ACETAMIDO-PHENYLBENZAMIDE DERIVATIVES AND METHODS OF USING THE SAME

RELATED APPLICATION

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 63/088,778, filed on October 7, 2020, the contents of which is incorporated herein in their entirety.

FIELD OF THE DISCLOSURE

[0002] The present disclosure relates to acetamido-phenylbenzamide derivatives which possess P-glycoprotein modulation activity and/or modulation activity against drug metabolizing enzyme cytochrome P450 (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) and are useful the treatment of the human or animal body. The present disclosure also relates to processes for the preparation of these compounds, to pharmaceutical compositions comprising them, and to their uses in the treatment of disorders in which the expression of P-glycoprotein and/or cytochrome P450 isoforms (*e.g.*, CYP3A4 or CYP3A5) is modulated (*e.g.*, in a cancer which has developed multi-drug resistance). The present disclosure also relates to the use of the compounds of the instant disclosure for improving oral bioavailability of therapeutics which are substrates of P-glycoprotein and/or cytochrome P450. The present disclosure also relates to the use of the compounds of the instant disclosure for increasing brain distribution of therapeutics which are substrates of P-glycoprotein and/or cytochrome P450.

BACKGROUND

[0003] Many anticancer agents (*e.g.*, vinca alkaloid, anthracycline, epipodophilotoxin, paclitaxel, and docetaxel) become ineffective when administered to a patient having multi-drug resistance (MDR) which has been caused by the presence of overexpressed P-glycoprotein. P-glycoprotein modulates intracellular accumulation of the administered anticancer agent by pumping the agent out of the tumor cell. Expression of the drug metabolizing CYP3A4 protein in breast, colorectal, esophageal tumors, and Ewing's sarcoma may curb the intracellular concentration of anticancer agents by forming metabolites with reduced antitumor activity. This action of CYP3A4 limits the

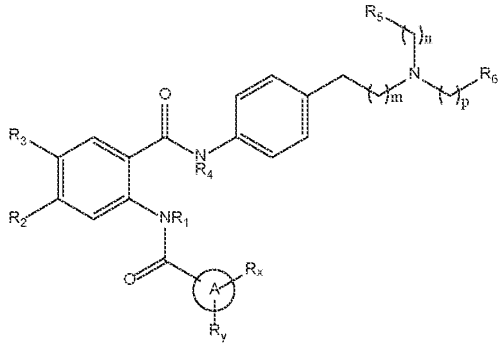
efficacy of anticancer agents or contributes to the development of resistance to these agents. Modulation of P-glycoprotein and/or cytochrome P450 enzymes (*e.g.*, CYP3A4) in the tumor cells may increase the sensitivity of these cells to anticancer agents.

[0004] P-glycoprotein is also expressed in normal healthy tissues, *e.g.* the small intestine. Intestinal P-glycoprotein does not allow its substrates to cross the epithelial cells lining the intestinal wall resulting in poor oral bioavailability of these substrates. Additionally, the anticancer agent may also suffer from first pass metabolism by cytochrome P450 enzymes (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) present in the small intestine as well as in the liver causing further reduction in their oral bioavailability. Accordingly, there is a need to enhance the bioavailability of anticancer agents by dual targeting modulation of P-glycoprotein and cytochrome P450 (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) enzymes.

[0005] The localization of P-glycoprotein in the endothelial cells of the blood-brain barrier also significantly limits the transport of P-glycoprotein substrates from the blood to the brain. Modulating P-glycoprotein at the blood-brain barrier may be beneficial in the treatment of a number of central nervous system (CNS) disorders, *e.g.*, a brain tumor such as glioblastoma. The conventional P-glycoprotein modulators, such as verapamil and cyclosporin A, cause serious adverse effects (*e.g.*, blood pressure decline and immunity suppression). Thus, several new P-glycoprotein modulators such as piperidine-2-carboxylate, acridine, piperazine-2,5-dione, anthranilic acid and methanodibenzosuberan derivatives have been developed. However, the newly introduced P-glycoprotein modulators have been reported to have toxicity and other adverse effects. This disclosure arises from a need to provide further compounds for the modulation of P-glycoprotein and cytochrome P450 (*e.g.*, CYP3A4 and CYP3A5 isoforms) enzymes that reduce serious adverse effects, while a) markedly enhancing the bioavailability of the substrates of these enzymes, including anticancer agents, b) overcoming the multi-drug resistance of tumors, and c) improving the delivery of the P-glycoprotein substrates to the brain.

SUMMARY

[0006] In one aspect, the present disclosure provides a compound of Formula (I):



(I),

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

A is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with oxo;

each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-C(O)N(R_{11})_2$, $-C(O)NR_{11}-S(O)_2R_{11}$, $-C(O)NR_{11}-S(O)_2-OR_{11}$, or $-C(O)NR_{11}-S(O)_2-N(R_{11})_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or $-C(O)R_7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, $-C(O)OR_{10}$, $-C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-O-(CH_2)_t-R_8$, $-NH-(CH_2)_t-R_8$, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently $-(CH_2)_0-$(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_0-(C_{6-10}$ aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$;

each R_{10} is independently halogen, -OH, $-NH_2$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

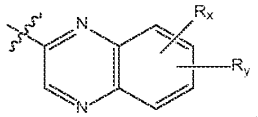
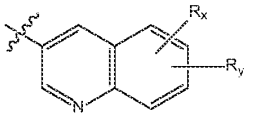
each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

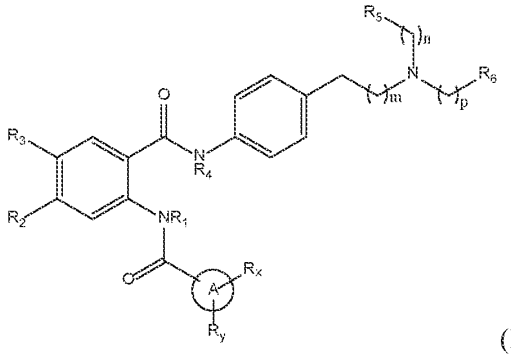
each n, m, and p is independently 0 or 1;

t is 1, 2, or 3; and

u is 0, 1, 2, or 3,

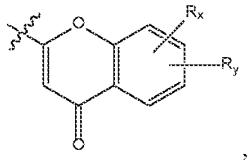
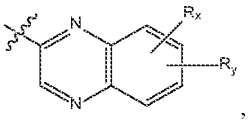
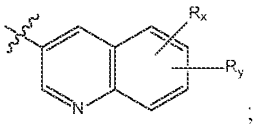
wherein when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not phenyl,  , or  .

[0007] In one aspect, the present disclosure provides a compound of Formula (I'):



(I'),

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

A is  ,  , or  ;

each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-C(O)N(R_{11})_2$, $-C(O)NR_{11}-S(O)_2R_{11}$, $-C(O)NR_{11}-S(O)_2-OR_{11}$, or $-C(O)NR_{11}-S(O)_2-N(R_{11})_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -

$C(O)R_7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, $-C(O)OR_{10}$, $-C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, $-O-(CH_2)_t-R_8$, $-NH-(CH_2)_t-R_8$, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently $-(CH_2)_u-$(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_u-(C_{6-10}$ aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$;

each R_{10} is independently halogen, -OH, $-NH_2$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and

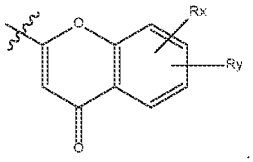
S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

each n, m, and p is independently 0 or 1;

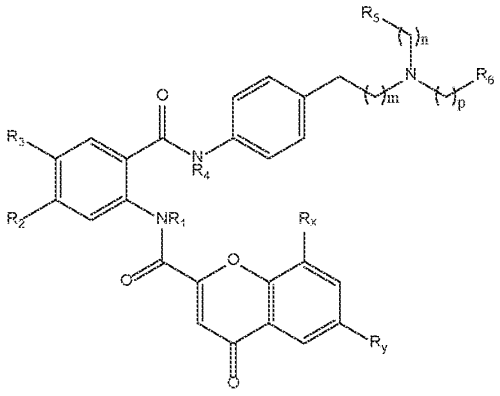
t is 1, 2, or 3; and

u is 0, 1, 2, or 3,

wherein when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl, A is 

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[0008] In one aspect, the present disclosure provides a compound of Formula (II):



(II),

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

each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -C(O)R_7, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, -NH_2, -CN, -C(O)R_{10}, -C(O)OR_{10}, -C(O)N(R_{10})$_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -O-(CH$_2$)$_t$-R_8, -NH-(CH$_2$)$_t$-R_8, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, -NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -SH, -S(C_{1-6} alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently -(CH$_2$)$_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or -(CH$_2$)$_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2;

each R_{10} is independently halogen, -OH, -NH_2, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

each n, m, and p is independently 0 or 1;

t is 1, 2, or 3; and

u is 0, 1, 2, or 3.

[0009] In one aspect, the present disclosure provides a compound obtainable by, or obtained by, a method for preparing a compound as described herein (*e.g.*, a method comprising one or more steps described in Schemes 1-10).

[0010] In one aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, and a pharmaceutically acceptable diluent or carrier.

[0011] In one aspect, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein (*e.g.*, the intermediate is selected from the intermediates described in Examples 1-284).

[0012] In one aspect, the present disclosure provides a method of modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*) and/or cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[0013] In one aspect, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[0014] In one aspect, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*) and/or cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*).

[0015] In one aspect, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[0016] In one aspect, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*) and/or cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*).

[0017] In one aspect, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[0018] In one aspect, the present disclosure provides a method of preparing a compound of the present disclosure.

[0019] In one aspect, the present disclosure provides a method of preparing a compound, comprising one or more steps described herein.

[0020] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to

be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

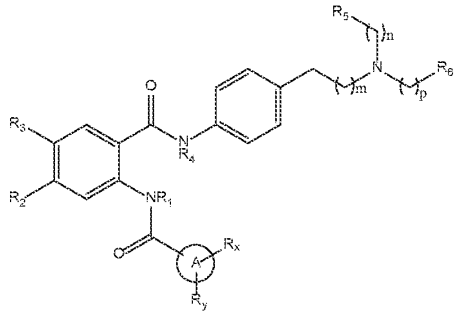
[0021] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION

[0022] The disclosure arises from a need to provide further compounds for the modulation of P-glycoprotein and/or cytochrome P450 (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) enzymes that reduce serious adverse effects, while markedly enhancing the bioavailability of drugs which are substrates of P-glycoprotein and/or cytochrome P450 (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) enzymes, including anticancer agents, antihypertensive agents, antiarrhythmics, HIV protease inhibitors, antibiotics, antimycotics, immunosuppressive agents, antidepressants, neuroleptics, antiepileptics, antacids, opioids, and antiemetics. The compounds of the instant disclosure can also be useful in overcoming multi-drug resistance caused by P-glycoprotein and/or cytochrome P450 (*e.g.*, CYP3A4) in cancer cells. The compounds of the instant disclosure can also be useful in modulating P-glycoprotein at the blood brain barrier, enabling brain penetration of drugs and improving the efficacy of these drugs in diseases of the brain (*e.g.*, a brain tumor). The compounds of the instant closure can also be useful for modulating P-glycoprotein in the capillaries of biliary canaliculi, thereby modulating the enterohepatic recirculation of P-glycoprotein substrate drugs affected by this phenomenon (*e.g.*, irinotecan). The compounds of the instant disclosure can also be useful for modulating P-glycoprotein expressed in the renal proximal tubule cells and affect the renal excretion of substrate drugs.

Compounds of the Present Disclosure

[0023] In one aspect, the present disclosure provides a compound of Formula (I):



(I),

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

A is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with oxo;

each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-C(O)N(R_{11})_2$, $-C(O)NR_{11}-S(O)_2R_{11}$, $-C(O)NR_{11}-S(O)_2-OR_{11}$, or $-C(O)NR_{11}-S(O)_2-N(R_{11})_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or $-C(O)R_7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, $-C(O)OR_{10}$, $-C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-O-(CH_2)_t-R_8$, $-NH-(CH_2)_t-R_8$, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently $-(CH_2)_0-$(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_0-(C_{6-10}$ aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$;

each R_{10} is independently halogen, -OH, $-NH_2$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

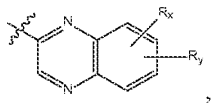
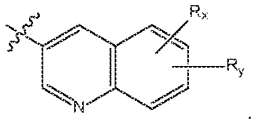
each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

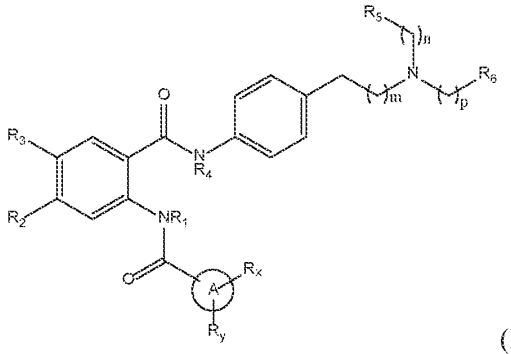
each n, m, and p is independently 0 or 1;

t is 1, 2, or 3; and

u is 0, 1, 2, or 3,

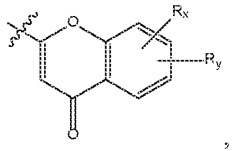
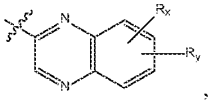
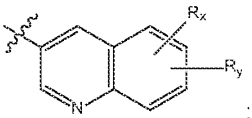
wherein R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not phenyl,  , or  .

[0024] In one aspect, the present disclosure provides a compound of Formula (I'):



(I'),

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

A is  ,  , or  ;

each R_X and R_Y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-C(O)N(R_{11})_2$, $-C(O)NR_{11}$-$S(O)_2R_{11}$, $-C(O)NR_{11}$-$S(O)_2$-OR_{11}, or $-C(O)NR_{11}$-$S(O)_2$-$N(R_{11})_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -

$C(O)R_7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, $-C(O)OR_{10}$, $-C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, $-O-(CH_2)_t-R_8$, $-NH-(CH_2)_t-R_8$, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently $-(CH_2)_u-$(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_u-(C_{6-10}$ aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$;

each R_{10} is independently halogen, -OH, $-NH_2$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and

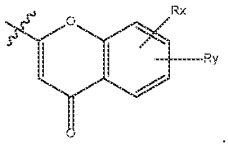
S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

each n, m, and p is independently 0 or 1;

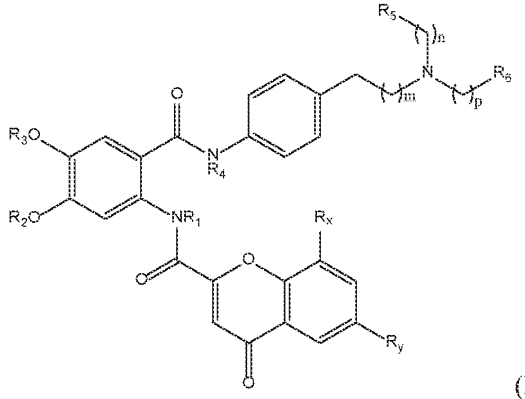
t is 1, 2, or 3; and

u is 0, 1, 2, or 3,

wherein R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl, A is 

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[0025] In one aspect, the present disclosure provides a compound of Formula (II):



(II),

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

each R_X and R_Y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -C(O)R_7, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, -NH_2, -CN, -C(O)R_{10}, -C(O)OR_{10}, -C(O)N(R_{10})$_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -O-(CH_2)$_t$-R_8, -NH-(CH_2)$_t$-R_8, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, -NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -SH, -S(C_{1-6} alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently -(CH_2)$_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or -(CH_2)$_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2;

each R_{10} is independently halogen, -OH, -NH_2, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

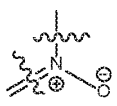
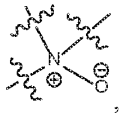
each n, m, and p is independently 0 or 1;

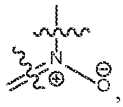
t is 1, 2, or 3; and

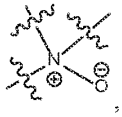
u is 0, 1, 2, or 3.

[0026] It is understood that, for a compound of Formula (I), (I'), or (II), **A**, $\mathbf{R_x}$, $\mathbf{R_y}$, $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$, $\mathbf{R_6}$, $\mathbf{R_7}$, $\mathbf{R_8}$, $\mathbf{R_9}$, $\mathbf{R_{10}}$, $\mathbf{R_{11}}$, **n**, **m**, **p**, **t**, and **u** can each be, where applicable, selected from the groups described herein, and any group described herein for any of **A**, $\mathbf{R_x}$, $\mathbf{R_y}$, $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$, $\mathbf{R_6}$, $\mathbf{R_7}$, $\mathbf{R_8}$, $\mathbf{R_9}$, $\mathbf{R_{10}}$, $\mathbf{R_{11}}$, **n**, **m**, **p**, **t**, and **u** can be combined, where applicable, with any group described herein for one or more of the remainder of **A**, $\mathbf{R_x}$, $\mathbf{R_y}$, $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$, $\mathbf{R_6}$, $\mathbf{R_7}$, $\mathbf{R_8}$, $\mathbf{R_9}$, $\mathbf{R_{10}}$, $\mathbf{R_{11}}$, **n**, **m**, **p**, **t**, and **u**.

[0027] In some embodiments, a N atom of the compound is an N-oxide.

[0028] In some embodiments, the N-oxide has the formula  or , wherein ≈ indicates attachment to the compound of Formula (I), (I'), or (II).

[0029] In some embodiments, the N-oxide has the formula , wherein ≈ indicates attachment to the compound of Formula (I), (I'), or (II).

[0030] In some embodiments, the N-oxide has the formula , wherein ~ indicates attachment to the compound of Formula (I), (I'), or (II).

[0031] In some embodiments, A is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with oxo.

[0032] In some embodiments, A is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[0033] In some embodiments, A is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with oxo.

[0034] In some embodiments, A is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[0035] In some embodiments, A is C_{3-10} cycloalkyl optionally substituted with oxo.

[0036] In some embodiments, A is C_3 cycloalkyl. In some embodiments, A is C_4 cycloalkyl. In some embodiments, A is C_5 cycloalkyl. In some embodiments, A is C_6 cycloalkyl. In some embodiments, A is C_7 cycloalkyl. In some embodiments, A is C_8 cycloalkyl. In some embodiments, A is C_9 cycloalkyl. In some embodiments, A is C_{10} cycloalkyl.

[0037] In some embodiments, A is C_3 cycloalkyl optionally substituted with oxo. In some embodiments, A is C_4 cycloalkyl optionally substituted with oxo. In some embodiments, A is C_5 cycloalkyl optionally substituted with oxo. In some embodiments, A is C_6 cycloalkyl optionally substituted with oxo. In some embodiments, A is C_7 cycloalkyl optionally substituted with oxo. In some embodiments, A is C_8 cycloalkyl optionally substituted with oxo. In some embodiments, A is C_9 cycloalkyl optionally substituted with oxo. In some embodiments, A is C_{10} cycloalkyl optionally substituted with oxo.

[0038] In some embodiments, A is C_3-C_7 monocyclic cycloalkyl. In some embodiments, A is C_3-C_7 monocyclic saturated cycloalkyl. In some embodiments, A is C_3-C_7 monocyclic partially saturated cycloalkyl. In some embodiments, A is C_9-C_{10} bicyclic cycloalkyl. In some

embodiments, A is C_9-C_{10} bicyclic saturated cycloalkyl. In some embodiments, A is C_9-C_{10} bicyclic partially saturated cycloalkyl. In some embodiments, A is C_8-C_{10} polycyclic cycloalkyl.

[0039] In some embodiments, A is C_3-C_7 monocyclic cycloalkyl optionally substituted with oxo. In some embodiments, A is C_3-C_7 monocyclic saturated cycloalkyl optionally substituted with oxo. In some embodiments, A is C_3-C_7 monocyclic partially saturated cycloalkyl optionally substituted with oxo. In some embodiments, A is C_9-C_{10} bicyclic cycloalkyl optionally substituted with oxo. In some embodiments, A is C_9-C_{10} bicyclic saturated cycloalkyl optionally substituted with oxo. In some embodiments, A is C_9-C_{10} bicyclic partially saturated cycloalkyl optionally substituted with oxo. In some embodiments, A is C_8-C_{10} polycyclic cycloalkyl optionally substituted with oxo.

[0040] In some embodiments, A is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[0041] In some embodiments, A is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo.

[0042] In some embodiments, A is 3-membered heterocyclyl comprising 1 heteroatom selected from N, O, and S. In some embodiments, A is 4-membered heterocyclyl comprising 1-2 heteroatoms selected from N, O, and S. In some embodiments, A is 5-membered heterocyclyl comprising 1-3 heteroatoms selected from N, O, and S. In some embodiments, A is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[0043] In some embodiments, A is 3-membered heterocyclyl comprising 1 heteroatom selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 4-membered heterocyclyl comprising 1-2 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 5-membered heterocyclyl comprising 1-3 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 7-membered heterocyclyl comprising 1-4 heteroatoms selected

from N, O, and S, optionally substituted with oxo. In some embodiments, A is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo.

[0044] In some embodiments, A is 7- to 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[0045] In some embodiments, A is 7- to 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo.

[0046] In some embodiments, A is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[0047] In some embodiments, A is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo. In some embodiments, A is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo.

[0048] In some embodiments, A is 8- to 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[0049] In some embodiments, A is 8- to 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with oxo.

[0050] In some embodiments, A is C_{6-10} aryl or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[0051] In some embodiments, A is C_{6-10} aryl. In some embodiments, A is C_5-C_6 aryl. In some embodiments, A is phenyl.

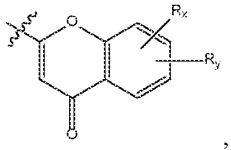
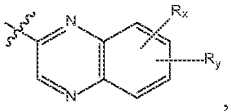
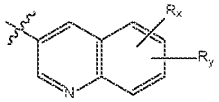
[0052] In some embodiments, A is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

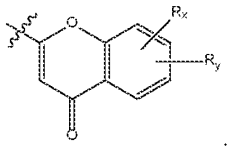
[0053] In some embodiments, A is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

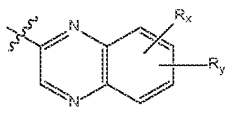
[0054] In some embodiments, A is 9- to 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

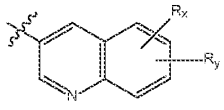
[0055] In some embodiments, A is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, A is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[0056] In some embodiments, A is 9- to 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[0057] In some embodiments, A is , , or .

[0058] In some embodiments, A is .

[0059] In some embodiments, A is .

[0060] In some embodiments, A is .

[0061] In some embodiments, each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$.

[0062] In some embodiments, each R_x and R_y is H.

[0063] In some embodiments, each R_x and R_y is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$.

[0064] In some embodiments, each R_x and R_y is independently H, C_{1-6} alkyl, or -OH.

[0065] In some embodiments, R_x is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$.

[0066] In some embodiments, R_x is H.

[0067] In some embodiments, R_x is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$.

[0068] In some embodiments, R_x is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkoxy.

[0069] In some embodiments, R_x is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0070] In some embodiments, R_x is C_{1-6} alkyl. In some embodiments, R_x is methyl. In some embodiments, R_x is ethyl. In some embodiments, R_x is propyl. In some embodiments, R_x is butyl. In some embodiments, R_x is pentyl. In some embodiments, R_x is hexyl. In some embodiments, R_x is isopropyl. In some embodiments, R_x is isobutyl. In some embodiments, R_x is isopentyl. In some embodiments, R_x is isohexyl. In some embodiments, R_x is secbutyl. In some embodiments, R_x is secpentyl. In some embodiments, R_x is sechexyl. In some embodiments, R_x is tertbutyl.

[0071] In some embodiments, R_x is C_{2-6} alkenyl. In some embodiments, R_x is C_2 alkenyl. In some embodiments, R_x is C_3 alkenyl. In some embodiments, R_x is C_4 alkenyl. In some embodiments, R_x is C_5 alkenyl. In some embodiments, R_x is C_6 alkenyl.

[0072] In some embodiments, R_x is C_{2-6} alkynyl. In some embodiments, R_x is C_2 alkynyl. In some embodiments, R_x is C_3 alkynyl. In some embodiments, R_x is C_4 alkynyl. In some embodiments, R_x is C_5 alkynyl. In some embodiments, R_x is C_6 alkynyl.

[0073] In some embodiments, R_x is C_{1-6} alkoxy. In some embodiments, R_x is methoxy. In some embodiments, R_x is ethoxy. In some embodiments, R_x is propoxy. In some embodiments, R_x is butoxy. In some embodiments, R_x is pentoxy. In some embodiments, R_x is hexoxy.

[0074] In some embodiments, R_X is halogen, -CN, -OH, or -NH_2.

[0075] In some embodiments, R_X is halogen. In some embodiments, R_X is F, Cl, Br, or I. In some embodiments, R_X is F, Cl, or Br. In some embodiments, R_X is F. In some embodiments, R_X is Cl. In some embodiments, R_X is Br. In some embodiments, R_X is I.

[0076] In some embodiments, R_X is -CN. In some embodiments, R_X is -OH. In some embodiments, R_X is -NH_2.

[0077] In some embodiments, each R_X is H, C_{1-6} alkyl, or -OH.

[0078] In some embodiments, R_Y is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or -NH_2.

[0079] In some embodiments, R_Y is H.

[0080] In some embodiments, R_Y is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or -NH_2.

[0081] In some embodiments, R_Y is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkoxy.

[0082] In some embodiments, R_Y is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0083] In some embodiments, R_Y is C_{1-6} alkyl. In some embodiments, R_Y is methyl. In some embodiments, R_Y is ethyl. In some embodiments, R_Y is propyl. In some embodiments, R_Y is butyl. In some embodiments, R_Y is pentyl. In some embodiments, R_Y is hexyl. In some embodiments, R_Y is isopropyl. In some embodiments, R_Y is isobutyl. In some embodiments, R_Y is isopentyl. In some embodiments, R_Y is isohexyl. In some embodiments, R_Y is secbutyl. In some embodiments, R_Y is secpentyl. In some embodiments, R_Y is sechexyl. In some embodiments, R_Y is tertbutyl.

[0084] In some embodiments, R_Y is C_{2-6} alkenyl. In some embodiments, R_Y is C_2 alkenyl. In some embodiments, R_Y is C_3 alkenyl. In some embodiments, R_Y is C_4 alkenyl. In some embodiments, R_Y is C_5 alkenyl. In some embodiments, R_Y is C_6 alkenyl.

[0085] In some embodiments, R_Y is C_{2-6} alkynyl. In some embodiments, R_Y is C_2 alkynyl. In some embodiments, R_Y is C_3 alkynyl. In some embodiments, R_Y is C_4 alkynyl. In some embodiments, R_Y is C_5 alkynyl. In some embodiments, R_Y is C_6 alkynyl.

[0086] In some embodiments, R_Y is C_{1-6} alkoxy. In some embodiments, R_Y is methoxy. In some embodiments, R_Y is ethoxy. In some embodiments, R_Y is propoxy. In some embodiments, R_Y is butoxy. In some embodiments, R_Y is pentoxy. In some embodiments, R_Y is hexoxy.

[0087] In some embodiments, R_Y is halogen, -CN, -OH, or -NH_2.

[0088] In some embodiments, R_y is halogen. In some embodiments, R_y is F, Cl, Br, or I. In some embodiments, R_y is F, Cl, or Br. In some embodiments, R_y is F. In some embodiments, R_y is Cl. In some embodiments, R_y is Br. In some embodiments, R_y is I.

[0089] In some embodiments, R_y is -CN. In some embodiments, R_y is -OH. In some embodiments, R_y is $-NH_2$.

[0090] In some embodiments, each R_y is H, C_{1-6} alkyl, or -OH.

[0091] In some embodiments, each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0092] In some embodiments, each R_1 and R_4 is independently H.

[0093] In some embodiments, each R_1 and R_4 is independently C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0094] In some embodiments, each R_1 and R_4 is independently H or C_{1-6} alkyl.

[0095] In some embodiments, R_1 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0096] In some embodiments, R_1 is H.

[0097] In some embodiments, R_1 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[0098] In some embodiments, R_1 is C_{1-6} alkyl. In some embodiments, R_1 is methyl. In some embodiments, R_1 is ethyl. In some embodiments, R_1 is propyl. In some embodiments, R_1 is butyl. In some embodiments, R_1 is pentyl. In some embodiments, R_1 is hexyl. In some embodiments, R_1 is isopropyl. In some embodiments, R_1 is isobutyl. In some embodiments, R_1 is isopentyl. In some embodiments, R_1 is isohexyl. In some embodiments, R_1 is secbutyl. In some embodiments, R_1 is secpentyl. In some embodiments, R_1 is sechexyl. In some embodiments, R_1 is tertbutyl.

[0099] In some embodiments, R_1 is C_{2-6} alkenyl. In some embodiments, R_1 is C_2 alkenyl. In some embodiments, R_1 is C_3 alkenyl. In some embodiments, R_1 is C_4 alkenyl. In some embodiments, R_1 is C_5 alkenyl. In some embodiments, R_1 is C_6 alkenyl.

[00100] In some embodiments, R_1 is C_{2-6} alkynyl. In some embodiments, R_1 is C_2 alkynyl. In some embodiments, R_1 is C_3 alkynyl. In some embodiments, R_1 is C_4 alkynyl. In some embodiments, R_1 is C_5 alkynyl. In some embodiments, R_1 is C_6 alkynyl.

[00101] In some embodiments, each R_1 is H or C_{1-6} alkyl.

[00102] In some embodiments, R_4 is H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00103] In some embodiments, R_4 is H.

[00104] In some embodiments, R_4 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00105] In some embodiments, R_4 is C_{1-6} alkyl. In some embodiments, R_4 is methyl. In some embodiments, R_4 is ethyl. In some embodiments, R_4 is propyl. In some embodiments, R_4 is butyl. In some embodiments, R_4 is pentyl. In some embodiments, R_4 is hexyl. In some embodiments, R_4 is isopropyl. In some embodiments, R_4 is isobutyl. In some embodiments, R_4 is isopentyl. In some embodiments, R_4 is isohexyl. In some embodiments, R_4 is secbutyl. In some embodiments, R_4 is secpentyl. In some embodiments, R_4 is sechexyl. In some embodiments, R_4 is tertbutyl.

[00106] In some embodiments, R_4 is C_{2-6} alkenyl. In some embodiments, R_4 is C_2 alkenyl. In some embodiments, R_4 is C_3 alkenyl. In some embodiments, R_4 is C_4 alkenyl. In some embodiments, R_4 is C_5 alkenyl. In some embodiments, R_4 is C_6 alkenyl.

[00107] In some embodiments, R_4 is C_{2-6} alkynyl. In some embodiments, R_4 is C_2 alkynyl. In some embodiments, R_4 is C_3 alkynyl. In some embodiments, R_4 is C_4 alkynyl. In some embodiments, R_4 is C_5 alkynyl. In some embodiments, R_4 is C_6 alkynyl.

[00108] In some embodiments, each R_4 is H or C_{1-6} alkyl.

[00109] In some embodiments, each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$, wherein either R_2 or R_3 is not H.

[00110] In some embodiments, each R_2 and R_3 is independently C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00111] In some embodiments, each R_2 and R_3 is independently -O-C_{1-6} alkyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, or -C(O)NR_{11}-S(O)$_2$$R_{11}$.

[00112] In some embodiments, either R_2 or R_3 is not H.

[00113] In some embodiments, R_2 is not H.

[00114] In some embodiments, R_3 is not H.

[00115] In some embodiments, R_2 is H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00116] In some embodiments, R_2 is H.

[00117] In some embodiments, R_2 is C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00118] In some embodiments, R_2 is C_{2-6} alkenyl or C_{2-6} alkynyl.

[00119] In some embodiments, R_2 is C_{2-6} alkenyl. In some embodiments, R_2 is C_2 alkenyl. In some embodiments, R_2 is C_3 alkenyl. In some embodiments, R_2 is C_4 alkenyl. In some embodiments, R_2 is C_5 alkenyl. In some embodiments, R_2 is C_6 alkenyl.

[00120] In some embodiments, R_2 is C_{2-6} alkynyl. In some embodiments, R_2 is C_2 alkynyl. In some embodiments, R_2 is C_3 alkynyl. In some embodiments, R_2 is C_4 alkynyl. In some embodiments, R_2 is C_5 alkynyl. In some embodiments, R_2 is C_6 alkynyl.

[00121] In some embodiments, R_2 is -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00122] In some embodiments, R_2 is -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, or -O-C_{2-6} alkynyl.

[00123] In some embodiments, R_2 is -O-C_{1-6} alkyl. In some embodiments, R_2 is -O-methyl. In some embodiments, R_2 is -O-ethyl. In some embodiments, R_2 is -O-propyl. In some embodiments, R_2 is -O-butyl. In some embodiments, R_2 is -O-pentyl. In some embodiments, R_2 is -O-hexyl. In some embodiments, R_2 is -O-isopropyl. In some embodiments, R_2 is -O-isobutyl. In some embodiments, R_2 is -O-isopentyl. In some embodiments, R_2 is -O-isohexyl. In some embodiments, R_2 is -O-secbutyl. In some embodiments, R_2 is -O-secpentyl. In some embodiments, R_2 is -O-sechexyl. In some embodiments, R_2 is -O-tertbutyl.

[00124] In some embodiments, R_2 is -O-C_{2-6} alkenyl. In some embodiments, R_2 is -O-C_2 alkenyl. In some embodiments, R_2 is -O-C_3 alkenyl. In some embodiments, R_2 is -O-C_4 alkenyl. In some embodiments, R_2 is -O-C_5 alkenyl. In some embodiments, R_2 is -O-C_6 alkenyl.

[00125] In some embodiments, R_2 is -O-C_{2-6} alkynyl. In some embodiments, R_2 is -O-C_2 alkynyl. In some embodiments, R_2 is -O-C_3 alkynyl. In some embodiments, R_2 is -O-C_4 alkynyl. In some embodiments, R_2 is -O-C_5 alkynyl. In some embodiments, R_2 is -O-C_6 alkynyl.

[00126] In some embodiments, R_2 is -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00127] In some embodiments, R_2 is -C(O)R_{11}, -C(O)OR_{11}, or -C(O)N(R_{11})$_2$.

[00128] In some embodiments, R_2 is -C(O)R_{11}. In some embodiments, R_2 is -C(O)OR_{11}. In some embodiments, R_2 is -C(O)N(R_{11})$_2$.

[00129] In some embodiments, R_2 is -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00130] In some embodiments, R_2 is -C(O)NR_{11}-S(O)$_2$$R_{11}$. In some embodiments, R_2 is -C(O)NR_{11}-S(O)$_2$-OR_{11}. In some embodiments, R_2 is -C(O)NR_{11}-S(O)$_2$-N(R_{11})$_2$.

[00131] In some embodiments, R_2 is -O-C_{1-6} alkyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, or -C(O)NR_{11}-S(O)$_2$$R_{11}$.

[00132] In some embodiments, R_3 is H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00133] In some embodiments, R_3 is H.

[00134] In some embodiments, R_3 is C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00135] In some embodiments, R_3 is C_{2-6} alkenyl or C_{2-6} alkynyl.

[00136] In some embodiments, R_3 is C_{2-6} alkenyl. In some embodiments, R_3 is C_2 alkenyl. In some embodiments, R_3 is C_3 alkenyl. In some embodiments, R_3 is C_4 alkenyl. In some embodiments, R_3 is C_5 alkenyl. In some embodiments, R_3 is C_6 alkenyl.

[00137] In some embodiments, R_3 is C_{2-6} alkynyl. In some embodiments, R_3 is C_2 alkynyl. In some embodiments, R_3 is C_3 alkynyl. In some embodiments, R_3 is C_4 alkynyl. In some embodiments, R_3 is C_5 alkynyl. In some embodiments, R_3 is C_6 alkynyl.

[00138] In some embodiments, R_3 is -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$.

[00139] In some embodiments, R_3 is -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, or -O-C_{2-6} alkynyl.

[00140] In some embodiments, R_3 is -O-C_{1-6} alkyl. In some embodiments, R_3 is -O-methyl. In some embodiments, R_3 is -O-ethyl. In some embodiments, R_3 is -O-propyl. In some embodiments, R_3 is -O-butyl. In some embodiments, R_3 is -O-pentyl. In some embodiments, R_3 is -O-hexyl. In some embodiments, R_3 is -O-isopropyl. In some embodiments, R_3 is -O-isobutyl. In some embodiments, R_3 is -O-isopentyl. In some embodiments, R_3 is -O-isohexyl. In some

embodiments, R_3 is -O-secbutyl. In some embodiments, R_3 is -O-secpentyl. In some embodiments, R_3 is -O-sechexyl. In some embodiments, R_3 is -O-tertbutyl.

[00141] In some embodiments, R_3 is -O-C_{2-6} alkenyl. In some embodiments, R_3 is -O-C_2 alkenyl. In some embodiments, R_3 is -O-C_3 alkenyl. In some embodiments, R_3 is -O-C_4 alkenyl. In some embodiments, R_3 is -O-C_5 alkenyl. In some embodiments, R_3 is -O-C_6 alkenyl.

[00142] In some embodiments, R_3 is -O-C_{2-6} alkynyl. In some embodiments, R_3 is -O-C_2 alkynyl. In some embodiments, R_3 is -O-C_3 alkynyl. In some embodiments, R_3 is -O-C_4 alkynyl. In some embodiments, R_3 is -O-C_5 alkynyl. In some embodiments, R_3 is -O-C_6 alkynyl.

[00143] In some embodiments, R_3 is -$C(O)R_{11}$, -$C(O)OR_{11}$, -$C(O)N(R_{11})_2$, -$C(O)NR_{11}$-$S(O)_2R_{11}$, -$C(O)NR_{11}$-$S(O)_2$-OR_{11}, or -$C(O)NR_{11}$-$S(O)_2$-$N(R_{11})_2$.

[00144] In some embodiments, R_3 is -$C(O)R_{11}$, -$C(O)OR_{11}$, or -$C(O)N(R_{11})_2$.

[00145] In some embodiments, R_3 is -$C(O)R_{11}$. In some embodiments, R_3 is -$C(O)OR_{11}$. In some embodiments, R_3 is -$C(O)N(R_{11})_2$.

[00146] In some embodiments, R_3 is -$C(O)NR_{11}$-$S(O)_2R_{11}$, -$C(O)NR_{11}$-$S(O)_2$-OR_{11}, or -$C(O)NR_{11}$-$S(O)_2$-$N(R_{11})_2$.

[00147] In some embodiments, R_3 is -$C(O)NR_{11}$-$S(O)_2R_{11}$. In some embodiments, R_3 is -$C(O)NR_{11}$-$S(O)_2$-OR_{11}. In some embodiments, R_3 is -$C(O)NR_{11}$-$S(O)_2$-$N(R_{11})_2$.

[00148] In some embodiments, R_3 is -O-C_{1-6} alkyl, -$C(O)R_{11}$, -$C(O)OR_{11}$, -$C(O)N(R_{11})_2$, or -$C(O)NR_{11}$-$S(O)_2R_{11}$.

[00149] In some embodiments, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -$C(O)R_7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7.

[00150] In some embodiments, each R_5 and R_6 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected

from N, O, and S, or -C(O)R_7, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7.

[00151] In some embodiments, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00152] In some embodiments, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00153] In some embodiments, each R_5 and R_6 is independently H.

[00154] In some embodiments, each R_5 and R_6 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00155] In some embodiments, each R_5 and R_6 is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00156] In some embodiments, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -C(O)R_7, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00157] In some embodiments, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00158] In some embodiments, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more R_7.

[00159] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is substituted with one or more R_7.

[00160] In some embodiments, R_5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00161] In some embodiments, R_5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00162] In some embodiments, R_5 is H.

[00163] In some embodiments, R_5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00164] In some embodiments, R_5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00165] In some embodiments, R_5 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_7.

[00166] In some embodiments, R_5 is C_{1-6} alkyl optionally substituted with one or more R_7. In some embodiments, R_5 is methyl optionally substituted with one or more R_7. In some embodiments, R_5 is ethyl optionally substituted with one or more R_7. In some embodiments, R_5 is propyl optionally substituted with one or more R_7. In some embodiments, R_5 is butyl optionally substituted with one or more R_7. In some embodiments, R_5 is pentyl optionally substituted with one or more R_7. In some embodiments, R_5 is hexyl optionally substituted with one or more R_7. In some embodiments, R_5 is isopropyl optionally substituted with one or more R_7. In some embodiments, R_5 is isobutyl optionally substituted with one or more R_7. In some embodiments, R_5 is isopentyl optionally substituted with one or more R_7. In some embodiments, R_5 is isohexyl optionally substituted with one or more R_7. In some embodiments, R_5 is secbutyl optionally substituted with one or more R_7. In some embodiments, R_5 is secpentyl optionally substituted with one or more R_7. In some embodiments, R_5 is sechexyl optionally substituted with one or more R_7. In some embodiments, R_5 is tertbutyl optionally substituted with one or more R_7.

[00167] In some embodiments, R_5 is C_{2-6} alkenyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_2 alkenyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_3 alkenyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_4 alkenyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_5 alkenyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_6 alkenyl optionally substituted with one or more R_7.

[00168] In some embodiments, R_5 is C_{2-6} alkynyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_2 alkynyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_3 alkynyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_4 alkynyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_5 alkynyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_6 alkynyl optionally substituted with one or more R_7.

[00169] In some embodiments, R_5 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one or more R_7.

[00170] In some embodiments, R_5 is C_{1-6} alkyl substituted with one or more R_7. In some embodiments, R_5 is methyl substituted with one or more R_7. In some embodiments, R_5 is ethyl substituted with one or more R_7. In some embodiments, R_5 is propyl substituted with one or more R_7. In some embodiments, R_5 is butyl substituted with one or more R_7. In some embodiments, R_5 is pentyl substituted with one or more R_7. In some embodiments, R_5 is hexyl substituted with one or more R_7. In some embodiments, R_5 is isopropyl substituted with one or more R_7. In some embodiments, R_5 is isobutyl substituted with one or more R_7. In some embodiments, R_5 is isopentyl substituted with one or more R_7. In some embodiments, R_5 is isohexyl substituted with one or more R_7. In some embodiments, R_5 is secbutyl substituted with one or more R_7. In some embodiments, R_5 is secpentyl substituted with one or more R_7. In some embodiments, R_5 is sechexyl substituted with one or more R_7. In some embodiments, R_5 is tertbutyl substituted with one or more R_7.

[00171] In some embodiments, R_5 is C_{2-6} alkenyl substituted with one or more R_7. In some embodiments, R_5 is C_2 alkenyl substituted with one or more R_7. In some embodiments, R_5 is C_3 alkenyl substituted with one or more R_7. In some embodiments, R_5 is C_4 alkenyl substituted with one or more R_7. In some embodiments, R_5 is C_5 alkenyl substituted with one or more R_7. In some embodiments, R_5 is C_6 alkenyl substituted with one or more R_7.

[00172] In some embodiments, R_5 is C_{2-6} alkynyl substituted with one or more R_7. In some embodiments, R_5 is C_2 alkynyl substituted with one or more R_7. In some embodiments, R_5 is C_3 alkynyl substituted with one or more R_7. In some embodiments, R_5 is C_4 alkynyl substituted with one or more R_7. In some embodiments, R_5 is C_5 alkynyl substituted with one or more R_7. In some embodiments, R_5 is C_6 alkynyl substituted with one or more R_7.

[00173] In some embodiments, R_5 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one R_7.

[00174] In some embodiments, R_5 is C_{1-6} alkyl substituted with one R_7. In some embodiments, R_5 is methyl substituted with one R_7. In some embodiments, R_5 is ethyl substituted with one R_7. In some embodiments, R_5 is propyl substituted with one R_7. In some embodiments, R_5 is butyl substituted with one R_7. In some embodiments, R_5 is pentyl substituted with one R_7. In some embodiments, R_5 is hexyl substituted with one R_7. In some embodiments, R_5 is isopropyl substituted with one R_7. In some embodiments, R_5 is isobutyl substituted with one R_7. In some embodiments, R_5 is isopentyl substituted with one R_7. In some embodiments, R_5 is isohexyl

substituted with one R_7. In some embodiments, R_5 is secbutyl substituted with one R_7. In some embodiments, R_5 is secpentyl substituted with one R_7. In some embodiments, R_5 is sechexyl substituted with one R_7. In some embodiments, R_5 is tertbutyl substituted with one R_7.

[00175] In some embodiments, R_5 is C_{2-6} alkenyl substituted with one R_7. In some embodiments, R_5 is C_2 alkenyl substituted with one R_7. In some embodiments, R_5 is C_3 alkenyl substituted with one R_7. In some embodiments, R_5 is C_4 alkenyl substituted with one R_7. In some embodiments, R_5 is C_5 alkenyl substituted with one R_7. In some embodiments, R_5 is C_6 alkenyl substituted with one R_7.

[00176] In some embodiments, R_5 is C_{2-6} alkynyl substituted with one R_7. In some embodiments, R_5 is C_2 alkynyl substituted with one R_7. In some embodiments, R_5 is C_3 alkynyl substituted with one R_7. In some embodiments, R_5 is C_4 alkynyl substituted with one R_7. In some embodiments, R_5 is C_5 alkynyl substituted with one R_7. In some embodiments, R_5 is C_6 alkynyl substituted with one R_7.

[00177] In some embodiments, R_5 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00178] In some embodiments, R_5 is C_{1-6} alkyl. In some embodiments, R_5 is methyl. In some embodiments, R_5 is ethyl. In some embodiments, R_5 is propyl. In some embodiments, R_5 is butyl. In some embodiments, R_5 is pentyl. In some embodiments, R_5 is hexyl. In some embodiments, R_5 is isopropyl. In some embodiments, R_5 is isobutyl. In some embodiments, R_5 is isopentyl. In some embodiments, R_5 is isohexyl. In some embodiments, R_5 is secbutyl. In some embodiments, R_5 is secpentyl. In some embodiments, R_5 is sechexyl. In some embodiments, R_5 is tertbutyl.

[00179] In some embodiments, R_5 is C_{2-6} alkenyl. In some embodiments, R_5 is C_2 alkenyl. In some embodiments, R_5 is C_3 alkenyl. In some embodiments, R_5 is C_4 alkenyl. In some embodiments, R_5 is C_5 alkenyl. In some embodiments, R_5 is C_6 alkenyl.

[00180] In some embodiments, R_5 is C_{2-6} alkynyl. In some embodiments, R_5 is C_2 alkynyl. In some embodiments, R_5 is C_3 alkynyl. In some embodiments, R_5 is C_4 alkynyl. In some embodiments, R_5 is C_5 alkynyl. In some embodiments, R_5 is C_6 alkynyl.

[00181] In some embodiments, R_5 is C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00182] In some embodiments, R_5 is C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00183] In some embodiments, R_5 is C_{3-10} cycloalkyl or 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more R_7.

[00184] In some embodiments, R_5 is C_{3-10} cycloalkyl or 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00185] In some embodiments, R_5 is C_{3-10} cycloalkyl optionally substituted with one or more R_7.

[00186] In some embodiments, R_5 is C_3 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_4 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_5 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_6 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_7 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_8 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_9 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_{10} cycloalkyl optionally substituted with one or more R_7.

[00187] In some embodiments, R_5 is C_3-C_7 monocyclic cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_3-C_7 monocyclic saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_3-C_7 monocyclic partially saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic partially saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_5 is C_8-C_{10} polycyclic cycloalkyl optionally substituted with one or more R_7.

[00188] In some embodiments, R_5 is C_{3-10} cycloalkyl substituted with one or more R_7.

[00189] In some embodiments, R_5 is C_3 cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_4 cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_5 cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_6 cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_7 cycloalkyl substituted with one

or more R_7. In some embodiments, R_5 is C_8 cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_9 cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_{10} cycloalkyl substituted with one or more R_7.

[00190] In some embodiments, R_5 is C_3-C_7 monocyclic cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_5 is C_8-C_{10} polycyclic cycloalkyl substituted with one or more R_7.

[00191] In some embodiments, R_5 is $C_{3\text{-}10}$ cycloalkyl substituted with one R_7.

[00192] In some embodiments, R_5 is C_3 cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_4 cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_5 cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_6 cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_7 cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_8 cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_9 cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_{10} cycloalkyl substituted with one R_7.

[00193] In some embodiments, R_5 is C_3-C_7 monocyclic cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one R_7. In some embodiments, R_5 is C_8-C_{10} polycyclic cycloalkyl substituted with one R_7.

[00194] In some embodiments, R_5 is $C_{3\text{-}10}$ cycloalkyl.

[00195] In some embodiments, R_5 is C_3 cycloalkyl. In some embodiments, R_5 is C_4 cycloalkyl. In some embodiments, R_5 is C_5 cycloalkyl. In some embodiments, R_5 is C_6 cycloalkyl. In some embodiments, R_5 is C_7 cycloalkyl. In some embodiments, R_5 is C_8 cycloalkyl. In some embodiments, R_5 is C_9 cycloalkyl. In some embodiments, R_5 is C_{10} cycloalkyl.

[00196] In some embodiments, R_5 is C_3-C_7 monocyclic cycloalkyl. In some embodiments, R_5 is C_3-C_7 monocyclic saturated cycloalkyl. In some embodiments, R_5 is C_3-C_7 monocyclic partially saturated cycloalkyl. In some embodiments, R_5 is C_9-C_{10} bicyclic cycloalkyl. In some embodiments, R_5 is C_9-C_{10} bicyclic saturated cycloalkyl. In some embodiments, R_5 is C_9-C_{10} bicyclic partially saturated cycloalkyl. In some embodiments, R_5 is C_8-C_{10} polycyclic cycloalkyl.

[00197] In some embodiments, R_5 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 12-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00198] In some embodiments, R_5 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some

embodiments, R_5 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 12-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00199] In some embodiments, R_5 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 12-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O,

and S, substituted with one R_7. In some embodiments, R_5 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00200] In some embodiments, R_5 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 12-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00201] In some embodiments, R_5 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 13-membered bicyclic

heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00202] In some embodiments, R_5 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00203] In some embodiments, R_5 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00204] In some embodiments, R_5 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is

8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00205] In some embodiments, R_5 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 12-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00206] In some embodiments, R_5 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 12-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00207] In some embodiments, R_5 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 12-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00208] In some embodiments, R_5 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 12-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00209] In some embodiments, R_5 is C_{6-10} aryl or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the aryl or heteroaryl is optionally substituted with one or more R_7.

[00210] In some embodiments, R_5 is C_{6-10} aryl or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00211] In some embodiments, R_5 is C_{6-10} aryl optionally substituted with one or more R_7.

[00212] In some embodiments, R_5 is C_{6-8} aryl optionally substituted with one or more R_7. In some embodiments, R_5 is phenyl optionally substituted with one or more R_7.

[00213] In some embodiments, R_5 is C_{6-8} aryl substituted with one or more R_7. In some embodiments, R_5 is phenyl substituted with one or more R_7.

[00214] In some embodiments, R_5 is C_{6-8} aryl substituted with one R_7. In some embodiments, R_5 is phenyl substituted with one R_7.

[00215] In some embodiments, R_5 is C_{6-10} aryl.

[00216] In some embodiments, R_5 is C_{6-8} aryl. In some embodiments, R_5 is phenyl.

[00217] In some embodiments, R_5 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 12-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00218] In some embodiments, R_5 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 12-membered heteroaryl comprising 1-4

heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00219] In some embodiments, R_5 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 12-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00220] In some embodiments, R_5 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 12-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00221] In some embodiments, R_5 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00222] In some embodiments, R_5 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00223] In some embodiments, R_5 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00224] In some embodiments, R_5 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00225] In some embodiments, R_5 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 9-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00226] In some embodiments, R_5 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 9-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00227] In some embodiments, R_5 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 9-

membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00228] In some embodiments, R_5 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 9-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00229] In some embodiments, R_5 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or $-C(O)R_7$, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00230] In some embodiments, R_5 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00231] In some embodiments, R_5 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more R_7.

[00232] In some embodiments, R_5 is cyclopropyl, piperidine, tetrahydropyran, morpholine, phenyl, pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole,

isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00233] In some embodiments, R_5 is cyclopropyl, piperidine, tetrahydropyran, or morpholine.

[00234] In some embodiments, R_5 is phenyl, pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00235] In some embodiments, R_5 is pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00236] In some embodiments, R_5 is pyridine or pyrimidine.

[00237] In some embodiments, R_5 is tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00238] In some embodiments, R_5 is tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, or imidazole.

[00239] In some embodiments, R_5 is 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00240] In some embodiments, R_5 is 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, or benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole.

[00241] In some embodiments, R_5 is 9H-carbazole.

[00242] In some embodiments, R_6 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00243] In some embodiments, R_6 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00244] In some embodiments, R_6 is H.

[00245] In some embodiments, R_6 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00246] In some embodiments, R_6 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00247] In some embodiments, R_6 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_7.

[00248] In some embodiments, R_6 is C_{1-6} alkyl optionally substituted with one or more R_7. In some embodiments, R_6 is methyl optionally substituted with one or more R_7. In some embodiments, R_6 is ethyl optionally substituted with one or more R_7. In some embodiments, R_6 is propyl optionally substituted with one or more R_7. In some embodiments, R_6 is butyl optionally substituted with one or more R_7. In some embodiments, R_6 is pentyl optionally substituted with one or more R_7. In some embodiments, R_6 is hexyl optionally substituted with one or more R_7. In some embodiments, R_6 is isopropyl optionally substituted with one or more R_7. In some embodiments, R_6 is isobutyl optionally substituted with one or more R_7. In some embodiments, R_6 is isopentyl optionally substituted with one or more R_7. In some embodiments, R_6 is isohexyl optionally substituted with one or more R_7. In some embodiments, R_6 is secbutyl optionally substituted with one or more R_7. In some embodiments, R_6 is secpentyl optionally

substituted with one or more R_7. In some embodiments, R_6 is sechexyl optionally substituted with one or more R_7. In some embodiments, R_6 is tertbutyl optionally substituted with one or more R_7.

[00249] In some embodiments, R_6 is C_{2-6} alkenyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_2 alkenyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_3 alkenyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_4 alkenyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_5 alkenyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_6 alkenyl optionally substituted with one or more R_7.

[00250] In some embodiments, R_6 is C_{2-6} alkynyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_2 alkynyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_3 alkynyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_4 alkynyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_5 alkynyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_6 alkynyl optionally substituted with one or more R_7.

[00251] In some embodiments, R_6 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one or more R_7.

[00252] In some embodiments, R_6 is C_{1-6} alkyl substituted with one or more R_7. In some embodiments, R_6 is methyl substituted with one or more R_7. In some embodiments, R_6 is ethyl substituted with one or more R_7. In some embodiments, R_6 is propyl substituted with one or more R_7. In some embodiments, R_6 is butyl substituted with one or more R_7. In some embodiments, R_6 is pentyl substituted with one or more R_7. In some embodiments, R_6 is hexyl substituted with one or more R_7. In some embodiments, R_6 is isopropyl substituted with one or more R_7. In some embodiments, R_6 is isobutyl substituted with one or more R_7. In some embodiments, R_6 is isopentyl substituted with one or more R_7. In some embodiments, R_6 is isohexyl substituted with one or more R_7. In some embodiments, R_6 is secbutyl substituted with one or more R_7. In some embodiments, R_6 is secpentyl substituted with one or more R_7. In some embodiments, R_6 is sechexyl substituted with one or more R_7. In some embodiments, R_6 is tertbutyl substituted with one or more R_7.

[00253] In some embodiments, R_6 is C_{2-6} alkenyl substituted with one or more R_7. In some embodiments, R_6 is C_2 alkenyl substituted with one or more R_7. In some embodiments, R_6 is C_3

alkenyl substituted with one or more R_7. In some embodiments, R_6 is C_4 alkenyl substituted with one or more R_7. In some embodiments, R_6 is C_5 alkenyl substituted with one or more R_7. In some embodiments, R_6 is C_6 alkenyl substituted with one or more R_7.

[00254] In some embodiments, R_6 is C_{2-6} alkynyl substituted with one or more R_7. In some embodiments, R_6 is C_2 alkynyl substituted with one or more R_7. In some embodiments, R_6 is C_3 alkynyl substituted with one or more R_7. In some embodiments, R_6 is C_4 alkynyl substituted with one or more R_7. In some embodiments, R_6 is C_5 alkynyl substituted with one or more R_7. In some embodiments, R_6 is C_6 alkynyl substituted with one or more R_7.

[00255] In some embodiments, R_6 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one R_7.

[00256] In some embodiments, R_6 is C_{1-6} alkyl substituted with one R_7. In some embodiments, R_6 is methyl substituted with one R_7. In some embodiments, R_6 is ethyl substituted with one R_7. In some embodiments, R_6 is propyl substituted with one R_7. In some embodiments, R_6 is butyl substituted with one R_7. In some embodiments, R_6 is pentyl substituted with one R_7. In some embodiments, R_6 is hexyl substituted with one R_7. In some embodiments, R_6 is isopropyl substituted with one R_7. In some embodiments, R_6 is isobutyl substituted with one R_7. In some embodiments, R_6 is isopentyl substituted with one R_7. In some embodiments, R_6 is isohexyl substituted with one R_7. In some embodiments, R_6 is secbutyl substituted with one R_7. In some embodiments, R_6 is secpentyl substituted with one R_7. In some embodiments, R_6 is sechexyl substituted with one R_7. In some embodiments, R_6 is tertbutyl substituted with one R_7.

[00257] In some embodiments, R_6 is C_{2-6} alkenyl substituted with one R_7. In some embodiments, R_6 is C_2 alkenyl substituted with one R_7. In some embodiments, R_6 is C_3 alkenyl substituted with one R_7. In some embodiments, R_6 is C_4 alkenyl substituted with one R_7. In some embodiments, R_6 is C_5 alkenyl substituted with one R_7. In some embodiments, R_6 is C_6 alkenyl substituted with one R_7.

[00258] In some embodiments, R_6 is C_{2-6} alkynyl substituted with one R_7. In some embodiments, R_6 is C_2 alkynyl substituted with one R_7. In some embodiments, R_6 is C_3 alkynyl substituted with one R_7. In some embodiments, R_6 is C_4 alkynyl substituted with one R_7. In some embodiments, R_6 is C_5 alkynyl substituted with one R_7. In some embodiments, R_6 is C_6 alkynyl substituted with one R_7.

[00259] In some embodiments, R_6 is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00260] In some embodiments, R_6 is C_{1-6} alkyl. In some embodiments, R_6 is methyl. In some embodiments, R_6 is ethyl. In some embodiments, R_6 is propyl. In some embodiments, R_6 is butyl. In some embodiments, R_6 is pentyl. In some embodiments, R_6 is hexyl. In some embodiments, R_6 is isopropyl. In some embodiments, R_6 is isobutyl. In some embodiments, R_6 is isopentyl. In some embodiments, R_6 is isohexyl. In some embodiments, R_6 is secbutyl. In some embodiments, R_6 is secpentyl. In some embodiments, R_6 is sechexyl. In some embodiments, R_6 is tertbutyl.

[00261] In some embodiments, R_6 is C_{2-6} alkenyl. In some embodiments, R_6 is C_2 alkenyl. In some embodiments, R_6 is C_3 alkenyl. In some embodiments, R_6 is C_4 alkenyl. In some embodiments, R_6 is C_5 alkenyl. In some embodiments, R_6 is C_6 alkenyl.

[00262] In some embodiments, R_6 is C_{2-6} alkynyl. In some embodiments, R_6 is C_2 alkynyl. In some embodiments, R_6 is C_3 alkynyl. In some embodiments, R_6 is C_4 alkynyl. In some embodiments, R_6 is C_5 alkynyl. In some embodiments, R_6 is C_6 alkynyl.

[00263] In some embodiments, R_6 is C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00264] In some embodiments, R_6 is C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00265] In some embodiments, R_6 is C_{3-10} cycloalkyl or 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more R_7.

[00266] In some embodiments, R_6 is C_{3-10} cycloalkyl or 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00267] In some embodiments, R_6 is C_{3-10} cycloalkyl optionally substituted with one or more R_7.

[00268] In some embodiments, R_6 is C_3 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_4 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_5 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_6 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_7 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_8 cycloalkyl optionally substituted with one or more R_7. In some

embodiments, R_6 is C_9 cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_{10} cycloalkyl optionally substituted with one or more R_7.

[00269] In some embodiments, R_6 is C_3-C_7 monocyclic cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_3-C_7 monocyclic saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_3-C_7 monocyclic partially saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic partially saturated cycloalkyl optionally substituted with one or more R_7. In some embodiments, R_6 is C_8-C_{10} polycyclic cycloalkyl optionally substituted with one or more R_7.

[00270] In some embodiments, R_6 is $C_{3\text{-}10}$ cycloalkyl substituted with one or more R_7.

[00271] In some embodiments, R_6 is C_3 cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_4 cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_5 cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_6 cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_7 cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_8 cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_9 cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_{10} cycloalkyl substituted with one or more R_7.

[00272] In some embodiments, R_6 is C_3-C_7 monocyclic cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one or more R_7. In some embodiments, R_6 is C_8-C_{10} polycyclic cycloalkyl substituted with one or more R_7.

[00273] In some embodiments, R_6 is $C_{3\text{-}10}$ cycloalkyl substituted with one R_7.

[00274] In some embodiments, R_6 is C_3 cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_4 cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_5 cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_6 cycloalkyl substituted with

one R_7. In some embodiments, R_6 is C_7 cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_8 cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_9 cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_{10} cycloalkyl substituted with one R_7.

[00275] In some embodiments, R_6 is C_3-C_7 monocyclic cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one R_7. In some embodiments, R_6 is C_8-C_{10} polycyclic cycloalkyl substituted with one R_7.

[00276] In some embodiments, R_6 is $C_{3\text{-}10}$ cycloalkyl.

[00277] In some embodiments, R_6 is C_3 cycloalkyl. In some embodiments, R_6 is C_4 cycloalkyl. In some embodiments, R_6 is C_5 cycloalkyl. In some embodiments, R_6 is C_6 cycloalkyl. In some embodiments, R_6 is C_7 cycloalkyl. In some embodiments, R_6 is C_8 cycloalkyl. In some embodiments, R_6 is C_9 cycloalkyl. In some embodiments, R_6 is C_{10} cycloalkyl.

[00278] In some embodiments, R_6 is C_3-C_7 monocyclic cycloalkyl. In some embodiments, R_6 is C_3-C_7 monocyclic saturated cycloalkyl. In some embodiments, R_6 is C_3-C_7 monocyclic partially saturated cycloalkyl. In some embodiments, R_6 is C_9-C_{10} bicyclic cycloalkyl. In some embodiments, R_6 is C_9-C_{10} bicyclic saturated cycloalkyl. In some embodiments, R_6 is C_9-C_{10} bicyclic partially saturated cycloalkyl. In some embodiments, R_6 is C_8-C_{10} polycyclic cycloalkyl.

[00279] In some embodiments, R_6 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with

one or more R_7. In some embodiments, R_6 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 12-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00280] In some embodiments, R_6 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 12-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00281] In some embodiments, R_6 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 12-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00282] In some embodiments, R_6 is 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 11-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 12-membered heterocyclyl comprising 1-4 heteroatoms

selected from N, O, and S. In some embodiments, R_6 is 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00283] In some embodiments, R_6 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00284] In some embodiments, R_6 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00285] In some embodiments, R_6 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00286] In some embodiments, R_6 is 7- to 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 7-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 8-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 9-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 10-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 11-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 12-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 13-membered bicyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00287] In some embodiments, R_6 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with

one or more R_7. In some embodiments, R_6 is 12-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00288] In some embodiments, R_6 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 12-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00289] In some embodiments, R_6 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 12-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00290] In some embodiments, R_6 is 9- to 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 9-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 10-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 11-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 12-membered polycyclic heterocyclyl

comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 13-membered polycyclic heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00291] In some embodiments, R_6 is C_{6-10} aryl or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the aryl or heteroaryl is optionally substituted with one or more R_7.

[00292] In some embodiments, R_6 is C_{6-10} aryl or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00293] In some embodiments, R_6 is C_{6-10} aryl optionally substituted with one or more R_7.

[00294] In some embodiments, R_6 is C_{6-8} aryl optionally substituted with one or more R_7. In some embodiments, R_6 is phenyl optionally substituted with one or more R_7.

[00295] In some embodiments, R_6 is C_{6-8} aryl substituted with one or more R_7. In some embodiments, R_6 is phenyl substituted with one or more R_7.

[00296] In some embodiments, R_6 is C_{6-8} aryl substituted with one R_7. In some embodiments, R_6 is phenyl substituted with one R_7.

[00297] In some embodiments, R_6 is C_{6-10} aryl.

[00298] In some embodiments, R_6 is C_{6-8} aryl. In some embodiments, R_6 is phenyl.

[00299] In some embodiments, R_6 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 12-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 13-

membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00300] In some embodiments, R_6 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 12-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00301] In some embodiments, R_6 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 12-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In

some embodiments, R_6 is 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00302] In some embodiments, R_6 is 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 11-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 12-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00303] In some embodiments, R_6 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00304] In some embodiments, R_6 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from

N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00305] In some embodiments, R_6 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00306] In some embodiments, R_6 is 9- to 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 9-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 10-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 11-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 12-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 13-membered bicyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00307] In some embodiments, R_6 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 9-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_6 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some

embodiments, R_6 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00308] In some embodiments, R_6 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 9-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_6 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00309] In some embodiments, R_6 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 9-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_6 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00310] In some embodiments, R_6 is 9- to 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 9-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 10-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 11-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 12-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_6 is 13-membered polycyclic heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00311] In some embodiments, R_6 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -C(O)R_7, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00312] In some embodiments, R_6 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

[00313] In some embodiments, R_6 is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more R_7.

[00314] In some embodiments, R_6 is cyclopropyl, piperidine, tetrahydropyran, morpholine, phenyl, pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00315] In some embodiments, R_6 is cyclopropyl, piperidine, tetrahydropyran, or morpholine.

[00316] In some embodiments, R_6 is phenyl, pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00317] In some embodiments, R_6 is pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00318] In some embodiments, R_6 is pyridine or pyrimidine.

[00319] In some embodiments, R_6 is tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00320] In some embodiments, R_6 is tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, or imidazole.

[00321] In some embodiments, R_6 is 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00322] In some embodiments, R_6 is 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, or benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole.

[00323] In some embodiments, R_6 is 9H-carbazole.

[00324] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7.

[00325] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00326] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00327] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00328] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00329] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00330] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00331] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00332] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00333] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00334] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00335] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered

heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00336] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00337] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00338] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00339] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 6-membered heterocyclyl

comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00340] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00341] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_7.

[00342] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00343] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to

which they are attached form a 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_7.

[00344] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_7.

[00345] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00346] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 6-membered

heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00347] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a piperidine, optionally substituted with one or more R_7.

[00348] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a piperidine, substituted with one or more R_7.

[00349] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a piperidine, substituted with one R_7.

[00350] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a piperidine.

[00351] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a tetrahydroquinoline, optionally substituted with one or more R_7.

[00352] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a tetrahydroquinoline, substituted with one or more R_7.

[00353] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a tetrahydroquinoline, substituted with one R_7.

[00354] In some embodiments, R_5 and R_6 together with the atoms to which they are attached form a tetrahydroquinoline.

[00355] In some embodiments, each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, $-C(O)OR_{10}$, $-C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-O-(CH_2)_t-R_8$, $-NH-(CH_2)_t-R_8$, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10}.

[00356] In some embodiments, each R_7 is independently oxo, halogen, -OH, -NH_2, -CN, -$C(O)R_{10}$, -$C(O)OR_{10}$, -$C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, -$NH(C_{1-6}$ alkyl), -$N(C_{1-6}$ alkyl)$_2$, -O-$(CH_2)_t$-R_8, -NH-$(CH_2)_t$-R_8, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00357] In some embodiments, R_7 is oxo, halogen, -OH, -NH_2, -CN, -$C(O)R_{10}$, -$C(O)OR_{10}$, -$C(O)N(R_{10})_2$, -O-$(CH_2)_t$-R_8, or -NH-$(CH_2)_t$-R_8.

[00358] In some embodiments, R_7 is oxo, halogen, -OH, -NH_2, or -CN.

[00359] In some embodiments, R_7 is oxo.

[00360] In some embodiments, R_7 is halogen. In some embodiments, R_7 is F, Cl, Br, or I. In some embodiments, R_7 is F, Cl, or Br. In some embodiments, R_7 is F. In some embodiments, R_7 is Cl. In some embodiments, R_7 is Br. In some embodiments, R_7 is I.

[00361] In some embodiments, R_7 is -OH. In some embodiments, R_7 is -NH_2. In some embodiments, R_7 is -CN.

[00362] In some embodiments, R_7 is -$C(O)R_{10}$, -$C(O)OR_{10}$, -$C(O)N(R_{10})_2$, -O-$(CH_2)_t$-R_8, or -NH-$(CH_2)_t$-R_8.

[00363] In some embodiments, R_7 is -$C(O)R_{10}$. In some embodiments, R_7 is -$C(O)OR_{10}$. In some embodiments, R_7 is -$C(O)N(R_{10})_2$. In some embodiments, R_7 is -O-$(CH_2)_t$-R_8. In some embodiments, R_7 is -NH-$(CH_2)_t$-R_8.

[00364] In some embodiments, R_7 is C_{1-6} alkoxy, -$NH(C_{1-6}$ alkyl), or -$N(C_{1-6}$ alkyl)$_2$.

[00365] In some embodiments, R_7 is C_{1-6} alkoxy. In some embodiments, R_7 is methoxy. In some embodiments, R_7 is ethoxy. In some embodiments, R_7 is propoxy. In some embodiments, R_7 is butoxy. In some embodiments, R_7 is pentoxy. In some embodiments, R_7 is hexoxy. In some embodiments, R_7 is isopropoxy. In some embodiments, R_7 is isobutoxy. In some embodiments, R_7 is isopentoxy. In some embodiments, R_7 is isohexoxy. In some embodiments, R_7 is secbutoxy. In some embodiments, R_7 is secpentoxy. In some embodiments, R_7 is sechexoxy. In some embodiments, R_7 is tertbutoxy.

[00366] In some embodiments, R_7 is -$NH(C_{1-6}$ alkyl) or -$N(C_{1-6}$ alkyl)$_2$. In some embodiments, R_7 is -$NH(C_{1-6}$ alkyl). In some embodiments, R_7 is -$N(C_{1-6}$ alkyl)$_2$.

[00367] In some embodiments, R_7 is C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or

5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10}.

[00368] In some embodiments, R_7 is C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00369] In some embodiments, R_7 is C_{1-3} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{10}.

[00370] In some embodiments, R_7 is C_{1-3} alkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is methyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is ethyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is propyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is isopropyl optionally substituted with one or more R_{10}.

[00371] In some embodiments, R_7 is C_{2-6} alkenyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_2 alkenyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_3 alkenyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_4 alkenyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_5 alkenyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_6 alkenyl optionally substituted with one or more R_{10}.

[00372] In some embodiments, R_7 is C_{2-6} alkynyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_2 alkynyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_3 alkynyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_4 alkynyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_5 alkynyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_6 alkynyl optionally substituted with one or more R_{10}.

[00373] In some embodiments, R_7 is C_{1-3} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one or more R_{10}.

[00374] In some embodiments, R_7 is C_{1-3} alkyl substituted with one or more R_{10}. In some embodiments, R_7 is methyl substituted with one or more R_{10}. In some embodiments, R_7 is ethyl substituted with one or more R_{10}. In some embodiments, R_7 is propyl substituted with one or more R_{10}. In some embodiments, R_7 is isopropyl substituted with one or more R_{10}.

[00375] In some embodiments, R_7 is C_{2-6} alkenyl substituted with one or more R_{10}. In some embodiments, R_7 is C_2 alkenyl substituted with one or more R_{10}. In some embodiments, R_7 is C_3 alkenyl substituted with one or more R_{10}. In some embodiments, R_7 is C_4 alkenyl substituted with one or more R_{10}. In some embodiments, R_7 is C_5 alkenyl substituted with one or more R_{10}. In some embodiments, R_7 is C_6 alkenyl substituted with one or more R_{10}.

[00376] In some embodiments, R_7 is C_{2-6} alkynyl substituted with one or more R_{10}. In some embodiments, R_7 is C_2 alkynyl substituted with one or more R_{10}. In some embodiments, R_7 is C_3 alkynyl substituted with one or more R_{10}. In some embodiments, R_7 is C_4 alkynyl substituted with one or more R_{10}. In some embodiments, R_7 is C_5 alkynyl substituted with one or more R_{10}. In some embodiments, R_7 is C_6 alkynyl substituted with one or more R_{10}.

[00377] In some embodiments, R_7 is C_{1-3} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one R_{10}.

[00378] In some embodiments, R_7 is C_{1-3} alkyl substituted with one R_{10}. In some embodiments, R_7 is methyl substituted with one R_{10}. In some embodiments, R_7 is ethyl substituted with one R_{10}. In some embodiments, R_7 is propyl substituted with one R_{10}. In some embodiments, R_7 is isopropyl substituted with one R_{10}.

[00379] In some embodiments, R_7 is C_{2-6} alkenyl substituted with one R_{10}. In some embodiments, R_7 is C_2 alkenyl substituted with one R_{10}. In some embodiments, R_7 is C_3 alkenyl substituted with one R_{10}. In some embodiments, R_7 is C_4 alkenyl substituted with one R_{10}. In some embodiments, R_7 is C_5 alkenyl substituted with one R_{10}. In some embodiments, R_7 is C_6 alkenyl substituted with one R_{10}.

[00380] In some embodiments, R_7 is C_{2-6} alkynyl substituted with one R_{10}. In some embodiments, R_7 is C_2 alkynyl substituted with one R_{10}. In some embodiments, R_7 is C_3 alkynyl substituted with one R_{10}. In some embodiments, R_7 is C_4 alkynyl substituted with one R_{10}. In some embodiments, R_7 is C_5 alkynyl substituted with one R_{10}. In some embodiments, R_7 is C_6 alkynyl substituted with one R_{10}.

[00381] In some embodiments, R_7 is C_{1-3} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00382] In some embodiments, R_7 is C_{1-3} alkyl. In some embodiments, R_7 is methyl. In some embodiments, R_7 is ethyl. In some embodiments, R_7 is propyl. In some embodiments, R_7 is isopropyl.

[00383] In some embodiments, R_7 is C_{2-6} alkenyl. In some embodiments, R_7 is C_2 alkenyl. In some embodiments, R_7 is C_3 alkenyl. In some embodiments, R_7 is C_4 alkenyl. In some embodiments, R_7 is C_5 alkenyl. In some embodiments, R_7 is C_6 alkenyl.

[00384] In some embodiments, R_7 is C_{2-6} alkynyl. In some embodiments, R_7 is C_2 alkynyl. In some embodiments, R_7 is C_3 alkynyl. In some embodiments, R_7 is C_4 alkynyl. In some embodiments, R_7 is C_5 alkynyl. In some embodiments, R_7 is C_6 alkynyl.

[00385] In some embodiments, R_7 is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10}.

[00386] In some embodiments, R_7 is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00387] In some embodiments, R_7 is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more R_{10}.

[00388] In some embodiments, R_7 is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00389] In some embodiments, R_7 is C_{3-10} cycloalkyl optionally substituted with one or more R_{10}.

[00390] In some embodiments, R_7 is C_3 cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_4 cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_5 cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_6 cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_7 cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_8 cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_9 cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_{10} cycloalkyl optionally substituted with one or more R_{10}.

[00391] In some embodiments, R_7 is C_3-C_7 monocyclic cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_3-C_7 monocyclic saturated cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_3-C_7 monocyclic partially

saturated cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic saturated cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic partially saturated cycloalkyl optionally substituted with one or more R_{10}. In some embodiments, R_7 is C_8-C_{10} polycyclic cycloalkyl optionally substituted with one or more R_{10}.

[00392] In some embodiments, R_7 is C_{3-10} cycloalkyl substituted with one or more R_{10}.

[00393] In some embodiments, R_7 is C_3 cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_4 cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_5 cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_6 cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_7 cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_8 cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_9 cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_{10} cycloalkyl substituted with one or more R_{10}.

[00394] In some embodiments, R_7 is C_3-C_7 monocyclic cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one or more R_{10}. In some embodiments, R_7 is C_8-C_{10} polycyclic cycloalkyl substituted with one or more R_{10}.

[00395] In some embodiments, R_7 is C_{3-10} cycloalkyl substituted with one R_{10}.

[00396] In some embodiments, R_7 is C_3 cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_4 cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_5 cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_6 cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_7 cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_8 cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_9 cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_{10} cycloalkyl substituted with one R_{10}.

[00397] In some embodiments, R_7 is C_3-C_7 monocyclic cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one R_{10}. In some embodiments, R_7 is C_8-C_{10} polycyclic cycloalkyl substituted with one R_{10}.

[00398] In some embodiments, R_7 is $C_{3\text{-}10}$ cycloalkyl.

[00399] In some embodiments, R_7 is C_3 cycloalkyl. In some embodiments, R_7 is C_4 cycloalkyl. In some embodiments, R_7 is C_5 cycloalkyl. In some embodiments, R_7 is C_6 cycloalkyl. In some embodiments, R_7 is C_7 cycloalkyl. In some embodiments, R_7 is C_8 cycloalkyl. In some embodiments, R_7 is C_9 cycloalkyl. In some embodiments, R_7 is C_{10} cycloalkyl.

[00400] In some embodiments, R_7 is C_3-C_7 monocyclic cycloalkyl. In some embodiments, R_7 is C_3-C_7 monocyclic saturated cycloalkyl. In some embodiments, R_7 is C_3-C_7 monocyclic partially saturated cycloalkyl. In some embodiments, R_7 is C_9-C_{10} bicyclic cycloalkyl. In some embodiments, R_7 is C_9-C_{10} bicyclic saturated cycloalkyl. In some embodiments, R_7 is C_9-C_{10} bicyclic partially saturated cycloalkyl. In some embodiments, R_7 is C_8-C_{10} polycyclic cycloalkyl.

[00401] In some embodiments, R_7 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 10-membered

heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}.

[00402] In some embodiments, R_7 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}.

[00403] In some embodiments, R_7 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}.

[00404] In some embodiments, R_7 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00405] In some embodiments, R_7 is C_{6-10} aryl or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the aryl or heteroaryl is optionally substituted with one or more R_{10}.

[00406] In some embodiments, R_7 is C_{6-10} aryl or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00407] In some embodiments, R_7 is C_{6-10} aryl optionally substituted with one or more R_{10}.

[00408] In some embodiments, R_7 is C_{6-8} aryl optionally substituted with one or more R_{10}. In some embodiments, R_7 is phenyl optionally substituted with one or more R_{10}.

[00409] In some embodiments, R_7 is C_{6-8} aryl substituted with one or more R_{10}. In some embodiments, R_7 is phenyl substituted with one or more R_{10}.

[00410] In some embodiments, R_7 is C_{6-8} aryl substituted with one R_{10}. In some embodiments, R_7 is phenyl substituted with one R_{10}.

[00411] In some embodiments, R_7 is C_{6-10} aryl.

[00412] In some embodiments, R_7 is C_{6-8} aryl. In some embodiments, R_7 is phenyl.

[00413] In some embodiments, R_7 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 7-membered heteroaryl comprising 1-4 heteroatoms selected

from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}. In some embodiments, R_7 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_{10}.

[00414] In some embodiments, R_7 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}. In some embodiments, R_7 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_{10}.

[00415] In some embodiments, R_7 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}. In some embodiments, R_7 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_{10}.

[00416] In some embodiments, R_7 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 6-membered heteroaryl

comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_7 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00417] In some embodiments, R_7 is cyclopropyl, piperidine, tetrahydropyran, morpholine, phenyl, pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00418] In some embodiments, R_7 is cyclopropyl, piperidine, tetrahydropyran, or morpholine.

[00419] In some embodiments, R_7 is phenyl, pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00420] In some embodiments, R_7 is pyridine, pyrimidine, tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00421] In some embodiments, R_7 is pyridine or pyrimidine.

[00422] In some embodiments, R_7 is tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00423] In some embodiments, R_7 is tetrazole, triazole, pyrazole, thiazole, oxazole, furan, pyrrole, isoxazole, or imidazole.

[00424] In some embodiments, R_7 is 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole, or 9H-carbazole.

[00425] In some embodiments, R_7 is 1,3-dihydro-2H-benzo[d]imidazol-2-one, indoline, indole, 2,3-diydrobenzofuran, 1H-benzo[d][1,2,3]triazole, 1H-indazole, imidazo[1,2-a]pyrazine, naphthalene, quinoline, 2,3-dihydrobenzo[b][1,4]dioxine, or benzo[d]oxazol-2(3H)-one, benzo[d]isoxazole.

[00426] In some embodiments, R_7 is 9H-carbazole.

[00427] In some embodiments, R_7 is oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, C_{1-6} alkyl, C_{2-6} alkynyl, $-O-(CH_2)_t-R_8$, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkynyl, aryl, or heteroaryl is optionally substituted with one or more R_{10}.

[00428] In some embodiments, R_7 is oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, C_{1-6} alkyl, C_{2-6} alkynyl, $-O-(CH_2)_t-R_8$, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkynyl, aryl, or heteroaryl is substituted with one or more R_{10}.

[00429] In some embodiments, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9.

[00430] In some embodiments, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00431] In some embodiments, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, -SH, or $-S(C_{1-6}$ alkyl), wherein the alkoxy or alkyl is optionally substituted by one or more R_9.

[00432] In some embodiments, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, -SH, or $-S(C_{1-6}$ alkyl), wherein the alkoxy or alkyl is substituted by one or more R_9.

[00433] In some embodiments, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, -SH, or $-S(C_{1-6}$ alkyl), wherein the alkoxy or alkyl is substituted by one R_9.

[00434] In some embodiments, R_8 is C_{1-6} alkoxy optionally substituted by one or more R_9.

[00435] In some embodiments, R_8 is C_{1-6} alkoxy-OH, wherein the alkoxy is optionally substituted by one or more R_9.

[00436] In some embodiments, R_8 is C_{1-6} alkoxy substituted by one or more R_9.

[00437] In some embodiments, R_8 is C_{1-6} alkoxy-OH, wherein the alkoxy is substituted by one or more R_9.

[00438] In some embodiments, R_8 is C_{1-6} alkoxy substituted by one R_9.

[00439] In some embodiments, R_8 is C_{1-6} alkoxy-OH, wherein the alkoxy is substituted by one R_9.

[00440] In some embodiments, R_8 is $-NH(C_{1-6}$ alkyl), wherein the alkyl is optionally substituted by one or more R_9.

[00441] In some embodiments, R_8 is $-N(C_{1-6}$ alkyl$)_2$, wherein the alkyl is optionally substituted by one or more R_9.

[00442] In some embodiments, R_8 is $-NH(C_{1-6}$ alkyl), wherein the alkyl is substituted by one or more R_9.

[00443] In some embodiments, R_8 is $-N(C_{1-6}$ alkyl$)_2$, wherein the alkyl is substituted by one or more R_9.

[00444] In some embodiments, R_8 is $-NH(C_{1-6}$ alkyl), wherein the alkyl is substituted by one R_9.

[00445] In some embodiments, R_8 is $-N(C_{1-6}$ alkyl$)_2$, wherein the alkyl is substituted by one R_9.

[00446] In some embodiments, R_8 is $-S(C_{1-6}$ alkyl), wherein the alkyl is optionally substituted by one or more R_9.

[00447] In some embodiments, R_8 is $-S(C_{1-6}$ alkyl), wherein the alkyl is substituted by one or more R_9.

[00448] In some embodiments, R_8 is $-S(C_{1-6}$ alkyl), wherein the alkyl is substituted by one R_9.

[00449] In some embodiments, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, -SH, $-S(C_{1-6}$ alkyl).

[00450] In some embodiments, R_8 is -OH, C_{1-6} alkoxy, or C_{1-6} alkoxy-OH.

[00451] In some embodiments, R_8 is -OH.

[00452] In some embodiments, R_8 is C_{1-6} alkoxy. In some embodiments, R_8 is methoxy. In some embodiments, R_8 is ethoxy. In some embodiments, R_8 is propoxy. In some embodiments, R_8 is butoxy. In some embodiments, R_8 is pentoxy. In some embodiments, R_8 is hexoxy. In some embodiments, R_8 is isopropoxy. In some embodiments, R_8 is isobutoxy. In some embodiments, R_8 is isopentoxy. In some embodiments, R_8 is isohexoxy. In some embodiments, R_8 is secbutoxy. In some embodiments, R_8 is secpentoxy. In some embodiments, R_8 is sechexoxy. In some embodiments, R_8 is tertbutoxy.

[00453] In some embodiments, R_8 is C_{1-6} alkoxy-OH. In some embodiments, R_8 is methoxy-OH. In some embodiments, R_8 is ethoxy-OH. In some embodiments, R_8 is propoxy-OH. In some embodiments, R_8 is butoxy-OH. In some embodiments, R_8 is pentoxy-OH. In some embodiments, R_8 is hexoxy-OH. In some embodiments, R_8 is isopropoxy-OH. In some embodiments, R_8 is isobutoxy-OH. In some embodiments, R_8 is isopentoxy-OH. In some embodiments, R_8 is isohexoxy-OH. In some embodiments, R_8 is secbutoxy-OH. In some embodiments, R_8 is secpentoxy-OH. In some embodiments, R_8 is sechexoxy-OH. In some embodiments, R_8 is tertbutoxy-OH.

[00454] In some embodiments, R_8 is $-NH_2$, $-NH(C_{1-6}$ alkyl), or $-N(C_{1-6}$ alkyl)$_2$.

[00455] In some embodiments, R_8 is $-NH_2$.

[00456] In some embodiments, R_8 is $-NH(C_{1-6}$ alkyl). In some embodiments, R_8 is -NH(methyl). In some embodiments, R_8 is -NH(ethyl). In some embodiments, R_8 is -NH(propyl). In some embodiments, R_8 is -NH(butyl). In some embodiments, R_8 is -NH(pentyl). In some embodiments, R_8 is -NH(hexyl). In some embodiments, R_8 is -NH(isopropyl). In some embodiments, R_8 is -NH(isobutyl). In some embodiments, R_8 is -NH(isopentyl). In some embodiments, R_8 is -NH(isohexyl). In some embodiments, R_8 is -NH(secbutyl). In some embodiments, R_8 is -NH(secpentyl). In some embodiments, R_8 is -NH(sechexyl). In some embodiments, R_8 is -NH(tertbutyl).

[00457] In some embodiments, R_8 is $-N(C_{1-6}$ alkyl)$_2$. In some embodiments, R_8 is $-N(methyl)_2$. In some embodiments, R_8 is $-N(ethyl)_2$. In some embodiments, R_8 is $-N(propyl)_2$. In some embodiments, R_8 is $-N(butyl)_2$. In some embodiments, R_8 is $-N(pentyl)_2$. In some embodiments, R_8 is $-N(hexyl)_2$. In some embodiments, R_8 is $-N(isopropyl)_2$. In some embodiments, R_8 is -

$N(isobutyl)_2$. In some embodiments, R_8 is $-N(isopentyl)_2$. In some embodiments, R_8 is $-N(isohexyl)_2$. In some embodiments, R_8 is $-N(secbutyl)_2$. In some embodiments, R_8 is $-N(secpentyl)_2$. In some embodiments, R_8 is $-N(sechexyl)_2$. In some embodiments, R_8 is $-N(tertbutyl)_2$.

[00458] In some embodiments, R_8 is -SH or $-S(C_{1-6}$ alkyl).

[00459] In some embodiments, R_8 is -SH.

[00460] In some embodiments, R_8 is $-S(C_{1-6}$ alkyl).

[00461] In some embodiments, R_8 is -S(methyl). In some embodiments, R_8 is -S(ethyl). In some embodiments, R_8 is -S(propyl). In some embodiments, R_8 is -S(butyl). In some embodiments, R_8 is -S(pentyl). In some embodiments, R_8 is -S(hexyl). In some embodiments, R_8 is -S(isopropyl). In some embodiments, R_8 is -S(isobutyl). In some embodiments, R_8 is -S(isopentyl). In some embodiments, R_8 is -S(isohexyl). In some embodiments, R_8 is -S(secbutyl). In some embodiments, R_8 is -S(secpentyl). In some embodiments, R_8 is -S(sechexyl). In some embodiments, R_8 is -S(tertbutyl).

[00462] In some embodiments, R_8 is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_9.

[00463] In some embodiments, R_8 is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00464] In some embodiments, R_8 is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with one or more R_9.

[00465] In some embodiments, R_8 is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00466] In some embodiments, R_8 is C_{3-10} cycloalkyl optionally substituted with one or more R_9.

[00467] In some embodiments, R_8 is C_3 cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_4 cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_5 cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_6 cycloalkyl optionally substituted with one or more R_9. In some

embodiments, R_8 is C_7 cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_8 cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_9 cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_{10} cycloalkyl optionally substituted with one or more R_9.

[00468] In some embodiments, R_8 is C_3-C_7 monocyclic cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_3-C_7 monocyclic saturated cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_3-C_7 monocyclic partially saturated cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic saturated cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic partially saturated cycloalkyl optionally substituted with one or more R_9. In some embodiments, R_8 is C_8-C_{10} polycyclic cycloalkyl optionally substituted with one or more R_9.

[00469] In some embodiments, R_8 is $C_{3\text{-}10}$ cycloalkyl substituted with one or more R_9.

[00470] In some embodiments, R_8 is C_3 cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_4 cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_5 cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_6 cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_7 cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_8 cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_9 cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_{10} cycloalkyl substituted with one or more R_9.

[00471] In some embodiments, R_8 is C_3-C_7 monocyclic cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one or more R_9. In some embodiments, R_8 is C_8-C_{10} polycyclic cycloalkyl substituted with one or more R_9.

[00472] In some embodiments, R_8 is $C_{3\text{-}10}$ cycloalkyl substituted with one R_9.

[00473] In some embodiments, R_8 is C_3 cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_4 cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_5 cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_6 cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_7 cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_8 cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_9 cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_{10} cycloalkyl substituted with one R_9.

[00474] In some embodiments, R_8 is C_3-C_7 monocyclic cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_3-C_7 monocyclic saturated cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_3-C_7 monocyclic partially saturated cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic saturated cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_9-C_{10} bicyclic partially saturated cycloalkyl substituted with one R_9. In some embodiments, R_8 is C_8-C_{10} polycyclic cycloalkyl substituted with one R_9.

[00475] In some embodiments, R_8 is $C_{3\text{-}10}$ cycloalkyl.

[00476] In some embodiments, R_8 is C_3 cycloalkyl. In some embodiments, R_8 is C_4 cycloalkyl. In some embodiments, R_8 is C_5 cycloalkyl. In some embodiments, R_8 is C_6 cycloalkyl. In some embodiments, R_8 is C_7 cycloalkyl. In some embodiments, R_8 is C_8 cycloalkyl. In some embodiments, R_8 is C_9 cycloalkyl. In some embodiments, R_8 is C_{10} cycloalkyl.

[00477] In some embodiments, R_8 is C_3-C_7 monocyclic cycloalkyl. In some embodiments, R_8 is C_3-C_7 monocyclic saturated cycloalkyl. In some embodiments, R_8 is C_3-C_7 monocyclic partially saturated cycloalkyl. In some embodiments, R_8 is C_9-C_{10} bicyclic cycloalkyl. In some embodiments, R_8 is C_9-C_{10} bicyclic saturated cycloalkyl. In some embodiments, R_8 is C_9-C_{10} bicyclic partially saturated cycloalkyl. In some embodiments, R_8 is C_8-C_{10} polycyclic cycloalkyl.

[00478] In some embodiments, R_8 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some

embodiments, R_8 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9.

[00479] In some embodiments, R_8 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9.

[00480] In some embodiments, R_8 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 7-membered heterocyclyl

comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9.

[00481] In some embodiments, R_8 is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00482] In some embodiments, R_8 is C_{6-10} aryl or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the aryl or heteroaryl is optionally substituted with one or more R_9.

[00483] In some embodiments, R_8 is C_{6-10} aryl or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00484] In some embodiments, R_8 is C_{6-10} aryl optionally substituted with one or more R_9.

[00485] In some embodiments, R_8 is C_{6-8} aryl optionally substituted with one or more R_9. In some embodiments, R_8 is phenyl optionally substituted with one or more R_9.

[00486] In some embodiments, R_8 is C_{6-8} aryl substituted with one or more R_9. In some embodiments, R_8 is phenyl substituted with one or more R_9.

[00487] In some embodiments, R_8 is C_{6-8} aryl substituted with one R_9. In some embodiments, R_8 is phenyl substituted with one R_9.

[00488] In some embodiments, R_8 is C_{6-10} aryl.

[00489] In some embodiments, R_8 is C_{6-8} aryl. In some embodiments, R_8 is phenyl.

[00490] In some embodiments, R_8 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9. In some embodiments, R_8 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more R_9.

[00491] In some embodiments, R_8 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9. In some embodiments, R_8 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more R_9.

[00492] In some embodiments, R_8 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 9-membered heteroaryl comprising 1-4

heteroatoms selected from N, O, and S, substituted with one R_9. In some embodiments, R_8 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one R_9.

[00493] In some embodiments, R_8 is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_8 is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00494] In some embodiments, R_8 is H, -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $-S(C_{1-6}$ alkyl), 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, heterocyclyl, or heteroaryl is optionally substituted by one or more R_9.

[00495] In some embodiments, R_8 is H, -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $-S(C_{1-6}$ alkyl), 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, heterocyclyl, or heteroaryl is substituted by one or more R_9.

[00496] In some embodiments, each R_9 is independently $-(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$.

[00497] In some embodiments, R_9 is $-(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_u$-(C_{6-10} aryl).

[00498] In some embodiments, R_9 is $-(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$.

[00499] In some embodiments, R_9 is $-(CH_2)_u$-(5-membered heteroaryl), wherein the heteroaryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_9 is $-(CH_2)_u$-(6-membered heteroaryl), wherein the heteroaryl is optionally substituted with one or

more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(7-membered heteroaryl), wherein the heteroaryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(8-membered heteroaryl), wherein the heteroaryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(9-membered heteroaryl), wherein the heteroaryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(10-membered heteroaryl), wherein the heteroaryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2.

[00500] In some embodiments, R_9 is -$(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one or more halogen, -CN, -OH, or -NH_2.

[00501] In some embodiments, R_9 is -$(CH_2)_u$-(5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one or more halogen, -CN, -OH, or -NH_2.

[00502] In some embodiments, R_9 is -$(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one halogen, -CN, -OH, or -NH_2.

[00503] In some embodiments, R_9 is -$(CH_2)_u$-(5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(6-membered heteroaryl comprising 1-4

heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S), wherein the heteroaryl is substituted with one halogen, -CN, -OH, or -NH_2.

[00504] In some embodiments, R_9 is -$(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S).

[00505] In some embodiments, R_9 is -$(CH_2)_u$-(5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S). In some embodiments, R_9 is -$(CH_2)_u$-(6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S). In some embodiments, R_9 is -$(CH_2)_u$-(7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S). In some embodiments, R_9 is -$(CH_2)_u$-(8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S). In some embodiments, R_9 is -$(CH_2)_u$-(9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S). In some embodiments, R_9 is -$(CH_2)_u$-(10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S).

[00506] In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-10} aryl), wherein the aryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-8} aryl), wherein the aryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(phenyl), wherein the phenyl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2.

[00507] In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-10} aryl), wherein the aryl is substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-8} aryl), wherein the aryl is substituted with one or more halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(phenyl), wherein the phenyl is substituted with one or more halogen, -CN, -OH, or -NH_2.

[00508] In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-10} aryl), wherein the aryl is substituted with one halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-8} aryl), wherein the aryl is substituted with one halogen, -CN, -OH, or -NH_2. In some embodiments, R_9 is -$(CH_2)_u$-(phenyl), wherein the phenyl is substituted with more halogen, -CN, -OH, or -NH_2.

[00509] In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-10} aryl). In some embodiments, R_9 is -$(CH_2)_u$-(C_{6-8} aryl). In some embodiments, R_9 is -$(CH_2)_u$-(phenyl).

[00510] In some embodiments, R_9 is -$(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or -$(CH_2)_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen or -OH.

[00511] In some embodiments, R_9 is -$(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or -$(CH_2)_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is substituted with one or more halogen or -OH.

[00512] In some embodiments, each R_{10} is independently halogen, -OH, -NH_2, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00513] In some embodiments, R_{10} is halogen, -OH, -NH_2, or -CN.

[00514] In some embodiments, R_{10} is halogen.

[00515] In some embodiments, R_{10} is F, Cl, Br, or I. In some embodiments, R_{10} is F, Cl, or Br.

[00516] In some embodiments, R_{10} is F. In some embodiments, R_{10} is Cl. In some embodiments, R_{10} is Br. In some embodiments, R_{10} is I.

[00517] In some embodiments, R_{10} is -OH. In some embodiments, R_{10} is -NH_2. In some embodiments, R_{10} is -CN.

[00518] In some embodiments, R_{10} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00519] In some embodiments, R_{10} is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} haloalkyl.

[00520] In some embodiments, R_{10} is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00521] In some embodiments, R_{10} is C_{1-6} alkyl. In some embodiments, R_{10} is methyl. In some embodiments, R_{10} is ethyl. In some embodiments, R_{10} is propyl. In some embodiments, R_{10} is

butyl. In some embodiments, R_{10} is pentyl. In some embodiments, R_{10} is hexyl. In some embodiments, R_{10} is isopropyl. In some embodiments, R_{10} is isobutyl. In some embodiments, R_{10} is isopentyl. In some embodiments, R_{10} is isohexyl. In some embodiments, R_{10} is secbutyl. In some embodiments, R_{10} is secpentyl. In some embodiments, R_{10} is sechexyl. In some embodiments, R_{10} is tertbutyl.

[00522] In some embodiments, R_{10} is C_{2-6} alkenyl. In some embodiments, R_{10} is C_2 alkenyl. In some embodiments, R_{10} is C_3 alkenyl. In some embodiments, R_{10} is C_4 alkenyl. In some embodiments, R_{10} is C_5 alkenyl. In some embodiments, R_{10} is C_6 alkenyl.

[00523] In some embodiments, R_{10} is C_{2-6} alkynyl. In some embodiments, R_{10} is C_2 alkynyl. In some embodiments, R_{10} is C_3 alkynyl. In some embodiments, R_{10} is C_4 alkynyl. In some embodiments, R_{10} is C_5 alkynyl. In some embodiments, R_{10} is C_6 alkynyl.

[00524] In some embodiments, R_{10} is C_{1-6} haloalkyl. In some embodiments, R_{10} is halomethyl. In some embodiments, R_{10} is haloethyl. In some embodiments, R_{10} is halopropyl. In some embodiments, R_{10} is halobutyl. In some embodiments, R_{10} is halopentyl. In some embodiments, R_{10} is halohexyl.

[00525] In some embodiments, R_{10} is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00526] In some embodiments, R_{10} is C_{3-10} cycloalkyl or 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00527] In some embodiments, R_{10} is C_{3-10} cycloalkyl.

[00528] In some embodiments, R_{10} is C_3 cycloalkyl. In some embodiments, R_{10} is C_4 cycloalkyl. In some embodiments, R_{10} is C_5 cycloalkyl. In some embodiments, R_{10} is C_6 cycloalkyl. In some embodiments, R_{10} is C_7 cycloalkyl. In some embodiments, R_{10} is C_8 cycloalkyl. In some embodiments, R_{10} is C_9 cycloalkyl. In some embodiments, R_{10} is C_{10} cycloalkyl.

[00529] In some embodiments, R_{10} is C_3-C_7 monocyclic cycloalkyl. In some embodiments, R_{10} is C_3-C_7 monocyclic saturated cycloalkyl. In some embodiments, R_{10} is C_3-C_7 monocyclic partially saturated cycloalkyl. In some embodiments, R_{10} is C_9-C_{10} bicyclic cycloalkyl. In some embodiments, R_{10} is C_9-C_{10} bicyclic saturated cycloalkyl. In some embodiments, R_{10} is C_9-C_{10} bicyclic partially saturated cycloalkyl. In some embodiments, R_{10} is C_8-C_{10} polycyclic cycloalkyl.

[00530] In some embodiments, R_{10} is 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 3-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00531] In some embodiments, R_{10} is C_{6-10} aryl or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00532] In some embodiments, R_{10} is C_{6-10} aryl.

[00533] In some embodiments, R_{10} is C_{6-8} aryl. In some embodiments, R_{10} is phenyl.

[00534] In some embodiments, R_{10} is 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{10} is 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00535] In some embodiments, R_{10} is C_{1-6} alkyl, C_{1-6} haloalkyl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00536] In some embodiments, each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O,

and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00537] In some embodiments, each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$.

[00538] In some embodiments, each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00539] In some embodiments, R_{11} is H

[00540] In some embodiments, R_{11} is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$.

[00541] In some embodiments, R_{11} is C_{1-6} alkyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is methyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is ethyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is propyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is butyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the

cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is pentyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is hexyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isopropyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isobutyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and

S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isopentyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isohexyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is secbutyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is secpentyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is sechexyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-

membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is tertbutyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$.

[00542] In some embodiments, R_{11} is C_{1-6} alkyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is methyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is ethyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-

membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is propyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is butyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is pentyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is hexyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isopropyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4

heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isobutyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isopentyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is isohexyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is secbutyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered

heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is secpentyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is sechexyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is tertbutyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$.

[00543] In some embodiments, R_{11} is C_{2-6} alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In

some embodiments, R_{11} is C_2 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_3 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_4 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_5 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_6 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the

cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$.

[00544] In some embodiments, R_{11} is C_{2-6} alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_2 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_3 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_4 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-}

$_6$ alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or -NH_2. In some embodiments, R_{11} is C_5 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or -NH_2. In some embodiments, R_{11} is C_6 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or -NH_2.

[00545] In some embodiments, R_{11} is C_{2-6} alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or -NH_2. In some embodiments, R_{11} is C_2 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or -NH_2. In some embodiments, R_{11} is C_3 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-

membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_4 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_5 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_6 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$.

[00546] In some embodiments, R_{11} is C_{2-6} alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected

from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_2 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_3 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_4 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_5 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$. In some embodiments, R_{11} is C_6 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl

comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$.

[00547] In some embodiments, R_{11} is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00548] In some embodiments, R_{11} is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00549] In some embodiments, R_{11} is C_{1-6} alkyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is methyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is ethyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is propyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is butyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is pentyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and

S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is hexyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isopropyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isobutyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isopentyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isohexyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is secbutyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is secpentyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is sechexyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is tertbutyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00550] In some embodiments, R_{11} is C_{1-6} alkyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl,

or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is methyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is ethyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is propyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is butyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is pentyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is hexyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isopropyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isobutyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isopentyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is isohexyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some

embodiments, R_{11} is secbutyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is secpentyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is sechexyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is tertbutyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00551] In some embodiments, R_{11} is C_{2-6} alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_2 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_3 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_4 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_5 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_6 alkenyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00552] In some embodiments, R_{11} is C_{2-6} alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_2 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_3 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_4 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_5 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_6 alkenyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00553] In some embodiments, R_{11} is C_{2-6} alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_2 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_3 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_4 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_5 alkynyl optionally substituted with one or more C_{3-10}

cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_6 alkynyl optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00554] In some embodiments, R_{11} is C_{2-6} alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_2 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_3 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_4 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_5 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S. In some embodiments, R_{11} is C_6 alkynyl substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00555] In some embodiments, R_{11} is C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl.

[00556] In some embodiments, R_{11} is C_{1-6} alkyl. In some embodiments, R_{11} is methyl. In some embodiments, R_{11} is ethyl. In some embodiments, R_{11} is propyl. In some embodiments, R_{11} is butyl. In some embodiments, R_{11} is pentyl. In some embodiments, R_{11} is hexyl. In some embodiments, R_{11} is isopropyl. In some embodiments, R_{11} is isobutyl. In some embodiments, R_{11} is isopentyl. In some embodiments, R_{11} is isohexyl. In some embodiments, R_{11} is secbutyl. In

some embodiments, R_{11} is secpentyl. In some embodiments, R_{11} is sechexyl. In some embodiments, R_{11} is tertbutyl.

[00557] In some embodiments, R_{11} is C_{2-6} alkenyl. In some embodiments, R_{11} is C_2 alkenyl. In some embodiments, R_{11} is C_3 alkenyl. In some embodiments, R_{11} is C_4 alkenyl. In some embodiments, R_{11} is C_5 alkenyl. In some embodiments, R_{11} is C_6 alkenyl.

[00558] In some embodiments, R_{11} is C_{2-6} alkynyl. In some embodiments, R_{11} is C_2 alkynyl. In some embodiments, R_{11} is C_3 alkynyl. In some embodiments, R_{11} is C_4 alkynyl. In some embodiments, R_{11} is C_5 alkynyl. In some embodiments, R_{11} is C_6 alkynyl.

[00559] In some embodiments, R_{11} is H or C_{1-6} alkyl optionally substituted with one or more 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, or oxo.

[00560] In some embodiments, R_{11} is H or C_{1-6} alkyl optionally substituted with one or more 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl, aryl, or heteroaryl is substituted with one or more 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, or oxo.

[00561] In some embodiments, R_{11} is H or C_{1-6} alkyl substituted with one or more 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, or oxo.

[00562] In some embodiments, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00563] In some embodiments, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00564] In some embodiments, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00565] In some embodiments, two R_{11} together with the atom to which they are attached form a 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00566] In some embodiments, two R_{11} together with the atom to which they are attached form a 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00567] In some embodiments, two R_{11} together with the atom to which they are attached form a 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00568] In some embodiments, two R_{11} together with the atom to which they are attached form a 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00569] In some embodiments, two R_{11} together with the atom to which they are attached form a 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00570] In some embodiments, two R_{11} together with the atom to which they are attached form a 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00571] In some embodiments, two R_{11} together with the atom to which they are attached form a 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00572] In some embodiments, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00573] In some embodiments, two R_{11} together with the atom to which they are attached form a 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00574] In some embodiments, two R_{11} together with the atom to which they are attached form a 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00575] In some embodiments, two R_{11} together with the atom to which they are attached form a 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00576] In some embodiments, two R_{11} together with the atom to which they are attached form a 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00577] In some embodiments, two R_{11} together with the atom to which they are attached form a 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00578] In some embodiments, two R_{11} together with the atom to which they are attached form a 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00579] In some embodiments, two R_{11} together with the atom to which they are attached form a 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00580] In some embodiments, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00581] In some embodiments, two R_{11} together with the atom to which they are attached form a 4-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00582] In some embodiments, two R_{11} together with the atom to which they are attached form a 5-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00583] In some embodiments, two R_{11} together with the atom to which they are attached form a 6-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00584] In some embodiments, two R_{11} together with the atom to which they are attached form a 7-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00585] In some embodiments, two R_{11} together with the atom to which they are attached form a 8-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00586] In some embodiments, two R_{11} together with the atom to which they are attached form a 9-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00587] In some embodiments, two R_{11} together with the atom to which they are attached form a 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S.

[00588] In some embodiments, two R_{11} together with the atom to which they are attached form a 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00589] In some embodiments, two R_{11} together with the atom to which they are attached form a 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00590] In some embodiments, two R_{11} together with the atom to which they are attached form a 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00591] In some embodiments, two R_{11} together with the atom to which they are attached form a 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00592] In some embodiments, two R_{11} together with the atom to which they are attached form a 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00593] In some embodiments, two R_{11} together with the atom to which they are attached form a 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00594] In some embodiments, two R_{11} together with the atom to which they are attached form a 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00595] In some embodiments, two R_{11} together with the atom to which they are attached form a 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00596] In some embodiments, two R_{11} together with the atom to which they are attached form a 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00597] In some embodiments, two R_{11} together with the atom to which they are attached form a 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00598] In some embodiments, two R_{11} together with the atom to which they are attached form a 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00599] In some embodiments, two R_{11} together with the atom to which they are attached form a 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00600] In some embodiments, two R_{11} together with the atom to which they are attached form a 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00601] In some embodiments, two R_{11} together with the atom to which they are attached form a 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00602] In some embodiments, two R_{11} together with the atom to which they are attached form a 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00603] In some embodiments, two R_{11} together with the atom to which they are attached form a 5-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00604] In some embodiments, two R_{11} together with the atom to which they are attached form a 6-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00605] In some embodiments, two R_{11} together with the atom to which they are attached form a 7-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00606] In some embodiments, two R_{11} together with the atom to which they are attached form a 8-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00607] In some embodiments, two R_{11} together with the atom to which they are attached form a 9-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00608] In some embodiments, two R_{11} together with the atom to which they are attached form a 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

[00609] In some embodiments, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S,

optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00610] In some embodiments, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

[00611] In some embodiments, each n, m, and p is independently 0 or 1. In some embodiments, each n, m, and p is independently 0. In some embodiments, each n, m, and p is independently 1.

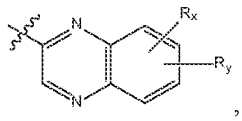
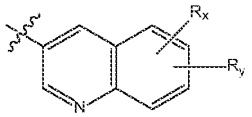
[00612] In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1.

[00613] In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1.

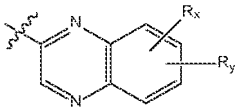
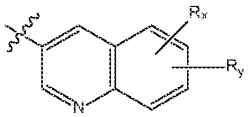
[00614] In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1.

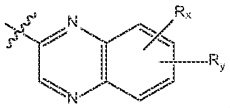
[00615] In some embodiments, t is 1, 2, or 3. In some embodiments, t is 1. In some embodiments, t is 2. In some embodiments, t is 3.

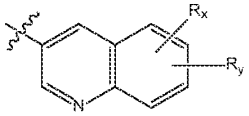
[00616] In some embodiments, u is 0, 1, 2, or 3. In some embodiments, u is 0. In some embodiments, u is 1. In some embodiments, u is 2. In some embodiments, u is 3.

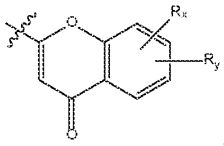
[00617] In some embodiments, when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not phenyl, , or .

[00618] In some embodiments, when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not phenyl.

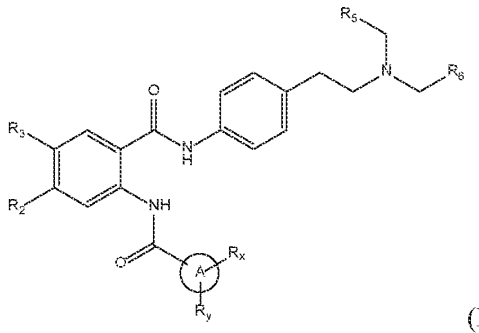
[00619] In some embodiments, when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not  or .

[00620] In some embodiments, when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not .

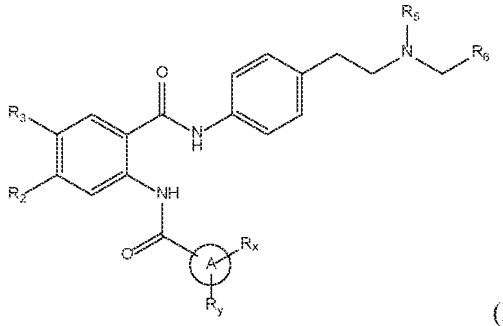
[00621] In some embodiments, when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not .

[00622] In some embodiments, when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is .

[00623] In some embodiments, the compound is of Formula (I-a) or (I-b):



(I-a), or



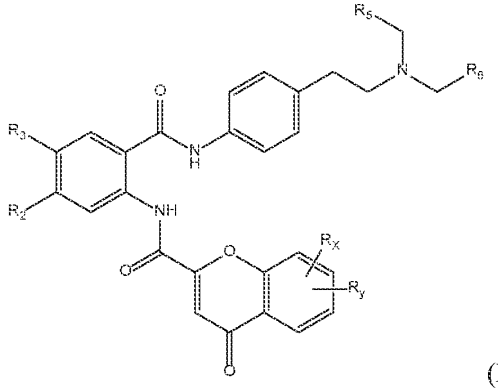
(I-b)

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

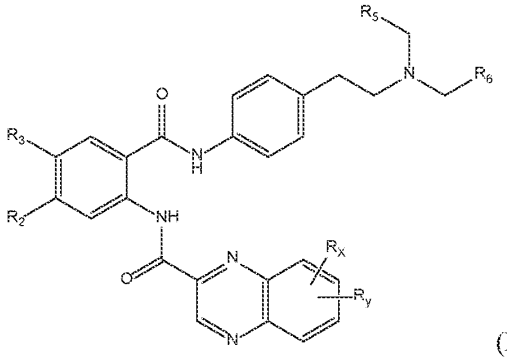
[00624] In some embodiments, the compound is of Formula (I-a) or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00625] In some embodiments, the compound is of Formula (I-b) or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

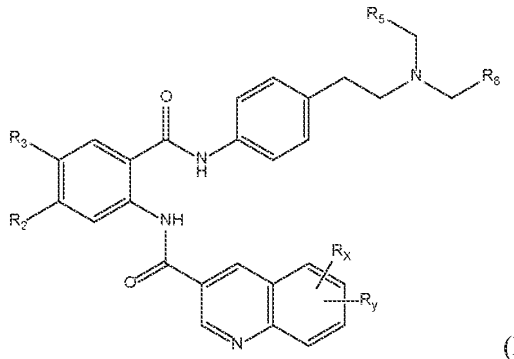
[00626] In some embodiments, the compound is of Formula (I-c), (I-d), or (I-e):



(I-c),



(I-d), or



(I-e)

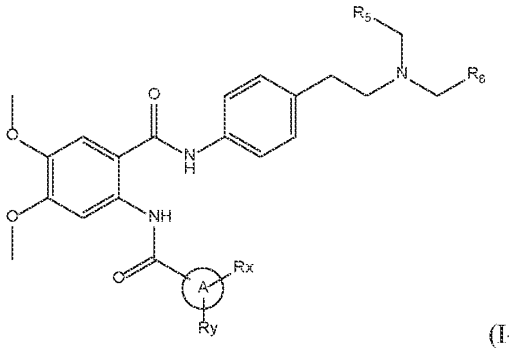
or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00627] In some embodiments, the compound is of Formula (I-c) or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

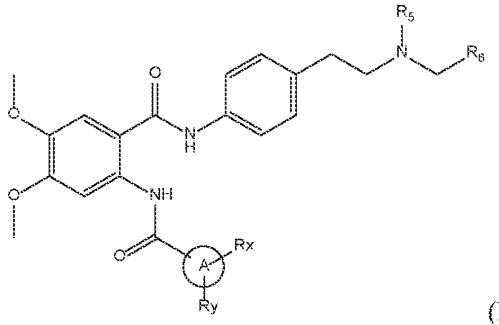
[00628] In some embodiments, the compound is of Formula (I-d) or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00629] In some embodiments, the compound is of Formula (I-e) or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00630] In some embodiments, the compound is of Formula (I-a') or (I-b'):



(I-a'), or



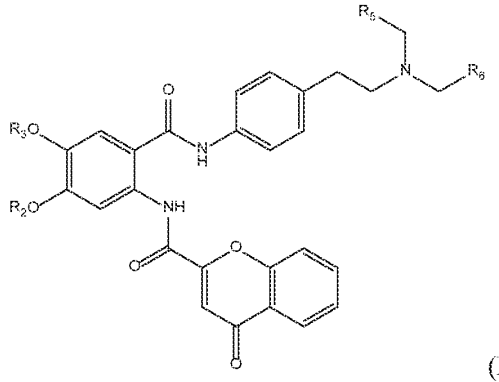
(I-b')

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00631] In some embodiments, the compound is of Formula (I-a') or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00632] In some embodiments, the compound is of Formula (I-b') or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00633] In some embodiments, the compound is of Formula (II-a):

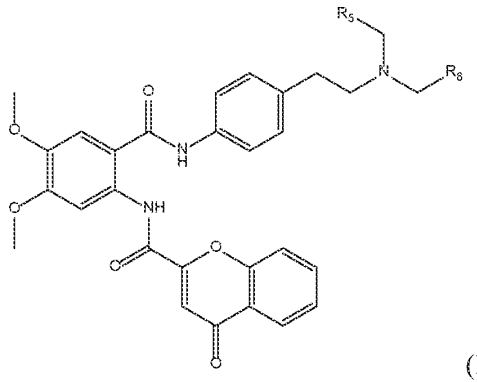


(II-a)

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00634] In some embodiments, the compound is of Formula (II-a) or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00635] In some embodiments, the compound is of Formula (II-a'):



(II-a')

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00636] In some embodiments, the compound is of Formula (II-a') or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00637] It is understood that, for a compound of any of the Formulae disclosed herein, **A**, R_X, R_Y, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, **n**, **m**, **p**, **t**, and **u** can each be, where applicable, selected from the groups described herein, and any group described herein for any of **A**, R_X, R_Y, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, **n**, **m**, **p**, **t**, and **u** can be combined, where applicable, with any group described herein for one or more of the remainder of **A**, R_X, R_Y, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, **n**, **m**, **p**, **t**, and **u**.

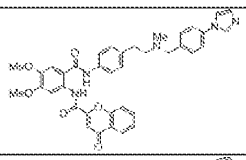
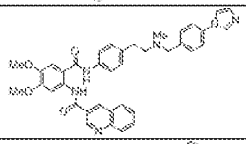
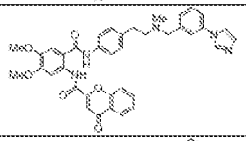
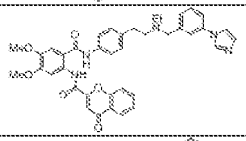
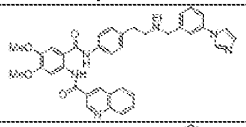
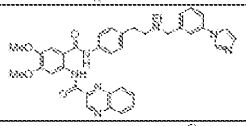
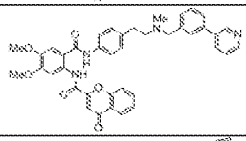
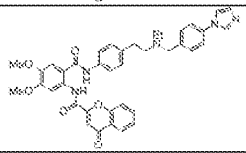
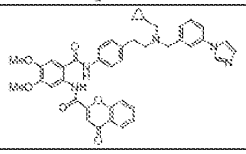
[00638] In some embodiments, the compound is selected from the compounds described in Table 1 and prodrugs and pharmaceutically acceptable salts thereof.

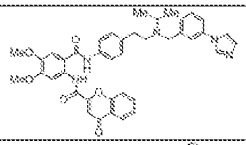
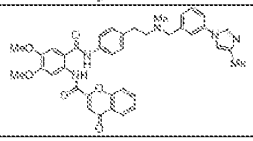
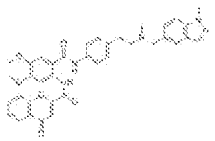
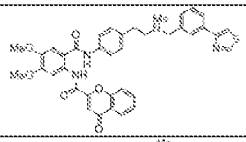
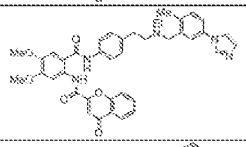
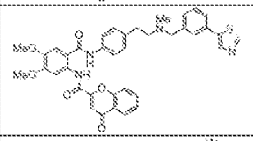
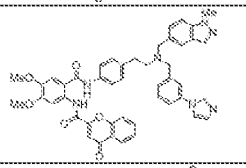
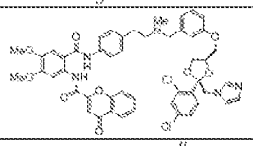
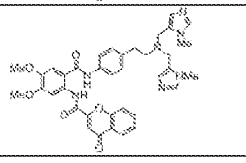
[00639] In some embodiments, the compound is selected from the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

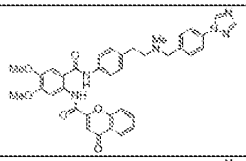
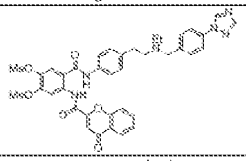
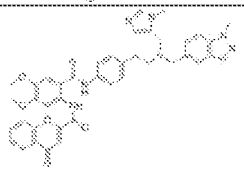
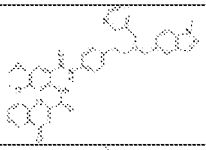
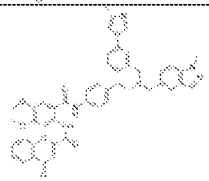
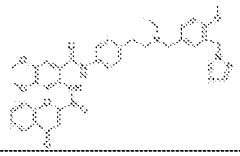
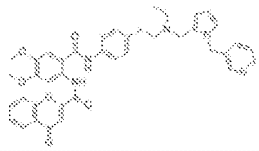
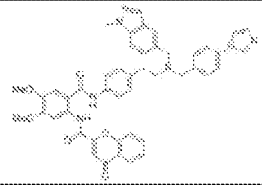
[00640] In some embodiments, the compound is selected from the prodrugs of compounds described in Table 1 and pharmaceutically acceptable salts thereof.

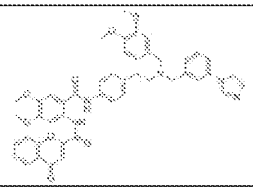
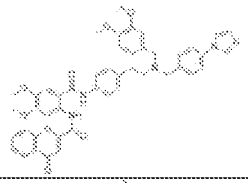
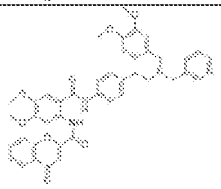
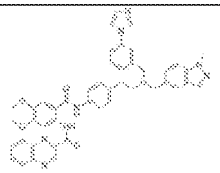
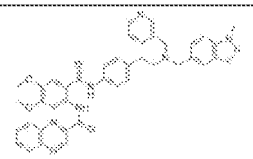
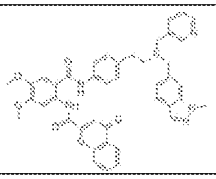
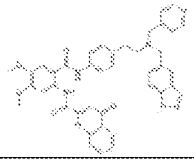
[00641] In some embodiments, the compound is selected from the compounds described in Table 1.

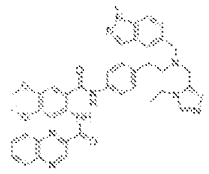
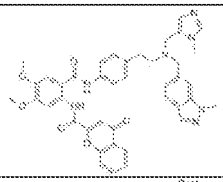
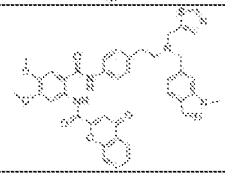
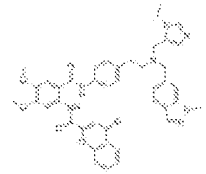
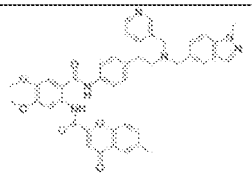
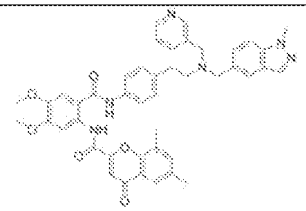
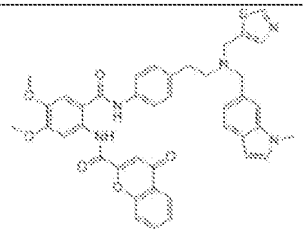
Table 1

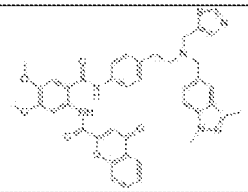
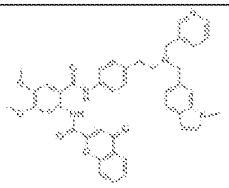
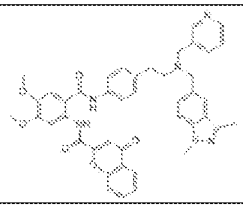
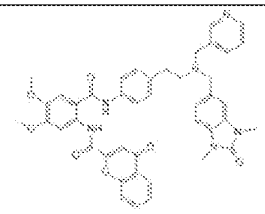
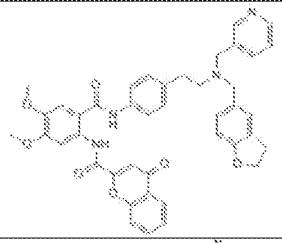
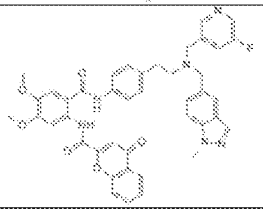
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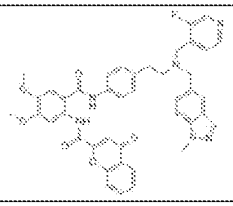
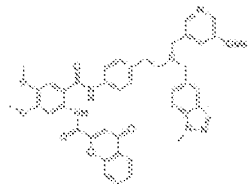
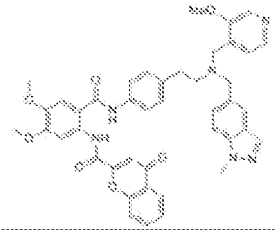
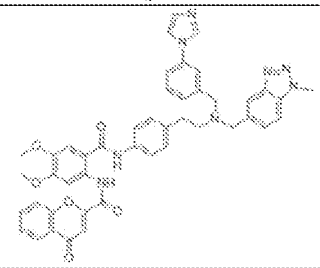
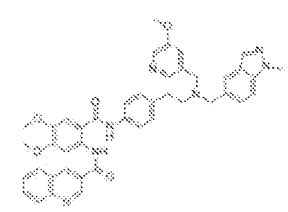
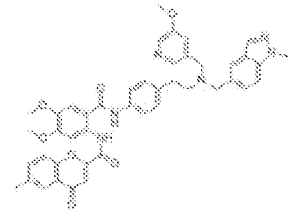
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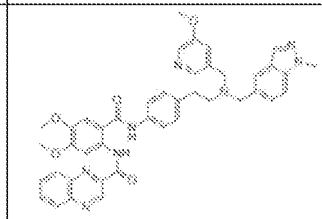
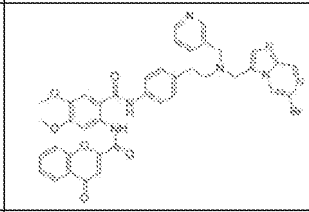
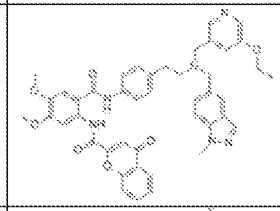
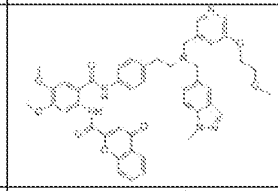
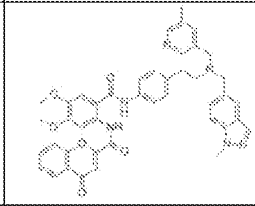
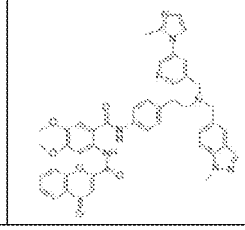
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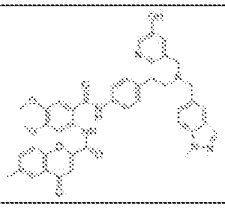
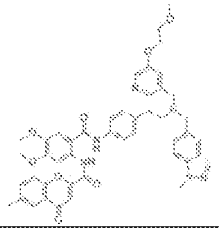
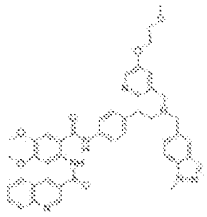
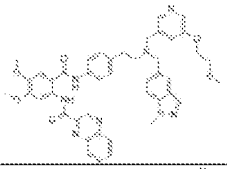
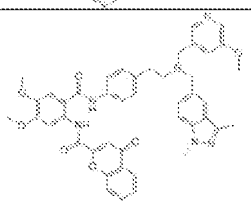
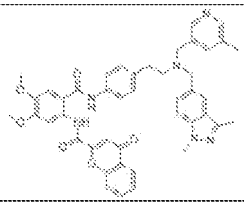
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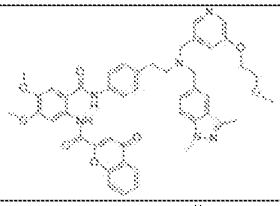
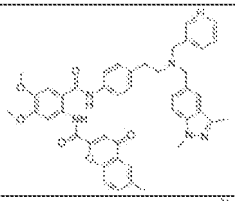
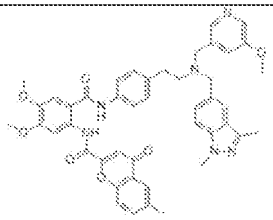
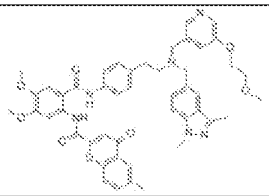
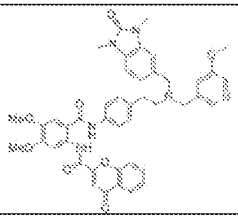
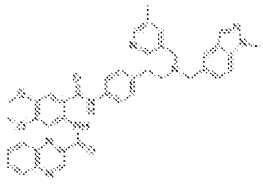
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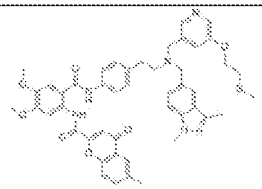
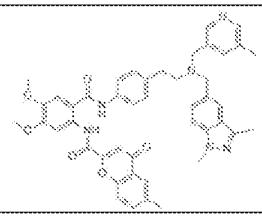
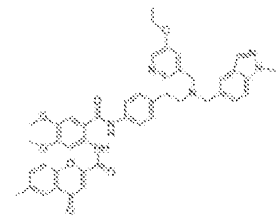
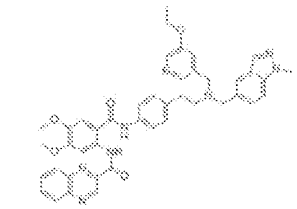
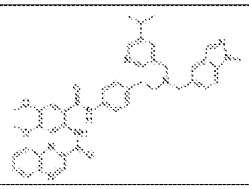
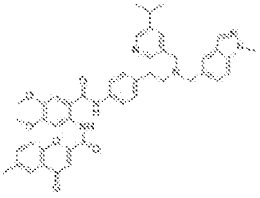
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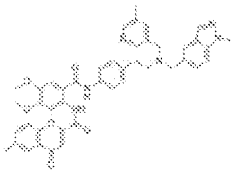
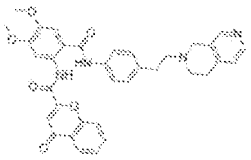
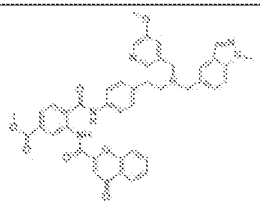
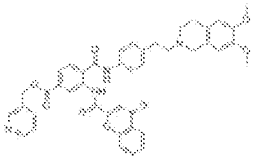
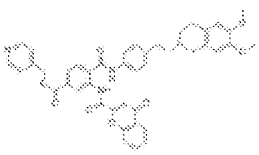
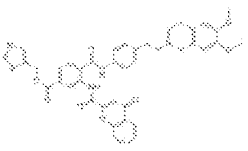
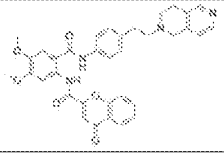
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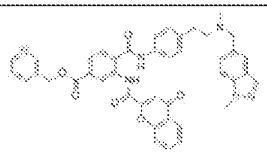
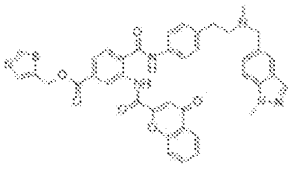
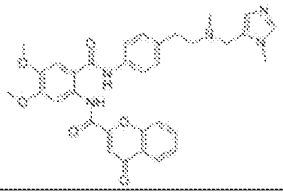
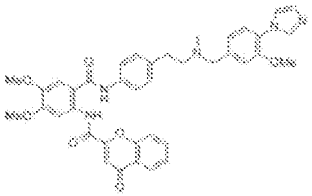
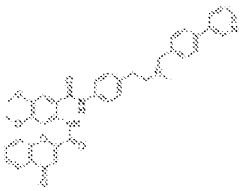
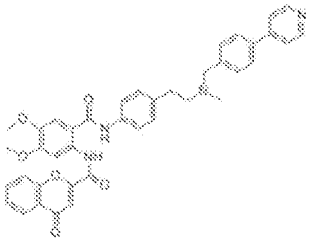
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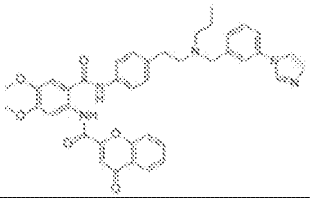
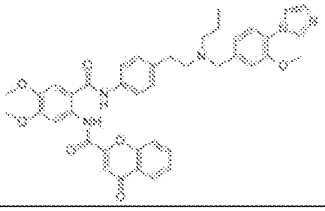
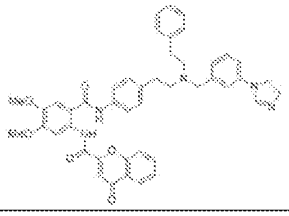
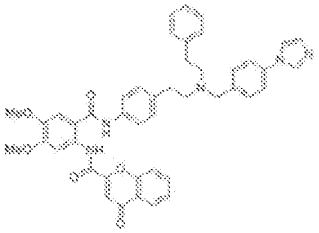
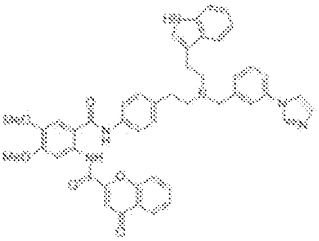
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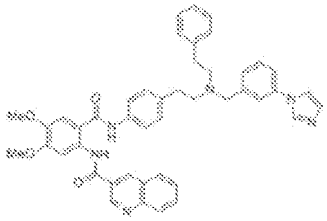
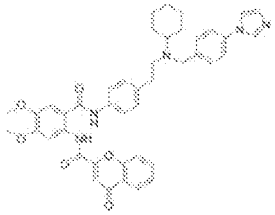
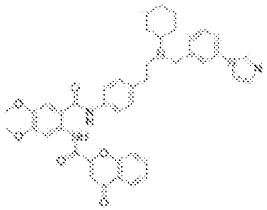
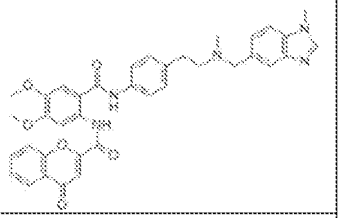
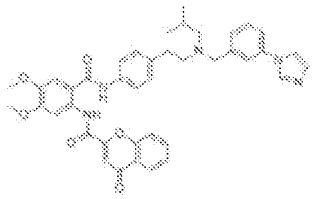
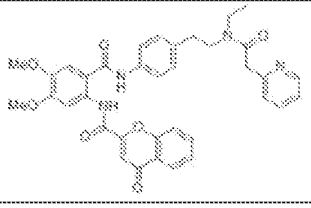
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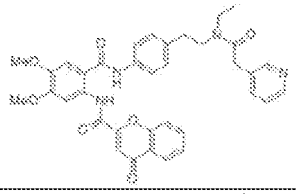
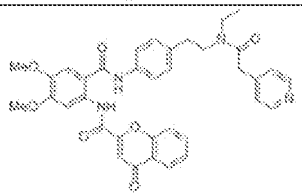
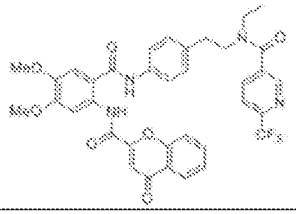
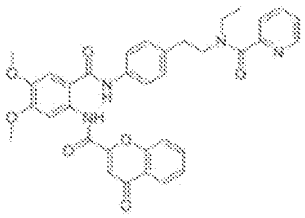
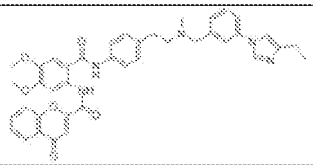
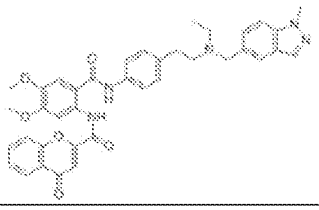
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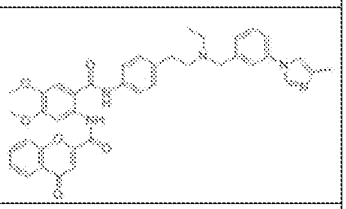
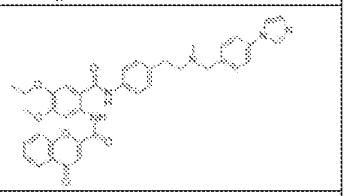
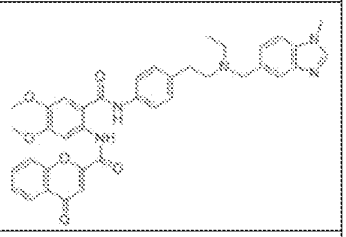
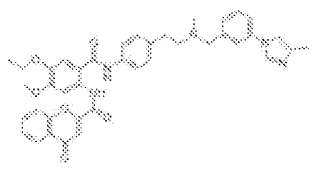
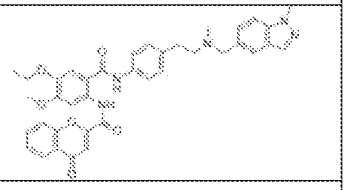
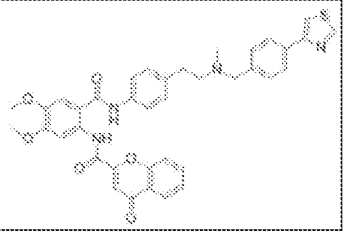
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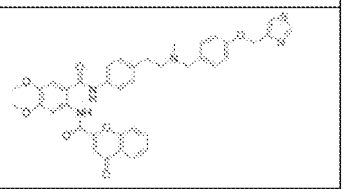
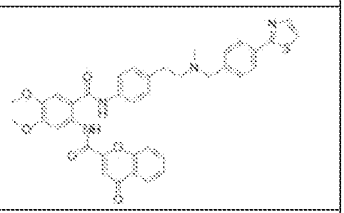
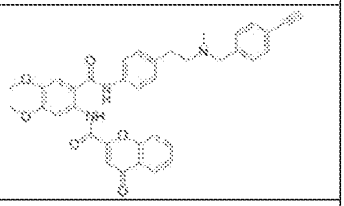
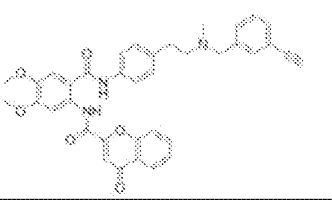
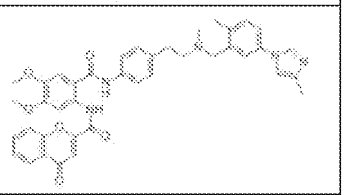
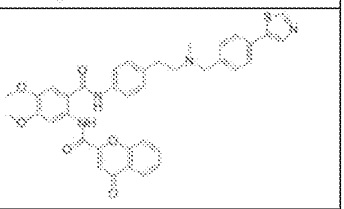
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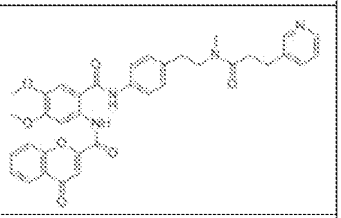
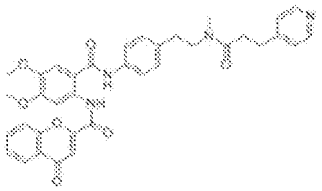
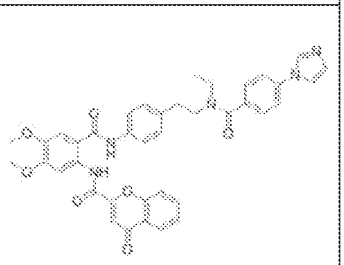
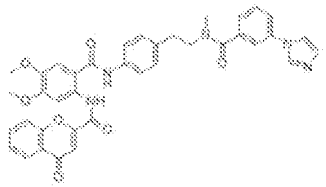
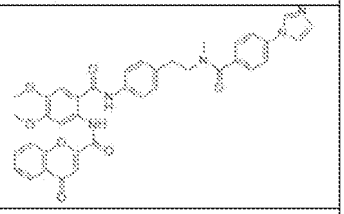
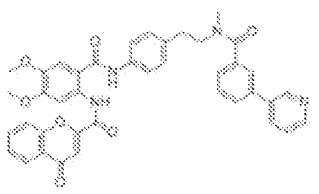
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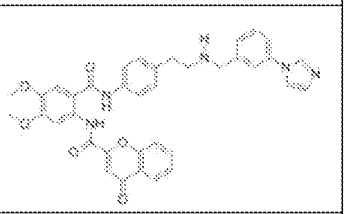
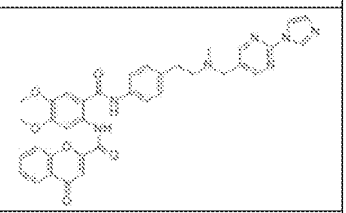
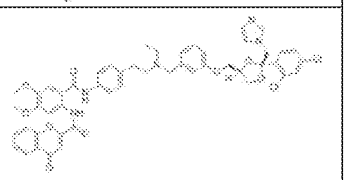
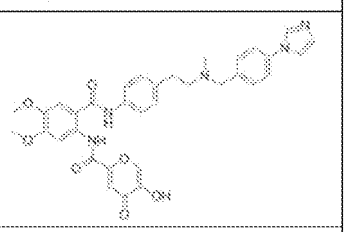
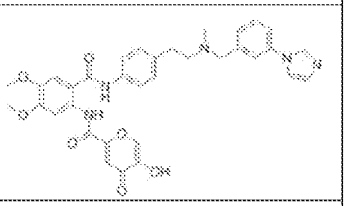
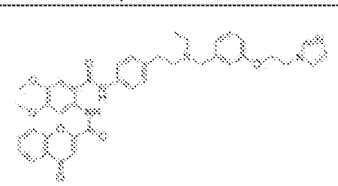
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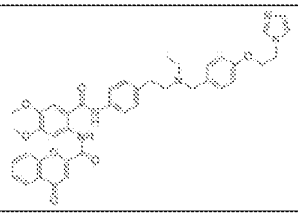
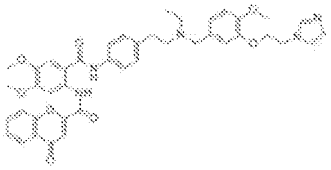
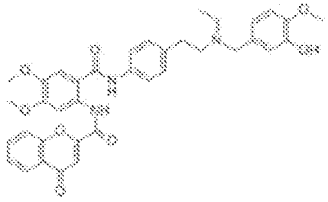
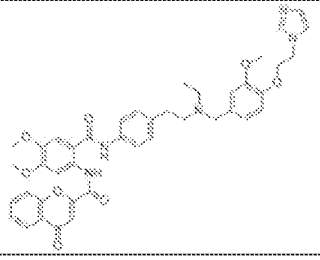
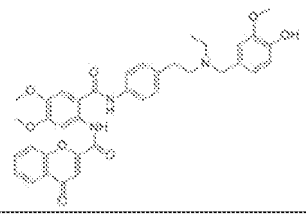
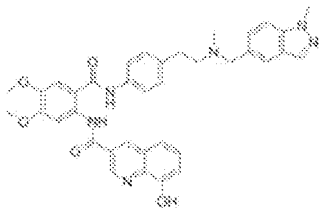
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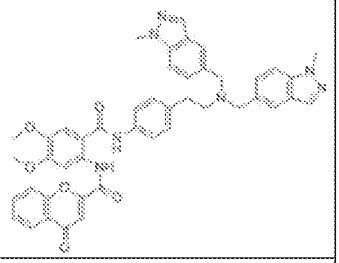
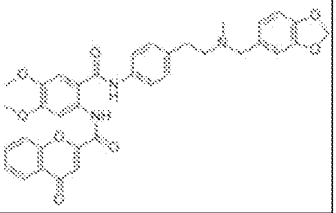
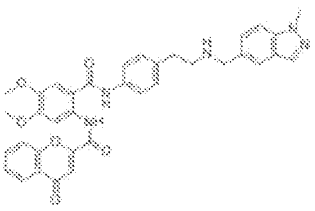
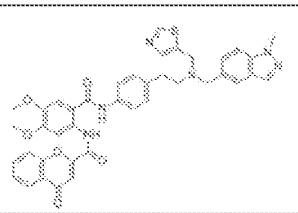
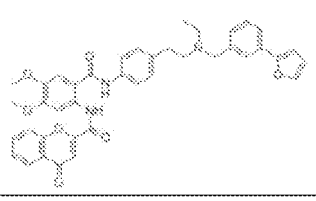
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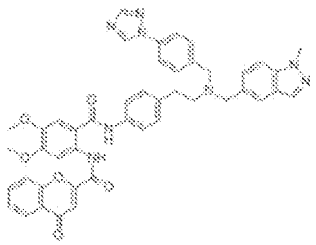
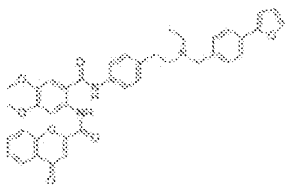
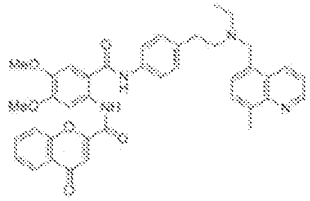
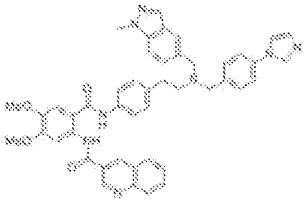
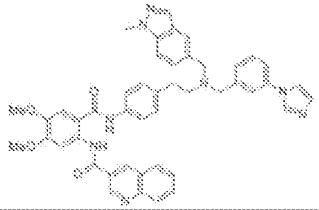
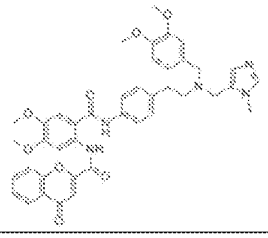
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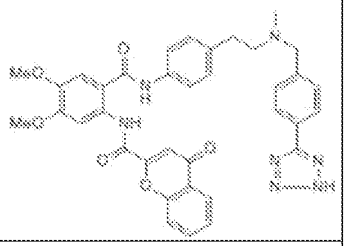
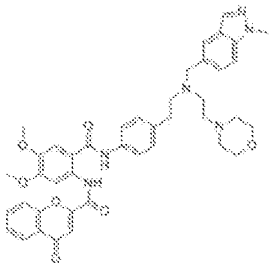
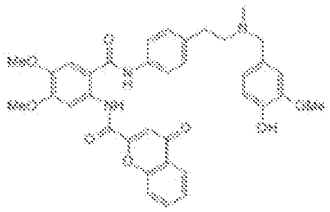
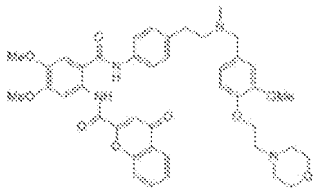
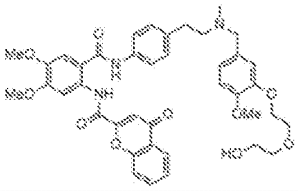
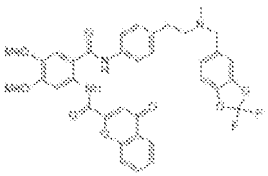
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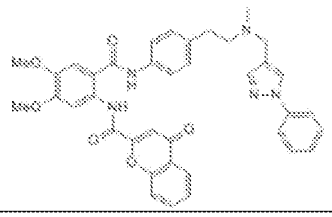
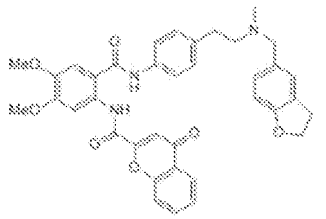
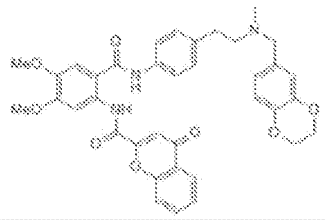
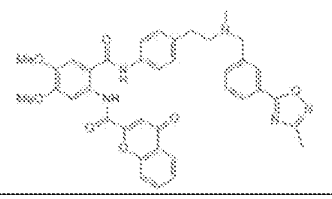
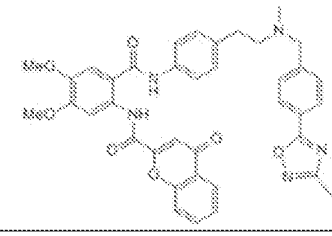
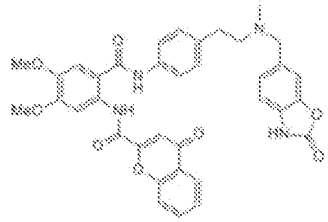
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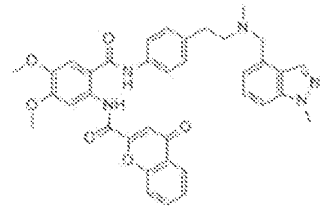
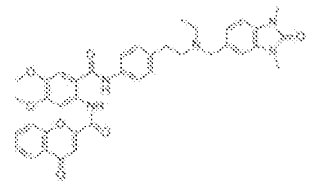
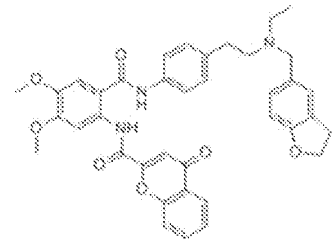
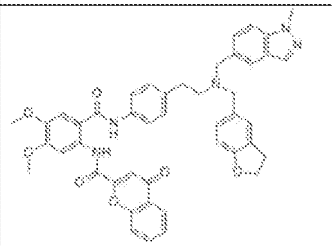
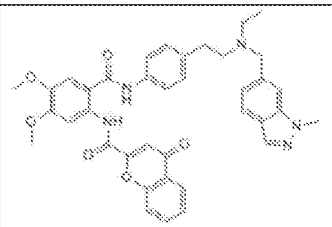
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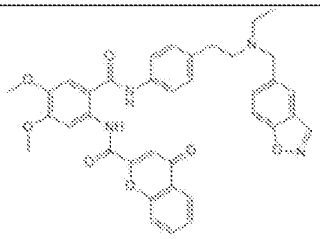
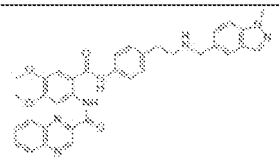
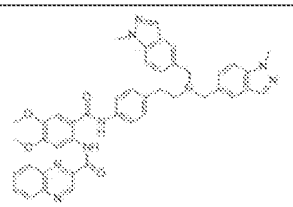
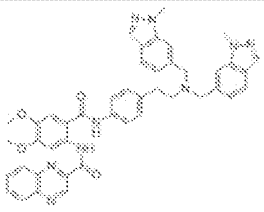
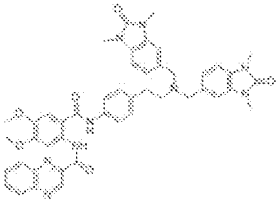
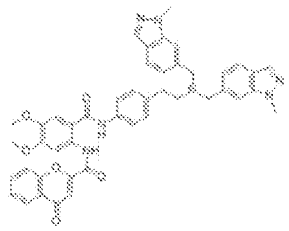
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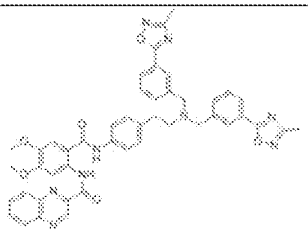
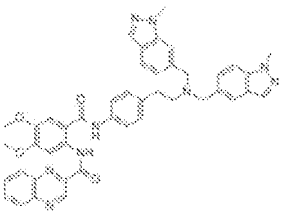
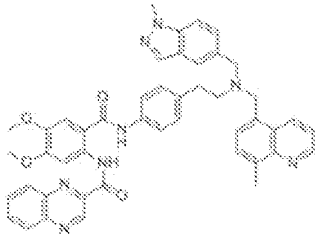
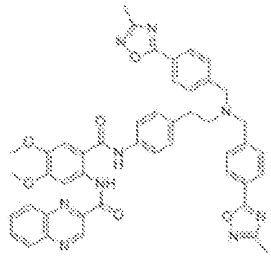
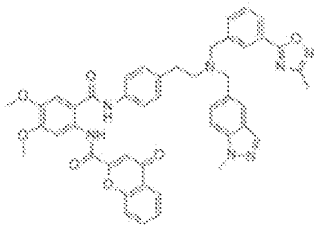
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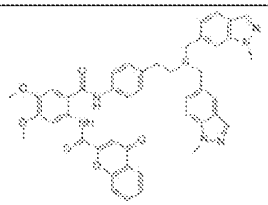
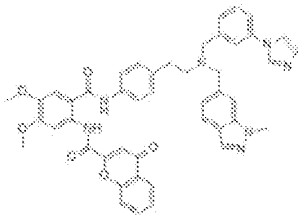
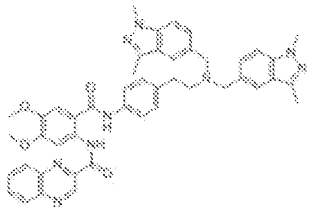
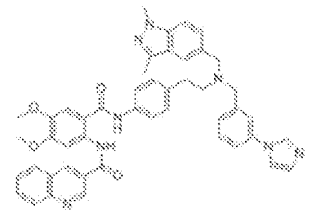
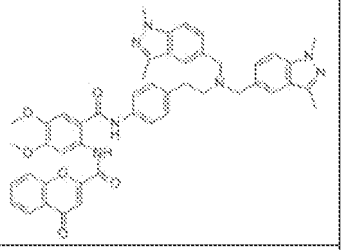
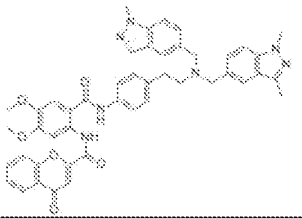
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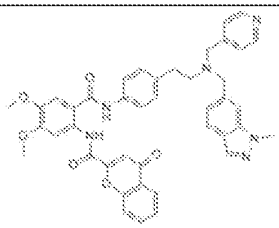
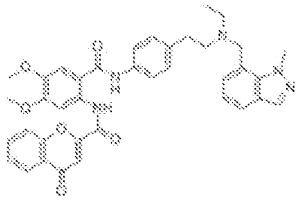
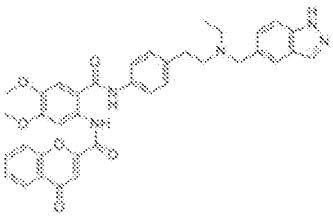
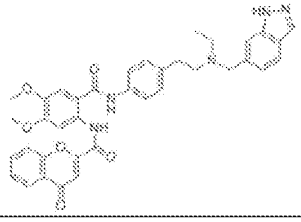
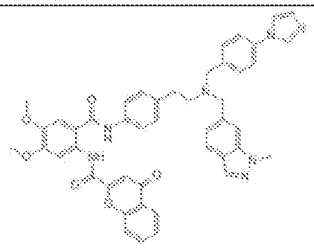
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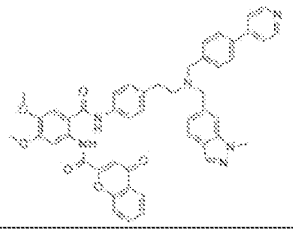
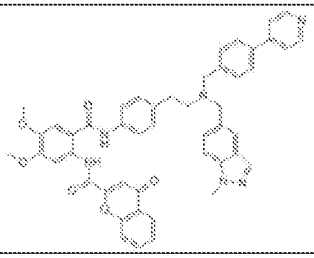
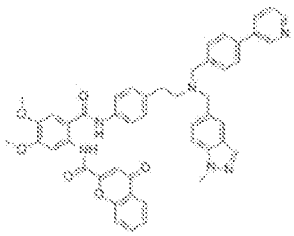
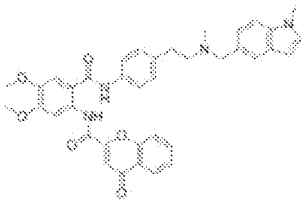
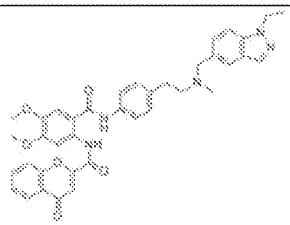
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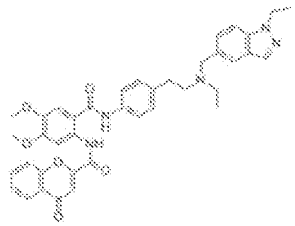
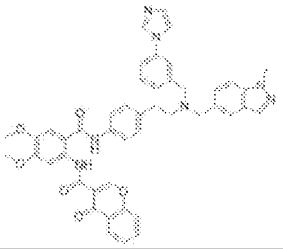
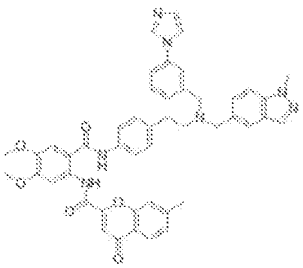
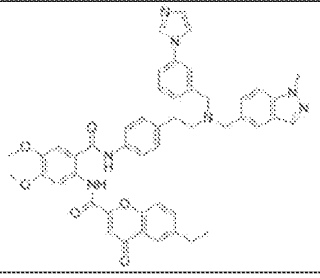
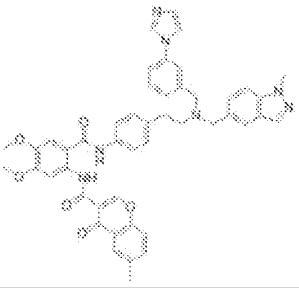
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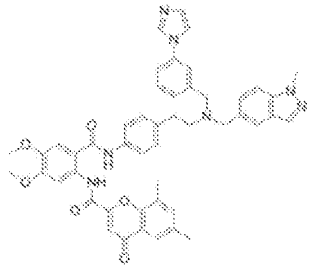
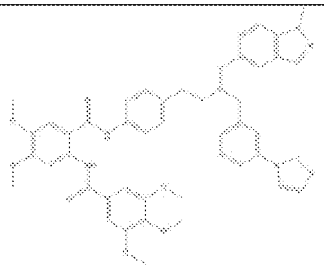
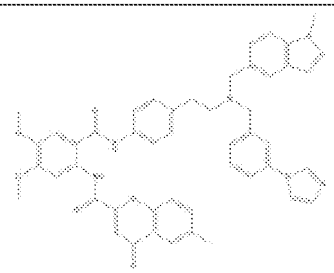
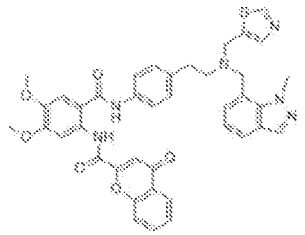
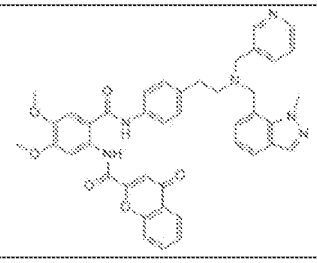
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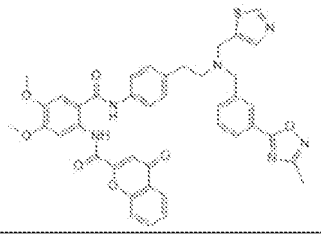
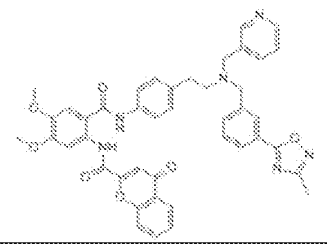
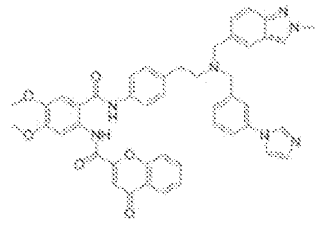
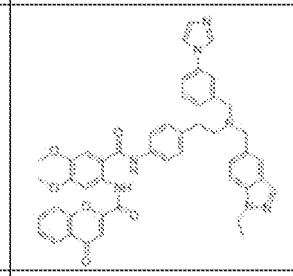
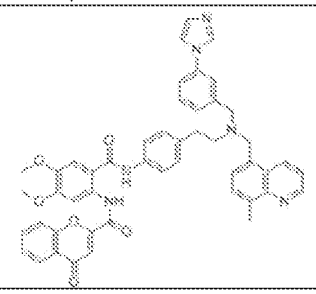
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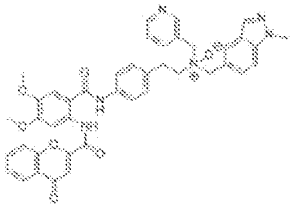
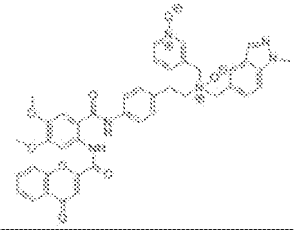
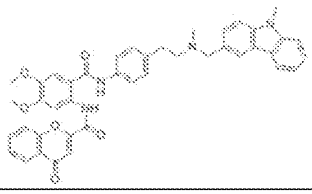
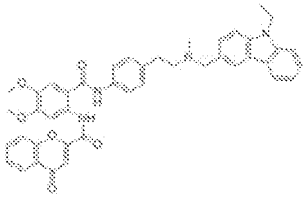
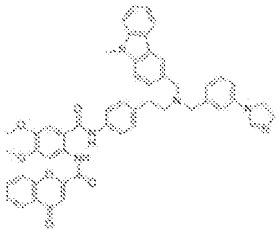
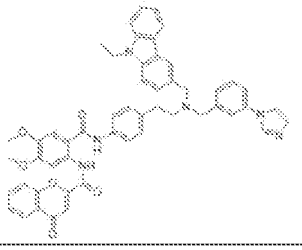
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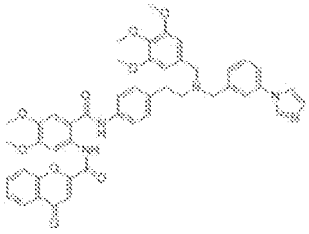
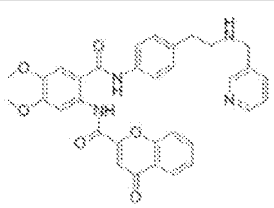
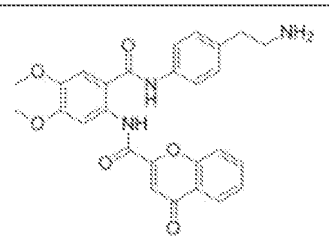
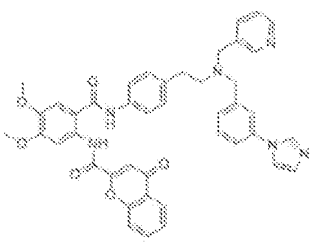
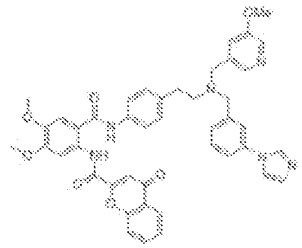
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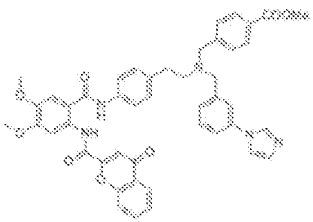
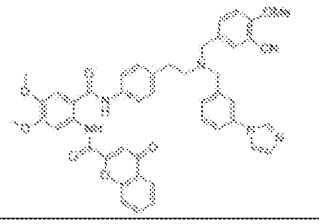
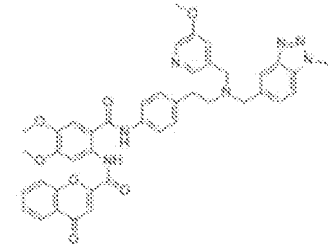
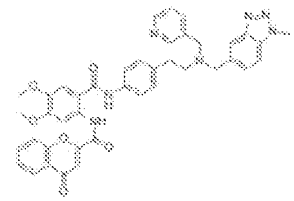
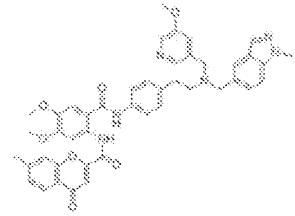
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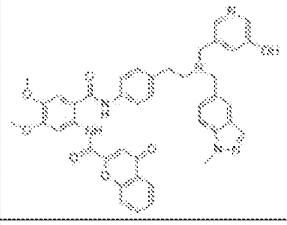
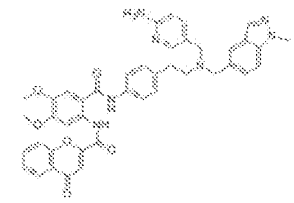
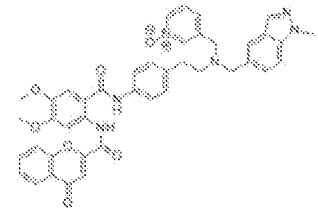
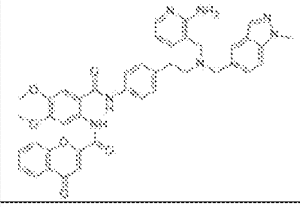
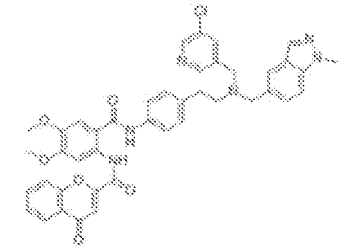
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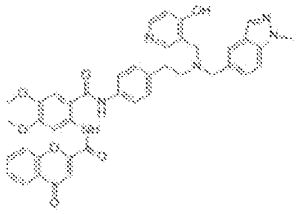
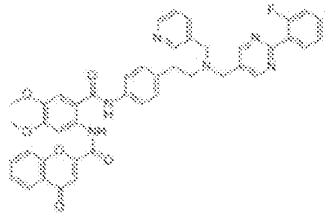
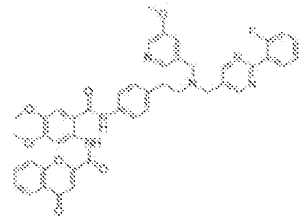
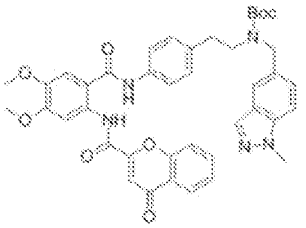
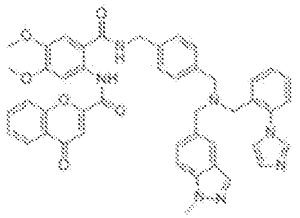
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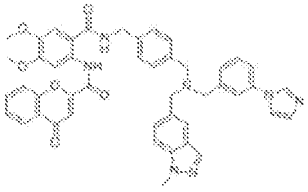
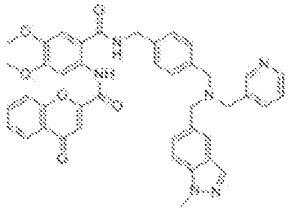
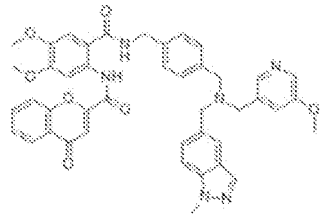
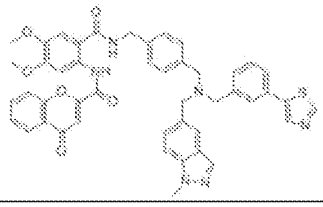
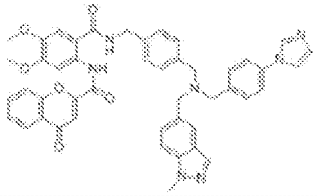
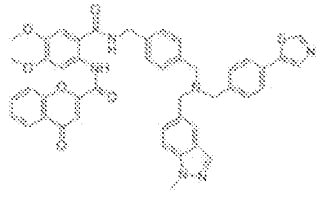
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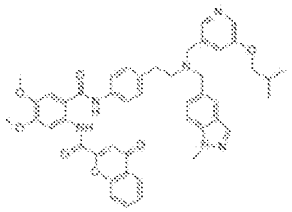
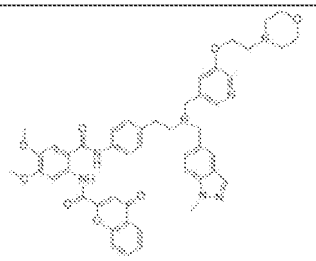
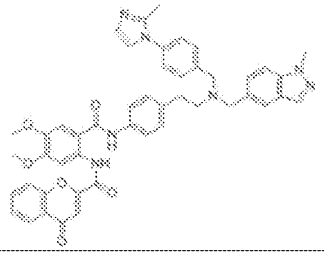
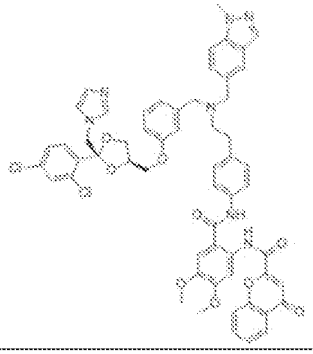
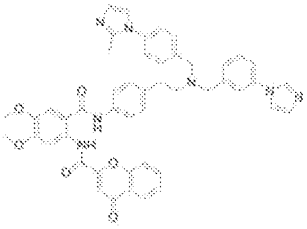
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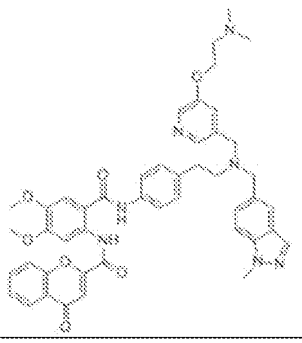
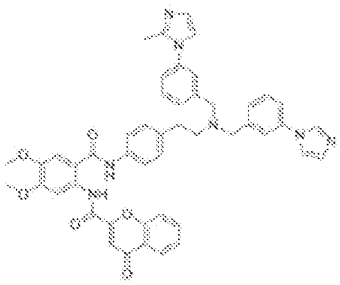
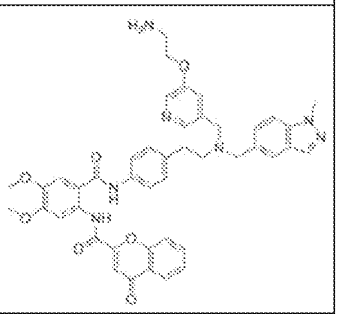
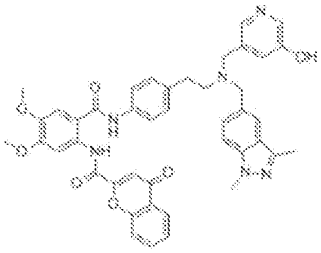
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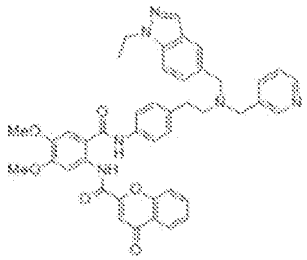
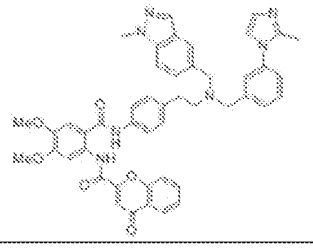
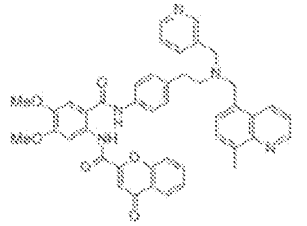
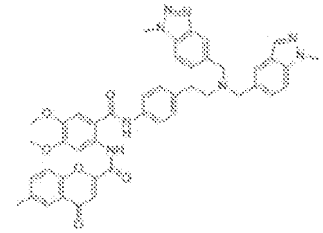
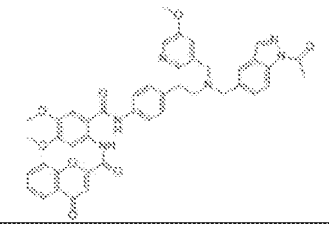
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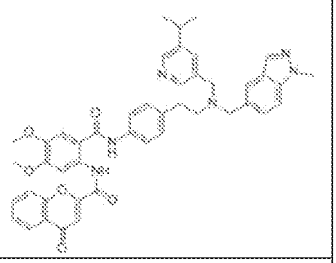
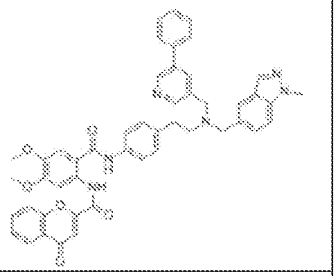
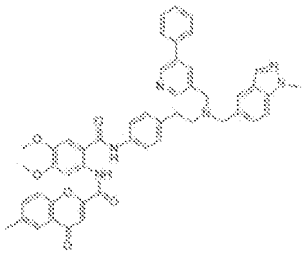
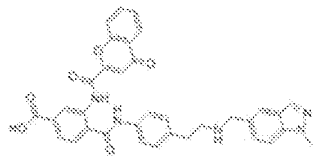
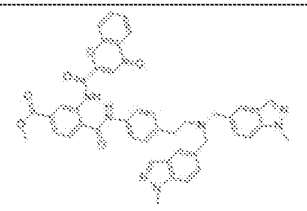
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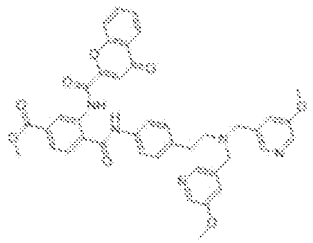
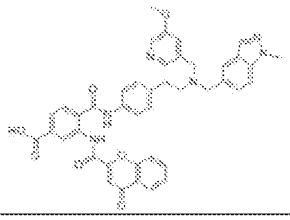
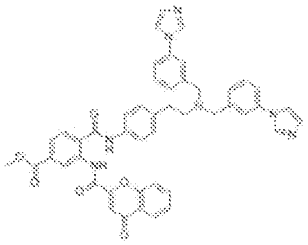
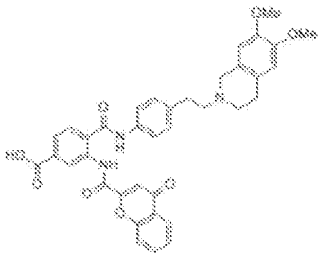
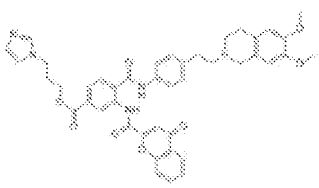
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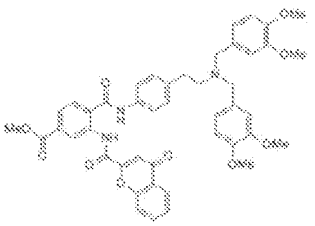
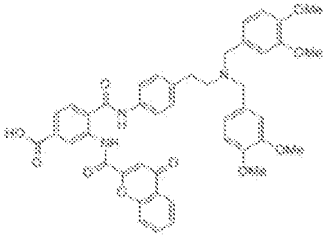
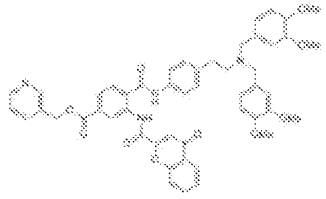
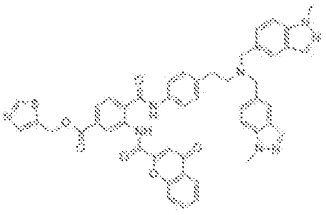
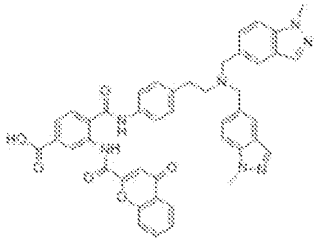
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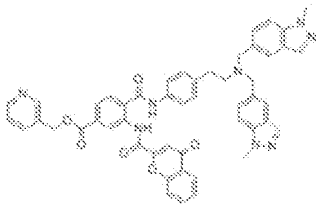
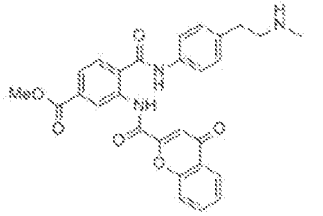
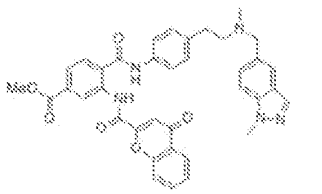
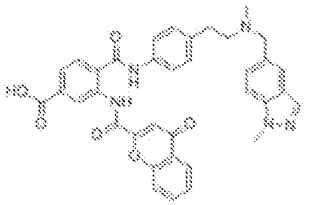
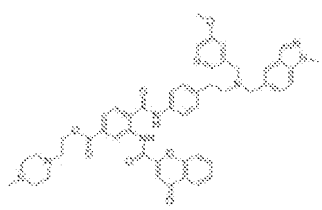
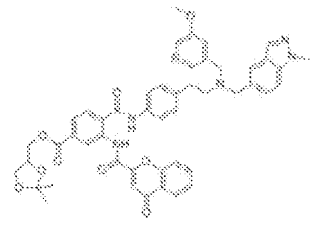
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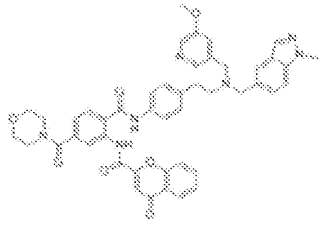
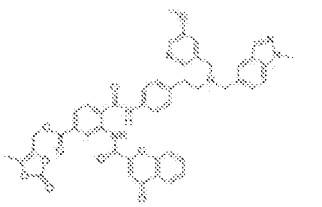
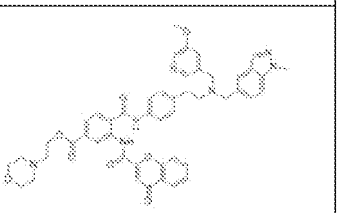
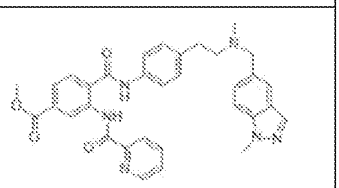
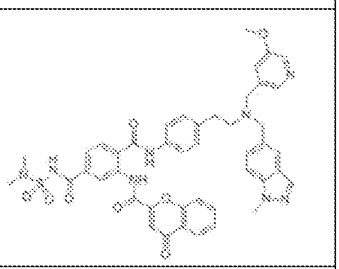
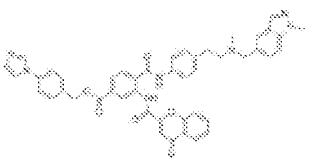
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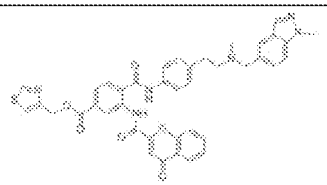
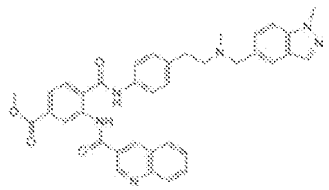
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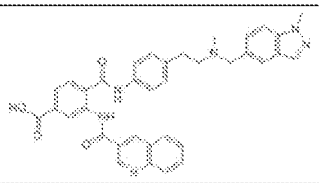
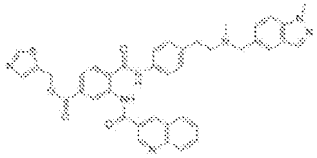
Cmpnd No.	Structure
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Cmpnd No.	Structure
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[00642] The present disclosure also encompasses compounds of the disclosure as defined herein which comprise one or more isotopic substitutions.

[00643] In some aspects, the present disclosure provides a compound being an isotopic derivative (*e.g.*, isotopically labeled compound) of any one of the compounds of the Formulae disclosed herein.

[00644] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1 and prodrugs and pharmaceutically acceptable salts thereof.

[00645] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[00646] In some embodiments, the compound is an isotopic derivative of any one of prodrugs of the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[00647] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1.

[00648] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivative can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[00649] In some embodiments, the isotopic derivative is a deuterium labeled compound.

[00650] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds of the Formulae disclosed herein.

[00651] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1 and prodrugs and pharmaceutically acceptable salts thereof.

[00652] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[00653] In some embodiments, the compound is a deuterium labeled compound of any one of the prodrugs of the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[00654] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1.

[00655] It is understood that the deuterium labeled compound comprises a deuterium atom having an abundance of deuterium that is substantially greater than the natural abundance of deuterium, which is 0.015%.

[00656] In some embodiments, the deuterium labeled compound has a deuterium enrichment factor for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). As used herein, the term "deuterium enrichment factor" means the ratio between the deuterium abundance and the natural abundance of a deuterium.

[00657] It is understood that the deuterium labeled compound can be prepared using any of a variety of art-recognized techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a deuterium labeled reagent for a non-deuterium labeled reagent.

[00658] A compound of the invention or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the invention. Further, substitution with deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, *e.g.*, increased *in vivo* half-life or reduced dosage requirements.

[00659] In some embodiments, the compound is a ^{18}F labeled compound.

[00660] In some embodiments, the compound is a ^{123}I labeled compound, a ^{124}I labeled compound, a ^{125}I labeled compound, a ^{129}I labeled compound, a ^{131}I labeled compound, a ^{135}I labeled compound, or any combination thereof.

[00661] In some embodiments, the compound is a ^{33}S labeled compound, a ^{34}S labeled compound, a ^{35}S labeled compound, a ^{36}S labeled compound, or any combination thereof.

[00662] It is understood that the ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{129}I, ^{131}I, ^{135}I, ^{3}S, ^{34}S, ^{35}S, and/or ^{36}S labeled compound, can be prepared using any of a variety of art-recognized techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{129}I, ^{131}I, ^{135}I, ^{3}S, ^{34}S, ^{35}S, and/or ^{36}S labeled reagent for a non-isotope labeled reagent.

[00663] A compound of the invention or a pharmaceutically acceptable salt or solvate thereof that contains one or more of the aforementioned ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{129}I, ^{131}I, ^{135}I, ^{3}S, ^{34}S, ^{35}S, and ^{36}S atom(s) is within the scope of the invention. Further, substitution with isotope (*e.g.*, ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{129}I, ^{131}I, ^{135}I, ^{3}S, ^{34}S, ^{35}S, and/or ^{36}S) may afford certain therapeutic advantages resulting from greater metabolic stability, *e.g.*, increased *in vivo* half-life or reduced dosage requirements.

Definitions

[00664] Unless otherwise stated, the following terms used in the specification and claims have the meanings set out below.

[00665] As use herein, the phrase "compound of the disclosure" refers to those compounds which are disclosed herein, both generically and specifically.

[00666] For the avoidance of doubt it is to be understood that, where in this specification a group is qualified by "described herein", the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

[00667] The various functional groups and substituents making up the compounds of any of the Formulae disclosed herein are typically chosen such that the molecular weight of the compound does not exceed 1000 daltons. More usually, the molecular weight of the compound will be less than 900, for example less than 800, or less than 750, or less than 700, or less than 650 daltons. More conveniently, the molecular weight is less than 600 and, for example, is 550 daltons or less.

[00668] As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl", "C_1-C_6 alkyl", or "C_{1-6} alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intends to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[00669] As used herein, the term "optionally substituted alkyl" refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[00670] As used herein, the term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkenyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkenyl groups containing three to six carbon atoms.

[00671] As used herein, the term "optionally substituted alkenyl" refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, halogen,

hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[00672] As used herein, the term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, "alkynyl" includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkynyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkynyl groups containing three to six carbon atoms.

[00673] As used herein, the term "optionally substituted alkynyl" refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[00674] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl

includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyl and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl.

[00675] As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon monocyclic or polycyclic (*e.g.*, fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (*e.g.*, C_3-C_{12} (or C_{3-12}), C_3-C_{10} (or C_{3-10}), or C_3-C_8 (or C_{3-8})). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, 1,2,3,4-tetrahydronaphthalenyl, and adamantyl.

[00676] As used herein, the term "heterocycloalkyl" or "heterocyclyl" refers to a saturated or partially unsaturated 3-8 membered monocyclic, 7-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, P, or Se), *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulphur, unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, oxiranyl, azetidinyl, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl, pyranyl, morpholinyl, tetrahydrothiopyranyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 1,4-dioxaspiro[4.5]decanyl, 1-oxaspiro[4.5]decanyl, 1-azaspiro[4.5]decanyl, 3'H-spiro[cyclohexane-1,1'-isobenzofuran]-yl, 7'H-spiro[cyclohexane-1,5'-furo[3,4-b]pyridin]-yl, 3'H-spiro[cyclohexane-1,1'-furo[3,4-c]pyridin]-yl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazolyl, 3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidinyl, 4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridinyl, 5,6,7,8-tetrahydropyrido[4,3-d]pyrimidinyl, 2-azaspiro[3.3]heptanyl, 2-methyl-2-azaspiro[3.3]heptanyl, 2-azaspiro[3.5]nonanyl, 2-methyl-2-azaspiro[3.5]nonanyl, 2-azaspiro[4.5]decanyl, 2-methyl-2-azaspiro[4.5]decanyl, 2-oxa-azaspiro[3.4]octanyl, 2-oxa-azaspiro[3.4]octan-6-yl, and the like. In the case of multicyclic heterocycloalkyl, only one of the rings in the heterocycloalkyl needs to be non-aromatic (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl).

[00677] As used herein, the term "aryl" includes groups with aromaticity, including "conjugated," or multicyclic systems with one or more aromatic rings and do not contain any

heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like. Conveniently, an aryl is phenyl.

[00678] As used herein, the term "heteroaryl" is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulphur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulphur heteroatoms may optionally be oxidised (*i.e.*, N→O and $S(O)_p$, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocyclyl is not more than 1. Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like. Heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, 4,5,6,7-tetrahydrobenzo[c]isoxazolyl).

[00679] Furthermore, the terms "aryl" and "heteroaryl" include multicyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

[00680] The cycloalkyl, heterocyclyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (*e.g.*, the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or

heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl such as benzo[d][1,3]dioxole-5-yl).

[00681] As used herein, the term "substituted," means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[00682] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[00683] When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[00684] As used herein, the term "hydroxy" or "hydroxyl" includes groups with an -OH or -O^-.

[00685] As used herein, the term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

[00686] The term "haloalkyl" or "haloalkoxyl" refers to an alkyl or alkoxyl substituted with one or more halogen atoms.

[00687] As used herein, the term "optionally substituted haloalkyl" refers to unsubstituted haloalkyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, hydroxyl,

alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[00688] As used herein, the term "alkoxy" or "alkoxyl" includes substituted and unsubstituted alkyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphhydryl, alkylthio, arylthio, thiocarboxylate, sulphates, alkylsulphinyl, sulphonato, sulphamoyl, sulphonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[00689] As used herein, the expressions "one or more of A, B, or C," "one or more A, B, or C," "one or more of A, B, and C," "one or more A, B, and C," "selected from the group consisting of A, B, and C", "selected from A, B, and C", and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[00690] It is to be understood that the present disclosure provides methods for the synthesis of the compounds of any of the Formulae disclosed herein. The present disclosure also provides

detailed methods for the synthesis of various disclosed compounds of the present disclosure according to the following schemes as well as those shown in the Examples.

[00691] It is to be understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[00692] It is to be understood that the synthetic processes of the disclosure can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00693] It is to be understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognised reference textbooks of organic synthesis known to those in the art

[00694] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups. One of ordinary skill in the art will recognise that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[00695] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of the compounds to provide such treatment or prophylaxis as is described herein, as well as use of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[00696] As used herein, the term "subject" is interchangeable with the term "subject in need thereof", both of which refer to a subject having a disease or having an increased risk of developing the disease. A "subject" includes a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In one embodiment, the mammal is a human. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (i.e., a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[00697] As used herein, the term "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the

administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model. It is to be appreciated that references to "treating" or "treatment" include the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) modulating the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (2) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[00698] It is to be understood that a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[00699] As used herein, the term "preventing," "prevent," or "protecting against" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[00700] It is to be understood that one skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the disclosure.

[00701] It is to be understood that, for the compounds of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[00702] It is to be understood that the compounds of any Formula disclosed herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (*e.g.*, amino) on a

substituted compound disclosed herein. Suitable anions include chloride, bromide, iodide, sulphate, bisulphate, sulphamate, nitrate, phosphate, citrate, methanesulphonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulphonate, and acetate (*e.g.*, trifluoroacetate).

[00703] As used herein, the term "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulphonic, acetic, ascorbic, benzene sulphonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulphonic, 1,2-ethane sulphonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulphonic, maleic, malic, mandelic, methane sulphonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulphamic, sulphanilic, sulphuric, tannic, tartaric, toluene sulphonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[00704] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt.

[00705] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulphonic acid, 2-naphthalenesulphonic acid, 4-toluenesulphonic acid, camphorsulphonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine,

triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, *e.g.*, 3:1, 2:1, 1:2, or 1:3.

[00706] It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[00707] A suitable pharmaceutically acceptable salt of a compound of the disclosure is, for example, an acid-addition salt of a compound of the disclosure which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, formic, citric methane sulphonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of a compound of the disclosure which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, diethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[00708] As used herein, the term "pharmaceutically acceptable anion" refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (*e.g.*, carboxylate) on a substituted compound disclosed herein. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion or diethylamine ion. The substituted compounds disclosed herein also include those salts containing quaternary nitrogen atoms.

[00709] It is to be understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. It is also to be understood that certain compounds of any of the Formulae disclosed herein may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. Nonlimiting examples of hydrates include monohydrates, dihydrates, trihydrate, semihydrate, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc. It is to be understood that the disclosure encompasses all such solvated forms that possess P-glycoprotein and/or cytochrome P450 (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) modulatory activity.

[00710] As used herein, the term "solvate" means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H_2O.

[00711] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[00712] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[00713] It will be understood that the compounds of any of the Formulae disclosed herein and any pharmaceutically acceptable salts thereof, comprise stereoisomers, mixtures of stereoisomers, polymorphs of all isomeric forms of said compounds.

[00714] As used herein, the term "isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images of each other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture."

[00715] As used herein, the term "chiral center" refers to a carbon atom bonded to four nonidentical substituents.

[00716] As used herein, the term "chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture." When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[00717] As used herein, the term "geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (*e.g.*, 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[00718] It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It is also to be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the disclosure may have geometric isomeric centers (E- and Z- isomers). It is to be understood that the present disclosure encompasses all optical, diastereoisomers and

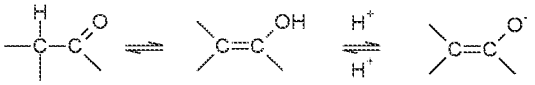
geometric isomers and mixtures thereof that possess P-glycoprotein and/or cytochrome P450 (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) modulatory activity.

[00719] It is to be understood that the structures and other compounds discussed in this disclosure include all atropic isomers thereof. It is also to be understood that not all atropic isomers may have the same level of activity.

[00720] As used herein, the term "atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[00721] As used herein, the term "tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerizations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[00722] For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by any of the Formulae disclosed herein. Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



[00723] Compounds of any of the Formulae disclosed herein containing an amine function may also form N-oxides. A reference herein to a compound of any of the Formulae disclosed herein that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidized to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocyclyl. N-oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a peracid (*e.g.* a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1977, 7, 509-514) in which the amine compound is reacted with meta-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[00724] It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[00725] As used herein, the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[00726] As used herein, the term "derivative" refers to compounds that have a common core structure and are substituted with various groups as described herein.

[00727] As used herein, the term "bioisostere" refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or

topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulphonamides, tetrazoles, sulphonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[00728] It is also to be understood that certain compounds of any of the Formulae disclosed herein may exhibit polymorphism, and that the disclosure encompasses all such forms, or mixtures thereof, which possess P-glycoprotein and/or cytochrome P450 (*e.g.*, CYP3A4 and/or CYP3A5 isoforms) modulatory activity. It is generally known that crystalline materials may be analysed using conventional techniques such as X-Ray Powder Diffraction analysis, Differential Scanning Calorimetry, Thermal Gravimetric Analysis, Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, Near Infrared (NIR) spectroscopy, solution and/or solid state nuclear magnetic resonance spectroscopy. The water content of such crystalline materials may be determined by Karl Fischer analysis.

[00729] The compounds of any of the Formulae disclosed herein may be administered in the form of a prodrug which is broken down in the human or animal body to release a compound of the disclosure. A prodrug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the disclosure. A prodrug can be formed when the compound of the disclosure contains a suitable group or substituent to which a property-modifying group can be attached. Examples of prodrugs include derivatives containing *in vivo* cleavable alkyl or acyl substituents at the ester or amide group in any of the Formulae disclosed herein.

[00730] Accordingly, the present disclosure includes those compounds of any of the Formulae disclosed herein as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a prodrug thereof. Accordingly, the present disclosure includes those compounds of any of the Formulae disclosed herein that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of any of the Formulae disclosed herein may be a synthetically-produced compound or a metabolically-produced compound.

[00731] A suitable pharmaceutically acceptable prodrug of a compound of any of the Formulae disclosed herein is one that is based on reasonable medical judgment as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity. Various forms of prodrug have been described, for example in the

following documents: a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985); c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991); d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992); e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984); g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[00732] A suitable pharmaceutically acceptable prodrug of a compound of any of the Formulae disclosed herein that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of any of the Formulae disclosed herein containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C_1-C_{10} alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C_1-C_{10} alkoxycarbonyl groups such as ethoxycarbonyl, N,N-(C_1-C_6 alkyl)$_2$carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C_1-C_4 alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[00733] A suitable pharmaceutically acceptable prodrug of a compound of any of the Formulae disclosed herein that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C_{1-4}alkylamine such as methylamine, a (C_1-C_4 alkyl)$_2$amine such as dimethylamine, N-ethyl-N-methylamine or diethylamine, a C_1-C_4 alkoxy-C_2-C_4 alkylamine such as 2-methoxyethylamine, a phenyl-C_1-C_4 alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

[00734] A suitable pharmaceutically acceptable prodrug of a compound of any of the Formulae disclosed herein that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C_1-C_{10} alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl,morpholinomethyl,piperazin-1-ylmethyl and 4-(C_1-C_4 alkyl)piperazin-1-ylmethyl.

[00735] The *in vivo* effects of a compound of any of the Formulae disclosed herein may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of any of the Formulae disclosed herein. As stated hereinbefore, the *in vivo* effects of a compound of any of the Formulae disclosed herein may also be exerted by way of metabolism of a precursor compound (a prodrug).

[00736] Suitably, the present disclosure excludes any individual compounds not possessing the biological activity defined herein.

Methods of Synthesis

[00737] In some aspects, the present disclosure provides a method of preparing a compound of the present disclosure.

[00738] In some aspects, the present disclosure provides a method of preparing a compound, comprising one or more steps as described herein.

[00739] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, or directly obtained by a method for preparing a compound as described herein.

[00740] In some aspects, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein.

[00741] The compounds of the present disclosure can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying schemes and examples.

[00742] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction

temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

[00743] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilized.

[00744] It will be appreciated that during the synthesis of the compounds of the disclosure in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed. For examples of protecting groups see one of the many general texts on the subject, for example, "*Protective Groups in Organic Synthesis*" by Theodora Green (John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule. Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[00745] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl, or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a

primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[00746] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[00747] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[00748] Once a compound of any of the Formulae disclosed herein has been synthesized by any one of the processes defined herein, the processes may then further comprise the additional steps of: (i) removing any protecting groups present; (ii) converting the compound into another compound of a Formula disclosed herein ; (iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or (iv) forming a prodrug thereof.

[00749] The resultant compounds of a Formula disclosed herein can be isolated and purified using techniques well known in the art.

[00750] Conveniently, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable solvents comprise but are not limited to hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran, cyclopentylmethyl ether (CPME), methyl tert-butyl ether (MTBE) or dioxane; glycol ethers, such as ethylene glycol monomethyl or

monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone, methylisobutylketone (MIBK) or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methylpyrrolidinone (NMP); nitriles, such as acetonitrile; sulphoxides, such as dimethyl sulphoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate or methyl acetate, or mixtures of the said solvents or mixtures with water.

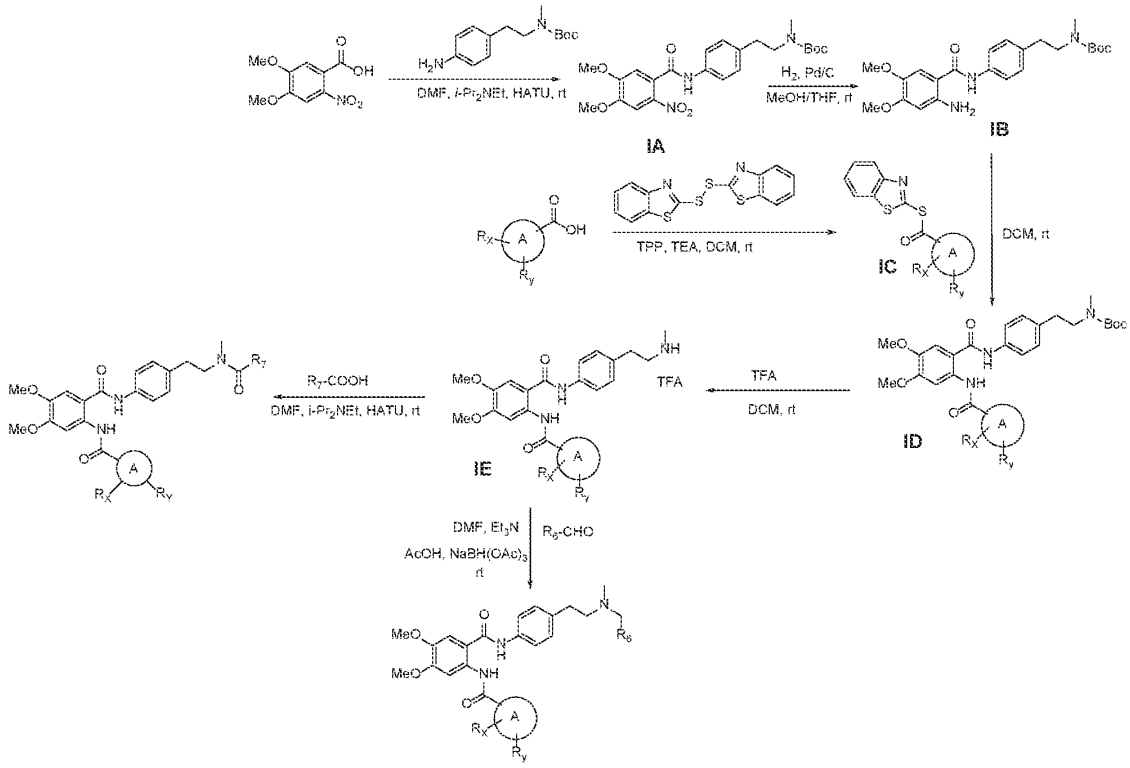
[00751] Reaction times are generally in the range between a fraction of a minute and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring.

[00752] Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present disclosure can be readily prepared. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

[00753] As will be understood by the person skilled in the art of organic synthesis, compounds of the present disclosure are readily accessible by various synthetic routes, some of which are exemplified in the accompanying schemes and examples. The skilled person will easily recognize which kind of reagents and reactions conditions are to be used and how they are to be applied and adapted in any particular instance – wherever necessary or useful – in order to obtain the compounds of the present disclosure. Furthermore, some of the compounds of the present disclosure can readily be synthesized by reacting other compounds of the present disclosure under suitable conditions, for instance, by converting one particular functional group being present in a compound of the present disclosure, or a suitable precursor molecule thereof, into another one by applying standard synthetic methods, like reduction, oxidation, addition or substitution reactions; those methods are well known to the skilled person. Likewise, the skilled person will apply – whenever necessary or useful – synthetic protecting (or protective) groups; suitable protecting groups as well as methods for introducing and removing them are well-known to the person skilled in the art of chemical synthesis and are described, in more detail, in, *e.g.*, P.G.M. Wuts, T.W. Greene, "*Greene's Protective Groups in Organic Synthesis*", 4th edition (2006) (John Wiley & Sons).

[00754] General routes for the preparation of a compound of the application are described in Schemes 1-10 herein. A person of skill in the art will understand that the general reagents used throughout the below schemes could be substituted with other standard reagents (*e.g.*, a couple reaction utilizing HATU could also utilize any suitable couple agent in replacement of HATU).

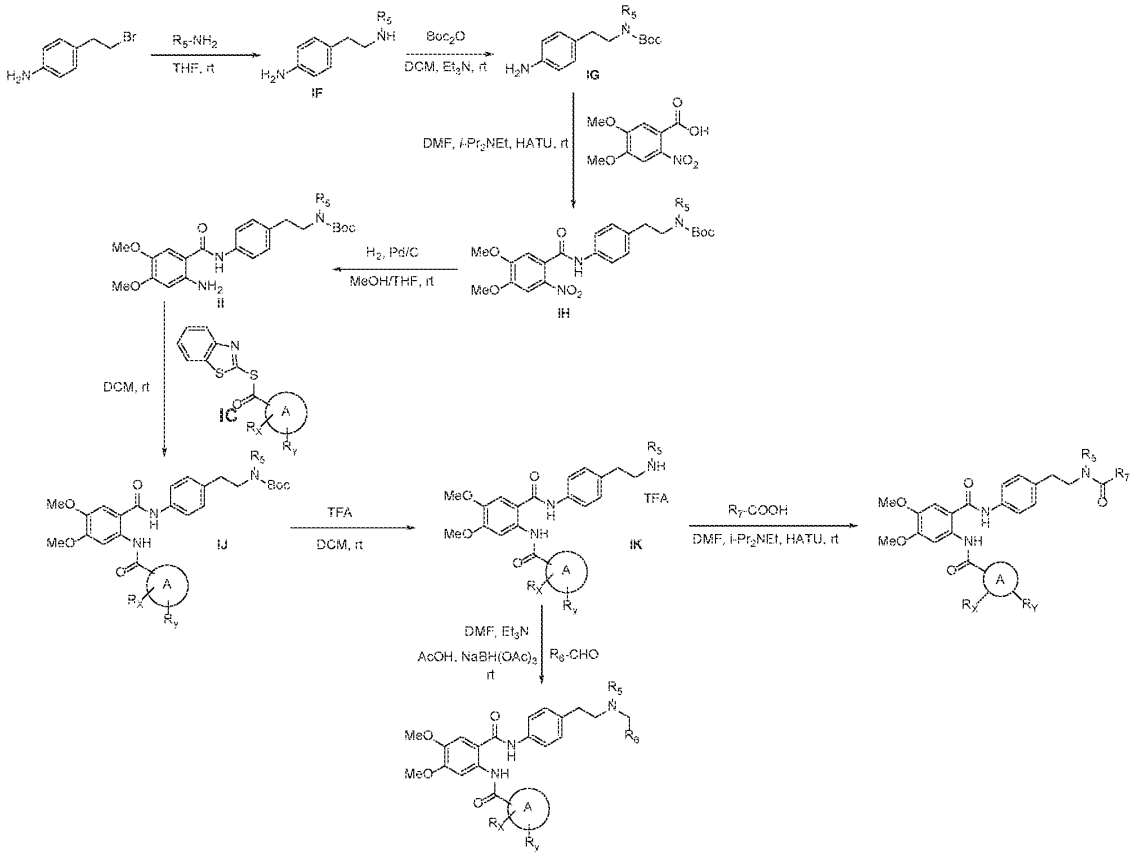
Scheme 1



General Procedure for Scheme 1.

[00755] Scheme 1 demonstrates the synthesis of compounds with R_5 = H, and R_2 and R_3 = methoxy as representative groups. 4,5-Dimethoxy-2-nitrobenzoic acid is coupled with 4-(*N*-Boc-2-(methylamino)ethyl)aniline to give intermediate **IA**. Hydrogenation of intermediate **IA** produced intermediate **IB**. Intermediate **IB** is coupled with various thioesters (**IC**) prepared by reacting the corresponding acids with benzothiazol-2-yl disulfide to produce intermediate **ID**. Acid activation via conversion into thioester is used herein. Intermediate **ID** was deprotected to yield intermediate **IE**. Finally, reductive amination of intermediate **IE** with various aldehydes R_5CHO or coupling with acids R_7CO_2H produces the target compounds.

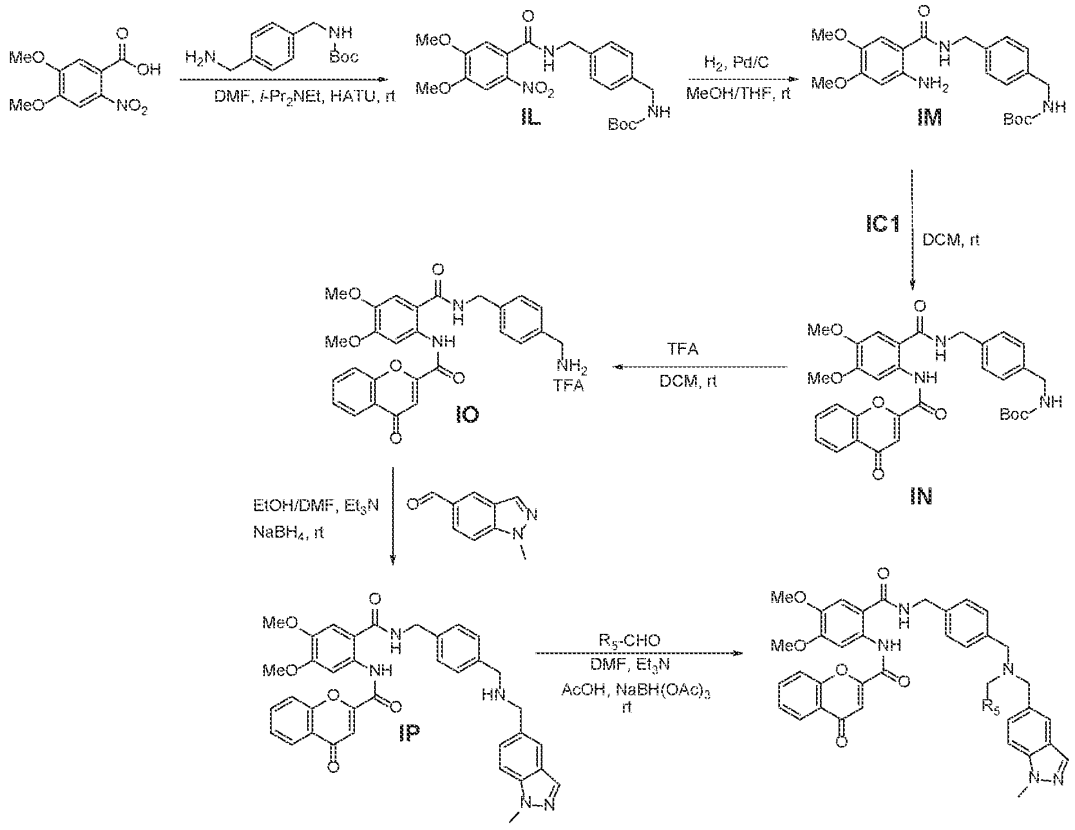
Scheme 2



General Procedure for Scheme 2

[00756] Scheme 2 describes the synthesis of compounds with general R_5, wherein R_5 is not H, and R_6, wherein R_6 is not H, groups, and R_2 and R_3 = methoxy as representative groups. R_5NH_2 is alkylated to produce intermediate **IF,** which is protected to form intermediate **IG**. Intermediate **IG** is then coupled with 4,5-dimethoxy-2-nitrobenzoic acid to produce intermediate **IH**. Hydrogenation of intermediate **IH** produced intermediate **II**. Intermediate **II** is coupled with various thioesters (**IC**), prepared by reacting the corresponding acids with benzothiazol-2-yl disulfide, to produce intermediate **IJ**. Intermediate **IJ** is then deprotected to yield intermediate **IK**. Reductive amination of Intermediate **IK** with various aldehydes R_6CHO or coupling with acids R_7CO_2H produces the target compounds.

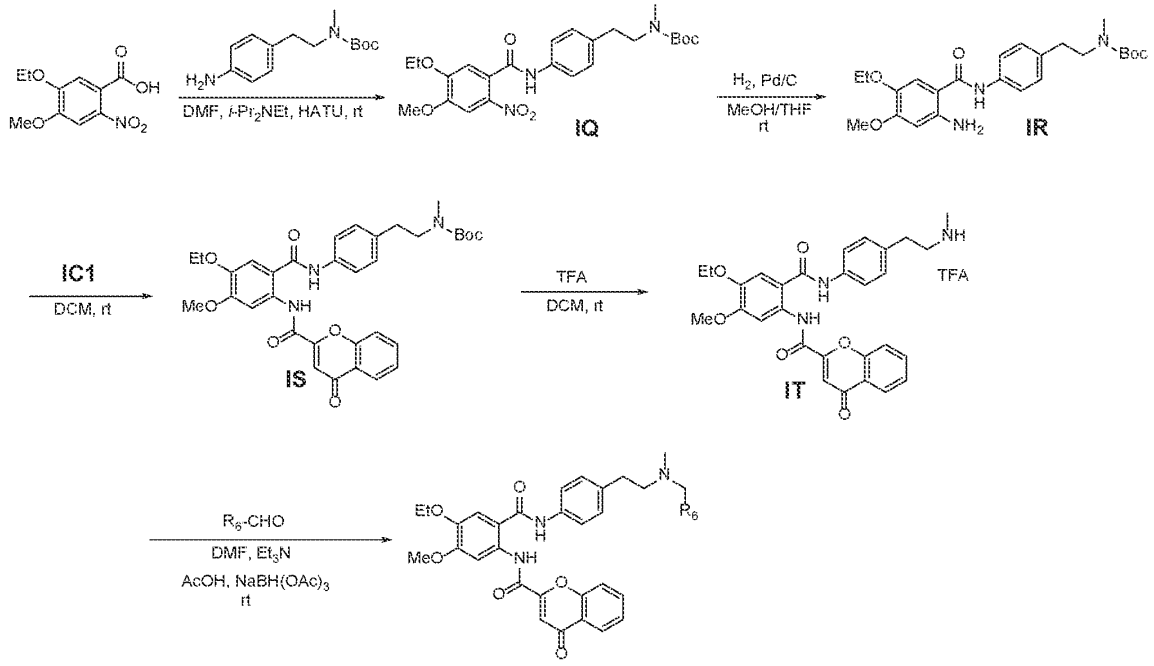
Scheme 3



General Procedure for Scheme 3

[00757] The synthesis of benzylamine derivatives with various R_5 groups, wherein R_6 is "N1-methylindazol-5-ylmethyl" and ring A is "chromone-2-yl" is presented in Scheme 3. 4,5-Dimethoxy-2-nitrobenzoic acid is coupled with 4-(Boc-aminomethyl)benzylamine to give intermediate **IL**. Hydrogenation of intermediate **IL** produces intermediate **IM**. Intermediate **IM** is then coupled with thioester (**IC1**), prepared from chromone-2-carboxylic acid, to produce intermediate **IN**, which is then converted to intermediate **IO** via deprotection of the Boc group. Reductive amination of intermediate **IO** produces intermediate **IP**, which is then subjected to another reductive amination with aldehydes (R_5CHO) containing different R_5 groups to yield the target compound.

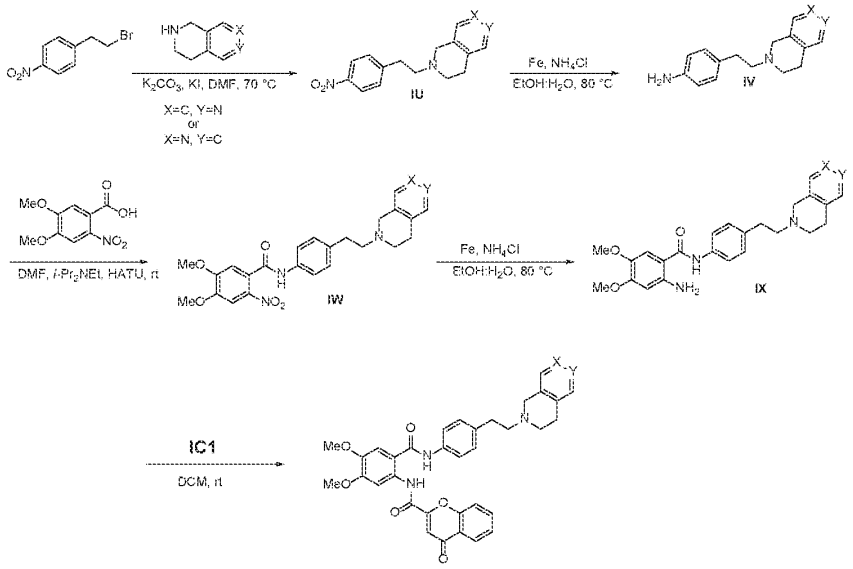
Scheme 4



General Procedure for Scheme 4

[00758] Scheme 4 demonstrates the synthesis of compounds with R_3 = ethoxy, R_2 = methoxy, and R_5 = methyl. 5-Ethoxy-4-methoxy-2-nitrobenzoic acid is coupled with 4-(*N*-boc-2-(methylamino)ethyl)aniline to give intermediate **IQ**. Intermediate **IQ** is subjected to hydrogenation to convert the nitro group to an amino group and produce intermediate **IR**. Intermediate **IR** is coupled with thioester (**IC1**) prepared from chromone-2-carboxylic acid to produce intermediate **IS**, which is then converted to intermediate **IT** via deprotection of the Boc group. Reductive amination of Intermediate **IT** produces the target compound.

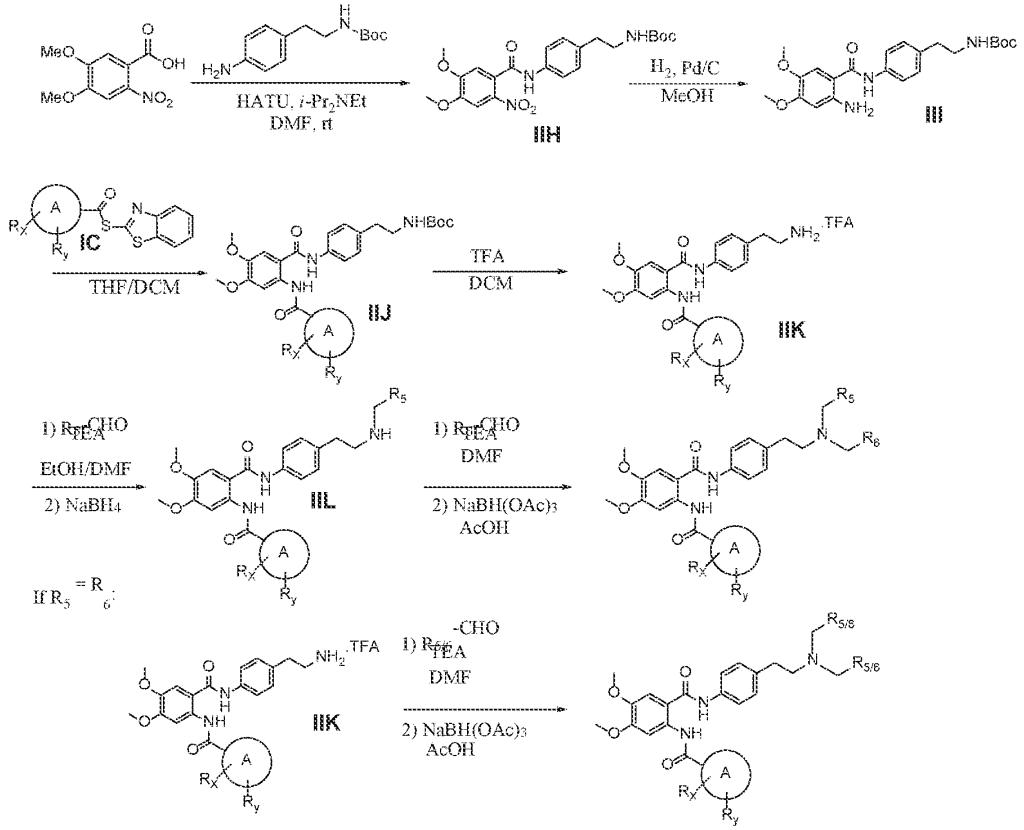
Scheme 5



General Procedure for Scheme 5

[00759] Scheme 5 demonstrates the synthesis of compounds with R_5 and R_6 together forming a six-membered heterocyclic ring. Tertrahydropyridopyridine is alkylated with 2-(4-nitrophenyl)ethylbromide to produce intermediate **IU**, which upon reduction produces intermediate **IV**. Intermediate **IV** is then coupled with 4,5-dimethoxy-2-nitrobenzoic acid to produce intermediate **IW**. The nitro intermediate **IW** is then converted to aniline intermediates **IX**. Intermediate **IX** is then coupled with thioester (**IC1**), prepared from chromone-2-carboxylic acid, to produce the target compound.

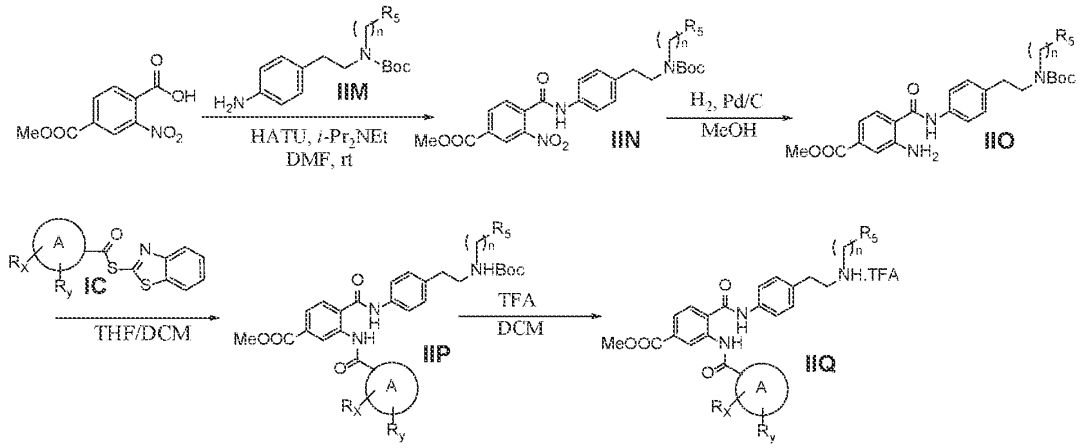
Scheme 6



General Procedure for Scheme 6

[00760] A general synthesis of target compounds with various ring A, R_5, and R_6 groups is described in Scheme 6. 4,5-Dimethoxy-2-nitrobenzoic acid is coupled with 4-(*N*-boc-2-aminoethyl)aniline to give intermediate **IIIH**. Intermediate **IIIH** is subjected to hydrogenation to convert the nitro group to an amino group and produce intermediate **III**. Intermediate **III** is coupled with various thioesters (**IC**), prepared by reacting the corresponding acids with benzothiazol-2-yl disulfide, to produce intermediate **IIJ**. Deprotection of Boc group in Intermediate **IIJ** yields intermediate **IIK**. Sequential reductive amination of intermediates **IIK** yields the target compound. When $R_5 = R_6$, the target compound can be synthesized from **IIK** in a one-pot synthesis using excess suitable aldehyde and reducing agent.

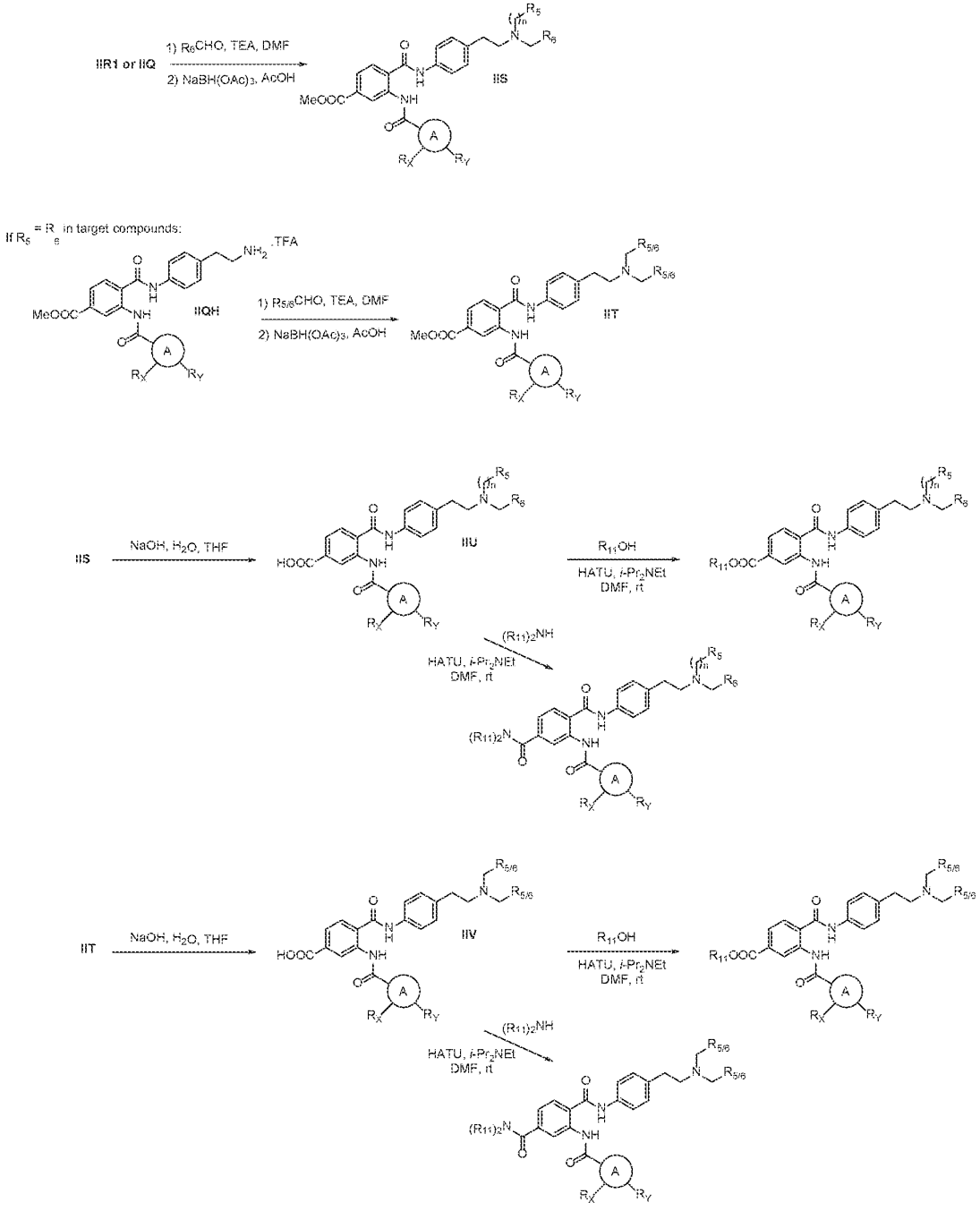
Scheme 7



General Procedure for Scheme 7

[00761] Scheme 7 demonstrates the synthesis of compounds with R_2 = COOMe, R_3 = H, and R_6 = H. Methyl 2-nitroterephthalate is coupled with compound **IIM** to give intermediate **IIN**. Intermediate **IIN** is subjected to hydrogenation to convert the nitro group to an amino group to produce intermediate **IIO**. Intermediate **IIO** is coupled with various thioesters (**IC**), prepared by reacting the corresponding acids with benzothiazol-2-yl disulfide, producing intermediate **IIP**. Intermediate **IIP** is then converted to the target examples via Boc-deprotection. The target compound also serves as intermediate **IIQ** for the additional syntheses.

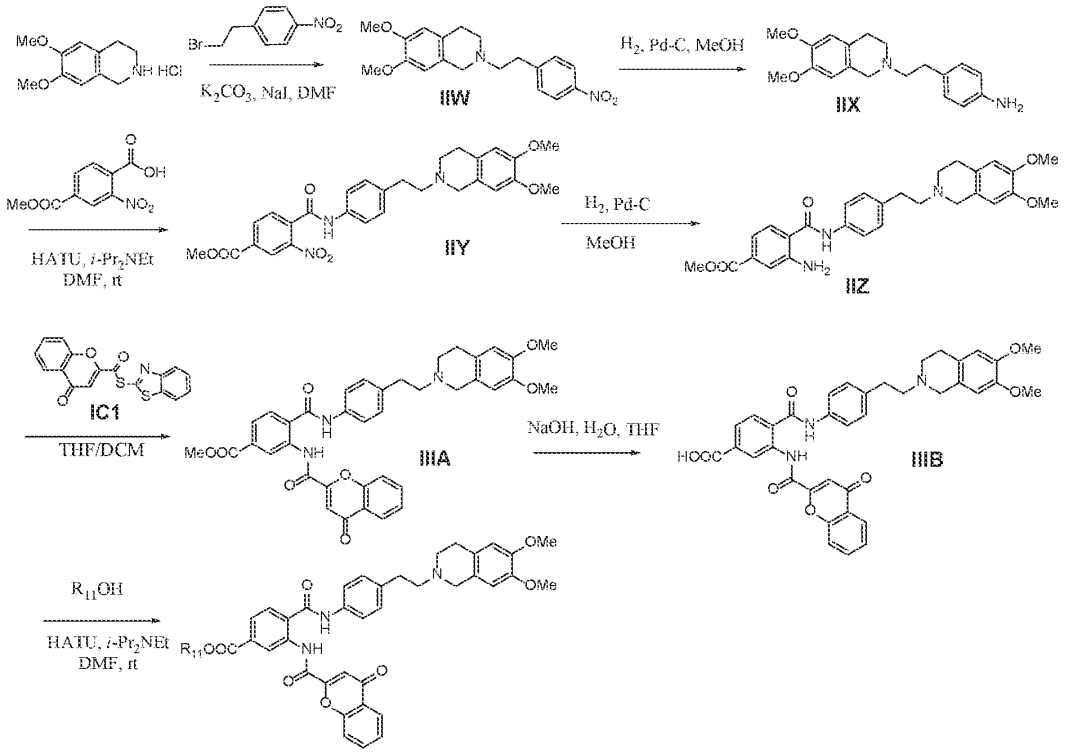
Scheme 8


IIR1 or IIQ
1) R6CHO, TEA, DMF
2) NaBH(OAc)3, AcOH
IIS
If R5 = R6 in target compounds:
IIQH
.TFA
1) R5/6CHO, TEA, DMF
2) NaBH(OAc)3, AcOH
IIT
IIS
NaOH, H2O, THF
IIU
R11OH
HATU, i-Pr2NEt
DMF, rt
(R11)2NH
IIT
IIV

General Procedure for Scheme 8

[00762] Scheme 8 depicts the synthesis of example compounds with R_2 being carboxylic acid, ester, or amide, and various R_5 and R_6 groups. Intermediate **IIQ** is reacted with various aldehydes R_6CHO to form intermediate **IIS** (*e.g.*, a target compound of the instant disclosure). When the target compound features the same R_5 and R_6, which are not H, intermediate **IIQH** (**IIQ** with n = 0 and R_5 = H) is reacted with an excess amount of the aldehyde ($R_{5/6}CHO$) to yield the target compound, which is also represented by intermediate **IIT**. To obtain compounds wherein R_2 = COOH, the methyl ester **IIS** or **IIT** is hydrolyzed in basic medium to yield the target compound, represented by intermediate **IIU** or **IIV**. Intermediate **IIU** or **IIV** is then coupled with an alcohol or an amine to yield the final target compounds.

Scheme 9



General Procedure for Scheme 9

[00763] Scheme 9 illustrates the synthesis of compounds with R_5 and R_6 together forming 6,7-dimethoxytetrahydroisoquinoline as a representative of a heterocyclic ring, with R_3 = H, and with R_2 being a carboxylic acid or a carboxylic acid derivative, such as an ester. 6,7-

Dimethoxytetrahydroisoquinoline is alkylated with 2-(4-nitrophenyl)ethylbromide followed by hydrogenation to produce intermediate **IIX**. Intermediate **IIX** is then coupled with methyl 2-nitroterephthalate to give intermediate **IIY**. Hydrogenation of intermediate **IIY** provided intermediate **IIZ**. Intermediate **IIZ** is then coupled with thioester (**IC1**), prepared from chromone-2-carboxylic acid, to produce intermediate **IIIA**, which is hydrolyzed in basic medium to give **IIIB**. Esterification of acid **IIIB** with various alcohols $R_{11}OH$ afforded the target compounds.

[00764] It should be understood that in the description and formulae shown above, the various groups are as defined herein, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds in the Schemes are mere representatives with elected substituents to illustrate the general synthetic methodology of a compound disclosed herein.

[00765] It is understood that a neutral compound of any of the Formulae disclosed herein may be converted to a salt (*e.g.*, sodium salt) using routine techniques in the art (*e.g.*, pH adjustment and, optionally, extraction (*e.g.*, into an organic phase)). Further, a salt (*e.g.*, sodium salt) of a compound of any of the Formulae disclosed herein may be converted to a neutral compound using routine techniques in the art (*e.g.*, pH adjustment and, optionally, extraction (*e.g.*, into an aqueous phase)).

Biological Assays

[00766] Compounds designed, selected and/or optimized by methods described above, once produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules can be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

[00767] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) *High Throughput Screening*, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[00768] Various *in vitro* or *in vivo* biological assays are may be suitable for detecting the effect of the compounds of the present disclosure. These *in vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[00769] P-glycoprotein modulatory activity may be determined by an assay wherein P-glycoprotein overexpressed cell lines are treated with increasing concentrations of a compound of the present disclosure and therapeutic agent for three days, followed by an MTT assay.

[00770] Cell growth percentage may be calculated with the following equation:

Cell growth percentage = $(T-T_0)/(C-T_0) \times 100\%$,

wherein T is OD of the test well exposure to Compound; C is OD of the control well without Compound treatment; and T_0 is OD at time zero. Cell growth inhibition curve and EC_{50} (measure of P-glycoprotein inhibition) may be obtained and fit to a nonlinear regression model using GraphPad Prism software (v6.0).

[00771] Cytochrome P450 activity may be determined by a P450-Glo™ assay (Promega) with human liver microsomes wherein the compounds of the present disclosure are dosed at different concentrations in buffer and incubated. Dose-response curve and IC_{50} data may be obtained and fit to a nonlinear regression model using GraphPad Prism software (v6.0).

[00772] In vivo activity in mice of the instant compounds may be determined by administering (*e.g.*, orally) compound to the mice at different concentrations.

[00773] Blood samples may be obtained via peripheral veins at determined time points and analyzed by LC-MS/MS.

[00774] In some embodiments, the biological assay is described in the Examples herein.

Pharmaceutical Compositions

[00775] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure as an active ingredient. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound of any of the Formulae disclosed herein, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, and one or more pharmaceutically acceptable carriers or excipients. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound selected from Table 1, or a pharmaceutically

acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, and one or more pharmaceutically acceptable carriers or excipients.

[00776] 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.

[00777] As used herein, the term "pharmaceutical composition" is a formulation containing the compounds of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[00778] It is to be understood that the present disclosure also provides pharmaceutical compositions comprising any compound described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[00779] As used herein, the term "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00780] As used herein, the term "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and

neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[00781] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00782] It is to be understood that a compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, a compound of the disclosure may be injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, a disease or disorder disclosed herein) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[00783] A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[00784] As used herein, the term "effective amount", refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or modulatory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[00785] It is to be understood that, for any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. It is to be understood that, for any compound, the effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[00786] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[00787] The compositions of the disclosure may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels,

or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing). In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[00788] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilising processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[00789] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor® EL or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by

including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00790] The formulation of the present disclosure may be in the form of an aqueous solution comprising an aqueous vehicle. The aqueous vehicle component may comprise water and at least one pharmaceutically acceptable excipient. Suitable acceptable excipients include those selected from the group consisting of a solubility enhancing agent, chelating agent, preservative, tonicity agent, viscosity/suspending agent, buffer, and pH modifying agent, and a mixture thereof.

[00791] Any suitable solubility enhancing agent can be used. Examples of a solubility enhancing agent include cyclodextrin, such as those selected from the group consisting of hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, randomly methylated-β-cyclodextrin, ethylated-β-cyclodextrin, triacetyl-β-cyclodextrin, peracetylated-β-cyclodextrin, carboxymethyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl-β-cyclodextrin, glucosyl-β-cyclodextrin, sulphated β-cyclodextrin (S-β-CD), maltosyl-β-cyclodextrin, β-cyclodextrin sulphobutyl ether, branched-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated-γ-cyclodextrin, and trimethyl-γ-cyclodextrin, and mixtures thereof.

[00792] Any suitable chelating agent can be used. Examples of a suitable chelating agent include those selected from the group consisting of ethylenediaminetetraacetic acid and metal salts thereof, disodium edetate, trisodium edetate, and tetrasodium edetate, and mixtures thereof.

[00793] Any suitable preservative can be used. Examples of a preservative include those selected from the group consisting of quaternary ammonium salts such as benzalkonium halides (preferably benzalkonium chloride), chlorhexidine gluconate, benzethonium chloride, cetyl pyridinium chloride, benzyl bromide, phenylmercury nitrate, phenylmercury acetate, phenylmercury neodecanoate, merthiolate, methylparaben, propylparaben, sorbic acid, potassium sorbate, sodium benzoate, sodium propionate, ethyl p-hydroxybenzoate, propylaminopropyl biguanide, and butyl-*p*-hydroxybenzoate, and sorbic acid, and mixtures thereof.

[00794] The aqueous vehicle may also include a tonicity agent to adjust the tonicity (osmotic pressure). The tonicity agent can be selected from the group consisting of a glycol (such as propylene glycol, diethylene glycol, triethylene glycol), glycerol, dextrose, glycerin, mannitol, potassium chloride, and sodium chloride, and a mixture thereof.

[00795] The aqueous vehicle may also contain a viscosity/suspending agent. Suitable viscosity/suspending agents include those selected from the group consisting of cellulose derivatives, such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, polyethylene glycols (such as polyethylene glycol 300, polyethylene glycol 400), carboxymethyl cellulose, hydroxypropylmethyl cellulose, and cross-linked acrylic acid polymers (carbomers), such as polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol (Carbopols - such as Carbopol 934, Carbopol 934P, Carbopol 971, Carbopol 974 and Carbopol 974P), and a mixture thereof.

[00796] In order to adjust the formulation to an acceptable pH (typically a pH range of about 5.0 to about 9.0, more preferably about 5.5 to about 8.5, particularly about 6.0 to about 8.5, about 7.0 to about 8.5, about 7.2 to about 7.7, about 7.1 to about 7.9, or about 7.5 to about 8.0), the formulation may contain a pH modifying agent. The pH modifying agent is typically a mineral acid or metal hydroxide base, selected from the group of potassium hydroxide, sodium hydroxide, and hydrochloric acid, and mixtures thereof, and preferably sodium hydroxide and/or hydrochloric acid. These acidic and/or basic pH modifying agents are added to adjust the formulation to the target acceptable pH range. Hence it may not be necessary to use both acid and base - depending on the formulation, the addition of one of the acid or base may be sufficient to bring the mixture to the desired pH range.

[00797] The aqueous vehicle may also contain a buffering agent to stabilize the pH. When used, the buffer is selected from the group consisting of a phosphate buffer (such as sodium dihydrogen phosphate and disodium hydrogen phosphate), a borate buffer (such as boric acid, or salts thereof including disodium tetraborate), a citrate buffer (such as citric acid, or salts thereof including sodium citrate), and ε-aminocaproic acid, and mixtures thereof.

[00798] The formulation may further comprise a wetting agent. Suitable classes of wetting agents include those selected from the group consisting of polyoxypropylene-polyoxyethylene block copolymers (poloxamers), polyethoxylated ethers of castor oils, polyoxyethylenated sorbitan esters (polysorbates), polymers of oxyethylated octyl phenol (Tyloxapol), polyoxyl 40 stearate, fatty acid glycol esters, fatty acid glyceryl esters, sucrose fatty esters, and polyoxyethylene fatty esters, and mixtures thereof.

[00799] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated

above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00800] The compounds of present disclosure can be formulated for oral administration in forms such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of present disclosure can also be formulated for intravenous (bolus or in-fusion), intraperitoneal, topical, subcutaneous, intramuscular or transdermal (*e.g.*, patch) administration, all using forms well known to those of ordinary skill in the pharmaceutical arts.

[00801] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00802] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebuliser.

[00803] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for

example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00804] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

[00805] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00806] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[00807] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the disclosure vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the symptoms of the disease or disorder disclosed herein and also preferably causing complete regression of the disease or

disorder. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In preferred aspects, dosages can range from about 1 mg/kg per day to about 1000 mg/kg per day. In an aspect, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m^2, and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. Improvement in survival and growth indicates regression. As used herein, the term "dosage effective manner" refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[00808] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[00809] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[00810] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[00811] The compositions of the disclosure may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

[00812] An effective amount of a compound of the present disclosure for use in therapy is an amount sufficient to modulate P-glycoprotein activity and/or cytochrome P450 activity in a disease or disorder referred to herein, slow the disease or disorder progression and/or reduce the symptoms associated with the disease or disorder.

[00813] The size of the dose for therapeutic or prophylactic purposes of a compound of any of the Formulae disclosed herein will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Methods of Use

[00814] In some aspects, the present disclosure provides a method of modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*) and/or cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00815] In some aspects, the present disclosure provides a method of modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00816] In some aspects, the present disclosure provides a method of modulating cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

[00817] In some embodiments, the P-glycoprotein activity is overexpressed. In some embodiments, the P-glycoprotein activity is under-expressed.

[00818] In some embodiments, the cytochrome P450 activity is overexpressed. In some embodiments, the cytochrome P450 activity is under-expressed.

[00819] In some embodiments, the cytochrome P450 activity is CYP3A4 activity.

[00820] In some embodiments, the cytochrome P450 activity is CYP3A5 activity.

[00821] In some embodiments, the modulation is inhibition.

[00822] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00823] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00824] In some aspects, the present disclosure provides a method of treating a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00825] In some aspects, the present disclosure provides a method of treating a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00826] In some embodiments, when the methods relate to preventing or prevention of a disease or disorder, the method comprises administering an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00827] In some embodiments, when the methods relate to treating or treatment of a disease or disorder, the method comprises administering a therapeutically effective amount or effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00828] In some embodiments, the disease or disorder is associated with an implicated P-glycoprotein activity (*e.g.*, overactivity or abnormal activity). In some embodiments, the disease

or disorder is a disease or disorder in which P-glycoprotein activity is implicated (*e.g.*, abnormal or elevated). In some embodiments, the disease or disorder is a disease or disorder in which multi-drug resistance is implicated due to P-glycoprotein activity. In some embodiments, the disease or disorder is a disease or disorder in which P-glycoprotein activity is implicated due to multi-drug resistance following cancer treatment.

[00829] In some embodiments, the disease or disorder is associated with an implicated cytochrome P450 activity (*e.g.*, overactivity or abnormal activity). In some embodiments, the disease or disorder is a disease or disorder in which cytochrome P450 activity is implicated (*e.g.*, abnormal or elevated). In some embodiments, the disease or disorder is a disease or disorder in which multi-drug resistance is implicated due to cytochrome P450 activity. In some embodiments, the disease or disorder is a disease or disorder in which cytochrome P450 activity is implicated due to multi-drug resistance following cancer treatment.

[00830] In some embodiments, the disease or disorder is a cell proliferative disorder.

[00831] In some embodiments, the cell proliferative disorder is a cancer.

[00832] In some embodiments, the cancer involves abnormal cell growth with the potential to invade or spread to other parts of the body.

[00833] In some embodiments, the cancer is a malignant tumor or neoplasm.

[00834] In some embodiments, the cancer is breast cancer, pancreatic cancer, non-small cell lung cancer, small cell lung cancer, ovarian cancer, epithelial ovarian cancer, AIDS-related Kaposi sarcoma, soft tissue sarcoma, leiomyosarcoma, esophageal cancer, melanoma, lymphoma, uterine cancer, peritoneal cancer, fallopian tube cancer, endometrial cancer, cervical cancer, thyroid cancer, gastric cancer, gastroesophageal junction cancer, urothelial cancer, bladder cancer, oropharynx cancer, hypopharynx cancer, larynx cancer, head and neck cancer, germ cell cancer/tumors, prostate cancer, colon cancer, rectal cancer, kidney cancer, cholangiocarcinoma (bile duct cancer), glioblastoma, squamous cell carcinoma, glioma, leukemia, or non-Hodgkin lymphoma.

[00835] In some embodiments, the cancer is breast cancer. In some embodiments, the breast cancer is metastatic breast cancer. In some embodiments, the breast cancer is carcinoma of the breast. In some embodiments, the breast cancer is triple-negative breast cancer.

[00836] In some embodiments, the cancer is lung cancer. In some embodiments, the lung cancer is non-small cell lung cancer. In some embodiments, the lung cancer is small cell lung cancer.

[00837] In some embodiments, the cancer is prostate cancer. In some embodiments, the prostate cancer is metastatic hormone resistant prostate cancer, castration naïve prostate cancer, or castration resistant prostate cancer. In some embodiments, the prostate cancer is metastatic hormone resistant prostate cancer. In some embodiments, the prostate cancer is carcinoma of the prostate.

[00838] In some embodiments, the cancer is ovarian cancer. In some embodiments, the cancer is carcinoma of the ovary.

[00839] In some embodiments, the cancer is AIDS-related Kaposi sarcoma.

[00840] In some embodiments, the cancer is pancreatic cancer. In some embodiments, the pancreatic cancer is adenocarcinoma of the pancreas.

[00841] In some embodiments, the cancer is bladder cancer, breast cancer, cervical cancer, esophageal cancer, gastric cancer, epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, head and neck cancer, squamous cell carcinoma of the head and neck (SCCHN), non-small cell lung cancer (NSCLC), castration naïve prostate cancer, castration resistant prostate cancer, metastatic hormone resistant prostate cancer (mHRPC), small cell lung cancer, soft tissue sarcoma, or uterine cancer.

[00842] In some embodiments, the cancer is breast cancer, non-small cell lung cancer, prostate cancer (including metastatic hormone resistant prostate cancer, castration naïve prostate cancer, or castration resistant prostate cancer), squamous cell carcinoma of the head and neck, or gastric cancer.

[00843] In some embodiments, the cancer is colorectal cancer.

[00844] In some embodiments, the cancer is an advanced malignancy. In some embodiments, the cancer is a primary or secondary cancer.

[00845] In some embodiments, the cancer is a solid tumor.

[00846] In some embodiments, the solid tumor is histologically or cytologically confirmed.

[00847] In some embodiments, the solid tumor is metastatic or unresectable.

[00848] In some embodiments, the subject is predisposed to the state, disorder, or condition (*e.g.*, presence of a genetic variant).

[00849] In some aspects, the present disclosure provides a method of treating or preventing a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable

prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00850] In some aspects, the present disclosure provides a method of treating or preventing a cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00851] In some aspects, the present disclosure provides a method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00852] In some aspects, the present disclosure provides a method of treating a cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition of the present disclosure.

[00853] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*) and/or cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*).

[00854] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*).

[00855] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in modulating cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*).

[00856] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[00857] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in treating a disease or disorder disclosed herein.

[00858] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in treating or preventing a cancer in a subject in need thereof.

[00859] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof for use in treating a cancer in a subject in need thereof.

[00860] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*) and/or cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*).

[00861] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for modulating P-glycoprotein activity (*e.g.*, *in vitro* or *in vivo*).

[00862] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for modulating cytochrome P450 activity (*e.g.*, *in vitro* or *in vivo*).

[00863] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[00864] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for treating a disease or disorder disclosed herein.

[00865] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer,

tautomer, or salt thereof in the manufacture of a medicament for treating or preventing a cancer in a subject in need thereof.

[00866] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof in the manufacture of a medicament for treating a cancer in a subject in need thereof.

[00867] The present disclosure therefore provides a method of modulating P-glycoprotein activity *in vitro* or *in vivo* and/or cytochrome P450 activity *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, as defined herein.

[00868] The present disclosure provides compounds that function as modulators of P-glycoprotein activity and/or cytochrome P450 activity. The present disclosure therefore provides a method of modulating P-glycoprotein activity *in vitro* or *in vivo* and/or cytochrome P450 activity *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, as defined herein.

[00869] The present disclosure provides compounds that function as modulators of P-glycoprotein activity. The present disclosure therefore provides a method of modulating P-glycoprotein activity *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, as defined herein.

[00870] The present disclosure therefore provides a method of modulating cytochrome P450 activity *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, as defined herein.

[00871] The present disclosure provides compounds that function as modulators of cytochrome P450 activity. The present disclosure therefore provides a method of modulating cytochrome P450 activity *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, as defined herein.

[00872] In some embodiments, the compounds of the present disclosure improve oral bioavailability of therapeutics which are substrates of P-glycoprotein and/or cytochrome P450.

[00873] In some embodiments, the compounds of the present disclosure improve oral bioavailability of therapeutics which are substrates of P-glycoprotein.

[00874] In some embodiments, the compounds of the present disclosure improve oral bioavailability of therapeutics which are substrates of cytochrome P450.

[00875] In some embodiments, the compounds of the present disclosure increase brain distribution of therapeutics which are substrates of P-glycoprotein and/or cytochrome P450.

[00876] In some embodiments, the compounds of the present disclosure increase brain distribution of therapeutics which are substrates of P-glycoprotein.

[00877] In some embodiments, the compounds of the present disclosure increase brain distribution of therapeutics which are substrates of cytochrome P450.

[00878] Effectiveness of compounds of the disclosure can be determined by industry-accepted assays/disease models according to standard practices of elucidating the same as described in the art and are found in the current general knowledge.

[00879] The present disclosure also provides a method of treating a disease or disorder in which P-glycoprotein activity and/or cytochrome P450 activity is implicated in a subject in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition as defined herein.

[00880] The present disclosure also provides a method of treating a disease or disorder in which P-glycoprotein activity is implicated in a subject in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition as defined herein.

[00881] The present disclosure also provides a method of treating a disease or disorder in which cytochrome P450 activity is implicated in a subject in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition as defined herein.

[00882] The present disclosure also provides a method of treating a disease or disorder in which P-glycoprotein activity and/or cytochrome P450 activity is implicated in a subject in need of such treatment, comprising administering to said patient an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition as defined herein.

[00883] The present disclosure also provides a method of treating a disease or disorder in which P-glycoprotein activity is implicated in a subject in need of such treatment, comprising administering to said patient an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition as defined herein.

[00884] The present disclosure also provides a method of treating a disease or disorder in which cytochrome P450 activity is implicated in a subject in need of such treatment, comprising administering to said patient an effective amount of a compound, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, or a pharmaceutical composition as defined herein.

[00885] Compounds of the present disclosure, or pharmaceutically acceptable salts thereof, may be administered alone as a sole therapy or can be administered in addition with one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

[00886] For example, therapeutic effectiveness may be enhanced by administration of an adjuvant (i.e. by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the individual is enhanced). Alternatively, by way of example only, the benefit experienced by an individual may be increased by administering a compound of any of the Formulae disclosed herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00887] In the instances wherein the compound of the present disclosure is administered in combination with other therapeutic agents, the compound of the disclosure need not be administered via the same route as other therapeutic agents, and may, because of different physical and chemical characteristics, be administered by a different route. For example, the compound of the disclosure may be administered orally to generate and maintain good blood

levels thereof, while the other therapeutic agent may be administered intravenously. The initial administration may be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

[00888] The particular choice of other therapeutic agent will depend upon the diagnosis of the attending physicians and their judgment of the condition of the individual and the appropriate treatment protocol. According to this aspect of the disclosure there is provided a combination for use in the treatment of a disease in which P-glycoprotein activity and/or cytochrome P450 activity is implicated comprising a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, and another suitable agent. According to this aspect of the disclosure there is provided a combination for use in the treatment of a disease in which P-glycoprotein activity is implicated comprising a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, and another suitable agent. According to this aspect of the disclosure there is provided a combination for use in the treatment of a disease in which cytochrome P450 activity is implicated comprising a compound of the disclosure as defined hereinbefore, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, and another suitable agent.

[00889] According to a further aspect of the disclosure there is provided a pharmaceutical composition which comprises a compound of the disclosure, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, in combination with another suitable agent, in association with a pharmaceutically acceptable diluent or carrier.

[00890] In addition to its use in therapeutic medicine, compounds of any of the Formulae disclosed herein and pharmaceutically acceptable salts thereof are also useful as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of modulators of P-glycoprotein and/or cytochrome P450 in laboratory animals such as dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

[00891] In addition to its use in therapeutic medicine, compounds of any of the Formulae disclosed herein and pharmaceutically acceptable salts thereof are also useful as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the

evaluation of the effects of modulators of P-glycoprotein in laboratory animals such as dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

[00892] In addition to its use in therapeutic medicine, compounds of any of the Formulae disclosed herein and pharmaceutically acceptable salts thereof are also useful as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of modulators of cytochrome P450 in laboratory animals such as dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

[00893] In any of the above-mentioned pharmaceutical composition, process, method, use, medicament, and manufacturing features of the instant disclosure, any of the alternate embodiments of macromolecules of the present disclosure described herein also apply.

[00894] The compounds of the disclosure or pharmaceutical compositions comprising these compounds may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or topically (i.e., at the site of desired action).

[00895] Routes of administration include, but are not limited to, oral (*e.g.* by ingestion); buccal; sublingual; transdermal (including, *e.g.*, by a patch, plaster, etc.); transmucosal (including, *e.g.*, by a patch, plaster, etc.); intranasal (*e.g.*, by nasal spray); ocular (*e.g.*, by eye drops); pulmonary (*e.g.*, by inhalation or insufflation therapy using, *e.g.*, via an aerosol, *e.g.*, through the mouth or nose); rectal (*e.g.*, by suppository or enema); vaginal (*e.g.*, by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intra-arterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

[00896] The disclosure having been described, the following examples are offered by way of illustration and not limitation.

EXAMPLES

[00897] For exemplary purpose, neutral compounds of any of the Formulae disclosed herein are synthesized and tested in the examples. It is understood that the neutral compounds of any of the Formulae disclosed herein may be converted to the corresponding pharmaceutically acceptable salts of the compounds using routine techniques in the art (*e.g.*, by saponification of an ester to

the carboxylic acid salt, or by hydrolyzing an amide to form a corresponding carboxylic acid and then converting the carboxylic acid to a carboxylic acid salt).

[00898] Nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz or 300 MHz as stated and at 300.3 K unless otherwise stated; the chemical shifts (δ) are reported in parts per million (ppm). Spectra were recorded using a Bruker or Varian instrument with 8, 16 or 32 scans.

[00899] LC-MS chromatograms and spectra were recorded using an Agilent 1200 or Shimadzu LC-20 AD&MS 2020 instrument using a C-18 column such as a Luna-C18 2.0x30 mm or Xbridge Shield RPC18 2.1x50 mm. Injection volumes were 0.7 – 8.0 µl and the flow rates were typically 0.8 or 1.2 ml/min. Detection methods were diode array (DAD) or evaporative light scattering (ELSD) as well as positive ion electrospray ionisation. MS range was 100 - 1000 Da. Solvents were gradients of water and acetonitrile both containing a modifier (typically 0.01 – 0.04 %) such as trifluoroacetic acid or ammonium carbonate.

Abbreviations:

ACN	Acetonitrile
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulphoxide
DMSO-d_6	Hexadeuterodimethylsulphoxide
eq.	Equivalents
ESI	Electrospray ionisation
EtOAc	Ethyl acetate
EtOH	Ethanol
H	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HCl	Hydrochloric acid
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
HPLC	High performance liquid chromatography
LC-MS	Liquid chromatography-mass spectrometry
MeOD	Methanol-d_4
MeOH	Methanol
$NaHCO_3$	Sodium bicarbonate

NaOH	Sodium hydroxide
Na_2SO_4	Sodium sulphate
Pd	Palladium
PPh_3	Triphenylphosphine
pet. ether	Petroleum ether
ppm	Parts per million
RM	Reaction mixture
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Example 1: Synthesis of Intermediates

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-nitrobenzamido)phenethyl)(methyl)carbamate Intermediate IA (Scheme 1)

[00900] To a stirred solution of 4,5-dimethoxy-2-nitrobenzoic acid (10.0 g, 44.01 mmol, 1.0 eq.) and *tert*-butyl (4-aminophenethyl) (methyl)carbamate (11.01 g, 44.01 mmol, 1.0 eq.) in DMF (150 mL) were added HATU (18.40 g, 48.41 mmol, 1.1 eq.) and DIPEA (18.36 mL, 132.03 mmol, 3.0 eq.) at room temperature. The reaction was monitored by LC/MS and after completion of the reaction, the reaction mixture was diluted with EtOAc and washed with 1 M HCl (2x), saturated $NaHCO_3$ (2x) and brine (2x). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford crude product. The crude material was purified by flash chromatography on silica gel using Heptane/Ethyl acetate (0-100% gradient) to afford the desired product **Intermediate IA** (14.5 g, 72%). ^{1}H NMR (400 MHz, DMSO-d^6) 1.34 (s, 9H), 2.71-2.75 (m, 5H), 3.36 (s, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 7.16 (d, J = 8 Hz, 2H), 7.25 (s, 1H), 7.57 (d, J = 8 Hz, 2H), 7.70 (s, 1H), 10.44 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 460.19

Synthesis of tert-Butyl (4-(2-amino-4,5-dimethoxybenzamido)phenethyl)(methyl)carbamate Intermediate IB (Scheme 1)

[00901] To a 1000 mL round bottom flask charged with **Intermediate IA** (14.0 g, 30.46 mmol, 1.0 eq.) and 10% Pd/C (324 mg, 3.046 mmol, 0.1 eq.), 500 mL of methanol/THF (1:1) was added at room temperature. The reaction mixture was pressurized with H_2 gas balloon and stirred at room temperature for 5 h. The reaction mixture was filtered through Celite pad and washed with methanol (2x). The filtrate was concentrated under vacuum to afford **Intermediate IB** (11.4 g, 87%) which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d^6) 1.33 (s,

9H), 2.75-2.78 (m, 5H), 3.39 (s, 2H), 3.86 (s, 3H), 3.90 (s, 3H), 5.24 (s, 2H), 7.19 (d, J = 8 Hz, 2H), 7.22 (s, 1H), 7.55-7.68 (m, 3H), 10.40 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 430.09

*Synthesis of Thioester IC (Scheme 1; **General Procedure AA**)*

[00902] To a stirred solution of acid (1.0 eq.), 2,2'-benzothiazole disulfide (1.1 eq.), PPh_3 (1.1 eq.) in DCM (200 mL) at room temperature, TEA (1 eq.) was added. The mixture was stirred overnight at room temperature. Heptane (500 mL) was added and the solid formed was filtered, rinsed with acetone, and dried under vacuum to afford the desired thioester which was used without further purification.

Synthesis of S-(benzo[d]thiazol-2-yl)4-oxo-4H-chromene-2-carbothioate (IC1, Scheme 1)

[00903] Using General Procedure **AA** and chromone-2-carboxylic acid (17.2 g) as the acid, 26.5 g of the title compound was obtained (86% yield). ^{1}H NMR (400 MHz, DMSO-d^6) 6.92 (s, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.51-7.56 (m, 2H), 7.72 (d, *J* = 8 Hz, 1H), 7.85-7.89 (m, 1H), 7.94 (d, *J* = 8 Hz, 2H), 8.05-8.06 (m, 2H); *m/z* (ESI+), $[M + H]^+$ = 340.14

Synthesis of S-(benzo[d]thiazol-2-yl)quinoline-3-carbothioate (IC2, Scheme 1)

[00904] Using General Procedure **AA** and quinoline-3-carboxylic acid (10.5 g) as the acid, 18.5 g of the title compound was obtained (63% yield). ^{1}H NMR (400 MHz, DMSO-d^6) 7.41-7.45 (m, 1H), 7.50-7.54 (m, 1H), 7.68-7.72 (m, 1H), 7.88-7.92 (m, 2H), 8.04-8.09 (m, 2H), 8.11-8.19 (m, 1H), 8.96 (s, 1H), 9.32 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 323.18

Synthesis of S-(benzo[d]thiazol-2-yl) 5-hydroxy-4-oxo-4H-pyran-2-carbothioate (IC3, Scheme 1)

[00905] Using General Procedure **AA** and 5-hydroxy-4-oxo-4H-pyran-2-carboxylic acid (5.0 g) as the acid, 6.4 g of the title compound was obtained (68% yield).

Synthesis of S-(benzo[d]thiazol-2-yl)-8-hydroxyquinoline-3-carbothioate (IC4, Scheme 1)

[00906] Using General Procedure **AA** and 8-hydroxyquinoline-3-carboxylic acid (6.0 g) as the acid, 5.6 g of the title compound was obtained (62% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) quinoxaline-2-carbothioate (IC5, Scheme 1)

[00907] Using General Procedure **AA** and quinoxaline-2-carboxylic acid (5.5 g) as the acid, 7.2 g of the title compound was obtained (70% yield). ^{1}H NMR (400 MHz, DMSO-d^6) 7.41-7.49 (m, 1H), 7.51-7.53 (m, 1H), 7.92-8.16 (m, 4H), 8.18-8.23 (m, 2H), 9.42 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 324.21

Synthesis of S-(Benzo[d]thiazol-2-yl) 6-methyl-4-oxo-4H-chromene-2-carbothioate (IC6, Scheme 1)

[00908] Using General Procedure **AA** and 6-methyl chromone-2-carboxylic acid (3.06 g) as the acid, 4.34 g of the title compound was obtained (82% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) 6,8-dimethyl-4-oxo-4H-chromene-2-carbothioate (IC7, Scheme 1)

[00909] Using General Procedure **AA** and 6,8-dimethyl chromone-2-carboxylic acid (3.27 g) as the acid, 4.35 g of the title compound was obtained (79% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) 6-ethyl-4-oxo-4H-chromene-2-carbothioate (IC8, Scheme 1)

[00910] Using General Procedure **AA** and 6-ethyl chromone-2-carboxylic acid (3.27 g) as the acid, 4.23 g of the title compound was obtained (77% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) 7-methyl-4-oxo-4H-chromene-2-carbothioate (IC9, Scheme 1)

[00911] Using General Procedure **AA** and 7-methyl chromone-2-carboxylic acid (3.06 g) as the acid, 4.41 g of the title compound was obtained (83% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) 6-methyl-4-oxo-4H-chromene-3-carbothioate (IC10, Scheme 1)

[00912] Using General Procedure **AA** and 6-methyl-chromone-3-carboxylic acid (3.06 g) as the acid, 3.9 g of the title compound was obtained (74% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) 4-oxo-4H-chromene-3-carbothioate (IC11, Scheme 1)

[00913] Using General Procedure **AA** and chromone-3-carboxylic acid (2.85 g) as the acid, 4.00 g of the title compound was obtained (79% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) 3,4,5-trimethoxybenzothioate (IC12, Scheme 1)

[00914] Using General Procedure **AA** and 3,4,5-trimethoxybenzoic acid (3.18 g) as the acid, 4.51 g of the title compound was obtained (83% yield).

Synthesis of S-(Benzo[d]thiazol-2-yl) pyridine-2-carbothioate (IC13, Scheme 1)

[00915] Using General Procedure **AA** and picolinic acid (1.85 g) as the acid, 3.24 g of the title compound was obtained (79% yield).

*Synthesis of Intermediate ID (Scheme 1; **General Procedure BB**)*

[00916] To a stirred solution of **IB** (1.0 eq.) in anhydrous DCM (150 mL) at room temperature was added **C** (1.3 eq.) and the stirring was continued overnight at room temperature. The mixture

was then diluted with heptane and the formed solid was filtered and dried to afford **ID** which was used without further purification.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2 carboxamido) benzamido) phenethyl) (methyl)carbamate (ID1, Scheme 1)

[00917] The General Procedure **BB** and intermediate **IC1** (6.5 g) was used to obtain 7.8 g of the title compound (88% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(quinoline-3-carboxamido) benzamido) phenethyl) (methyl) carbamate (ID2, Scheme 1)

[00918] The General Procedure **BB** and intermediate **IC2** (3.0 g) was used to obtain 6.2 g of the title compound (72% yield).

Synthesis of tert-Butyl (4-(2-(5-hydroxy-4-oxo-4H-pyran-2-carboxamido)-4,5-dimethoxybenzamido) phenethyl) (methyl) carbamate (ID3, Scheme 1)

[00919] The General Procedure **BB** and intermediate **IC3** (3.51 g) was used to obtain 3.8 g of the title compound (76% yield).

Synthesis of tert-Butyl (4-(2-(8-hydroxyquinoline-3-carboxamido)-4,5-dimethoxybenzamido) phenethyl) (methyl) carbamate (ID4, Scheme 1)

[00920] The General Procedure **BB** and intermediate **IC4** (2.87 g) was used to obtain 2.9 g of the title compound (74% yield).

*Synthesis of Intermediate IE (Scheme 1; **General Procedure CC**)*

[00921] To a cooled suspension of **ID** in DCM (50 mL) at 0 °C, was added TFA (100 eq.) dropwise. The reaction mixture was then stirred at room temperature for 1 h. After completion of the reaction (monitored by LC/MS), the mixture was concentrated under vacuum. To the residue, acetonitrile was added resulting in a precipitate. After volatiles were removed, acetonitrile was added again and the mixture was concentrated. To the obtained solid residue, a small amount of DCM (20 mL) was added followed by a copious amount of heptanes. The resulting precipitate was collected by filtration and washed with heptanes to afford intermediate **IE** which was used without further purification.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(methylamino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IE1, Scheme 1)

[00922] The General Procedure **CC** and intermediate **ID1** (7.8 g) was used to obtain 6.5 g of the title compound (81% yield).

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(methylamino) ethyl) phenyl) carbamoyl) phenyl) quinoline-3-carboxamide trifluoroacetate salt (IE2, Scheme 1).

[00923] The General Procedure **CC** and intermediate **ID2** (6.2 g) was used to obtain 5.5 g of the title compound (87% yield).

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(methylamino)ethyl)phenyl)carbamoyl)phenyl)-5-hydroxy-4-oxo-4H-pyran-2-carboxamide trifluoroacetate salt (IE3, Scheme 1).

[00924] The General Procedure **CC** and intermediate **ID3** (3.8 g) was used to obtain 3.2 g of the title compound (82% yield).

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(methylamino)ethyl)phenyl)carbamoyl)phenyl)-8-hydroxyquinoline-3-carboxamide trifluoroacetate salt (IE4, Scheme 1).

[00925] The General Procedure **CC** and intermediate **ID4** (2.9 g) was used to obtain 2.5 g of the title compound (84% yield).

Reductive Amination (Scheme 1; ***General Procedure DD)***

[00926] To a clean 40 mL vial, a mixture of intermediate **IE** (1 eq.), aldehyde (1 eq.), and Et_3N (2.5 eq.) in anhydrous DMF (5 mL) was stirred at room temperature for 4 h. Then, acetic acid (3 eq.) followed by sodium triacetoxyborohydride (3.0 eq.) were added and the stirring was continued overnight at room temperature. Upon completion of the reaction (checked by LC/MS), the reaction mixture was diluted with DCM, and washed with brine (2x). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the crude product which was then purified by reverse phase-HPLC to give the final compound as a TFA salt which was converted to free base by dissolving the compound in 10% MeOH/DCM, followed by extraction with 1.0 M NaOH, drying over anhydrous sodium sulfate, filtration, and removal of the solvent under vacuum.

General Procedure EE *For the Amide Formation (Scheme 1)*

[00927] To a stirred solution of acid (0.16 mmol, 1.0 eq.) and **IE1** (0.16 mmol, 1.0 eq.) in DMF (5 mL) were added HATU (0.18 mmol, 1.1 eq.) and DIPEA (0.48 mmol, 3.0 eq.) at room temperature. The reaction mixture was monitored by LC/MS and after completion of the reaction, the mixture was diluted with EtOAc, and washed with 1 M HCl (2x), saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford crude product which was purified via RP (reverse phase)-HPLC to give the desired compound as a TFA salt which was converted to free base by dissolving the compound in 10%

MeOH/DCM, followed by extraction with 1.0 M NaOH, drying over anhydrous sodium sulfate, filtration, and removal of the solvent under vacuum.

The final Compound Nos. 25-55 were synthesized according to Scheme 2.

General Procedure 2A *for Step 1 of Scheme 2*

[00928] 4-(2-bromoethyl) aniline (2.5 mmol, 1.0 eq.) and the corresponding primary amine (10 mmol, 4.0 eq.) were dissolved in 20 mL anhydrous THF. The mixture was left to stir for overnight at room temperature. The reaction mixture was monitored by LC/MS and after completion of the reaction, the reaction mixture was concentrated under vacuum to afford secondary amine **IF** which was used without further purification.

Synthesis of 4-(2-(Ethylamino)ethyl)aniline (IF1, Scheme 2)

[00929] The title compound was obtained following General Procedure **2A** and using ethylamine.

Synthesis of 4-(2-(Propylamino)ethyl)aniline (IF2, Scheme 2)

[00930] The title compound was obtained following General Procedure **2A** and *n*-propylamine.

Synthesis of 4-(2-(Isobutylamino)ethyl)aniline (IF3, Scheme 2)

[00931] The title compound was obtained following General Procedure **2A** and 2-methylpropan-1-amine.

Synthesis of 4-(2-(Isopropylamino)ethyl)aniline (IF4, Scheme 2)

[00932] The title compound was obtained following General Procedure **2A** and *iso*propylamine.

Synthesis of 4-(2-((Cyclopropylmethyl)amino)ethyl)aniline (IF5, Scheme 2)

[00933] The title compound was obtained following General Procedure **2A** and cyclopropylmethanamine.

Synthesis of 4-(2-(Phenethylamino)ethyl)aniline (IF6, Scheme 2)

[00934] The title compound was obtained following General Procedure **2A** and 2-phenylethan-1-amine.

Synthesis of 4-(2-(Cyclohexylamino)ethyl)aniline (IF7, Scheme 2)

[00935] The title compound was obtained following General Procedure **2A** and cyclohexanamine.

Synthesis of 4-(2-((2-(1H-indol-3-yl)ethyl)amino)ethyl)aniline (IF8, Scheme 2)

[00936] The title compound was obtained following General Procedure **2A** and 2-(1H-indol-3-yl)ethan-1-amine.

General Procedure 2B for Step 2 of Scheme 2

[00937] To an ice-cooled (0 °C) solution of secondary amine **IF** (2.0 mmol, 1.0 eq.) in 20 mL anhydrous DCM was added Boc anhydride (2.2 mmol, 1.1 eq.). The reaction mixture was stirred overnight at room temperature and after completion of the reaction, the volatiles were removed by vacuum. The residue obtained was triturated with *n*-heptane and then filtered to afford intermediate **IG** which was used without further purification.

General Procedure 2C for Step 3 of Scheme 2

[00938] To a stirred solution of 4,5-dimethoxy-2-nitrobenzoic acid (5.5 mmol, 1.0 eq.) and intermediate **IG** (5.5 mmol, 1.0 eq.) in 50 mL DMF were added HATU (6.05 mmol, 1.1 eq.) and DIPEA (16.5 mmol, 3.0 eq.) at room temperature. The reaction mixture was monitored by LC/MS, and after completion of the reaction, the reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ (2x) and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford crude product, which was purified by flash chromatography on silica gel using MeOH/DCM (0-10% gradient) to afford intermediate **IH**.

General Procedure 2D for Step 4 of Scheme 2

[00939] To a clean round bottom flask charged with **IH** (4.5 mmol, 1.0 eq.) and 10% Pd/C (0.45 mmol, 0.1 eq., 10.0% by wt%) and 30 mL methanol/THF (1:1) was stirred at room temperature. The reaction mixture was pressurized with H_2 gas balloon and stirred at room temperature for 5 h. The reaction mixture was then filtered through celite pad, washed with methanol (2x) and the filtrate was concentrated under vacuum to afford intermediate **II** which was used without further purification.

General Procedure 2E for Step 5 of Scheme 2

[00940] To a stirred solution of **II** (0.6 mmol, 1.0 eq.) in anhydrous DCM (15 mL) was added **IC** (0.78 mmol, 1.3 eq.) at room temperature and the stirring was continued overnight at room temperature. The reaction mixture was then diluted with heptane resulting in a precipitate which was collected and dried to afford intermediate **IJ** which was used without further purification.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) (ethyl)carbamate (IJ1, Scheme 2)

[00941] Using General Procedure **2E**, **II1** (0.25 g) and **IC1** (0.24 g), 0.29 g of the title compound was obtained (83% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(quinoline-3-carboxamido) benzamido) phenethyl) (ethyl)carbamate (IJ2, Scheme 2).

[00942] Using General Procedure **2E**, **II1** (0.25 g) and **IC2** (0.23 g), 0.289 g of the title compound was obtained (86% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(quinoxaline-2-carboxamido) benzamido) phenethyl) (ethyl) carbamate (IJ3, Scheme 2)

[00943] Using General Procedure **2E**, **II1** (0.25 g) and **IC5** (0.23 g), 0.275 g of the title compound was obtained (81% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) (propyl) carbamate (IJ4, Scheme 2)

[00944] Using General Procedure **2E**, **II2** (0.25 g) and **IC1** (0.24 g), 0.280 g of the title compound was obtained (81% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) (isobutyl) carbamate (IJ5, Scheme 2)

[00945] Using General Procedure **2E**, **II3** (0.25 g) and **IC1** (0.234 g), 0.290 g of the title compound was obtained (85% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) (isopropyl) carbamate (IJ6, Scheme 2)

[00946] Using General Procedure **2E**, **II4** (0.25 g) and **IC1** (0.241 g), 0.279 g of the title compound was obtained (81% yield).

Synthesis of tert-Butyl (cyclopropylmethyl)(4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido)benzamido)phenethyl)carbamate (IJ7, Scheme 2)

[00947] Using General Procedure **2E**, **II5** (0.25 g) and **IC1** (0.235 g), 0.295 g of the title compound was obtained (86% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) (phenethyl) carbamate (IJ8, Scheme 2)

[00948] Using General Procedure **2E**, **II6** (0.3 g) and **IC1** (0.255 g), 0.35 g of the title compound was obtained (88% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(quinoline-3-carboxamido) benzamido) phenethyl) (ethyl)carbamate (IJ9, Scheme 2)

[00949] Using General Procedure **2E**, **II6** (0.3 g) and **IC2** (0.242 g), 0.326 g of the title compound was obtained (84% yield).

Synthesis of tert-Butyl cyclohexyl(4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) carbamate (IJ10, Scheme 2)

[00950] Using General Procedure **2E**, **II7** (0.25 g) and **IC1** (0.22 g), 0.285 g of the title compound was obtained (85% yield).

Synthesis of tert-Butyl (2-(1H-indol-3-yl) ethyl) (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) carbamate (IJ11, Scheme 2)

[00951] Using General Procedure **2E**, **II8** (0.25 g) and **IC1** (0.197 g), 0.275 g of the title compound was obtained (84% yield).

***General Procedure 2F** for Step 6 of Scheme 2*

[00952] To an ice-cooed (0 °C) suspension of intermediate **IJ** (0.5 mmol, 1 eq.) in DCM (5 mL) was added TFA (50 mmol, 100 eq.) dropwise. The reaction mixture was then stirred at room temperature for 1 h. After completion of the reaction (monitored by LC/MS), the mixture was concentrated under vacuum. To the residue, acetonitrile was added resulting in a precipitate. After volatiles were removed, acetonitrile was added again, and the mixture was concentrated. To the obtained solid residue, a small amount of DCM was added followed by a copious amount of heptane. The resulting precipitate was collected by filtration and washed with heptane to afford intermediate **IK** which was used without further purification.

Synthesis of N-(2-((4-(2-(Ethylamino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK1, Scheme 2)

[00953] Following the General Procedure **2F** with **IJ1** (0.25 g), 0.215 g of the title compound was obtained (84% yield).

Synthesis of N-(2-((4-(2-(Ethylamino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl) quinoline-3-carboxamide trifluoroacetate salt (IK2, Scheme 2)

[00954] Following the General Procedure **2F** with **IJ2** (0.25 g), 0.23 g of the title compound was obtained (89% yield).

Synthesis of N-(2-((4-(2-(Ethylamino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl) quinoxaline-2-carboxamidetrifluoroacetate salt (IK3, Scheme 2)

[00955] Following the General Procedure **2F** with **IJ3** (0.25 g), 0.235 g of the title compound was obtained (91% yield).

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(propylamino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK4, Scheme 2)

[00956] Following the General Procedure **2F** with **IJ4** (0.25 g), 0.218 g of the title compound was obtained (85% yield).

Synthesis of N-(2-((4-(2-(Isobutylamino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK5, Scheme 2)

[00957] Following the General Procedure **2F** with **IJ5** (0.25 g), 0.238 g of the title compound was obtained (93% yield).

Synthesis of N-(2-((4-(2-(Isopropylamino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK6, Scheme 2)

[00958] Following the General Procedure **2F** with **IJ6** (0.25 g), 0.222 g of the title compound was obtained (87% yield).

Synthesis of N-(-(2-((4-(2-((Cyclopropylmethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK7, Scheme 2)

[00959] Following the General Procedure **2F** with **IJ7** (0.25 g), 0.243 g of the title compound was obtained (95% yield).

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(phenethylamino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK8, Scheme 2)

[00960] Following the General Procedure **2F** with **IJ8** (0.25 g), 0.233 g of the title compound was obtained (91% yield).

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(phenethylamino) ethyl) phenyl) carbamoyl) phenyl) quinoline-3-carboxamide trifluoroacetate salt (IK9, Scheme 2)

[00961] Following the General Procedure **2F** with **IJ9** (0.25 g), 0.218 g of the title compound was obtained (85% yield).

Synthesis of N-(2-((4-(2-(Cyclohexylamino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK10, Scheme 2)

[00962] Following the General Procedure **2F** with **IJ10** (0.25 g), 0.242 g of the title compound was obtained (95% yield).

Synthesis of N-(2-((4-(2-((2-(1H-indol-3-yl)ethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt (IK11, Scheme 2)

[00963] Following the General Procedure **2F** with **IJ11** (0.25 g), 0.236 g of the title compound was obtained (92% yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-nitrobenzamido) phenethyl) (methyl)carbamate IL (Scheme 3)

[00964] To a stirred solution of 4,5-dimethoxy-2-nitrobenzoic acid (3.33 g, 14.67 mmol, 1.0 eq.) and *tert*-butyl (4-(aminomethyl)benzyl)carbamate (3.67 g, 14.67 mmol, 1.0 eq.) in DMF (50 mL) were added HATU (6.13 g, 16.13 mmol, 1.1 eq.) and DIPEA (6.12 mL, 44.01 mmol, 3.0 eq.) at room temperature. The reaction mixture was stirred overnight. The reaction was monitored by LC/MS, after completion of the reaction, the reaction mixture was diluted with EtOAc, and washed with 1 M HCl (2x), saturated $NaHCO_3$ (2x) and brine (2x). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford crude product. The crude material was purified by flash chromatography on silica gel using Heptane/Ethylacetate (0-100% gradient) to afford the desired product **IL** (5.78 g, 87% yield).

Synthesis of tert-Butyl (4-((2-amino-4,5-dimethoxybenzamido)methyl)benzyl)carbamate IM (Scheme 3)

[00965] To a 250 mL round bottom flask charged with **IL** (5.7 g, 12.8 mmol, 1.0 eq.) and 10% Pd/C (136 mg, 1.28 mmol, 10.0% wt%), 150 mL of methanol / THF (50:50) was added at room temperature. Reaction mixture was pressurized with H_2 gas balloon and stirred at room temperature for 5 h, reaction mixture was filtered through Celite pad, followed by washing of Celite pad with methanol (2 times) and filtrate was concentrated under vacuum to afford **IM** (4.8 g, 90% yield) which was used without further purification.

Synthesis of tert-Butyl (4-((4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) methyl) benzyl) carbamate IN (Scheme 3)

[00966] To a clean 250 mL round bottom flask was added **IM** (4.5 g, 10.8 mmol, 1.0 eq.) and a stir bar. The compound was then dissolved in anhydrous DCM (75 mL). To the stirring mixture was then added **IC1** (4.78 g, 14.09 mmol, 1.3 eq.) and the reaction was stirred at room temperature for overnight. The mixture was then diluted with Heptane (150 mL) and the formed solid was filtered off to afford **IN** (5.1 g, 81% yield) which was used without further purification.

Synthesis of N-(2-((4-(Aminomethyl)benzyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt IO (Scheme 3)

[00967] To a 250 mL round bottom flask, **IN** (5.0 g, 8.5 mmol, 1 eq.) was suspended in DCM (100 mL) and stirred. The mixture was cooled to 0°C, then TFA (65.1 mL, 850 mmol, 100 eq.) was added dropwise creating a clear brown solution. The mixture was stirred at room temperature for 1 h. Reaction mixture was monitored with LC/MS, after completion of the reaction, the mixture was concentrated under vacuum. ACN (250 mL) was added and a precipitate formed. The volatiles were then removed and more ACN (500 mL) was added and evaporated off leaving a solid. A small amount of DCM (50 mL) was then added to suspend the solid and then to it was added a copious amount of heptane. The resulting precipitate was collected by filtration and washed with heptane to afford compound **IO** (4.2 g, 82% yield).

Synthesis of N-(4,5-Dimethoxy-2-((4-((((1-methyl-1H-indazol-5-yl)methyl)amino)methyl)benzyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide IP (Scheme 3)

[00968] To a clean 250 mL round bottom flask equipped with a stir bar were added **IO** (4.0 g, 6.65 mmol, 1.0 eq.), 1-methyl-1H-indazole-5-carbaldehyde (1.59 g, 9.97 mmol, 1.50 eq.), 25% EtOH in DMF (100 mL), and TEA (4.65 mL, 33.25 mmol, 5.0 eq.). The mixture was stirred at 70 °C for 30 min then left to stir at room temperature for 4 h. Sodium borohydride (1.26 g, 33.25 mmol, 5.0 eq.) was then added, and the mixture was stirred for 5-10 min. The reaction was then quenched with MeOH (25 mL), diluted with DCM (250 mL) and washed with water (2x) and brine (2x), the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude material was purified via flash chromatography on silica gel using Methanol/DCM (0-10% gradient) to afford **IP** (2.65 g, 64% yield).

Synthesis of tert-Butyl (4-(5-ethoxy-4-methoxy-2-nitrobenzamido) phenethyl) (methyl) carbamate IQ (Scheme 4)

[00969] To a stirred solution of 5-ethoxy-4-methoxy-2-nitrobenzoic acid (3.53 g, 14.67 mmol, 1.0 eq.) and *tert*-butyl (4-aminophenethyl) (methyl)carbamate (3.67 g, 14.67 mmol, 1.0 eq.) in DMF (50 mL) were added HATU (6.13 g, 16.13 mmol, 1.1 eq.) and DIPEA (6.12 mL, 44.01 mmol, 3.0 eq.) at room temperature. Reaction mixture was stirred for overnight. The reaction was monitored with LC/MS, after completion of the reaction, reaction mixture was diluted with EtOAc, and washed with 1 M HCl (2x), saturated $NaHCO_3$ (2x) and brine (2x). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford crude product. The crude

material was purified via flash chromatography on silica gel using Heptane/Ethylacetate (0% - 100% gradient) to afford 2.8 g of **IQ** (41% yield).

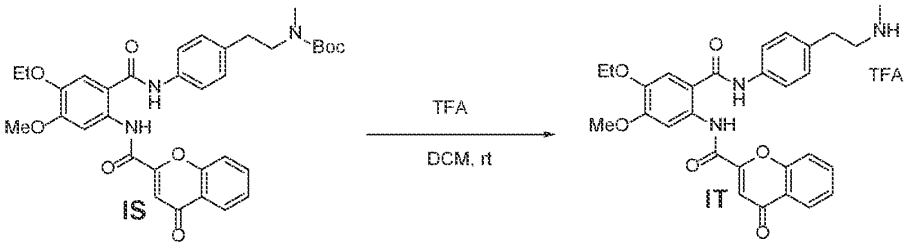
Synthesis of tert-Butyl (4-(2-amino-5-ethoxy-4-methoxybenzamido) phenethyl) (methyl)carbamate IR (Scheme 4)

[00970] To a 250 mL round bottom flask charged with **IQ** (2.8 g, 6.4 mmol, 1.0 eq.) and 10% Pd/C (68 mg, 0.64 mmol, 10.0% wt%), 50 mL of methanol / THF (50:50) was added at room temperature. Reaction mixture was pressurized with H_2 gas balloon and stirred at room temperature for 5 h, reaction mixture was filtered through Celite pad, followed by washing of Celite pad with methanol (2x) and filtrate was concentrated under vacuum to afford 1.9 g of **IR** (68% yield) which was used without further purification.

Synthesis of tert-Butyl (4-(5-ethoxy-4-methoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl) (methyl)carbamate IS (Scheme 4)

[00971] To a clean 250 mL round bottom flask was added **IR** (1.8 g, 4.06 mmol, 1.0 eq.) and a stir bar. The compound was then dissolved in anhydrous DCM (50 mL). To the stirring mixture was then added **IC1** (1.79 g, 5.28 mmol, 1.3 eq.) and the reaction was stirred at room temperature overnight. The mixture was then diluted with heptane (150 mL) and the formed solid was filtered off to afford 2.1 g of **IS** (87% yield) which was used without further purification.

Synthesis of N-(4-Ethoxy-5-methoxy-2-((4-(2-(methylamino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt IT (Scheme 4)



[00972] To a 250 mL round bottom flask, **IS** (2.0 g, 3.25 mmol, 1 eq.) was suspended in DCM (25 mL) and stirred. The mixture was cooled to 0 °C, then TFA (24.88 mL, 100 eq.) was added dropwise creating a clear brown solution. The mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by LC/MS), the mixture was concentrated under vacuum. To the residue, acetonitrile (100 mL) was added resulting in a precipitate. After

volatiles were removed, acetonitrile (200 mL) was added again and the mixture was concentrated. To the obtained solid residue, a small amount of DCM (20 mL) was added to form a suspension followed by a copious amount of heptane. The resulting precipitate was collected by filtration and washed with heptane to afford 1.6 g of **IT** (80% yield) which was used without further purification.

General Procedure GG *for Synthesis of Intermediate* ***IU*** *(Scheme 5)*

[00973] To a clean 40 mL vial charged with stirring bar, amine (2.0 mmol, 1.0 eq.), KI (0.4 mmol, 0.2 eq.) and K_2CO_3 (2.2 mmol, 1.1 eq.) were stirred in anhydrous DMF (3 mL). Amine (2.0 mmol, 1.0 eq.) was added, and the mixture was heated to 70 °C for 24 h. The reaction was monitored by LC/MS. After completion, the reaction mixture was allowed to cool to room temperature and was then filtered, washed with DCM and was concentrated under vacuum to afford intermediate **IU** which was used without further purification.

Synthesis of 2-(4-nitrophenethyl)-1,2,3,4-tetrahydro-2,7-naphthyridine (IU1, Scheme 5)

[00974] The General Procedure **GG** was used to obtain 0.42 g of the title compound (74% yield).

Synthesis of 2-(4-nitrophenethyl)-1,2,3,4-tetrahydro-2,6-naphthyridine (IU2, Scheme 5)

[00975] The General Procedure **GG** was used to obtain 0.92 g of the title compound (61% yield).

General Procedure HH *for Synthesis of Intermediate* ***IV*** *(Scheme 5)*

[00976] To a clean 40 mL vial charged with a stirring bar, intermediate **IU** (1.77 mmol, 1.0 eq.), Fe (17.7 mmol, 10 eq.) and NH_4Cl (3.55 mmol, 2.0 eq.) were mixed in a mixture of water (1.5 mL) and Ethanol (10 mL). The mixture was heated at 90°C for 1h. The reaction was checked by LC/MS for completion. The mixture was filtered while hot and filter pad was washed with ethyl acetate (100 mL) followed by 20 mL MeOH. The filtrate was washed with sat. $NaHCO_3$ and brine, then dried under anhydrous Na_2SO_4 and concentrated under vacuum to afford intermediate **IV** which was used without further purification.

Synthesis of 4-(2-(3,4-dihydro-2,7-naphthyridin-2(1H)-yl)ethyl)aniline (IV1, Scheme 5)

[00977] The General Procedure **HH**, intermediate **IU1** (0.5 g) was used to obtain 0.35 g of the title compound (78% yield).

Synthesis of 4-(2-(3,4-dihydro-2,6-naphthyridin-2(1H)-yl)ethyl)aniline (IV2, Scheme 5)

[00978] The General Procedure **HH**, intermediate **IU2** (0.5 g) was used to obtain 0.34 g of the title compound (76% yield).

General Procedure II *for Step 3 of Scheme 5*

[00979] To a stirred solution of 4,5-dimethoxy-2-nitrobenzoic acid (1.0 mmol, 1.0 eq.) and intermediate **IV** (1.0 mmol, 1.0 eq.) in 5 mL DMF were added HATU (1.1 mmol, 1.1 eq.) and DIPEA (3.0 mmol, 3.0 eq.) at room temperature. The reaction mixture was monitored by LC/MS, and after completion of the reaction, the reaction mixture was diluted with EtOAc, washed with water (2x) and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated to afford crude product, which was purified by flash chromatography on silica gel using MeOH/DCM (0-10% gradient) to afford intermediate **IW**.

Synthesis of N-(4-(2-(3,4-Dihydro-2,7-naphthyridin-2(1H)-yl)ethyl)phenyl)-4,5-dimethoxy-2-nitrobenzamide (IW1, Scheme 5)

[00980] Following the General Procedure **II**, intermediate **IV1** (0.25 g) was used to obtain 0.114 g of the title compound (25 % yield)

Synthesis of N-(4-(2-(3,4-Dihydro-2,6-naphthyridin-2(1H)-yl)ethyl)phenyl)-4,5-dimethoxy-2-nitrobenzamide (IW2, Scheme 5)

[00981] Following the General Procedure **II**, intermediate **IV2** (0.25 g) was used to obtain 0.12 g of the title compound (32 % yield)

Synthesis of 2-Amino-N-(4-(2-(3,4-dihydro-2,7-naphthyridin-2(1H)-yl)ethyl)phenyl)-4,5-dimethoxybenzamide (IX1, Scheme 5)

[00982] Following the General Procedure **HH**, intermediate **IW1** (0.16 g) was used to obtain 0.1 g of the title compound (92 % yield)

Synthesis of 2-Amino-N-(4-(2-(3,4-dihydro-2,6-naphthyridin-2(1H)-yl)ethyl)phenyl)-4,5-dimethoxybenzamide (IX2, Scheme 5)

[00983] Following the General Procedure **HH**, intermediate **IW2** (0.15 g) was used to obtain 0.09 g of the title compound (83 % yield)

Synthesis of tert-Butyl 3-(4,5-dimethoxy-2-nitrobenzamido)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate IY (Scheme 6)

[00984] Following the General Procedure **2C**, 4,5-dimethoxy-2-nitrobenzoic acid (0.5 g) and *tert*-butyl 3-amino-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.55 g) were used to obtain 0.39 g of the title compound (39 % yield).

Synthesis of tert-Butyl 3-(2-amino-4,5-dimethoxybenzamido)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate IZ (Scheme 6)

[00985] Following the General Procedure **2D**, intermediate **IY** (0.39 g) was used to obtain 0.19 g of the title compound (51 % yield).

Synthesis of tert-Butyl 3-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido)benzamido)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate IIA (Scheme 6)

[00986] Following the General Procedure **BB**, intermediate **IZ** (0.19 g) was used to obtain 0.2 g of the title compound (72 % yield).

Synthesis of N-(4,5-Dimethoxy-2-((5,6,7,8-tetrahydro-1,6-naphthyridin-3-yl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide trifluoroacetate salt IIB (Scheme 6)

[00987] Following the General Procedure **CC**, intermediate **IIA** (0.2 g) was used to obtain 0.15 g of the title compound (75 % yield).

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-nitrobenzamido)phenethyl)carbamate (IIH) (Scheme 6)

[00988] A round-bottom flask was charged with 4,5-dimethoxy-2-nitrobenzoic acid (12.0 g, 52.9 mmol, 1.00 eq.), *tert*-butyl (4-aminophenethyl)carbamate (13.1 g, 55.5 mmol, 1.05 eq.), HATU (22.1 g, 58.2 mmol, 1.10 eq.) and DMF (100 mL). The mixture was cooled to 0 °C and stirred for 10 min. DIPEA (26.25 ml, 158.7 mmol, 3.0 eq.) was added slowly and the stirring was continued at room temperature for 2-24 h. The reaction mixture was then diluted with DCM (400 mL), and the organic layer was washed with 300 mL water (2x), and 100 mL brine (2x), briefly dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to about 200 mL. Heptane (400 mL) was then added, and the mixture was stirred as the product continued to precipitate. The product was then filtered, washed with 40% DCM/heptane, and dried under vacuum overnight to give 20.5 g of intermediate **IIH** as an off-white solid (87% yield). ^{1}H NMR (400MHz, DMSO-d^6): 1.38 (s, 9H), 2.65 (t, J = 12, 2H), 3.01 (t, J = 12, 2H), 3.89 (s, 3H), 3.92 (s, 3H), 6.87-6.89 (m, 1H), 7.16 (d, J = 8, 2H), 7.26 (s, 1H), 7.57 (d, J = 8, 2H), 7.70 (s, 1H), 10.43 (s, 1H); m/z (ESI+), $[M + Na]^+$ = 468.41

Synthesis of tert-Butyl (4-(2-amino-4,5-dimethoxybenzamido)phenethyl)carbamate (III) (Scheme 6)

[00989] To a clean, dry hydrogenation flask were added compound **IIH** (2.5 g, 5.65 mmol, 1.0 eq.), 10% palladium on activated carbon (297 mg, 0.28 mmol, 0.05 eq.), and MeOH (50 mL).

The flask was then charged with hydrogen at 50 psi and shook for 3 h. The reaction mixture was then filtered on celite and concentrated under vacuum to afford the crude product, which was then purified by flash chromatography on silica gel (EtOAc/Heptane) to afford 4.2 g of compound **III** as an off-white solid (89% yield).

*Synthesis of Intermediate **IIJ** (Scheme 6; **General Procedure SS**)*

[00990] A round-bottom flask was charged with intermediate **IC** (6.6 mmol, 1.1 eq.) and either DCM or 50% THF/DCM mixture (150 mL). The mixture was stirred either at room temperature or at refluxing temperature until all the solids dissolved. To a clean, dry 40 mL vial, intermediate **III** (2.5 g, 6.0 mmol, 1.00 eq.) and DCM (20 mL) were added, and the mixture was stirred at room temperature until all the solids dissolved then added to the round-bottom flask containing intermediate **IC**. The reaction mixture was stirred at room temperature overnight. If a precipitate was formed, the solid was filtered and dried under vacuum; if not, the reaction mixture was concentrated under vacuum and the product was purified by flash chromatography on silica gel (EtOAc/Heptane) to give intermediate **IIJ**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido)benzamido) phenethyl)carbamate (IIJ1, Scheme 6)

[00991] 2.24 g of compound **IC1** was used to synthesize 2.36 g of the title compound (67% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(6-methyl-4-oxo-4H-chromene-2-carboxamido) benzamido)phenethyl)carbamate (IIJ2, Scheme 6)

[00992] 2.33 g of compound **IC6** was used to synthesize 2.55 g of the title compound (71% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(2-(6,8-dimethyl-4-oxo-4H-chromene-2-carboxamido)-4,5-dimethoxybenzamido)phenethyl)carbamate (IIJ3, Scheme 6)

[00993] 2.42 g of compound **IC7** was used to synthesize 2.40 g of the title compound (65% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(2-(6-ethyl-4-oxo-4H-chromene-2-carboxamido)-4,5-dimethoxybenzamido)phenethyl)carbamate (IIJ4, Scheme 6)

[00994] 2.42 g of compound **IC8** was used to synthesize 2.60 g of the title compound (70% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(7-methyl-4-oxo-4H-chromene-2-carboxamido)benzamido)phenethyl)carbamate (IIJ5, Scheme 6)

[00995] 2.33 g of compound **IC9** was used to synthesize 2.60 g of the title compound (72% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(6-methyl-4-oxo-4H-chromene-3-carboxamido)benzamido)phenethyl)carbamate (IIJ6, Scheme 6)

[00996] 2.33 g of compound **IC10** was used to synthesize 2.3 g of the title compound (64% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-3-carboxamido)benzamido) phenethyl)carbamate (IIJ7, Scheme 6)

[00997] 2.24 g of compound **IC11** was used to synthesize 2.1 g of the title compound (60% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(quinoline-3-carboxamido)benzamido)phenethyl) carbamate (IIJ8, Scheme 6)

[00998] 2.13 g of compound **IC2** was used to synthesize 2.2 g of the title compound (64% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(quinoxaline-2-carboxamido)benzamido) phenethyl)carbamate (IIJ9, Scheme 6)

[00999] 2.13 g of compound **IC5** was used to synthesize 2.5 g of the title compound (73% yield) according to the General Procedure **SS**.

Synthesis of tert-Butyl (4-(4,5-dimethoxy-2-(3,4,5-trimethoxybenzamido)benzamido)phenethyl) carbamate (IIJ10, Scheme 6)

[001000] 2.38 g of compound **IC12** was used to synthesize 2.4 g of the title compound (66% yield) according to the General Procedure **SS**.

*Synthesis of Intermediate **IIK** (Scheme 6; **General Procedure TT**)*

[001001] A round-bottom flask was charged with intermediate **IIJ** (3-5 mmol, 1.0 eq.) and a mixture of TFA and DCM (1: 2 v/v, 30-50 mL). The mixture was stirred at room temperature for 3-24 h. The solution was then diluted with MeOH (100 mL) and concentrated under vacuum. The residue was then suspended in heptane, filtered, and dried to give intermediate **IIK**, which was used without further purification or purified by reverse phase HPLC (0.1% TFA in water/ACN).

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4H-chromene-2-carboxamide trifluoroacetate (IIK2, Scheme 6)

[001002] 2.40 g of compound **IIJ2** was used to synthesize 1.80 g of the title compound (93% yield) according to the General Procedure **TT**.

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6,8-dimethyl-4-oxo-4H-chromene-2-carboxamide trifluoroacetate (IIK3, Scheme 6)

[001003] 2.30 g of compound **IIJ3** was used to synthesize 1.95 g of the title compound (83% yield) according to the General Procedure **TT**.

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-ethyl-4-oxo-4H-chromene-2-carboxamide trifluoroacetate (IIK4, Scheme 6)

[001004] 2.46 g of compound **IIJ4** was used to synthesize 2.24 g of the title compound (89% yield) according to the General Procedure **TT**.

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-7-methyl-4-oxo-4H-chromene-2-carboxamide trifluoroacetate (IIK5, Scheme 6)

[001005] 2.40 g of compound **IIJ5** was used to synthesize 2.30 g of the title compound (93% yield) according to the General Procedure **TT**.

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4H-chromene-3-carboxamide trifluoroacetate (IIK6, Scheme 6)

[001006] 1.80 g of compound **IIJ6** was used to synthesize 1.55 g of the title compound (84% yield) according to the General Procedure **TT**.

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-3-carboxamide trifluoroacetate (IIK7, Scheme 6)

[001007] 1.76 g of compound **IIJ7** was used to synthesize 1.60 g of the title compound (89% yield) according to the General Procedure **TT**.

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoline-3-carboxamide trifluoroacetate (IIK8, Scheme 6)

[001008] 2.0 g of compound **IIJ8** was used to synthesize 1.75 g of the title compound (86% yield) according to the General Procedure **TT**.

Synthesis of N-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide trifluoroacetate (IIK9, Scheme 6)

[001009] 2.43 g of compound **IIJ9** was used to synthesize 2.2 g of the title compound (88% yield) according to the General Procedure **TT**.

Synthesis of N-(4-(2-Aminoethyl)phenyl)-4,5-dimethoxy-2-(3,4,5-trimethoxybenzamido) benzamide trifluoroacetate (IIK10, Scheme 6)

[001010] 2.13 g of compound **IIJ10** was used to synthesize 1.9 g of the title compound (87% yield) according to the General Procedure **TT**.

*Synthesis of Intermediate IIL (Scheme 6; **General Procedure UU**)*

[001011] To a clean, dry 40 mL vial equipped with a stir bar were added intermediate **IIK** (0.30 mmol, 1.0 eq.), the aldehyde R_2CHO (0.45 mmol, 1.50 eq.), 25% EtOH in DMF (10 mL), and TEA (0.2 mL, 1.5 mmol, 5.0 eq.). The mixture was vortexed and heated using a heat gun till all the solids dissolve. The mixture was then cooled to room temperature and stirred for 3 h. Sodium borohydride (57 mg, 1.5 mmol, 5.0 eq.) was then added, and the mixture was vortexed and stirred for 5-10 min. The reaction was then slowly quenched with MeOH, acidified with TFA, filtered, and purified by reverse phase HPLC (0.1% TFA in water/ACN) to give intermediate **IIL**. Alternately, the reaction was slowly quenched with MeOH, precipitated with water, and filtered. The solid collected by filtration was purified by flash chromatography on silica gel (MeOH/DCM) to give intermediate **IIL** as a free base.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL2, Scheme 6)

[001012] 180 mg of compound **IIK1** and 72 mg of 1-methyl-1*H*-indazole-6-carbaldehyde were used to synthesize 124 mg of the title compound (65% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-indol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL3, Scheme 6)

[001013] 180 mg of compound **IIK1** and 72 mg of 1-methyl-1*H*-indole-6-carbaldehyde were used to synthesize 112 mg of the title compound (59% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1,3-dimethyl-1H-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL4, Scheme 6)

[001014] 180 mg of compound **IIK1** and 78 mg of 1,3-dimethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 131 mg of the title compound (67% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((2,3-dihydrobenzofuran-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL5, Scheme 6)

[001015] 180 mg of compound **IIK1** and 68 mg of 2,3-dihydrobenzofuran-5-carbaldehyde were used to synthesize 114 mg of the title compound (61% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL6, Scheme 6)

[001016] 180 mg of compound **IIK1** and 86 mg of 1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[d]imidazole-5-carbaldehyde were used to synthesize 127 mg of the title compound (64% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-benzo[d][1,2,3]triazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL7, Scheme 6)

[001017] 180 mg of compound **IIK1** and 72 mg of 1-methyl-1*H*-benzo[d][1,2,3]triazole-5-carbaldehyde were used to synthesize 110 mg of the title compound (58% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((6-bromoimidazo[1,2-a]pyrazin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL8, Scheme 6)

[001018] 180 mg of compound **IIK1** and 102 mg of 6-bromoimidazo[1,2-a]pyrazine-3-carbaldehyde were used to synthesize 120 mg of the title compound (57% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-7-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL9, Scheme 6)

[001019] 180 mg of compound **IIK1** and 72 mg of 1-methyl-1*H*-indazole-7-carbaldehyde were used to synthesize 123 mg of the title compound (65% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((8-methylquinolin-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL10, Scheme 6)

[001020] 180 mg of compound **IIK1** and 102 mg of 8-methylquinoline-5-carbaldehyde were used to synthesize 131 mg of the title compound (68% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((3,4-dimethoxyphenyl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL12, Scheme 6)

[001021] 180 mg of compound **IIK1** and 75 mg of veratraldehyde were used to synthesize 113 mg of the title compound (59% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4H-chromene-2-carboxamide (IIL13, Scheme 6)

[001022] 185 mg of compound **IIK2** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 112 mg of the title compound (58% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1,3-dimethyl-1H-indazol-5-yl)methyl)amino) ethyl)phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4H-chromene-2-carboxamide (IIL14, Scheme 6)

[001023] 185 mg of compound **IIK2** and 78 mg of 1,3-dimethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 135 mg of the title compound (68% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-6,8-dimethyl-4-oxo-4H-chromene-2-carboxamide (IIL15, Scheme 6)

[001024] 189 mg of compound **IIK3** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 108 mg of the title compound (54% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-6-Ethyl-4-oxo-4H-chromene-2-carboxamide (IIL16, Scheme 6)

[001025] 189 mg of compound **IIK4** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 119 mg of the title compound (60% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-7-methyl-4-oxo-4H-chromene-2-carboxamide (IIL17, Scheme 6)

185 mg of compound **IIK5** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 122 mg of the title compound (63% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4H-chromene-3-carboxamide (IIL18, Scheme 6)

[001026] 185 mg of compound **IIK6** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 125 mg of the title compound (64% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-3-carboxamide (IIL19, Scheme 6)

[001027] 180 mg of compound **IIK7** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 117 mg of the title compound (62% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-quinoline-3-carboxamide (IIL20, Scheme 6)

[001028] 176 mg of compound **IIK8** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 125 mg of the title compound (69% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-quinoline-3-carboxamide (IIL21, Scheme 6)

[001029] 176 mg of compound **IIK8** and 78 mg of 1,3-dimethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 131 mg of the title compound (69% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-ethyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL23, Scheme 6)

[001030] 180 mg of compound **IIK1** and 78 mg of 1-ethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 108 mg of the title compound (56% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-(N-((1-acetyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL24, Scheme 6)

[001031] 180 mg of compound **IIK1** and 86 mg of 1-acetyl-1H-indazole-5-carbaldehyde were used to synthesize 107 mg of the title compound (54% yield) according to the General Procedure **UU**.

Synthesis of N-(4,5-Dimethoxy-2-((4-(2-((3-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)amino)ethyl) phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (IIL25, Scheme 6)

[001032] 180 mg of compound **IIK1** and 85 mg of 3-(3-methyl-1,2,4-oxadiazol-5-yl)benzaldehyde were used to synthesize 98 mg of the title compound (50% yield) according to the General Procedure **UU**.

Synthesis of N-(2-((4-(2-(((2-(2-Fluorophenyl)pyrimidin-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide (IIL26, Scheme 6)

[001033] 180 mg of compound **IIK1** and 91 mg of 2-(2-fluorophenyl)pyrimidine-5-carbaldehyde were used to synthesize 105 mg of the title compound (52% yield) according to the General Procedure **UU**.

Synthesis of 4,5-Dimethoxy-N-(4-(2-(((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl)phenyl)-2-(3,4,5-trimethoxybenzamido)benzamide (IIL27, Scheme 6)

[001034] 187 mg of compound **IIK10** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 113 mg of the title compound (57% yield) according to the General Procedure **UU**.

*Synthesis of Final Compounds (Scheme 6; **General Procedure VV**)*

[001035] To a clean, dry 40 mL vial equipped with a stir bar were added Intermediate **IIL** (0.1 mmol, 1.0 eq.), aldehyde R_3CHO (0.2 mmol, 2.0 eq.), DMF (3.5 mL), and TEA (65 µL, 0.5 mmol, 5.0 eq.). The mixture was stirred at room temperature for 3 h. To the reaction mixture were added HOAc (57 µL, 1.0 mmol, 10.0 eq) and sodium triacetoxyborohydride (41 mg, 0.2 mmol, 1.5 eq.), and the mixture was stirred overnight or until it is determined by LC/MS that most of the starting material was converted to the desired product. The mixture was then diluted with 5% TFA/MeOH up to 5 mL, filtered using a syringe-driven filter unit, and purified by

reverse phase HPLC (0.1% TFA in water/ACN) to give the pure final compound as a TFA salt which was converted to free base by dissolving the compound in 10% MeOH/DCM, followed by extraction with 1.0 M NaOH, drying over anhydrous sodium sulfate, filtration, and removal of the solvent under vacuum. Alternately, the reaction was precipitated with water and filtered. The solid collected by filtration was purified by flash chromatography on silica gel (MeOH/DCM) to obtain final compound as a free base.

*Synthesis of Final Compounds with $R_2 = R_3$ (Scheme 6; **General Procedure WW**)*

[001036] To a clean, dry 40 mL vial equipped with a stir bar were added compound **IIK** (0.1 mmol, 1.0 eq.), aldehyde R_3CHO (0.4 mmol, 4.0 eq.), DMF (3.5 mL), and TEA (65 µL, 0.5 mmol, 5.0 eq.). The mixture was stirred at room temperature for 3 h. To the reaction mixture were added HOAc (57 µL, 1.0 mmol, 10.0 eq) and sodium triacetoxyborohydride (84 mg, 0.4 mmol, 4.0 eq.), and the mixture was stirred overnight or until it is determined by LC/MS that most of the compound **IIK** was converted to the product. The mixture was then diluted with 5% TFA/MeOH up to 5 mL, filtered using a syringe-driven filter unit, and purified by reverse phase HPLC (0.1% TFA in water/ACN) to give the pure final compound as a TFA salt which was converted to free base by dissolving the compound in 10% MeOH/DCM, followed by extraction with 1.0 M NaOH, drying over anhydrous sodium sulfate, filtration, and removal of the solvent under vacuum.

*Synthesis of Intermediate IIN (Scheme 7; **General Procedure XX**)*

[001037] A round-bottom flask was charged with 4-(methoxycarbonyl)-2-nitrobenzoic acid (3.38 g, 15.0 mmol, 1.00 eq.), Intermediate **IIN** (15.75 mmol, 1.05 eq.), HATU (6.27 g, 16.5 mmol, 1.10 eq.) and DMF (40 mL). The mixture was cooled to 0 °C and stirred for 10 min. DIPEA (7.5 ml, 45 mmol, 3.0 eq.) was added slowly and the stirring was continued at room temperature for 2-24 h. The reaction mixture was then diluted with DCM (200 mL), and the organic layer was washed with 150 mL water (2x), and 50 mL brine (2x), briefly dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The product was purified by flash chromatography on silica gel (MeOH/DCM) to give intermediate **IIN**.

Synthesis of tert-Butyl (4-(4-methoxycarbonyl-2-nitrobenzamido)phenethyl)carbamate (IIN1, Scheme 7)

[001038] 3.72 g of *tert*-butyl (4-aminophenethyl)carbamate (**IIM1**) was used to synthesize 5.4 g of the title compound (81% yield) according to the General Procedure **XX**.

Synthesis of tert-Butyl (4-(4-methoxycarbonyl-2-nitrobenzamido)phenethyl)(methyl)carbamate (IIN2, Scheme 7)

[001039] 3.94 g of *tert*-Butyl (4-aminophenethyl)(methyl)carbamate (**IIM2**) was used to synthesize 5.7 g of the title compound (83% yield) according to the General Procedure **XX**. ^{1}H NMR (400 MHz, DMSO-d_6) 1.33 (s, 9H), 2.53-2.72 (m, 2H), 2.72 (s, 3H), 3.23 (s, 2H), 4.85 (s, 2H), 6.47 (d, , J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H); *m/z* (ESI+), $[M + H]^+$ = 251.32.

*Synthesis of Intermediate IIO (Scheme 7; **General Procedure YY**)*

[001040] To a clean, dry hydrogenation flask were added compound **IIN** (5.0 mmol, 1.0 eq.), 10% palladium on activated carbon (265 mg, 0.25 mmol, 0.05 eq.), and MeOH (50 mL). The flask was then charged with hydrogen at 50 psi and shook for 3 h. The reaction mixture was then filtered on celite and concentrated under vacuum to afford the product, which was used either without purification or purified by flash chromatography on silica gel.

Synthesis of tert-Butyl (4-(4-methoxycarbonyl-2-aminobenzamido)phenethyl)carbamate (IIO1, Scheme 7)

[001041] 2.22 g of Intermediate **IIN1** was used to synthesize 1.6 g of the title compound (77% yield) according to the General Procedure **YY**.

Synthesis of tert-Butyl (4-(4-methoxycarbonyl-2-aminobenzamido)phenethyl)(methyl)carbamate (IIO2, Scheme 7)

[001042] 1.28 g of Intermediate **IIO1** was used to synthesize 1.5 g of the title compound (70% yield) according to the General Procedure **YY**.

*Synthesis of Intermediate IIP (Scheme 7; **General Procedure ZZ**)*

[001043] A round-bottom flask was charged with intermediate **IC** (6.6 mmol, 1.1 eq.) and 50% THF/DCM mixture (150 mL). The mixture was stirred either at room temperature or at refluxing temperature until all the solids dissolved. To a clean, dry 40 mL vial, intermediate **IIO** (6.0 mmol, 1.00 eq.) and DCM (20 mL) were added, and the mixture was stirred at room temperature until all the solids dissolved then added to the round-bottom flask containing intermediate **IC**. The reaction mixture was stirred at room temperature overnight, then the reaction mixture was concentrated under vacuum, and the residue was suspended in minimal amount of DCM or 50% DCM/heptane, filtered, dried under vacuum, and used without further purification.

Synthesis of Methyl 4-((4-(2-((tert-butoxycarbonyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4H-chromene-2-carboxamido)benzoate (IIP1, Scheme 7)

[001044] 2.48 g of compound **IIO1** and 2.24 g of compound **IC1** were used to synthesize 2.2 g of the title compound (63% yield) according to the General Procedure **ZZ**.

Synthesis of Methyl 4-((4-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4H-chromene-2-carboxamido)benzoate (IIP2, Scheme 7)

[001045] 2.56 g of compound **IIO2** and 2.24 g of compound **IC1** were used to synthesize 2.41 g of the title compound (67% yield) according to the General Procedure **ZZ**.

Synthesis of Methyl 4-((4-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)phenyl)carbamoyl)-3-(quinoline-3-carboxamido)benzoate (IIP3, Scheme 7)

[001046] 2.56 g of compound **IIO2** and 2.13 g of compound **IC2** were used to synthesize 2.16 g of the title compound (62% yield) according to the General Procedure **ZZ**.

Synthesis of Methyl 4-((4-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)phenyl)carbamoyl)-3-(picolinamido)benzoate (IIP4, Scheme 7)

[001047] 2.56 g of compound **IIO2** and 1.80 g of compound **IC13** were used to synthesize 2.04 g of the title compound (64% yield) according to the General Procedure **ZZ**.

*Synthesis of Intermediate IIQ (Scheme 7, **General Procedure AAA**)*

[001048] A round-bottom flask was charged with intermediate **IIP** (3.0 mmol, 1.0 eq.) and a mixture of TFA and DCM (1: 2 v/v, 30-50 mL). The mixture was stirred at room temperature for 3-24 h. The solution was then diluted with MeOH (100 mL) and concentrated under vacuum. The residue was then suspended in heptane, filtered, and dried to give intermediate **IIQ**, which was used without further purification or purified by reverse phase HPLC (0.1% TFA in water/ACN) if biological data were to be obtained.

*Synthesis of Methyl 4-((4-(2-aminoethyl)phenyl)carbamoyl)-3-(4-oxo-4H-chromene-2-carboxamido)benzoate trifluoroacetate (**IIQ1**, Scheme 7)*

[001049] 1.76 g of compound **IIP1** was used to synthesize 1.60 g of the title compound (89% yield) according to the General Procedure **AAA**.

*Synthesis of Methyl 4-((4-(2-(methylamino)ethyl)phenyl)carbamoyl)-3-(quinoline-3-carboxamido)benzoate trifluoroacetate (**IIQ3**, Scheme 7)*

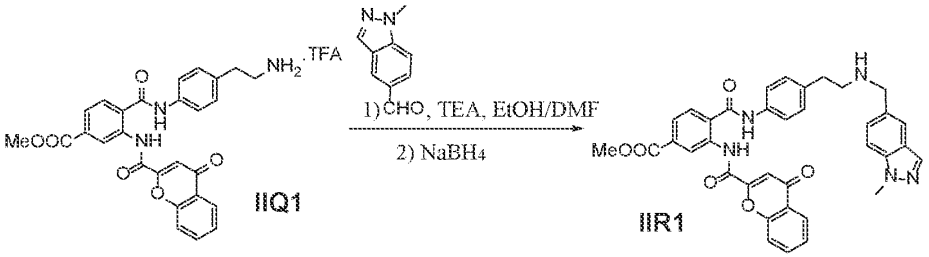
[001050] 1.75 g of compound **IIP3** was used to synthesize 1.57 g of the title compound (88% yield) according to the General Procedure **AAA**.

*Synthesis of Methyl 4-((4-(2-(methylamino)ethyl)phenyl)carbamoyl)-3-(picolinamido)benzoate trifluoroacetate (**IIQ4**, Scheme 7)*

[001051] 1.60 g of compound **IIP4** was used to synthesize 1.29 g of the title compound (79% yield) according to the General Procedure **AAA**.

*Synthesis of Methyl 4-((4-(2-(((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl) phenyl)carbamoyl)-3-(4-oxo-4H-chromene-2-carboxamido)benzoate (**IIR1**, Scheme 10)*

Scheme 10



[001052] A round-bottom flask was charged with intermediate **IIQ1** (1.2 g, 2.0 mmol, 1.0 eq.), 1-methyl-1*H*-indazole-5-carbaldehyde (480 mg, 3.0 mmol, 1.50 eq.), 25% EtOH in DMF (70 mL), and TEA (1.35 mL, 10 mmol, 5.0 eq.). The mixture was heated till all the solids dissolve. The mixture was then cooled to room temperature and stirred for 3 h. Sodium borohydride (228 mg, 6.0 mmol, 3.0 eq.) was then added, and the mixture was stirred for 5-10 min. The reaction was slowly quenched with MeOH, precipitated with water, and filtered. The solid collected by filtration was purified by flash chromatography on silica gel (MeOH/DCM) to give 545 mg of intermediate **IIR1** (43% yield).

*Synthesis of Intermediate **IIS** or **IIT** (Scheme 8; **General Procedure BBB**)*

[001053] A round-bottom flask was charged with Intermediate **IIQ** or **IIR1** (0.8 mmol, 1.0 eq.), aldehyde R_6CHO (1.2 mmol, 1.5 eq.), DMF (30 mL), and TEA (0.5 mL, 4.0 mmol, 5.0 eq.). The mixture was stirred at room temperature for 3 h. To the reaction mixture were added HOAc (0.45 mL, 8.0 mmol, 10.0 eq) and sodium triacetoxyborohydride (252 mg, 1.2 mmol, 1.5 eq.), and the mixture was stirred overnight or until it is determined by LC/MS that most of the starting material was converted to the product. The reaction mixture was then precipitated with water and filtered, and the solid collected by filtration was purified by flash chromatography on silica gel (MeOH/DCM) to give intermediate **IIS** as a free base. To synthesize Intermediate **IIT**, the same procedure was used using Intermediate **IIQH** with increased amounts of the aldehyde $R_{5/6}CHO$ (2.4 mmol, 3.0 eq.) and sodium triacetoxyborohydride (504 mg, 2.4 mmol, 3.0 eq.).

*Synthesis of Intermediate **IIU** or **IIV** (Scheme 8; **General Procedure CCC**)*

[001054] A clean, dry 40 mL vial was charged with Intermediate **IIS** or **IIT** (0.3 mmol, 1.0 eq.), THF (2.1 mL), and 1.0 M NaOH (0.9 mL, 0.9 mmol, 3.0 eq.). The mixture was stirred at room temperature for 3-4 h with frequent monitoring of the reaction by LC/MS to check for both reaction completion and product degradation. The product was then precipitated by adding 1.0 M HCl (6 mL), filtered, washed with water, dried under vacuum, and used without further purification.

*Synthesis of Final Compounds (Scheme 8; **General Procedure DDD**)*

[001055] A round-bottom flask was charged with Intermediate **IIU** or **IIV** (0.1 mmol, 1.00 eq.), alcohol $R_{11}OH$ or amine $(R_{11})_2NH$ (0.25 mmol, 2.5 eq.), HATU (42 mg, 0.11 mmol, 1.10 eq.) and DMF (4.0 mL). The mixture was stirred for 10 min. DIPEA (50 µL, 0.3 mmol, 3.0 eq.) was added slowly and the stirring was continued at room temperature overnight. The product was separated by reverse phase HPLC (0.1% TFA in water/ACN), re-purified using reverse phase HPLC when necessary, then dissolved in 10% MeOH/DCM (50 mL) and extracted with saturated sodium bicarbonate (2 x 50 mL) and brine (1 x 50 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated under vacuum to give the product as a free base.

*Synthesis of 6,7-Dimethoxy-2-(4-nitrophenethyl)-1,2,3,4-tetrahydroisoquinoline (**IIW**) (Scheme 9)*

[001056] A round-bottom flask was charged with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (6.59 mg, 29 mmol, 1.02 eq.), 1-(2-bromoethyl)-4-nitrobenzene (6.41 mg, 28 mmol, 1.0 eq.), anhydrous potassium carbonate (11.7 g, 85 mmol, 3.0 eq.), sodium iodide (5.16 g, 34 mmol, 1.2 eq.), and DMF (100 mL). and the reaction mixture was heated at 80 °C and stirred for 4 h then stirred at room temperature overnight. Upon reaction completion, the mixture was diluted with DCM (500 mL) and washed with water (2 x 400 mL) and brine (2 x 200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to afford 7.52 g of Intermediate **IIW** (79% yield), which was used without further purification.

*Synthesis of 4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)aniline (**IIX**) (Scheme 9)*

[001057] To a clean, dry hydrogenation flask were added Intermediate **IIW** (1.71 g, 5.0 mmol, 1.0 eq.), 10% palladium on activated carbon (265 mg, 0.25 mmol, 0.05 eq.), and MeOH (50 mL).

The flask was then charged with hydrogen at 50 psi and shook for 3 h. The reaction mixture was then filtered on celite and concentrated under vacuum to afford 2.76 g of the product (88% yield), which was used without further purification.

Synthesis of Methyl 4-((4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)carbamoyl)-3-nitrobenzoate (IIY) (Scheme 9)

[001058] A round-bottom flask was charged with 4-(methoxycarbonyl)-2-nitrobenzoic acid (1.92 g, 8.5 mmol, 1.00 eq.), intermediate **IIX** (2.65 g, 8.5 mmol, 1.05 eq.), HATU (3.55 g, 9.35 mmol, 1.10 eq.) and DMF (30 mL). The mixture was cooled to 0 °C and stirred for 10 min. DIPEA (4.2 ml, 25.5 mmol, 3.0 eq.) was added slowly and the stirring was continued at room temperature overnight. The reaction mixture was then diluted with DCM (200 mL), and the organic layer was washed with 150 mL water (2x), and 50 mL brine (2x), briefly dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The product was purified by flash chromatography on silica gel (EtOAc/Heptane) to afford 2.37 g of intermediate **IIN** (54% yield).

Synthesis of Methyl 3-amino-4-((4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)carbamoyl)benzoate (IIZ) (Scheme 9)

[001059] To a clean, dry hydrogenation flask were added Intermediate **IIY** (2.33 g, 4.5 mmol, 1.0 eq.), 10% palladium on activated carbon (244 mg, 0.23 mmol, 0.05 eq.), and MeOH (50 mL). The flask was then charged with hydrogen at 50 psi and shook for 3 h. The reaction mixture was then filtered on celite and concentrated under vacuum to afford 1.86 g of the product (85% yield), which was used without further purification.

*Synthesis of Methyl 4-((4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)carbamoyl)-3-(4-oxo-4H-chromene-2-carboxamido)benzoate (**IIIA**) (Scheme 9)*

[001060] A round-bottom flask was charged with intermediate **IC** (1.12 g, 3.3 mmol, 1.1 eq.) and 50% THF/DCM mixture (75 mL). The mixture was stirred either at room temperature or at refluxing temperature until all the solids dissolved. To a clean, dry 40 mL vial, intermediate **IIZ** (1.46 g, 3.0 mmol, 1.00 eq.) and DCM (10 mL) were added, and the mixture was stirred at room temperature until all the solids dissolved then added to the round-bottom flask containing intermediate **IC**. The reaction mixture was stirred at room temperature overnight, then the reaction mixture was concentrated under vacuum, and the residue was purified using flash chromatography (MeOH/DCM) to afford 1.06 g of Intermediate **IIIA** (54% yield).

*Synthesis of Final Compounds (Scheme 9; **General Procedure EEE**)*

[001061] A round-bottom flask was charged with Intermediate **IIIB** (0.14 mmol, 1.00 eq.), alcohol R_2OH (0.35 mmol, 2.5 eq.), HATU (57 mg, 0.15 mmol, 1.07 eq.) and DMF (4.0 mL). The mixture was stirred for 10 min. DIPEA (75 µL, 0.45 mmol, 3.0 eq.) was added slowly and the stirring was continued at room temperature overnight. The product was separated by reverse phase HPLC (0.1% TFA in water/ACN), re-purified using reverse phase HPLC when necessary, then dissolved in 10% MeOH/DCM (50 mL) and extracted with saturated sodium bicarbonate (2 x 50 mL) and brine (1 x 50 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated under vacuum to give the product as a free base.

Example 2: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl)benzyl)(methyl)amino)ethyl)phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001062] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.028 g 4-(1H-Imidazol-1-yl) benzaldehyde, the title compound was obtained in 0.05 g (47% yield).

Example 3: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)quinoline-3-carboxamide

[001063] Using the General Procedure **DD**, 0.1 g intermediate **IE2** and 0.028 g 4-(1H-Imidazol-1-yl) benzaldehyde, the title compound was obtained in 0.06 g (64% yield).

Example 4: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001064] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.028 g 3-(1H-Imidazol-1-yl) benzaldehyde, the title compound was obtained in 0.058 g (55% yield).

Example 5: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(3-(pyridin-3-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001065] Using the General Procedure **DD**, 0.12 g intermediate **IE1** and 0.0355 g 3-(pyridin-3-yl) benzaldehyde, the title compound was obtained in 0.09 g (69% yield).

Example 6: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-methyl-1H-imidazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001066] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.0178 g 1-methyl-1H-imidazole-5-carbaldehyde, the title compound was obtained in 0.065 g (67% yield).

Example 7: Synthesis of *N*-(2-((4-(2-((4-(1H-imidazol-1-yl)-3-methoxybenzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001067] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.032 g 4-(1H-imidazol-1-yl)-3-methoxybenzaldehyde, the title compound was obtained in 0.063 g (56% yield).

Example 8: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl (4-(pyridin-3-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001068] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.029 g 4-(pyridin-3-yl) benzaldehyde, the title compound was obtained in 0.048 g (44% yield). ^{1}H NMR (400 MHz, DMSO-d^6) 2.22 (s, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.77 (t, *J* = 8.0 Hz, 2H), 3.58 (s, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 6.91 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.41-7.66 (m, 8H), 7.82-7.86 (m, 1H), 8.00-8.06 (m, 2H), 8.31 (s, 1H), 8.51 (dd, *J* = 1.6 Hz, 1H), 8.84 (dd, *J* = 1.6 Hz, 1H), 10.32 (s, 1H), 12.99 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 669.18.

Example 9: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl (4-(pyridin-4-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001069] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.029 g 4-(pyridin-4-yl)benzaldehyde, the title compound was obtained in 0.055 g (51% yield). ^{1}H NMR (400 MHz, DMSO-d^6) 2.23 (s, 3H), 2.61 (t, *J* = 12.0 Hz, 2H), 2.77 (t, *J* = 12.0 Hz, 2H), 3.59 (s, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 6.90 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.48-7.85 (m, 10H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.31 (s, 1H), 8.57 (d, *J* = 4.0 Hz, 2H), 10.27 (s, 1H), 12.98 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 669.21.

Example 10: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl (3-(4-methyl-1H-imidazol-1-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001070] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.03 g 3-(4-methyl-1H-imidazol-1-yl)benzaldehyde, the title compound was obtained in 0.067 g (62% yield).

Example 11: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-methyl-1H-indazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001071] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.026 g 1-methyl-1H-indazole-5-carbaldehyde, the title compound was obtained in 0.069 g (66% yield). ^{1}H NMR (400 MHz, DMSO-d^6) 2.21 (s, 3H), 2.61 (t, *J* = 8 Hz, 2H), 2.76 (t, *J* = 8.0 Hz, 2H), 3.62 (s, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 6.92 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.30 (dd, *J* = 1.2 Hz,

1H), 7.50-7.66 (m, 7H), 7.83-7.87 (m, 1H), 7.94 (s, 1H), 8.04 (dd, J = 1.6 Hz, 1H), 8.31 (s, 1H), 10.32 (s, 1H), 12.95 (s, 1H); m/z (ESI+), $[M + H]^+$ = 646.21.

Example 12: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-methyl-1H-benzo[*d*]imidazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001072] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.026 g 1-methyl-1H-benzo[*d*]imidazole-5-carbaldehyde, the title compound was obtained in 0.065 g (62% yield).

Example 13: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-methyl-1H-benzo[*d*]imidazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001073] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.032 g 3-(4-ethyl-1H-imidazol-1-yl)benzaldehyde, the title compound was obtained in 0.052 g (47% yield).

Example 14: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(4-(thiazol-4-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001074] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.031 g 4-(thiazol-4-yl)benzaldehyde, the title compound was obtained in 0.052 g (48% yield).

Example 15: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl (4-(thiazol-4-ylmethoxy) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001075] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.035 g 4-(thiazol-4-ylmethoxy)benzaldehyde, the title compound was obtained in 0.048 g (42% yield).

Example 16: Synthesis of *N*-(4,5-dimethoxy-2-((4-(2-(methyl(3-(thiazol-4-yl)benzyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001076] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.031 g 3-(thiazol-4-yl)benzaldehyde, the title compound was obtained in 0.06 g (55% yield).

Example 17: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(4-(thiazol-2-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001077] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.031 g 4-(thiazol-2-yl)benzaldehyde, the title compound was obtained in 0.060 g (55% yield).

Example 18: Synthesis of *N*-(2-((4-(2-((4-Ethynylbenzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001078] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.021 g 4-ethynylbenzaldehyde, the title compound was obtained in 0.074 g (75% yield).

Example 19: Synthesis of *N*-(2-((4-(2-((3-Ethynylbenzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001079] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.021 g 3-ethynylbenzaldehyde, the title compound was obtained in 0.072 g (73% yield).

Example 20: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(4-(thiazol-4-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001080] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.031 g 3-(thiazol-4-yl)benzaldehyde, the title compound was obtained in 0.062 g (57% yield).

Example 21: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(2-methyl-5-(4-methyl-1H-imidazol-1-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001081] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.032 g 2-methyl-5-(4-methyl-1H-imidazol-1-yl)benzaldehyde, the title compound was obtained in 0.059 g (53% yield).

Example 22: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(4-(thiazol-5-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001082] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.031 g 4-(thiazol-5-yl)benzaldehyde, the title compound was obtained in 0.064 g (59% yield).

Example 23: Synthesis of *N*-(2-((4-(2-(((2-(1H-Imidazol-1-yl) pyrimidin-5-yl) methyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001083] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.028 g 2-(1H-imidazol-1-yl)pyrimidine-5-carbaldehyde, the title compound was obtained in 0.07 g (66% yield).

Example 24: Synthesis of *N*-(2-((4-(2-((3-(((2S,4R)-2-((1H-imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl) methoxy) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001084] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.07 g 3-(((2S,4R)-2-((1H-imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)benzaldehyde, the title compound was obtained in 0.052 g (35% yield).

Example 25: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-5-hydroxy-4-oxo-4H-pyran-2-carboxamide

[001085] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.029 g 4-(1H-imidazol-1-yl)benzaldehyde, the title compound was obtained in 0.055 g (52% yield).

Example 26: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-5-hydroxy-4-oxo-4H-pyran-2-carboxamide

[001086] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.029 g 3-(1H-imidazol-1-yl)benzaldehyde, the title compound was obtained in 0.06 g (56% yield).

Example 27: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-methyl-1H-indazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl) phenyl)-8-hydroxyquinoline-3-carboxamide

[001087] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.026 g 1-methyl-1H-indazole-5-carbaldehyde, the title compound was obtained in 0.068 g (65% yield).

Example 28: Synthesis of *N*-(2-((4-(2-((4-(1H-1,2,4-Triazol-1-yl) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001088] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.028 g 4-(1H-1,2,4-triazol-1-yl)benzaldehyde, the title compound was obtained in 0.066 g (62% yield).

Example 29: Synthesis of *N*-(2-((4-(2-((Benzo[*d*][1,3]dioxol-5-ylmethyl)(methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001089] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.024 g benzo[d][1,3]dioxole-5-carbaldehyde, the title compound was obtained in 0.072 g (70% yield).

Example 30: Synthesis of *N*-(2-((4-(2-((4-(2H-Tetrazol-5-yl) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001090] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.028 g 4-(2H-tetrazol-5-yl)benzaldehyde, the title compound was obtained in 0.055 g (52% yield).

Example 31: Synthesis of *N*-(2-((4-(2-((4-Hydroxy-3-methoxybenzyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001091] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.024 g 4-hydroxy-3-methoxybenzaldehyde, the title compound was obtained in 0.056 g (54% yield).

Example 32: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((3-methoxy-4-(2-morpholinoethoxy) benzyl) (methyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001092] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.043 g 3-methoxy-4-(2-morpholinoethoxy)benzaldehyde, the title compound was obtained in 0.065 g (54% yield).

Example 33: Synthesis of *N*-(2-((4-(2-((4-(2-(2-Hydroxyethoxy)ethoxy)-3-methoxybenzyl) (methyl) amino) ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001093] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.039 g 4-(2-(2-hydroxyethoxy)ethoxy)-3-methoxybenzaldehyde, the title compound was obtained in 0.045 g (38% yield).

Example 34: Synthesis of *N*-(2-((4-(2-(((2,2-Difluorobenzo[*d*][1,3]dioxol-5-yl)methyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001094] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.03 g 2,2-difluorobenzo[*d*][1,3]dioxole-5-carbaldehyde, the title compound was obtained in 0.072 g (66% yield).

Example 35: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-phenyl-1H-pyrazol-4-yl)methyl)amino) ethyl) phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001095] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.028 g 1-phenyl-1H-pyrazole-4-carbaldehyde, the title compound was obtained in 0.064 g (60% yield).

Example 36: Synthesis of *N*-(2-((4-(2-(((2,3-Dihydrobenzofuran-5-yl)methyl)(methyl)amino)ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001096] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.024 g 2,3-dihydrobenzofuran-5-carbaldehyde, the title compound was obtained in 0.038 g (37% yield).

Example 37: Synthesis of *N*-(2-((4-(2-(((2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)(methyl)amino) ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001097] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.026 g 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbaldehyde, the title compound was obtained in 0.072 g (68% yield).

Example 38: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(3-(3-methyl-1,2,4-oxadiazol-5-yl) benzyl) amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001098] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.03 g 3-(3-methyl-1,2,4-oxadiazol-5-yl)benzaldehyde, the title compound was obtained in 0.067 g (61% yield).

Example 39: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl(4-(3-methyl-1,2,4-oxadiazol-5-yl) benzyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001099] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.03 g 4-(3-methyl-1,2,4-oxadiazol-5-yl)benzaldehyde, the title compound was obtained in 0.06 g (55% yield).

Example 40: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((2-oxo-2,3-dihydrobenzo[*d*]oxazol-6-yl) methyl) amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001100] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.026 g 2-oxo-2,3-dihydrobenzo[*d*]oxazole-6-carbaldehyde, the title compound was obtained in 0.059 g (56% yield).

Example 41: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-methyl-1H-indazol-4-yl) methyl) amino) ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001101] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.026 g 1-methyl-1H-indazole-4-carbaldehyde, the title compound was obtained in 0.072 g (69% yield).

Example 42: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((1-methyl-1H-indol-5-yl) methyl) amino) ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001102] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.025 g 1-methyl-1H-indole-5-carbaldehyde, the title compound was obtained in 0.059 g (57% yield).

Example 43: Synthesis of *N*-(2-((4-(2-(((1-Ethyl-1H-indazol-5-yl) methyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001103] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.028 g 1-ethyl-1H-indazole-5-carbaldehyde, the title compound was obtained in 0.045 g (42% yield).

Example 44: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(methyl((9-methyl-9H-carbazol-3-yl) methyl) amino) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001104] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.034 g 9-methyl-9H-carbazole-3-carbaldehyde, the title compound was obtained in 0.069 g (61% yield).

Example 45: Synthesis of *N*-(2-((4-(2-(((9-Ethyl-9H-carbazol-3-yl) methyl) (methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001105] Using the General Procedure **DD**, 0.1 g intermediate **IE1** and 0.036 g 9-ethyl-9H-carbazole-3-carbaldehyde, the title compound was obtained in 0.065 g (57% yield).

Example 46: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(*N*-methyl-3-(pyridin-3-yl) propanamido) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001106] Using the General Procedure **EE**, 0.1 g intermediate **IE1** and 0.024 g 3-(pyridin-3-yl)propanoic acid, the title compound was obtained in 0.082 g (80% yield).

Example 47: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(*N*-methyl-3-(pyridin-4-yl) propanamido) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001107] Using the General Procedure **EE**, 0.1 g intermediate **IE1** and 0.024 g 3-(pyridin-4-yl)propanoic acid, the title compound was obtained in 0.083 g (81% yield).

Example 48: Synthesis of *N*-(2-((4-(2-(3-(1H-imidazol-1-yl)-*N*-methylbenzamido) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001108] Using the General Procedure **EE**, 0.1 g intermediate **IE1** and 0.03 g 3-(1H-imidazol-1-yl)benzoic acid, the title compound was obtained in 0.088 g (81% yield).

Example 49: Synthesis of *N*-(2-((4-(2-(4-(1H-Imidazol-1-yl)-*N*-methylbenzamido) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001109] Using the General Procedure **EE**, 0.1 g intermediate **IE1** and 0.03 g 4-(1H-imidazol-1-yl)benzoic acid, the title compound was obtained in 0.078 g (72% yield).

Example 50: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(*N*-methyl-3-(pyridin-3-yl) benzamido) ethyl) phenyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001110] Using the General Procedure **EE**, 0.1 g intermediate **IE1** and 0.032 g 3-(pyridin-3-yl)benzoic acid, the title compound was obtained in 0.079 g (72% yield).

Example 51: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001111] Following the General Procedure **DD** with **IK1** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.02 g), 0.035 g of the title compound was obtained (44% yield).

Example 52: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)quinoline-3-carboxamide

[001112] Following the General Procedure **DD** with **IK2** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.021 g), 0.041 g of the title compound was obtained (51% yield).

Example 53: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001113] Following the General Procedure **DD** with **IK3** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.021 g), 0.045 g of the title compound was obtained (57% yield).

Example 54: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl) benzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001114] Following the General Procedure **DD** with **IK1** (0.075 g) and 4-(1H-imidazol-1-yl) benzaldehyde (0.02 g), 0.039 g of the title compound was obtained (49% yield).

Example 55: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (propyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001115] Following the General Procedure **DD** with **IK4** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.02 g), 0.028 g of the title compound was obtained (35% yield)

Example 56: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl)-3-methoxybenzyl) (propyl) amino) ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001116] Following the General Procedure **DD** with **IK4** (0.075g) and 4-(1H-imidazol-1-yl)-3-methoxybenzaldehyde (0.023 g), 0.035 g of the title compound was obtained (42% yield).

Example 57: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (cyclopropylmethyl) amino) ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001117] Following the General Procedure **DD** with **IK7** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.019 g), 0.032 g of the title compound was obtained (40% yield).

Example 58: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (phenethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001118] Following the General Procedure **DD** with **IK8** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.018 g), 0.039 g of the title compound was obtained (49% yield).

Example 59: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl) benzyl) (phenethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001119] Following the General Procedure **DD** with **IK8** (0.075 g) and 4-(1H-imidazol-1-yl) benzaldehyde (0.018 g), 0.035 g of the title compound was obtained (44% yield).

Example 60: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl)benzyl)(2-(1H-indol-3-yl) ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001120] Following the General Procedure **DD** with **IK11** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.017 g), 0.04 g of the title compound was obtained (51% yield).

Example 61: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (phenethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)quinoline-3-carboxamide

[001121] Following the General Procedure **DD** with **IK9** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.018 g), 0.035 g of the title compound was obtained (44% yield).

Example 62: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl) benzyl) (cyclohexyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001122] Following the General Procedure **DD** with **IK10** (0.075 g) and 4-(1H-imidazol-1-yl) benzaldehyde (0.018 g), 0.03 g of the title compound was obtained (38% yield).

Example 63: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (cyclohexyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001123] Following the General Procedure **DD** with **IK10** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.018 g), 0.032 g of the title compound was obtained (40% yield).

Example 64: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (isopropyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001124] Following the General Procedure **DD** with **IK6** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.02 g), 0.025 g of the title compound was obtained (31% yield).

Example 65: Synthesis of *N*-(2-((4-(2-((3-(1H-Imidazol-1-yl) benzyl) (isobutyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001125] Following the General Procedure **DD** with **IK5** (0.075 g) and 3-(1H-imidazol-1-yl) benzaldehyde (0.019 g), 0.039 g of the title compound was obtained (52% yield).

Example 66: Synthesis of *N*-(2-((4-(2-(Ethyl((1-methyl-1H-indazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001126] Following the General Procedure **DD** with **IK1** (0.05 g) and 1-methyl-1H-indazole-5-carbaldehyde (0.013 g), 0.02 g of the title compound was obtained (38% yield).

Example 67: Synthesis of *N*-(2-((4-(2-(Ethyl(3-(4-methyl-1H-imidazol-1-yl) benzyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001127] Following the General Procedure **DD** with **IK1** (0.05 g) and 3-(4-methyl-1H-imidazol-1-yl)benzaldehyde (0.015 g), 0.019 g of the title compound was obtained (34% yield).

Example 68: Synthesis of *N*-(2-((4-(2-(Ethyl((1-methyl-1H-benzo[*d*]imidazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001128] Following the General Procedure **DD** with **IK1** (0.05 g) and 1-methyl-1H-benzo[*d*]imidazole-5-carbaldehyde (0.013 g), 0.022 g of the title compound was obtained (42% yield).

Example 69: Synthesis of *N*-(2-((4-(2-((5-(1H-Imidazol-1-yl)-2-methylbenzyl) (ethyl) amino) ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001129] Following the General Procedure **DD** with **IK1** (0.05 g) and 5-(1H-imidazol-1-yl)-2-methylbenzaldehyde (0.015 g), 0.026 g of the title compound was obtained (47% yield).

Example 70: Synthesis of *N*-(2-((4-(2-((3-(((2S,4R)-2-((1H-Imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)benzyl)(ethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001130] Following the General Procedure **DD** with **IK1** (0.05 g) and 3-(((2S,4R)-2-((1H-imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)benzaldehyde (0.034 g), 0.028 g of the title compound was obtained (37% yield).

Example 71: Synthesis of *N*-(2-((4-(2-((3-(2-(1H-Imidazol-1-yl) ethoxy) benzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001131] Following the General Procedure **DD** with **IK1** (0.05 g) and 3-(2-(1H-imidazol-1-yl)ethoxy)benzaldehyde (0.017 g), 0.027 g of the title compound was obtained (47% yield).

Example 72: Synthesis of *N*-(2-((4-(2-((4-(2-(1H-Imidazol-1-yl) ethoxy) benzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001132] Following the General Procedure **DD** with **IK1** (0.05 g) and 4-(2-(1H-imidazol-1-yl)ethoxy)benzaldehyde (0.017 g), 0.029 g of the title compound was obtained (50% yield).

Example 73: Synthesis of *N*-(2-((4-(2-((3-(2-(1H-Imidazol-1-yl)ethoxy)-4-methoxybenzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001133] Following the General Procedure **DD** with **IK1** (0.05 g) and 3-(2-(1H-imidazol-1-yl)ethoxy)-4-methoxybenzaldehyde (0.019 g), 0.02 g of the title compound was obtained (33% yield).

Example 74: Synthesis of *N*-(2-((4-(2-(Ethyl(3-hydroxy-4-methoxybenzyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001134] Following the General Procedure **DD** with **IK1** (0.05 g) and 3-hydroxy-4-methoxybenzaldehyde (0.012 g), 0.027 g of the title compound was obtained (52% yield).

Example 75: Synthesis of *N*-(2-((4-(2-((4-(2-(1H-Imidazol-1-yl)ethoxy)-3-methoxybenzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001135] Following the General Procedure **DD** with **IK1** (0.05 g) and 4-(2-(1H-imidazol-1-yl)ethoxy)-3-methoxybenzaldehyde (0.019 g), 0.015 g of the title compound was obtained (32% yield).

Example 76: Synthesis of *N*-(2-((4-(2-(Ethyl(4-hydroxy-3-methoxybenzyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001136] Following the General Procedure **DD** with **IK1** (0.05 g) and 4-hydroxy-3-methoxybenzaldehyde (0.012 g), 0.023 g of the title compound was obtained (38% yield).

Example 77: Synthesis of *N*-(2-((4-(2-((4-(1H-1,2,4-Triazol-1-yl) benzyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001137] Following the General Procedure **DD** with **IK1** (0.05 g) and 4-(1H-1,2,4-triazol-1-yl)benzaldehyde (0.014 g), 0.026 g of the title compound was obtained (48% yield).

Example 78: Synthesis of *N*-(2-((4-(2-((4-((1H-1,2,4-Triazol-1-yl)methyl)-3-methoxybenzyl) (ethyl) amino) ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001138] Following the General Procedure **DD** with **IK1** (0.05 g) and 3-((1H-1,2,4-triazol-1-yl)methyl)-4-methoxybenzaldehyde (0.017 g), 0.028 g of the title compound was obtained (49% yield).

Example 79: Synthesis of *N*-(2-((4-(2-(Ethyl(3-(furan-2-yl)benzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001139] Following the General Procedure **DD** with **IK1** (0.05 g) and 3-(furan-2-yl)benzaldehyde (0.014 g), 0.031 g of the title compound was obtained (58% yield).

Example 80: Synthesis of *N*-(2-((4-(2-(Ethyl(4-(furan-2-yl)benzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001140] Following the General Procedure **DD** with **IK1** (0.05 g) and 4-(furan-2-yl)benzaldehyde (0.014 g), 0.035 g of the title compound was obtained (65% yield).

Example 81: Synthesis of *N*-(2-((4-(2-(Ethyl((1-(pyridin-3-ylmethyl)-1H-pyrrol-2-yl) methyl) amino) ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001141] Following the General Procedure **DD** with **IK1** (0.05 g) and 1-(pyridin-3-ylmethyl)-1H-pyrrole-2-carbaldehyde (0.015 g), 0.023 g of the title compound was obtained (42% yield).

Example 82: Synthesis of *N*-(2-((4-(2-(Ethyl((8-methylquinolin-5-yl) methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001142] Following the General Procedure **DD** with **IK1** (0.05 g) and 8-methylquinoline-5-carbaldehyde (0.0137 g), 0.033 g of the title compound was obtained (61% yield).

Example 83: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazol-5-yl) methyl) (ethyl) amino) ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001143] Following the General Procedure **DD** with **IK1** (0.05 g) and 1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[*d*]imidazole-5-carbaldehyde (0.015 g), 0.025 g of the title compound was obtained (45% yield).

Example 84: Synthesis of *N*-(2-((4-(2-(((2,3-Dihydrobenzofuran-5-yl)methyl) (ethyl) amino) ethyl) phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001144] Following the General Procedure **DD** with **IK1** (0.05 g) and 2,3-dihydrobenzofuran-5-carbaldehyde (0.012 g), 0.029 g of the title compound was obtained (56% yield).

Example 85: Synthesis of *N*-(2-((4-(2-(Ethyl((1-methyl-1H-indazol-6-yl) methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001145] Following the General Procedure **DD** with **IK1** (0.05 g) and 1-methyl-1H-indazole-6-carbaldehyde (0.013 g), 0.032 g of the title compound was obtained (61% yield).

Example 86: Synthesis of *N*-(2-((4-(2-((Benzo[*d*]isoxazol-5-ylmethyl) (ethyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001146] Following the General Procedure **DD** with **IK1** (0.05 g) and benzo[*d*]isoxazole-5-carbaldehyde (0.012 g), 0.02 g of the title compound was obtained (38% yield).

Example 87: Synthesis of *N*-(2-((4-(2-(Ethyl((1-methyl-1H-indazol-7-yl) methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001147] Following the General Procedure **DD** with **IK1** (0.05 g) and 1-methyl-1H-indazole-7-carbaldehyde (0.013 g), 0.031 g of the title compound was obtained (59% yield).

Example 88: Synthesis of *N*-(2-((4-(2-(((1H-Indazol-5-yl)methyl)(ethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001148] Following the General Procedure **DD** with **IK1** (0.05 g) and 1H-indazole-5-carbaldehyde (0.012 g), 0.028 g of the title compound was obtained (54% yield).

Example 89: Synthesis of *N*-(2-((4-(2-(((1H-Indazol-6-yl)methyl)(ethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001149] Following the General Procedure **DD** with **IK1** (0.05 g) and 1H-indazole-6-carbaldehyde (0.012 g), 0.022 g of the title compound was obtained (43% yield).

Example 90: Synthesis of *N*-(2-((4-(2-(Ethyl((1-ethyl-1H-indazol-5-yl) methyl) amino) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001150] Following the General Procedure **DD** with **IK1** (0.05 g) and 1-ethyl-1H-indazole-5-carbaldehyde (0.014 g), 0.026 g of the title compound was obtained (48% yield).

Example 91: Synthesis of *N*-(2-((4-(2-(*N*-Ethyl-2-(pyridin-2-yl)acetamido)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001151] Following the General Procedure **EE** with **IK1** (0.08 g) and 2-(pyridin-2-yl)acetic acid (0.018 g), 0.062 g of the title compound was obtained (76% yield).

Example 92: Synthesis of *N*-(2-((4-(2-(*N*-Ethyl-2-(pyridin-3-yl)acetamido)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001152] Following the General Procedure **EE** with **IK1** (0.08 g) and 2-(pyridin-3-yl)acetic acid (0.018 g), 0.07 g of the title compound was obtained (85% yield).

Example 93: Synthesis of *N*-(2-((4-(2-(*N*-Ethyl-2-(pyridin-4-yl)acetamido)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001153] Following the General Procedure **EE** with **IK1** (0.08 g) and 2-(pyridin-4-yl)acetic acid (0.018 g), 0.065 g of the title compound was obtained (79% yield).

Example 94: Synthesis of *N*-(4-(4,5-Dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl)-N-ethyl-6-(trifluoromethyl)nicotinamide

[001154] Following the General Procedure **EE** with **IK1** (0.08 g) and 6-(trifluoromethyl)nicotinic acid (0.024 g), 0.06 g of the title compound was obtained (68% yield).

Example 95: Synthesis of *N*-(4-(4,5-Dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido) benzamido) phenethyl)-N-ethylpicolinamide

[001155] Following the General Procedure **EE** with **IK1** (0.08 g) and picolinic acid (0.016 g), 0.065 g of the title compound was obtained (81% yield).

Example 96: Synthesis of *N*-(2-((4-(2-(*N*-Ethyl-4-(1H-imidazol-1-yl) benzamido) ethyl) phenyl) carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001156] Following the General Procedure **EE** with **IK1** (0.08 g) and 4-(1H-imidazol-1-yl)benzoic acid (0.024 g), 0.07 g of the title compound was obtained (79% yield).

Example 97: Synthesis of *N*-(2-((4-(((2-(1H-Imidazol-1-yl)benzyl)((1-methyl-1H-indazol-5-yl)methyl)amino)methyl)benzyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001157] Following the General Procedure **DD** with **IP** (0.1 g) and 2-(1H-imidazol-1-yl)benzaldehyde (0.027 g), 0.085 g of the title compound was obtained (68% yield).

Example 98: Synthesis of *N*-(2-((4-(((3-(1H-Imidazol-1-yl)benzyl)((1-methyl-1H-indazol-5-yl)methyl)amino)methyl)benzyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001158] Following the General Procedure **DD** with **IP** (0.1 g) and 3-(1H-imidazol-1-yl)benzaldehyde (0.027 g), 0.09 g of the title compound was obtained (72% yield).

Example 99: Synthesis of *N*-(4,5-Dimethoxy-2-((4-((((1-methyl-1H-indazol-5-yl) methyl) (pyridin-3-yl methyl) amino) methyl) benzyl) carbamoyl) phenyl)-4-oxo-4H-chromene-2-carboxamide

[001159] Following the General Procedure **DD** with **IP** (0.1 g) and nicotinaldehyde (0.017 g), 0.08 g of the title compound was obtained (70% yield).

Example 100: Synthesis of *N*-(4,5-Dimethoxy-2-((4-((((5-methoxypyridin-3-yl)methyl)((1-methyl-1H-indazol-5-yl)methyl)amino)methyl)benzyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001160] Following the General Procedure **DD** with **IP** (0.1 g) and 5-methoxynicotinaldehyde (0.022 g), 0.078 g of the title compound was obtained (65% yield).

Example 101: Synthesis of *N*-(4,5-Dimethoxy-2-((4-((((1-methyl-1H-indazol-5-yl)methyl)(3-(thiazol-5-yl)benzyl)amino)methyl)benzyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001161] Following the General Procedure **DD** with **IP** (0.1 g) and 3-(thiazol-5-yl)benzaldehyde (0.03 g), 0.095 g of the title compound was obtained (75% yield).

Example 102: Synthesis of *N*-(2-((4-(((4-(1H-Imidazol-1-yl)benzyl)((1-methyl-1H-indazol-5-yl)methyl)amino)methyl)benzyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001162] Following the General Procedure **DD** with **IP** (0.1 g) and 4-(1H-imidazol-1-yl)benzaldehyde (0.027 g), 0.083 g of the title compound was obtained (65% yield).

Example 103: Synthesis of *N*-(4,5-Dimethoxy-2-((4-((((1-methyl-1H-indazol-5-yl)methyl)(4-(thiazol-5-yl)benzyl)amino)methyl)benzyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001163] Following the General Procedure **DD** with **IP** (0.1 g) and 4-(thiazol-5-yl)benzaldehyde (0.03 g), 0.08 g of the title compound was obtained (63% yield).

Example 104: Synthesis of *N*-(2-((4-(2-((4-(1H-Imidazol-1-yl) benzyl) (methyl)amino) ethyl) phenyl) carbamoyl)-4-ethoxy-5-methoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001164] Following the General Procedure **DD** with **IT** (0.1 g) and 4-(1H-imidazol-1-yl)benzaldehyde (0.027 g), 0.07 g of the title compound was obtained (66% yield).

Example 105: Synthesis of *N*-(4-Ethoxy-5-methoxy-2-((4-(2-(methyl(3-(4-methyl-1H-imidazol-1-yl) benzyl) amino) ethyl) phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001165] Following the General Procedure **DD** with **IT** (0.1 g) and 3-(4-methyl-1H-imidazol-1-yl)benzaldehyde (0.029 g), 0.054 g of the title compound was obtained (50% yield).

Example 106: Synthesis of *N*-(4-Ethoxy-5-methoxy-2-((4-(2-(methyl((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide

[001166] Following the General Procedure **DD** with **IT** (0.1 g) and 1-methyl-1H-indazole-5-carbaldehyde (0.025 g), 0.065 g of the title compound was obtained (62% yield).

Example 107: Synthesis of *N*-(2-((4-(2-(3,4-Dihydro-2,7-naphthyridin-2(1H)-yl)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001167] Following the General Procedure **BB**, 0.073 g of intermediate **IW1** was used to obtain 0.043 g of the title compound (42% yield).

Example 108: Synthesis of *N*-(2-((4-(2-(3,4-Dihydro-2,6-naphthyridin-2(1H)-yl)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4H-chromene-2-carboxamide

[001168] Following the General Procedure **BB**, 0.073 g of intermediate **IW2** was used to obtain 0.03 g of the title compound (27% yield).

Example 109: Synthesis of *N*-(2-((4-(2-Aminoethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide trifluoroacetate (IIK1)

[001169] 2.05 g of compound **IIJ1** was used to synthesize 1.9 g of the title compound (90% yield) according to the General Procedure **TT**.

Example 110: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(*N*-((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide (IIL1)

[001170] 180 mg of compound **IIK1** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 120 mg of the title compound (63% yield), which was obtained as a free base after purification by flash chromatography, according to the General Procedure **UU**.

Example 111: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(*N*-((3-(1*H*-imidazol-1-yl)phenyl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide (IIL11)

[001171] 180 mg of compound **IIK1** and 78 mg of 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 123 mg of the title compound (64% yield), which was obtained as a free base after purification by flash chromatography, according to the General Procedure **UU**.

Example 112: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(*N*-((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-quinoxaline-2-carboxamide (IIL22)

[001172] 176 mg of compound **IIK9** and 72 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 121 mg of the title compound (65% yield), which was obtained as a free base after purification by flash chromatography, according to the General Procedure **UU**.

Example 113: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001173] 180 mg of compound **IIK1** and 48 mg of nicotinaldehyde were used to synthesize 85 mg of the title compound (49% yield), which was obtained as a free base after purification by flash chromatography, according to the General Procedure **UU**.

Example 114: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001174] 63 mg intermediate **IIL1** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 32 mg of the title compound (41% yield) according to the General Procedure **VV**.

Example 115: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-imidazol-5-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001175] 63 mg intermediate **IIL1** and 22 mg 1-methyl-1*H*-imidazole-5-carbaldehyde were used to synthesize 30 mg of the title compound (41% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d$_6$), 2.65 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 7.0 Hz, 2H), 3.43 (s, 3H), 3.61 (s, 2H), 3.72 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 3.99 (s, 3H), 6.86 (s, 1H), 6.94 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 8.6, 1.5 Hz, 1H), 7.50-7.61 (m, 8H), 7.86 (m, 1H), 7.98 (d, J = 0.8 Hz, 1H), 8.07 (dd, J = 8.0, 1.6 Hz, 1H), 8.33 (s, 1H), 10.33 (s, 1H), 12.98 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 726.31.

Example 116: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001176] 63 mg intermediate **IIL1** and 22 mg nicotinaldehyde were used to synthesize 37 mg of the title compound (51% yield) according to the General Procedure **VV**.

Example 117: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((3-(4-methyl-1*H*-imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001177] 63 mg intermediate **IIL1** and 37 mg 3-(4-methyl-1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 29 mg of the title compound (36% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d$_6$) 2.21 (s, 3H), 2.67 (t, J = 8 Hz, 2H), 2.82 (t, J = 12 Hz, 2H), 3.71 (s, 2H), 3.76 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 6.82 (s, 1H), 6.85 (s, 1H), 7.15-7.19 (m, 3H), 7.32-7.73 (m, 13H), 7.95 (s, 1H), 8.03 (dd, J = 1.6 Hz, 1H), 8.33 (s, 1H), 10.36 (s, 1H), 12.96 (s, 1H); m/z (ESI+), $[M + H]^+$ = 802.21

Example 118: Synthesis of *N*-(2-((4-(2-((4-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001178] 63 mg intermediate **IIL1** and 35 mg 4-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 31 mg of the title compound (39% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d$_6$) 2.67 (t, J = 6.4 Hz, 2H), 2.84 (t, J = 6.4 Hz, 2H), 3.69 (s, 2H), 3.74 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 6.93 (s, 1H), 7.06 (s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.47-7.59 (m, 7H), 7.63 (d, J = 8.0 Hz, 2H), 7.67 (s, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.96 (s, 1H), 8.04 (d, J = 7.6 Hz, 1H), 8.19 (s, 1H), 8.33 (s, 1H), 10.37 (s, 1H), 12.97 (s, 1H); m/z (ESI+), $[M + H]^+$ = 788.13

Example 119: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(pyridin-4-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001179] 63 mg intermediate **IIL1** and 22 mg isonicotinaldehyde were used to synthesize 33 mg of the title compound (46% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d$_6$) 2.62 (t, J = 16 Hz, 2H), 2.79 (t, J = 12 Hz, 2H), 3.64 (s, 2H), 3.72 (s, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 3.95 (s, 3H), 6.91 (s, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H),

7.33 (dd, *J* = 1.6 Hz, 1H), 7.46-7.57 (m, 5H), 7.61 (d, *J* = 8 Hz, 2H), 7.72-.7.77 (m, 1H), 7.94 (s, 1H), 8.02 (dd, *J* = 1.6 Hz, 1H), 8.32 (s, 1H), 8.44 (d, *J* = 4 Hz, 2H), 10.33 (s, 1H), 13.00 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 31.51, 34.73, 54.19, 55.05, 55.51, 57.00, 108.83, 110.30, 111.46, 112.87, 117.72, 119.51, 120.95, 122.85, 122.90, 123.03, 124.49, 125.55, 126.58, 128.38, 130.35, 131.47, 132.46, 134.48, 135.66, 135.95, 138.51, 144.05, 148.88, 151.02, 154.21, 154.64, 156.06, 166.27, 176.68; *m/z* (ESI+), $[M + H]^+$ = 713.21.

Example 120: Synthesis of *N*-(2-((4-(2-(((5-Fluoropyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001180] 63 mg intermediate **IIL1** and 25 mg 5-fluoronicotinaldehyde were used to synthesize 28 mg of the title compound (38% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.64 (t, *J* = 16.0 Hz, 2H), 2.80 (t, *J* = 12.0 Hz, 2H), 3.70 (s, 2H), 3.73 (s, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.91 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.30 (dd, *J* = 1.6 Hz, 1H), 7.48-7.56 (m, 6H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.75-.7.79 (m, 1H), 7.94 (s, 1H), 8.03 (dd, *J* = 1.6 Hz, 1H), 8.32 (s, 1H), 8.38-8.39 (m, 2H), 10.35 (s, 1H), 12.96 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d^6) 31.41, 34.73, 53.91, 55.09, 55.52, 56.93, 108.84, 110.30, 117.72, 119.52, 120.77, 122.90, 123.05, 126.57, 128.34, 130.30, 131.47, 132.35, 134.52, 135.43, 135.72, 135.88, 137.07, 138.50, 145.26, 154.24, 154.68, 166.26, 176.70; *m/z* (ESI+), $[M + H]^+$ = 741.22.

Example 121: Synthesis of *N*-(2-((4-(2-(((3-Fluoropyridin-4-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001181] 63 mg intermediate **IIL1** and 25 mg 3-fluoroisonicotinaldehyde were used to synthesize 35 mg of the title compound (47% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.68 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 3.75 (s, 2H), 3.78 (s, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 6.94 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.35 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.39 (t, *J* = 5.6 Hz, 1H), 7.49-7.59 (m, 5H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.75-7.80 (m, 1H), 7.96 (d, *J* = 0.8 Hz, 1H), 8.05 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.34 (s, 1H), 8.35 (s, 1H), 8.46 (d, *J* = 1.6 Hz, 1H), 10.37 (s, 1H), 12.99 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 741.32.

Example 122: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001182] 63 mg intermediate **IIL1** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 37 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 123: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((3-methoxypyridin-4-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001183] 63 mg intermediate **IIL1** and 28 mg 3-methoxyisonicotinaldehyde were used to synthesize 40 mg of the title compound (53% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.65 (t, J = 12.0 Hz, 2H), 2.80 (t, J = 12 Hz, 2H), 3.63 (s, 2H), 3.76 (s, 3H), 3.85 (s, 6H), 3.89 (s, 3H), 3.95 (s, 3H), 6.92 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.27-7.28 (m, 2H), 7.33-7.64 (m, 9H), 7.74 (t, J = 12 Hz, 1H), 7.93 (s, 1H), 8.03 (d, J = 4 Hz, 1H), 8.11 (d, J = 4 Hz, 1H), 8.24 (s, 1H), 8.32 (s, 1H), 10.32 (s, 1H), 12.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 31.74, 34.72, 49.48, 54.35, 54.73, 55.07, 55.52, 57.26, 103.88, 108.78, 110.30, 111.49, 112.93, 117.73, 119.39, 120.94, 122.35, 122.88, 123.04, 124.49, 125.55, 126.55, 128.44, 130.53, 131.44, 132.44, 134.50, 135.46, 135.67, 136.03, 138.49, 141.66, 144.07, 151.02, 152.88, 154.23, 154.66, 156.08, 166.28, 176.69; *m/z* (ESI+), $[M + H]^+$ = 753.15.

Example 124: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(thiazol-5-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001184] 63 mg intermediate **IIL1** and 23 mg thiazole-5-carbaldehyde were used to synthesize 29 mg of the title compound (40% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.66 (t, J = 12.0 Hz, 2H), 2.80 (t, J = 12.0 Hz, 2H), 3.77 (s, 2H), 3.84 (s, 3H), 3.86 (s, 2H), 3.88 (s, 3H), 3.96 (s, 3H), 6.91 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.35 (dd, J = 1.2 Hz, 1H), 7.45-7.63 (m, 8H), 7.77-7.81 (m, 1H), 7.75-.7.79 (m, 1H), 7.93 (s, 1H), 8.03 (dd, J = 1.6 Hz, 1H), 8.31 (s, 1H), 9.05 (s, 1H), 10.33 (s, 1H), 12.97 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 31.84, 34.74, 51.71, 54.05, 55.07, 55.51, 56.90, 108.69, 110.31, 115.60, 117.73, 119.43, 120.89, 122.91, 123.04, 124.51, 125.60, 126.74, 128.37, 130.76, 131.45, 132.39, 134.55, 135.62, 136.13, 138.50, 152.95, 154.24, 154.34, 156.08, 166.25, 176.69; *m/z* (ESI+), $[M + H]^+$ = 729.22.

Example 125: Synthesis of *N*-(2-((4-(2-((4-(1*H*-1,2,4-Triazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001185] 63 mg intermediate **IIL1** and 35 mg 4-(1*H*-1,2,4-Triazol-1-yl)benzaldehyde were used to synthesize 34 mg of the title compound (43% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.64 (t, *J* = 16.0 Hz, 2H), 2.80 (t, *J* = 16.0 Hz, 2H), 3.69 (s, 2H), 3.72 (s, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 6.91 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 4.0 Hz, 1H), 7.34-7.63 (m, 9H), 7.68-7.73 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.95 (s, 1H), 8.00-8.03 (m, 1H), 8.16 (s, 1H), 9.20 (s, 1H), 10.35 (s, 1H), 12.97 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 789.23.

Example 126: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(2-morpholinoethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001186] 63 mg intermediate **IIL1** and 26 mg 2-morpholinoacetaldehyde were used to synthesize 33 mg of the title compound (44% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.29 (t, *J* = 8.0 Hz, 4H), 2.37 (t, *J* = 12.0 Hz, 2H), 2.59 (t, *J* = 12.0 Hz, 2H), 2.67-2.75 (m, 4H), 3.49 (t, *J* = 8.0 Hz, 4H), 3.72 (s, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 3.97 (s, 3H), 6.91 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 12.0 Hz, 1H), 7.49-7.64 (m, 7H), 7.80-7.84 (m, 1H), 7.93 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 8.30 (s, 1H), 10.26 (s, 1H), 12.97 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 745.19.

Example 127: Synthesis of *N*-(2-((4-(2-(((2,3-Dihydrobenzofuran-5-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001187] 63 mg intermediate **IIL1** and 30 mg 2,3-dihydrobenzofuran-5-carbaldehyde were used to synthesize 35 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 128: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001188] 63 mg intermediate **IIL1** and 32 mg 1-methyl-1*H*-indazole-6-carbaldehyde were used to synthesize 29 mg of the title compound (37% yield) according to the General Procedure **VV**.

Example 129: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001189] 63 mg intermediate **IIL1** and 35 mg 1,3-dimethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 41 mg of the title compound (52% yield) according to the General Procedure **VV**.

Example 130: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(4-(pyridin-4-yl)benzyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001190] 63 mg intermediate **IIL1** and 37 mg 4-(pyridin-4-yl)benzaldehyde were used to synthesize 38 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 131: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(4-(pyridin-3-yl)benzyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001191] 63 mg intermediate **IIL1** and 37 mg 4-(pyridin-3-yl)benzaldehyde were used to synthesize 32 mg of the title compound (40% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d^6) 2.66 (t, J = 12.0 Hz, 2H), 2.81 (t, J = 12.0 Hz, 2H), 3.69 (s, 2H), 3.73 (s, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 6.91 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.35-7.69 (m, 16H), 7.97-8.02 (m, 3H), 8.32 (s, 1H), 8.49 (dd, J = 1.6 Hz, 1H), 8.83 (s, 1H), 10.34 (s, 1H), 12.98 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 799.49.

Example 132: Synthesis of *N*-(2-((4-(2-(((5-Ethoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001192] 63 mg intermediate **IIL1** and 30 mg 5-ethoxynicotinaldehyde were used to synthesize 39 mg of the title compound (51% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d$_6$) 1.27 (t, J = 8.0 Hz, 3H), 2.67 (t, J = 12.0 Hz, 2H), 2.81 (t, J = 12.0 Hz, 2H), 3.67 (s, 2H), 3.70 (s, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 3.96 (q, 2H), 6.94 (s, 1H), 7.14-7.20 (m, 3H), 7.29 (dd, J = 4.0 Hz, 1H), 7.48-7.74 (m, 8H), 7.94 (s, 1H), 8.04-8.11 (m, 3H), 8.34 (s, 1H), 10.37 (s, 1H), 12.97 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 767.50.

Example 133: Synthesis of *N*-(2-((4-(2-(((5-Hydroxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001193] 63 mg intermediate **IIL1** and 25 mg 5-hydroxynicotinaldehyde were used to synthesize 36 mg of the title compound (49% yield) according to the General Procedure **VV**. ^{1}H NMR (400

MHz, DMSO-d_6) 2.65 (t, J = 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 3.64 (s, 2H), 3.70 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 6.94 (s, 1H), 7.13-7.17 (m, 3H), 7.33 (dd, J = 8.6, 1.5 Hz, 1H), 7.51-7.59 (m, 5H), 7.63 (d, J = 8.4 Hz, 2H), 7.82 (t, J = 7.8 Hz, 1H), 7.96 (d, J = 0.8 Hz, 1H), 8.01 (s, 2H), 8.06 (dd, J = 8.0, 1.6 Hz, 1H), 8.34 (s, 1H), 9.84 (brs, 1H), 10.36 (s, 1H), 12.97 (s, 1H); m/z (ESI+), $[M + H]^+$ = 739.32.

Example 134: Synthesis of *N*-(2-((4-(2-(((6-Aminopyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001194] 63 mg intermediate **IIL1** and 25 mg 6-aminonicotinaldehyde were used to synthesize 37 mg of the title compound (50% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6), 2.62 (t, J = 7.3 Hz, 2H), 2.79 (t, J = 7.2 Hz, 2H), 3.48 (s, 2H), 3.66 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 3.97 (s, 3H), 5.76 (s, 2H), 6.42 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.30-7.34 (m, 2H), 7.51-7.58 (m, 5H), 7.62 (d, J = 8.4 Hz, 2H), 7.79-7.85 (m, 2H), 7.95 (d, J = 0.4 Hz, 1H), 8.06 (dd, J = 7.8, 1.4 Hz, 1H), 8.34 (s, 1H), 10.36 (s, 1H), 12.98 (s, 1H); m/z (ESI+), $[M + H]^+$ = 738.22.

Example 135: Synthesis of 3-(((4-(4,5-Dimethoxy-2-(4-oxo-4*H*-chromene-2-carboxamido)benzamido)phenethyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)methyl)pyridine 1-oxide

[001195] 63 mg intermediate **IIL1** and 25 mg 3-formylpyridine 1-oxide were used to synthesize 34 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 136: Synthesis of *N*-(2-((4-(2-(((2-Aminopyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001196] 63 mg intermediate **IIL1** and 25 mg 2-aminonicotinaldehyde were used to synthesize 31 mg of the title compound (42% yield) according to the General Procedure **VV**.

Example 137: Synthesis of *N*-(2-((4-(2-(((5-Chloropyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001197] 63 mg intermediate **IIL1** and 28 mg 5-chloronicotinaldehyde were used to synthesize 38 mg of the title compound (50% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.64 (t, J = 12.0 Hz, 2H), 2.80-2.88 (m, 3H), 3.66 (s, 2H), 3.68 (s, 2H), 3.86 (s,

3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.93 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.28 (dd, *J* = 8.0 Hz, 1H), 7.48-7.59 (m, 6H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.74-7.78 (m, 1H), 7.93 (s, 1H), 8.03 (dd, *J* = 1.2 Hz, 1H), 8.29 (s, 1H), 8.32 (s, 2H), 10.35 (s, 1H), 12.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 22.92, 30.26, 31.44, 34.73, 53.84, 55.10, 55.51, 56.88, 108.73, 110.33, 111.54, 117.72, 119.42, 120.68, 122.90, 124.53, 125.61, 126.54, 128.34, 130.53, 131.43, 132.31, 133.09, 133.99, 134.51, 135.94, 138.49, 142.26, 144.09, 146.82, 151.01, 154.24, 154.68, 156.10, 176.69; *m/z* (ESI+), $[M + H]^+$ = 765.22.

Example 138: Synthesis of *N*-(2-((4-(2-(((4-Hydroxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001198] 63 mg intermediate **IIL1** and 25 mg 4-hydroxynicotinaldehyde were used to synthesize 42 mg of the title compound (57% yield) according to the General Procedure **VV**.

Example 139: Synthesis of *N*-(2-((4-(2-(((5-Isobutoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001199] 63 mg intermediate **IIL1** and 36 mg 5-isobutoxynicotinaldehyde were used to synthesize 39 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 140: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-(2-methoxyethoxy)pyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001200] 63 mg intermediate **IIL1** and 36 mg 5-(2-methoxyethoxy)nicotinaldehyde were used to synthesize 34 mg of the title compound (43% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.65 (t, *J* = 8.0 Hz, 2H), 2.80 (t, *J* = 12.0 Hz, 2H), 3.23 (s, 3H), 3.60-3.62 (m, 2H), 3.66 (s, 2H), 3.69 (s, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 4.07-4.09 (m, 2H), 6.93 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 1H), 7.28-7.31 (m, 1H), 7.47-7.75 (m, 8H), 7.93 (s, 1H), 8.02 (dd, *J* = 1.6 Hz, 1H), 8.11 (s, 2H), 8.33 (s, 1H), 10.34 (s, 1H), 12.97 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 797.23.

Example 141: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((5-(2-morpholinoethoxy)pyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001201] 63 mg intermediate **IIL1** and 47 mg 5-(2-morpholinoethoxy)nicotinaldehyde were used to synthesize 30 mg of the title compound (35% yield) according to the General Procedure **VV**.

Example 142: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((4-(2-methyl-1*H*-imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001202] 63 mg intermediate **IIL1** and 37 mg 4-(2-methyl-1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 31 mg of the title compound (39% yield) according to the General Procedure **VV**.

Example 143: Synthesis of *N*-(2-((4-(2-((3-(((*2S,4R*)-2-((1*H*-Imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001203] 63 mg intermediate **IIL1** and 80 mg 3-(((*2S,4R*)-2-((1*H*-imidazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methoxy)benzaldehyde were used to synthesize 37 mg of the title compound (35% yield) according to the General Procedure **VV**.

Example 144: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((5-methylpyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001204] 63 mg intermediate **IIL1** and 24 mg 5-methylnicotinaldehyde were used to synthesize 28 mg of the title compound (38% yield) according to the General Procedure **VV**.

Example 145: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-(2-methyl-1*H*-imidazol-1-yl)pyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001205] 63 mg intermediate **IIL1** and 38 mg 5-(2-methyl-1*H*-imidazol-1-yl)nicotinaldehyde were used to synthesize 35 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 146: Synthesis of *N*-(2-((4-(2-(((5-(2-(Dimethylamino)ethoxy)pyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001206] 63 mg intermediate **IIL1** and 39 mg 5-(2-(dimethylamino)ethoxy)nicotinaldehyde were used to synthesize 36 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 147: Synthesis of *N*-(2-((4-(2-(((5-(2-Aminoethoxy)pyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001207] 64 mg intermediate **IIL1** and 33 mg 5-(2-aminoethoxy)nicotinaldehyde were used to synthesize 31 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 148: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((3-(2-methyl-1*H*-imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001208] 63 mg intermediate **IIL1** and 37 mg 3-(2-methyl-1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 40 mg of the title compound (50% yield) according to the General Procedure **VV**.

Example 149: Synthesis of *N*-(2-((4-(2-(((5-*i*-Propylpyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001209] 63 mg intermediate **IIL1** and 30 mg 5-isopropylnicotinaldehyde were used to synthesize 37 mg of the title compound (48% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 1.15 (s, 3H), 1.17 (s, 3H), 2.64 (t, J = 16.0 Hz, 2H), 2.80-2.88 (m, 3H), 3.66 (s, 2H), 3.68 (s, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.93 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.28 (dd, J = 8.0 Hz, 1H), 7.48-7.59 (m, 6H), 7.62 (d, J = 8.0 Hz, 2H), 7.74-7.78 (m, 1H), 7.93 (s, 1H), 8.03 (dd, J = 1.2 Hz, 1H), 8.29 (s, 1H), 8.32 (s, 2H), 10.35 (s, 1H), 12.94 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 22.92, 30.26, 31.44, 34.73, 53.84, 55.10, 55.51, 56.88, 108.73, 110.33, 111.54, 117.72, 119.42, 120.68, 122.90, 124.53, 125.61, 126.54, 128.34, 130.53, 131.43, 132.31, 133.09, 133.99, 134.51, 135.94, 138.49, 142.26, 144.09, 146.82, 151.01, 154.24, 154.68, 156.10, 176.69; *m/z* (ESI+), $[M + H]^+$ = 765.22.

Example 150: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-Methyl-1*H*-indazol-5-yl)methyl)((5-phenylpyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001210] 63 mg intermediate **IIL1** and 37 mg 5-phenylnicotinaldehyde were used to synthesize 34 mg of the title compound (43% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.74 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 6.6 Hz, 2H), 3.74 (s, 2H), 3.78 (s, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 6.93 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.32 (m, 2H), 7.43-7.51 (m, 5H), 7.54 (s, 1H), 7.57 (m, 1H), 7.61-7.67 (m, 5H), 7.90 (s, 1H), 7.94 (s, 1H), 8.02 (d, J = 7.2 Hz, 1H), 8.35 (s, 1H), 8.52 (s, 1H), 8.70 (s, 1H), 10.38 (s, 1H), 12.96 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 799.23.

Example 151: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-6-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001211] 63 mg intermediate **IIL2** and 22 mg nicotinaldehyde were used to synthesize 38 mg of the title compound (53% yield) according to the General Procedure **VV**.

Example 152: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001212] 63 mg intermediate **IIL2** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 39 mg of the title compound (50% yield) according to the General Procedure **VV**.

Example 153: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-6-yl)methyl)(pyridin-4-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001213] 63 mg intermediate **IIL2** and 22 mg isonicotinaldehyde were used to synthesize 39 mg of the title compound (51% yield) according to the General Procedure **VV**.

Example 154: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-imidazol-5-yl)methyl)((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001214] 63 mg intermediate **IIL2** and 22 mg 1-methyl-1*H*-imidazole-5-carbaldehyde were used to synthesize 36 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 155: Synthesis of *N*-(2-((4-(2-((4-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001215] 63 mg intermediate **IIL2** and 35 mg 4-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 32 mg of the title compound (41% yield) according to the General Procedure **VV**.

Example 156: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-6-yl)methyl)(4-(pyridin-4-yl)benzyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001216] 63 mg intermediate **IIL2** and 37 mg 4-(pyridin-4-yl)benzaldehyde were used to synthesize 31 mg of the title compound (39% yield) according to the General Procedure **VV**.

Example 157: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-6-yl)methyl)(thiazol-5-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001217] 63 mg intermediate **IIL2** and 23 mg thiazole-5-carbaldehyde were used to synthesize 32 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 158: Synthesis of *N*-(2-((4-(2-(((1-Ethyl-1*H*-imidazol-5-yl)methyl)((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001218] 63 mg intermediate **IIL2** and 25 mg 1-ethyl-1*H*-imidazole-5-carbaldehyde were used to synthesize 36 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 159: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indol-6-yl)methyl)(thiazol-5-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001219] 63 mg intermediate **IIL3** and 23 mg thiazole-5-carbaldehyde were used to synthesize 33 mg of the title compound (45% yield) according to the General Procedure **VV**.

Example 160: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indol-6-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001220] 63 mg intermediate **IIL3** and 22 mg nicotinaldehyde were used to synthesize 28 mg of the title compound (39% yield) according to the General Procedure **VV**.

Example 161: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)(thiazol-5-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001221] 64 mg intermediate **IIL4** and 23 mg thiazole-5-carbaldehyde were used to synthesize 36 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 162: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001222] 64 mg intermediate **IIL4** and 22 mg nicotinaldehyde were used to synthesize 32 mg of the title compound (43% yield) according to the General Procedure **VV**.

Example 163: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001223] 64 mg intermediate **IIL4** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 37 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 164: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-hydroxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001224] 64 mg intermediate **IIL4** and 25 mg 5-hydroxynicotinaldehyde were used to synthesize 36 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 165: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-methylpyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001225] 64 mg intermediate **IIL4** and 24 mg 5-methylnicotinaldehyde were used to synthesize 30 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 166: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-(2-methoxyethoxy)pyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001226] 64 mg intermediate **IIL4** and 36 mg 5-(2-methoxyethoxy)nicotinaldehyde were used to synthesize 36 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 167: Synthesis of *N*-(2-((4-(2-(((2,3-Dihydrobenzofuran-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001227] 62 mg intermediate **IIL5** and 22 mg nicotinaldehyde were used to synthesize 33 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 168: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001228] 66 mg intermediate **IIL6** and 22 mg nicotinaldehyde were used to synthesize 38 mg of the title compound (50% yield) according to the General Procedure **VV**.

Example 169: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001229] 66 mg intermediate **IIL6** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 36 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 170: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001230] 63 mg intermediate **IIL7** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 39 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 171: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001231] 63 mg intermediate **IIL7** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 31 mg of the title compound (41% yield) according to the General Procedure **VV**.

Example 172: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001232] 63 mg intermediate **IIL7** and 22 mg nicotinaldehyde were used to synthesize 31 mg of the title compound (43% yield) according to the General Procedure **VV**.

Example 173: Synthesis of *N*-(2-((4-(2-(((6-Bromoimidazo[1,2-a]pyrazin-3-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001233] 70 mg intermediate **IIL8** and 22 mg nicotinaldehyde were used to synthesize 32 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 174: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-7-yl)methyl)(thiazol-5-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001234] 63 mg intermediate **IIL9** and 23 mg thiazole-5-carbaldehyde were used to synthesize 33 mg of the title compound (45% yield) according to the General Procedure **VV**.

Example 175: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-7-yl)methyl)(thiazol-5-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001235] 63 mg intermediate **IIL9** and 22 mg nicotinaldehyde were used to synthesize 34 mg of the title compound (47% yield) according to the General Procedure **VV**.

Example 176: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((8-methylquinolin-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001236] 64 mg intermediate **IIL10** and 35 mg 3-(1*H*-Imidazol-1-yl)benzaldehyde were used to synthesize 41 mg of the title compound (51% yield) according to the General Procedure **VV**.

Example 177: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((8-methylquinolin-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001237] 64 mg intermediate **IIL10** and 22 mg nicotinaldehyde were used to synthesize 36 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 178: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-ethyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001238] 64 mg intermediate **IIL11** and 35 mg 1-ethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 32 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 179: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((9-methyl-9*H*-carbazol-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001239] 64 mg intermediate **IIL11** and 42 mg 9-methyl-9*H*-carbazole-3-carbaldehyde were used to synthesize 29 mg of the title compound (35% yield) according to the General Procedure **VV**.

Example 180: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((9-ethyl-9*H*-carbazol-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001240] 64 mg intermediate **IIL11** and 45 mg 9-ethyl-9*H*-carbazole-3-carbaldehyde were used to synthesize 31 mg of the title compound (36% yield) according to the General Procedure **VV**.

Example 181: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)(3,4,5-trimethoxybenzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001241] 64 mg intermediate **IIL11** and 39 mg 3,4,5-trimethoxybenzaldehyde were used to synthesize 37 mg of the title compound (45% yield) according to the General Procedure **VV**.

Example 182: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001242] 64 mg intermediate **IIL11** and 22 mg nicotinaldehyde were used to synthesize 32 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 183: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001243] 64 mg intermediate **IIL11** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 33 mg of the title compound (43% yield) according to the General Procedure **VV**.

Example 184: Synthesis of Methyl 4-(((3-(1*H*-imidazol-1-yl)benzyl)(4-(4,5-dimethoxy-2-(4-oxo-4*H*-chromene-2-carboxamido)benzamido)phenethyl)amino)methyl)benzoate

[001244] 64 mg intermediate **IIL11** and 33 mg methyl 4-formylbenzoate were used to synthesize 36 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 185: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)(3-cyano-4-methoxybenzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001245] 64 mg intermediate **IIL11** and 32 mg 5-formyl-2-methoxybenzonitrile were used to synthesize 30 mg of the title compound (38% yield) according to the General Procedure **VV**.

Example 186: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)(4-(2-methyl-1*H*-imidazol-1-yl)benzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001246] 64 mg intermediate **IIL11** and 37 mg 4-(2-methyl-1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 39 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 187: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)(3-(2-methyl-1*H*-imidazol-1-yl)benzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001247] 64 mg intermediate **IIL11** and 37 mg 3-(2-methyl-1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 38 mg of the title compound (47% yield) according to the General Procedure **VV**.

Example 188: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)(3,4-dimethoxybenzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001248] 63 mg intermediate **IIL12** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 40 mg of the title compound (50% yield) according to the General Procedure **VV**.

Example 189: Synthesis of *N*-(2-((4-(2-((4-(1*H*-Imidazol-1-yl)benzyl)(3,4-dimethoxybenzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001249] 63 mg intermediate **IIL12** and 35 mg 4-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 31 mg of the title compound (39% yield) according to the General Procedure **VV**.

Example 190: Synthesis of *N*-(2-((4-(2-((3,4-Dimethoxybenzyl)((1-methyl-1*H*-imidazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001250] 63 mg intermediate **IIL12** and 22 mg 1-methyl-1*H*-imidazole-5-carbaldehyde were used to synthesize 36 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 191: Synthesis of *N*-(2-((4-(2-((3,4-Dimethoxybenzyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001251] 63 mg intermediate **IIL12** and 22 mg nicotinaldehyde were used to synthesize 35 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 192: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001252] 64 mg intermediate **IIL13** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 32 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 193: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001253] 64 mg intermediate **IIL13** and 22 mg nicotinaldehyde were used to synthesize 36 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 194: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001254] 64 mg intermediate **IIL13** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 32 mg of the title compound (42% yield) according to the General Procedure **VV**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.38 (s, 3H), 2.66 (t, J = 12.0 Hz, 2H), 2.79 (t, J = 12.0 Hz, 2H), 3.67 (s, 2H), 3.69 (s, 2H), 3.76 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 3.94 (s, 3H), 6.88 (s, 1H), 7.13 (d, J = 8.0 Hz, 2H), 7.22 (s, 1H), 7.28-7.62 (m, 8H), 7.81 (s, 1H), 7.92 (s, 1H), 8.11 (d, J = 8.0 Hz, 2H), 8.30 (s, 1H), 10.32 (s, 1H), 12.92 (s, 1H); *m/z* (ESI+), $[M + H]^+$ = 767.12.

Example 195: Synthesis of *N*-(2-((4-(2-(((5-Hydroxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001255] 64 mg intermediate **IIL13** and 25 mg 5-hydroxynicotinaldehyde were used to synthesize 33 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 196: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-(2-methoxyethoxy)pyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001256] 64 mg intermediate **IIL13** and 36 mg 5-(2-methoxyethoxy)nicotinaldehyde were used to synthesize 34 mg of the title compound (42% yield) according to the General Procedure **VV**.

Example 197: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001257] 64 mg intermediate **IIL13** and 32 mg 1-methyl-1*H*-benzo[*d*][1,2,3]triazole-5-carbaldehyde were used to synthesize 29 mg of the title compound (37% yield) according to the General Procedure **VV**.

Example 198: Synthesis of *N*-(2-((4-(2-(((5-Ethoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001258] 64 mg intermediate **IIL13** and 30 mg 5-ethoxynicotinaldehyde were used to synthesize 33 mg of the title compound (42% yield) according to the General Procedure **VV**.

Example 199: Synthesis of *N*-(2-((4-(2-(((5-*i*-Propylpyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001259] 64 mg intermediate **IIL13** and 30 mg 5-isopropylnicotinaldehyde were used to synthesize 32 mg of the title compound (41% yield) according to the General Procedure **VV**.

Example 200: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((5-methylpyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001260] 64 mg intermediate **IIL13** and 24 mg 5-methylnicotinaldehyde were used to synthesize 38 mg of the title compound (51% yield) according to the General Procedure **VV**.

Example 201: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((5-phenylpyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001261] 64 mg intermediate **IIL13** and 37 mg 5-phenylnicotinaldehyde were used to synthesize 36 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 202: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001262] 65 mg intermediate **IIL14** and 22 mg nicotinaldehyde were used to synthesize 31 mg of the title compound (41% yield) according to the General Procedure **VV**.

Example 203: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001263] 65 mg intermediate **IIL14** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 36 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 204: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-(2-methoxyethoxy)pyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001264] 65 mg intermediate **IIL14** and 36 mg 5-(2-methoxyethoxy)nicotinaldehyde were used to synthesize 39 mg of the title compound (47% yield) according to the General Procedure **VV**.

Example 205: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-(2-(methylthio)ethoxy)pyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001265] 65 mg intermediate **IIL14** and 40 mg 5-(2-(methylthio)ethoxy)nicotinaldehyde were used to synthesize 37 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 206: Synthesis of *N*-(2-((4-(2-(((1,3-Dimethyl-1*H*-indazol-5-yl)methyl)((5-methylpyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001266] 65 mg intermediate **IIL14** and 24 mg 5-methylnicotinaldehyde were used to synthesize 38 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 207: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6,8-dimethyl-4-oxo-4*H*-chromene-2-carboxamide

[001267] 65 mg intermediate **IIL15** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 30 mg of the title compound (37% yield) according to the General Procedure **VV**.

Example 208: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-6,8-dimethyl-4-oxo-4*H*-chromene-2-carboxamide

[001268] 65 mg intermediate **IIL15** and 22 mg nicotinaldehyde were used to synthesize 35 mg of the title compound (47% yield) according to the General Procedure **VV**.

Example 209: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-ethyl-4-oxo-4*H*-chromene-2-carboxamide

[001269] 65 mg intermediate **IIL16** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 31 mg of the title compound (38% yield) according to the General Procedure **VV**.

Example 210: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-7-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001270] 64 mg intermediate **IIL17** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 29 mg of the title compound (36% yield) according to the General Procedure **VV**.

Example 211: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-7-methyl-4-oxo-4*H*-chromene-2-carboxamide

[001271] 64 mg intermediate **IIL17** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 38 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 212: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-6-methyl-4-oxo-4*H*-chromene-3-carboxamide

[001272] 64 mg intermediate **IIL18** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 37 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 213: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-3-carboxamide

[001273] 63 mg intermediate **IIL19** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 39 mg of the title compound (50% yield) according to the General Procedure **VV**.

Example 214: Synthesis of *N*-(2-((4-(2-((4-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoline-3-carboxamide

[001274] 61 mg intermediate **IIL20** and 35 mg 4-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 30 mg of the title compound (39% yield) according to the General Procedure **VV**.

Example 215: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoline-3-carboxamide

[001275] 61 mg intermediate **IIL20** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 31 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 216: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoline-3-carboxamide

[001276] 61 mg intermediate **IIL20** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 33 mg of the title compound (45% yield) according to the General Procedure **VV**.

Example 217: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-(2-methoxyethoxy)pyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoline-3-carboxamide

[001277] 61 mg intermediate **IIL20** and 32 g 5-(2-methoxyethoxy)nicotinaldehyde were used to synthesize 34 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 218: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1,3-dimethyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoline-3-carboxamide

[001278] 62 mg intermediate **IIL21** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 36 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 219: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001279] 61 mg intermediate **IIL22** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 35 mg of the title compound (45% yield) according to the General Procedure **VV**.

Example 220: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoxaline-2-carboxamide

[001280] 61 mg intermediate **IIL22** and 22 mg nicotinaldehyde were used to synthesize 33 mg of the title compound (47% yield) according to the General Procedure **VV**.

Example 221: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoxaline-2-carboxamide

[001281] 61 mg intermediate **IIL22** and 32 g 1-methyl-1*H*-indazole-6-carbaldehyde were used to synthesize 35 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 222: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((8-methylquinolin-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoxaline-2-carboxamide

[001282] 61 mg intermediate **IIL22** and 34 mg 8-methylquinoline-5-carbaldehyde were used to synthesize 34 mg of the title compound (44% yield) according to the General Procedure **VV**.

Example 223: Synthesis of *N*-(2-((4-(2-(((1-Ethyl-1*H*-imidazol-5-yl)methyl)((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001283] 61 mg intermediate **IIL22** and 25 mg 1-ethyl-1*H*-imidazole-5-carbaldehyde were used to synthesize 35 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 224: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoxaline-2-carboxamide

[001284] 61 mg intermediate **IIL22** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 38 mg of the title compound (52% yield) according to the General Procedure **VV**.

Example 225: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((5-(2-methoxyethoxy)pyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoxaline-2-carboxamide

[001285] 61 mg intermediate **IIL22** and 32 mg 5-(2-methoxyethoxy)nicotinaldehyde were used to synthesize 31 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 226: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-(((1-methyl-1*H*-indazol-5-yl)methyl)((5-methylpyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)quinoxaline-2-carboxamide

[001286] 61 mg intermediate **IIL22** and 24 mg 5-methylnicotinaldehyde were used to synthesize 33 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 227: Synthesis of *N*-(2-((4-(2-(((5-Ethoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001287] 61 mg intermediate **IIL22** and 30 mg 5-ethoxynicotinaldehyde were used to synthesize 32 mg of the title compound (43% yield) according to the General Procedure **VV**.

Example 228: Synthesis of *N*-(2-((4-(2-(((5-*i*-Propylpyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001288] 61 mg intermediate **IIL22** and 30 mg 5-isopropylnicotinaldehyde were used to synthesize 36 mg of the title compound (48% yield) according to the General Procedure **VV**.

Example 229: Synthesis of *N*-(2-((4-(2-(((1-Ethyl-1*H*-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001289] 64 mg intermediate **IIL23** and 22 mg nicotinaldehyde were used to synthesize 31 mg of the title compound (42% yield) according to the General Procedure **VV**.

Example 230: Synthesis of *N*-(2-((4-(2-(((1-Acetyl-1*H*-indazol-5-yl)methyl)((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001290] 65 mg intermediate **IIL24** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 36 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 231: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((3-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001291] 65 mg intermediate **IIL25** and 32 mg 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 32 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 232: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((3-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)(thiazol-5-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001292] 65 mg intermediate **IIL25** and 23 mg thiazole-5-carbaldehyde were used to synthesize 37 mg of the title compound (49% yield) according to the General Procedure **VV**.

Example 233: Synthesis of *N*-(4,5-Dimethoxy-2-((4-(2-((3-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001293] 65 mg intermediate **IIL25** and 22 mg nicotinaldehyde were used to synthesize 31 mg of the title compound (41% yield) according to the General Procedure **VV**.

Example 234: Synthesis of *N*-(2-((4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((2-methyl-2*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001294] 64 mg intermediate **IIL11** and 32 mg 2-methyl-2H-indazole-5-carbaldehyde were used to synthesize 30 mg of the title compound (38% yield) according to the General Procedure **VV**.

Example 235: Synthesis of *N*-(2-((4-(2-(((2-(2-Fluorophenyl)pyrimidin-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001295] 67 mg intermediate **IIL26** and 22 mg nicotinaldehyde were used to synthesize 35 mg of the title compound (46% yield) according to the General Procedure **VV**.

Example 236: Synthesis of *N*-(2-((4-(2-(((2-(2-Fluorophenyl)pyrimidin-5-yl)methyl)((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001296] 67 mg intermediate **IIL26** and 28 mg 5-methoxynicotinaldehyde were used to synthesize 32 mg of the title compound (40% yield) according to the General Procedure **VV**.

Example 237: Synthesis of *N*-(4-(2-((3-(1*H*-Imidazol-1-yl)benzyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)-4,5-dimethoxy-2-(3,4,5-trimethoxybenzamido)benzamide

[001297] 65 mg intermediate **IIL27** and 35 mg 3-(1*H*-imidazol-1-yl)benzaldehyde were used to synthesize 34 mg of the title compound (42% yield) according to the General Procedure **VV**.

Example 238: Synthesis of *N*-(2-((4-(2-(Bis((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001298] 60 mg intermediate **IIK1** and 64 mg 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 29 mg of the title compound (37% yield) according to the General Procedure **WW**. ^{1}H NMR (400 MHz, DMSO-d_6) 2.65 (t, J = 12.0 Hz, 2H), 2.81 (t, J = 12.0 Hz, 2H), 3.73 (s, 4H), 3.87 (s, 3H), 3.90 (s, 3H), 3.97 (s, 6H), 6.93 (s, 1H), 7.12 (d, J = 8 Hz, 3H), 7.35 (dd, J = 1.6 Hz, 2H), 7.46-7.73 (m, 10H), 7.95 (s, 2H), 8.03 (dd, J = 1.6 Hz, 1H), 8.33 (s, 1H), 10.35 (s, 1H), 12.96 (s, 1H); m/z (ESI+), $[M + H]^+$ = 776.20.

Example 239: Synthesis of *N*-(2-((4-(2-(Bis((1-methyl-1*H*-imidazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001299] 60 mg intermediate **IIK1** and 44 mg 1-methyl-1*H*-imidazole-5-carbaldehyde were used to synthesize 33 mg of the title compound (49% yield) according to the General Procedure **WW**.

Example 240: Synthesis of *N*-(2-((4-(2-(Bis((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001300] 60 mg intermediate **IIK1** and 64 mg 1-methyl-1*H*-indazole-6-carbaldehyde were used to synthesize 31 mg of the title compound (37% yield) according to the General Procedure **WW**.

Example 241: Synthesis of *N*-(2-((4-(2-(Bis((1,3-dimethyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001301] 60 mg intermediate **IIK1** and 70 mg 1,3-dimethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 34 mg of the title compound (44% yield) according to the General Procedure **WW**.

Example 242: Synthesis of *N*-(2-((4-(2-(Bis((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001302] 59 mg intermediate **IIK22** and 64 mg 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 35 mg of the title compound (46% yield) according to the General Procedure **WW**.

Example 243: Synthesis of *N*-(2-((4-(2-(Bis((1-methyl-1*H*-indazol-6-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001303] 59 mg intermediate **IIK22** and 64 mg 1-methyl-1*H*-indazole-6-carbaldehyde were used to synthesize 30 mg of the title compound (40% yield) according to the General Procedure **WW**.

Example 244: Synthesis of *N*-(2-((4-(2-(Bis((1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001304] 59 mg intermediate **IIK22** and 76 mg 1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[d]imidazole-5-carbaldehyde were used to synthesize 33 mg of the title compound (40% yield) according to the General Procedure **WW**.

Example 245: Synthesis of *N*-(2-((4-(2-(Bis((1,3-dimethyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001305] 59 mg intermediate **IIK22** and 70 mg 1,3-dimethyl-1*H*-indazole-5-carbaldehyde were used to synthesize 32 mg of the title compound (41% yield) according to the General Procedure **WW**.

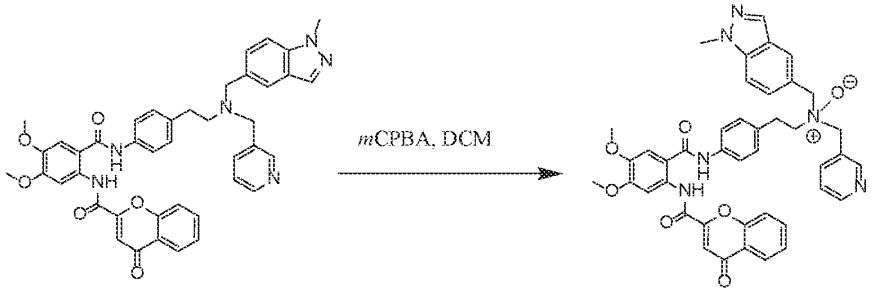
Example 246: Synthesis of *N*-(2-((4-(2-(Bis(3-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

[001306] 59 mg intermediate **IIK22** and 75 mg 3-(3-methyl-1,2,4-oxadiazol-5-yl)benzaldehyde were used to synthesize 29 mg of the title compound (36% yield) according to the General Procedure **WW**.

Example 247: Synthesis of *N*-(2-((4-(2-(Bis(4-(3-methyl-1,2,4-oxadiazol-5-yl)benzyl)amino)ethyl)phenyl)carbamoyl)-4,5-dimethoxyphenyl)quinoxaline-2-carboxamide

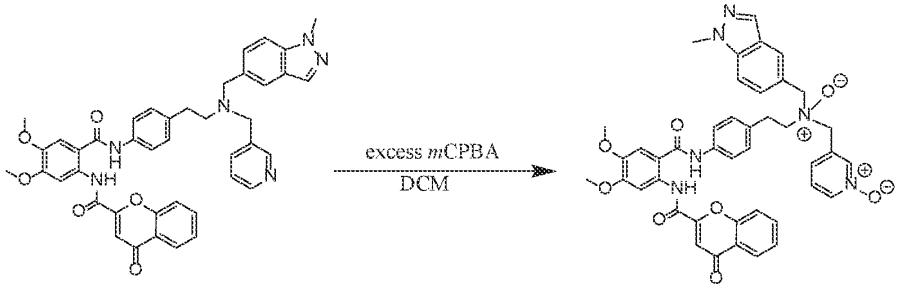
[001307] 59 mg intermediate **IIK22** and 75 mg 4-(3-methyl-1,2,4-oxadiazol-5-yl)benzaldehyde were used to synthesize 31 mg of the title compound (38% yield) according to the General Procedure **WW**.

Example 248: Synthesis of 2-(4-(4,5-Dimethoxy-2-(4-oxo-4*H*-chromene-2-carboxamido)benzamido)phenyl)-*N*-((1-methyl-1*H*-indazol-5-yl)methyl)-*N*-(pyridin-3-ylmethyl)ethan-1-amine oxide



[001308] A 40 mL vial was charged with N-(4,5-dimethoxy-2-((4-(2-(((1-methyl-1H-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (72 mg, 0.1 mmol, 1 eq.) and DCM (4.0 mL). The mixture was cooled down to 0 °C and then 70-75% *m*CPBA (30 mg, ~ 0.12 mmol, 1.2 eq.) was added and the mixture was stirred for 30 min. Upon reaction completion, the mixture was concentrated under vacuum and the residue was dissolved in 4 mL 5% TFA/MeOH/DMF and purified by reverse phase HPLC (0.1% TFA in water/ACN) to give 2-(4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido)benzamido)phenyl)-N-((1-methyl-1H-indazol-5-yl)methyl)-N-(pyridin-3-ylmethyl)ethan-1-amine oxide as a TFA salt. The free base form of 2-(4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido)benzamido)phenyl)-N-((1-methyl-1H-indazol-5-yl)methyl)-N-(pyridin-3-ylmethyl)ethan-1-amine oxide was obtained upon dissolving it in 10% MeOH/DCM, extraction with 1 M NaOH, drying over anhydrous sodium sulfate, and removal of the solvent under vacuum affording 29 mg of the title compound (39% yield).

Example 249: Synthesis of 2-(4-(4,5-Dimethoxy-2-(4-oxo-4*H*-chromene-2-carboxamido)benzamido)phenyl)-*N*-((1-methyl-1*H*-indazol-5-yl)methyl)-*N*-((1-oxidopyridin-3-yl)methyl)ethan-1-amine oxide



[001309] A 40 mL vial was charged with N-(4,5-dimethoxy-2-((4-(2-(((1-methyl-1H-indazol-5-yl)methyl)(pyridin-3-ylmethyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (72 mg, 0.1 mmol, 1 eq.) and DCM (4.0 mL). The mixture was cooled down to 0 °C and then 70-75% *m*CPBA (60 mg, ~ 0.34 mmol, 2.4 eq.) was added and the mixture was stirred for 30 min. Upon reaction completion, the mixture was concentrated under vacuum and the residue was dissolved in 4 mL 5% TFA/MeOH/DMF and purified by reverse phase HPLC (0.1% TFA in water/ACN) to give compound 2-(4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido)benzamido)phenyl)-N-((1-methyl-1H-indazol-5-yl)methyl)-N-((1-oxidopyridin-3-yl)methyl)ethan-1-amine oxide as a TFA salt. The free base form of 2-(4-(4,5-dimethoxy-2-(4-oxo-4H-chromene-2-carboxamido)benzamido)phenyl)-N-((1-methyl-1H-indazol-5-yl)methyl)-N-((1-oxidopyridin-3-yl)methyl)ethan-1-amine oxide was obtained upon dissolving in 10% MeOH/DCM, extraction with 1 M NaOH, drying over anhydrous sodium sulfate, and removal of the solvent under vacuum to afford 33 mg of the title compound (44% yield).

Example 250: Synthesis of Methyl 4-((4-(2-(methylamino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate trifluoroacetate (IIQ2)

[001310] 1.80 g of compound **IIP2** was used to synthesize 1.69 g of the title compound (92% yield) according to the General Procedure **AAA**.

Example 251: Synthesis of Methyl 4-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate (IIS1)

[001311] 503 mg of compound **IIR1** and 164 mg of 5-methoxynicotinaldehyde were used to synthesize 320 mg of the title compound (53% yield) according to the General Procedure **BBB**.

Example 252: Synthesis of Methyl 4-((4-(2-(methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate (IIS2)

[001312] 490 mg of compound **IIQ2** and 192 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 262 mg of the title compound (51% yield) according to the General Procedure **BBB**.

Example 253: Synthesis of Methyl 4-((4-(2-(methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(quinoline-3-carboxamido)benzoate (IIS3)

[001313] 477 mg of compound **IIQ3** and 192 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 241 mg of the title compound (48% yield) according to the General Procedure **BBB**.

Example 254: Synthesis of Methyl 4-((4-(2-(methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(picolinamido)benzoate (IIS4)

[001314] 345 mg of compound **IIQ4** and 192 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 231 mg of the title compound (50% yield) according to the General Procedure **BBB**.

Example 255: Synthesis of Methyl 4-((4-(2-(bis((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate (IIT1)

[001315] 479 mg of compound **IIQ1** and 384 mg of 1-methyl-1*H*-indazole-5-carbaldehyde were used to synthesize 314 mg of the title compound (51% yield) according to the General Procedure **BBB**.

Example 256: Synthesis of Methyl 4-((4-(2-(bis(3,4-dimethoxybenzyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate (IIT2)

[001316] 479 mg of compound **IIQ1** and 399 mg of veratraldehyde were used to synthesize 287 mg of the title compound (46% yield) according to the General Procedure **BBB**.

Example 257: Synthesis of Methyl 4-((4-(2-(bis((5-methoxypyridin-3-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001317] 479 mg of compound **IIQ1** and 329 mg of 5-methoxynicotinaldehyde were used to synthesize 231 mg of the title compound (40% yield) according to the General Procedure **BBB**.

Example 258: Synthesis of Methyl 4-((4-(2-(bis(3-(1*H*-imidazol-1-yl)benzyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001318] 479 mg of compound **IIQ1** and 413 mg of 3-(1H-imidazol-1-yl)benzaldehyde were used to synthesize 298 mg of the title compound (47% yield) according to the General Procedure **BBB**.

Example 259: Synthesis of 4-((4-(2-(((1-Methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoic acid

[001319] 189 mg of compound **IIR1** was used to synthesize 139 mg of the title compound (76% yield) according to the General Procedure **CCC**.

Example 260: Synthesis of 4-((4-(2-(((5-Methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoic acid (IIU1)

[001320] 225 mg of compound **IIS1** was used to synthesize 154 mg of the title compound (70% yield) according to the General Procedure **CCC**.

Example 261: Synthesis of 4-((4-(2-(Methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoic acid (IIU2)

[001321] 193 mg of compound **IIS2** was used to synthesize 142 mg of the title compound (75% yield) according to the General Procedure **CCC**.

Example 262: Synthesis of 4-((4-(2-(Methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(quinoline-3-carboxamido)benzoic acid (IIU3)

[001322] 188 mg of compound **IIS3** was used to synthesize 134 mg of the title compound (73% yield) according to the General Procedure **CCC**.

Example 263: Synthesis of 4-((4-(2-(Bis((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoic acid (IIV1)

[001323] 232 mg of compound **IIT1** was used to synthesize 157 mg of the title compound (69% yield) according to the General Procedure **CCC**.

Example 264: Synthesis of 4-((4-(2-(Bis(3,4-dimethoxybenzyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoic acid (IIV2)

[001324] 236 mg of compound **IIT2** was used to synthesize 164 mg of the title compound (71% yield) according to the General Procedure **CCC**.

Example 265: Synthesis of 2-(4-Methylpiperazin-1-yl)ethyl 4-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001325] 74 mg of compound **IIU1** and 36 mg of 2-(4-methylpiperazin-1-yl)ethan-1-ol were used to synthesize 39 mg of the title compound (45% yield) according to the General Procedure **DDD**.

Example 266: Synthesis of (2,2-Dimethyl-1,3-dioxolan-4-yl)methyl 4-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001326] 74 mg of compound **IIU1** and 33 mg of (2,2-dimethyl-1,3-dioxolan-4-yl)methanol were used to synthesize 34 mg of the title compound (40% yield) according to the General Procedure **DDD**.

Example 267: Synthesis of (2-Oxo-1,3-dioxol-4-yl)methyl 4-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001327] 74 mg of compound **IIU1** and 33 mg of 4-(hydroxymethyl)-5-methyl-1,3-dioxol-2-one were used to synthesize 38 mg of the title compound (46% yield) according to the General Procedure **DDD**.

Example 268: Synthesis of 2-Morpholinoethyl 4-((4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001328] 74 mg of compound **IIU1** and 33 mg of 2-morpholinoethan-1-ol were used to synthesize 32 mg of the title compound (38% yield) according to the General Procedure **DDD**.

Example 269: Synthesis of Pyridin-3-ylmethyl 4-((4-(2-(methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001329] 63 mg of compound **IIU2** and 28 mg of pyridin-3-ylmethanol were used to synthesize 31 mg of the title compound (43% yield) according to the General Procedure **DDD**.

Example 270: Synthesis of Thiazol-5-ylmethyl 4-((4-(2-(methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001330] 63 mg of compound **IIU2** and 29 mg of thiazol-5-ylmethanol were used to synthesize 34 mg of the title compound (47% yield) according to the General Procedure **DDD**.

Example 271: Synthesis of 4-(1*H*-Imidazol-1-yl)benzyl 4-((4-(2-(methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001331] 63 mg of compound **IIU2** and 44 mg of (4-(1*H*-imidazol-1-yl)phenyl)methanol were used to synthesize 38 mg of the title compound (48% yield) according to the General Procedure **DDD**.

Example 272: Synthesis of Thiazol-4-ylmethyl 4-((4-(2-(methyl((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001332] 63 mg of compound **IIU2** and 29 mg of thiazol-4-ylmethanol were used to synthesize 29 mg of the title compound (40% yield) according to the General Procedure **DDD**.

Example 273: Synthesis of Thiazol-5-ylmethyl 4-((4-(2-(methyl((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(quinoline-3-carboxamido)benzoate

[001333] 61 mg of compound **IIU3** and 29 mg of thiazol-5-ylmethanol were used to synthesize 32 mg of the title compound (45% yield) according to the General Procedure **DDD**.

Example 274: Synthesis of Thiazol-4-ylmethyl 4-((4-(2-(bis((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001334] 76 mg of compound **IIV1** and 29 mg of thiazol-4-ylmethanol were used to synthesize 37 mg of the title compound (43% yield) according to the General Procedure **DDD**.

Example 275: Synthesis of Pyridin-3-ylmethyl 4-((4-(2-(bis((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001335] 76 mg of compound **IIV1** and 28 mg of pyridin-3-ylmethanol were used to synthesize 30 mg of the title compound (35% yield) according to the General Procedure **DDD**.

Example 276: Synthesis of Pyridin-3-ylmethyl 4-((4-(2-(bis(3,4-dimethoxybenzyl)amino)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001336] 77 mg of compound **IIV2** and 28 mg of pyridin-3-ylmethanol were used to synthesize 41 mg of the title compound (48% yield) according to the General Procedure **DDD**.

Example 277: Synthesis of *N*-(2-((4-(2-(((5-Methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)-5-(morpholine-4-carbonyl)phenyl)-4-oxo-4*H*-chromene-2-carboxamide

[001337] 74 mg of compound **IIU1** and 22 mg of morpholine were used to synthesize 28 mg of the title compound (35% yield) according to the General Procedure **DDD**.

Example 278: Synthesis of *N*-(*N*,*N*-Dimethylsulfamoyl)-*N1*-(4-(2-(((5-methoxypyridin-3-yl)methyl)((1-methyl-1*H*-indazol-5-yl)methyl)amino)ethyl)phenyl)-2-(4-oxo-4*H*-chromene-2-carboxamido)terephthalamide

[001338] 74 mg of compound **IIU1** and 31 mg of *N*,*N*-dimethylsulfamide were used to synthesize 33 mg of the title compound (39% yield) according to the General Procedure **DDD**.

Example 279: Synthesis of 4-((4-(2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)carbamoyl)-3-(4-oxo-4H-chromene-2-carboxamido)benzoic acid (IIIB)

[001339] A clean, dry 40 mL vial was charged with Intermediate **IIIA** (991 g, 1.5 mmol, 1.0 eq.), THF (10.5 mL), and 1.0 M NaOH (4.5 mL, 4.5 mmol, 3.0 eq.). The mixture was stirred at room temperature for 3-4 h with frequent monitoring of the reaction by LC/MS to check for both reaction completion and product degradation. The product was then precipitated by adding 1.0 M HCl (30 mL), filtered, washed with water, dried under vacuum to give 498 g of Intermediate **IIIB**, which was used without further purification.

Example 280: Synthesis of Pyridin-3-ylmethyl 4-((4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001340] 97 mg of compound **IIIB1** and 38 mg of pyridin-3-ylmethanol were used to synthesize 42 mg of the title compound (38% yield) according to the General Procedure **EEE**.

Example 281: Synthesis of Pyridin-4-ylmethyl 4-((4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001341] 97 mg of compound **IIIB1** and 38 mg of pyridin-4-ylmethanol were used to synthesize 46 mg of the title compound (41% yield) according to the General Procedure **EEE**.

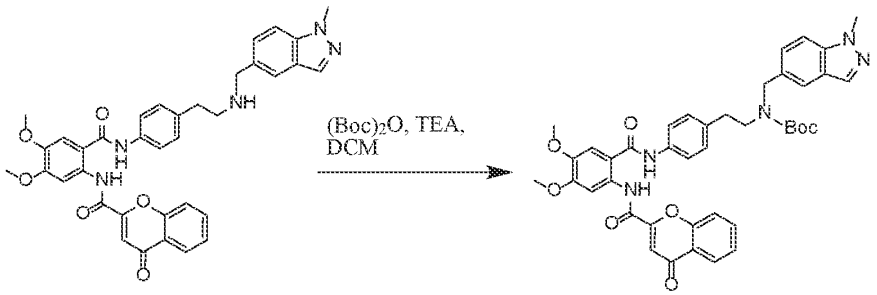
Example 282: Synthesis of Thiazol-5-ylmethyl 4-((4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001342] 97 mg of compound **IIIB1** and 40 mg of thiazol-5-ylmethanol were used to synthesize 44 mg of the title compound (39% yield) according to the General Procedure **EEE**.

Example 283: Synthesis of 3-(1*H*-Imidazol-1-yl)propyl 4-((4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)ethyl)phenyl)carbamoyl)-3-(4-oxo-4*H*-chromene-2-carboxamido)benzoate

[001343] 97 mg of compound **IIIB1** and 44 mg of 3-(1H-imidazol-1-yl)propan-1-ol were used to synthesize 40 mg of the title compound (35% yield) according to the General Procedure **EEE**.

Example 284: Synthesis of *tert*-Butyl (4-(4,5-dimethoxy-2-(4-oxo-4*H*-chromene-2-carboxamido)benzamido)phenethyl)((1-methyl-1*H*-indazol-5-yl)methyl)carbamate



[001344] A clean, dry 40 mL vial was charged with N-(4,5-dimethoxy-2-((4-(2-(((1-methyl-1H-indazol-5-yl)methyl)amino)ethyl)phenyl)carbamoyl)phenyl)-4-oxo-4H-chromene-2-carboxamide (63 mg, 0.15 mmol, 1.0 eq.), di-*tert*-butyl dicarbonate (35 mg, 0.16 mmol, 1.1 eq.), and DCM (30 mL). TEA (62 µL, 0.45 mmol, 0.3 eq.) was added to the reaction mixture at 0 °C, and the reaction mixture was stirred overnight. The mixture was then concentrated under vacuum and the residue was purified by flash chromatography on silica gel (MeOH/DCM) to give 41 mg of the title compound (37% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) 1.41 (s, 9H), 2.74 (s, 2H), 3.31 (s, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 4.02 (s, 3H), 4.46 (s, 2H), 6.93 (s, 1H), 7.19 (s, 2H), 7.29-7.32 (m, 1H), 7.53-7.57 (m, 2H), 7.59-7.68 (m, 5H), 7.87 (t, J = 16.0 Hz, 1H), 8.02 (s, 1H), 8.06 (dd, J = 1.6 Hz, 1H), 8.08 (dd, J = 1.6 Hz, 1H), 8.31 (s, 1H), 10.34 (s, 1H), 12.96 (s, 1H); m/z (ESI+), $[M + H]^+$ =732.29.

Example 285. Determination of P-glycoprotein Inhibitory Activity

[001345] A P-glycoprotein overexpressing cell line derived from the human uterine sarcoma cell line MES-SA (i.e., MES-SA/DX5 cells (ATCC)) was seeded by stepwise exposures to increasing concentrations of doxorubicin, in a 96-well plate at 6,500 cells/100 µL media (McCoy's 5A + 10% FBS) in each well. The cells were incubated overnight at 37 °C, 5% CO_2. Compounds were diluted in a separate 96-well plate to yield 11x of final concentration (final Compound concentrations were 0, 5, 20, 80, 320, and 1280 nM and the final docetaxel concentration was 100 nM or the final paclitaxel concentration was 200 nM). DMSO was used as a negative control and known P-glycoprotein inhibitor, encequidar methane sulfonic acid monohydrate (HM30181A), was used as a positive control. 10 µL of the 11x dilutions was added to the appropriate well, P-glycoprotein inhibition wells comprised Compound + docetaxel (or Compound + paclitaxel). The compound toxicity wells comprised 1280 nM Compound + 10 µL of culture media. Treated cells were incubated for 3 days at 37 °C, 5% CO_2.

[001346] T_0 value (reflecting the starting number of cells upon Compound treatment) of 3 wells of cells was determined by performing the following steps 1-4 as described below.

1. 10 µL MTT (5 mg/mL in PBS) was added to each well and incubated for 1.5 hours at 37 °C, 5% CO_2.

2. Culture media was removed and 100 µL of DMSO was added to each well.

3. The plate was gently shook until all purple MTT formazan crystals were dissolved. OD_{540} was then measured using microplate reader.

4. Cell growth percentage was calculated with the following equation:

Cell growth percentage = $(T-T_0)/(C-T_0)$ x 100%,

wherein T is OD of the test well exposure to Compound; C is OD of the control well without Compound treatment; and T_0 is OD at time zero. Cell growth inhibition curve and EC_{50} (measure of P-glycoprotein inhibition) were obtained by fitting the data to nonlinear regression model using GraphPad Prism software (v6.0).

Example 286. Determination of CYP3A4 Inhibitory Activity

[001347] Test compounds, DMSO (negative control), and ketoconazole (positive control) were diluted to 4x final concentrations in water. The standard final Compound concentrations were 37, 111, 333, 1000, and 3000 nM. 12.5 µL of the Compound dilutions were transferred to a white 96-well plate. 1450 µL (enough for a whole plate) of 4x assay buffer (400 mM potassium phosphate buffer (10 mL 1M potassium phosphate buffer: 8.02 mL 1M K_2HPO_4 + 1.98 mL 1M

KH_2PO_4 (1.4g K_2HPO_4 + 0.27g KH_2PO_4 in 10 mL H_2O), 32 μM Luciferin-IPA (Promega V9002)) 580 μl of 1 M K_3PO_4 buffer, 870 μL H_2O, 14 μL of 3 mM Luciferin-IPA, and 18 μL of human liver microsome (Sigma M0317-1VL) was made. 12.5 μL of 4x assay buffer was added to each well. For the well of blank control, 12.5 μL of 4x assay buffer without liver microsome was added. The plate was incubated at room temperature for 15 minutes. 2.75 mL NADPH buffer was made as follows: 2.42 mL H_2O, 275 μL solution A and 55 μL solution B (NADPH regeneration system, Promega V9510). 25 μL of the buffer was added to each well. The plates were incubated at 37 °C for 11 minutes. 50 μL of luciferin detection reagent (Promega V9002) was added and the plates were incubated at room temperature for 5 minutes. The plate was read with a luminometer.

[001348] The dose-response curve and IC_{50} were obtained by fitting data to nonlinear regression model using GraphPad Prism software (v6.0).

[001349] For EC_{50} or IC_{50} values shown in Table A, "A" means EC_{50} or IC_{50} < 100 nM; "B" means EC_{50} or IC_{50} ranging between 100 nM and 250 nM; "C" means EC_{50} or IC_{50} ranging between 250 nM and 500 nM; "D" means EC_{50} or IC_{50} ranging between 500 nM and 1000 nM; "E" means EC_{50} or IC_{50} > 1000 nM; "Nd" means Not determined.

Table A.

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
1	B	B
2	A	B
3	A	B
4	A	B
5	A	B
6	A	B
7	A	D
8	B	B
9	A	B
10	A	C
11	A	D
12	A	E
13	A	E
14	C	B
15	C	D
16	A	C
17	C	A

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
18	C	A
19	B	C
20	A	B
21	B	A
22	A	A
23	A	C
24	A	B
25	A	C
26	A	C
27	A	B
28	A	B
29	B	B
30	A	D
31	A	C
32	B	A
33	A	A
34	A	B

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
35	A	E
36	A	B
37	B	B
38	A	B
39	A	C
40	A	C
41	A	B
42	B	C
43	A	B
44	A	B
45	A	C
46	A	C
47	A	C
48	A	B
49	B	C
50	B	B
51	A	C
52	A	C
53	A	B
54	A	B
55	A	B
56	A	C
57	A	C
58	A	D
59	B	B
60	A	C
61	A	C
62	A	D
63	A	D
64	A	B
65	A	B
66	A	B
67	A	B
68	A	B
69	A	B
70	A	B
71	A	D
72	A	A
73	A	C
74	A	C
75	A	C

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
76	B	E
77	A	C
78	A	D
79	B	B
80	A	D
81	A	E
82	A	C
83	A	A
84	A	E
85	A	C
86	E	C
87	D	B
88	E	D
89	E	E
90	B	C
91	B	B
92	C	Nd
93	C	Nd
94	C	Nd
95	C	Nd
96	D	Nd
97	C	Nd
98	E	E
99	E	C
100	E	Nd
101	E	Nd
102	C	Nd
103	D	Nd
104	E	Nd
105	A	B
106	A	E
107	A	B
108	E	C
109	E	E
110	E	D
111	A	E
112	E	E
113	E	E
114	E	E
115	C	E
116	A	E

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
117	B	C
118	E	C
119	E	B
120	E	B
121	E	Nd
122	E	D
123	E	A
124	E	C
125	C	B
126	C	D
127	D	A
128	E	D
129	E	E
130	D	A
131	D	C
132	D	B
133	B	E
134	E	B
135	A	D
136	D	E
137	A	E
138	A	E
139	A	E
140	A	E
141	A	E
142	A	E
143	A	E
144	A	E
145	A	D
146	A	D
147	B	A
148	E	E
149	B	E
150	B	Nd
151	E	Nd
152	D	Nd
153	B	Nd
154	C	Nd
155	A	E
156	D	Nd
157	A	E

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
158	D	Nd
159	E	Nd
160	B	Nd
161	A	E
162	A	E
163	A	E
164	A	E
165	E	E
166	A	Nd
167	A	E
168	A	E
169	A	E
170	A	E
171	D	Nd
172	A	E
173	A	E
174	E	Nd
175	B	Nd
176	A	Nd
177	C	A
178	A	Nd
179	B	C
180	A	E
181	A	E
182	B	A
183	B	Nd
184	B	E
185	A	E
186	B	B
187	B	E
188	A	E
189	A	E
190	A	E
191	A	E
192	A	E
193	E	Nd
194	C	Nd
195	C	Nd
196	C	Nd
197	A	E
198	E	Nd

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
199	A	D
200	C	E
201	C	D
202	B	D
203	B	C
204	B	C
205	B	D
206	C	E
207	A	B
208	A	E
209	A	Nd
210	B	Nd
211	E	Nd
212	E	E
213	B	A
214	C	E
215	E	E
216	B	B
217	B	B
218	C	B
219	C	B
220	D	B
221	B	C
222	B	B
223	C	B
224	B	E
225	B	E
226	B	E
227	A	D
228	E	E
229	B	C
230	C	B
231	E	E
232	D	A
233	D	B
234	C	B
235	D	B
236	E	E
237	E	B
238	E	E
239	B	E

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
240	B	C
241	A	E
242	E	C
243	E	E
244	D	E
245	E	C
246	E	E
247	C	B
248	B	C
249	B	E
250	B	B
251	A	E
252	B	C
253	A	D
254	A	E
255	D	E
256	E	E
257	B	E
258	B	A
259	E	E
260	D	A
261	E	E
262	D	A
263	B	E
264	E	E
265	D	E
266	B	E
267	E	E
268	B	E
269	E	Nd
270	A	E
271	E	E
272	E	C
273	E	Nd
274	E	Nd
275	E	Nd
276	E	Nd
277	C	E
278	D	C
279	C	Nd
280	A	B

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
281	A	E
282	E	Nd
283	A	D
Elacridar	A	E
Tariquidar	A	E
Encequidar methane sulfonic acid	A	E

Cmpnd No.	P-glycoprotein EC_{50} (nM)	CYP3A4 IC_{50} (nM)
monohydrate		
Verapamil	E	E
Ketoconazole	E	B
Ritonavir	E	A

Example 287. Oral Absorption of Docetaxel in Mice

[001350] In vivo activity of the compounds of the present disclosure was performed as follows: Eighteen 7- to 9-week-old CD-1 mice were fasted overnight prior to drug administration while they were allowed free access to water and were fed 4 hours post dosing. Mice were divided into four groups of three to five rats each.

[001351] All four test groups were orally administered as seen in Table B.

Table B. Compound Dosage and Formulation

Compound	Dosage	Formulation
Docetaxel	10 mg/kg	2 mg/mL: 13% tween 80 + 7% kolliphor® EL + 80% purified water
Compound 16	80 mg/kg	16 mg/mL: 4% DMSO + 0.27% MSA + 95.73% (30% propylene glycol + 70% purified water + 0.02% conc. HCl)
Compound 48	20 mg/kg	4 mg/mL: 9.2% DMSO + 0.8% MSA + 90% [13% tween 80 + 7% kolliphor® EL + 80% (30% propylene glycol + 70% purified water + 0.02% conc. HCl)])
Control (Vehicle)		9.2% DMSO + 0.8% MSA + 90% [13% tween 80 + 7% kolliphor® EL + 80% (30% propylene glycol + 70% purified water + 0.02% conc. HCl)]
Encequidar methanesulfonic acid monohydrate	10 mg/kg	4 mg/mL: 5% DMSO + 95% (30% propylene glycol + 70% purified water + 0.02% conc. HCl)

[001352] Blood samples (approx. 30-50 µL) were obtained via peripheral veins of each mouse before (0) and 0.25, 0.5, 1, 2, 4, and 8 hours after docetaxel administration for control group (entry 1, Table C) and at 0.25, 0.5, 1, 2, 4, and 8 hours after docetaxel administration for rest of the groups (entries 2-4, Table C). Blood samples were treated with EDTA-K2 as anti-coagulant and placed on ice until centrifugation. Each blood sample was centrifuged at 4 °C, 3000g for 15 min within 0.5 hour from plasma collection. An aliquot of 20 µL plasma sample was protein precipitated with 100 µL IS (Internal Standard) solution (100 ng/mL labetalol + 100 ng/mL tolbutamide in acetonitrile, 1:1), the mixture was vortex-mixed and centrifuged at 4000 rpm for 15 min at 4 °C. An aliquot of 80 µL sample was transferred to a sample plate and mixed with 80 µL water, then the plate was shook at 800 rpm for 10 min. 1-10 µL of the supernatant was then injected for LC-MS/MS analysis under the following conditions:

Instrument: LCMS 6500;

MS conditions: ESI, positive;

Column: Waters ACQUITY UPLC BEH C18 2.1x50 mm, 1.7 μm;

Mobile phase A: 0.1% formic acid in water; and

Mobile phase B: 0.1% formic acid in acetonitrile.

Table C. Pharmacokinetic Parameters of Oral Docetaxel

Entry	Compound	$AUC_{0\text{-}inf}$ (ng·h/mL)[1]	T_{max} (h)[2]	C_{max} (ng/mL)[3]
1	Control	207 ± 144	0.417 ± 0.144	166 ± 131
2	Encequidar methanesulfonic acid monohydrate	698 ± 238	0.700 ± 0.274	316 ± 98.1
3	Compound 48	1031 ± 384	0.600 ± 0.224	540 ± 272
4	Compound 16	1350 ± 619	3.700 ± 2.95	174 ± 52.5

[1] Area under the curve of plasma concentration
[2] Time at the maximum plasma concentration
[3] Maximum plasma concentration

[001353] The compounds of the instant disclosure (*e.g.*, Compound 48 and Compound 16) increased the systemic bioavailability of orally dosed docetaxel by 5-fold and by 6.5-fold, respectively whereas with encequidar methanesulfonic acid monohydrate a 3.4-fold increase in the systemic bioavailability of docetaxel was found, as compared to when there was no inhibitor.

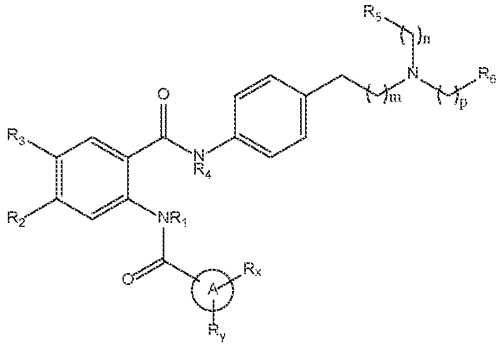
EQUIVALENTS

[001354] The details of one or more embodiments of the invention are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

[001355] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the invention to the precise form disclosed, but by the claims appended hereto.

CLAIMS

1. A compound of Formula (I):



(I)

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

A is C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl or heterocyclyl is optionally substituted with oxo;

each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-C(O)N(R_{11})_2$, $-C(O)NR_{11}$-$S(O)_2R_{11}$, $-C(O)NR_{11}$-$S(O)_2$-OR_{11}, or $-C(O)NR_{11}$-$S(O)_2$-$N(R_{11})_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -$C(O)R_7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, $-C(O)OR_{10}$, $-C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, $-O-(CH_2)_t-R_8$, $-NH-(CH_2)_t-R_8$, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl)$_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently $-(CH_2)_0-$(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_0-(C_{6-10}$ aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$;

each R_{10} is independently halogen, -OH, $-NH_2$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

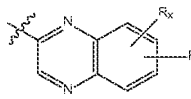
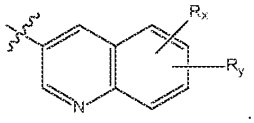
each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

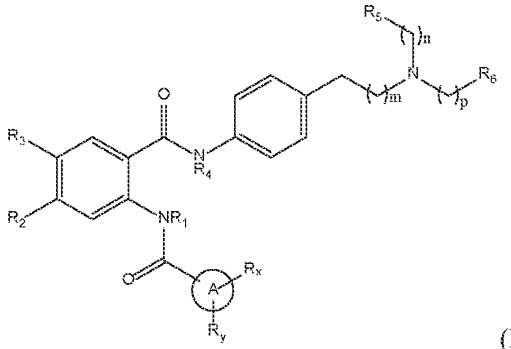
each n, m, and p is independently 0 or 1;

t is 1, 2, or 3; and

u is 0, 1, 2, or 3,

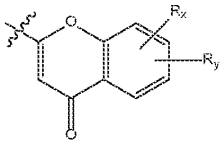
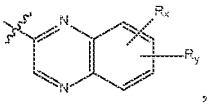
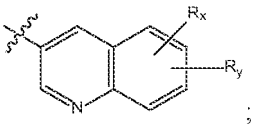
wherein R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not phenyl,  , or  .

2. A compound of Formula (I):



(I)

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

A is  ,  , or  ;

each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -O-C_{1-6} alkyl, -O-C_{2-6} alkenyl, -O-C_{2-6} alkynyl, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-C(O)N(R_{11})_2$, $-C(O)NR_{11}-S(O)_2R_{11}$, $-C(O)NR_{11}-S(O)_2-OR_{11}$, or $-C(O)NR_{11}-S(O)_2-N(R_{11})_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -

$C(O)R_7$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, $-C(O)OR_{10}$, $-C(O)N(R_{10})_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, $-O-(CH_2)_t-R_8$, $-NH-(CH_2)_t-R_8$, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl$)_2$, -SH, $-S(C_{1-6}$ alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently $-(CH_2)_u-$(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or $-(CH_2)_u-(C_{6-10}$ aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or $-NH_2$;

each R_{10} is independently halogen, -OH, $-NH_2$, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and

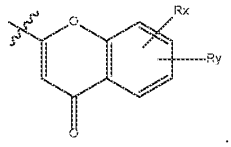
S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

each n, m, and p is independently 0 or 1;

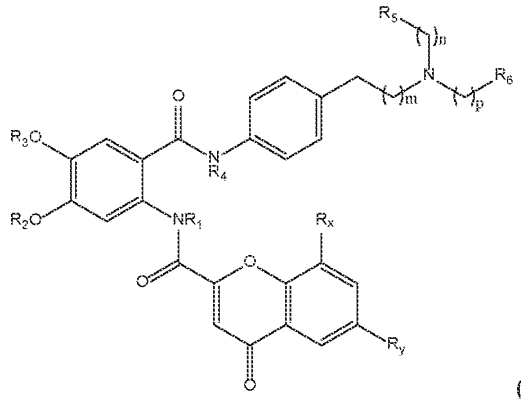
t is 1, 2, or 3; and

u is 0, 1, 2, or 3,

wherein R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl, A is 

.

3. A compound of Formula (II):



(II)

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

each R_x and R_y is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, halogen, -CN, -OH, or $-NH_2$;

each R_1 and R_4 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl;

each R_2 and R_3 is independently H, C_{2-6} alkenyl, C_{2-6} alkynyl, -C(O)R_{11}, -C(O)OR_{11}, -C(O)N(R_{11})$_2$, -C(O)NR_{11}-S(O)$_2$$R_{11}$, -C(O)N$R_{11}$-S(O)$_2$-O$R_{11}$, or -C(O)N$R_{11}$-S(O)$_2$-N($R_{11}$)$_2$, wherein either R_2 or R_3 is not H;

each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or -C(O)R_7, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7, or

R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more R_7;

each R_7 is independently oxo, halogen, -OH, -NH_2, -CN, -C(O)R_{10}, -C(O)OR_{10}, -C(O)N(R_{10})$_2$, C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -O-(CH_2)$_t$-R_8, -NH-(CH_2)$_t$-R_8, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{10};

R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, -NH_2, -NH(C_{1-6} alkyl), -N(C_{1-6} alkyl)$_2$, -SH, -S(C_{1-6} alkyl), C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted by one or more R_9;

each R_9 is independently -(CH_2)$_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or -(CH_2)$_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen, -CN, -OH, or -NH_2;

each R_{10} is independently halogen, -OH, -NH_2, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S;

each R_{11} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, halogen, -CN, -OH, or $-NH_2$, or

two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$;

each n, m, and p is independently 0 or 1;

t is 1, 2, or 3; and

u is 0, 1, 2, or 3.

4. The compound of any one of preceding claims, wherein each R_x and R_y is independently H, C_{1-6} alkyl, or -OH.

5. The compound of any one of preceding claims, each R_1 and R_4 is independently H or C_{1-6} alkyl.

6. The compound of claim 1 or 2, each R_2 and R_3 is independently -O-C_{1-6} alkyl, $-C(O)R_{11}$, $-C(O)OR_{11}$, $-C(O)N(R_{11})_2$, or $-C(O)NR_{11}$-$S(O)_2R_{11}$.

7. The compound of any one of preceding claims, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, or $-C(O)R_7$, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

8. The compound of any one of preceding claims, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_7.

9. The compound of any one of preceding claims, each R_5 and R_6 is independently H, C_{1-6} alkyl, C_{3-10} cycloalkyl, 3- to 13-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 13-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more R_7.

10. The compound of any one of preceding claims, R_5 and R_6 together with the atoms to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl or heteroaryl is substituted with one or more R_7.

11. The compound of any one of preceding claims, each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, C_{1-3} alkyl, C_{2-6} alkynyl, $-O-(CH_2)_t-R_8$, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkynyl, aryl, or heteroaryl is optionally substituted with one or more R_{10}.

12. The compound of any one of preceding claims, each R_7 is independently oxo, halogen, -OH, $-NH_2$, -CN, $-C(O)R_{10}$, C_{1-3} alkyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $-O-(CH_2)_t-R_8$, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkyl, alkynyl, aryl, or heteroaryl is substituted with one or more R_{10}.

13. The compound of any one of preceding claims, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, $-NH_2$, $-N(C_{1-6}$ alkyl$)_2$, $-S(C_{1-6}$ alkyl), 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected

from N, O, and S, wherein the alkoxy, alkyl, heterocyclyl, or heteroaryl is optionally substituted by one or more R_9.

14. The compound of any one of preceding claims, R_8 is -OH, C_{1-6} alkoxy, C_{1-6} alkoxy-OH, -NH_2, -N(C_{1-6} alkyl)$_2$, –S(C_{1-6} alkyl), 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the alkoxy, alkyl, heterocyclyl, or heteroaryl is substituted by one or more R_9.

15. The compound of any one of preceding claims, each R_9 is independently -$(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or -$(CH_2)_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is optionally substituted with one or more halogen or -OH.

16. The compound of any one of preceding claims, each R_9 is independently -$(CH_2)_u$-(5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S) or -$(CH_2)_u$-(C_{6-10} aryl), wherein the heteroaryl or aryl is substituted with one or more halogen or -OH.

17. The compound of any one of preceding claims, each R_{10} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S.

18. The compound of any one of preceding claims, each R_{11} is independently H, C_{1-6} alkyl optionally substituted with one or more 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, or oxo.

19. The compound of any one of preceding claims, each R_{11} is independently H, C_{1-6} alkyl optionally substituted with one or more 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising

1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl, aryl, or heteroaryl is substituted with one or more 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, or oxo.

20. The compound of any one of preceding claims, each R_{11} is independently H, C_{1-6} alkyl substituted with one or more 3- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, C_{6-10} aryl, or 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, wherein the heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more 5- to 10-membered heteroaryl comprising 1-4 heteroatoms selected from N, O, and S, C_{1-6} alkyl, or oxo.

21. The compound of any one of preceding claims, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, optionally substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

22. The compound of any one of preceding claims, two R_{11} together with the atom to which they are attached form a 4- to 10-membered heterocyclyl comprising 1-4 heteroatoms selected from N, O, and S, substituted with one or more C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, -OH, or $-NH_2$.

23. The compound of any one of preceding claims, each n is 0.

24. The compound of any one of preceding claims, each n is 1.

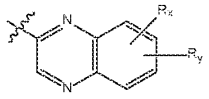
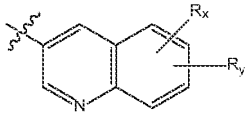
25. The compound of any one of preceding claims, each m is 0.

26. The compound of any one of preceding claims, each m is 1.

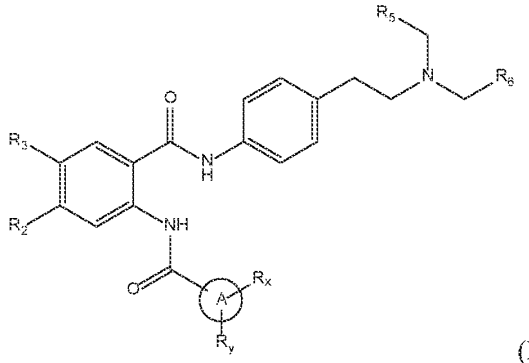
27. The compound of any one of preceding claims, each p is 0.

28. The compound of any one of preceding claims, each p is 1.

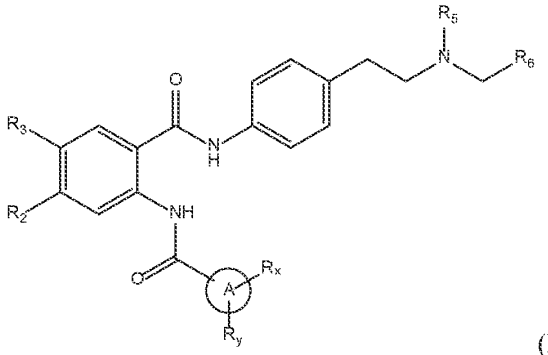
29. The compound of any one of preceding claims, wherein either R_2 or R_3 is not H.

30. The compound of any one of preceding claims, wherein when R_5 and R_6 together with the atoms to which they are attached form a heterocyclyl or heteroaryl, A is not  or .

31. The compound of claim 1 or 2, wherein the compound is of Formula (I-a) or (I-b):



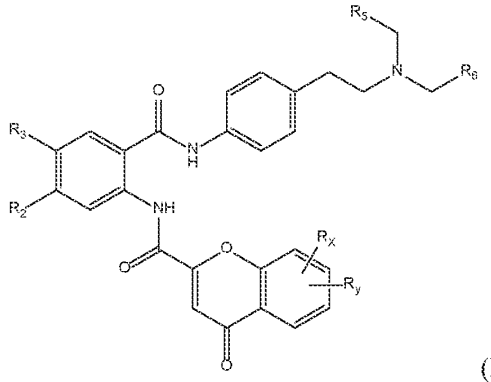
(I-a), or



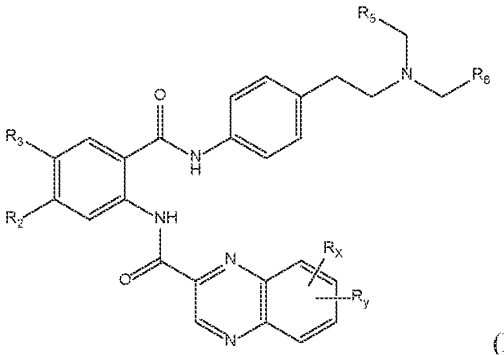
(I-b)

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

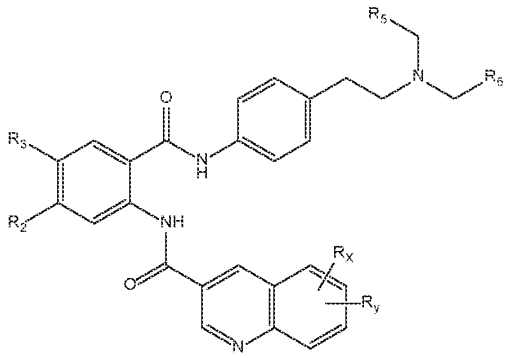
32. The compound of claim 1 or 2, wherein the compound is of Formula (I-c), (I-d), or (I-e):



(I-c),



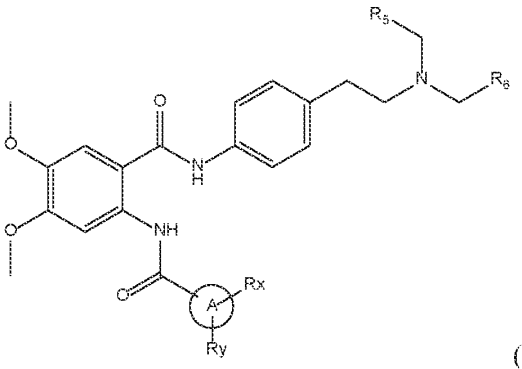
(I-d), or



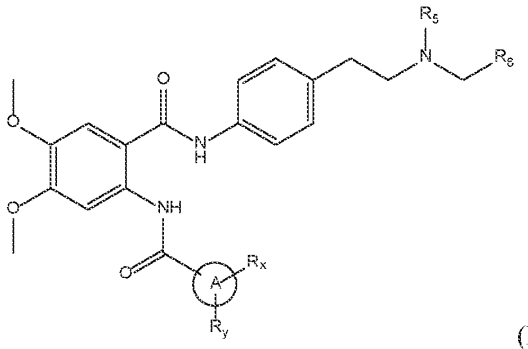
(I-e)

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

33. The compound of claim 1 or 2, wherein the compound is of Formula (I-a') or (I-b'):



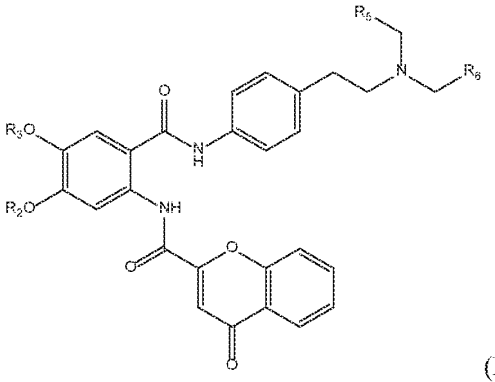
(I-a'), or



(I-b')

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

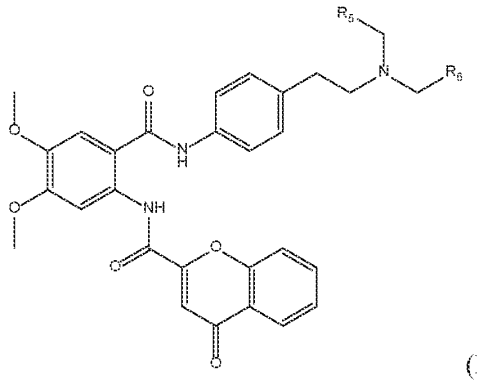
34. The compound of any one of claims 1-3, wherein the compound is of Formula (II-a):



(II-a)

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

35. The compound of any one of claims 1-3, wherein the compound is of Formula (II-a'):



(II-a')

or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof.

36. The compounds of any one of claims 1-3, wherein the compound is selected from Table 1.

37. A pharmaceutical composition comprising a compound of any one of claims 1-36, or a pharmaceutically acceptable prodrug, solvate, enantiomer, stereoisomer, tautomer, or salt thereof, and a pharmaceutically acceptable diluent or carrier.

38. A method of modulating P-glycoprotein activity and/or cytochrome P450 activity, comprising contacting a cell with an effective amount of a compound of any one of claims 1-36 or a pharmaceutical composition of claim 37.

39. A method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-36 or a pharmaceutical composition of claim 37.

40. A method of treating or preventing a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-36 or a pharmaceutical composition of claim 37.

41. A compound of any one of claims 1-36 or a pharmaceutical composition of claim 37, for use in modulating P-glycoprotein activity and/or cytochrome P450 activity.

42. A compound of any one of claims 1-36 or a pharmaceutical composition of claim 37, for use in treating or preventing a disease or disorder disclosed herein.

43. A compound of any one of claims 1-36 or a pharmaceutical composition of claim 37, for use in treating or preventing a cancer.

44. Use of a compound of any one of claims 1-36 or a pharmaceutical composition of claim 37, in the manufacture of a medicament for modulating P-glycoprotein activity and/or cytochrome P450 activity.

45. Use of a compound of any one of claims 1-36 or a pharmaceutical composition of claim 37, in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

46. Use of a compound of any one of claims 1-36 or a pharmaceutical composition of claim 37, in the manufacture of a medicament for treating or preventing a cancer.