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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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(54) **Title:** QUINAZOLINONE HSD17B13 INHIBITORS AND USES THEREOF

(57) **Abstract:** Described herein are HSD17B13 inhibitors and pharmaceutical compositions comprising said inhibitors. The subject compounds and compositions are useful for the treatment of liver disease, metabolic disease, or cardiovascular disease, such as NAFLD or NASH, or drug induced liver injury (DILI).

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QUINAZOLINONE HSD17B13 INHIBITORS AND USES THEREOF

CROSS-REFERENCE

[0001] This patent application claims the benefit of US Provisional Application No. 63/056,168, filed July 24, 2020 and US Provisional Application No. 63/113,557, filed November 13, 2020; each of which is incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Nonalcoholic fatty liver diseases (NAFLDs) including NASH (nonalcoholic steatohepatitis) are considered to be hepatic manifestations of the metabolic syndrome and are characterized by the accumulation of triglycerides in the liver of patients without a history of excessive alcohol consumption. The majority of patients with NAFLD are obese or morbidly obese and have accompanying insulin resistance. The incidence of NAFLD/NASH has been rapidly increasing worldwide consistent with the increased prevalence of obesity, and it is currently the most common chronic liver disease.

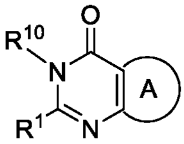
[0003] NAFLD is classified into simple steatosis, in which only hepatic steatosis is observed, and NASH, in which intralobular inflammation and ballooning degeneration of hepatocytes is observed along with hepatic steatosis. The proportion of patients with NAFLD who have NASH is still not clear but might range from 20-40%. NASH is a progressive disease and may lead to liver cirrhosis and hepatocellular carcinoma. Twenty percent of NASH patients are reported to develop cirrhosis, and 30-40% of patients with NASH cirrhosis experience liver-related death. Recently, NASH has become the third most common indication for liver transplantation in the United States. Currently, the principal treatment for NAFLD/NASH is lifestyle modification by diet and exercise. However, pharmacological therapy is indispensable because obese patients with NAFLD often have difficulty maintaining improved lifestyles.

[0004] 17β-Hydroxysteroid dehydrogenases (HSD17Bs) comprise a large family of 15 members some of which involved in sex hormone metabolism. Some HSD17Bs enzymes also play key roles in cholesterol and fatty acid metabolism. A recent study showed that hydroxysteroid 17β-dehydrogenase 13 (HSD17B13), an enzyme with unknown biological function, is a novel liver-specific lipid droplet (LD)-associated protein in mouse and humans. HSD17B13 expression is markedly upregulated in patients and mice with non-alcoholic fatty liver disease (NAFLD). Hepatic overexpression of HSD17B13 promotes lipid accumulation in the liver. HSD17B13 could also have potential as a biomarker of chronic liver disease, such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) (for example: steatosis, nonalcoholic steatohepatitis (NASH), NASH-fibrosis, or cirrhosis), steatohepatitis, and liver cancer.

SUMMARY OF THE INVENTION

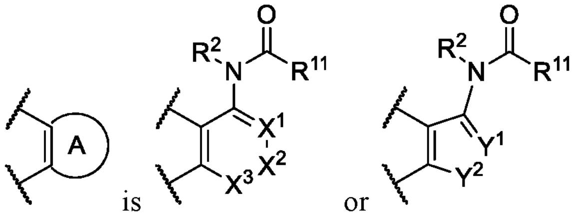
[0005] Provided herein are methods, compounds, and compositions useful for reducing expression or activity of HSD17B13 in a subject in need thereof. Also, provided herein are methods, compounds, and compositions comprising HSD17B13 specific inhibitors, which can be useful in reducing the morbidity of HSD17B13-related diseases or conditions in a subject in need thereof. Such methods, compounds, and compositions can be useful, for example, to treat, prevent, delay or ameliorate liver disease, metabolic disease, or cardiovascular disease.

[0006] Disclosed herein is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (II),

wherein:



X^1 is N or CR^{X1};

R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^2 is N or CR^{X2};

R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^3 is N or CR^{X3};

R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^1 is N or CR^{Y1};

R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^2 is S, O, or NR^{Y2};

R^{Y2} is hydrogen, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^1 is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, or heteroaryl;

R^2 is hydrogen, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^{10} is C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{10a};

each R^{10a} is independently deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH_2, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2R^a$, -NO_2, -NR^cR^d, -NHS(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH_2, -S(=O)$_2NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or two R^{10a} on the same carbon are taken together to form an oxo;

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a};

each R^{11a} is independently deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH_2, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2R^a$, -NO_2, -NR^cR^d, -NHS(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -S(=O)$_2NR^b$C(=O)R^a, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH_2, -S(=O)$_2NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or two R^{11a} on the same carbon are taken together to form an oxo;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -

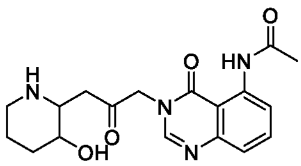
OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl; and

each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

provided that the compound of Formula (II) is not: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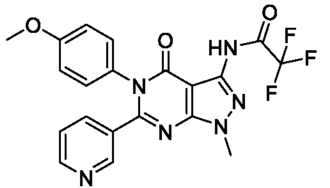
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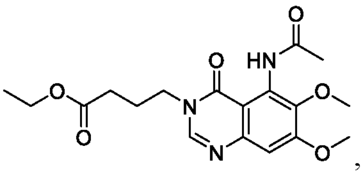
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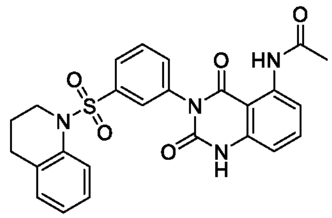
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[0007] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0008] Also disclosed herein is a method of treating a disease in a subject in need thereof, the method comprising administering a pharmaceutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein. In some embodiments of a method of treating a disease, the disease is a liver disease, a metabolic disease, or a cardiovascular disease. In some embodiments of a method of treating a disease, the disease is NAFLD. In some embodiments of a method of treating a disease, the disease is NASH. In some embodiments of a method of treating a disease, the disease is drug induced liver injury (DILI). In some embodiments of a method of treating a disease, the disease is associated with HSD17B13. In some embodiments of a method of treating a disease, the diseases is alcoholic liver disease. In some embodiments of a method of treating a disease, the disease is cirrhosis. In some embodiments of a method of treating a disease, the disease is decompensated portal hypertension.

INCORPORATION BY REFERENCE

[0009] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0010] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0011] Reference throughout this specification to “some embodiments” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0012] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0013] “oxo” refers to =O.

[0014] “Carboxyl” refers to -COOH.

[0015] “Alkyl” refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-

1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" or "$C_{1\text{-}6}$alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, the alkyl is a $C_{1\text{-}10}$alkyl. In some embodiments, the alkyl is a $C_{1\text{-}6}$alkyl. In some embodiments, the alkyl is a $C_{1\text{-}5}$alkyl. In some embodiments, the alkyl is a $C_{1\text{-}4}$alkyl. In some embodiments, the alkyl is a $C_{1\text{-}3}$alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0016] "Alkenyl" refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl ($-CH=CH_2$), 1-propenyl ($-CH_2CH=CH_2$), isopropenyl [$-C(CH_3)=CH_2$], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkenyl" or "$C_{2\text{-}6}$alkenyl", means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkenyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0017] "Alkynyl" refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as "C_2-C_6 alkynyl" or "$C_{2\text{-}6}$alkynyl", means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkynyl" where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -

CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0018] “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkylene is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0019] “Alkoxy” refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, COOMe, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0020] “Aryl” refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0021] “Cycloalkyl” refers to a partially or fully saturated, monocyclic or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (C_3-C_{15} cycloalkyl or C_3-C_{15} cycloalkenyl), from three to ten carbon atoms (C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl), from three to eight carbon atoms (C_3-C_8 cycloalkyl or C_3-C_8

cycloalkenyl), from three to six carbon atoms (C_3-C_6 cycloalkyl or C_3-C_6 cycloalkenyl), from three to five carbon atoms (C_3-C_5 cycloalkyl or C_3-C_5 cycloalkenyl), or three to four carbon atoms (C_3-C_4 cycloalkyl or C_3-C_4 cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0022] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0023] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0024] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0025] "Aminoalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0026] "Deuteroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more deuteriums. In some embodiments, the alkyl is substituted with one deuterium. In some embodiments, the alkyl is substituted with one, two, or three deuteriums. In some embodiments, the alkyl is substituted with one, two, three, four, five, or six deuteriums. Deuteroalkyl include, for example, CD_3, CH_2D, CHD_2, CH_2CD_3, CD_2CD_3, $CHDCD_3$, CH_2CH_2D, or CH_2CHD_2. In some embodiments, the deuteroalkyl is CD_3.

[0027] "Heterocycloalkyl" refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (C_2-C_{15} heterocycloalkyl or C_2-C_{15} heterocycloalkenyl), from two to ten carbon atoms (C_2-C_{10} heterocycloalkyl or C_2-C_{10} heterocycloalkenyl), from two to eight carbon atoms (C_2-C_8 heterocycloalkyl or C_2-C_8 heterocycloalkenyl), from two to seven carbon atoms (C_2-C_7 heterocycloalkyl or C_2-C_7 heterocycloalkenyl), from two to six carbon atoms (C_2-C_6 heterocycloalkyl or C_2-C_7 heterocycloalkenyl), from two to five carbon atoms (C_2-C_5 heterocycloalkyl or C_2-C_5 heterocycloalkenyl), or two to four carbon atoms (C_2-C_4 heterocycloalkyl or C_2-C_4 heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidinyl, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Unless otherwise noted, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-

membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0028] “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, $-CF_3$, -OH, -OMe, $-NH_2$, or $-NO_2$. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, $-CF_3$, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0029] The term “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” means either “alkyl” or “substituted alkyl” as defined above. Further, an optionally substituted group may be un-substituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), mono-substituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., $-CH_2CHF_2$, $-CH_2CF_3$, $-CF_2CH_3$, $-CFHCHF_2$, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially ad infinitum) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0030] An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0031] “Treatment” of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition, subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition. In some embodiments, treatment also includes prophylactic treatment (e.g., administration of a composition described herein when an individual is suspected to be suffering from a liver disease, e.g., NAFLD).

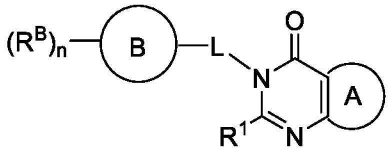
[0032] “Synergy” or “synergize” refers to an effect of a combination that is greater than additive of the effects of each component alone at the same doses.

[0033] “HSD17B13” means hydroxysteroid 17-beta dehydrogenase 13 and refers to any nucleic acid of HSD17B13. For example, in some embodiments, HSD17B13 includes a DNA sequence encoding HSD17B13, an RNA sequence transcribed from DNA encoding HSD17B13 (including genomic DNA comprising introns and exons). HSD17B13 can also refer to any amino acid sequence of HSD17B13 (may include secondary or tertiary structures of the protein molecule), encoded by a DNA sequence and/or RNA sequence. The target may be referred to in either upper or lower case.

Compounds

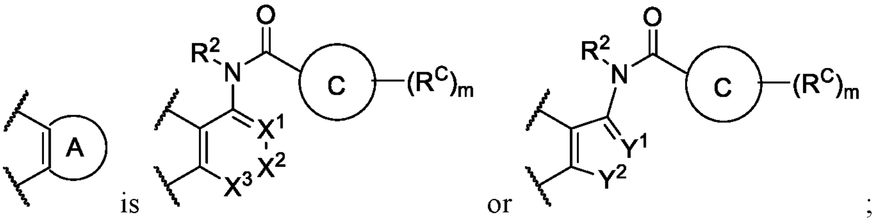
[0034] Described herein are compounds of Formula (I) and (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof useful in the treatment of liver diseases. In some embodiments, the liver disease is NAFLD.

[0035] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:



X^1 is N or CR^{X1};

R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^2 is N or CR^{X2};

R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^3 is N or CR^{X3};

R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^1 is N or CR^{Y1};

R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^2 is S, O, or NR^{Y2};

R^{Y2} is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^1 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, or heteroaryl;

R^2 is hydrogen, -S(=O)R^a, -S(=O)$_2$R^a, -S(=O)$_2$NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

L is -(CR^{3}R^4)$_p$-;

each R^3 and each R^4 are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

p is 0-4;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH$_2$, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2$R^a, -NO$_2$, -NR^{c}R^d, -NHS(=O)$_2$R^a, -S(=O)$_2$NR^{c}R^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^{c}R^d, -OC(=O)NR^{c}R^d, -NR^{b}C(=O)NR^{c}R^d, -NR^{b}C(=O)R^a, -NR^{b}C(=O)OR^b, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl;

n is 1-4;

Ring C is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH$_2$, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2$R^a, -NO$_2$, -NR^{c}R^d, -NHS(=O)$_2$R^a, -S(=O)$_2$NR^{c}R^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^{c}R^d, -OC(=O)NR^{c}R^d, -NR^{b}C(=O)NR^{c}R^d, -NR^{b}C(=O)R^a, -NR^{b}C(=O)OR^b, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl;

m is 1-4;

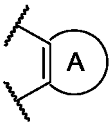
each R^a is independently C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C$_1$-C$_6$alkyl(cycloalkyl), C$_1$-C$_6$alkyl(heterocycloalkyl), C$_1$-C$_6$alkyl(aryl), or C$_1$-C$_6$alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl; and

each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl.

[0036] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,



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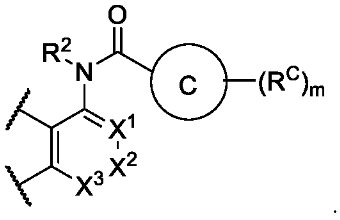

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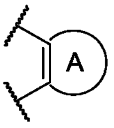
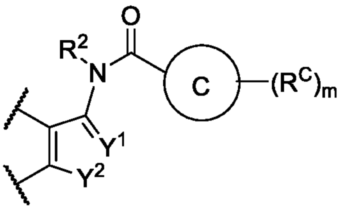
[0037] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^1 is N. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^1 is CR^{X1}.

[0038] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^2 is N. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^2 is CR^{X2}.

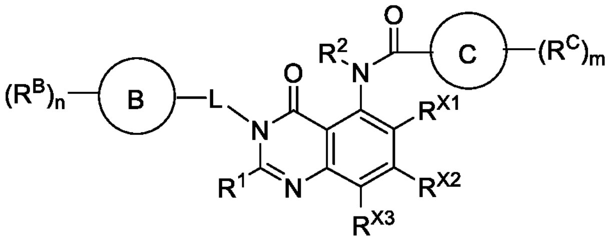
[0039] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^3 is N. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^3 is CR^{X3}.

[0040] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,  is  .

[0041] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^1 is N. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^1 is CR^{Y1}.

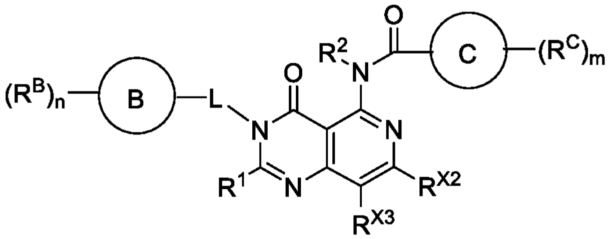
[0042] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is S. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is O. In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is NR^{Y2}.

[0043] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (Ia)



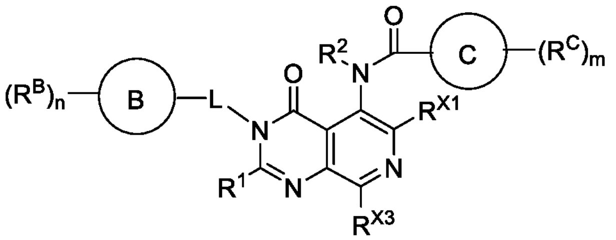
Formula (Ia).

[0044] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (Ib)



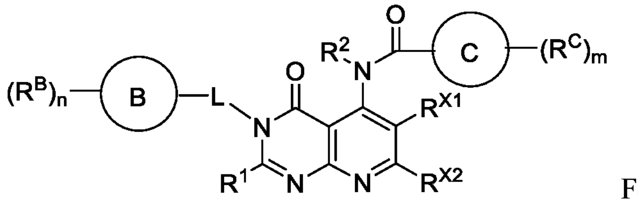
Formula (Ib).

[0045] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (Ic)



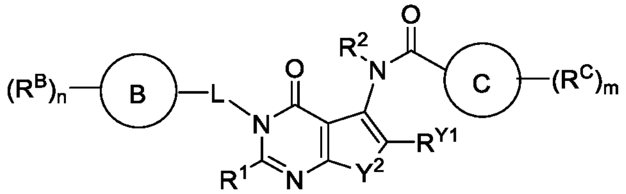
Formula (Ic).

[0046] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (Id)



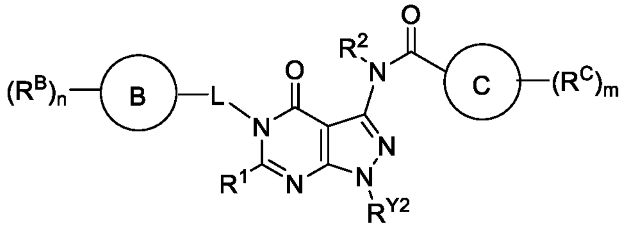
Formula (Id).

[0047] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (Ie)



Formula (Ie).

[0048] In some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (If)



Formula (If).

[0049] In some embodiments of a compound of Formula (I), (Ia), (Ic), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ic), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ic), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ic), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), (Ia), (Ic), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen.

[0050] In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or

C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Id), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen.

[0051] In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), (Ia), (Ib), or (Ic), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen.

[0052] In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is O. In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is S. In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is NR^{Y2}.

[0053] In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I) or (Ie), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen.

[0054] In some embodiments of a compound of Formula (I), (Ie), or (If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (I), (Ie), or

(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), (Ie), or (If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is hydrogen. In some embodiments of a compound of Formula (I), (Ie), or (If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is C_1-C_6alkyl.

[0055] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen, deuterium, halogen, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen.

[0056] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is C_1-C_6alkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen.

[0057] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 0-2. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 1 or 2. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 2. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 1. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, p is 0.

[0058] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^3 and each R^4 are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^3 and each R^4 are independently hydrogen, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^3 and each R^4 are independently hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^3

and each R^4 are independently hydrogen or halogen. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^3 and each R^4 are hydrogen.

[0059] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring B is aryl or heteroaryl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring B is cycloalkyl or heterocycloalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring B is aryl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring B is heteroaryl.

[0060] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH$_2$, -NR^{c}R^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently hydrogen, halogen, -OR^a, or C_1-C_6alkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently -OR^a.

[0061] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 2. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 1. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, n is 1 or 2.

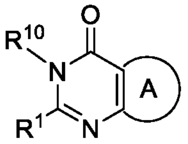
[0062] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring C is cycloalkyl or heterocycloalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring C is aryl or heteroaryl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring C is aryl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Ring C is heteroaryl.

[0063] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH$_2$, -NR^{c}R^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^C is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^C is independently hydrogen, halogen, -OH, or

C_1-C_6alkyl. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^C is independently halogen or -OH.

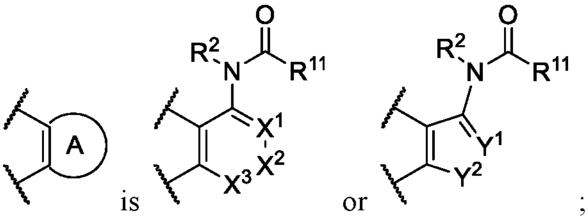
[0064] In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, m is 1 or 2. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, m is 1. In some embodiments of a compound of Formula (I) or (Ia)-(If), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, m is 2.

[0065] Also disclosed herein is a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (II),

wherein:



X^1 is N or CR^{X1};

R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^2 is N or CR^{X2};

R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^3 is N or CR^{X3};

R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^1 is N or CR^{Y1};

R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^2 is S, O, or NR^{Y2};

R^{Y2} is hydrogen, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^1 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, or heteroaryl;

R^2 is hydrogen, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2$NR^cR^d, -C(=O)R^a, -C(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^{10} is C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{10a};

each R^{10a} is independently deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH_2, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2R^a$, -NO_2, -NR^cR^d, -NHS(=O)$_2R^a$, -S(=O)$_2$NR^cR^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH_2, -S(=O)$_2$NH_2, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or two R^{10a} on the same carbon are taken together to form an oxo;

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a};

each R^{11a} is independently deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH_2, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2R^a$, -NO_2, -NR^cR^d, -NHS(=O)$_2R^a$, -S(=O)$_2$NR^cR^d, -S(=O)$_2$NR^bC(=O)R^a, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH_2, -S(=O)$_2$NH_2, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or two R^{11a} on the same carbon are taken together to form an oxo;

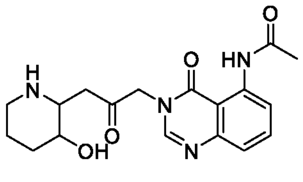
each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl; and

each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

provided that the compound of Formula (II) is not: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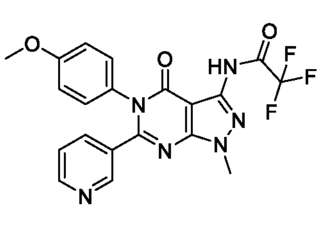
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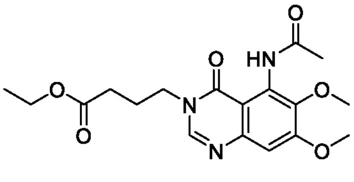
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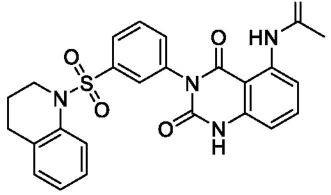
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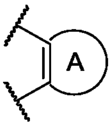
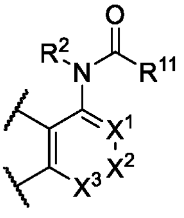
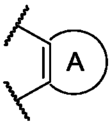
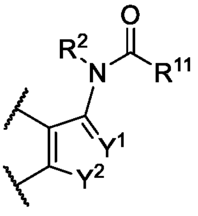
[0066] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,  is  .

[0067] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^1 is N. In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^1 is CR^{X1}.

[0068] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^2 is N. In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^2 is CR^{X2}.

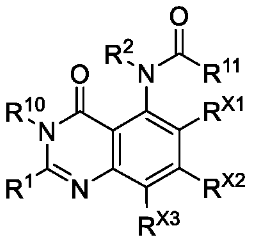
[0069] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^3 is N. In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, X^3 is CR^{X3}.

[0070] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,  is  .

[0071] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^1 is N. In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^1 is CR^{Y1}.

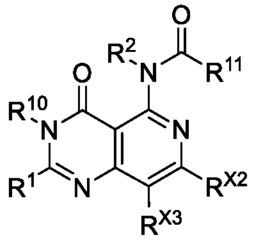
[0072] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is S. In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is O. In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is NR^{Y2}.

[0073] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (IIa)

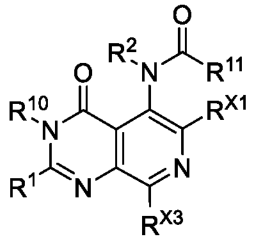


Formula (IIa).

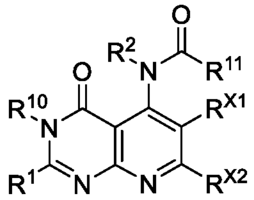
[0074] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (IIb)


Formula (IIb).

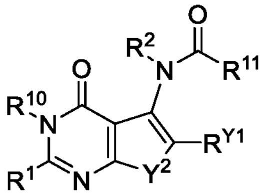
[0075] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (IIc)


Formula (IIc).

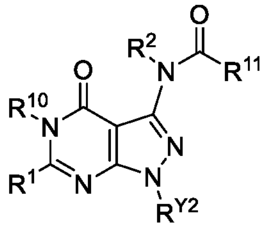
[0076] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (IId)


Formula (IId).

[0077] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (IIe)


Formula (IIe).

[0078] In some embodiments of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, the compound is of Formula (IIf)


Formula (IIf).

[0079] In some embodiments of a compound of Formula (II), (IIa), (IIc), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIc), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIc), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIc), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (II), (IIa), (IIc), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X1} is hydrogen.

[0080] In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IId), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X2} is hydrogen.

[0081] In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (II), (IIa), (IIb), or (IIc), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{X3} is hydrogen.

[0082] In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is O. In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is S. In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, Y^2 is NR^{Y2}.

[0083] In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or cycloalkyl. In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, deuterium, halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen, halogen, or C_1-C_6alkyl. In some embodiments of a compound of Formula (II) or (IIe), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y1} is hydrogen.

[0084] In some embodiments of a compound of Formula (II), (IIe), or (IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl. In some embodiments of a compound of Formula (II), (IIe), or (IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (II), (IIe), or (IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is hydrogen. In some embodiments of a compound of Formula (II), (IIe), or (IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{Y2} is C_1-C_6alkyl.

[0085] In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen, deuterium, halogen, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^1 is hydrogen.

[0086] In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is C_1-C_6alkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^2 is hydrogen.

[0087] In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{10} is C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, or C_2-C_{10}alkynyl; wherein the alkyl, alkenyl, and alkynyl are optionally independently substituted with one, two, or three R^{10a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{10} is C_1-C_{10}alkyl optionally independently substituted with one, two, or three R^{10a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{10} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{10a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{10} is aryl, heteroaryl, C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{10a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{10} is C_1-C_{10}alkyl(aryl); wherein the alkyl and aryl are optionally independently substituted with one, two, or three R^{10a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{10} is C_1-C_{10}alkyl(aryl); wherein the aryl is optionally substituted with one, two, or three R^{10a}.

[0088] In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{10a} is independently hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-OP(=O)OH_2$, $-NR^cR^d$, $-C(=O)R^a$, $-OC(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, $-S(=O)_2Me$, $-NH_2$, $-S(=O)_2NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{10a} is independently hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, $-S(=O)_2Me$, $-NH_2$, $-S(=O)_2NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{10a} is independently hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, C_1-C_6alkyl, or C_1-C_6haloalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, $-S(=O)_2Me$, $-NH_2$, $-S(=O)_2NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or

C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{10a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{10a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^B is independently hydrogen, halogen, -OR^a, or C_1-C_6alkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{10a} is independently -OR^a.

[0089] In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl; wherein the alkyl, alkenyl, alkynyl are optionally independently substituted with one, two, or three R^{11a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{11} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{11} is aryl, heteroaryl, C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{11} is aryl optionally independently substituted with one, two, or three R^{11a}. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^{11} is C_1-C_{10}alkyl(aryl) or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a}.

[0090] In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH$_2$, -NR^{c}R^d, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C$_1$-C$_6$alkyl, or C$_1$-C$_6$haloalkyl; wherein the alkyl is optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, or C$_1$-C$_6$deuteroalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C$_1$-C$_6$alkyl, or C$_1$-C$_6$haloalkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently hydrogen, halogen, -OH, or C$_1$-C$_6$alkyl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently halogen or -OH. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently aryl or heteroaryl. In some embodiments of a compound of Formula (II) or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^{11a} is independently heteroaryl.

[0091] In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, or cycloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C$_1$-C$_6$alkyl or C$_1$-C$_6$haloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^a is independently C$_1$-C$_6$alkyl.

[0092] In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen,

C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is hydrogen. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^b is independently C_1-C_6alkyl.

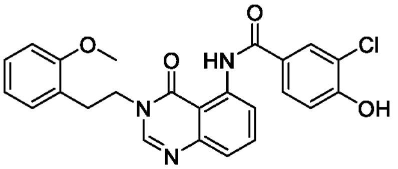
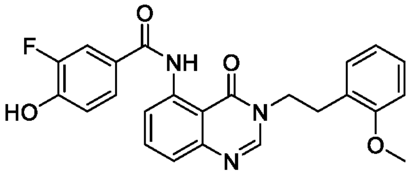
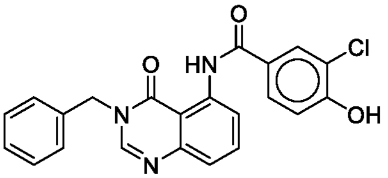
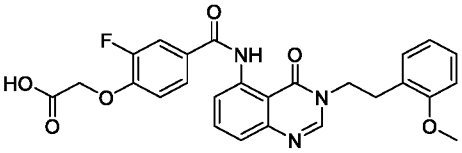
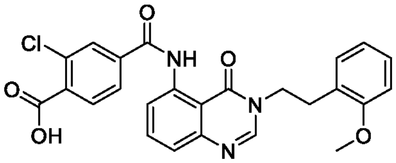
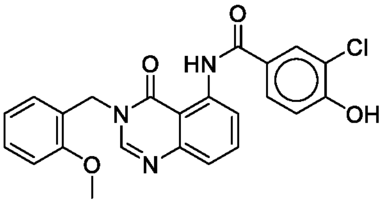
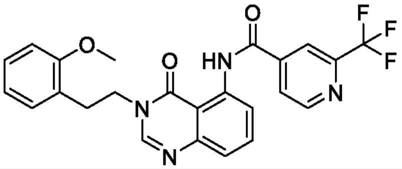
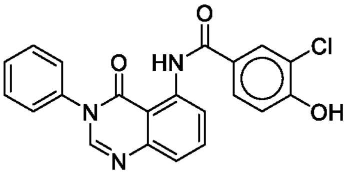
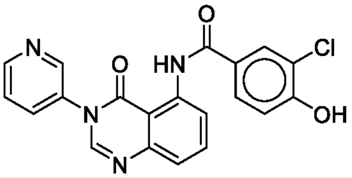
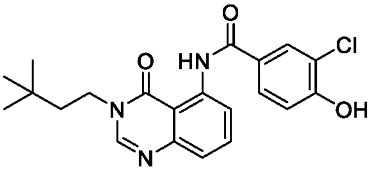
[0093] In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, cycloalkyl, or heterocycloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or cycloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d is independently hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d is independently hydrogen or C_1-C_6alkyl. In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, each R^c and R^d is hydrogen.

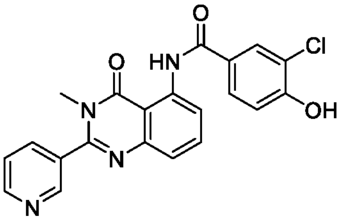
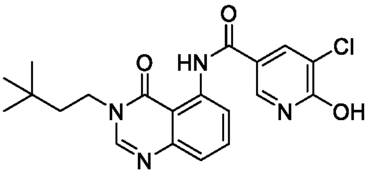
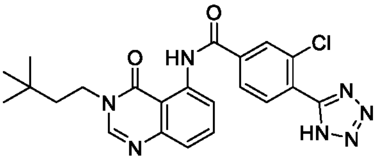
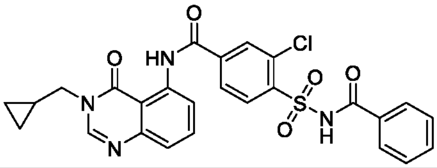
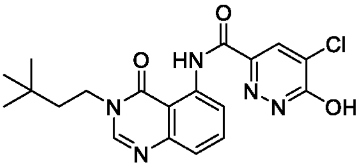
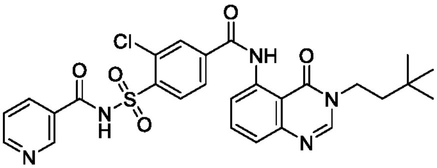
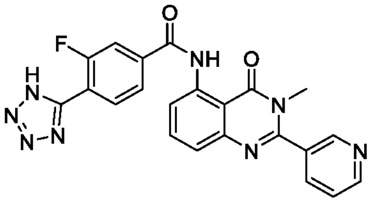
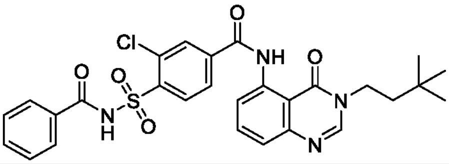
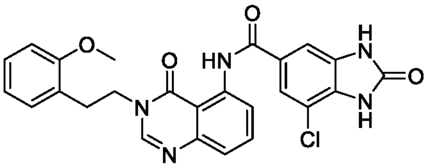
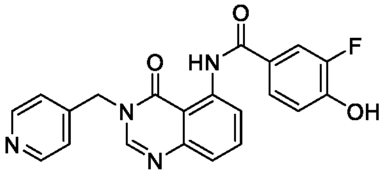
[0094] In some embodiments of a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one, two, or three halogen, C_1-C_6alkyl, or C_1-C_6haloalkyl.

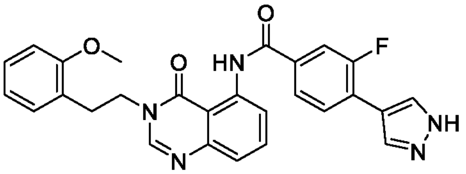
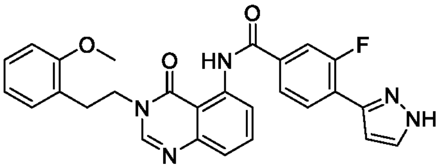
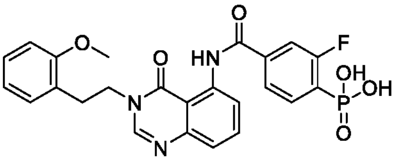
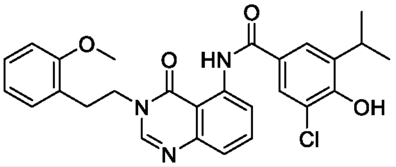
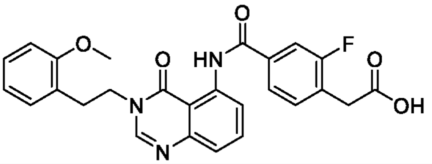
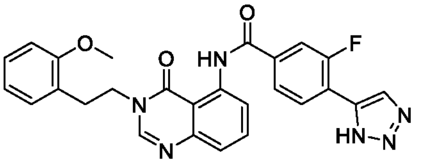
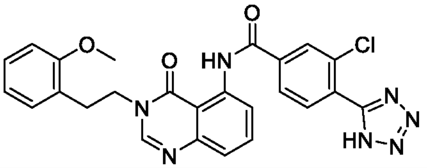
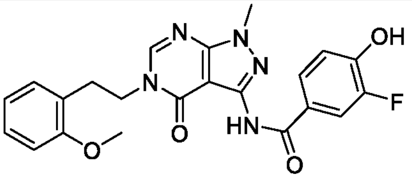
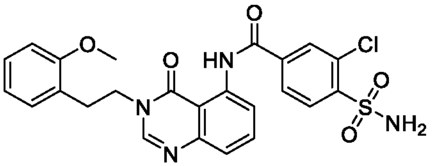
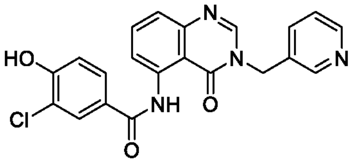
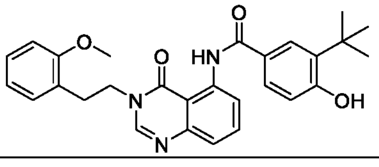
[0095] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

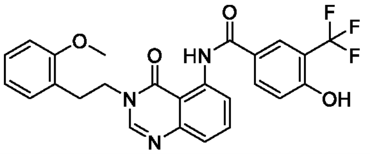
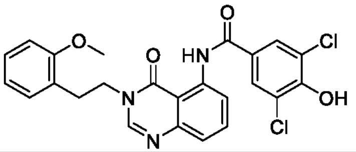
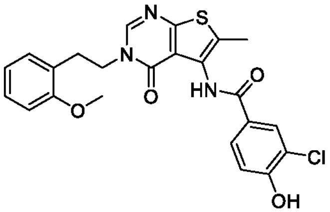
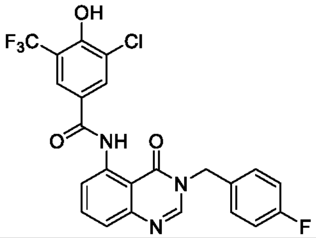
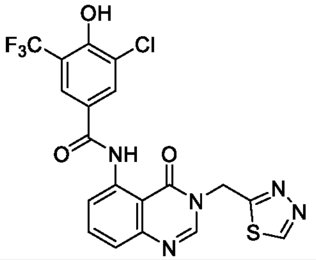
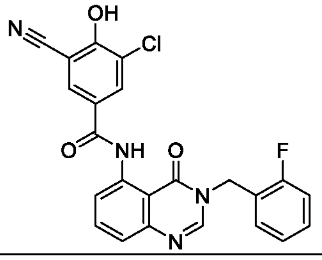
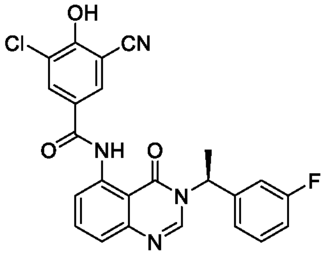
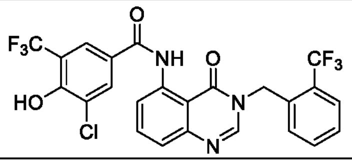
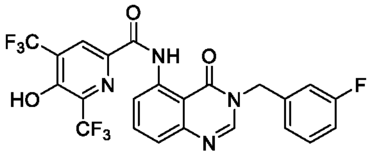
[0096] Described herein is a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, selected from a compound in Table 1.

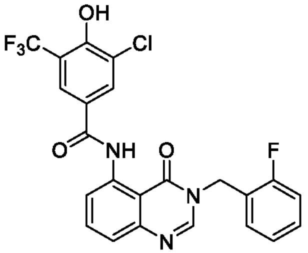
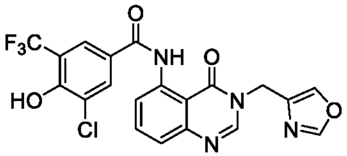
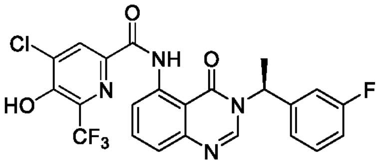
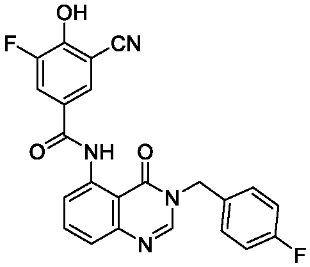
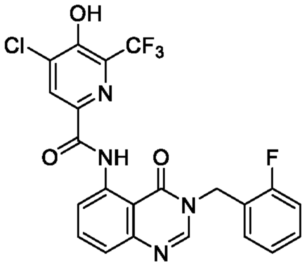
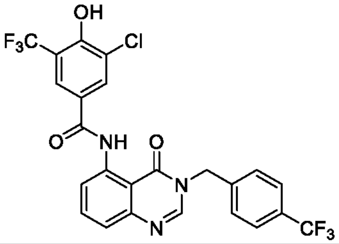
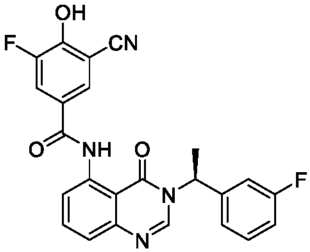
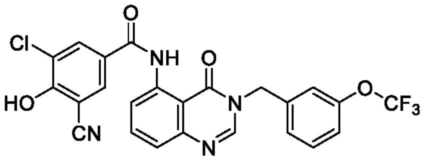
Table 1. Exemplary compounds

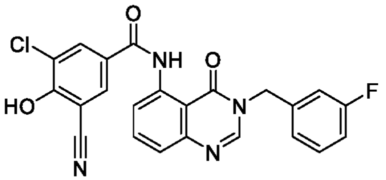
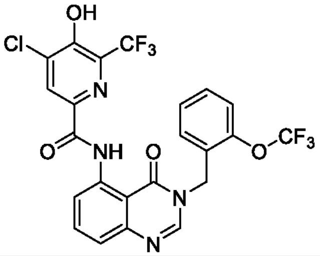
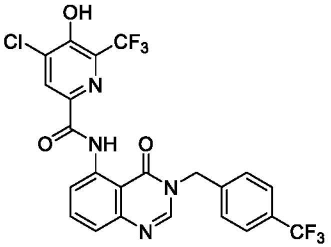
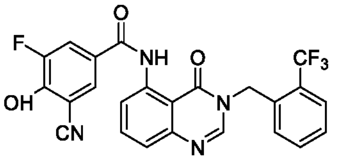
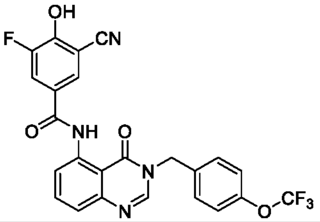
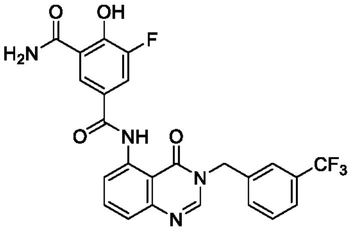
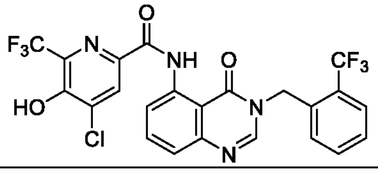
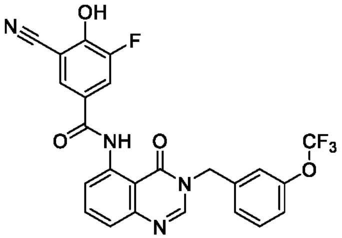
Example	Structure	Name
1		3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
2		3-fluoro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
3		N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-hydroxybenzamide
4		2-(2-fluoro-4-((3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamoyl)phenoxy)acetic acid
5		2-chloro-4-((3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamoyl)benzoic acid
6		3-chloro-4-hydroxy-N-(3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
7		N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-2-(trifluoromethyl)isonicotinamide
8		3-chloro-4-hydroxy-N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl)benzamide
9		3-chloro-4-hydroxy-N-(4-oxo-3-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)benzamide
10		3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxybenzamide

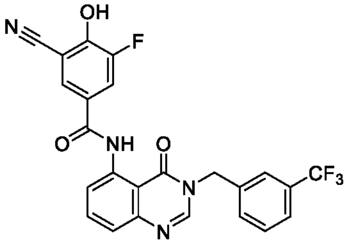
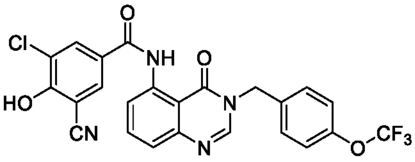
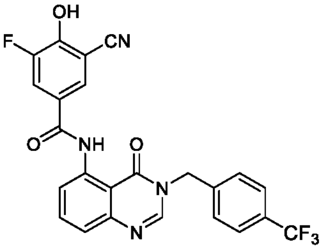
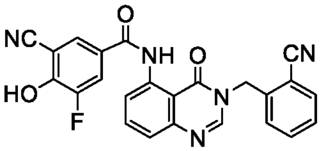
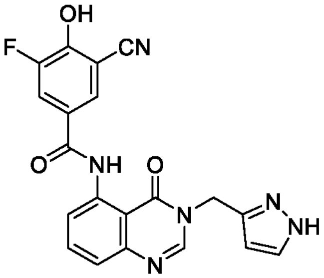
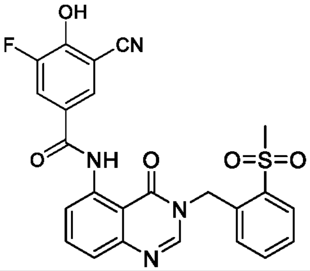
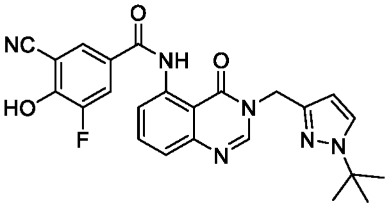
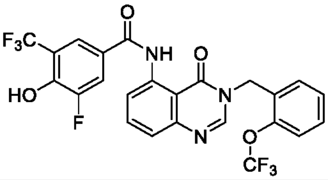
Example	Structure	Name
11		3-chloro-4-hydroxy-N-(3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)benzamide
12		5-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-6-hydroxynicotinamide
13		3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-(1H-tetrazol-5-yl)benzamide
14		4-(N-benzoylsulfamoyl)-3-chloro-N-(3-(cyclopropylmethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
15		5-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-6-hydroxypyridazine-3-carboxamide
16		N-((2-chloro-4-((3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamoyl)phenyl)sulfonyl)nicotinamide
17		3-fluoro-N-(3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)-4-(1H-tetrazol-5-yl)benzamide
18		4-(N-benzoylsulfamoyl)-3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
19		7-chloro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carboxamide
20		3-fluoro-4-hydroxy-N-(4-oxo-3-(pyridin-4-ylmethyl)-3,4-dihydroquinazolin-5-yl)benzamide

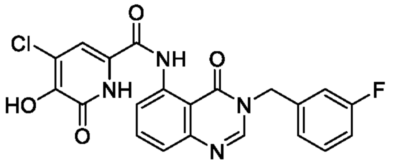
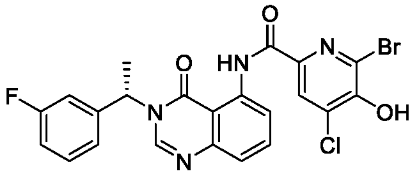
Example	Structure	Name
21		3-fluoro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-(1H-pyrazol-4-yl)benzamide
22		3-fluoro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-(1H-pyrazol-3-yl)benzamide
23		(2-fluoro-4-((3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamoyl)phenyl)phosphonic acid
24		3-chloro-4-hydroxy-5-isopropyl-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
25		2-(2-fluoro-4-((3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamoyl)phenyl)acetic acid
26		3-fluoro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-(1H-1,2,3-triazol-5-yl)benzamide
27		3-chloro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-(1H-tetrazol-5-yl)benzamide
28		3-fluoro-4-hydroxy-N-(5-(2-methoxyphenethyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzamide
29		3-chloro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-sulfamoylbenzamide
30		3-chloro-4-hydroxy-N-(4-oxo-3-(pyridin-3-ylmethyl)-3,4-dihydroquinazolin-5-yl)benzamide
31		3-(tert-butyl)-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide

Example	Structure	Name
32		4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-3-(trifluoromethyl)benzamide
33		3,5-dichloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
34		3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-6-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-5-yl)benzamide
35		3-chloro-N-(3-(4-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxy-5-(trifluoromethyl)benzamide
36		N-(3-((1,3,4-thiadiazol-2-yl)methyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-hydroxy-5-(trifluoromethyl)benzamide
37		3-chloro-5-cyano-N-(3-(2-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxybenzamide
38		(S)-3-chloro-5-cyano-N-(3-(1-(3-fluorophenyl)ethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxybenzamide
39		3-chloro-4-hydroxy-N-(4-oxo-3-(2-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)-5-(trifluoromethyl)benzamide
40		N-(3-(3-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-5-hydroxy-4,6-bis(trifluoromethyl)picolinamide

Example	Structure	Name
41		3-chloro-N-(3-(2-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxy-5-(trifluoromethyl)benzamide
42		3,5-dichloro-4-hydroxy-N-(3-(oxazol-4-ylmethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
43		(S)-4-chloro-N-(3-(1-(3-fluorophenyl)ethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-5-hydroxy-6-(trifluoromethyl)picolinamide
44		3-cyano-5-fluoro-N-(3-(4-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxybenzamide
45		4-chloro-N-(3-(2-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-5-hydroxy-6-(trifluoromethyl)picolinamide
46		3-chloro-4-hydroxy-*N*-(4-oxo-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)-5-(trifluoromethyl)benzamide
47		(S)-3-cyano-5-fluoro-N-(3-(1-(3-fluorophenyl)ethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxybenzamide
48		3-chloro-5-cyano-4-hydroxy-*N*-(4-oxo-3-(3-(trifluoromethoxy)benzyl)-3,4-dihydroquinazolin-5-yl)benzamide

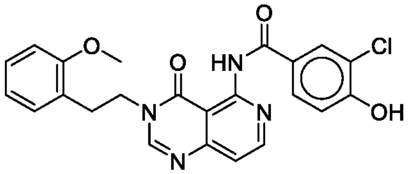
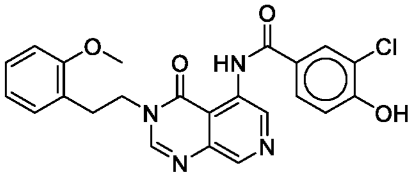
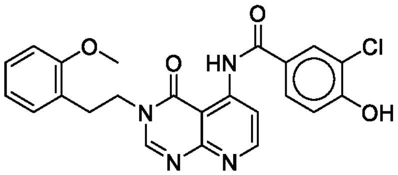
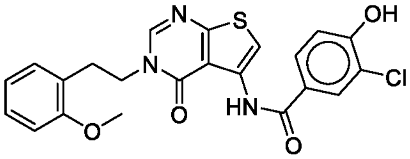
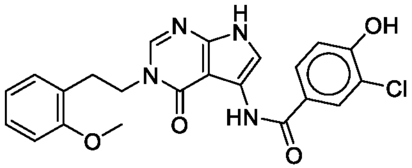
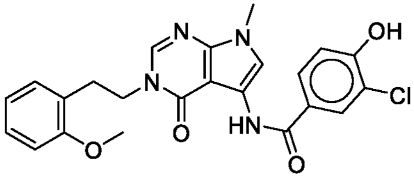
Example	**Structure**	**Name**
49		3-chloro-5-cyano-*N*-(3-(3-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxybenzamide
50		4-chloro-5-hydroxy-*N*-(4-oxo-3-(2-(trifluoromethoxy)benzyl)-3,4-dihydroquinazolin-5-yl)-6-(trifluoromethyl)picolinamide
51		4-chloro-5-hydroxy-*N*-(4-oxo-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)-6-(trifluoromethyl)picolinamide
52		3-cyano-5-fluoro-4-hydroxy-*N*-(4-oxo-3-(2-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)benzamide
53		3-cyano-5-fluoro-4-hydroxy-*N*-(4-oxo-3-(4-(trifluoromethoxy)benzyl)-3,4-dihydroquinazolin-5-yl)benzamide
54		5-fluoro-4-hydroxy-*N*1-(4-oxo-3-(3-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)isophthalamide
55		4-chloro-5-hydroxy-*N*-(4-oxo-3-(2-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)-6-(trifluoromethyl)picolinamide
56		3-cyano-5-fluoro-4-hydroxy-*N*-(4-oxo-3-(3-(trifluoromethoxy)benzyl)-3,4-dihydroquinazolin-5-yl)benzamide

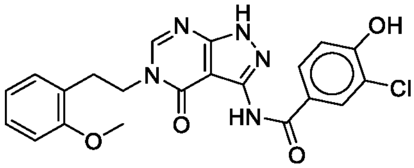
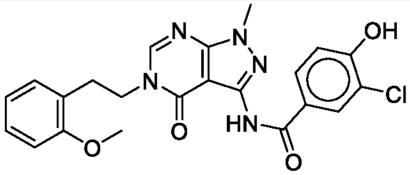
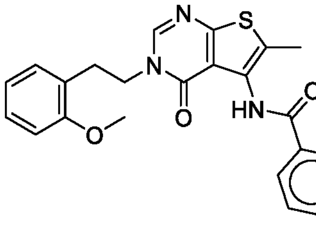
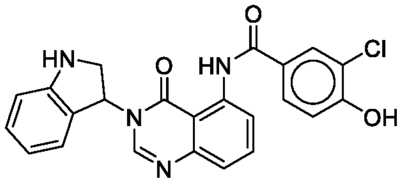
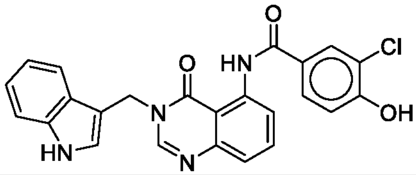
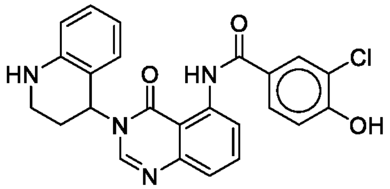
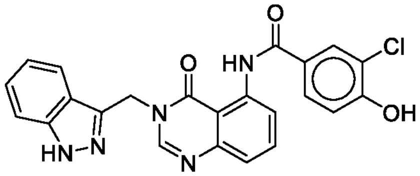
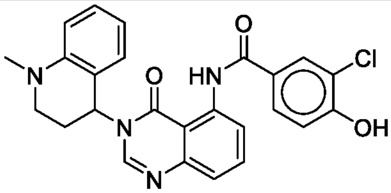
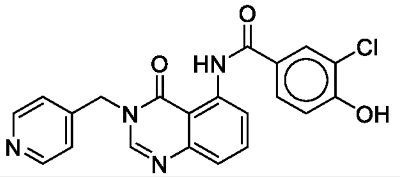
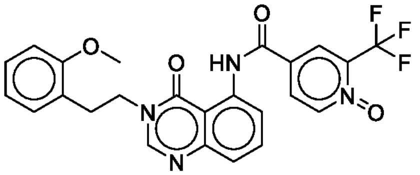
Example	Structure	Name
57		3-cyano-5-fluoro-4-hydroxy-*N*-(4-oxo-3-(3-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)benzamide
58		3-chloro-5-cyano-4-hydroxy-*N*-(4-oxo-3-(4-(trifluoromethoxy)benzyl)-3,4-dihydroquinazolin-5-yl)benzamide
59		3-cyano-5-fluoro-4-hydroxy-*N*-(4-oxo-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-5-yl)benzamide
60		3-cyano-*N*-{3-[(2-cyanophenyl)methyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-5-fluoro-4-hydroxybenzamide
61		*N*-(3-((1H-pyrazol-3-yl)methyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-3-cyano-5-fluoro-4-hydroxybenzamide
62		3-cyano-5-fluoro-4-hydroxy-N-(3-(2-(methylsulfonyl)benzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
63		N-(3-((1-(tert-butyl)-1H-pyrazol-3-yl)methyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-3-cyano-5-fluoro-4-hydroxybenzamide
64		3-fluoro-4-hydroxy-N-(4-oxo-3-(2-(trifluoromethoxy)benzyl)-3,4-dihydroquinazolin-5-yl)-5-(trifluoromethyl)benzamide

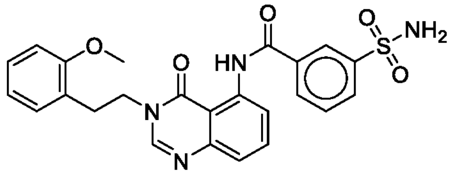
Example	Structure	Name
65		4-chloro-N-(3-(3-fluorobenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-5-hydroxy-6-oxo-1,6-dihydropyridine-2-carboxamide
66		6-bromo-4-chloro-N-{3-[(1S)-1-(3-fluorophenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-5-hydroxypyridine-2-carboxamide

[0097] Described herein is a compound of Formula (I), (Ia)-(If), (II), or (IIa)-(IIf), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, selected from a compound in Table 1a.

Table 1a. Exemplary compounds

Structure	Name
	3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)benzamide
	3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydropyrido[3,4-d]pyrimidin-5-yl)benzamide
	3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-5-yl)benzamide
	3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-5-yl)benzamide
	3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)benzamide
	3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-7-methyl-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)benzamide

	3-chloro-4-hydroxy-N-(5-(2-methoxyphenethyl)-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzamide
	3-chloro-4-hydroxy-N-(5-(2-methoxyphenethyl)-1-methyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-3-yl)benzamide
	3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-6-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidin-5-yl)benzamide
	3-chloro-4-hydroxy-N-(3-(indolin-3-yl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
	N-(3-((1H-indol-3-yl)methyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-hydroxybenzamide
	3-chloro-4-hydroxy-N-(4-oxo-3-(1,2,3,4-tetrahydroquinolin-4-yl)-3,4-dihydroquinazolin-5-yl)benzamide
	N-(3-((1H-indazol-3-yl)methyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-hydroxybenzamide
	3-chloro-4-hydroxy-N-(3-(1-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide
	3-chloro-4-hydroxy-N-(4-oxo-3-(pyridin-4-ylmethyl)-3,4-dihydroquinazolin-5-yl)benzamide
	4-((3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamoyl)-2-(trifluoromethyl)pyridine 1-oxide

	N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-3-sulfamoylbenzamide

Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[0098] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Labeled compounds

[0099] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, *i.e.*, ^2H, produces certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements.

[00100] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00101] In some embodiments, the labeled compounds described herein are used for measuring in vitro and in vivo binding of unlabeled HSD17B13 inhibitors.

Pharmaceutically acceptable salts

[00102] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00103] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or a solvate, or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00104] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ-hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylateundeconate and xylenesulfonate.

[00105] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein, solvate, or stereoisomer thereof and their pharmaceutically acceptable acid addition salts.

[00106] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^{+}(C_{1\text{-}4}\ \text{alkyl})_4$, and the like.

[00107] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[00108] In some embodiments, the compounds described herein exist as solvates. The invention provides for methods of treating diseases by administering such solvates. The invention further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00109] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or methanol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Tautomers

[00110] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Method of Treatment

[00111] Provided herein are methods of inhibiting HSD17B13 expression or activity, which can be useful for treating, preventing, or ameliorating a disease associated with HSD17B13 in a subject in need thereof, such as NAFLD or NASH, by administration of a compound that targets HSD17B13, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

[00112] Provided herein are methods of inhibiting expression or activity of HSD17B13 in a cell comprising contacting the cell with a HSD17B13 inhibitor disclosed or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, thereby inhibiting expression or activity of HSD17B13 in the cell. In some embodiments, the cell is a hepatocyte cell. In some embodiments, the cell is in the liver. In some embodiments, the cell is in the liver of a subject who has, or is at risk of having a disease, disorder, condition, symptom, or physiological marker associated with a liver disease, metabolic disease, or cardiovascular disease or disorder. In some embodiments, the cells are the adipocytes or monocytes from a subject who has or is at risk of having a disease. In some embodiments, the cells are the lymphocytes from a subject who has or is at risk of having a disease. In some embodiments, the liver disease, metabolic disease, or cardiovascular disease or disorder is metabolic syndrome, fatty liver disease, chronic liver disease, liver cirrhosis, hepatic steatosis, steatohepatitis, nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, nonalcoholic steatohepatitis (NASH), fulminant Wilson’s disease, rapidly fibrosing hepatitis C viral injury, and decompensated portal vein hypertension. In some embodiments, the liver disease, metabolic disease, or cardiovascular disease or disorder is NASH.

[00113] In some embodiments, the liver disease is primary biliary cirrhosis or primary sclerosing cholangitis.

[00114] Provided herein are methods of treating, preventing, delaying the onset, slowing the progression, or ameliorating one or more diseases, disorders, conditions, symptoms, or physiological markers associated with HSD17B13 comprising administering to a subject in need thereof a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the subject in need thereof is identified as having, or at risk of having, the disease, disorder, condition, symptom or physiological marker. In some embodiments, the liver disease, metabolic disease, or cardiovascular disease or disorder is metabolic syndrome, liver disease, fatty liver disease, chronic liver disease, liver cirrhosis, hepatic steatosis, steatohepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH). In some embodiments, the liver disease, metabolic disease, or cardiovascular disease or disorder is NASH.

[00115] Provided herein are methods of reducing, improving, or regulating hepatic steatosis, liver fibrosis, triglyceride synthesis, lipid levels, hepatic lipids, ALT levels, NAFLD Activity Score (NAS), cholesterol levels, or triglyceride levels, or a combination thereof, in a subject in need thereof comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating hepatic steatosis in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating liver fibrosis in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating triglyceride synthesis in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating lipid levels in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating hepatic lipids in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating ALT levels in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating NAFLD Activity Score in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating cholesterol levels in the individual. In some embodiments, the compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, is provided for use in reducing, improving, or regulating triglyceride levels in the individual. In some embodiments, the subject is identified as having, or at risk of having a disease, disorder, condition, symptom, or physiological marker associated with a liver disease, metabolic disease, or cardiovascular disease or disorder. In some embodiments, the liver disease, metabolic disease, or cardiovascular disease or disorder is metabolic syndrome, liver disease, fatty liver disease, chronic liver disease, liver cirrhosis, hepatic steatosis, steatohepatitis, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH). In some embodiments, the liver disease, metabolic disease, or cardiovascular disease or disorder is NASH.

[00116] Provided herein are methods for treating, preventing, or delaying onset drug induced liver injury (DILI) in a subject in need thereof. In some embodiments, the liver injury is steatohepatitis. Also provided herein are methods for treating, preventing, or delaying onset drug induced steatohepatitis (DISH) in a subject in need thereof. In some embodiments, the subject in need thereof is receiving chemotherapy for treating cancer. In some embodiments, the subject in need thereof is receiving a treatment for a cardiovascular disease. In some embodiments, the subject in need thereof is receiving treatment for a psychiatric disease/condition. In some embodiments, the subject in need thereof is receiving treatment for pain. In some embodiments, the subject in need thereof is receiving treatment for arthritis. In some embodiments, the chemotherapy is tamoxifen, toremifene, irinotecan, methotrexate, fluorouracil (5-FU), or any combination thereof. In some embodiments, the subject in need thereof is receiving amiodarone, perhexiline, propranolol, or any combination thereof. In some embodiments, the subject in need thereof is receiving amitriptyline, clozapine, or any combination thereof. In some embodiments, the subject in need thereof is receiving methotrexate, pirprofen, or any combinations thereof.

Dosing

[00117] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00118] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of or risk factor for the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition. In one aspect, prophylactic treatments include administering to a mammal having patatin-like phospholipase domain-containing 3 (PNPLA3) polymorphism, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent liver damages. The 148 Isoleucine to Methionine protein variant (I148M) of patatin-like phospholipase domain-containing 3 (PNPLA3), a protein is expressed in the liver and is involved in lipid metabolism, has recently been identified as a major determinant of liver fat content. Several studies confirmed that the I148M variant predisposes towards the full spectrum of liver damage associated with fatty liver: from simple steatosis to steatohepatitis and progressive fibrosis. Furthermore, the I148M variant represents a major determinant of progression of alcohol related steatohepatitis to cirrhosis, and to influence fibrogenesis and related clinical outcomes in chronic hepatitis C virus hepatitis, and possibly chronic hepatitis B virus hepatitis, hereditary hemochromatosis and primary sclerosing cholangitis. In some embodiments, PNPLA3 polymorphism is used to predict liver disease progression.

[00119] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00120] In certain embodiments wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00121] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent or daily treatment on a long-term basis upon any recurrence of symptoms.

[00122] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00123] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00124] In one embodiment, the daily dosages appropriate for the compound described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00125] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{10} and the ED_{90}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED_{50} with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00126] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00127] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day.

[00128] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the subject every 12 hours; (v) the compound is administered to the subject every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

Routes of Administration

[00129] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[00130] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

Pharmaceutical Compositions/Formulations

[00131] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In one embodiment, the compounds of this invention may be administered to animals. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

[00132] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington’s Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00133] In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

[00134] The pharmaceutical compositions described herein are administered to a subject by appropriate administration routes, including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, liquids, gels, syrups, elixirs, slurries, suspensions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid oral dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, powders, dragees, effervescent formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00135] Pharmaceutical compositions including compounds described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or compression processes.

[00136] Pharmaceutical compositions for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents are added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. In some embodiments, dyestuffs or pigments are added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00137] Pharmaceutical compositions that are administered orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added.

[00138] Pharmaceutical compositions for parental use are formulated as infusions or injections. In some embodiments, the pharmaceutical composition suitable for injection or infusion includes sterile aqueous solutions, or dispersions, or sterile powders comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof. In some embodiments, the pharmaceutical composition comprises a liquid carrier. In some embodiments, the liquid carrier is a solvent or liquid dispersion medium comprising, for example, water, saline, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and any combinations thereof. In some embodiments, the pharmaceutical compositions further comprise a preservative to prevent growth of microorganisms.

Combination

[00139] Disclosed herein are method of treating a liver disease, metabolic disease, or cardiovascular disease using a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, in combination with an additional therapeutic agent.

[00140] In some embodiments, the additional therapeutic agent is used for the treatment of diabetes or diabetes related disorder or conditions.

[00141] In some instances, the additional therapeutic agent comprises a statin, an insulin sensitizing drug, an insulin secretagogue, an alpha-glucosidase inhibitor, a GLP agonist, a GIP agonist, a THR beta agonist, a PDE inhibitor, a DPP-4 inhibitor (such as sitagliptin, vildagliptin, saxagliptin, linagliptin, anaglptin, teneligliptin, alogliptin, gemiglptin, or dutoglpitin), a catecholamine (such as epinephrine, norepinephrine, or dopamine), peroxisome proliferator-activated receptor (PPAR)-gamma agonist (*e.g.,* a thiazolidinedione (TZD) [such as pioglitazone, rosiglitazone, rivoglitazone, or troglitazone], aleglitazar, farglitazar, muraglitazar, or tesaglitazar), peroxisome proliferator-activated receptor (PPAR)-alpha agonist, peroxisome proliferator-activated receptor (PPAR)-delta agonist, a farnesoid X receptor (FXR) agonist (e.g., obeticholic acid), or a combination thereof. In some cases, the statin is a HMG-CoA reductase inhibitor. In other instances, additional therapeutic agents include fish oil, fibrate, vitamins such as niacin, retinoic acid (e.g., 9 cis-retinoic acid), nicotinamide ribonucleoside or its analogs thereof, or combinations thereof. In other instances, additional therapeutic agents include ACC inhibitors, FGF19 and FGF21 mimics, CCR2/CCR5 antagonists, or combinations thereof.

[00142] In some embodiments, the additional therapeutic agent is vivitrol.

[00143] In some embodiments, the additional therapeutic agent is a statin such as a HMG-CoA reductase inhibitor, fish oil, fibrate, niacin or a combination thereof. In other instances, the additional therapeutic agent is a dyslipidemia drug that prevent lipid absorption such as orlistat.

[00144] In some embodiments, the additional therapeutic agent is a vitamin such as retinoic acid or tocopheryl acetate for the treatment of diabetes and diabetes related disorder or condition such as lowering elevated body weight and/or lowering elevated blood glucose from food intake.

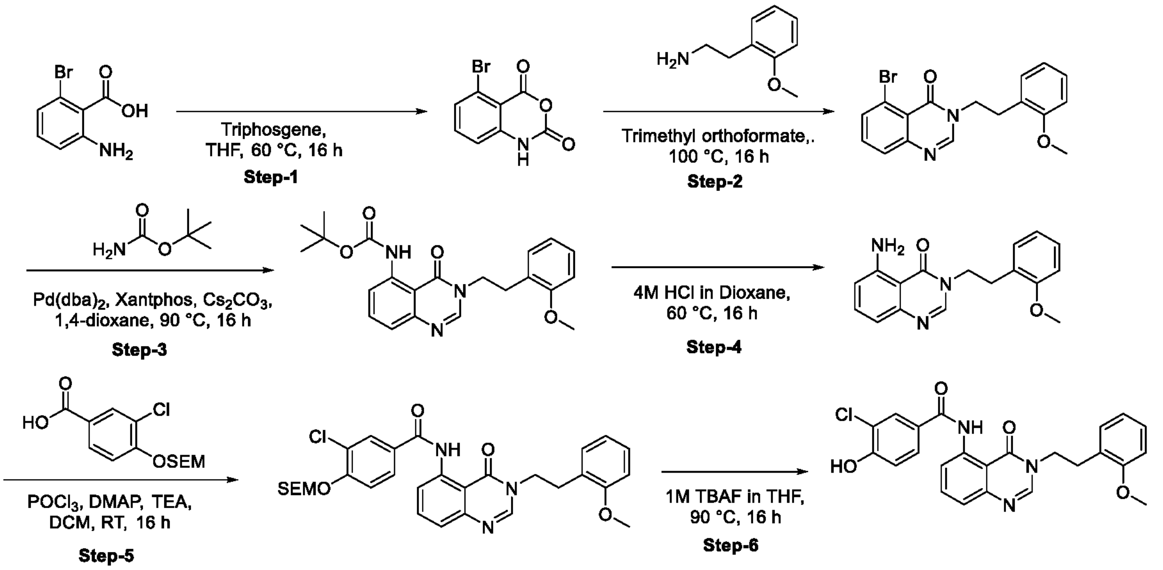
[00145] In some embodiments, the additional therapeutic agent is a glucose-lowering agent. In some embodiments, the additional therapeutic agent is an anti-obesity agent. In some embodiments, the additional therapeutic agent is selected from among a peroxisome proliferator activated receptor (PPAR) agonist (gamma, dual, or pan), a dipeptidyl peptidase (IV) inhibitor, a glucagon-like peptide-1 (GLP-I) analog, insulin or an insulin analog, an insulin secretagogue, a sodium glucose co-transporter 2 (SGLT2) inhibitor, a glucophage, a human amylin analog, a biguanide, an alpha-glucosidase inhibitor, a meglitinide, a thiazolidinedione, and sulfonylurea. In some embodiments, the additional therapeutic agent is metformin, sitagliptin, saxaglitpin, repaglinide, nateglinide, exenatide, liraglutide, insulin lispro, insulin aspart, insulin glargine, insulin detemir, insulin isophane, and glucagon-like peptide 1, or any combination thereof. In some embodiments, the additional therapeutic agent is a lipid-lowering agent.

[00146] In some embodiments, the additional therapeutic agent is an antioxidant, corticosteroid such as budesonide, anti-tumor necrosis factor (TNF), or a combination thereof.

[00147] In some embodiments, the additional therapeutic agent is administered at the same time as the compound disclosed herein. In some embodiments, the additional therapeutic agent and the compound disclosed herein are administered sequentially. In some embodiments, the additional therapeutic agent is administered less frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered more frequently than the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered prior than the administration of the compound disclosed herein. In some embodiments, the additional therapeutic agent is administered after the administration of the compound disclosed herein.

EXAMPLE

Example 1: 3-chloro-4-hydroxy-*N*-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide



Step 1: Synthesis of 5-bromo-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione

[00148] To a suspension of 2-amino-6-bromobenzoic acid (2.00 g, 9.26 mmol) in tetrahydrofuran (20.0 mL) was added solid triphosgene (2.75 g, 9.26 mmol) at ambient temperature and heated to 60°C for 16 h. The reaction mixture was evaporated under *vacuo*. The obtained solid was triturated with diethyl ether to afford 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione as off-white solid (1.8 g; 80.33%). LCMS (ES) *m/z* calcd. for C8H4BrNO3, 242.03; found, 243.9 (M+2H).

Step 2: Synthesis of 5-bromo-3-(2-methoxyphenethyl)quinazolin-4(3H)-one

[00149] To a suspension of 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione (0.5 g, 2.07 mmol) in trimethoxymethane (5.00 mL) was added 2-(2-methoxyphenyl)ethan-1-amine (312 mg, 2.07 mmol) at ambient temperature and then heated to 100 °C for 16 h. The reaction mixture was evaporated in *vacuo*. The obtained solid was triturated with diethyl ether to afford 5-bromo-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (0.65 g, 87.6%) as off-white solid. LCMS (ES) *m/z* calcd. for C17H15BrN2O2, 359.22; found, 361.1 (M+2H).

Step 3: Synthesis of tert-butyl (3-(2-methoxyphenethyl)-4-oxo-3,4-dihydro quinazolin-5-yl)carbamate

[00150] A stirred solution of 5-bromo-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (500 mg, 1.39 mmol) and tert-butyl carbamate (489 mg, 4.18 mmol) in 1,4-dioxane (10.0 mL) was purged with argon for 10 minutes. This was followed by the addition of 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.32 g, 0.55 mmol), cesium carbonate (1.36 g, 4.18 mmol) and Bis(dibenzylideneacetone)palladium(0) (0.16 g, 0.27 mmol). The resulting reaction mixture was heated to and maintained at 100 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated under *vacuo*. The crude material was purified by flash column chromatography. Pure fractions were collected and concentrated to afford tert-butyl N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamate (0.5 g, 91%) as yellow solid. LCMS (ES) *m/z* calcd. for $C_{22}H_{25}N_3O_4$, 395.46; found, 396.2 (M+H).

Step 4: Synthesis of 5-amino-3-(2-methoxyphenethyl)quinazolin-4(3H)-one

[00151] To a solid tert-butyl N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamate (0.5 g, 1.26 mmol) was added 4 *M* hydrogen chloride in 1,4-Dioxane (15.8 mL, 63.2 mmol) at 0 °C. The resulting reaction mixture was heated to and maintained at 60 °C for 16 h. After completion of the reaction, the reaction mixture was concentrated in *vacuo*. The obtained residue was triturated with diethyl ether (2 x 25 mL) and dried under *vacuo* to afford 5-amino-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (0.4 g, crude) as yellow solid. LCMS (ES) *m/z* calcd. for $C_{17}H_{17}N_3O_2$, 295.34; found, 296.2 (M+H).

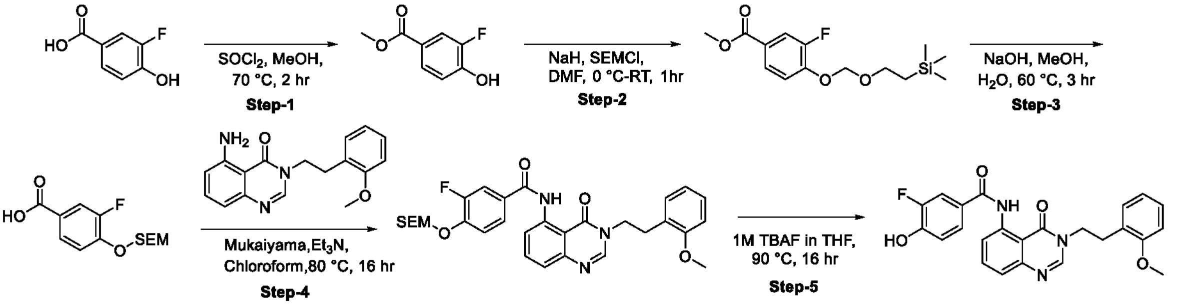
Step 5: Synthesis of 3-chloro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)benzamide

[00152] To a stirred solution of 3-chloro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzoic acid (0.23 g, 0.76 mmol) and 5-amino-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (0.15 g, 0.51 mmol) dissolved in dichloromethane (5 mL) was added *N,N*-Diisopropylethylamine (1.82 mL, 10.2 mmol), N,N-dimethylpyridin-4-amine (12.4 mg, 0.1 mmol) and phosphoryl trichloride (0.14 mL, 1.52 mmol) in dichloromethane (0.5 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 30 minutes. After completion of the reaction, the reaction mixture was concentrated in *vacuo* to get crude product. The crude material was purified by flash column chromatography. Pure fractions were collected and concentrated to afford 3-chloro-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide (0.29 g, 18.6 %) as off-white sold. LCMS (ES) *m/z* calcd. for $C_{30}H_{34}ClN_3O_5Si$, 580.15; found, 582.2 (M+2H).

Step 6: Synthesis of 3-chloro-4-hydroxy-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide

[00153] To a solution of 3-chloro-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide (0.07 g, 0.121 mmol) in tetrahydrofuran (1.00 mL) was added 1M tetrabutylammonium fluoride in tetrahydrofuran (0.7 mL, 2.42 mmol) at ambient temperature and then heated to and maintained at 60 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated in *vacuo.* The crude material was purified by flash column chromatography. Pure fractions were collected and concentrated to afford 3-chloro-4-hydroxy-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}benzamide as off-white solid (0.025 g, 46%). LCMS (ES) *m/z* calcd. for C24H20ClN3O4, 449.89; found, 450.1 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 11.12 (s, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 7.93 (s, 2H), 7.81-7.77 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19-7.15 (m, 2H), 7.09 (d, *J* = 6.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.83-6.79 (m, 1H), 4.23 (t, *J* = 6.0 Hz, 2H), 3.53 (s, 3H), 3.02 (t, *J* = 6.0 Hz, 2H).

Example 2: Synthesis of 3-fluoro-4-hydroxy-N-{3-[2-(2-methoxyphenyl) ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}benzamide



Step 1: Synthesis of methyl 3-fluoro-4-hydroxybenzoate

[00154] To a stirred solution of 3-fluoro-4-hydroxybenzoic acid (4.00 g, 25.6 mmol) in methanol (80 mL) was added thionyl chloride (12.0 mL, 16.5 mmol) drop-wise at 0 °C. The reaction mixture was heated at 70 °C for 2 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (200 mL), washed with saturated sodium bicarbonate (50 mL), water (50 mL) and brine solution (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and evaporated to afford methyl 3-fluoro-4-hydroxybenzoate as orange gum (4.0 g). LCMS (ES) m/z calcd. For C8H7FO3, 170.0; found, 171.1 (M+H).

Step 2: Synthesis of methyl 3-fluoro-4-{[2-(trimethylsilyl)ethoxy]methoxy} benzoate

[00155] To a stirred solution of methyl 3-fluoro-4-hydroxybenzoate (4.00 g, 23.5 mmol) dissolved in DMF (40.0 mL) was added sodium hydride (1.08g, 28.2 mmol) portion wise at 0 °C. The reaction mixture was stirred at ambient temperature for 30 min. Then the reaction mixture was added drop-wise [2-(chloromethoxy)ethyl]trimethylsilane (4.5 mL, 25.9 mmol) . The reaction mixture was stirred at ambient temperature for 1 h. After completion of the reaction, the reaction mixture was poured into ice-cold water (50 mL), extracted with ethyl acetate (2 x100 mL). The organic phase was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, filtered and evaporated to afford the methyl 3-fluoro-4-{[2-(trimethylsilyl) ethoxy]methoxy}benzoate orange colored gum (6.5g, crude). LCMS (ES) m/z calcd. For C14H21FO4Si, 300.1; found, 301.1 (M+H).

Step 3: synthesis of 3-fluoro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzoic acid

[00156] To a stirred solution of methyl 3-fluoro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzoate (6.5 g, 21.5 mmol) in methanol (80.0 mL) and water (20.0 mL) was added sodium hydroxide (2.6 g, 64.9 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was concentrated, and the residue was dissolved in water (40 mL) and acidified with 1*N* HCl (*p*H = 4). The resulting precipitate was collected by filtration and dried under *vacuum* to afford the crude 3-fluoro-4-{[2-(trimethylsilyl) ethoxy]methoxy}benzoic acid as a white solid (6 g). LCMS (ES) *m/z* calcd. for C13H19FO4Si, 286.1; found, 285.0 (M-H).

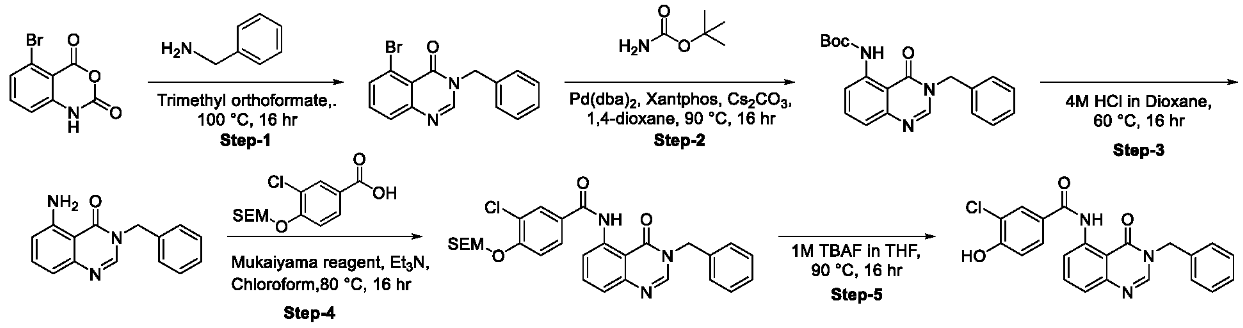
Step 4: Synthesis of 3-fluoro-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide

[00157] A stirred solution of 3-fluoro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzoic acid (0.727g, 2.54 mmol), triethylamine (1.52 mL, 8.26 mmol) and 2-chloro-1-methylpyridinium iodide (1.07 g, 4.95 mmol) in chloroform (15.0 mL) was purged with nitrogen for 5 mins. The reaction mixture was added 5-amino-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (500 mg, 1.69 mmol) and heated to 80 °C for 18 h. After completion, the reaction mixture was quenched with ice cold water (50 mL) and extracted with ethyl acetate (2 x 150 mL) and washed with brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated to afford the crude product. The crude material was purified by flash chromatography. Purification resulted in 3-fluoro-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide (0.45g, 47%) (LCMS (ES) *m/z* calcd. for C30H34FN3O5Si, 563.2; found, 564.2 (M+H).

Step 5: Synthesis of 3-fluoro-4-hydroxy-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}benzamide

[00158] To a stirred solution of 3-fluoro-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide (0.45g, 0.798 mmol) in tetrahydrofuran (6.0 mL) was added a solution of *tetrabutylammonium fluoride* (7.98 mL, 7.98 mmol. The reaction mixture was heated to 90 °C for 16 h. After completion, the reaction mixture was added with water (30 mL), extracted with ethyl acetate (2 x 50 mL). The organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to afford the crude product. The crude material was purified by flash chromatography. Purification resulted in 3-fluoro-4-hydroxy-N-{3-[2-(2-methoxyphenyl) ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}benzamide (0.2 g, 58%) (LCMS (ES) *m/z* calcd. for C24H20FN3O4, 433.1; found, 434.1 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 11.2-10.4 (bs, 1H), 8.71 (d, *J* = 8.0 Hz, 1H), 7.91 (S, 1H), 7.91-7.77 (m, 1H), 7.72-7.67 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19-7.13 (m, 2H), 7.09 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 6.83-6.79 (m, 1H), 4.24 (t, J = 5.6 Hz, 2H), 3.52 (S, 3H), 3.02 (t, J = 5.6Hz, 2H).

Example 3: Synthesis of N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-hydroxybenzamide



Step 1: Synthesis of 3-benzyl-5-bromo-3,4-dihydroquinazolin-4-one

[00159] To a suspension of 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione (1.00 g, 4.13 mmol) in trimethoxymethane (6.00 mL) was added 1-phenylmethanamine (0.45 g, 4.13 mmol). The reaction mixture was heated at 90 °C for 16 h. After completion, the reaction mixture was added with water (50 mL), extracted with ethyl acetate (2 x 100 mL). The organic phase was washed with brine solution (30 mL), dried over anhydrous sodium sulfate, filtered and evaporate under vacuum to get the crude. The crude material was purified by flash chromatography. Purification resulted in pure 3-benzyl-5-bromo-3,4-dihydroquinazolin-4-one (850 mg, 2.70 mmol) as a yellow colored compound. LCMS (ES) m/z calcd. for $C_{15}H_{11}BrN_2O$, 316.0; found, 317.0 (M+H).

Step 2: Synthesis of tert-butyl N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate

[00160] A suspension of 3-benzyl-5-bromo-3,4-dihydroquinazolin-4-one (860 mg, 2.73 mmol), tert-butyl carbamate (959 mg, 8.19 mmol) and tert-butyl carbamate (959 mg, 8.19 mmol) in 1,4-dioxane (10.0 mL) was purged with nitrogen. Then the reaction was added with [5-(diphenylphosphanyl)-9,9-dimethyl-9H-xanthen-4-yl]diphenylphosphane (0.63 g, 1.09 mmol) and bis((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one)palladium (314 mg, 0.546 mmol). The reaction mass was heated at 100 °C for 16 h. The reaction mixture was filtered through celite bed, washed with ethyl acetate (2 x 50 mL), the filtrate was evaporated to get crude. The crude material was purified by flash chromatography. Purification resulted in tert-butyl N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate (750 mg, 2.13 mmol) as yellow gum. LCMS (ES) m/z calcd. for $C_{20}H_{21}N_3O_3$, 351.1; found, 352.2 (M+H).

Step 3: Synthesis of 5-amino-3-benzyl-3,4-dihydroquinazolin-4-one

[00161] To the solid tert-butyl N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate (750 mg, 2.13 mmol) was added 4M HCl in 1,4-Dioxane (7.00 mL). The reaction mass was heated at 80 °C for 3 hr. After completion of the reaction it was evaporated in vacuo, the obtained residue was triturated with diethyl ether (2 x 25 mL) and dried under vacuum to afford 5-amino-3-benzyl-3,4-dihydroquinazolin-4-one (650 mg, Crude) as yellow solid. LCMS (ES) m/z calcd. for $C_{15}H_{13}N_3O$, 251.11; found, 252.11 (M+H).

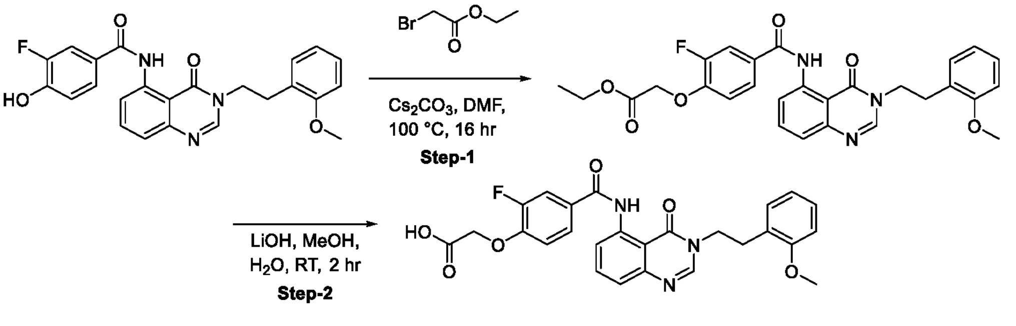
Step 4: Synthesis of N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide

[00162] A solution of 3-chloro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzoic acid (603 mg, 1.99 mmol), triethylamine (1.84 mL, 9.95 mmol) and 2-chloro-1-methylpyridiniumiodide (1.29 g, 5.97 mmol) in chloroform (10 mL) was purged with nitrogen for 5 min. The reaction mixture was then added 5-amino-3-benzyl-3,4-dihydroquinazolin-4-one (500 mg, 1.99 mmol). After addition, the reaction was heated to 80 °C for 16 h. After completion of the reaction, the reaction mixture was quenched with ice-cold water (50 mL), extracted with dichloromethane (2 x 150 mL), washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered and evaporate under vacuum to get the crude. The crude material was purified by flash chromatography. Purification resulted in N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide (650 mg, 1.21 mmol) as yellow solid. LCMS (ES) m/z calcd. for $C28H30ClN3O4Si$, 535.17; found, 536.2 (M+H).

Step 5: Synthesis of N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-hydroxybenzamide

[00163] To a stirred solution of N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide (0.65g, 1.12 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammoniumfluoride (12.1 mL, 12.1 mmol). The reaction mixture was heated at 90 °C for 16 h. After completion, the reaction mixture was added to water (50 mL) and extracted with ethyl acetate (2 x 150 mL). The organic phase was washed with brine (50 mL), dried over anhydrous sodium sulphate, filtered, and evaporated to get the crude. The crude material was purified by flash chromatography. Purification resulted in N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)-3-chloro-4-hydroxybenzamide (0.1 g, 21%) (LCMS) m/z calcd. For $C22H16ClN3O3$, 405.09; found, 405.9 (M+H). ^{1}H NMR (400 MHz, DMSO-d6) δ 12.91 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.58 (s, 1H), 7.90 (S, 1H), 7.84-7.80 (m, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.41-7.13 (m, 6H), 7.12 (d, J = 8.4 Hz, 1H), 5.25 (s, 2H).

Example 4: Synthesis of 2-[2-fluoro-4-({3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamoyl)phenoxy]acetic acid



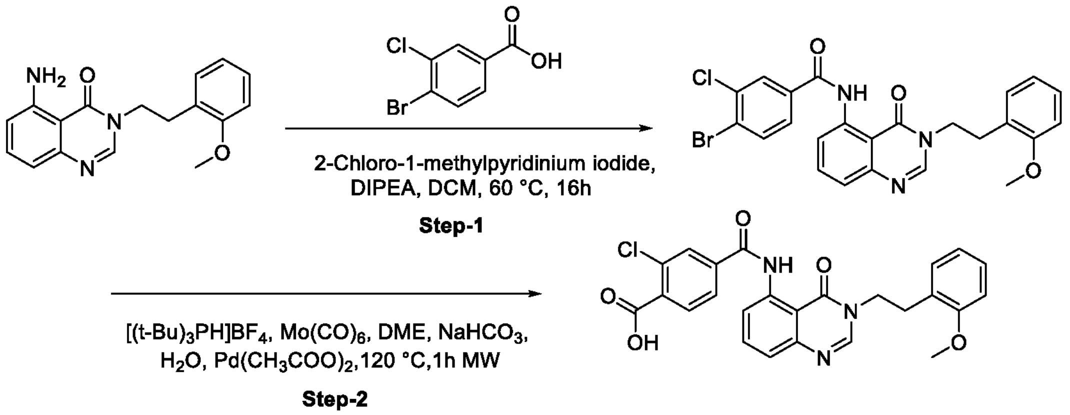
Step 1: Synthesis of ethyl 2-[2-fluoro-4-({3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamoyl)phenoxy]acetate

[00164] To a solution of 3-fluoro-4-hydroxy-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}benzamide (60 mg, 0.138 mmol) in DMF (3 ml) was added cesium carbonate (135 mg, 0.415 mmol) and ethyl 2-bromoacetate (34.7 mg, 208 µmol). Reaction mixture was heated at 100 °C for 12 h. After completion, the reaction mixture was added to water (20 mL), extracted with ethyl acetate (2x50 mL) and washed with brine (25 mL). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated under *vacuum* to afford ethyl 2-[2-fluoro-4-({3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamoyl)phenoxy]acetate (40 mg, 56%) as white solid. LCMS (ES) *m/z* calcd. for C28H26FN3O6, 519.18; found, 520.2 (M+H).

Step 2: Synthesis of 2-[2-fluoro-4-({3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamoyl)phenoxy]acetic acid

[00165] To a solution of ethyl 2-[2-fluoro-4-({3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamoyl)phenoxy]acetate (40 mg, 0.138 mmol) in methanol (8 mL) and water (4 mL) was added lithium hydroxide (3.98 mg, 0.166 mmol). The Reaction mixture was stirred at room temperature for 2 h. After completion of the reaction, the reaction mixture was concentrated, the residue was dissolved in water (10 mL) and acidified with 1*N* HCl (pH = 4). The precipitate formed was filtered, washed with water (2X5 mL) and dried under *vacuum* to afford 2-[2-fluoro-4-({3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamoyl)phenoxy]acetic acid (20 mg, 30%) as off-white solid. LCMS (ES) *m/z* calcd. for C26H22FN3O6, 491.1; found, 492.0 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.71 (d, J = 8.0 Hz, 1H), 7.92 (S, 1H), 7.82-7.75 (m, 3H), 7.37-7.31 (m, 2H), 7.18-7.15 (m, 1H), 7.08 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.82-6.79 (m, 2H), 4.92 (S, 2H), 4.23 (m, 2H), 3.41 (s, 3H), 3.02 (s, 2H).

Example 5: Synthesis of 2-chloro-4-((3-(2-methoxyphenethyl)-4-oxo-3,4-dihydro quinazolin-5-yl)carbamoyl)cyclohexa-1,5-diene-1-carboxylic acid



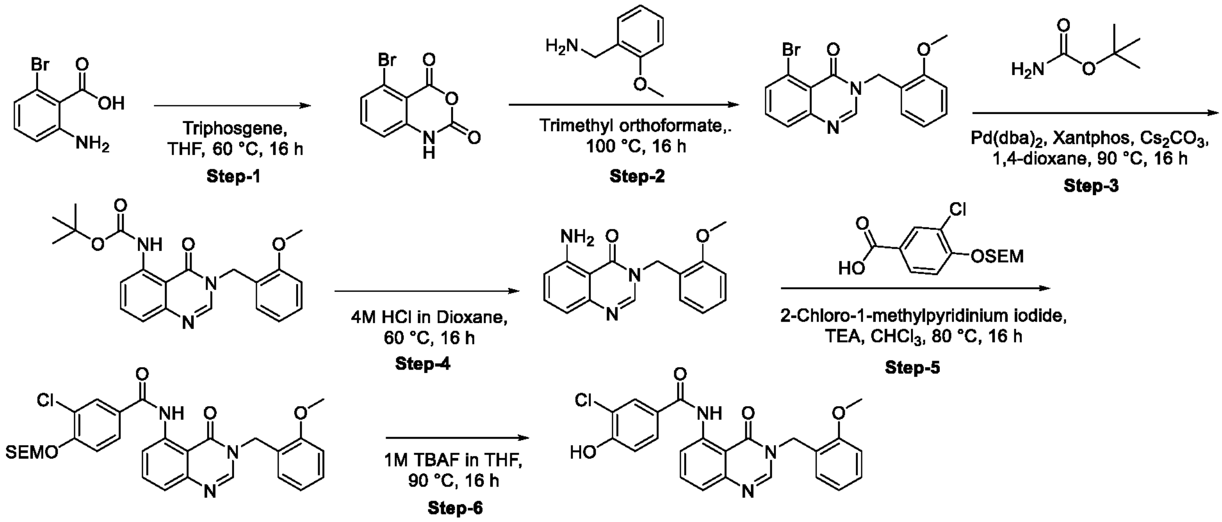
Step 1: Synthesis of 4-bromo-3-chloro-N-(3-(2-methoxyphenethyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide

[00166] To a stirred solution of 4-bromo-3-chlorobenzoic acid (500 mg, 2.12 mmol) in dichloromethane (3.0 mL) was added 2-chloro-1-methylpyridin-1-ium iodide (1.63 g, 3 eq., 6.37 mmol), ethylbis(propan-2-yl)amine (1.14 mL, 3 eq., 6.37 mmol) and 5-amino-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (502 mg, 0.8 eq., 1.70 mmol) at room temperature. After addition, the reaction mixture was heated to 60 °C for 16 h. The reaction mixture was diluted with ice-water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. The crude material was purified by flash chromatography. Purification resulted in 4-bromo-3-chloro-N-{3-[2-(2-methoxyphenyl) ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}benzamide (0.38 g, 34%) as yellow solid. LCMS (ES) *m/z* calcd. for C24H19BrClN3O3, 513.03; found, 513.8 (M+H).

Step 2: Synthesis of 2-chloro-4-((3-(2-methoxyphenethyl)-4-oxo-3,4-dihydro quinazolin-5-yl)carbamoyl)cyclohexa-1,5-diene-1-carboxylic acid

[00167] To a stirred solution of 4-bromo-3-chloro-N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}benzamide (100 mg, 195 µmol) in 1,2-dimethoxyethane (1.0 mL) was added tert-butylphosphaniumtetrafluoroborate (11.3 mg, 0.039 mmol), hexacarbonyl molybdenum(0) (103 mg, 0.39 mmol), sodium carbonate (24.6 mg, 0.293 mmol) in water (0.5 mL) and palladium acetate (2.2 mg, 0.0975 mmol) was heated at 120 °C in microwave for 15 mins. After completion of the reaction, the reaction mixture was poured into water (20 ml) and extracted with dichloromethane (3 x10 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated in *vacuo* to result in crude. The crude was purified by reverse phase preparative HPLC. Pure fractions were collected and evaporated in *vacuo* to afford pure 2-chloro-4-({3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}carbamoyl)benzoic acid (0.013 g; 13%) as white solid. LCMS (ES) *m/z* calcd. for C25H20ClN3O5, 477.1; found, 478.1 (M+H). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.26 (s, 1H), 8.71 (s, 1H), 8.04-7.95 (m, 4H), 7.83 (t, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.017-7.08 (m, 2H), 6.86-6.81 (m, 3H), 4.23 (bs, 2H), 3.52 (s, 3H), 3.02 (bs, 2H).

Example 6: Synthesis of 3-chloro-4-hydroxy-N-(3-(2-methoxybenzyl)-4-oxo-3,4-dihydro quinazolin-5-yl)benzamide



Step 1: Synthesis of 5-bromo-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione

[00168] To a suspension of 2-amino-6-bromobenzoic acid (2.00 g, 9.26 mmol) in tetrahydrofuran (20.0 mL) was added solid triphosgene (2.75 g, 9.26 mmol) at ambient temperature and after addition the reaction mixture was heated to 60 °C for 16 h. Evaporation of the reaction mixture resulted in solid which was purified by trituration in diethyl ether. This afforded 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione as off-white solid (1.8g; 80.3%). LCMS (ES) *m/z* calcd. for C8H4BrNO3, 240.9; found, 241.9 (M+H).

Step 2: Synthesis of 5-bromo-3-(2-methoxybenzyl)quinazolin-4(3H)-one

[00169] To a suspension of 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione (1.00 g, 4.13 mmol) in trimethoxymethane (5.00 mL) was added 1-(2-methoxyphenyl)methanamine (567 mg, 4.13 mmol) at ambient temperature and then heated to 100 °C for 16 h. The reaction mixture was evaporated under *vacuo*. The resulting solid was triturated with diethyl ether to afford pure 5-bromo-3-(2-methoxybenzyl)quinazolin-4(3H)-one) as off-white solid. LCMS (ES) *m/z* calcd. for C16H13BrN2O2, 344.0; found, 345.0 (M+H).

Step 3: Synthesis of tert-butyl (3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate

[00170] A stirred solution of 5-bromo-3-[(2-methoxyphenyl)methyl]-3,4-dihydroquinazolin-4-one (800 mg, 2.32 mmol) and tert-butyl carbamate (500 mg, 1.07 mmol) in 1,4-dioxane (10.0 mL) was purged with argon for 10 mins. This was followed by the addition of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.53 g, 0.92 mmol), cesium carbonate (1.36 g, 4.18 mmol) and bis(dibenzylideneacetone)palladium(0) (0.267 g, 0.464 mmol). The resulting reaction mixture was heated to 100 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated in *vacuo.* The crude material was purified by combi flash chromatography. Purification resulted in tert-butyl (3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate (0.5 g, 82%) as yellow solid. LCMS (ES) *m/z* calcd. for C21H23N3O4, 381.2; found, 382.2 (M+H).

Step 4: Synthesis of 5-amino-3-(2-methoxybenzyl)quinazolin-4(3H)-one

[00171] To a solid of tert-butyl N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate (500 mg, 1.42 mmol) was added 4 M HCl in 1,4-dioxane (15.8 mL, 63.2 mmol) at 0 °C. The resulting reaction mixture was heated to 60 °C for 16 h. After completion of the reaction, the reaction mixture was concentrated in *vacuo*. The obtained residue was triturated with diethyl ether (2 x 25 mL) and dried under vacuum to afford 5-amino-3-(2-methoxybenzyl)quinazolin-4(3H)-one (0.42 g) as yellow solid. LCMS (ES) *m/z* calcd. for C16H15N3O2, 281.1; found, 282.1 (M+H)

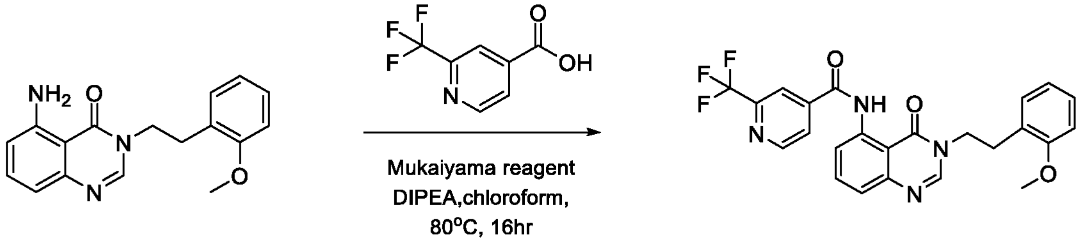
Step 5: Synthesis of 3-chloro-N-(3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)benzamide

[00172] A stirred solution of 3-chloro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzoic acid (0.72 g, 2.38 mmol) in chloroform (5.0 mL) was purged with nitrogen for 10 mins. This was followed by the addition of triethylamine (1.54 mL, 8.26 mmol), 2-Chloro-1-methylpyridinium iodide (1.54 g, 7.14 mmol) and 5-amino-3-(2-methoxybenzyl)quinazolin-4(3H)-one (0.53 g, 1.9 mmol) at ambient temperature. The resulting reaction mixture was heated to 80 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated under *vacuo.* The crude material was purified by flash chromatography. Purification resulted in 3-chloro-N-(3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)benzamide as an off white solid (0.52 g, 31%). LCMS (ES) *m/z* calcd. For C29H32ClN3O5Si, 565.18; found, 566.2 (M+H).

Step 6: Synthesis of 3-chloro-4-hydroxy-N-(3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide

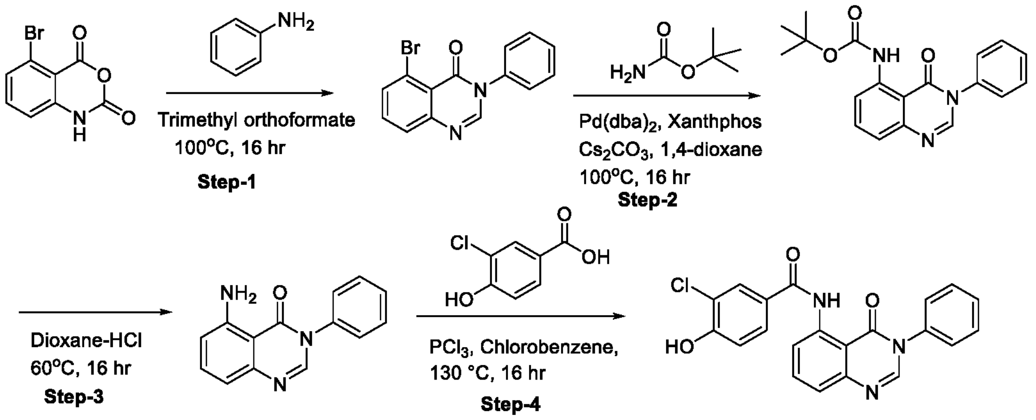
[00173] To a solution of 3-chloro-N-{3-[(2-methoxyphenyl)methyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzamide (0.3 g, 0.530 mmol) in tetrahydrofuran (1.00 mL) was added 1M tetrabutylammonium fluoride in tetrahydrofuran (2.3 mL, 7.95 mmol) at ambient temperature and then heated to 60 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated under *vacuo*. The crude material was purified by flash chromatography. Purification resulted in 3-chloro-4-hydroxy-N-(3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-5-yl)benzamide as off-white solid (0.025 g, 46%). LCMS (ES) *m/z* calcd. For C23H18ClN3O4, 435.1; found, 436.1 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 11.13 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.47 (s, 1H), 7.90 (s, 1H), 7.82 (t, J = 12 Hz, 1H), 7.75(d, J = 8 Hz, 1H), 7.39 (d, J = 8 Hz, 1H), 7.29 (t, J = 8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 2H) ,7.04 (d, J = 8 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 5.17 (s, 2H), 3.83 (s, 3H).

Example 7: Synthesis of N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-2-(trifluoromethyl)pyridine-4-carboxamide



[00174] To a stirred solution of 2-(trifluoromethyl)pyridine-4-carboxylic acid (300 mg, 1.57 mmol) and 5-amino-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (464 mg, 1.57 mmol) in chloroform (5 mL) under nitrogen atmosphere was added ethylbis(propan-2-yl)amine (1.45 mL, 8.26 mmol) and 2-chloro-1-methylpyridin-1-ium iodide (1.20 g, 4.71 mmol) and stirred at 80 °C for 16 h. Reaction was monitored by LCMS and TLC. After completion of reaction, the reaction mixture was quenched with ice-cold water (50 mL) and extracted with ethyl acetate (50 mL) and organic layer was washed with brine solution (2 X 25 mL) and dried over anhydrous sodium sulphate, filtered and concentrated under *vacuum*. The crude material was purified by flash column chromatography. Purification afforded N-{3-[2-(2-methoxyphenyl)ethyl]-4-oxo-3,4-dihydroquinazolin-5-yl}-2-(trifluoromethyl)pyridine-4-carboxamide (65.0 mg, 8%) as off-white solid. LCMS (ES) *m/z* calcd. for C24H19F3N4O3, 468.1; found, 467.0 (M-H). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.42 (s, 1 H), 9.11 (d, J=5.2Hz, 1H), 8.71 (d, J=8 Hz, 1H), 8.284 (s, 1H), 8.18 (d, J=4.4Hz, 1H), 7.98 (s, 1H), 7.86 (t, 1H), 7.4 (d, J=8, 1H), 7.17 (t, 1H), 7.09 (d, J=7.2, 1H), 6.88-6.79 (m, 2H), 4.25-4.22 (t, 2H), 3.52 (s, 3H), 3.03-3.00 (t, 2H).

Example 8: Synthesis of 3-chloro-4-hydroxy-N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl)benzamide



Step 1: Synthesis of 5-bromo-3-phenyl-3,4-dihydroquinazolin-4-one

[00175] To a stirred solution of 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione (1.00 g, 4.13 mmol) in trimethoxymethane (3 ml) was added aniline (385 mg, 4.13 mmol) and stirred at 100 °C for 16 h. The separated solid was washed with n-pentane to get 5-bromo-3-phenyl-3,4-dihydroquinazolin-4-one as off-white solid. LCMS (ES) *m/z* calcd. for C14H9BrN2O, 301.99; found, 303.0 (M+H).

Step 2: Synthesis of tert-butyl N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl) carbamate

[00176] A suspension of 5-bromo-3-phenyl-3,4-dihydroquinazolin-4-one (1.10 g, 3.65 mmol) and tert-butyl N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl)carbamate (1.20 g, 3.56 mmol) in 1,4-dioxane (10.0 mL) was purged with nitrogen. Then added [5-(diphenylphosphanyl)-9,9-dimethyl-9H-xanthen-4-yl]diphenylphosphane (845 mg, 1.46 mmol) and bis((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) palladium (420 mg, 0.731 mmol). The reaction mass was stirred at 100 °C for 16 h. The reaction mixture was filtered through celite bed, washed with ethyl acetate (2 x 50 mL), the filtrate was washed with water (20 mL), brine solution (20 mL), dried over sodium sulphate, filtered and concentrated to get crude product as brown gum. The crude product was purified flash column chromatography. Purification resulted in tert-butyl N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl)carbamate as white solid. (1.2 g, 97.3%). LCMS (ES) *m/z* calcd. for C19H19N3O3, 337.1; found, 338.1 (M+H).

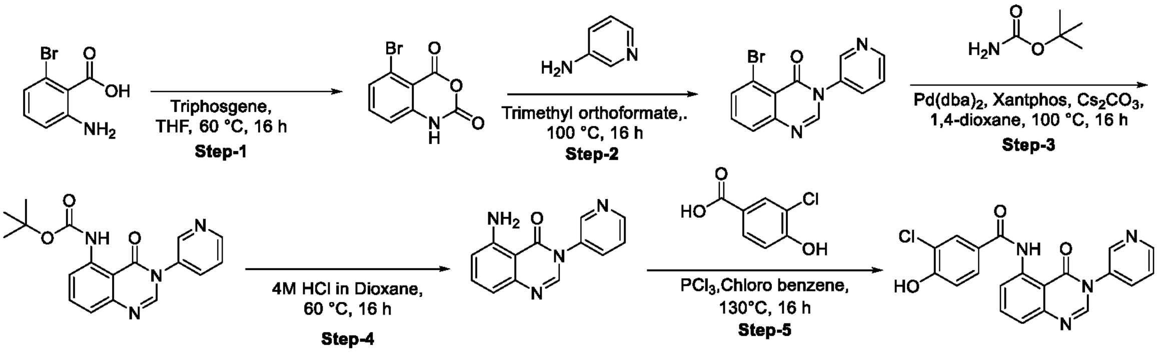
Step 3: Synthesis of 5-amino-3-phenyl-3,4-dihydroquinazolin-4-one

[00177] To a solid of tert-butyl N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl)carbamate (1.5 g,4.45 mmol)) was added 4 M HCl in 1,4-dioxane (30 mL, 125 mmol) at 0 °C. The resulting reaction mixture was heated to 60 °C for 16 h. After completion of the reaction, the reaction mixture was concentrated under *vacuo*. The obtained residue was triturated with diethyl ether (2 x 25 mL) and dried under *vacuo* to afford 5-amino-3-[2-(2-methoxyphenyl)ethyl]-3,4-dihydroquinazolin-4-one (950 mg, 90%) as pale yellow solid. LCMS (ES) *m/z* calcd. for C14H11N3O, 237.1; found, 238.1 (M+H).

Step 4: Synthesis of 3-chloro-4-hydroxy-N-(4-oxo-3-phenyl-3,4-dihydroquinazolin-5-yl)benzamide

[00178] To a stirred solution of 5-amino-3-phenyl-3,4-dihydroquinazolin-4-one (500 mg, 2.11 mmol), 3-chloro-4-hydroxybenzoic acid (364 mg, 2.11 mmol) in chlorobenzene (7 ml) was added trichlorophosphane (145 mg) and stirred at 130 °C for 16 h. Reaction was cooled to room temperature and quenched with sodium bicarbonate solution and extracted with ethyl acetate (100 ml). The organic layer was washed with brine solution and dried over anhydrous sodium sulphate, filtered, and concentrated. The crude product was purified by flash column chromatography. Purification resulted in 3-chloro-4-hydroxy-N-(4-oxo-3-phenyl-3,4-dihydro quinazolin-5-yl)benzamide as off-white solid (10 mg, 1.21%). LCMS (ES) *m/z* calcd. For C21H14ClN3O3, 391.07; found, 392.1 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (s, 1H), 11.10 (s, 1H), 8.79 (d, *J* = 8.4 Hz, 1 H), 8.36 (s, 1H), 7.89 (d, J=11.2 Hz, 2H), 7.7 (d, J=8 Hz, 1 H), 7.58 (m, 4H), 7.44 (d, J=8 Hz, 1H), 7.10 (d, J=8 Hz, 1H).

Example 9: Synthesis of 3-chloro-4-hydroxy-N-(4-oxo-3-(pyridin-3-yl)-3,4-dihydro quinazolin-5-yl)benzamide



Step 1: Synthesis of 5-bromo-2*H*-benzo[*d*][1,3]oxazine-2,4(1*H*)-dione

[00179] To a stirred solution of 2-amino-6-bromobenzoic acid (2.00 g, 9.26 mmol) in tetrahydrofuran (20.0 mL) was added solid triphosgene (2.75 g, 9.26 mmol) at ambient temperature and then heated to 60 °C for 16 h. The reaction mixture was evaporated in *vacuo*. The separated solid was triturated with diethyl ether to afford 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione as off white solid (1.8 g; 80.3%). LCMS (ES) *m/z* calcd. For C8H4BrNO3, 240.9; found, 241.9 (M+H).

Step 2: Synthesis of 5-bromo-3-(pyridin-3-yl)quinazolin-4(3H)-one

[00180] To a stirred solution of 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione (1.00 g, 4.13 mmol) in trimethoxymethane (5.00 mL) was added pyridin-3-amine (0.778 g , 8.26 mmol) at ambient temperature and heated at 100 °C for 16 h. The reaction mixture was evaporated in *vacuo*. The separated solid was triturated with diethyl ether to afford 5-bromo-3-(pyridin-3-yl)-3,4-dihydroquinazolin-4-one as off-white solid. LCMS (ES) *m/z* calcd. for, C13H8BrN3O, 300.99; found, 302.0 (M+H).

Step 3: Synthesis of tert-butyl (4-oxo-3-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl) carbamate

[00181] A stirred solution of 5-bromo-3-(pyridin-3-yl)-3,4-dihydroquinazolin-4-one (0.5 g, 1.65 mmol) and tert-butyl carbamate (0.6 g, 1.51 mmol) in 1,4-dioxane (10.0 mL) was purged with argon for 10 minutes. This was followed by the addition of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.326 g, 0.57 mmol), cesium carbonate (1.36 g, 4.18 mmol) and bis(dibenzylideneacetone)palladium(0) (0.167 g, 0.282 mmol). The resulting reaction mixture was heated to 100 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated under *vacuo*. The crude material was purified by flash column chromatography.

Purification afforded tert-butyl N-[4-oxo-3-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl]carbamate (0.6 g, 85%) as off-white solid. LCMS (ES) *m/z* calcd. for C18H18N4O3, 338.14; found, 339.2 (M+H).

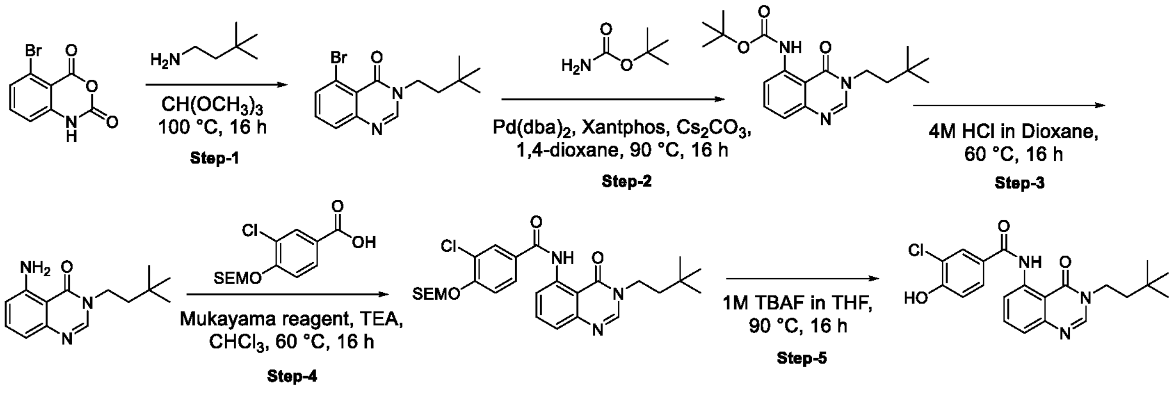
Step 4: Synthesis of 5-amino-3-(pyridin-3-yl)quinazolin-4(3H)-one

[00182] To a solid of tert-butyl N-(3-benzyl-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate (0.5 g, 1.42 mmol) was added 4 M HCl in 1,4-dioxane (15.8 mL, 63.2 mmol) at 0 °C. The resulting reaction mixture was heated to 60 °C for 16 h. After completion of the reaction, the reaction mixture was concentrated under vacuum. The obtained residue was triturated with diethyl ether (2 x 25 mL) and dried under *vacuo* to afford 5-amino-3-[(2-methoxyphenyl)methyl]-3,4-dihydroquinazolin-4-one (420 mg, quantitative) as brown solid. LCMS (ES) *m/z* calcd. for C13H10N4O, 238.01; found, 239.1 (M+H).

Step 5: Synthesis of 3-chloro-4-hydroxy-N-(4-oxo-3-(pyridin-3-yl)-3,4-dihydro quinazolin-5-yl)benzamide

[00183] To a stirred solution of 3-chloro-4-hydroxybenzoic acid (0.118 g ,1.09 mmol) and 5-amino-3-(pyridin-3-yl)-3,4-dihydroquinazolin-4-one.hydrochloride (0.25 g, 0.91 mmol) in chlorobenzene (5.0 mL) was added trichlorophosphane (0.39 ml , 0.45 mmol) at ambient temperature. The resulting mixture was then heated to 130 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with dichloromethane (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulphate, and concentrated under *vacuo to result in crude.* The crude material was purified by reverse phase Prep-HPLC. Pure fractions were collected and concentrated to afford 3-chloro-4-hydroxy-N-[4-oxo-3-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl]benzamide (32.0 mg, 8%). LCMS (ES) *m/z* calcd. for C20H13ClN4O3, 390.07; found, 391.0 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 11.12 (s, 1H), 8.81-8.78 (m, 2H), 8.72 (d, J = 4.4 Hz, 1H), 8.80-8.78 (m, 2H), 8.436 (s, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.92-7.87 (m, 2H), 7.72-7.64 (m, 2H), 7.46 (d, J = 8.4 Hz, 1H) ,7.10 (d, J = 8.8 Hz, 1H).

Example 10: 3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydro quinazolin-5-yl)-4-hydroxybenzamide



Step 1: Synthesis of 5-bromo-3-(3,3-dimethylbutyl)quinazolin-4(3H)-one

[00184] To a suspension of 5-bromo-2,4-dihydro-1H-3,1-benzoxazine-2,4-dione (1.00 g, 4.13 mmol), 3,3-dimethylbutan-1-amine hydrochloride (569 mg, 4.13 mmol) in trimethoxymethane (10.0 mL) was added triethylamine (0.861 mL, 6.20 mmol) at ambient temperature and then heated to 100 °C for 16 h. The reaction mixture was evaporated under *vacuo*. The crude material was purified by flash column chomatography using ethyl acetate-hexane gradient (required product elutes at around 25% ethyl acetate-hexane). Purification afforded 5-bromo-3-(3,3-dimethylbutyl)quinazolin-4(3H)-one (0.65 g, 50.8%) as off-white solid. LCMS (ES) *m/z* calcd. for C14H17BrN2O, 310.05; found, 311.1 (M+H).

Step 2: Synthesis of tert-butyl (3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydro quinazolin-5-yl)carbamate

[00185] To a stirred solution of 5-bromo-3-(3,3-dimethylbutyl)-3,4-dihydroquinazolin-4-one (0.65 g, 2.10 mmol) and tert -butyl carbamate (0.5 g, 4.20 mmol) in 1,4-dioxane (10.0 mL) was added cesium carbonate (2.05 g, 6.31 mmol). Then the reaction mixture was purged with argon for 10 minutes. This was followed by the addition of 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (0.48 g, 0.841 mmol), and Bis(dibenzylideneacetone)palladium(0) (0.2 g, 0.42 mmol). The resulting reaction mixture was heated to 100 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulfate, and concentrated under ***vacuo***. The crude material was purified by flash column chromatography using ethyl acetate-hexane gradient (required product elutes at around 20% ethyl acetate-hexane). Purification afforded tert-butyl (3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)carbamate (0.6 g, 82.6%) as yellow solid. LCMS (ES) *m/z* calcd. for C19H27N3O3, 345.2; found, 346.3 (M+H).

Step 3: Synthesis of 5-amino-3-(3,3-dimethylbutyl)quinazolin-4(3H)-one

[00186] To a solid of tert-butyl N-[3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl]carbamate (0.43g, 1.26 mmol) was added *4M* HCl in 1,4-Dioxane (10.9 mL, 43.4 mmol) at 0 °C. The resulting reaction mixture was heated to 60 °C for 16 h. After completion of the reaction, the reaction mixture was concentrated under *vacuo*. The obtained residue was triturated with diethyl ether (2 x 25 mL) and dried under *vacuo* to afford 5-amino-3-(3,3-dimethylbutyl)-3,4-dihydroquinazolin-4-one hydrochloride (0.45 g, quantitative) as yellow solid. LCMS (ES) *m/z* calcd. for C14H19N3O, 245.15; found, 246.2 (M+H).

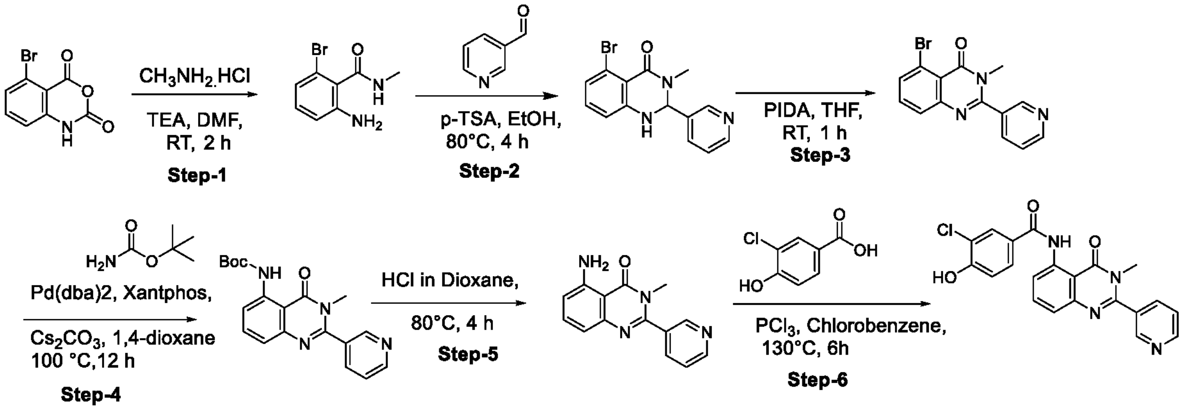
Step 4: Synthesis of 3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydro quinazolin-5-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)benzamide

[00187] To a stirred solution of 3-chloro-4-{[2-(trimethylsilyl)ethoxy]methoxy}benzoic acid (0.58 g, 1.92 mmol) and Triethylamine (1.1 mL, 7.98 mmol) in dichloromethane was added 2-chloro-1-methylpyridin-1-ium iodide (1.22 g, 4.79 mmol). The reaction mixture was degassed with nitrogen for 5 minutes. The reaction mixture was added with 5-amino-3-(3,3-dimethylbutyl)-3,4-dihydroquinazolin-4-one hydrochloride (0.45g, 1.6 mmol). The reaction mixture was heated to 60 °C for 16 h. After completion of reaction, the reaction mixture was poured into water (50 mL) and extracted with dichloromethane (3 x 100 mL). The organic phase was washed with water, brine, dried over anhydrous sodium sulfate, and concentrated under vacuo. The crude material was purified by flash column chromatography using ethyl acetate-hexane gradient (required product elutes at around 30% ethyl acetate-hexane). Purification resulted in 3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-((2-(trimethylsilyl) ethoxy)methoxy)benzamide (0.4 g, 47.25 %) as off-white sold. LCMS (ES) m/z calcd. for C27H36ClN3O4Si, 529.2; found, 530.3 (M+H).

Step 5: Synthesis of 3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydro quinazolin-5-yl)-4-hydroxybenzamide

[00188] To a solution of 3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-((2-(trimethylsilyl)ethoxy)methoxy)benzamide (0.4 g, 0.75 mmol) in tetrahydrofuran (5.00 mL) was added 1*M* tetrabutylammonium fluoride in tetrahydrofuran (7.5 mL, 7.5 mmol) at ambient temperature and then heated to 90 °C for 16 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulfate, and concentrated under *vacuo*. The crude material was purified by flash column chromatography using ethyl acetate-hexane gradient (required product elutes at around 35% ethyl acetate-hexane). Purification resulted in 3-chloro-N-(3-(3,3-dimethylbutyl)-4-oxo-3,4-dihydroquinazolin-5-yl)-4-hydroxybenzamide as off-white solid (0.125 g, 41.4%). LCMS (ES) *m/z* calcd. for C21H22ClN3O3, 399.1; found, 399.9 (M+H), ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.47 (s, 1H), 7.94 (s, 1H), 7.82-7.80 (m, 2H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 4.03 (m, 2H), 1.62 (m, 2H) 0.98 (s, 9H).

Example 11. Synthesis of 3-chloro-4-hydroxy-N-(3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)benzamide



Step-1: Synthesis of 2-amino-6-bromo-N-methylbenzamide

[00189] A stirred solution of 5-bromo-2H-benzo[d][1,3]oxazine-2,4(1H)-dione (1.50 g, 6.20 mmol) in N,N-dimethylformamide (20.0 mL) was added Methylamine.HCl (2.09 g, 31.0 mmol) and Triethylamine (4.36 mL, 31.0 mmol). The resulting reaction mixture was stirred at 50 °C for 6 h. After completion of the reaction, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with water, brine solution, dried over anhydrous sodium sulfate, and concentrated under vacuo to afford 2-amino-6-bromo-N-methylbenzamide as a brown color solid (1.10 g, 78 %); LCMS (ES) m/z calcd. for C8H9BrN2O, 229.99; found, 231.0 (M+ H).

Step-2: Synthesis of 5-bromo-3-methyl-2-(pyridin-3-yl)-2,3-dihydro quinazolin-4(1H)-one

[00190] To a stirred solution of 2-amino-6-bromo-N-methylbenzamide (1.10 g, 4.80 mmol) in ethanol (20.0 mL) was added pyridine-3-carbaldehyde (0.787 g, 7.35 mmol), p-TSA (0.165 g, 0.960 mmol) and $MgSO_4$ (2.00 g, 16.6 mmol) under nitrogen atmosphere at room temperature. Allow the reaction mass to 80 °C for 4 h. Progress of the reaction was monitored by TLC. After completion of reaction, reaction mass was concentrated under vacuo to get thepyridine-3-carbaldehyde as brown solid (0.787 g, 51%); LCMS (ES) m/z calcd. for $C14H12BrN3O$, 317.0; found, 318.0 (m+H).

Step-3: Synthesis of 5-bromo-3-methyl-2-(pyridin-3-yl)quinazolin-4(3H)-one

To a stirred solution of 5-bromo-3-methyl-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (1.50 g, 4.71 mmol) in oxolane (10.0 mL) and added PIDA (2.28 g, , 7.07 mmol) and stirred at room temperature for 1 h. Progress of the reaction was monitored by LCMS, after completion of reaction, reaction mass was quenched with water (10.0 mL) and washed with sodium bicarbonate (10 mL), water (10 mL) .The organic layer was washed brine, dried over anhydrous sodium sulphate, filtered and evaporated in vacuo to obtain crude. The crude was purified by flash chromatography using ethyl acetate-hexane gradient to afford pure 5-bromo-3-methyl-2-(pyridin-3-yl)-3,4-dihydroquinazolin-4-one as brown colour solid (0.900 g, 60% yield) . LCMS (ES) m/z calcd. for $C14H10BrN3O$, 317.0; found, 318.1(M+H).

Step-4: Synthesis of tert-butyl (3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydro quinazolin-5-yl)carbamate

[00191] To a stirred solution of 5-bromo-3-methyl-2-(pyridin-3-yl)quinazolin-4(3H)-one (0.5 g, 1.58 mmol) and tert-butyl carbamate (0.556 g, 4.74 mmol) in 1,4-dioxane (10.0 mL) were added cesium carbonate (1.55 g, 4.74 mmol) and Xanthphos (0.366 g, 0.633 mmol) then degassed under nitrogen gas for 10 min. To this added bis((1E,4E)-1,5-diphenylpenta-1,4-dien-3-one) palladium (182 mg, 0.316 mmol) and allowed to stirred at 100 °C for 12 h. Progress of the reaction was monitored by TLC and LCMS, after completion of reaction, reaction mass was filtered through celite bed and concentrated to get the crude product. The crude material was purified by flash chromatography using ethyl acetate-hexane gradient to afford tert-butyl (3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)carbamate as yellow colour solid (400 mg, 72%). LCMS (ES) m/z calcd. For $C19H20N4O3$, 352.1; found, 353.0 (M+H).

Step-5: Synthesis of 5-amino-3-methyl-2-(pyridin-3-yl)quinazolin-4(3H)-one

[00192] To a stirred solution of tert-butyl (3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)carbamate (557 mg, 1.58 mmol) in 1,4-dioxane (4.0 mL) and added 1,4-dioxane hydrochloride (4.00 mL) and heat the reaction mass to 80 °C for 6 h. Progress of the reaction was monitored by TLC , after completion of reaction, reaction mass was concentrated to get the 5-amino-3-methyl-2-(pyridin-3-yl)quinazolin-4(3H)-one as yellow solid (200 mg, 50%). LCMS (ES) m/z calcd. For $C14H12N4O$, 252.1; found, 253.1 (M+H).

Step-6: Synthesis of 3-chloro-4-hydroxy-N-(3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)benzamide

[00193] To a solution of 3-chloro-4-hydroxybenzoic acid (145 mg, 0.839 mmol) and 5-amino-3-methyl-2-(pyridin-3-yl)quinazolin-4(3H)-one (0.212 g, 0.839 mmol) in chlorobenzene (10 mL) under nitrogen at room temperature was added $PCl3$ (0.08 g, 0.588 mmol) and heat the reaction mass to 130 °C for 6 h. TLC monitored progress of the reaction and LCMS, after completion of reaction, reaction mass was quenched with water and filter the solid, and dry to get the crude product. The crude was purified by Preparative-HPLC (Column: Inertsil C18, (250 mm X 20mm X 5mic), Mobile Phase-A: 0.1% TFA in water Mobile Phase-B: Acetonitrile, Flow rate-19 mL/min]. Pure fraction was concentrated to get the 3-chloro-4-hydroxy-N-(3-methyl-4-oxo-2-(pyridin-3-yl)-3,4-dihydroquinazolin-5-yl)benzamide as yellow solid (30.0 mg, 8.7%). LCMS (ES) m/z calcd. for C21H15ClN4O3, 406.08; found, 407.1 [M+H]; 1H NMR (400 MHz, DMSO-d6): 1H NMR (400 MHz, DMSO-d6) δ 13.31 (s, 1H), 11.16 (s, 1H), 8.89 (s, 1H), 8.76 (d, J = 6.4 Hz, 2H), 8.16 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H), 7.82-7.78 (m, 2H), 7.65-7.58 (m, 1H), 7.39 (d, J = 7.6, 1H), 7.16 (d, J = 8.4, 1H), 3.41 (s, 3H).

[00194] The following compounds were synthesized as described in Examples 1-11.

Ex.	**Spectral data**
12	LCMS (ES) *m/z* calcd. for C20H21ClN4O3, 400.1; found, 401.3 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 12.92 (s, 1H), 12.72 (s, 1H), 8.64 (d, *J*=8.4 Hz,1H,), 8.50 (s, 1H), 8.11 (d, *J*=25.2 Hz, 1H), 8.08 (m, 1H), 7.83 (t, *J*=15.2 Hz, 1H), 7.40 (d, *J*=7.6 Hz, 1H), 4.04 (m, 2H), 1.65 (t, *J*=5.2 Hz, 2H), 0.98 (s, 10H).
13	LCMS (ES) *m/z* calcd. for $C_{22}H_{22}ClN_7O_2$, 451.15; found, 452.3 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.29 (s, 1H), 8.74 (d, *J*=7.6Hz,1H), 8.51 (s 1H), 8.2 (s, 1H), 8.1 (m, 2H), 7.88-7.84 (t, 1H), 7.45 (d, *J*= 8.4 Hz, 1H), 4.06-4.02 (t, *J*= 8, 2H), 1.64-1.60 (t, 2H), 0.98 (s, 9H).
14	LCMS (ES) *m/z* calcd. for $C_{26}H_{21}ClN_4O_5S$ 536.1; found, 537.3 (M+H). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.26 (s, 2H), 8.72 (d, *J* = 8 Hz, 1H), 8.5 (s, 1H), 8.41 (d, *J* = 8 Hz, 1H), 8.14 - 8.11 (m, 2H), 7.92 - 7.85(m, 3H), 7.64 - 7.60 (m, 1H), 7.50 - 7.44 (m, 3H), 3.89 (d, *J* = 8 Hz, 2H), 1.32 (s, 1H), 0.51 - 0.45 (m, 4H).
15	LCMS (ES) *m/z* calcd. for $C_{19}H_{20}ClN_5O_3$, 401.13; found, 402.3 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.06 (s, 1H), 13.39 (s, 1H), 8.76 (d, 8.4 Hz, 1H), 8.46 (s, 1H), 8.2 (s, 1H), 7.84-7.80 (t, 1H), 7.41 (d, *J*= 8.4 Hz, 1H), 4.03-3.99 (t, 2H), 1.62-1.59 (t, *J*= 8.0 Hz, 2H), 0.98 (s, 9H,).
16	LCMS (ES) *m/z* calcd. for $C_{27}H_{26}ClN_5O_5S$, 567.13; found, 568.3 (M+H). 1H-NMR (400 MHz, DMSO-d_6): δ 13.22 (s, 1H), 9.08 (s, 1H), 8.77 (s, 1H), 8.72 (d, *J*=8.4 Hz, 1H), 8.50 (m, 2H), 8.31 (d, *J*=8Hz, 1H), 8.04-8.00 (m, 3H), 7.85 (t, 1H), 7.67 (s, 1H), 7.43 (d, *J*=8Hz, 1H), 4.03 (m, 2H), 1.61(m, 2H), 0.97 (s, 9H).
17	LCMS (ES) *m/z* calcd. for $C_{22}H_{15}FN_8O_2$, 442.1; found, 443.0 (M+H). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.3 (s, 1H), 8.91 (s, 1H), 8.82-8.78 (m, 2H), 8.34 (t, *J*=7.6Hz 1H), 8.16 (d, *J*=4Hz, 1H), 8.05-8.02 (m, 2H), 7.97 (t, *J* = 9.2 Hz, 1H), 7.62-7.20 (m, 1H), 7.48 (d, J=8.4 Hz 1H), 3.45 (s, 3H).
18	LCMS (ES), Calcd. For $C_{28}H_{27}ClN_4O_5S$, 566.1; found-*m/z*- 567.3 (M+H). 1H-NMR (400 MHz, DMSO-d_6): δ 13.25 (s, 1H), 8.7 (d, *J*=8 Hz, 1H), 8.50 (s, 1H), 8.41 (d, *J*=8Hz, 1H), 8.13 (s, 2H), 7.9-7.86 (m, 4H), 7.61(t, 1H), 7.5-7.43 (m, 3H), 4.03 (m, 2H), 1.61(m, 2H), 0.97 (s, 9H).
19	LCMS (ES) *m/z* calcd. for C25H20ClN5O4, 489.1; found, 490.1 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.1 (s, 1H), 11.8-11.2 (m, 2H), 8.76 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.64 (br s, 1H), 7.52 (br s, 1H), 7.34-7.32 (m, 1H), 7.19-7.17 (m, 1H), 7.13-7.11 (m, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 1H), 4.25 (t, *J* = 6.8 Hz, 2H), 3.54 (s, 3H), 3.04 (t, *J* = 6.4 Hz, 2H).
20	LCMS (ES) *m/z* calcd. for C21H15FN4O3, 390.1; found, 391.2 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (s, 1H), 10.80 (s, 1H), 8.75 (d, *J*=8.4 Hz, 1H), 8.59 (d, *J*=16.4 Hz, 3H), 7.87 (t, *J*=8.4 Hz, 1H), 7.72 (m, 2H), 7.53 (s, 2H), 7.42 (d, *J*=8 Hz, 1H), 7.10 (t, *J*=16.8 Hz, 1H), 5.37 (s, 2H).
21	LCMS (ES) *m/z* calcd. for C27H22FN5O3, 483.17; found, 484.3 (M+H).

Ex.	Spectral data
	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 2H) 8.75 (d, *J*=8 Hz, 1H), 8.32 (s, 1H), 8.05 (t, *J*=19.2 Hz, 2H), 7.93 (s, 1H), 7.80 (m, 3H), 7.34 (d, *J*=8.4 Hz, 1H), 7.17 (t, *J*=8 Hz, 1H), 7.09 (d, *J*=7.2 Hz, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 6.82 (t, *J*=7.2 Hz, 1H), 4.25 (s, 2H), 3.52 (s, 3H), 3.03 (s, 2H).
22	LCMS (ES) *m/z* calcd. for C27H22FN5O3, 483.17; found, 484.3 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 2H) 8.75 (d, *J*=8 Hz, 2H), 8.22 (s, 1H), 7.94 (s, 1H), 7.84 (m, 3H), 7.35 (d, 1H, *J*=8 Hz, 1H), 7.17 (t, *J*=15.6 Hz, 1H), 7.09 (d, *J*=7.6 Hz, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 6.80 (m, 2H), 4.25 (m, 2H), 3.53 (s, 3H), 3.03 (m, 2H).
23	LCMS (ES), Calcd. For $C_{24}H_{21}FN_3O_6P$, 497.12; found- *m/z*- 498.2 (M+H). 1H-NMR (400 MHz, DMSO-d_6): δ 13.19 (s, 1H), 8.64 (s, 1H), 7.91 (s, 1H), 7.7 (m, 4H), 7.28 (m, 2H), 7.18 (t, 1H), 7.09 (d, 8 Hz, 1H), 6.88 (d, 8 Hz, 1H), 6.8 (t, 1H), 3.53 (s, 3H), 4.22 (t, 2H), 3.01(t, 2H).
24	LCMS (ES) *m/z* calcd. for C27H26ClN3O4, 491.97; found, 492.3 (M+H), 99.35 % at 260 nm. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1 H), 9.98 (s, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.83-7.77 (m, 3H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.19-7.15 (m, 1H), 7.11 (d, *J* = 6.4 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.84-6.80 (m, 1H), 4.22 (t, *J* = 6.4 Hz, 2H), 3.56 (s, 3H), 3.39-3.34 (m, 1H), 3.04 (t, *J* = 6.4 Hz, 2H), 1.25 (d, *J* = 7.2 Hz, 6H).
25	LCMS (ES) *m/z* calcd. for C26H22FN3O5, 475.5; found, 476.3 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H). 8.73 (d, *J*=7.6 Hz, 1H), 7.94 (s, 1H), 7.81 (t, *J*= 16 Hz, 2H), 7.76 (d, *J*=7.2 Hz, 1H), 7.69 (d, *J*=10.4 Hz, 1H), 7.65 (t, *J*=15.6 Hz, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 7.17 (t, *J*=14.8 Hz, 1H), 7.08 (d, *J*=6.4 Hz, 1H), 6.87 (d, *J*=8 Hz, 1H), 6.80 (t, *J*=14.4 Hz, 1H), 4.24 (t, *J*=12 Hz, 2H), 3.74 (s, 2H), 3.53 (s, 3H), 3.02 (t, *J*=12.8 Hz, 2H).
26	LCMS (ES), Calcd. For $C_{26}H_{21}FN_6O_3$, 484.17; found *m/z*-485.3 (M+H). ^{1}H-NMR-(400 MHz, DMSO-d_6): δ 13.26 (s, 1 H), 8.76 (d, *J*=8, 1H), 8.3 (s, 2H), 7.95-7.81 (m, 4H), 7.36 (d, *J*=8, 1H), 7.17 (d, *J*=8, 1H), 7.10 (d, *J*=7.2, 1H), 6.89-6.82 (m, 2H), 4.26 (t, 2H), 3.54 (s, 3H), 3.04 (t, 2H).
27	LCMS (ES), calcd. for $C_{25}H_{20}ClN_7O_3$, 501.1; found *m/z*-502.1 (M+H). 1H-NMR (400 MHz, DMSO-d_6): δ 13.30 (s, 1H), 8.74 (d, *J*=8 Hz, 1H), 8.19 (s, 1H), 8.11(m, 2H), 7.97 (s, 1H), 7.84 (t, 1H), 7.38 (d, *J*=8Hz, 1H), 7.17 (t, 1H), 7.09 (d, *J*=7.2Hz, 1H), 6.87 (d, *J*=8.4Hz, 1H), 6.81 (t, 1H), 4.24 (br s, 2H), 3.53 (s, 3H), 3.02 (t, 2H).
28	LCMS (ES) *m/z* calcd. for C22H20FN5O4, 437.4; found, 438.1 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 10.29 (s, 1H), 7.87 (s, 1H), 7.76 (d, *J*=12 Hz, 1H), 7.69 (d, *J*=8.4 Hz, 1H), 7.19 (t, *J*=15.2 Hz, 1H), 7.05 (t, *J*=13.2, 2H), 6.89 (d, *J*=8 Hz, 1H), 6.82 (t, *J*=14.4 Hz, 1H), 4.06 (d, *J*=6.4 Hz, 2H), 3.81 (s, 3H), 3.60 (s, 3H), 2.88 (t, *J*=13.2 Hz, 2H).
29	LCMS (ES) *m/z* calcd. For C24H21ClN4O5S, 512.09; found, 513 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (s, 1H), 8.7 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8 Hz, 1H), 8.1 (s, 1H), 8.06-7.96 (m, 1H), 7.83-7.80 (m, 4H), 7.37 (d, *J* = 8 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 4.22 (t, *J* = 6 Hz, 2H), 3.53 (s, 3H), 3.02 (t, *J* = 6 Hz, 1H).
30	LCMS (ES) *m/z* calcd. For C21H15ClN4O3, 406.08; found, 407 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (s, 1H), 11.09 (s, 1H), 8.75-8.71 (m, 2H), 8.63 (s, 1H), 8.57 (s, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.90 (s, 1H), 7.84 (t, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 5.32 (s, 2H).
31	LCMS (ES) *m/z* calcd. for C28H29N3O4, 471.22; found, 472.2 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1 H), 10.26 (s, 1H), 8.75 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 2H), 7.92-7.51 (m, 1H), 7.70 (d, *J* = 8.4

Ex.	Spectral data
	Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.19-7.15 (m, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.84-6.80 (m, 1H), 4.20 (t, *J* = 6.0 Hz, 2H), 3.52 (s, 3H), 3.02 (t, *J* = 6.0 Hz, 2H), 1.41 (s, 9H).
32	LCMS (ES) *m/z* calcd. for C25H20F3N3O4, 483.14; found, 484.0 (M+H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 13.13 (s, 1 H), 8.72 (d, *J* = 7.6 Hz, 1H), 8.14 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.93 (s, 1H), 7.80-7.69 (m, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.20-7.14 (m, 2H), 7.09 (d, *J* = 6.4 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.87-6.79 (m, 2H), 4.22 (m, 2H), 3.52 (s, 3H), 3.01 (m, 2H).
34	LCMS (ES) *m/z* calcd. For C23H20ClN3O4S, 469.09; found, 470.2 (M+H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.84 (s, 1H), 9.83 (s, 1H), 8.03 (s, 1H), 7.80 (d, *J* = 12.8 Hz, 2H), 7.21-7.17 (m, 1H), 7.05 (d, *J* =6 Hz, 2H), 6.90-6.80 (m, 2H), 4.09 (t, 2H), 3.57 (s, 3H), 2.92 (t, 2H), 2.29 (s, 3H).
35	LCMS (ES): *m/z* calcd. For C23H14ClF4N3O3, 491.07; found 492.0 (M+H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): 1H NMR (400 MHz, DMSO-d6): δ 13.00 (s, 1H), 8.71 (d, *J* = 8.0 Hz, 1H), 8.65 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 7.87-7.83 (m, 1H), 7.51-7.47 (m, 2H), 7.42 (d, *J* = 8 Hz, 1H), 7.21-7.17 (m, 2H), 5.25 (s, 2H).
36	LCMS (ES): *m/z* calcd. For C19H11ClF3N5O3S, 481.02; found, 482.0 (M+H). ^{1}H NMR (400 MHz, DMSO- *d*$_6$): δ 12.84 (s, 1H), 11.80-11.20 (bs, 1H), 9.60 (s, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.66 (s, 1H), 8.17 (s, 1H), 8.08 (s, 1H), 7.90-7.88 (m, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 5.75 (s, 2H).
37	LCMS (ES): *m/z* calcd. For C23H14ClFN4O3, 448.07; found 449.0 (M+H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 12.55 (s, 1H), 8.73 (d, *J* = 8.0 Hz, 1H), 8.54 (s, 1H), 7.81-7.77 (m, 2H), 7.72-7.71 (m, 1H), 7.39-7.32 (m, 3H), 7.27-7.17 (m, 2H), 5.32 (s, 2H).
38	LCMS (ES): *m/z* calcd. For C24H16ClFN4O3, 462.09; found, 461.1(M-H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): *δ* 12.94 (s, 1H), 8.68 (d, *J* = 8.0 Hz, 1H), 8.44 (s, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.86-7.82 (m, 1H), 7.42–7.39 (m, 2H), 7.33-7.30 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.17 – 7.13 (m, 1H), 6.22–6.17 (m, 1H), 1.86 (d, *J* = 7.2 Hz, 3H).
39	LCMS (ES): *m/z* calcd. For C24H14ClF6N3O3, 541.06; found 542.0 (M+H), 99.77 % at 245 nm. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 12.93 (s, 1H), 11.80-11.20 (bs, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.61 (s, 1H), 8.14 (s, 1H), 8.05 (s, 1H), 7.93-7.89 (m, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.63-7.59 (m, 1H), 7.55-7.49 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 5.47 (s, 2H). Purity: 99.7 % at 254 nm.
40	LCMS (ES): *m/z* calcd. For C23H13F7N4O3, 526.0; found, 527.1 (M+H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$); δ 13.45 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.61 (s, 1H), 8.08 (s, 1H), 7.79-7.75 (m, 1H), 7.39-7.28 (m, 4H), 7.18-7.12 (m, 1H), 5.17 (s, 2H).
41	LCMS (ES): *m/z* calcd. For C23H14ClF4N3O3, 491.07; found 492.0 (M+H). ^{1}HNMR (400 MHz, DMSO-*d*$_6$): δ 12.67 (bs, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.55 (s, 2H), 7.88 (bs, 1H), 7.82-778 (m, 1H), 7.32-7.41-7.32 (m, 3H), 7.26-7.17 (m, 2H), 5.30 (s, 2H).
42	LCMS (ES): *m/z* calcd. For C20H12ClF3N4O4: 464.05; found, 465.0 (M+H). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 12.92 (bs, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.55 (s, 1H), 8.37 (s, 1H), 8.18-8.14 (m, 2 H), 8.07 (bs, 1H), 7.88-7.83 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 5.21 (s, 2H).
43	LCMS (ES): *m/z* calcd. For C23H15ClF4N4O3, 506.08; found, 505.0 (M-H).

Ex.	Spectral data
	^{1}H NMR (400 MHz, DMSO d_6): δ 13.72 (s, 1H), 8.83 (d, J = 8.0 Hz, 1H), 8.50 (s, 1H), 8.28 (s, 1H), 7.83-7.79 (m, 1H), 7.40–7.25 (m, 4H), 7.18-7.12 (m, 1H), 6.03 (d, J = 7.2 Hz, 1H), 1.87 (d, J = 6.8 Hz, 3H).
44	LCMS (ES): *m/z* calcd. for C23H14F2N4O3 432.1; found, 431.1(M-H). 1H NMR (400 MHz, DMSO d_6): δ 12.93 (s, 1H), 8.68 (d, J = 8.0 Hz, 1H), 8.63 (s, 1H), 8.00 (s, 1H), 7.97 (m, 1H), 7.87 (m, 1H), 7.49-7.43 (m, 3H), 7.22-7.17 (m, 2H), 5.27 (s, 2H).
45	LCMS (ES): *m/z* calcd. for C22H13ClF4N4O3; 492.06 found, 493.1 (M+H). ^{1}H NMR (400 MHz, DMSO d_6): δ 13.70 (s, 1H), 8.84 (d, J = 8.0 Hz, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 7.86-7.82 (m, 1H), 7.47-7.35 (m, 3H), 7.25-7.16 (m, 2H), 5.25 (s, 2H). Purity: 98.8 % at 254 nm.
46	LCMS (ES) *m/z* calcd. for C24H14ClF6N3O3, 541.06; found, 542.0 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 11.58 (bs, 1H), 8.72-8.67 (m, 2H), 8.17 (m, 1H) 8.09-8.08 (m, 1H) 7.88 (t, J = 8.4 Hz, 1H) 7.73 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.6 Hz, 1H), 5.37 (s, 2H).
47	LCMS (ES) *m/z* calcd. C24H16F2N4O3, 446.1; found, 445.1 (M-1). HPLC purity: 99.3 % at 254 nm. 1H NMR (400 MHz, DMSO *d6*); δ 12.98 (s, 1H), 8.72 (d, J = 1.2 Hz, 1H), 8.46 (s, 1H), 8.02-7.98 (m, 2H), 7.87 (t, J = 8.4 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.35 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 0.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.24-6.23 (m, 1H), 1.88 (d, J = 7.2 Hz, 3H).
48	LCMS (ES) m/z calcd. For C24H14ClF3N4O4, 514; found 515.1 (M+H), 99.4 % at 240 nm 1H NMR (400 MHz, DMSO-d6); δ 12.87 (bs, 1H), 8.71-8.66 (m, 2H), 8.15 (d, J= 2 Hz, 1H), 8.09 (d, J = 2 Hz, 1H), 7.90-7.85 (m, 1H), 7.52-7.50 (m, 2H), 7.46-7.41 (m, 2H), 7.33 (d, J=8.4 Hz, 1H), 5.32 (s, 2H).
49	LCMS (ES) m/z calcd. for C23H14ClFN4O3; 448.0; found, 449.0 (M+H). ^{1}H NMR (400 MHz, DMSO-*d6*); δ 12.87 (s, 1H), 8.66 (d, J = 8.0 Hz, 1H), 8.60 (s, 1H), 8.14-8.06 (m, 2H), 7.87-7.82 (m, 1H), 7.43-7.36 (m, 2H), 7.26-7.10 (m, 3H), 5.27 (s, 2H).
50	LCMS (ES)*m/z* calcd. For C23H13ClF6N4O4, 558.05; found, 559.0 (M+H), 1H NMR (400 MHz, DMSO-*d6*); δ 13.66 (s, 1H), 8.85 (d, J=7.6, Hz, 1H), 8.56 (s, 1H), 8.33 (s, 1H), 7.85 (t, J=8.4, Hz, 1H), 7.48-7.33 (m, 5H), 5.29 (s, 2H).
51	LCMS (ES) m/z calcd. for C23H13ClF6N4O3, 542.06; found 543.0 [M+H]$^+$. 1HNMR (400 MHz, DMSO-d6); δ 13.66 (s, 1H), 8.82 (d, J=8 Hz, 1H), 8.64 (s, 1H), 8.32 (s, 1 H), 7.83 (t, J= 8.2 Hz, 1H), 7.62-7.71 (m, 4H), 7.40 (d, J=8 Hz, 1H), 5.28 (s, 2H). Purity: 98.0% at 240 nm.
52	LCMS (ES) m/z calcd. for C24H14F4N4O3, 482.1; found 483.1 [M+H]$^+$. 1HNMR (400 MHz, DMSO-d6): δ 12.74 (s, 1H), 8.68 (d, J=8 Hz, 1H), 8.54 (s, 1H), 7.80-7.88 (m, 4H), 7.52-7.58 (m, 1H), 7.45-7.51 (m, 2H), 7.11 (d, J=7.6 Hz, 1H), 5.45 (s, 2H).
53	LCMS (ES) m/z calcd. For C24H14F4N4O4, 498; found 499.0 (M+H), 1H NMR (400 MHz, DMSO-d6): δ 12.82 (s, 1H), 8.68 (d, J = 8 Hz, 1H), 8.61 (s, 1H), 7.92-7.84 (m, 3H), 7.52 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8Hz 1H), 7.35 (d, J=8.4 Hz, 2H), 5.29 (s, 2H). Purity 99.8 % at 230 nm;
54	LCMS (ES) *m/z* calcd. For C24H16F4N4O4, 500.11; found, 499.1 (M-1). 1H NMR (400 MHz, DMSO-*d6*); δ 12.82 (s,1H), 8.72-8.69 (m, 3H), 8.43 (s, 1H), 8.28 (bs, 1H), 7.90-7.83 (m, 3H), 7.69-7.68 (m, 2H), 7.60- 7.59 (m, 1H), 7.44 (d, J = 8.0 Hz, 1H), 5.36 (s, 2H).
55	LCMS (ES) m/z calcd. for C23H13ClF6N4O3, 542.06; found 543.0 [M+H]$^+$.

Ex.	**Spectral data**
	1HNMR (400 MHz, DMSO-d6): δ 13.63 (s, 1 H), 8.87-8.85 (d, *J* = 8 Hz,1 H), 8.57 (s, 1 H), 8.34 (s, 1 H), 7.90-7.86 (t, *J* = 8.4 Hz, 1 H),7.83-7.81 (d, *J* = 8 Hz, 1 H), 7.60-7.58 (m, 1 H), 7.53-7.46 (m, 2 H), 7.17-7.15 (d, *J* = 7.6 Hz, 1 H), 5.43 (s, 2 H).
56	LCMS (ES) m/z calcd. for C24H14F4N4O4; 498.4; found, 499.1 (M+H). 1H NMR (400 MHz, DMSO-d6); δ 12.90 (s, 1H), 8.70 (d, *J* = 8.0 Hz, 1H), 8.66 (s, 1H), 7.94-7.98 (m, 2H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.52-7.40 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 1H), 5.33 (s, 2H).
57	LCMS (ES) *m/z* calcd. For C24H14F4N4O3, 482.10; found, 483.1 (M+1), 1H NMR (400 MHz, DMSO-*d*6); δ 12.89 (s, 1H), 8.70-8.69 (m, 2H), 7.95-7.80 (m, 4H), 7.70-7.60 (m, 3H), 7.45 (d, J=7.2 Hz, 1H), 5.37 (s, 2H).
58	LCMS (ES) *m/z* calcd. For C24H14ClF3N4O4, 514.07; found 515.0 (M+H), 98.69 % at 230 nm. 1H NMR (400 MHz, DMSO-d6); δ 12.54 (s, 1H), 8.71 (d, *J* = 8.8 Hz, 1H), 8.56 (s, 1H), 7.80-7.77 (m, 3H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45-7.35 (m, 3H), 5.28 (s, 2H).
59	LCMS (ES) *m/z* calcd. for C24H14F4N4O3, 482.1; found, 483.1 (M+H). 1H NMR (400 MHz, DMSO d6); δ 12.84 (s, 1H), 8.68-8.63 (m, 2H), 7.94 (d, *J* = 12.8 Hz, 2H), 7.85 (t, *J* = 8.0 Hz, 1H), 7.7 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 5.37 (s, 2H).
60	LCMS (ES) m/z calcd. for C24H14FN5O3, 439.11; found, 440.1 (M+H). 1H NMR (400 MHz, DMSO-d6); δ 12.80 (s, 1H), 8.69 (d, J= 7.6 Hz, 1H), 8.63 (s, 1H), 7.95 - 7.87 (m, 4H), 7.69 - 7.65 (m, 1H), 7.54 - 7.47 (m, 2H), 7.40 (d, J= 8 Hz, 1H), 5.47 (s, 2H).
61	LCMS (ES) *m/z* calcd. For C20H13FN6O3, 404.1; found 405.1 (M+H). 1H NMR (400 MHz, DMSO-d6); δ 12.97 (s, 1H), 12.75 (bs, 1H), 8.70 (d, *J* = 7.6 Hz, 1H), 8.52 (s, 1H), 8.00 - 7.96 (m, 2H), 7.86 (t, *J* = 8 Hz, 1H), 7.69 (bs, 1H), 7.44 - 7.42 (m, 1H), 6.30 (d, J = 2Hz, 1H), 5.28 (s, 2H).
62	LCMS (ES) *m/z* calcd. C24H17FN4O5S, 492.09; found, 493.0 (M+H). ^{1}H NMR (400 MHz, DMSO *d*6) *δ* 12.76 (s, 1H), 8.69 (d, *J* = 8.0 Hz, 1H), 8.63 (s, 1H), 8.0 (d, *J* = 6.8 Hz, 1H), 7.85(t, *J* = 4.0 Hz, 3H), 7.60 (d, *J* = 4.0 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 5.6 (s, 2H), 3.47 (s, 3H).
63	LCMS (ES) *m/z* calcd. for C24H21FN6O3 460.17; found, 461.1 (M+H), ^{1}H NMR (400 MHz, DMSO-*d*$_6$) *δ* 13.00 (s, 1H), 8.695 (d, *J* = 8 Hz, 1H), 8.5 (s, 1H), 8.01-7.97 (m, 2H), 7.86 (t, *J* = 8 Hz ,1H), 7.7 (d, *J* = 2.4 Hz, 1H), 7.4 (d, *J* = 7.6 Hz, 1H), 6.25 (d, *J* = 2.4 Hz, 1H), 5.25 (s, 2H), 1.5 (s, 9H).
64	LCMS (ES) m/z calcd. for C24H14F7N3O4, 541.09; found 542.0 [M+H] ^{1}HNMR (400 MHz, DMSO-d6): δ 12.97 (s, 1 H), 11.960 (br, 1 H), 8.69 (d, *J*= 8 Hz, 1 H), 8.57 (s, 1 H), 7.46-7.83(m, 3 H), 7.32-7.86 (m, 5 H), 5.31 (s, 2 H).
65	LCMS (ES) m/z calcd. for C21H14ClFN4O4, 440.07; found 441.1 [M+H]$^+$. 1HNMR (400 MHz, DMSO-d6): δ 13.40 (s, 1H), 8.84 (d, *J* = 8 Hz, 1H), 8.58 (s, 1H), 7.82 (t, *J* = 8 Hz, 1H), 7.53 (s, 1H),7.45-7.37 (m, 3H), 7.30-7.23 (m, 3H), 7.15-7.13 (m, 1H), 5.25 (s, 2H).

Example A: NADH detection assay for evaluation of HSD17ß13 activity and identification of inhibitors

[00195] The fluorescence based Leukotriene B3 (LTB3) assay monitors the fluorescence of NADH, which is generated from NAD+ during the dehydrogenation of the substrate LTB3. The reactions were performed in a 384-well plates (Greiner; #655076) in a 20 µl reaction volume containing the following reagents (final concentrations): 25 μM LTB3 (Cayman; #20109); 3 mM NAD$^+$ (Sigma; #N0623); 125 nM HSD17B13 enzyme (in-house; *E. coli* expressed His-tagged, purified, soluble protein); 1 M potassium phosphate buffer, pH 7.4; and 1% DMSO. Reactions were initiated by co-addition of NAD+ and enzyme, and monitored for 1 hour at 26.5°C. Generation of NADH was measured as the fluorescence signal (Excitation at 340 nm and Emission at 445 nm) at 1 hour minus the baseline fluorescence at t=0. Fluorescence signals in the absence of LTB3 (negative control values), were subtracted from all values so that the results reflected substrate-dependent production of NADH. NADH standards were included to allow the conversion of relative fluorescence units into rates of enzyme activity. Enzyme activity in the presence of test compounds was expressed as a percentage of the uninhibited enzyme activity, and plotted versus inhibitor concentration. Non-linear regression was performed using a four-parameter logistic model and Microsoft Excel Solver software Ten concentrations of inhibitor were tested in duplicate (in the range of 30 μM – 2.5 nM), and two independent concentration response assays were performed.

Example B: Estrone detection assay for evaluation of HSD17ß13 activity and identification of inhibitors

[00196] The liquid chromatography/mass spectrometry (LC/MS) estrone detection assay monitors the conversion of estradiol to estrone by HSD17B13. This assay was undertaken in a 96wp format (Eppendorf deep well Plate 96/500) in an 80μl reaction volume containing: 4μM of Estradiol (E2; Cayman; #10006315), 6mM NAD$^+$ (Sigma; #N0623) and 30 nM HSD17B13 enzyme (in-house; *E. coli* expressed His-tagged, purified, soluble protein) in a reaction containing 1M potassium phosphate buffer pH 7.4, with 0.5% vehicle (DMSO). Reactions were incubated for 2 hours at 26.5°C, and estradiol (E2) conversion to estrone (E1) was quantitated by LC-MS/MS based analyte detection for both E2 and E1 using LCMS grade reagents.

[00197] Reactions were terminated by the addition of two volumes of acetonitrile (MeCN; LCMS grade; CAS# 75/05/8) containing deuterated (D4)-E1 used as internal standard (Clear Synth; #CS-T-54273; 500 ng/mL final concentration). Samples were applied to pre-prepared Bond Elut-C18 extraction cartridges (3 mL; Agilent; #12102028), washed and eluted in MeCN. Eluates were dried under nitrogen and re-suspended in 60% methanol (LCMS grade methanol; CAS# 67/56/1) before submission for analysis. Aqueous linearity for E2 and E1 were included for quantification.

[00198] Analysis of samples was undertaken on a XBridge BEH C18 column (Waters; #186003033) using 0.1% Diethyl Amine in MeCN (mobile phase A; DEA CAS# 109-89-7) and 0.1% Diethyl Amine in milli-Q water (mobile phase B) in a 3min gradient allowing 25%B. Analytes were detected in negative mode using MRM analysis, with E2 having a RT of 1.85min and E1 having a RT of 2min. Activity of the enzyme, in the absence of NAD$^+$, was used to evaluate specificity of conversion. Enzyme activity in the presence of test samples was expressed as a percentage of the uninhibited enzyme activity, and plotted versus inhibitor concentration. Non-linear regression was performed using a four-parameter logistic model and GraphPad Prism software (GraphPad Software, La Jolla, CA). All assessments were undertaken in duplicate evaluations and pooled during extraction process and subsequently injected as duplicates for LC-MS/MS analysis.

[00199] The data for both examples is shown in table 2 below:

Table 2:

Ex.	**IC$_{50}$ with LTB3 (μM)**	**IC$_{50}$ with Estradiol (μM)**
1	A	A
2	A	A
3	A	A
4	D	C
5	D	C
6	A	A
7	D	D
8	D	B
9	D	B
10	A	A
11	B	B
12	NT	C
13	NT	C
14	B	C
15	D	C
16	C	C
17	D	D
18	D	C
19	B	D
20	D	B
21	D	D
22	B	D
23	D	D
24	D	D
25	D	C
26	D	C
27	B	C
28	C	B
29	D	D
30	A	A
31	D	D
32	A	A
33	B	B
34	A	A
35	NT	B
36	NT	C
37	NT	B
38	NT	B
39	NT	B
40	NT	B
41	NT	B
42	NT	C
43	NT	B
44	NT	A
45	NT	B
46	NT	B

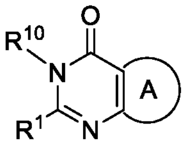
Ex.	**IC_{50} with LTB3 (µM)**	**IC_{50} with Estradiol (µM)**
47	NT	A
48	NT	B
49	NT	B
50	NT	B
51	NT	C
52	NT	A
53	NT	B
54	NT	C
55	NT	B
56	NT	B
57	NT	A
58	NT	B
59	NT	A
60	NT	A
61	NT	B
62	NT	B
63	NT	B
64	NT	A
65	NT	D

IC_{50} with LTB3	**IC_{50} with Estradiol**
A is less than or equal to 1 µM; B is more than 1 µM and less than or equal to 5 µM; C is more than 5 µM and less than or equal to 10 µM; D is more than 10 µM. NT: not tested	A is less than or equal to 0.1 µM; B is more than 0.1 µM and less than or equal to 1 µM; C is more than 1 µM and less than or equal to 10 µM; D is more than 10 µM. NT: not tested

CLAIMS

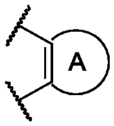
WHAT IS CLAIMED IS:

1. A compound of Formula (II), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (II),

wherein:



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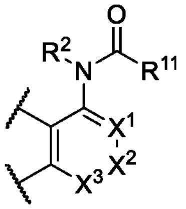
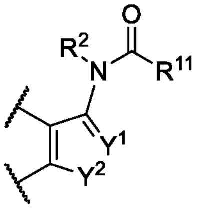


or



;

X^1 is N or CR^{X1};

R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^2 is N or CR^{X2};

R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X^3 is N or CR^{X3};

R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^1 is N or CR^{Y1};

R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Y^2 is S, O, or NR^{Y2};

R^{Y2} is hydrogen, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^1 is hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, or heteroaryl;

R^2 is hydrogen, -S(=O)R^a, -S(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -C(=O)R^a, -C(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R^{10} is C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{10a};

each R^{10a} is independently deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH_2, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2R^a$, -NO_2, -NR^cR^d, -NHS(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH_2, -S(=O)$_2NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or two R^{10a} on the same carbon are taken together to form an oxo;

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a};

each R^{11a} is independently deuterium, halogen, -CN, -OH, -OR^a, -OP(=O)OH_2, -SH, -SR^a, -S(=O)R^a, -S(=O)$_2R^a$, -NO_2, -NR^cR^d, -NHS(=O)$_2R^a$, -S(=O)$_2NR^cR^d$, -S(=O)$_2NR^b$C(=O)R^a, -C(=O)R^a, -OC(=O)R^a, -C(=O)OR^b, -OC(=O)OR^b, -C(=O)NR^cR^d, -OC(=O)NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH_2, -S(=O)$_2NH_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_1-C_6aminoalkyl;

or two R^{11a} on the same carbon are taken together to form an oxo;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -

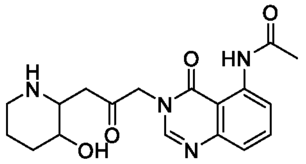
OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl;

each R^b is independently hydrogen, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C$_1$-C$_6$alkyl(cycloalkyl), C$_1$-C$_6$alkyl(heterocycloalkyl), C$_1$-C$_6$alkyl(aryl), or C$_1$-C$_6$alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three deuterium, oxo, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl; and

each R^c and R^d are independently hydrogen, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, C$_2$-C$_6$alkenyl, C$_2$-C$_6$alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C$_1$-C$_6$alkyl(cycloalkyl), C$_1$-C$_6$alkyl(heterocycloalkyl), C$_1$-C$_6$alkyl(aryl), or C$_1$-C$_6$alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one, two, or three oxo, deuterium, halogen, -CN, -OH, -OMe, -S(=O)Me, -S(=O)$_2$Me, -NH$_2$, -S(=O)$_2$NH$_2$, -C(=O)Me, -C(=O)OH, -C(=O)OMe, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, or C$_1$-C$_6$aminoalkyl;

provided that the compound of Formula (II) is not: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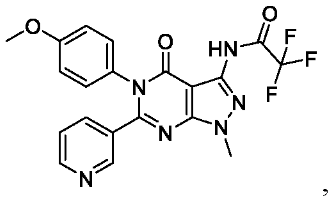
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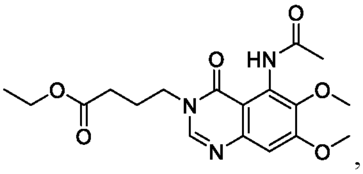
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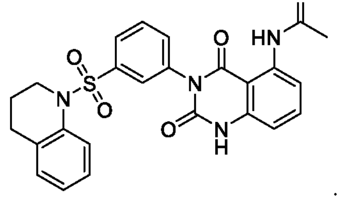
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2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

   X^1 is N.

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

   X^1 is CR^{X1}.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

X^2 is N.

5. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
X^2 is CR^{X2}.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
X^3 is N.

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
X^3 is CR^{X3}.

8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
Y^1 is N.

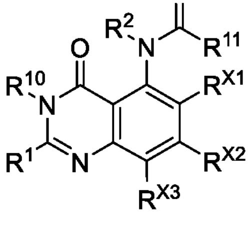
9. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
Y^1 is CR^{Y1}.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
Y^2 is S.

11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
Y^2 is O.

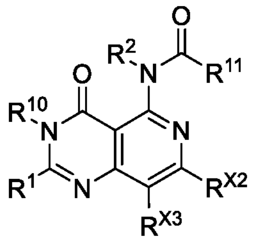
12. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
Y^2 is NR^{Y2}.

13. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound of Formula (II) is Formula (IIa):



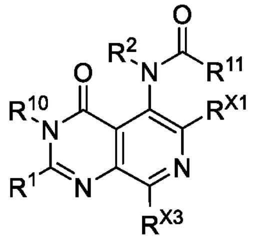
Formula (IIa).

14. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound of Formula (II) is Formula (IIb):



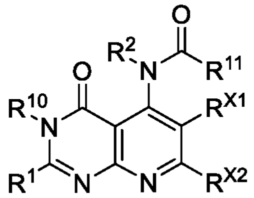
Formula (IIb).

15. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound of Formula (II) is Formula (IIc):



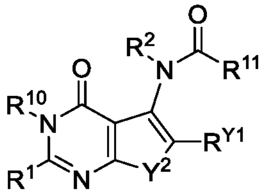
Formula (IIc).

16. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound of Formula (II) is Formula (IId):



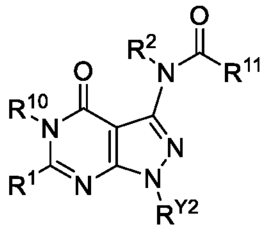
Formula (IId).

17. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound of Formula (II) is Formula (IIe):



Formula (IIe).

18. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound of Formula (II) is Formula (IIf):



Formula (IIf).

19. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{X1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl.

20. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{X1} is hydrogen.

21. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{X2} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl.

22. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{X2} is hydrogen.

23. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{X3} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl.

24. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{X3} is hydrogen.

25. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
Y^2 is S.

26. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
Y^2 is NR^{Y2}.

27. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{Y1} is hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl;

28. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{Y1} is hydrogen or C_1-C_6alkyl.

29. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{Y1} is hydrogen.

30. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{Y2} is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, or C_1-C_6hydroxyalkyl.

31. The compound of any of the preceding claims, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:
R^{Y2} is hydrogen or C_1-C_6alkyl.

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^1 is hydrogen.

33. The compound of any one of claims 1-32, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^2 is hydrogen.

34. The compound of any one of claims 1-33, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{10} is C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, or C_2-C_{10}alkynyl; wherein the alkyl, alkenyl, and alkynyl are optionally independently substituted with one, two, or three R^{10a}.

35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{10} is C_1-C_{10}alkyl optionally substituted with one, two, or three R^{10a}.

36. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{10} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{10a}.

37. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{10} is aryl, heteroaryl, C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{10a}.

38. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{10} is C_1-C_{10}alkyl(aryl); wherein the alkyl and aryl are optionally independently substituted with one, two, or three R^{10a}.

39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{10a} is independently deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl.

40. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{10a} is independently deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl.

41. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{10a} is independently halogen, -OR^a, or C_1-C_6alkyl.

42. The compound of any one of claims 1-41, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{10a} is independently -OR^a.

43. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{11} is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_2-C_6alkenyl, or C_2-C_6alkynyl; wherein the alkyl, alkenyl, alkynyl are optionally substituted with one, two, or three R^{11a}.

44. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{11} is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_{10}alkyl(cycloalkyl), C_1-C_{10}alkyl(heterocycloalkyl), C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a}.

45. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{11} is aryl, heteroaryl, C_1-C_{10}alkyl(aryl), or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a}.

46. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{11} is aryl optionally substituted with one, two, or three R^{11a}.

47. The compound of any one of claims 1-42, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{11} is C_1-C_{10}alkyl(aryl) or C_1-C_{10}alkyl(heteroaryl); wherein the alkyl, aryl, and heteroaryl are optionally independently substituted with one, two, or three R^{11a}.

48. The compound of any one of claims 1-47, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{11a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl.

49. The compound of any one of claims 1-48, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{11a} is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, C_1-C_6alkyl, or C_1-C_6haloalkyl.

50. The compound of any one of claims 1-49, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{11a} is independently hydrogen, halogen, -OH, or C_1-C_6alkyl.

51. The compound of any one of claims 1-50, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{11a} is independently halogen or -OH.

52. A compound selected from a compound found in table 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

53. A pharmaceutical composition comprising a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

54. A method of treating a disease in a subject in need thereof, the method comprising administering a pharmaceutically effective amount of a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition of claim 53.

55. The method of claim 54, wherein the disease is a liver disease, a metabolic disease, or a cardiovascular disease.

56. The method of claim 54 or 55, wherein the disease is NAFLD.

57. The method of claim 54 or 55, wherein the disease is NASH.

58. The method of claim 54 or 55, wherein the disease is drug induced liver injury (DILI).

59. The method of claim 54 or 55, wherein the disease is associated with HSD17B13.

60. The method of claim 54 or 55, wherein the diseases is alcoholic liver disease.

61. The method of claim 54 or 55, wherein the disease is cirrhosis.

62. The method of claim 54 or 55, wherein the disease is decompensated portal hypertension.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/042999

A. CLASSIFICATION OF SUBJECT MATTER

A61P 1/16 (2006.01) C07D 239/88 (2006.01) C07D 239/90 (2006.01) C07D 239/91 (2006.01) C07D 401/04 (2006.01) C07D 401/06 (2006.01) C07D 401/12 (2006.01) C07D 401/14 (2006.01) C07D 403/04 (2006.01) C07D 403/06 (2006.01) C07D 403/12 (2006.01) C07D 413/06 (2006.01) C07D 471/04 (2006.01) C07D 487/04 (2006.01) C07D 495/04 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

REGISTRY and CAPLUS: substructure search conducted based on the pyrimidinone motif in formula II

Applicant/Inventor Search: DOCDB, DWP and internal databases provided by IP Australia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

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

* Special categories of cited documents:

"A"	document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"D"	document cited by the applicant in the international application		
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 September 2021	Date of mailing of the international search report 30 September 2021
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	**Authorised officer** Kelsey Horvath AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262832917

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2021/042999**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0010537 A1 (HANAMURA et al.) 11 January 2007 paragraphs [0054]-[0059], pg. 4; paragraph [0307], pg. 21; example 108, paragraphs [3074]-[3076], pg. 220; paragraph [0930], pg. 59	1, 3, 5, 7, 13, 19-24, 33-51, 53-55, 59
A	WO 2007/000655 A2 (ORCHID RESEARCH LABORATORIES LIMITED) 04 January 2007 ln 14 pg. 1 - ln 2 pg. 2; ln 20 pg. 11 - ln 9 pg. 12; ln 25 pg. 19 - ln 3 pg. 20; compound 41, pg. 31	1-51, 53-62
A	US 2694711 A (AMERICAN CYANAMID CO.) 16 November 1954 ln 18-47, col. 1; example 35, ln 7-39, col. 12	1-51, 53-62
A	CHAO, Q. et al., “Substituted Isoquinolines and Quinazolines as Potential Antiinflammatory Agents. Synthesis and Biological Evaluation of Inhibitors of Tumor Necrosis Factor α”, J. Med. Chem., 1999, vol. 42, no. 19, pages 3860-3873 compound 51, scheme 6, pg. 3863; table 1, pg. 3866; figure 1, pg. 3867	1-51, 53-62

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/042999

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☒ Claims Nos.: **52**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See Supplemental Box

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

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

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of **Box II**
The claim does not comply with Rule 6.2(a) because it relies on references to the description.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2007/0010537 A1	11 January 2007	US 2007010537 A1	11 Jan 2007
		CA 2536313 A1	03 Mar 2005
		EP 1657238 A1	17 May 2006
		JP 2005097276 A	14 Apr 2005
		WO 2005019188 A1	03 Mar 2005
WO 2007/000655 A2	04 January 2007	WO 2007000655 A2	04 Jan 2007
		EP 1896476 A2	12 Mar 2008
		JP 2008543968 A	04 Dec 2008
		US 2009163521 A1	25 Jun 2009
US 2694711 A	16 November 1954	US 2694711 A	16 Nov 1954

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.