Title: COMPOSITION AND METHODS FOR INHIBITING MAMMALIAN STERILE 20-LIKE KINASE 1

Abstract: Disclosed herein are compounds, compositions, and methods of their use for the treatment of diabetes.
COMPOSITION AND METHODS FOR INHIBITING MAMMALIAN STERILE 20-LIKE KINASE 1

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/184,813, filed on June 25, 2015, U.S. Provisional Application No. 62/184,781, filed on June 25, 2015, and U.S. Provisional Application No. 62/258,634, filed on November 23, 2015, which are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Beta cells of the pancreas produce insulin, which is required for cells to take up glucose. Under normal conditions, blood glucose levels rise after eating, triggering pancreatic insulin release. However, in subjects with insulin dependent diabetes mellitus (type 1 diabetes (TID)), beta cells are damaged by autoimmune inflammation, leading to an insufficiency of insulin. In contrast, subjects with non-insulin-dependent diabetes mellitus (type 2 diabetes (T2D)), have normal or high levels of insulin, but a resistance to insulin in peripheral tissues. Beta cells are not able increase secretion of insulin to overcome this resistance. Apoptosis of beta cells occurs in both type I and type II diabetes. Therapies for both TID and T2D include those that require strict dietary regimens and/or drugs that are often not well tolerated long term, both of which make adherence to these therapies challenging for patients. Thus, additional and/or alternative therapies are desirable.

SUMMARY OF THE INVENTION

[0003] Disclosed herein are compounds, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, that modulate an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. Further disclosed herein are compounds, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, that inhibit the activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. Also disclosed herein are methods of treating a metabolic condition in a subject comprising administering to the subject a compound described herein that modulates an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. In some embodiments, the metabolic condition is diabetes mellitus. In some embodiments, the metabolic condition is selected from type 1 diabetes mellitus and type 2 diabetes mellitus. In some embodiments, the metabolic condition is type 1 diabetes mellitus. In some embodiments, the metabolic condition is type 2 diabetes mellitus. In some embodiments, the compound inhibits the activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a
homolog thereof. In some embodiments, the activity is selected from a phosphorylation activity, an inflammatory activity, a cleavage activity, an apoptotic activity, a ubiquinating activity, a mitochondrial activity, and combinations thereof. In some embodiments, the compound inhibits phosphorylation of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof. In some embodiments, the protein downstream is selected from a transcription factor, a kinase, and a histone. In some embodiments, the transcription factor is pancreatic and duodenal homeobox 1 (PDX-1) or a homolog thereof. In some embodiments, the histone is histone 2B (H2B). In some embodiments, the kinase is a Janus kinase (JNK). In some embodiments, the compound inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof. In some embodiments, the protein downstream is a caspase. In some embodiments, the caspase is selected from caspase 9, caspase 3 and MST1. In some embodiments, the compound inhibits apoptotic activity of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof. In some embodiments, the protein downstream is selected from JNK, Bim, Bax, Bcl-2, homologs thereof, and combinations thereof. In some embodiments, the compound is neratinib.

[0004] Further disclosed herein are methods of treating an inflammatory condition in a subject comprising administering to the subject a compound that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. Also disclosed herein are methods of treating an autoimmune disorder in a subject comprising administering to the subject a compound that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. In some embodiments, the compound is neratinib.

[0005] In some embodiments of the methods described herein, the compound is a compound of Formula (I) having the structure:

\[
\text{Formula (I)};
\]

wherein:

- \(\equiv\) is a single or double bond;
- \(X\) is \(-0-, \text{N}(H)-,\) or \(-\text{CH}_2-\);
R¹ and R² are each independently C₁₆alkyl; or R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;

R³ is C₁-alkyl;

each R⁴ is independently halogen, C₁₆alkyl, C₁₆alkoxy, C₁₆haloalkyl, or -CN;

R⁵ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from halogen, C₁₆alkyl, C₁₆alkoxy, C₁₆haloalkyl, Ci.

ehaloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃₋₆cycloalkyl, and phenyl;

R⁶ is H or C₁₆alkyl;

n is 0, 1, 2, or 3; and

p is 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments of the methods described herein, the compound is a compound of Formula (I) wherein p is 1. In some embodiments of the methods described herein, the compound is a compound of Formula (I) wherein n is 1 or 2. In some embodiments of the methods described herein, the compound is a compound of Formula (I) wherein each R⁴ is independently halogen or C₁₆alkyl. In some embodiments of the methods described herein, the compound is a compound having the structure of Formula (Ia):

![Formula (Ia)](image)

In some embodiments of the methods described herein, the compound is a compound having the structure of Formula (lb):

![Formula (lb)](image)

In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R¹ and R² are each independently C₁₆alkyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R¹
and R² are each -CH₃. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁵ is heteroaryl and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₆cycloalkyl, and phenyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁵ is unsubstituted pyridyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁵ is pyridyl substituted by one substituent selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₆cycloalkyl, and phenyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁵ is pyridyl substituted by -CH₃. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁵ is aryl and wherein aryl is unsubstituted or substituted by one or more substituents selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₆cycloalkyl, and phenyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁵ is unsubstituted phenyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁵ is phenyl substituted by one substituent selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₆cycloalkyl, and phenyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁴ is halogen or Ci₆alkyl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁴ is halogen. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R⁴ is -Cl. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein X is -0-. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein X is -N(H)-. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein X is -CH₂-. In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein R³ is -CH₂CH₃. In some embodiments of the methods described herein, the compound is a compound of Formula
In some embodiments of the methods described herein, the compound is a compound of Formula (I), (la), or (lb) wherein \( \equiv \) is a single bond. Also disclosed herein is a method of treating a metabolic condition in a subject comprising administering neratinib to the subject. Further disclosed herein is a method of treating diabetes mellitus in a subject comprising administering neratinib to the subject.

Also disclosed herein is a compound of Formula (II) having the structure:

\[
\text{Formula (II);}
\]

wherein:

- \( X \) is -0-, -N(H)-, or -CH\(_2\)-;
- \( R^1 \) and \( R^2 \) are each independently \( C_{1-6} \)alkyl; or \( R^1 \) and \( R^2 \) together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;
- \( R^3 \) is \( C_{1-6} \)alkyl;
- each \( R^4 \) is independently halogen, \( C_{1-6} \)alkyl, \( C_{1-6} \)alkoxy, \( C_{1-6} \)haloalkyl, or -CN;
- \( R^5 \) is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one or more substituents selected from halogen, \( C_{1-6} \)alkyl, \( C_{1-6} \)alkoxy, \( C_{1-6} \)haloalkyl, \( C_{1-6} \)haloalkoxy, -OH, -CH\(_2\)OH, -CN, -CO\(_2\)R\(_6\), \( C_{3-6} \)cycloalkyl, and phenyl;
- \( R^6 \) is \( H \) or \( C_{1-6} \)alkyl;
- \( n \) is 0, 1, 2, or 3; and
- \( p \) is 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments is a compound of Formula (II), wherein \( p \) is 1. In some embodiments is a compound of Formula (II), wherein \( n \) is 1 or 2. In some embodiments is a compound of Formula (II), wherein each \( R^4 \) is independently halogen or \( C_{1-6} \)alkyl. In some embodiments is a compound having the structure of Formula (IIa):
[0010] In some embodiments is a compound having the structure of Formula (lib):

![Formular (lib)](image)

[0011] In some embodiments is a compound of Formula (II), (Ia), or (lib), wherein $R^1$ and $R^2$ are each independently $C_{1-6}$alkyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^1$ and $R^2$ are each -CH$_3$. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^1$ and $R^2$ together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is heteroaryl and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$haloalkyl, $C_{1-6}$haloalkoxy, -OH, -CH$_2$OH, -CN, -CO$_2$R$^6$, $C_{3-6}$cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is unsubstituted pyridyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is pyridyl substituted by one substituent selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$haloalkyl, $C_{1-6}$haloalkoxy, -OH, -CH$_2$OH, -CN, -CO$_2$R$^6$, $C_{3-6}$cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is pyridyl substituted by $C_{1-6}$alkyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is pyridyl substituted by -CH$_3$. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is aryl and wherein aryl is unsubstituted or substituted by one or more substituents selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$haloalkyl, $C_{1-6}$haloalkoxy, -OH, -CH$_2$OH, -CN, -CO$_2$R$^6$, $C_{3-6}$cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is unsubstituted phenyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^5$ is phenyl substituted by one substituent selected from halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$haloalkyl, $C_{1-6}$haloalkoxy, -OH, -CH$_2$OH, -CN, -CO$_2$R$^6$, $C_{3-6}$cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^4$ is halogen or $C_{1-6}$alkyl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^4$ is halogen. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $R^4$ is -Cl. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $X$ is -OH. In some embodiments is a compound of Formula (II), (Ila), or (lib), wherein $X$ is -N(H)-. In some
embodiments is a compound of Formula (II), (Ha), or (lib), wherein X is -CH₂-. In some embodiments is a compound of Formula (II), (Ha), or (lib), wherein R³ is -CH₂CH₃.

[0012] Also provided herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a pharmaceutically acceptable excipient.

[0013] Further disclosed herein is a method of treating cancer in a subject comprising administering to the subject a compound described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a pharmaceutically acceptable excipient.

**BRIEF DESCRIPTION OF THE DRAWINGS**

[0014] FIG. 1 depicts a pathway of MST1 molecular activity.
[0015] FIG. 2 shows expressions of apoptotic proteins downstream of MST1 activity were modulated by a non-selective MST1 inhibitor and a selective MST1 inhibitor.
[0016] FIG. 3 shows beta cell apoptosis decreased with exposure to increasing concentrations of neratinib.
[0017] FIG. 4 shows neratinib attenuated hyperglycemia in T1D model mice.
[0018] FIG. 5 shows neratinib improved responses to acute glucose challenge in T1D model mice.
[0019] FIG. 6 shows neratinib reduced blood glucose in T1D model mice.
[0020] FIG. 7 shows neratinib increased serum insulin in T1D model mice.
[0021] FIG. 8 shows anti-apoptotic activity of neratinib in beta cells.
[0022] FIG. 9 shows anti-apoptotic activity of neratinib in beta cells.

**DETAILED DESCRIPTION OF THE INVENTION**

[0023] Mammalian Sterile 20-like Kinase 1 (MST1) is upregulated in beta cells of islets in the pancreas that are exposed to a diabetogenic milieu, such as islets of type 2 diabetes patients and mice with mutant leptin receptors (db/db mice). Beta cell specific MST1 deficiency prevents loss of glucose regulation and beta cell mass induced by streptozotocin. MST1 mediates beta cell death via effects on mitochondria, pancreatic and duodenal homeobox 1 (PDX-1), and histone targets (see, e.g. FIG. 1). Therefore, MST1 inhibitors can serve as a therapeutic agent for patients with diabetes. In some embodiments, the MST1 inhibitor is neratinib.

[0024] Neratinib (also known as HKI-272) was identified as an inhibitor of MST1 kinase activity. Neratinib has been previously developed as an EGFR/HER-2 inhibitor, its use intended for breast cancer. Desirable pharmacokinetics and safety have been confirmed in human patients.
However, neratinib as a modulator of MST1 and its use for treating diabetes, inflammatory conditions and autoimmune disorders is unprecedented.

[0025] Beta cell apoptosis was found to decrease with exposure to increasing concentrations of neratinib (see FIG. 3). Neratinib attenuated hyperglycemia in TID model mice treated with streptozotocin (STZ) (see FIG. 4) and improved responses to acute glucose challenge in the TID model mice (see FIG. 5). Neratinib reduced blood glucose and increased serum insulin in TID model mice (see FIGS. 6-7).

[0026] Since diabetes is associated with and may be at least partially caused by autoimmune and inflammatory activity, the compounds described herein may have therapeutic potential for non-diabetes autoimmune and inflammatory conditions as well. In some embodiments, the MST1 inhibitor is neratinib.

Definitions

[0027] 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.

[0028] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. 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.

[0029] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0030] "Amino" refers to the -NH₂ radical.
"Cyano" or "nitrile" refers to the -CN radical.
"Hydroxy" or "hydroxyl" refers to the -OH radical.
"Nitro" refers to the -NO2 radical.
"Oxo" refers to the =O substituent.
"Oxime" refers to the =N-OH substituent.
"Thioxo" refers to the =S substituent.
"Alkyl" refers to a straight or branched hydrocarbon chain radical, has from one to twelve carbon atoms, and is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is referred to as a C1-C12 alkyl, likewise, for example, an alkyl comprising up to 6 carbon atoms is a C1-C6 alkyl. Alkyl groups include, but are not limited to, methyl, ethyl, i-propyl, 1-methylethyl (iso-propyl), i-butyl, t-butyl, s-butyl, s-pentyl, 1,1-dimethylethyl (t-butyl), 2-methylhexyl, vinyl alkyl, propynyl, and the like. Alkyl comprising unsaturations include alkenyl and alkynyl groups. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted as described below.
"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain, as described for alkyl above. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted as described below.
"Alkoxy" refers to a radical of the formula -ORa where Ra is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted as described below.
"Aryl" refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 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 or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.
"Cycloalkyl" or "carbocycle" refers to a stable, non-aromatic, monocyclic or polycyclic carbocyclic ring, which may include fused or bridged ring systems, which is saturated or
unsaturated. Representative cycloalkyls or carbocycles include, but are not limited to, 
cycloalkyls having from three to fifteen carbon atoms, from three to ten carbon atoms, from three 
to eight carbon atoms, from three to six carbon atoms, from three to five carbon atoms, or three 
to four carbon atoms. Monocyclic cycloalkyls or carbocycles include, for example, cyclopropyl, 
cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls or 
carbocycles 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. Unless otherwise stated specifically in the specification, a 
cycloalkyl or carbocycle group may be optionally substituted.

[0042] "Fused" refers to any ring structure described herein which is fused to an existing ring 
structure. When the fused ring is a heterocyclic ring or a heteroaryl ring, any carbon atom on the 
existing ring structure which becomes part of the fused heterocyclic ring or the fused heteroaryl 
ring may be replaced with a nitrogen atom.

[0043] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo.

[0044] "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. Unless stated otherwise specifically in the specification, a 
haloalkyl group may be optionally substituted.

[0045] "Haloalkoxy" similarly refers to a radical of the formula -OR_a where R_a is a haloalkyl 
radical as defined. Unless stated otherwise specifically in the specification, a haloalkoxy group 
may be optionally substituted as described below.

[0046] "Heterocycloalkyl" or "heterocyclic" or "heterocyclic ring" or "heterocycle" refers to a 
stable 3- to 24-membered non-aromatic 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. Unless stated otherwise specifically in the specification, the heterocyclic radical may be a 
monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged 
ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclic radical may be 
optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclic 
radical may be partially or fully saturated. Examples of such heterocyclic radicals include, but 
are not limited to, azetidinyl, dioxolanyl, thi-enyl[1,3]dithianyl, decahydroisoquinolyl, 
imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, 
octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrroloidinyl, oxazolidinyl, 
piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl,
tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 12-crown-4, 15-crown-5, 18-crown-6, 21-crown-7, aza-18-crown-6, diaza-18-crown-6, aza-21-crown-7, and diaza-21-crown-7. Unless stated otherwise specifically in the specification, a heterocycl group may be optionally substituted. 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, heterocy cloalkyls 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). Unless stated otherwise specifically in the specification, a heterocycloalkyl group may be optionally substituted.

[0047] The term "heteroaryl" as used herein, alone or in combination, refers to optionally substituted aromatic monoradicals containing from about five to about twenty skeletal ring atoms, where one or more of the ring atoms is a heteroatom independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but not limited to these atoms and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments in which two or more heteroatoms are present in the ring, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others. The term heteroaryl includes optionally substituted fused and non-fused heteroaryl radicals having at least one heteroatom. The term heteroaryl also includes fused and non-fused heteroaryl s having from five to about twelve skeletal ring atoms, as well as those having from five to about ten skeletal ring atoms. Bonding to a heteroaryl group can be via a carbon atom or a heteroatom. Thus, as a non-limiting example, an imidazol group may be attached to a parent molecule via any of its carbon atoms (imidazol-2-yl, imidazol-4-yl or imidazol-5-yl), or its nitrogen atoms (imidazol-1-yl or imidazol-3-yl). Likewise, a heteroaryl group may be further substituted via any or all of its carbon atoms, and/or any or all of its heteroatoms. A fused heteroaryl radical may contain from two to four fused rings where the ring of attachment is a heteroaromatic ring and the other individual rings may be alicyclic, heterocyclic, aromatic, heteroaromatic or any combination thereof. A non-limiting example of a single ring heteroaryl group includes pyridyl; fused ring heteroaryl groups include benzimidazolyl, quinolinyl, acridinyl; and a non-fused bi-heteroaryl group includes bipyridinyl. Further examples of heteroaryl s include, without limitation, furanyl, thi enyl, oxazolyl, acridinyl, azepinyl, phenazinyl, benzimidazolyl, benzindolyl, benzofurananyl, benzofuranononyl, benzoazolyl, benzothiazolyl, benzothiadiazolyl, benzo thiophenyl, benzoazidazolyl, benzodioxolyl,
benzo[£][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzotriazolyl, benzodioxolyl, benzodioxinyl, benzyopyranyl, benzopyranonyl, benzothenyl (benzothiophenyl), benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanonyl, imidazolyl, indolyl, isoaxazolyl, isoquinolinyl, indoliziny1, indazolyl, isoindolyl, indoliny1, isoindoliny1, indoliziny1, isothiazolyl, isoindolyloxadiazolyl, indazolyl, naphthyridinyl, oxadiazolyl, 2-oxazepiny1, oxirany1, 1-oxidopyridinyl, 1-oxidopyrimidiny1, 1-oxidopyrazinyl, 1-oxidopyridaziny1, 1-phenyl-1H-pyrroly1, phenothiazinyl, phenoxazinyl, pyridinyl, pyridaziny1, pyrimidy1, pyrazinyl, pyrroly1, pyraziny1, pyrazolyl, puriny1, phthalaziny1, pteridiny1, quinoliny1, quinazoliny1, quinoxaliny1, quinuclidiny1, triazolyl, tetrazolyl, thiazolyl, triaziny1, thiadiazolyl, tetrahydroquinolinyl, thiazolyl, and thiophenyl and the like, and their oxides, such as for example pyridyl-N-oxide. Illustrative examples of heteroaryl groups include the following moieties:

All the above groups may be either substituted or unsubstituted. The term "substituted" as used herein means any of the above groups (e.g., alkyl, alky1ene, alkoxy, aryl, cycloalkyl, haloalkyl, heterocycl1 and/or heteroaryl) may be further functionalized wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atom substituent. Unless stated specifically in the specification, a substituted group may include one or more substituents selected from: oxo, amino, -C0 2H, nitrile, nitro, hydroxyl, thiooxy, alkyl, alky1ene, alkoxy, aryl, cycloalkyl, heterocycl1, heteroaryl, dialkylamines, arylamines, alkylarylamines, diarylamines, trialkylammonium (-N+R3), N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsily1 groups, dialkylarylsily1 groups, alkyldia1yrsily1 groups, triarylsily1 groups, perfluoroalkyl or perfluoroalkoxy, for example, trifluoromethyl or trifluoromethoxy.

"Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbony1, carboxy1, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with -NH2, -NRg=C(=0)NRh, -NRg=S02Rg, -OC(=0)NRh, -ORg, -SRg, -SORg, =SO2Rg, -OSO2Rg, -S02ORg, =NS02Rg, and -S02NRh. In the foregoing, Rg and Rh are the
same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclylalkyl, heteroaryl, N-heteroaryl and/or heteroarylalkyl. In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents. Furthermore, any of the above groups may be substituted to include one or more internal oxygen, sulfur, or nitrogen atoms. For example, an alkyl group may be substituted with one or more internal oxygen atoms to form an ether or polyether group. Similarly, an alkyl group may be substituted with one or more internal sulfur atoms to form a thioether, disulfide, etc.

[0049] 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$_2$CH$_3$), fully substituted (e.g., -CF$_2$CF$_3$), mono-substituted (e.g., -CH$_2$CH$_3$F) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., -CH$_2$CHF$_2$, -CH$_2$CF$_3$, -CF$_2$CH$_3$, -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 substition 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.

[0050] 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.

[0051] As used herein, MST1, a cleaved product thereof, a homolog thereof, a modification thereof (e.g. phosphorylation), complexes thereof, and a splice variant thereof, may be used interchangeably, unless otherwise specified. MST1, also known as Stk4, is a serine/threonine kinase. Homologs thereof may be selected from mammalian sterile 20-like kinase 2, Ste-20, and p21-activated kinase (Pak).

[0052] "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 other
embodiments, treatment also includes prophylactic treatment (e.g., administration of a
composition described herein when an individual is suspected to be suffering from a bacterial
infection).

[0053] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the
same molecule. The compounds presented herein may exist as tautomers. 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. Some examples of tautomeric
interconversions include:

![Tautomeric Interconversions](image)

[0054] A "metabolite" of a compound disclosed herein is a derivative of that compound that is
formed when the compound is metabolized. The term "active metabolite" refers to a biologically
active derivative of a compound that is formed when the compound is metabolized. The term
"metabolized," as used herein, refers to the sum of the processes (including, but not limited to,
hydrolysis reactions and reactions catalyzed by enzymes, such as, oxidation reactions) by which
a particular substance is changed by an organism. Thus, enzymes may produce specific structural
alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and
reductive reactions while uridine diphosphate glucuronyl transferases catalyze the transfer of an
activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids,
amines and free sulphhydryl groups. Further information on metabolism may be obtained from The
compounds disclosed herein can be identified either by administration of compounds to a host
and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in
vitro and analysis of the resulting compounds. Both methods are well known in the art. In some
embodiments, metabolites of a compound are formed by oxidative processes and correspond to
the corresponding hydroxy-containing compound. In some embodiments, a compound is
metabolized to pharmacologically active metabolites.
Compounds

[0055] In some embodiments is a compound of Formula (I), (Ia), (lb), (II), (Ha), or (lib) that modulates an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. In some embodiments is a compound of Formula (I), (Ia), (lb), (II), (Ha), or (lib) that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. In some embodiments is a compound of Formula (I), (Ia), (lb), (II), (Ha), or (lib) that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof; wherein the activity is selected from a phosphorylation activity, an inflammatory activity, a cleavage activity, an apoptotic activity, a ubiquitinating activity, a mitochondrial activity, and combinations thereof. In some embodiments is a compound of Formula (I), (Ia), (lb), (II), (Ha), or (lib) that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof; wherein the compound inhibits phosphorylation of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof. In some embodiments is a compound of Formula (I), (Ia), (lb), (II), (Ha), or (lib) that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof; wherein the compound inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof. In some embodiments is a compound of Formula (I), (Ia), (lb), (II), (Ha), or (lib) that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof; wherein the compound inhibits apoptotic activity of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof.

[0056] In some embodiments provided herein, is a compound of Formula (I) having the structure:

![Formula (I)](image)

wherein:

- $\equiv$ is a single or double bond;
- $X$ is $\equiv$, $\equiv$, $\equiv$, or $\equiv$.
R¹ and R² are each independently C₁₋₆alkyl; or R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;

R³ is C₁₋₆alkyl;
each R⁴ is independently halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, or -CN;
R⁵ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃₋₆cycloalkyl, and phenyl;
R⁶ is H or C₁₋₆alkyl;
n is 0, 1, 2, or 3; and
p is 1, 2, or 3;
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0057] In some embodiments is a compound of Formula (I), wherein p is 1. In some embodiments is a compound of Formula (I), wherein p is 2. In some embodiments is a compound of Formula (I), wherein p is 3. In some embodiments is a compound of Formula (I), wherein n is 0. In some embodiments is a compound of Formula (I), wherein n is 1. In some embodiments is a compound of Formula (I), wherein n is 2. In some embodiments is a compound of Formula (I), wherein n is 1 or 2. In some embodiments is a compound of Formula (I), wherein n is 3. In some embodiments is a compound of Formula (I), wherein each R⁴ is halogen. In some embodiments is a compound of Formula (I), wherein each R⁴ is independently -Cl or -Br. In some embodiments is a compound of Formula (I), wherein each R⁴ is -Cl. In some embodiments is a compound of Formula (I), wherein each R⁴ is -Br. In some embodiments is a compound of Formula (I), wherein each R⁴ is C₁₋₆alkyl. In some embodiments is a compound of Formula (I), wherein each R⁴ is -CH₃. In some embodiments is a compound of Formula (I), wherein each R⁴ is independently halogen or C₁₋₆alkyl. In some embodiments is a compound of Formula (I), wherein each R⁴ is independently -Cl or -CH₃. In some embodiments is a compound of Formula (I), wherein each R⁴ is C₁₋₆alkoxy. In some embodiments is a compound of Formula (I), wherein each R⁴ is C₁₋₆haloalkoxy. In some embodiments is a compound of Formula (I), wherein each R⁴ is -CN. In some embodiments is a compound of Formula (I), wherein R¹ and R² are each independently C₁₋₆alkyl. In some embodiments is a compound of Formula (I), wherein R¹ and R² are each -CH₃. In some embodiments is a compound of Formula (I), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments is a compound of Formula (I), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a piperidine ring. In some embodiments is a compound of Formula (I), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form an optionally substituted piperazine ring. In some embodiments is...
a compound of Formula (I), wherein R and R₂ together with the nitrogen to which they are
attached are combined to form a morpholine ring. In some embodiments is a compound of
Formula (I), wherein R₅ is heteroaryl and wherein heteroaryl is unsubstituted or substituted by
one or more substituents selected from halogen, Cᵬ₆ alkyl, Cᵬ₆ alkoxy, Cᵬ₆ haloalkyl, Cᵬ
haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R₆, C₃₆ cycloalkyl, and phenyl. In some embodiments is a
compound of Formula (I), wherein R₅ is heteroaryl and wherein heteroaryl is substituted by one
substituent selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, -
CH₂OH, -CN, -CO₂R₆, C₃₋₆ cycloalkyl, and phenyl. In some embodiments is a compound of
Formula (I), wherein R₅ is unsubstituted pyridyl. In some embodiments is a compound of
Formula (I), wherein R₅ is pyridyl substituted by one or more substituents selected from halogen,
C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R₆, C₃₋₆
haloalkyl, and phenyl. In some embodiments is a compound of Formula (I), wherein R₅ is
pyridyl substituted by one substituent selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkyl,
C₁₋₆ haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R₆, C₃₋₆ cycloalkyl, and phenyl. In some embodiments
is a compound of Formula (I), wherein R₅ is pyridyl substituted by Ci₋₆ alkyl. In some
embodiments is a compound of Formula (I), wherein R₅ is pyridyl substituted by -CH₃. In some
embodiments is a compound of Formula (I), wherein R₅ is pyridyl substituted by halogen. In
some embodiments is a compound of Formula (I), wherein R₅ is pyridyl substituted by -Cl. In
some embodiments is a compound of Formula (I), wherein R₅ is pyridyl substituted by -Br. In
some embodiments is a compound of Formula (I), wherein R₅ is pyridyl substituted by Ci₋₆
alkoxy. In some embodiments is a compound of Formula (I), wherein R₅ is pyridyl substituted
by Ci₋₆ haloalkyl. In some embodiments is a compound of Formula (I), wherein R₅ is pyridyl
substituted by Ci₋₆ haloalkoxy. In some embodiments is a compound of Formula (I), wherein R₅ is
pyridyl substituted by -OH. In some embodiments is a compound of Formula (I), wherein R₅ is
pyridyl substituted by -CH₂OH. In some embodiments is a compound of Formula (I), wherein R₅ is
pyridyl substituted by -CN. In some embodiments is a compound of Formula (I), wherein R₅ is
pyridyl substituted by -CO₂R₆. In some embodiments is a compound of Formula (I), wherein R₅ is
pyridyl substituted by C₃₋₆ cycloalkyl. In some embodiments is a compound of Formula (I),
wherein R₅ is pyridyl substituted by phenyl. In some embodiments is a compound of Formula (I),
wherein R₅ is aryl and wherein aryl is unsubstituted or substituted by one or more substituents
selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, Ci₋₆ haloalkyl, Ci₋₆ haloalkoxy, -OH, -CH₂OH, -CN,
-CO₂R₆, C₃₋₆ cycloalkyl, and phenyl. In some embodiments is a compound of Formula (I),
wherein R₅ is unsubstituted phenyl. In some embodiments is a compound of Formula (I), wherein
R₅ is phenyl substituted by one or more substituents selected from halogen, Ci₋₆ alkyl, Ci₋₆ alkoxy,
Ci₋₆ haloalkyl, Ci₋₆ haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R₆, C₃₋₆ cycloalkyl, and phenyl. In some
embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by one substituent selected from halogen, C1-C6alkyl, C1-C6alkoxy, C1-C6haloalkyl, C1-C6haloalkoxy, -OH, -CH2OH, -CN, -C02R6, C3-C6cycloalkyl, and phenyl. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by C1-C6alkyl. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by -CH3. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by halogen. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by -Cl. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by -Br. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by C1-C6alkoxy. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by C1-C6haloalkyl. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by C1-C6haloalkoxy. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by -OH. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by -CH2OH. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by -CN. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by C3-C6cycloalkyl. In some embodiments is a compound of Formula (I), wherein R5 is phenyl substituted by phenyl. In some embodiments is a compound of Formula (I), wherein X is -0-. In some embodiments is a compound of Formula (I), wherein X is -N(H)-. In some embodiments is a compound of Formula (I), wherein X is -CH2-. In some embodiments is a compound of Formula (I), wherein R3 is -CH2CH3. In some embodiments is a compound of Formula (I), wherein is a single bond. In some embodiments is a compound of Formula (I), wherein is a double bond.

[0058] In some embodiments provided herein, is a compound of Formula (la) having the structure:

![Formula (la)](image)

wherein:

- is a single or double bond;
- X is -O-, -N(H)-, or -CH2-;
R¹ and R² are each independently C₁₋₆alkyl; or R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;

R³ is C₁₋₆alkyl;

R⁴ is halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, or -CN;

R⁵ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₋₆cycloalkyl, and phenyl; and

R⁶ is H or C₁₋₆alkyl;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0059] In some embodiments is a compound of Formula (la), wherein R⁴ is halogen. In some embodiments is a compound of Formula (la), wherein R⁴ is -CI. In some embodiments is a compound of Formula (la), wherein R⁴ is -Br. In some embodiments is a compound of Formula (la), wherein R⁴ is C₁₋₆alkyl. In some embodiments is a compound of Formula (la), wherein R⁴ is -CH₃. In some embodiments is a compound of Formula (la), wherein R⁴ is C₁₋₆alkoxy. In some embodiments is a compound of Formula (la), wherein R⁴ is C₁₋₆haloalkyl. In some embodiments is a compound of Formula (la), wherein R⁴ is -CN. In some embodiments is a compound of Formula (la), wherein R¹ and R² are each independently C₁₋₆alkyl. In some embodiments is a compound of Formula (la), wherein R¹ and R² are each -CH₃. In some embodiments is a compound of Formula (la), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments is a compound of Formula (la), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a piperidine ring. In some embodiments is a compound of Formula (la), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a piperazine ring. In some embodiments is a compound of Formula (la), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a morpholine ring. In some embodiments is a compound of Formula (la), wherein R⁵ is heteroaryl and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (la), wherein R⁵ is heteroaryl and wherein heteroaryl is substituted by one substituent selected from halogen, C¹₋₆alkyl, C¹₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (la), wherein R⁵ is unsubstituted pyridyl. In some embodiments is a compound of Formula (la), wherein R⁵ is pyridyl substituted by one or more substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -C0₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of
Formula (la), wherein R₅ is pyridyl substituted by one substituent selected from halogen, C₆alkyl, C₆alkoxy, C₆haloalkyl, C₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by C₁₋₆alkyl. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by -CH₃. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by halogen. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by -Cl. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by -Br. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by C₁₋₆alkoxy. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by C₁₋₆haloalkyl. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by C₁₋₆haloalkoxy. In some embodiments is a compound of Formula (la), wherein R₅ is pyridyl substituted by C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (la), wherein R₅ is unsubstituted phenyl. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by one or more substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by one substituent selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, C₁₋₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by -CH₃. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by halogen. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by -Cl. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by -Br. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by C₁₋₆alkoxy. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by C₁₋₆haloalkyl. In some embodiments is a compound of Formula (la), wherein R₅ is phenyl substituted by C₁₋₆haloalkoxy. In some embodiments is a compound of
Formula (la), wherein R⁵ is phenyl substituted by -OH. In some embodiments is a compound of Formula (la), wherein R⁵ is phenyl substituted by -CH₂OH. In some embodiments is a compound of Formula (la), wherein R⁵ is phenyl substituted by -CN. In some embodiments is a compound of Formula (la), wherein R⁵ is phenyl substituted by -C₀₂R⁶. In some embodiments is a compound of Formula (la), wherein R⁵ is phenyl substituted by C₃₆cycloalkyl. In some embodiments is a compound of Formula (la), wherein R⁵ is phenyl substituted by phenyl. In some embodiments is a compound of Formula (la), wherein X is -0-. In some embodiments is a compound of Formula (la), wherein X is -N(H)-. In some embodiments is a compound of Formula (la), wherein X is -CH₂-. In some embodiments is a compound of Formula (la), wherein R³ is -CH₂CH₃. In some embodiments is a compound of Formula (la), wherein == is a single bond. In some embodiments is a compound of Formula (la), wherein == is a double bond.

[0060] In some embodiments provided herein, is a compound of Formula (lb) having the structure:

![Structure Diagram](image_url)

wherein:

== is a single or double bond;

X is -0-, -N(H)-, or -CH₂-;

R¹ and R² are each independently Cᵢ₋₆alkyl; or R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;

R³ is Cᵢ₋₆alkyl;

R⁴ is halogen, Cᵢ₋₆alkyl, Cᵢ₋₆alkoxy, Cᵢ₋₆haloalkyl, or -CN;

R⁵ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, Ci.

e haloalkoxy, -OH, -CH₂OH, -CN, C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl; and

R⁶ is H or Cᵢ₋₆alkyl;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0061] In some embodiments is a compound of Formula (lb), wherein R⁴ is halogen. In some embodiments is a compound of Formula (lb), wherein R⁴ is -Cl. In some embodiments is a compound of Formula (lb), wherein R⁴ is -Br. In some embodiments is a compound of Formula
(lb), wherein R^4 is C_{6}alkyl. In some embodiments is a compound of Formula (lb), wherein R^4 is -CH_{3}. In some embodiments is a compound of Formula (lb), wherein R^4 is C_{6}alkoxy. In some embodiments is a compound of Formula (lb), wherein R^4 is C_{6}haloalkyl. In some embodiments is a compound of Formula (lb), wherein R^4 is -CN. In some embodiments is a compound of Formula (lb), wherein R^1 and R^2 are each independently C_{6}alkyl. In some embodiments is a compound of Formula (lb), wherein R^1 and R^2 are each -CH_{3}. In some embodiments is a compound of Formula (lb), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments is a compound of Formula (lb), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a piped dine ring. In some embodiments is a compound of Formula (lb), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a piperazine ring. In some embodiments is a compound of Formula (lb), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a morpholine ring. In some embodiments is a compound of Formula (lb), wherein R^5 is heteroaryl and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, C_{6}alkyl, C_{6}alkoxy, C_{6}haloalkyl, C_{6}haloalkoxy, -OH, -CH_{2}OH, -CN, -C_{0,2}R^6, C_{3,6}cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lb), wherein R^5 is heteroaryl and wherein heteroaryl is substituted by one substituent selected from halogen, C_{1,6}alkyl, C_{1,6}alkoxy, C_{1,6}haloalkyl, C_{1,6}haloalkoxy, -OH, -CH_{2}OH, -CN, -C_{0,2}R^6, C_{3,6}cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by one substituent selected from halogen, C_{6}alkyl, C_{6}alkoxy, C_{6}haloalkyl, C_{6}haloalkoxy, -OH, -CH_{2}OH, -CN, -C_{0,2}R^6, C_{3,6}cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by C_{6}alkyl. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by -CH_{3}. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by halogen. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by -Cl. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by -Br. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by C_{6}alkoxy. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by C_{6}haloalkyl. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by C_{6}haloalkoxy. In some embodiments is a compound of Formula (lb), wherein R^5 is pyridyl substituted by -OH. In some embodiments is a compound of
Formula (lb), wherein R\textsuperscript{5} is pyridyl substituted by -CH\textsubscript{2}OH. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is pyridyl substituted by -CN. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is pyridyl substituted by -C0\textsubscript{2}R\textsuperscript{6}. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is pyridyl substituted by C\textsubscript{3,6}cycloalkyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is pyridyl substituted by phenyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is aryl and wherein aryl is unsubstituted or substituted by one or more substituents selected from halogen, C\textsubscript{1,6}alkyl, C\textsubscript{6}alkoxy, C\textsubscript{1,6}haloalkyl, C\textsubscript{1,6}h haloalkoxy, -OH, -CH\textsubscript{2}OH, -CN, -C0\textsubscript{2}R\textsuperscript{6}, C\textsubscript{3,6}cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is unsubstituted phenyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by one or more substituents selected from halogen, C\textsubscript{1,6}alkyl, C\textsubscript{1,6}alkoxy, C\textsubscript{6}h haloalkyl, C\textsubscript{6}haloalkoxy, -OH, -CH\textsubscript{2}OH, -CN, -C0\textsubscript{2}R\textsuperscript{6}, C\textsubscript{3,6}cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by one substituent selected from halogen, C\textsubscript{6}alkyl, C\textsubscript{6}alkoxy, C\textsubscript{6}haloalkyl, C\textsubscript{6}haloalkoxy, -OH, -CH\textsubscript{2}OH, -CN, -C0\textsubscript{2}R\textsuperscript{6}, C\textsubscript{3,6}cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by C\textsubscript{6}alkyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by -CH\textsubscript{3}. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by halogen. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by -Cl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by -Br. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by C\textsubscript{6}alkoxy. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by C\textsubscript{6}h haloalkyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by C\textsubscript{6}h haloalkoxy. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by -OH. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by -CH\textsubscript{2}OH. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by -CN. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by -C0\textsubscript{2}R\textsuperscript{6}. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by C\textsubscript{3,6}cycloalkyl. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{5} is phenyl substituted by phenyl. In some embodiments is a compound of Formula (lb), wherein X is -0-. In some embodiments is a compound of Formula (lb), wherein X is -N(H)-. In some embodiments is a compound of Formula (lb), wherein X is -CH\textsubscript{2}-. In some embodiments is a compound of Formula (lb), wherein R\textsuperscript{3} is -CH\textsubscript{2}CH\textsubscript{3}. In some embodiments is a compound of Formula (lb), wherein \textsuperscript{===} is a single bond. In some embodiments is a compound of Formula (lb), wherein \textsuperscript{==} is a double bond.
In some embodiments provided herein, is a compound of Formula (II) having the structure:

![Formula (II)](image)

wherein:

- **X** is -0-, -N(H)-, or -CH₂-;
- **R₁** and **R₂** are each independently Cl₆alkyl; or **R₁** and **R₂** together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;
- **R³** is Cl₆alkyl;
- each **R⁴** is independently halogen, Cl₂alkyl, Cl₆alkoxy, Cl₆haloalkyl, or -CN;
- **R⁵** is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one or more substituents selected from halogen, C₁₆alkyl, Cl₆alkoxy, Cl₆haloalkyl, Cl₆ehaloalkoxy, -OH, -CH₂OH, -CN, -CO₂R₆, C₃cycloalkyl, and phenyl;
- **R⁶** is H or Cl₆alkyl;
- **n** is 0, 1, 2, or 3; and
- **p** is 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In some embodiments is a compound of Formula (II), wherein **p** is 1. In some embodiments is a compound of Formula (II), wherein **p** is 2. In some embodiments is a compound of Formula (II), wherein **p** is 3. In some embodiments is a compound of Formula (II), wherein **n** is 0. In some embodiments is a compound of Formula (II), wherein **n** is 1. In some embodiments is a compound of Formula (II), wherein **n** is 2. In some embodiments is a compound of Formula (II), wherein **n** is 1 or 2. In some embodiments is a compound of Formula (II), wherein **n** is 3. In some embodiments is a compound of Formula (II), wherein each **R⁴** is halogen. In some embodiments is a compound of Formula (II), wherein each **R⁴** is independently -Cl or -Br. In some embodiments is a compound of Formula (II), wherein each **R⁴** is -Cl. In some embodiments is a compound of Formula (II), wherein each **R⁴** is -Br. In some embodiments is a compound of Formula (II), wherein each **R⁴** is Cl₂alkyl. In some embodiments is a compound of Formula (II), wherein each **R⁴** is -CH₃. In some embodiments is a compound of Formula (II), wherein each **R⁴** is independently halogen or Cl₆alkyl. In some embodiments is a compound of
Formula (II), wherein each R^4 is independently -Cl or -CH₃. In some embodiments is a compound of Formula (II), wherein each R^4 is Ci-6alkoxy. In some embodiments is a compound of Formula (II), wherein each R^4 is Ci-6haloalkyl. In some embodiments is a compound of Formula (II), wherein each R^4 is -CN. In some embodiments is a compound of Formula (II), wherein R^1 and R^2 are each independently Ci₆alkyl. In some embodiments is a compound of Formula (II), wherein R^1 and R^2 are each -CH₃. In some embodiments is a compound of Formula (II), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments is a compound of Formula (II), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a piperidine ring. In some embodiments is a compound of Formula (II), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a piperazine ring. In some embodiments is a compound of Formula (II), wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a morpholine ring. In some embodiments is a compound of Formula (II), wherein R^5 is heteroaryl and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R^5 is heteroaryl and wherein heteroaryl is substituted by one substituent selected from halogen, C₁₋₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R^5 is pyridyl substituted by one substituent selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R^5 is pyridyl substituted by one substituent selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R^5 is pyridyl substituted by one substituent selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₋₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R^5 is pyridyl substituted by -OH.
is pyridyl substituted by -CH₂OH. In some embodiments is a compound of Formula (II), wherein R⁵ is pyridyl substituted by -CN. In some embodiments is a compound of Formula (II), wherein R⁵ is pyridyl substituted by -C₀₂R⁶. In some embodiments is a compound of Formula (II), wherein R⁵ is pyridyl substituted by C₃₆cycloalkyl. In some embodiments is a compound of Formula (II), wherein R⁵ is pyridyl substituted by phenyl. In some embodiments is a compound of Formula (II), wherein R⁵ is aryl and wherein aryl is unsubstituted or substituted by one or more substituents selected from halogen, C₁₆alkyl, C₁₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R⁵ is unsubstituted phenyl. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by one or more substituents selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by one substituent selected from halogen, Ci₆alkyl, Ci₆alkoxy, Ci₆haloalkyl, Ci₆haloalkoxy, -OH, -CH₂OH, -CN, -C₀₂R⁶, C₃₆cycloalkyl, and phenyl. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by -CH₃. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by halogen. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by -Cl. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by -Br. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by Cl. Ci₆alkoxy. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by Ci₆haloalkyl. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by Ci₆haloalkoxy. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by -OH. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by -CH₂OH. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by -CN. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by -C₀₂R⁶. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by C₃₆cycloalkyl. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by phenyl. In some embodiments is a compound of Formula (II), wherein R⁵ is phenyl substituted by X is -0-. In some embodiments is a compound of Formula (II), wherein X is -N(H)-. In some embodiments is a compound of Formula (II), wherein X is -CH₂-. In some embodiments is a compound of Formula (II), wherein R³ is -CH₂CH₃. [0064] In some embodiments provided herein, is a compound of Formula (Iia) having the structure:
wherein:
X is -O-, -N(H)-, or -CH₂-;
R¹ and R² are each independently Cᵢ₋₆alkyl; or R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;
R³ is C₁₋₆alkyl;
R⁴ is halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, or -CN;
R⁵ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, Ci. ehaloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃₋₆cycloalkyl, and phenyl; and
R⁶ is H or C₁₋₆alkyl;
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0065] In some embodiments is a compound of Formula (Ila), wherein R⁴ is halogen. In some embodiments is a compound of Formula (Ila), wherein R⁴ is -Cl. In some embodiments is a compound of Formula (Ila), wherein R⁴ is -Br. In some embodiments is a compound of Formula (Ila), wherein R⁴ is C₁₋₆alkyl. In some embodiments is a compound of Formula (Ila), wherein R⁴ is -CH₃. In some embodiments is a compound of Formula (Ila), wherein R⁴ is Ci.₆alkoxy. In some embodiments is a compound of Formula (Ila), wherein R⁴ is Ci.₆haloalkyl. In some embodiments is a compound of Formula (Ila), wherein R⁴ is -CN. In some embodiments is a compound of Formula (Ila), wherein R¹ and R² are each independently Ci.₆alkyl. In some embodiments is a compound of Formula (Ila), wherein R¹ and R² are each -CH₃. In some embodiments is a compound of Formula (Ila), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments is a compound of Formula (Ila), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a piperidine ring. In some embodiments is a compound of Formula (Ila), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a morpholine ring. In some embodiments is a compound of Formula (Ila), wherein R⁵ is heteroaryl.
and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, \( \text{Ci}_{6}\text{-alkyl}, \text{Ci}_{6}\text{-alkoxy}, \text{Ci}_{6}\text{-haloalkyl}, \text{Ci}_{6}\text{-haloalkoxy}, -\text{OH}, -\text{CH}_2\text{OH}, -\text{CN}, -\text{C}_0\text{,}_2\text{R}_6, \text{C}_3\text{-cycloalkyl}, \) and phenyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is heteroaryl and wherein heteroaryl is substituted by one substituent selected from halogen, \( \text{Ci}_{6}\text{-alkyl}, \text{Ci}_{6}\text{-alkoxy}, \text{Ci}_{6}\text{-haloalkyl}, \text{Ci}_{6}\text{-haloalkoxy}, -\text{OH}, -\text{CH}_2\text{OH}, -\text{CN}, -\text{C}_0\text{,}_2\text{R}_6, \text{C}_3\text{-cycloalkyl}, \) and phenyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is unsubstituted pyridyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by one or more substituents selected from halogen, \( \text{Ci}_{6}\text{-alkyl}, \text{Ci}_{6}\text{-alkoxy}, \text{Ci}_{6}\text{-haloalkyl}, \text{Ci}_{6}\text{-haloalkoxy}, -\text{OH}, -\text{CH}_2\text{OH}, -\text{CN}, -\text{C}_0\text{,}_2\text{R}_6, \text{C}_3\text{-cycloalkyl}, \) and phenyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by -\text{CH}_3. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by -\text{Cl}. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by -\text{Br}. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by \( \text{Ci}_{6}\text{-alkoxy} \). In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by \( \text{Ci}_{6}\text{-haloalkyl} \). In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by \( \text{Ci}_{6}\text{-haloalkoxy} \). In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by -\text{OH}. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by -\text{CH}_2\text{OH}. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by -\text{CN}. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by -\text{C}_0\text{,}_2\text{R}_6. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by \( \text{C}_3\text{-cycloalkyl} \). In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is pyridyl substituted by phenyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is aryl and wherein aryl is unsubstituted or substituted by one or more substituents selected from halogen, \( \text{Ci}_{6}\text{-alkyl}, \text{Ci}_{6}\text{-alkoxy}, \text{Ci}_{6}\text{-haloalkyl}, \text{Ci}_{6}\text{-haloalkoxy}, -\text{OH}, -\text{CH}_2\text{OH}, -\text{CN}, -\text{C}_0\text{,}_2\text{R}_6, \text{C}_3\text{-cycloalkyl}, \) and phenyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is unsubstituted phenyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is phenyl substituted by one or more substituents selected from halogen, \( \text{Ci}_{6}\text{-alkyl}, \text{Ci}_{6}\text{-alkoxy}, \text{Ci}_{6}\text{-haloalkyl}, \text{Ci}_{6}\text{-haloalkoxy}, -\text{OH}, -\text{CH}_2\text{OH}, -\text{CN}, -\text{C}_0\text{,}_2\text{R}_6, \text{C}_3\text{-cycloalkyl}, \) and phenyl. In some embodiments is a compound of Formula (Ia), wherein \( R^5 \) is phenyl substituted by one substituent selected from halogen, \( \text{Ci}_{6}\text{-alkyl}, \text{Ci}_{6}\text{-alkoxy}, \text{Ci}_{6}\text{-haloalkyl}, \text{Ci}_{6}\text{-haloalkoxy}, -\text{OH}, -
CH$_2$OH, -CN, -CO$_2$R$_6$, C$_3$-$\delta$ cycloalkyl, and phenyl. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by C$_i$-$\delta$ alkyl. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by -CH$_3$. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by halogen. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by -Cl. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by -Br. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by C$_i$-$\delta$ alkoxy. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by C$_i$-$\delta$ haloalkyl. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by C$_i$-$\delta$ haloalkoxy. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by -OH. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by -CH$_2$OH. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by -CN. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by -C0$_2$R$_6$. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by C$_3$-$\delta$ Cycloalkyl. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by phenyl. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is phenyl substituted by X. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is N(H)-. In some embodiments is a compound of Formula (Ila), wherein X is -CH$_2$-. In some embodiments is a compound of Formula (Ila), wherein R$_5$ is -CH$_2$CH$_3$.

[0066] In some embodiments provided herein, is a compound of Formula (lib) having the structure:

![Formula (lib)](image)

wherein:

X is -0-, -N(H)-, or -CH$_2$-;

R$^1$ and R$^2$ are each independently C$_i$-$\delta$ alkyl; or R$^1$ and R$^2$ together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;

R$^3$ is C$_i$-$\delta$ alkyl;

R$^4$ is halogen, C$_1$-$\delta$ alkyl, C$_i$-$\delta$ alkoxy, C$_i$-$\delta$ haloalkyl, or -CN;
R⁵ is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from halogen, Ci-6alkyl, Ci-6alkoxy, Ci-6haloalkyl, C₁-sixhaloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃-sixcycloalkyl, and phenyl; and R⁶ is H or Ci-6alkyl; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0067] In some embodiments is a compound of Formula (lib), wherein R⁴ is halogen. In some embodiments is a compound of Formula (lib), wherein R⁴ is -Cl. In some embodiments is a compound of Formula (lib), wherein R⁴ is -Br. In some embodiments is a compound of Formula (lib), wherein R⁴ is Ci-6alkyl. In some embodiments is a compound of Formula (lib), wherein R⁴ is Ci-6haloalkyl. In some embodiments is a compound of Formula (lib), wherein R⁴ is -CH₃. In some embodiments is a compound of Formula (lib), wherein R⁴ is Ci-6alkoxy. In some embodiments is a compound of Formula (lib), wherein R⁴ is -CN. In some embodiments is a compound of Formula (lib), wherein R¹ and R² are each independently Ci-6alkyl. In some embodiments is a compound of Formula (lib), wherein R¹ and R² are each -CH₃. In some embodiments is a compound of Formula (lib), wherein R¹ together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring. In some embodiments is a compound of Formula (lib), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a piperidine ring. In some embodiments is a compound of Formula (lib), wherein R¹ and R² together with the nitrogen to which they are attached are combined to form a morpholine ring. In some embodiments is a compound of Formula (lib), wherein R⁵ is heteroaryl and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, Ci-6alkyl, Ci-6alkoxy, Ci-6haloalkyl, Ci-6haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃-sixcycloalkyl, and phenyl. In some embodiments is a compound of Formula (lib), wherein R⁵ is heteroaryl and wherein heteroaryl is substituted by one substituent selected from halogen, Ci-6alkyl, Ci-6alkoxy, Ci-6haloalkyl, Ci-6haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃-sixcycloalkyl, and phenyl. In some embodiments is a compound of Formula (lib), wherein R⁵ is unsubstituted pyridyl. In some embodiments is a compound of Formula (lib), wherein R⁵ is pyridyl substituted by one or more substituents selected from halogen, Ci-6alkyl, Ci-6alkoxy, Ci-6haloalkyl, Ci-6haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃-sixcycloalkyl, and phenyl. In some embodiments is a compound of Formula (lib), wherein R⁵ is pyridyl substituted by Ci-6alkyl. In some embodiments is a compound of Formula (lib), wherein
R^5 is pyridyl substituted by -CH_3. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by halogen. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by -Cl. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by -Br. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by Ci_6alkoxy. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by Ci-6haloalkyl. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by Ci-6haloalkoxy. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by -OH. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by -CH_2OH. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by -CN. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by -C0_2R^6. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by C_3-6cycloalkyl. In some embodiments is a compound of Formula (lib), wherein R^5 is pyridyl substituted by phenyl. In some embodiments is a compound of Formula (lib), wherein R^5 is aryl and wherein aryl is unsubstituted or substituted by one or more substituents selected from halogen, Ci_6alkyl, Ci_6alkoxy, Ci_6haloalkyl, Ci_6haloalkoxy, -OH, -CH_2OH, -CN, -C0_2R^6, C_3-6cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lib), wherein R^5 is unsubstituted phenyl. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by one or more substituents selected from halogen, Ci_6alkyl, Ci_6alkoxy, Ci_6haloalkyl, Ci_6haloalkoxy, -OH, -CH_2OH, -CN, -C0_2R^6, C_3-6cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by one substituent selected from halogen, C_1-6alkyl, C_1-6alkoxy, C_i-6haloalkyl, C_i-6haloalkoxy, -OH, -CH_2OH, -CN, -C0_2R^6, C_3-6cycloalkyl, and phenyl. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by C_i-6alkyl. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by -CH_3. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by halogen. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by -Cl. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by -Br. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by Ci_6alkoxy. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by Ci-6haloalkyl. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by Ci_6haloalkoxy. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by -OH. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by -CH_2OH. In some embodiments is a compound of Formula (lib), wherein R^5 is phenyl substituted by -CN. In some embodiments is a compound of Formula (lib), wherein R^5 is
phenyl substituted by -C0₂R⁶. In some embodiments is a compound of Formula (lib), wherein R⁵ is phenyl substituted by C₃₅cycloalkyl. In some embodiments is a compound of Formula (lib), wherein R⁵ is phenyl substituted by phenyl. In some embodiments is a compound of Formula (lib), wherein X is -0-. In some embodiments is a compound of Formula (lib), wherein X is -N(H)-. In some embodiments is a compound of Formula (lib), wherein X is -CH₂-. In some embodiments is a compound of Formula (lib), wherein R₃ is -CH₂CH₃.

[0068] In some embodiments is a compound, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, having the structure selected from:
Preparation of Compounds

Compounds of Formula (I), (la), (lb), (II), (Ila), or (lib) may be synthesized using standard synthetic reactions known to those of skill in the art or using methods known in the art. The reactions can be employed in a linear sequence to provide the compounds or they may be
used to synthesize fragments which are subsequently joined by the methods known in the art. Also described herein are pharmaceutically acceptable salts, pharmaceutically acceptable solvates, and pharmaceutically acceptable prodrugs of such compounds. Pharmaceutical compositions comprising at least one such compound or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically active metabolite or pharmaceutically acceptable prodrug of such compound, and a pharmaceutically acceptable excipient are also provided.

[0070] The starting material used for the synthesis of the compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Aldrich Chemical Co. (Milwaukee, Wisconsin), Bachem (Torrance, California), or Sigma Chemical Co. (St. Louis, Mo.). The compounds described herein, and other related compounds having different substituents can be synthesized using techniques and materials known to those of skill in the art, such as described, for example, in March, ADVANCED ORGANIC CHEMISTRY 4th Ed., (Wiley 1992); Carey and Sundberg, ADVANCED ORGANIC CHEMISTRY 4th Ed., Vols. A and B (Plenum 2000, 2001); Green and Wuts, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS 3rd Ed., (Wiley 1999); Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989); (all of which are incorporated by reference in their entirety). General methods for the preparation of compound as disclosed herein may be derived from known reactions in the field, and the reactions may be modified by the use of appropriate reagents and conditions, as would be recognized by the skilled person, for the introduction of the various moieties found in the formulae as provided herein.

[0071] The products of the reactions may be isolated and purified, if desired, using conventional techniques, including, but not limited to, filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0072] Compounds described herein may be prepared as a single isomer or a mixture of isomers.

[0073] The starting materials and intermediates for the compounds of this invention may be prepared by the application or adaptation of the methods described herein, their obvious chemical equivalents, or, for example, as described in literature such as The Science of Synthesis, Volumes 1-8. Editors E. M. Carreira et al. Thieme publishers (2001-2008).
Further Forms of Compounds Disclosed Herein

Isomers

Furthermore, 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, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. 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 (e.g., crystalline diastereomeric salts). 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

In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In certain embodiments, the compounds described herein exist as partially or fully deuterated 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 of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chloride, such as $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^5$N, $^{18}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, and $^{36}$Cl, respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvate, hydrate or derivatives 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 $^3$H and $^{14}$C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., $^3$H 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., $^2$H, produces certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

[0076] 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.

Pharmaceutically acceptable salts

[0077] 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.

[0078] 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 of the invention, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0079] 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, dodecyl sulfate, 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-naphthalenesulfonate, 2-naphthalenesulfonate, 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, tosylate undeconate and xylenesulfonate.

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-toluensulfonic 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 of the invention and their pharmaceutically acceptable acid addition salts.

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+(Ci4 alkyl)4, and the like.
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**

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.

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 alcohohates 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.

**Methods**

Disclosed herein is a compound of Formula (I), (la), (lb), (II), (Ha), or (lib) that modulates an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. Further disclosed herein is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (IIa), or (lib). In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (IIa), or (lib), wherein the metabolic condition is diabetes mellitus. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (IIa), or (lib), wherein the metabolic condition is type 1 diabetes mellitus. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (IIa), or (lib), wherein the metabolic condition is type 2 diabetes mellitus.
In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is selected from a phosphorylation activity, an inflammatory activity, a cleavage activity, an apoptotic activity, a ubiquitinating activity, a mitochondrial activity, and combinations thereof. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is phosphorylation activity. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is an inflammatory activity. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is a cleavage activity. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is an apoptotic activity. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is a ubiquitinating activity. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ia), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ia), or (lib) inhibits the activity of the mammalian sterile 20-like kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is an inflammatory activity.
kinase 1 (MST1), the cleaved product thereof, or the homolog thereof, and the activity is a
mitochondrial activity.

[0087] In some embodiments is a method of treating a metabolic condition in a subject
comprising administering to the subject a compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib),
wherein the compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib) inhibits phosphorylation of a
protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product
thereof, or the homolog thereof. In some embodiments is a method of treating a metabolic
condition in a subject comprising administering to the subject a compound of Formula (I), (Ia),
(Ib), (II), (IIa), or (lib), wherein the compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib)
inhibits phosphorylation of a protein downstream of the activity of the mammalian sterile 20-like
kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is
selected from a transcription factor, a kinase, and a histone. In some embodiments is a method of
treating a metabolic condition in a subject comprising administering to the subject a compound of
Formula (I), (Ia), (lb), (II), (IIa), or (lib), wherein the compound of Formula (I), (Ia), (lb), (II),
(IIa), or (lib) inhibits phosphorylation of a protein downstream of the activity of the mammalian
sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein
downstream is a transcription factor. In some embodiments is a method of treating a metabolic
condition in a subject comprising administering to the subject a compound of Formula (I), (Ia),
(lb), (II), (IIa), or (lib), wherein the compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib)
inhibits phosphorylation of a protein downstream of the activity of the mammalian sterile 20-like
kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is a
transcription factor and the transcription factor is pancreatic and duodenal homeobox 1 (PDX-1)
or a homolog thereof. In some embodiments is a method of treating a metabolic condition in a
subject comprising administering to the subject a compound of Formula (I), (Ia), (lb), (II), (IIa),
or (lib), wherein the compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib) inhibits
phosphorylation of a protein downstream of the activity of the mammalian sterile 20-like kinase
1, the cleaved product thereof, or the homolog thereof, and the protein downstream is a kinase. In
some embodiments is a method of treating a metabolic condition in a subject comprising
administering to the subject a compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib), wherein the
compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib) inhibits phosphorylation of a protein
downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product
thereof, or the homolog thereof, and the protein downstream is Janus kinase. In some
embodiments is a method of treating a metabolic condition in a subject comprising administering
to the subject a compound of Formula (I), (Ia), (lb), (II), (IIa), or (lib), wherein the compound of
Formula (I), (Ia), (lb), (II), (IIa), or (lib) inhibits phosphorylation of a protein downstream of the
activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is a histone. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ila), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) inhibits phosphorylation of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is a histone and the histone is histone 2B.

[0088] In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ila), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ila), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is caspase. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ila), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is selected from caspase 9, caspase 3, and MST1.

In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ila), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is caspase 9. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ila), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is caspase 3. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (la), (lb), (II), (Ila), or (lib), wherein the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is MST1.
In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib), wherein the compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib) inhibits apoptotic activity of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib), wherein the compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib) inhibits apoptotic activity of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is selected from INK, Bim, Bax, Bcl-2, homologs thereof, and combinations thereof. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib), wherein the compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib) inhibits apoptotic activity of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is Bim. In some embodiments is a method of treating a metabolic condition in a subject comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib), wherein the compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib) inhibits apoptotic activity of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof, and the protein downstream is Bcl-2.

Also disclosed herein in some embodiments is a method of treating an inflammatory condition in a subject comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib).

Also disclosed herein in some embodiments is a method of treating an autoimmune disorder in a subject comprising administering to the subject a compound of Formula (I), (Ia), (Ib), (II), (IIa), or (lib).
[0092] Also disclosed herein is a method of treating cancer in a subject comprising administering to the subject a compound of Formula (I), (Ia), (lb), (II), (Ia), or (lib), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a pharmaceutically acceptable excipient. Further disclosed herein is a method of treating cancer in a subject comprising administering to the subject a compound of Formula (II), (Ila), or (lib), or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a pharmaceutically acceptable excipient.

[0093] In some embodiments of the methods described herein the compound is neratinib.

[0094] In some embodiments of the methods described herein the compound has the structure:
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0095] In some embodiments, the compounds of Formula (I), (la), (lb), (II), (Ila), or (lib) described herein inhibit the activity of the MST1 directly or indirectly. In some embodiments, the compounds of Formula (I), (la), (lb), (II), (Ila), or (lib) described herein inhibit a protein upstream of MST1. As used herein, the term "upstream" indicates a protein that has activity that effects MST1 expression or activity. In some embodiments, the compounds of Formula (I), (la), (lb), (II), (Ila), or (lib) described herein inhibit a protein downstream of MST1. As used herein, the term "downstream" indicates a protein that has activity that is affected by MST1 expression or activity. In some embodiments, the protein upstream or the protein downstream is a component of a Hippo signaling pathway.

[0096] In some embodiments, provided herein is a compound, or pharmaceutically acceptable salt, solvate, or prodrug thereof, selected from:

[0097] In some embodiments, the compounds described herein may inhibit an activity of MST1. The activity may be selected from a phosphorylation activity, an inflammatory activity, a cleavage activity, an apoptotic activity, a ubiquinating activity, a mitochondrial activity, and combinations thereof. The activity may be an activity directed toward MST1. The activity may
be directed toward a non-MST1 protein or substrate. The activity may be selected from auto-
phosphorylation.

[0098] In some embodiments, the compounds described herein may inhibit phosphorylation of a
protein downstream of the activity of MST1. The compounds described herein may inhibit
phosphorylation of a protein upstream of the activity of MST1. The protein downstream may be
selected from a transcription factor, a kinase, a histone. The transcription factor may be
pancreatic and duodenal homeobox 1 (PDX-1) or a homolog thereof. The histone may be histone
2B (H2B). The kinase may be a Janus kinase (INK). The compounds described herein may
inhibit cleavage of a protein downstream of the activity of the MST1. The protein downstream
may be an apoptotic protein. The protein downstream may be a caspase. The caspase may be an
initiator caspase. The caspase may be an effector caspase. The caspase may be selected from
caspase 9, caspase 3 and MST1. The compounds described herein may inhibit apoptotic activity
of a protein downstream of the activity of the MST1. The protein downstream may be selected
from JNK, Bim, Bax, Bcl-2, homologs thereof, and combinations thereof.

[0099] Further disclosed herein are methods of treating a metabolic condition in a subject
comprising administering a compound described herein, or a pharmaceutically acceptable salt,
solvate, or prodrug thereof, to the subject. Disclosed herein are methods of treating diabetes
mellitus in a subject comprising administering a compound described herein, or a
pharmaceutically acceptable salt, solvate, or prodrug thereof, to the subject.

[0100] Further disclosed herein are methods of treating a metabolic condition in a subject
comprising administering neratinib to the subject. Disclosed herein are methods of treating
diabetes mellitus in a subject comprising administering neratinib to the subject.

[0101] The metabolic condition may be a metabolic disease, a metabolic disorder or a
symptom thereof. The metabolic condition may acute. The metabolic condition may be chronic.
The metabolic condition may be a risk for a metabolic disease. The metabolic condition may be a
pre-metabolic condition. For example, the subject may be insulin insensitive or have high
blood glucose levels, but not diagnosed with diabetes mellitus.

[0102] The metabolic condition may be diabetes mellitus. The method of claim 1, wherein the
metabolic condition is selected from type 1 diabetes mellitus and type 2 diabetes mellitus.
Diabetes mellitus may include, type I diabetes, type 2 diabetes, gestational diabetes, and
pre-diabetes. The diabetes mellitus may be caused by a disease of the pancreas, a surgery or a
medication.

[0103] In some embodiments, the metabolic condition may be one or more symptoms and/or
conditions of a metabolic disease/disorder. Examples of diabetes/metabolic related conditions
include, but are not limited to, diabetic retinopathy, diabetic nephropathy, diabetic heart disease,
diabetic foot disorders, diabetic neuropathy, macrovascular disease, diabetic cardiomyopathy, infection and diabetic ketoacidosis. Diabetic neuropathy may include, but is not limited to symmetric polyneuropathy, autonomic neuropathy, radiculopathy, cranial neuropathy, and mononeuropathy.

Further disclosed herein are methods of treating an inflammatory condition in a subject comprising administering to the subject a compound described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. In some embodiments are methods of treating an inflammatory condition in a subject comprising administering to the subject a compound described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof, wherein the compound is neratinib. In some embodiments, the inflammatory condition is selected from, but not limited to, Alzheimer's, arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis), asthma, atherosclerosis, Crohn's disease, colitis, dermatitis, fibromyalgia, hepatitis, irritable bowel syndrome (IBS), Parkinson's disease, celiac disease, lupus, chronic obstructive pulmonary disease, and psoriasis.

In some embodiments, the method further comprises treating the subject with an additional therapy. In some embodiments, the additional therapy is a therapy for the treatment of diabetes mellitus. In some embodiments, the additional therapy is a sulfonylurea. In some embodiments, the additional therapy is a thiazolidine. In some embodiments, the additional therapy is a dipeptidyl peptidase-4 (DPP-4) inhibitor. In some embodiments, the additional therapy is selected from metformin, sitagliptin, exenatide, colesevelam, sitagliptin, metformin, glipizide, glimepiride, canagliflozin, insulin, rosiglitazone, saxagliptin, alogliptin, chlorpropamide, glibenclamide, gliclazide, glumetazamide, miglitol, pioglitazone, repaglinide, simvastatin, tolazamide, tolbutamide, vildagliptin, and combinations thereof.

Disclosed herein are methods of treating an autoimmune disorder in a subject comprising administering to the subject a compound described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof. In some embodiments is a method of treating an autoimmune disorder in a subject comprising administering to the subject a compound described herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof, wherein the compound is neratinib. In some embodiments, the autoimmune disorder is selected from, but are not limited to, acute disseminated encephalomyelitis, alopecia areata, antiphospholipid syndrome, autoimmune cardiomyopathy,
autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune progesterone dermatitis, autoimmune thrombocytopenic purpura, autoimmune urticaria, autoimmune uveitis, Behcet's disease, Celiac disease, cold agglutinin disease, Crohn's disease, dermatomyositis, diabetes mellitus type 1, eosinophilic fasciitis, gastrointestinal pemphigoid, Goodpasture's syndrome, Grave's disease, Guillain-Barre syndrome, Hashimoto's encephalopathy, Hashimoto's thyroiditis, idiopathic thrombocytopenic purpura, lupus erythematosus, Miller-Fisher syndrome, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, narcolepsy, pemphigus vulgaris, pernicious anemia, polymyositis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, relapsing polychondritis, rheumatoid arthritis, rheumatic fever, Sjogren's syndrome, temporal arteritis, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease, vasculitis, and Wegener's granulomatosis.

[00107] In some embodiments, the compounds described herein may inhibit an activity of MST1. In some embodiments, the compounds described herein may inhibit an activity of MST2. In some embodiments, the compounds described herein may inhibit an activity of MST1 and MST2. The activity may be selected from a phosphorylation activity, an inflammatory activity, a cleavage activity, an apoptotic activity, a ubiquinating activity, a mitochondrial activity, and combinations thereof. The activity may be an activity directed toward MST1. The activity may be directed toward a non-MST1 protein or substrate. The activity may be selected from auto-phosphorylation.

**Pharmaceutical Compositions/Formulations**

[00108] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients 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 & Wilkins, 1999), herein incorporated by reference for such disclosure.

[00109] Provided herein are pharmaceutical compositions that include a compound of Formula (I), (la), (lb), (II), (Ha), or (lib) and at least one pharmaceutically acceptable inactive ingredient.
In some embodiments, the compounds described herein are administered as pharmaceutical compositions in which a compound of Formula (I), (la), (lb), (II), (Ha), or (lib) is mixed with other active ingredients, as in combination therapy. In other embodiments, the pharmaceutical compositions include other medicinal or pharmaceutical agents, carriers, adjuvants, preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In yet other embodiments, the pharmaceutical compositions include other therapeutically valuable substances.

A pharmaceutical composition, as used herein, refers to a mixture of a compound of Formula (I), (la), (lb), (II), (Ha), or (lib) with other chemical components (i.e. pharmaceutically acceptable inactive ingredients), such as carriers, excipients, 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, or one or more combination thereof. The pharmaceutical composition facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. In some embodiments, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

The pharmaceutical formulations 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, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

Pharmaceutical compositions including a compound of Formula (I), (la), (lb), (II), (IIa), or (lib) 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.
Routes of Administration

[00113] Suitable routes of administration include, but are not limited to, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, 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/or intranasal injections.

[00114] In certain embodiments, a compound of Formula (I), (Ia), (Ib), (II), (Ha), or (lib) is administered in a local rather than systemic manner, for example, via topical application of the compound directly on to skin, or intravenously, or subcutaneously, 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. 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 (e.g., as a patch, an ointment, or in combination with a wound dressing, or as a wash or a spray). In alternative embodiments, a formulation is administered systemically (e.g., by injection, or as a pill).

Methods of Dosing

[00115] For 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 clinical trial.

[00116] 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 a patient, 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 the disease being treated and is currently in remission, a pharmaceutical composition comprising a
compound of Formula (I), (la), (lb), (II), (Ila), or (lib) in order to prevent a return of the symptoms of the disease or condition.

[00117] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compound of Formula (I), (la), (lb), (II), (Ila), or (lib) is 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.

[00118] In certain embodiments wherein a patient's status does improve, the dose of drug being administered may be 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%.

[00119] In certain embodiments the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug diversion"). In specific embodiments, the length of the drug diversion 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 diversion 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%. After a suitable length of time, the normal dosing schedule is optionally reinstated.

[00120] In some embodiments, 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 treatment on a long-term basis upon any recurrence of symptoms.

[00121] 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 can nevertheless be 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. 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 over
a short period of time) or at appropriate intervals, for example as two, three, four or more sub-
doses per day.

[00122] In some embodiments, as a patient is started on a regimen of an antiviral compound, the
patient is also weaned off (e.g., step-wise decrease in dose) a second treatment regimen.

[00123] In one embodiment, the daily dosages appropriate for a compound of Formula (I), (Ia),
(lb), (II), (Ha), or (lib) described herein are from about 0.01 to about 10 mg/kg per body weight.
In specific embodiments, an indicated daily dosage in a large mammal, including, but not limited
to, humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered in
divided doses, including, but not limited to, up to four times a day. In one embodiment, the daily
dosage is administered in extended release form. In certain embodiments, suitable unit dosage
forms for oral administration comprise from about 1 to 500 mg active ingredient. In other
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.

[00124] 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_{50} and the ED_{50}. 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.

**EXAMPLES**

[00125] These examples are provided for illustrative purposes only and not to limit the scope of
the claims provided herein. The starting materials and reagents used for the synthesis of the
compounds described herein may be synthesized or can be obtained from commercial sources, such as, but not limited to, Sigma-Aldrich, Acros Organics, Fluka, and Fischer Scientific.

**Example 1: Synthesis of N-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (5)**

![Chemical structure of compound 5]

Step 1: **6-Amino-4-chloro-7-ethoxyquinoline-3-carbonitrile (2)**

Step 2: **N-(4-Chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (1)** (1.53 g, 5.27 mmol) was suspended and stirred in 10 mL of water and the reaction flask was placed in a 0 °C ice-water bath. Concentrated HCl (15 mL) was added dropwise with stirring over 10 min. The reaction flask was placed in a 50 °C oil bath and reaction progress was monitored by LCMS until -90% conversion, at which point competing byproducts began to appear as observed by LCMS. The reaction was stirred in a 0 °C ice-water bath and was quenched with saturated NaHCO₃. The product was extracted into EtOAc and evaporated to dryness. The crude product (1.2 g of -85:15 product: starting material, -4.85 mmol) was taken on to the next step without further purification.

**Step 2: N-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (3)**

4-(Dimethylamino)butanoic acid hydrochloride (1.95 g, 11.6 mmol) was suspended in EtOAc (20 mL) and DMF (0.08 mL, 1.0 mmol) under argon in a 0 °C ice-water bath. Oxalyl chloride (0.870 mL, 10.2 mmol) was added dropwise over 5 minutes and the suspension was stirred in the ice-water bath for 20 minutes. The bath was removed and the reaction was allowed...
to stir at ambient temperature for 2 h then was placed into a 0 °C ice-water bath. A solution of 2 (1.20 g, 4.85 mmol) in NMP was then added and the reaction was allowed to stir in the ice-water bath for 90 minutes. The reaction was quenched by the addition of water (40 mL), washed with EtOAc (50 mL) and the organic layer was extracted with 1 N HCl (30 mL). The combined aqueous layers were basified to pH 11 with 10 N NaOH to precipitate the product. The product (1.18 g) was collected via filtration as a yellow solid and was used in the next step without purification. NMR shows >90% purity. H NMR (400 MHz, Methanol-d₄) δ 9.16 (s, 1H), 8.83 (s, 1H), 7.49 (s, 1H), 4.39 (q, J = 6.9 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.52 - 2.43 (m, 2H), 2.32 (s, 6H), 1.95 (p, J = 7.5 Hz, 2H), 1.58 (t, J = 7.0 Hz, 3H). MS-ESI (m/z) calcd for [C₈H₂ICIN₄O₂ + H]⁺ 361.14; found: 361.15.

[00130] Step 3: 3-chloro-4-((3-methylpyridin-2-yl)methoxy)aniline (4)

[00131] 4-Amino-2-chlorophenol (72 mg, 0.50 mmol), 2-(chloromethyl)-3-methylpyridine (100 mg, 0.56 mmol) and cesium carbonate (0.82 g, 2.5 mmol) were stirred in acetonitrile (2.5 mmol) at ambient temperature overnight. [Note: when chloromethyl-substituted heterocycles were not available, the chloride was formed from the alcohol and SOCl₂]. The suspension was filtered and evaporated to dryness before being purified by gradient flash chromatography (0 to 100% EtOAc in hexanes with 0.1% trimethylamine). The major peak by UV was collected and its identity was checked on LCMS to ensure it was the desired product; m/z of 249.1 (M+1⁺) was observed. This product was taken to the next step without further characterization.

[00132] Step 4: N-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (5)

[00133] Compound 3 (18 mg, 0.05 mmol), pyridine-hydrochloride (6 mg, 0.05 mmol) and Compound 4 (12.5 mg, 0.05 mmol) were stirred in isopropanol (0.5 mL) in a heating block at 75 °C for 16h. After cooling to ambient temperature, the reaction mixture was diluted with MeOH to dissolve all components and purified by preparative HPLC to yield the product (5, 7.23 mg) as the bis-TFA salt. 1HNMR (400 MHz, Methanol-d₄) δ 9.09 (s, 1H), 8.77 (s, 1H), 8.49 (d, J = 5.2
Hz, (1H), 7.98 (d, J = 7.9 Hz, 1H), 7.59 - 7.53 (m, 2H), 7.44 - 7.34 (m, 3H), 5.44 (s, 2H), 4.40 (q, J = 7.0 Hz, 2H), 3.29 - 3.20 (m, 2H), 2.93 (s, 6H), 2.74 (t, J = 6.9 Hz, 2H), 2.55 (s, 3H), 2.12 (dt, J = 15.2, 7.1 Hz, 2H), 1.59 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for \([\text{C}_3\text{H}_13\text{ClN}_6\text{O}_3 + \text{H}]^+\) 573.24; found: 573.24.

[00134] Examples 2-83 were prepared according to a similar procedure as described for Example 1:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image" alt="Structure 2" /></td>
<td>(^1\text{H} \text{NMR} (400 \text{ MHz, Methanol-d}<em>4) \delta 9.03 (s, 1H), 8.65 (s, 1H), 8.54 (d, J = 6.9 Hz, 1H), 7.77 (s, 1H), 7.55 (d, J = 8.19 Hz, 1H), 7.36 (d, J = 9.4 Hz, 1H), 7.36 - 7.27 (m, 3H), 5.28 (s, 2H), 4.40 (q, J = 6.9 Hz, 2H), 3.40 - 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, J = 6.8 Hz, 2H), 2.32 - 2.13 (m, 2H), 1.58 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for ([\text{C}</em>{20}\text{H}_{32}\text{ClN}_6\text{O}_3 + \text{H}]^+) 593.18; found: 593.20.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 3" /></td>
<td>(^1\text{H} \text{NMR} (400 \text{ MHz, Methanol-d}<em>4) \delta 9.03 (s, 1H), 8.68 (s, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.57 - 7.40 (m, 2H), 7.37 (d, J = 6.19 Hz, 1H), 7.36 - 7.27 (m, 2H), 5.25 (s, 2H), 4.40 (q, J = 6.9 Hz, 2H), 3.40 - 3.25 (m, 2H), 2.94 (s, 6H), 2.75 (t, J = 6.4 Hz, 2H), 2.30 - 2.13 (m, 2H), 1.59 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for ([\text{C}</em>{30}\text{H}_{30}\text{BrClN}_6\text{O}_3 + \text{H}]^+) 637.13; found: 637.20.</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 4" /></td>
<td>(^1\text{H} \text{NMR} (400 \text{ MHz, Methanol-d}<em>4) \delta 9.05 (s, 1H), 8.71 (s, 1H), 8.01 (q, J = 7.9 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.48 - 7.36 (m, 2H), 7.26 (d, J = 6.2 Hz, 1H), 7.05 (dd, J = 8.3, 2.2 Hz, 1H), 5.26 (s, 2H), 4.40 (q, J = 6.9 Hz, 2H), 3.40 - 3.26 (m, 2H), 2.94 (s, 6H), 2.74 (t, J = 6.8 Hz, 2H), 2.30 - 2.13 (m, 2H), 1.59 (t, J = 6.8 Hz, 3H); MS-ESI (m/z) calcd for ([\text{C}</em>{30}\text{H}_{30}\text{ClF}_5\text{N}_6\text{O}_3 + \text{H}]^+) 577.20; found: 577.20.</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 5" /></td>
<td>(^1\text{H} \text{NMR} (400 \text{ MHz, Methanol-d}<em>4) \delta 9.05 (s, 1H), 8.71 (s, 1H), 8.09 (t, J = 7.8 Hz, 1H), 7.98 - 7.70 (m, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 6.2 Hz, 1H), 7.48 - 7.37 (m, 2H), 7.28 (d, J = 8.8 Hz, 1H), 5.24 (s, 2H), 4.40 (q, J = 6.4 Hz, 2H), 3.40 - 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, J = 6.9 Hz, 2H), 2.28 - 2.13 (m, 2H), 1.59 (t, J = 6.9 Hz, 3H); MS-ESI (m/z) calcd for ([\text{C}</em>{30}\text{H}_{30}\text{ClN}_6\text{O}_3 + \text{H}]^+) 585.08; found: 585.20.</td>
</tr>
</tbody>
</table>
[Chemical structures and NMR data]

**6**

\(^1\)H NMR (400 MHz, Methanol-d\(_4\)) \(\delta 9.08\) (s, 1H), 8.75 (s, 1H), 7.98 – 7.71 (m, 1H), 7.57 (s, 1H), 7.65 – 7.37 (m, 2H), 7.27 (d, \(J = 8.8\) Hz, 1H), 7.20 (d, \(J = 7.34\) Hz, 1H), 6.75 (d, \(J = 8.3\) Hz, 1H), 5.24 (s, 2H), 4.41 (q, \(J = 6.9\) Hz, 2H), 3.94 (s, 3H), 3.40 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, \(J = 6.9\) Hz, 2H), 2.28 – 2.12 (m, 2H), 1.60 (t, \(J = 6.9\) Hz, 3H); MS-ESI (m/z) calcld for \([C_{31}H_{35}ClN_3O_4 + H]^+\) 589.23; found: 589.20.

**7**

\(^1\)H NMR (400 MHz, Methanol-d\(_4\)) \(\delta 9.04\) (s, 1H), 8.69 (s, 1H), 7.89 (t, \(J = 7.8\) Hz, 1H), 7.66 (s, 1H), 7.55 (d, \(J = 8.1\) Hz, 1H), 7.44 (d, \(J = 7.9\) Hz, 1H), 7.36 – 7.30 (m, 2H), 7.26 (s, 1H), 5.26 (s, 2H), 4.40 (q, \(J = 6.9\) Hz, 2H), 3.40 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, \(J = 6.8\) Hz, 2H), 2.32 – 2.14 (m, 2H), 1.58 (t, \(J = 6.9\) Hz, 3H); MS-ESI (m/z) calcld for \([C_{30}H_{30}ClN_3O_3 + H]^+\) 593.18; found: 593.20.

**8**

\(^1\)H NMR (400 MHz, Methanol-d\(_4\)) \(\delta 9.13\) (s, 1H), 8.81 (s, 1H), 8.66 (d, \(J = 5.3\) Hz, 1H), 8.10 (td, \(J = 7.8, 1.7\) Hz, 1H), 7.84 (d, \(J = 7.9\) Hz, 1H), 7.62 (d, \(J = 2.5\) Hz, 1H), 7.60 – 7.53 (m, 1H), 7.44 – 7.39 (m, 2H), 7.31 (d, \(J = 8.8\) Hz, 1H), 5.42 (s, 2H), 4.41 (q, \(J = 7.0\) Hz, 2H), 3.34 – 3.29 (m, 6H), 3.29 – 3.19 (m, 2H), 2.74 (t, \(J = 6.9\) Hz, 2H), 2.12 (dt, \(J = 14.9, 7.1\) Hz, 2H), 1.59 (t, \(J = 7.0\) Hz, 3H); MS-ESI (m/z) calcld for \([C_{30}H_{31}ClN_3O_3 + H]^+\) 559.22; found: 280.26 (z = 2).

**9**

\(^1\)H NMR (400 MHz, Methanol-d\(_4\)) \(\delta 9.11\) (s, 1H), 8.80 (s, 1H), 8.66 – 8.59 (m, 1H), 8.03 (td, \(J = 7.8, 1.8\) Hz, 1H), 7.76 (d, \(J = 7.9\) Hz, 1H), 7.52 (dd, \(J = 7.6, 1.2\) Hz, 1H), 7.40 – 7.28 (m, 3H), 7.25 (dd, \(J = 8.6, 1.1\) Hz, 1H), 5.38 (s, 2H), 4.41 (q, \(J = 7.0\) Hz, 2H), 3.28 – 3.18 (m, 2H), 2.93 (s, 6H), 2.73 (t, \(J = 6.9\) Hz, 2H), 2.16 – 2.08 (m, \(J = 14.8, 7.1\) Hz, 2H), 1.59 (t, \(J = 7.0\) Hz, 3H); \(^19\)F NMR (376 MHz, Methanol-d\(_4\)) \(\delta -132.89\); MS-ESI (m/z) calcld for \([C_{30}H_{30}F_2N_6O_3 + H]^+\) 543.25; found: 272.22 (z = 2).

**10**

\(^1\)H NMR (400 MHz, Methanol-d\(_4\)) \(\delta 9.12\) (s, 1H), 8.78 (s, 1H), 8.55 (d, \(J = 5.5\) Hz, 1H), 7.74 (s, 1H), 7.61 (d, \(J = 2.5\) Hz, 1H), 7.54 (d, \(J = 5.5\) Hz, 1H), 7.44 – 7.37 (m, 2H), 7.30 (d, \(J = 8.8\) Hz, 1H), 5.43 (s, 2H), 4.41 (q, \(J = 7.0\) Hz, 2H), 3.28 – 3.20 (m, 2H), 2.93 (s, 6H), 2.74 (t, \(J = 6.9\) Hz, 2H), 2.55 (s, 3H), 2.12 (dt, \(J = 14.9, 7.0\) Hz, 2H), 1.59 (t, \(J = 7.0\) Hz, 3H); MS-ESI (m/z) calcld for \([C_{31}H_{35}ClN_3O_3 + H]^+\) 573.24; found: 573.28.
**11**

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.08 (s, 1H), 8.76 (s, 1H), 8.47 (s, 1H), 7.86 (d, $J$ = 7.9 Hz, 1H), 7.68 (d, $J$ = 8.1 Hz, 1H), 7.57 (d, $J$ = 2.3 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.28 (d, $J$ = 8.8 Hz, 1H), 5.34 (s, 2H), 4.40 (q, $J$ = 6.9 Hz, 2H), 3.27 – 3.21 (m, 2H), 2.93 (s, 6H), 2.73 (t, $J$ = 6.8 Hz, 2H), 2.43 (s, 3H), 2.12 (p, $J$ = 7.1 Hz, 2H), 1.58 (t, $J$ = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C$_{31}$H$_{33}$ClN$_6$O$_3$ + H]$^+$ 573.24; found: 573.33.

**12**

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.11 (s, 1H), 8.77 (s, 1H), 8.03 (t, $J$ = 7.8 Hz, 1H), 7.69 (d, $J$ = 7.8 Hz, 1H), 7.59 (d, $J$ = 2.5 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.30 (d, $J$ = 8.8 Hz, 1H), 5.38 (s, 2H), 4.41 (q, $J$ = 7.0 Hz, 2H), 3.29 – 3.21 (m, 2H), 2.93 (s, 6H), 2.74 (t, $J$ = 6.9 Hz, 2H), 2.67 (s, 3H), 2.12 (dt, $J$ = 14.8, 6.9 Hz, 2H), 1.59 (t, $J$ = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C$_{31}$H$_{33}$ClN$_6$O$_3$ + H]$^+$ 573.24; found: 573.26.

**13**

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.08 (s, 1H), 8.75 (s, 1H), 8.49 (d, $J$ = 2.7 Hz, 1H), 7.77 – 7.64 (m, 3H), 7.57 (d, $J$ = 2.5 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.27 (d, $J$ = 8.8 Hz, 1H), 5.33 (s, 2H), 4.40 (q, $J$ = 7.0 Hz, 2H), 3.25 (dd, $J$ = 9.0, 7.0 Hz, 2H), 2.93 (s, 6H), 2.73 (t, $J$ = 6.9 Hz, 2H), 2.18 – 2.06 (m, 2H), 1.58 (t, $J$ = 7.0 Hz, 3H); $^{17}$F NMR (376 MHz, Methanol-d$_4$) $\delta$ -131.24; MS-ESI (m/z) calcd for [C$_{33}$H$_{32}$ClF$_3$N$_6$O$_3$ + H]$^+$ 577.21; found: 577.22.

**14**

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.06 (s, 1H), 8.72 (s, 1H), 8.58 (d, $J$ = 2.3 Hz, 1H), 7.93 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.69 (d, $J$ = 8.5 Hz, 1H), 7.55 (d, $J$ = 2.5 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.25 (d, $J$ = 8.8 Hz, 1H), 5.33 (s, 2H), 4.39 (q, $J$ = 6.8 Hz, 2H), 3.28 – 3.21 (m, 2H), 2.93 (s, 6H), 2.73 (t, $J$ = 6.9 Hz, 2H), 2.12 (dt, $J$ = 15.0, 7.0 Hz, 2H), 1.58 (t, $J$ = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C$_{35}$H$_{30}$Cl$_2$N$_6$O$_3$ + H]$^+$ 593.18; found: 593.14.

**15**

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.08 (d, $J$ = 1.2 Hz, 1H), 8.76 (d, $J$ = 1.3 Hz, 1H), 8.62 – 8.55 (m, 1H), 8.20 – 8.13 (m, 1H), 7.54 (s, 1H), 7.44 – 7.33 (m, 4H), 5.45 (d, $J$ = 1.3 Hz, 2H), 4.42 (q, $J$ = 6.9 Hz, 2H), 3.30 – 3.23 (m, 2H), 2.95 (s, 6H), 2.80 – 2.68 (m, 2H), 2.14 (dt, $J$ = 14.9, 7.5 Hz, 2H), 1.60 (t, $J$ = 6.7, 3H); MS-ESI (m/z) calcd for [C$_{36}$H$_{30}$BrClN$_6$O$_3$ + H]$^+$ 637.13; found: 320.08 ($\varepsilon$ = 2).
\[ ^1H \text{NMR (400 MHz, Methanol-}d_4) \delta 9.07 (d, J = 1.3 Hz, 1H), 8.76 (d, J = 1.4 Hz, 1H), 8.52 – 8.42 (m, 1H), 7.74 (t, J = 9.1 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.44 – 7.35 (m, 2H), 5.40 (t, J = 1.7 Hz, 2H), 4.46 – 4.37 (m, 2H), 3.31 – 3.22 (m, 2H), 2.95 (d, J = 1.5 Hz, 6H), 2.75 (td, J = 7.1, 1.5 Hz, 2H), 2.22 – 2.05 (m, 2H), 1.60 (td, J = 7.1, 1.6 Hz, 3H); \]^19F NMR (376 MHz, Methanol-d_4) \delta -125.66; MS-ESI (m/z) calcd for [C_{38}H_{36}ClF_3N_6O_3 + H]^+ 577.21; found: 289.3 (z = 2).

\[ ^1H \text{NMR (400 MHz, Methanol-}d_4) \delta 9.07 (s, 1H), 8.86 (d, J = 5.1 Hz, 1H), 8.76 (s, 1H), 8.28 (d, J = 7.8 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.53 (d, J = 2.4 Hz, 1H), 7.41 – 7.31 (m, 3H), 5.48 (s, 2H), 4.42 (q, J = 7.0 Hz, 2H), 3.29 – 3.23 (m, 2H), 2.95 (s, 6H), 2.75 (t, J = 6.8 Hz, 2H), 2.14 (dt, J = 14.3, 7.6 Hz, 2H), 1.60 (t, J = 7.0 Hz, 3H); \]^19F NMR (376 MHz, Methanol-d_4) \delta -61.50; MS-ESI (m/z) calcd for [C_{33}H_{36}ClF_3N_6O_3 + H]^+ 627.21; found: 627.15.

\[ ^1H \text{NMR (400 MHz, Methanol-}d_4) \delta 9.10 (s, 1H), 8.79 (s, 1H), 8.21 (d, J = 4.4 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.43 – 7.31 (m, 3H), 5.38 (s, 2H), 4.40 (q, J = 6.6 Hz, 2H), 3.98 (s, 3H), 3.28 – 3.22 (m, 2H), 2.93 (s, 6H), 2.80 – 2.69 (m, 2H), 2.22 – 2.05 (m, 2H), 1.58 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C_{31}H_{31}ClN_5O_4 + H]^+ 589.23; found: 295.31 (z = 2).

\[ ^1H \text{NMR (400 MHz, Methanol-}d_4) \delta 9.03 (s, 1H), 8.86 (s, 1H), 8.77 – 8.69 (m, 1H), 8.35 – 8.26 (m, 1H), 7.69 – 7.60 (m, 1H), 7.57 – 7.48 (m, 1H), 7.45 – 7.31 (m, 3H), 5.50 (s, 2H), 4.41 (q, J = 8.9 Hz, 2H), 3.31 – 3.21 (m, 2H), 2.95 (s, 2H), 2.80 – 2.68 (m, 6H), 2.20 – 2.06 (m, 2H), 1.60 (t, J = 9.0 Hz, 3H); MS-ESI (m/z) calcd for [C_{31}H_{31}ClN_5O_3 + H]^+ 584.22; found: 292.81 (z = 2).

\[ ^1H \text{NMR (400 MHz, Methanol-}d_4) \delta 9.13 (s, 1H), 8.75 (s, 1H), 8.55 (d, J = 5.5 Hz, 1H), 8.12 (d, J = 7.1 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.46 (d, J = 9.0 Hz, 1H), 7.38 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 4.42 (q, J = 7.2 Hz, 2H), 3.31 – 3.22 (m, 2H), 2.95 (s, 6H), 2.76 (t, J = 6.1 Hz, 2H), 2.55 (s, 3H), 2.20 – 2.09 (m, 2H), 1.61 (t, J = 6.9 Hz, 3H); MS-ESI (m/z) calcd for [C_{31}H_{31}N_5O_3 + H]^+ 539.28; found: 270.4 (z = 2).
1H NMR (400 MHz, Methanol-d4) δ 9.12 (s, 1H), 8.76 (s, 1H), 8.58 – 8.49 (m, 1H), 8.13 – 8.03 (m, 1H), 7.69 – 7.60 (m, 1H), 7.42 – 7.19 (m, 4H), 5.44 (s, 2H), 4.51 – 4.34 (m, 2H), 3.29 – 3.21 (m, 2H), 2.95 (s, 6H), 2.80 – 2.70 (m, 2H), 2.56 (s, 3H), 2.32 (s, 3H), 2.21 – 2.10 (m, 2H), 1.66 – 1.55 (m, 3H); MS-ESI (m/z) calced for [C12H10NO3 + H]+: 553.29; found: 553.27.

1H NMR (400 MHz, Methanol-d4) δ 9.12 (s, 1H), 8.79 (s, 1H), 8.59 – 8.51 (m, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.51 – 7.24 (m, 4H), 5.51 (s, 2H), 4.43 (q, J = 6.5 Hz, 2H), 3.30 – 3.21 (m, 2H), 2.94 (s, 6H), 2.80 – 2.69 (m, 2H), 2.56 (s, 3H), 2.21 – 2.07 (m, 2H), 1.60 (t, J = 6.9 Hz, 3H); 19F NMR (376 MHz, Methanol-d4) δ -132.47; MS-ESI (m/z) calced for [C31H33FN6O3 + H]+: 557.27; found: 279.36 (z = 2).

1H NMR (400 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.78 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.66 (dd, J = 7.8, 5.1 Hz, 1H), 7.52 (t, J = 8.9 Hz, 1H), 7.41 (s, 1H), 7.22 – 7.09 (m, 2H), 5.46 (s, 2H), 4.43 (q, J = 7.0 Hz, 2H), 3.31 – 3.23 (m, 2H), 2.95 (s, 6H), 2.77 (t, J = 6.9 Hz, 2H), 2.55 (s, 3H), 2.15 (dt, J = 15.2, 7.0 Hz, 2H), 1.61 (t, J = 7.0 Hz, 3H); 19F NMR (376 MHz, Methanol-d4) δ -120.09; MS-ESI (m/z) calced for [C31H33FN6O3 + H]+: 557.27; found: 279.36 (z = 2).

1H NMR (400 MHz, Methanol-d4) δ 9.12 (s, 1H), 8.80 (s, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.06 – 7.97 (m, 1H), 7.77 – 7.69 (m, 1H), 7.61 (dd, J = 10.5, 5.0 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.42 – 7.32 (m, 2H), 5.47 (s, 2H), 4.43 (q, J = 7.0 Hz, 4H), 3.28 – 3.20 (m, 2H), 2.95 (s, 6H), 2.80 – 2.68 (m, 2H), 2.58 (s, 3H), 2.19 – 2.05 (m, 2H), 1.61 (t, J = 7.1 Hz, 3H); MS-ESI (m/z) calced for [C31H33BrN6O3 + H]+: 617.19; found: 310.08 (z = 2).

1H NMR (400 MHz, Methanol-d4) δ 9.19 (s, 1H), 8.80 (s, 1H), 8.57 (d, J = 5.2 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.48 – 7.44 (m, 1H), 7.43 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 5.50 (s, 2H), 4.44 (q, J = 7.0 Hz, 2H), 3.31 – 3.22 (m, 2H), 2.95 (s, 6H), 2.77 (t, J = 6.8 Hz, 2H), 2.56 (s, 3H), 2.15 (dt, J = 14.2, 6.8 Hz, 2H), 1.61 (t, J = 7.1 Hz, 3H); MS-ESI (m/z) calced for [C31H33ClN6O3 + H]+: 573.24; found: 573.13.

1H NMR (400 MHz, Methanol-d4) δ 9.00 (s, 1H), 8.71 (s, 1H), 8.53 – 8.48 (m, 1H), 8.09 – 8.02 (m, 1H), 7.67 – 7.60 (m, 1H), 7.46 – 7.39 (m, 3H), 5.43 (s, 2H), 4.41 (q, J = 6.6 Hz, 2H), 3.31 – 3.20 (m, 2H), 2.95 (s, 6H), 2.79 – 2.69 (m, 2H), 2.60 (s, 3H), 2.20 – 2.07 (m, 2H), 1.60 (t, J = 8.1 Hz, 3H); MS-ESI
(m/z) caleld for \([\text{C}_{31}\text{H}_{32}\text{Cl}_{2}\text{N}_{6}\text{O}_{2} + \text{H}]^-\) 607.20; found: 304.33 (z = 2).

1H NMR (400 MHz, Methanol-d4) \(\delta\) 9.08 (s, 1H), 8.77 (s, 1H), 8.51 – 8.44 (m, 1H), 7.89 (d, \(J = 5.3\) Hz, 1H), 7.80 (s, 1H), 7.76 – 7.68 (m, 1H), 7.56 – 7.46 (m, 2H), 7.40 (s, 1H), 5.51 (s, 2H), 4.48 – 4.36 (m, 2H), 3.29 – 3.21 (m, 2H), 2.94 (s, 6H), 2.82 – 2.69 (m, 2H), 2.56 (s, 3H), 2.19 – 2.06 (m, 2H), 1.65 – 1.54 (m, 3H); MS-ESI (m/z) caleld for \([\text{C}_{32}\text{H}_{33}\text{N}_{2}\text{O}_{3}+\text{H}]^-\) 564.27; found: 564.41.

1H NMR (400 MHz, Methanol-d4) \(\delta\) 9.10 (s, 1H), 8.76 (s, 1H), 8.60 – 8.53 (m, 1H), 8.22 – 8.14 (m, 1H), 7.77 – 7.68 (m, 1H), 7.39 (s, 1H), 7.28 (d, \(J = 8.6\) Hz, 1H), 7.18 (s, 1H), 7.05 (d, \(J = 9.2\) Hz, 1H), 5.45 (s, 2H), 4.42 (q, \(J = 7.1\) Hz, 2H), 3.88 (s, 3H), 3.32 – 3.22 (m, 2H), 2.95 (s, 6H), 2.80 – 2.71 (m, 2H), 2.55 (s, 3H), 2.20 – 2.08 (m, 2H), 1.60 (t, \(J = 6.9\) Hz, 3H); MS-ESI (m/z) caleld for \([\text{C}_{32}\text{H}_{33}\text{N}_{2}\text{O}_{3}+\text{H}]^-\) 569.29; found: 569.36.

MS-ESI (m/z) caleld for \([\text{C}_{32}\text{H}_{33}\text{N}_{2}\text{O}_{3}+\text{H}]^-\) 564.27; found: 564.34.

1H NMR (400 MHz, Methanol-d4) \(\delta\) 9.16 (s, 1H), 8.74 (s, 1H), 8.61 – 8.52 (m, 1H), 8.15 (d, \(J = 11.0\) Hz, 1H), 7.74 – 7.66 (m, 1H), 7.44 – 7.34 (m, 2H), 7.19 (s, 1H), 7.13 (d, \(J = 2.1\) Hz, 1H), 5.46 (s, 2H), 4.43 (q, \(J = 6.2\) Hz, 4H), 3.31 – 3.21 (m, 2H), 2.95 (s, 6H), 2.83 – 2.72 (m, 2H), 2.56 (s, 3H), 2.34 (s, 2H), 2.21 – 2.09 (m, 2H), 1.66 – 1.56 (m, 3H); MS-ESI (m/z) caleld for \([\text{C}_{32}\text{H}_{36}\text{N}_{6}\text{O}_{3}+\text{H}]^-\) 553.29; found: 553.38.

1H NMR (400 MHz, Methanol-d4) \(\delta\) 9.14 (s, 1H), 8.79 (s, 1H), 8.67 – 8.57 (m, 1H), 8.39 – 8.27 (m, 1H), 7.92 – 7.81 (m, 1H), 7.42 (s, 1H), 7.24 (s, 2H), 5.35 (s, 2H), 4.47 – 4.34 (m, 2H), 3.31 – 2.25 (m, 2H), 2.97 (s, 6H), 2.82 – 2.67 (m, 2H), 2.55 (s, 3H), 2.39 (s, 6H), 2.24 – 2.07 (m, 2H), 1.67 – 1.53 (m, 3H); MS-ESI (m/z) caleld for \([\text{C}_{33}\text{H}_{38}\text{N}_{6}\text{O}_{3}+\text{H}]^-\) 567.31; found:
<table>
<thead>
<tr>
<th>33</th>
<th>567.38.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.17 (s, 1H), 8.75 (s, 1H), 8.56 (d, $J$ = 5.1 Hz, 1H), 8.16 (d, $J$ = 8.0 Hz, 1H), 7.71 (t, $J$ = 6.3 Hz, 1H), 7.39 (s, 1H), 7.27 (d, $J$ = 8.6 Hz, 1H), 7.12 (d, $J$ = 8.7 Hz, 1H), 5.45 (s, 2H), 4.43 (q, $J$ = 6.9 Hz, 2H), 3.27 (dd, $J$ = 9.8, 6.9 Hz, 2H), 2.95 (s, 6H), 2.76 (t, $J$ = 6.9 Hz, 2H), 2.57 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H), 2.21 – 2.10 (m, 2H), 1.61 (t, $J$ = 6.8 Hz, 3H); MS-ESI (m/z) calcld for [C$</em>{33}$H$_{38}$N$_6$O$_3$ + H]$^+$ 567.31; found: 567.58.</td>
</tr>
</tbody>
</table>

| 34 | ![Chemical Structure](image2.png) | $^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.15 (s, 1H), 8.75 (s, 1H), 8.54 (d, $J$ = 5.4 Hz, 1H), 8.13 – 8.04 (m, 1H), 7.69 – 7.59 (m, 1H), 7.38 (s, 1H), 7.21 (s, 1H), 7.14 (s, 1H), 5.42 (s, 2H), 4.43 (q, $J$ = 6.4, 5.9 Hz, 2H), 3.32 – 3.22 (m, 2H), 2.95 (s, 6H), 2.81 – 2.71 (m, 2H), 2.56 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 2.16 (d, $J$ = 7.8 Hz, 2H), 1.61 (t, $J$ = 6.9 Hz, 3H); MS-ESI (m/z) calcld for [C$_{33}$H$_{38}$N$_6$O$_3$ + H]$^+$ 567.31; found: 567.32. |

| 35 | ![Chemical Structure](image3.png) | $^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.06 (s, 1H), 8.74 (s, 1H), 7.55 (d, $J$ = 6.78 Hz, 1H), 7.53 (t, $J$ = 6.2 Hz, 1H), 7.55 (d, $J$ = 8.1 Hz, 1H), 7.44 (d, $J$ = 7.9 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.26 (s, 1H), 5.44 (s, 2H), 4.41 (q, $J$ = 6.9 Hz, 2H), 3.40 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, $J$ = 6.4 Hz, 2H), 2.32 – 2.13 (m, 2H), 1.59 (t, $J$ = 6.9 Hz, 3H); MS-ESI (m/z) calcld for [C$_{32}$H$_{30}$Cl$_2$N$_6$O$_3$ + H]$^+$ 593.15; found: 593.15. |

| 36 | ![Chemical Structure](image4.png) | $^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.08 (s, 1H), 8.83 (d, $J$ = 6.2 Hz, 1H), 8.73 (d, $J$ = 7.8 Hz, 1H), 7.95 (s, 1H), 7.72 (d, $J$ = 7.2 Hz, 1H), 7.59 (t, $J$ = 6.2 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.29 (d, $J$ = 8.3 Hz, 1H), 5.46 (s, 2H), 4.40 (q, $J$ = 6.3 Hz, 2H), 3.40 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, $J$ = 6.9 Hz, 2H), 2.28 – 2.14 (m, 2H), 1.60 (t, $J$ = 6.1 Hz, 3H); MS-ESI (m/z) calcld for [C$_{31}$H$_{29}$Cl$_2$N$_6$O$_3$ + H]$^+$ 584.21; found: 584.2. |

| 37 | ![Chemical Structure](image5.png) | $^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.05 (s, 1H), 8.74 (s, 1H), 8.60 (d, $J$ = 6.2 Hz, 1H), 7.60 (dd, $J$ = 6.4, 2.60 Hz, 2H), 7.50 – 7.30 (m, 4H), 5.49 (s, 2H), 4.41 (q, $J$ = 6.9 Hz, 2H), 4.12 (s, 3H), 3.40 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, $J$ = 6.4 Hz, 2H), 2.28 – 2.15 (m, 2H), 1.60 (t, $J$ = 6.9 Hz, 3H); MS-ESI (m/z) calcld for [C$_{31}$H$_{30}$Cl$_2$N$_6$O$_4$ + H]$^+$ 589.23; found: 589.20. |

<p>| 38 | <img src="image6.png" alt="Chemical Structure" /> | $^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.09 (s, 1H), 8.77 (s, 1H), 7.64 (d, $J$ = 6.2 Hz, 1H), 7.60 (d, $J$ = 6.4 Hz, 2H), 7.50 – 7.40 (m, 3H), 5.59 (s, 2H), 4.41 (q, $J$ = 6.9 Hz, 2H), 3.40 – 3.26 (m, 2H), 2.95 (s, 6H), 2.75 (t, $J$ = 6.2 Hz, 2H), 2.28 – 2.15 (m, 2H), 1.70-1.59 (m, 6H); MS-ESI (m/z) calcld for [C$</em>{33}$H$_{34}$Cl$_2$N$_6$O$_3$ + H]$^+$ 583.22; found: 583.20. |</p>
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<th>Image</th>
<th>Chemical Structure</th>
<th>NMR Data</th>
<th>MS-ESI Data</th>
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<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.08 (s, 1H), 8.75 (s, 1H), 7.53 (d, $J = 6.8$ Hz, 1H), 7.39 (d, $J = 6.4$ Hz, 1H), 7.50 – 7.40 (m, 3H), 5.13 (s, 2H), 4.41 (q, $J = 6.8$ Hz, 2H), 3.40 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, $J = 6.4$ Hz, 2H), 2.50 (s, 3H), 2.28 – 2.13 (m, 2H), 1.59 (t, $J = 6.9$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{31}$ClN$_6$O$_4$ + H]$^+$ 563.21; found: 563.25.</td>
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<td><img src="image2" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.05 (s, 1H), 8.73 (s, 1H), 7.52 (d, $J = 6.4$ Hz, 1H), 7.52 (d, $J = 6.9$ Hz, 1H), 7.50 – 7.34 (m, 3H), 5.25 (s, 2H), 4.38 (q, $J = 6.1$ Hz, 2H), 3.40 – 3.25 (m, 2H), 2.91 (s, 6H), 2.71 (t, $J = 4.67$ Hz, 2H), 2.28 – 2.13 (m, 3H), 1.56 (t, $J = 6.9$ Hz, 3H), 1.08 – 0.95 (m, 4H); MS-ESI (m/z) calc for [C$</em>{31}$H$_{33}$ClN$_6$O$_4$ + H]$^+$ 589.23; found: 589.23.</td>
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<tr>
<td>41</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.08 (s, 1H), 8.69 (s, 1H), 8.58 (d, $J = 6.7$ Hz, 1H), 8.27 (s, 1H), 7.90 – 7.75 (m, 1H), 7.55 (s, 1H), 7.41 (d, $J = 7.2$ Hz, 1H), 7.48 – 7.37 (m, 3H), 5.50 (s, 2H), 4.38 (q, $J = 6.9$ Hz, 2H), 3.40 – 3.26 (m, 2H), 2.91 (s, 6H), 2.72 (t, $J = 6.9$ Hz, 2H), 2.64 (s, 3H), 2.28 – 2.14 (m, 2H), 1.60 (t, $J = 6.1$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{31}$H$_{33}$ClN$_6$O$_4$ + H]$^+$ 612.24; found: 612.3.</td>
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<td><img src="image4" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.11 (s, 1H), 8.75 (s, 1H), 8.18 (dd, $J = 6.7$, 6.1 Hz, 2H), 8.27 (s, 1H), 7.90 – 7.80 (m, 2H), 7.60 (d, $J = 6.4$ Hz, 1H), 7.48 – 7.37 (m, 3H), 5.60 (s, 2H), 4.48 (q, $J = 6.2$ Hz, 2H), 3.40 – 3.26 (m, 2H), 2.93 (s, 9H), 2.72 (t, $J = 6.2$ Hz, 2H), 2.28 – 2.14 (m, 2H), 1.60 (t, $J = 6.4$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{33}$ClN$_6$O$_4$ + H]$^+$ 624.24; found: 624.19.</td>
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<td>43</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.08 (s, 1H), 8.74 (s, 1H), 7.87 (d, $J = 6.8$ Hz, 1H), 7.54 (d, $J = 6.2$ Hz, 1H), 7.40 – 7.34 (m, 3H), 7.30 (d, $J = 8.8$ Hz, 1H), 5.20 (s, 2H), 4.41 (q, $J = 6.9$ Hz, 2H), 4.49 – 4.32 (m, 4H), 3.42 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, $J = 6.4$ Hz, 2H), 2.28 – 2.13 (m, 2H), 1.60 (t, $J = 6.2$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{31}$H$_{33}$ClN$_6$O$_4$ + H]$^+$ 617.22; found: 617.10.</td>
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<tr>
<td>44</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.09 (s, 1H), 8.75 (s, 1H), 8.45 (s, 1H), 7.73 (d, $J = 8.04$ Hz, 2H), 7.55 (s, 1H), 7.50 – 7.40 (m, 3H), 5.56 (s, 2H), 4.41 (q, $J = 6.1$ Hz, 2H), 3.40 – 3.26 (m, 2H), 2.94 (s, 6H), 2.75 (t, $J = 6.9$ Hz, 2H), 2.28 – 2.13 (m, 3H), 1.60 (t, $J = 6.9$ Hz, 3H), 1.08 – 0.95 (m, 4H); MS-ESI (m/z) calc for [C$</em>{33}$H$_{35}$ClN$_6$O$_4$ + H]$^+$ 599.25; found: 599.20.</td>
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**45**

$^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.15 (s, 1H), 8.81 (s, 1H), 8.45 (s, 1H), 8.59 (dd, $J = 8.04$, 5.53 Hz, 1H), 8.21 (d, $J = 7.86$ Hz, 1H), 7.80 – 7.61 (m, 1H), 7.50 – 7.45 (m, 3H), 5.52 (s, 2H), 4.42 (q, $J = 6.95$ Hz, 2H), 3.40 – 3.26 (m, 2H), 3.00 – 2.95 (m, 8H), 2.75 (t, $J = 6.44$ Hz, 2H), 2.28 – 2.15 (m, 2H), 1.60 (t, $J = 6.44$ Hz, 3H), 1.36 (t, $J = 7.54$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{32}$H$_{35}$ClN$_6$O$_3$ + H]$^+$ 587.25; found: 587.20.

**46**

$^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.04 (s, 1H), 8.72 (s, 1H), 7.64 – 7.14 (m, 9H), 5.25 (s, 2H), 4.50 – 4.24 (m, 2H), 2.92 (s, 6H), 2.82 – 2.61 (m, 2H), 2.26 – 1.93 (m, 2H), 1.70 – 1.44 (m, 3H).

**47**

$^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.14 (s, 1H), 8.76 (s, 1H), 8.71 – 8.65 (m, 1H), 8.17 (td, $J = 7.8$, 1.7 Hz, 1H), 7.85 (d, $J = 7.9$ Hz, 1H), 7.64 (dd, $J = 7.6$, 5.3 Hz, 1H), 7.44 (d, $J = 9.0$ Hz, 2H), 7.39 (s, 1H), 7.21 (d, $J = 9.0$ Hz, 2H), 5.40 (s, 2H), 4.42 (t, $J = 7.0$ Hz, 2H), 3.28 – 3.19 (m, 2H), 2.92 (s, 6H), 2.74 (s, 2H), 2.21 – 2.04 (m, 2H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{30}$H$_{32}$N$_6$O$_5$ + H]$^+$ 525.26; found: 263.25 (z = 2).

**48**

$^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.12 (s, 1H), 8.76 (s, 1H), 8.64 (d, $J = 5.2$ Hz, 1H), 8.12 – 8.00 (m, 1H), 7.79 (d, $J = 7.9$ Hz, 1H), 7.61 – 7.51 (m, 1H), 7.37 (s, 1H), 7.33 – 7.23 (m, 2H), 7.10 (dd, $J = 8.7$, 1.8 Hz, 1H), 5.35 (s, 2H), 4.40 (t, $J = 7.1$ Hz, 2H), 3.24 (ddd, $J = 10.2$, 5.5, 1.8 Hz, 2H), 2.93 (s, 6H), 2.74 (t, $J = 6.9$ Hz, 2H), 2.37 (s, 2H), 2.12 (p, $J = 7.0$, 6.3 Hz, 2H), 2.15 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{31}$H$_{33}$N$_6$O$_5$ + H]$^+$ 539.28; found: 270.27 (z = 2).

**49**

$^1$H NMR (400 MHz, Methanol-d$_4$) δ 9.13 (s, 1H), 8.89 – 8.85 (m, 1H), 8.78 (s, 1H), 8.72 (dd, $J = 5.4$, 1.5 Hz, 1H), 8.41 (dt, $J = 8.1$, 1.7 Hz, 1H), 7.84 (ddd, $J = 8.1$, 5.4, 0.9 Hz, 1H), 7.60 (d, $J = 2.5$ Hz, 1H), 7.43 (dd, $J = 8.7$, 2.5 Hz, 1H), 7.39 (s, 1H), 7.35 (d, $J = 8.8$ Hz, 1H), 5.45 (s, 2H), 4.41 (q, $J = 7.0$ Hz, 2H), 3.29 – 3.19 (m, 2H), 2.93 (s, 6H), 2.74 (t, $J = 7.0$ Hz, 2H), 2.17 – 2.07 (m, 2H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{30}$H$_{31}$ClN$_6$O$_5$ + H]$^+$ 559.22; found: 280.26 (z = 2).
50

$^1$H NMR (400 MHz, Methanol-$d_4$) δ 9.12 (s, 1H), 8.83 – 8.74 (m, 3H), 8.06 – 8.00 (m, 2H), 7.63 (d, $J = 2.3$ Hz, 1H), 7.45 – 7.37 (m, 2H), 7.31 (dd, $J = 8.9$, 1.2 Hz, 1H), 5.56 (s, 2H), 4.41 (q, $J = 6.9$ Hz, 2H), 3.28 – 3.20 (m, 2H), 2.93 (s, 6H), 2.74 (t, $J = 7.0$ Hz, 2H), 2.18 – 2.04 (m, 2H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{30}$H$_{31}$CIN$_3$O$_4$ + H$^+$] 559.22; found: 280.26 ($z = 2$).

51

$^1$H NMR (400 MHz, Methanol-$d_4$) δ 9.14 (s, 1H), 8.86 (s, 1H), 8.76 (s, 1H), 8.72 (dd, $J = 5.5$, 1.5 Hz, 1H), 8.42 (d, $J = 8.2$ Hz, 1H), 7.89 – 7.82 (m, 1H), 7.44 (d, $J = 8.9$ Hz, 2H), 7.38 (s, 1H), 7.21 (d, $J = 8.8$ Hz, 2H), 5.38 (s, 2H), 4.41 (q, $J = 7.0$ Hz, 2H), 3.29 – 3.21 (m, 2H), 2.93 (s, 6H), 2.74 (t, $J = 7.0$ Hz, 2H), 2.18 – 2.05 (m, 2H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{30}$H$_{32}$N$_4$O$_3$ + H$^+$] 525.26; found: 263.25 ($z = 2$).

52

$^1$H NMR (400 MHz, Methanol-$d_4$) δ 9.08 (s, 1H), 8.76 (d, $J = 1.8$ Hz, 1H), 8.46 (d, $J = 8.6$ Hz, 1H), 8.07 (d, $J = 8.8$ Hz, 1H), 8.02 – 7.95 (m, 1H), 7.88 – 7.80 (m, 2H), 7.68 – 7.63 (m, 1H), 7.59 (d, $J = 2.4$ Hz, 1H), 7.41 – 7.28 (m, 3H), 5.54 (s, 2H), 4.40 (q, $J = 7.0$ Hz, 2H), 3.27 – 3.19 (m, 2H), 2.92 (d, $J = 1.8$ Hz, 6H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.18 – 2.03 (m, 2H), 1.58 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{31}$H$_{33}$ClN$_3$O$_3$ + H$^+$] 609.24; found: 609.26.

53

MS-ESI (m/z) calcd for [C$_{31}$H$_{36}$ClF$_5$N$_3$O$_3$ + H$^+$] 627.21; found: 627.09.

54

$^1$H NMR (400 MHz, Methanol-$d_4$) δ 8.10 (t, $J = 7.6$ Hz, 2H), 7.93 (t, $J = 9.1$ Hz, 2H), 7.77 (d, $J = 7.8$ Hz, 2H), 7.39 – 7.24 (m, 1H), 7.24 – 7.13 (m, 3H), 7.03 (dd, $J = 9.0$, 2.6 Hz, 1H), 5.41 (s, 1H), 5.30 (s, 3H), 4.39 (q, $J = 7.2$ Hz, 1H), 3.35 (s, 2H), 3.28 – 3.19 (m, 1H), 2.92 (s, 2H), 2.73 (t, $J = 6.9$ Hz, 1H), 2.12 (s, 6H), 1.58 (t, $J = 6.9$ Hz, 1H); MS-ESI (m/z) calcd for [C$_{31}$H$_{36}$ClF$_5$N$_3$O$_3$ + H$^+$] 627.21; found: 627.10.

55

$^1$H NMR (400 MHz, Methanol-$d_4$) δ 9.03 (s, 1H), 8.86 (s, 2H), 8.67 (s, 1H), 7.98 (d, $J = 16.8$ Hz, 1H), 7.71 (s, 1H), 7.56 (s, 1H), 7.41 – 7.28 (m, 3H), 5.45 (s, 2H), 4.41 (d, $J = 7.1$ Hz, 2H), 3.37 (d, $J = 2.0$ Hz, 1H), 3.25 (d, $J = 7.9$ Hz, 2H), 2.95 (d, $J = 2.2$ Hz, 6H), 2.75 (s, 2H), 2.14 (s, 2H), 1.60 (d, $J = 14.4$ Hz, 3H).
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<td>^1H NMR (400 MHz, Methanol-d_4) δ 9.08 (d, J = 1.9 Hz, 1H), 8.75 (d, J = 2.0 Hz, 1H), 8.25 (d, J = 2.7 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 8.7, 2.8 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.30 – 7.24 (m, 1H), 5.26 (d, J = 2.0 Hz, 2H), 4.40 (q, J = 7.0 Hz, 2H), 4.16 (qd, J = 6.9, 2.0 Hz, 2H), 3.25 (ddd, J = 8.0, 6.5, 2.1 Hz, 2H), 2.93 (d, J = 1.9 Hz, 6H), 2.73 (t, J = 6.9 Hz, 2H), 2.12 (p, J = 7.1 Hz, 2H), 1.58 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calc'd for [C_{35}H_{37}ClN_{7}O_{4} + H]^+ 603.25; found: 603.18.</td>
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65\[\text{H NMR (400 MHz, Methanol-d₄) } \delta 9.09 \text{ (s, 1H), 8.75 (s, 1H), 8.64 (d, } J = 1.8 \text{ Hz, 1H), 8.56 (s, 1H), 8.28 (d, } J = 1.9 \text{ Hz, 1H), 7.56 (d, } J = 2.3 \text{ Hz, 1H), 7.44 - 7.33 \text{ (m, 3H), 5.45 (s, 2H), 4.87 (s, 7H), 4.40 (q, } J = 7.0 \text{ Hz, 2H), 3.99 (s, 3H), 3.29 - 3.20 \text{ (m, 2H), 2.92 (s, 5H), 2.73 (t, } J = 6.9 \text{ Hz, 2H), 2.12 (dt, } J = 14.6, 7.0 \text{ Hz, 2H), 1.58 (t, } J = 6.9 \text{ Hz, 3H); MS-ESI (m/z) calc for } [\text{C}_{36}\text{H}_{35}\text{ClN6O}_{5}\text{]+}^+ 637.13; \text{ found: 637.10.}\]

66\[\text{H NMR (400 MHz, Methanol-d₄) } \delta 9.04 \text{ (s, 1H), 8.68 (s, 1H), 7.48 (d, } J = 2.6 \text{ Hz, 1H), 7.39 - 7.29 \text{ (m, 2H), 7.17 (d, } J = 8.8 \text{ Hz, 1H), 5.49 (s, 2H), 4.86 (s, 6H), 4.39 (q, } J = 6.9 \text{ Hz, 2H), 4.22 (t, } J = 5.9 \text{ Hz, 2H), 3.35 (s, 1H), 3.32 - 3.20 \text{ (m, 3H), 2.92 (s, 9H), 2.73 (t, } J = 6.9 \text{ Hz, 2H), 2.42 (s, 3H), 2.31 (s, 3H), 2.12 (dt, } J = 14.7, 7.0 \text{ Hz, 2H), 1.58 (t, } J = 7.0 \text{ Hz, 3H); MS-ESI (m/z) calc for } [\text{C}_{31}\text{H}_{35}\text{ClN6O}_{5}\text{]+}^+ 591.12; \text{ found: 591.12.}\]

67\[\text{H NMR (400 MHz, Methanol-d₄) } \delta 9.06 \text{ (s, 1H), 8.75 (s, 1H), 7.59 (d, } J = 2.2 \text{ Hz, 1H), 7.51 (d, } J = 2.3 \text{ Hz, 1H), 7.40 - 7.30 \text{ (m, 3H), 6.43 (d, } J = 2.3 \text{ Hz, 1H), 5.19 (s, 2H), 4.40 (q, } J = 7.0 \text{ Hz, 2H), 3.91 (s, 3H), 3.27 - 3.18 \text{ (m, 2H), 2.93 (s, 5H), 2.73 (t, } J = 6.8 \text{ Hz, 2H), 2.12 (p, } J = 7.2 \text{ Hz, 2H), 1.59 (t, } J = 7.0 \text{ Hz, 3H); MS-ESI (m/z) calc for } [\text{C}_{29}\text{H}_{32}\text{ClN-O}_{4}\text{]+}^+ 562.23; \text{ found: 562.10.}\]

68\[\text{H NMR (400 MHz, Methanol-d₄) } \delta 9.20 \text{ (s, 1H), 9.01 (s, 1H), 8.67 (s, 1H), 8.02 (d, } J = 8.4 \text{ Hz, 1H), 7.87 - 7.79 \text{ (m, 1H), 7.53 (d, } J = 2.0 \text{ Hz, 1H), 7.35 (d, } J = 7.3 \text{ Hz, 3H), 5.57 (s, 2H), 4.39 (d, } J = 7.3 \text{ Hz, 2H), 3.35 (d, } J = 2.0 \text{ Hz, 2H), 3.24 (t, } J = 7.9 \text{ Hz, 2H), 2.93 (d, } J = 2.2 \text{ Hz, 5H), 2.73 (t, } J = 6.9 \text{ Hz, 2H), 2.12 (s, 2H), 1.58 (t, } J = 7.1 \text{ Hz, 3H); MS-ESI (m/z) calc for } [\text{C}_{29}\text{H}_{36}\text{ClN-O}_{4}\text{]+}^+ 560.21; \text{ found: 560.15.}\]

69\[\text{H NMR (400 MHz, Methanol-d₄) } \delta 9.03 \text{ (s, 1H), 8.69 (s, 1H), 8.27 (s, 1H), 8.06 (s, 1H), 7.51 (d, } J = 2.1 \text{ Hz, 1H), 7.39 - 7.28 \text{ (m, 3H), 5.19 (s, 2H), 4.39 (q, } J = 7.0 \text{ Hz, 2H), 3.35 (d, } J = 1.3 \text{ Hz, 1H), 3.29 - 3.20 \text{ (m, 2H), 2.93 (s, 6H), 2.73 (t, } J = 6.9 \text{ Hz, 2H), 2.12 (p, } J = 7.0 \text{ Hz, 2H), 1.58 (t, } J = 7.0 \text{ Hz, 3H); MS-ESI (m/z) calc for } [\text{C}_{28}\text{H}_{35}\text{ClN-O}_{4}\text{]+}^+ 549.19; \text{ found: 549.15.}\]
70

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.03 (s, 1H), 8.69 (s, 1H), 8.27 (s, 1H), 8.06 (s, 1H), 7.51 (d, $J = 2.1$ Hz, 1H), 7.39$ - $ 7.28 (m, 3H), 5.19 (s, 2H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.35 (d, $J = 1.3$ Hz, 1H), 3.29$ - $ 3.20 (m, 2H), 2.93 (s, 6H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.12 (p, $J = 7.0$ Hz, 2H), 1.58 (t, $J = 7.0$ Hz, 3H); MS-ESI ($m/z$) calcd for [C$_{30}$H$_{34}$CIN-O$_4$+H]$^+$ 592.24; found: 592.20.

71

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.10 (d, $J = 2.0$ Hz, 1H), 8.81$ - $ 8.75 (m, 1H), 8.53 (d, $J = 4.8$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.57 (s, 1H), 7.50$ - $ 7.35 (m, 4H), 7.16 (d, $J = 2.0$ Hz, 1H), 5.49 (d, $J = 1.7$ Hz, 2H), 4.45$ - $ 4.35 (m, 2H), 3.75$ - $ 3.60 (m, 2H), 3.34$ - $ 3.19 (m, 3H), 2.95$ - $ 2.89 (m, 6H), 2.73 (td, $J = 6.9, 1.7$ Hz, 2H), 2.12 (q, $J = 7.6$ Hz, 2H), 1.58 (ddd, $J = 8.1, 6.9, 1.9$ Hz, 3H); MS-ESI ($m/z$) calcd for C$_{32}$H$_{31}$CIN$_6$O$_7$+H$^+$ 599.24; found: 599.10.

72

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.11 (d, $J = 4.5$ Hz, 1H), 8.81$ - $ 8.75 (m, 6H), 8.50 (d, $J = 4.9$ Hz, 1H), 8.08 (d, $J = 8.5$ Hz, 1H), 7.55 (s, 1H), 7.48$ - $ 7.32 (m, 4H), 7.15 (d, $J = 2.0$ Hz, 1H), 5.45 (d, $J = 1.7$ Hz, 2H), 4.42$ - $ 4.35 (m, 2H), 3.72$ - $ 3.60 (m, 2H), 3.35$ - $ 3.15 (m, 3H), 2.95$ - $ 2.80 (m, 6H), 2.72 (td, $J = 6.6, 1.7$ Hz, 2H), 2.10 (q, $J = 7.4$ Hz, 2H), 1.56 (ddd, $J = 8.1, 6.4, 1.8$ Hz, 3H); MS-ESI ($m/z$) calcd for C$_{30}$H$_{33}$CIN$_6$O$_7$+H$^+$ 635.25; found: 635.20.

73

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.02 (d, $J = 3.6$ Hz, 1H), 8.70 (s, 1H), 7.78$ - $ 7.70 (m, 2H), 7.53 (s, 1H), 7.38$ - $ 7.30 (m, 5H), 6.86 (d, $J = 3.4$ Hz, 1H), 5.38 (d, $J = 3.4$ Hz, 2H), 4.39 (s, 2H), 3.31 (d, $J = 9.7$ Hz, 6H), 3.24 (s, 1H), 2.93 (d, $J = 3.2$ Hz, 5H), 2.73 (s, 2H), 2.41 (d, $J = 3.5$ Hz, 3H), 2.11 (s, 2H), 1.58 (q, $J = 6.0$ Hz, 3H); MS-ESI ($m/z$) calcd for [C$_{36}$H$_{35}$CIN$_6$O$_7$+H]$^+$ 639.24; found: 639.15.

74

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.16$ - $ 9.11 (m, 1H), 8.74 (d, $J = 1.4$ Hz, 1H), 8.50 (d, $J = 5.3$ Hz, 1H), 8.01 (d, $J = 7.7$ Hz, 1H), 7.63$ - $ 7.51 (m, 3H), 7.38 (d, $J = 1.2$ Hz, 1H), 7.26 (d, $J = 9.3$ Hz, 1H), 5.42 (s, 2H), 4.41 (q, $J = 6.9$ Hz, 2H), 3.32 (s, 2H), 3.30$ - $ 3.21 (m, 1H), 2.93 (s, 5H), 2.75 (t, $J = 6.9$ Hz, 2H), 2.52 (s, 3H), 2.14 (q, $J = 7.8$ Hz, 2H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI ($m/z$) calcd for [C$_{31}$H$_{31}$BrN$_6$O$_7$+H]$^+$ 617.18; found: 617.15.
| 75 | \[\text{H NMR (400 MHz, Methanol-\text{d}_4)} \delta 9.15 - 9.10 (m, 1H), 8.77 (s, 1H), 8.47 (d, J = 4.9 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.69 (s, 1H), 7.58 (s, 1H), 7.51 (t, J = 6.6 Hz, 1H), 7.40 (s, 1H), 5.46 – 5.41 (m, 2H), 4.86 (d, J = 4.7 Hz, 5H), 4.46 – 4.36 (m, 2H), 3.34 – 3.21 (m, 5H), 2.93 (d, J = 1.9 Hz, 5H), 2.74 (t, J = 7.0 Hz, 2H), 2.53 (s, 3H), 2.14 (q, J = 7.8 Hz, 2H), 1.63 – 1.54 (m, 3H); MS-ESI (m/z) calcd for [C\textsubscript{31}H\textsubscript{27}Cl\textsubscript{5}N\textsubscript{6}O\textsubscript{3}+H]\textsuperscript{+} 607.19; found: 607.15. |
| 76 | \[\text{H NMR (400 MHz, Methanol-\text{d}_4)} \delta 9.02 (s, 1H), 8.69 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.35 (d, J = 6.2 Hz, 3H), 5.31 (s, 2H), 4.39 (d, J = 7.4 Hz, 2H), 3.34 – 3.20 (m, 4H), 2.92 (t, J = 2.0 Hz, 6H), 2.73 (t, J = 7.0 Hz, 2H), 2.45 (d, J = 2.1 Hz, 3H), 2.11 (d, J = 9.5 Hz, 2H), 1.58 (t, J = 7.1 Hz, 3H); MS-ESI (m/z) calcd for [C\textsubscript{31}H\textsubscript{26}BrCl\textsubscript{5}N\textsubscript{6}O\textsubscript{3}+H]\textsuperscript{+} 651.14; found: 327.04 (z = 2). |
| 77 | \[\text{H NMR (400 MHz, Methanol-\text{d}_4)} \delta 9.09 (s, 1H), 8.70 (s, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.37 (s, 1H), 7.32 (s, 1H), 7.15 (s, 1H), 5.25 (d, J = 2.1 Hz, 2H), 4.40 (d, J = 7.5 Hz, 2H), 3.31 (d, J = 9.8 Hz, 3H), 2.94 (d, J = 1.6 Hz, 5H), 2.75 (s, 3H), 2.42 (d, J = 1.8 Hz, 3H), 2.13 (s, 2H), 1.58 (t, J = 6.9 Hz, 3H); MS-ESI (m/z) calcd for [C\textsubscript{31}H\textsubscript{27}Cl\textsubscript{5}N\textsubscript{6}O\textsubscript{3}+H]\textsuperscript{+} 651.14; found: 327.04 (z = 2). |
| 78 | \[\text{H NMR (400 MHz, Methanol-\text{d}_4)} \delta 9.16 (s, 1H), 8.79 (s, 1H), 8.59 (d, J = 5.5 Hz, 1H), 8.23 (dd, J = 8.0, 1.5 Hz, 1H), 7.76 (dd, J = 7.9, 5.4 Hz, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 7.35 (s, 1H), 5.53 (s, 2H), 4.41 (q, J = 6.9 Hz, 3H), 3.27 – 3.21 (m, 3H), 2.92 (s, 7H), 2.74 (t, J = 7.0 Hz, 2H), 2.58 (s, 3H), 2.33 (s, 3H), 2.16 – 2.07 (m, 3H), 1.58 (t, J = 7.0 Hz, 4H); MS-ESI (m/z) calcd for [C\textsubscript{31}H\textsubscript{27}Cl\textsubscript{5}N\textsubscript{6}O\textsubscript{3}+H]\textsuperscript{+} 587.25; found: 294.37 (z = 2). |
| 79 | \[\text{H NMR (400 MHz, Methanol-\text{d}_4)} \delta 9.14 (s, 1H), 8.79 (s, 1H), 8.52 – 8.45 (m, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 9.7 Hz, 2H), 7.53 (dd, J = 7.8, 5.1 Hz, 1H), 7.40 (s, 1H), 2.57 – 2.50 (m, 4H), 5.45 (s, 2H), 2.14 (dt, J = 14.9, 7.1 Hz, 2H), 4.47 – 4.36 (m, 3H), 1.64 – 1.56 (m, 4H), 2.94 (s, 6H), 2.75 (t, J = |
80

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.14 (s, 1H), 8.81 (s, 1H), 8.53 (ddd, $J = 5.3$, 1.5, 0.7 Hz, 1H), 8.08 (ddd, $J = 7.9$, 1.6, 0.8 Hz, 1H), 7.64 (dd, $J = 7.8$, 5.2 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.41 (s, 1H), 5.49 (s, 2H), 4.90 (s, 25H), 4.41 (q, $J = 7.0$ Hz, 2H), 3.35 – 3.21 (m, 13H), 2.93 (s, 6H), 2.74 (t, $J = 6.9$ Hz, 2H), 2.55 (s, 3H), 2.19 – 2.07 (m, 2H), 1.61 (s, 1H); MS-ESI ($m/z$) calcld for $[C_{31}H_{35}F_3N_6O_7]^+$ 623.25; found: 312.32 ($z = 2$).

81

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.11 (s, 1H), 8.85 – 8.79 (m, 1H), 8.74 (s, 1H), 8.24 (d, $J = 8.0$ Hz, 1H), 7.63 (dd, $J = 8.0$, 4.9 Hz, 1H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.36 (s, 1H), 7.28 (d, $J = 2.8$ Hz, 1H), 7.12 (dd, $J = 8.8$, 2.8 Hz, 1H), 5.41 (s, 2H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.28 – 3.20 (m, 3H), 2.92 (s, 7H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.11 (dt, $J = 15.0$, 7.1 Hz, 2H), 1.58 (t, $J = 7.0$ Hz, 3H); MS-ESI ($m/z$) calcld for $[C_{31}H_{35}ClF_3N_6O_7]^+$ 627.20; found: 314.35 ($z = 2$).

82

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.12 (s, 1H), 8.77 – 8.68 (m, 2H), 8.36 (dd, $J = 7.9$, 1.7 Hz, 1H), 7.59 – 7.45 (m, 2H), 7.37 (s, 1H), 7.26 (d, $J = 2.8$ Hz, 1H), 7.09 (dd, $J = 8.8$, 2.8 Hz, 1H), 5.58 (s, 2H), 4.97 – 4.78 (m, 3H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.89 (s, 3H), 3.29 – 3.19 (m, 3H), 2.92 (s, 6H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.11 (dt, $J = 14.4$, 7.0 Hz, 2H), 1.57 (t, $J = 7.0$ Hz, 3H); MS-ESI ($m/z$) calcld for $[C_{31}H_{35}ClN_6O_7]^+$ 617.22; found: 617.24.

83

$^1$H NMR (400 MHz, Methanol-$d_4$) $\delta$ 9.16 (s, 1H), 8.80 (s, 1H), 8.60 (s, 1H), 8.28 (d, $J = 7.8$ Hz, 1H), 7.74 – 7.66 (m, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 7.39 (d, $J = 2.9$ Hz, 2H), 7.21 (dd, $J = 8.9$, 2.7 Hz, 1H), 5.46 (s, 2H), 4.96 – 4.86 (m, 1H), 4.83 (s, 2H), 4.40 (q, $J = 7.0$ Hz, 2H), 3.29 – 3.18 (m, 2H), 2.91 (s, 6H), 2.72 (t, $J = 6.9$ Hz, 2H), 2.11 (dt, $J = 14.8$, 7.0 Hz, 2H), 1.57 (t, $J = 6.9$ Hz, 3H), 1.37 – 1.24 (m, 2H), 0.88 (t, $J = 7.1$ Hz, 1H); MS-ESI ($m/z$) calcld for $[C_{31}H_{35}ClN_6O_7]^+$ 589.23; found: 589.7.
Example 84: Synthesis of \(N\)-\((4\)-(3-chloro-4-\((3\)-methylpyridin-2-yl\)methoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)acetamide

\[
\text{\[00135\]} \quad \text{\[00135\] \(N\)-\((4\)-(3-chloro-4-\((3\)-methylpyridin-2-yl\)methoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)acetamide \ was prepared by a similar procedure to that described for example 1 by coupling Compound 1 with Compound 4. H NMR (400 MHz, Methanol-\(d_4\)) \(\delta\) 9.09 (s, 1H), 8.78 (d, \(J = 1.2\) Hz, 1H), 8.51 (d, \(J = 5.2\) Hz, 1H), 8.00 (d, \(J = 7.8\) Hz, 1H), 7.58 (d, \(J = 7.8\) Hz, 2H), 7.42 (d, \(J = 1.4\) Hz, 2H), 7.37 (d, \(J = 1.1\) Hz, 1H), 5.47 (s, 2H), 4.42 (q, \(J = 7.3\) Hz, 2H), 2.56 (s, 3H), 2.30 (d, \(J = 1.3\) Hz, 3H), 1.61 (t, \(J = 6.9\) Hz, 3H); MS-ESI (\(m/z\)) calcd for [\(C_{27}H_{24}CIN_5O_3 + H\)]\(^+\) 502.16; found: 502.18.
\]

\[
\text{\[00136\]} \quad \text{\[00136\] Examples 85-89 were prepared according to a similar procedure as described for Example 84:}
\]

<table>
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<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>85</td>
<td><img src="image" alt="Structure" /></td>
<td>(^1)H NMR (400 MHz, Methanol-(d_4)) (\delta) 9.06 (s, 1H), 8.73 (s, 1H), 8.60 (d, (J = 4.9) Hz, 1H), 7.96 (td, (J = 7.8), 1.8 Hz, 1H), 7.75 (d, (J = 7.9) Hz, 1H), 7.58 (d, (J = 2.6) Hz, 1H), 7.45 (dd, (J = 7.3), 5.0 Hz, 1H), 7.38 (dd, (J = 8.7), 2.6 Hz, 1H), 7.35 (s, 1H), 7.28 (d, (J = 8.8) Hz, 1H), 5.36 (s, 2H), 4.41 (q, (J = 7.0) Hz, 2H), 2.30 (s, 3H), 1.61 (t, (J = 7.0) Hz, 3H); MS-ESI ((m/z)) calcd for [(C_{23}H_{21}CIN_5O_3 + H)](^+) 488.15; found: 488.19.</td>
</tr>
<tr>
<td>86</td>
<td><img src="image" alt="Structure" /></td>
<td>(^1)H NMR (400 MHz, Methanol-(d_4)) (\delta) 9.07 (s, 1H), 8.74 (s, 1H), 7.47 (d, (J = 6.9) Hz, 2H), 7.42 ~ 7.36 (m, 4H), 7.35 ~ 7.30 (m, 2H), 7.13 (d, (J = 9.0) Hz, 2H), 5.16 (s, 2H), 4.40 (q, (J = 7.0) Hz, 2H), 2.28 (s, 3H), 1.59 (t, (J = 7.0) Hz, 3H); MS-ESI ((m/z)) calcd for [(C_{23}H_{24}N_5O_3 + H)](^+) 453.19; found: 453.21.</td>
</tr>
<tr>
<td>87</td>
<td><img src="image" alt="Structure" /></td>
<td>(^1)H NMR (400 MHz, Methanol-(d_4)) (\delta) 9.08 (s, 1H), 8.77 (s, 1H), 7.49 ~ 7.28 (m, 7H), 7.13 (ddd, (J = 8.4), 2.5, 0.9 Hz, 1H), 7.08 (t, (J = 2.2) Hz, 1H), 7.04 (ddd, (J = 7.8), 2.0, 0.9 Hz, 1H), 5.14 (s, 2H), 4.40 (q, (J = 7.0) Hz, 2H), 2.28 (s, 3H), 1.59 (t, (J = 7.0) Hz, 3H); MS-ESI ((m/z)) calcd for [(C_{22}H_{22}N_5O_3 + H)](^+) 453.19; found: 453.21.</td>
</tr>
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Example 90: Synthesis of (E)-N-(4-(3-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-enamide (7)

[00137] Step 1: (E)-N-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-enamide (6)

[00138] (E)-N-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-enamide (6) was prepared following the procedure of Example 1. Step 2, starting with (2E)-4-(dimethylamino)but-2-enoic acid hydrochloride. 1H NMR (400 MHz, Methanol-d_4) δ 9.29 (s, 1H), 8.87 (s, 1H), 7.54 (s, 1H), 7.09 - 6.96 (m, 1H), 6.57 (d, J = 15.6 Hz, 1H), 4.42 (q, J = 7.3, 6.9 Hz, 2H), 3.23 (d, J = 6.5 Hz, 2H), 2.32 (s, 6H), 1.60 (t, J = 7.0 Hz, 3H). MS-ESI (m/z) calcd for [C_{26}H_{23}ClN_{6}O_{3} + H]^+ 359.13; found: 359.14.
Step 2: (E)-N-(4-(3-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-enamide (7) was prepared by a similar procedure to that described for example 1 by coupling Compound 6 with Compound 4.

$\text{H NMR (400 MHz, Methanol-d}_4\text{) } \delta 9.23 (s, 1H), 8.81 (s, 1H), 8.58 (d, J = 4.7 Hz, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.72 (dd, J = 7.8, 5.4 Hz, 1H), 7.63 (d, J = 2.2 Hz, 1H), 7.51 - 7.41 (m, 3H), 7.01 (dt, J = 14.5, 7.1 Hz, 1H), 6.86 (d, J = 15.3 Hz, 1H), 5.53 (s, 2H), 4.44 (q, J = 7.0 Hz, 2H), 4.05 (d, J = 7.0 Hz, 2H), 2.96 (s, 6H), 2.59 (s, 3H); MS-ESI (m/z) calcd for [C$_{37}$H$_{27}$ClN$_6$O$_3$ + H]$^+$ 571.22; found: 571.28.

Example 91: Synthesis of (E)-N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-enamide (9) was prepared by a similar procedure to that described for example 90 by coupling Compound 6 with Compound 8. Compound 8 was prepared in a similar manner as outlined in example 1, step 3. H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.09 (s, 1H), 8.78 (d, J = 1.2 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 1.4 Hz, 2H), 7.37 (d, J = 1.1 Hz, 1H), 5.47 (s, 2H), 4.42 (q, J = 7.3 Hz, 2H), 2.56 (s, 3H), 2.30 (d, J = 1.3 Hz, 3H), 1.61 (t, J = 6.9 Hz, 3H); MS-ESI (m/z) calcd for [C$_{27}$H$_{24}$ClN$_2$O$_3$ + H]$^+$ 502.16; found: 502.18.
Examples 92-94 were prepared according to a similar procedure as described for examples 90 and 91:

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<tbody>
<tr>
<td>92</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.17 (s, 1H), 8.72 (s, 1H), 8.52 (d, $J = 5.5$ Hz, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 7.68 (s, 1H), 7.38 (s, 1H), 7.25 (d, $J = 8.6$ Hz, 1H), 7.15 (s, 1H), 7.06 – 6.98 (m, 1H), 6.83 (d, $J = 15.3$ Hz, 1H), 5.42 (s, 2H), 4.87 (s, 4H), 4.41 (d, $J = 7.1$ Hz, 2H), 4.02 (d, $J = 7.2$ Hz, 2H), 3.85 (s, 3H), 3.33 (s, 9H), 2.94 (s, 6H), 2.53 (s, 3H), 1.58 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$</em>{32}$H$_{34}$N$_6$O$_4$+H]$^+$ 567.26; found: 567.23.</td>
</tr>
<tr>
<td>93</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.26 (s, 1H), 8.77 (s, 1H), 8.62 (d, $J = 5.7$ Hz, 2H), 8.32 (d, $J = 7.9$ Hz, 2H), 7.84 (dd, $J = 7.9, 5.6$ Hz, 2H), 7.41 (t, $J = 4.3$ Hz, 3H), 7.26 – 7.13 (m, 3H), 7.00 (dt, $J = 14.4, 7.1$ Hz, 1H), 6.89 – 6.83 (m, 1H), 5.53 (s, 2H), 4.44 (q, $J = 7.0$ Hz, 3H), 4.04 (d, $J = 7.2$ Hz, 3H), 2.95 (s, 7H), 2.57 (s, 4H), 2.35 (s, 4H), 1.60 (t, $J = 7.0$ Hz, 5H); MS-ESI (m/z) calcd for [C$</em>{32}$H$_{34}$N$_6$O$_3$+H]$^+$ 551.27; found: 276.38 (z = 2).</td>
</tr>
<tr>
<td>94</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) δ 9.20 (s, 1H), 8.71 (s, 1H), 8.54 – 8.48 (m, 1H), 8.10 (d, $J = 8.0$ Hz, 1H), 7.65 (dd, $J = 7.9, 5.3$ Hz, 1H), 7.36 (s, 1H), 7.17 (s, 1H), 7.09 (s, 1H), 7.02 – 6.89 (m, 1H), 6.80 (dt, $J = 15.2, 1.0$ Hz, 1H), 5.40 (s, 2H), 4.88 (s, 1H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.99 (dd, $J = 7.2, 1.2$ Hz, 2H), 3.31 (s, 1H), 2.91 (d, $J = 2.2$ Hz, 6H), 2.52 (s, 4H), 2.24 (d, $J = 17.8$ Hz, 7H), 1.56 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$</em>{33}$H$_{36}$N$_6$O$_3$+H]$^+$ 565.28; found: 283.39 (z = 2).</td>
</tr>
</tbody>
</table>
Example 95: Synthesis of N-(4-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(pyrrolidin-1-yl)butanamide (11)

A 1 dram vial with a stir bar is charged with compound 10 (30 mg, 0.067 mmol, 1.0 equiv), 4-(pyrrolidin-1-yl)butanoic acid hydrochloride (27 mg, 0.14 mmol, 2.0 equiv), EDC-HCl (33 mg, 0.17 mmol, 2.5 equiv), 48 mg DIPEA (0.37 mmol, 5.5 equiv) and CH$_2$C$_3$H$_2$. DMAP (1.5 mg, 0.012 mmol, 0.2 equiv) is added, the reaction vial is capped and stirred for at room temperature for 18 h. The reaction is quenched with the addition of 2 mL of saturated NH$_4$C$_1$ and is extracted with CH$_2$C$_3$H$_2$ (2 × 2 mL). The combined organic layer is washed with brine and evaporated. The crude residue is purified by gradient flash column chromatography (2 to 20% MeOH in CH$_2$C$_3$H$_2$) to yield the product as a yellow solid (32 mg, 82%). H NMR (400 MHz, CDCl$_3$) $\delta$ 9.06 (s, 1H), 8.60 (d, $J = 4.3$ Hz, 1H), 8.46 (s, 1H), 8.38 (s, 1H), 7.90 (s, 1H), 7.77 (td, $J = 7.6$, 1.7 Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 7.29 - 7.18 (m, 3H), 6.99 (d, $J = 8.4$ Hz, 1H), 6.90 (d, $J = 8.5$ Hz, 1H), 5.27 (s, 2H), 4.26 (q, $J = 6.9$ Hz, 2H), 2.70 - 2.45 (m, 8H), 1.95 (p, $J = 7.2$ Hz, 2H), 1.85 - 1.71 (m, 4H), 1.55 (t, $J = 6.9$ Hz, 3H); MS-ESI (m/z) calcd for [C$_{32}$H$_{33}$C$_{1}$N$_{6}$O$_{7}^+$ + H]$^{+}$ 585.24; found: 293.19 ($z = 2$).

Examples 96-106 were prepared according to a similar procedure as described for example 95:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td><img src="image" alt="Structure" /></td>
<td>H NMR (400 MHz, CDCl$<em>3$) $\delta$ 9.06 (s, 1H), 8.61 (d, $J = 4.5$ Hz, 1H), 8.50 (s, 1H), 7.82 - 7.65 (m, 3H), 7.34 - 7.24 (m, 3H), 7.08 (dd, $J = 8.7$, 2.6 Hz, 1H), 6.97 (d, $J = 8.8$ Hz, 1H), 5.30 (s, 2H), 4.28 (q, $J = 7.0$ Hz, 2H), 2.88 (s, 2H), 2.77 (s, 2H), 2.51 (s, 6H), 1.61 - 1.52 (m, 3H); MS-ESI (m/z) calcd for [C$</em>{29}$H$<em>{32}$ClN$</em>{6}$O$_{3}$ + H]$^{+}$ 545.21; found: 545.16.</td>
</tr>
</tbody>
</table>
\(^1\)H NMR (400 MHz, Methanol-d₄) \(\delta\) 9.09 (s, 1H), 8.79 (s, 1H), 8.61 (d, \(J = 5.1\) Hz, 1H), 7.99 (td, \(J = 7.8, 1.8\) Hz, 1H), 7.77 (d, \(J = 7.8\) Hz, 1H), 7.59 (d, \(J = 2.5\) Hz, 1H), 7.50 – 7.45 (m, 1H), 7.41 – 7.36 (m, 2H), 7.29 (d, \(J = 8.9\) Hz, 1H), 5.37 (s, 2H), 4.41 (q, \(J = 6.9\) Hz, 2H), 3.58 (d, \(J = 12.3\) Hz, 2H), 3.24 – 3.15 (m, 2H), 2.95 (t, \(J = 12.5\) Hz, 2H), 2.73 (t, \(J = 6.9\) Hz, 2H), 2.20 – 2.07 (m, 2H), 1.96 (d, \(J = 14.8\) Hz, 2H), 1.80 (dd, \(J = 35.2, 14.7\) Hz, 3H), 1.59 (t, \(J = 7.0\) Hz, 3H), 1.52 (d, \(J = 14.9\) Hz, 1H); MS-ESI (m/z) calc for \([\text{C}_{13}\text{H}_{23}\text{ClN}_6\text{O}_7 + H]\)^+ 599.25; found: 599.21.

\(^1\)H NMR (400 MHz, Methanol-d₄) \(\delta\) 9.14 (s, 1H), 8.81 (s, 1H), 8.68 (d, \(J = 4.9\) Hz, 1H), 8.15 (td, \(J = 7.8, 1.7\) Hz, 1H), 7.88 (d, \(J = 7.9\) Hz, 1H), 7.67 – 7.58 (m, 2H), 7.45 – 7.38 (m, 2H), 7.32 (d, \(J = 8.8\) Hz, 1H), 5.44 (s, 2H), 4.41 (q, \(J = 7.0\) Hz, 2H), 3.46 (s, 4H), 3.34 (s, 4H), 3.06 (dd, \(J = 9.0, 6.5\) Hz, 2H), 2.91 (s, 3H), 2.71 (t, \(J = 7.0\) Hz, 2H), 2.08 (p, \(J = 7.1\) Hz, 2H), 1.59 (t, \(J = 7.0\) Hz, 3H); MS-ESI (m/z) calc for \([\text{C}_{16}\text{H}_{25}\text{ClN}_3\text{O}_3 + H]\)^+ 614.26; found: 614.31.

\(^1\)H NMR (400 MHz, Methanol-d₄) \(\delta\) 9.13 (s, 1H), 8.81 (s, 1H), 8.67 (d, \(J = 4.4\) Hz, 1H), 8.12 (td, \(J = 7.8, 1.7\) Hz, 1H), 7.86 (d, \(J = 7.9\) Hz, 1H), 7.64 – 7.56 (m, 2H), 7.45 – 7.38 (m, 2H), 7.31 (d, \(J = 8.8\) Hz, 1H), 5.43 (s, 2H), 4.41 (q, \(J = 7.0\) Hz, 2H), 4.06 (d, \(J = 12.9\) Hz, 2H), 3.78 (t, \(J = 12.5\) Hz, 2H), 3.55 (d, \(J = 12.4\) Hz, 2H), 3.31 – 3.24 (m, 2H), 3.23 – 3.08 (m, 2H), 2.74 (t, \(J = 6.9\) Hz, 2H), 2.22 – 2.07 (m, 2H), 1.59 (t, \(J = 6.9\) Hz, 3H); MS-ESI (m/z) calc for \([\text{C}_{12}\text{H}_{25}\text{ClN}_3\text{O}_5 + H]\)^+ 601.23; found: 601.21.

\(^1\)H NMR (400 MHz, Methanol-d₄) \(\delta\) 9.07 (s, 1H), 8.80 (s, 1H), 8.63 (d, \(J = 4.4\) Hz, 1H), 8.04 (td, \(J = 7.8, 1.7\) Hz, 1H), 7.81 (d, \(J = 7.9\) Hz, 1H), 7.60 (d, \(J = 2.6\) Hz, 1H), 7.56 – 7.46 (m, 1H), 7.41 (dd, \(J = 8.7, 2.6\) Hz, 1H), 7.35 (s, 1H), 7.29 (d, \(J = 8.8\) Hz, 1H), 5.39 (s, 2H), 4.40 (q, \(J = 7.0\) Hz, 2H), 2.53 (t, \(J = 7.3\) Hz, 2H), 1.77 (b, \(J = 7.4\) Hz, 2H), 1.59 (t, \(J = 7.0\) Hz, 3H), 1.04 (t, \(J = 7.4\) Hz, 3H); MS-ESI (m/z) calc for \([\text{C}_{20}\text{H}_{23}\text{ClN}_5\text{O}_3 + H]\)^+ 516.18; found: 516.25.

\(^1\)H NMR (400 MHz, Methanol-d₄) \(\delta\) 9.10 (s, 1H), 8.80 (s, 1H), 8.63 (d, \(J = 4.3\) Hz, 1H), 8.04 (td, \(J = 7.8, 1.7\) Hz, 1H), 7.85 – 7.77 (m, 1H), 7.61 (d, \(J = 2.5\) Hz, 1H), 7.52 (ddd, \(J = 7.7, 5.1, 1.2\) Hz, 1H), 7.41 (dd, \(J = 8.7, 2.6\) Hz, 1H), 7.35 (s, 1H), 7.30 (d, \(J = 8.8\) Hz, 1H), 5.40 (s, 2H), 4.40 (q, \(J = 7.0\) Hz, 2H), 2.57 (q, \(J = 7.5\) Hz, 2H), 1.59 (t, \(J = 7.0\) Hz, 3H), 1.24 (t, \(J = 7.5\) Hz,
1H NMR (400 MHz, Methanol-d4) δ 9.07 (s, 1H), 8.77 (s, 1H), 8.60 (d, J = 5.0 Hz, 1H), 7.97 (td, J = 7.7, 1.8 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 2.6 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.39 (dd, J = 8.8, 2.6 Hz, 1H), 7.34 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 5.36 (s, 2H), 4.40 (q, J = 7.0 Hz, 2H), 3.49 (t, J = 6.2 Hz, 2H), 3.35 (s, 3H), 2.62 (t, J = 7.3 Hz, 2H), 2.03 – 1.92 (m, 2H), 1.59 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C2H2Cl3N2O5 + H]+ 546.19; found: 546.23.

1H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 8.73 (s, 1H), 8.58 (d, J = 5.1 Hz, 1H), 7.94 (td, J = 7.6, 1.7 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 2.6 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.37 (dd, J = 8.7, 2.6 Hz, 1H), 7.33 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.39 (q, J = 6.9 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 1.81 – 1.68 (m, 2H), 1.66 – 1.52 (m, 4H), 1.38 – 1.22 (m, 2H), 0.92 (d, J = 6.6 Hz, 6H); MS-ESI (m/z) calcd for [C6H12O2Cl3N2 + H]+ 558.23; found: 558.29.

1H NMR (400 MHz, Methanol-d4) δ 8.98 (s, 1H), 8.74 (s, 1H), 8.59 (d, J = 5.2 Hz, 1H), 7.95 (td, J = 7.8, 1.7 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.37 (dd, J = 8.7, 2.6 Hz, 1H), 7.33 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 4.38 (q, J = 7.0 Hz, 2H), 2.41 (d, J = 6.9 Hz, 2H), 1.94 – 1.64 (m, 5H), 1.58 (t, J = 7.0 Hz, 3H), 1.40 – 1.16 (m, 4H), 1.09 (d, J = 11.8 Hz, 2H); MS-ESI (m/z) calcd for [C2H2Cl3N2O5 + H]+ 570.23; found: 570.35.

1H NMR (400 MHz, CDCl3) δ 9.11 (s, 1H), 8.60 (d, J = 4.5 Hz, 1H), 8.38 (s, 1H), 8.12 (s, 1H), 7.77 (td, J = 7.7, 1.8 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.48 – 7.36 (m, 5H), 7.34 – 7.23 (m, 2H), 7.20 – 7.13 (m, 2H), 6.89 (dd, J = 8.7, 2.3 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H), 4.03 (q, J = 6.9 Hz, 2H), 3.84 (s, 2H), 1.26 (t, J = 6.9 Hz, 3H); MS-ESI (m/z) calcd for [C6H12Cl3N2O5 + H]+ 564.18; found: 282.66 (z = 2).

1H NMR (400 MHz, CDCl3) δ 9.29 (s, 1H), 8.84 (s, 1H), 8.59 (d, J = 4.5 Hz, 1H), 8.44 (s, 1H), 8.87 (d, J = 7.4 Hz, 2H), 7.76 (td, J = 7.6, 1.8 Hz, 1H), 7.70 – 7.57 (m, 2H), 7.57 – 7.44 (m, 2H), 7.33 – 7.19 (m, 2H), 7.04 (dd, J = 8.7, 2.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 5.25 (s, 2H), 4.33 (q, J = 6.9 Hz, 2H), 1.58 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C3H4Cl3N2O5 + H]+ 550.16; found: 275.67 (z = 2).
Example 107: Synthesis of N-(4-(3-chloro-4-(2-(pyridin-2-yl)ethyl)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (14)

[00145] Step 1: 3-chloro-4-(pyridin-2-ylethynyl)aniline (12)

2-Ethynylpyridine (0.57 mL, 5.6 mmol), 4-iodo-3-chloroaniline (1.01 g, 4.0 mmol), PdCl$_2$(PPh)$_3$)$_2$ (281 mg, 0.4 mmol), copper (I) iodide (152 mg, 0.8 mmol), trimethylamine (5.6 mL, 40 mmol) and DMF (4.5 mL) were added to a vial with a stirbar and the mixture was sparged with Argon. The reaction mixture was heated in a 90 °C heating block for 45 min then cooled to ambient temperature. The mixture was partitioned between water and ethyl acetate, and the organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The crude product was purified by gradient flash column chromatography from 0 - 100% EtOAc in hexanes to yield 660 mg (72%) of 3-chloro-4-(pyridin-2-ylethynyl)aniline (12) as a yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.61 (s, 1H), 7.69 (t, $J$ = 7.7 Hz, 1H), 7.54 (d, $J$ = 7.8 Hz, 1H), 7.41 (d, $J$ = 8.4 Hz, 1H), 7.26 - 7.21 (m, 1H), 6.72 (s, 1H), 6.53 (d, $J$ = 8.4 Hz, 1H), 3.95 (br s, 2H).

[00146] Step 2: 3-chloro-4-(2-(pyridin-2-yl)ethyl)aniline (13)

To a Parr shaker hydrogenation apparatus was added 12 (650 mg, 2.47 mmol), 10% Pd/C (50 mg) and EtOAc (15 mL). The reaction flask was filled to 80 psi with H$_2$ and the reaction was shaken for 16 h. After offgassing the H$_2$, the reaction mixture was passed through a pad of Celite then the crude product was purified by gradient flash column chromatography from 0 - 100% EtOAc in hexane. 3-chloro-4-(2-(pyridin-2-yl)ethyl)aniline (13) was isolated as a
yellow solid, 343 mg (1.47 mmol, 60%). 1H NMR (400 MHz, CDC\textsubscript{13}) \(\delta\) 8.58 (ddd, \(J = 5.0, 1.9, 0.9\) Hz, 1H), 7.63 (td, \(J = 7.7, 1.9\) Hz, 1H), 7.21 - 7.11 (m, 2H), 6.95 (d, \(J = 8.2\) Hz, 1H), 6.72 (d, \(J = 2.4\) Hz, 1H), 6.49 (dd, \(J = 8.1, 2.4\) Hz, 1H), 3.79 (br s, 2H), 3.16 - 2.99 (m, 4H).

[00149] Step 3: \(N\)-(4-(3-chloro-4-(2-(pyridin-2-yl)ethyl)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (14)

\[
\begin{align*}
\text{HN} & \quad \text{NH} \\
\text{O} & \quad \text{Cl} \\
\text{CN} & \quad \text{Cl} \\
\text{ElO} & \quad \text{Cl} \\
\text{N} & \quad \text{NH} \\
\text{NH} & \quad \text{NH} \\
\text{O} & \quad \text{Cl} \\
\text{CN} & \quad \text{Cl}
\end{align*}
\]

\[\text{HN} \rightarrow \text{py-HCl} / \text{PrOH}\]

[00150] \(N\)-(4-(3-chloro-4-(2-(pyridin-2-yl)ethyl)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (14) was prepared by a similar procedure to that described for example 1 by coupling Compound 3 with Compound 13. \(^1\)H NMR (400 MHz, Methanol-d\textsubscript{4}) \(\delta\) 9.11 (s, 1H), 8.78 (s, 1H), 8.67 (d, \(J = 5.8\) Hz, 1H), 8.38 (tt, \(J = 8.0, 2.0\) Hz, 1H), 7.88 - 7.81 (m, 1H), 7.81 - 7.75 (m, 1H), 7.50 (s, 1H), 7.42 (s, 1H), 7.36 - 7.27 (m, 2H), 4.41 (q, \(J = 6.7\) Hz, 2H), 3.46 - 3.39 (m, 2H), 3.38 - 3.33 (m, 2H), 3.28 - 3.20 (m, 2H), 2.92 (s, 6H), 2.73 (t, \(J = 6.9\) Hz, 2H), 2.12 (p, \(J = 7.1\) Hz, 2H), 1.58 (t, \(J = 7.0\) Hz, 3H). MS-ESI (m/z) calcd for [C\textsubscript{3}H\textsubscript{35}ClN\textsubscript{6}0\textsubscript{2} + H]\textsuperscript{+} 557.24; found: 279.24 (z = 2).

Example 108: Synthesis of \(N\)-(2-chloro-4-(3-cyano-6-(4-(dimethylamino)butanamido)-7-ethoxyquinolin-4-ylamino)phenyl)-3-methylpicolinamide (15)

[00151] Step 1: \(N\)-(2-chloro-4-nitrophenyl)-3-methylpicolinamide (13)

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{CO} & \quad \text{O} \\
\text{N} & \quad \text{NH}_2 \\
\text{O} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N}
\end{align*}
\]

1) ClC(O)C(O)Cl

2) \(\text{O}_2\text{N}

[00152] 3-Methylpyridine-2-carboxylic acid (206 mg, 1.5 mmol) was stirred in dry CH\textsubscript{2}C\textsubscript{12} (3 mL) under argon in a 0 °C ice-water bath. Oxalyl chloride (570 mg, 4.5 mmol) was added...
dropwise by syringe and the reaction was allowed to warm to ambient temperature and stir for 16 h, at which point the solvent was evaporated under reduced pressure and the residue was redissolved in 5 mL of CH₂Cl₂. 2-Chloro-4-nitroaniline (172 mg, 1 mmol) was added as a solid and the reaction mixture was stirred at ambient temperature under argon for 2.5 h. The solvent was removed under reduced pressure and the resulting crude product was purified by gradient flash column chromatography with 0 - 100% EtOAc in hexanes to yield N-(2-chloro-4-nitrophenyl)-3-methylpicolinamide (13) as a yellow solid (98 mg, 34%). H NMR (400 MHz, CDCl₃) δ 11.38 (s, 1H), 8.91 (d, J = 9.2 Hz, 1H), 8.59 - 8.48 (m, 1H), 8.35 (d, J = 2.6 Hz, 1H), 8.21 (dd, J = 9.2, 2.6 Hz, 1H), 7.70 (dd, J = 7.7, 1.5 Hz, 1H), 7.45 (dd, J = 7.8, 4.6 Hz, 1H), 2.82 (s, 3H).

[00153] Step 2: N-(4-amino-2-chlorophenyl)-3-methylpicolinamide (14)

[00154] Compound 13 (98 mg, 0.34 mmol), zinc dust (230 mg, 3.5 mmol), ammonium chloride (45 mg, 0.85 mmol), methanol (5 mL) and water (1 mL) were stirred in a vial at ambient temperature for 16 h, then the mixture was filtered through filter paper and the solvents were removed under reduced pressure. The crude product was purified by gradient flash column chromatography with 0 - 100% EtOAc in hexanes with 0.1% triethylamine, to give N-(4-amino-2-chlorophenyl)-3-methylpicolinamide (14) (28 mg, 31%) as a yellow solid. LCMS (found 262.1, M+H+).

[00155] Step 3: N-(2-chloro-4-(3-cyano-6-(4-(dimethylamino)butanamido)-7-ethoxyquinolin-4-ylamino)phenyl)-3-methylpicolinamide (15)

[00156] N-(2-chloro-4-(3-cyano-6-(4-(dimethylamino)butanamido)-7-ethoxyquinolin-4-ylamino)phenyl)-3-methylpicolinamide (15) was prepared by a similar procedure to that described for example 1 by coupling Compound 3 with Compound 14. H NMR (400 MHz, Methanol-d₄) δ 9.06 (s, 1H), 8.74 (s, 1H), 8.67 (d, J = 8.8 Hz, 1H), 8.58 (d, J = 4.5 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.62 - 7.51 (m, 2H), 7.45 - 7.37 (m, 2H), 4.42 (q, J = 7.2 Hz, 2H), 2.94 (s, 3H).
6H), 2.81 (s, 3H), 2.75 (t, J = 6.8 Hz, 2H), 2.20 - 2.06 (m, 2H), 1.60 (t, J = 7.0 Hz, 3H), 2H are unresolved and under the MeOD peak; MS-ESI (m/z) calcd for [C_{31}H_{32}ClN_{7}O_{3} + H]^+ 586.24; found: 586.2 (z = 2).

Example 109: Synthesis of N-(2-chloro-4-(3-cyano-6-(4-(dimethylamino)butanamido)-7-ethoxyquinolin-4-ylamino)phenyl)benzamide

![Image](image)

[00157] *N*-((2-chloro-4-(3-cyano-6-(4-(dimethylamino)butanamido)-7-ethoxyquinolin-4-ylamino)phenyl)benzamide was prepared by a similar procedure to that described for example 108 starting with benzoic acid in step 1. ^H NMR (400 MHz, Methanol-d$_4$) δ 9.09 (s, 1H), 8.79 (s, 1H), 8.08 - 7.97 (m, 3H), 7.68 - 7.48 (m, 4H), 7.48 - 7.38 (m, 2H), 4.41 (q, J = 6.9 Hz, 2H), 3.27 - 3.21 (m, 2H), 2.92 (s, 6H), 2.74 (t, J = 6.9 Hz, 2H), 2.19 - 2.04 (m, 2H), 1.59 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C_{31}H_{32}ClN_{7}O_{3} + H]^+ 571.22; found: 286.26 (z = 2).

Example 110: Synthesis of N-(4-(6-acetamido-3-cyano-7-ethoxyquinolin-4-ylamino)-2-chlorophenyl)benzamide

![Image](image)

[00158] *N*-(4-(6-acetamido-3-cyano-7-ethoxyquinolin-4-ylamino)-2-chlorophenyl)benzamide was prepared by a similar procedure to that described for example 1 by coupling Compound 1 with Compound 14. ^H NMR (400 MHz, Methanol-d$_4$) δ 9.13 (s, 1H), 8.87 (s, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 2.4 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.52 - 7.46 (m, 1H), 7.35 (s, 1H), 4.42 (q, J = 7.0 Hz, 2H), 2.29 (s, 3H), 1.61 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C_{27}H_{22}ClN_{5}O_{3} + H]^+ 500.15; found: 500.29.
Example 111: Synthesis of N-(4-(3-chloro-4-(pyridin-2-ylmethylamino)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (16)

[00159] Step 1: 2-Chloro-4-nitro-N-(pyridin-2-ylmethyl)aniline (B)

[00160] 3-Chloro-4-fluoronitrobenzene (3.51 g, 20.0 mmol) and triethylamine (4.18 mL, 30.0 mmol) are dissolved in 20 mL of DMF in a round bottom flask charged with a stir bar. 2-(aminomethyl)pyridine is added via syringe and the reaction is allowed to stir under argon for 18h. The reaction is stopped by the addition of water (100 mL) and the resulting mixture is filtered and washed with more water to yield 5.149 g of compound B as a yellow solid which is taken onto the next step without further purification.

[00161] Step 2: 2-Chloro-Nl-(pyridin-2-ylmethyl)benzene-l,4-diamine (C)

[00162] A round bottom flask is charged with 527 mg (2.0 mmol) of compound B, 500 mg of activated carbon, 16.2 mg (0.1 mmol) of FeCl₃, and 20 mL of ethanol and the flask is sparged with argon. Hydrazine monohydrate (400 mg, 8.0 mmol) is added by syringe and the reaction mixture is stirred under argon at 60 °C. After 17h, the reaction is cooled to room temperature and filtered through Celite, washing with methanol. The filtrate is evaporated and the resulting residue is purified by automated flash column chromatography (0 to 100% EtOAc in hexanes) to yield 113 mg (24%) of compound C as an off-white solid. 1H NMR (400 MHz, CDCl₃) δ 8.67 - 8.49 (m, 1H), 7.71 - 7.53 (m, 1H), 7.33 (t, J = 6.4 Hz, 1H), 7.18 (dt, J = 7.3, 4.8 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.50 (dt, J = 13.6, 8.7 Hz, 2H), 4.47 (d, J = 5.0 Hz, 2H), 4.07 - 3.62 (m, 3H).

[00163] Step 3: N-(4-(3-chloro-4-(pyridin-2-ylmethylamino)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (16)
N-(4-(3-chloro-4-(pyridin-2-ylmethylamino)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-((dimethylamino)butanamide (16) was prepared by a similar procedure to that described for example 1 by coupling Compound 3 with Compound C. 

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.10 (s, 1H), 8.74 (s, 1H), 8.65 (d, $J = 4.8$ Hz, 1H), 8.22 - 8.11 (m, 1H), 7.74 (d, $J = 8.2$ Hz, 1H), 7.64 (t, $J = 6.5$ Hz, 1H), 7.50 - 7.43 (m, 1H), 7.36 (s, 1H), 7.22 - 7.14 (m, 1H), 6.65 (d, $J = 8.8$ Hz, 1H), 4.80 (s, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.30 - 3.20 (m, 2H), 2.93 (s, 6H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.12 (p, $J = 7.3$ Hz, 2H), 1.58 (t, $J = 6.9$ Hz, 3H); MS-ESI ($m/z$) calcd for [C$_{30}$H$_{32}$CIN$_7$O$_2$ + H]$^+$ 558.24; found: 279.78 ($z = 2$).

Examples 112-114 were prepared according to a similar procedure as described for example 111:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>112</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.06 (s, 1H), 8.71 (d, $J = 1.4$ Hz, 1H), 8.58 (ddd, $J = 5.2$, 1.7, 0.9 Hz, 1H), 7.96 (td, $J = 7.8$, 1.7 Hz, 1H), 7.62 (dt, $J = 7.9$, 1.0 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.34 (s, 1H), 7.10 (dd, $J = 8.7$, 2.4 Hz, 1H), 6.56 (d, $J = 8.8$ Hz, 1H), 4.85 (q, $J = 7.0$ Hz, 1H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.27 - 3.20 (m, 2H), 2.92 (d, $J = 1.7$ Hz, 6H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.17 - 2.06 (m, 2H), 1.67 (d, $J = 6.8$ Hz, 3H), 1.57 (t, $J = 7.0$ Hz, 3H); MS-ESI ($m/z$) calcd for [C$</em>{31}$H$_{34}$CIN$_7$O$_2$ + H]$^+$ 572.25; found: 572.20.</td>
</tr>
<tr>
<td>113</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.04 (s, 1H), 8.69 (s, 1H), 8.59 (ddd, $J = 5.1$, 1.7, 0.9 Hz, 1H), 7.98 (t, $J = 7.8$ Hz, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.49 - 7.40 (m, 2H), 7.33 (s, 1H), 6.98 - 6.91 (m, 1H), 6.11 (d, $J = 8.8$ Hz, 1H), 4.38 (q, $J = 7.0$ Hz, 2H), 3.27 - 3.19 (m, 2H), 2.92 (s, 6H), 2.72 (t, $J = 7.0$ Hz, 2H), 2.11 (dt, $J = 15.0$, 7.1 Hz, 2H), 1.81 (s, 6H), 1.57 (t, $J = 7.0$ Hz, 3H); MS-ESI ($m/z$) calcd for [C$</em>{32}$H$_{36}$CIN$_7$O$_2$ + H]$^+$ 586.27; found: 586.21.</td>
</tr>
</tbody>
</table>
Example 115: Synthesis of N-(3-cyano-7-ethoxy-4-(phenylamino)quinolin-6-yl)acetamide

![Chemical Structure](image)

**Analytical Data**

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 10.44 (s, 1H), 9.02 (s, 1H), 8.85 (dd, $J = 8.7, 7.3$ Hz, 2H), 8.56 (t, $J = 7.4$ Hz, 1H), 8.49 (d, $J = 7.7$ Hz, 2H), 5.95 (q, $J = 7.0$ Hz, 2H), 5.26 (s, 3H), 3.75 (s, 3H), 3.13 (t, $J = 7.0$ Hz, 3H).</td>
</tr>
<tr>
<td>117</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.04 (s, 1H), 8.76 (s, 1H), 7.50 (td, $J = 8.1, 6.2$ Hz, 1H), 7.36 (s, 1H), 7.27 - 7.12 (m, 3H), 4.40 (q, $J = 7.0$ Hz, 2H), 2.28 (s, 3H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calcd for [C$</em>{20}$H$<em>{17}$F$</em>{11}$N$_3$O$_2$ + H]$:^+$ 365.14; found: 365.21.</td>
</tr>
<tr>
<td>118</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.08 (s, 1H), 8.76 (s, 1H), 7.56 - 7.46 (m, 2H), 7.36 (s, 1H), 7.35 - 7.28 (m, 2H), 4.40 (q, $J = 7.0$ Hz, 2H), 2.28 (s, 3H), 1.59 (t, $J = 7.0$ Hz, 3H).</td>
</tr>
</tbody>
</table>
119

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.06 (s, 1H), 8.74 (s, 1H), 7.52 – 7.44 (m, 2H), 7.33 (s, 1H), 7.25 (t, $J$ = 8.6 Hz, 2H), 4.40 (q, $J$ = 7.0 Hz, 2H), 2.28 (s, 3H), 1.59 (t, $J$ = 7.0 Hz, 3H); MS-ESI ($m/z$) calc'd for [C$_{20}$H$_{21}$FN$_4$O$_2$ + H]$^+$ 365.14; found: 365.21.

120

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.08 (s, 1H), 8.75 (s, 1H), 7.34 (s, 4H), 7.33 (s, 1H), 4.40 (q, $J$ = 7.0 Hz, 2H), 2.44 (s, 3H), 2.28 (s, 3H), 1.59 (t, $J$ = 7.0 Hz, 3H); MS-ESI ($m/z$) calc'd for [C$_{21}$H$_{20}$N$_4$O$_2$ + H]$^+$ 361.17; found: 361.24.

121

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.05 (s, 1H), 8.71 (s, 1H), 7.37 (d, $J$ = 8.9 Hz, 2H), 7.32 (s, 1H), 7.05 (d, $J$ = 8.9 Hz, 2H), 4.39 (q, $J$ = 7.0 Hz, 2H), 3.87 (s, 3H), 2.28 (s, 3H), 1.59 (t, $J$ = 7.0 Hz, 3H); MS-ESI ($m/z$) calc'd for [C$_{21}$H$_{20}$N$_4$O$_2$ + H]$^+$ 377.16; found: 377.21.

122

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.07 (s, 1H), 8.78 (s, 1H), 7.52 (d, $J$ = 8.7 Hz, 2H), 7.43 (d, $J$ = 8.7 Hz, 2H), 7.35 (s, 1H), 4.40 (q, $J$ = 7.0 Hz, 2H), 2.28 (s, 3H), 1.59 (t, $J$ = 7.0 Hz, 3H); MS-ESI ($m/z$) calc'd for [C$_{21}$H$_{20}$CIN$_3$O$_2$ + H]$^+$ 381.11; found: 381.11.

123

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.08 (s, 1H), 8.79 (d, $J$ = 1.4 Hz, 1H), 7.53 (d, $J$ = 2.3 Hz, 1H), 7.39 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.34 (s, 1H), 7.26 (d, $J$ = 8.6 Hz, 1H), 4.40 (q, $J$ = 7.0 Hz, 2H), 3.91 – 3.82 (m, 4H), 3.14 – 3.08 (m, 4H), 2.28 (s, 3H), 1.59 (t, $J$ = 7.0 Hz, 3H); MS-ESI ($m/z$) calc'd for [C$_{22}$H$_{22}$CIN$_3$O$_2$ + H]$^+$ 466.16; found: 466.18.

124

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.10 (s, 1H), 8.85 (s, 1H), 7.80 (d, $J$ = 8.3 Hz, 2H), 7.59 (d, $J$ = 8.1 Hz, 2H), 7.39 (s, 1H), 4.41 (q, $J$ = 7.0 Hz, 2H), 2.28 (s, 3H), 1.60 (t, $J$ = 7.0 Hz, 3H); MS-ESI ($m/z$) calc'd for [C$_{21}$H$_{17}$F$_3$N$_3$O$_2$ + H]$^+$ 415.14; found: 415.21.

125

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.09 (s, 1H), 8.81 (s, 1H), 7.57 (d, $J$ = 8.9 Hz, 2H), 7.43 (d, $J$ = 8.3 Hz, 2H), 7.39 (d, $J$ = 2.6 Hz, 1H), 4.40 (q, $J$ = 7.0 Hz, 2H), 2.28 (s, 3H), 1.59 (t, $J$ = 7.0 Hz, 3H); MS-ESI ($m/z$) calc'd for [C$_{21}$H$_{17}$F$_3$N$_3$O$_2$ + H]$^+$ 431.13; found: 431.18.
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>NMR Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.08 (s, 1H), 8.76 (s, 1H), 7.76 (d, $J = 8.5$ Hz, 2H), 7.69 (dd, $J = 8.3$, 1.3 Hz, 2H), 7.54 – 7.43 (m, 4H), 7.41 – 7.31 (m, 2H), 4.40 (q, $J = 7.0$ Hz, 2H), 2.28 (s, 3H), 1.60 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{22}$N$_2$O$_2$ + H]$^+$ 423.18; found: 423.16.</td>
</tr>
<tr>
<td>127</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.11 (s, 1H), 8.83 (d, $J = 1.4$ Hz, 1H), 7.55 – 7.32 (m, 5H), 4.41 (q, $J = 7.0$ Hz, 2H), 2.28 (d, $J = 1.4$ Hz, 3H), 1.64 – 1.54 (m, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{17}$ClN$_2$O$_2$ + H]$^+$ 381.11; found: 381.18.</td>
</tr>
<tr>
<td>128</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.11 (s, 1H), 8.85 (s, 1H), 7.86 (t, $J = 1.9$ Hz, 1H), 7.82 – 7.66 (m, 3H), 7.39 (s, 1H), 4.42 (q, $J = 7.0$ Hz, 2H), 2.28 (s, 3H), 1.60 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{24}$N$_2$O$_2$ + H]$^+$ 372.15; found: 372.19.</td>
</tr>
<tr>
<td>129</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.05 (s, 1H), 8.85 (s, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.2$ Hz, 2H), 7.41 (s, 1H), 4.41 (q, $J = 6.9$ Hz, 2H), 2.27 (s, 3H), 1.59 (t, $J = 7.0$ Hz, 3H).</td>
</tr>
<tr>
<td>130</td>
<td><img src="image5" alt="Structure Image" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.05 (s, 1H), 8.72 (s, 1H), 7.39 (t, $J = 7.7$ Hz, 1H), 7.33 (s, 1H), 7.31 – 7.18 (m, 3H), 4.39 (q, $J = 7.0$ Hz, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{23}$N$_2$O$_2$ + H]$^+$ 361.17; found: 361.24.</td>
</tr>
<tr>
<td>131</td>
<td><img src="image6" alt="Structure Image" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.06 (s, 1H), 8.73 (s, 1H), 7.43 – 7.32 (m, 2H), 7.04 – 6.92 (m, 3H), 4.37 (q, $J = 7.0$ Hz, 2H), 3.83 (s, 3H), 2.29 (s, 3H), 1.59 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{23}$N$_2$O$_2$ + H]$^+$ 377.16; found: 377.21.</td>
</tr>
<tr>
<td>132</td>
<td><img src="image7" alt="Structure Image" /></td>
<td>$^1$H NMR (400 MHz, Methanol-d$<em>4$) $\delta$ 9.13 (s, 1H), 8.84 (s, 1H), 7.84 – 7.67 (m, 4H), 7.42 (s, 1H), 4.41 (q, $J = 6.9$ Hz, 2H), 2.29 (s, 3H), 1.60 (t, $J = 7.0$ Hz, 3H); MS-ESI (m/z) calc for [C$</em>{29}$H$_{24}$F$_3$N$_2$O$_2$ + H]$^+$ 415.14; found: 415.21.</td>
</tr>
</tbody>
</table>
Example 137: Synthesis of N-(4-(3-chlorophenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (18)

![Chemical Structure](image)

**Example 137**

**Step 1:** 6-Amino-4-(3-chlorophenylamino)-7-ethoxyquinoline-3-carbonitrile (17)
Compound 17 was prepared according to a similar procedure as described for Compound 2 (example 1) beginning with the compound described as Example 127. Compound 17 was used without further purification.

Step 2: N-(4-(3-Chlorophenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (18)

\[
\text{HNMR (400 MHz, Methanol-d}_4\text{) } \delta 9.10 (s, 1H), 8.78 (s, 1H), 7.52 - 7.44 (m, 3H), 7.43 (s, 1H), 7.38 (dt, } J = 7.5, 1.8 \text{ Hz, 1H}), 4.39 (q, } J = 7.0 \text{ Hz, 2H), 3.28 - 3.20 (m, 2H), 2.92 (s, 6H), 2.74 (t, } J = 6.9 \text{ Hz, 2H), 2.18 - 2.06 (m, 2H), 1.58 (t, } J = 7.0 \text{ Hz, 3H); MS-ESI (m/z) calcd for [C}_{24}\text{H}_{26}\text{C1N}_5\text{O}_2^+ + H]^+ 452.18; found: 452.17.\]

Examples 138-139 were prepared according to a similar procedure as described for example 137:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>^1H NMR (400 MHz, Methanol-d\textsubscript{4}) δ 9.08 (s, 1H), 8.75 (s, 1H), 7.59 - 7.47 (m, 1H), 7.46 - 7.31 (m, 2H), 7.28 - 7.16 (m, 1H), 4.40 (q, } J = 7.8, 7.0 \text{ Hz, 2H), 3.97 (s, 3H), 2.93 (s, 6H), 2.79 - 2.68 (m, 2H), 2.13 (dd, } J = 14.9, 7.7 \text{ Hz, 2H), 1.58 (t, } J = 8.3 \text{ Hz, 3H), 1.40 - 1.29 (m, 2H).}</td>
</tr>
<tr>
<td>139</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>^1H NMR (400 MHz, Methanol-d\textsubscript{4}) δ 9.13 (s, 1H), 8.72 (d, } J = 0.7 \text{ Hz, 1H), 8.53 (d, } J = 5.3 \text{ Hz, 1H), 8.12 (d, } J = 7.9 \text{ Hz, 1H), 7.71 - 7.63 (m, 1H), 7.36 (d, } J = 8.9 \text{ Hz, 2H), 7.17 (d, } J = 2.8 \text{ Hz, 1H), 7.09 (dd, } J = 8.6, 2.7 \text{ Hz, 1H), 5.43 (s, 2H), 4.40 (q, } J = 7.0 \text{ Hz, 2H), 3.31 (dq, } J = 3.2, 1.6 \text{ Hz, 23H), 2.93 (d, } J = 0.8 \text{ Hz, 6H), 2.74 (t, } J = 6.9 \text{ Hz, 2H), 2.53 (s, 3H), 2.32 (s, 3H), 2.14 (q, } J = 7.4 \text{ Hz, 2H), 1.58 (t, } J = 7.0 \text{ Hz, 3H); MS-ESI (m/z) calcd for [C}<em>{25}\text{H}</em>{29}\text{N}_5\text{O}_3^+ + H]^+ 448.23; found: 277.83.}</td>
</tr>
</tbody>
</table>
Example 140: Synthesis of 4-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino)-7-ethoxy-6-(methylamino)quinoline-3-carbonitrile (20)

[00173] To a stirred suspension of 6-amino-4-((3-chloro-4-(pyridin-2-ylmethoxy)phenyl)amino)-7-ethoxyquinoline-3-carbonitrile (19) (30 mg, 0.067 mmol) and sodium bicarbonate (6 mg, 0.07 mmol) in DMF (0.75 mL) is added iodomethane (11 mg, 0.08 mmol) and the reaction is stirred at room temperature. After 2 h, the reaction is stopped with the addition of water (2 mL) and extracted into CH₂Cl₂ (2 × 2 mL). The combined organic layer is washed with brine and evaporated. The resulting crude residue is purified by automatic flash column chromatography (2% to 8% methanol in CH₂Cl₂) to give 4-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino)-7-ethoxy-6-(methylamino)quinoline-3-carbonitrile (20) (1.8 mg, 6%) as a yellow solid.

H NMR (400 MHz, Methanol-d₄) δ 8.58 (d, J = 5.3 Hz, 1H), 8.26 (s, 1H), 7.96 - 7.89 (m, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.44 - 7.37 (m, 2H), 7.25 - 7.13 (m, 3H), 7.02 (s, 1H), 5.31 (s, 2H), 4.30 (q, J = 7.0 Hz, 2H), 2.95 (s, 3H), 1.55 (t, J = 6.9 Hz, 3H); MS-ESI (m/z) calcd for [C₂₅H₂₂ClN₂O₂ + H]⁺ 460.15; found: 230.55 (z = 2).

[00174] Examples 141-142 were prepared according to a similar procedure as described for example 140:

<table>
<thead>
<tr>
<th>Ex.</th>
<th>Structure</th>
<th>Analytical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>141</td>
<td><img src="image1" alt="Structure" /></td>
<td>'H NMR (400 MHz, CDCl₃) δ 8.60 (d, J = 4.8 Hz, 1H), 7.88 - 7.66 (m, 3H), 7.55 (s, 1H), 7.39 (dd, J = 11.7, 7.0 Hz, 3H), 7.22 (d, J = 7.5 Hz, 3H), 7.05 (d, J = 2.5 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 6.81 (dd, J = 8.3, 2.5 Hz, 1H), 6.50 (s, 1H), 5.30 (s, 2H), 5.16 (s, 2H), 3.90 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 6.9 Hz, 3H); MS-ESI (m/z) calcd for [C₁₉H₁₅ClN₂O₂ + H]⁺ 356.18; found: 268.68 (z = 2).</td>
</tr>
<tr>
<td>142</td>
<td><img src="image2" alt="Structure" /></td>
<td>'H NMR (400 MHz, CDCl₃) δ 8.59 (dt, J = 4.8, 1.4 Hz, 1H), 7.91 - 7.64 (m, 3H), 7.57 (s, 1H), 7.46 - 7.05 (m, 13H), 6.99 - 6.81 (m, 2H), 6.54 (s, 1H), 5.30 (s, 2H), 5.21 (s, 2H), 4.70 (s, 1H), 4.47 (s, 2H), 3.93 (q, J = 7.0 Hz, 2H), 1.33 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C₁₉H₁₃ClN₂O₄ + H]⁺ 626.23; found: 313.67 (z = 2).</td>
</tr>
</tbody>
</table>
Example 143: Synthesis of $N$-(4-(3-chloro-4-(3-methylpyridin-2-yl)oxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (22)

[00175] Step 1: 2-Chloro-4-(3-methylpyridin-2-yl)oxy)aniline (21)

4-amino-3-chlorophenol (0.5 g, 3.5 mmol) was combined with 2-Fluoro-3-methylpyridine (0.387 g, 3.5 mmol), DMSO (10 mL) and cesium carbonate (1.47 g, 4.17 mmol). The reaction mixture was stirred at 80 °C for 15 h. The reaction was cooled to room temperature and the suspension was filtered. The filtrate partitioned between ethyl acetate (25 mL) and water (20 mL), the organic layer was washed with brine (20 mL), dried over sodium sulfate, and concentrated in vacuum. The resulting was purified by automatic flash column chromatography (1 to 5% methanol in CH$_2$Cl$_2$) yielding the product; $m/z$ of 235.1 (M+1$^+$) was observed. This product was taken to the next step without further characterization.

[00177] Step 2: $N$-(4-(3-chloro-4-(3-methylpyridin-2-yl)oxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (22)

$N$-(4-(3-chloro-4-(3-methylpyridin-2-yl)oxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (22) was prepared by a similar procedure to that described for example 1 by coupling Compound 3 with 2-chloro-4-((3-methylpyridin-2-yl)oxy)aniline (21). $\text{H NMR}$ (400 MHz, Methanol-$d_4$) $\delta$ 9.15 (s, 1H), 8.77 (s, 1H), 8.05 - 7.98 (m, 1H), 7.75 (ddd, $J = 7.4$, 1.9, 1.0 Hz, 1H), 7.57 (d, $J = 8.7$ Hz, 1H), 7.38 (s, 1H), 7.32 (d, $J = 2.6$ Hz, 1H), 7.19 - 7.10
(m, 2H), 4.97 - 4.73 (m, 3H), 4.40 (q, J = 7.0 Hz, 2H), 3.30 - 3.19 (m, 2H), 2.92 (s, 6H), 2.73 (t, J = 6.9 Hz, 2H), 2.33 (s, 3H), 2.18 - 2.06 (m, 2H), 1.57 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C_{30}H_{31}ClN_{6}O_{3} + H]^+ 559.21; found: 280.32 (z = 2).

**Example 144: Synthesis of N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-3-cyanoquinolin-6-yl)-4-(dimethylamino)butanamide (30)**

![Chemical Structure](image)

**[00179]** Step 1: N-(4-((2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)amino)phenyl)acetamide (23)

![Chemical Structure](image)

**[00180]** A suspension of N-(4-aminophenyl)acetamide (5 g, 33.3 mmol) in 100 mL of isopropanol was heated at 50 °C for 10 min at which point 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (6.2 g, 33.3 mmol) was added. The resulting suspension was heated at 80 °C for 1 h before being cooled to room temperature. The solid was filtered, washed well with ether, and dried in vacuo to provide compound 23 (8 g, 78%) as a brown solid that was immediately used in the next step.

**[00181]** Step 2: N-(4-Oxo-1,4-dihydroquinolin-6-yl)acetamide (24)

![Chemical Structure](image)

**[00182]** A suspension of compound 23 (8 g, 26.3 mmol) in 135 mL of diphenyl ether was heated at 240 °C for 18 h. The mixture was cooled to room temperature and filtered. The resulting brown solid was washed with ether and dried in vacuo to provide N-(4-oxo-1,4-dihydroquinolin-6-yl)acetamide (24) (2 g, 37%) as a brown solid that was used without further purification.
Step 3: \(N-\text{(3-bromo-4-oxo-1,4-dihydroquinolin-6-yl)acetamide} \) (25)

To a stirred suspension of compound 24 (2 g, 9.89 mmol) in AcOH (30 mL) was added dropwise a solution of \(\text{Br}_2\) (0.5 mL, 9.89 mmol) over 10 min, the resulting reaction mixture was stirred at rt for 1 h. The resulting solid was collected, washed with cooled EtOH (30 mL), and dried under reduced pressure to give a title compound; mlz of 245.74 (M+1\(^+\)). This product was taken to the next step without further characterization.

Step 4: \(N-\text{(3-cyano-4-oxo-1,4-dihydroquinolin-6-yl)acetamide} \) (26)

Compound 25 (1 g, 3.55 mmol), CuCN (636 mg, 7.11 mmol) and Cul (169 mg, 0.887 mmol) were suspended in DMF (15 mL) under nitrogen. The reaction mixture stirred and heated 130-140 °C for 6 h and then cooled rt. The resulting mixture filtered through a celite pad and celite pad was washed with 50 mL of DMF. The combined filtrate was concentrated. The residue was suspended in 50% EtOH/EtOAc (50 mL), stirred and heated to 70 °C for 1 h. After cooled to room temperature, the resulting solid was collected washed with 50% EtOH/EtOAc (25 mL) and dried at 50 °C to give \(N-\text{(3-cyano-4-oxo-1,4-dihydroquinolin-6-yl)acetamide} \) (26); mlz of 215.1 (M+1\(^+\)). This product was taken to the next step without further characterization.

Step 5: \(N-\text{(4-chloro-3-cyanoquinolin-6-yl)acetamide} \) (27)

\(N-\text{(3-cyano-4-oxo-1,4-dihydroquinolin-6-yl)acetamide} \) (800 mg, 3.52 mmol) was added to 10 mL of thionyl chloride. Three drops of DMF were added, and the mixture was heated at 125 °C for 3 h. The mixture was cooled to room temperature, and the solvent was removed in vacuo. The derived solid was taken up in \(\text{CH}_2\text{Cl}_2\) (50 mL) and poured into saturated \(\text{NaHCO}_3\) (100 mL). The layers were separated, and the aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to provide the title compound; mlz of 245.74 (M+1\(^+\)). This product was used in next step without further purification.
Step 6: N-(4-((2-Chloro-4-((3-methylpyridin-2-yl)methoxy)phenyl)amino)-3-cyanoquinolin-6-yl)acetamide (28)

N-(4-((2-Chloro-4-((3-methylpyridin-2-yl)methoxy)phenyl)amino)-3-cyanoquinolin-6-yl)acetamide (28) was prepared by a similar procedure to that described for example 1 by coupling Compound 27 with Compound 8. 

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ 9.06 (s, 1H), 8.73 (s, 1H), 8.60 (d, $J$ = 4.9 Hz, 1H), 7.96 (td, $J$ = 7.8, 1.8 Hz, 1H), 7.75 (d, $J$ = 7.9 Hz, 1H), 7.58 (d, $J$ = 2.6 Hz, 1H), 7.45 (dd, $J$ = 7.3, 5.0 Hz, 1H), 7.38 (dd, $J$ = 8.7, 2.6 Hz, 1H), 7.35 (s, 1H), 7.28 (d, $J$ = 8.8 Hz, 1H), 5.36 (s, 2H), 2.30 (s, 3H), 2.06 (s, 3H); MS-ESI (m/z) calcd for [C$_{25}$H$_{20}$ClN$_5$O$_2$ + H]$^+$ 458.13; found: 458.1

Step 7: 6-Amino-4-((2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenyl)amino)quinoline-3-carbonitrile (29)

6-Amino-4-((2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenyl)amino)quinoline-3-carbonitrile (29) was prepared by a similar procedure that described in example 1 step 1. The crude 6-amino-4-((2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenyl)amino)quinoline-3-carbonitrile (29) was taken on to the next step without further purification.

Step 8: N-(4-(2-Chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-3-cyanoquinolin-6-yl)-4-(dimethylamino)butanamide (30)
Example 145: Synthesis of N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-7-ethoxy-3-formylquinolin-6-yl)-4-(dimethylamino)butanamide (31)

Diisobutylaluminium hydride solution (0.1 mL of 2 M solution in hexane) was added drop wise over a period of 5 min to a vigorously stirred solution of N-(4-((2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)butanamide (example 25) (50 mg, 0.08 mmol) in anhydrous dichloromethane (10 mL) under nitrogen at -78 °C. After the mixture was stirred for an additional 30 min. excess reagent was quenched by addition of methanol (1 mL) followed by 5% HCl (5 mL). The resulting mixture was allowed to warm to rt and the organic layer was removed. The aqueous layer was extracted with dichloromethane (10 mL), the combined organic layers, washed with brine (10 mL), dried over anhydrous Na2SO4 and the solvent was evaporated under vacuum, to afford the crude aldehyde which was purified by prep-HPLC to N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-7-ethoxy-3-formylquinolin-6-yl)-4-(dimethylamino)butanamide (31). H NMR (400 MHz, Methanol-d4) δ 10.00 (s, 1H), 9.03 (s, 1H), 8.68 (s, 1H), 8.48 (d, J = 4.9 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.55 - 7.40 (m, 3H), 7.35 (s, 1H), 7.21 (dd, J = 8.8, 2.8 Hz, 1H), 5.36 (s, 2H), 4.92 (d, J = 8.4 Hz, 1H), 4.39 (q, J = 7.0 Hz, 2H), 3.19 - 3.10 (m, 2H), 2.87 (s, 6H), 2.62 - 2.46 (m, 5H), 1.98 (dt, J = 15.1, 6.9 Hz, 2H), 1.55 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C19H20ClN5O2 + H]+ 576.23; found: 576.29.
Example 146: Synthesis of N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-7-ethoxyquinazolin-6-yl)-4-(dimethylamino)butanamide (36)

[00196] Step 1: 4-Chloro-7-ethoxy-6-nitroquinazoline (33)

[00197] A suspension of 7-ethoxy-6-nitro-1,8a-dihydroquinazolin-4(4aH)-one (32) (314 mg, 1.34 mmol) in POCl₃ (15 mL) was heated to reflux for 1 h. The clear solution was then evaporated by N₂ stream and the residue was dissolved in CH₂Cl₂ and washed with aqueous NaHCO₃. The organic layer was dried and the solvent removed to obtain 4-chloro-7-ethoxy-6-nitroquinazoline (33); H NMR (CDCl₃, 400 MHz) δ 9.07 (s, 1H), 8.62 (s, 1H), 7.54 (s, 1H), 4.37 (q, J = 7.0 Hz, 2H), 1.57 (t, J = 7.0 Hz, 3H).

[00198] Step 2: N-(4-Oxo-1,4-dihydroquinolin-6-yl)acetamide (34)

[00199] 4-Chloro-7-ethoxy-6-nitroquinazoline (33) (100 mg, 0.214 mmol) and compound 8 (98 mg, 0.395 mmol) in i-PrOH (16 mL) were heated to reflux and cone HCl (3 drops) was added. The mixture was stirred and refluxed for 6 h and then basified by addition of Et₃N. The solvent was removed under reduced pressure, the solid residue was dissolved in Et₂O and filtered, then the solvent was removed under reduced pressure and the residue was further dissolved in AcOEt and washed with H₂O. The organic layer was evaporated to dryness to give N-(4-Oxo-1,4-dihydroquinolin-6-yl)acetamide (34) that was used in the next step without further purifications.
[00200] Step 3: A^-{(2-Chloro-4-((3-methylpyridin-2-yl)methoxy)phenyl)-7-ethoxyquinazoline-4,6-diamine (35)

\[
\begin{align*}
\text{34} & \quad \text{O}_2\text{N} \quad \text{EtO} \\
\text{H} & \quad \text{HN} \\
\text{35} & \quad \text{H}_2\text{N} \\
\end{align*}
\]

[00201] N-(4-Oxo-1,4-dihydroquinolin-6-yl)acetamide (34) (100 mg, 1.00 mmol) was dissolved in acetone/saturated aqueous NH_4Cl (5 mL each) at room temperature. Zinc nanopowder (42 mg, 0.643) was added, and the mixture was stirred vigorously for 30 min. The mixture was diluted with EtOAc (50 mL) and filtered to remove the Zn salts. The organic phase was washed with saturated aqueous NaHCO_3 (20 mL) and saturated aqueous NaCl (10mL). The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated to obtain N^4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenyl)-7-ethoxyquinazoline-4,6-diamine (35).

[00202] Step 4: N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-7-ethoxyquinazolin-6-yl)-4-(dimethylamino)butanamide (36)

\[
\begin{align*}
\text{35} & \quad \text{Cl} \\
\text{36} & \quad \text{N} \\
\end{align*}
\]

[00203] N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)-7-ethoxyquinazolin-6-yl)-4-(dimethylamino)butanamide (36) was prepared according to a similar procedure as described for example 95. H NMR (400 MHz, Methanol-^\text{d}) \delta 9.17 (s, 1H), 8.62 (s, 1H), 8.50 (d, J = 5.0 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.60 - 7.46 (m, 2H), 7.40 (d, J = 2.8 Hz, 1H), 7.29 (s, 1H), 7.21 (dd, J = 8.9, 2.8 Hz, 1H), 5.39 (s, 2H), 4.42 (q, J = 7.0 Hz, 2H), 3.32 - 3.23 (m, 2H), 2.95 (s, 6H), 2.76 (t, J = 6.9 Hz, 2H), 2.52 (s, 3H), 2.15 (dt, J = 15.1, 7.1 Hz, 2H), 1.60 (t, J = 7.0 Hz, 3H); MS-ESI (m/z) calcd for [C_{29}H_{33}CIN_6O_3 + H]^+ 549.23; found: 549.2.
Example 147: Synthesis of N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)quinolin-6-yl)-4-(dimethylamino)butanamide

\[ \text{N-(4-(2-chloro-4-((3-methylpyridin-2-yl)methoxy)phenylamino)quinolin-6-yl)-4-(dimethylamino)butanamide (147) was prepared according to a similar procedure as described for example 144.} \]

\[
\begin{align*}
\text{H NMR} & \quad (400 \text{ MHz, Methanol-}^d) & \delta & \quad 8.87 (d, J = 2.0 \text{ Hz, } 1\text{H}), \quad 8.52 (d, J = 5.3 \text{ Hz, } 1\text{H}), \quad 8.32 (dd, J = 7.0, 1.8 \text{ Hz, } 1\text{H}), \quad 8.06 - 7.95 \text{ (m, } 2\text{H}), \quad 7.91 (dd, J = 9.2, 1.7 \text{ Hz, } 1\text{H}), \quad 7.65 - 7.55 \text{ (m, } 2\text{H}), \quad 7.52 - 7.38 \text{ (m, } 2\text{H}), \quad 6.82 (dd, J = 6.9, 1.8 \text{ Hz, } 1\text{H}), \quad 5.49 - 5.44 \text{ (m, } 2\text{H}), \quad 3.32 - 3.21 \text{ (m, } 7\text{H}), \quad 2.96 - 2.91 \text{ (m, } 6\text{H}), \quad 2.67 (td, J = 7.0, 1.7 \text{ Hz, } 2\text{H}), \quad 2.59 - 2.53 \text{ (m, } 3\text{H}), \quad 2.20 - 2.07 \text{ (m, } 2\text{H}); \quad \text{MS-ESI} \quad (m/z) \quad \text{calcd for [C}_{28}\text{H}_{30}\text{ClN}_5\text{O}_2+H]^+ \quad 504.21; \quad \text{found: 504.2.}
\end{align*}
\]

Example 148: Synthesis of 1-(4-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-3-cyclohexylurea (37)

\[
\text{To a stirred solution of 6-amino-4-((3-chloro-4-(pyridin-2-ylmethoxy)phenyl)amino)-7-ethoxyquinoline-3-carbonitrile (19) and DIPEA (31 mg, 0.23 mmol) in THF (0.75 mL) is added cyclohexyl isocyanate (0.05 mL) and the reaction is stirred at room temperature for 2 days. At this point, the reaction is evaporated and purified by preparative HPLC (10\% to 60\% MeCN in water, +0.1\% TFA). The starting material is reisolated as well as a very minor peak corresponding to the desired product, yielding 0.8 mg (2\%) of 1-(4-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-3-cyclohexylurea (37) as a solid.} \]

\[
\begin{align*}
\text{H NMR} & \quad (400 \text{ MHz, Methanol-}^d) & \delta & \quad 8.99 (s, 1\text{H}), \quad 8.73 (s, 1\text{H}), \quad 8.59 (d, J = 5.0 \text{ Hz, } 1\text{H}), \quad 7.96 (td, J = 7.8, 1.8 \text{ Hz, } 1\text{H}), \quad 7.75 (d, J = 8.0 \text{ Hz, } 1\text{H}), \quad 7.59 (d, J = 2.5 \text{ Hz, } 1\text{H}), \quad 7.47 - 7.42 \text{ (m, } 1\text{H}), \quad 7.39 (dd, J = 8.7, 2.6 \text{ Hz, } 1\text{H}), \quad 7.31 - 7.26 \text{ (m, } 2\text{H}), \quad 5.36 (s, 2\text{H}), \quad 4.40 (q, J = 7.0 \text{ Hz, } 2\text{H}), \quad 3.70 - 3.55 \text{ (m, } 1\text{H}), \quad 2.01 - 1.90 \text{ (m, } 2\text{H}), \quad 1.82 - 1.70 \text{ (m, } 2\text{H}), \quad 1.61 (t, J = 6.9 \text{ Hz, } 3\text{H}), \quad 1.47 - 1.34 \text{ (m, } 2\text{H}), \quad 1.34 - 1.20 \text{ (m, } 4\text{H}).
\end{align*}
\]
Example 149: MST1/MST2 Biochemical LanthaScreen Eu kinase binding assay

MST1 and MST2 biochemical LanthaScreen Eu Kinase Binding Assay was based on the binding and displacement of kinase tracer to the kinase of interest. Compounds in 1000X DMSO stock solution was dispensed using automated dispensing system (Labcyte) to 384 well Corning Microplate at 15nL, 5uL of Kinase buffer A was added to each well. Plates were shaken and incubated for 1min to ensure well dissolution of compounds. Kinase/Antibody mixture was added at a final concentration of 5nM and 2nM and kinase tracer 222 solution at a final concentration of 100nM in a total volume of 20 uL. Plates were incubated for 1.5hrs in dark at room temperature and assay plates were scanned on Envision plate reader with excitation:

340nM and kinase Tracer Emission at 665nM. IC50 data is shown in Table 1.

Table 1 - MST1/EGFR/MAP4K4 Binding Assays

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<td>Kinase Binding assay- MST1 IC₅₀ (nM)</td>
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A = IC_{50} less than 100 nM; B = IC_{50} greater than or equal to 100 nM and less than 1 µM; C = IC_{50} greater than or equal to 1 µM and less than 10 µM; NT = not tested

**Example 150: Nucview488 cell based assay**

[N00207] Nucview488 cell based assay was carried out in INS1 beta cells, using a membrane-permeable fluorogenic caspase substrate to detect caspase-3/7 activity in living cells without inhibiting activity of the caspase. Compounds in 1000X DMSO stock solution was dispensed using automated dispensing system (Labcyte) to 384 well Corning Microplate at 25nL, cells were added to the assay plate at 10k cells/well in 25uL of the completed growth media, 24 hours later, Nucview488 substrate/Thapsigargin mixture in cell growth media was added to a final concentration of 1uM and 25nM, respectively at 25uL total volume. 16 hours later, cells were fixed with 3% PFA and stained with 0.2ug/mL Hoechst33342 and plates were scanned and fluorescence was detected and qualified through imaging software Cellomics.

**Example 151: Neratinib inhibits high glucose/palmitate induced apoptotic activity in beta cells**

[N00208] Freshly isolated human islets from a single donor were exposed to high glucose and palmitate (HG/Pal) to induce apoptosis. Phosphorylated MST1 (pMST1) and cleaved caspase 3 (CI Casp3) was readily induced under these conditions, indicating apoptotic activity was triggered by the treatment (FIG. 8, Lane 4). However, MST1 phosphorylation and induction of cleaved caspase 3 was inhibited by 25 µM neratinib, indicating neratinib anti-apoptotic activity (FIG. 8, Lane 6).

**Example 152: Neratinib inhibits cytokine induced apoptotic activity in beta cells**

[N00209] Freshly isolated human islets from a single donor were stressed with a combination of proinflammatory cytokines interleukin 1 beta (IL-1β) and interferon gamma (IFN-γ). Islets exhibited an increase in MST1 phosphorylation and strong increase in Caspase 3 cleavage (CI Casp3) (FIG. 9, lane 4). Both 10 µM and 25 µM neratinib treatment inhibited MST1 phosphorylation and Caspase 3 cleavage (FIG. 9, lanes 5 and 6).
What is claimed is:

1. A method of treating a metabolic condition in a subject comprising administering to the subject a compound that modulates an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof.

2. The method of claim 1, wherein the metabolic condition is diabetes mellitus.

3. The method of claim 2, wherein the metabolic condition is type 1 diabetes mellitus.

4. The method of claim 2, wherein the metabolic condition is type 2 diabetes mellitus.

5. The method of any one of claims 1-4, wherein the compound inhibits the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof.

6. The method of claim 5, wherein the activity is selected from a phosphorylation activity, an inflammatory activity, a cleavage activity, an apoptotic activity, a ubiquitinating activity, a mitochondrial activity, and combinations thereof.

7. The method of any one of claims 1-4, wherein the compound inhibits phosphorylation of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof.

8. The method of claim 7, wherein the protein downstream is selected from a transcription factor, a kinase, and a histone.

9. The method of claim 8, wherein the transcription factor is pancreatic and duodenal homeobox 1 (PDX-1) or a homolog thereof.

10. The method of claim 8, wherein the histone is histone 2B (H2B).

11. The method of claim 8, wherein the kinase is a Janus kinase (INK).

12. The method of any one of claims 1-4, wherein the compound inhibits cleavage of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof.

13. The method of claim 12, wherein the protein downstream is a caspase.
14. The method of claim 13, wherein the caspase is selected from caspase 9, caspase 3 and MST1.

15. The method of any one of claims 1-4, wherein the compound inhibits apoptotic activity of a protein downstream of the activity of the mammalian sterile 20-like kinase 1, the cleaved product thereof, or the homolog thereof.

16. The method of claim 15, wherein the protein downstream is selected from INK, Bim, Bax, Bcl-2, homologs thereof, and combinations thereof.

17. A method of treating an inflammatory condition in a subject comprising administering to the subject a compound that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof.

18. A method of treating an autoimmune disorder in a subject comprising administering to the subject a compound that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof.

19. A method for use in liver, corneal, or skin regeneration in a subject comprising administering to the subject a compound that inhibits an activity of a mammalian sterile 20-like kinase 1 (MST1), a cleaved product thereof, or a homolog thereof.

20. The method of any one of claims 1-19, wherein the compound is a compound of Formula (I) having the structure:

![Formula (I)](image-url)

wherein:

- 
- is a single or double bond;
- X is -O-, -N(H)-, or -CH₂-;
- R¹ and R² are each independently C₁-alkyl; or R¹ and R² together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;
- R³ is C₁-alkyl;
- each R⁴ is independently halogen, C₁-alkyl, C₁-alkoxy, C₁-haloalkyl, or -CN;
R^5 is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted by one or more substituents selected from halogen, Ci-6alkyl, Ci-6alkoxy, Ci-6haloalkyl, Ci.

eh haloalkoxy, -OH, -CH_2OH, -CN, -CO_2R^6, C_3-6cycloalkyl, and phenyl;

R^6 is H or Ci_6alkyl;

n is 0, 1, 2, or 3; and

p is 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

21. The method of claim 20, wherein p is 1.

22. The method of claim 20 or claim 21, wherein n is 1 or 2.

23. The method of any one of claims 20-22, wherein each R^4 is independently halogen or Ci.

24. The method of any one of claims 20-23 having the structure of Formula (la):

\[\text{Formula (la).}\]

25. The method of any one of claims 20-23 having the structure of Formula (lb):

\[\text{Formula (lb).}\]

26. The method of any one of claims 20-25, wherein R^1 and R^2 are each independently Ci_6alkyl.

27. The method of any one of claims 20-26, wherein R^1 and R^2 are each -CH_3.

28. The method of any one of claims 20-25, wherein R^1 and R^2 together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring.
29. The method of any one of claims 20-28, wherein R^5 is heteroaryl and wherein heteroaryl is unsubstituted or substituted by one or more substituents selected from halogen, C_ialkyl, C_ialkoxy, C_ihaloalkyl, C_i-haloalkoxy, -OH, -CH_2OH, -CN, -CO_2R^6, C_3cycloalkyl, and phenyl.

30. The method of claim 29, wherein R^5 is unsubstituted pyridyl.

31. The method of claim 29, wherein R^5 is pyridyl substituted by one substituent selected from halogen, C_ialkyl, C_ialkoxy, C_i-haloalkyl, C_i-haloalkoxy, -OH, -CH_2OH, -CN, -CO_2R^6, C_3cycloalkyl, and phenyl.

32. The method of claim 31, wherein R^5 is pyridyl substituted by C_ialkyl.

33. The method of claim 32, wherein R^5 is pyridyl substituted by -CH_3.

34. The method of any one of claims 20-28, wherein R^5 is aryl and wherein aryl is unsubstituted or substituted by one or more substituents selected from halogen, C_ialkyl, C_ialkoxy, C_i-haloalkyl, C_i-haloalkoxy, -OH, -CH_2OH, -CN, -CO_2R^6, C_3cycloalkyl, and phenyl.

35. The method of claim 34, wherein R^5 is unsubstituted phenyl.

36. The method of claim 34, wherein R^5 is phenyl and wherein phenyl is substituted by one substituent selected from halogen, C_ialkyl, C_ialkoxy, C_i-haloalkyl, C_i-haloalkoxy, -OH, -CH_2OH, -CN, -CO_2R^6, C_3cycloalkyl, and phenyl.

37. The method of any one of claims 20-36, wherein R^4 is halogen or C_ialkyl.

38. The method of any one of claims 20-36, wherein R^4 is halogen.

39. The method of any one of claims 20-36, wherein R^4 is -Cl.

40. The method of any one of claims 20-39, wherein X is -O-.

41. The method of any one of claims 20-39, wherein X is -N(H)-.

42. The method of any one of claims 20-39, wherein X is -CH_2-.

43. The method of any one of claims 20-42, wherein R^3 is -CH_2CH_3.

44. The method of any one of claims 20-43, wherein is a single bond.

45. The method of any one of claims 20-43, wherein is a double bond.
46. The method of any one of claims 1-19, wherein the compound is selected from:
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

47. The method of any one of claims 1-19, wherein the compound is neratinib.

48. A method of treating a metabolic condition in a subject comprising administering neratinib to the subject.
49. A method of treating diabetes mellitus in a subject comprising administering neratinib to the subject.

50. A compound of Formula (II) having the structure:

![Formula (II)](attachment)

wherein:

- \( X \) is -0-, -N(H)-, or -CH\(_2\)-;
- \( R^1 \) and \( R^2 \) are each independently \( C_{1-6}\)alkyl; or \( R^1 \) and \( R^2 \) together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring;
- \( R^3 \) is \( C_{1-6}\)alkyl;
- each \( R^4 \) is independently halogen, \( C_{1-6}\)alkyl, \( C_{1-6}\)alkoxy, \( C_{1-6}\)haloalkyl, or -CN;
- \( R^5 \) is aryl or heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one or more substituents selected from halogen, \( C_{1-6}\)alkyl, \( C_{1-6}\)alkoxy, \( C_{1-6}\)haloalkyl, \( C_i \)ehaloalkoxy, -OH, -CH\(_2\)OH, -CN, -C\(_2\)R\(_6\), C\(_3\)alkyl, cycloalkyl, and phenyl;
- \( R^6 \) is H or \( C_{1-6}\)alkyl;
- \( n \) is 0, 1, 2, or 3; and
- \( p \) is 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

51. The compound of claim 50, wherein \( p \) is 1.

52. The compound of claim 50 or claim 51, wherein \( n \) is 1 or 2.

53. The compound of any one of claims 50-52, wherein each \( R^4 \) is independently halogen or \( C_{1-6}\)alkyl.

54. The compound of any one of claims 50-53 having the structure of Formula (Ila):
55. The compound of any one of claims 50-53 having the structure of Formula (Iia):

![Formula (Iia).]

56. The compound of any one of claims 50-55, wherein R₁ and R₂ are each independently C₆alkyl.

57. The compound of any one of claims 50-56, wherein R₁ and R₂ are each -CH₃.

58. The compound of any one of claims 50-55, wherein R₁ and R₂ together with the nitrogen to which they are attached are combined to form a heterocycloalkyl ring.

59. The compound of any one of claims 50-58, wherein R₅ is heteroaryl and wherein heteroaryl is unsubstituted or substituted with one or more substituents selected from halogen, C₆alkyl, C₆alkoxy, C₆haloalkyl, C₆haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R₆, C₃,₆cycloalkyl, and phenyl.

60. The compound of claim 59, wherein R₅ is unsubstituted pyridyl.

61. The compound of claim 59, wherein R₅ is pyridyl substituted by one substituent selected from halogen, C₆alkyl, C₆alkoxy, C₆haloalkyl, C₆haloalkoxy, -OH, -CH₂OH, -CN, -CO₂R₆, C₃,₆cycloalkyl, and phenyl.

62. The compound of claim 61, wherein R₅ is pyridyl substituted by C₆alkyl.

63. The compound of claim 62, wherein R₅ is pyridyl substituted by -CH₃.
64. The compound of any one of claims 50-58, wherein R⁵ is aryl and wherein aryl is unsubstituted or substituted with one or more substituents selected from halogen, Cᵢ₆alkyl, Cᵢ₆alkoxy, Cᵢ₆haloalkyl, Cᵢ₆ehaloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃₋₆cycloalkyl, and phenyl.

65. The compound of claim 64, wherein R⁵ is unsubstituted phenyl.

66. The compound of claim 64, wherein R⁵ is phenyl and wherein phenyl is substituted by one substituent selected from halogen, Cᵢ₆alkyl, Cᵢ₆alkoxy, Cᵢ₆haloalkyl, Cᵢ₆ehaloalkoxy, -OH, -CH₂OH, -CN, -CO₂R⁶, C₃₋₆cycloalkyl, and phenyl.

67. The compound of any one of claims 50-66, wherein R⁴ is halogen or Cᵢ₆alkyl.

68. The compound of any one of claims 50-66, wherein R⁴ is halogen.

69. The compound of any one of claims 50-66, wherein R⁴ is -Cl.

70. The compound of any one of claims 50-69, wherein X is -0-.

71. The compound of any one of claims 50-69, wherein X is -N(H)-.

72. The compound of any one of claims 50-69, wherein X is -CH₂-.

73. The compound of any one of claims 50-72, wherein R³ is -CH₂CH₃.

74. A compound, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, selected from:
75. A pharmaceutical composition comprising a compound of any one of claims 50-74, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a pharmaceutically acceptable excipient.

76. A method of treating cancer in a subject comprising administering to the subject a compound of any one of claims 50-74, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.
FIG. 6

Glucose (mg/dL)

~56% normalized

CONTROL  STZ  STZ + DRUG

FIG. 7

Insulin (ng/mL)

-100% increase

CONTROL  STZ  STZ + DRUG
FIG. 8

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pMST1

Cl Casp3

Actin

FIG. 9

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pMST1

Cl Casp3

Actin
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

**IPC (8)** - A61 K 31/4725; A61 K 31/47; A61 K 31/4709; A61 K 31/496; C12N 9/12 (2016.01)

**CPC** - A61K 31/4725; A61K 31/47; A61K 31/4709; A61K 31/496; C12N 9/12 (2016.08)

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)

**IPC** - A61 K 31/47; A61 K 31/4709; A61 K 31/4725; A61 K 31/496; C12N 9/12 (2016.01)

**CPC** - A61 K 31/47; A61 K 31/4709; A61 K 31/4725; A61 K 31/496; C12N 9/12 (2016.08)

**USPC** - 424/133.1; 514/210; 18; 514/218; 514/228.2; 514/303; IPC(8) - A61 K 31/47; A61 K 31/4709; A61 K 31/4725; A61 K 31/496; C12N 9/12; CPC - A61 K 31/47; A61K 31/4709; A61K 31/4725; A61K 31/496; C12N 9/12 (keyword delimited)

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

**USPC** - 424/133.1; 514/210; 18; 514/218; 514/228.2; 514/303; IPC(8) - A61 K 31/47; A61 K 31/4709; A61 K 31/4725; A61 K 31/496; C12N 9/12; CPC - A61 K 31/47; A61K 31/4709; A61K 31/4725; A61K 31/496; C12N 9/12 (keyword delimited)

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

Orbit, Google Patents, Google Scholar, PubChem

Search terms used: neratinib, metabolic, kinase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>WO 2014/187964 A2 (UNIVERSITY OF BREMEN) 27 November 2014 (27.11.2014) entire document</td>
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Further documents are listed in the continuation of Box C.

Special categories of cited documents:

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

**E** earlier application or patent but published on or after the international filing date

**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)

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

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

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

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

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

**Z** document member of the same patent family

Date of the actual completion of the international search

11 August 2016

Date of mailing of the international search report

08 SEP 2016

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA-US, Commissioner for Patents

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Form PCT/ISA/210 (second sheet) (January 2015)
### Box No. II  Observations where certain claims were found unseachable (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:

2. □ Claims Nos.:
   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:

3. ☑ Claims Nos.: 20-47, 53-73, 75, 76
   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.