The invention is directed to Compounds of Formula 1 and pharmaceutically acceptable salts or solvates thereof, as well as methods of treating using the compounds, methods for screening for inhibitor compounds and methods for identifying treatment regimens.
CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 61/413,972, filed November 15, 2010, which is incorporated herein by reference.

SEQUENCE LISTING

[0002] This application incorporates by reference in its entirety the Sequence Listing entitled "10-027_SequenceListing.txt" (14.5 KB) which was created November 15, 2011 and filed herewith on November 15, 2011.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] This invention relates to the field of protein kinases and inhibitors thereof. In particular, the invention relates to inhibitors of Phosphatidylinositol 3-kinase (PI3Kα) signaling pathways, screening assays to identify PI3Kα selective inhibitors, and methods for treating cancer patients with PI3Kα selective inhibitors, PI3Kβ selective inhibitors, mammalian target of rapamycin (mTOR) kinase inhibitors and combinations thereof.

Background of the Invention

[0004] Phosphatidylinositol 3-kinases (PI 3-kinases or PI3Ks) are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. PI3Ks are a family of related intracellular signal transducer enzymes capable of phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns). Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by PI3KCA gene represents the catalytic subunit, which uses ATP to phosphorylate phosphatidylinositol (PtdIns), PtdIns4P and PtdIns(4,5)P2.

[0005] Phosphatidylinositol 3-kinase (PI3Ka), a dual specificity protein kinase, is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by this gene represents the catalytic subunit, which uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. PTEN, a tumor suppressor which inhibits cell growth through multiple mechanisms, can dephosphorylate PIP3, the major product of PI3KCA.
PIP3, in turn, is required for translocation of protein kinase B (AKT1, PKB) to the cell membrane, where it is phosphorylated and activated by upstream kinases. The effect of PTEN on cell death is mediated through the PI3KCA/AKT1 pathway.


[0007] The mammalian target, mTOR, is a protein kinase that integrates both extracellular and intracellular signals of cellular growth, proliferation, and survival. Extracellular mitogenic growth factor signaling from cell surface receptors and intracellular pathways that convey hypoxic stress, energy and nutrient status all converge at mTOR. mTOR exists in two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is a key mediator of transcription and cell growth (via its substrates p70S6 kinase and 4E-BP1) and promotes cell survival via the serum and glucocorticoid-activated kinase SGK, whereas mTORC2 promotes activation of the pro-survival kinase AKT. Given its central role in cellular growth, proliferation and survival, it is perhaps not surprising that mTOR signaling is frequently dysregulated in cancer and other diseases (Bjornsti and Houghton Rev Cancer 2004, 4(5), 335-48; Houghton and Huang Microbiol Immunol 2004, 279, 339-59; Inoki, Corradetti et al. Nat Genet 2005, 37(1), 19-24).
mTOR is a member of the PIKK (PI3K-related Kinase) family of atypical kinases which includes ATM, ATR, and DNAPK, and its catalytic domain is homologous to that of PI3K. Dyregulation of PI3K signaling is a common function of tumor cells. In general, mTOR inhibition may be considered as a strategy in many of the tumor types in which PI3K signaling is implicated such as those discussed below.


Brief Description of the Drawings

[0010] FIG. 1 depicts Western Blots used to determine IC\textsubscript{50} of a PI3K-a selective compound measuring PI3K pathway inhibition in two distinct cell lines harboring two different genetic PI3K-a mutations.

[0011] FIG. 2A depicts a graph measuring PI3K pathway inhibition of a PI3K-a selective compound in PIK3CA H1047R models and in PIK3CA E545L models.
[0012] FIG. 2B depicts a graph measuring PI3K pathway inhibition of a dual PI3K-
(x/mTOR selective compound in PIK3CA H1047R models and in PIK3CA E545L models.

[0013] FIG. 2C depicts a graph measuring PI3K pathway inhibition of a PI3K-a
selective compound in PIK3CA H1047R models and in PIK3CA E545L models.

[0014] FIG. 2D depicts a graph measuring PI3K pathway inhibition of a dual PI3K-
a/mTOR selective compound in PIK3CA H1047R models and in PIK3CA E545L models.

[0015] FIG. 3A depicts a graph illustrating the effects of PI3K-β selective compound on
the inhibition of PI3K pathway inhibition by a PI3K-a selective compound in a cell line
harboring a PI3K-a mutation (E545K).

[0016] FIG. 3B depicts a graph illustrating the effects of PI3K-β selective compound on
the inhibition of PI3K pathway inhibition by a PI3K-a selective compound in a cell line
harboring a wild-type PI3K-a.

[0017] FIG. 3C depicts a graph illustrating the effects of PI3K-β selective compound on
the inhibition of PI3K pathway inhibition by a PI3K-a selective compound in a cell line
harboring a PI3K-a mutation (H1047R).

[0018] FIG. 4A depicts a bar chart representing the effect a PI3K-β selective compound
has on PI3K pathway inhibition in various cell lines in the presence of a PI3K-a selective
compound.

[0019] FIG. 4B depicts a bar chart representing the effect a PI3K-β selective compound
has on PI3K pathway inhibition in various cell lines in the presence of a PI3K-a selective
compound.

[0020] FIG. 4C depicts a bar chart representing the effect a PI3K-β selective compound
has on PI3K pathway inhibition in various cell lines in the presence of a PI3K-a selective
compound.

[0021] FIG. 4D depicts a bar chart representing the effect a PI3K-β selective compound
has on PI3K pathway inhibition in various cell lines in the presence of a pan PI3K inhibitor
compound.

SUMMARY OF THE INVENTION

[0022] The following only summarizes certain aspects of the invention and is not
intended to be limiting in nature. These aspects and other aspects and embodiments are
described more fully below. All references cited in this specification are hereby incorporated
by reference in their entirety. In the event of a discrepancy between the express disclosure of
this specification and the references incorporated by reference, the express disclosure of this specification shall control.

[0023] We recognized the important role of PI3K and mTOR in biological processes and disease states and, therefore, realized that inhibitors of these protein kinases would be desirable. Accordingly, the invention provides compounds that inhibit, regulate, and/or modulate PI3K and/or mTOR that are useful in the treatment of hyperproliferative diseases, such as cancer, in mammals. This invention also provides methods of making the compound, methods of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

[0024] The important role of PI3K-a and mTOR in biological processes and disease states was recognized and, therefore, realized that inhibitors of these protein kinases would be desirable. Accordingly, the invention provides treatment methods, methods for selectively screening compounds that are selective towards cancers that are mediated by specific genetic lesions in PI3CA and methods for identifying a treatment regimen for patients with cancer. In other aspects, the present invention provides compounds that inhibit, regulate, and/or modulate PI3K-a and/or mTOR and are useful in the treatment of hyperproliferative diseases, such as cancer, in mammals, for example, humans.

[0025] A first aspect of the invention provides a compound of Formula I:

```
I
```

or a single stereoisomer or mixture of isomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof, where

R⁴ is phenyl optionally substituted with one, two, or three R⁶ groups; or
R⁴ is heteroaryl optionally substituted with one, two, or three R⁷;
R² is -NR³R⁴;
R³ is hydrogen, alkyl, or alkoxycarbonylalkyl; and R⁴ is optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; or
R^3 and R^4 together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10e};

HET is

(a) a saturated or partially unsaturated, but non-aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen where the remaining ring atoms are carbon; or

(b) a partially unsaturated, but not aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and which ring is fused to a benzo ring; or

(c) a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and where each ring of the 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic; or

(d) a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon where each ring of the bicyclic 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic, and where the bicyclic 7- to 11-membered ring is fused to a benzo ring;

R^{5b} and R^{5c} are independently hydrogen or alkyl;

R^{5b} is hydrogen or halo;

R^{5b} is hydrogen, amino, or halo;

R^{5d}, R^{5e}, R^{5f}, and R^{5g} are hydrogen;

each R^{6}, when R^{6} is present, is independently nitro; cyano; halo; alkyl; alkenyl; alkynyl; haloalkyl; -OR^{8a}; -NR^{8a}R^{8a}; -C(0)NR^{8a}R^{8a}; -NR^{8a}C(0)OR^{8a}; -NR^{8a}C(0)R^{8a}; -NR^{8a}S(0)_{2}R^{8a}; -NR^{8a}C(0)NR^{8a}R^{8a}; carboxy, -C(0)OR^{9}; alkylcarbonyl; alkyl substituted with one or two -C(0)NR^{8a}R^{8a}; heteroaryl optionally substituted with 1, 2, or 3 R^{14}; or optionally substituted heterocycloalkyl;
each R^7, when R^7 is present, is independently oxo; nitro; alkyl; alkenyl; alkynyl; halo; haloalkyl; hydroxyalkyl; alkoxyalkyl; alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, or optionally substituted phenyl.

R^8 is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, or haloalkyl;

R^{8a} is hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, cyanoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;

R^9 is alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, or optionally substituted heterocycloalkylalkyl;

R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, and R^{10f} are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy; cyano; alkoxycarbonyl; carboxy; amino; alkylamino; dialkylamino; C(0)R; C(0)NR; optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted heteroaryl; or optionally substituted heteroarylalkyl; or two of R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, and R^{10f} when attached to the same carbon form oxo, imino, or thiono;

R^{11} hydrogen, alkyl, or alkenyl;

R^{11a} hydrogen, alkyl, or alkenyl;

R^{12} is alkyl, or optionally substituted heteroaryl;

R^{13} is alkyl or haloalkyl; and

each R^{14}, when R^{14} is present, is independently amino, alkylamino, dialkylamino, acylamino, halo, hydroxy, alkyl, haloalkyl, hydroxyalkyl, aminealkyl, alkylaminoalkyl, dialkylaminolalkyl, alkoxyacylonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, or optionally substituted phenyl.
In a second aspect, the invention is directed to a pharmaceutical composition which comprises 1) a compound of Formula I or a single stereoisomer or mixture of isomers thereof, optionally as a pharmaceutically acceptable salt thereof and 2) a pharmaceutically acceptable carrier, excipient, or diluent.

In a third aspect of the invention is a method of inhibiting the *in vivo* activity of PI3K and additionally optionally mTOR, the method comprising administering to a patient an effective PI3K-inhibiting and additionally optionally mTOR-inhibiting amount of a Compound of Formula Ia Compound of Formula I or a single stereoisomer or mixture of stereoisomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof or pharmaceutical composition thereof.

In a fourth aspect, the Invention provides a method for treating a disease, disorder, or syndrome which method comprises administering to a patient a therapeutically effective amount of a compound of Formula I or a single stereoisomer or mixture of isomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I or a single stereoisomer or mixture of isomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0026] In a fifth aspect, the Invention provides a method for making a Compound of Formula 1(a) which method comprises

(a) reacting the following intermediate, or a salt thereof:

![Chemical Structure](image)

where X is halo and R¹ is as defined in the Summary of the Invention for a Compound of Formula I; with an intermediate of formula R²H where R² is as defined in the Summary of the Invention for a Compound of Formula I to yield a Compound of the Invention of Formula 1(a)
and optionally separating individual isomers; and optionally modifying any of the $R^1$ and $R^2$ groups; and optionally forming a pharmacetically acceptable salt thereof; or

(b) reacting the following intermediate, or a salt thereof:

![Chemical structure]

where $R$ is halo or -$\text{B(OR')}_2$ (where both $R'$ are hydrogen or the two $R'$ together form a boronic ester), and $R^2$ is as defined in the Summary of the Invention for a Compound of Formula I; with an intermediate of formula $R^1Y$ where $Y$ is halo when $R$ is -$\text{B(OR)}_2$ and $Y$ is -$\text{B(OR')}_2$ when $R$ is halo, and $R^2$ is as defined in the Summary of the Invention for a Compound of Formula I to yield a Compound of the Invention for a Compound of Formula I(a); and optionally separating individual isomers; and optionally modifying any of the $R^1$ and $R^2$ groups; and optionally forming a pharmacetically acceptable salt, hydrate, solvate or combination thereof.

[0027] A sixth aspect of the invention provides a method for treating a subject having a tumor. The method comprises: (a) administering a PI3K-α selective inhibitor, a dual PI3K-α/mTOR selective inhibitor, or a combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor to the subject if said tumor comprises a mutation in a PI3K-α kinase domain; or (b) administering a combination of a PI3K-α selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-α/mTOR selective inhibitor, or aPDK-β selective inhibitor, to said subject if said tumor comprises a mutation in a PI3K-α helical domain.

[0028] In a seventh aspect, the present invention provides a method for identifying a selective inhibitor of a PI3K isozyme, the method comprising: (a) contacting a first cell bearing a first mutation in a PI3K-α with a candidate inhibitor; (b) contacting a second cell bearing a wild type PI3K-α, a PTEN null mutation, or a second mutation in said PI3K-α with the candidate inhibitor; and (c) measuring AKT phosphorylation in said first and said second cells, wherein decreased AKT phosphorylation in said first cell when compared to said second cell identifies said candidate inhibitor as a selective PI3K-α inhibitor.

[0029] In an eighth aspect, the present invention provides for a method for determining a treatment regimen for a cancer patient having a tumor comprising a PI3K-α, the method comprising: determining the presence or absence of a mutation in amino acids 1047 and/or 545 of said PI3K-α; wherein if said PI3K-α has a mutation at position 1047, said method comprises administering to the cancer patient a therapeutically effective amount of a PI3K-α
selective inhibitor compound, or a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor; or wherein if said PI3K-a has a mutation at position 545, said method comprises administering to the cancer patient a therapeutically effective amount of a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, or a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor.

[0030] In still further aspects of the above methods, the cell used to diagnose, treat or screen against includes a cancer or tumor cell obtained from a tumor or cancer derived from: breast cancer, mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B cell lymphoma, rhabdomyosarcoma, ovarian cancer, endometrial cancer, cervical cancer, non-small cell lung carcinoma, small cell lung carcinoma, adenocarcinoma, colon cancer, rectal cancer, gastric carcinoma, hepatocellular carcinoma, melanoma, mantle cell lymphoma, pancreatic cancer, prostate carcinoma, thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, glioblastoma, or head and neck cancer.

[0031] In these and other aspects and as embodied herein, the PI3K-a selective inhibitor, the dual PI3K-a/mTOR selective inhibitor, or the combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor can be a Compound of Formula I and of Table I. The combination variant can alternatively comprise a Compound of Formula I or of Table I with an appropriately active inhibiting agent known to the skilled artisan.

DETAILED DESCRIPTION OF THE INVENTION


Abbreviations and Definitions

[0033] The following abbreviations and terms have the indicated meanings throughout:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>conc</td>
<td>concentrated</td>
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<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>Abbreviation</td>
<td>Meaning</td>
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<tr>
<td>dd</td>
<td>doublet of doublet</td>
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<tr>
<td>dt</td>
<td>doublet of triplet</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIEA or DIPEA</td>
<td>$N,N$-di-isopropyl-$N$-ethyamine</td>
</tr>
<tr>
<td>DMA</td>
<td>$N,N$-dimethylacetamide</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphano)ferrocene</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact ionization</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
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<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>GC/MS</td>
<td>gas chromatography/mass spectrometry</td>
</tr>
<tr>
<td>h or hr</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HATU</td>
<td>2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>L</td>
<td>liter(s)</td>
</tr>
<tr>
<td>LC/MS</td>
<td>liquid chromatography/mass spectrometry</td>
</tr>
<tr>
<td>M</td>
<td>molar or molarity</td>
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<td>m</td>
<td>Multiplet</td>
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<td>mg</td>
<td>milligram(s)</td>
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<td>MHz</td>
<td>megahertz (frequency)</td>
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<td>min</td>
<td>minute(s)</td>
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<td>mol</td>
<td>mole(s)</td>
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<tr>
<td>MS</td>
<td>mass spectral analysis</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl</td>
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<td>N</td>
<td>normal or normality</td>
</tr>
<tr>
<td>nM</td>
<td>Nanomolar</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
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<tr>
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<td>Quartet</td>
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<tr>
<td>quant</td>
<td>quantitative</td>
</tr>
<tr>
<td>r</td>
<td>Room temperature</td>
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<td>s</td>
<td>Singlet</td>
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<tr>
<td>t or tr</td>
<td>Triplet</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
</tbody>
</table>

[0034] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond, "—" means a single or double bond. The symbol "ΛΛΛ" refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, E- or Z-, of the double bond is ambiguous. When a group is depicted removed from its parent Formula, the "〜" symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural Formula.

[0035] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual Formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, -CH₂CH₂-. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.
If a group "R" is depicted as "floating" on a ring system, as for example in the Formula:

\[
\begin{array}{c}
\text{Br} \\
\text{H}
\end{array}
\]

then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

If a group "R" is depicted as floating on a fused or bridged ring system, as for example in the Formula:

\[
\begin{array}{c}
\text{R} \\
\text{H}
\end{array}
\]

then, unless otherwise defined, a substituent "R" may reside on any atom of the fused or bridged ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the Formula above), implied hydrogen (for example as in the Formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the Formula above, "Z" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused or bridged ring system.

When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the Formula:

\[
\begin{array}{c}
\text{(R)}_y \\
\text{H}
\end{array}
\]

where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring structure with the depicted ring as for example in the Formula:
"Acyl" means a -C(0)R radical where R is alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl, as defined herein, e.g., acetyl, trifluoromethylcarbonyl, or 2-methoxyethylcarbonyl, and the like.

"Acylamino" means a -NRR' radical where R is hydrogen, hydroxy, alkyl, or alkoxy and R' is acyl, as defined herein.

"Acyloxy" means an -OR radical where R is acyl, as defined herein, e.g., cyanomethylcarbonyloxy, and the like.

"Administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., surgery, radiation, and chemotherapy, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

"Alkenyl" means a means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to 6 carbon atoms which radical contains at least one double bond, e.g., ethenyl, propenyl, 1-but-3-enyl, and 1-pent-3-enyl, and the like.

"Alkoxy" means an -OR group where R is alkyl group as defined herein. Examples include methoxy, ethoxy, propoxy, isopropoxy, and the like.

"Alkoxyalkyl" means an alkyl group, as defined herein, substituted with at least one, specifically one, two, or three, alkoxy groups as defined herein. Representative examples include methoxymethyl and the like.

"Alkoxy carbonyl" means a -C(0)R group where R is alkoxy, as defined herein.

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to 6 carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), or pentyl (including all isomeric forms), and the like.

"Alkylamino" means an -NHR group where R is alkyl, as defined herein.

"Alkylaminoalkyl" means an alkyl group substituted with one or two alkylamino groups, as defined herein.
"Alkylaminoalkyloxy" means an -OR group where R is alkylaminoalkyl, as defined herein.

"Alkylcarbonyl" means a -C(0)R group where R is alkyl, as defined herein.

"Alkylsulfonyl" means an -S(0)2R group where R is alkyl, as defined herein.

"Alkylsulfonylalkyl" means an alkyl group, as defined herein, substituted with at least one, preferably one or two, alkylsulfonyl groups, as defined herein.

"Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to 6 carbon atoms which radical contains at least one triple bond, e.g., ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

"Amino" means -NH2.

"Aminoalkyl" means an alkyl group substituted with at least one, specifically one, two or three, amino groups.

"Aminoalkyloxy" means an -OR group where R is aminoalkyl, as defined herein.

"Aminocarbonyl" means a -C(0)NH2 group.

"Alkylaminocarbonyl" means a -C(0)NHR group where R is alkyl as defined herein.

"Aryl" means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. Representative examples include phenyl, naphthyl, and indanyl, and the like.

"Arylalkyl" means an alkyl radical, as defined herein, substituted with one or two aryl groups, as defined herein, e.g., benzyl and phenethyl, and the like.

"Arylalkyloxy" means an -OR group where R is arylalkyl, as defined herein.

"Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma,
carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochonfronoma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, menigioma, gia, sarcoma);

Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-theal cell tumors, SertoliLeydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell", a "tumor" or "tumor cell" as provided herein, includes a cell or group of cells afflicted by any one of the above-identified conditions.
"Cyanoalkyl" means an alkyl group, as defined herein, substituted with one or two cyano groups.

"Cycoalkyl" means a monocyclic or fused or bridged bicyclic or tricyclic, saturated or partially unsaturated (but not aromatic), monovalent hydrocarbon radical of three to ten carbon ring atoms. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. More specifically, the term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohex-3-enyl, or (1r,3r,5/7?,?,7?)-tricyclo[3.3.1.137]decan-2-yl, and the like.

"Cycoalkylalkyl" means an alkyl group substituted with at least one, specifically one or two, cycloalkyl group(s) as defined herein.

"Dialkylamino" means a -NRR' radical where R and R’ are alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamo, diethylamino, N,N'-methylpropylamino or N,N'-methylethylamino, and the like.

"Dialkylaminoalkyl" means an alkyl group substituted with one or two dialkylamino groups, as defined herein.

"Dialkylaminoalkyloxy" means an -OR group where R is dialkylaminoalkyl, as defined herein. Representative examples include 2-(N,N-diethylamino)-ethyloxy, and the like.

"Dialkylaminocarbonyl" means a -C(0)NRR' group where R and R' are alkyl as defined herein.

"Halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

"Haloalkoxy" means an -OR group where R’ is haloalkyl as defined herein, e.g., trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

"Haloalkyl" mean an alkyl group substituted with one or more halogens, specifically 1, 2, 3, 4, 5, or 6 halo atoms, e.g., trifluoromethyl, 2-chloroethyl, and 2,2-difluoroethyl, and the like.

"Heteroaryl" means a monocyclic or fused or bridged bicyclic monovalent radical of 5 to 14 ring atoms containing one or more, specifically one, two, three, or four ring heteroatoms where each heteroatom is independently -O-, -S(O)\(_n\)\(^{-}\) (n is 0, 1, or 2), -NH-, -N=, or N-oxide, with the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising the bicyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group.
Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. More specifically, the term heteroaryl includes, but is not limited to, 1,2,4-triazolyl, 1,3,5-triazolyl, phthalimidyl, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1\(H\)-indolyl (including, for example, 2,3-dihydro-1\(H\)-indol-2-yl or 2,3-dihydro-1\(H\)-indol-5-yl, and the like), isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzodioxol-4-yl, benzofuranyl, cinnolinyl, indoliziny1, naphthyridin-3-yl, phthalazin-3-yl, phthalazin-4-yl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, oxazolyl, isooxazolyl, oxadiazolyl, benzoxazolyl, quinolinolyl, isoquinolynl, tetrahydroisoquinolinolyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, 2,3-dihydrobenzofuranyl, benzo[d][1,3]dioxolyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, thiazolyl, isothiazolyl, thiadiazolyl, benzothiazolyl, benzothienyl, and the derivatives thereof, or N-oxide or a protected derivative thereof. The term "5- or 6-membered heteroaryl" describes a subset of the term "heteroaryl."

"Heteroarylalkyl" means an alkyl group, as defined herein, substituted with at least one, specifically one or two heteroaryl group(s), as defined herein.

"Heterocycloalkyl" means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused or bridged, bicyclic or tricyclic group of 5 to 12 ring atoms in which one or more, specifically one, two, three, or four ring heteroatoms where each heteroatom is independently O, S(0)\(n\) (\(n\) is 0, 1, or 2), -N=, or -NH-, the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. When the point of valency is located on a nitrogen atom, \(\text{R}^y\) is absent. More specifically the term heterocycloalkyl includes, but is not limited to, azetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1\(H\)-pyrrolyl, piperidinyl, 4-piperidonyl, morpholynl, piperazinyl, 2-oxopiperazinyl, tetrahydropryranyl, 2-oxopiperidinyl, thiomorpholynl, thiamorpholynl, perhydroazepinyl, pyrazolidinyl, imidazolyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolynl, oxazolidinyl, isoxazolidinyl, thiazolynl, thiazolidinyl, quinclidinyl, isothiazolidinyl, octahydrocyclopenta[c]pyrrolyl, octahydropyridinyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuryl, tetrahydropyrany1, (3a\(\beta\),6aS)-5-
methyloctahydrocyclopenta[c]pyrrolyl, and (3aS,6aR)-5-methyl-1,2,3,3a,4,6a-
hexahydrocyclopenta[c]pyrrolyl, and the derivatives thereof and N-oxide or a protected
derivative thereof.

"Heterocycloalkylalkyl" means an alkyl radical, as defined herein, substituted
with one or two heterocycloalkyl groups, as defined herein, e.g., morpholinylmethyl,
N-pyrrolidinylethyl, and 3-α-n-azetidinyl)propyl, and the like.

"Heterocycloalkyloxy" means an -OR group where R is heterocycloalkyl, as
defined herein.

"Hydroxyalkyl" means an alkyl group, as defined herein, substituted with at least
one, preferably 1, 2, 3, or 4, hydroxy groups.

"Phenylalkyl" means an alkyl group, as defined herein, substituted with one or
two phenyl groups.

"Phenylalkyloxy" means an -OR group where R is phenylalkyl, as defined herein.

"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. One of ordinary skill in the
art would understand that with respect to any molecule described as containing one or more
optional substituents, only sterically practical and/or synthetically feasible compounds are
meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term,
unless stated otherwise. A list of exemplary optional substitutions is presented below in the
definition of "substituted."

"Optionally substituted aryl" means an aryl group, as defined herein, optionally
substituted with one, two, or three substituents independently acyl, acylamino, acyloxy, alkyl,
haloalkyl, alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxyacarbonyl, alkenyloxycarbonyl,
amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl,
dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfanyl, alkylsulfonyl, aminosulfonyl,
alkylaminosulfonyl, dialkylaminosulfonylethyl, alkylsulfonylamino, or aminoalkoxy; or aryl is
pentafluorophenyl. Within the optional substituents on "aryl", the alkyl and alkenyl, either
alone or as part of another group (including, for example, the alkyl in alkoxyacarbonyl), are
independently optionally substituted with one, two, three, four, or five halo.

"Optionally substituted arylalkyl" means an alkyl group, as defined herein,
substituted with optionally substituted aryl, as defined herein.
"Optionally substituted cycloalkyl" means a cycloalkyl group, as defined herein, substituted with one, two, or three groups independently acyl, acyloxy, acylamino, alkyl, haloalkyl, alkenyl, alkoxy, alkenyloxy, alkoxyacylboryl, alkenyloxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonlamino, halo, hydroxy, amino, alkenylamine, dialkylamine, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, nitro, alkoxyalkyloxy, amidalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, carboxy, or cyano. Within the above optional substituents on "cycloalkyl", the alkyl and alkenyl, either alone or as part of another substituent on the cycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkenyloxy, or haloalkylsulfonyl.

"Optionally substituted cycloalkylalkyl" means an alkyl group substituted with at least one, specifically one or two, optionally substituted cycloalkyl groups, as defined herein.

"Optionally substituted heteroaryl" means a heteroaryl group optionally substituted with one, two, or three substituents independently acyl, acylamino, acyloxy, alkyl, haloalkyl, alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxyacylboryl, alkenyloxycarbonyl, amino, alkenylamine, dialkylamine, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonlamino, amidalkoxy, alkylaminoalkoxy, or dialkylaminoalkoxy. Within the optional substituents on "heteroaryl", the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alkoxyacylboryl), are independently optionally substituted with one, two, three, four, or five halo.

"Optionally substituted heteroarylalkyl" means an alkyl group, as defined herein, substituted with at least one, specifically one or two, optionally substituted heteroaryl group(s), as defined herein.

"Optionally substituted heterocycloalkyl" means a heterocycloalkyl group, as defined herein, optionally substituted with one, two, or three substituents independently acyl, acylamino, acyloxy, haloalkyl, alkyl, alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxyacylboryl, alkenyloxycarbonyl, amino, alkenylamine, dialkylamine, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, alkylsulfonlamino, amidalkoxy, or phenylalkyl. Within the optional substituents on "heterocycloalkyl", the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl
in alkoxy carbonyl), are independently optionally substituted with one, two, three, four, or five halo.

[0090] "Optionally substituted heterocycloalkylalkyl" means an alkyl group, as defined herein, substituted with at least one, specifically one or two, optionally substituted heterocycloalkyl group(s) as defined herein.

[0091] "Optionally substituted phenyl" means a phenyl group optionally substituted with one, two, or three substituents independently acyl, acylamino, acyloxy, alkyl, haloalkyl, alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxy carbonyl, alkenyloxycarbonyl, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, or aminoalkoxy, or aryl is pentafluorophenyl. Within the optional substituents on "phenyl", the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alkoxy carbonyl), are independently optionally substituted with one, two, three, four, or five halo.

[0092] "Optionally substituted phenylalkyl" means an alkyl group, as defined herein, substituted with one or two optionally substituted phenyl groups, as defined herein.

[0093] "Optionally substituted phenylsulfonyl" means an \(-\text{S(0)}_2\text{R}\) group where \(\text{R}\) is optionally substituted phenyl, as defined herein.

[0094] "Oxo" means an oxygen which is attached via a double bond.

[0095] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0096] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released in vivo. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design per se was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.
"Oligonucleotide" or "oligonucleotide probes" or "polynucleotide" or "nucleotide" or "nucleic acid" refer to a biological polymer molecule comprised of two or more deoxyribonucleotides or ribonucleotides, preferably more than three, and usually more than ten. The exact size will depend on many factors, which in turn depends on the ultimate function or use of the oligonucleotide. The oligonucleotide may be generated in any manner, including chemical synthesis, DNA replication, reverse transcription, or a combination thereof.

"Oligonucleotide having a nucleotide sequence encoding a gene" or "a nucleic acid sequence encoding" a specified polypeptide refer to a nucleic acid sequence comprising the coding region of a gene or in other words the nucleic acid sequence which encodes a gene product. The coding region may be present in either a cDNA, genomic DNA or RNA form. When present in a DNA form, the oligonucleotide may be single-stranded (i.e., the sense strand) or double-stranded. Suitable expression control sequences or elements such as enhancers/promoters, splice junctions, polyadenylation signals, etc. may be placed in close proximity to the coding region of the gene if needed to permit proper initiation of transcription and/or correct processing of the primary RNA transcript. Alternatively, the coding region utilized in the expression vectors of the present invention may contain endogenous enhancers/promoters, splice junctions, intervening sequences, polyadenylation signals, etc. or a combination of both endogenous and exogenous control elements.

"Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a specific embodiment the patient is a mammal, and in a more specific embodiment the patient is human.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid,
propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic 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, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

[00102] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Specific salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tromethamine, N-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. "Platin(s)," and "platin-containing agent(s)" include, for example, cisplatin, carboplatin, and oxaliplatin.

[00103] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.
"Preventing" or "prevention" of a disease, disorder, or syndrome includes inhibiting the disease from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome.

"Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) inhibiting the disease, disorder, or syndrome, i.e., arresting its development; and (ii) relieving the disease, disorder, or syndrome, i.e., causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

Generally, the procedures for cell cultures, infection, molecular biology methods and the like are common methods used in the art. Such standard techniques can be found in reference manuals such as for example, Sambrook et al. (1989, Molecular Cloning-A Laboratory Manual, Cold Spring Harbor. Laboratories), Herdewijn, ed., Oligonucleotide Synthesis: Methods and Applications (Methods in Molecular Biology), Humana Press, Totowa, N.J., 2004.and Ausubel et al. (1994, Current Protocols in Molecular Biology, Wiley, New York), all these references are incorporated by reference herein in their entireties.

Generally, procedures for production and use of antibodies, for example, immunoprecipitation, ELISA, and other uses of antibodies and related immunology methods and the like are common methods used in the art. Such standard techniques can be found in reference manuals such as for example, Kohler & Milstein (1975) Nature 256:495-497; Kozbor, et al. (1983) Immunology Today 4:72; Cole, et al., pp. 77-96 in Monoclonal Antibodies and Cancer Therapy (1985); Coligan (1991) Current Protocols in Immunology; Harlow & Lane (1988) Antibodies: A Laboratory Manual; and Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) all of these documents are incorporated herein in their entireties.

Embodiments of the Invention

The following paragraphs present a number of embodiments of compounds of the invention. In each instance the embodiment includes both the recited compounds, as well as a
single stereoisomer or mixture of stereoisomers thereof, as well as a pharmaceutically acceptable salt thereof.

[00109] **Embodiments (A1):** In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is hydrogen or alkyl and \( R^{5a}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I. In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is alkyl and \( R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I.

[00110] **Embodiments (A2):** In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is hydrogen, amino, or halo and \( R^{5a}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I. In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is halo and \( R^{5a}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I. In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is fluoro and \( R^{5a}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I.

[00111] **Embodiments (A3):** In another embodiment, the Compound of Formula I is that where \( R^{5c} \) is hydrogen or alkyl and \( R^{5a}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I. In another embodiment, the Compound of Formula I is that where \( R^{5c} \) is alkyl and \( R^{5a}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I.

[00112] **Embodiments (A4):** In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is hydrogen or halo and \( R^{5a}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5b} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I. In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is halo and \( R^{5a}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5h} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I. In another embodiment, the Compound of Formula I is that where \( R^{5b} \) is fluoro and \( R^{5a}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^{5g} \), and \( R^{5b} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I.
Embodiment (B): Another embodiment of the Invention is directed to a Compound of Formula 1(a)

\[
\begin{align*}
R^1 & \quad R^2 \\
\end{align*}
\]

where \(R^1, R^2,\) and all other groups are as defined in the Summary of the Invention for a Compound of Formula 1.

Embodiment (Bl): In another embodiment, the Compound is according to Formula 1(a) where

- \(R^1\) is phenyl substituted with one or two \(R^6\) groups; or
- \(R^1\) is heteroaryl optionally substituted with one, two, or three \(R^7;\)
- \(R^2\) is \(-NR^3R^4;\)
- \(R^3\) is hydrogen, alkyl, or alkoxy carbonylalkyl; and \(R^4\) is optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenyl alkyl, or optionally substituted heteroaryl alkyl; or
- \(R^3\) and \(R^4\) together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with \(R^{10g}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e},\) and \(R^{10f};\)

HET is

(a) a saturated or partially unsaturated, but non-aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen where the remaining ring atoms are carbon; or

(b) a partially unsaturated, but not aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and which ring is fused to a benzo ring; or

(c) a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and where each ring of the 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic; or
(d) a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon where each ring of the bicyclic 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic, and where the bicyclic 7- to 11-membered ring is fused to a benzo ring;

each R^6, when R^6 is present, is independently nitro, -NR^8R^8o, -C(0)NR^8R^8o, -NR^8C(0)OR^9, or heteroaryl optionally substituted with 1, 2, or 3 R^14;

each R^7, when present, is independently alkyl, cycloalkyl, halo, -NR^8R^8o, -C(0)NR^8R^8o,
- NR^8C(0)OR^9, -NR^8C(0)R^9, -NR^8S(0)R^8a, or -S(0)R^8aNR^8R^9;

R^8 is hydrogen, alkyl, or alkenyl;

R^8a is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;

R^9 is alkyl or haloalkyl; and

R^10, R^10a, R^10b, R^10c, R^10d, R^10e, and R^10f are independently hydrogen, halo, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkyamino, dialkylamino, -C(0)R^12, -C(0)NR^11R^11a,

optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenyloxy, optionally substituted phenyloxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; or two of R^10, R^10a, R^10b, R^10c, R^10d, R^10e, and R^10f when attached to the same carbon form oxo, imino, or thiono;

R^11 hydrogen, alkyl, or alkenyl;

R^11a hydrogen, alkyl, or alkenyl;

R^12 is alkyl, or optionally substituted heteroaryl; and

each R^14, when present, is halo, alkyl, or alkoxy carbonyl.

[00115] Embodiment (Bla) : In another embodiment, the Compound is according to Formula 1(a) where

R^1 is phenyl substituted with one or two R^6 groups; or

R^1 is heteroaryl optionally substituted with one, two, or three R^7;

R^2 is -NR^3R^4;
$R^3$ is hydrogen, alkyl, or alkoxy carbonylalkyl; and $R^4$ is cycloalkyl, phenylalkyl, heteroarylalkyl, phenyl, or phenyl substituted with one or two alkyl; or $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with $R^6$, $R^{10a}$, $R^{10b}$, $R^{10c}$, $R^{10d}$, $R^{10e}$, and $R^{10f}$;

HET is

(a) a saturated or partially unsaturated, but non-aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen where the remaining ring atoms are carbon; or

(b) a partially unsaturated, but not aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and which ring is fused to a benzo ring; or

(c) a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and where each ring of the 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic; or

(d) a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon where each ring of the bicyclic 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic, and where the bicyclic 7- to 11-membered ring is fused to a benzo ring;

each $R^6$, when $R^6$ is present, is independently nitro, -NR$^8$R$^{8a}$, -C(0)NR$^8$R$^{8a}$, -NR$^8$C(0)OR$^9$, or heteroaryl optionally substituted with 1, 2, or 3 $R^{14}$;

each $R^7$, when present, is independently alkyl, cycloalkyl, halo, -NR$^8$R$^{8a}$, -C(0)NR$^8$R$^{8a}$, -NR$^8$C(0)OR$^9$, -NR$^8$C(0)R$^9$, -NR$^8$S(0)$_2$R$^{8a}$, or -S(0)$_2$NR$^8$R$^9$;

$R^8$ is hydrogen, alkyl, or alkenyl;

$R^{8a}$ is hydrogen, alkyl, haloalkyl, heterocycloalkyl, or phenylalkyl;

$R^9$ is alkyl or haloalkyl; and
R₁₀, R₁₀a, R₁₀b, R₁₀c, R₁₀d, R₁₀e, and R₁₀f are independently hydrogen, halo, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfanyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, -C(0)R₁₂, -C(0)NR₁₁₁₈, cycloalkyl, cycloalkylalkyl, phenyl, phenylalkyl, phenoxy, phenyloxyalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl where the ring portion of any R₁₀, R₁₀a, R₁₀b, R₁₀c, R₁₀d, R₁₀e, and R₁₀f phenyl, phenylalkyl, phenoxy, phenyloxyalkyl, heteroaryl, or heteroarylalkyl is optionally substituted with one, two, or three groups which are independently halo, hydroxy, nitro, alkyl, haloalkyl, alkylcarbonyl, alkoxy, amino, alkylamino, dialkylamino, or cycloalkyl; or two of R₁₀, R₁₀a, R₁₀b, R₁₀c, R₁₀d, R₁₀e, and R₁₀f when attached to the same carbon form oxo, imino, or thiono;

R₁¹ hydrogen, alkyl, or alkenyl;
R₁¹¹a hydrogen, alkyl, or alkenyl;
R₁¹₂ is alkyl, or optionally substituted heteroaryl; and each R₁¹₄, when present, is halo, alkyl, or alkoxy carbonyl.

[00116] Embodiment (B2): In another embodiment, the Compound is according to Formula 1(a) where

R¹ is as defined in the Summary of the Invention for a Compound of Formula 1;
R² is -NR³R⁴ where R³ is hydrogen, alkyl, or alkoxy carbonylalkyl; and R⁴ is optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted heteroarylalkyl; or
R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET and HET is indolin-l-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-l-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with R₁₀, R₁₀₄, and R₁₀₅; or
R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (a):

![Diagram](image-url)

(a);

where Z is a bond, -C(O)-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R²)-, -C(R₁₀e)(R₁₀f)-, or C₂₋₃-alkylene; or
R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (b):

\[
\begin{align*}
&\text{(b)}; \\
&\text{where} \quad (a) \quad R^{20} \text{ and } R^{20c} \text{ or } R^{20} \text{ and } R^{20d} \text{ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety; or} \\
&(b) \quad R^{20a} \text{ and } R^{20c} \text{ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety; or} \\
&(c) \quad R^{20a} \text{ and } R^{20b} \text{ together with the carbon to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety; where the cycloalkyl and heterocycloalkyl are optionally substituted with } R^{10} \text{ and } R^{10a}; \text{ and the remaining of } R^{20}, R^{20a}, R^{20b}, R^{20c}, \text{ and } R^{20d} \text{ are hydrogen; or} \\
\end{align*}
\]

R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (b):

\[
\begin{align*}
&\text{(b)}; \\
&\text{where } R^{20} \text{ and } R^{20d} \text{ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl and } R^{20a} \text{ and } R^{20c} \text{ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a tricyclic moiety where the cycloalkyl and heterocycloalkyl are optionally substituted with } R^{10} \text{ and } R^{10a}; \text{ and } R^{20b} \text{ is hydrogen; or} \\
\end{align*}
\]

R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c):

\[
\begin{align*}
&\text{(c)}; \\
&\text{and} \\
&31
\end{align*}
\]
(a) $R^{20}$ and $R^{20d}$ or $R^{20}$ and $R^{20e}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety.

(b) $R^{20e}$ and $R^{20f}$ together with the carbons to which they are bonded form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety.

(c) $R^{20}$ and $R^{20a}$ or $R^{20a}$ and $R^{20c}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety; where the cycloalkyl and heterocycloalkyl are optionally substituted with $R^{10}$ and $R^{10a}$; and where the remaining of $R^{20}$, $R^{20a}$, $R^{20c}$, $R^{20d}$, $R^{20e}$, and $R^{20f}$ are $R^{10}$, $R^{10a}$, $R^{10c}$, $R^{10d}$, $R^{10e}$, and $R^{10f}$, respectively; or $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (d), (e), or (f):

![Diagram](attachment:image.png)

$R^{10}$, $R^{10a}$, $R^{10b}$, $R^{10c}$, $R^{10d}$, $R^{10e}$, and $R^{10f}$ are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy; cyano; alkoxycarbonyl; carboxy; amino; alkylamino; dialkylamino; $-C(0)R^{12}$; $-C(0)NR^{11a}$; optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted phenylalkyl; optionally substituted phenylalkyl; optionally substituted heterocycloalkyl; optionally substituted heterocycloalkylalkyl; optionally substituted heteroaryl; or optionally substituted heteroarylalkyl; or two of $R^{10}$, $R^{10a}$, $R^{10b}$, $R^{10c}$, $R^{10d}$, $R^{10e}$, and $R^{10f}$ when attached to the same carbon form oxo, imino, or thiono;

$R^{11}$ hydrogen, alkyl, or alkenyl;
$R^{11a}$ hydrogen, alkyl, or alkenyl; and $R^{12}$ is alkyl, or optionally substituted heteroaryl.

**Embodiment (B2a):** In another embodiment, the Compound is according to Formula I(a) where $R^1$ is phenyl substituted with one or two $R^6$ groups; or $R^1$ is heteroaryl optionally substituted with one, two, or three $R^7$.
R\textsuperscript{2} is \(-\text{NR}^3\text{R}^4\) where \(\text{R}^3\) is hydrogen, alkyl, or alkoxy carbonylalkyl; and \(\text{R}^4\) is optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted heteroarylalkyl; or

R\textsuperscript{2} is \(-\text{NR}^3\text{R}^4\) where \(\text{R}^3\) and \(\text{R}^4\) together with the nitrogen to which they are attached form HET and HET is indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with \(\text{R}^{10}\), \(\text{R}^{10a}\), and \(\text{R}^{10b}\); or

R\textsuperscript{2} is \(-\text{NR}^3\text{R}^4\) where \(\text{R}^3\) and \(\text{R}^4\) together with the nitrogen to which they are attached form HET according to formula (a):

where \(Z\) is a bond, \(-\text{C}(\text{O})\)-, \(-\text{O}\)-, \(-\text{S}\)-, \(-\text{S(O)}\)-, \(-\text{S(0)}\)-, \(-\text{N(}\text{R}^3\text{)}\)-, \(-\text{C(}\text{R}^{10}\text{)}(\text{R}^{10f})\)-, or \(\text{C}_{2,3}\)-alkylene; or

R\textsuperscript{2} is \(-\text{NR}^3\text{R}^4\) where \(\text{R}^3\) and \(\text{R}^4\) together with the nitrogen to which they are attached form HET according to formula (b):

where

(a) \(\text{R}^{20}\) and \(\text{R}^{20c}\) or \(\text{R}^{20}\) and \(\text{R}^{20d}\) together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety; or
(b) \(\text{R}^{20a}\) and \(\text{R}^{20c}\) together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety; or
(c) \(\text{R}^{20a}\) and \(\text{R}^{20b}\) together with the carbon to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety;

where the cycloalkyl and heterocycloalkyl are optionally substituted with \(\text{R}^{10}\) and \(\text{R}^{10a}\); and the remaining of \(\text{R}^{20}\), \(\text{R}^{20a}\), \(\text{R}^{20b}\), \(\text{R}^{20c}\), and \(\text{R}^{20d}\) are hydrogen; or
R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (b):

\[ \text{HET} \]

where R^{20} and R^{20d} together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl and R^{20a} and R^{20c} together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a tricyclic moiety where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; and and R^{20b} is hydrogen; or

R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (c):

\[ \text{HET} \]

where

(a) R^{20} and R^{20d} or R^{20} and R^{20c} together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety
(b) R^{20e} and R^{20f} together with the carbons to which they are bonded form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety,
(c) R^{20} and R^{20a} or R^{20a} and R^{20c} together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety;

where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; and the remaining of R^{20}, R^{20a}, R^{20e}, R^{20d}, R^{20c}, and R^{20f} are R^{10}, R^{10a}, R^{10e}, R^{10d}, R^{10e}, and R^{10f}, respectively; or

R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (d), (e), or (f):
each R^6^, when present, is independently nitro, -NR^8^R^8^a, -C(0)NR^8^R^8^a, -NR^8^C(0)OR^9^, or heteroaryl optionally substituted with 1, 2, or 3 R^1^;  
each R^7^, when present, is independently alkyl, cycloalkyl, -NR^8^R^8^a, -C(0)NR^8^R^8^a,  
-NR^8^C(0)OR^9^, or -NR^8^C(0)R^9^;  
R^8^ is hydrogen, alkyl, or alkenyl;  
R^8^a is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;  
R^9^ is alkyl or haloalkyl; and  
R^1^, R^10^a, R^10^b, R^10^c, R^10^d, and R^10^e are independently hydrogen, alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonfyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, -C(0)R^1^2^, -C(0)NR^1^1^R^1^1^a^, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenol, optionally substituted phenyl alkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl;  
or R^10^a and R^10^b together form oxo; or R^10^e and R^10^f together form oxo;  
R^2^ is hydrogen, alkyl, haloalkyl, haloalkenyl, hydroxy alkyl, alkylsulfonfyl, hydroxy, alkoxy, alkoxy carbonyl, -C(0)R^1^2^, -C(0)NR^1^1^R^1^1^a^, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenol, optionally substituted phenylalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkyl;  
R^1^ is phenyl substituted with one or two R^6^ groups; or  
R^1^ is heteroaryl optionally substituted with one, two, or three R^7^;
R^2 is -NR^3R^4 where R^3 is hydrogen, alkyl, or alkoxy carbonylalkyl; and R^4 is optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted heteroarylalkyl; or

R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET and HET is indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with R^{10}, R^{10a}, and R^{10b}; or

R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (a):

(a);

where Z is a bond, -C(O)-, -O-, -S-, -S(O)_, -S(O)_2-, -N(R^{10e})(R^{10f})-, or C\_2\_3-alkylene; R^z is hydrogen, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylsulfonyl, hydroxy, alkoxy, alkoxy carbonyl, -C(O)R^{12}, -C(O)NR^{11}R^{11a}, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and R^{10}, R^{10a}, R^{10b}, R^{10c}, and R^{10d} are independently hydrogen, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, -C(O)R^{12}, -C(O)NR^{11}R^{11a}, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenyloxy, optionally substituted phenyloxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkyl; or R^{10a} and R^{10b} together form oxo; or R^{10e} and R^{10f} together form oxo; or

R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (b):

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where
(a) $R_{20}^0$ and $R_{20}^{20c}$ or $R_{20}^{20}$ and $R_{20}^{20d}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety; or
(b) $R_{20}^{20a}$ and $R_{20}^{20c}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety; or
(c) $R_{20}^{20a}$ and $R_{20}^{20b}$ together with the carbon to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety;
where the cycloalkyl and heterocycloalkyl are optionally substituted with $R^{10}$ and $R^{10a}$ where $R^{10}$ and $R^{10a}$ are independently hydroxy, alkyl, haloalkyl, or optionally substituted phenyl; and the remaining of $R_{20}^0$, $R_{20}^{20a}$, $R_{20}^{20b}$, $R_{20}^{20c}$, and $R_{20}^{20d}$ are hydrogen; or
$R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (b):

where $R_{20}^0$ and $R_{20}^{20d}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl and $R_{20}^{20a}$ and $R_{20}^{20c}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a tricyclic moiety, and where the cycloalkyl and heterocycloalkyl are optionally substituted with $R^{10}$ and $R^{10a}$; and $R_{20}^{20b}$ is hydrogen; or
$R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (c):
where

(d) $R^{20}$ and $R^{20d}$ or $R^{20}$ and $R^{20c}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety

(e) $R^{20e}$ and $R^{20f}$ together with the carbons to which they are bonded form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety.

(f) $R^{20}$ and $R^{20a}$ or $R^{20a}$ and $R^{20e}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety;

where the cycloalkyl is optionally substituted with $R^{10}$ and $R^{10a}$ where $R^{10}$ and $R^{10a}$ are independently alkyl or together form oxo; and the remaining of $R^{20}$, $R^{20a}$, $R^{20c}$, $R^{20d}$, $R^{20e}$, and $R^{20f}$ are $R^{10}$, $R^{10a}$, $R^{10c}$, $R^{10d}$, $R^{10e}$, and $R^{10f}$, respectively, and the $R^{10}$, $R^{10a}$, $R^{10c}$, $R^{10d}$, $R^{10e}$, and $R^{10f}$ are independently hydrogen, hydroxy, alkyl, halo, haloalkyl, hydroxyalkyl, optionally substituted phenyl, or amino, or $R^{10e}$ and $R^{10f}$ together form oxo; or

$R^{2}$ is $-NR^{3}R^{4}$ where $R^{3}$ and $R^{4}$ together with the nitrogen to which they are attached form HET according to formula (d), (e), or (f):

![Diagram](image-url)

where $R^{10}$, $R^{10a}$, $R^{10b}$, $R^{10c}$, $R^{10d}$, and $R^{10e}$ are independently hydrogen, hydroxy, alkyl, haloalkyl, or optionally substituted phenyl; or, in formula (d) and (f), $R^{10e}$ and $R^{10f}$ together form oxo;

each $R^{6}$, when present, is independently nitro, $-NR^{8}R^{8a}$, $-C(0)NR^{8}R^{8a}$, $-NR^{8}C(0)OR$; or heteroaryl optionally substituted with 1, 2, or 3 $R^{14}$;

each $R^{7}$, when present, is independently alkyl, cycloalkyl, $-NR^{8}R^{8a}$, $-C(0)NR^{8}R^{8a}$, $-NR^{8}C(0)OR$; or $-NR^{8}C(0)R$; $R^{8}$ is hydrogen, alkyl, or alkenyl;

$R^{8a}$ is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;

$R^{9}$ is alkyl or haloalkyl; and

$R^{11}$ hydrogen, alkyl, or alkenyl;

$R^{11a}$ hydrogen, alkyl, or alkenyl;

$R^{12}$ is alkyl, or optionally substituted heteroaryl; and

each $R^{14}$, when present, is halo, alkyl, or alkoxy carbonyl.
[00119] Embodiments (C): In another embodiment, the Compound is according to Formula 1(a) where R^1 is heteroaryl optionally substituted with one, two, or three R^7; and R^2, R^7 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is heteroaryl optionally substituted with one or two R^7; and R^2, R^7 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is heteroaryl substituted with one or two R^7; and R^2, R^7 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.

[00120] Embodiments (C1): In another embodiment, the Compound is according to Formula 1(a) where R^1 is a 9-membered heteroaryl optionally substituted with one, two, or three R^7; and R^2, R^7 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is a 9-membered heteroaryl optionally substituted with one or two R^7; and R^2, R^7 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is a 9-membered heteroaryl substituted with one or two R^7; and R^2, R^7 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.

[00121] Embodiments (C2): In another embodiment, the Compound is according to Formula 1(a) where R^1 is benzimidazolyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, thiazolo[4,5-b]pyridinyl, or thiazolo[5,4-b]pyridinyl where R^1 is optionally substituted with one or two R^7; and R^2, R^7 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is benzimidazolyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, thiazolo[4,5-b]pyridinyl, or thiazolo[5,4-b]pyridinyl where R^1 is optionally substituted with one or two R^7; each R^7, when present, is alkyl, haloalkyl, cycloalkyl, -NR^8R^8a, or -NR^8C(0)OR^9; and R^8, R^8a, R^9, R^2 and all other groups are as defined in the Summary of the
Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R\textsuperscript{1} is benzimidazolyl, 1H-imidazo[4,5-&]pyridinyl, 3H-imidazo[4,5-b]pyridinyl, thiazolo[4,5-b]pyridinyl, or thiazolo[5,4-b]pyridinyl where R\textsuperscript{1} is optionally substituted with one or two R\textsuperscript{7}; each R\textsuperscript{7}, when present, is alkyl, haloalkyl, cycloalkyl, -NR\textsuperscript{8}R\textsuperscript{8a}, or -NR\textsuperscript{8}C(0)OR \textsuperscript{9}; R\textsuperscript{8} is hydrogen; R\textsuperscript{8a} is hydrogen, alkyl, or haloalkyl; R\textsuperscript{9} is alkyl; and R\textsuperscript{2} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R\textsuperscript{1} is benzimidazolyl, 1H-imidazo[4,5-b]pyridinyl, 3H-imidazo[4,5-fr]pyridinyl, thiazolo[4,5-b]pyridinyl, or thiazolo[5,4-b]pyridinyl where R\textsuperscript{1} is optionally substituted with one or two R\textsuperscript{7}; each R\textsuperscript{7}, when present, is alkyl, haloalkyl, cycloalkyl, -NR\textsuperscript{8}R\textsuperscript{8a}, or -NR\textsuperscript{8}C(0)OR \textsuperscript{9}; R\textsuperscript{8} is hydrogen; R\textsuperscript{8a} is hydrogen, C\textsubscript{i-3}-alkyl, or haloalkyl; R\textsuperscript{9} is C\textsuperscript{\textalpha}-alkyl; and R\textsuperscript{2} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R\textsuperscript{1} is benzimidazol-6-yl, 2-methyl-benzimidazol-6-yl, 2-cyclopropyl-benzimidazol-6-yl, 2-trifluormethyl-benzimidazol-6-yl, 2-amino-benzimidazol-6-yl, 2-(2,2,2-trifluoroethylamino)-benzimidazol-6-yl, 2-(2-monofluoroethylamino)-benzimidazol-6-yl, 2-(2,2-difluoroethylamino)-benzimidazol-6-yl, 2-(methoxycarbonylamino)-benzimidazol-6-yl, imidazo[4,5-b]pyridin-6-yl, 2-methyl-imidazo[4,5-b]pyridin-6-yl, 2-amino-imidazo[4,5-b]pyridin-6-yl, 2-cyclopropyl-imidazo[4,5-b]pyridin-6-yl, or 2-trifluormethyl-imidazo[4,5-b]pyridin-6-yl; and R\textsuperscript{2} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.

[00122] Embodiments (C3): In another embodiment, the Compound is according to Formula 1(b)

![Chemical Structure](image)

where R\textsuperscript{2} and R\textsuperscript{7}, when present, are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(b) where R\textsuperscript{7}, when
present, is alkyl, haloalkyl, cycloalkyl, -NR^8R^8a, or -NR^8C(0)OR^9; R^2, R^8, R^8a, R^9, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(b) where R^7, when present, is alkyl, haloalkyl, cycloalkyl, -NR^8R^8a, or -NR^8C(0)OR^9; R^8 is hydrogen; R^8a is hydrogen, alkyl, or haloalkyl; R^9 is alkyl; and R^2 is as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(b) where R^7, when present, is C^1,3-alkyl, haloalkyl, cycloalkyl, -NR^8R^8a, or -NR^8C(0)OR^9; R^2, R^8, R^8a, R^9, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(c1) or 1(c2) where R^2 and R^7 are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(c1) or 1(c2) where R^7, when present, is alkyl, haloalkyl, cycloalkyl, -NR^8R^8a, or -NR^8C(0)OR^9; R^2, R^8, R^8a, R^9, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(c1) or 1(c2) where R^7, when present, is alkyl, haloalkyl, cycloalkyl, -NR^8R^8a, or -NR^8C(0)OR^9; R^8 is hydrogen; R^8a is hydrogen, alkyl, or haloalkyl; R^9 is alkyl; and R^2 is as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(c1) or 1(c2) where R^7, when present, is C^1,3-alkyl, haloalkyl, cycloalkyl, -NR^8R^8a, or -NR^8C(0)OR^9; R^8 is hydrogen; R^8a is hydrogen, C^1,3-alkyl, or haloalkyl; R^9 is C^1,3-alkyl; and R^2 is as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.
Embodiments (C5): In another embodiment, the Compound is according to Formula I(d1) or I(d2)

\[
(R^7)_{0-1} N - R^2 (R^7)_{0-1} N - R^2
\]

where \( R^2 \) and \( R^7 \) are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula I(d1) or I(d2) where \( R^7 \), when present, is alkyl, haloalkyl, cycloalkyl, \(-NR^8 R^8a\) or \(-NR^8 C(0)OR^9\); \( R^2, R^8, R^8a, R^9 \), and all other groups are as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula I(d1) or I(d2) where \( R^7 \), when present, is alkyl, haloalkyl, cycloalkyl, \(-NR^8 R^8a\) or \(-NR^8 C(0)OR^9\); \( R^8 \) is hydrogen; \( R^8a \) is hydrogen, alkyl, or haloalkyl; \( R^9 \) is alkyl; and \( R^2 \) is as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula I(d1) or I(d2) where \( R^7 \), when present, is \( C_{1,3}\)-alkyl, haloalkyl, cycloalkyl, \(-NR^8 R^8a\) or \(-NR^8 C(0)OR^9\); \( R^8 \) is hydrogen; \( R^8a \) is hydrogen, \( C^8\)-alkyl, or haloalkyl; \( R^9 \) is \( C_{1,3}\)-alkyl; and \( R^2 \) is as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.

Embodiments (C6): In another embodiment, the Compound is according to Formula I(a) where \( R^1 \) is a 6-membered heteroaryl optionally substituted with one, two, or three \( R^7 \); and \( R^2, R^7 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula I(a) where \( R^1 \) is a 6-membered heteroaryl optionally substituted with one or two \( R^7 \); and \( R^2, R^7 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula I(a) where \( R^1 \) is a 6-membered heteroaryl substituted with one or two \( R^7 \); and \( R^2, R^7 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula I(a) where
R is pyrazinyl, pyridazinyl, pyridinyl, or pyrimidinyl where R is optionally substituted with one or two R^7; and R^9, R^2, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R is pyrazinyl, pyridazinyl, pyridinyl, or pyrimidinyl where R is substituted with one or two R^7; and R^2, R^7, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazinyl, pyridazinyl, pyridinyl, or pyrimidinyl where R^1 is optionally substituted with one or two R^7; R^7 is halo, optionally substituted heteroaryl, -NR^8S(0)R^8, -S(0)NR^8R^9, -C(0)NR^8R^8, -NR^8R^8; R^2, R^8, R^8, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazinyl, pyridazinyl, pyridinyl, or pyrimidinyl where R^1 is optionally substituted with one or two R^7; R^7 is halo, optionally substituted heteroaryl, -NR^8S(0)R^8, -S(0)NR^8R^8, -C(0)NR^8R^8, R^2, R^8, R^8, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazinyl, pyridazinyl, pyridinyl, or pyrimidinyl where R^1 is optionally substituted with one or two R^7; R^7 is optionally substituted heteroaryl, -C(0)NR^8R^8, R^2, R^8, R^8, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazinyl, pyridazinyl, pyridinyl, or pyrimidinyl where R^1 is optionally substituted with one or two R^7; R^7 is optionally substituted heteroaryl, -C(0)NR^8R^8, R^2, R^8, R^8, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazinyl, pyridazinyl, pyridinyl, or pyrimidinyl where R^1 is optionally substituted with one or two R^7; R^7 is optionally substituted heteroaryl, -C(0)NR^8R^8, or -NR^8R^8; R^2, R^8, R^8, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.
4-methylaminocarbonyl-pyridin-3-yl, or 4-(imidazol-2-yl)-pyridin-3-yl; and R² is as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R¹ is pyridin-3-yl optionally substituted with one, two, or three R⁷; and R², R⁷ and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R¹ is pyridin-3-yl optionally substituted with one or two R⁷; and R², R⁷ and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R¹ is pyridin-3-yl where R¹ is optionally substituted with one or two R⁷; R⁷ is halo, alkoxy, -NR⁸S(0)₂R⁸₄, -S(0)₂NR⁸R⁹, -C(0)NR⁸R⁸₄, or -NR⁸S(0)₂R⁸₄; R², R⁸, R⁸₄, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R¹ is pyridin-3-yl where R¹ is optionally substituted with one or two R⁷; R⁷ is halo, alkoxy, -NR⁸S(0)₂R⁸₄, -S(0)₂NR⁸R⁹, -C(0)NR⁸R⁸₄, or -NR⁸S(0)₂R⁸₄; each R⁸ is hydrogen; each R⁸₄ is independently hydrogen or alkyl; R⁹ is hydrogen or alkyl; R² and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3.

Embodiments (C7): In another embodiment, the Compound is according to Formula 1(a) where R¹ is a 5-membered heteroaryl optionally substituted with one or two R⁷; and R², R⁷ and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R¹ is a 5-membered heteroaryl substituted with one or two R⁷; and R⁴, R¹ and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R¹ is pyrazolyl or thiazolyl, where R¹ is optionally substituted with one or two R⁷; and R², R⁷ and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula
1(a) where R^1 is pyrazolyl or thiazolyl, where R^1 is optionally substituted with one or two R^7; each R^7, when present, is alkyl, -NR^8_R^8a, or -NR^8C(0)R^9; and R^2, R^8, R^8a, R^9, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazolyl or thiazolyl, where R^1 is optionally substituted with one or two R^7; each R^7, when present, is alkyl, -NR^8_R^8a, or -NR^8C(0)R^9; R^8 is hydrogen; R^8a is hydrogen, alkyl, or benzyl; R^9 is alkyl; and R^2 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazolyl or thiazolyl, where R^1 is optionally substituted with one or two R^7; each R^7, when present, is C_{i-3}-alkyl, -NR^8_R^8a, or -NR^8C(0)R^9; R^8 is hydrogen; R^8a is hydrogen, C_{i-3}-alkyl, or benzyl; R^9 is C_{i-3}-alkyl; and R^2 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, 5-phenylmethylamino-pyrazol-3-yl, 5-amino-pyrazol-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, 2-methylcarbonylamino-thiazol-5-yl, or 2-amino-thiazol-5-yl; and R^2 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.

[00128] Embodiments (C8): In another embodiment, the Compound is according to Formula 1(a) where R^1 is phenyl substituted with one, two, or three R^6 groups; each R^6 is independently nitro; cyano; halo; alkyl; alkenyl; alkynyl; haloalkyl; -OR^8i; -NR^8_R^8a; -C(0)NR^8_R^8a; -NR^8C(0)OR^9; -NR^8C(0)R^9; -NR^8S(0)_2R^8; -NR^8C(0)NR_R^8a; carboxy, -C(0)OR^9; alkylcarbonyl; alkyl substituted with one or two -C(0)NR^8_R^8a; heteroaryl optionally substituted with 1, 2, or 3 R^{14}; or optionally substituted heterocycloalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is phenyl substituted with one or two R^6 groups; each R^6 is independently nitro; cyano; halo; alkyl; alkenyl; alkynyl; haloalkyl; -OR^8a; -NR^8_R^8a; -C(0)NR^8_R^8a; -NR^8C(0)OR^9; -NR^8C(0)R^9; -NR^8S(0)_2R^8a; -NR^8C(0)NR_R^8a; carboxy, -C(0)OR^9; alkylcarbonyl; alkyl substituted with one or two -C(0)NR^8_R^8a; heteroaryl optionally substituted with 1, 2, or 3 R^{14}; or optionally substituted
heterocycloalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.

[00129] Embodiments (C8a): In another embodiment, the Compound is according to Formula 1(a) where R^1 is phenyl substituted with one or two R^6 groups; each R^6 is independently -OR^{8a}; -NR^{8a}R^{8a}; -C(0)NR^{8a}R^{8a}; or heteroaryl optionally substituted with 1, 2, or 3 R^{14}; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is phenyl substituted with one or two R^6 groups; each R^6 is independently -OR^{8a}; -NR^{8a}R^{8a}; -C(0)NR^{8a}R^{8a}; or heteroaryl optionally substituted with 1, 2, or 3 R^{14}; R^8 is hydrogen or alkyl; R^{8a} is hydrogen, alkyl, haloalkyl, or optionally substituted heterocycloalkyl; R^{14}, when present, is halo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3. In another embodiment, the Compound is according to Formula 1(a) where R^1 is phenyl substituted with one or two R^6 groups; each R^6 is independently 2,2-difluoroethylaminocarbonyl, N-pyrrolidin-1-ylaminocarbonyl, N-pyrrolidin-2-ylaminocarbonyl, N-pyrrolidin-3-ylaminocarbonyl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, benzimidazol-2-yl, 5-fluorobenzimidazol-2-yl, or benzimidazol-6-yl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, and B3.

[00130] Embodiments (D): In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 is hydrogen, alkyl, or alkoxy carbonylalkyl; and R^4 is optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted heteroarylalkyl; and R^1 all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00131] Embodiments (Dl): In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 is alkoxy carbonylalkyl; R^4 is optionally substituted phenylalkyl; and R^1 all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a)
where R^2 is -NR^3R^4 and R^3 is alkoxy carbonylalkyl; R^4 is phenylalkyl; and R^1 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 is ethoxycarbonylmethyl; R^4 is benzyl; and R^1 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

Embodiments (D2): In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 is hydrogen; and R^4 is optionally substituted phenyl; and R^1 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 is hydrogen; and R^4 is phenyl optionally substituted with alkyl; and R^1 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

Embodiments (D3): In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 is alkyl; and R^4 is optionally substituted phenylalkyl; and R^1 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 is alkyl; and R^4 is phenylalkyl optionally substituted with alkyl; and R^1 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 is methyl, ethyl, n-propyl, isopropyl, or n-butyl; and R^4 is 1-phenylethyl, 2-phenylethyl, phenylethyl, 3-methyl-phenylethyl and R^1 and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).
[00134]  **Embodiments (D4):** In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) is alkyl; and \( R^4 \) is optionally substituted heteroarylalkyl; and \( R^1 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) is alkyl; and \( R^4 \) is heteroarylalkyl; and \( R^1 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) is methyl; and \( R^4 \) is pyridinylmethyl; and \( R^1 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00135]  **Embodiments (D5):** In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) is hydrogen; and \( R^4 \) is optionally substituted cycloalkyl; and \( R^1 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) is hydrogen; and \( R^4 \) is cycloalkyl; and \( R^1 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) is hydrogen; and \( R^4 \) is \((1r,3r,5 R,7/?)-tricyclo[3.3.1.1^3^7]decan-2-yl\); and \( R^1 \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00136]  **Embodiment (D6):** In another embodiment, the Compound is according to Formula 1(a) where

- \( R^1 \) is phenyl substituted with one or two \( R^6 \) groups independently nitro, \(-NR^8R^8\), \(-C(0)NR^8R^8\), \(-NR^8C(0)OR^9\), or heteroaryl optionally substituted with 1, 2, or 3 \( R^{14} \); or
- \( R^1 \) is heteroaryl optionally substituted with one, two, or three \( R^3 \);
- \( R^2 \) is \(-NR^3R^4 \) where \( R^3 \) is hydrogen, alkyl, or alkoxy carbonylalkyl; and \( R^4 \) is optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, or optionally substituted heteroarylalkyl;

\( \text{R}^{1,2,3,4,5,6,7,8,9,10,11,12,13,14} \) as defined throughout.
each R^7, when present, is independently alkyl, -NR^8R^8_a, -C(0)NR^8R^8_a, -NR^8C(0)OR^9, or -NR^8C(0)OR^9;
R^8 is hydrogen, alkyl, or alkenyl;
R^8_a is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;
R^9 is alkyl or haloalkyl; and
each R^1, when present, is halo, alkyl, or alkoxy carbonyl.

[00137] Embodiments (E): In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with R^{10}, R^{10_a}, R^{10_b}, R^{10_c}, R^{10_d}, R^{10_e}, and R^{10_f}; and HET, R^{10}, R^{10_a}, R^{10_b}, R^{10_c}, R^{10_d}, R^{10_e}, R^{10_f} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B 2, B2a, B3, (C)-C(8), and (C8a).

[00138] Embodiments (El): In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with R^{10}, R^{10_a}, R^{10_b}, R^{10_c}, R^{10_d}, R^{10_e}, and R^{10_f}; HET is a saturated or partially unsaturated, but non-aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen where the remaining ring atoms are carbon; and R^{10}, R^{10_a}, R^{10_b}, R^{10_c}, R^{10_d}, R^{10_e}, R^{10_f} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00139] Embodiments (E2): In another embodiment, the Compound is according to Formula I(a) where R^3 and R^4 together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with R^{10}, R^{10_a}, R^{10_b}, R^{10_c}, R^{10_d}, R^{10_e}, and R^{10_f}; HET is a partially unsaturated, but not aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and which ring is fused to a benzo ring; and R^{10}, R^{10_a}, R^{10_b}, R^{10_c}, R^{10_d}, R^{10_e}, and R^{10_f} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^3 and R^4 together with the nitrogen to which they are attached form HET optionally substituted on any substitutable
atom of the ring with \( R_{10} \), \( R_{10a} \), and \( R_{10b} \); \( R_{10} \), \( R_{10d} \), \( R_{10c} \), and \( R_{10f} \) are hydrogen; HET is a partially unsaturated, but not aromatic, monocyclic 5- to 8-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and which ring is fused to a benzo ring; and \( R_{10} \), \( R_{10a} \), \( R_{10b} \), and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

**Embodiments (E3):** In another embodiment, the Compound is according to Formula 1(a) where \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with \( R_{10} \), \( R_{10a} \), \( R_{10b} \), \( R_{10c} \), \( R_{10d} \), \( R_{10e} \), and \( R_{10f} \); HET is a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and where each ring of the 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic; and \( R_{10} \), \( R_{10a} \), \( R_{10c} \), \( R_{10b} \), \( R_{10d} \), \( R_{10e} \), and \( R_{10f} \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with \( R_{10} \), \( R_{10a} \), and \( R_{10b} \); \( R_{10c} \), \( R_{10d} \), \( R_{10e} \), and \( R_{10f} \) are hydrogen; HET is a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon and where each ring of the 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic; and \( R_{10} \), \( R_{10a} \), and \( R_{10b} \) and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

**Embodiments (E4):** In another embodiment, the Compound is according to Formula 1(a) where \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with \( R_{10} \), \( R_{10a} \), \( R_{10b} \), \( R_{10c} \), \( R_{10d} \), \( R_{10e} \), and \( R_{10f} \); HET is a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon where each ring of the bicyclic 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic,
and where the bicyclic 7- to 11-membered ring is fused to a benzo ring; and R^{10}, R^{10d}, R^{10e}, R^{10f}, R^{10c}, R^{10a}, and R^{10b} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(C)(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R^3 and R^4 together with the nitrogen to which they are attached form HET optionally substituted on any substitutable atom of the ring with R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, and R^{10f}; HET is a fused, bridged, or spirocyclic, bicyclic 7- to 11-membered ring optionally containing an additional one or two ring heteroatoms which are independently oxygen, sulfur, or nitrogen and the remaining ring atoms are carbon where each ring of the bicyclic 7- to 11-membered ring is saturated or partially unsaturated but not fully aromatic, and where the bicyclic 7- to 11-membered ring is fused to a benzo ring; R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10f} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(C)(8), and (C8a).

[00142] Embodiments (E): In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET and HET is indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with R^{10}, R^{10a}, and R^{10b}; and R^{10}, R^{10a}, R^{10b} and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(C)(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET and HET is indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with R^{10}, R^{10a}, and R^{10b}; R^{10} is hydrogen or phenyl; R^{10a} and R^{10b} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(C)(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET and HET is indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with R^{10}, R^{10a}, and R^{10b}; R^{10}, R^{10a} and
R\textsuperscript{a,b} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

**Embodiments (F2):** In another embodiment, the Compound is according to Formula I(a) where

R\textsuperscript{1} is phenyl substituted with one or two R\textsuperscript{6} groups independently nitro, -NR\textsuperscript{8}R\textsuperscript{8a}, -C(0)NR\textsuperscript{8}R\textsuperscript{8a}, -NR\textsuperscript{8}C(0)OR\textsuperscript{9}, or heteroaryl optionally substituted with 1, 2, or 3 R\textsuperscript{14}; or

R\textsuperscript{1} is heteroaryl optionally substituted with one, two, or three R\textsuperscript{7};

R\textsuperscript{2} is -NR\textsuperscript{3}R\textsuperscript{4} and R\textsuperscript{3} and R\textsuperscript{4} together with the nitrogen to which they are attached form HET and HET is indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with R\textsuperscript{10}, R\textsuperscript{10a}, and R\textsuperscript{10b}; each R\textsuperscript{7}, when present, is independently alkyl, -NR\textsuperscript{8}R\textsuperscript{8a}, -C(0)NR\textsuperscript{8}R\textsuperscript{8a}, -NR\textsuperscript{8}C(0)OR\textsuperscript{9}, or -NR\textsuperscript{8}C(0)R\textsuperscript{9};

R\textsuperscript{8} is hydrogen, alkyl, or alkenyl;

R\textsuperscript{8a} is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;

R\textsuperscript{9} is alkyl or haloalkyl; and

R\textsuperscript{10}, R\textsuperscript{10a}, and R\textsuperscript{10b} are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy; cyano; alkoxy carbonyl; carboxy; amino; alkylamino; dialkylamino; -C(0)R\textsuperscript{12}; -C(0)NR\textsuperscript{11}R\textsuperscript{11a}; optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted phenyloxy; optionally substituted phenyloxyalkyl; optionally substituted heterocycloalkyl; optionally substituted heteroaryl; or optionally substituted heteroarylalkyl; or two of R\textsuperscript{10}, R\textsuperscript{10a}, R\textsuperscript{10b}, R\textsuperscript{10c}, R\textsuperscript{10d}, R\textsuperscript{10e}, and R\textsuperscript{10f} when attached to the same carbon form oxo;

R\textsuperscript{11} hydrogen, alkyl, or alkenyl;

R\textsuperscript{11a} hydrogen, alkyl, or alkenyl;

R\textsuperscript{12} is alkyl, or optionally substituted heteroaryl; and

each R\textsuperscript{14}, when present, is halo, alkyl, or alkoxy carbonyl.

**Embodiments (F2):** In another embodiment, the Compound is according to Formula I(a) where
R\(^1\) is phenyl substituted with one or two R\(^6\) groups independently nitro, -NR\(^8\)R\(^{9a}\), -C(0)NR\(^8\)R\(^{8a}\), -NR\(^8\)C(0)OR\(^9\), or heteroaryl optionally substituted with 1, 2, or 3 R\(^{14}\); or R\(^1\) is heteroaryl optionally substituted with one, two, or three R\(^7\);

R\(^2\) is -NR\(^3\)R\(^4\) and R\(^3\) and R\(^4\) together with the nitrogen to which they are attached form HET and HET is indolin-1-yl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, or 1,2,3,4-tetrahydro-1,4-epiminonaphth-9-yl, where any substitutable atom on HET is optionally substituted with R\(^{10}\), R\(^{10a}\), and R\(^{10b}\); each R\(^7\), when present, is independently alkyl, -NR\(^8\)R\(^{8a}\), -C(0)NR\(^8\)R\(^{8a}\), -NR\(^8\)C(0)OR\(^9\), or -NR\(^8\)C(0)R\(^9\);

R\(^8\) is hydrogen, alkyl, or alkenyl;

R\(^{8a}\) is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;

R\(^9\) is alkyl or haloalkyl; and

R\(^{10}\), R\(^{10a}\), and R\(^{10b}\) are independently hydrogen, alkyl, or optionally substituted phenyl;

R\(^{11}\) is hydrogen, alkyl, or alkenyl;

R\(^{11a}\) is hydrogen, alkyl, or alkenyl;

R\(^{12}\) is alkyl, or optionally substituted heteroaryl; and

each R\(^{14}\), when present, is halo, alkyl, or alkoxy carbonyl.

**Embodiments (G):** In another embodiment, the Compound is according to Formula 1(a) where R\(^2\) is -NR\(^3\)R\(^4\) and R\(^3\) and R\(^4\) together with the nitrogen to which they are attached form HET according to formula (a):

\[
\begin{align*}
\text{Z} & \quad \text{R}(\text{Z})_{\text{R}_{\text{10}}} \\
\text{R} & \quad \text{R}_{\text{10}} \\
\text{R} & \quad \text{R}_{\text{10d}} \\
\text{R} & \quad \text{R}_{\text{10c}} \\
\text{R} & \quad \text{R}_{\text{10b}} \\
\end{align*}
\]

(a);

where Z is a bond, -C(0)-, -0-, -S-, -S(O)-, -S(0)-, -N(R\(^{10}\))(-C(R\(^{10e}\))(R\(^{10f}\))=, or C\(_{2,3}\)-alkylene; R\(^2\) is hydrogen, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylsulfonyl, hydroxy, alkoxy, alkoxy carbonyl, -C(0)R\(^{12}\), -C(0)NR\(^{11}\)R\(^{11a}\), optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R\(^{10}\), R\(^{10a}\), R\(^{10b}\), R\(^{10c}\), R\(^{10d}\), R\(^{10e}\), and R\(^{10f}\) are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkythio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy; cyano; alkoxy carbonyl;
carboxy; amino; alkylamino; dialkylamino; -C(0)R_1^2; -C(0)NR_r^a; optionally substituted
cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally
substituted phenylalkyl; optionally substituted phenyloxy; optionally substituted
phenyloxyalkyl; optionally substituted heterocycloalkyl; optionally substituted
heterocycloalkylalkyl; optionally substituted heteroaryl; or optionally substituted
heteroarylalkyl; or R^{10a} and R^{10b} together form oxo; and all other groups are as defined in the
Summary of the Invention for a Compound of Formula I or as defined in any one of
embodiments B, Bl, B1a, B2, B2a, B3, (C)-C(8), and (C8a).

[00146] Embodiments (G1): In another embodiment, the Compound is according to
Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are
attached form HET according to formula (a):

\[
\begin{align*}
\text{(a);} \\
\text{where } Z \text{ is a bond; } R^{10}, R^{10a}, R^{10b}, R^{10c}, \text{ and } R^{10d} \text{ are independently hydrogen; halo; alkyl;}
\text{haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy;}
cyano; alkoxyacarbonyl; carboxy; amino; alkylamino; dialkylamino; -C(0)R^{12};
-C(0)NR^{11}R^{11a}; \text{ optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl;}
\text{optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted
phenyloxy; optionally substituted phenyloxyalkyl; optionally substituted heterocycloalkyl;}
\text{optionally substituted heterocycloalkylalkyl; optionally substituted heteroaryl; or optionally substituted
heteroarylalkyl; or } R^{10a} \text{ and } R^{10b} \text{ together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of}
\text{embodiments B, Bl, B1a, B2, B2a, B3, (C)-C(8), and (C8a).}
\end{align*}
\]

[00147] Embodiments (Gla): In another embodiment, the Compound is according to
Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are
attached form HET according to formula (a) where Z is a bond; one of R^{10}, R^{10a}, R^{10b}, R^{10c}, and
R^{10d} is alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy,
alkoxy, haloalkoxy, cyano, alkoxyacarbonyl, carboxy, amino, alkylamino, dialkylamino,
-C(0)R^{12}, -C(0)NR^{11}R^{11a}, optionally substituted cycloalkyl, optionally substituted
cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted
phenyloxy, optionally substituted phenyloxyalkyl, optionally substituted
heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; the remaining of R_{10}^{a}, R_{10}^{b}, R_{10}^{c}, and R_{10}^{d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

**[00148] Embodiments (Gib):** In another embodiment, the Compound is according to Formula 1(a) where R_{2} is -NR_{3}R_{4} and R_{3} and R_{4} together with the nitrogen to which they are attached form HET according to formula (a) where Z is bond; R_{10}^{a} is hydrogen, hydroxy, optionally substituted phenyl, or optionally substituted phenylalkyl; R_{10}^{b}, R_{10}^{c}, and R_{10}^{d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R_{2} is -NR_{3}R_{4} and R_{3} and R_{4} together with the nitrogen to which they are attached form HET according to formula (a) where Z is bond; R_{10}^{b} is alkyl, optionally substituted phenyl, or optionally substituted phenylalkyl; R_{10}^{a}, R_{10}^{b}, R_{10}^{c}, and R_{10}^{d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

**[00149] Embodiments (G2):** In another embodiment, the Compound is according to Formula 1(a) where R_{2} is -NR_{3}R_{4} and R_{3} and R_{4} together with the nitrogen to which they are attached form HET according to formula (a):

![Diagram](image_url)

(a);

where Z is -O-; R_{10}^{0}, R_{10}^{a}, R_{10}^{b}, R_{10}^{c}, and R_{10}^{d} are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxo; haloalkoxy; cyano; alkoxy carbonyl; carboxy; amino; alkylamino; dialkylamino; -C(0)R_{12}; -C(0)NR_{11}R_{11}; optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted phenyloxy; optionally substituted phenyloxyalkyl; optionally substituted heteroaryl; optionally substituted heteroarylalkyl; optionally substituted heterocycloalkyl; optionally substituted heterocycloalkylalkyl; optionally substituted heteroarylalkyl; or R_{10}^{a} and R_{10}^{b} together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I. In another
embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ and $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (a) where $Z$ is $-O-$; $R^{10}$, $R^{10a}$, $R^{10b}$, $R^{10c}$, and $R^{10d}$ are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00150] Embodiments (G2a): In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ and $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (a) where $Z$ is $-O-$; one of $R^{10}$, $R^{10a}$, $R^{10b}$, $R^{10c}$, and $R^{10d}$ is alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, $-C(0)R^{12}$, $-C(0)NR^{11}R^{11a}$, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenoxy, optionally substituted phenoxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylmethyl; the remaining of $R^{10}$, $R^{10a}$, $R^{10b}$, $R^{10c}$, and $R^{10d}$ are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00151] Embodiments (G2b): In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ and $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (a) where $Z$ is $-O-$; $R^{10a}$ is optionally substituted phenyloxyalkyl; $R^{10}$, $R^{10a}$, $R^{10b}$, $R^{10c}$, and $R^{10d}$ are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00152] Embodiments (G3): In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ and $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (a):

(a);
where \( Z \) is \(-S-, -S(O)-, \) or \(-S(0)\) \(_2^-\); \( R_{10}, R_{10a}, R_{10b}, R_{10c}, \) and \( R_{10d} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00153] Embodiments (G4): In another embodiment, the Compound is according to Formula I(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET according to formula (a):

![Diagram](https://via.placeholder.com/150)

(a);

where \( Z \) is \(-N(R^2)\); \( R^5 \) is hydrogen, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylsulfonyl, hydroxy, alkoxy, alkoxy carbonyl, \(-C(0)R \) \(_{12}^2\), \(-C(0)NR_{11}^3R_{12}^4\), optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; \( R_{10}, R_{10a}, R_{10b}, R_{10c}, \) and \( R_{10d} \) are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkythio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy; cyano; alkoxy carbonyl; carboxy; amino; alkylamino; dialkylamino; \(-C(0)R \) \(_{12}^2\); \(-C(0)NR_{11}^3R_{12}^4\); optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted phenyloxy; optionally substituted phenyloxy alkyl; optionally substituted heterocycloalkyl; optionally substituted heterocycloalkylalkyl; optionally substituted heterocycloalkylalkyl; optionally substituted heterocycloalkylalkyl; or optionally substituted heteroarylalkyl; or \( R_{10a} \) and \( R_{10b} \) together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where \( R^2 \) is \(-NR^3R^4 \) and \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET according to formula (a) where \( Z \) is \(-N(R^2)\); \( R_{10}, R_{10a}, R_{10b}, R_{10c}, \) and \( R_{10d} \) are hydrogen; \( R^5 \) is hydrogen, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylsulfonyl, hydroxy, alkoxy, alkoxy carbonyl, \(-C(0)R \) \(_{12}^2\), \(-C(0)NR_{11}^3R_{12}^4\), optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and all other groups are as defined in the
Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, B1a, B2, B2a, B3, (C)-(C)(8), and (C8a).

[00154] Embodiments (G4a): In another embodiment, the Compound is according to Formula I(a) where R² is -NR³R⁴ and R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (a) where Z is -N(R²)⁻; one of R², R₁₀, R₁₀b, R₁₀b, R₁₀c, and R₁₀d is not hydrogen; the remaining of R², R₁₀, R₁₀a, R₁₀b, R₁₀c, and R₁₀d are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, B1a, B2, B2a, B3, (C)-(C)(8), and (C8a).

[00155] Embodiments (G4b): In another embodiment, the Compound is according to Formula I(a) where R² is -NR³R⁴ and R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (a) where Z is -N(R²)⁻; R² is alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylsulfonyl, hydroxy, alkoxy, alkoxy carbonyl, -C(0)R₁₂, -C(0)NR₁₁a, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylmethyl; R₁₀, R₁₀a, R₁₀b, R₁₀c, and R₁₀d are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, B1a, B2, B2a, B3, (C)-(C)(8), and (C8a).

[00156] Embodiments (G4c): In another embodiment, the Compound is according to Formula I(a) where R² is -NR³R⁴ and R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (a) where Z is -N(R²)⁻; R² is alkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heteroaryl, or -C(0)R₁₂; R₁₀, R₁₀a, R₁₀b, R₁₀c, and R₁₀d are hydrogen; and R₁₂ and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, B1a, B2, B2a, B3, (C)-(C)(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R² is -NR³R⁴ and R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (a) where Z is -N(R²)⁻; R² is alkyl; or R² is phenyl optionally substituted with one, two, or three groups which are independently halo, haloalkyl, hydroxy, alkyl, alkoxy, alkylcarbonyl, and nitro; or R² is phenylmethyl optionally substituted with one, two, or three groups which are independently halo, haloalkyl, hydroxy, alkyl, alkoxy, alkylcarbonyl, or nitro; or R² is
heteroaryl optionally substituted with one, two, or three groups which are independently halo, haloalkyl, hydroxy, alkyl, alkoxy, alkylcarbonyl, or nitro; and R\text{h0}, R\text{i0a}, R\text{i0b}, R\text{l0c}, and R\text{l0d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00157] **Embodiments (G4d):** In another embodiment, the Compound is according to Formula I(a) where R\text{2} is -NR\text{3}R\text{4} and R\text{3} and R\text{4} together with the nitrogen to which they are attached form HET according to formula (a) where Z is -N(R\text{5})--; R\text{10} and R\text{2} are independently alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylsulfonyl, hydroxy, alkoxy, alkoxycarbonyl, -C(0)R\text{12}, -C(0)NR\text{11}R\text{10a}, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R\text{10a}, R\text{i0b}, R\text{l0c}, and R\text{l0d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00158] **Embodiments (G4e):** In another embodiment, the Compound is according to Formula I(a) where R\text{2} is -NR\text{3}R\text{4} and R\text{3} and R\text{4} together with the nitrogen to which they are attached form HET according to formula (a) where Z is -N(R\text{5})--; R\text{10} is optionally substituted phenyl; R\text{2} is alkyl or optionally substituted phenyl; R\text{10a}, R\text{i0b}, R\text{l0c}, and R\text{l0d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R\text{2} is -NR\text{3}R\text{4} and R\text{3} and R\text{4} together with the nitrogen to which they are attached form HET according to formula (a) where Z is -N(R\text{5})--; R\text{10} is phenyl optionally substituted with one, two, or three groups which are independently halo, haloalkyl, hydroxy, alkyl, alkoxy, alkylcarbonyl, or nitro; R\text{2} is alkyl, or phenyl optionally substituted with one, two, or three groups which are independently halo, haloalkyl, hydroxy, alkyl, alkoxy, alkylcarbonyl, or nitro; R\text{10a}, R\text{i0b}, R\text{l0c}, and R\text{l0d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00159] **Embodiments (G4f):** In another embodiment, the Compound is according to Formula I(a) where R\text{2} is -NR\text{3}R\text{4} and R\text{3} and R\text{4} together with the nitrogen to which they are
attached form HET according to formula (a) where Z is \(-\text{N}(\text{R}^5)\); \(\text{R}^2\) is alkyl; \(\text{R}^{10a}\) and \(\text{R}^{10b}\) together form oxo; \(\text{R}^{10}, \text{R}^{10c},\) and \(\text{R}^{10d}\) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00160] Embodiments (G5): In another embodiment, the Compound is according to Formula 1(a) where \(\text{R}^2\) is \(-\text{NR}^3\text{R}^4\) and \(\text{R}^3\) and \(\text{R}^4\) together with the nitrogen to which they are attached form HET according to formula (a):

![Chemical Structure](image)

(a);

where Z is \(-\text{C}(\text{R}^{10e})(\text{R}^{10f})\); \(\text{R}^{10}, \text{R}^{10a}, \text{R}^{10b}, \text{R}^{10c}, \text{R}^{10d}, \text{R}^{10e},\) and \(\text{R}^{10f}\) are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; halooalkoxy; cyano; alkoxyalkenyl; carboxyl; amino; alkylamino; dialkylaminoo; \(-\text{C}(0)\text{R}^{12}\); \(-\text{C}(0)\text{NR}^{11}\text{R}^{11a}\); optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted phenyloxy; optionally substituted phenyloxyalkyl; optionally substituted heterocycloalkyl; optionally substituted heterocycloalkylalkyl; optionally substituted heteroaryl; or optionally substituted heteroarylalkyl; or \(\text{R}^{10a}\) and \(\text{R}^{10b}\) together form oxo; or \(\text{R}^{10e}\) and \(\text{R}^{10f}\) together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \(\text{R}^2\) is \(-\text{NR}^3\text{R}^4\) and \(\text{R}^3\) and \(\text{R}^4\) together with the nitrogen to which they are attached form HET according to formula (a) where Z is \(-\text{C}(\text{R}^{10c})(\text{R}^{10f})\); \(\text{R}^{10}, \text{R}^{10a}, \text{R}^{10b}, \text{R}^{10c}, \text{R}^{10d}, \text{R}^{10e},\) and \(\text{R}^{10f}\) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \(\text{R}^2\) is \(-\text{NR}^3\text{R}^4\) and \(\text{R}^3\) and \(\text{R}^4\) together with the nitrogen to which they are attached form HET according to formula (a) where Z is \(-\text{C}(\text{R}^{10e})(\text{R}^{10f})\); \(\text{R}^{10c}\) and \(\text{R}^{10f}\) together form oxo; \(\text{R}^{10}, \text{R}^{10a}, \text{R}^{10b}, \text{R}^{10c},\) and \(\text{R}^{10d}\) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).
Embodiments (G5a): In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (a) where Z is -C(R^lo(R^{10f}), one of R^{lo}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, and R^{10f} is alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, -C(0)R^{12}, -C(0)NR^{11R^{11a}}, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenyloxy, optionally substituted phenoxycarbonyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; the remaining of R^{io}, R^{1oa}, R^{1ob}, R^{1oc}, R^{1od}, R^{1oe}, and R^{1of} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

Embodiments (G5b): In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (a) where Z is -C(R^{10e}(R^{10f})), one of R^{lo}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, and R^{10f} is alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, cyano, alkoxy carbonyl, -C(0)NR^{11R^{11a}}, optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenyloxy, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; the remaining of R^{io}, R^{1oa}, R^{1ob}, R^{1oc}, R^{1od}, R^{1oe}, and R^{1of} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (a) where Z is -C(R^{10e}(R^{10f})), one of R^{lo}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, and R^{10f} is alkyl; halo; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; cyano; alkoxy carbonyl; -C(0)NR^{11R^{11a}}, phenyl optionally substituted with one, two, or three groups which are independently alkyl, amino, halo, haloalkyl, alkoxy, or haloalkoxy; phenylalkyl optionally substituted with one, two, or three groups which are alkyl, amino, halo, haloalkyl, alkoxy, or haloalkoxy; phenyloxy optionally substituted with one, two, or three groups which are alkyl, amino, halo, haloalkyl, alkoxy, or haloalkoxy; cycloalkyl; heterocycloalkyl; heteroaryl optionally
substituted with one or two groups which are independently alkyl or cycloalkyl; the
remaining of R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, and R^{10f} are hydrogen; R^{11} and R^{11a} are
independently hydrogen or alkyl; and all other groups are as defined in the Summary of the Invention for a
Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(8), and (C8a).

[00163] Embodiments (G5c): In another embodiment, the Compound is according to
Formula I(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are
attached form HET according to formula (a) where Z is -C(R^{10e})(R^{10f})-; two of R^{10}, R^{10a}, R^{10b},
R^{10c}, R^{10d}, R^{10e}, and R^{10f} are independently alkyl, halo, haloalkyl, hydroxyalkyl, hydroxy,
cyano, -C(0)NR^{11}R^{11a}, or optionally substituted phenyl; the remaining of R^{10}, R^{10a}, R^{10b}, R^{10c},
R^{10d}, R^{10e}, and R^{10f} are hydrogen; and all other groups are as defined in the Summary of the
invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(8), and (C8a). In another embodiment, the Compound is according to
Formula I(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are
attached form HET according to formula (a) where Z is -C(R^{10e})(R^{10f})-; two of R^{10}, R^{10a}, R^{10b},
R^{10c}, R^{10d}, R^{10e}, and R^{10f} are independently alkyl; halo; haloalkyl; hydroxyalkyl; hydroxy;
cyano; -C(0)NR^{11}R^{11a}; or phenyl optionally substituted with one or two halo, alkyl,
haloalkyl, or alkoxy; R^{11} and R^{11a} are independently hydrogen or alkyl; the remaining of R^{10},
R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10e}, and R^{10f} are hydrogen; and all other groups are as defined in the
Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(8), and (C8a).

[00164] Embodiments (G5d): In another embodiment, the Compound is according to
Formula I(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are
attached form HET according to formula (a) where Z is -C(R^{10e})(R^{10f})-; one of R^{10}, R^{10a}, R^{10b},
R^{10c}, and R^{10d} is optionally substituted phenyl; R^{10e} and R^{10f} together form oxo; the remaining
of R^{10}, R^{10a}, R^{10b}, R^{10c}, and R^{10d} are hydrogen; and all other groups are as defined in the
Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(8), and (C8a). In another embodiment, the
Compound is according to Formula I(a) where R^2 is -NR^3R^4 and R^3 and R^4 together with the nitrogen to which they are
attached form HET according to formula (a) where Z is -C(R^{10e})(R^{10f})-; one of R^{10}, R^{10a}, R^{10b},
R^{10c}, and R^{10d} is phenyl optionally substituted with one or two halo; R^{10e} and R^{10f} together form oxo; the remaining of R^{10}, R^{10a}, R^{10b}, R^{10c}, and R^{10d}
are hydrogen; and all other groups are as defined in the Summary of the Invention for a
Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00165] Embodiments (G5e): In another embodiment, the Compound is according to Formula I(a) where \( R^2 \) is \(-\text{NR}^3\text{R}^4 \) and \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET according to formula (a) where \( Z \) is \(-\text{C}(R^{10c})(R^{10f})\); one of \( R^{10a}, R^{10a}, \text{R}^{10b}, R^{10c} \), \( R^{10e} \), and \( R^{10d} \) is optionally substituted phenyl; \( R^{10e} \) and \( R^{10f} \) are each halo; the remaining of \( R^{10}, R^{10a}, R^{10b}, R^{10c}, \) and \( R^{10d} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00166] Embodiments (G6): In another embodiment, the Compound is according to Formula I(a) where \( R^2 \) is \(-\text{NR}^3\text{R}^4 \) and \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET according to formula (a):

\[
\begin{align*}
R^{10a} & \quad Z \quad R^{10c} \\
R^{10b} & \quad R^{10d} \\
R^{10} & \quad N
\end{align*}
\]

(a);

where \( Z \) is \( C_{2,3} \)-alkylene; \( R^{10}, R^{10a}, R^{10b}, R^{10c}, \) and \( R^{10d} \) are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy; cyano; alkoxy carbonyl; carboxy; amino; alkylamino; dialkylamino; \(-\text{C}(0)\text{R}^{12}; -\text{C}(0)\text{NR}^{11}\text{R}^{11a} \); optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted phenyloxy; optionally substituted phenyloxyalkyl; optionally substituted heterocycloalkyl; optionally substituted heterocycloalkylalkyl; optionally substituted heteroaryl; or optionally substituted heteroarylalkyl; or \( R^{10a} \) and \( R^{10b} \) together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00167] Embodiments (G6a): In another embodiment, the Compound is according to Formula I(a) where \( R^2 \) is \(-\text{NR}^3\text{R}^4 \) and \( R^3 \) and \( R^4 \) together with the nitrogen to which they are attached form HET according to formula (a) where \( Z \) is \( C_{2,3} \)-alkylene; one of \( R^{10}, R^{10a}, R^{10b}, R^{10c}, \) and \( R^{10d} \) is alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, \(-\text{C}(0)\text{R}^{12}; -\text{C}(0)\text{NR}^{11}\text{R}^{11a} \); optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl,
optionally substituted phenyloxy, optionally substituted phenyloxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroaryalkyl; or R\textsubscript{10}\textsuperscript{a} and R\textsubscript{10}\textsuperscript{b} together form oxo; the remaining of R\textsubscript{10}, R\textsubscript{10}\textsuperscript{a}, R\textsubscript{10}\textsuperscript{b}, R\textsubscript{10}\textsuperscript{c}, and R\textsubscript{10}\textsuperscript{d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00168] **Embodiments (G6b):** In another embodiment, the Compound is according to Formula 1(a) where R\textsuperscript{2} is -NR\textsuperscript{3}R\textsuperscript{4} and R\textsuperscript{3} and R\textsuperscript{4} together with the nitrogen to which they are attached form HET according to formula (a) where Z is C\textsubscript{2-3}-alkylene; R\textsuperscript{10} is hydrogen or optionally substituted phenyl; and R\textsubscript{10}\textsuperscript{a}, R\textsubscript{10}\textsuperscript{b}, R\textsubscript{10}\textsuperscript{c}, and R\textsubscript{10}\textsuperscript{d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R\textsuperscript{2} is -NR\textsuperscript{3}R\textsuperscript{4} and R\textsuperscript{3} and R\textsuperscript{4} together with the nitrogen to which they are attached form HET according to formula (a) where Z is C\textsubscript{2,5}-alkylene; R\textsuperscript{10} is hydrogen or phenyl; and R\textsuperscript{10}\textsuperscript{a}, R\textsuperscript{10}\textsuperscript{b}, R\textsuperscript{10}\textsuperscript{c}, and R\textsuperscript{10}\textsuperscript{d} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00169] **Embodiments (G7):** In another embodiment, the Compound is according to Formula 1(a) where

R\textsuperscript{1} is phenyl substituted with one or two R\textsuperscript{5} groups which are independently nitro, -NR\textsuperscript{8}R\textsuperscript{8a}, -C(0)NR\textsuperscript{8}R\textsuperscript{8a}, -NR\textsuperscript{8}C(0)OR\textsuperscript{9}, or heteroaryl optionally substituted with 1, 2, or 3 R\textsuperscript{14}; or R\textsuperscript{1} is heteroaryl optionally substituted with one, two, or three R\textsuperscript{7};

R\textsuperscript{2} is -NR\textsuperscript{3}R\textsuperscript{4} and R\textsuperscript{3} and R\textsuperscript{4} together with the nitrogen to which they are attached form HET according to formula (a):

![Diagram](image)

(a);

where Z is a bond, -C(O)-, -O-, -S-, -S(O)-, -S(O)\textsubscript{2}-, -N(R\textsuperscript{5})-, -C(R\textsuperscript{10})\textsuperscript{c}(R\textsuperscript{10})\textsuperscript{d}, or C\textsubscript{2-3}-alkylene; R\textsuperscript{5} is hydrogen, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylsulfonyl, hydroxy, alkoxy, alkoxy carbonyl, -C(0)R\textsuperscript{12}, -C(0)NR\textsuperscript{11}R\textsuperscript{11a}, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted...
phenylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroarylalkyl; 

R\textsuperscript{10}, R\textsuperscript{10a}, R\textsuperscript{10b}, R\textsuperscript{10c}, R\textsuperscript{10d}, and R\textsuperscript{10f} are independently hydrogen; halo; alkyl; haloalkyl; haloalkenyl; hydroxyalkyl; alkylthio; alkylsulfonyl; hydroxy; alkoxy; haloalkoxy; cyano; alkoxy carbonyl; carboxy; amino; alkyaminio; dialkylaminio; -C(\text{O})R\textsuperscript{11}; -C(\text{O})NR\textsuperscript{11a}; optionally substituted cycloalkyl; optionally substituted cycloalkylalkyl; optionally substituted phenyl; optionally substituted phenylalkyl; optionally substituted phenyloxy; optionally substituted phenyloxyalkyl; optionally substituted heterocycloalkylalkyl; optionally substituted heteroaryl; or optionally substituted heteroarylalkyl; or R\textsuperscript{10a} and R\textsuperscript{10b} together form oxo; or R\textsuperscript{10c} and R\textsuperscript{10f} together form oxo; 

R\textsuperscript{11} hydrogen, alkyl, or alkenyl; 

R\textsuperscript{11a} hydrogen, alkyl, or alkenyl; 

R\textsuperscript{12} is alkyl, or optionally substituted heteroaryl; and 

each R\textsuperscript{14}, when present, is halo, alkyl, or alkoxy carbonyl. 

**Embodiments (H):** In another embodiment, the Compound is according to Formula 1(a) where R\textsuperscript{2} is -NR\textsuperscript{3}R\textsuperscript{4} where R\textsuperscript{3} and R\textsuperscript{4} together with the nitrogen to which they are attached form HET according to formula (b): 

![Diagram](b); 

where 

(a) R\textsuperscript{20} and R\textsuperscript{20c} or R\textsuperscript{20} and R\textsuperscript{20d} together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety; or 

(b) R\textsuperscript{20a} and R\textsuperscript{20c} together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety; or 

(c) R\textsuperscript{20a} and R\textsuperscript{20b} together with the carbon to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety; 

where the cycloalkyl and heterocycloalkyl are optionally substituted with R\textsuperscript{10} and R\textsuperscript{10a} and the R\textsuperscript{10} and R\textsuperscript{10a} are independently hydrogen, alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl,
carboxy, amino, alkylamino, dialkylamino, \(-\text{C}(0)\text{R}^{12}, \text{C}(0)\text{NR}^{1}\text{R}^{\text{lla}}\), optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenoxy, optionally substituted phenoxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and the remaining of \(\text{R}^{20}, \text{R}^{20a}, \text{R}^{20b}, \text{R}^{20c}, \text{R}^{20d}\) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(8), and (C8a).

[00171] Embodiments (HI): In another embodiment, the Compound is according to Formula I(a) where \(\text{R}^{2}\) is \(-\text{NR}^{3}\text{R}^{4}\) where \(\text{R}^{3}\) and \(\text{R}^{4}\) together with the nitrogen to which they are attached form HET according to formula (b) where \(\text{R}^{20a}\) and \(\text{R}^{20e}\) together with the carbons to which they are bonded form cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety and where the cycloalkyl and heterocycloalkyl are optionally substituted with \(\text{R}^{10}\) and \(\text{R}^{10a}\); \(\text{R}^{20}, \text{R}^{20b}\), and \(\text{R}^{20d}\) are hydrogen; \(\text{R}^{10}\) and \(\text{R}^{10a}\) are independently hydrogen, alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkythio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxycarbonyl, carboxy, amino, alkylamino, dialkylamino, \(-\text{C}(0)\text{R}^{12}, -\text{C}(0)\text{NR}^{1}\text{R}^{\text{lla}}\), optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenoxy, optionally substituted phenyloxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where \(\text{R}^{2}\) is \(-\text{NR}^{3}\text{R}^{4}\) where \(\text{R}^{3}\) and \(\text{R}^{4}\) together with the nitrogen to which they are attached form HET according to formula (b) and is
octahydrocyclopenta[c]pyrrolyl, octahydropyrrolo[3,4-c]pyrrolyl, (3aR,6aS)-5-methyloctahydrocyclopenta[c]pyrrolyl, or (3aS,6aR)-5-methyl-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrolyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00172] Embodiments (H2): In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (b) where R²⁰ and R²⁰d together with the carbons to which they are bonded form a cycloalkyl or heterocyloalkyl such that HET is a bridged bicyclic moiety and where the cycloalkyl and heterocyloalkyl are optionally substituted with R₁₀ and R₁₀a; R²₀a, R²₀b, and R²₀c are hydrogen; R₁₀ and R₁₀a are independently hydrogen, alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkythio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxycarbonyl, carboxy, amino, alkylamino, dialkylamino, -C(0)R₁₂, -C(0)NR₁₁R₁₁a, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenyloxy, optionally substituted phenyloxalkyl, optionally substituted heteroaryl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroarylalkyl, and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00173] Embodiments (H3): In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (b) where R²⁰ and R²⁰b together with the carbon to which they are bonded form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R₁₀ and R₁₀a; and R₂₀, R₂₀c, and R₂₀d are hydrogen; R₁₀ and R₁₀a are independently hydrogen,
alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, -C(0)R, -C(0)NR, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenyloxy, optionally substituted phenyloxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (b) where R²⁰ and R²₀b together with the carbon to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R¹⁰ and R¹₀a; and R¹₀, R¹₀a, R²⁰, R²₀c, and R²₀d are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

**Embodiments (H4):** In another embodiment, the Compound is according to Formula I(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (b) where R²⁰ and R²₀c together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R¹⁰c and R¹₀a; and R²₀a, R²₀b, and R²₀d are hydrogen; R¹₀ and R¹₀a are independently hydrogen, alkyl, halo, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, hydroxy, alkoxy, haloalkoxy, cyano, alkoxy carbonyl, carboxy, amino, alkylamino, dialkylamino, -C(0)R, -C(0)NR, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenoxy, optionally substituted phenoxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (b) where R²⁰ and R²₀c together with the carbons
to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with $R^{10}$ and $R^{10a}$; and $R^{10}, R^{10a}, R^{20a}, R^{20b}$, and $R^{20d}$ are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-(C8), and (C8a).

**Embodiments (H5):** In another embodiment, the Compound is according to Formula 1(a) where

$R^1$ is phenyl substituted with one or two $R^6$ groups which are independently nitro, $-NR^8R^8a$, $-C(0)NR^8R^8a$, $-NR^8C(0)OR^9$, or heteroaryl optionally substituted with 1, 2, or 3 $R^{14}$; or

$R^1$ is heteroaryl optionally substituted with one, two, or three $R^7$;

$R^2$ is $-NR^3R^3$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (b):

![Diagram](b)

where

(a) $R^{20}$ and $R^{20c}$ or $R^{20}$ and $R^{20d}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety; or

(b) $R^{20a}$ and $R^{20e}$ together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety; or

(c) $R^{20a}$ and $R^{20b}$ together with the carbon to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety;

where the cycloalkyl and heterocycloalkyl are optionally substituted with $R^{10}$ and $R^{10a}$ where

$R^{10}$ and $R^{10a}$ are independently hydroxy, alkyl, haloalkyl, or optionally substituted phenyl; and the remaining of $R^{20}$, $R^{20a}$, $R^{20b}$, $R^{20c}$, and $R^{20d}$ are hydrogen;

each $R^7$, when present, is independently alkyl, $-NR^8R^8a$, $-C(0)NR^8R^8a$, $-NR^8C(0)OR^9$, or $-NR^8C(0)R^9$;

$R^8$ is hydrogen, alkyl, or alkenyl;

$R^{8a}$ is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;

$R^9$ is alkyl or haloalkyl; and

each $R^{14}$, when present, is halo, alkyl, or alkoxy carbonyl.
Embodiments (R): In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (b):

\[
\begin{align*}
\text{(b)}; \\
& R^{20a} \ \\
& R^{20b} \ \\
& R^{20d} \ \\
& R^{20c}
\end{align*}
\]

where \( R^{20} \) and \( R^{20d} \) together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl and \( R^{20a} \) and \( R^{20c} \) together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a tricyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with \( R^{10} \) and \( R^{10a} \); and \( R^{20b} \) is hydrogen; and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

Embodiments (J): In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (c):

\[
\begin{align*}
\text{(c)}; \\
& R^{20a} \ \\
& R^{20b} \ \\
& R^{20d} \ \\
& R^{20c} \ \\
& R^{20e} \ \\
& R^{20f}
\end{align*}
\]

(a) \( R^{20} \) and \( R^{20d} \) or \( R^{20} \) and \( R^{20c} \) together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety

(b) \( R^{20e} \) and \( R^{20f} \) together with the carbons to which they are bonded form cycloalkyl or heterocycloalkyl such that HET is a spirocyclic bicyclic moiety,

(c) \( R^{20} \) and \( R^{20a} \) or \( R^{20a} \) and \( R^{20c} \) together with the carbons to which they are bonded form a cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety;

where the cycloalkyl and heterocycloalkyl are optionally substituted with \( R^{10} \) and \( R^{10a} \); and the remaining of \( R^{20}, R^{20a}, R^{20c}, R^{20d}, R^{20e}, \) and \( R^{20f} \) are \( R^{10}, R^{10a}, R^{10c}, R^{10d}, R^{10e}, R^{10f}, \) and \( R^{10h} \), respectively; each \( R^{10} \), each \( R^{10a}, R^{10e}, R^{10d}, R^{10e}, R^{10f}, \) and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).
[00178] **Embodiments (Jl):** In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is -NR$^3$R$^4$ where $R^3$ and R$^4$ together with the nitrogen to which they are attached form HET according to formula (c) where $R^{20}$ and $R^{20d}$ together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety and where the cycloalkyl and heterocycloalkyl are optionally substituted with $R^{10}$ and $R^{10a}$; and $R^{20a}$, $R^{20c}$, $R^{20e}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively; $R^{10}$, each $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is -NR$^3$R$^4$ where $R^3$ and R$^4$ together with the nitrogen to which they are attached form HET according to formula (c) where $R^{20}$ and $R^{20d}$ together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20e}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10c}$ are hydrogen, $R^{10e}$ and $R^{10f}$ together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00179] **Embodiments (Jl a):** In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is -NR$^3$R$^4$ where $R^3$ and R$^4$ together with the nitrogen to which they are attached form HET according to formula (c) where $R^{20}$ and $R^{20d}$ together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20e}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10c}$ are hydrogen, $R^{10e}$ and $R^{10f}$ together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00180] **Embodiments (Jib):** In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is -NR$^3$R$^4$ where $R^3$ and R$^4$ together with the nitrogen to which they are attached form HET according to formula (c) where $R^{20}$ and $R^{20d}$ together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20e}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10c}$ are hydrogen, $R^{10e}$ is hydrogen, hydroxy, or alkyl, and $R^{10f}$ is hydrogen, hydroxy, alkyl, haloalkyl, hydroxyalkyl, amino, halo, or optionally substituted phenyl; and all other groups are as defined in the Summary of the Invention for a Compound.
of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00181] **Embodiments (Jlc)**: In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is -NR\(^3\)R\(^4 \) where R\(^3 \) and R\(^4 \) together with the nitrogen to which they are attached form HET according to formula (c) where R\(^{20} \) and R\(^{20d} \) together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and R\(^{20a} \), R\(^{20c} \), R\(^{20e} \), and R\(^{20f} \) are R\(^{10a} \), R\(^{10c} \), R\(^{10e} \), and R\(^{10f} \), respectively, where R\(^{10a} \) and R\(^{10f} \) are hydrogen, R\(^{10c} \) is hydrogen, and R\(^{10f} \) is hydroxy; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is -NR\(^3\)R\(^4 \) where R\(^3 \) and R\(^4 \) together with the nitrogen to which they are attached form HET according to formula (c) where R\(^{20} \) and R\(^{20d} \) together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and R\(^{20a} \), R\(^{20c} \), R\(^{20e} \), and R\(^{20f} \) are R\(^{10a} \), R\(^{10c} \), R\(^{10e} \), and R\(^{10f} \), respectively, where R\(^{10a} \) and R\(^{10f} \) are hydrogen, R\(^{10c} \) is hydroxy, and R\(^{10f} \) is haloalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^2 \) is -NR\(^3\)R\(^4 \) where R\(^3 \) and R\(^4 \) together with the nitrogen to which they are attached form HET according to formula (c) where R\(^{20} \) and R\(^{20d} \) together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and R\(^{20a} \), R\(^{20c} \), R\(^{20e} \), and R\(^{20f} \) are R\(^{10a} \), R\(^{10c} \), R\(^{10e} \), and R\(^{10f} \), respectively, where R\(^{10a} \) and R\(^{10f} \) are hydrogen, R\(^{10c} \) is hydroxy, and R\(^{10f} \) is alkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to
Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (c) where $R^{20}$ and $R^{20d}$ together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20c}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10e}$ are hydrogen, $R^{10e}$ is alkyl, and $R^{10f}$ is halo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20e}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10e}$ are hydrogen, $R^{10e}$ is hydroxy, and $R^{10f}$ is phenyl optionally substituted with one or two halo or haloalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20e}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10e}$ are hydrogen, $R^{10e}$ is hydrogen, and $R^{10f}$ is haloalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20c}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10e}$ are hydrogen, $R^{10e}$ is hydroxy, and $R^{10f}$ is hydroxyalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and $R^{20a}$, $R^{20c}$, $R^{20c}$, and $R^{20f}$ are $R^{10a}$, $R^{10c}$, $R^{10e}$, and $R^{10f}$, respectively, where $R^{10a}$ and $R^{10e}$ are hydrogen, $R^{10e}$ is hydroxy, and $R^{10f}$ is hydroxyalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).
cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and R^{20a}, R^{20c}, R^{20e}, and R^{20f} are R^{10a}, R^{10c}, R^{10e}, and R^{10f}, respectively, where R^{10a} and R^{10c} are hydrogen, R^{10e} is hydrogen, and R^{10f} is amino; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (c) where R^{20} and R^{20d} together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET forms a bridged bicyclic moiety; and R^{20a}, R^{20c}, R^{20e}, and R^{20f} are R^{10a}, R^{10c}, R^{10e}, and R^{10f}, respectively, where R^{10a}, R^{10e}, and R^{10e} are hydrogen, and R^{10f} is hydroxyalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00182] ** embodiments (J2): In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (c) where R^{20} and R^{20f} together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; and R^{20a}, R^{20d}, R^{20e}, and R^{20f} are R^{10a}, R^{10d}, R^{10e}, and R^{10f}, respectively; R^{10}, each R^{10a}, R^{10d}, R^{10e}, and R^{10f}, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (c) where R^{20} and R^{20c} together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a bridged bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; and R^{20a}, R^{20d}, R^{20e}, and R^{20f} are R^{10a}, R^{10d}, R^{10e}, and R^{10f}, respectively where each R^{0a}, R^{10d}, R^{0e}, and R^{10f} are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00183] ** embodiments (J3): In another embodiment, the Compound is according to Formula I(a) where R^2 is -NR^3R^4 where R^3 and R^4 together with the nitrogen to which they are attached form HET according to formula (c) where R^{20e} and R^{20f} together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a
spirocyclic bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; and R^{20}, R^{20a}, R^{20e}, and R^{20d} are R^{10}, R^{10a}, R^{10c}, and R^{10d}, respectively; each R^{1}, each R^{10a}, R^{10c}, and R^{10d}, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00184] Embodiments (J4): In another embodiment, the Compound is according to Formula I(a) where R^{2} is -NR^{3}R^{4} where R^{3} and R^{4} together with the nitrogen to which they are attached form HET according to formula (c) where R^{20} and R^{20a} together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; and R^{20c}, R^{20d}, R^{20e}, and R^{20f} are R^{10c}, R^{10d}, R^{10e}, and R^{10f}, respectively; R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10e}, R^{10f}, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^{2} is -NR^{3}R^{4} where R^{3} and R^{4} together with the nitrogen to which they are attached form HET according to formula (c) where R^{20} and R^{20a} together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; R^{20c}, R^{20d}, R^{20e}, and R^{20f} are R^{10c}, R^{10d}, R^{10e}, and R^{10f}, respectively and R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10e}, and R^{10f} are hydrogen; R^{10}, R^{10a}, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00185] Embodiments (J5): In another embodiment, the Compound is according to Formula I(a) where R^{2} is -NR^{3}R^{4} where R^{3} and R^{4} together with the nitrogen to which they are attached form HET according to formula (c) where R^{20a} and R^{20c} together with the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety, where the cycloalkyl and heterocycloalkyl are optionally substituted with R^{10} and R^{10a}; and R^{20}, R^{20a}, R^{20d}, and R^{20f} are R^{10c}, R^{10d}, and R^{10f}, respectively; each R^{10}, R^{10a}, R^{10b}, R^{10c}, R^{10d}, R^{10f}, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula I(a) where R^{2} is -NR^{3}R^{4} where R^{3} and R^{4} together with the nitrogen to which they are attached form HET according to formula (c) where R^{20a} and R^{20c} together with
the carbons to which they are attached form cycloalkyl or heterocycloalkyl such that HET is a fused bicyclic moiety; and \( R^{20}, R^{20c}, R^{20d}, \) and \( R^{20f} \) are \( R^{10}, R^{10c}, R^{10d}, \) and \( R^{10f} \), respectively and \( R^{10}, R^{10c}, R^{10d}, \) and \( R^{10f} \) are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00186] **Embodiment (J6):** In another embodiment, the Compound is according to Formula 1(a) where \( R^{2} \) is \(-NR^{3}R^{4}\) where \( R^{3} \) and \( R^{4} \) together with the nitrogen to which they are attached form HET according to formula (c) which is according to formula (g)

![Diagram](g)

where \( R^{10e}, R^{10f} \), and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00187] **Embodiment (J6a):** In another embodiment, the Compound is according to Formula 1(a) where \( R^{2} \) is \(-NR^{3}R^{4}\) where \( R^{3} \) and \( R^{4} \) together with the nitrogen to which they are attached form HET according to formula (c) which is according to formula (g) where \( R^{10e} \) is hydrogen, alkyl, halo, haloalkyl, hydroxy, or optionally substituted phenyl; \( R^{10f} \) is hydrogen, hydroxy, amino, alkyl, hydroxyalkyl, or haloalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \( R^{2} \) is \(-NR^{3}R^{4}\) where \( R^{3} \) and \( R^{4} \) together with the nitrogen to which they are attached form HET according to formula (c) which is according to formula (g) where \( R^{10e} \) is hydrogen, alkyl, halo, haloalkyl, hydroxy, or phenyl optionally substituted with one or two groups which are halo or haloalkyl; \( R^{10f} \) is hydrogen, hydroxy, amino, alkyl, hydroxyalkyl, or haloalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00188] **Embodiment (J6b):** In another embodiment, the Compound is according to Formula 1(a) where \( R^{2} \) is \(-NR^{3}R^{4}\) where \( R^{3} \) and \( R^{4} \) together with the nitrogen to which they are attached form HET according to formula (c) which is according to formula (g) where \( R^{10e} \) and \( R^{10f} \) together form o xo; and all other groups are as defined in the Summary of the
Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00189] Embodiment (J7): In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h)

(h)

where R₁⁰, R₁⁰c, R₁⁰f, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment of embodiment (J7), the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where one of R₁⁰, R₁⁰c, and R₁⁰f is not hydrogen and the others are as defined in embodiment (J7); and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00190] Embodiment (J7a): In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where R₁⁰ is hydrogen; R₁⁰c is -C(0)NH₂, hydroxy, alkoxy, cyano, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted phenyl, optionally substituted phenylalkyl, optionally substituted phenyloxy, or optionally substituted heteroaryl; and R₁⁰f is hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where R₁⁰ is hydrogen; R₁⁰c is -C(0)NH₂, hydroxy, alkoxy, cyano, alkyl, haloalkyl, haloalkenyl, hydroxyalkyl, alkylthio, alkylsulfonyl, cycloalkyl, heterocycloalkyl, phenyl optionally substituted with one or two halo, phenylalkyl optionally substituted with one or two halo,
phenyloxy optionally substituted with one or two halo, heteroaryl optionally substituted with one alkyl or cycloalkyl; and $R_{10}^{ef}$ is hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00191] **Embodiment (J7b):** In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where $R_{10}^i$ is alkyl, or optionally substituted phenyl; $R_{10e}^{io}$ is hydroxy, alkyl, haloalkyl, or cyano; and $R_{10f}^{io}$ is hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where $R_{10}^i$ is alkyl, or phenyl optionally substituted with one or two groups which are independently halo, or haloalkyl; $R_{10e}^{io}$ is hydroxy, alkyl, haloalkyl, or cyano; and $R_{10f}^{io}$ is hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00192] **Embodiment (J7c):** In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where $R_{10e}^{io}$ and $R_{10f}^{io}$ together form oxo; and $R_{10}^i$ and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where $R_{10}^i$ is hydrogen, or optionally substituted phenyl; $R_{10e}^{io}$ and $R_{10f}^{io}$ together form oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where $R^2$ is $-NR^3R^4$ where $R^3$ and $R^4$ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where $R_{10}^i$ is hydrogen, or phenyl optionally substituted with one or two halo; $R_{10e}^{io}$ and $R_{10f}^{io}$ together form
oxo; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00193] **Embodiment (J7d):** In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where R₁⁰ is alkyl, haloalkyl, alkoxycarbonyl, or optionally substituted phenyl; R₁⁰ε and R₁⁰f are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where R₁⁰ is alkyl, haloalkyl, alkoxycarbonyl, or phenyl optionally substituted with one, two, or three groups which are independently dialkylamino, alkyl, halo, haloalkyl, or alkoxy; R₁⁰ε and R₁⁰f are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00194] **Embodiment (J7e):** In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where R₁⁰ is optionally substituted phenyl; R₁⁰ε is hydroxy, or halo; and R₁⁰f is alkyl, halo, haloalkyl, or hydroxyalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where R₁⁰ is phenyl optionally substituted with one or two halo; R₁⁰ε is hydroxy, or halo; and R₁⁰f is alkyl, halo, haloalkyl, or hydroxyalkyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00195] **Embodiment (J7f):** In another embodiment, the Compound is according to Formula 1(a) where R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h)
where \(R^{10}\) is hydrogen; \(R^{10c}\) is hydroxy, halo, alkyl, or cyano; and \(R^{10f}\) is alkyl, haloalkyl, halo, \(-\text{C}(0)\text{NH}_{2}\), or optionally substituted phenyl; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound is according to Formula 1(a) where \(R^2\) is \(-\text{NR}^3\text{R}^4\) where \(R^3\) and \(R^4\) together with the nitrogen to which they are attached form HET according to formula (c) which is further according to formula (h) where \(R^{10}\) is hydrogen; \(R^{10c}\) is hydroxy, halo, alkyl, or cyano; and \(R^{10f}\) is alkyl, haloalkyl, halo, \(-\text{C}(0)\text{NH}_{2}\), or phenyl optionally substituted with one or two groups which are independently halo, alkyl, haloalkyl, or alkoxy; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00196] Embodiments (J8v). In another embodiment, the Compound is according to Formula 1(a) where \(R^2\) is \(-\text{NR}^3\text{R}^4\) where \(R^3\) and \(R^4\) together with the nitrogen to which they are attached form HET according to formula (c):

(a) \(R^{20}\) and \(R^{20d}\) or \(R^{20}\) and \(R^{20c}\) together with the carbons to which they are bonded form a cycloalkyl such that HET is a bridged moiety.

(b) \(R^{20c}\) and \(R^{20f}\) together with the carbons to which they are bonded form cycloalkyl such that HET is a spirocyclic moiety.

(c) \(R^{20}\) and \(R^{20a}\) or \(R^{20a}\) and \(R^{20c}\) together with the carbons to which they are bonded form a cycloalkyl such that HET is a fused bicyclic moiety;

where the cycloalkyl is optionally substituted with \(R^{10}\) and \(R^{10a}\) where \(R^{10}\) and \(R^{10a}\) are independently alkyl or together form oxo; and the remaining of \(R^{20}\), \(R^{20a}\), \(R^{20c}\), \(R^{20d}\), \(R^{20e}\), and \(R^{20f}\) are \(R^{10}\), \(R^{10a}\), \(R^{10c}\), \(R^{10d}\), \(R^{10e}\), and \(R^{10f}\), respectively, where \(R^{10}, R^{10a}, R^{10c}, R^{10d}, R^{10e},\) and \(R^{10f}\) are independently hydrogen, hydroxy, alkyl, halo, haloalkyl, hydroxyalkyl, optionally substituted phenyl, or amino, or \(R^{10c}\) and \(R^{10f}\) together form oxo;

each \(R^7\), when present, is independently alkyl, \(-\text{NR}^8\text{R}^{8a}, -\text{C}(0)\text{NR}^8\text{R}^{8a}, -\text{NR}^8\text{C}(0)\text{OR}^9\), or \(-\text{NR}^8\text{C}(0)\text{OR}^9\);

\(R^8\) is hydrogen, alkyl, or alkenyl;
R^8 is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;
R^9 is alkyl or haloalkyl; and
each R^1^4, when present, is halo, alkyl, or alkoxy carbonyl.

[00197] **Embodiments (K):** In another embodiment, the Compound of Formula is according to Formula I where R^2^ is -NR^3^R^4^ where R^3^ and R^4^ together with the nitrogen to which they are attached form HET according to formula (d), (e), or (f):

![Diagram](image-url)

where all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound of Formula is according to Formula I where R^2^ is -NR^3^R^4^ where R^3^ and R^4^ together with the nitrogen to which they are attached form HET according to formula (d) or (f) where R^10^ is optionally substituted phenyl, R^10c^ and R^10f^ together form oxo, and R^10a^, R^10c^, and R^10d^ are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a). In another embodiment, the Compound of Formula is according to Formula I where R^2^ is -NR^3^R^4^ where R^3^ and R^4^ together with the nitrogen to which they are attached form HET according to formula (e) where R^10^ or R^10e^ is optionally substituted phenyl, and the remaining of R^10^, R^10a^, R^10c^, R^10d^, R^10e^, and R^10f^ are hydrogen; and all other groups are as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00198] **Embodiments (K):** In another embodiment, the Compound of Formula is according to Formula I where

R^1^ is phenyl substituted with one or two R^6^ groups independently which are independently nitro, -NR^8^R^8a^, -C(0)NR^8^R^8a^, -NR^8C(0)OR^9^, or heteroaryl optionally substituted with 1, 2, or 3 R^1^; or
R^1^ is heteroaryl optionally substituted with one, two, or three R^7^;
R² is -NR³R⁴ where R³ and R⁴ together with the nitrogen to which they are attached form HET according to formula (d), (e), or (f):

![Chemical Structures](image)

where R¹⁰, R¹⁰a, R¹⁰c, R¹⁰d, R¹⁰e, and R¹⁰f are independently hydrogen, hydroxy, alkyl, haloalkyl, or optionally substituted phenyl; or, in formula (d) or (f), R¹⁰e and R¹⁰f together form oxo;

each R⁷, when present, is independently alkyl, -NR₈R₈a, -C(0)NR₈R₈a, -NR₈C(0)OR₉, or -NR₈C(0)R₉;

R⁸ is hydrogen, alkyl, or alkenyl;

R₈a is hydrogen, alkyl, haloalkyl, optionally substituted heterocycloalkyl, or optionally substituted phenylalkyl;

R₉ is alkyl or haloalkyl; and
each R¹⁴, when present, is halo, alkyl, or alkoxy carbonyl.

[00199] In another embodiment (L), the Compound is according to Formula 1(e)

![Chemical Structure](image)

where R¹⁰, R¹⁰a, R¹⁰b, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B'1, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00200] In another embodiment (M), the Compound of Formula I is according to Formula 1(f)
where $R^{10}$, $R^{10a}$, and $R^{10b}$, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00201] In another embodiment (N), the Compound of Formula I is according to Formula Kg)

![Diagram](1(g)

where $R^{1}$, $R^{1a}$, and $R^{1b}$, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00202] In another embodiment (P), the Compound of Formula I is according to Formula 1(h)

![Diagram](1(h)

where $R^{10}$, $R^{10a}$, and $R^{10b}$, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, B1, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

[00203] In another embodiment (Q), the Compound of Formula I is according to Formula I(P)

![Diagram](I(P)

where each $R^i$, when $R^i$ is present, is independently alkyl, alkoxy, or halo; and $R^{10c}$, $R^{10f}$, and all other groups are independently as defined in the Summary of the Invention for a
Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

In another embodiment (Q1), the Compound of Formula I is according to Formula I(n)

where each Rₐ, when Rₐ is present, is independently alkyl, alkoxy, or halo; and R₁₀ₑ, R₁₀ᶠ, and all other groups are independently as defined in the Summary of the Invention for a Compound of Formula I or as defined in any one of embodiments B, Bl, Bla, B2, B2a, B3, (C)-C(8), and (C8a).

In another embodiment, any one of the Compound of Formulae 1, 1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(p), and I(n) is that where R¹ and/or R² are independently as defined in any one of the above embodiments.

Embodiment (U): Another embodiment provides a pharmaceutical composition which comprises 1) a compound, as a single stereoisomer or mixture of isomers thereof, according to any one of Formula I, (1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(p), and I(n) or according to any one of the above embodiments or a compound in Table 1, optionally as a pharmaceutically acceptable salt thereof, and 2) a pharmaceutically acceptable carrier, excipient, and/or diluent thereof.

Embodiment (V): Another embodiment is a method of treating disease, disorder, or syndrome where the disease is associated with uncontrolled, abnormal, and/or unwanted cellular activities effected directly or indirectly by PI3K and/or mTOR which method comprises administering to a human in need thereof a therapeutically effective amount of a Compound of any of Formula I, (1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(p), and I(n), a Compound of any one of the above embodiments, or a Compound from Table 1, optionally as a pharmaceutically acceptable salt or pharmaceutical composition thereof. In another embodiment of embodiment (V), the disease is cancer. In another embodiment of embodiment (V), the disease is cancer and the Compound is of Formula 1(a) or a Compound from Table 1.
[00208] **Embodiment (W):** Another embodiment is directed to a method of treating a disease, disorder, or syndrome which method comprises administering to a patient a therapeutically effective amount of a Compound of any of Formula I, (1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(p), and I(n), a Compound of any one of the above embodiments, or a Compound from Table 1, optionally as a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a Compound of Formula I, (1(a), 1(b), 1(c), 1(d), 1(e), 1(f), 1(g), 1(h), I(p), and I(n), a Compound of any one of the above embodiments, or a Compound from Table 1, and a pharmaceutically acceptable carrier, excipient, or diluent. In another embodiment of embodiment (W), the disease is cancer. In another embodiment of embodiment (W), the disease is cancer and the Compound is of Formula 1(a) or a Compound from Table 1.

[00209] In another embodiment of any of the embodiments of Embodiment (W), the cancer is breast cancer, mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B cell lymphoma, rhabdomyosarcoma, ovarian cancer, endometrial cancer, cervical cancer, non small cell lung carcinoma, small cell lung carcinoma, adenocarcinoma, colon cancer, rectal cancer, gastric carcinoma, hepatocellular carcinoma, mantle cell lymphoma melanoma, pancreatic cancer, prostate carcinoma, thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, glioblastoma, or head and neck cancer.

[00210] **Embodiment (X):** Another embodiment is directed to a therapeutic method for treating a subject having a tumor. Phosphatidylinositol 3-kinases (PI 3-kinases or PBKs) are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. PBKs are a family of related intracellular signal transducer enzymes capable of phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns). Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by PBKCA gene represents the catalytic subunit, which uses ATP to phosphorylate phosphatidylinositols (PtdIns), PtdIns4P and PtdIns(4,5)P2.

[00211] In the present invention, reference to position within the amino acid sequence of PBKa is made referring to SEQ ID NO: 1. Reference to positions within the nucleotide sequence of the PBKa is made referring to SEQ ID NO:2. Specific amino acids in the wild type protein sequence are described using single letter amino acid designation followed by
the position in the protein sequence, for example E545 indicates that position 545 is glutamic acid. To represent a substitution at a particular position, the substituted amino acid follows the position, for example E545K indicates that the glutamic acid at position 545 is replaced with a lysine.

[00212] As used herein, the term "subject" refers to a mammal, preferably a human mammal, that can be afflicted by a cancer disease. Typically, the terms "subject" and "patient" are used herein interchangeably in reference to a human individual. In various embodiments, reference to human PDK-a in the various methods and description of genetic variants herein refers to the human PI3K-πI0 a catalytic subunit. In some embodiments a gene which encodes an exemplary PI3K-a is illustrated in GenBank Accession No. NG 012113 located on chromosome 3 at map coordinates 3q26.3. Other synonyms include: MGC142161; MGC142163; πI0-alpha; PDKa.

[00213] In one illustrative embodiment, a mature PI3K-a protein sequence is encoded by a mRNA (NCBI Accession No. NM 006218, version NM 006218.2 GI: 54792081.)

[00214] Activation of PI3K signaling occurs in the majority of human cancers. Mechanisms of pathway dysregulation include over-expression or mutational activation of upstream receptor tyrosine kinases or components of the pathway including PI3K-a and inactivation the lipid phosphatase PTEN. Mutations in PI3K-a occur most frequently at hotspots in the helical domain (E542K, E545K) or kinase domain (H1047R). The effects of different PI3K pathway-activating genetic lesions are not equivalent. PTEN-null tumor cells demonstrate high basal pAKT levels while PI3K-a mutant cells are either RAS-dependent with low basal levels of pAKT (E545K) or RAS-independent with more variable levels of pAKT (H1047R) (Vasudevan, 2009; Zhao, 2008; Mandelker, 2009; Pang, 2009).

[00215] The high frequency of PI3K pathway activation in human tumors has lead to the development of PI3K inhibitors as cancer therapeutics. First generation compounds are largely pan-PI3K inhibitors that target more than one class I PI3K isoform (PI3K-α, PBKβ, PI3K5, and PI3Kγ) or related protein kinases such as mTOR. In order to identify genetic lesions which sensitize cells to PI3K inhibitors, investigators have profiled panels of tumor cell line with using protein phosphorylation or cell growth/viability as readouts. In general, mutational activation of PI3K-a, lack of PTEN function, and HER2 over-expression were found to sensitize cells to pan-PI3K compounds while mutational activation of KRAS lead to desensitization (Serra, 2008; Brachmann, 2009; O'Brien, 2010).
Despite increased attention, the genetic backgrounds where inhibition of specific PI3K isoymes would block cell signaling and growth and provide therapeutic benefit are less well defined. For PTEN-negative tumors, specific inhibition of PBKβ (but not PBKa) using RNAi or selective inhibitors (e.g. TGX-221, EXEL-04214154) blocks basal AKT phosphorylation and cell growth (Wee, 2008, Edgar, 2010). For PI3K-a mutant/PTEN positive tumors, inhibition of PI3Kβ has little effect while PI3Ka knockdown by siRNA reduces basal AKT phosphorylation and cell growth (Wee, 2009), however differential effects in H1047R vs. E545K cells have not been reported.

In this regard, therapeutic methods for treating subjects having a tumor comprise: (a) administering a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to the subject if the tumor comprises a mutation in a PI3K-a kinase domain; or (b) administering a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a PI3K-β selective inhibitor, to the subject if the tumor comprises a mutation in a PI3K-a helical domain.

In some embodiments, the tumors being treated can include one or more of breast cancer, mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B cell lymphoma, rhabdomyosarcoma, ovarian cancer, endometrial cancer, cervical cancer, non small cell lung carcinoma, small cell lung carcinoma, adenocarcinoma, colon cancer, rectal cancer, gastric carcinoma, hepatocellular carcinoma, melanoma, pancreatic cancer, prostate carcinoma, thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, glioblastoma, or head and neck cancer.

In some embodiments of the present invention, the therapeutic method first requires a tumor sample from the subject, wherein the sample can be any tumor tissue sample that is believed to contain a tumor cell. In some embodiments, subjects in need of a cancer treatment have often been diagnosed as having a tumor or cancer and samples of such tumor or cancer can be readily obtained using standard oncological methods known in the art. In some embodiments, the tumor cell obtained from the patient can be obtained using laparoscopic, endoscopic or surgical means, for example, a direct incision into a tumor mass as located and/or identified using any screening means, for example, direct palpation, radiographic or tomographic means, e.g. MRI or CT/PET Scans.
In some embodiments, the tumor cells can be cultured from a biopsied tissue for further screening assays or other methods described herein. For example, >100 mg of non-necrotic, non-contaminated tissue can harvested from the patient by any suitable biopsy or surgical procedure known in the art. Biopsy sample preparation can generally proceed under sterile conditions, for example, under a Laminar Flow Hood which should be turned on at least 20 minutes before use. Reagent grade ethanol is used to wipe down the surface of the hood prior to beginning the sample preparation. The tumor is then removed, under sterile conditions, from the shipping container and is minced with sterile scissors. If the specimen arrives already minced, the individual tumor tissue pieces should be divided into groups. Using sterile forceps, each undivided tissue section is then placed in 3 ml sterile growth medium (Standard F-10 medium containing 17% calf serum and a standard amount of Penicillin and Streptomycin) and systematically minced by using two sterile scalpels in a scissor-like motion, or mechanically equivalent manual or automated opposing incisor blades. This cross-cutting motion is important because the technique creates smooth cut edges on the resulting tumor multicellular particulates. Preferably but not necessarily, the tumor particulates each measure 1 mm³. After each tumor quarter has been minced, the particles are plated in culture flasks using sterile pasteur pipettes (9 explants per T-25 or 20 particulates per T-75 flask). Each flask is then labeled with the patient's code, the date of explantation and any other distinguishing data.

The explants can be evenly distributed across the bottom surface of the flask, with initial inverted incubation in a 37°C incubator for 5-10 minutes, followed by addition of about 5-10 niL sterile growth medium and further incubation in the normal, non-inverted position. Flasks are placed in a 35°C, non-C0₂ incubator. Flasks should be checked daily for growth and contamination. Over a period of a few weeks, with weekly removal and replacement of 5 ml of growth medium, the explants will foster growth of cells into a monolayer. With respect to the culturing of tumor cells, (without wishing to be bound by any particular theory), maintaining the malignant cells within a multicellular particulate of the originating tissue, growth of the tumor cells themselves is facilitated versus the overgrowth of fibroblasts (or other unwanted cells) which tends to occur when suspended tumor cells are grown in culture.

The use of the above procedure to form a cell monolayer culture maximizes the growth of malignant cells from the tissue sample, and thus optimizes ensuing tissue culture assay of chemotherapeutic action of various agents to be tested. Enhanced growth of actual
malignant cells is only one aspect of the present invention, however; another important feature is the growth rate monitoring system used to oversee growth of the monolayer once formed. Once a primary culture and its derived secondary monolayer tissue culture has been initiated, the growth of the cells is monitored to ascertain the time to initiate the chemotherapy assay and to determine the growth rate of the cultured cells.

[00223] The tumor cell whether a primary tumor cell or cultured tumor cells can then be interrogated to determine whether the isolated tumor cell from the subject contains a mutation in the kinase domain or in the helical domain. Once the sequencing data for each sample of nucleic acid has been confirmed, the sequence itself can be read to determine whether or not the tumor cell has a mutation in a kinase domain and/or the helical domain of PI3K-a. In some embodiments, the nucleotide sequence can be converted into a protein amino acid sequence of a mature, full length PI3K pi 10-a subunit or fragment thereof containing the amino acids representative of the diagnostic mutations described herein. Purely for the purposes of the present application, the PI3KCA or PI3K pi 10-a catalytic subunit is herein referred to as PI3K-a. The designation of such should not be confused with the regulatory p85-a subunit.

[00224] While several embodiments herein have exemplified human PI3K-a, other PI3K-a subunit encoding nucleotides and full length amino acid sequences are readily available from depository of bioinformatic databases such as NCBI, UniProtKB -Swiss-Prot and TrEMBL-, UniRef, UniParc and the like. In some embodiments, the methods to identify a protein sequence of PI3K-a can employ a nucleic acid-based approach or a protein based approach. In both respects, the determination of whether a mutation in PI3K-a kinase domain or catalytic domain can be readily performed using assays that are well known in the field of identifying genetic mutations. As used herein, for exemplary purposes only, full length human PI3K-a is shown in SEQ ID 1.

[00225] As used herein, the kinase domain of a human PI3K-a (PI3KCA) includes the kinase domain located in axon 20 which spans approximately from amino acid 699-1064 of SEQ ID NO: 1. In some embodiments, the methods of the present invention identifies whether the subject's tumor cell has a mutation at position 1047. In some embodiments, the mutation in the kinase domain includes a substitution of histidine to arginine at position 1047 of SEQ ID NO: 1.

[00226] In some embodiments, once the subject has been identified as having a tumor cell with a mutation in the kinase domain, for example, a mutation at amino acid 1047 of SEQ ID
the patient can be administered with a PI3K-a selective inhibitor. If the subject contains a mutation wherein histidine (H) is replaced with arginine (R) at position 1047 of SEQ ID NO:1, the subject is administered with a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, a combination of a PI3K-a selective inhibitor or a mTOR selective inhibitor.

In some embodiments, a mutation of the helical domain in a subject's tumor cell can be used as a basis to treat the subject's tumor with a composition that does not include a PI3K-a selective inhibitor alone. As used herein, the helical domain refers to a domain in PI3K-a that spans approximately from amino acid 526 to 696 of SEQ ID NO: 1. In some embodiments, specific mutations in the helical domain can include a mutation at positions 542 and/or 545 of SEQ ID NO:1. If the subject contains a mutation wherein glutamic acid (E) is replaced with lysine (K) at positions 542 and/or 545 of SEQ ID NO: 1, the subject is administered with a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, a combination of a PI3K-a selective inhibitor or a mTOR selective inhibitor.

In some embodiments, the subject's tumor cell or cells have been used in one or more assays to determine the amino acid sequence directly or from sequence information obtained from nucleic acids encoding the PI3K-a. If the subject's tumor cell contains a mutation in the helical domain, the subject can be administered with one or more of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a PI3K-β selective inhibitor.

In some embodiments, PI3K-a selective inhibitors, dual PI3K-a/mTOR selective inhibitors and mTOR inhibitors can be selected from Table 1 below. In some embodiments, PI3K-a selective inhibitors, dual PI3K-a/mTOR selective inhibitors and mTOR inhibitors useful in the present inventive methods described in embodiments (X), (Y) and (Z) infra include those disclosed in International Patent Application Nos. PCT/US2006/039574 filed October 9, 2006 and PCT/US2006/039734 filed October 9, 2006. Both of these International Patent Applications are incorporated herein by reference in their entireties.

In some embodiments, a dual PI3K-a/mTOR selective inhibitor can include any one of:
[00231] In some embodiments, the PI3K-α selective inhibitor can include any one of the following PI3K-α selective inhibitor compounds:
In various embodiments of the present invention, the variously described inhibitors can be administered to a subject having a tumor or cancer in pharmaceutical compositions according to the invention. The pharmaceutical composition can include a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, a combination of a PI3K-a selective inhibitor or a mTOR selective inhibitor if the subject's tumor comprises a mutation in a PI3K-a kinase domain; or a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-ct/mTOR selective inhibitor, or a PI3K-β selective inhibitor, to the subject if the subject's tumor comprises a mutation in a PI3K-a helical domain. Each of these inhibitors can also include a pharmaceutically acceptable carrier, excipient, or diluent. In certain other specific embodiments, administration is by the oral route. Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, specifically in unit dosage forms suitable for simple administration of precise dosages.

The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/ an active agent, and, in addition, may include
pharmaceutically acceptable carriers and adjuvants, etc can be administered in tablet, capsule, liquid, powder, nutritional bar or effervescent form. "pharmaceutically acceptable" refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Methods of preparation of formulations for various forms of administration are known in the art and discussed in detail in Remington's Pharmaceutical Sciences, Eighteenth Edition (1990), incorporated herein by reference.

[00235] Dosages of the pharmaceutical composition of the present invention necessary to achieve a therapeutically effect may depend upon several factors. A "therapeutically effective amount" of a compound of the disclosed invention is the quantity which, when administered to a subject having a disease or disorder, results in regression of the disease or disorder or symptoms thereof, optionally including reduction in adverse side-effects in the subject when compared to another similarly prescribed medicine.

[00236] The amount of the disclosed compound to be administered to a subject will depend on the particular disorder, the mode of administration, co-administered compounds, if any, and the characteristics of the subject, such as general health, other diseases, age, sex, genotype, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. In some instances, a higher dosage is first prescribed to be titrated to a tolerable dose in which the subject does not experience overtly negative side effects which would result in cessation of treatment. In some embodiments, the dose of the compounds of the present invention can range in an amount of 0.001 mg/kg to about 100 mg/kg per day administered in single doses, multiple doses or in controlled release formulations. In some embodiments, therapeutically effective amounts of the disclosed compounds are administered typically in a range between about 0.01 mg/kg per day and about 50 mg/kg per day, and preferably between 0.1 mg/kg per day and about 10 mg/kg/day.

[00237] In some embodiments, the therapeutic method for treating a subject having a tumor can optionally comprise administering a compound of the present invention in addition to another chemotherapeutic agent. Among the many chemotherapeutic agents which may be used in combination with a compound of the present invention are anti-neoplastic agents. Anti-neoplastic agents may induce anti-neoplastic effects in a cell-cycle specific manner, i.e.,
are phase specific and act at a specific phase of the cell cycle, or bind DNA and act in a non-cell-cycle specific manner, i.e., are non-cell cycle specific and operate by other mechanisms. Both types of anti-neoplastic agents may be employed in combination with the compounds of the present invention.

[00238] Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines, alkyl sulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclines, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

[00239] Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

[00240] Platinum coordination complexes are non-phase specific anti-neoplastic agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

[00241] Alkylating agents are non-phase anti-neoplastic specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, and hydroxyl groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

[00242] Antibiotic chemotherapeutic agents are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death.
Examples of antibiotic antineoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins. Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G₂ phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mercaptopurine and thioguanine.

Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,1 1-ethylenedioxy-20-camptothecin.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues believed to be useful in the treatment of neoplasms include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrozole, vorazole, and exemestane useful in the treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene useful in the treatment of hormone dependent breast carcinoma; and gonadotropin-releasing hormone.
(GnRH) and analogues thereof which stimulate the release of luteinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors are those inhibitors which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation or survival. Signal transduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3 domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes. In some embodiments, the additional chemotherapeutic agent can include an inhibitor to other PI3K catalytic subunits (PI3K-β, PI3K-δ, or PI3K-γ), or regulatory units, for example, TGX-221, or Pan PI3K selective inhibitors, for example, PI-103 and PIK-75 at the dosages described above. As used herein TGX-221 ((CAS No. 663619-89-4) 7-methyl-2-(4-morpholinyl)-9-[l-(phenylamino)ethyl]-4H-pyrido[1,2-alpyrimidin-4-one) is a potent, selective, and cell permeable inhibitor of PI3K ριιθβ having

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\text{and is commercially available from Cayman Chemicals, Catalog No. 10007349 (Ann Arbor, MI, USA).} \]

As used herein, PI-103 ((CAS No. 371935-74-9) 3-[4-(4-morpholinyl)pyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl]-phenol) is a cell-permeable, ATP-competitive inhibitor of phosphatidylinositol 3-kinase (PI3K) family members with selectivity toward DNA-PK, PI3K (pi 10a), and mTOR having the structure:

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\text{and is commercially available from Cayman Chemicals, Catalogue No. 10009209 (Ann Arbor MI, USA).} \]

As used herein, PIK-75 ((CAS 372196-67-3), 2-memyl-5-nitro-2-[6-bromoimidazo[1,2-a]pyridin-3-yl)methylene]-l-methylhydrazide-
benzenesulfonic acid) is a PI3K kinase inhibitor having the structure:

![Chemical Structure]

and is commercially available from Cayman Chemicals, Catalog No. 10009210 (Ann Arbor, MI, USA).

**[00247] Embodiment (Y):** Another embodiment is directed to a method for identifying a selective inhibitor of a PI3K isozyme, the method comprising: (a) contacting a first cell bearing a first mutation in a PI3K-a with a candidate inhibitor; (b) contacting a second cell bearing a wild type PI3K-a, a PTEN null mutation, or a second mutation in said PI3K-a with the candidate inhibitor; and (c) measuring AKT phosphorylation in said first and said second cells, wherein decreased AKT phosphorylation in said first cell when compared to said second cell identifies said candidate inhibitor as a selective PI3K-a inhibitor.

**[00248]** As noted above, the newly discovered association between selective genetic mutations and increased sensitivities of some cancers to specific inhibitors renders a particular genetic background more susceptible to one or more types of inhibitors than others. This association between genetic backgrounds and susceptibilities of certain cancers provides an attractive and convenient cellular platform for identification of new selective inhibitors to PI3K kinases (e.g. via screening assays to detect compounds or entities that inhibit phosphorylation in a PI3K-dependent manner). As will be appreciated by those of ordinary skill in the art, any kind of compounds or agents can be tested using the inventive screening methods. A candidate inhibitor compound may be a synthetic or natural compound; it may be a single molecule, a mixture of different molecules or a complex of at least two molecules. A candidate inhibitor can comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl, hydroxyl, ether, or carboxyl group, for example at least two of the functional chemical groups. The candidate inhibitor often comprises cyclical carbon or heterocycloalkyl structures and/or aromatic or heteroaromatic structures substituted with one or more of the above functional groups. Candidate inhibitors are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs, or combinations thereof. In certain embodiments, the inventive methods are used for testing one or more candidate inhibitor compounds. In other embodiments, the inventive methods are used for screening collections or libraries of candidate inhibitor compounds. As used herein, the term "collection" refers to any set of
compounds, molecules or agents, while the term "library" refers to any set of compounds, molecules or agents that are structural analogs.

[00249] Libraries of candidate inhibitor compounds that can be screened using the methods of the present invention may be either prepared or purchased from a number of companies. Synthetic compound libraries are commercially available from, for example, Comgenex (Princeton, N.J.), Brandon Associates (Merrimack, N.H.), Microsource (New Milford, Conn.), and Aldrich (Milwaukee, Wis.). Libraries of candidate inhibitor compounds have also been developed by and are commercially available from large chemical companies. Additionally, natural collections, synthetically produced libraries and compounds are readily modified through conventional chemical, physical, and biochemical means.

[00250] Cells to be used in the practice of the screening methods described herein may be primary cells, secondary cells, or immortalized cells (e.g., established cell lines). They may be prepared by techniques well known in the art (for example, cells may be obtained by fine needle biopsy from a patient or a healthy donor) or purchased from immunological and microbiological commercial resources (for example, from the American Type Culture Collection (ATCC), Manassas, Va.). Alternatively or additionally, cells may be genetically engineered to contain, for example, a gene of interest. In a first set of cells, the cells possess a genetic mutation in PI3K-a kinase domain, for example, H1047R. In a second set of cells to be used in the screening assays, the second set of cells possess a genetic mutation in a different kinase catalytic subunit, (for example, a mutation in a helical domain, for example, at E542K and/or E545K, or in a different regulatory protein, for example Phosphatase and Tensin Homolog (PTEN). When a candidate inhibitor inhibits phosphorylation, (for example AKT phosphorylation) to a higher degree in the cell possessing the PI3K-a kinase domain genetic mutation when compared to a cell possessing a genetic mutation in a different kinase catalytic subunit, (for example a mutation in a helical domain, for example, at positions E542K and/or E545K, or in a different regulatory protein), then the candidate inhibitor is a selective inhibitor for cancers or tumors that harbor activation mutations in PI3K-a. Conversely, PI3K-a-selective compounds inhibit AKT phosphorylation, PI3K pathway activation, and cell proliferation with greater potency in tumor cells harboring the PI3K-a-H1047R mutation compared to PTEN negative, PI3K-a wild-type, and PI3K-a-E542K and/or E545K backgrounds. Both PTEN inactivation and KRAS activation desensitize cells to the growth inhibitory effects of PI3K-a-selective compounds. A wild-type PI3K-a is illustratively provided in SEQ ID NO: 1 and is encoded by a mRNA of SEQ ID NO: 2.
In some embodiments, the first and second cells used in the screening assay have different genetic backgrounds. In one embodiment, the first cell group has a genetic mutation in a PI3K-α kinase domain. In an illustrative embodiment, the genetic mutation in the first cell group includes a mutation in a mRNA (NCBI Accession No. NM 006218, version NM 006218.2 GI: 54792081 herein disclosed as SEQ ID NO: 2 which encodes a full length PI3K-α having a mutation in the kinase domain. In one embodiment, an exemplary mutation is at a codon (3296, 3297 and 3298), in the kinase domain of SEQ ID NO: 2, wherein the codon is mutated to provide an amino acid other than a histidine at position 1047 of PI3K-α. The second cell group lacks the mutation of the first test cell group. In one embodiment, an exemplary mutation is at a codon (1790, 1791 and 1792), in the helical domain of SEQ ID NO: 2, wherein the codon is mutated to provide an amino acid other than a glutamic acid at position 545 of PI3K-α. In one exemplary mutation, the glutamic acid at 542 or 545 is mutated to lysine (E545K). This mutation has also been previously reported to be a particularly oncogenic mutation in the PI3K/AKT signaling pathway.

In some embodiments, the second cell group can harbor a mutation in PTEN.

In some embodiments, the first cell group can include various cell lines, including cancer cell lines, for example breast cancer cell lines that may be commercially available from the American Type Culture Collection ((ATCC) American Type Culture Collection, Manassas, VA.) bearing the H1047R het genetic mutation of PI3K-α. In some embodiments, the first cell can include HCT-116, T-47D, MDA-MB-453, SIGOV-3, BT-20 or LS H74T cell lines. In some embodiments, the second cell can include MCF-7, PC3 MCI-H460, SK-BR-3, PC-3, MDA-MB-468, SK-BR-3, MDA-MB-231T, or A549. Each specific cell line can be maintained according to instructions provided upon purchase and are commonly available through the ATCC. The table below provides exemplary first and second cell groups for use in the inventive methods described herein.

In some embodiments, the first cell group and second cell group can also include non-tumor cell lines that have been transformed with a mutant PI3K-α catalytic subunit, for example. H1047R het or E545K PI3K-α catalytic subunit. Methods of introducing nucleic acids and vectors into isolated cells and the culture and selection of transformed host cells in vitro are known in the art and include the use of calcium chloride-mediated transformation, transduction, conjugation, triparental mating, DEAE, dextran-mediated transfection,
infection, membrane fusion with liposomes, high velocity bombardment with DNA-coated microprojectiles, direct microinjection into single cells, and electroporation (see, e.g., Sambrook et al., supra; Davis et al., Basic Methods in Molecular Biology, 2ed ed., McGraw-Hill Professional, 1995; and Neumann et al., EMBO J., 1: 841 (1982)). There are several methods for eukaryotic cell transformation, either transiently or stably using a variety of expression vectors. Methods for mutating a cell-line, for example NIH 3T3 cells by amplifying a sequence of DNA encoding the mutated PI3K-a catalytic subunit of interest. The amplified PCR mutant PI3K-a construct can be cloned into a viral expression vector, for example, pSX2neo, a Moloney murine leukemia virus (MLV) long terminal repeat-driven expression vector made by inserting a simian virus 40 early promoter-neomycin phosphotransferase gene into pSX2, designed to express high levels of 10A1 MLV Env. Transformation of NIH 3T3 cells can be performed by transfection with a different CaP04 coprecipitation technique. After reaching confluence the cells can be transferred into a medium containing 5% FBS without dexamethasone. Morphologically transformed cells can be separated and isolated from mixtures of transformed and nontransformed Env-plasmid-transfected cells by excising the transformed foci from the cell layer with a small-bore pipette (a Pasteur pipette drawn out over a flame to give a fine tip) and aspiration of the foci by the use of a rubber bulb attached to a pipette.

[00255] In some embodiments, the methods described herein require that the cells be tested in the presence of a candidate inhibitor, wherein the candidate inhibitor is added to separate exemplary assay wells, each well containing either the first or second cells. The amount of candidate inhibitor can vary, such that a range of inhibitory activities can be determined for the determination of an IC50 for that candidate inhibitor. This can easily be achieved by serially diluting the compound in an appropriate solvent, for example, DMSO and then in the culture medium in which the first and second cells are being incubated in. In some embodiments, the concentration of the candidate inhibitor can range from about 1 pM to about 1 mM concentration. In some embodiments, the candidate inhibitors are added in amounts ranging from about 0.5 nM to about 10 μM. The incubation of candidate inhibitor with first and second cell groups can vary, typically ranging from about 30 minutes to about 60 hours. Exemplary inhibition assay conditions are provided in the Examples section below.

[00256] In some embodiments, in assays in which PI3K and/or mTOR mediated activity is being measured, the first and/or second cells can be stimulated with a growth factor. The
selection of growth factor is mediated by the requirements of the cell line, for example, illustrative growth factors can include VEGF, IGF, insulin and heregulin.

[00257] In some embodiments, the inhibitory activity of the candidate compounds can be measured using a variety of cellular activities. When cancer cell lines are being used, the inhibition of PI3K mediated activity, e.g. AKT phosphorylation (both at residues S473 and T308), AKT activation, cellular proliferation, and apoptosis resistance in the cells can all be measured. In some embodiments, the amount of AKT phosphorylation in the first and second cell groups can be measured using a phopho-specific antibody (for example AKT1 (phospho S473, Cat. No. ab8932, AKT1 (phospho T308) Cat. No. ab66134) which are commercially available from AbCam, Cambridge, MA. Other methods for measuring the inhibition of PI3K-a activity in the first and second cell groups are described in Donahue, A.C. et al., *Measuring phosphorylated Akt and other phosphoinositide 3-kinase-regulated phosphoproteins in primary lymphocytes*. Methods Enzymol. 2007(434):131-154 which is incorporated herein by reference in its entirety.

[00258] Embodiment (Z): In another embodiment, the invention provides a method for determining a treatment regimen for a cancer patient having a tumor comprising a PI3K-a, the method comprising:

- determining the presence or absence of a mutation in amino acids 1047 and/or 545 of the PI3K-a;

wherein if the PI3K-a has a mutation at position 1047, the method comprises administering to the cancer patient a therapeutically effective amount of a PI3K-a selective inhibitor compound; or

wherein if the PI3K-a has a mutation at position 545, the method comprises administering to the cancer patient a therapeutically effective amount of a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PBK-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor.

[00259] In another embodiment, the invention provides a method for determining a treatment regimen for a cancer patient having a tumor comprising a PI3K-a, the method comprising:

- determining the presence or absence of a mutation in amino acids 1047 and/or 545 of the PI3K-a;
wherein if the PI3K-a has a mutation at position 1047, the method comprises administering to the cancer patient a therapeutically effective amount of a PI3K-a selective inhibitor compound, a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor; or

wherein if the PI3K-α has a mutation at position 545, the method comprises administering to the cancer patient a therapeutically effective amount of a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor.

[00260] In another embodiment, the invention provides a method for determining a treatment regimen for a cancer patient having a tumor comprising a PI3K-a, the method comprising:

determining the presence or absence of a mutation in amino acids 1047 and/or 542 and/or 545 of the PI3K-a;

wherein if the PI3K-a has a mutation at position 1047, the method comprises administering to the cancer patient a therapeutically effective amount of a PI3K-a selective inhibitor compound, a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor; or

wherein if the PI3K-a has a mutation at position 545, the method comprises administering to the cancer patient a therapeutically effective amount of a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor.

[00261] The method of the invention can be used to identify cancer patient populations more likely to benefit from treatment with PDKα-selective inhibitors as well as patient populations less likely to benefit.

[00262] The invention can be used to further define genetic markers or gene expression signatures which identify PDKα inhibitor sensitive tumor subtypes by extended in vitro cell line profiling and in vivo pharmacodynamic and efficacy studies.

[00263] In some embodiments, a method for determining a treatment regimen for a cancer patient having the exemplified cancers herein can be readily performed on the basis of the differential activity of PI3K-a selective inhibitors in cancers having a PI3K-a mutated background described herein. In patients in which a tumor cell has been analyzed and assayed to determine whether the tumor harbors a PI3Kα mutation in the kinase domain, for example, a mutation resulting in H1047R, greater efficacy and treatment improvement can be
achieved by tailoring a treatment comprising a PI3K-a selective inhibitor. For patients, who have a tumor which does not harbor a mutation in PI3Kα kinase domain, the treatment may require adopting a different treatment regimen, for example, by focusing on delivery of a combination of PI3K-a selective inhibitors and a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor. As indicated above, the PI3K-a selective inhibitors, mTOR selective inhibitors and dual PI3K-a/mTOR selective inhibitors are exemplified in Table 1 and in the detailed description herein.

[00264] In some embodiments, methods for determining a treatment regimen comprises determining the presence of a mutation in amino acids 1047 and/or 542 and/or 545 of the PI3K-a in the subject’s tumor as set forth in SEQ ID NO: 1. In some embodiments, the mutation to the kinase domain can include a mutation to H1047 of SEQ ID NO: 1 mutating to H1047R.

[00265] In some embodiments of the invention comprises determining the presence or absence of a mutation in amino acids 1047 and/or 542 and/or 545 of the PI3K-a which includes isolating a nucleic acid sample encoding said PI3K-a or isolating said PI3K-a or a fragment thereof from the tumor.

[00266] In some embodiments, the mutation to the helical domain can include a mutation to E542 of SEQ ID NO:1 mutating to E542K. In another embodiment, the mutation to the helical domain can include a mutation to E545 mutating to E545K. Exemplary mutations in the helical domain can include a mutation at position 542 and/or 545 of SEQ ID NO:1.

[00267] In some embodiments, methods for determining a treatment regimen comprises determining the presence of a mutation in amino acids 1047 and/or 545 of the PI3K-a in the subject’s tumor. This step can be achieved in a variety of ways, using nucleic acid approaches, protein separation approaches or direct immunological approaches using mutation specific antibodies. In some embodiments, presence of a mutation in amino acids 1047 and/or 545 of the PI3K-a in the subject’s tumor can be determined using any suitable method for the sequence analysis of amino acids. Examples of suitable techniques include, but are not limited to, western blot analysis, immunoprecipitation, radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

[00268] In the present invention, reference to position within the amino acid sequence of PI3Ka is made referring to SEQ ID NO: 1. Reference to positions within the nucleotide sequence of the PI3Ka is made referring to SEQ ID NO:2. Specific amino acids in the wild
type protein sequence are described using single letter amino acid designation followed by the position in the protein sequence, for example E545 indicates that position 545 is glutamic acid. To represent a substitution at a particular position, the substituted amino acid follows the position, for example E545K indicates that the glutamic acid at position 545 is replaced with a lysine.

[00269] Determining the presence or absence of mutations in the sequence of the PI3K-a peptide sequence is generally determined using in vitro methods wherein a tumor sample is used which has been removed from the body of a patient.

[00270] Determining the presence or absence of mutations in the amino acid sequence of PI3Ka or a portion thereof, can be done using any suitable method. For example the nucleotide sequence of PI3Ka or a portion thereof maybe determined and the amino acid sequence deduced from the nucleotide sequence or a PI3K-a protein can be interrogated directly.

[00271] The nucleotide sequence of the PI3K-α, or a portion thereof, may be determined using any method for the sequence analysis of nucleic acids. Methods for identification of sequence mutation in genes are well known in the art and the mutations in the PI3Ka can be identified by any suitable method. These methods include, but are not limited to, dynamic allele-specific hybridization; the use of molecular beacons; enzyme-based methods, using for example DNA ligase, DNA polymerase or nucleases; PCR based methods, whole genome sequencing; partial genome sequencing; exome sequencing; nucleic acid probe hybridization; and restriction enzyme digestion analysis.

[00272] Methods of Direct DNA sequencing are well known in the art, see for example: Current Protocols in Molecular Biology, edited by Fred M. Ausubel, Roger Brent, Robert E. Kingston, David D. Moore, J. G. Seidman, John A. Smith, Kevin Struhl, and Molecular Cloning: A Laboratory Manual, Joe Sambrook, David W Russel, 3rd edition, Cold Spring Harbor Laboratory Press). These sequencing protocols include for example, the use of radioactively labeled nucleotides, and nucleotides labeled with a fluorescent dye.

[00273] For example, Barbi, S. et al., used the following protocol to sequence the helical domain (exon 9) and the kinase domain (exon 20) of PI3K-a. Normal and tumor DNA was extracted from paraffin-embedded tissue, and amplified using fluorescent dye-labeled primers, the following primer pairs. Primer sequences need to be chosen to uniquely select for a region of DNA, avoiding the possibility of mishybridization to a similar sequence nearby. A commonly used method is BLAST search whereby all the possible regions to
which a primer may bind can be seen. Both the nucleotide sequence as well as the primer itself can be BLAST searched. The free NCBI tool Primer-BLAST integrates primer design tool and BLAST search into one application, so does commercial software product such as Beacon Designer, (Premier Biosoft International, Palo Alto California). Mononucleotide repeats should be avoided, as loop formation can occur and contribute to mishybridization. In addition, computer programs are readily available to aid in design of suitable primers. In certain embodiments the nucleic acid probe is labeled for use in a Southern hybridization assay. The nucleic acid probe may be radioactively labeled, fluorescently labeled or is immunologically detectable, in particular is a digoxygenin-labeled (Roche Diagnostics GmbH, Mannheim).

[00274] In some embodiments, determining the presence of a helical domain mutation in exon 9 can be achieved using an exemplary forward primer and reverse primer, including, for example: GGGAAAAATATGACAAAGAAAGC (SEQ ID NO: 3) and CTGAGATCAGCCAAATTCAGTT (SEQ ID NO: 4) respectively and a sequencing primer can include TAGCTAGAGACAATGAATTAAGGGAAA (SEQ ID NO: 5), for determining a mutation in the kinase domain in exon 20, an exemplary set of primers can include forward and reverse primers CTCAATGATGCTTGGCTCTG (SEQ ID NO: 6) and TGGATCCAGGTGATGGTTC (SEQ ID NO: 7) respectively and the sequencing primer can include TTGATGACATGGCATACTCG (SEQ ID NO: 8). The amplification products were sequenced. (Barbi, S. et al. J. Experimental and Clinical Cancer Research 2010, 29:32) The sequences are then compared and differences between the wild type PI3K-α sequence and the sequence of the tumor PI3K-a. The assay could also be performed by only amplifying the tumor DNA and comparing the sequence with the sequence of SEQ ID NO:1.

[00275] In some embodiments, the present invention provides polynucleotide sequences comprising polynucleotide sequences in whole or in part from SEQ ID NO: 2 that are capable of hybridizing to the helical region, or the kinase domain of PI3K-a under conditions of high stringency. "High stringency conditions" when used in reference to nucleic acid hybridization comprise conditions equivalent to binding or hybridization at 42°C in a solution consisting of 5 times SSPE (43.8 g/l NaCl, 6.9 g/l NaH₂PO₄·H₂O and 1.85 g/l EDTA, pH adjusted to 7.4 with NaOH), 0.5% SDS, 5 x Denhardt's reagent and 100 µg/mL denatured salmon sperm DNA followed by washing in a solution comprising 0.1 x SSPE, 1.0% SDS at 42°C when a probe of about 500 nucleotides in length is employed.
In some embodiments, the polynucleotides can include sequences complementary to nucleic acid sequences that encode in whole or in part PI3K-α or PI3K-α having specific mutations as described herein. The terms "complementary" and "complementarity" refer to polynucleotides (i.e., a sequence of nucleotides) related by the base-pairing rules. For example, for the sequence "A-G-T," is complementary to the sequence "T-C-A."

Complementarity may be "partial," in which only some of the nucleic acids' bases are matched according to the base pairing rules. Or, there may be "complete" or "total" complementarity between the nucleic acids. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands. This is of particular importance in amplification reactions, as well as detection methods which depend upon binding between nucleic acids.

In some embodiments, the present invention provides polynucleotide sequences comprising polynucleotide sequences in whole or in part from SEQ ID NO: 2 that are capable of hybridizing to the helical region, or the kinase domain ofPI3K-α under conditions of high stringency. In some embodiments, the polynucleotides can include sequences complementary to nucleic acid sequences that encode in whole or in part PI3K-α or PI3K-α having specific mutations as described herein. The terms "complementary" and "complementarity" refer to polynucleotides (i.e., a sequence of nucleotides) related by the base-pairing rules. For example, for the sequence "A-G-T," is complementary to the sequence "T-C-A."

Complementarity may be "partial," in which only some of the nucleic acids' bases are matched according to the base pairing rules. Or, there may be "complete" or "total" complementarity between the nucleic acids. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands. This is of particular importance in amplification reactions, as well as detection methods which depend upon binding between nucleic acids.

The term "homology" when used in relation to nucleic acids refers to a degree of complementarity. There may be partial homology or complete homology (i.e., identity).

"Sequence identity" refers to a measure of relatedness between two or more nucleic acids or proteins, and is given as a percentage with reference to the total comparison length. The identity calculation takes into account those nucleotide or amino acid residues that are identical and in the same relative positions in their respective larger sequences. Calculations of identity may be performed by algorithms contained within computer programs such as "GAP" (Genetics Computer Group, Madison, Wis.) and "ALIGN" (DNASter, Madison,
A partially complementary sequence is one that at least partially inhibits (or competes with) a completely complementary sequence from hybridizing to a target nucleic acid is referred to using the functional term "substantially homologous." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or Northern blot, solution hybridization and the like) under conditions of low stringency. A substantially homologous sequence or probe will compete for and inhibit the binding (i.e., the hybridization) of a sequence which is completely homologous to a target under conditions of low stringency. This is not to say that conditions of low stringency are such that non-specific binding is permitted; low stringency conditions require that the binding of two sequences to one another be a specific (i.e., selective) interaction. The absence of non-specific binding may be tested by the use of a second target which lacks even a partial degree of complementarity (e.g., less than about 30% identity); in the absence of non-specific binding the probe will not hybridize to the second non-complementary target.

In preferred embodiments, hybridization conditions are based on the melting temperature (Tm) of the nucleic acid binding complex and confer a defined "stringency." The term "hybridization" refers to the pairing of complementary nucleic acids. Hybridization and the strength of hybridization (i.e., the strength of the association between the nucleic acids) is impacted by such factors as the degree of complementary between the nucleic acids, stringency of the conditions involved, the Tm of the formed hybrid, and the G:C ratio within the nucleic acids. A single molecule that contains pairing of complementary nucleic acids within its structure is said to be "self-hybridized."

The term "Tm" refers to the "melting temperature" of a nucleic acid. The melting temperature is the temperature at which a population of double-stranded nucleic acid molecules becomes half dissociated into single strands. The equation for calculating the Tm of nucleic acids is well known in the art. As indicated by standard references, a simple estimate of the Tm value may be calculated by the equation: Tm =81.5+0.41(% G+C), when a nucleic acid is in aqueous solution at 1 M NaCl. The term "stringency" refers to the conditions of temperature, ionic strength, and the presence of other compounds such as organic solvents, under which nucleic acid hybridizations are conducted. With "high stringency" conditions, nucleic acid base pairing will occur only between nucleic acid fragments that have a high frequency of complementary base sequences.
In addition, sequence mutations in the PI3Kα can be determined using any sequence-specific nucleic acid detection method allowing detection of single-nucleotide variation, in particular any such method involving complementary base pairing. In some embodiments, the method requires determining the presence or absence of a mutation in amino acids 1047 and/or 542 and/or 545 of the PI3K-a in the tumor which may include the steps of isolating a nucleic acid sample encoding said PI3K-a or isolating said PI3K-a or a fragment thereof from said tumor and determining if the nucleic acid sample has a mutation at position 542 and/or 545 and/or 1047 as set forth in SEQ ID NO:1. For example, to determine if the PI3K-a comprises a E545 mutation, the sequence of PI3K-a peptide or a portion thereof comprising nucleotides 1790, 1791 and 1792 of SEQ ID NO:2 (codon corresponding with position 545 in the amino acid sequence), is used in a polymerase chain reaction (PCR) where the oligonucleotide primers allow the amplification of PI3Ka only if the nucleotide at position 1790 is G. If no reaction product is formed then the amino acid at position 545 is mutated. In another example the oligonucleotide primers are designed to allow the amplification of the to allow amplification if the nucleotide at position 3297 is A (codon comprising nucleotides 3296, 3297 and 3298 corresponds with position 1047 of the amino acid sequence). If no reaction product is formed using those primers then the amino acid at position 545 is mutated. Methods for performing PCR are known in the art (see Current Protocols in Molecular Biology, edited by Fred M. Ausubel, Roger Brent, Robert E. Kingston, David D. Moore, J. G. Seidman, John A. Smith, Kevin Struhl, and; Molecular Cloning: A Laboratory Manual, Joe Sambrook, David W Russel, 3rd edition, Cold Spring Harbor Laboratory Press).

Dynamic allele-specific hybridization (DASH) genotyping takes advantage of the differences in the melting temperature in DNA that results from the instability of mismatched base pairs. This technique is well suited to automation. In the first step, a DNA segment is amplified and attached to a bead through a PCR reaction with a biotinylated primer. In the second step, the amplified product is attached to a streptavidin column and washed with NaOH to remove the un-biotinylated strand. An sequence-specific oligonucleotide is then added in the presence of a molecule that fluoresces when bound to double-stranded DNA. The intensity is then measured as temperature is increased until the Tm can be determined. A single nucleotide change will result in a lower than expected Tm (Howell W., Jobs M., Gyllensten U., Brookes A. (1999) Dynamic allele-specific hybridization. A new method for scoring single nucleotide polymorphisms. Nat Biotechnol. 17(1):87-8). Because DASH
genotyping is measuring a quantifiable change in Tm, it is capable of measuring all types of
mutations, not just SNPs. Other benefits of DASH include its ability to work with label free
probes and its simple design and performance conditions.

[00283] Molecular beacons can also be used to detect mutations in a DNA sequences
Molecular beacons makes use of a specifically engineered single-stranded oligonucleotide
probe. The oligonucleotide is designed such that there are complementary regions at each end
and a probe sequence located in between. This design allows the probe to take on a hairpin,
or stem-loop, structure in its natural, isolated state. Attached to one end of the probe is a
fluorophore and to the other end a fluorescence quencher. Because of the stem-loop structure
of the probe, the fluorophore is in close proximity to the quencher, thus preventing the
molecule from emitting any fluorescence. The molecule is also engineered such that only the
probe sequence is complementary to the to the genomic DNA that will be used in the assay
(Abravaya K., Huff J., Marshall R., Merchant B., Mullen C. , Schneider G., and Robinson J.
Med. 41:468-474). If the probe sequence of the molecular beacon encounters its target
genomic DNA during the assay, it will anneal and hybridize. Because of the length of the
probe sequence, the hairpin segment of the probe will denatured in favor of forming a longer,
more stable probe-target hybrid. This conformational change permits the fluorophore and
quencher to be free of their tight proximity due to the hairpin association, allowing the
molecule to fluoresce. If on the other hand, the probe sequence encounters a target sequence
with as little as one non-complementary nucleotide, the molecular beacon will preferentially
stay in its natural hairpin state and no fluorescence will be observed, as the fluorophore
remains quenched. The unique design of these molecular beacons allows for a simple
diagnostic assay to identify SNPs at a given location. If a molecular beacon is designed to
match a wild-type allele and another to match a mutant of the allele, the two can be used to
identify the genotype of an individual. If only the first probe's fluorophore wavelength is
detected during the assay then the individual is homozygous to the wild type. If only the
second probe's wavelength is detected then the individual is homozygous to the mutant allele.
Finally, if both wavelengths are detected, then both molecular beacons must be hybridizing to
their complements and thus the individual must contain both alleles and be heterozygous.

[00284] Enzyme-based nucleic acid methods are also suitable and contemplated for
determining mutations in the PI3K-a nucleotide sequence. For example, Restriction fragment
length polymorphism (RFLP) (discussed in greater detail below) can be used to detect single
nucleotide differences. SNP-RFLP makes use of the many different restriction endonucleases and their high affinity to unique and specific restriction sites. By performing a digestion on a genomic sample and determining fragment lengths through a gel assay it is possible to ascertain whether or not the enzymes cut the expected restriction sites. A failure to cut the genomic sample results in an identifiably larger than expected fragment implying that there is a mutation at the point of the restriction site which is rendering it protected from nuclease activity.

[00285] The term “functionally equivalent codon” is used herein to refer to codons that encode the same amino acid, such as the six codons for arginine.

[00286] In one embodiment of the invention, the method comprises at least one nucleic acid probe or oligonucleotide for determining the sequence of the codon that encodes amino acid 1047. In another embodiment the method comprises at least one nucleic acid probe or oligonucleotide for determining the sequence of the codon that encodes amino acid 545. The oligonucleotide is a PCR primer, preferably a set of PCR primers which allows amplification of a PI3Ka nucleic acid sequence fragment only if the codon which encodes amino acid 1047 encodes a histidine. In another method, the PCR primer or set of PCR primers allows the amplification of nucleic acid sequence fragment only if the codon which encodes amino acid 545 encodes a glutamic acid. Determination of suitable PCR primers is routine in the art, (Current Protocols in Molecular Biology, edited by Fred M. Ausubel, Roger Brent, Robert E. Kingston, David D. Moore, J. G. Seidman, John A. Smith, Kevin Struhl; Looseleaf: 0-471-650338-X; CD-ROM: 0-471-30661-4). In addition, computer programs are readily available to aid in design of suitable primers. In certain embodiments the nucleic acid probe is labeled for use in a Southern hybridization assay. The nucleic acid probe may be radioactively labeled, fluorescently labeled or is immunologically detectable, in particular is a digoxygenin-labeled (Roche Diagnostics GmbH, Mannheim).

[00287] U.S. Patent Publication 20010016323 discloses methods for detecting point mutations using a fluorescently labeled oligonucleotidemeric probe and fluorescence resonance energy transfer. A point mutation leading to a base mismatch between the probe and the target DNA strand causes the melting temperature of the complex to be lower than the melting temperature for the probe and the target if the probe and target were perfectly matched.

[00288] Other suitable methods for detecting single point mutations include those disclosed in, for example, U.S. Patent Publication 2002010665, which involves the use of
oligonucleotide probes in array format. Such arrays can include one or more of SEQ ID Nos:3-8. U.S. Patent Publication 20020177157 discloses additional methods for detecting point mutations.

[00289] A polynucleotide carrying a point mutation leading to a mutation of PI3K-a kinase domain, for example, H1047R that is the subject of this invention can be identified using one or more of a number of available techniques. However, detection is not limited to the techniques described herein and the methods and compositions of the invention are not limited to these methods, which are provided for exemplary purposes only. Polynucleotide and oligonucleotide probes are also disclosed herein and are within the scope of the invention, and these probes are suitable for one or more of the techniques described below. These include allele-specific oligonucleotide hybridization (ASO), which, in one embodiment, is a diagnostic mutation detection method wherein hybridization with a pair of oligonucleotides corresponding to alleles of a known mutation is used to detect the mutation. Another suitable method is denaturing high performance liquid chromatography (DHPLC), which is a liquid chromatography method designed to identify mutations and polymorphisms based on detection of heteroduplex formation between mismatched nucleotides. Under specified conditions, heteroduplexes elute from the column earlier than homoduplexes because of reduced melting temperature. Analysis can then be performed on individual samples.

[00290] An amplified region of the DNA containing the mutation or the wild-type sequence can be analyzed by DHPLC. Use of DHPLC is described in U.S. Pat. Nos. 5,795,976 and 6,453,244, both of which are incorporated herein by reference. A suitable method is that provided by Transgenomic, Inc. (Omaha, Nebr.) using the Transgenomic WAVE® System.

[00291] For ASO, a region of genomic DNA or cDNA containing the PI3K-a mutation (H1047R and/or E545K) is amplified by PCR and transferred onto duplicating membranes. This can be performed by dot/slot blotting, spotting by hand, or digestion and Southern blotting. The membranes are prehybridized, then hybridized with a radiolabeled or deoxyxygenin (DIG) labeled oligonucleotide to either the mutant or wild-type sequences. For the DIG label, detection is performed using chemiluminescent or colorimetric methods. The membranes are then washed with increasing stringency until the ASO is washed from the non-specific sequence. Following autoradiographic exposure, the products are scored for the level of hybridization to each oligonucleotide. Optimally, controls are included for the normal
and mutant sequence on each filter to confirm correct stringency, and a negative PCR control

is used to check for contamination in the PCR.

[00292] The size of the ASO probe is not limited except by technical parameters of the art. Generally, too short a probe will not be unique to the location, and too long a probe may cause loss of sensitivity. The oligonucleotides are preferably 15-21 nucleotides in length, with the mismatch towards the center of the oligonucleotide.

[00293] The region of sample DNA on which ASO hybridization is performed to detect the mutation of this invention is preferably amplified by PCR using a forward primer, For exon 9 (to identify the H1047R mutation) the forward primer and reverse primers can include

GGGAAAAATATGACAAAGAAAGC (SEQ ID NO: 3) and
CTGAGATCAGCCAAATTCAGTT (SEQ ID NO: 4) respectively and the sequencing primer can include TAGCTAGAGACAATGAATTAAGGGAAA (SEQ ID NO: 5).

[00294] For exon 20 the forward and reverse primers can include:

CTCAATGATGCTTGGCTCTG (SEQ ID NO: 6) and TGGAATCCAGAGTGAGCTTTC (SEQ ID NO: 7) respectively. and the sequencing primer can include:

TTGATGACATTGCATACATTG (SEQ ID NO: 8). The amplification product can be sequenced. (Barbi, S. et al. J. Experimental and Clinical Cancer Research 2010, 29:32 incorporated by reference herein in its entirety). The sequences can then be compared and differences between the wild type PIK3-a sequence and the sequence of the tumor PIK3-a are determined. The presence or absence of a mutation in PIK3-a can also be determined by comparing the sequence of the tumor PIK3-a and comparing the sequence with the sequence of SEQ ID NO: 1.

[00295] In this case, amplification by PCR or a comparable method is not necessary but can optionally be performed.

[00296] Optionally, one or more than one of the amplified regions described above, (including the 306 nucleotide region generated using primers of SEQ ID NO: 3-8, or shorter portions of either of these regions, can be analyzed by sequencing in order to detect the mutation. Sequencing can be performed as is routine in the art. The only limitation on choice of the region to be sequenced, in order to identify the presence of the mutation, is that the region selected for sequencing must include the nucleotide that is the subject of the mutation, The size of the region selected for sequencing is not limited except by technical parameters as is known in the art, and longer regions comprising part or all of the DNA or RNA between selected amplified regions using the primers SEQ ID NOs: 3 & 4 and 6 & 7 disclosed herein
Variations of the methods disclosed above are also suitable for detecting the mutation. For example, in a variation of ASO, the ASO's are given homopolymer tails with terminal deoxyribonucleotidyl transferase, spotted onto nylon membrane, and covalently bound by UV irradiation. The target DNA is amplified with biotinylated primers and hybridized to the membrane containing the immobilized oligonucleotides, followed by detection. An example of this reverse dot blot technique is the INNO-LIPA kit from Innogenetics (Belgium).

With the identification and sequencing of the mutated gene and the gene product, i.e. SEQ ID NO:1 having a mutation at E545K and H1047R, probes and antibodies raised to the gene product can be used in a variety of hybridization and immunological assays to screen for and detect the presence of either a normal or mutated gene or gene product.

Expression of the mutated gene in heterologous cell systems can be used to demonstrate structure function relationships. Ligating the DNA sequence into a plasmid expression vector to transfect cells is a useful method to test the influence of the mutation on various cellular biochemical parameters. Plasmid expression vectors containing either the entire normal or mutant human or mouse sequence or portions thereof, can be used in in vitro mutagenesis experiments which will identify portions of the protein crucial for regulatory function.

The DNA sequence can be manipulated in studies to understand the expression of the gene and its product, and to achieve production of large quantities of the protein for functional analysis, for antibody production, and for patient therapy. Changes in the sequence may or may not alter the expression pattern in terms of relative quantities, tissue-specificity and functional properties.

A number of methods are available for analysis of variant (e.g., mutant or polymorphic) nucleic acid sequences. Assays for detections polymorphisms or mutations fall into several categories, including, but not limited to direct sequencing assays, fragment polymorphism assays, hybridization assays, and computer based data analysis. Protocols and commercially available kits or services for performing multiple variations of these assays are commercially available and known to those of skill in the art. In some embodiments, assays are performed in combination or in combined parts (e.g., different reagents or technologies from several assays are combined to yield one assay). The following illustrative assays may be used to screen and identify nucleic acid molecules containing the mutations of PI3K-a
mutation of interest.

**Fragment Length Polymorphism Assays**

[00302] In some embodiments of the present invention, variant sequences are detected using a fragment length polymorphism assay. In a fragment length polymorphism assay, a unique DNA banding pattern based on cleaving the DNA at a series of positions is generated using an enzyme (e.g., a restriction enzyme or a CLEAVASE I [Third Wave Technologies, Madison, Wis.] enzyme). DNA fragments from a sample containing a SNP or a mutation will have a different banding pattern than wild type.

**PCR Assays**

[00303] In some embodiments of the present invention, variant sequences are detected using a PCR-based assay. In some embodiments, the PCR assay comprises the use of oligonucleotide nucleic acid primers that hybridize only to the variant or wild type allele of PI3K-a (e.g., to the region of mutation or multiple mutations). Both sets of primers are used to amplify a sample of DNA. If only the mutant primers result in a PCR product, then the subject's tumor or cancer expresses a somatic mutation in an PI3K-a mutation allele. PCR amplification conditions are tailored to the specific oligonucleotide primers or oligonucleotide probes used, the quality and type of DNA or RNA being screened, and other well known variables that can be controlled using appropriate reagents and/or PCR cycling conditions known to those of ordinary skill in the art.

**RFLP Assays**

[00304] In some embodiments of the present invention, variant sequences are detected using a restriction fragment length polymorphism assay (RFLP). The region of interest is first isolated using PCR. The PCR products are then cleaved with restriction enzymes known to give a unique length fragment for a given polymorphism. The restriction-enzyme digested PCR products are separated by agarose gel electrophoresis and visualized by ethidium bromide staining. The length of the fragments is compared to molecular weight markers and fragments generated from wild-type and mutant controls.

**Direct Sequencing Assays**

[00305] In some embodiments of the present invention, variant sequences are detected
using a direct sequencing technique. In these assays, DNA samples are first isolated from a subject using any suitable method. In some embodiments, the region of interest is cloned into a suitable vector and amplified by growth in a host cell (e.g., a bacteria). In other embodiments, DNA in the region of interest is amplified using PCR.

Following amplification, DNA in the region of interest (e.g., the region containing the SNP or mutation of interest) is sequenced using any suitable method, including but not limited to manual sequencing using radioactive marker nucleotides, or automated sequencing. The results of the sequencing are displayed using any suitable method. The sequence is examined and the presence or absence of a given SNP or mutation is determined.

CFLP Assays

In other embodiments, variant sequences are detected using a CLEAVASE fragment length polymorphism assay (CFLP; Third Wave Technologies, Madison, Wis.; See e.g., U.S. Pat. Nos. 5,843,654; 5,843,669; 5,719,208; and 5,888,780; each of which is herein incorporated by reference). This assay is based on the observation that when single strands of DNA fold on themselves, they assume higher order structures that are highly individual to the precise sequence of the DNA molecule. These secondary structures involve partially duplexed regions of DNA such that single stranded regions are juxtaposed with double stranded DNA hairpins. The CLEAVASE I enzyme, is a structure-specific, thermostable nuclease that recognizes and cleaves the junctions between these single-stranded and double-stranded regions. The region of interest is first isolated, for example, using PCR. Then, DNA strands are separated by heating. Next, the reactions are cooled to allow intra-strand secondary structure to form. The PCR products are then treated with the CLEAVASE I enzyme to generate a series of fragments that are unique to a given SNP or mutation. The CLEAVASE enzyme treated PCR products are separated and detected (e.g., by agarose gel electrophoresis) and visualized (e.g., by ethidium bromide staining). The length of the fragments is compared to molecular weight markers and fragments generated from wild-type and mutant controls.

Hybridization Assays

In some embodiments of the present invention, variant sequences are detected by hybridization analysis in a hybridization assay. In a hybridization assay, the presence or absence of a given mutation is determined based on the ability of the DNA from the sample
to hybridize to a complementary DNA molecule (e.g., a oligonucleotide probe or probes as illustrated herein). A variety of hybridization assays using a variety of technologies for hybridization and detection are available. Relevant and useful hybridization assays for practicing the methods of the present invention are provided below.

**Direct Detection of Hybridization**

[00309] In some embodiments, hybridization of a probe to the sequence of interest (e.g., a SNP or mutation) is detected directly by visualizing a bound probe (e.g., a Northern or Southern assay; See e.g., Ausabel et al. (eds.) (1991) Current Protocols in Molecular Biology, John Wiley & Sons, NY). In these assays, genomic DNA (Southern) or RNA (Northern) is isolated from a subject. The DNA or RNA is then cleaved with a series of restriction enzymes that cleave infrequently in the genome and not near any of the markers being assayed. The DNA or RNA is then separated (e.g., on an agarose gel) and transferred to a membrane. A labeled (e.g., by incorporating a radiolabeled) probe or probes specific for the SNP or mutation being detected is allowed to contact the membrane under a condition or low, medium, or high stringency conditions. The unbound probe is removed and the presence of binding is detected by visualizing the labeled probe.

**Detection of Hybridization Using "DNA Chip" Assays**

[00310] In some embodiments of the present invention, variant sequences are detected using a DNA chip hybridization assay. In this assay, a series of oligonucleotide probes are affixed to a solid support. The oligonucleotide probes are designed to be unique to a given SNP or mutation. The DNA sample of interest is contacted with the DNA "chip" and hybridization is detected.

[00311] In some embodiments, an illustrative and commercially available DNA chip assay can include a GENECHIP® (commercially available from Affymetrix, Santa Clara, CA, USA); See e.g., U.S. Pat. Nos. 6,045,996; 5,925,525; and 5,858,659; each of which is herein incorporated by reference) assay. The GENECHIP® technology uses miniaturized, high-density arrays of oligonucleotide probes affixed to a "chip." Probe arrays are manufactured by Affymetrix's light-directed chemical synthesis process, which combines solid-phase chemical synthesis with photolithographic fabrication techniques employed in the semiconductor industry. Using a series of photolithographic masks to define chip exposure sites, followed by specific chemical synthesis steps, the process constructs high-density
arrays of oligonucleotides, with each probe in a predefined position in the array. Multiple probe arrays are synthesized simultaneously on a large glass wafer. The wafers are then diced, and individual probe arrays are packaged in injection-molded plastic cartridges, which protect them from the environment and serve as chambers for hybridization.

[00312] The nucleic acid to be analyzed is isolated, amplified by PCR, and labeled with a fluorescent reporter group. The labeled DNA is then incubated with the array using a fluidics station. The array is then inserted into the scanner, where patterns of hybridization are detected. The hybridization data are collected as light emitted from the fluorescent reporter groups already incorporated into the target, which is bound to the probe array. Probes that perfectly match the target generally produce stronger signals than those that have mismatches. Since the sequence and position of each probe on the array are known, by complementarity, the identity of the target nucleic acid applied to the probe array can be determined.

Enzymatic Detection of Hybridization

[00313] In some embodiments of the present invention, hybridization can be detected by enzymatic cleavage of specific structures (INVADER assay, Third Wave Technologies; See e.g., U.S. Pat. Nos. 5,846,717, 6,090,543; 6,001,567; 5,985,557; and 5,994,069; each of which is herein incorporated by reference). The INVADER assay detects specific DNA and RNA sequences by using structure-specific enzymes to cleave a complex formed by the hybridization of overlapping oligonucleotide probes. Elevated temperature and an excess of one of the probes enable multiple probes to be cleaved for each target sequence present without temperature cycling. These cleaved probes then direct cleavage of a second labeled probe. The secondary probe oligonucleotide can be 5'-end labeled with fluorescein that is quenched by an internal dye. Upon cleavage, the de-quenched fluorescein labeled product may be detected using a standard fluorescence plate reader. The INVADER assay detects specific mutations in unamplified genomic DNA. The isolated DNA sample is contacted with the first probe specific either for a mutation of the present invention or wild type PI3K-a sequence and allowed to hybridize. Then a secondary probe, specific to the first probe, and containing the fluorescein label, is hybridized and the enzyme is added. Binding is detected by using a fluorescent plate reader and comparing the signal of the test sample to known positive and negative controls.

[00314] In some embodiments, hybridization of a bound probe is detected using a TaqMan
assay (PE Biosystems, Foster City, Calif.; See e.g., U.S. Pat. Nos. 5,962,233 and 5,538,848, each of which is herein incorporated by reference). The assay is performed during a PCR reaction. The TaqMan assay exploits the 5'-3' exonuclease activity of the AMPLITAQ GOLD DNA polymerase. A probe, specific for a given allele or mutation, is included in the PCR reaction. The probe consists of an oligonucleotide with a 5'-reporter dye (e.g., a fluorescent dye) and a 3'-quencher dye. During PCR, if the probe is bound to its target, the 5'-3' nucleolytic activity of the AMPLITAQ GOLD polymerase cleaves the probe between the reporter and the quencher dye. The separation of the reporter dye from the quencher dye results in an increase of fluorescence. The signal accumulates with each cycle of PCR and can be monitored with a fluorometer.

[00315] In accordance with the present invention, diagnostic kits are also provided which will include the reagents necessary for the above-described diagnostic screens. For example, kits may be provided which include oligonucleotide probes or PCR primers are present for the detection and/or amplification of mutant PI3K-a and comparable wild-type PI3K-a related nucleotide sequences. Again, such probes may be labeled for easier detection of specific hybridization. As appropriate to the various diagnostic embodiments described above, the oligonucleotide probes in such kits may be immobilized to substrates and appropriate controls may be provided. Examples of such oligonucleotide probes include oligonucleotides comprising or consisting of at least one of SEQ ID NOs: 3&4 and 6&7.

[00316] Determining the presence or absence of mutations in the amino acid sequence of PI3Ka can be determined using any method for the sequence analysis of amino acids. Non-limiting examples include: western blot analysis or ELISA assays, or direct protein sequencing of the PI3Ka in the subject's tumor. In some embodiments, particularly useful antibodies have selectivity for wild type PI3K-a versus the mutant PI3Kα, for example, an antibody useful in the assay would bind to wild type PI3K-α, or a portion wild type PBKα, but not to a PI3Ka having a mutation at the amino acid of interest. Particularly useful antibodies could include antibodies which bind the wild type PI3Ka which has histidine at position 1047 but does not bind a mutant PI3Ka which has an amino acid other than histidine, such as arginine, in other words the antibody would specifically bind to an epitope comprising histidine at position 1047. Likewise, particularly useful are antibodies which bind the wild type PI3Ka which has glutamic acid at position 545 but does not bind a mutant PI3Ka which has an amino acid other than glutamic acid at position 545, such as lysine at that position.
Another embodiment of the invention provides a method comprising the use of at least one antibody which binds selectively to the wild type PI3Ka protein as compared with binding to a mutated form of PDKa. Alternately, the antibody binds selectively to a mutated form of PDKa as compared with binding to the wild type PI3Ka protein and can differentiate between wild-type PI3Ka and PI3Ka-H1047R or between wild-type PDKa and PI3Ka-E545K. Methods for isolating suitable amounts of target protein from a complex mixture in relatively small amounts (less than 1 mg) are commonly known by those skilled in the art. In one illustrative embodiment, a tumor cell or plurality of tumor cells from a subject's tumor or cancer are lysed using commonly available lysing reagents in the presence of protease inhibitors. The lysate is cleared and the supernatant is either electrophoresed and subjected to a Western Blot using mutation specific antibodies, or alternatively, the mutated PI3Ka-H1047R or PI3Ka-E545K proteins are selectively immunoprecipitated and further dissociated from the capture antibody and subjected to Western Blotting or protein sequenced directly.

"Antibody" includes, any immunoglobulin molecule that recognizes and specifically binds to a target, such as a protein, polypeptide, peptide, carbohydrate, polynucleotide, lipid, etc., through at least one antigen recognition site within the variable region of the immunoglobulin molecule. As used herein, the term is used in the broadest sense and encompasses intact polyclonal antibodies, intact monoclonal antibodies, antibody fragments (such as Fab, Fab', F(ab')2, and Fv fragments), single chain Fv (scFv) mutants, multispecific antibodies such as bispecific antibodies generated from at least two intact antibodies, fusion proteins comprising an antibody portion, and any other modified immunoglobulin molecule comprising an antibody portion so long as the antibodies exhibit the desired biological activity. An antibody can be of any the five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, or subclasses (isotypes) thereof (e.g. IgGl, IgG2, IgG3, IgG4, IgAl and IgA2), based on the identity of their heavy-chain constant domains referred to as alpha, delta, epsilon, gamma, and mu, respectively. The different classes of immunoglobulins have different and well known subunit structures and three-dimensional configurations. Antibodies can be naked or conjugated to other molecules such as toxins, radioisotopes, and the like.

"Antibody fragment" can refer to a portion of an intact antibody. Examples of antibody fragments include, but are not limited to, linear antibodies; single-chain antibody
molecules; Fc or Fc' peptides, Fab and Fab fragments, and multispecific antibodies formed from antibody fragments.

"Chimeric antibodies" refers to antibodies wherein the amino acid sequence of the immunoglobulin molecule is derived from two or more species. Typically, the variable region of both light and heavy chains corresponds to the variable region of antibodies derived from one species of mammals (e.g. mouse, rat, rabbit, etc) with the desired specificity, affinity, and capability while the constant regions are homologous to the sequences in antibodies derived from another (usually human) to avoid eliciting an immune response in that species.

"Humanized" forms of non-human (e.g., rabbit) antibodies include chimeric antibodies that contain minimal sequence, or no sequence, derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. Most often, the humanized antibody can comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a nonhuman immunoglobulin and all or substantially all of the FR residues are those of a human immunoglobulin sequence. The humanized antibody can also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Methods used to generate humanized antibodies are well known in the field of immunology and molecular biology.

"Hybrid antibodies" can include immunoglobulin molecules in which pairs of heavy and light chains from antibodies with different antigenic determinant regions are assembled together so that two different epitopes or two different antigens can be recognized and bound by the resulting tetramer.

The term "epitope" or "antigenic determinant" are used interchangeably herein and refer to that portion of an antigen capable of being recognized and specifically bound by a particular antibody. When the antigen is a polypeptide, epitopes can be formed both from contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained upon protein
denaturing, whereas epitopes formed by tertiary folding are typically lost upon protein
denaturing. An epitope typically includes at least 3-5, and more usually, at least 5 or 8-10
amino acids in a unique spatial conformation.

[00324] "Specifically binds" to or shows "specific binding" towards an epitope means that
the antibody reacts or associates more frequently, and/or more rapidly, and/or greater
duration, and/or with greater affinity with the epitope than with alternative substances.

Preparation of Antibodies

**Polyclonal Antibodies**

[00325] Polyclonal antibodies are preferably raised in animals by multiple subcutaneous
(sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. Alternatively,
antigen may be injected directly into the animal's lymph node (see Kilpatrick et al.,
Hybridoma, 16:381-389, 1997). An improved antibody response may be obtained by
conjugating the relevant antigen to a protein that is immunogenic in the species to be
immunized, e.g., keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or
soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example,
maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-
hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride or other
agents known in the art.

[00326] Animals are immunized against the antigen, immunogenic conjugates or
derivatives by combining, e.g., 100 µg of the protein or conjugate (for mice) with 3 volumes
of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One
month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or
conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. At 7-14
days post-booster injection, the animals are bled and the serum is assayed for antibody titer.
Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the
conjugate of the same antigen, but conjugated through a different cross-linking reagent.
Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating
agents such as alum are suitably used to enhance the immune response.

**Monoclonal Antibodies**

[00327] Monoclonal antibodies can be made using the hybridoma method first described
by Kohler et al., Nature, 256:495 (1975), or by recombinant DNA methods. In the hybridoma
method, a mouse or other appropriate host animal, such as rats, hamster or macaque monkey, is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)). The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells and are sensitive to a medium. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)). Exemplary murine myeloma lines include those derived from MOP-21 and M. C.-ll mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, Calif. USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Md. USA. Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). The binding affinity of the monoclonal antibody can be determined, for example, by BIAdcore or Scatchard analysis (Munson et al., Anal. Biochem., 107:220 (1980)).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones can be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEMO or RPMI 1640 medium. In addition, the hybridoma cells can be grown in vivo as ascites tumors in an animal. The monoclonal antibodies secreted by the
subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

Recombinant Production of Antibodies

[00330] The amino acid sequence of an immunoglobulin of interest can be determined by direct protein sequencing, and suitable encoding nucleotide sequences can be designed according to a universal codon table.

[00331] Alternatively, DNA encoding the monoclonal antibodies can be isolated and sequenced from the hybridoma cells using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). Sequence determination will generally require isolation of at least a portion of the gene or cDNA of interest. Usually this requires cloning the DNA or mRNA encoding the monoclonal antibodies. Cloning is carried out using standard techniques (see, e.g., Sambrook et al. (1989) Molecular Cloning: A Laboratory Guide, Vols 1-3, Cold Spring Harbor Press, which is incorporated herein by reference). For example, a cDNA library can be constructed by reverse transcription of polyA+ mRNA, preferably membrane-associated mRNA, and the library screened using probes specific for human immunoglobulin polypeptide gene sequences. In a preferred embodiment, the polymerase chain reaction (PCR) is used to amplify cDNAs (or portions of full-length cDNAs) encoding an immunoglobulin gene segment of interest (e.g., a light chain variable segment). The amplified sequences can be cloned readily into any suitable vector, e.g., expression vectors, minigene vectors, or phage display vectors. It will be appreciated that the particular method of cloning used is not critical, so long as it is possible to determine the sequence of some portion of the immunoglobulin polypeptide of interest.

[00332] One source for RNA used for cloning and sequencing is a hybridoma produced by obtaining a B cell from the transgenic mouse and fusing the B cell to an immortal cell. An advantage of using hybridomas is that they can be easily screened, and a hybridoma that produces a human monoclonal antibody of interest selected. Alternatively, RNA can be isolated from B cells (or whole spleen) of the immunized animal. When sources other than hybridomas are used, it may be desirable to screen for sequences encoding immunoglobulins or immunoglobulin polypeptides with specific binding characteristics. One method for such screening is the use of phage display technology. Phage display is described in e.g., Dower et
al., WO 91/17271, McCafferty et al., WO 92/01047, and Caton and Koprowski, Proc. Natl. Acad. Sci. USA, 87:6450-6454 (1990), each of which is incorporated herein by reference. In one embodiment using phage display technology, cDNA from an immunized transgenic mouse (e.g., total spleen cDNA) is isolated, PCR is used to amplify cDNA sequences that encode a portion of an immunoglobulin polypeptide, e.g., CDR regions, and the amplified sequences are inserted into a phage vector. cDNAs encoding peptides of interest, e.g., variable region peptides with desired binding characteristics, are identified by standard techniques such as panning. The sequence of the amplified or cloned nucleic acid is then determined. Typically the sequence encoding an entire variable region of the immunoglobulin polypeptide is determined, however, sometimes only a portion of a variable region need be sequenced, for example, the CDR-encoding portion. Typically the sequenced portion will be at least 30 bases in length, and more often bases coding for at least about one-third or at least about one-half of the length of the variable region will be sequenced. Sequencing can be carried out on clones isolated from a cDNA library or, when PCR is used, after subcloning the amplified sequence or by direct PCR sequencing of the amplified segment. Sequencing is carried out using standard techniques (see, e.g., Sambrook et al. (1989) Molecular Cloning: A Laboratory Guide, Vols 1-3, Cold Spring Harbor Press, and Sanger, F. et al. (1977) Proc. Natl. Acad. Sci. USA 74: 5463-5467, which is incorporated herein by reference). By comparing the sequence of the cloned nucleic acid with published sequences of human immunoglobulin genes and cDNAs, an artisan can determine readily, depending on the region sequenced, (i) the germline segment usage of the hybridoma immunoglobulin polypeptide (including the isotype of the heavy chain) and (ii) the sequence of the heavy and light chain variable regions, including sequences resulting from N-region addition and the process of somatic mutation. One source of immunoglobulin gene sequence information is the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Md.

[00333] Once isolated, the DNA may be operably linked to expression control sequences or placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to direct the synthesis of monoclonal antibodies in the recombinant host cells.

[00334] Expression control sequences denote DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences
that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome-binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

[00335] Nucleic acid is operably linked when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome-binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, operably linked means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking can be accomplished by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers can be used in accordance with conventional practice.

[00336] Cell, cell line, and cell culture are often used interchangeably and all such designations include progeny. Transformants and transformed cells include the primary subject cell and cultures derived therefrom without regard for the number of transfers. It also is understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Mutant progeny that have the same function or biological activity as screened for in the originally transformed cell are included.

[00337] Isolated nucleic acids also are provided that encode specific antibodies, optionally operably linked to control sequences recognized by a host cell, vectors and host cells comprising the nucleic acids, and recombinant techniques for the production of the antibodies, which may comprise culturing the host cell so that the nucleic acid is expressed and, optionally, recovering the antibody from the host cell culture or culture medium.

[00338] A variety of vectors are known in the art. Vector components can include one or more of the following: a signal sequence (that, for example, can direct secretion of the antibody), an origin of replication, one or more selective marker genes (that, for example, can confer antibiotic or other drug resistance, complement auxotrophic deficiencies, or supply critical nutrients not available in the media), an enhancer element, a promoter, and a transcription termination sequence, all of which are well known in the art.

[00339] Suitable host cells include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include eubacteria, such as Gram-negative or Gram-positive organisms, for
example, Enterohacteriaceae such as Escherichia, e.g., E. coli, Enterobacter, Erwinia, Klebsiella, Proteus, Salmonella, e.g., Salmonella typhimurium, Serratia, e.g., Serratia marcescans, and Shigella, as well as Bacilli such as B. subtilis and B. licheniformis, Pseudomonas, and Streptomyces. In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors. Saccharomyces cerevisiae, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available, such as Pichia, e.g. P. pastoris, Schizosaccharomyces pombe; Kluyveromyces, Yarrowia; Candida; Trichoderma reesia; Neurospora crassa; Schwanniomyces such as Schwanniomyces occidentalis; and filamentous fungi such as, e.g., Neurospora, Penicillium, Tolypocladium, and Aspergillus hosts such as A. niger.

[00340] Suitable host cells for the expression of glycosylated antibodies are derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as Spodoptera frugiperda (caterpillar), Aedes aegypti (mosquito), Aedes albopictus (mosquito), Drosophila melanogaster (fruitfly), and Bombyx mori have been identified. A variety of viral strains for transfection of such cells are publicly available, e.g., the L-I variant of Autographa californica NPV and the Bm-5 strain of Bombyx mori NPV.

[00341] However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become routine. Examples of useful mammalian host cell-lines are Chinese hamster ovary cells, including CHOKI cells (ATCC CCL61) and Chinese hamster ovary cells/DHFR (DXB-11, DG-44; Urlaub et al, Proc. Natl. Acad. Sci. USA 77: 4216 (1980)); monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, [Graham et al., J. Gen Virol. 36: 59 (1977)]; baby hamster kidney cells (BHK, ATCC CCL 10); mouse Sertoli cells (TM4, Mather, Biol. Reprod. 23: 243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (WI38, ATCC CCL 75); human hepatoma cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., Annals N.Y. Acad. Sci. 383: 44-68 (1982)); MRC 5 cells and FS4 cells.
The host cells can be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., Meth. Enz. 58: 44 (1979), Barnes et al., Anal. Biochem. 102: 255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO90103430; WO 87/00195; or U.S. Pat. Re. No. 30,985 can be used as culture media for the host cells. Any of these media can be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as Gentamycin.TM. drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements also can be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the artisan.

The antibody composition can be purified using, for example, hydroxylapatite chromatography, cation or anion exchange chromatography, or preferably affinity chromatography, using the antigen of interest or protein A or protein G as an affinity ligand. Protein A can be used to purify antibodies that are based on human .gamma.1, .gamma.2, or .gamma.4 heavy chains (Lindmark et al., J. Immunol. Meth. 62: 1-13 (1983)). Protein G is recommended for all mouse isotypes and for human .gamma.3 (Guss et al., 20 EMBO J. 5: 15671575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a CH3 domain, the Bakerbond ABX.TM. resin (J. T. Baker, Phillipsburg, 25 NJ.) is useful for purification. Other techniques for protein purification such as ethanol precipitation, Reverse Phase HPLC, chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also possible depending on the specific binding agent or antibody to be recovered.

The term "epitope" or "antigenic determinant" are used interchangeably herein and refer to that portion of an antigen capable of being recognized and specifically bound by a particular antibody. When the antigen is a polypeptide, epitopes can be formed both from
contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding are typically lost upon protein denaturing. An epitope typically includes at least 3-5, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

"Specifically binds" to or shows "specific binding" towards an epitope means that the antibody reacts or associates more frequently, and/or more rapidly, and/or greater duration, and/or with greater affinity with the epitope than with alternative substances.

In some embodiments, once the subject's tumor has been analyzed to determine whether the tumor harbors a wild type PI3K-a versus a mutant PI3K-a, for example, PI3K-a E545K or PI3K-a H1047R, using any one or more of the assays and methods described above, a treatment regimen can be prepared for the subject. If the subject's tumor harbors a PDK-a having a mutation at position 1047, (for example, H1047R), the treatment regimen comprises administering to the subject a therapeutically effective amount of a PI3K-α selective inhibitor compound, or a dual PI3K-α/mTOR selective inhibitor, or a combination of a PI3K-α selective inhibitor or a mTOR selective inhibitor. If the subject's tumor harbors a PI3K-a having a mutation at position 545, (for example, E545K), the treatment regimen comprises administering to the subject a therapeutically effective amount of a combination of a PI3K-α selective inhibitor and a PDK-β selective inhibitor, a dual PI3K-α/mTOR selective inhibitor, or a combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor.

Embody (AZ): In another embodiment, the present invention provides kits comprising materials useful for carrying out the methods of the invention. The diagnostic/screening procedures described herein may be performed by diagnostic laboratories, experimental laboratories, or practitioners. The invention provides kits which can be used in these different settings.

Basic materials and reagents required for identifying a PI3K-a mutation in a subject's tumor or cancer according to methods of the present invention may be assembled together in a kit. In certain embodiments, the kit comprises at least one PI3K-a amino acid sequence determining reagent that specifically detects a mutation in a nucleic acid or protein obtained from a subject's tumor disclosed herein, and instructions for using the kit according to one or more methods of the invention. Each kit necessarily comprises reagents which render the procedure specific. Thus, for detecting mRNA harboring the PI3K-a H1047R or E545K mutation, the reagent will comprise a nucleic acid probe complementary to mRNA,
such as, for example, a cDNA or an oligonucleotide. The nucleic acid probe may or may not be immobilized on a substrate surface (e.g., a microarray). For detecting a polypeptide product encoded by at least one PI3K-a mutation gene, the reagent will comprise an antibody that specifically binds to the mutated PI3K-a or a wild-type PI3K-a.

Depending on the procedure, the kit may further comprise one or more of: extraction buffer and/or reagents, amplification buffer and/or reagents, hybridization buffer and/or reagents, immunodetection buffer and/or reagents, labeling buffer and/or reagents, and detection means. Protocols for using these buffers and reagents for performing different steps of the procedure may also be included in the kit.

Reagents may be supplied in a solid (e.g., lyophilized) or liquid form. Kits of the present invention may optionally comprise one or more receptacles for mixing samples and/or reagents (e.g., vial, ampoule, test tube, ELISA plate, culture plate, flask or bottle) for each individual buffer and/or reagent. Each component will generally be suitable as aliquoted in its respective container or provided in a concentrated form. Other containers suitable for conducting certain steps for the disclosed methods may also be provided. The individual containers of the kit are preferably maintained in close confinement for commercial sale.

In certain embodiments, the kits of the present invention further comprise control samples. For example, a kit may include samples of total mRNA derived from tissue of various physiological states, such as, for example, wild-type PI3K-α, PI3K-α H1047R mRNA or PI3K-α E545K mRNA to be used as controls. In other embodiments, the inventive kits comprise at least one prostate disease expression profile map as described herein for use as comparison template. Preferably, the expression profile map is digital information stored in a computer-readable medium.

Instructions for using the kit according to one or more methods of the invention may comprise instructions for processing the prostate tissue sample and/or performing the test, instructions for interpreting the results as well as a notice in the form prescribed by a governmental agency (e.g., FDA) regulating the manufacture, use or sale of pharmaceuticals or biological products.

**Representative Compounds**

Representative compounds of Formula I are depicted below. The examples are merely illustrative and do not limit the scope of the invention in any way. Compounds of the invention are named according to systematic application of the nomenclature rules agreed
upon by the International Union of Pure and Applied Chemistry (IUPAC), International
Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts
Service (CAS). Specifically, names in Table 1 were generated using ACD/Labs naming
software 8.00 release, product version 8.08 or higher.

### Table 1

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>6-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}pyridazin-3-amine</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>methyl 6-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}-1H-benzimidazol-2-yl)carbamate</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>5-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}pyrimidin-2-amine</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>5-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}pyrazin-2-amine</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure Image" /></td>
<td>N-(5-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}-1,3-thiazol-2-yl)acetamide</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure Image" /></td>
<td>5-{4-[(4-(trifluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}pyrazin-2-amine</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure Image" /></td>
<td>7-[4-(1H-imidazol-2-yl)phenyl]-4-{4-(trifluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Structure Image" /></td>
<td>4-{4-(methylpiperidin-1-yl)carbonyl}-7-(1,3-thiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
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</table>
| 9 | ![Structure Image](image9) | 3-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}-N-(phenylmethyl)-1H-pyrazol-5-
<table>
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<tr>
<td>10</td>
<td><img src="image1.png" alt="Structure 10" /></td>
<td>3-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-pyrazol-5-amine</td>
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<tr>
<td>11</td>
<td><img src="image2.png" alt="Structure 11" /></td>
<td>methyl [6-([2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>12</td>
<td><img src="image3.png" alt="Structure 12" /></td>
<td>methyl [6-([2-(4-fluorophenyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
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<tr>
<td>13</td>
<td><img src="image4.png" alt="Structure 13" /></td>
<td>methyl [6-([4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>14</td>
<td><img src="image5.png" alt="Structure 14" /></td>
<td>methyl [6-([2-(4-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>15</td>
<td><img src="image6.png" alt="Structure 15" /></td>
<td>methyl [6-([4-(fluoromethyl)-4-hydroxypiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>16</td>
<td><img src="image7.png" alt="Structure 16" /></td>
<td>methyl [6-([2-(3,4-difluorophenyl)-4-oxopiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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<tr>
<td>17</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(±)-methyl [5-[(4-[[2R,4S]-2-(4-fluorophenyl)-4-hydroxy piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>18</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>methyl [6-[(4-hydroxy-4-[[3-(trifluoromethyl)phenyl]piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>19</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>methyl [6-[(4-difluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>20</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>methyl [6-[(4-[[3-(endo)-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>21</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>methyl [6-[(4-cyanopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
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<tr>
<td>22</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>methyl [6-[(4-hydroxy-4-(trifluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
</tr>
<tr>
<td>23</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>1-[[7-(2-amino-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)yl]carbonyl]-4-methylpiperidin-4-ol</td>
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<td>24</td>
<td><img src="image8.png" alt="Structure" /></td>
<td>methyl [6-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
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<tr>
<td>25</td>
<td><img src="image9.png" alt="Structure" /></td>
<td>methyl [6-[(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate</td>
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<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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<tr>
<td>26</td>
<td><img src="image" alt="Structure 26" /></td>
<td>6-(4-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-amine</td>
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<tr>
<td>27</td>
<td><img src="image" alt="Structure 27" /></td>
<td>1-[[7-(2-amino-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]-2-(3,4-difluorophenyl)piperidin-4-one</td>
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<tr>
<td>28</td>
<td><img src="image" alt="Structure 28" /></td>
<td>1-[[7-(2-amino-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]-2-(3-fluorophenyl)piperidin-4-one</td>
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<tr>
<td>29</td>
<td><img src="image" alt="Structure 29" /></td>
<td>N-ethyl-6-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-amine</td>
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<tr>
<td>30</td>
<td><img src="image" alt="Structure 30" /></td>
<td>1-[[7-[2-(ethylamino)-1H-benzimidazol-6-yl]-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]-2-(3-fluorophenyl)piperidin-4-one</td>
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<tr>
<td>31</td>
<td><img src="image" alt="Structure 31" /></td>
<td>2-(3-fluorophenyl)-1-[[7-[2-[[2,2,2-trifluoroethyl]amino]-1H-benzimidazol-5-yl]-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]piperidin-4-one</td>
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<tr>
<td>32</td>
<td><img src="image" alt="Structure 32" /></td>
<td>1-[[7-[2-[[2-fluoroethyl]amino]-1H-benzimidazol-5-yl]-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]-2-(3-fluorophenyl)piperidin-4-one</td>
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<td>33</td>
<td><img src="image" alt="Structure 33" /></td>
<td>6-(4-[[4-(1,1-difluoroethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-N-ethyl-1H-benzimidazol-2-amine</td>
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<td>Entry No.</td>
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<tr>
<td>34</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>methyl [6-(4-[(4-(1,1)-difluoroethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>35</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>methyl [6-(4-[(4-(2-fluoroethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>36</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>methyl [6-(4-[(4-(fluoromethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>37</td>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>methyl [6-(4-[(2-(4-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>38</td>
<td><img src="image5.png" alt="Structure Image" /></td>
<td>methyl [6-(4-[(4-(fluoromethyl)-4-hydroxypiperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>39</td>
<td><img src="image6.png" alt="Structure Image" /></td>
<td>methyl [6-(4-[(2-(3,4-difluorophenyl)-4-oxopiperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>40</td>
<td><img src="image7.png" alt="Structure Image" /></td>
<td>methyl [6-(4-[(4-cyanopiperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>41</td>
<td><img src="image1" alt="" /></td>
<td>methyl (6-{(4-methylpiperidin-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl)carbamate</td>
</tr>
<tr>
<td>42</td>
<td><img src="image2" alt="" /></td>
<td>6-{(4-{(4-(1,1-difluoroethyl)piperidin-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl)carbamate</td>
</tr>
<tr>
<td>43</td>
<td><img src="image3" alt="" /></td>
<td>6-{(4-{(4-(difluoromethyl)piperidin-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl)carbamate</td>
</tr>
<tr>
<td>44</td>
<td><img src="image4" alt="" /></td>
<td>6-{(4-{(4-(2-fluoroethyl)piperidin-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl)carbamate</td>
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<td>45</td>
<td><img src="image5" alt="" /></td>
<td>6-{(4-{(4-(fluoromethyl)piperidin-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl)carbamate</td>
</tr>
<tr>
<td>46</td>
<td><img src="image6" alt="" /></td>
<td>1-{(7-(2-amino-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl)piperidine-4-carbonitrile</td>
</tr>
<tr>
<td>47</td>
<td><img src="image7" alt="" /></td>
<td>1-{(7-(2-amino-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl)piperidine-4-carboxamide</td>
</tr>
<tr>
<td>48</td>
<td><img src="image8" alt="" /></td>
<td>1-{(7-(2-amino-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl)-2-(3-fluorophenyl)piperidin-4-one</td>
</tr>
<tr>
<td>49</td>
<td><img src="image9" alt="" /></td>
<td>8-{(7-(2-amino-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl)-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(endo)-ol</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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<tr>
<td>50</td>
<td><img src="image" alt="Structure" /></td>
<td>$N$-[5-(4-[(4-(fluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-benzimidazol-2-yl]acetamide</td>
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<tr>
<td>51</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(3-fluorophenyl)-1-[[7-(2-methyl-3H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]piperidin-4-one</td>
</tr>
<tr>
<td>52</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(3-fluorophenyl)-1-[[7-(3H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]piperidin-4-one</td>
</tr>
<tr>
<td>53</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(3,4-difluorophenyl)-1-[[7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]piperidin-4-one</td>
</tr>
<tr>
<td>54</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(4-fluorophenyl)-1-[[7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]piperidin-4-one</td>
</tr>
<tr>
<td>55</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(3-fluorophenyl)-1-[[7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]piperidin-4-one</td>
</tr>
<tr>
<td>Entry No.</td>
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</tr>
<tr>
<td>56</td>
<td>(2R)-2-(4-fluorophenyl)-1-((7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl)piperidin-4-one</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>(2S)-2-(4-fluorophenyl)-1-((7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl)piperidin-4-one</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>4-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-7-[4-(1H-imidazol-2-yl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
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</tr>
<tr>
<td>59</td>
<td>8-[[7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(endo)-ol</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>7-[4-(1H-imidazol-2-yl)phenyl]-4-[[4-methylpiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
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</tr>
<tr>
<td>61</td>
<td>1-[[7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl)piperidine-4-carbonitrile</td>
<td></td>
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<tr>
<td>62</td>
<td>4-[[4-(difluoromethyl)piperidin-1-yl]carbonyl]-7-[4-(1H-imidazol-2-yl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>1-[[7-[6-(1H-imidazol-2-yl)pyridin-3-yl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl)piperidine-4-carbonitrile</td>
<td></td>
</tr>
<tr>
<td>Entry No.</td>
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<td>Name</td>
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</tr>
<tr>
<td>64</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-(2,2-difluoroethyl)-4-(4-[[2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide</td>
</tr>
<tr>
<td>65</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[[2S]-2-phenylpiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>66</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[[2R]-2-phenylpiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>67</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>4-[[4,4-difluoropiperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>68</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]piperidin-4-ol</td>
</tr>
<tr>
<td>69</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>4-[[4-[[4-chlorophenyl]methyl]piperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>70</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>4-[[4-[[4-chlorophenyl]oxy]piperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>71</td>
<td><img src="image8.png" alt="Structure" /></td>
<td>1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-4,4'-bipiperidine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>72</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>4-[(3-ethylpiperidin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoaxepine</td>
</tr>
<tr>
<td>73</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>4-[(2-(4-fluorophenyl)piperidin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoaxepine</td>
</tr>
<tr>
<td>74</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>ethyl (3S)-1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoaxepin-4(5H)-yl]carbonyl]piperidine-3-carboxylate</td>
</tr>
<tr>
<td>75</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>ethyl 1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoaxepin-4(5H)-yl]carbonyl]piperidine-2-carboxylate</td>
</tr>
<tr>
<td>76</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>4-[(5-ethyl-2-methylpiperidin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoaxepine</td>
</tr>
<tr>
<td>77</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>8-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoaxepin-4(5H)-yl]carbonyl]-8-azabicyclo[3.2.1]octan-3-(endo)-amine</td>
</tr>
<tr>
<td>78</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>(3R)-1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoaxepin-4(5H)-yl]carbonyl]pyrrolidin-3-ol</td>
</tr>
<tr>
<td>79</td>
<td><img src="image8.png" alt="Structure" /></td>
<td>4-methyl-1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoaxepin-4(5H)-yl]carbonyl]piperidin-4-ol</td>
</tr>
<tr>
<td>80</td>
<td><img src="image9.png" alt="Structure" /></td>
<td>(±)-7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4aS,8aR)-octahydroisoquinolin-2(1H)-ylcarbonyl]-2,3,4,5-tetrahydro-1,4-benzoaxepine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>81</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>4-{{[2-(3-fluorophenyl)piperidin-1-yl]carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
<tr>
<td>82</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>(3S)-1-{{[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl}pyrrolidin-3-ol}</td>
</tr>
<tr>
<td>83</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>4-{{[4-fluoro-4-methylpiperidin-1-yl]carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
<tr>
<td>84</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>4-{{hexahydrocyclopenta[c]pyrrolo[2(1H)-yl]carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
<tr>
<td>85</td>
<td><img src="image5" alt="Structure Image" /></td>
<td>4-{{3,4-dihydroquinolin-1(2H)-yl}carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
<tr>
<td>86</td>
<td><img src="image6" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-(piperidin-1-yl)carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
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<td>87</td>
<td><img src="image7" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-(pyrroloidin-1-yl)carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
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<td>88</td>
<td><img src="image8" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-{{[3-methylpiperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
<tr>
<td>89</td>
<td><img src="image9" alt="Structure Image" /></td>
<td>4-{azepan-1-yl}carbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
</tr>
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<td>90</td>
<td><img src="image10" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-5-yl)-4-{{[3aR,6aS]-5-methylhexahydrocyclopenta[c]pyrrol-2(3H)-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepine}</td>
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<tr>
<td>Entry No.</td>
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<td>Name</td>
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<tr>
<td>91</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>(±)-7-(2-methyl-1H-benimidazol-5-yl)-4-{{{3aS,6aR}-5-methyl-3a,4,6a-tetrahydrocyclopenta[c]pyrrolo-2(1H)-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>92</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>N-methyl-7-(2-methyl-1H-benimidazol-6-yl)-N-(phenylmethyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>93</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>N-methyl-7-(2-methyl-1H-benimidazol-6-yl)-N-(2-phenylethyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>94</td>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benimidazol-6-yl)-4-{{{2-(phenylmethyl)pyrrolidin-1-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>95</td>
<td><img src="image5.png" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benimidazol-6-yl)-4-{{{2-phenylpyrrolidin-1-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
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<td>96</td>
<td><img src="image6.png" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benimidazol-6-yl)-4-{{{2-phenylpiperidin-1-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>97</td>
<td><img src="image7.png" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benimidazol-6-yl)-4-{{{3-phenylpiperidin-1-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
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<tr>
<td>98</td>
<td><img src="image8.png" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benimidazol-6-yl)-4-{{{3-phenylpyrrolidin-1-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
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<tr>
<td>Entry No.</td>
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<td>99</td>
<td><img src="image1" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(2-methylpyrrolidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
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<tr>
<td>100</td>
<td><img src="image2" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(3-(phenylmethyl)pyrrolidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
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<td>101</td>
<td><img src="image3" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(1-oxothiomorpholin-4-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
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<td>102</td>
<td><img src="image4" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[[4-(methylsulfonyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>103</td>
<td><img src="image5" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-N-(1-methylethyl)-N-(phenylmethyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>104</td>
<td><img src="image6" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(2-phenylmethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>105</td>
<td><img src="image7" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-(methoxy)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>106</td>
<td><img src="image8" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(3-phenylmethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>107</td>
<td><img src="image9" alt="Structure" /></td>
<td>4-(2-azabicyclo[2.2.1]hept-2-ylcarbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
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</tr>
<tr>
<td>108</td>
<td><img src="image1.png" alt="Structure Image" /></td>
<td>1-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}carbonyl}piperidin-3-ol</td>
</tr>
<tr>
<td>109</td>
<td><img src="image2.png" alt="Structure Image" /></td>
<td>N-methyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-[(1R)-1-phenylethyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>110</td>
<td><img src="image3.png" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-{{5-phenylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl}carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>111</td>
<td><img src="image4.png" alt="Structure Image" /></td>
<td>1-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}carbonyl}-2-phenylpiperidin-4-one</td>
</tr>
<tr>
<td>112</td>
<td><img src="image5.png" alt="Structure Image" /></td>
<td>(8-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}carbonyl}-8-azabicyclo[3.2.1]oct-3-(endo)-yl)methanol</td>
</tr>
<tr>
<td>113</td>
<td><img src="image6.png" alt="Structure Image" /></td>
<td>4-{{3,4-dihydroisoquinolin-2(1H)-y1carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>114</td>
<td><img src="image7.png" alt="Structure Image" /></td>
<td>4-{{2-(3,4-difluorophenyl)piperidin-1-yl}carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>115</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>4-((2-[3,5-bis(trifluoromethyl)phenyl]piperidin-1-yl)carbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>116</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>4-((2-(3-chloro-5-fluorophenyl)piperidin-1-yl)carbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>117</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>4-((2-(4-fluoro-2-methylphenyl)piperidin-1-yl)carbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>118</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>4-((2-(4-fluoro-3-methylphenyl)piperidin-1-yl)carbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>119</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>2-(3,4-difluorophenyl)-1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(SH)-yl]carbonyl]-4-(trifluoromethyl)piperidin-4-ol</td>
</tr>
<tr>
<td>120</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-((2-[4-(trifluoromethyl)phenyl]piperidin-1-yl)carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>121</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>2-(3,4-difluorophenyl)-1-{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}carbonyl}piperidin-4-one</td>
</tr>
<tr>
<td>122</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-5-yl)-4-{(2-phenylazepan-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>123</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>4-{(2-(3-fluoro-4-methylphenyl)piperidin-1-yl)carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>124</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>4-{(2-(3-chlorophenyl)piperidin-1-yl)carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>125</td>
<td><img src="image5" alt="Structure Image" /></td>
<td>2-(3-fluorophenyl)-1-{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}carbonyl}piperidin-4-one</td>
</tr>
<tr>
<td>126</td>
<td><img src="image6" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-{(2-(2-methylphenyl)piperidin-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>127</td>
<td><img src="image7" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-{(2-[3-(trifluoromethyl)phenyl]piperidin-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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<tr>
<td>128</td>
<td><img src="image1" alt="Structure" /></td>
<td>4-{[2-(3-chloro-4-fluorophenyl)piperidin-1-yl][carbonyl]}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>129</td>
<td><img src="image2" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-{[2-(3,4,5-trifluorophenyl)piperidin-1-yl][carbonyl]}-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>130</td>
<td><img src="image3" alt="Structure" /></td>
<td>4-{[2-(3,5difluorophenyl)piperidin-1-yl][carbonyl]}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>131</td>
<td><img src="image4" alt="Structure" /></td>
<td>N,N-dimethyl-4-(1-{[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl][carbonyl]}piperidin-2-yl)aniline</td>
</tr>
<tr>
<td>132</td>
<td><img src="image5" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-(morpholin-4-ylcarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine</td>
</tr>
<tr>
<td>133</td>
<td><img src="image6" alt="Structure" /></td>
<td>(+)-(2R,4R)-4-methyl-1-{[7-(2-methyl-1H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl][carbonyl]}-2-phenylpiperidin-4-ol</td>
</tr>
<tr>
<td>134</td>
<td><img src="image7" alt="Structure" /></td>
<td>(+)-(2R,4S)-4-methyl-1-{[7-(2-methyl-1H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl][carbonyl]}-2-phenylpiperidin-4-ol</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>135</td>
<td><img src="image135" alt="Structure 135" /></td>
<td>4-methyl-1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl]piperidine-4-carboxamide</td>
</tr>
<tr>
<td>136</td>
<td><img src="image136" alt="Structure 136" /></td>
<td>(±)-(2R,4S)-2-(4-fluorophenyl)-1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl]piperidin-4-ol</td>
</tr>
<tr>
<td>137</td>
<td><img src="image137" alt="Structure 137" /></td>
<td>4-[[4-(difluoromethylidene)piperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>138</td>
<td><img src="image138" alt="Structure 138" /></td>
<td>4-[[4,4-difluoro-2-phenylpiperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>139</td>
<td><img src="image139" alt="Structure 139" /></td>
<td>2-(1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl]piperidin-4-yl)propan-2-ol</td>
</tr>
<tr>
<td>140</td>
<td><img src="image140" alt="Structure 140" /></td>
<td>(±)-(2R,4S)-2-(3,4-difluorophenyl)-1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl]piperidin-4-ol</td>
</tr>
<tr>
<td>141</td>
<td><img src="image141" alt="Structure 141" /></td>
<td>1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl]-4-[4-( trifluoromethyl)phenyl]piperidin-4-ol</td>
</tr>
<tr>
<td>142</td>
<td><img src="image142" alt="Structure 142" /></td>
<td>4-(4-fluorophenyl)-1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl]piperidin-4-ol</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>143</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>9-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl][carbonyl]-1,2,3,4-tetrahydro-1,4-epiminonaphthalene</td>
</tr>
<tr>
<td>144</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-{{4-methyl-2-phenylpiperazin-1-yl][carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>145</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>4-{{2,4-diphenylpiperazin-1-yl}[carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>146</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>1-methyl-4-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl}[carbonyl]piperazin-2-one</td>
</tr>
<tr>
<td>147</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>(±)-4-{{2R,4S}-2-(3,4-difluorophenyl)-4-(fluoromethyl)piperidin-1-yl[carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>148</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>(±)-(2R,4R)-2-(3,4-difluorophenyl)-1-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl[carbonyl]piperidine-4-carbonitrile</td>
</tr>
<tr>
<td>149</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-N-{{1r,3r,5R,7R-tricyclo[3.3.1.1-3,7-dec-2-yl]-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>150</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-((4-[(trifluoromethyl)pyridin-2-yl)piperazin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>151</td>
<td><img src="image" alt="Structure" /></td>
<td>ethyl N-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl}[carbonyl]-N-(phenylmethyl)glycinate</td>
</tr>
<tr>
<td>152</td>
<td><img src="image" alt="Structure" /></td>
<td>4-((4-[(2-chloro-6-fluorophenyl)methyl]piperazin-1-yl)carbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>153</td>
<td><img src="image" alt="Structure" /></td>
<td>N-methyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-[(3-methylphenyl)methyl]-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>154</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[[2-[(4-methylphenyl)oxy]methyl]morpholin-4-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>155</td>
<td><img src="image" alt="Structure" /></td>
<td>4-ethyl-9-{{7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl}-3,9-diazaspiro[5.5]undecan-2-one</td>
</tr>
<tr>
<td>156</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-(octahydroisoquinolin-2(1H)-ylcarbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>157</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-phenyl-3,6-dihydropyridin-1(2H)-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>158</td>
<td><img src="image" alt="Structure" /></td>
<td>4-((4-(furan-2-yl)carbonyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>159</td>
<td><img src="image" alt="Structure" /></td>
<td>4-[(4-(2-chlorophenyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>160</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-[3-(methyloxy)phenyl]piperazin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>161</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-pyrazin-2-yl)piperazin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>162</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-(5-methyl-1,2,4-oxadiazol-3-yl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>163</td>
<td><img src="image" alt="Structure" /></td>
<td>4-[(4-[5-cyclopropyl-1,2,4-oxadiazol-3-yl)piperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>164</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-N-(4-pentylphenyl)-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>165</td>
<td><img src="image" alt="Structure" /></td>
<td>4-[(4-(2-fluorophenyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>166</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-pyrimidin-2-yl)piperazin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>167</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(azocan-1-ylcarbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>168</td>
<td><img src="image" alt="Structure" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-(4-nitrophenyl)piperazin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
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</tr>
<tr>
<td>169</td>
<td><img src="image1" alt="Structure Image" /></td>
<td>1-[4-(4-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl)piperazin-1-yl]phenyl]ethanone</td>
</tr>
<tr>
<td>170</td>
<td><img src="image2" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-phenylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>171</td>
<td><img src="image3" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-(phenylmethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>172</td>
<td><img src="image4" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-pyridin-2-yl)piperazin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>173</td>
<td><img src="image5" alt="Structure Image" /></td>
<td>N-butyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-(phenylmethyl)-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>174</td>
<td><img src="image6" alt="Structure Image" /></td>
<td>7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-phenylpiperazin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>175</td>
<td><img src="image7" alt="Structure Image" /></td>
<td>4-[(4-(4-fluorophenyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>176</td>
<td><img src="image8" alt="Structure Image" /></td>
<td>4-[(4-(3-chlorophenyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine</td>
</tr>
<tr>
<td>177</td>
<td><img src="image9" alt="Structure Image" /></td>
<td>N-ethyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-(phenylmethyl)-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxamide</td>
</tr>
<tr>
<td>178</td>
<td><img src="image10" alt="Structure Image" /></td>
<td>8-[(7-(1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(endo)-ol</td>
</tr>
<tr>
<td>Entry No.</td>
<td>Structure</td>
<td>Name</td>
</tr>
<tr>
<td>----------</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>179</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>8-({7-[2-(ethylamino)-1H-imidazo[4,5-b]pyridin-6-yl]-2,3-dihydro-1.4-benzoazepin-4(5H)-yl</td>
</tr>
<tr>
<td>180</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>8-{[7-{6-amino-5-[3-aminoazetidin-1-yl]sulfonyl</td>
</tr>
<tr>
<td>181</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>IV-[2-chloro-5-(4-[[3-hydroxy-3-(trifluoromethyl)]-8-azabicyclo[3.2.1]oct-8-yl</td>
</tr>
</tbody>
</table>

**General Administration**

[00354] In one aspect, the invention provides pharmaceutical compositions comprising an inhibitor of PI3K and/or mTOR according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other specific embodiments, administration is by the oral route. Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities.

Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, specifically in unit dosage forms suitable for simple administration of precise dosages.

[00355] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include carriers and adjuvants, etc.

[00356] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic
agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, etc.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a cross linked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at
least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, t alc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[00362] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[00363] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[00364] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.
Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

The compounds of the invention, or their pharmaceutically acceptable salts or solvates, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70
kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

**UTILITY**

Compounds of the Invention have activity for PI3K-alpha, mTOR, or for both. Compounds of this invention have been tested using the assays described in Biological Examples 1 and 3 and have been determined to be inhibitors of PI3K-alpha, mTOR, or for both. Suitable *in vitro* assays for measuring PI3K, mTORC1, and mTORC2 activity and the inhibition thereof by compounds are known in the art. For further details of an *in vitro* assay for measuring PI3K and mTOR activity see Biological Examples, Example 1, 2, and 3 *infra.* Cell-based assays for measurement of *in vitro* efficacy in treatment of cancer are known in the art. In addition, assays are described in Biological Examples, Example 5 and 6, *infra.* Suitable *in vivo* models for cancer are known to those of ordinary skill in the art. For further details of *in vivo* models for prostate adenocarcinoma, glioblastoma, lung carcinoma, and melanoma, see Biological Examples 7, 8, 9, 10, 11, 12, and 13, *infra.* Following the examples disclosed herein, as well as that disclosed in the art, a person of ordinary skill in the art can determine the activity of a compound of this invention.

Compounds of Formula I are useful for treating diseases, particularly cancer in which activity against PI3K-alpha, mTOR, or both contributes to the pathology and/or symptomatology of the disease. For example, cancer in which activity against PI3K-alpha, mTOR, or both contributes to its pathology and/or symptomatology include breast cancer, mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B cell lymphoma, rhabdomyosarcoma, ovarian cancer, endometrial cancer, cervical cancer, non small cell lung carcinoma, small cell lung carcinoma, adenocarcinoma, colon
cancer, rectal cancer, gastric carcinoma, hepatocellular carcinoma, melanoma, mantle cell lymphoma, pancreatic cancer, prostate carcinoma, thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, glioblastoma, or head and neck cancer.

[00374] Compounds of the invention are also useful as inhibitors of PI3Ka and/or mTOR \textit{in vivo} for studying the \textit{in vivo} role of PI3Ka and/or mTOR in biological processes, including the diseases described herein. Accordingly, the invention also comprises a method of inhibiting PI3Ka and/or mTOR \textit{in vivo} comprising administering a compound or composition of the invention to a mammal.

**General Synthesis**

[00375] Compounds of this invention can be made by the synthetic procedures described below. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.), or Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as 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), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates of the reaction 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.

[00376] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure and over a temperature range from about -78 °C to about 150 °C, more specifically from about 0 °C to about 125 °C and more specifically at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of hydrogenation), all reactions are performed under an atmosphere of nitrogen.

[00377] Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These
modified functional groups regenerate original functional groups by routine manipulation or
in vivo. Amides and esters of the compounds of the present invention may be prepared
according to conventional methods. A thorough discussion of prodrugs is provided in T.
Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S.
Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche,
American Pharmaceutical Association and Pergamon Press, 1987, both of which are
incorporated herein by reference for all purposes.

[00378] The compounds of the invention, or their pharmaceutically acceptable salts, may
have asymmetric carbon atoms or quaternized nitrogen atoms in their structure. Compounds
of the Invention that may be prepared through the syntheses described herein may exist as
single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The
compounds may also exist as geometric isomers. All such single stereoisomers, racemates
and mixtures thereof, and geometric isomers are intended to be within the scope of this
invention.

[00379] Some of the compounds of the invention contain an active ketone -C(0)CF₃ and
may exist in part or in whole as the -C(OH₂)CF₃ form. Regardless of whether the compound
is drawn as the -C(0)CF₃ or -C(OH₂)CF₃ form, both are included within the scope of the
Invention. Although an individual compound may be drawn as the -C(0)CF₃ form, one of
ordinary skill in the art would understand that the compound may exist in part or in whole as
the -C(OH₂)CF₃ form and that the ratio of the two forms may vary depending on the
compound and the conditions in which it exists.

[00380] Some of the compounds of the invention may exist as tautomers. For example,
where a ketone or aldehyde is present, the molecule may exist in the enol form; where an
amide is present, the molecule may exist as the imidic acid; and where an enamine is present,
the molecule may exist as an imine. All such tautomers are within the scope of the invention.
Further, for example, in this application R¹ can be 5-oxo-1H-1,2,4-triazol-3-yl, depicted
structurally below:

Both 5-oxo-1H-1,2,4-triazol-3-yl and the above structure 1 include, and are equivalent to,
3-hydroxy-4H-1,2,4-triazol-5-yl and its structure 2:
Regardless of which structure or which terminology is used, each tautomer is included within the scope of the Invention.

[00381] The present invention also includes N-oxide derivatives and protected derivatives of compounds of the Invention. For example, when compounds of the Invention contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. When compounds of the Invention contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable "protecting group" or "protective group". A comprehensive list of suitable protective groups can be found in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of the Invention can be prepared by methods well known in the art.

[00382] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents or by converting one enantiomer to the other by asymmetric transformation. For a mixture of enantiomers,
enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[00383] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[00384] The chemistry for the preparation of the compounds of this invention is known to those skilled in the art. In fact, there may be more than one process to prepare the compounds of the invention. The following examples illustrate but do not limit the invention. All references cited herein are incorporated by reference in their entirety.

[00385] An intermediate of formula 4 where PG is a nitrogen-protecting group, R^5_a and R^5_c are independently hydrogen or alkyl, R^5_h is hydrogen or halo, R^5_b is hydrogen, amino, or halo, and R^5_d, R^5_e, R^5_f, and R^5_g are hydrogen can be prepared according to Scheme I.

Scheme 1

[00386] In particular, an intermediate of formula 4a can be prepared according to Scheme Ia.

Scheme 1a

[00387] An intermediate of formula 1a is commercially available or can be prepared using methods known to one of ordinary skill in the art. In particular an intermediate of formula 1a where R^5_h is hydrogen and R^5_b is hydrogen, bromo, or chloro is commercially available. An intermediate of formula 1a where R^5_h is hydrogen and R^5_b is bromo, chloro, iodo, or fluoro is commercially available. An intermediate of formula 1a where R^5_h is fluoro and R^5_b is hydrogen can be prepared using procedures described in J. of Med. Chem., 2004, 47(12), 3163-3179. An intermediate of formula 1a where R^5_h is hydrogen and R^5_b is amino can be
prepared from the corresponding, commercially-available nitro intermediate using procedures known to one of ordinary skill in the art.

[00388] An intermediate of formula 2a where \( R^{5a} \) is hydrogen or methyl is commercially available. The intermediate of formula 1a is treated with an intermediate of formula 2a in the presence of a reducing agent such as sodium borohydrate, in a solvent(s) such as tetrahydrofuran and/or methanol and allowed to react at a temperature of about 40 °C for approximately 4 hours. The solvent is then removed and the reaction is taken up in a solvent(s) such as ethyl acetate and/or saturated sodium bicarbonate. To this suspension a nitrogen-protecting group precursor, such as di-tert-butyl dicarbonate, is added and the mixture is allowed to stir at room temperature overnight to yield an intermediate of formula 3a where PG is a nitrogen-protecting group.

[00389] Intermediate 3a is then treated with a catalyst, such as triphenylphosphine, in the presence of a dehydrating agent such as diisopropyl azodicarboxylate, in a solvent such as DCM. The reaction is allowed to proceed at room temperature for approximately 12 hours and the resulting product is optionally purified by column chromatography to yield an intermediate of formula 4a. Alternatively, the intermediate of formula 4a can be prepared by treating the intermediate of formula 3a with Burgess' reagent.

[00390] An intermediate of formula 5 where PG is a nitrogen-protecting group, \( R^{5a} \) and \( R^{5c} \) are independently hydrogen or alkyl, \( R^{5h} \) is hydrogen or halo, \( R^{5b} \) is hydrogen, amino, or halo, \( R^{5e}, R^{5f}, \) and \( R^{5g} \) are hydrogen, and \( R^1 \) is as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to Scheme 2.

**Scheme 2**

![Scheme 2](image)

where the intermediate of formula 4 is prepared as described in Scheme 1.

[00391] In particular, an intermediate of formula 5a where \( R^{5a} \) is hydrogen or alkyl, \( R^{5h} \) is hydrogen or halo, \( R^{5b} \) is hydrogen, amino, or halo, and \( R^1 \) is as defined in the Summary of the Invention for a Compound of Formula I, can be prepared according to Scheme 2a.

**Scheme 2a**
The intermediate of formula 4a, prepared as described in Scheme 1a, is treated with a boronic acid of formula \(-\text{B}({\text{OR}}')_2\) (where both \(\text{R}'\) are hydrogen or the two \(\text{R}'\) together form a boronic ester), which is commercially available or can be prepared using procedures known to one of ordinary skill in the art. The reaction is carried out in the presence of a catalyst such as \(\text{Pd(dppf)Cl}_2\), a base such as potassium carbonate, and in a solvent such as DME at about 80 °C for about 2 hours. The product can then be purified by chromatography to yield an intermediate of formula 5a.

Alternatively, an intermediate of formula 5, as defined above, can be prepared as described in Scheme 4.

**Scheme 4**

An intermediate of formula 13, where PG is a nitrogen-protecting group and \(\text{R}^1\) is as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to Scheme 4a.

**Scheme 4a**

An intermediate of formula 13, where PG is a nitrogen-protecting group, is prepared as described in Scheme 1a. 13 is treated with triisopropylborate in a solvent such as THF at a temperature of about -60 °C, followed by dropwise addition of a base such as n-butyllithium in tetrahydrofuran. The reaction was allowed to proceed for about 30 minutes, was treated with an acid such as hydrochloric acid, and allowed to warm to room temperature to yield an intermediate of formula 14a. Intermediate 14a is then treated with an intermediate of formula \(\text{R'}\text{X}\) (where \(\text{X}\) is a halide, and which is commercially available or can be prepared using procedures known to one of ordinary skill in the art), in the presence of a base such as
potassium carbonate, in the presence of a catalyst such as tetrakis(triphenylphosphine)palladium(0), and in a solvent(s) such as 1,2-dimethoxyethane and/or water. The reaction is allowed to proceed under nitrogen and stirred at reflux for about 3 hours to yield an intermediate of formula 5b.

A Compound of the Invention of Formula I where R<sup>5a</sup> and R<sup>5c</sup> are independently hydrogen or alkyl, R<sup>5h</sup> is hydrogen or halo, R<sup>5b</sup> is hydrogen, amino, or halo, R<sup>5e</sup>, R<sup>5f</sup>, and R<sup>5g</sup> are hydrogen, and R<sup>1</sup> and R<sup>2</sup> are as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to Scheme 5.

**Scheme 5**

![](image)

where X is halo.

In particular, a Compound of Formula I(j) where R<sup>5a</sup> is hydrogen or alkyl, R<sup>5h</sup> is hydrogen or halo, R<sup>5b</sup> is hydrogen, amino, or halo, and R<sup>1</sup> and R<sup>2</sup> are as defined in the Summary of the Invention for a Compound of Formula I can be prepared as described in Scheme 5a.

**Scheme 5a**

![](image)

The protecting group on the intermediate of formula 5a is removed. When the protecting group is Boc, it can be removed with HCl to yield an intermediate of formula 6a. The intermediate of formula 7(a) where X is halo is prepared using procedures known to one of ordinary skill in the art. The intermediate of formula R<sup>2</sup>H is commercially available or can be prepared using procedures described herein or procedures known to one of ordinary skill in the art. The intermediate of formula 6a is then treated with R<sup>2</sup>H, in the presence of a base such as Hiinig’s base, in a solvent such as DMF, at a temperature of about 50 °C. The product can be purified by column chromatography to yield an intermediate of Formula I(j).

In particular, a Compound of Formula I(k) where R<sup>1</sup> and R<sup>2</sup> are as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to Scheme 5b.
protecting group on intermediate of formula 5b, prepared as described in Scheme 4a, is removed. When the protecting group is Boc, it can be removed with HCl to yield an intermediate of formula 6b. Intermediate 7b is then prepared using procedures known to one of ordinary skill in the art. Intermediate 7b is then treated with an intermediate of R2H using conditions known to one or ordinary skill in the art to yield a Compound of Formula I(k).

A compound of the invention where R5a, R5b, R5c, R5d, R5e, R5f, R5g, and R5h are hydrogen; R1 is benzimidazol-6-yl substituted at the 2-position with one R7; R7 is alkyl; and R2 is as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to Scheme 6.

**Scheme 6**

A Compound of Formula I(y) where and R2 is as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to Scheme 7a.

**Scheme 7a**

The Compound of Formula I(x), prepared using procedures according to Scheme 5b, is treated with a base such as LiOH, in a solvent(s) such as THF and/or water to yield the hydrolyzed Compound of Formula I(y).

A Compound of Formula I where R1, R2, R5a, R5b, R5c, R5d, R5e, R5f, R5g, and R5h are as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to the following scheme (where X is halo) using procedures known to one of ordinary skill in the art.
A Compound of Formula I where \( R^1, R^2, R^5d, R^5e, R^5f, R^5g \), and \( R^5h \) are as defined in the Summary of the Invention for a Compound of Formula I can be prepared according to the following scheme where \( R \) is \(-B(OR')_2\) (where both \( R' \) are hydrogen or the two \( R' \) together form a boronic ester) and \( Y \) is halo, or \( R \) is halo and \( Y \) is \(-B(OR')_2\) (where both \( R' \) are hydrogen or the two \( R' \) together form a boronic ester) using Suzuki coupling procedures known to one of ordinary skill in the art.

**Synthetic Examples**

**Reagent Preparation 1**

[00401] STEP 1: To a solution of tert-butyl 2-oxopiperidine-1-carboxylate (0.30 g, 1.51 mmol) in tetrahydrofuran (8 mL) cooled to -78 °C was added slowly over 15 minutes 0.3 M 3,4,5-trifluorophenylmagnesium bromide in tetrahydrofuran (3.30 mL, 1.66 mmol) and the mixture was then allowed to warm to 25 °C over 30 minutes. The reaction mixture was poured slowly into an ice cold solution of 0.5 N hydrochloric acid (100 mL), and extracted twice with ethyl acetate (2x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by silica gel column chromatography (diethyl ether/hexanes 1:4) to give tert-butyl 5-oxo-5-(3,4,5-trifluorophenyl)pentylcarbamate (0.18 g, 36% yield). MS (EI) for \( C_{16}H_{20}F_3NO_3 \): 332 (MH⁺).

[00402] STEP 2: Tert-butyl 5-oxo-5-(3,4,5-trifluorophenyl)pentylcarbamate (0.18 g, 0.54 mmol) was stirred in trifluoroacetic acid/dichloromethane 1:1 (8 mL) for 1 hour then concentrated. The residue was dissolved in ethyl acetate (40 mL) and washed with saturated sodium chloride/2M aqueous sodium hydroxide 10:1 (11 mL), then dried over anhydrous
sodium sulfate, filtered and concentrated to provide 5-amino-l-(3,4,5-trifluorophenyl)pentan-1-one (0.11 g, 88% yield) as an oil. MS (EI) for C_{11}H_{12}F_{3}NO: 232 (MH^+).

STEP 3: To 5-amino-l-(3,4,5-trifluorophenyl)pentan-1-one (0.11 g, 0.48 mmol) in tetrahydrofuran/methanol 4:1 (10 mL) was added in portions over 20 minutes solid sodium borohydride (0.20 g, 5.0 mmol) and stirring was continued 18 hours at 25 °C. The reaction mixture was concentrated then taken into ethyl acetate (40 mL), washed with saturated sodium chloride/2 N aqueous sodium hydroxide 10:1 (11 mL) then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:1) to give 2-(3,4,5-trifluorophenyl)piperidine (0.70 g, 68% yield) as an oil. ^1H NMR (400 MHz, CDC1_3): 7.01 (m, 2H), 3.52 (m, IH), 3.17 (m, IH) 2.77 (m, IH), 2.07 (br s, IH), 1.88 (m, IH), 1.74 (m, IH), 1.64 (m, IH), 1.55-1.35 (m, 3H).

Using analogous synthetic techniques and substituting with alternative starting materials in step 1 the following reagents were prepared. Alternative starting materials were purchased from commercial sources unless otherwise indicated.

2-(3-chloro-4-fluorophenyl)piperidine. Prepared according to the method of reagent preparation 1 using 3-chloro-4-fluorophenylmagnesium bromide in step 1. MS (EI) for C_{11}H_{13}ClF_N: 214 (MH^+).

2-(3,5-difluorophenyl)piperidine. Prepared according to the method of reagent preparation 1 using 3,4-difluorophenylmagnesium bromide in step 1. MS (EI) for C_{11}H_{13}F_{2}N: 198 (MH^+).

2-(4-fluoro-3-methylphenyl)piperidine. Prepared according to the method of reagent preparation 1 using 4-fluoro-3-methylphenylmagnesium bromide in step 1. ^1H NMR (400 MHz, CDC1_3): 7.19 (dd, IH), 7.11 (m, IH), 6.92 (t, IH), 3.54 (m, IH), 3.17 (m, IH), 2.76 (m, IH), 2.25 (d, 3H), 1.89 (m, 2H), 1.75 (m, IH), 1.66 (m, IH), 1.48 (m, 2H).

2-(4-chlorophenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 4-chlorophenylmagnesium bromide in step 1. MS (EI) for C_{11}H_{14}ClN: 196 (MH^+).

2-(3,4-difluorophenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 3,4-difluorophenylmagnesium bromide in step 1. ^1H NMR (400 MHz, CDC1_3): 7.64 (m, IH), 7.49 (m, IH), 7.15 (m, IH), 3.83 (m, 2H), 2.57 (m, 2H), 1.84 (m, 2H), 1.67 (m, 2H).

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[00410] 2-(4-chloro-3-fluorophenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 4-chloro-3-fluorophenylmagnesium bromide in step 1. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.59 (dd, 1H), 7.49 (dd, 1H), 7.38 (tr, 1H), 3.84 (m, 2H), 2.56 (m, 2H), 1.84 (m, 2H), 1.67 (m, 2H).

[00411] 2-(3,5-bis(trifluoromethyl)phenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 3,5-bis(trifluoromethyl)phenylmagnesium bromide in step 1. MS (EI) for C\(_{13}\)H\(_{13}\)F\(_6\)N: 298 (MH\(^+\)).

[00412] 2-(3-chloro-5-fluorophenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 3-chloro-5-fluorophenylmagnesium bromide in step 1. MS (EI) for C\(_{11}\)H\(_{13}\)ClF: 214 (MH\(^+\)).

[00413] 2-(4-(trifluoromethoxy)phenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 4-trifluoromethoxyphenylmagnesium bromide in step 1. MS (EI) for C\(_{14}\)H\(_{14}\)F\(_3\)NO: 246 (MH\(^+\)).

[00414] 2-(3-fluoro-4-methoxyphenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 3-fluoro-4-methoxyphenylmagnesium bromide in step 1. MS (EI) for C\(_{13}\)H\(_{16}\)FNO: 210 (MET).

[00415] 2-(2-fluorophenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 2-fluorophenylmagnesium bromide in step 1. MS (EI) for C\(_{12}\)H\(_{14}\)FN: 180 (MH\(^+\)).

[00416] 2-(4-(trifluoromethyl)phenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 4-trifluoromethylphenylmagnesium chloride in step 1. MS (EI) for C\(_{12}\)H\(_{14}\)F\(_3\)N: 230 (MH\(^+\)).

[00417] 2-(3-fluoro-4-methylphenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 3-fluoro-4-methylphenylmagnesium bromide in step 1. MS (EI) for C\(_{12}\)H\(_{16}\)FN: 194 (MH\(^+\)).

[00418] 2-(3,4-dichlorophenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 3,4-dichlorophenylmagnesium bromide in step 1. MS (EI) for C\(_{11}\)H\(_{13}\)Cl\(_2\)N: 230 (MH\(^+\)).

[00419] 2-(4-fluoro-2-methylphenyl)piperidine. Synthesized according to the method of reagent preparation 1 using 4-fluoro-2-methylphenylmagnesium bromide in step 1. MS (EI) for C\(_{12}\)H\(_{16}\)FN: 194 (MH\(^+\)).
Reagent Preparation 2

(±)-(2R,4S)-2-phenylpiperidin-4-ylmethanol

[00420] STEP 1: A suspension of potassium tert-butoxide (1.25 g, 11.1 mmol) and methyltriphenylphosphonium bromide (3.86 g, 1.1 mmol) in tetrahydrofuran (100 mL) was stirred at 40 °C for 30 minutes. The mixture was then cooled to room temperature and a solution of tert-butyl 4-oxo-2-phenylpiperidine-1-carboxylate (2.35 g, 8.5 mmol) in tetrahydrofuran (30 mL) was added slowly. The reaction mixture was stirred at 40 °C for 24 hours. The mixture was cooled to room temperature and quenched by the addition of water and diluted with ethyl acetate (250 mL). The organic layer was separated then washed with water, 10% aqueous citric acid and brine, dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography on silica gel (hexane:ethyl acetate 95:5 to 9:1) provided tert-butyl 4-methylene-2-phenylpiperidine-1-carboxylate (2.24 g, 96%). H NMR (400 MHz, CDC13): 7.31 (m, 4H), 7.21 (m, 1H), 5.48 (br d, 1H), 4.84 (dd, 2H), 4.07 (br dd, 1H), 2.85 (br, t, 1H), 2.78 (dtr, 1H), 2.64 (dd, 1H), 2.28 (dtr, 1H), 2.20 (br d, 1H), 1.42 (s, 9H). GC/MS (EI) for C17H25N03: 273 (M+).

[00421] STEP 2: To solution of tert-butyl 4-methylene-2-phenylpiperidine-1-carboxylate (2.20 g, 8.04 mmol) in tetrahydrofuran (50 mL) at 0 °C was added borane-tetrahydrofuran complex (1M solution in tetrahydrofuran) (12.1 mL, 12.1 mmol) and the reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was allowed to warm to room temperature then stirred for an additional 2 hours. It was cooled to 0 °C and 2M aqueous sodium hydroxide (8.0 mL, 16.0 mmol) was added slowly followed by the slow addition of 30% aqueous hydrogen peroxide (5.5 mL, 48.4 mmol). The mixture was stirred for another hour then diluted with water (100 mL) and partitioned with ethyl acetate (250 mL). The organic layer was separated and washed with 2M aqueous sodium thiosulfate (100 mL), brine, dried over anhydrous sodium sulfate, filtered and concentrated. Column chromatography in silica gel (chloroform:methanol 9:1 to 4:1) provided tert-butyl 4-(hydroxymethyl)-2-phenylpiperidine-1-carboxylate (1.86 g, 79%). H NMR (400 MHz, CDCl3): 7.30 (m, 2H), 7.20 (m, 3H), 4.86 (dd, 1H), 4.04 (m, 1H), 3.62 (m, 0.5H), 3.44 (m, 3H), 3.24 (m, 1H), 2.12 (m, 0.5H), 1.93 (m, 1H), 1.64 (m, 2H), 1.42 (m, 1H), 1.26 (s, 9H). GC/MS (EI) for C17H25N03: 235 (M-tBu+).
STEP 3: To a solution of tert-butyl 4-(hydroxymethyl)-2-phenylpiperidine-1-carboxylate (0.29 g, 1.00 mmol) in dichloromethane (50 mL) was added trifluoroacetic acid (10 mL) and the reaction mixture was heated to reflux. After cooling to room temperature the solvent was evaporated. The residue was twice taken into 50% ethyl acetate in toluene then concentrated (2x100 mL) and the resulting solid then dried to give (±)-(2R,4S)-2-phenylpiperidin-4-ylmethanol as the trifluoroacetic acid salt (0.26 g, quantitative). MS (EI) for C_{12}H_{17}NO: 192 (MH⁺).

Reagent Preparation 3
2-(trifluoromethyl)piperidine

A mixture of 2-(trifluoromethyl)pyridine (0.38 g, 2.60 mmol) and platinum oxide (0.04 g, 0.18 mmol) in acetic acid (15 mL) and concentrated hydrochloric acid (2 mL) was hydrogenated in a Parr apparatus at 40 psi for 3 d. Filtration through celite and concentration of the filtrate provided 2-(trifluoromethyl)piperidine as hydrochloride salt which was used without further purification. ¹H NMR (400 MHz, methanol-d₄): 4.18 (m, 1H), 3.50 (m, 1H), 3.15 (m, 1H), 2.16 (m, 1H), 1.99 (m, 2H), 1.71 (m, 3H).

Using analogous synthetic techniques and substituting with alternative starting reagents the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

4-cyclopropylpiperidine. Prepared as hydrochloride salt according to reagent preparation 3 by using 4-cyclopropylpyridine. MS (EI) for C₃H₇N: 125 (M⁺).

Reagent Preparation 4
tert-butyl 8-azabicyclo[3.2.1]octan-3-(endo)-ylcarbamate

STEP 1: To a 5 L round-bottom flask was added 8-methyl-8-azabicyclo[3.2.1]octan-3-endo-amine (432 g, 3.1 mol), 2 L of dry 1,4-dioxane, 675 mL of deionized water and 468 g of dry triethylamine. Di-tert-butyl dicarbonate (solution in 1.2 L of dioxane) was added dropwise to the stirring solution at room temperature over 16 h. The reaction mixture was concentrated and the resulting residue suspended in 2.5 L of methylene chloride, then washed twice with 1 L of water, dried with anhydrous magnesium sulfate, filtered, and volatile organics removed by rotary evaporation to yield 617 g (83%) of tert-butyl 8-methyl-8-azabicyclo[3.2.1]octan-3-ylcarbamate (mp 79-81 °C).

STEP 2: To a 5 L round-bottom flask was added 480 g (2.0 mol) of tert-butyl 8-methyl-8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate, 2 L of toluene, and 69 g (0.5 mol) of potassium carbonate. 2,2,2-Trichloroethyl chloroformate (347 mL, 2.4 mol) was added
dropwise at room temperature over 6 h and the reaction heated at reflux temperature for 8 h.
After the solution was cooled to room temperature, 1.2 L of water was added to the reaction
solution and stirred 0.5 h. The organic layer was separated and washed with 1 L of brine,
dried with anhydrous magnesium sulfate, filtered, and concentrated to yield a cloudy oil. The
oil was titrated with 700 mL of a 3:2 ethyl ether/hexanes solution to yield 280 g (mp 131-135
°C) of 2,2,2-trichloroethyl 3-endo-(tert-butoxycarbonylamino)-8-azabicyclo[3.2.1]octane-8-
carboxylate as a solid that was collected by filtration. The mother liquor was concentrated
and titrated further to yield a less pure sample of the Troc protected diamine (129 g, mp 116-
118 °C).

STEP 3: To a 5 L round-bottom flask was added 360 g (0.9 mol) of 2,2,2-
trichloroethyl 3-endo-(tert-butoxycarbonylamino)-8-azabicyclo[3.2.1]octane-8-
carboxylate, 2.8 L of methanol and 675 g (12.6 mol) of ammonium chloride. The solution was heated to
reflux and 387 g (7.5 mol) of zinc dust was carefully added in small portions over 0.5 h.
Upon complete addition of the zinc dust, the reaction was heated at reflux temperature for 2 h
then cooled to room temperature. The reaction filtered through a thin pad of Celite 545, and
the methanol removed by rotary evaporation. The resulting solid was dissolved in 800 mL of
methylene chloride and stirred with 600 mL of concentrated ammonium hydroxide for 0.5 h.
The organic layer was separated, washed with 600 mL of water, dried with anhydrous
magnesium sulfate, filtered, and concentrated to yield an oil. The residue was dissolved in
200 mL of methylene chloride and 1 L of ethyl ether then filtered. The resulting solution was
chilled to 0 °C and 215 mL of 4 N hydrogen chloride in dioxane was added slowly, dropwise
over 0.5 h, being sure to maintain the reaction solution temperature close to 0 °C. After the
addition was complete, 200 mL of methylene chloride and 1.4 L of ethyl ether were added to
the cooled solution and a pale white precipitate formed. The resulting solid was collected by
filtration to yield 173 g (85%) of tert-butyl 8-azabicyclo[3.2.1]octan-3-endo-ylcarbamate
hydrochloride salt.

4-methylpiperidin-4-ol

STEP 1: To a solution of methyl magnesium bromide (6.00 mmol) in ethyl ether
(27 mL) was added 1-benzyl-piperidin-4-one (0.53 g, 0.28 mmol) at 0 °C followed by
tetrahydrofuran (10 mL). The reaction mixture was warmed to room temperature and stirred
for 18 h. Saturated ammonium chloride was added and the aqueous layer was extracted with
ethyl acetate (3 x). The combined organic extracts were dried over sodium sulfate, filtered
and concentrated. Column chromatography on silica (2-10% methanol in dichloromethane) afforded 1-benzyl-4-methylpiperidin-4-ol (0.42 g, 72% yield).

**STEP 2:** A mixture of 1-benzyl-4-methylpiperidin-4-ol (0.20 g, 0.97 mmol) and 10% palladium on carbon in methanol was hydrogenated in a Parr apparatus at 35 psi for 18 h. Then a solution of 4M hydrochloric acid in dioxane (0.1 mL) was added and the mixture was filtered through celite. The filtrate was concentrated and dried to give 4-methylpiperidin-4-ol as hydrochloride salt (0.10 g, 89% yield). \(^1\)H NMR (400 MHz, methanol-\(d_4\)): 3.23 (m, 4H), 1.77 (m, 4H), 1.29 (s, 3H).

**Reagent Preparation 6**

4-(difluoromethyl)piperidine

**STEP 1:** To a solution of tert-butyl (4-hydroxymethyl)piperidine-l-carboxylate (0.52 g, 2.40 mmol, (J. Labelled Compounds and Radiopharmaceuticals 1999, 42, 1289-1300) in dichloromethane (20 mL) was added Dess-Martin-periodinane (1.13 g, 2.66 mmol), and the mixture was stirred at room temperature for 2 h. A 10% aqueous solution of sodium thiosulfate (20 mL) was added followed by saturated sodium bicarbonate (20 mL), and the biphasic mixture was stirred at room temperature for 45 min. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x). The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over sodium sulfate then filtered and concentrated to afford tert-butyl 4-formylpiperidine-l-carboxylate. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 9.67 (s, 1H), 3.99 (m, 2H), 2.93 (m, 2H), 2.42 (m, 1H), 1.89 (m, 2H), 1.55 (m, 2H), 1.46 (s, 9H).

**STEP 2:** To a solution of DAST (1.16 g, 7.20 mmol) in dichloromethane (30 mL) was added a solution of tert-butyl 4-formylpiperidine-l-carboxylate (0.51 g, 2.40 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. A 5% aqueous solution of sodium bicarbonate was added, the layers were separated, the organic layer was washed with saturated sodium bicarbonate, and brine, dried over sodium sulfate, filtered and concentrated to provide tert-butyl 4-(difluoromethyl)piperidine-l-carboxylate. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 5.59 (m, 1H), 4.20 (m, 2H), 2.69 (m, 2H), 1.91 (m, 1H), 1.74 (m, 2H), 1.46 (s, 9H), 1.34 (m, 2H).

**STEP 3:** A solution of tert-butyl 4-(difluoromethyl)piperidine-l-carboxylate in trifluoroacetic acid was stirred at room temperature for 1 h then concentrated and dried to give 4-(difluoromethyl)piperidine as the trifluoroacetate salt. \(^1\)H NMR (400 MHz, CDCl\(_3\)):

\[
\begin{align*}
5.67 & \text{ (m, 1H)} \\
3.55 & \text{ (m, 2H)} \\
2.96 & \text{ (m, 2H)} \\
2.04 & \text{ (m, 3H)} \\
1.80 & \text{ (m, 2H)}
\end{align*}
\]
Reagent Preparation 7
4-(fluoromethyl)piperidine

[00434] A solution of tert-butyl 4-(fluoromethyl)piperidine-l-carboxylate (J. Labelled Compounds and Radiopharmaceuticals 1999, 42, 1289-1300) in trifluoroacetic acid was stirred at room temperature for 1 h and then concentrated and dried to give 4-(fluoromethyl)piperidine as the trifluoroacetate salt. 1H NMR (400 MHz, CDC1₃): 4.33 (dd, 2H), 3.49 (m, 2H), 2.92 (m, 2H), 2.07 (m, 1H), 1.97 (m, 2H), 1.64 (m, 2H).

Reagent Preparation 8
4-fluoro-4-methylpiperidine

[00435] STEP 1: To a solution of 4-benzyl-4-methylpiperidine-4-ol (0.16 g, 0.76 mmol) (reagent preparation 5, step 1) in dichloromethane (10 mL) was added DAST (0.37 g, 2.30 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. A 5% aqueous solution of sodium bicarbonate was added, the layers were separated, the organic layer was washed with saturated sodium bicarbonate, and brine, dried over sodium sulfate, filtered and concentrated to provide a mixture of 4-benzyl-4-fluoro-4-methylpiperidine and 4-benzyl-4-methyl-1,2,3,6-tetrahydropyridine. The mixture was dissolved in acetone (15 mL) and water (3 mL) then osmium tetroxide (0.25 mL of a 4% aqueous solution, 0.04 mmol) and N-methylmorpholine N-oxide (0.11 g, 0.91 mmol) were added at 0 °C. The solution was kept in a freezer at -20 °C for 3 d then warmed to room temperature and 10% aqueous sodium thiosulfate was added. The biphasic mixture was stirred for 90 min at room temperature. Dichloromethane was added, the mixture was filtered through celite and the organic layer was washed with 1M hydrochloric acid, dried over sodium sulfate, filtered and concentrated to give a 4-benzyl-4-fluoro-4-methylpiperidine.

[00436] STEP 2: A suspension of 4-benzyl-4-fluoro-4-methylpiperidine as obtained in step 1 and 10% palladium on carbon in methanol was hydrogenated in a Parr apparatus at 40 psi for 18 h. The mixture was filtered through celite and the filtrate concentrated to give 4-fluoro-4-methylpiperidine which was used without further purification. MS (El) for C₆H₇F₂N: 118 (MH⁺).

Reagent Preparation 9
4-(l,l-difluoroethyl)piperidine

[00437] STEP 1: To a solution of DAST (1.83 g, 11.35 mmol) in dichloromethane (30 mL) was added 4-acetylpyridine (1.00 g, 8.25 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 d. More DAST (0.61 g, 3.78 mmol) was added
and stirring was continued for 1 d. A 5% aqueous solution of sodium bicarbonate was added, the layers were separated and the organic layer was washed with saturated sodium bicarbonate, and brine then dried over sodium sulfate, filtered and concentrated to provide a 5:1 mixture of 4-(1,1-difluoroethyl)pyridine and 4-acetylpyridine.

[00438] STEP 2: The mixture was dissolved in methanol (10 mL) and 1 M hydrochloric acid (10 mL) then catalytic platinum oxide was added and the resulting suspension was hydrogenated in a Parr apparatus at 40 psi for 3 d. Filtration through celite and concentration of the filtrate gave a complex mixture containing 20% of the desired 4-(1,1-difluoroethyl)piperidine as the hydrochloride salt which was used without further purification.

Reagent Preparation 10

(3aR,6aS)-5-methyloctahydrocyclopenta[c]pyrrole

[00439] STEP 1: (3aR,6aS)-tert-Butyl 5-methylenehexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (Tetrahedron 1993, 49(23), 5047-54) (107 mg, 0.48 mmol) was taken into methanol (1 mL) followed by addition of platinum oxide (10 mg) and the mixture was sparged with hydrogen gas at 1 atm for 10 minutes then allowed to stir under an atmosphere of hydrogen for 12 h. The mixture was filtered through a celite pad and the filtrate concentrated. The residue was taken into a minimum of ethyl acetate then filtered through a silica gel pad using 100% ethyl acetate. The filtrate was concentrated and dried to give (3aR,6aS)-½rf-butyl 5-methyl hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate as a colorless oil, 5-methyl endo/exo isomer mixture (98.6 mg, 92% yield). GC-MS (EI) for C_{13}H_{23}N_{0.2}; 225 (M+).

[00440] STEP 2: (3aR,6aS)-tert-butyl 5-methyl hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (98.6 mg, 0.44 mmol) was taken into a minimum of neat TFA and the solution was allowed to stand for 30 minutes at room temperature. The mixture was then concentrated and the residue taken into methanol and concentrated again then dried. The residue thus obtained was taken into methanol (5 mL) and basified using Bio-Rad AG-IX hydroxide form resin. The mixture was then filtered and concentrated and dried to give (3aR,6aS)-5-methyloctahydrocyclopenta[c]pyrrole (27.9 mg, 55%) as an amorphous residue.

Reagent Preparation 11

(±)-(3aR,6aS)-5-methyl-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrole
STEP 1: (3aR,6aS)-tert-Butyl 5-methylenehexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (Tetrahedron 1993, 49(23), 5047-54) (114 mg, 0.51 mmol) was taken into a minimum of neat TFA and the solution was allowed to stand for 30 minutes at room temperature. The mixture was then concentrated and the residue taken into methanol and concentrated again then dried. The residue thus obtained was taken into methanol (5 mL) and basified using Bio-Rad AG-IX hydroxide form resin. The mixture was then filtered and concentrated and dried to give impure (±)-(3aR,6aS')-5-methyl-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrole (93 mg) as an amorphous residue that was used without further purification.

Reagent Preparation 12
4-(methylthio)piperidine

STEP 1: To a solution of tert-butyl 4-hydroxypiperidine-l-carboxylate (4.0 g, 20.0 mmol) and triethylamine (4.0 g, 40 mmol) in dichloromethane (50 mL) was added methanesulfonyl chloride (2.8 g, 24.4 mmol) at 0 °C. The solution was stirred at 0 °C for 10 min, then at room temperature for 2 h. The reaction mixture was partitioned between 10% citric acid and ethyl acetate. The organic layer was washed with sodium bicarbonate, and brine, dried over sodium sulfate, filtered and concentrated to give tert-butyl 4-(methylsulfonyloxy)piperidine-l-carboxylate (6.4 g, quantitative yield). MS (EI) for C_{11}H_{11}NO_5S: 279 (M^+).

STEP 2: A solution of tert-butyl 4-(methylsulfonyloxy)piperidine-l-carboxylate (2.0 g, 7.2 mmol) and sodium thiomethoxide (1.0 g, 14.4 mmol) in methanol (30 mL) was refluxed for 15 h and then concentrated. The residue was partitioned between water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate and the combined organic extracts washed with brine, dried over sodium sulfate, filtered and concentrated. Column chromatography on silica (3% ethyl acetate in hexanes) afforded tert-butyl 4-(methylthio)piperidine-l-carboxylate (0.98 g, 58% yield) as a colorless oil. MS (EI) for C_{11}H_{21}NO_2S: 231 (M^+).

STEP 3: A solution of tert-butyl 4-(methylthio)piperidine-l-carboxylate (63 mg, 0.27 mmol) in methanol (1 mL) and 4 N hydrogen chloride in dioxane (4 mL) was refluxed for 2 min and then concentrated and dried to provide 4-(methylthio)piperidine hydrochloride as a colorless oil.
Reagent Preparation 13

thiomorpholine-1-oxide


Reagent Preparation 14

4-(methylsulfonyl)piperidine

[00446] STEP 1: To a solution of tert-butyl 4-(methylthio)piperidine-1-carboxylate (280 mg, 1.2 mmol) (reagent preparation 12, step 2) in dichloromethane (8 mL) was added m-chloroperbenzoic acid (835 mg, 4,8 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 15 h. The reaction mixture was partitioned between 1N sodium hydroxide and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to give tert-butyl 4-(methylsulfonyl)piperidine-1-carboxylate (290 mg, 92% yield). MS (EI) for C11H13NOS: 206 (M-tBu+).

[00447] STEP 2: A solution tert-butyl 4-(methylsulfonyl)piperidine-1-carboxylate (100 mg, 0.38 mmol) in methanol (1 mL) and 4 N hydrogen chloride in dioxane (4 mL) was refluxed for 2 min and then concentrated to provide 4-(methylthio)piperidine hydrochloride salt as a colorless solid. MS (EI) for C6H13NOS: 163 (M+).

Reagent Preparation 15

3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(endo)-ol

[00448] Step 1: Trimethyl(trifluoromethyl)silane (0.32 g, 2.25 mmol) was added to a mixture of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 2.2 mmol), cesium carbonate (1.1 g, 3.4 mmol) in N,N-dimethylformamide (5 mL) at 0°C. The resulting mixture was warmed to room temperature and stirred for two hours. The mixture was diluted with ethyl acetate (80 mL), washed with water (3 x 50 mL) then brine (50 mL), dried over sodium sulfate, filtered, and concentrated. The residue was taken into methanol (20 mL) and potassium carbonate (0.62 g, 4.5 mmol) was added then stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate (150 mL) then filtered and concentrated. The residue was purified by silica gel chromatography (10% to 25% ethyl acetate in hexanes gradient) to give tert-butyl 3-(endo)-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.36 g, 55% yield), GC-MS (EI) for C13H29F3NO5: 295 (M+).

[00449] Step 2: tert-Butyl 3-(en/0)-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate 1(0.36 g, 1.2 mmol) was taken into acetonitrile (2 mL)
and 4 M hydrogen chloride in 1,4-dioxane (2 mL) then stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(endo)-ol hydrochloride (0.28 g, 100% yield). MS (EI) for C₁₈H₂₃F₃NO: 196 (MH⁺).

**Reagent Preparation 16**

3-methyl-8-azabicyclo[3.2.1]octan-3-(endo)-ol

[00450] Step 1: Methylmagnesium bromide (3 M solution in ether, 2.7 mmol) was added to a solution of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 2.2 mmol), in tetrahydrofuran (20 mL) at 0 °C and the resulting mixture was stirred one hour. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (20 mL) then partitioned with ethyl acetate (80 mL). The organic portion was separated, washed with water, then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (5% to 35% ethyl acetate in hexanes gradient) to give tert-butyl 3-(endo)-hydroxy-3-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (0.22 g, 41% yield), GC-MS (EI) for C₁₃H₂₃NO₃: 241 (M⁺).

[00451] Step 2: tert-Butyl 3-(endo)-hydroxy-3-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (0.22 g, 1.2 mmol) was taken into acetonitrile (1 mL), and 4 M hydrogen chloride in 1,4-dioxane (1 mL) then stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 3-methyl-8-azabicyclo[3.2.1]octan-3-(endo)-ol hydrochloride salt (0.16 g, 100% yield). MS (EI) for C₈H₁₂F₃NO: 142 (MH⁺).

**Reagent Preparation 17**

3-fluoro-3-(endo)-methyl-8-azabicyclo[3.2.1]octane

[00452] Step 1: Dimethylaminosulfur trifluoride (81 mg, 0.61 mmol) was added to a solution of tert-butyl 3-(en<io>)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.21 mmol) (reagent preparation 18, step 2) in dichloromethane (2 mL) at 0 °C, and the resulting mixture was stirred one hour. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (10 mL) then partitioned with dichloromethane (20 mL). The organic portion was separated, washed with water, then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (5% to 35% ethyl acetate in hexanes gradient) to give tert-butyl 3-fluoro-3-(enifo)-methyl-8-
azabicyclo[3.2.1]octane-8-carboxylate (28 mg, 56% yield), GC-MS (EI) for C$_3$H$_{22}$FN0$_2$: 243 (M$^+$).

[00453] Step 2: A mixture of tert-butyl 3-fluoro-3-(en<io)-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (0.22 g, 1.2 mmol), acetonitrile (1 mL) and 4 M hydrogen chloride in 1,4-dioxane (1 mL) was stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 3-fluoro-3-(en<io)-methyl-8-azabicyclo[3.2.1]octane hydrochloride salt (20 mg, 100% yield). MS (EI) for C$_3$H$_{23}$FN: 144 (MH$^+$).

Reagent Preparation 18

8-azabicyclo[3.2.1]octan-3-(en<io)-ylmethanol

[00454] Step 1: Potassium tert-butoxide (0.62 g, 5.5 mmol) was added to a suspension of methyltriphenylphosphonium bromide (1.98 g, 5.5 mmol) in tetrahydrofuran (20 mL) and the resulting mixture was stirred at room temperature for one hour. A solution of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 2.2 mmol) in tetrahydrofuran (5 mL) was then added and the resulting mixture was stirred at 35°C for two hours. The mixture was cooled, diluted with hexane (100 mL), filtered, and the filtrate was washed with water then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to give tert-butyl 3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (0.45 g, 91% yield). GC-MS (EI) for C$_{13}$H$_{23}$N0$_2$: 223 (M$^+$).

[00455] Step 2: Borane (1 M solution in tetrahydrofuran, 1.79 mL) was added to a solution of tert-butyl 3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (0.20 g, 0.87 mmol) in tetrahydrofuran (20 mL) at 0°C. The reaction mixture was slowly warmed to room temperature and stirred for 18 hours. It was then cooled to 0 °C, followed by sequential addition of 2 M sodium hydroxide solution (1 mL) and hydrogen peroxide solution (30% in water, 0.46 mL). The mixture was warmed to room temperature and stirred for 1.5 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL), diluted with water (20 mL) and partitioned with ethyl acetate (20 mL). The organic portion was separated and washed twice with saturated sodium bisulfite solution (20 mL), water then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (20% to 90% ethyl acetate hexanes gradient) to give tert-butyl 3-(endo)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (0.19 g, 88% yield), GC-MS (EI) for C$_{13}$H$_{23}$N0$_3$: 241 (M$^+$).
Step 3: A mixture of tert-butyl 3-(endo)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.21 mmol), acetonitrile (1 mL), and 4 M hydrogen chloride in 1,4-dioxane (1 mL) was stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 8-azabicyclo[3.2.1]octan-3-(endo)-ylmethanol hydrochloride salt (36 mg, 100% yield). MS (EI) for C₈H₁₅FN: 144 (MH⁺).

Reagent Preparation 19

3-(endo)-(fluoromethyl)-8-azabicyclo[3.2.1]octane

Step 1: Methanesulfonyl chloride (154 mg, 1.35 mmol) was added to a mixture of tert-butyl 3-(endo)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (325 mg, 1.4 mmol) (reagent preparation 18, step 2), triethylamine (136 mg, 1.4 mmol), and 1,4-diazabicyclo[2.2.2]octane (31 mg, 0.28 mmol) in toluene (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 minutes, and at room temperature for another 15 minutes. The reaction mixture was quenched with a cold mixture of water and ethyl acetate. The organic portion was separated, washed with water, then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (5% to 25% ethyl acetate in hexanes gradient) to give tert-butyl 3-(endo-methylsulfonyloxy)methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (330 mg, 77% yield), GC-MS (EI) for C₁₄H₂₅N₀₅S: 319 (M⁺).

Step 2: A mixture of tert-butyl 3-(endo-methylsulfonyloxy)methyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (330 mg, 1.0 mmol), triethylamine (136 mg, 1.4 mmol), and tetrabutylammonium fluoride hexahydrate (489 mg, 1.3 mmol) in tetrahydrofuran (10 mL) was stirred at 60 °C for 18 hours. The reaction mixture was cooled, concentrated and the residue purified by silica gel chromatography (5% to 15% ethyl acetate in hexanes gradient) to give tert-butyl 3-(endo)-(fluoromethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (120 mg, 36% yield), GC-MS (EI) for C₁₃H₂₂FN0₂: 243 (M⁺).

Step 3: A mixture of tert-butyl 3-(endo)-(fluoromethyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 0.21 mmol), acetonitrile (1 mL), and 4 M hydrogen chloride in 1,4-dioxane (1 mL) was stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 3-(endo)-(fluoromethyl)-8-azabicyclo[3.2.1]octane hydrochloride salt (37 mg, 100% yield). MS (EI) for C₈H₁₅FN: 144 (MH⁺).
Reagent Preparation 20

[00460] STEP 1: Benzyl 2-(4-fluorophenyl)-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate was prepared according to the method in (Tetrahedron Lett., 1986, 27, 4549-4552) using 4-methoxypyridine (29.8 mL, 290 mmol), benzyl chloroformate (50.0 mL, 350 mmol) and 4-fluorophenyl magnesium bromide (0.8 M solution in THF), (450 mL, 0.36 mmol), to yield (81 g, 86% yield) of the title compound. MS (EI) for C_{19}H_{18}FNO: 194 (MH+).

[00461] STEP 2: Benzyl 2-(4-fluorophenyl)-4-oxopiperidine-1-carboxylate was prepared according to the method described in (J. Am. Chem. Soc., 2001, 66, 2181-2182) using benzyl 2-(4-fluorophenyl)-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate (16.5 g, 50.7 mmol) and zinc dust (9.8 g, 150 mmol) to afford (16.0 g, 96% yield) of the title compound. H NMR (400 MHz, CDCl₃): 7.39-7.32 (m, 5H), 7.21 (m, 2H), 7.00 (t, 2H), 5.82 (br s, 1H), 5.21 (dd, 2H), 4.28 (br s, 1H), 3.15 (m, 1H), 2.92 (m, 1H), 2.88 (dd, 1H), 2.54 (m, 1H), 2.37 (m, 1H). MS (EI) for C_{19}H_{18}FNO: 328 (MH+).

[00462] STEP 3: A solution of benzyl 2-(4-fluorophenyl)-4-oxopiperidine-1-carboxylate (4.75 g, 14.50 mmol) in a mixture of ethyl acetate and tetrahydrofuran (1:1, 100 mL) was hydrogenated in the presence of 10% Pd/C at atmospheric pressure over 12h. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in ethyl acetate (250 mL) and washed twice with saturated aqueous bicarbonate (100 mL), brine, then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dried to give 2-(4-fluorophenyl)piperidin-4-one (2.8 g, quantitative). MS (EI) for C_{11}H_{12}FNO: 194 (MH+).

[00463] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00464] 2-(3,4-difluorophenyl)piperidin-4-one. Synthesized according to the method of reagent preparation 20 using 3,4-difluorophenylmagnesium bromide in step 1. MS (EI) for C_{14}H_{14}F₂NO: 212 (MH+).

[00465] 2-(3-fluorophenyl)piperidin-4-one. Synthesized according to the method of reagent preparation 20 using 3-fluorophenylmagnesium bromide in step 1. MS (EI) for C_{13}H_{12}FNO: 194 (MH+)
**Reagent Preparation 21**

2-(3,4-difluorophenyl)-4-(trifluoromethyl)piperidin-4-ol

[00466] STEP 1: To a solution of benzyl 2-(3,4-difluorophenyl)-4-oxopiperidine-1-carboxylate (0.21 g, 0.60 mmol) (reagent preparation 20, step 2) in dimethylformamide (4.0 mL) at 0 °C was added cesium carbonate (0.30 g, 0.90 mmol), followed by the addition of trimethyl(trifluoromethyl)silane (0.35 mL, 2.40 mmol). The reaction mixture was stirred at room temperature for 12 hours then partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate then filtered and concentrated. To a solution of the residue in methanol was added potassium carbonate (0.16 g, 1.19 mmol) and the reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate and washed with 1M aqueous hydrochloric acid, brine, dried over anhydrous magnesium sulfate then filtered and concentrated to give benzyl 2-(3,4-difluorophenyl)-4-hydroxy-4-(trifluoromethyl)piperidine-1-carboxylate (0.24 g, quantitative).

[00467] STEP 2: A solution of benzyl 2-(3,4-difluorophenyl)-4-hydroxy-4-(trifluoromethyl)piperidine-1-carboxylate (0.24 g, 0.60 mmol) in methanol (100 mL) was hydrogenated in the presence of catalytic 10% palladium on carbon at atmospheric pressure for 12h. The catalyst was filtered off and the filtrate was concentrated and dried to give 2-(3,4-difluorophenyl)-4-(trifluoromethyl)piperidin-4-ol (0.13 g, 78%). MS (EI) for C_{12}H_{12}F_{5}NO: 282 (MH^+).

**Reagent Preparation 22**

4-(2,2-difluoroethyl)piperidine

[00468] STEP 1: To a solution of tert-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (0.6 g, 2.6 mmol) in dichloromethane (30 mL) was added Dess-Martin-periodinane (1.2 g, 2.8 mmol), and the mixture was stirred at room temperature for 90 min. A 10% aqueous solution of sodium thiosulfate (15 mL) was added followed by saturated sodium bicarbonate (15 mL), and the biphasic mixture was stirred at room temperature for 1 h. The layers were separated, the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with saturated sodium bicarbonate, and brine, dried over sodium sulfate, filtered and concentrated to afford tert-butyl 4-(oxoethyl)piperidine-1-carboxylate that was used directly without further purification.

[00469] STEP 2: To a solution of tert-butyl 4-(oxoethyl)piperidine-1-carboxylate as obtained in step 1 in dichloromethane (50 mL) was added DAST (1.2 g, 7.8 mmol) at 0 °C.
The reaction mixture was warmed to room temperature and stirred for 17 h. A 5% aqueous solution of sodium bicarbonate was added and the layers were separated. The organic layer was washed with saturated sodium bicarbonate, and brine, dried over sodium sulfate, filtered and concentrated to provide tert-butyl 4-(2,2-difluoroethyl)piperidine-1-carboxylate that was used directly without further purification.

STEP 3: tert-Butyl 4-(2,2-difluoroethyl)piperidine-1-carboxylate as obtained in step 2 was dissolved in a minimum of trifluoroacetic acid and the resulting solution was stirred at room temperature for 2 h. The solution was then concentrated to give 4-(2,2-difluoroethyl)piperidine as the trifluoroacetate salt. MS (EI) for C12H13F2N: 150 (MH+).

Reagent Preparation 23

(±)-(2R,4R)-4-methyl-2-phenylpiperidin-4-ol and (±)-(2R,4S)-4-methyl-2-phenylpiperidin-4-ol

STEP 1: Methylmagnesium bromide (3 M solution in ether, 1.2 mL, 3.6 mmol) was added to a solution of tert-butyl 4-oxo-2-phenylpiperidine-1-carboxylate (328 mg, 1.2 mmol), in tetrahydrofuran (20 mL) at 0 °C and the resulting mixture was stirred at this temperature one hour. The reaction mixture was then quenched with saturated aqueous ammonium chloride solution (20 mL) and diluted with ethyl acetate (80 mL). The organic portion was separated, washed with water, then brine solution, dried over sodium sulfate, filtered and concentrated. The residue purified by silica gel chromatography (25% to 70% ethyl acetate in hexane gradient) to give the first eluting isomer assigned as (±)-tert-butyl (2R,4S)-4-methyl-2-phenylpiperidin-4-ol-1-carboxylate (100 mg, 29% yield), LC-MS for C12H23N03: 292 (MH+); and the second eluting isomer assigned as (±)-tert-butyl (2R,4R)-4-methyl-2-phenylpiperidin-4-ol-1-carboxylate (120 mg, 35% yield), MS (EI) for C12H23N03: 292 (MH+).

STEP 2: (±)-tert-butyl (2R,4S)-4-methyl-2-phenylpiperidin-4-ol-1-carboxylate (37 mg, 0.13 mmol) was taken into a minimum of neat TFA and allowed to stand at room temperature for 15 minutes. The solution was concentrated and taken into ethanol (5 mL) then concentrated and the residue dried to give (2R,4S)-4-methyl-2-phenylpiperidin-4-ol trifluoroacetate salt as an amorphous residue. MS (EI) for C12H17NO: 192 (MH+).

In the same manner (±)-(2R,4R)-4-methyl-2-phenylpiperidin-4-ol trifluoroacetate salt was prepared. MS (EI) for C12H17NO: 192 (MH+).
Reagent Preparation 24

4-(trifluoromethyl)piperidin-4-ol

[00474] STEP 1: To a solution of tert-butyl 4-oxopiperidine-1-carboxylate (0.6 g, 3.0 mmol) and cesium carbonate (1.1 g, 3.3 mmol) in dimethylformamide (10 mL) was added dropwise trimethyl(trifluoromethyl)silane (2 mL, 13.5 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with diethyl ether (100 ml) washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford tert-butyl 4-(trifluoromethyl)-4-(trimethylsilyloxy)piperidine-l-carboxylate (0.512 g, 50% yield) as an orange residue that was used without further purification. MS (EI) for C_{14}H_{26}F_{3}N0_{3}Si: 341 (MH^+).

[00475] STEP 2: To a solution of tert-butyl 4-(trifluoromethyl)-4-(trimethylsilyloxy)piperidine-l-carboxylate (0.512 g, 1.50 mmol), in methanol (10 mL) was potassium carbonate (0.25 g, 1.81 mmol). The resulting mixture was stirred at room temperature for 12 hours. Filtration and concentration provided an orange residue that was purified by silica gel chromatography (97:3 dichloromethane:methanol) to give tert-butyl 4-hydroxy-4-(trifluoromethyl)piperidine-l-carboxylate (0.07 g, 14% yield). MS (EI) for C_{11}H_{18}F_{3}N0: 269 (MET^+).

[00476] STEP 3: To a solution of tert-butyl 4-hydroxy-4-(trifluoromethyl)piperidine-l-carboxylate (0.07 g, 0.26 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL). The resulting mixture was stirred at room temperature for 30 minutes. Concentration and drying afforded 4-(trifluoromethyl)piperidin-4-ol (0.044 g, 100%). MS (EI) for C_{6}HioF_{3}N0: 269 (MH^+).

Reagent Preparation 25

4-methylpiperidine-4-carbonitrile

[00477] STEP 1: Trifluoroacetic acid anhydride (75 uL, 0.82 mmol) was added to a mixture of tert-butyl 4-carbamoyl-4-methylpiperidine-l-carboxylate (100 mg, 0.41 mmol) and pyridine (118 uL, 1.6 mmol) in tetrahydrofuran (2 mL), and the resulting mixture was stirred at room temperature for one hour. The mixture was concentrated then taken into ethyl acetate (20 mL) and partitioned with 0.5 M hydrochloric acid. The organic layer was washed with water then brine, dried over sodium sulfate, filtered, and concentrated to provide a 1:1 mixture of tert-butyl 4-cyano-4-methylpiperidine-l-carboxylate and tert-butyl 4-carbamoyl-4-methylpiperidine-l-carboxylate (100 mg) that was carried forward without further
purification. GC-MS (EI) for \( \text{C}_7\text{H}_{15}\text{N}_2\text{O}_2 \) (tert-butyl 4-cyano-4-methylpiperidine-1-carboxylate): 224 (M+).

[00478] STEP 2: tert-Butyl 4-cyano-4-methylpiperidine-1-carboxylate as obtained in step 1 (100 mg, 0.21 mmol), acetonitrile (1 mL), and 4 M hydrogen chloride in 1,4-dioxane (1 mL) were combined and stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 4-methylpiperidine-4-carboxamide hydrochloride salt (56 mg) contaminated with 4-methylpiperidine-4-carboxamide hydrochloride salt. MS (EI) for \( \text{C}_7\text{H}_{15}\text{N}_2 \) (4-methylpiperidine-4-carboxamide): 125 (MH+).

Reagent Preparation 26
8-azabicyclo[3.2.1]octan-3-ol

[00479] STEP 1: Sodium borohydride (178 mg, 4.7 mmol) was added to a solution of tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 2.2 mmol) in ethanol (10 mL), and the resulting mixture was stirred at room temperature for one hour. The mixture was quenched with saturated ammonium chloride solution (30 mL), and extracted with ethyl acetate (3x 20 mL). The combined extract was washed with water then brine, dried over sodium sulfate, filtered and concentrated to give tert-butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (463 mg, 92% yield) as a mixture of endo and exo stereoisomers. GC-MS (EI) for \( \text{C}_{12}\text{H}_{21}\text{N}_2 \): 227 (M+).

[00480] STEP 2: tert-Butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate as obtained in step 1 (100 mg, 2.0 mmol), acetonitrile (2 mL) and 4 M hydrogen chloride in 1,4-dioxane (2 mL) were combined and stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 8-azabicyclo[3.2.1]octan-3-ol hydrochloride salt (71 mg, 100% yield). MS (EI) for \( \text{C}_7\text{H}_{13}\text{NO} \): 128 (MH+).

Reagent Preparation 27
3-(endo)-methyl-8-azabicyclo[3.2.1]octane

[00481] STEP 1: A mixture of tert-butyl 3-methylene-8-azabicyclo[3.2.1]octane-8-carboxylate (0.10 g, 0.44 mmol) (reagent preparation 18), 10% palladium on charcoal (10 mg) and ethanol (15 mL) was hydrogenated in a Parr apparatus at 40 psi for 18 hours. The mixture was filtered and concentrated then dried to give tert-butyl 3-(endo)-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (96 mg, 95% yield); GC-MS (EI) for \( \text{C}_{13}\text{H}_{23}\text{N}_2\text{O}_2 \): 225 (M+).

[00482] STEP 2: A mixture of tert-butyl 3-(endo)-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (96 mg, 0.43 mmol), acetonitrile (1 mL), and 4 M hydrogen chloride in 1,4-
dioxane (1 mL) was stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give 3-(endo)-methyl-8-azabicyclo[3.2.1]octane hydrochloride salt (68 mg, 100% yield). MS (EI) for C₈H₁₅N: 126 (MH⁺).

Reagent Preparation 28

(±)-(2R,4S)-2-(3,4-difluorophenyl)piperidin-4-ol

[00483] STEP 1: A solution of benzyl 2-(3,4-difluorophenyl)-4-oxo-3,4-dihydropyridine-l(2H)-carboxylate (6.70 g, 19.50 mmol) (reagent preparation 20) in methanol (100 mL) was hydrogenated with catalytic 10% palladium on carbon in a Parr shaker at 35 psi. The catalyst was filtered off and the filtrate was concentrated then dried to give (±)-(2R,4S)-2-(3,4-difluorophenyl)piperidin-4-ol (4.2 g, quantitative). ¹H NMR (400 MHz, d₆-DMSO): 7.33 (m, 1H), 7.28 (m, 1H), 7.02 (m, 1H), 5.00 (t, 1H), 4.49 (d, 1H), 3.91 (m, 1H), 3.77 (m, 1H), 3.21 (m, 1H), 2.11 (2t, 1H), 1.95 (2q, 1H), 1.70 (m, 1H), 1.50 (m, 1H). MS (EI) for C₁₁H₁₃F₂NO: 214 (MH⁺).

[00484] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 the following reagents were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00485] (±)-(2R,4S)-2-(4-fluorophenyl)piperidin-4-ol. Synthesized according to the method of reagent preparation 28 starting with benzyl 6-(4-fluorophenyl)-4-oxo-3,4-dihydropyridine-l(2H)-carboxylate (reagent preparation 20). MS (EI) for C₁₁H₁₄FNO: 194 (M⁺).

Reagent Preparation 29

4,4-difluoro-2-phenylpiperidine

[00486] STEP 1: To a solution of tert-butyl 4-oxo-2-phenylpiperidine-l-carboxylate (0.20 g, 0.73 mmol), in dichloromethane (50 mL) at 0 °C was slowly added bis (2-methoxyethyl) aminosulfur trifluoride (0.16 mL, 0.87 mmol) and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 12 hours, then quenched by the addition of saturated aqueous ammonium chloride and partitioned with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. Silica gel chromatography of the residue (hexanes:ethyl acetate 4:1) provided tert-butyl 4,4-difluoro-2-phenylpiperidine-l-carboxylate (0.17 g, 81%). GC-MS (EI) for C₁₆H₂₁F₂NO₈: 241 (M-tBu⁺).

[00487] STEP 2: To a solution of tert-butyl 4,4-difluoro-2-phenylpiperidine-l-carboxylate (0.17 g, 0.57 mmol) in methanol (5 mL) was added 4M hydrogen chloride in dioxane (5 mL).
The reaction mixture was stirred at room temperature for 4 hours then concentrated and the residue was tritivated with diethyl ether. The white solid was collected by filtration and dried to give 4,4-difluoro-2-phenylpiperidine as the hydrochloride salt (93 mg, 70 %). GC-MS (EI) for C_{11}H_{13}F_{2}N: 197 (MH^+).

**Reagent Preparation 30**

**1,3-diphenylpiperazine**

[00488] **STEP 1:** A solution of tert-butyl 3-phenylpiperazine-1-carboxylate (0.95 g, 3.6 mmol), benzyl chloroformate (0.85 g, 5.0 mmol) and diisopropylethylamine (1.0 g, 7.7 mmol) in dioxane (20 mL) was heated to 95 °C for 3 hours. After cooling, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate (50 mL) and brine (25 mL). After drying over anhydrous sodium sulfate, filtration and concentration, the residue was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:8) to give 1-benzyl 4-tert-butyl 2-phenylpiperazine-1,4-dicarboxylate (0.84 g, 59% yield).

[00489] **STEP 2:** To 1-benzyl 4-tert-butyl 2-phenylpiperazine-1,4-dicarboxylate (0.84 g, 2.12 mmol) in dichloromethane (5.0 mL) added drop wise trifluoroacetic acid (5.0 mL) and maintained at 25 °C for 90 minutes. The reaction mixture was concentrated, and the residue dissolved in ethyl acetate (60 mL). The solution was washed with saturated aqueous sodium carbonate (30 mL) and brine (20 mL), and then dried over anhydrous sodium sulfate, filtered and concentrated to yield benzyl 2-phenylpiperazine-1-carboxylate (0.59 g, 94% yield). MS (EI) for C_{8}H_{10}O_{2}N: 297 (MH^+).

[00490] **STEP 3:** A solution of benzyl 2-phenylpiperazine-1-carboxylate (0.17 g., 0.58 mmol), bromobenzene (0.37 g, 2.37 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.06 g, 0.06 mmol), sodium tert-butoxide (0.20 g, 2.0 mmol) and 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (0.25 g, 0.64 mmol) in benzene (20 mL) was heated to 80 °C for 4.5 hours. After cooling, the reaction was diluted with ethyl acetate (60 mL), and washed with water (2x 30 mL), then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:4) to give benzyl 2,4-diphenylpiperazine-1-carboxylate (0.17 g, 79% yield) as an oil. MS (EI) for C_{24}H_{24}N_{2}O_{2}: 373 (MH^+).

[00491] **STEP 4:** A solution of benzyl 2,4-diphenylpiperazine-1-carboxylate (0.17 g, 0.45 mmol) and 5% Pd on carbon (0.1 g) in tetrahydrofuran/methanol 5:1 (10 mL) was stirred under hydrogen (1 atm) for 4.5 hours. The reaction was filtered through celite and
concentrated to give the title compound 1,3-diphenylpiperizine (0.10 g, 93% yield) as an oil. MS (EI) for C_{16}H_{18}N_{2}: 239 (MH^+).

Reagent Preparation 31

(±)-(2R,4R)-2-(4-fluorophenyl)piperidin-4-ol

STEP 1: A mixture of benzyl 2-(4-fluorophenyl)-4-oxo-3,4-dihydropyridine-1-carboxylate (1.00 g, 3.07 mmol) (reagent preparation 20) and 5% Pd on carbon (0.1 g) in acetic acid:methanol 1:10 (20 mL) was hydrogenated at 45 psi using a Parr apparatus for 16 hours. The catalyst was removed by filtering through Celite, and the filtrate concentrated to give (±)-(25,4R)-2-(4-fluorophenyl)piperidin-4-ol as an oil. The material was taken into chloroform (100 mL) and di-tert-butyl dicarbonate (0.74 g, 3.4 mmol) was added, followed by the dropwise addition of diisopropylethylamine (1.5 g, 12 mmol). The reaction was warmed to reflux for 10 minutes, then allowed to cool to 25°C over 30 minutes. The organic solution was washed with 0.1M aqueous hydrochloric acid (45 mL), water (50 mL) and saturated sodium bicarbonate (50 mL), then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate:hexanes, 1:1) to give (±)-(25,4R)-tert-butyl 2-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate (0.59 g, 65% yield). H NMR (400 MHz, d_{6}-DMSO): 7.25 (m, 2H), 7.10 (m, 2H), 4.96 (t, 1H), 4.46 (d, 1H), 3.90 (m, 1H), 3.77 (m, 1H), 3.23 (dt, 1H), 2.06 (m, 1H), 1.95 (m, 1H) 1.73 (m, 1H), 1.45 (m, 1H), 1.29 (s, 9H).

STEP 2: To (±)-(2S,4#)-tert-butyl 2-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate (0.55 g, 1.90 mmol) in tetrahydrofuran (20 mL) was added methanesulfonyl chloride (0.158 g, 2.05 mmg), followed by dropwise addition of diisopropylethylamine (0.50 g, 3.9 mmol) and N,N-dimethylpyridin-4-amine (10 mg). After 30 minutes the reaction was diluted with ethyl acetate (50 mL) and washed with 0.1 M hydrochloric acid (25 mL) then saturated sodium bicarbonate (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate:hexanes, 1:4) to give (±)-(2S,4R)-tert-butyl 2-(4-fluorophenyl)-4-(methylsulfonyloxy)piperidine-1-carboxylate (0.62 g, 88% yield). ^{1}H NMR (400 MHz, CDC_{13}): 5.79 (dd, 1H), 7.05 (t, 2H), 5.38 (d, 1H), 5.14 (m, 1H), 4.14 (m, 1H), 3.25 (m, 1H), 2.68 (m, 1H), 2.59 (s, 3H), 2.21 9M, 1H), 1.93 (m, 2H), 1.42 (s, 9H).

STEP 3: A solution of (±)-(2S,4R)-tert-butyl 2-(4-fluorophenyl)-4-(methylsulfonyloxy)piperidine-1-carboxylate (0.30 g, 0.80 mmol) and sodium acetate (0.33 g, 4.0 mmol) in dimethylsulfoxide (15 mL) was heated to 90°C for 2.5 hours. After cooling, the
reaction mixture was diluted with ethyl acetate (40 mL), and washed with water (25 mL) and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate:hexanes 1:10) to give (±)-(2R,4R)-tert-butyl 4-acetoxy-2-(4-fluorophenyl)piperidine-1-carboxylate (150 mg, 49% yield). 

**[00495]** STEP 4: A suspension of (±)-(2R,4R)-tert-butyl 4-acetoxy-2-(4-fluorophenyl)piperidine-1-carboxylate (150 mg, 0.40 mmol) and potassium carbonate (1.0 g) in methanol:water 10:1 (11 mL) was stirred for 1 hour then diluted with ethyl acetate (40 mL) and washed with water (25 mL) and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give (±)-(2R,4R)-tert-butyl 2-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate (117 mg, 99% yield). 

**[00496]** STEP 5: To (±)-(2R,4R)-tert-butyl 2-(4-fluorophenyl)-4-hydroxypiperidine-1-carboxylate (0.10 g, 0.34 mmol) in dichloromethane (10 mL) added trifluoroacetic acid: dichloromethane 1:4 (5 mL) and the mixture was stirred at 25 °C for 30 minutes. The solution was concentrated and dried to give title compound (±)-(2R,4R)-2-(4-fluorophenyl)piperidine-4-ol (105 mg, 99% yield) as the trifluoracetic acid salt. 

**[00497]** STEP 1: To a solution of tert-butyl 3-methylene-8-azabicyclo[3.2.1]octane-3-ol carboxylate (0.9 g, 4.0 mmol) (reagent preparation 18, step 1) in acetone (16 mL) and water (4 mL) was added osmium tetroxide (0.25 mL of a 4% aqueous solution, 0.04 mmol) and N-methylmorpholine N-oxide (1.4 g, 12.0 mmol). The reaction mixture was stirred at room temperature for 15 h, concentrated, and the residue was partitioned between 20% citric acid and ethyl acetate. The organic layer was washed twice with brine, dried over sodium sulfate, filtered and concentrated to give tert-butyl 3-(hydroxy)-3-(endo)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-carboxylate (1.0 g, quantitative yield). MS (EI) for C_{13}H_{23}NO_4: 257 (M+).
STEP 2: A solution of tert-butyl 3-(hydroxy)-3-(enJo)-(hydroxymethyl)-8-azabicyclo[3.2.1]octane-carboxylate (50 mg, 0.20 mmol) in dichloromethane (1 mL) and trifluoroacetic acid (1 mL) was stirred at room temperature for 1 h and then concentrated and dried to give 3-(en<io)-(hydroxymethyl)-8-azabicyclo[3.2.1]octan-3-ol as the trifluoroacetate salt, which was used without further purification.

Reagent Preparation 33

(±)-(2R,4S)-2-(3,4-difluorophenyl)-4-(fluoromethyl)piperidine

STEP 1: Potassium tert-butoxide (0.81 g, 7.2 mmol) was added to a suspension of methyltriphenylphosphonium bromide (2.58 g, 7.2 mmol) in tetrahydrofuran (20 mL) and the resulting mixture was stirred at room temperature for one hour. A solution of phenylmethyl 2-(3,4-difluorophenyl)-4-oxopiperidine-1-carboxylate (1.00 g, 2.9 mmol) (reagent preparation 20) in tetrahydrofuran (5 mL) was added and the resulting mixture was stirred at 35°C for two hours. The mixture was cooled, diluted with hexane (100 mL), filtered, and the filtrate washed with water then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to give phenylmethyl 2-(3,4-difluorophenyl)-4-methylidene piperidine-1-carboxylate (0.79 g, 79% yield), MS (EI) for C_{20}H_{19}F_2NO_2: 344 (MH^+).

STEP 2: A solution of borane (1 M in tetrahydrofuran, 4.58 mL) was added to a solution of phenylmethyl 2-(3,4-difluorophenyl)-4-methylidene piperidine-1-carboxylate (0.79 g, 2.3 mmol) in tetrahydrofuran (20 mL) at 0°C. The reaction mixture was slowly warmed to room temperature and stirred for 18 hours. The mixture was then cooled to 0°C, and 2M sodium hydroxide solution (2.6 mL, 5.2 mmol) then hydrogen peroxide solution (30% in water, 1.2 mL) were added sequentially. The mixture was warmed to room temperature and stirred for 1.5 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL), diluted with water (20 mL), and partitioned with ethyl acetate (20 mL). The organic portion was separated and washed twice with saturated sodium bisulfite solution (20 mL), water, then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (20% to 90% ethyl acetate in hexanes gradient) to give (±)-phenylmethyl (2R,4S)-2-(3,4-difluorophenyl)-4-(hydroxymethyl)piperidine-1-carboxylate (0.57 g, 69% yield), MS (EI) for C_{20}H_{21}F_2NO_3: 362 (MH^+).

STEP 3: Methanesulfonfyl chloride (74 mg, 0.65 mmol) was added to a mixture of (±)-phenylmethyl (2R,4S)-2-(3,4-difluorophenyl)-4-(hydroxymethyl)piperidine-1-
carboxylate (233 mg, 0.64 mmol), triethylamine (233 mg, 1.7 mmol), and 1,4-
diazabicyclo[2.2.2]octane (15 mg, 0.13 mmol) in toluene (10 mL) at 0 °C, and the resulting
mixture was stirred at 0 °C for 15 minutes, and at room temperature for another 15 minutes.
The reaction mixture was then quenched with a cold mixture of water and ethyl acetate. The
organic portion was separated, washed with water, then brine, dried over sodium sulfate,
filtered and concentrated. The residue was purified by silica gel chromatography (5% to 25%
ethyl acetate in hexanes gradient) to give (±)-phenylmethyl (2R,4S)-2-(3,4-difluorophenyl)-4-
{[(methylsulfonyl)oxy]methyl}piperidine-1-carboxylate (271 mg, 96% yield). MS (EI) for
C_{21}H_{23}F_{2}N_{5}S: 440 (MH^+).

STEP 4: A mixture of (±)-phenylmethyl (2R,4S)-2-(3,4-difluorophenyl)-4-
{[(methylsulfonyl)oxy]methyl}piperidine-1-carboxylate (200 mg, 0.46 mmol), and cesium
fluoride (190 mg, 1.3 mmol) in dimethyl sulfoxide (2 mL) was stirred at 100 °C for 18 hours.
The reaction mixture was cooled and purified directly by silica gel chromatography (5% to
25% ethyl acetate in hexanes gradient) to give (±)-phenylmethyl (2i?,4S)-2-(3,4-
difluorophenyl)-4-(fluoromethyl)piperidine-1-carboxylate (85 mg, 51% yield). MS (EI) for
C_{20}H_{2}F_{3}N_{2}: 364 (MH^+).

STEP 5: A mixture of (±)-phenylmethyl (2R,4S)-2-(3,4-difluorophenyl)-4-
(fluoromethyl)piperidine-1-carboxylate (85 mg, 0.23 mmol), 10% palladium on carbon (85
mg) and ethyl acetate (5 mL) in a 100 mL flask was stirred under 1 atmosphere of hydrogen
at room temperature for three days. The mixture was filtered and the filtrate concentrated and
dried to give (±)-(2R,4S)-2-(3,4-difluorophenyl)-4-(fluoromethyl)piperidine (39 mg, 73%
yield), MS (EI) for C_{12}H_{14}F_{3}N: 230 (MH^+).

Reagent Preparation 34

(±)-(2R,4R)-2-(3,4-difluorophenyl)piperidine-4-carbonitrile

Step 1: Methanesulfonyl chloride (1.0 g, 3.2 mmol) was added to a mixture of (±)-1,1-
dimethylethyl (2i?,4S)-2-(3,4-difluorophenyl)-4-hydroxypiperidine-1-carboxylate (1.00 g,
3.0 mmol) (obtained by conducting reagent preparation 28 in the presence of di-tert-butyl
dicarbonate) and triethylamine (0.70 g, 7.0 mmol), in tetrahydrofuran (25 mL) at 0 °C, and
the resulting mixture was at room temperature for two hours. The reaction mixture was then
quenched with a cold mixture of water and ethyl acetate. The organic portion was separated,
washed with 5% sodium hydroxide, 0.5M hydrochloric acid, water then brine, dried over
sodium sulfate, filtered and concentrated. The residue was purified by silica gel
chromatography (5% to 75% ethyl acetate in hexanes gradient) to give (±)-1,1-dimethylethyl (2R,4S)-2-(3,4-difluorophenyl)-4-[(methylsulfonf)oxy]piperidine-1-carboxylate (1.2 g, 88% yield). MS (EI) for C₁₇H₂₃F₂NO₅S: 392 (MH⁺).

[00505] STEP 2: A mixture of (±)-1,1-dimethylethyl (2R,4S)-2-(3,4-difluorophenyl)-4-[(methylsulfonf)oxy]piperidine-1-carboxylate (0.72 g, 1.8 mmol), and potassium cyanide (0.33 g, 3.7 mmol) in N,N-dimethylformamide (3.3 mL) was stirred at 90 °C for 18 hours. The reaction mixture was cooled, diluted with ethyl acetate (50 mL), washed twice with 5% lithium chloride solution (30 mL), then brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (5% to 25% ethyl acetate in hexanes gradient) to give (±)-1,1-dimethylethyl (2R,4R)-4-cyano-2-(3,4-difluorophenyl)piperidine-1-carboxylate (165 mg, 30% yield). MS (EI) for C₁₇H₂₃F₂N₂O₂: 323 (MH⁺).

[00506] STEP 3: A mixture of (±)-1,1-dimethylethyl (2R,4R)-4-cyano-2-(3,4-difluorophenyl)piperidine-1-carboxylate (65 mg, 0.20 mmol), acetonitrile (2 mL), and 4 M hydrogen chloride in 1,4-dioxane (2 mL) was stirred at 70 °C for 15 minutes. The reaction mixture was concentrated and dried to give (±)-(2R,4R)-4-(3,4-difluorophenyl)piperidine-4-carbonitrile hydrochloride salt (50 mg, 96% yield); MS (EI) for C₁₂H₁₂F₂N₂: 223 (MH⁺).

Reagent Preparation 35

*tert-butyl* 6-bromo-2-(tert-butoxycarbonyl(methoxycarbonyl)amino)-1-**H**-benzo[<]imidazole-1-carboxylate

[00507] STEP 1: To a slurry of 4-bromobenzene-1,2-diamine (2.1 g, 11 mmol), 1,2-dimethoxylethane (20 mL) and methanol (5 mL) was added 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (4.0 g, 19 mmol). The reaction mixture was heated (105 °C) for 12 h and then diluted with ethyl ether (100 mL). The resulting precipitate was collected by filtration and rinsed with ethyl ether (2 x 25 mL) to provide methyl 6-bromo-1**H**-benzo[J]imidazol-2-ylcarbamate (2.3 g, 77% yield). MS (EI) for C₉H₃BrN₅O₂: 271 (MH⁺).

[00508] STEP 2: To a cooled (0 °C) slurry of 6-bromo-1**H**-benzo[d]imidazol-2-ylcarbamate (2.3 g, 8.5 mmol), di-tert-butyl dicarbonate (4.5 g, 20 mmol), DIPEA (5.9 mL, 34 mmol) and chloroform (30 mL) was added DMAP (0.36 g, 2.9 mmol). The reaction mixture was stirred for 2 h at ambient temperature and then partitioned between dichloromethane (50 mL) and saturated aqueous ammonium chloride (50 mL). The organic layer was then washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered
and concentrated. Column chromatography on silica (10-25% ethyl acetate in hexanes) provided tert-butyl 6-bromo-2-(tert-butoxycarbonyl(methoxycarbonyl)amino)-1H-benzo[d]imidazole-1-carboxylate (2.3 g, 58% yield) as a red-brown solid. MS (EI) for C_{9}H_{24}BrN_{3}O_{6} 471 (MH⁺).

Reagent Preparation 36

3-(4-bromophenyl)-l-(tetrahydro-2'H-pyran-2-yl)-lH-pyrazole

[00509] STEP 1: To a heated (80 °C) solution of 3-(4-bromophenyl)-1H-pyrazole (1.0 g, 4.5 mmol) and trifluoroacetic acid (0.02 mL, 0.23 mmol) in toluene (5 mL) was added 3,4-dihydro-2'H-pyran (0.43 mL, 4.7 mol) over 1 hour. The reaction mixture was stirred for an additional hour and was then concentrated and dried to provide 3-(4-bromophenyl)-l-(tetrahydro-2'H-pyran-2-yl)-lH-pyrazole (1.3 g, 94% yield). MS (EI) for C_{9}H_{13}BrN_{2}O : 308 (MH⁺).

Reagent Preparation 37

4-(fluoromethyl)-4-hydroxypiperidine-l-carbonyl chloride

[00510] STEP 1: To a solution of tert-butyl 4-hydroxy-4-(hydroxymethyl)piperidine-l-carboxylate (Bioorganic & Medicinal Chemistry Letters 2008, 18(21), 5804-5808) (400 mg, 1.73 mmol) and DIPEA (1.2 mL, 7.0 mmol) in THF (10 mL) cooled to 0 °C was added thionyl chloride (0.65 mL, 8.6 mmol) in a dropwise manner and the mixture was stirred at this temperature for 1 h. The mixture was then paritioned with saturated aqueous sodium bicarbonate and ethyl acetate. The organic phase was extracted with ethyl acetate (3x) and the combined organic layers were washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated to afford 1,1-dimethylethyl 1,3-dioxo-2-thia-8-azaspiro[4.5]decane-8-carboxylate 2-oxide (562 mg) as an amber oil that was used without further purification. GC-MS (EI) for C_{9}H_{10}O_{5}S : 277 (M⁺).

[00511] STEP 2: 1,1-dimethylethyl 1,3-dioxo-2-thia-8-azaspiro[4.5]decane-8-carboxylate 2-oxide as obtained in step 1 (555 mg) was taken into acetonitrile (20 mL) followed by addition of sodium periodate (642 mg, 3.0 mmol), water (5 mL), and ruthenium (II) chloride hydrate (5 mg) and the mixture was stirred for 3 h at room temperature. The mixture was then concentrated and the residue partitioned with ethyl acetate and water. The organic phase was washed with water (2x) and brine followed by drying over anhydrous sodium sulfate, filtration and concentration. The residue was purified by silica gel chromatography (30% ethyl acetate in hexanes) to give 1,1-dimethylethyl 1,3-dioxo-2-thia-8-azaspiro[4.5]decane-8-carboxylate 2,2-dioxide (500 mg, 98% yield) as a yellow crystalline solid. ¹H NMR
(400mHz, CDC\textsubscript{13}): 4.44 (s, 2H), 4.03 (br, 2H), 3.16 (br tr, 2H), 2.21 (d, 2H), 1.76 (m, 2H), 1.46 (s, 9H).

STEP 3: 1,1-dimethylethyl 1,3-dioxa-2-thia-8-azaspiro[4.5]decan-8-carboxylate 2,2-dioxide (500 mg, 1.7 mmol) was taken into THF (5 mL) followed by addition of TBAF (1M in THF, 1.8 mL) and the resulting solution was stirred for 3h at 40 °C. The mixture was then cooled and partitioned with ethyl acetate and 20% aqueous citric acid. The organic solution was washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated to afford tert-butyl 4-(fluoromethyl)-4-hydroxypiperidine-1-carboxylate (350 mg, 88% yield). GC-MS (EI) for C\textsubscript{11}H\textsubscript{20}FNO\textsubscript{3}: 233 (M\textsuperscript{+}). BOC-group deprotection was carried out in a manner well established in the literature (see, Greene and Wuts, Protective Groups in Organic Synthesis, Wiley-Interscience) to give 4-(fluoromethyl)piperidin-4-ol hydrochloride salt as a colorless solid.

STEP 4: 4-(Fluoromethyl)piperidin-4-ol hydrochloride (233 mg, 1.37 mmol) was suspended in dichloromethane (3 mL) followed by addition of DIPEA (0.6 mL, 3.4 mmol) and the slurry obtained added in portions over several minutes to a solution of phosgene (20W% in toluene, 0.75 mL) diluted into dichloromethane (5 mL) and the mixture was allowed to stir at this temperature for 15 minutes. The mixture was then concentrated and the residue partitioned with ethyl acetate and water. The organic solution was washed 0.5M hydrochloric acid, brine then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (3:1 ethyl ether:hexanes) to give 4-(fluoromethyl)-4-hydroxypiperidine-1-carbonyl chloride (100 mg, 37% yield) as a colorless amorphous residue. GC-MS (EI) for C\textsubscript{7}H\textsubscript{11}FNO\textsubscript{2}Cl: 196 (M\textsuperscript{+}).

Using analogous synthetic techniques and substituting with alternative starting materials in step 4 the following reagents were prepared. Alternative starting materials were purchased from commercial sources unless otherwise indicated.

4-methylpiperidine-1-carbonyl chloride. Synthesized according to the method of reagent preparation 37 by using 4-methylpiperidine in step 4. H NMR (400 MHz, CDC\textsubscript{13}): 4.28, (d, 1H), 2.95 (dt, 2H), 1.75 to 1.56 (m, 3H), 1.27 to 1.10 (m, 2H), 0.97 (d, 3H), GC-MS for C\textsubscript{8}H\textsubscript{12}ClN\textsubscript{0}: 161 (M\textsuperscript{+}).

4-cyanopiperidine-1-carbonyl chloride. Synthesized according to the method of reagent preparation 37 by using piperidine-4-carbonitrile in step 4. GC-MS for C\textsubscript{7}H\textsubscript{9}ClN\textsubscript{2}O: 172 (M\textsuperscript{+}).
4-(trifluoromethyl)piperidine-1-carbonyl chloride. Synthesized according to reagent preparation 37 by using 4-(trifluoromethyl)piperidine in step 4. GC-MS (EI) for C₇H₉CIF₃N0₂: 215 (M⁺).

4-(1,1-difluoroethyl)piperidine-1-carbonyl chloride. Synthesized according to reagent preparation 37 by using 4-(1,1-difluoroethyl)piperidine (reagent preparation 9) in step 4. GC-MS (EI) for C₈H₁₅CIF₂N0₂: 211 (M⁺).

4-(2-fluoroethyl)piperidine-1-carbonyl chloride. Synthesized according to reagent preparation 37 by using 4-(2-fluoroethyl)piperidine (WO 9746553) in step 4. GC-MS (EI) for C₉H₁₅CIF₂N0₂: 193 (M⁺).


2-(4-fluorophenyl)piperidine-1-carbonyl chloride. Synthesized according to the method of reagent preparation 37 using 2-(4-fluorophenyl)piperidine in step 4. GC-MS (EI) for C₁₂H₁₅CIFNO₂: 241 (M⁺).

2-(3-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride. Synthesized according to the method of reagent preparation 37 using 2-(3-fluorophenyl)piperidin-4-one (reagent preparation 20) in step 4. ^1H NMR (400 MHz, CDC1₃): 7.37 (dd, IH), 7.07 (d, IH), 7.02 (t, IH), 5.98 (br s, IH), 4.40 (m, IH), 3.36 (br d, IH), 3.04 (t, IH), 2.98 (dd, IH), 2.64 (m, IH), 2.46 (br d, IH). GC-MS (EI) for C₁₂HnClFNO₂: 255 (M⁺).

2-(4-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride. Synthesized according to the method of reagent preparation 37 using 2-(4-fluorophenyl)piperidin-4-one (reagent preparation 20) in step 4. GC-MS (EI) for C₁₂HnClFNO₂: 255 (M⁺).

2-(3,4-difluorophenyl)-4-oxopiperidine-1-carbonyl chloride. Synthesized according to the method of reagent preparation 37 using 2-(3,4-difluorophenyl)piperidin-4-one (reagent preparation 20) in step 4. ^1H NMR (400 MHz, CDC1₃): 7.18 (dd, IH), 7.13 (m, IH), 7.02 (m, IH), 5.94 (br s, IH), 4.42 (m, IH), 3.33 (br d, IH), 2.98 (m, 2H), 2.65 (m, IH), 2.46 (br d, IH). GC/MS (EI) for C₁₂HnClFNO₂: 255 (M⁺). GC-MS (EI) for C₁₂HnClFNO₂: 273 (M⁺).

4-(fluoromethyl)piperidine-1-carbonyl chloride. Synthesized according to the method of reagent preparation 37 using 4-(fluoromethyl)piperidine (reagent preparation 7) in step 4. GC-MS (EI) for C₇H₇CIFNO₂: 180 (M⁺).

Step 1: To a cooled (0 °C) solution of 5-bromopyridine-2,3-diamine (5.0 g, 27 mmol) in NMP (20 mL) was added isothiocyanatoethane (2.3 mL, 26 mmol). The resulting solution was heated (65 °C) for four hours and then cooled to ambient temperature before 1,3-diisopropylcarbodiimide (4.2 mL, 27 mmol) was added. The reaction mixture was stirred for 18 hours, diluted with water and the resulting suspension was collected by filtration. Trituration with ethyl acetate provided 6-bromo-N-ethyl-3H-imidazo[4,5-b]pyridin-2-amine (4.8 g, 75% yield) as a brown solid. 1H NMR (400 MHz, d6-DMSO) δ 11.41 (bs, IH), 7.91 (s, IH), 7.53 (s, IH), 7.17 (s, IH), 3.33 (q, 2H), 1.17 (t, 3H); MS (ES) for C8H9BrN4: 241 (MH+).

Step 2: To a cooled (0 °C) solution of 6-bromo-N-ethyl-3H-imidazo[4,5-b]pyridin-2-amine (0.36 g, 1.5 mmol) in DMF was added NaH (60% dispersion in mineral oil, 0.060 g, 1.5 mmol) portion wise over 15 minutes. The reaction mixture was stirred for 15 minutes and then chloro(methoxy)methane (0.12 mL, 1.5 mmol) was added dropwise over 15 minutes. The resulting slurry was allowed to warm to ambient temperature and was stirred for two hours and was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by silica gel chromatography provided both 6-bromo-N-ethyl-N,3-bis(methoxymethyl)-3H-imidazo[4,5-b]pyridin-2-amine (0.091 g, 18%) and 6-bromo-N-ethyl-3-(methoxymethyl)-3H-imidazo[4,5-b]pyridin-2-amine (0.15 g, 35% yield). Bisprotected product: MS (ES) for Cj2H17BrN4O2: 329 (MH+). Monoprotected product: 1H NMR (400 MHz, CDC13) δ 8.03 (d, IH), 7.73 (d, IH), 5.42 (s, 2H), 4.98 (s, IH), 3.59 (q, 2H), 3.36 (s, 3H), 1.34 (t, 3H); MS (ES) for C11H13BrN4O: 285 (MH+).

Reagent Preparation 39: N-(5-bromo-2-chloropyridin-3-yl)methanesulfonamide

STEP 1: A solution of 5-bromo-2-chloropyridin-3-amine (1.0 g, 4.8 mmol) and diisopropylethylamine (1.85 mL, 10.6 mmol) in dichloromethane (25 mL) was cooled to 0 °C, and then methanesulfonyl chloride (750 uL, 9.6 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 15 min and was then warmed to rt. After stirring for 2 h, water was added, and then the biphasic mixture was partitioned. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was then dissolved in dioxane (10 mL) and water (10 mL). Potassium carbonate (2.76 g, 20 mmol) was added, and
the reaction mixture was stirred for 15 h at rt. Water was then added to the mixture which was subsequently acidified with aqueous citric acid (10%). The aqueous mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (gradient, 100% hexanes to 50% hexanes : 50% ethyl acetate) to provide N-(5-bromo-2-chloropyridin-3-yl)methanesulfonamide (520 mg, 1.82 mmol, 38% yield) as a light pink solid. H NMR (400 MHz, CDCl₃) δ 8.27 (d, 1H), 8.14 (d, 1H), 6.83 (br s, 1H), 3.11 (s, 3H); MS (EI) for C₆H₄BrClN₂O₂S: 285, 287, 289 (Br + Cl isotopes, MH⁺).

Reagent Preparation: 40: tert-butyl 1-(2-amino-5-bromopyridin-3-ylsulfonfonyl)azetidin-3-ylcarbamate

To a solution of tert-butyl azetidin-3-ylcarbamate (64 mg, 0.37 mmol) and potassium carbonate (102 mg, 0.74 mmol) in dioxane (2 mL) and water (400 uL) was added 2-amino-5-bromopyridine-3-sulfonfonyl chloride (100 mg, 0.37 mmol, prepared according to the methods in WO2008 144463). The reaction mixture was stirred for 1 h at room temperature then quenched by addition of saturated aqueous sodium bicarbonate, and the aqueous solution was extracted twice with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to provide tert-butyl 1-(2-amino-5-bromopyridin-3-ylsulfonfonyl)azetidin-3-ylcarbamate (120 mg, 0.30 mmol, 80% yield) as a white solid. H NMR (400 MHz, CDCl₃) δ 8.31 (d, 1H), 8.00 (d, 1H), 5.76 (br s, 2H), 4.80 (br s, 1H), 4.50-4.36 (m, 1H), 4.11 (t, 2H), 3.75 (t, 2H), 1.42 (s, 9H); MS (EI) for C₁₇H₁₉BrN₄O₄S: 407, 409 (Br isotopes, MH⁺).

Synthetic Example 1: 4-(azepan-1-ylcarbonyl)-7-(2-methyl-1 H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine.

[00526] STEP 1: To 5-bromo-2-methylbenzimidazole (38 g, 180 mmol) in THF (400 mL) was added di-tert-butyl dicarbonate (39 g, 189 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated. Ethyl acetate (400 mL) was added to the residue, and the solution was washed with 10% aqueous citric acid (2 x 100 mL), water (100 mL), and brine (100 mL), dried over sodium sulfate, and concentrated. Column chromatography on silica (gradient 20-30% ethyl acetate in hexane) provided 1,1-dimethyl 6-bromo-2-methyl-l H-benzimidazole-1-carboxylate (27 g, 48% yield) as a beige solid. MS (EI) for C₁₇H₁₉BrN₂O₂: 312 (MH⁺).

[00527] STEP 2: A solution of 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (30.0 g, 91.4 mmol) and triisopropyl borate (22.4 g, 119
mmol) in THF (300 mL) was cooled to -78 °C, and a 2.5M solution of n-butyllithium in hexanes (47.6 mL, 119 mmol) was added dropwise over 40 min at this temperature. The reaction mixture was stirred at -78 °C for an additional 30 min, then quenched by dropwise addition of 2 N hydrochloric acid (80 mL), and allowed to warm up to room temperature. Ethyl acetate (100 mL) and water (100 mL) were added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with water, dried over sodium sulfate, and concentrated. Hexane (200 mL) was added to the residue and the mixture was stirred overnight. The precipitate was filtered, washed several times with hexane, and dried to give (4-[(1,1-dimethylethyl)oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (23.4 g, 87%) as a colorless solid. MS (EI) for C_{17}H_{17}N_{3}O: 280 (MH^+).

**[00528]** STEP 3: A suspension of 1,1-dimethylethyl 6-bromo-2-methyl-1H-benzimidazole-1-carboxylate (11.3 g, 36 mmol), (4-[(1,1-dimethylethyl)oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (11.7 g, 40 mmol), dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (3.0 g, 10 mol %) in dioxane (115 mL) and water (28.5 mL) was degassed with nitrogen, and then diisopropylethylamine (18.6 g, 144 mmol) was added. The reaction mixture was stirred at 90 °C for 220 min, cooled to room temperature, and concentrated. Column chromatography on silica of the residue (gradient 25-30% ethyl acetate in hexane) afforded 1,1-dimethyl 7-(1-[(1,1-dimethylethyl)oxy]carbonyl]-2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (13.2 g, 76% yield) as an amorphous solid. MS (EI) for C_{27}H_{33}N_{3}O: 480(MH^+).

**[00529]** STEP 4: A solution of 1,1-dimethyl 7-(1-[(1,1-dimethylethyl)oxy]carbonyl]-2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (13.1 g, 27 mmol) in a mixture of methanol (20 mL) and 4 N hydrogen chloride in dioxane (30 mL) was refluxed for 15 min. After cooling to room temperature ethyl ether (100 mL) was added, and the reaction mixture was concentrated. Another portion of ethyl ether (100 mL) was added, the precipitate was filtered off, washed several times with ethyl ether, and dried to give 7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine dihydrochloride (8.9 g, 93% yield) as a light beige solid. 1HNMR (400 MHz, CD$_3$OD); 7.93(s, 1H), 7.86-7.67(m, 4H), 7.28(s, 1H), 4.54(s, 2H), 4.33-4.23(m, 2H), 3.65-3.54(m, 2H), 2.91(s, 3H); MS (EI) for C$_7$H$_{17}$N$_3$O : 280 (MH^+).
STEP 5: 7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine dihydrochloride (6.95 g, 19.73 mmol) was suspended in dichloromethane (100 mL) and cooled to 0 °C. To the resulting mixture was added DIPEA (19 mL, 109 mmol) followed by allyl chloroformate (4.6 mL, 43.4 mmol) and stirring was continued at 0 °C for 30 minutes then warmed to room temperature. The reaction mixture was then charged with additional DIPEA (3.4 mL) and allyl chloroformate (1 mL) then stirred an additional 30 minutes at room temperature. The resulting solution was then concentrated and the residue azeotroped once from methanol (100 mL). The residue was then taken back into methanol (100 mL) followed by portionwise addition of 2 M aqueous sodium hydroxide (20 mL) and the mixture was allowed to stir for 1 h at room temperature. The solution was then concentrated and the residue partitioned with chloroform and dilute brine. The organic phase was then dried over anhydrous sodium sulfate, filtered and concentrated to give prop-2-en-1-yl 7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxylate as an amorphous residue which was carried forward directly into step 6.

STEP 6: prop-2-en-1-yl 7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxylate as obtained in step 5 was taken into THF (100 mL) followed by addition of pyridine (2.5 mL, 30 mmol) and di-tert-butyl dicarbonate (4.9 g, 22.4 mmol) and the mixture was allowed to stir at room temperature over 12 h. The resulting solution was concentrated and the residue partitioned with ethyl acetate and 10% aqueous citric acid. The organic phase was washed twice with additional 10% aqueous citric acid then brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography using 3:2 to 4:1 ethyl acetate in hexanes as eluent to afford 7-[1-[(1,1-dimethylethoxy)carbonyl]-2-methyl-1H-benzimidazol-6-yl]-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxylic acid 2-propenyl ester (10.2 g) as a pale yellow amorphous residue. MS (EI) for C_{15}H_{29}N_{3}O_{5}: 465 (MH+).

STEP 7: 7-[1-[(1,1-dimethylethoxy)carbonyl]-2-methyl-1H-benzimidazol-6-yl]-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxylic acid 2-propenyl ester (110 mg, 0.27 mmol) was taken into THF (1 mL) followed by addition of sodium triacetoxyborohydride (254 mg, 1.2 mmol) then tetrakis(triphenylphosphine)palladium (0) (6.1 mg, 0.005 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was diluted with chloroform and partitioned with dilute aqueous sodium bicarbonate. The aqueous phase was extracted twice with chloroform and the combined organic layers were dried over anhydrous sodium sulfate then filtered and concentrated to give crude 1,1-dimethylethyl 2-methyl-6-(2,3,4,5-
tetrahydro-1,4-benzoxazepin-7-yl)-H-benzimidazole-1-carboxylate (109.5 mg) as an amorphous residue. MS (EI) for C_{22}H_{23}N_{3}O_{3}: 380 (MH^+).

[00533] STEP 8: Phosgene (20 W% in toluene) (190 uL, 0.38 mmol) was added by syringe to a 0 °C cooled solution of pyridine (100 uL, 1.2 mmol) in chloroform (3 mL) followed by addition of 1,1-dimethylethyl 2-methyl-6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-H-benzimidazole-1-carboxylate as obtained in step 7 as a solution in chloroform (1 mL). The mixture was stirred for 15 minutes at 0 °C then partitioned with 10% aqueous citric acid. The organic phase was washed over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by silica gel chromatography to give 1,1-dimethylethyl 6-[4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-IH-benzimidazole-1-carboxylate (62.6 mg, 59% yield) as a yellow amorphous residue. MS (EI) for C_{23}H_{24}CIN_{3}O_{4}: 442 (MH^+).

STEP 9: 1,1-dimethylethyl 6-[4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-H-benzimidazole-1-carboxylate (33 mg, 0.08 mmol) was taken into dichloromethane (1.5 mL) followed by addition of homopiperidine (0.1 mL, 0.89 mmol) and the mixture was allowed to stir for 12 h at room temperature. The mixture was then concentrated and the residue partitioned with ethyl acetate and 10% aqueous citric acid. The organic phase was separated and dried over magnesium sulfate then filtered and concentrated. The residue obtained was taken into trifluoroacetic acid (1 mL) and allowed to stand for 1 h at room temperature. The solution was then concentrated and the residue taken into a minimum of aqueous acetonitrile and purified by preparative reverse phase HPLC. Lyophilization of the combined pure fractions afforded 4-(azepan-1-ylcarbonyl)-7-(2-methyl-1 H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (18 mg) as an amorphous solid. H NMR (400 MHz, de-DMSO): 7.91 (s, 1H), 7.83 (d, 1H), 7.76 (dd, 1H), 7.64 (d, 1H), 7.55 (dd, 1H), 7.06 (d, 1H), 4.42 (s, 2H), 4.22 (br s, 2H); 3.55 (br s, 2H) 3.29 (tr, 4H), 2.64 (s, 3H), 1.65 (br s, 4H), 1.49 (br s, 4H). MS (EI) for C_{24}H_{28}N_{4}O_{2}: 406 (MH^+).

[00534] Using analogous synthetic techniques and substituting with alternative starting reagents in step 9 the following compounds of the invention were prepared. Protecting group introduction and removal steps were conducted as required according to literature techniques appropriate for a given protecting group (see for example: Greene and Wuts, Protective Groups in Organic Synthetic, Wiley-Interscience). Alternative starting materials were obtained commercially unless otherwise indicated.

[00535] 4-(hexahydrocyclopenta[c]pyrrol-2(1 H)-ylcarbonyl)-7-(2-methyl-1 H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method
of example 1 by using octahydrocyclopenta[c]pyrrole in step 9. \textsuperscript{1}H NMR (400 MHz, methanol\textsuperscript{a}): 7.64 (m, IH), 7.54-7.42 (m, 4H), 7.02 (d, IH), 4.53 (s, 2H), 4.21 (m, 2H), 3.71 (m, 2H), 3.55 (m, 2H), 3.20 (m, 2H), 2.62 (m, 2H), 2.59 (s, 3H), 1.86-1.69 (m, 3H), 1.58 (m, IH), 1.44 (m, 2H); MS (EI) for C\textsubscript{25}H\textsubscript{28}N\textsubscript{4}O\textsubscript{2}: 417 (MH\textsuperscript{+}).

[00536] 4-(3,4-dihydroquinolin-1(2 H)-ylcarbonyl)-7-(2-methyl-1 H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 1,2,3,4-tetrahydroquinoline in step 9. \textsuperscript{1}H NMR (400 MHz, methanol-d\textsubscript{4}): 7.59 (m, IH), 7.51 (d, IH), 7.45 (dd, IH), 7.38 (dd, IH), 7.19 (d, IH), 7.03 (d, IH), 7.00-6.85 (m, 3H), 4.50 (s, 2H), 4.19 (m, 2H), 3.72 (m, 2H), 3.52 (m, 2H), 2.80 (t, 2H), 2.59 (s, 3H), 1.92 (m, 2H); MS (EI) for C\textsubscript{27}H\textsubscript{26}N\textsubscript{4}O\textsubscript{2}: 439 (MH\textsuperscript{+}).

[00537] 7-(2-methyl-1 H-benzimidazol-6-yl)-4-[(2-phenylpyrrolidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 2-benzylpyrrolidine in step 9. \textsuperscript{1}H NMR (400 MHz, methanol-d\textsubscript{4}): 7.65 (m, IH), 7.57-7.42 (m, 4H), 7.21-7.03 (m, 6H), 4.56 (m, 2H), 4.32 (m, IH), 4.16 (m, 2H), 3.77 (m, IH), 3.65 (m, IH), 3.44 (m, IH), 3.34 (m, IH), 2.90 (m, IH), 2.58 (t, 2H), 2.50 (m, IH), 1.84 (m, 2H), 1.60 (m, 2H); MS (EI) for C\textsubscript{25}H\textsubscript{30}N\textsubscript{4}O\textsubscript{2}: 467 (MH\textsuperscript{+}).

[00538] 7-(2-methyl-1 H-benzimidazol-6-yl)-4-[(2-phenylpyrrolidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine acetate. Prepared according to the method of example 1 by using 2-phenylpyrrolidine in step 9. \textsuperscript{1}H NMR (400 MHz, methanol-d\textsubscript{4}): 7.66 (m, IH), 7.53 (m, 2H), 7.46 (m, 2H), 7.14 (m, 2H), 7.04 (m, 4H), 4.95 (m, 2H), 4.14 (m, 2H), 3.88 (m, IH), 3.70 (m, 2H), 3.61 (m, IH), 2.57 (s, 3H), 2.34 (m, IH), 2.00 (m, IH), 1.98 (s, 3H), 1.86 (m, IH), 1.70 (m, IH); MS (EI) for C\textsubscript{25}H\textsubscript{26}N\textsubscript{4}O\textsubscript{2}: 453 (MH\textsuperscript{+}).

[00539] 7-(2-methyl-1 H-benzimidazol-6-yl)-4-[(2-phenylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the trifluoroacetate salt according to the method of example 1 by using 2-phenylpiperidine in step 9. \textsuperscript{1}H NMR (400 MHz, methanol-d\textsubscript{4}): 7.80-7.65 (m, 3H), 7.50 (dd, IH), 7.32 (d, IH), 7.27-7.11 (m, 5H), 7.07 (d, IH), 4.65 (m, IH), 4.57 (s, 2H), 4.20 (m, 2H), 3.78 (m, 2H), 3.37 (m, IH), 3.16 (m, IH), 2.86 (s, 3H), 2.05 (m, IH), 1.87 (m, IH), 1.75-1.54 (m, 4H); MS (EI) for C\textsubscript{25}H\textsubscript{30}N\textsubscript{4}O\textsubscript{2}: 467 (MH\textsuperscript{+}).

[00540] 7-(2-methyl-1 H-benzimidazol-6-yl)-4-[(3-phenylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the acetate salt according to the method of example 1 by using 3-phenylpiperidine in step 9. \textsuperscript{1}H NMR (400 MHz, methanol-d\textsubscript{4}): 7.58 (d, IH), 7.49 (m, 2H), 7.42 (dd, IH), 7.32 (dd, IH), 7.16-7.03 (m, 5H), 7.01 (d, IH), 4.51 (s,
7-(2-methyl-1H-benzimidazol-6-yl)-4-[(3-phenylpyrrolidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the acetate salt according to the method of example 1 by using 3-phenylpyrrolidine in step 9. H NMR (400 MHz, methanol-d₄): 7.04 (s, 1H), 7.50 (m, 2H), 7.46 (dd, 1H), 7.36 (dd, 1H), 7.26-7.12 (m, 5H), 7.04 (d, 1H), 4.61 (m, 1H), 4.58 (s, 2H), 4.31 (m, 1H), 4.15 (m, 1H), 3.85 (m, 1H), 3.66 (m, 2H), 3.61 (m, 2H), 3.35 (m, 1H), 2.60 (s, 3H), 2.26 (m, 1H), 2.01 (m, 1H), 1.97 (s, 3H); MS (EI) for C₂₉H₂₈N₄O₂: 453 (M⁺).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(2-methylpyrrolidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the acetate salt according to the method of example 1 by using 2-methylpyrrolidine in step 9. H NMR (400 MHz, methanol-d₄): 7.55 (m, 1H), 7.45-7.32 (m, 4H), 6.94 (d, 1H), 4.44 (m, 2H), 4.19 (m, 1H), 4.04 (m, 1H), 3.87 (m, 1H), 3.65 (m, 1H), 3.59-3.46 (m, 2H), 3.26 (m, 1H), 2.49 (s, 3H), 2.02 (m, 1H), 1.89 (s, 3H), 1.80 (m, 1H), 1.58 (m, 1H), 1.38 (m, 1H), 0.98 (d, 3H); MS (EI) for C₂₃H₂₆N₄O₂: 391 (M⁺).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(3-(phenylmethyl)pyrrolidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the acetate salt according to the method of example 1 by using 3-benzylpyrrolidine in step 9. H NMR (400 MHz, methanol-d₄): 7.65 (m, 1H), 7.54-7.42 (m, 4H), 7.16-7.06 (m, 5H), 7.01 (d, 1H), 4.52 (m, 2H), 4.24 (m, 1H), 4.14 (m, 1H), 3.74 (m, 1H), 3.63 (m, 1H), 3.45 (m, 2H), 3.34 (m, 1H), 3.17 (m, 1H), 2.65 (m, 2H), 2.58 (s, 3H), 2.37 (m, 1H), 1.99 (s, 3H), 1.93 (m, 1H), 1.60 (m, 1H); MS (EI) for C₂₉H₃₀N₄O₂: 467 (M⁺).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(l-oxothiomorpholin-4-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-(methylsulfinyl)piperidine (synthesized according to reagent preparation 13) in step 9. H NMR (400 MHz, DMSO-d₆): 7.63 (m, 1H), 7.58 (d, 1H), 7.48 (m, 2H), 7.36 (dd, 1H), 7.00 (d, 1H), 4.48 (s, 2H), 4.19 (m, 2H), 3.62 (m, 4H), 3.66 (m, 2H), 2.96 (m, 2H), 2.72 (m, 2H), 1.86 (s, 3H); MS (EI) for C₂₂H₂₄N₄O₂S: 425 (M⁺).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-(methylsulfonyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-(methylsulfonyl)piperidine (synthesized according to reagent preparation 14) in step 9. H NMR (400 MHz, DMSO-d₆): 12.27 (br. s, 1H), 7.64 (m, 1H), 7.55 (m, 1H), 7.48 (m, 2H), 7.37 (m, 1H), 7.01 (m, 1H), 4.46 (s, 2H), 4.19 (m, 2H), 3.68 (m,
2H), 3.62 (m, 2H), 2.94 (m, 3H), 2.81 (m, 2H), 1.99 (m, 2H), 1.91 (m, IH), 1.60 (m, 2H); MS (EI) for C\(_{24}\)H\(_{28}\)N\(_4\)O\(_4\)S: 469 (MH\(^+\)).

[00546] 7-(2-methyl-1H-benzimidazol-6-yl)-N-[(1-methylethyl)-N-(phenylmethyl)-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxamide. Prepared according to the method of example 1 by using N-benzylpropan-2-amine in step 9. \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): 12.27 (br s, IH), 7.64 (m, IH), 7.55 (m, IH), 7.48 (m, 2H), 7.37 (m, IH), 7.01 (m, IH), 4.46 (s, 2H), 4.19 (m, 2H), 3.68 (m, 2H), 3.62 (m, 2H), 2.94 (m, 3H), 2.81 (m, 2H), 1.99 (m, 2H), 1.91 (m, IH), 1.60 (m, 2H); MS (EI) for C\(_{24}\)H\(_{28}\)N\(_4\)O\(_4\)S: 469 (MH\(^+\)).

[00547] 7-(2-methyl-1H-benzimidazol-6-yl)-4-[(2-(phenylmethyl)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepine. Prepared as the free base as described in example 1 using racemic 2-benzylpiperidine in step 9. \(^1\)H NMR (400 MHz, methanol-d\(_4\)): 7.49 (s, IH), 7.43-7.36 (m, 2H), 7.32-7.27 (m, 2H), 7.08-6.90 (m, 6H), 4.19 (s, 2H), 4.13-4.04 (m, 2H), 3.73-3.66 (m, IH), 3.45-3.32 (m, 2H), 3.30-3.23 (m, IH), 3.17-3.07 (m, 1H), 2.89-2.82 (m, IH), 2.74-2.67 (m, IH), 2.49 (s, 3H), 1.77-1.38 (m, 6H); MS (EI) for C\(_{30}\)H\(_{32}\)N\(_4\)O\(_2\): 481 (MH\(^+\)).

[00548] 7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-methoxy)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepine. Prepared as described in example 1 using 4-methoxypiperidine in step 9. \(^1\)H NMR (400 MHz, methanol-d\(_4\)): 7.57 (s, IH), 7.47-7.34 (m, 4H), 6.96 (d, IH), 4.41 (s, 2H), 4.12 (t, 2H), 3.61 (t, 2H), 3.48-3.40 (m, 2H), 3.39-3.31 (m, IH), 3.27 (s, 3H), 2.96 (t, 2H), 1.88-1.81 (m, 2H), 1.53-1.42 (m, 2H); MS (EI) for C\(_{24}\)H\(_{28}\)N\(_4\)O\(_3\): 421 (MH\(^+\)).

[00549] 7-(2-methyl-1H-benzimidazol-6-yl)-4-[(3-phenylmethyl)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepine. Prepared as described in example 1 using racemic 3-benzylpiperidine in step 9. \(^1\)H NMR (400 MHz, methanol-d\(_4\)): 7.62 (s, IH), 7.51-7.38 (m, 4H), 7.13-7.04 (m, 3H), 7.01-6.96 (m, 3H), 4.45-4.34 (m, 2H), 4.07 (t, 2H), 3.60-3.43 (m, 4H), 2.80-2.72 (m, IH), 2.57 (s, 3H), 2.50-2.42 (t, IH), 2.37 (d, 2H), 1.80-1.61 (m, 3H), 1.55-1.46 (m, IH), 1.15-1.05 (m, IH); MS (EI) for C\(_{30}\)H\(_{32}\)N\(_4\)O\(_2\): 481 (MH\(^+\)).

[00550] 4-(2-azabicyclo[2.2.1]hept-2-yl]carbonyl}-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine. Prepared as the free base as described in example 1 using 2-azabicyclo[2.2.1]heptane in step 9. \(^1\)H NMR (400 MHz, d\(_6\)-DMSO): 12.26 (br s, IH), 7.72-7.43 (m, 4H), 7.35 (d, IH), 6.99 (d, IH), 4.47 (s, 2H), 4.24 (m, IH), 4.12 (m, IH), 3.96 (s, IH), 3.71-3.43 (m, 4H), 2.81 (d, IH), 2.51 (s, 3H), 1.84-1.75 (m, 1H), 1.62-1.52 (m, 2H), 1.48-1.41 (d, 2H), 1.39-1.28 (m, 2H); MS (EI) for C\(_{24}\)H\(_{28}\)N\(_4\)O\(_2\): 403 (MH\(^+\)).
1-(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl)piperidin-3-ol. Prepared as described in example 1 using racemic 3-hydroxy pip eridine step 9. \(^1\)H NMR (400 MHz, methanol-d4): 7.65 (s, IH), 7.55-7.50 (m, 2H), 7.48-7.42 (m, 2H), 7.03 (d, IH), 4.50 (s, 2H), 4.19 (m, 2H), 3.75-3.66 (m, 3H), 3.55 (m, IH), 3.37 (m, IH), 2.99 (m, IH), 2.87 (m, IH), 2.58 (s, 3H), 1.93 (m, IH), 1.82 (m, IH), 1.60-1.44 (m, 2H); MS (EI) for C\(_{23}\)H\(_{26}\)N\(_{4}\)O\(_2\): 407 (MH\(^+\)).

**[00552]** \(N\)-methyl-7-(2-methyl-1H-benzimidazol-6-yl)-7V-{[(IR)-1-phenylethyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. Prepared as the free base as described in example 1 using (R)-N-methyl-1-phenylethanamine step 9. \(^1\)H NMR (400 MHz, methanol-d4): 7.60 (s, IH), 7.53-7.45 (m, 2H), 7.38-7.32 (m, 2H), 7.30-7.17 (m, 5H), 7.05 (d, IH), 5.11 (q, IH), 4.62 (s, 2H), 4.51 (br, s, 2H), 4.25 (m, IH), 3.70 (m, 1H), 2.65 (s, 3H), 2.59 (s, 3H), 1.54 (d, 3H); MS (EI) for C\(_{22}\)H\(_{23}\)N\(_{4}\)O\(_2\): 441 (MH\(^+\)).

**[00553]** 7-(2-methyl-1H-benzimidazol-6-yl)-4-(piperidin-1-ylcarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using piperidine in step 9. MS (EI) for C\(_{23}\)H\(_{26}\)N\(_{4}\)O\(_2\): 391 (MH\(^+\)).

**[00554]** 7-(2-methyl-1H-benzimidazol-6-yl)-4-(pyrrolidin-1-ylcarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using pyrrolidine in step 9. MS (EI) for C\(_{22}\)H\(_{24}\)N\(_{4}\)O\(_2\): 377 (MH\(^+\)).

**[00555]** 7-(2-methyl-1H-benzimidazol-6-yl)-4-{[(3-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using racemic 3-methylpiperidine in step 9. MS (EI) for C\(_{24}\)H\(_{28}\)N\(_{4}\)O\(_2\): 406 (MH\(^+\)).

**[00556]** 7-(2-methyl-1H-benzimidazol-5-yl)-4-[(3a/?6aS)-5-methylhexahydrocyclopenta[c]pyrrol-2(1H)-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized as a 4:1 mixture of 5-methyl isomers according to the method of example 1 using (3aR,6aS)-5-methyloctahydrocyclopenta[c]pyrrole (reagent preparation 10) in step 9. \(^1\)H NMR (400 MHz, methanol-cU): 7.85 (s, IH), 7.76-7.75 (d, 2H), 7.54 (s, IH), 7.48 (dd, IH), 7.05 (dd, IH), 4.56 (s, 2H), 4.24 (m, 2H), 3.75 (m, 2H), 3.59 (minor isomer, dd, 0.5H), 3.40 (major isomer, dd, 1.5H), 3.32 (major isomer, dd, 1.5H), 3.14 (minor isomer, dd, 0.5H), 2.71 (minor isomer, br, 0.5H), 2.59 (major isomer, br, 1.5H), 2.06-1.98 (m, 2H), 1.97-1.88 (m, IH), 1.62 (minor isomer, dd, 0.5H), 1.01-0.9 (m, 4.5H). MS (EI) for C\(_{26}\)H\(_{30}\)N\(_{4}\)O\(_2\): 432 (MH\(^+\)).

**[00557]** (±)-7-(2-methyl-1H-benzimidazol-5-yl)-4-{[(3a5,6a/?)-5-methyl-3,3a,4,6a-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine.
Synthesized according to the method of example 1 using (±)-(3aR,6aS)-5-methyl-1,2,3,3a,4,6a-hexahydrocyclopenta[c]pyrrole (reagent preparation 11) in step 9. H NMR (400 MHz, d<sub>6</sub>-DMSO): 7.91 (s, IH), 7.82 (d, IH), 7.75 (dd, IH), 7.59 (d, IH), 7.54 (dd, IH), 7.04 (d, IH), 7.19 (s, IH), 4.49 (s, 2H), 4.21 (m, 2H), 3.61 (m, 2H), 3.21 (br, IH), 3.18 (d, IH), 3.04 (dd, IH), 2.74 (tr, IH), 2.44 (dd, IH), 2.01 (d, IH), 1.65 (s, 3H). MS (EI) for C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>2</sub>: 430 (MH<sup>+</sup>).

**[00558]** 4-[(4,4-difluoropiperidin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4,4-difluoropiperidine in step 9. H NMR (400 MHz, methanol-d<sub>4</sub>): 7.65 (d, IH), 7.54 (d, IH), 7.52 (d, IH), 7.47 (dd, IH), 7.44 (dd, IH), 7.04 (d, IH), 4.54 (s, 2H), 4.22 (m, 2H), 3.73 (m, 2H), 3.38 (m, 4H), 2.59 (s, 3H), 2.02 (m, 4H); MS (EI) for C<sub>23</sub>H<sub>24</sub>F<sub>2</sub>N<sub>4</sub>O<sub>2</sub>: 427 (MH<sup>+</sup>).

**[00559]** 1-[(7-(2-memyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl)piperidin-4-ol. Prepared according to the method of example 1 by using 4-piperidin-4-ol in step 9. H NMR (400 MHz, CDCl<sub>3</sub>): 7.60 (s, IH), 7.53 (d, IH), 7.41 (m, 2H), 7.35 (m, IH), 7.07 (d, IH), 4.45 (s, 2H), 4.21 (m, 2H), 3.89 (m, IH), 3.72 (m, 2H), 3.63 (m, 2H), 3.00 (m, 2H), 2.64 (m, 3H), 1.96 (m, 2H), 1.61 (m, 2H); MS (EI) for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>: 407 (MH<sup>+</sup>).

**[00560]** 4-{[4-(4-chlorophenyl)methyl]piperidin-1-yl}carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-(4-chlorobenzyl)piperidine in step 9. H NMR (400 MHz, methanol-d<sub>4</sub>): 7.64 (s, IH), 7.52 (d, IH), 7.50 (d, IH), 7.46 (dd, IH), 7.41 (dd, IH), 7.21 (d, 2H), 7.12 (d, 2H), 7.03 (d, IH), 4.48 (s, 2H), 4.19 (m, 2H), 3.67 (m, 4H), 2.76 (m, 2H), 2.59 (s, 3H), 2.55 (d, 2H), 1.71 (m, IH), 1.61 (m, 2H), 1.27 (m, 2H); MS (EI) for C<sub>30</sub>H<sub>31</sub>CIN<sub>4</sub>O<sub>2</sub>: 515 (MH<sup>+</sup>).

**[00561]** 4-{[4-(4-chlorophenyl)oxy]piperidin-1-yl}carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-(4-chlorophenoxy)piperidine in step 9. H NMR (400 MHz, methanol-d<sub>4</sub>): 7.64 (s, IH), 7.51 (m, 2H), 7.47 (dd, 1H), 7.42 (dd, IH), 7.23 (m, 2H), 7.04 (d, IH), 6.93 (m, 2H), 4.55 (m, IH), 4.52 (s, 2H), 4.21 (m, 2H), 3.71 (m, 2H), 3.54 (m, 2H), 3.20 (m, 2H), 2.58 (s, 3H), 2.01 (m, 2H), 1.76 (m, 2H); MS (EI) for C<sub>29</sub>H<sub>29</sub>CIN<sub>4</sub>O<sub>2</sub>: 517 (MH<sup>+</sup>).

**[00562]** 1-{[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl}-4,4'-bipiperidine. Prepared as the acetate salt according to the method of...
example 1 by using 4,4'-bipiperidine in step 9. H NMR (400 MHz, methanol-d$_4$): 7.64 (s, IH), 7.51 (m, 2H), 7.47 (dd, IH), 7.42 (d, IH), 7.04 (d, IH), 4.50 (s, 2H), 4.20 (m, 2H), 3.74 (m, 2H), 3.68 (m, 2H), 3.37 (m, 2H), 2.92 (m, 2H), 2.81 (m, 2H), 2.58 (s, 3H), 1.95 (m, 2H), 1.37 (m, 2H), 1.52-1.23 (m, 6H); MS (EI) for C$_{28}$H$_{32}$N$_4$O$_2$: 474 (MH$^+$).

[00563] 4-{(3-ethylpiperidin-1-yl)carbonyl}-7-(2-methyl-1 H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine. Prepared according to the method of example 1 by using racemic 3-ethylpiperidine in step 9. H NMR (400 MHz, methanol-d$_4$): 7.64 (s, IH), 7.51 (m, 2H), 7.47 (dd, IH), 7.42 (d, IH), 7.04 (d, IH), 4.50 (s, 2H), 4.21 (m, 2H), 3.67 (m, 2H), 3.62 (m, 2H), 2.79 (m, IH), 2.58 (s, 3H), 2.46 (m, IH), 1.90 (m, IH), 1.70 (m, IH), 1.56 (m, IH), 1.42 (m, IH), 1.17 (m, 2H), 1.07 (m, IH), 0.80 (t, 3H); MS (EI) for C$_{25}$H$_{30}$N$_4$O$_2$: 419 (MH$^+$).

[00564] 4-{[2-(4-fluorophenyl)piperidin-1-yl]carbonyl}-7-(2-methyl-1 H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine. Prepared according to the method of example 1 by using racemic 2-(4-fluorophenyl)piperidine in step 9. MS (EI) for C$_9$H$_{29}$N$_4$O$_2$: 485 (MH$^+$).

[00565] ethyl (35)-l-{[7-(2-methyl-1 H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl}piperidine-3-carboxylate. Prepared according to the method of example 1 by using (5)-ethyl piperidine-3-carboxylate in step 9. H NMR (400 MHz, methanol-cL): 7.67 (s, IH), 7.53 (m, 2H), 7.47 (m, 2H), 7.04 (d, IH), 4.51 (s, 2H), 4.20 (m, 2H), 3.96 (m, 2H), 3.69 (m, 3H), 3.49 (m, IH), 3.09 (m, IH), 2.97 (m, IH), 2.61 (m, IH), 2.60 (s, 3H), 2.01 (m, IH), 1.81-1.53 (m, 3H), 1.10 (t, 3H); MS (EI) for C$_{26}$H$_{30}$N$_4$O$_4$: 463 (MH$^+$).

[00566] ethyl 1-{[7-(2-methyl-1 H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl}piperidine-2-carboxylate. Prepared according to the method of example 1 by using racemic ethyl piperidine-2-carboxylate in step 9. H NMR (400 MHz, methanol-d$_4$): 7.65 (s, IH), 7.51 (m, 2H), 7.44 (m, 2H), 7.04 (d, IH), 4.52 (m, 2H), 4.28 (m, IH), 4.21 (m, IH), 4.08 (m, 2H), 3.70 (m, 2H), 2.58 (s, 3H), 2.05 (m, IH), 1.81 (m, IH), 1.64 (m, 2H), 1.49 (m, IH), 1.13 (t, 3H); MS (EI) for C$_{26}$H$_{30}$N$_4$O$_4$: 463 (MH$^+$).

[00567] 4-{(5-ethyl-2-methylpiperidin-1-yl)carbonyl}]-7-(2-methyl-1 H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine. Prepared according to the method of example 1 by using racemic 5-ethyl-2-methylpiperidine in step 9. H NMR (400 MHz, methanol-d$_4$): 7.64 (s, IH), 7.50 (m, 2H), 7.43 (m, 2H), 7.04 (d, IH), 4.46 (s, 2H), 4.21 (m, 2H), 4.06 (m, IH), 3.65 (m, 2H), 3.42 (m, IH), 2.68 (m, IH), 2.58 (s, 3H), 1.77 (m, IH), 1.70 (m, IH), 1.56 (m, IH), 1.39 (m, IH), 1.31 (m, IH), 1.18 (d, 3H), 0.81 (t, 3H); MS (EI) for C$_{26}$H$_{32}$N$_4$O$_2$: 433 (MH$^+$).
8-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-8-azabicyclo[3.2.1]octan-3-(endo)-amine. Prepared as the acetate salt according to the method of example 1 by using tert-butyl 8-azabicyclo[3.2.1]octan-3-(endo)-ylcarbamate (synthesized according to reagent preparation 4) in step 9. $^1$H NMR (400 MHz, methanol-d$_4$): 7.64 (s, IH), 7.50 (m, 2H), 7.44 (m, 2H), 7.03 (d, IH), 4.62 (s, 2H), 4.24 (m, 2H), 4.15 (m, 2H), 3.77 (m, 2H), 3.46 (m, IH), 2.58 (s, 3H), 2.55 (m, 2H), 2.05 (m, 2H), 1.92 (s, 3H), 1.75 (m, 2H), 1.60 (m, 2H); MS (EI) for C$_{28}$H$_{30}$N$_4$O$_2$: 432 (MH$^+$).

(3R)-l-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]pyrrolidin-3-ol. Prepared according to the method of example 1 by using (fl)-pyrrolidin-3-ol in step 9. $^1$H NMR (400 MHz, methanol-d$_4$): 7.64 (s, IH), 7.51 (m, 2H), 7.44 (m, 2H), 7.03 (d, IH), 4.56 (s, 2H), 4.36 (m, IH), 4.28 (m, IH), 4.17 (m, IH), 3.80-3.60 (m, 4H), 3.38 (m, 2H), 2.58 (s, 3H), 1.90 (m, 2H); MS (EI) for C$_{28}$H$_{28}$N$_4$O$_2$: 393 (MH$^+$).

4-methyl-1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]piperidin-4-ol. Prepared according to the method of example 1 by using 4-methylpiperidin-4-ol (synthesized according to reagent preparation 5) in step 9. $^1$H NMR (400 MHz, methanol-d$_4$): 7.64 (s, IH), 7.50 (m, 2H), 7.43 (m, 2H), 7.03 (d, IH), 4.49 (s, 2H), 4.20 (m, IH), 3.68 (m, 2H), 3.39 (m, 2H), 3.24 (m, 2H), 2.58 (s, 3H), 1.61 (m, 4H), 1.23 (s, 3H); MS (EI) for C$_{28}$H$_{28}$N$_4$O$_2$: 421 (MH$^+$).

(±)-7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4aS,8aR)-octahydroisoquinolin-2(1H)-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using racemic (4aS,8aR/-)decahydroisoquinoline in step 9. $^1$H NMR (400 MHz, methanol-d$_4$): $^1$H NMR (400 MHz, methanol-d$_4$): 7.66 (s, IH), 7.52 (m, 2H), 7.48 (dd, IH), 7.44 (dd, IH), 7.05 (d, IH), 4.73 (d, IH), 4.62 (d, IH), 4.13 (m, 2H), 3.95 (m, IH), 3.82 (m, IH), 3.21 (m, IH), 2.66 (m, IH), 2.58 (s, 3H), 2.44 (m, IH), 1.83 (m, IH), 1.78-1.54 (m, 6H), 1.35 (m, IH), 1.21 (m, 2H), 1.06 (m, 2H), 0.87 (m, IH); MS (EI) for C$_{29}$H$_{31}$N$_4$O$_2$: 445 (MH$^+$).

4-[(2-(3-fluorophenyl)piperidin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using racemic 2-(3-fluorophenyl)piperidine in step 9. $^1$H NMR (400 MHz, methanol-d$_4$): 7.59 (s, IH), 7.50 (d, IH), 7.47 (d, IH), 7.35 (m, 2H), 7.20 (m, IH), 7.05 (d, IH), 7.03 (d, IH), 6.97 (m, IH), 6.86 (m, IH), 4.60 (m, 2H), 4.56 (m, IH), 4.21 (m, IH), 4.12 (ml 2H), 3.76 (m, 2H), 3.23 (m, 2H), 2.58 (s, 3H), 1.99 (m, IH), 1.88 (m, IH), 1.70 (m, 2H), 1.60 (m, 2H); MS (EI) for C$_{29}$H$_{32}$N$_4$O$_2$: 485 (MH$^+$).
(35)-l-\{7-(2-methyl-1\textsubscript{H}-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5\textsubscript{H})-yl\}pyrrolidin-3-ol. Prepared according to the method of example 1 by using (S)-pyrrolidin-3-ol in step 9.  

\textbf{H} NMR (400 MHz, methanol-d\textsubscript{4}): 7.64 (s, IH), 7.51 (m, 2H), 7.44 (m, 2H), 7.03 (d, IH), 4.56 (m, 2H), 4.36 (m, IH), 4.28 (m, IH), 4.18 (m, IH), 3.81-3.60 (m, 4H), 3.38 (m, IH), 3.24 (m, IH), 2.58 (s, 3H), 1.92 (m, 2H); MS (EI) for C\textsubscript{22}H\textsubscript{24}N\textsubscript{4}O\textsubscript{3}: 393 (MH\textsuperscript{+}).

4-\{(4-fluoro-4-methylpiperidin-1-yl)carbonyl\}-7-(2-methyl-1\textsubscript{H}-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-fluoro-4-methylpiperidine (synthesized according to reagent preparation 8) in step 9.  

\textbf{H} NMR (400 MHz, methanol-c\textsubscript{6}U): 7.69 (s, IH), 7.58 (d, IH), 7.50 (m, 3H), 7.04 (d, IH), 4.51 (s, 2H), 4.20 (m, 2H), 3.70 (m, 2H), 3.49 (m, 2H), 3.15 (m, 2H), 2.65 (s, 3H), 1.75 (m, 4H), 1.36 (d, 3H); MS (EI) for C\textsubscript{23}H\textsubscript{27}FN\textsubscript{4}O\textsubscript{2}: 423 (MH\textsuperscript{+}).

7-(2-methyl-1\textsubscript{H}-benzimidazol-6-yl)-4-\{[(2R)-2-phenylpiperidin-1-yl]carbonyl\}-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared by chiral preparative HPLC separation of racemic 7-(2-methyl-1\textsubscript{H}-benzimidazol-6-yl)-4-\{(2-phenylpiperidin-1-yl)carbonyl\}-2,3,4,5-tetrahydro-1,4-benzoxazepine (example 1) using a SHIMADZU LC-20AD apparatus equipped with a Chiralpak AD-H, 25 cm x 4.6 mm column using a mobile phase of ethanol:methanol 1:1 and flow rate of 18.0 mL/min and detection at 220 nm. The isomer with retention time 11.20 min. was assigned as the (R)-enantiomer. Chiral analytical HPLC was carried out using a SHIMADZU LC-20AD apparatus equipped with a Chiralpak AD-H, 25 cm x 4.6 mm column using a mobile phase of ethanol:methanol 1:1 and flow rate of 0.7 mL/min with detection at 254/220 nm. This isomer gave a retention time 9.51 min and ee >99%. MS (EI) C\textsubscript{24}H\textsubscript{30}N\textsubscript{4}O\textsubscript{2}: 467 (MH\textsuperscript{+}).

7-(2-methyl-1\textsubscript{H}-benzimidazol-6-yl)-4-\{[(25)-2-phenylpiperidin-1-yl]carbonyl\}-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared by chiral preparative HPLC separation of racemic 7-(2-methyl-1\textsubscript{H}-benzimidazol-6-yl)-4-\{(2-phenylpiperidin-1-yl)carbonyl\}-2,3,4,5-tetrahydro-1,4-benzoxazepine (example 1) using a SHIMADZU LC-20AD apparatus equipped with a Chiralpak AD-H, 25 cm x 4.6 mm column using a mobile phase of ethanol:methanol 1:1 and flow rate of 18.0 mL/min and detection at 220 nm. The isomer with retention time 11.20 min. was assigned as the (S)-enantiomer. Chiral analytical HPLC was carried out using a SHIMADZU LC-20AD apparatus equipped with a Chiralpak AD-H, 25 cm x 4.6 mm column using a mobile phase of ethanol:methanol 1:1 and flow rate of 0.7
niL/min with detection at 254/220 nm. This isomer gave a retention time 13.30 min and ee >99%. MS (EI) C_{9}H_{19}N_{2}O_{2}+: 467 (MH⁺).

[00577] 7-(2-Methyl-1H-benzimidazol-6-yl)-4-[(5-phenylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using commercially available 2-phenyl-octahydro-pyrrolo[3,4-c]pyrrole in step 9. (400 MHz, methanol-d_4): 7.61 (br, IH), 7.50 to 7.45 (m, 2H), 7.44 (dd, IH), 7.37 (dd, IH), 7.12 (t, 2H), 7.03 (t, IH), 6.62 (d, 2H), 4.54 (s, 2H), 4.21 (m, 2H), 3.77 to 3.69 (m, 4H), 3.48 to 3.66 (m, 2H), 3.19 (dd, 2H), 3.04 to 2.95 (2H), 2.57 (s, 3H); MS (EI) for C_{30}H_{28}N_{2}O_{3}: 494 (MH⁺).

[00578] 1-[(7-(2-Methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-2-phenylpiperidin-4-one. Prepared according to the method of example 1 by using 2-phenylpiperidin-4-one in step 9. 400 MHz, methanol-d_4): 7.61 (s, IH), 7.50 (d, IH), 7.47 (dd, IH), 7.40 (d, IH), 7.35 (dd, IH), 7.28 to 7.17 (m, 5H), 7.04 (d, IH), 5.23 (t, IH), 4.61 (s, 2H), 4.22 (m, 2H), 3.80 (m, 4H), 3.37 (m, 2H), 2.93 (m, 2H), 2.66 (m, IH), 2.58 (s, 3H), 2.34 (dd, IH); MS (EI) for Molecular Formula C_{29}H_{28}N_{4}O_{3}: 481 (MH⁺).

[00579] 8-[(7-(2-Methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-8-azabicyclo[3.2.1]octan-3-(enio)-yl)methanol. Prepared according to the method of example 1 using 8-azabicyclo[3.2.1]octan-3-(endo)-ylmethanol hydrochloride (reagent preparation 18) in step 9. (400 MHz, methanol-d_4): 7.64 (br, IH), 7.54 to 7.50 (m, 2H), 7.45 (dd, IH), 7.43 (dd, IH), 7.05 (d, IH), 4.60 (s, 2H), 4.22 (m, 2H), 4.07 (br, 2H), 3.77 (m, 2H), 3.55 (d, 2H), 2.58 (s, 3H), 2.24 to 2.15 (m, 2H), 1.95 to 1.87 (m, 2H), 1.66 to 1.54 (m, 4H); MS (EI) for C_{29}H_{30}N_{4}O_{3}: 447 (MH⁺).

**Synthetic Example 2**

5-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}pyrimidin-2-amine

[00580] STEP 1: 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (10 g, 30.5 mmol) was taken into hot ethanol (10 mL) followed by addition of 4M hydrogen chloride in dioxane solution (2.1 eq, 16 mL) and the resulting solution was allowed to slowly cool to ambient temperature over one hour. An excess of ethyl ether was then added and the resulting slurry was filtered. The filter cake was washed with ethyl ether and dried to give 7-bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (7.9 g, 98% yield) as a colorless crystalline solid. MS (EI) for C_{9}H_{10}NOBr: 229 (MH⁺).
STEP 2: 7-bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (3.0 g, 11.34 mmol) was suspended in dichloromethane (30 mL) followed by addition of DIPEA (3 mL, 34 mmol) and pyridine (4 mL, 49 mmol) and the resulting partially heterogeneous mixture was added portionwise over 5 minutes to a 0 °C cooled solution of phosgene (20 W% in toluene, 15 mL, 28 mmol) in dichloromethane (15 mL). The resulting mixture was then allowed to slowly warm to room temperature over 30 minutes then concentrated. The residue was partitioned with ethyl acetate and water and the organic phase washed twice with 1M aqueous hydrochloric acid then brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carbonyl chloride (3.35 g) as a pale yellow oil. MS (EI) for C_{13}H_{23}BrNO: 319 (MH+).

STEP 3: 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carbonyl chloride as obtained in step 2 was taken into dichloromethane (35 mL) followed by portionwise addition of 4-methylpiperidine (3.5 mL, 28.4 mmol) over 5 minutes. The resulting mixture was stirred an additional 5 minutes then concentrated. The residue was partitioned with ethyl acetate and water and the organic phase washed with 1M aqueous hydrochloric acid then brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 7-bromo-4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine (3.91 g) as a clear oil. MS (EI) for C_{15}H_{22}BrClNO: 292 (MH+).

STEP 4: 7-bromo-4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine as obtained in step 3 (3.91 g, 11.07 mmol) was azeotroped twice from warm heptane then taken into anhydrous THF and cooled to -78 °C under nitrogen. Triisopropyl borate (3.3 mL, 14.4 mmol) was added by syringe followed by dropwise addition of n-butyllithium (2.5M in hexane, 5.8 mL, 14.4 mmol) over 30 minutes. The mixture was allowed to stir an additional 30 minutes at -78 °C then quenched by careful addition of 2M aqueous hydrochloric acid (10 mL) and warmed to room temperature. The mixture was stirred for 1 h at room temperature then concentrated to remove THF. The resulting aqueous mixture was then diluted with additional water and basified to pH greater than 12 by addition of 50% aqueous sodium hydroxide. The aqueous mixture was extracted once with ethyl ether then acidified to pH 1 by addition of concentrated aqueous hydrochloric acid. The acidic mixture was extracted once with ethyl acetate then washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford 4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-yl) boronic acid (2.86 g, 81% yield). MS (EI) for C_{16}H_{23}BrN_{2}O: 319 (MH+).
STEP 5: To a mixture of 2-amino-5-bromopyrimidine (65 mg, 0.37 mmol), {4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-7-yl} boronic acid (100 mg, 0.31 mmol) and potassium carbonate (215 mg, 1.6 mmol) in DMA (5.0 mL) and water (0.5 mL) was added dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (23 mg, 0.03 mmol). The reaction mixture was stirred at 95 °C for 2.5 hours and then partitioned between dichloromethane (10 mL) and 1M aqueous sodium hydroxide (10 mL). The organic layer was separated and washed with brine (10 mL) then dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel using 2% methanol in dichloromethane as eluent and the combined product containing fractions were concentrated. The residue thus obtained was taken into a minimum of acetonitrile and purified by preparative reverse phase HPLC to afford 5-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyrimidin-2-amine (24 mg) as an amorphous solid. 1H NMR (400 MHz, DMSO-d6): 8.51 (s, 2H), 7.47 (d, 1H), 7.42 (dd, 1H), 6.98 (d, 1H), 6.75 (s, 2H), 4.39 (s, 2H), 4.12-4.18 (m, 2H), 3.46-3.59 (m, 4H), 2.70 (t, 2H), 1.42-1.61 (m, 3H), 1.04-1.18 (m, 2H), 0.91 (d, 3H); MS (EI) for C24H15SN5O2: 368 (MH+).

[00584] Using analogous synthetic techniques and substituting with alternative starting reagents in step 5 then conducting protecting group removal as required according to literature techniques appropriate for a given protecting group (see for example: Greene and Wuts, Protective Groups in Organic Synthetic, Wiley-Interscience) the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00585] 5-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyrazin-2-amine. Synthesized according to the method of example 2 using 5-bromopyrazin-2-amine in step 5. 1H NMR (400 MHz, d6-DMSO): 8.44 (s, 1H), 7.99 (s, 1H), 7.79 (d, 1H), 7.71 (dd, 1H), 6.97 (d, 1H), 4.39 (s, 2H), 4.17 (br s, 2H), 3.57 (br s, 2H), 3.51 (d, 2H), 2.68 (tr, 2H), 1.56 (d, 2H), 1.49 (m, 1H), 1.11 (q, 2H), 0.92 (d, 3H). MS (EI) for C20H25N5O2: 368 (MH+).

[00586] 6-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridazin-3-amine. Synthesized according to the method of example 2 using 6-bromopyridazin-3-amine in step 5. 1H NMR (400 MHz, d6-DMSO): 8.49 (br s, 2H), 8.33 (d, 1H), 7.84 (d, 1H), 7.76 (dd, 1H), 7.49 (d, 1H), 7.05 (d, 1H), 4.44 (s, 2H), 4.24 (m, 2H), 3.60
methyl (6-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l H-benzimidazol-2-yl)carbamate. Synthesized according to the method of example 2 using tert-butyl 6-bromo-2-((tert-butoxycarbonyl)(methoxycarbonyl)amino)-l H-benzo[1]imidazole-1-carboxylate (reagent preparation 35) in step 5. H NMR (400 MHz, CD3OD): 7.61 (s, 1H), 7.44-7.51 (m, 3H), 7.38 (d, 1H), 7.02 (d, 1H), 4.90 (s, 3H), 4.48-4.63 (m, 2H), 4.17-4.21 (m, 2H), 3.64-3.72 (m, 2H), 3.5 (d, 2H), 2.82 (t, 2H), 1.51-1.70 (m, 3H), 1.15-1.52, (m, 2H), 0.94 (d, 3H); MS (EI) for C20H25N5O2: 368 (MH+).

**Synthetic Example 3**

**N-(5-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,3-thiazol-2-yl)acetamide**

**[00588]**  
**STEP 1:** A mixture of N-(5-bromothiazol-2-yl)acetamide (1.00 g, 4.52 mmol), (4-[(1,1-dimethylethyl)oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (example 1, step 2) (1.54 g, 5.43 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.33 g, 0.40 mmol), potassium carbonate (2.50 g, 18.1 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was degassed with nitrogen for 5 minutes and then stirred at 93°C for 18 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (80 mL), filtered over celite. The filtrate was washed with brine (2 x 50 mL), dried over sodium sulfate, filtered, concentrated. The residue was purified by flash chromatography (20% to 80% ethyl acetate-hexane gradient) to give 1,1-dimethylethyl 7-[2-(acetylamino)-1,3-thiazol-5-yl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (0.99 g, 2.54 mmol, 56.2% yield); MS (EI) for C16H23N3O4: 290 (MH+).

**[00589]**  
**STEP 2:** A mixture of 1,1-dimethylethyl 7-[2-(acetylamino)-1,3-thiazol-5-yl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (0.29 g, 0.75 mmol), in methanol (2 mL) and 4 M hydrogen chloride in 1,4-dioxane (2 mL) was stirred at 70°C for 15 minutes. The reaction mixture was cooled and concentrated, and dried in vacuum to give the de-protected product N-[5-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,3-thiazol-2-yl]acetamide hydrochloride (0.24 g, 0.24 mmol, 99% yield); MS (EI) for C14H15N3O2S: 290 (MH+).

**[00590]**  
**STEP 3:** 4-Methylpiperidine-1-carboxyl chloride (reagent preparation 37) (103 mg, 0.64 mmol) was added to a mixture of N-[5-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,3-thiazol-2-yl]acetamide hydrochloride, (173 mg, 0.53 mmol) and potassium carbonate
(374 mg, 2.7 mmol) in N,N-dimethylformamide (2 mL). The resulting mixture was stirred at room temperature for 18 hours, then methanol (2 mL) was added and concentrated. The residue was diluted with ethyl ether (40 mL), a solid was collected by filtration, and washed with ether and water to give N-(5-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1,3-thiazol-2-yl)acetamide (140 mg, 0.34 mol, 63% yield). H NMR (400 MHz, DMSO-d$_6$): 7.58 (s, 1H), 7.35 to 7.32 (m, 2H), 6.91 (d, 1H), 4.36 (s, 2H), 4.12 (br, 2H), 3.54 to 3.47 (m, 4H), 2.71 to 2.65 (m, 2H), 2.00 (s, 3H), 1.60 to 1.43 (m, 3H), 1.16 to 1.067 (m, 2H), 0.92 (d, 3H); MS (El) for C$_2$H$_{26}$N$_4$O$_5$S: 415 (MH$^+$).

**Synthetic Example 4**

7-[4-(1H-imidazol-2-yl)phenyl]-4-[(4-(trifluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepine

[00591] STEP 1: 1,1-Dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxylate (5.0 g, 20.1 mmol), bis(pinacolato)diboron (5.6 g, 22.1 mmol), potassium acetate (5.9 g, 60.2 mmol) and [1,1’-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (440 mg, 0.62 mmol) were heated in DMSO (5 mL) solution at 80 °C for 1.5 h. The mixture was then cooled to room temperature and diluted with an excess of ethyl acetate and filtered through a bed of celite. The filtrate was partitioned with 1M aqueous hydrochloric acid and the organic phase washed with brine and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated and the residue purified by silica chromatography using 4:1 hexanes:ethyl acetate as eluent to give tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzoazepine-4(5)-carboxylate (7.6 g, 100%). H NMR (400 MHz, CDCl$_3$): 7.77 (s, 0.4H), 7.67 (s, 1H), 7.65 (s, 0.6H), 7.04-6.98 (m, 1H), 4.54 (s, 0.7H), 4.43 (s, 1.3H), 4.09-4.01 (m, 2H), 3.79 (dd, 2H), 1.40 (br s, 9H), 1.26 (s, 12H). MS (El) for C$_{20}$H$_{30}$BNO$_5$S: 376 (MH$^+$).

[00592] STEP 2: To a solution of 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzoxazepine benzoazepin-4(5 H)-carboxylate (3.0 g, 8.00 mmol) in dichloromethane (90 mL) was added trifluoroacetic acid (10 mL) and the reaction mixture was heated to reflux. After cooling to room temperature the solvent was evaporated and the residue was taken into ethyl acetate (250 mL). The solution was partitioned with saturated aqueous sodium bicarbonate (200 mL) and the organic layer was separated. It was washed again with saturated aqueous bicarbonate (150 mL) then brine. The combined aqueous phase was extracted once with ethyl acetate (200 mL). The combined organic phases were then washed with brine, dried over anhydrous anhydrous sodium sulfate,
filtered and concentrated to give 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine (2.1 g, 96%). MS (EI) for C_{23}H_{25}N_3O_3: 276 (MH+).

STEP 3: 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoazepine (2.2 g, 8.0 mmol) was taken into dichloromethane (30 mL) followed by addition of DIPEA (40 mmol, 7 mL) then 4-trifluoromethylpiperidine hydrochloride salt (1.55 g, 8.2 mmol). The mixture was allowed to stir 30 minutes at room temperature then concentrated. The residue was partitioned with ethyl acetate and 5% aqueous citric acid. The organic phase was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated to give 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)-2,3-dihydro-1,4-benzoazepine-4(5 H)-carbonyl chloride (3.0 g) as a pale yellow amorphous residue.

STEP 4: 7-(4,4,5,5-Tetramethyl-1,3,2-dioxaboralan-2-yl)-2,3-dihydro-1,4-benzoazepine-4(5 H)-carbonyl chloride (3 g) was obtained in step 3 was taken into dichloromethane (50 mL) followed by addition of DIPEA (40 mmol, 7 mL) then 4-trifluoromethylpiperidine hydrochloride salt (1.55 g, 8.2 mmol). The mixture was allowed to stir 30 minutes at room temperature then concentrated. The residue was partitioned with ethyl acetate and 5% aqueous citric acid. The organic phase was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated to give 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)-4-{{(4-(trifluoromethyl)piperidin-1-yl)carbonyl}2,3,4,5-tetrahydro-1,4-benzoazepine. MS (EI) for C_{22}H_{30}BF_3N_2O_4Cl: 455 (MH+).

STEP 5: 2-(4-bromophenyl)imidazole (5.3 g, 23.76 mmol) was taken into THF (100 mL) followed by addition of DIPEA (5 mL, 28.5 mmol) and isobutyl chloroformate (3.4 mL, 26.1 mmol) and the resulting solution was stirred for 30 minutes at room temperature. The solution was then concentrated and the residue partitioned with ethyl acetate and water. The organic phase was washed once with 10% aqueous citric acid, brine then dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (2.5:1 hexanes:ethyl acetate) to give isobutyl 2-(4-bromophenyl)-1 H-imidazole-1-carboxylate (3.5 g, 46% yield) as an amorphous residue.

STEP 6: To a solution of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)-4-{{(4-(trifluoromethyl)piperidin-1-yl)carbonyl}2,3,4,5-tetrahydro-1,4-benzoazepine (0.4 g, 0.88 mmol) and isobutyl 2-(4-bromophenyl)-1 H-imidazole-1-carboxylate (0.6 g, 1.86 mmol) in dioxane (4 mL) and water (0.5 mL) was added diisopropylethylamine (0.34 g, 2.64 mmol).
The solution was sparged with \( \text{N}_2(g) \) for ten minutes before the addition of dichloro[1,1-bis-(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (0.072 g, 0.072 mmol)]. The resulting suspension was heated at 120 °C for 2 hours in a sealed tube on a CEM Explorer microwave synthesizer. On cooling to room temperature the mixture was diluted with ethyl acetate (100 mL), washed with saturated sodium bicarbonate (70 mL), brine (50 mL) then dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography (97:3 dichloromethane/methanol) then preparative reverse phase HPLC of the combined product containing fractions (0.1% aqueous ammonium acetate-acetonitrile) to afford 7-[(4-(1H-imidazol-2-yl)phenyl]-4-[(4-(trifluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine (0.058 g, 12% yield) as a white solid. \( ^1\text{H} \) NMR (400 MHz, methanol-\( d_4 \)): 7.92 (d, 2H), 7.70 (d, 2H), 7.58-7.50 (m, 2H), 7.15 (s, 2H), 7.05 (d, 1H), 4.52 (s, 2H), 4.22 (t, 2H), 3.77 (d, 2H), 3.71 (t, 2H), 2.87 (t, 2H), 2.39 (m, 1H), 1.86 (d, 2H), 1.59 (m, 2H); MS (EI) for \( \text{C}_{23}\text{H}_{25}\text{F}_3\text{N}_4\text{O}_2 \): 471 (MH\(^+\)).

Using analogous synthetic techniques and substituting with alternative starting reagents in step 6 and conducting subsequent protecting group removal as required according to literature techniques appropriate for a given protecting group (see for example: Greene and Wuts, Protective Groups in Organic Synthesis, Wiley-Interscience) the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

5-(4-[(4-(trifluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)pyrazin-2-amine. Synthesized according to the method of example 4 using 5-bromopyrazin-2-amine in step 6. \( ^1\text{H} \) NMR (400 MHz, \( d_6 \)-DMSO): 8.43 (d, 1H), 7.92 (d, 1H), 7.78 (d, 1H), 7.70 (dd, 1H), 6.95 (d, 1H), 6.53 (br s, 2H), 4.42 (s, 2H), 4.18 (m, 2H), 3.58 (m, 4H), 2.74 (t, 2H), 1.74 (d, 2H), 1.46 (m, 2H). MS (EI) for \( \text{C}_{29}\text{H}_{32}\text{F}_3\text{N}_5\text{O}_2 \): 422 (MH\(^+\)).

**Synthetic Example 5**

4-[(4-methylpiperidin-1-yl)carbonyl]-7-[(1,3-thiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

STEP 1: A solution of \text{tert}-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[\text{l}][1,4]oxazepine-4(5 \text{ H})-carboxylate (73 mg, 0.19 mol), 5-bromothiazole (40 mg, 0.26 mmol), \text{i}-\text{Bis(diphenylphosphino)}ferrocene dichloropalladium(II) (22 mg, 0.03 mmol) and potassium carbonate (0.14 g, 1.0 mmol) in \( N\text{ N}\)-dimethylacetamide/water 5:1
(5.5 mL) was heated to 90 °C for 1 hour. The cooled reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (30 mL) and brine (20 mL), and then dried over anhydrous sodium sulfate and concentrated. Purified by silica gel column chromatography (ethyl acetate/hexanes, 1:2) to give tert-butyl 7-(thiazol-5-yl)-2,3-dihydrobenzol[1,4]oxazepine-4(5 H)-carboxylate (44 mg, 70% yield). MS (EI) for C_{19}H_{23}N_{3}O_{2}S: 358 (MH+).

[00600] STEP 2: To tert-butyl 7-(thiazol-5-yl)-2,3-dihydrobenzol[1,4]oxazepine-4(5 H)-carboxylate (41 mg, 0.12 mmol) in methanol (5.0 mL) added 4.0 M hydrogen chloride in dioxane (3.0 mL) and the mixture stirred at 25 °C for 20 minutes then concentrated to give 7-(thiazol-5-yl)-2,3,4,5-tetrahydrobenzol[1,4]oxazepine hydrochloride as obtained in step 2 in dichloromethane (20 mL) at -20 °C added 20% phosgene in toluene (0.25 mL, 0.50 mmol) followed by addition of triethylamine (0.35 mL, 25 mmol). The reaction was allowed to warm to 25 °C and stand for 18 h. The mixture was then concentrated to give 7-(thiazol-5-yl)-2,3-dihydrobenzol[1,4]oxazepine-4(5 H)-carbonyl chloride.

[00601] STEP 3: To a suspension of 7-(thiazol-5-yl)-2,3,4,5-tetrahydrobenzol[1,4]oxazepine hydrochloride as obtained in step 2 in dichloromethane (20 mL) at -20 °C added 20% phosgene in toluene (0.25 mL, 0.50 mmol) followed by addition of triethylamine (0.35 mL, 25 mmol). The reaction was allowed to warm to 25 °C and stand for 2 hours. The reaction mixture was concentrated and the residue taken into ethyl acetate (50 mL) then washed with saturated aqueous sodium bicarbonate (25 mL) and brine (20 mL). The organic solution was dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by preparative reverse phase HPLC (0.1% aqueous ammonium acetate-acetonitrile). Pure fractions were concentrated and the residue was taken up in acetonitrile (2 mL) and 4.0 M hydrochloric acid (0.05 mL) then concentrated and dried to afford 4-{[(4-methylpiperidin-1-yl)carbonyl]-7-(1,3-thiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (3.9 mg, 6.5% yield) as the hydrochloride salt. 1H NMR (400 MHz, CDCl₃): 8.83 (br s, 1H), 8.03 (br s, 1H), 7.43 (s, 1H), 7.41 (d, 1H), 7.06 (d, 1H), 4.39 (s, 2H), 4.19 (m, 2H), 3.79-3.60 (m, 4H), 2.76 (t, 2H), 1.65 (d, 2H), 1.56 (br s, 1H), 1.22 (m, 2H), 0.98 (d, 3H); MS (EI) for C_{19}H_{23}N_{3}O_{2}S: 358 (MH+).
Synthetic Example 6

3-{4-[4-(methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl} N-(phenylmethyl)-1 H-pyrazol-5-amine.

[00603] STEP 1: n-Butyllithium (2.5 M in hexane, 2.31 mL, 5.8 mmol) was added to a solution of 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (1.56 g, 4.76 mmol) in tetrahydrofuran (20 mL) and the resulting mixture was stirred at -78 °C for one hour. A solution of N-methoxy-N-methylacetamide (0.97 g, 9.4 mmol) in tetrahydrofuran (5 mL) was added to the reaction mixture dropwise then warmed to room temperature and stirred for an additional hour. Water (50 mL) was added and the resulting mixture was extracted with ethyl acetate (3x 40 mL). The combined organic extract was washed with water, then brine solution (80 mL each), dried over sodium sulfate, filtered, concentrated to give 1,1-dimethylethyl 7-acetyl-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (1.34 g, 97% yield); MS (EI) for C_{16}H_{21}N0_4: 292 (MH+).

[00604] STEP 2: A solution of 1,1-dimethylethyl 7-acetyl-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (1.34 g, 4.60 mmol) in tetrahydrofuran (5 mL) was added to a suspension of sodium hydride (60% oil suspension, 0.80 g, 13.3 mmol) in tetrahydrofuran (20 mL) and the resulting mixture was stirred at room temperature for 5 minutes. Dimethyl carbonate (5 mL) was added and the resulting mixture was stirred at 65 °C for twenty minutes. Then the reaction mixture was cooled, quenched with ice (20 g) and aqueous ammonium chloride (20 mL) then extracted with ethyl acetate (3x 40 mL). The combined organic extract was washed with water, then brine solution (80 mL each), dried over sodium sulfate, filtered, concentrated, and purified by silica gel chromatography (25% ethyl acetate in hexanes) to give 1,1-dimethylethyl 7-[3-(methoxy)-3-oxopropanoyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.94 g, 59% yield); MS (EI) for C_{18}H_{25}N0_4: 350 (MH+).

[00605] STEP 3: A mixture of 1,1-dimethylethyl 7-[3-(methoxy)-3-oxopropanoyl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (300 mg, 0.86 mmol) and benzylamine (92 mg, 0.86 mmol) in o-xylene (3 mL) was stirred at 150 °C for one hour. The reaction mixture was cooled and purified directly by silica gel chromatography (50% ethyl acetate in hexanes) to give 1,1-dimethylethyl 7-[3-oxo-3-[phenylmethyl]amino]propanoyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (220 mg, 60% yield); MS (EI) for C_{24}H_{28}N_2O_5: 425 (MH+).

[00606] STEP 4: A mixture of 1,1-dimethylethyl 7-[3-oxo-3-[phenylmethyl]amino]propanoyl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (180
mg, 0.42 mmol) and Lawesson's reagent (177 mg, 0.44 mmol) in 1,4-dioxane (2 mL) was stirred at 65 °C for two hours. The reaction mixture was cooled and purified directly by silica gel chromatography (25% ethyl acetate in hexanes) to give 1,1-dimethylethyl 7-{3-[phenylmethyl]amino}-3-thioxopropanoyl]-2,3-dihydro-1,4-benzoazepine-4(5 H)-carboxylate (155 mg, 83% yield). MS (EI) for C\textsubscript{24}H\textsubscript{28}N\textsubscript{2}O\textsubscript{4}: 441 (MH\textsuperscript{+}).

**STEP 5:** A mixture of 1,1-dimethylethyl 7-{3-[phenylmethyl]amino}-3-thioxopropanoyl]-2,3-dihydro-1,4-benzoazepine-4(5 H)-carboxylate (155 mg, 0.35 mmol), hydrazine monohydrate (66 mg, 0.59 mmol), acetic acid and Lawesson's reagent (63 mg, 1.0 mmol) in ethanol (5 mL) was stirred at 78 °C for one hour. The reaction mixture was cooled, concentrated and the residue purified directly by silica gel chromatography (5% methanol in dichloromethane) to give 1,1-dimethylethyl 7-[5-{(phenylmethyl)amino]-1 H-pyrazol-3-yl]-2,3-dihydro-1,4-benzoazepine-4(5 H)-carboxylate (92 mg, 62% yield). MS (EI) for C\textsubscript{24}H\textsubscript{28}N\textsubscript{4}O\textsubscript{3}: 421 (MH\textsuperscript{+}).

**STEP 6** A mixture of 1,1-dimethylethyl 7-[5-{(phenylmethyl)amino]-1 H-pyrazol-3-yl]-2,3-dihydro-1,4-benzoazepine-4(5 H)-carboxylate (92 mg, 0.22 mmol) in acetonitrile (2 mL) and 4 M hydrogen chloride in 1,4-dioxane (2 mL) was stirred at 70 °C for 10 minutes. The reaction mixture was allowed to cool then concentrated and the residue suspended in N,N-dimethylformamide (2 mL). Triethylamine (123 mg, 1.21 mmol), then 4-methylpiperidine-l-carbonyl chloride (reagent preparation 37) (35 mg, 0.22 mmol) were added and the resulting mixture was stirred at room temperature for 18 hours. The crude mixture diluted with methanol (6 mL) and purified by preparative reverse phase HPLC to give 3-[4-{(4-methylpiperidin- 1-yl)carbonyl]-2,3,4,5-tetrahydro- 1,4-benzoazepin-7-yl l]-N-(phenylmethyl)-1 H-pyrazol-5-amine (56 mg, 57% yield), (400 MHz, methanol-d\textsubscript{4}): 7.49 (br, 1H), 7.45 (dd, 1H), 7.39 (d, 2H), 7.30 (t, 2H), 7.22 (dd, 1H), 6.96 (d, 1H), 5.81 (s, 1H), 4.43 (s, 2H), 4.33 (s, 2H), 4.17 (m, 2H), 3.66 to 3.59 (m, 4H), 2.80 (t, 2H), 1.67 to 1.50 (m, 3H), 1.24 to 1.12 (m, 2H), 0.96 (d, 3H); MS (EI) for C\textsubscript{26}H\textsubscript{31}N\textsubscript{3}O\textsubscript{2}: 446 (MH\textsuperscript{+}).

**Synthetic Example 7**

3-[4-{(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl l]-N-(phenylmethyl)-1 H-pyrazol-5-amine

**[00609]** A mixture of 3-[4-{(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl l}-N-(phenylmethyl)-1 H-pyrazol-5-amine (example 6) (39 mg, 0.088 mmol), 10% palladium on charcoal (37 mg) and methanol (15 mL) was hydrogenated in a
Parr apparatus at 45 psi for 18 hours. The suspension was filtered, concentrated and the residue purified by preparative reverse phase HPLC to give 3-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}-H-pyrazol-5-amine (17 mg, 55% yield).  

**Synthetic Example 8**

**methyl [6-(4-(fluoromethyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-lH-benzimidazol-2-yl]carbamate**

**STEP 1:** (4-{{1,1-dimethylethyl}oxycarbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (example 1, step 2) (2.22 g, 7.57 mmol) and 4-bromo-2-nitroaniline (1.56 g, 7.20 mmol) were taken into dioxane (20 mL), water (4 mL) and DIPEA (5.4 mL, 31 mmol) followed by addition of dichloro[1,1'-biphenyl-phosphino]ferrocenepalladium (II) dichloromethane adduct (322 mg, 0.39 mmol) and the mixture was heated to 95 °C for 2 h. The mixture was cooled to room temperature and partitioned with ethyl acetate and 10% aqueous citric acid. The biphasic mixture was filtered through a celite pad and the organic filtrate was washed once with 0.5M aqueous hydrochloric acid, brine then dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography to give 1,1-dimethylethyl 7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (2.01 g, 69% yield) as a yellow crystalline solid.

**STEP 2:** 1,1-Dimethylethyl 7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (3.3 g, 8.56 mmol) and 10% palladium on carbon (300 mg) were suspended in ethanol (100 mL) and the mixture was hydrogenated at 50 psi using a Parr apparatus for 12 h. The mixture was filtered through a celite pad and the filtrate concentrated. The residue was taken into acetic acid (25 mL) followed by addition of 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (2.3 g, 11.15 mmol) and the resulting mixture heated to 80 °C for 30 minutes. The mixture was cooled to room temperature then concentrated and partitioned with ethyl ether (60 mL) and dilute aqueous sodium bicarbonate. The biphasic mixture was allowed to stand for several minutes until a precipitate formed. The solid was collected by filtration, washed with water then ethyl ether and dried to give 1,1-dimethylethyl 7-(2-[(methylxoy)carbonyl]amino]-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (69 mg, 55% yield).
benzoxazepine-4(5 H)-carboxylate (2.98 g, 80% yield) as a white solid. MS (EI) for C_{23}H_{26}N_{4}O_{5}: 439 (MH+).

[00612] STEP 3: 1,1-Dimethylethyl 7-(2-{[(methylx)carbonyl] amino }-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (517 mg, 1.18 mmol) was taken into methanol (2 mL) and 4M hydrogen chloride in dioxane (2 mL) and the mixture was allowed to stand at room temperature for 30 minutes. The suspension obtained was diluted with excess ethyl ether and the solid collected by filtration to give methyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-benzimidazol-2-yl]carbamate dihydrochloride salt (462 mg, 95% yield) as a white solid. MS (EI) for C_{18}H_{18}N_{4}O_{3}: 339 (MH+).

[00613] STEP 4: Methyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-benzimidazol-2-yl]carbamate dihydrochloride salt (51.7 mg, 0.13 mmol) was taken into DMF (1 mL) and dichloromethane (1 mL) followed by addition of DIPEA (88 uL, 0.52 mmol) and the mixture was cooled to 0 °C. 4-(Fluoromethyl)piperidine-1-carbonyl chloride (reagent preparation 37) (33 mg, 0.13 mmol) was added to the mixture in a minimum of dichloromethane then stirred for 30 minutes. The mixture was partitioned with ethyl acetate and water and the organic phase washed twice with water, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (4:1 ethyl acetatemethanol to give methyl [6-(4-{[4-(fluoromethyl)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-benzimidazol-2-yl]carbamate (40.3 mg, 66% yield) as a white solid. H NMR (400 MHz, d_{6}-DMSO): 7.58 (s, 1H), 7.47 (s, 1H), 7.45-7.42 (m, 2H), 7.31 (dd, 1H), 7.02 (d, 1H), 4.42 (s, 2H), 4.37 (d, 1H), 4.26 (d, 1H), 4.17 (br s, 1H), 3.77 (s, 3H), 3.60 (br m, 4H), 2.75 (tr, 2H), 1.85 (br, 1H), 1.63 (d, 2H), 1.25 (q, 2H). MS (EI) for C_{25}H_{28}FN_{5}O_{4}: 483 (MH+).

[00614] Using analogous synthetic techniques and substituting with alternative starting reagents in step 4 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00615] methyl [6-(4-{[2-(4-fluorophenyl)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-benzimidazol-2-yl]carbamate. Synthesized according to the method of example 8 using 2-(4-fluorophenyl)-piperidine-l-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, d_{6}-DMSO): 11.70 (br s 1H), 7.57 (d, 1H), 7.45 (m, 2H), 7.40 (d, 1H), 7.28-7.22 (m, 3H), 7.08-7.01 (m, 3H), 4.59 (m, 1H), 4.52 (dd, 2H), 4.14 (m, 2H), 3.76 (s, 3H), 3.63 (t, 2H), 3.22 (m, 1H), 3.02 (m, 1H), 1.98 (m, 1H), 1.79 (m, 1H), 1.57 (m, 2H), 1.48 (m, 2H). MS (EI) C_{30}H_{30}FN_{5}O_{4}: 544 (MH+).
methyl \([6-(4-{[2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl})-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l\)H-benzimidazol-2-yl]carbamate. Synthesized according to the method of example 8 using 2-(3-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. \(^1\)H NMR (400 MHz, d6-DMSO): 11.58 (br d, IH), 7.55 (d, IH), 7.50 (d, IH), 7.42 (dd, IH), 7.41 (d, IH), 7.27 (m, 2H), 7.11-7.02 (m, 3H), 6.99 (d, IH), 5.19 (t, IH), 4.56 (s, 2H), 4.18 (m, 2H), 3.76 (s, 3H), 3.66 (m, 4H), 2.82 (m, 2H), 2.58 (m, IH), 2.31 (m IH). MS (EI) for C\(_{37}\)H\(_{48}\)FN\(_2\)O\(_5\): 558 (MH\(^+\)).

methyl \([6-(4-{[2-(4-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl})-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l\)H-benzimidazol-2-yl]carbamate. Synthesized according to the method of example 8 using 2-(4-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. \(^1\)H NMR (400 MHz, d6-DMSO): 7.58 (d, IH), 7.51 (s, IH), 7.44 (dd, 2H), 7.30-7.26 (m, 3H), 7.04 (q, 3H), 5.20 (tr, IH), 4.57 (dd AB, 2H), 4.26-4.16 (m, 2H), 3.76 (s, 3H), 3.71-3.65 (m, 3H), 3.34-3.28 (m, IH), 2.86 (d q, 2H), 2.65-2.57 (m, IH), 2.30 (d, IH). MS (EI) for C\(_{39}\)H\(_{49}\)F\(_2\)N\(_2\)O\(_5\): 559 (MH\(^+\)).

methyl \([6-(4-{[4-(fluoromethyl)-4-hydroxypiperidin-1-yl]carbonyl})-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l\)H-benzimidazol-2-yl]carbamate. Synthesized according to the method of example 8 using 4-(fluoromethyl)-4-hydroxypiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, d6-DMSO): 7.69 (d, IH), 7.58 (d, IH), 7.50 (d, IH), 7.49 (dd, IH), 7.44 (dd, IH), 7.03 (d, IH), 4.44 (s, 2H), 4.19 (br s, 2H), 4.16 (d, 2H), 3.84 (s, 3H), 3.60 (br s, 2H), 3.36 (d, 2H), 3.07 (tr, 2H), 2.71 (dd, IH), 1.56 (d tr, 2H), 1.43 (d, 2H). MS (EI) for C\(_{29}\)H\(_{28}\)FN\(_2\)O\(_5\): 499 (MH\(^+\)).

methyl \([6-(4-{[2-(3,4-difluorophenyl)-4-oxopiperidin-1-yl]carbonyl})-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l\)H-benzimidazol-2-yl]carbamate. Synthesized according to the method of example 8 using 2-(3,4-difluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, d6-DMSO): 7.58 (s, IH), 7.53 (s, IH), 7.44 (d, 2H), 7.35-7.25 (m, 3H), 7.11 (br, IH), 7.01 (d, IH), 5.16 (tr, IH), 4.58 (dd AB, 2H), 4.26-4.15 (m, 2H), 3.76 (s, 3H), 3.73-3.63 (m, 3H), 3.45 (m, IH), 2.83 (d, 2H), 2.64-2.55 (m, IH), 2.35 (d, IH). MS (EI) for C\(_{39}\)H\(_{47}\)F\(_2\)N\(_2\)O\(_5\): 578 (MH\(^+\)).

**Synthetic Example 9**

(±)-methyl \([5-(4-[[2R,4S]-2-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l\)H-benzimidazol-2-yl]carbamate

**STEP 1:** Methyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-lH-benzimidazol-2-yl]carbamate dihydrochloride salt (example 8, step 3) (503 mg, 1.2 mmol) was suspended
in dichloromethane (15 mL) followed by addition of DDPEA (1.2 mL, 6.9 mmol) and the mixture was stirred for 5 minutes. Phosgene (20 W% in toluene, 0.7 mL, 1.3 mmol) was then added and the mixture was stirred at room temperature an additional 1h. The mixture was then concentrated and partitioned with ethyl acetate and 10% aqueous citric acid. The bisphasic mixture was filtered and the organic filtrate was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. The residue thus obtained was triturated with ethyl ether and the resulting suspension was filtered and the filter cake washed with additional ethyl ether and dried to give methyl 5-[4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l H-benzimidazol-2-carboxylate (133 mg, 27 % yield) as a light tan solid that was carried forward without further purification. MS (EI) for C_{19}H_{17}Cl_{1}N_{4}O_{4}: 401 (MHT).

[00621] STEP 2: Methyl 5-[4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l H-benzimidazol-2-carboxylate (133 mg, 0.33 mmol) as obtained in step 1 was taken in to N,N-dimethylacetamide (1 mL) followed by addition of DIPEA (0.23 mL, 1.32 mmol) and racemic (2R,4S)-2-(4-fluorophenyl)piperidin-4-ol hydrochloride salt (reagent preparation 28) (75.5 mg, 0.33 mmol) and the mixture was stirred for 1h at room temperature. Racemic (2R,4S)-2-(4-fluorophenyl)piperidin-4-ol hydrochloride salt (80 mg) was added to the mixture at this point and the mixture was stirred an additional 1h followed then by addition of another aliquot of the piperidine reagent (56 mg) and the mixture was allowed to stir an additional 12h. The mixture was partitioned with ethyl acetate and 10% aqueous citric acid. The bisphasic mixture was filtered and the organic filtrate was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. The residue was chromatographed on silica gel (7.5% ethanol in ethyl acetate) to give 26 mg of residue after concentration of product containing fractions. Purification of the residue by preparative reverse phase HPLC afforded (±)-methyl 5-[4-{[(2R,4S)-2-(4-fluorophenyl)-4-hydroxypiperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l H-benzimidazol-2-yl] carbamate (6.4 mg) as a colorless solid. H NMR (400 MHz, d_{4}-methanol): 7.68 (s, IH), 7.56 (s, 2H), 7.45 (s, IH), 7.43 (d, IH), 7.02-6.96 (m, 3H), 6.65 (t, 2H), 4.60 (dd AB, 2H), 4.04 (m, 2H), 3.92 (dd, IH), 3.86 (s, 3H), 3.81 (br, IH), 3.69-3.63 (m, 2H), 3.40-3.36 (m, IH), 2.75 (tr, IH), 1.94-1.88 (m, 2H), 1.44 (q, IH).. MS (EI) for C_{29}H_{29}F_{6}N_{4}O_{3}: 502 (MH^+).

**Synthetic Example 10**

**methyl 6-[4-{4-hydroxy-4-[3-(trifluoromethyl)phenyl)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-l H-benzimidazol-2-yl] carbamate**
STEP 1: A solution of 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carbonyl chloride (example 2) (0.400 g, 1.38 mmol), 4-(3-(trifluoromethyl)phenyl)piperidin-4-ol (0.371 g, 1.51 mmol), and diisopropylethylamine (0.535 g, 4.14 mmol) in dichloromethane (3 mL) was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate (50 mL), washed with 10% citric acid (20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate. Filtration and concentration afforded 1-[(7-bromo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-4-[3-(trifluoromethyl)phenyl]piperidin-4-ol (0.688 g, 100%) as a white solid that was used without further purification. MS (EI) for C_{22}H_{22}BrF_{3}N_{2}O_{3}: 500 (MH^+).

STEP 2: To a solution of 1-[(7-bromo-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-4-[3-(trifluoromethyl)phenyl]piperidin-4-ol (0.200 g, 1.38 mmol) and 2-nitro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.365 g, 1.38 mmol) in dioxane (24 mL) and water (3.00 mL) was added tribasic potassium phosphate (0.413 g, 1.79 mmol). The solution was sparged with N_{2}(g) for ten minutes before the addition of dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium] (II) dichloromethane adduct (0.023 g, 10 mol%). The resulting suspension was heated at 90 °C for 2 hours in a sealed tube vessel. On cooling to room temperature the mixture was diluted with ethyl acetate (50 mL), washed with water (50 mL) and then dried over anhydrous sodium sulfate. Filtration and concentration afforded a crude orange oil that was purified by silica gel chromatography (7:3 hexanes/ethyl acetate) to provide 1-[(7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-4-[3-(trifluoromethyl)phenyl]piperidin-4-ol (0.200 g, 26% yield) as an orange oil. MS (EI) for C_{28}H_{27}F_{3}N_{4}O_{3}: 557 (MH^+).

STEP 3: To a solution of 1-[(7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-4-[3-(trifluoromethyl)phenyl]piperidin-4-ol (0.200 g, 0.359 mmol) in methanol (40 mL) was added 10% palladium on carbon (0.200 g). The solution was sparged with N_{2}(g) for five minutes before being placed on a Parr shaker and degassed. The resulting suspension was shaken for 3 hours under H_{2}(g) at 30 psi. Filtration and concentration afforded 1-[(7-(3,4-diaminophenyl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-1-[3-(trifluoromethyl)phenyl]piperidin-4-ol (0.156 g, 84% yield) as crude brown oil that was used without further purification. MS (EI) for C_{28}H_{29}F_{3}N_{4}O_{3}: 527 (MH^+).

STEP 4: To a solution of 1-[(7-(3,4-diaminophenyl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-1-[3-(trifluoromethyl)phenyl]piperidin-4-ol (0.156 g, 0.148 mmol) in glacial acetic acid (3 mL) was added 1,3-bis(methoxycarbonyl)-2-methyl-2-
thiopseudoura (0.040 g, 0.193 mmol). The reaction mixture was stirred at 80 °C for 3 h and then concentrated. Ethan ace tate (50 mL) was added to the residue, and the solution was washed with saturated sodium bicarbonate (50 mL) and then dried over anhydrous sodium sulfate. Filtration and concentration afforded a brown residue that was purified by silica gel chromatography (95:5 dichloromethane/methanol). Product containing fractions were combined and concentrated and the residue taken up in a 1:1 solution of methanol and acetonitrile (4 mL). The resulting precipitate was collected by filtration, washed with diethyl ether and dried to give methyl 6-[4-{4-(4-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate (0.042 g, 52% yield) as a white solid. H NMR (400 MHz, d_6-DMSO): 12.01-11.77 (br s, 1H), 11.43-11.19 (br s, IH), 7.38-7.84 (s, IH), 7.80-7.76 (d, IH), 7.62-7.52 (m, 4H), 7.46-7.39 (m, 2H), 7.33-7.29 (d, IH), 7.03-6.99 (d, IH), 5.33-5.31 (s, IH), 4.50-4.47 (s, 2H), 4.22-4.17 (s, 2H), 3.77-3.74 (s, 3H), 3.67-3.62 (s, 2H), 3.52-3.45 (d, 2H), 3.25-3.15 (t, 2H), 2.06-1.95 (t, 2H), 1.63-1.55 (d, 2H); MS (EI) for C_{29}H_{24}F_{2}N_{6}O_{2}^+: 610 (MH^+).

[00626] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00627] methyl 6-[4-[(4-difluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate. Prepared according to the method of example 10 by using 4-(difluoromethyl)piperidine (reagent preparation 6) in step 1. H NMR (400 MHz, DMSO-d_6): 11.72 (br s, IH), 7.58 (s, IH), 7.48 (s, IH), 7.43 (d, 2H), 7.31 (d, IH), 7.00 (d, IH), 5.93 (m, IH), 4.43 (s, 2H), 4.17 (m, 2H), 3.76 (s, 3H), 3.60 (m, 4H), 2.75 (m, 2H), 1.99 (m, IH), 1.65 (m, 2H), 1.36 (m, 2H); MS (EI) for C_{29}H_{24}F_{2}N_{6}O_{2}^+: 500 (MH^+).

Synthetic Example 11

Methyl 6-[4-[(4-cyanopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate

STEP 1: 1,1-dimethylethyl 7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (example 8, step 1) (6.0 g, 15.6 mmol) was taken into warm methanol (50 mL) followed by addition of 4M hydrogen chloride in dioxane (50 mL) in portions and the warm solution was allowed to slowly cool to room temperature over lh. The mixture was diluted with ethyl ether (100 mL) and the yellow solid was collected by filtration and dried to give 2-nitro-4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)aniline hydrochloride salt (3.61 g, 72% yield) as a yellow solid. H NMR (400 MHz, D_2O): 7.79 (s,
1H), 7.44 (d, 1H), 7.29 (s, 1H), 7.26 (d, 1H), 7.02 (d, 1H), 6.82 (d, 1H), 4.34 (s, 2H), 4.32 (br m, 2H), 3.67 (br m, ... The aqueous mixture was then partitioned with hexanes then filtered. The filter cake was washed with water then hexanes

[00628] STEP 2: 2-nitro-4-(2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)aniline hydrochloride salt (3.61 g, 11.2 mmol) and DEPEA (5.2 mL, 30 mmol) were taken into dichloromethane (50 mL) followed by dropwise addition of allyl chloroformate (1.23 mL, 11.2 mmol) over 5 minutes. The mixture was allowed to stir 30 minutes at room temperature then concentrated. The residue was partitioned with ethyl acetate and 10% aqueous citric acid and the organic solution washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated to give prop-2-en-1-yl 7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoazepine-4(5 H)-carboxylate (4.2 g, 100% yield) as a red amorphous residue. MS (EI) for C₂₇H₂₉N₅O₅: 370 (MH⁺).

[00629] STEP 3: Prop-2-en-1-yl 7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoazepine-4(5 H)-carboxylate (4.2 g, 11.2 mmol) was taken into glacial acetic acid (25 mL) and the solution was warmed to 45°C. Tin (II) chloride (8.51 g, 44.8 mmol) was added in portions over 5 minutes and the mixture was allowed to stir at this temperature for 6h. The mixture was then cooled to room temperature and diluted with MTBE (100 mL). 50% aqueous sodium hydroxide was then added in small portions with stirring until complete precipitation of tin salts occurred. Anhydrous sodium sulfate was then added in portions until the precipitated salts formed a fine granular solid and the mixture was filtered. The filter cake was washed with additional MTBE and the combined organic filtrate was concentrated. The residue was partitioned with ethyl acetate and saturated aqueous sodium bicarbonate. 50% aqueous sodium hydroxide was added to the biphasic mixture in portions until the aqueous pH was 9-10. The layers were then separated and the organic solution washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated to provide prop-2-en-1-yl 7-(3,4-diaminophenyl)-2,3-dihydro-1,4-benzoazepine-4(5 H)-carboxylate (2.7 g, 71% yield) as a yellow solid. MS (EI) for C₂₇H₂₉N₅O₅: 340 (MH⁺).

[00630] STEP 4: Prop-2-en-1-yl 7-(3,4-diaminophenyl)-2,3-dihydro-1,4-benzoazepine-4(5H)-carboxylate (2.7 g, 7.96 mmol) was taken into glacial acetic acid (15 mL) followed by addition of 1,3-(dimethoxycarbonyl)-2-methyl-2-thiopseudourea (1.81 g, 8.8 mmol) and the mixture was heated to 80°C for 30 minutes then concentrated to a thick residue. The residue was treated with saturated aqueous sodium bicarbonate and the aqueous mixture basified with portionwise addition of solid sodium bicarbonate with pH 8-9. The aqueous mixture was then partitioned with hexanes then filtered. The filter cake was washed with water then hexanes
and dried to give prop-2-en-l-yl 7-(2-[[methyloxy]carbonyl]amino)-1 H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (3.46 g, 100% yield) as a pale yellow solid.

[00631] STEP 5: Prop-2-en-l-yl 7-(2-[[methyloxy]carbonyl]amino)-1 H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (3.46 g, 7.96 mmol) was suspended in THF (75 mL) followed by addition of di-tert-butyl dicarbonate (4.3 g, 19.9 mmol) and pyridine (2 mL, 23.9 mmol). The mixture was stirred at room temperature 1h then warmed to reflux for an additional hour. The solution was then cooled to room temperature and concentrated. The residue was partitioned with ethyl acetate and 10% aqueous citric acid and the organic solution washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (ethyl acetate:hexanes 1:1) to provide N,N'-di-BOC prop-2-en-l-yl 7-(2-[[methyloxy]carbonyl]amino)-1 H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (3.3 g, 67% yield) as an impure amorphous residue. MS (EI) for C_{32}H_{38}N_{4}O_{9}: 624 (MH^+).

[00632] STEP 6: W-di-BOC prop-2-en-l-yl 7-(2-[[methyloxy]carbonyl] amino)-1H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (3.3 g, 5.3 mmol) was taken into THF (30 mL) followed by addition of sodium triacetoxyborohydride (5.6 g, 26.5 mmol) and palladium tetrakis-triphenylphosphine (612 mg) and the mixture was stirred for 30 minutes at room temperature. The mixture was concentrated and the residue partitioned with chloroform and saturated aqueous sodium bicarbonate. The biphasic mixture was saturated with solid sodium chloride and the aqueous phase extracted twice with chloroform. The combined organic solution was then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (100% ethyl acetate to 10% methanol in chloroform) to afford N,N'-di-BOC methyl [5-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-benzimidazol-2-yl] carbamate (830 mg, 29% yield) as an amorphous residue. MS (EI) for C_{38}H_{34}N_{4}O_{7}: 540 (MH^+).

[00633] STEP 7: To a solution of triphosgene (137 mg, 0.56 mmol) in THF (5 mL) was added a solution of N,N'-di-BOC methyl [5-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-benzimidazol-2-yl] carbamate (830 mg, 1.54 mmol), DIPEA (0.4 mL, 2.3 mmol) and pyridine (15 uL, 0.15 mmol) in THF (10 mL) in a dropwise manner over 5 minutes. The mixture was stirred an addition 10 minutes then concentrated. The residue was partitioned with ethyl acetate and 10% aqueous citric acid and the organic solution washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was chromatographed.
on silica gel (ethyl acetate:hexanes 2:3) to provide N,N’-di-BOC methyl [5-[4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl]carbamate (384 mg, 41% yield). MS (EI) for C_{29}H_{33}C_{11}N_{9}O_{9}: 602 (MH^+).

**[00634]** STEP 8: A mixture of N,N’-di-BOC methyl [5-[4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl]carbamate (40 mg, 0.07 mmol), 4-cyanopiperidine hydrochloride (20 mg, 0.14 mmol), and diisopropylethylamine (0.13 mL, 0.14 mmol), in dichloromethane (2 mL) was stirred at room temperature for one hour. The mixture was concentrated and purified directly by silica gel chromatography (0-15% methanol-dichloromethane) to give N,N’-di-BOC methyl [6-[(4-cyanopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl]carbamate as an amorphous residue.

**[00635]** STEP 9: A solution of N,N’-di-BOC methyl [6-[(4-cyanopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl]carbamate as obtained in step 8 was taken into trifluoroacetic acid (0.2 mL) and dichloroethane (1.8 mL) was stirred at room temperature for one hour. The reaction mixture was concentrated and purified by preparative reverse phase HPLC to give methyl [6-[(4-cyanopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl]carbamate (4.6 mg) as an amorphous solid.

H NMR (400 MHz, methanol-d4): 7.57 (br, 1H), 7.51 (br, 1H), 7.43 (dd, 2H), 7.31 (dd, 1H), 7.01 (d, 1H), 4.44 (s, 2H), 4.17 (m, 2H), 3.75 (s, 3H), 3.59 (m, 2H), 3.40 to 3.27 (m, 2H), 3.10 to 2.96 (m, 3H), 1.93 to 1.86 (m, 2H), 1.79 to 1.69 (m, 2H); MS (EI) for C_{25}H_{26}N_{9}O_{4}: 475 (MH^+).

**[00636]** Using analogous synthetic techniques and substituting with alternative starting reagents in step 8 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

**[00637]** Methyl [6-4-{[3-(e-i/o)-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(en<io)-ol]carbonyl }-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl]carbamate. Prepared according to the method of example 11 by using 3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(en<io)-ol hydrochloride (reagent preparation 15) in step 8. H NMR (400 MHz, methanol-d4): 7.60 (br, 1H), 7.48 to 7.43 (m, 3H), 7.37 (dd, 1H), 7.02 (d, 1H), 4.58 (s, 2H), 4.22 (m, 2H), 4.16 (br, 2H), 3.85 (s, 3H), 3.75 (m, 2H), 2.21 to 2.11 (m, 4H), 1.92 to 1.85 (m, 2H), 1.79 (d, 2H); MS (EI) for C_{27}H_{29}F_{3}N_{5}O_{5}: 560 (MH^+).

**[00638]** Methyl [6-4-{[4-hydroxy-4-(trifluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl]carbamate. Prepared according to
the method of example 11 by using 4-(trifluoromethyl)piperidin-4-ol hydrochloride (reagent preparation 24) in step 8. **H** NMR (400 MHz, methanol-d$_4$): 7.61 (d, IH), 7.52 (d, IH), 7.48 to 7.44 (m, 2H), 7.38 (dd, IH), 7.02 (d, IH), 4.51 (s, 2H), 4.20 (m, 2H), 3.85 (s, 3H), 3.70 (m, 2H), 3.61 (d, 2H), 3.18 (dd, 2H), 1.84 (dt, 2H), 1.70 (d, 2H); MS (EI) for C$_{5}$H$_{12}$F$_{3}$N$_{5}$O$_{5}$: 534 (MH$^+$).

[00639] 1-[[7-(2-amino-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-4-methylpiperidin-4-ol. Prepared according to the method of example 11 by using 4-methylpiperidin-4-ol (reagent preparation 5) in step 8. Isolated as a co-product in step 9. **H** NMR (400 MHz, methanol-d$_4$): 7.46 (d, IH), 7.44 to 7.41 (m, 2H), 7.32 (dd, IH), 7.28 (d, IH), 7.02 (d, IH), 4.48 (s, 2H), 4.19 (m, 2H), 3.68 (m, 2H), 3.43 to 3.21 (m, 4H), 1.66 to 1.53 (m, 4H), 1.23 (s, 3H); MS (EI) for C$_{23}$H$_{27}$N$_{5}$O$_{3}$: 422 (MH$^+$).

[00640] Methyl (6-{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl)carbamate. Prepared according to the method of example 11 by using 4-methylpiperidin-4-ol hydrochloride (reagent preparation 5) in step 8. **H** NMR (400 MHz, methanol-d$_4$): 7.43 (d, IH), 7.48 to 7.44 (m, 3H), 7.38 (dd, IH), 7.03 (d, IH), 4.48 (s, 2H), 4.19 (m, 2H), 3.85 (s, 3H), 3.64 (m, 2H), 3.43 to 3.22 (m, 4H), 1.67 to 1.53 (m, 4H), 1.23 (s, 3H); MS (EI) for C$_{25}$H$_{29}$N$_{5}$O$_{5}$: 480 (MH$^+$).

[00641] Methyl (6-{4-[3-oxo-8-azabicyclo[3.2.1]octan-3-one]-carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl)carbamate. Prepared according to the method of example 11 by using 8-azabicyclo[3.2.1]octan-3-one hydrochloride in step 8. **H** NMR (400 MHz, methanol-d$_4$): 7.60 (br, IH), 7.53 (br, IH), 7.47-7.43 (m, 2H), 7.37 (d, IH), 7.04 (d, IH), 4.68 (s, 2H), 4.38 to 4.31 (m, 2H), 4.28 to 4.20 (m, 2H), 3.87 (s, 3H), 3.86 to 3.84 (m, 2H), 2.86 (dd, 2H), 2.30 (d, 2H), 2.08-2.01 (m, 2H), 1.70 to 1.63 (m, 2H); MS (EI) for C$_{26}$H$_{27}$N$_{5}$O$_{5}$: 490 (MH$^+$).

**Synthetic Example 12**

6-(4-[(4-fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-amine

[00642] STEP 1: To a solution of methyl [6-(4-[(4-fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl]carbamate (example 8) (181 mg, 0.38 mmol, in methanol (6 mL) was added a 2 M aqueous solution of potassium hydroxide (6 mL), and the resulting mixture was stirred at 65 °C overnight. The pH was adjusted to 9 with 1 N aqueous hydrochloric acid, ethyl acetate was added (50 mL), and the organic layer was washed with brine (2 x 25 mL), dried over sodium sulfate, filtered
and concentrated. Purification by preparative reverse phase HPLC (0.1% aqueous ammonium acetate-acetonitrile) provided the title compound as the acetate salt (56 mg, 31% yield) as a colorless solid. H NMR (400 MHz, methanol-d₄): 7.47 (m, 1H), 7.43 (m, 2H), 7.30 (m, 2H), 7.02 (d, 1H), 4.48 (s, 2H), 4.29 (dd, 2H), 4.19 (m, 2H), 3.71 (m, 4H), 2.85 (m, 2H), 1.95 (s, 3H), 1.87 (m, 1H), 1.72 (m, 2H), 1.36 (m, 2H); MS (EI) for C₂₃H₂₆FN₅O₂: 424 (MH⁺).

**Synthetic Example 13**

1-[[7-(2-amino-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-2-(3,4-difluorophenyl)piperidin-4-one

[00643] STEP 1: A solution of 1,1-dimethylethyl 7-(4-amino-3-nitrophenyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (example 8, step 1) (2.3 g, 6.0 mmol), in acetic acid (20 mL) and ethyl acetate (20 mL) was hydrogenated at 45 psi over 10% Pd-C (1.0 g) for 1 h using a Parr apparatus. The catalyst was filtered off and the filtrate was concentrated to give 1,1-dimethylethyl 7-(3,4-diaminophenyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (2.0 g, 94% yield) as a light yellow oil. MS (EI) for C₂₀H₂₃N₅O₃: 356 (MH⁺).

[00644] STEP 2: To a solution of 1,1-dimethylethyl 7-(3,4-diaminophenyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (2.0 g, 5.6 mmol) in acetic acid (20 mL) was added 1,3-bis(benzyloxycarbonyl)-2-methyl-2-thiopseudourea (2.4 g, 6.7 mmol) and the resulting mixture was heated (60 °C). After 12 h the reaction mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was then washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography on silica (0 to 50% ethyl acetate/hexanes) provided 1,1-dimethylethyl 7-[2-(((phenylmethyl)oxy]carbonyl)amino]-1H-benzimidazol-6-yl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (1.3 g, 45% yield) as a brown solid. MS (EI) for C₂₀H₂₀N₄O₅: 515 (MH⁺).

[00645] STEP 3: TFA (3 mL) was added to 1,1-dimethylethyl 7-[2-(((phenylmethyl)oxy]carbonyl)amino]-1H-benzimidazol-6-yl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.95 g, 1.9 mmol) and the resulting solution was heated (50 °C). After 1 h the reaction mixture was concentrated and azeotroped with ethyl acetate (3x 30 mL) to afford phenylmethyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-benzimidazol-2-yl] carbamate bis-trifluoroacetate salt (0.48 g, 49% yield) as a brown solid. MS (EI) for C₂₄H₂₂N₄O₃F₂: 415 (MH⁺).

[00646] STEP 4: To a solution of phenylmethyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-benzimidazol-2-yl]carbamate bis-trifluoroacetate salt (0.40 g, 0.95 mmol) and
DBPEA (0.66 mL, 3.8 mmol) in DMF (3 mL) was added 2-(3,4-difluorophenyl)-4-oxopiperidine-l-carbonyl chloride (reagent preparation 37) (0.26 g, 0.95 mmol), and the resulting mixture was heated (50 °C). After 2 h, the reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Column chromatography on silica with 1-10% (8% reagent ammonium hydroxide in methanol):dichloromethane yielded phenylmethyl [6-(4-{2-(3,4-difluorophenyl)-4-oxopiperidin-1-yl} carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1 H-benzimidazol-2-yl] carbamate (0.35 g, 57% yield) as a waxy solid. MS (El) for C_{36}H_{31}F_{2}N_{5}O{5}: 652 (MH+).

STEP 5: A solution of phenylmethyl [6-(4-{2-(3,4-difluorophenyl)-4-oxopiperidin-1-yl} carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-H-benzimidazol-2-yl] carbamate (0.11 g, 0.17 mmol) in acetic acid (5 mL) was hydrogenated at 1 atm over 10% Pd-C (0.1 g) for 2 h. The catalyst was filtered off and the filtrate was concentrated. The resulting brown residue was dissolved in methanol and purified by preparative reverse phase HPLC to afford 1-{[7-(2-amino-1 H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl} carbonyl]-2-(3,4-difluorophenyl)piperidin-4-one (0.007 g, 8% yield) as a pale yellow solid. H NMR (400 MHz, CDC13): 7.02-7.29 (m, 8H), 6.98 (d, 1H), 6.94 (d, 1H), 5.27 (t, 1H), 4.43-4.46 (m, 2H), 4.16-4.30 (m, 2H), 3.70-3.85 (m, 3H), 3.21-3.31 (m, 1H), 2.79-2.99 (m, 2H), 2.51-2.61 (m, 1H), 2.32 (d, 1H); MS (El) for C_{28}H_{25}F_{2}N_{5}O_{3}: 518 (MH+).

Using analogous synthetic techniques and substituting with alternative starting reagents in step 4 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

1-{[7-(2-amino-1 H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl} carbonyl]-2-(3-fluorophenyl)piperidin-4-one. Synthesized according to the method of example 13 using 2-(3-fluorophenyl)-4-oxopiperidine-l-carbonyl chloride in step 4. H NMR (400 mHz, DMSO-d6): δ 6.85-7.30 (m, 10H), 5.33 (t, 1H), 4.50 (s, 2H), 4.16-4.31 (m, 2H), 3.73-3.86 (m, 3H), 3.23 (t, 1H), 2.82-3.01 (m, 2H), 2.52-2.65 (m, 1H), 2.31 (d, 1H); MS (El) for C_{28}H_{26}FN_{5}O_{3}: 500 (MH+).

Synthetic Example 14

1-{[7-(2-[2-fluoroethyl]amino]-Lff-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl} carbonyl]-2-(3-fluorophenyl)piperidin-4-one

STEP 1: 2-Fluoroethylamine hydrochloride salt (282.4 mg, 2.83 mmol) was suspended in 1:1 THF:DCM (6 mL) followed by addition of DIPEA (2.5 mL, 14.35 mmol).
The mixture was cooled to 0 °C followed by slow addition of thiophosgene (217 uL, 2.8 mmol) by syringe over five minutes then allowed to slowly warm to room temperature over 30 minutes. 4-Bromobenzene-1,2-diamine (530 mg, 2.8 mmol) was then added and the reaction mixture was allowed to stir at room temperature over an additional 12 h. The mixture was concentrated and the residue partitioned with ethyl acetate and 10% aqueous citric acid. The organic phase was washed twice with additional 10% aqueous citric acid then brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude mixture of thiourea thus obtained was taken into THF (15 mL) followed by addition of mercury (II) oxide (640 mg, 2.95 mmol). The mixture was brought to reflux for 6 h then stirred an additional 60 h at room temperature. The crude mixture was filtered through a bed of celite with ethyl acetate washing and the filtrate concentrated then taken back into ethyl acetate. The organic solution was washed once with 1M aqueous hydrochloric acid and the organic phase discarded. The aqueous phase was filtered to remove trace insoluble residue and the filtrate basified to pH 9-10 by dropwise addition of 50% aqueous sodium hydroxide. The aqueous phase was then extracted once with ethyl acetate and the organic solution was washed with brine then dried over anhydrous sodium sulfate, filtered and concentrated to afford crude 5-bromo-N-(2-fluoroethyl)-IH-benzo[d]imidazol-2-amine (390 mg, 53% yield) which was carried forward without further purification. MS (EI) for C$_9$H$_9$BrFN$_3$: 258, 260 (MH$^+$).

STEP 2: 5-bromo-N-(2-fluoroethyl)-IH-benzo[d]imidazol-2-amine (390 mg, 1.51 mmol) thus obtained in step 1 was taken into THF (15 mL) followed by addition of DIPEA (600 uL, 3.4 mmol) and isobutyl chloroformate (400 uL, 3.06 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was concentrated and the residue partitioned with ethyl acetate and 10% aqueous citric acid. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography to afford isobutyl 5-bromo-2-(2-fluoroethylamino)-IH-benzo[d]imidazole-1-carboxylate (290 mg, 54% yield) as a colorless crystalline solid. MS (EI) for C$_4$H$_7$BrFN$_3$O$_2$: 358, 360 (MH$^+$).

STEP 3: Isobutyl 5-bromo-2-(2-fluoroethylamino)-IH-benzo[J]imidazole-1-carboxylate (55 mg, 0.15 mmol) and (4-{{[(1,l-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)borynic acid (example 1, step 2) (50 mg, 0.17 mmol) were taken into dioxane (1 mL) and water (0.2 mL) followed by addition of dichloro[l,l-bis-(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (8.5 mg) and DIPEA (0.11 mL, 0.6 mmol) and the mixture was heated to 85 °C for 12 h. The mixture was then
cooled and diluted with ethyl acetate then dried over anhydrous sodium sulfate and filtered through a plug of silica gel with an ethyl acetate wash. The organic solution was then concentrated to an oil. The residue was taken into THF (2 mL) followed by sequential addition of DIPEA (0.05 mL, 0.29 mmol) and isobutyl chloroformate (0.01 mL, 0.08 mmol) then the mixture was stirred for 30 minutes. The mixture was concentrated and the residue purified by silica gel chromatography (1.5:1 hexanes:ethyl acetate) to give 1,1-dimethylethyl 7-(2-[(2-fluoroethyl)amino]-l-[(2-methylpropyl)oxy]carbonyl]-IH-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (59.4 mg, 75% yield) as a colorless amorphous residue. MS (EI) for C_{28}H_{53}FN_{4.5}: 528 (MH^+).

**STEP 4** 1,1-Dimethylethyl 7-(2-[(2-fluoroethyl)amino]-l-[(2-methylpropyl)oxy]carbonyl]-IH-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (59.4 mg, 0.11 mmol) was taken into neat TFA (1 mL) and allowed to stand for 1 h at room temperature then concentrated and dried. The residue was taken into THF (5 mL) followed by addition of DIPEA (0.2 mL, 1.1 mmol) followed by addition of 2-(3-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) (29 mg, 0.11 mmol) in a minimum of THF and the resulting solution was stirred at room temperature for 30 minutes. The mixture was then concentrated and taken up into methanol (5 mL) followed by addition of solid potassium carbonate (80 mg, 0.56 mmol) and stirring was continued for 30 minutes. The mixture was then concentrated and partitioned with ethyl acetate and brine. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated. The residue thus obtained was triturated with ethyl ether and the solid collected by filtration and dried to afford 1-{7-[2-[(2-fluoroethyl)amino]-IH-benzimidazol-5-yl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-y|carbonyl}x-2-(3-fluorophenyl)piperidin-4-one (46.4 mg, 75% yield).

**1H NMR (400 MHz, d_6-DMSO):** 7.51 (s, 1H), 7.42 (d, 1H), 7.36 (s, 1H), 7.31 (q, 1H), 7.18 (d, 1H), 7.12-7.03 (m, 4H), 6.99 (d, 1H), 5.20 (tr, 1H), 4.66 (tr, 1H), 4.57 (dd AB, 2H), 4.54 (tr, 1H), 4.20 (br m, 2H), 3.75-3.56 (br m, 6H), 2.86 (m, 2H), 2.60 (m, 1H), 2.33 (br d, 1H).

MS (EI) for C_{30}H_{29}FN_{5}O_{3}: 547 (MH^+).

**Using analogous synthetic techniques and substituting with alternative starting reagents in steps 1 and/or 4 the following compounds of the invention were prepared.**

**Alternative starting materials were obtained commercially unless otherwise indicated.**

**2-(3-fluorophenyl)- 1- {[7- {2-[(2,2,2-trifluoroethyl)amino]-1H-benzimidazol-5-yl}]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl} piperidin-4-one.** Synthesized according to the method of example 14 using 2,2,2-trifluoroethylamine hydrochloride salt in step 1.
NMR (400 MHz, d$_6$-DMSO): 7.52 (d, 1H), 7.44-7.35 (m, 3H), 7.30 (q, 1H), 7.25-7.20 (m, 1H), 7.17-7.03 (m, 4H), 6.99 (d, 1H), 5.20 (br s, 1H), 4.58 (dd AB, 2H), 4.25-4.14 (m, 4H), 3.68 (br d, 3H), 2.91-2.80 (m, 2H), 2.64-2.56 (m, 1H), 2.33 (d, 1H). MS (EI) for C$_{30}$H$_{27}$F$_4$N$_5$O$_3$: 583 (MH$^+$).

[00656]  N-ethyl-6-(4-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-benzimidazol-2-amine. Synthesized according to the method of example 14 using ethyl isothiocyanate in step 1 and 4-(fluoromethyl)piperidine-1-carbonyl chloride (reagent preparation 37) in step 4. MS (EI) C$_{25}$H$_{30}$FN$_5$O$_2$: 452 (MH$^+$).

[00657]  1-(7-[2-(ethylamino)-1H-benzimidazol-6-yl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl)-2-(3-fluorophenyl)piperidin-4-one. Prepared as the acetate salt according to the method of example 14 using ethyl isothiocyanate in step 1. H NMR (400 MHz, DMSO-d$_6$): 10.78 (br.s, 1H), 7.50 (br.s, 1H), 7.41 (d, 1H), 7.30 (m, 2H), 7.16-7.02 (m, 5H), 6.98 (d, 1H), 6.59 (t, 1H), 5.19 (t, 1H), 4.57 (m, 2H), 4.19 (m, 2H), 3.67 (m, 3H), 2.85 (m, 2H), 2.60 (m, 1H), 2.33 (m, 1H), 1.91 (s, 3H), 1.17 (t, 3H); MS (EI) for C$_{30}$H$_{30}$FN$_5$O$_3$: 528 (MH$^+$).

[00658]  6-(4-[[4-(1,1-difluoroethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-N-ethyl-1H-benzimidazol-2-amine. Prepared as the acetate salt according to the method of example 14 by using ethyl isothiocyanate in step 1 and 4-(1,1-difluoroethyl)piperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, methanol-d$_4$): 7.47 (d, 1H), 7.45-7.41 (m, 2H), 7.33 (dd, 1H), 7.29 (d, 1H), 7.02 (d, 1H), 4.49 (s, 2H), 4.20 (m, 2H), 3.77 (m, 2H), 3.69 (m, 2H), 3.44 (q, 2H), 2.82 (m, 2H), 1.96 (s, 3H), 1.80 (m, 2H), 1.55 (t, 3H), 1.48 (m, 2H), 1.32 (t, 3H); MS (EI) for C$_{26}$H$_{33}$F$_2$N$_5$O$_2$: 484 (MH$^+$).

**Synthetic Example 15**

Methyl [6-(4-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-imidazo[4,5-b]pyridin-2-yl]carbamate.

[00659]  STEP 1: A mixture of 2-amino-5-bromo-3-nitropyridine (0.70 g, 3.2 mmol), (4-[[1,1-dimethylethyl]oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (example 1, step 2) (1.0 g, 3.1 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (0.15 mg, 0.2 mmol), diisopropylethylamine (1.8 g, 14 mmol) in 50% aqueous 1,4-dioxane (40 mL) was degassed with nitrogen for 5 minutes and then stirred at 90°C for one hour. The
reaction mixture was cooled to room temperature, diluted with ethyl acetate (80 mL) then filtered over celite. The filtrate was washed twice with brine (50 mL), filtered and the filtrate dried over sodium sulfate, filtered again and concentrated. The residue was purified by silica gel chromatography (25% to 95% ethyl acetate in hexanes gradient) to give 1,1-dimethylethyl 7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.58 g, 48% yield); MS (EI) for C_{19}H_{22}N_{4}O_{5}: 389 (MH^+).

[00660] STEP 2: A mixture of 1,1-dimethylethyl 7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (0.58 g, 1.5 mmol), palladium (10% on charcoal, 0.50 g) and methanol (30 mL) was hydrogenated in a Parr apparatus at 45 psi for 18 hours. The mixture was filtered then concentrated and dried to give 1,1-dimethylethyl 7-(5,6-diaminopyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.51 g, 96% yield), MS (EI) for C_{13}H_{21}N_{4}O_{3}: 357 (MH^+).

[00661] STEP 3: To a solution of 1,1-dimethylethyl 7-(5,6-diaminopyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (0.51 g, 1.4 mmol) in acetic acid (5 mL) was added 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (0.3 g, 1.4 mmol). The reaction mixture was heated 65 °C for 18 h and then concentrated. The resulting residue was suspended in water and basified with portion wise addition of solid sodium bicarbonate. After complete neutralization of the aqueous mixture the insoluble solid was collected by filtration and washed with water then 50% ethyl acetate in hexanes and the filter cake dried to give 1,1-dimethylethyl 7-(2-[[methyloxy]carbonyl]amino)-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.52 g, 83% yield), MS (EI) for C_{21}H_{25}N_{3}O_{5}: 440 (MH^+).

[00662] STEP 4: To a mixture of 1,1-dimethylethyl 7-([methyloxy]carbonyl] amino)-3H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (0.52 g, 1.2 mmol) was taken into acetonitrile (5 mL) followed by addition of 4M hydrogen chloride in 1,4-dioxane (5 mL) and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated to give a white solid. It was washed with ether then dried to give methyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl]carbamate hydrochloride salt (0.40 g, 100% yield), MS (EI) for C_{17}H_{27}N_{3}O_{3}: 340 (MH^+).

[00663] STEP 5: A mixture of 4-(fluoromethyl)piperidine-1-carbonyl chloride (reagent preparation 37) (24 mg, 0.13 mmol), methyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl]carbamate hydrochloride (34 mg, 0.091 mmol), and diisoproylethylamine (59 mg, 0.45 mmol) in dichloromethane (0.5 mL) and N,N-
dimethylformamide (0.5 mL) was stirred at room temperature for one hour. The reaction mixture was concentrated then dissolved in methanol (2 mL) and purified directly by preparative reverse phase HPLC to give methyl [6-(4-({4-(fluoromethyl)piperidin-1-yl}carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-IH-imidazo[4,5-b]pyridin-2-yl]carbamate, (21 mg, 48 % yield), (400 MHz, DMSO-d$_6$): 8.41 (br, IH), 7.87 (s, IH), 7.54 to 7.44 (m, 2H), 7.05 (d, IH), 4.45 (s, 2H), 4.31 (dd, 2H), 4.19 (m, 2H), 3.67 to 3.55 (m, 4H), 2.74 (t, 2H), 1.84 (br, IH), 1.67 to 1.58 (m, 2H), 1.29 to 1.18 (m, 2H); MS (EI) for C$_{29}$H$_{25}$FN$_{6}$O$_5$: 559 (MH$^+$).

Using analogous synthetic techniques and substituting with alternative starting reagents in step 5 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

methyl [6-(4-([4-(1,1-difluoroethyl)piperidin-1-yl}carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-imidazo[4,5-b]pyridin-2-yl]carbamate. Prepared as the trifluoroacetate salt according to the method of example 15 by using 4-(1,1-difluoroethyl)piperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, DMSO-d$_6$): 8.48 (s, IH), 7.99 (s, IH), 7.56 (s, IH), 7.49 (d, IH), 7.06 (d, IH), 4.46 (s, 2H), 4.21 (m, 2H), 3.80 (s, 3H), 3.62 (m, 4H), 2.73 (m, 2H), 1.70 (m, 2H), 1.56 (t, 3H), 1.35 (m, 2H); MS (EI) for C$_{25}$H$_{29}$F$_2$N$_6$O$_5$: 515 (MH$^+$).

methyl [6-(4-([4-(2-fluoroethyl)piperidin-1-yl}carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1 H-imidazo[4,5-b]pyridin-2-yl]carbamate. Prepared as the acetate salt according to the method of example 15 by using 4-(2-fluoroethyl)piperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, DMSO-d$_6$): 8.40 (s, IH), 7.86 (s, IH), 7.52 (s, IH), 7.46 (d, IH), 7.04 (d, IH), 4.57 (m, IH), 4.44 (m, 3H), 4.19 (m, 2H), 3.77 (s, 3H), 3.56 (m, 4H), 2.71 (m, 3H), 1.62 (m, 4H), 1.19 (m, 2H); MS (EI) for C$_{25}$H$_{29}$F$_2$N$_6$O$_5$: 497 (MH$^+$).

methyl [6-(4-([2-(4-fluorophenyl)-4-oxopiperidin-1-yl}carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-E]pyridin-2-yl]carbamate. Prepared according to the method of example 15 by using 2-(4-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, DMSO-d$_6$): 8.39 (br, 1H), 7.87 (s, IH), 7.57 (d, IH), 7.48 (d, IH), 7.28 (m, 2H), 7.07 (m, 2H), 5.20 (t, IH), 4.59 (dd, 2H), 4.22 (m, 2H), 3.74 (s, 3H), 3.68 (m, 4H), 2.92 to 2.79 (m, 2H), 2.66 to 2.55 (m, 2H), 2.31 (dd, 2H); MS (EI) for C$_{25}$H$_{27}$FN$_6$O$_5$: 559 (MH$^+$).
methyl 6-((4-(fluoromethyl)-4-hydroxypiperidin-1-yl)carbonyl) -2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-1 H-imidazo[4,5-b]pyridin-2-yl]carbamate. Prepared according to the method of example 15 by using 4-(fluoromethyl)-4-hydroxypiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, DMSO-d$_6$): 8.41 (br, 1H), 7.88 (s, 1H), 7.53 (br 1H), 7.47 (dd, 2H), 7.05 (d, 1H), 4.45 (s, 2H), 4.19 (m, 2H), 4.15 (d, 2H), 3.78 (s, 3H), 3.59 (m, 2H), 3.41 (m, 2H), 3.08 (t, 2H), 1.62 to 1.50 (m, 2H), 1.46 to 1.41 (m, 2H); MS (EI) for C$_{24}$H$_{27}$FN$_2$O$_5$: 499 (MH$^+$).

methyl 6-(6-{2-(3,4-difluorophenyl)-4-oxopiperidin-1-yl)carbonyl} -2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-1 H-imidazo[4,5-b]pyridin-2-yl]carbamate. Prepared according to the method of example 15 by using 2-(3,4-difluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, DMSO-d$_6$): 8.41 (s, 1H), 7.88 (s, 1H), 7.59 (br, 1H), 7.33 (m, 1H), 7.29 (m, 2H), 7.05 (d, 1H), 5.15 (t, 1H), 4.60 (dd, 2H), 4.22 (m, 2H), 3.77 (s, 3H), 3.75 to 3.61 (m, 4H), 2.82 (m, 2H), 2.59 (m, 1H), 2.39 (dd, 1H); MS (EI) for C$_{29}$H$_{26}$F$_2$N$_6$O$_5$: 577 (MH$^+$).

methyl 6-{6-[(4-cyanopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl}-1 H-imidazo[4,5-b]pyridin-2-yl]carbamate. Prepared according to the method of example 15 by using 4-cyanopiperidine-1-carbonyl chloride (reagent preparation 37) in step 4. H NMR (400 MHz, methanol-d$_4$): 8.43 (br, 1H), 7.86 (br, 1H), 7.55 (br, 1H), 7.46 (dd, 1H), 7.04 (d, 1H), 4.47 (s, 2H), 4.20 (m, 2H), 3.78 (s, 3H), 3.60 (m, 2H), 3.44 to 3.27 (m, 2H), 3.06 to 2.97 (m, 3H), 1.93 to 1.85 (m, 2H), 1.79 to 1.69 (m, 2H); MS (EI) for C$_{24}$H$_{25}$N$_7$O$_4$: 476 (MH$^+$).

**Synthetic Example 16**

**methyl (6-{6-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl]carbamate**

STEP 1: To a mixture of 5-bromo-3-nitropyridin-2-amine (0.69 g, 3.2 mmol), 4-{4-methylpiperidine-1-yl)carbonyl}-2,3,4,5-tetrahydro-1,4-benzoazepine -7-yl) boronic acid (1.0 g, 3.2 mmol) (example 2, step 4), potassium bicarbonate (1.3 g, 2.3 mmol) and DIPEA (1.1 mL, 6.3 mmol) in DMA (12 mL) and water (3 mL) was added dichloro[1,1-bis(diphenyl-phosphino)ferrocenepalladium (II) dichloromethane adduct (0.12 g, 0.16 mmol). The reaction mixture was stirred at 99 °C for 12 hours and then partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2x 30 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The resulting brown residue was suspended in methanol (20 mL), filtered and...
washed with ethyl ether (2x 30 mL) to afford 5-{4-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}-3-nitropyridin-2-amine (1.0 g, 77% yield) as a yellow solid. MS (EI) for C_{21}H_{25}N_5O_4: 412 (MH^+)

**[00672]** STEP 2: To a slurry of 5-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-3-nitropyridin-2-amine (1.0 g, 2.4 mmol), 10% Pd-C (0.1 g) and ethanol (15 mL) was added ammonium formate (1.5 g, 24 mmol) portionwise over 1 hour. The reaction mixture was stirred for an additional hour and the catalyst was removed by filtration. Concentration of the filtrate followed by purification by silica gel column chromatography (0-5% methanol in dichloromethane) provided 5-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridine-2,3-diamine (0.67 g, 72% yield) as a pale yellow foam. MS (EI) for C_{21}H_{25}N_5O_2: 382 (MH^+)

**[00673]** STEP 3: To a solution of 5-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridine-2,3-diamine (0.21 g, 0.55 mmol) in acetic acid (5 mL) was added 1,3-bis(methoxycarbonyl)-2-methyl-2-fliopseudourea (0.17 g, 0.82 mmol) and the resulting mixture was heated at 80 °C. After 12 h the reaction mixture was diluted with ethyl ether (5 mL) and the resulting precipitate was collected by filtration. The resulting brown filter cake was dissolved in methanol and purified by preparative reverse phase HPLC to afford methyl (6-[(4-methylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl)carbamate (0.030 g, 12% yield) as a pale yellow solid. H NMR (400 MHz, DMSO-d_6): 12.02 (bs, 1H), 8.44 (s, 1H), 7.85 (s, 1H), 7.38-7.55 (m, 2H), 6.96-7.06 (m, 1H), 4.36-4.44 (m, 2H), 4.06-4.22 (m, 2H), 3.76 (s, 3H), 3.44-3.60 (m, 4H), 2.68 (t, 2H) 1.43-1.61 (m, 3H), 1.20 (q, 2H), 0.90 (d, 3H); MS (EI) for C_{24}H_{28}N_6O_4: 465 (MH^+).

**Synthetic Example 17**

1-{[7-(2-amino-1H-imidazo[4,5-6]pyridin-1H-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl}piperidine-4-carboxamide and 1-{[7-(2-amino-1H-imidazo[4,5-6]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5^)-yl]carbonyl}piperidine-4-carbonitrile

**[00674]** STEP 1: A mixture of methyl (6-4-[(4-cyanopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-imidazo[4,5-b]pyridin-2-yl)carbamate (example 15) (50 mg, 0.11 mmol) was taken into methanol (1 mL) followed by addition of 1M aqueous potassium hydroxide solution (1 mL) and the mixture was stirred at 70°C for 18 hours. The reaction mixture was then cooled to room temperature, adjusted to pH 10 with 6 M hydrochloric acid solution then concentrated to remove methanol, diluted with water (10 mL)
and extracted with ethyl acetate (3x 10 mL). The combined extract was dried over sodium sulfate then filtered and concentrated. The residue, composed of a mixture of the corresponding carbonitrile and carboxamide, was purified by preparative reverse phase HPLC to give 1-[(7-(2-aminol Himidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5 H)-yl]carbonyl]piperidine-4-carboxamide (2.7 mg, 6% yield); 1H NMR (400 MHz, methanol-d₄): 8.15 (br, 1H), 7.67 (br, 1H), 7.48 (br, 1H), 7.44 (dd, 1H), 7.94 (d, 1H), 4.50 (s, 2H), 4.21 (m, 2H), 3.75 to 3.69 (m, 4H), 2.84 (t, 2H), 2.45 to 2.38 (m, 1H), 1.83 to 1.67 (m, 4H); MS (EI) for C₂₂H₂₅N₇O₃·436 (MH⁺); and 1-[(7-(2-aminol Himidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5 H)-yl]carbamate (3.9 mg, 9% yield); (400 MHz, methanol-d₄): 8.16 (br, 1H), 7.66 (br, 1H), 7.48 (br, 1H), 7.43 (dd, 1H), 7.04 (d, 1H), 4.50 (s, 2H), 4.21 (m, 2H), 3.70 (m, 2H), 3.47 (m, 2H), 3.14 (m, 2H), 2.99 (m, 1H), 1.95 (m, 2H), 3.83 (m, 2H), MS (EI) for C₂₂H₂₅N₇O₃·418 (MH⁺).

Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

6-(4-[(4-(1,1-difluoroethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-l H-imidazo[4,5-b]pyridin-2-amine. Prepared as the acetate salt according to the method of example 17 by using methyl [6-(4-[(4-(1,1-difluoroethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-l H-imidazo[4,5-b]pyridin-2-yl]carbamate (example 15) in step 1. H NMR (400 MHz, DMSO-d₆): 8.11 (s, 1H), 7.52 (m, 2H), 7.44 (m, 1H), 7.00 (d, 1H), 6.64 (s, 2H), 4.44 (s, 2H), 4.17 (m, 2H), 3.62 (m, 4H), 2.72 (m, 2H), 1.99 (m, 1H), 1.70 (m, 2H), 1.57 (t, 3H), 1.37 (m, 2H); MS (EI) for C₂₃H₂₄F₂N₆O₂·457 (MH⁺).

6-(4-[(4-(difluoromethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-l H-imidazo[4,5-b]pyridin-2-amine. Prepared as the acetate salt according to the method of example 17 by using methyl [6-(4-[(4-(difluoromethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-l H-imidazo[4,5-b]pyridin-2-yl]carbamate (example 15) in step 1. H NMR (400 MHz, methanol-d₄): 8.15 (d, 1H), 7.65 (d, 1H), 7.48 (d, 1H), 7.43 (dd, 1H), 7.05 (d, 1H), 5.71 (m, 1H), 4.51 (s, 2H), 4.21 (m, 2H), 3.74 (m, 2H), 3.69 (m, 2H), 2.85 (m, 2H), 1.97 (m, 1H), 1.96 (s, 3H), 1.75 (m, 2H), 1.47 (m, 2H); MS (EI) for C₂₂H₂₄F₂N₆O₂·443 (MH⁺).

6-(4-[(4-(2-fluoroethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)-l H-imidazo[4,5-Z]pyridin-2-amine. Prepared as acetate salt according to

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the method of example 17 by using methyl [6-(4-{{[4-(2-fluoroethyl)piperidin-1-y]carbonyl}]-
2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl]carbamate
(example 15) in step 1. ^1^H NMR (400 MHz, methanol-d4): 8.15 (s, IH), 7.66 (s, IH), 7.58 (d,
IH), 7.436 (dd, IH), 7.05 (d, IH), 4.56 (m, IH), 4.49 (s, 2H), 4.44 (m, IH), 3.69 (m, 4H),
2.84 (m, 2H), 1.97 (s, 3H), 1.78-1.59 (m, 5H), 1.28 (m, 2H); MS (EI) for C_{23}H_{23}FN_{6}O_{2}: 439
(MH^+).

[00679] 6-(4-{{[4-(fluoromethyl)piperidin-1-y]carbonyl}]-2,3,4,5-tetrahydro-1,4-
benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-amine. Synthesized according to the method
of example 17 using methyl [6-(4-{{[4-(fluoromethyl)piperidin-1-y]carbonyl}]-2,3,4,5-
tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl]carbamate (example 15) in
step 1. ^1^H NMR (400 MHz, DMSO-d6): 8.12 (br, IH), 7.53 (s, IH), 7.49 (br, IH), 7.44 (dd,
IH), 7.00 (d, IH), 4.42 (s, 2H), 4.31 (dd, 2H), 4.17 (m, 2H), 3.62 to 3.54 (m, 4H), 2.74 (t,
2H), 1.83 (br, IH), 1.65 to 1.59 (m, 2H), 1.31 to 1.19 (m, 2H); MS (EI) for C_{22}H_{22}FN_{6}O_{2}: 425
(MH^+).

**Synthetic Example 18**

1-{{[7-(2-amino-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-
yl]carbonyl}-2-(3-fluorophenyl)piperidin-4-one

[00680] STEP 1: To a solution of 1,1-dimethylethyl 7-(5,6-diaminopyridin-3-yl)-2,3-
dihydro-1,4-benzoxazepine-4(5H)-carboxylate (example 15, step 2) (0.23 g, 0.65 mmol) in
acetic acid (10 mL) was added 1,3-bis(benzylxycarbonyl)-2-methyl-2-thiopseudourea (0.27
g, 0.76 mmol) and the resulting mixture was heated at 50 °C. After 4 h the reaction mixture
was concentrated then suspended in ethyl acetate (10 mL). Filtration followed by washing the
cake with ethyl acetate (2 x 10 mL) provided 1,1-dimethylethyl 7-[2-
{{[phenylmethyl]oxy}carbonyl}amino]-1H-imidazo[4,5-b]pyridin-6-yl]-2,3-dihydro-
1,4-benzoxazepine-4(5H)-carboxylate (0.3 g, 91% yield) as a white solid. MS (EI) for
C_{28}H_{29}N_{5}O_{5}: 516 (MH^+).

[00681] STEP 2: To a solution of 1,1-dimethylethyl 7-[2-
{{[phenylmethyl]oxy}carbonyl}amino]-1H-imidazo[4,5-b]pyridin-6-yl]-2,3-dihydro-1,4-
benzoxazepine-4(5H)-carboxylate (0.49 g, 1.9 mmol) in dichloromethane (10 mL) was added
trifluoroacetic acid (10 mL) and the resulting solution was heated at 50 °C. After 1 h the
reaction mixture was concentrated and the residue was concentrated three times from ethyl
acetate (30 mL) to afford phenylmethyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-

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imidazo[4,5-b]pyridin-2-yl]carbamate as the bis-trifluoroacetate salt (0.48 g, 95% yield). MS (EI) for C\textsubscript{23}H\textsubscript{21}N\textsubscript{5}O\textsubscript{3}: 416 (MH\textsuperscript{+}).

[00682] STEP 3: To a solution of phenylmethyl [6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl]carbamate bis-trifluoroacetate salt (0.40 g, 0.75 mmol) and DIPEA (1.0 mL, 5.7 mmol) in DMF (10 mL) was added 2-(3-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) (0.31 g, 1.2 mmol) and the resulting mixture was heated at 50 °C. After 12 h, the reaction mixture was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with brine (30 mL), dried over anhydrous magnesium sulfate then filtered and concentrated. Column chromatography on silica (1-10% isopropanol in dichloromethane) yielded phenylmethyl [6-(4-[[2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridin-2-yl]carbamate (0.15 g, 31% yield) as a waxy solid. MS (EI) for C\textsubscript{35}H\textsubscript{31}FN\textsubscript{6}O\textsubscript{5}: 635 (MH\textsuperscript{+}).

[00683] STEP 4: A solution of phenylmethyl [6-(4-[[2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-&]pyridin-2-yl]carbamate (0.15 g, 0.24 mmol) in acetic acid (5 mL) was hydrogenated at 1 atm over 10% palladium on carbon (0.15 g) for 18 h. The catalyst was removed by filtration and the filtrate was concentrated. The resulting brown residue was dissolved in methanol and purified by preparative reverse phase HPLC to afford 1-[[7-(2-amino-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-2-(3-fluorophenyl)piperidin-4-one (46 mg, 39% yield) as a pale yellow solid. \textsuperscript{1}H NMR (400 MHz, CDC\textsubscript{13}): 11.44 (bs, 1H), 8.17 (s, 1H), 6.97-7.60 (m, 7H), 6.75 (s, 1H), 5.18 (t, 1H), 4.51-4.66 (m, 2H), 4.13-4.30 (m, 2H), 3.56-3.78 (m, 3H), 3.21-3.31 (m, 1H), 2.79-2.99 (m, 2H), 2.51-2.61 (m, 1H), 2.32 (d, 1H); MS (EI) for C\textsubscript{27}H\textsubscript{25}FN\textsubscript{6}O\textsubscript{3}: 501 (MH\textsuperscript{+}).

[00684] Using analogous synthetic techniques and substituting with alternative starting reagents in step 3 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00685] 8-[[7-(2-amino-1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-(endo)-ol. Synthesized as the hydrochloride salt according to the method of example 18 using 3-hydroxy-3-(endo)-(trifluoromethyl)-8-azabicyclo[3.2.1]octane-8-carbonyl chloride (reagent preparation 37) in step 3. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): 8.58 (bs, 2H), 8.34 (s, 1H), 7.90 (s, 1H), 7.54 (s,
1H), 7.49 (d, 1H), 7.03 (d, 1H), 5.85 (s, 1H), 4.19-4.27 (m, 2H), 4.00-4.08 (m, 2H), 3.31-3.48
(m, 2H), 1.95-2.10 (m, 4H), 1.67-1.81 (m, 4H); MS (EI) for C_{21}H_{25}F3N_{6}O_{5}: 503 (MH^+).

**Synthetic Example 19**

**N-[5-(4-{[4-(fluoromethyl)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-
7-yl)-1H-benzimidazol-2-yl]acetamide**

[00686] **STEP 1**: 4-bromobenzene-1,2-diamine (1.02 g, 5.45 mmol) was taken into 50%
aqueous methanol (25 mL) followed by slow addition of cyanogen bromide (1.73 g, 16.35
mmol) and the mixture was allowed to stir at room temperature over 12 h. The mixture was
then concentrated to approximately 50% volume, diluted with water and brought to neutral
pH by addition of 2 M aqueous sodium hydroxide. The aqueous mixture was then partitioned
with ethyl acetate and the organic solution washed with brine, dried over anhydrous sodium
sulfate, filtered and concentrated to give 6-bromo-1 H-benzimidazol-2-amine (1.67 g) as a red
amorphous residue. MS (EI) for C_{7}H_{6}BrN_{3}: 213 (MH^+).

[00687] **STEP 2**: 6-Bromo-1 H-benzimidazol-2-amine as obtained in step 1 was taken into
THF (40 mL) followed by addition of di-tert-butyl dicarbonate (1.5 g, 6.86 mmol) and the
resulting solution was stirred for 30 minutes at room temperature then concentrated. The
residue was suspended in hexanes and the crystalline solid collected by filtration and dried to
give a mixture of tert-butyl 2-amino-6-bromo-1 H-benzimidazole-1-carboxylate and tert-butyl
2-amino-6-bromo-1 H-benzimidazole-1-carboxylate (1.17 g, 69% yield over 2 steps). MS (EI)
for C_{12}H_{16}BrN_{3}O_{2}: 256 (M-t-Bu^+).

[00688] **STEP 3**: BOC-protected 6-Bromo-1 H-benzimidazol-2-amine as obtained in step 2
as a mixture of N1,N3 isomers (52 mg, 0.17 mmol) was taken into THF (2 mL) followed by
addition of DIPEA (60 uL, 0.34 mmol) then acetic anhydride (32 uL, 0.34 mmol) and the
mixture was brought to reflux for 12h. The resulting solution was concentrated and the
residue taken into TFA then allowed to stand for 1h at room temperature. The solution was
concentrated and the residue partitioned with an ethyl ether/hexane mixture and saturated
aqueous sodium bicarbonate. The resulting suspension was filtered and the filter cake washed
with water then hexanes and dried to give N-(6-bromo-1 H-benzimidazol-2-yl)acetamide
(37.2 mg, 88% yield). 1H NMR (400 MHz, d_{6}-DMSO): 7.60 (d, 1H), 7.39 (d, 1H), 7.21 (dd,
1H), 2.16 (s, 3H).

[00689] **STEP 4**: (4-[1-(1-dimethylethyl)oxycarbonyl]-2,3,4,5-tetrahydro-1,4-
benzoxazepin-7-yl)boronic acid (Example 1, step 2) (1.07 g, 3.64 mmol) was dissolved into
4M hydrogen chloride in dioxane and the resulting solution was allowed to stir at room
temperature for 1.3 h. The heterogeneous mixture was then diluted with ethyl ether (100 mL) and the solid collected by filtration to give 2,3,4,5-tetrahydro-1,4-benzoazepin-7-ylboronic acid hydrochloride salt (791 mg, 95%). \(^1\)H NMR (400 MHz, D\(_2\)O): 7.79 (dd, 1H), 7.74 (d, 1H), 7.21 (d, 1H), 4.47 (s, 2H), 4.36 (m, 2H), 3.69 (m, 2H).

[00690] STEP 5: 2,3,4,5-tetrahydro-1,4-benzoazepin-7-ylboronic acid hydrochloride salt (188 mg, 0.82 mmol) was taken into 50% aqueous THF (2 mL) followed by addition of solid sodium bicarbonate (360 mg, 4.3 mmol) then 4-(fluoromethyl)piperidine-1-carbonyl chloride (reagent preparation 37) (218 mg, 1.21 mmol) in a minimum of THF. The mixture was stirred at room temperature over 1 h then partitioned with 0.5M aqueous hydrochloric acid and ethyl acetate. The organic solution was then brine washed, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was taken into isopropyl acetate and extracted once with 1M aqueous sodium hydroxide. The aqueous solution was then acidified to pH 2 using concentrated hydrochloric acid and extracted once with ethyl acetate then brine washed, dried over anhydrous sodium sulfate, filtered and concentrated to provide (4-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)boronic acid (143 mg, 52% yield) as an amorphous residue. MS (EI) for C\(_{25}\)H\(_{24}\)BrFN\(_5\)O\(_3\): 337 (MH\(^+\)).

[00691] STEP 6: (4-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)boronic acid (67.2 mg, 0.2 mmol), N-(6-bromo-1H-benzimidazol-2-yl)acetamide (34.8 mg, 0.14 mmol) and dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (6 mg) was taken into dioxane (0.5 mL) followed by addition of water (0.1 mL) and DIPEA (0.14 mL). The resulting mixture was heated in a sealable vessel at 85°C for 12 h then cooled to room temperature. The mixture was diluted with ethyl acetate, dried over anhydrous sodium sulfate and filtered through a silica plug with an ethyl acetate wash. The organic filtrate was washed once with 1M aqueous sodium hydroxide, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (100% ethyl acetate to 4:1 ethyl acetate:ethanol) to give N-[5-[[4-(fluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl]-1H-benzimidazol-2-yl)acetamide as a colorless solid. \(^1\)H NMR (400 MHz, oVmethanol): 7.64 (dd, 1H), 7.51-7.48 (m, 2H), 7.46 (dd, 1H), 7.40 (dd, 1H), 7.03 (d, 1H), 4.49 (s, 2H), 4.35 (d, 1H), 4.23 (d, 1H), 4.19 (m, 2H), 3.74 (d, 2H), 3.68 (m, 2H), 2.85 (br tr, 2H), 2.25 (s, 3H), 1.88 (br, 1H), 1.71 (d, 2H), 1.36 (d q, 2H). MS (EI) for C\(_{25}\)H\(_{38}\)F\(_{10}\)N\(_5\)O\(_3\): 337 (MH\(^+\)).
Using analogous synthetic techniques and substituting with alternative starting reagents in steps 5 and 6 then conducting protecting group removal as required according to literature techniques appropriate for a given protecting group (see for example: Greene and Wuts, Protective Groups in Organic Synthetic, Wiley-Interscience) the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

8-[[7-[2-(ethylamino)-1H-imidazo[4,5-b]pyridin-6-yl]-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol. Synthesized according to the method of example 19 using 3-hydroxy-3-(trifluoromethyl)-8-azabic cyclo[3.2.1]octane-8-carbonyl chloride (reagent preparation 37) in step 5 and 6-bromo-N-ethyl-l-(methoxymethyl)-1H-imidazo[4,5-b]pyridin-2-amine (reagent preparation 38) in step 6. H NMR (400 MHz, d₆-DMSO) δ 11.03 (s, 1H), 8.08 (d, 1H), 7.49 (m, 3H), 7.11 (s, 1H), 6.99 (d, 1H), 5.83 (s, 2H), 4.51 (s, 2H), 4.19 (m, 2H), 4.05 (m, 2H), 3.66 (m, 2H), 3.34 (q, 2H), 2.04 (m, 4H), 1.74 (m, 4H), 1.18 (t, 3H); MS (ES) for C₂₆H₂₉F₄N₆O₂S: 531 (MH⁺).

8-[[7- [6-amino-5-[(3-aminoazetidin-1-yl)sulfonfyl]pyridin-3-yl]-2,3-dihydro-1,4-benzoazepin-4(5H)-yl]carbonyl]-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol. Synthesized according to the method of example 19 using 3-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octane-8-carbonyl chloride (reagent preparation 37) in step 5 and tert-butyl l-(2-amino-5-bromopyridin-3-ylsulfonyl)azetidin-3-ylcarbamate (reagent preparation 40) in step 6. H NMR (400 MHz, d₆-DMSO) δ 8.56 (d, 1H), 7.93 (d, 1H), 7.47 (d, 1H), 7.44 (dd, 1H), 6.99 (d, 1H), 6.76 (bs, 2H), 5.82 (bs, 1H), 4.52 (s, 2H), 4.21 (m, 2H), 4.04 (m, 2H), 3.88 (t, 2H), 3.67 (m, 2H), 3.57 (m, 1H), 3.38 (t, 2H), 2.04 (m, 4H), 1.73 (m, 4H); MS (ES) for C₂₆H₂₈F₄N₆O₅S: 597 (MH⁺).

N-[2-chloro-5-(4-[(3-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]oct-8-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)pyridin-3-yl]methanesulfonamide. Synthesized according to the method of example 19 using 3-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octane-8-carbonyl chloride (reagent preparation 37) in step 5 and N-(5-bromo-2-chloropyridin-3-yl)methanesulfonamide (reagent preparation 39) in step 6. H NMR (400 MHz, d₆-DMSO) δ 9.84 (s, 1H), 8.49 (s, 1H), 8.01 (s, 1H), 7.58 (s, 1H), 7.53 (d, 1H), 7.04 (d, 1H), 5.82 (s, 2H), 4.54 (s, 2H), 4.25 (s, 2H), 4.03 (s, 2H), 3.68 (s, 2H), 3.15 (s, 3H), 2.02 (m, 4H), 1.72 (m, 4H); MS (ES) for C₂₄H₂₆ClF₃N₄O₂S: 575 (MH⁺).
Synthetic Example 20

2-(3-fluorophenyl)-1-[[7-(3H4imidazo[4,5-6]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5£T)-yl]carbonyl]piperidin-4-one

[00692] STEP 1: A suspension of 5-bromopyridine-2,3-diamine (3.00 g, 15.9 mmol) in trimethoxymethane (20 mL) was heated to 95 °C for one hour. After cooling to room temperature the solid was collected by filtration, and then washed with diethyl ether to give 6-bromo-l H-imidazole[4,5-b]pyridine (3.00 g, 95% yield) as a tan solid.

[00693] STEP 2: A solution of 6-bromo-l H-imidazole[4,5-b]pyridine (3.00 g, 15 mmol) and diisopropylethylamine (5.8 g, 45 mmol) in dimethylformamide (20 mL) was cooled to -10 °C followed by dropwise addition of isobutyl chloroformate (2.18 g, 16 mmol) and the mixture was stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate (80 mL) and washed with 0.1 N aqueous hydrochloric acid (50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give isobutyl 6-bromo-l H-imidazo[4,5-&]pyridine-1-carboxylate (4.3 g, 96% yield) as a tan solid. MS (EI) for C₁₁H₁₂BrN₃O₂: 299 (MH⁺).

[00694] STEP 3: A flask was charged with isobutyl 6-bromo-l H-imidazo[4,5-b]pyridine-1-carboxylate (2.00 g, 6.82 mmol), 4-[(l,l-dimethylethyl)oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (example 1, step 2) (2.00 g, 6.82 mmol), dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (0.14 g, 0.17 mmol), and diisopropylethylamine (3.50 g, 27.2 mmol) in dry dioxane (60 mL) and the mixture heated to 95 °C for 24 hours. The resulting mixture was diluted with ethyl acetate (100 mL) then washed with water (50 mL), 10% aqueous citric acid (50 mL) and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/hexane, 1:1) to give 1,1-dimethylethyl 7-[[2-methylpropyl)oxy]carbonyl]-1H-imidazo[4,5-b]pyridine-6-yl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (1.45 g, 46% yield) as a brown oil. MS (EI) for C₂₅H₂₇N₄O₂: 467 (MH⁺).

[00695] STEP 4: To a solution of 1,1-dimethylethyl 7-[[2-methylpropyl)oxy]carbonyl]-1 H-imidazo[4,5-6]pyridine-6-yl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (0.40 g, 0.86 mmol) in chloroform (4 mL) was added dropwise trifluoroacetic acid (5 mL) and the solution then warmed to 80 °C for 45 minutes. After cooling, the solution was concentrated and dried to give 2-methylpropyl 6-(2,3,4,5-
tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridine-1-carboxylate (0.37 g, 90% yield) as the trifuoroacetic acid salt. MS (EI) for C_{20}H_{25}N_{4}O_{3}: 367 (MH+).

[00696] STEP 5: A solution of 2-methylpropyl 6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-b]pyridine-1-carboxylate trifuoroacetic acid salt (0.20 g, 0.53 mmol), 2-(3-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) (0.13 g, 0.51 mmol) and diisopropylethylamine (3.0 g, 23 mmol) in N,N-dimethylformamide (8 mL) was heated to 65 °C for 18 hours. The resulting mixture was diluted with ethyl acetate (50 mL) and washed with water (2×25 mL) and once with brine (15 mL) then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (acetone/ethyl acetate, 1:4) to give 2-methylpropyl 6-(4-{[2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl }-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-Z7]pyridine-1-carboxylate (0.19 g, 64% yield). MS (EI) for C_{35}H_{35}FN_{3}O_{5}: 586 (MH+).

[00697] STEP 6: 2-methylpropyl 6-(4-{[2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl }-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-£]pyridine-1-carboxylate (0.19 g, 0.32 mmol) and potassium carbonate (0.20 g, 1.4 mmol) in methanol (10 mL) was stirred for 45 minutes at 25 °C. The mixture was diluted with ethyl acetate (80 mL) washed with water (50 mL) and brine (25 mL), then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (methanol/ethyl acetate 1:10). Residue obtained by the concentration of product containing fractions was stirred 18 hours at 25 °C in diethyl ether (20 mL) and the solid product thus formed was isolated by filtration to give 2-(3-fluorophenyl)-l-{{[7-(3H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl}piperidin-4-one (0.45 g, 27% yield). H NMR (400 MHz, d_{6}-DMSO): 8.62 (s, IH), 8.47 (s, IH), 8.18 (s, IH), 7.69 (d, IH), 7.57 (d, IH), 7.24 (q, IH), 7.10-7.01 (m, 4H), 5.19 (t, IH), 4.61 (m, 2H), 4.24 (m, 2H), 3.72 (m, 3H), 3.41 (m, 2H), 2.84 (m, 2H), 2.61 (m, IH), 2.34 (d, IH); MS (EI) for C_{27}H_{24}FN_{3}O_{3}: 486 (MH+).

[00698] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 the following compounds of the invention were prepared.

[00699] 2-(3-fluorophenyl)-l-{{[7-(2-methyl-3 H-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5 H)-yl]carbonyl}piperidin-4-one. Prepared according to the method of example 20 by using triethyl orthoacetate in step 1. H NMR (400 MHz, d_{6}-DMSO): 12.69 (d, IH), 8.49 (dd, IH), 8.00 (dd, IH), 7.65 (s, IH), 7.55 (d, IH), 7.28 (q, IH), 7.05 (m, 4H), 6.65 (t, IH), 5.79 (m, 2H), 2.34 (t, 4H), 1.91 (t, 4H), 1.56 (t, 4H), 1.25 (t, 4H).
5.18 (t, 1H), 4.61 (m, 2H), 4.22 (m, 2H), 3.71 (m, 3H), 3.38 (m, 5H), 2.84 (m, 2H), 2.52 (d, 2H), 2.35 (m, 1H). MS (EI) for C_{28}H_{26}FN_{3}O_{3} : 500 (MH\(^+\)).

**Synthetic Example 21**

1-(7-[4 -{(m-imidazoI-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}carbonyl)piperidine-4-carbonitrile

[00700] STEP 1: 2-(4-Bromophenyl)imidazole (330 mg, 1.48 mmol) was suspended in THF (10mL) and DMAP (194 mg, 1.59 mmol) then di-tert-butyl di carbonate (366 mg, 1.68 mmol) were sequentially added. The mixture was stirred for 1h then concentrated and partitioned with ethyl acetate and 10% aqueous citric acid. The organic solution was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated to afford 1,1-dimethylethyl 2-(4-bromophenyl)-1H-imidazol-1-carboxylate (457 mg, 96% yield) as an oil.

[00701] STEP 2: 1,1-Dimethylethyl 2-(4-bromophenyl)-1 H-imidazole-1-carboxylate (457 mg, 1.41 mmol) and (4-{[(l,l-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (example 1, step 2) (456 mg, 1.55 mmol) were taken into dioxane (5 mL) and water (1 mL) followed by addition of DIPEA (1.1 mL, 6.2 mmol) and dichloro[l,1-bis(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (58 mg) then the mixture was heated at 80 °C over 12h. The mixture was cooled then partitioned with ethyl acetate and 10% aqueous citric acid. The organic solution was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. The residue thus obtained was taken into methanol (10 mL) followed by addition of sodium hydroxide (180 mg, 4.5 mmol) in water (1 mL). The mixture was stirred at room temperature for 30 minutes then neutralized by addition of 10% aqueous citric acid then concentrated. The aqueous residue was partitioned with ethyl acetate and saturated aqueous sodium bicarbonate and the organic solution was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated to give 1,1-dimethylethyl 7-[4-(1 H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (490 mg, 89 % yield). MS (EI) for C_{23}H_{25}N_{3}O_{3} : 392 (MH\(^+\)).

[00702] STEP 3: 1,1-dimethylethyl 7-[4-(1 H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (490 mg, 1.25 mmol) was taken into dichloromethane (20 mL) followed by sequential addition of DIPEA (0.4 mL, 2.3 mmol) and isobutyl chloroformate (0.18 mL, 1.4 mmol) and the mixture was stirred at room temperature for 30 minutes. The mixture was concentrated then partitioned with ethyl acetate and 10% aqueous citric acid. The organic solution was washed with brine, dried over anhydrous sodium sulfate
then filtered and concentrated. The residue thus obtained was taken into TFA (5 mL) and
allowed to stand for 30 minutes at room temperature. The mixture was concentrated and
the residue was partitioned with ethyl acetate and saturated aqueous sodium bicarbonate and the
organic solution was washed with brine, dried over anhydrous sodium sulfate and then filtered
and concentrated to give 2-methylpropyl 2-[4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)phenyl]-1 H-imidazole-l-carboxylate (361 mg, 65% yield). MS (EI) for C_{23}H_{23}N_3O_3: 392 (MH^+).

STEP 4: 2-methylpropyl 2-[4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)phenyl]-1 H-imidazole-l-carboxylate (361 mg, 0.92 mmol) was taken into dichloromethane (5 mL) followed by addition of DIPEA (0.32 mL, 1.84 mmol). The solution thus obtained was added slowly by syringe over several minutes to a solution of phosgene (20 W% in toluene, 0.49 mL, 0.93 mmol) diluted in dichloromethane (5 mL) and cooled to 0 °C. The resulting mixture was stirred for 5 minutes then allowed to warm to room temperature and concentrated. The residue was taken back into dichloromethane (5 mL) followed by addition of DIPEA (0.48 mL, 2.76 mmol) and 4-cyanopiperidine hydrochloride salt (156 mg, 1.06 mmol) then stirred for 12h. The mixture was concentrated then partitioned with ethyl acetate and 10% aqueous citric acid. The organic solution was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by silica gel chromatography (100% ethyl acetate) to give 2-methylpropyl 2-((4-{4-[4-cyanopiperidin-1-yl]carbonyl}2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)phenyl)-1 H-imidazole-l-carboxylate (296 mg, 61% yield) as a crystalline solid. MS (EI) for C_{30}H_{33}N_5O_4: 529 (MH^+).

STEP 5: 2-Methylpropyl 2-((4-{4-[4-cyanopiperidin-1-yl]carbonyl}2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)phenyl)-1 H-imidazole-l-carboxylate (296 mg, 0.56 mmol) was taken into methanol (10 mL), THF (2 mL) and water (0.5 mL) then warmed to give a homogeneous solution. Potassium carbonate (160 mg, 1.15 mmol) and the mixture was stirred for 30 minutes. The mixture was then concentrated and partitioned with ethyl acetate and 10% aqueous citric acid. The organic solution was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by silica gel chromatography (10% ethanol in ethyl acetate) to give 1-{7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro- 1,4-benzoxazepin-4(5H)-yl carbonyl}piperidine-4-carbonitrile (155 mg, 65% yield). H NMR (400 MHz, d_4-methanol): 7.92 (d, 2H), 7.69 (d, 2H), 7.56 (d, 1H), 7.51 (dd, 1H), 7.15 (s, 2H), 7.04 (d, 1H), 4.51 (s, 2H), 4.21 (tr, 2H), 3.70 (tr, 2H), 3.49-3.43
[00705] Using analogous synthetic techniques and substituting with alternative starting reagents in step 4 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00706] 4-{{4-(fluoromethyl)pipedin-1-yl carbonyl}-7-{{4-(1H-imidazol-2-yl) phenyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 21 using 4-(fluoromethyl)piperidin (reagent preparation 7) in step 4. H NMR (400 MHz, d$_4$-methanol): 8.00 (d, 2H), 7.71 (d, 2H), 7.60 (d, IH), 7.55 (dd, IH), 7.16 (br, 2H), 7.02 (d, IH), 4.44 (s, 2H), 4.37 (d, IH), 4.26 (d, IH), 4.20 (br s, 2H), 3.59-3.56 (m, 4H), 2.74 (tr, 2H), 1.83 (br, IH), 1.62 (d, 2H), 1.26 (br q, 2H). M S (EI) for C$_{23}$H$_{27}$N$_4$O$_2$: 429 (MH$^+$).

**Synthetic Example 22**

2-(4-fluorophenyl)-1-{{7-[4-lff-imidazol-2-yl]phenyl}-2,3-dihydro-1,4-benzoxazepine-4(5Z7)-yl}carbonyl piperidin-4-one

[00707] STEP 1: A solution of isobutyl 2-(4-bromophenyl)-1 H-imidazole-1-carboxylate (example 4, step 5) (0.50 g, 1.55 mmol), (4-{{[[1,1-dimethylethyl]oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}boronic acid (example 1, step 2) (0.63 g, 1.70 mmol) and diisopropylethylamine (1.50 mL, 8.50 mmol) in 20% aqueous 1,4-dioxane (10 mL) was deoxygenated for 5 minutes by bubbling nitrogen gas into it, followed by the addition of 1,1-dimethylethyl palladium(II) complex with dichloromethane (70 mg, 0.085 mmol). The reaction mixture was heated to 80°C for 2 hours. On cooling to room temperature the mixture was diluted with ethyl acetate (250 mL) then filtered through a pad of Celite. The organic filtrate was washed with 10% aqueous citric acid (50 mL), brine then dried over anhydrous sodium sulfate, filtered and concentrated. Silica gel column chromatography (hexane-ethyl acetate 9:1 to 7:3) provided 1,1-dimethylethyl 7-[4-(1-[{{2-methylpropyl]oxy} carbonyl}]-1H-imidazol-2-yl]phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.32 g, 43%). H NMR (400 MHz, d$_6$-DMSO): 7.73 (d, IH), 7.67 (s, 4H), 7.56 (m, 2H), 7.14 (d, IH), 7.08 (m, IH), 4.56 (br s, IH), 4.51 (br s, 2H), 4.13 (br s, IH), 4.08 (m, 2H), 3.74 (m, 2H), 1.86 (m, IH), 1.34 (s, IH), 1.32 (s, 9H), 0.77 (d, 6H). M S (EI) for C$_{28}$H$_{33}$N$_3$O$_5$: 492 (MH$^+$).

[00708] STEP 2: To a solution of 1,1-dimethylethyl 7-[4-(1-{{2-methylpropyl]oxy} carbonyl}]-1H-imidazol-2-yl]phenyl]-2,3-dihydro-1,4-benzoxazepine-
4(5H)-carboxylate (0.30 g, 0.61 mmol) in dichloromethane (100 mL) was added
trifluoroacetic acid (20 mL) and the reaction mixture was heated to reflux. After cooling to
room temperature the solvent was evaporated. The residue was dissolved in ethyl acetate (250
mL). The organic layer was washed with saturated aqueous sodium bicarbonate (2x 100 mL),
brine, dried over anhydrous sodium sulfate then filtered and concentrated to give 2-
methylpropyl 2-[4-(2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)phenyl] -IH-imidazole- 1-
carboxylate (0.22 g, 86%). 1H NMR (400 MHz, d-DMSO): 12.48 (s, 1H), 7.68-7.61 (m,
2H), 7.30 (m, 1H), 7.15 (d, 1H), 7.10 (m, 3H), 7.04 (d, 2H), 5.20 (t, 1H), 4.62 (s, 2H), 4.24 (m, 2H), 4.04 (d, 2H), 3.68 (m, 3H), 3.40 (m, 1H), 2.86 (m, 2H), 2.61 (m, 1H), 2.32 (2t, 1H), 1.86 (m, 1H), 0.76 (m, 6H). MS (EI) for C_{35}H_{25}FN_{3}O_{5}: 611 (MH^+).

[00709] STEP 3: To a solution 2-methylpropyl 2-[4-(2,3,4,5-tetrahydro-1,4-benzoazepin-
7-yl)phenyl]-IH-imidazole-1-carboxylate (0.22 g, 0.56 mmol) and diisopropylethylamine
(0.50 mL, 2.81 mmol) in dimethylformamide (10 mL) at 0 °C a solution of 2-(4-
fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) (0.15 g, 0.59
mmol) in tetrahydrofuran (5 mL) was added and the reaction mixture was stirred for 2 hours
at room temperature. The mixture was diluted with ethyl acetate (250 mL) and partitioned
with water (100 mL). The organic layer was separated and washed with water (50 mL), 10%
aqueous citric acid (50 mL), brine then dried over anhydrous sodium sulfate, filtered and
concentrated. Column chromatography (hexane-acetone 4:1 to 7:3) provided 2-methylpropyl
2-[4-(2-(4-fluorophenyl)-4-oxopiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-
benzoazepin-7-yl)phenyl]-IH-imidazole-1-carboxylate (0.28 g, 80%). 1H NMR (400 MHz,
d_6-DMSO): 7.73 (d, 1H), 7.68-7.61 (m, 4H), 7.62 (d, 1H), 7.54 (dd, 1H), 7.30 (m, 1H), 7.15
(d, 1H), 7.10 (m, 3H), 7.04 (d, 2H), 5.20 (t, 1H), 4.62 (s, 2H), 4.24 (m, 2H), 4.04 (d, 2H),
3.68 (m, 3H), 3.40 (m, 1H), 2.86 (m, 2H), 2.61 (m, 1H), 2.32 (2t, 1H), 1.86 (m, 1H), 0.76 (m,
6H). MS (EI) for C_{35}H_{35}FN_{3}O_{5}: 611 (MH^+).

[00710] STEP 4: To a solution of 2-methylpropyl 2-[4-(4-[[2-(4-fluorophenyl)-4-
oxopiperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)phenyl]-IH-
imidazole-1-carboxylate (0.27 g, 0.44 mmol) in methanol (50 mL) was added potassium
bicarbonate (0.37 g, 2.65 mmol) at 0 °C and the reaction mixture was stirred for 2 hours at
room temperature. The solid was filtered off and the pH of the resulting solution was adjusted
to 6-7 by addition of glacial acetic acid. The solvent was evaporated and the residue was
dissolved in ethyl acetate (250 mL), washed with saturated aqueous sodium bicarbonate (2x
50 mL), brine and dried over anhydrous sodium sulfate, filtered and concentrated. The
precipitating product was collected by filtration, washed with hexane and dried to give 2-(4-
fluorophenyl)-1-((7-[4-(1 IH-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoazepin-4(5 H)-
yl)carbonyl)piperidin-4-one (0.19 g, 86 %). 1H NMR (400 MHz, d_6-DMSO): 12.48 (s, 1H),
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8.00 (d, 2H), 7.68 (d, 2H), 7.61 (d, IH), 7.55 (dd, IH), 7.31-7.26 (m, 3H), 7.10-6.92 (m, 4H), 5.20 (t, IH), 4.59 (s, ... Prepared according to the method of example 22 by using 3-hydroxy-3-(endo)-(trifluoromethyl)-8-

[00711] Using analogous synthetic techniques and substituting with alternative starting reagents in step 3 the following compounds of the invention were prepared.

[00712] (2R)-2-(4-fluorophenyl)-l-(7-[4-(1 H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoazepin-4(5 H)-y1)carbonyl)piperidin-4-one. Isolated by preparative chiral HPLC separation of the racemate using a SHIMADZU LC-8A apparatus equipped with a Chiralpak AD-H, 25 cm x 2.0 cm column using a mobile phase of hexane:2-propanol 4:1 and flow rate of 18.0 mL/min, detection at 220 nm. The isomer with retention time 26.0 min was assigned as the (R)-enantiomer. Chiral Analytical HPLC using a SHIMADZU LC-20AD apparatus equipped with a Chiralpak AD-H, 25 cm x 4.6 mm column using a mobile phase of ethanol:methanol 1:1 and flow rate of 0.7 mL/min, detection 254/220 nm gave a retention time 8.76 min and 98% enantiomeric excess. MS (EI) for C_{30}H_{27}F_{14}O_{3}: 511 (MH+).

[00713] (25)-2-(4-fluorophenyl)-l-(7-[4-(1 H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoazepin-4(5 H)-y1)carbonyl)piperidin-4-one. Isolated by preparative chiral HPLC separation of the racemate using a SHIMADZU LC-8A apparatus equipped with a Chiralpak AD-H, 25 cm x 2.0 cm column using a mobile phase of hexane:2-propanol 4:1 and flow rate of 18.0 mL/min, detection at 220 nm. The isomer with retention time 47.0 min was assigned as the (S)-enantiomer. Chiral Analytical HPLC using a SHIMADZU LC-20AD apparatus equipped with a Chiralpak AD-H, 25 cm x 4.6 mm column using a mobile phase of ethanol:methanol 1:1 and flow rate of 0.7 mL/min, detection 254/220 nm gave a retention time 11.20 min and 96% enantiomeric excess. MS (EI) for C_{30}H_{27}F_{14}O_{3}: 511 (MH+).

[00714] 2-(3-fluorophenyl)-l-(7-[4-(1 H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoazepin-4(5 H)-y1)carbonyl)piperidin-4-one. Synthesized according to the method of example 22 using 2-(3-fluorophenyl)-4-oxopiperidine-l-carbonyl chloride (reagent preparation 37) in step 3. H NMR (400 MHz, d_6-DMSO): 12.50 (br s, IH), 8.00 (d, 2H), 7.67 (d, 2H), 7.61 (d, IH), 7.55 (dd, IH), 7.32 (m, IH), 7.25 (br s, IH), 7.13-7.04 (m, 4H), 7.02 (d, IH), 5.20 (t, IH), 4.60 (s, 2H), 4.23 (m, 2H), 3.68 (m, 3H), 3.40 (m, IH), 2.85 (m, 2H), 2.60 (m, IH), 2.33 (2m, IH). MS (EI) C_{30}H_{27}F_{14}O_{3}: 511 (MH+).

[00715] 8-(7-[4-(1 H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoazepin-4(5 H)-y1)carbonyl)-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol. Prepared according to the method of example 22 by using 3-hydroxy-3-(endo)-(trifluoromethyl)-8-
azabicyclo[3.2.1]octane-8-carbonyl chloride (reagent preparation 37) in step 3. 

**H NMR** (400 MHz, methanol-d$_4$): 7.92 (m, 2H), 7.68 (m, 2H), 7.51 (m, 2H), 7.14 (s, 2H), 7.05 (m, 1H), 4.59 (s, 2H), 4.23 (m, 2H), 4.16 (m, 2H), 3.76 (m, 2H), 2.22-2.12 (m, 4H), 1.88 (m, 2H), 1.80 (m, 2H); MS (EI) for C$_{27}$H$_{32}$F$_3$N$_4$O$_3$: 513 (MH$^+$).

**[00716]** 2-(3,4-difluorophenyl)-1-({7-[4-(1H-imidazol-2-yl)phenyl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl}carbonyl)piperidin-4-one. Prepared according to the method of example 22 by using 2-(3,4-difluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) in step 3. 

**1H NMR** (400 MHz, d$_6$-DMSO): 12.55 (s, 1H), 8.00 (d, 2H), 7.70 (d, 2H), 7.63 (d, 1H), 7.55 (m, 1H), 7.35 - 7.26 (m, 2H), 7.13 - 7.10 (m, 2H), 7.02 (d, 1H), 5.14 (t,1H), 4.59 (m, 2H), 4.22 (m, 2H), 3.73 - 3.64 (m, 3H), 3.46 (m, 1H), 2.83 (d, 2H0, 2.59 (m, IH), 2.34 (m, 1H). MS (EI) for C$_{30}$H$_{26}$F$_2$N$_4$O$_3$: 529 (MH$^+$).

**Synthetic Example 23**

4-([4-(difluoromethyl)piperidin-1-yl]carbonyl)-7-[4-(1H-imidazol-2-yl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine

**[00717]** STEP 1: A suspension of isobutyl 2-(4-bromophenyl)-1H-imidazole-1-carboxylate (example 4, step 5) (72 mg, 0.22 mmol), bis(pinacolato)diboron (85 mg, 0.33 mmol), potassium acetate (109 mg, 1.11 mmol), and dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (18 mg, 0.02 mmol) in dimethyl sulfoxide (2 mL) was degassed with nitrogen, and then stirred at 90 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through celite. The filtrate was washed with water (lx) and brine (lx), dried over sodium sulfate, and concentrated to give crude 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1 H-imidazole which was used for the next step without further purification. MS (EI) for C$_{51}$H$_{49}$BN$_2$O$_{12}$: 271 (MH$^+$)

**[00718]** STEP 2: A mixture of 7-bromo-4-([4-(difluoromethyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine (78 mg, 0.20 mmol) (example 2, step 3), 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1 H-imidazole (0.20 mmol), cesium carbonate (325 mg, 1.00 mmol), and dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (16 mg, 0.02 mmol) in dioxane (5.0 mL) and water (0.5 mL) was degassed with nitrogen, and then stirred at 90 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through celite. The filtrate was washed with water (lx) and brine (lx), dried over sodium sulfate, filtered and concentrated. Purification by preparative reverse phase HPLC (0.1% aqueous trifluoroacetic acid-
acetonitrile) provided the title compound (4 mg, 4% yield). $^1$H NMR (400 MHz, methanol-$d_4$): 7.97 (d, 2H), 7.91 (d, 2H), 7.66 (s, 2H), 7.62 (d, IH), 7.57 (dd, IH), 7.08 (d, IH), 5.72 (m, IH), 4.53 (s, 2H), 4.24 (m, 2H), 3.72 (m, 4H), 2.84 (m, 2H), 2.00 (m, IH), 1.76 (m, 2H), 1.49 (m, 2H); MS (EI) for C$_2$H$_{16}$F$_2$N$_4$O$_2$: 453 (MH$^+$).

Synthetic Example 24

1-({[(7-6-(lf-imidazol-2-yl)pyridin-3-yl)2,3-dihydro-1,4-benzoxazepin-4(5 H)-yl]carbonyl}piperidine-4-carbonitrile

[00719] STEP 1: A mixture of (4-{{[(1,1-dimethylethyl)oxycarbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}boronic acid (example 1, step 2) (500 mg, 1.7 mmol), 5-bromopicolinaldehyde (380 mg, 2.0 mmol), cesium carbonate (1.66 g, 5.0 mmol), and dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium] (II) dichloromethane adduct (125 mg, 0.17 mmol) in dioxane (5.0 mL) and water (1.0 mL) was degassed with nitrogen, and then stirred at 90 °C with microwave irradiation for 30 min. The reaction mixture was cooled to room temperature, and partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2x), the combined organic layers were washed with brine (1x), dried over sodium sulfate, filtered and concentrated. Column chromatography on silica (hexanes/ethyl acetate 4:1) provided 1,1-dimethylethyl 7-(6-formylpyridin-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-carboxylate (580 mg, 96% yield) as a colorless solid. MS (EI) for C$_{20}$H$_{22}$N$_4$O$_4$: 355 (MH$^+$).

[00720] STEP 2: A solution of 1,1-dimethylethyl 7-(6-formylpyridin-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5 H)-carboxylate (580 mg, 1.6 mmol), ammonium acetate (1.85 g, 24.0 mmol), and glyoxal (0.25 mL of a 40% wt solution in water, 3.2 mmol) in ethanol (10 mL) was stirred at 70 °C for 45 min. The reaction mixture was cooled to room temperature, and partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2x), the combined organic layers were washed with brine (1x), dried over sodium sulfate, filtered and concentrated. Column chromatography on silica chloroform/methanol 9:1) afforded 1,1-dimethylethyl 7-[6-(1 H-imidazol-2-yl)pyridin-3-yl]-2,3-dihydro-1,4-benzoxazepin-4(5 H)-carboxylate (580 mg, 92% yield) as a brown solid. MS (EI) for C$_{22}$H$_{24}$N$_4$O$_3$: 393 (MH$^+$).

[00721] STEP 3: A solution of 1,1-dimethylethyl 7-[6-(1 H-imidazol-2-yl)pyridin-3-yl]-2,3-dihydro-1,4-benzoxazepin-4(5 H)-carboxylate (50 mg, 0.13 mmol) in a mixture of methanol (2 mL) and 4N hydrochloric acid in dioxane (2 mL) was refluxed for 5 min. After
cooling to room temperature and the reaction mixture was concentrated. The residue was then concentrated from chloroform (3x) and dried to give crude 7-[6-(IH-imidazol-2-yl)pyridin-3-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine.

[00722] STEP 4: The 7-[6-(1 H-imidazol-2-yl)pyridin-3-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine as obtained in step 3 was dissolved in dichloromethane (2 mL), diisopropylethylamine (0.12 mL, 0.65 mmol) was added, followed by addition of phosgene (0.07 mL of a 20% solution in toluene, 0.13 mmol). The reaction mixture was stirred at room temperature for 30 min and then concentrated to afford crude 7-[6-(1H-imidazol-2-yl)pyridin-3-yl]-2,3-dihydro-1,4-benzoxazepin-4(5H)-carboxylate (3.5 g, 9.1 mmol, example 26, step 1).

[00723] STEP 5: Dichloromethane (2 mL) was added to 7-[6-(1 H-imidazol-2-yl)pyridin-3-yl]-2,3-dihydro-1,4-benzoxazepin-4(5 H)-carbonyl chloride was obtained in step 4 followed by diisopropylethylamine (0.12 mL, 0.65 mmol) and 4-cyanopiperidine hydrochloride (25 mg, 0.16 mmol). The mixture was stirred at room temperature for 30 min and then concentrated. Purification of the residue by preparative reverse phase HPLC (0.1% aqueous ammonium acetate-acetonitrile) provided the title compound (18 mg, 32% yield) as a colorless solid. H NMR (400 MHz, DMSO-d$_6$): 12.84 (br. s, 1H), 8.86 (d, 1H), 8.11 (m, 2H), 7.71 (d, 1H), 7.61 (dd, 1H), 7.25 (br. s, 1H), 7.10 (br. s, 1H), 7.06 (d, 1H), 4.49 (s, 2H), 4.23 (m, 2H), 3.61 (m, 2H), 3.30 (m, 2H), 3.00 (m, 3H), 1.87 (m, 2H), 1.73 (m, 2H); MS (EI) for C$_{24}$H$_{24}$N$_6$O$_2$: 429 (MH$^+$).

Example 25: 8-{[7-(IH-imidazo[4,5-b]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl}-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol.

[00724] STEP 1: A suspension of 5-bromo-3-nitropyridin-2-amine (4.84 g, 22.2 mmol), 4-[[1,1-dimethylethyl]oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (6.51 g, 22.2 mmol), dichloro[l,l-bis(diphenyl)phosphino]ferrocenepalladium (II) dichloromethane adduct (1.60 g, 10 mol %) in dioxane (75 mL) and water (15 mL) was degassed with nitrogen, and then cesium carbonate (14.46 g, 44.4 mmol) was added. The reaction mixture was stirred at 90 °C overnight. The mixture was cooled to room temperature, water (150 mL) was added and stirred for 30 min to give a precipitate. The product 1,1-dimethylethyl 7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (8.1 g, 94% yield) was collected by filtration, dried under vacuum. MS (EI) for C$_9$H$_{22}$N$_4$O$_5$: 387.1(MH$^+$).

[00725] STEP 2: A mixture of 1,1-dimethylethyl 7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5 H)-carboxylate (3.5 g, 9.1 mmol, example 26, step 1) in
methanol (75 mL) and 4N hydrogen chloride in dioxane (11 mL) was stirred at 50 °C for 1.5 h and then concentrated. The resulting residue was triturated with a 10% methanol in diethyl ether solution (50 mL) to provide 3-nitro-5-(2,3,4,5-tetrahydro-1,4-benzoazepin-7-yl)pyridin-2-amine dihydrochloride (3.1 g, 95%) as a red solid. \[^1\text{H}\] NMR (400 MHz, \text{d}_6^*\text{DMSO}) \(\delta\) 9.76 (bs, 2H), 8.80 (d, 1H), 8.60 (s, 1H), 7.90 (s, 1H), 7.73 (dd, 1H), 7.16 (d, 1H), 4.39 (bs, 2H), 4.25 (bs, 2H), 3.48 (bs, 2H); MS (EI) for C\(_{24}\)H\(_{14}\)N\(_5\)O\(_3\): 488 (MH\(^+\)).

[00726] STEP 3: To a solution of 1,1-dimethylethyl 7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoazepine-4(5 \text{H})-carboxylate (1.1 g, 3.1 mmol) and DIPEA (2.7 mL, 16 mmol) in THF (10 mL) and NMP (5 mL) was added 3-hydroxy-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octane-8-carbonyl chloride (reagent preparation 37, 0.81 g, 3.1 mmol). The reaction mixture was heated (50 °C) for four hours and partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography provided 8-{[7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoazepine-4(5 \text{H})-yl]carbonyl}-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octane-8-carbonyl chloride (reagent preparation 37, 0.81 g, 3.1 mmol). The reaction mixture was heated (50 °C) for four hours and partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography provided 8-{[7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoazepine-4(5 \text{H})-yl]carbonyl}-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol (1.1 g, 69% yield) as red oil. MS (ES) for C\(_{23}\)H\(_{24}\)F\(_3\)N\(_5\)O\(_3\): 507.2 (MH\(^+\)).

[00727] STEP 4: A slurry of 8-{[7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoazepin-4(5 \text{H})-yl]carbonyl}]-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol (1.1 g, 2.2 mmol), Pd/C (5% wt./wt., 0.20 g) and acetic acid (40 mL) was subjected to an atmosphere of hydrogen (45 PSI) using a Parr apparatus. After 2 hours the reaction mixture was filtered through Celite and concentrated to give 8-{[7-(5,6-diaminopyridin-3-yl)-2,3-dihydro-1,4-benzoazepin-4(5 \text{H})-yl]carbonyl}-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol (0.95, 92% yield) as an orange oil. MS (ES) for C\(_{23}\)H\(_{20}\)F\(_3\)N\(_5\)O\(_3\): 478 (MH\(^+\)).

[00728] STEP 5: A slurry of 8-{[7-(5,6-diaminopyridin-3-yl)-2,3-dihydro-1,4-benzoazepin-4(5 \text{H})-yl]carbonyl}]-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol (0.22 g, 0.46 mmol) and trimethyl orthoformate (3.5 mL) was heated (105 °C) for 30 minutes. The reaction mixture was diluted with ethyl ether and the resulting precipitate was collected by filtration. Purification by preparative reverse phase HPLC provided 8-{[7-(1H-imidazo[4,5-b]pyridin-6-yl)-2,3-dimdro-1,4-benzoazepin-4(5H)-yl]carbonyl}-3-(trifluoromethyl)-8-azabicyclo[3.2.1]octan-3-ol (64 mg, 29% yield) as a white solid. \[^1\text{H}\] NMR (400 MHz, \text{d}_6^*\text{DMSO}) \(\delta\) 9.39 (s, 1H), 8.87 (s, 1H), 8.44 (s, 1H), 7.66 (s, 1H), 7.62 (dd, 1H), 7.07 (d, 1H), 5.81 (bs, 1H), 4.57 (s, 2H), 4.26 (s, 2H), 4.05 (s, 2H), 3.70 (s, 2H), 2.03 (m, 4H), 1.74 (m, 4H); MS (ES) for C\(_{24}\)H\(_{20}\)F\(_3\)N\(_5\)O\(_3\): 488 (MH\(^+\)).
Synthetic Example 26

\(N\)-(2,2-difluoroethyl)-4-(4-{[2-(3-fluorophenyl)-4-oxopiperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide

[00729]  STEP 1: To a solution of 4-(methoxycarbonyl)phenylboronic acid (6.0 g, 33 mmol), potassium bicarbonate (9.1 g, 92 mmol), 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (10 g, 31 mmol) and DIPEA (16 mL, 92 mmol) in dioxane (27 mL) and water (3 mL) was added dichloro[1,1-bis(diphenylphosphino)ferrocenepalladium (II) dichloromethane adduct (1.3 g, 1.8 mmol). The biphasic mixture was then heated at 90 °C for 2 h then partitioned with ethyl acetate and 1M hydrochloric acid. The organic layer was washed with 1M sodium hydroxide solution then dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (25% ethyl acetate in hexanes) to provide 1,1-dimethylethyl 7-{4-[(methyloxy)carbonyl]phenyl}-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (7.5 g, 64% yield) as a pale yellow solid. MS (EI) for \(C_{26}H_{23}FN_6O_3\) : 384 (MH\(^+\)).

[00730]  STEP 2: To a slurry of 1,1-dimethylethyl 7-{4-[(methyloxy)carbonyl]phenyl}-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (9.8 g, 26 mmol) in tetrahydrofuran (40 mL) was added a solution of lithium hydroxide (3.1 g, 130 mmol) in water (15 mL). The resulting mixture was heated at 60 °C for 18 h then partitioned between ethyl acetate (100 mL) and 1M hydrochloric acid (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by silica gel column chromatography (5% methanol in dichloromethane) provided 4-(4-[[1,1-dimethylethyl]oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoic acid (8.1 g, 85% yield). MS (EI) for \(C_{25}H_{22}N_5O_5\) : 370 (MH\(^+\)).

[00731]  STEP 3: To a cooled (0 °C) solution of 4-(4-[[1,1-dimethylethyl]oxy]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoic acid (0.95 g, 2.6 mmol), pyridine (1.3 mL, 15 mmol) and oxalyl chloride (0.44 mL, 5.1 mmol) in toluene (10 mL) was added dimethylformamide (0.01 mL, 0.1 mmol) and the resulting mixture was warmed to room temperature. After 24 h the reaction mixture was concentrated to provide 1,1-dimethylethyl 7-[4-(chlorocarbonyl)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (1.0 g, 100%) as a brown oil. MS (EI) for \(C_{28}H_{30}ClNO_4\) : 388 (MH\(^+\)).

[00732]  STEP 4: To a solution of 1,1-dimethylethyl 7-[4-(chlorocarbonyl)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (1.0 g, 2.6 mmol) and DIPEA (2.2 mL, 13
mmol) in tetrahydrofuran (10 mL) was added 2,2-difluoroethylamine (0.21 g, 2.6 mmol). The reaction mixture was stirred for 2 h and then partitioned between ethyl acetate (20 mL) and 1M hydrochloric acid (20 mL). The organic layer was washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by column chromatography on silica (30% ethyl acetate in hexanes) provided 1,1-dimethylethyl 7-(4-[(2,2-difluoroethyl)amino]carbonyl)phenyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.95 g, 85% yield). MS (EI) for C_{23}H_{26}F_{2}N_{2}O_{4}: 433 (MH^+).

[00733] STEP 5: To a slurry of 1,1-dimethylethyl 7-(4-[(2,2-difluoroethyl)amino]carbonyl)phenyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.95 g, 2.2 mmol) and methanol (30 mL) was added hydrogen chloride (4 M in dioxane, 3.3 mL, 13 mmol). The reaction mixture was heated (50 °C) for 1.5 hours then concentrated. The resulting residue was suspended in ethyl ether (15 mL) and the solid collected by filtration to give N-(2,2-difluoroethyl)-4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide hydrochloride salt (0.65 g, 80% yield) as a white solid. MS (EI) for C_{18}H_{18}F_{2}N_{2}O_{2}: 333 (MH^+).

[00734] STEP 6: To a slurry of N-(2,2-difluoroethyl)-4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide hydrochloride (0.19 g, 0.51 mmol), DIPEA (0.45 mL, 2.6 mL) and tetrahydrofuran (3 mL) was added 2-(3-fluorophenyl)-4-oxopiperidine-1-carbonyl chloride (reagent preparation 37) (0.13 g, 0.51 mmol). The reaction mixture was heated (50 °C) for 3 h and then concentrated. Purification by preparative reverse phase HPLC provided N-(2,2-difluoroethyl)-4-(2-(3-fluorophenyl)-4-oxopiperidin-1-yl)carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide (37 mg, 13% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): 7.82 (d, 2H), 7.55 (d, 2H), 7.47 (dd, 1H), 7.20-7.34 (m, 3H), 7.13 (d, 1H), 6.93-7.06 (m, 3H), 6.43 (t, 1H), 5.99 (tt, 1H), 5.34-5.40 (m, 1H), 4.54 (s, 2H), 4.20-4.30 (m, 2H), 3.73-3.93 (m, 5H), 3.20-3.30 (m, 1H), 2.84-3.06 (m, 2H), 2.54-2.64 (m, 1H), 2.32 (d, 1H); MS (EI) for C_{30}H_{28}F_{3}N_{3}O_{4}: 552 (MH^*).

**Synthetic Example 27**

4-[[2-(3-fluoro-4-methylphenyl)piperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

[00735] STEP 1: 7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine dihydrobromide (prepared as in step 5 example 1) (9.16 g, 20.76 mmol) was suspended in dichloromethane (100mL) followed by addition of DIPEA (12.6 mL, 72.7 mmol) and pyridine (1.7 mL, 20.8 mmol). Di-tert-butyl dicarbonate (10.0 g, 45.7 mmol) and
the solution was stirred for 12 h at room temperature. The mixture was concentrated and the residue partitioned with ethyl acetate and 10% aqueous citric acid. The organic phase was washed twice with additional 10% aqueous citric acid then brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue of 1,1-dimethyl 7-((1,1-dimethylethyl)oxy)carbonyl-2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate was taken into methanol (100 mL) followed by addition of sodium hydroxide (1.0 g, 25 mmol) in water (10 mL). The mixture was stirred for 1 h at room temperature then concentrated. The residue was partitioned with ethyl acetate and 1:1 brine: 10% aqueous citric acid. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give 1,1-dimethylethyl 7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (9.6 g) as an amorphous residue. MS (EI) for C_{23}H_{33}N_{3}O_{3}: 380(MH^+).

[00736] STEP 2: 1,1-dimethylethyl 7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate as prepared in step 1 (9.6 g) was taken into dichloromethane (100 mL) followed by sequential addition of DEPEA (4.3 mL, 24.9 mmol) and isobutyl chloroformate (2.7 mL, 20.8 mmol). The mixture was stirred for 1 h at room temperature then partitioned with 0.5 N aqueous hydrochloric acid. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford 1,1-dimethylethyl 7-(2-methyl-1-[(2-methylpropyl)oxy]carbonyl]-1H-benzimidazol-6-yl-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (10.3 g) as an amorphous residue. MS (EI) for C_{27}H_{33}N_{3}O_{3}: 480(MH^+).

[00737] STEP 3: 1,1-dimethylethyl 7-(2-methyl-1-[(2-methylpropyl)oxy]carbonyl]-1H-benzimidazol-6-yl-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate as obtained in step 2 (10.3 g) was taken into 1:1 TFA:dichloromethane (100 mL) and the resulting solution was stirred for 1 h at room temperature then concentrated. The residue was treated with saturated aqueous sodium bicarbonate (100 mL) and the aqueous mixture was treated with portion wise solid sodium bicarbonate until pH 8.5. The aqueous mixture was then saturated with sodium chloride and partitioned with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated then dried in vacuo. The residue was taken into 1:1 ethyl acetate/ethyl ether then washed with dilute aqueous sodium bicarbonate, water then brine and dried over anhydrous sodium sulfate. Silica gel was added to the mixture and stirred for 5 minutes then filtered through a celite bed. The filtrate was concentrated to
provide 2-methylpropyl 2-methyl-6-(2,3,4,5-tetramethyl-1,4-benzoxazepin-7-yl)-1H-benzimidazole-1-carboxylate (6.8 g, 86% overall yield).

[00738] Step 4: Phosgene (20 W% in toluene, 9.5 mL) was diluted into dichloromethane (40 mL) and the resulting solution cooled to 0 °C. 2-Methylpropyl 2-methyl-6-(2,3,4,5-tetramethyl-1,4-benzoxazepin-7-yl)-1H-benzimidazole-1-carboxylate as obtained in step 3 (6.8 g, 17.9 mmol) was taken into dichloromethane (30 mL) followed by addition of DEPEA (7.8 mL, 44.8 mmol) and the resulting solution was slowly added to the cooled phosgene solution over 5 minutes by addition funnel. The mixture was stirred an additional 5 minutes at 0 °C then allowed to warm to room temperature and concentrated. The residue was partitioned with ethyl acetate and 10% aqueous citric acid then washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography using 50% ethyl acetate in hexanes as eluent to give 2-methylpropyl 6-{4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-benzimidazole-1-carboxylate (3.73 g) as an amorphous solid.

[00739] STEP 5: 2-Methylpropyl 6-{4-(chlorocarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-benzimidazole-1-carboxylate (150 mg, 0.38 mmol) and 2-(3-fluoro-4-methylphenyl)piperidine (reagent preparation 1) (80 mg, 0.41 mmol) were taken into THF (3.5 mL) followed by addition of diisopropylethylamine (0.33 mL, 1.9 mmol) and the resulting solution was heated to reflux for 3h. The mixture was then cooled to room temperature and partitioned with ethyl acetate and 20% aqueous citric acid. The organic phase was separated, dried over sodium sulfate then filtered and concentrated. The residue obtained was taken up into methanol (5 mL) followed by addition of solid potassium carbonate (518 mg, 3.75 mmol) and the mixture was stirred for 12 h at room temperature. The mixture was then concentrated and the residue taken into a minimum of aqueous acetonitrile and purified by preparative reverse phase HPLC. Lyophilization of the combined pure fraction afforded 4-[[2-(3-fluoro-4-methylphenyl)piperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (23 mg) as an amorphous solid.

H NMR (400 MHz, d6-DMSO): 12.18 (br s, 1H), 7.59 (br s, 1H), 7.47 (dd, 2H), 7.40 (d, 1H), 7.27 (dd, 1H), 7.12 (t, 1H), 7.01 (d, 1H), 6.96 (d, 2H), 4.59 (m, 1H), 4.40 (dd, 2H), 4.18 (m, 2H), 3.53 (m, 2H), 3.21 (m, 1H), 3.00 (m, 1H), 2.50 (s, 3H), 2.24 (s, 3H), 1.96 (m, 1H), 1.79 (m, 1H), 1.62-1.38 (m, 4H). MS (EI) for C30H13F1N6O2: 499 (MH+).

[00740] Using analogous synthetic techniques and substituting with alternative starting reagents in steps 2 and/or 5 the following compounds of the invention were prepared.
Protecting group introduction and removal steps were conducted as required according to literature techniques appropriate for a given protecting group (see for example: Greene and Wuts, Protective Groups in Organic Synthetic, Wiley-Interscience). Alternative starting materials were obtained commercially unless otherwise indicated.

**[00741]** 7-(2-methyl-1H-benzimidazol-6-yl)-4-[(2-(methylphenyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic 2-o-tolylpiperidine in step 5. \(^1\)H NMR (400 MHz, de-DMSO): 7.88 (s, 1H), 7.79 (d, 1H), 7.73 (dd, 1H), 7.63 (m, 1H), 7.56 (dd, 1H), 7.26 (d, 1H), 7.11 (d, 1H), 7.06 (d, 1H), 7.04 (d, 1H), 6.91 (m, 1H), 6.81 (t, 1H), 4.68 (dd, 2H), 4.17 - 4.10 (m, 3H), 3.87 - 3.78 (m, 1H), 3.68 (m, 1H), 3.60 (m, 1H), 3.47 (m, 1H), 2.77 (s, 1H), 2.25 (s, 1H), 1.77 - 1.60 (m, 4H), 1.39 (m, 2H); MS (EI) for C\(_{33}\)H\(_{27}\)F\(_3\)N\(_4\)O\(_2\): 521 (MH\(^+\)).

**[00742]** 7-(2-methyl-1H-benzimidazol-6-yl)-4-[(2-(3-(trifluoromethyl)phenyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic 2-(3-(trifluoromethyl)phenyl)piperidine in step 5. \(^1\)H NMR (400 MHz, d\(_6\)-DMSO): 7.85 (s, 1H), 7.77 (d, 1H) 7.66 (d, 1H), 7.56-7.43 (m, 5H), 7.05 (d, 1H), 4.61 (q, 2H), 4.51 (t, 1H), 4.18 (m, 2H), 3.78-3.44 (m, 5H), 3.10 (br s, 2H), 2.77 (s, 3H), 1.88-1.82 (m, 2H), 1.63 (br s, 2H), 1.52 (br m, 2H); MS (EI) for C\(_{30}\)H\(_{29}\)F\(_3\)N\(_4\)O\(_2\): 535 (MH\(^+\)).

**[00743]** 4-[(2-(3-chloro-4-fluorophenyl)piperidin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic 2-(3-chloro-4-fluorophenyl)piperidine in step 5. \(^1\)H NMR (400 MHz, d\(_6\)-DMSO): 7.86 (s, 1H), 7.79 (d, 1H), 7.67 (d, 1H), 7.56 (m, 2H), 7.32 (d, 1H), 7.25-7.19 (m, 2H), 7.05 (d, 1H), 4.56 (q, 2H), 4.43 (t, 1H), 4.23-4.16 (m, 2H), 3.75-3.64 (m, 3H), 3.09 (t, 2H), 2.78 (s, 3H), 1.84-1.78 (m, 2H), 1.61 (br s, 2H), 1.50 (br m, 2H); MS (EI) for C\(_{29}\)H\(_{28}\)C\(_1\)FN\(_4\)O\(_2\): 519 (MH\(^+\)).

**[00744]** 7-(2-methyl-1H-benzimidazol-6-yl)-4-[(2-(3,4,5-trifluorophenyl)piperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic 2-(3,4,5-trifluorophenyl)piperidine in step 5. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.61 (br s, 1H), 7.55 (br d, 1H), 7.46 (dd, 1H), 7.37-7.44 (m, 3H), 7.09 (d, 1H), 6.88 (dd, 2H), 4.59-4.47 (m, 3H), 4.22-4.08 (m, 2H), 3.77 (m, 2H), 3.26-3.17 (m, 2H), 2.65 (s, 3H), 1.85 (m, 2H), 1.62 (m, 4H); MS (EI) for C\(_{29}\)H\(_{27}\)F\(_3\)N\(_4\)O\(_2\): 521 (MH\(^+\)).
Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic 2-(3,5-difluorophenyl)piperidine in step 5. H NMR (400 MHz, d<sub>6</sub>-DMSO): 7.85 (s, IH), 7.78 (d, IH), 7.67 (d, IH), 7.56 (m, 2H), 7.06 (d, IH), 6.98 (t, IH), 6.89 (d, IH), 7.58 (q, 2H), 4.45 (t, IH), 4.23-4.17 (m, 2H), 3.78-3.65 (m, 3H), 3.11 (brs, 2H), 2.78 (s, 3H), 1.81 (m, 2H), 1.61 (brs, 2H), 1.50 (m, 2H); MS (EI) for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>: 498 (MH<sup>+</sup>).

**N,N'-dimethyl-4-{1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl)carbonyl]piperidin-2-yl}aniline.** Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic N,N'-dimethyl-4-(piperidin-2-yl)aniline in step 5. MS (EI) for C<sub>34</sub>H<sub>38</sub>N<sub>4</sub>O<sub>2</sub>: 503 (MH<sup>+</sup>).

**7-(2-methyl-1H-benzimidazol-6-yl)-4-(morpholin-4-ylcarbonyl)-2,3,4,5-tetrahydro-1,4-benzoazepine.** Prepared according to the method of example 27 by using methyl chloroformate in step 2 and morpholine in step 5. H NMR (400 MHz, d<sub>6</sub>-DMSO): 7.88 (s, IH), 7.81 (d, IH), 7.24 (m, 2H), 7.62 (d, IH), 7.55 (dd, IH), 7.04 (d, IH), 4.51 (s, IH), 4.23 (t, IH), 3.65-3.58 (m, 6H), 3.12 (t, 4H), 2.74 (s, 3H); MS (EI) for C<sub>24</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>: 393 (MH<sup>+</sup>).

**(+)-(2R,4R)-4-methyl-1-{7-(2-methyl-1H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl}carbonyl}-2-phenylpiperidin-4-ol.** Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic (2R,4R)-4-methyl-2-phenylpiperidin-4-ol (reagent preparation 23) in step 5. H NMR (400 MHz, d<sub>4</sub>-methanol): 7.79 (s, IH), 7.73 (s, IH), 7.51-7.49 (m, 2H), 7.13 (d, 2H), 7.07-6.97 (m, 4H), 4.67 (dd AB, 2H), 4.38 (dd AB, 2H), 4.17 (tr AB, 2H), 4.03-3.96 (m, IH), 3.78 (d, tr AB, 2H), 3.29-3.25 (m, 2H), 2.84 (s, 3H), 1.89-1.82 (m, IH), 1.77-1.62 (m, 3H), 1.17 (s, 3H); MS (EI) for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>: 498 (MH<sup>+</sup>).

**(+)-(2R,4S)-4-methyl-1-{7-(2-methyl-1H-benzimidazol-5-yl)-2,3-dihydro-1,4-benzoazepin-4(5H)-yl}carbonyl}-2-phenylpiperidin-4-ol.** Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic (2R,4S)-4-methyl-2-phenylpiperidin-4-ol (reagent preparation 23) in step 5. H NMR (400 MHz, d<sub>4</sub>-methanol): 7.81 (s, IH), 7.74 (m, 2H), 7.51 (dd AB, 2H), 7.38 (d, IH), 7.18 (d, 2H), 7.12-7.05 (m, 4H), 4.62 (dd AB, 2H), 4.36 (dd AB, 2H), 4.22-4.10 (m, 2H), 3.22-3.15 (m, IH), 2.86 (s, 3H), 1.95-1.90 (m, IH), 1.84-1.72 (m, 3H), 1.70 (s, 3H); MS (EI) for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>3</sub>: 498 (MH<sup>+</sup>).
1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-4-[4-(trifluoromethyl)phenyl]piperidin-4-ol. Prepared according to the method of example 27 by using 4-(4-(trifluoromethyl)phenyl)piperidin-4-ol in step 5. H NMR (400 MHz, methanol-d$_4$): 7.66 (s, 1H), 7.65 (d, 1H), 7.55 (m, 3H), 7.51 (d, 1H), 7.47 (dd, 1H), 7.42 (dd, 1H), 7.06 (d, 1H), 4.46 (s, 2H), 4.24 (m, 2H), 3.74 (m, 2H), 3.64 (m, 2H), 3.38-3.24 (m, 2H), 2.58 (s, 3H), 2.11 (m, 2H), 1.70 (m, 2H); MS (EI) for C$_{28}$H$_{29}$F$_3$N$_4$O$_3$: 551 (MH$^+$).

4-(4-fluorophenyl)-1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 27 by using racemic 1-methyl-3-phenylpiperazine in step 5. MS (EI) for C$_{29}$H$_3$i$_2$N$_5$: 482 (MH$^+$).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-methyl-2-phenylpiperazin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 27 by using racemic 1-methyl-3-phenylpiperazine in step 5. MS (EI) for C$_{34}$H$_{33}$N$_5$: 544 (MH$^+$).

4-[(2,4-diphenylpiperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 27 by using racemic 1,3-diphenylpiperazine in step 5. H NMR (400 MHz, d$_6$-DMSO): 7.89 (s, 1H), 7.81 (d, 1H), 7.72 (m, 1H), 7.59-7.56 (m, 2H), 7.38 (d, 2H), 7.26 - 7.17 (m, 5H), 7.07 (d, 1H), 6.92 (d, 2H), 6.78 (t, 1H), 4.78 (t, 1H), 4.61 (s, 2H), 4.23 (t, 2H), 3.67-3.62 (m, 2H), 3.42-3.27 (m, 4H), 3.13 (m, 1H). MS (EI) for C$_{34}$H$_{33}$N$_5$: 544 (MH$^+$).

1-methyl-4-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]piperazin-2-one. Prepared as described in example 27 using 1-methylpiperazin-2-one in step 5. H NMR (400 MHz, methanol-d$_4$): 7.65 (s, 1H), 7.54-7.41 (m, 4H), 7.04 (d, 1H), 4.55 (s, 2H), 4.22 (t, 2H), 3.94 (s, 2H), 3.73 (t, 2H), 3.54 (t, 2H), 3.44 (t, 2H), 2.96 (s, 3H), 2.58 (s, 3H); MS (EI) for C$_{23}$H$_{29}$N$_5$: 420 (MH$^+$).

2-(1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]piperidin-4-yl)propan-2-ol. Prepared according to the method of example 27 by using 2-(piperidin-4-yl)propan-2-ol in step 5. H NMR (400 MHz, d$_6$-DMSO): 12.30 (br s, 1H), 7.62 (br m, 1H), 7.51 (dd, 1H), 7.46 (dd, 2H), 7.34 (d, 1H), 7.01 (d, 1H), 4.43 (s, 2H), 4.14 (m, 3H), 3.63 (d, 2H), 3.56 (m, 2H), 2.63 (t, 2H), 2.52 (s, 3H), 1.66 (d, 2H), 1.32 (dd, 1H), 1.21 (m, 2H), 1.03 (s, 6H). MS (EI) for C$_{26}$H$_{32}$N$_4$: 449 (MH$^+$).
Prepared according to the method of example 27 by using (±)-(2R,4S)-2-(3,4-difluorophenyl)piperidin-4-ol (reagent preparation 28) in step 5. H NMR (400 MHz, d<sub>6</sub>-DMSO): 7.62 (s, IH), 7.60 (d, IH), 7.47 (d, IH), 7.38 (d, IH), 7.08 (d, IH), 7.04-6.96 (m, 4H), 5.08 (t, IH), 4.08 (m, 2H), 4.02 (m, 2H), 3.64 (m, 2H), 3.30 (m, 2H), 2.51 (s, 3H), 1.90 (m, 2H), 1.64 (m, IH), 1.44 (m, 2H). MS (EI) C<sub>29</sub>H<sub>28</sub>F<sub>2</sub>N<sub>4</sub>O<sub>3</sub>: 519 (MH<sup>+</sup>).

Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(3,4-difluorophenyl)piperidine (reagent preparation 1) in step 5. H NMR (400 MHz, d<sub>6</sub>-DMSO): 12.24 (s, IH), 7.67 (s, 0.25H), 7.54 (m, 0.5H), 7.51 (0.25H), 7.49-7.46 (s, 2.5H), 7.44 (d, 0.5H), 7.29 (dt, IH), 7.26-7.19 (m, 2H), 7.05 (br m, IH), 7.01 (dd, IH), 4.58 (dd, IH), 4.46 (m, IH), 4.14 (m IH), 3.66 (m, IH), 3.30 (m, IH), 3.10 (m, 2H), 2.51 (s, 3H), 1.89 (m, IH), 1.78 (m, IH), 1.60 (m 3H), 1.48 (m, 3H). MS (El) for C<sub>29</sub>H<sub>28</sub>F<sub>2</sub>N<sub>4</sub>O<sub>3</sub>: 503 (MH<sup>+</sup>).

Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(3,5-bis(trifluoromethyl)phenyl)piperidine (reagent preparation 1) in step 5. H NMR (400 MHz, d<sub>6</sub>-DMSO): 7.83 (s, 1H), 7.80 (s, 3H), 7.73 (d, IH), 7.62 (m, IH), 7.58 (d, IH), 7.52 (dd, IH), 7.01 (d, IH), 4.63 (dd, 2H), 4.42 (m, IH), 4.18 (m IH), 3.72 (m IH), 3.62 (m, IH), 2.52 (s, 3H), 1.81 (m, IH), 1.70 (m, 6H), 1.50 (m, 2H). MS (El) for C<sub>31</sub>H<sub>28</sub>F<sub>6</sub>N<sub>4</sub>O<sub>2</sub>: 603 (MH<sup>+</sup>).

Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(3-chloro-5-fluorophenyl)piperidine (reagent preparation 1) in step 5. H NMR (400 MHz, d<sub>6</sub>-DMSO): 7.85 (d, IH), 7.78 (d, IH), 7.67 (dd, IH), 7.56 (s, 1.5H), 7.53 (d, 0.5H), 7.17 (2t, IH), 7.08 (s, IH), 7.05 (d, IH), 6.99 (br d, IH), 4.60 (dd, 2H), 4.39 (t, IH), 4.23 (m, IH), 4.16 (m, IH), 3.70 (m, IH), 3.10 (m, IH), 2.55 (s, 3H), 1.79 (m, 2H), 1.62 (m, 2H), 1.48 (m, 4H). MS (EI) for C<sub>29</sub>H<sub>28</sub>CIF<sub>3</sub>N<sub>4</sub>O<sub>2</sub>: 520 (MH<sup>+</sup>).
methylphenyl)piperidine (reagent preparation 1) in step 5. \[^1\text{H}\]NMR (400 MHz, CDCl\(_3\)): 9.28 (br s, 1H), 7.69 (br, 0.5H), 7.49 (d, 2H), 7.46 (br m, 1.5H), 7.40 (d, IH), 7.08 (d, IH), 7.04 (t, IH), 6.70 (d, IH), 6.49 (t, IH), 4.67 (dd, 2H), 4.24 (d, 2H), 4.04 (m, 2H), 3.78 (m 2H), 3.46 (m, IH), 2.89 (m, IH), 2.63 (s, 3H), 2.34 (s, 3H), 1.72 (m, 3H), 1.48 (m, 2H). MS (EI) for C\(_{20}\)H\(_{31}\)FN\(_4\)O\(_2\): 499 (MH\(^+\)).

[00761] 4-[[2-(4-fluoro-3-methylphenyl)piperidin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(4-fluoro-3-methylphenyl)piperidine (reagent preparation 1) in step 5. \[^1\text{H}\]NMR (400 MHz, CDCl\(_3\)): 7.54 (d, IH), 7.49 (s, IH), 7.43 (dd, IH), 7.28 (dd, IH), 7.19 (br s, IH), 7.07 (d, IH), 7.03 (m, 2H), 6.88 (t, IH), 4.68 (s, IH), 4.50 (s, 2H), 4.24 (m, IH), 4.18 (m, IH), 3.84 (m, IH), 3.68 (m, IH), 3.44 (m, IH), 3.21 (m, IH), 2.52 (s, 3H), 2.20 (s, 3H), 1.98 (m, IH), 1.88 (m, IH), 1.71 (m, IH), 1.58 (m, 3H). MS (EI) for C\(_{30}\)H\(_{41}\)FN\(_4\)O\(_3\): 499 (MH\(^+\)).

[00762] 2-(3,4-difluorophenyl)-1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-4-(trifluoromethyl)piperidin-4-ol. Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(3,4-difluorophenyl)-4-(trifluoromethyl)piperidin-4-ol (reagent preparation 21) in step 5. \[^1\text{H}\]NMR (400 MHz, d\(_6\)-DMSO): 12.22 (br s, IH), 7.59 (br m, IH), 7.46 (d, 2H), 7.36 (dd, IH), 7.33 (s, IH), 7.26 (m 2H), 7.19 (m, IH), 7.00 (d, IH), 5.76 (s, IH), 4.96 (t, IH), 4.49 (s, 2H), 4.18 (m, 2H), 3.59 (m, 2H), 2.52 (s, 3H), 2.30 (m, 2H), 2.00 (m, 2H), 1.84 (m, IH), 1.64 (m, IH). MS (EI) for C\(_{30}\)H\(_{27}\)F\(_5\)N\(_4\)O\(_3\): 587 (MH\(^+\)).

[00763] 7-(2-methyl-1H-benzimidazol-6-yl)-4-[[2-(4-(trifluoromethyl)phenyl)piperidin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(4-(trifluoromethyl)phenyl)piperidine (reagent preparation 1) in step 5. \[^1\text{H}\]NMR (400 MHz, d\(_4\)-methanol): 7.61 (d, IH), 7.51 (d, IH), 7.47 (dd, IH), 7.41 (d, IH), 7.39 (br s, 4H), 7.34 (dd, IH), 7.04 (d, IH), 4.62 (d, 2H), 4.52 (m, IH), 4.24 (m, IH), 4.12 (m, IH), 3.78 (t, IH), 3.24 (m, IH), 2.59 (s, 3H), 1.91 (m, 3H), 1.72 (m, 2H), 1.61 (m, 3H). MS (EI) for C\(_{39}\)H\(_{29}\)F\(_5\)N\(_4\)O\(_3\): 535 (MH\(^+\)).

[00764] 2-(3,4-difluorophenyl)-1-[[7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]piperidin-4-one. Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(3,4-difluorophenyl)piperidin-4-one (reagent preparation 20) in step 5. \[^1\text{H}\]NMR (400 MHz, d\(_4\)-methanol): 7.64 (d, IH), 7.51 (t, IH), 7.48 (m, 2H), 7.39 (dd, IH), 7.18 (m, IH), 7.07-7.01 (m, 3H), 5.18 (t, IH), 4.90 (dd,
2H), 4.23 (m, 2H), 3.79 (t (2H), 3.78 (m, IH), 3.50 (m, IH), 2.86 (d, 2H), 2.67 (m, IH), 2.58 (s, 3H), 2.42 (2t, IH). MS (EI) for C_{29}H_{29}F_2N_4O_3: 517 (MH^+).

[00765] (+)-(2R,4S)-2-(4-fluorophenyl)-l-[(7-(2-methyl-l H-benimidazol-6-yl)-2,3-dihydro-l,4-benzoxazepin-4(5 H)-yl]carbonyl]piperidin-4-ol. Synthesized according to the method of example 27 using (+)-(2R,4S)-2-(4-fluorophenyl)piperidin-4-ol (reagent preparation 28) in step 5. H NMR (400 MHz, d$_4$-MeOH): 7.65 (s, 1H), 7.56 (d, IH), 7.52 (t, IH), 7.49 (d, IH), 7.43 (dd, IH), 7.11 (dd, 2H), 7.04 (d, IH), 6.75 (t, 2H), 4.62 (s, 2H), 4.10 (m, IH), 4.01 (dd, 2H), 3.84 (m, IH), 3.74 (m 2H), 3.48 (2t, IH), 2.82 (t, IH), 2.58 (s, 3H). MS (EI) for C$_{29}$H$_{29}$F$_N$O$_{3}$: 501 (MH^+).

[00766] 4-[(4,4-difluoro-2-phenylpiperidin-1-yl)carbonyl]-7-(2-methyl-1H-benimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 27 using 4-(difluoromethylene)piperidine (see, WO2005009943) in step 5. H NMR (400 MHz, d$_4$-MeOH): 7.64 (m, IH), 7.52 (d and s, 2H), 7.45 (m, 2H), 7.03 (d, IH), 4.52 (s, 2H), 4.20 (m, 2H), 3.70 (m, 2H), 3.24 (m, 2H), 2.58 (s, 3H), 2.24 (m, 6H). MS (EI) for C$_{24}$H$_{24}$F$_2$N$_4$O$_2$: 439 (MH^+).

[00767] 4-[(4,4-difluoro-2-phenylpiperidin-1-yl)carbonyl]-7-(2-methyl-l H-benimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 27 using 4,4-difluoro-2-phenylpiperidine (reagent preparation 29) in step 5. H NMR (400 MHz, d$_4$-MeOH): 7.49 (br s, IH), 7.41 (d, IH), 7.38 (dd, IH), 7.25 (d, IH), 7.24 (t, IH), 7.17 (d, IH), 7.15 (d, IH), 7.09-7.03 (m, 3H), 6.93 (d, IH), 4.56 (s, 2H), 4.49 (m, IH), 4.09 (m, IH), 3.99 (m, IH), 3.69 (m, 2H), 3.30 (m, 2H), 2.49 (s, 3H), 2.28 (m, IH), 2.08 (m, 3H). MS (EI) for C$_{24}$H$_{24}$F$_2$N$_4$O$_2$: 503 (MH^+).

[00768] 7-(2-methyl-l H-benimidazol-5-yl)-4-[(2-phenylazepan-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-phenylazepane in step 5. H NMR (400 MHz, d$_6$-DMSO): 12.22 (br s, IH), 7.62 (br s, 0.5 H), 7.50 (br m, IH), 7.44 (dd, IH), 7.30-7.23 (m, 5.5H), 7.18 (m, 2H), 6.97 d, IH), 5.06 (m, IH), 4.34 (s, 2H), 4.10 (m, 2H), 3.78 (dd, IH), 3.49 (m, 2H), 3.10 (m, IH), 2.49 (s, 3H), 2.34 (m, IH), 1.66 (m, 5H), 1.40 (dd, IH), 1.29 (m, IH). MS (EI) for C_{30}H_{32}N_4O_2: 481 (MH^+).

[00769] 4-[(2-3-chlorophenyl)piperidin-1-yl]carbonyl]-7-(2-methyl-l H-benimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(3-chlorophenyl)piperidine in step 5. MS (EI) for C$_{29}$H$_{29}$ClN$_4$O$_2$: 502 (MH^+).
2-(3-fluorophenyl)-1-[(7-(2-methyl-1H-benimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl)piperidin-4-one. Synthesized according to the method of example 27 using methyl chloroformate in step 2 and 2-(3-fluorophenyl)piperidin-4-one (reagent preparation 20) in step 5. MS (EI) for C_{29}H_{26}FN_{10}O_3: 499 (MH^+).

4-Methyl-1-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl)piperidine-4-carboxamide. Prepared according to the method of example 27 by using 4-methylpiperidine-4-carboxamide (synthesized according to the procedure disclosed in WO2008011499) in step 5. h NMR (400 MHz, methanol-d_4): 7.59 (br, IH), 7.43 to 7.32 (m, 4H), 6.93 (d, IH), 4.38 (s, 2H), 4.01 (m, 2H), 3.57 (m, 2H), 3.37 to 3.30 (m, 2H), 3.00 (t, 2H), 2.45 (s, 3H), 2.01 to 1.93 (m, 2H), 1.44 to 1.36 (m, 2H), 1.12 (s, 3H); MS (EI) for 3/4 H_{29}N_{10}O_3: 448 (MH^+).

(±)-(2R,4S)-2-(3,4-difluorophenyl)-4-(fluoromethyl)piperidine-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazine. Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic (2R,4S)-2-(3,4-difluorophenyl)-4-(fluoromethyl)piperidine (reagent preparation 33) in step 5. h NMR (400 MHz, methanol-d_4): 7.65 (s, IH), 7.56 to 7.47 (m, 3H), 7.43 (dd, IH), 7.04 (d, IH), 7.00 to 6.94 (m, IH), 6.92 to 6.87 (m, 2H), 4.70 (q, 2H), 4.30 (dd, 2H), 4.17 to 4.02 (m, 2H), 4.01 to 3.87 (m, 2H), 3.78 to 3.72 (m, IH), 3.59 to 3.53 (m, IH), 2.83, (t, IH), 2.57 (s, 3H), 2.00 to 1.92 (m, IH), 1.85 to 1.78 (m, 2H), 1.68 to 1.55 (m, IH), 1.33 (dd, IH); MS (EI) for C_{30}H_{29}F_{13}N_{5}O_2: 535 (MH^+).

(±)-(2R,4S)-2-(3,4-difluorophenyl)-l-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl)piperidine-4-carbonitrile. Prepared according to the method of example 27 by using methyl chloroformate in step 2 and racemic (2R,4S)-2-(3,4-difluorophenyl)piperidine-4-carbonitrile hydrochloride (reagent preparation 34) in step 5. h NMR (400 MHz, methanol-d_4): 7.61 (br, IH), 7.52 to 7.45 (m, 2H), 7.36 to 7.31 (m, 2H), 7.20 to 7.14 (m, IH), 7.09 to 7.01 (m, 3H), 4.68 to 4.66 (m, IH), 4.60 (d, 2H), 4.25 to 4.09 (m, 2H), 3.78 (dd, 2H), 3.48 to 3.41 (m, IH), 3.26 to 3.18 (m, IH), 3.02 to 2.96 (m, IH), 2.57 (s, 3H), 2.33 to 2.26 (m, IH), 2.12 to 1.93 (m, 4H); MS (EI) for C_{30}H_{27}F_{2}N_{5}O_2: 528 (MH^+).

9-[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]carbonyl]-1,2,3,4-tetrahydro-1,4-epiminonaphthalene. Synthesized according to the method of example 27 using 1,2,3,4-tetrahydro-1,4-epiminonaphthalene in step 5. h NMR (400 MHz, DMSO-d_6): δ 12.24 (bs, IH), 7.08-7.74 (m, 9H), 6.97 (d, IH), 4.98 (s, 2H), 4.50
Synthetic Example 28

7\(^2\)-methyl-1H-benzimidazol-6-yl)-4-[(4\(^{y}\)rim^ din-2-ylpiperazin-1-yl)carbonyl]-2,3,4,5- 
tetrahydro-1,4-benzoxazepine

**[00775]**

STEP 1: To a solution of 1,1-dimethylethyl 6-{4-(chlorocarbonyl)-2,3,4,5- 
tetrahydro-1,4-benzoxepin-7-yl)-1 H-benzimidazole-1-carboxylate (5.5mg, 16 \(\mu\)mol) and 2- 
(piperazin-1-yl)pyrimidine (7.9 mg, 48 \(\mu\)mol) in anhydrous DCM (2 mL) was added PL- 
DIPAM (85mg, 3.27 mmol/g loading, 315 \(\mu\)mol, Polymer Labs) and the reaction mixture was 
shaken overnight at room temperature. The resulting mixture was drained into PL-PETA 
(55mg, 2.7 mmol/g loading, 175 \(\mu\)mol, Polymer Labs) and PL-MIA; (35 mg, 2.65 mmol/g 
loading, 104 \(\mu\)mol, Polymer Labs). The reaction mixture was shaken overnight at room 
temperature, drained and the resin was washed with 3.0 mL of methanol. The combined 
methanol solution was transferred to a 2 dram vial and concentrated under reduced pressure. 
The resulting oil was dissolved in methanol (2 mL) followed by the addition of 4 N 
anhydrous hydrogen chloride in dioxane (0.5 mL, Aldrich). The mixture was shaken at room 
temperature for an additional 18 hours. The resulting solution was concentrated under 
reduced pressure to give 7-(2-methyl-1H-benzimidazol-6-yl)-4-{[4-pyrimidin-2-ylpiperazin-
1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C\(_{26}\)H\(_{27}\)N\(_6\)O\(_2\): 470.5 (MH\(^+\)).

**[00776]** The compound was analyzed by LC-MS (Mux) and demonstrated purity 
requirement was measured above 80% AUC based on UV absorbance.

**[00777]** Using the above automated synthesis technique and substituting with alternative 
starting amines the following compounds of the invention were prepared. Alternative starting 
materials were obtained commercially unless otherwise indicated. All compounds of the 
invention demonstrated purity requirement was measured above 80% AUC based on UV 
absorbance.

**[00778]** 4-(azocan-1-ylcarbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro- 
1,4-benzoxazepine. MS (EI) for C\(_{23}\)H\(_{30}\)N\(_4\)O\(_2\): 419.5 (MH\(^+\)).

**[00779]** 7-(2-methyl-1H-benzimidazol-6-yl)-4-{[4-(phenylpiperazin-1-yl)carbonyl]-2,3,4,5- 
tetrahydro-1,4-benzoxazepine. MS (EI) for C\(_{23}\)H\(_{29}\)N\(_5\)O\(_2\): 468.6 (MH\(^+\)).

**[00780]** 4-{[4-(4-fluorophenyl)piperazin-1-yl]carbonyl}-7-(2-methyl-1H-benzimidazol-6- 
yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C\(_{28}\)H\(_{28}\)F\(_N_5\)O\(_2\): 486.6 (MH\(^+\)).
7-(2-methyl-1H-benzimidazol-6-yl)-4-([4-(4-nitrophenyl)piperazin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{28}H_{32}N_{4}O_{2}: 457.6 (MH^+).

1-(4-(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl)piperazin-1-yl)phenyl)ethanone. MS (EI) for C_{39}H_{31}N_{5}O_{3}: 510.6 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-phenylpiperidin-1-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{29}H_{33}N_{4}O_{2}: 467.6 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-([4-(phenylmethyl)piperidin-1-yl]carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{39}H_{32}N_{4}O_{2}: 481.6 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-pyrindin-2-yl)piperazin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{27}H_{28}N_{6}O_{2}: 469.6 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-(octahydroquinolin-1(2H)-yl)carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{25}H_{32}N_{4}O_{2}: 445.6 (MH^+).

N-ethyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-(phenylmethyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. MS (EI) for C_{37}H_{32}N_{4}O_{2}: 441.5 (MH^+).

N-butyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-(phenylmethyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. MS (EI) for C_{39}H_{32}N_{4}O_{2}: 469.6 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-phenyl-3,6-dihydropyridin-1(2H)-yl)carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{29}H_{28}N_{4}O_{2}: 486.5 (MH^+).

4-[(4-(furan-2-yl)carbonyl)piperazin-1-yl]carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{27}H_{27}N_{5}O_{4}: 485 (MH^+).

4-[(4-(3-chlorophenyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{28}H_{28}ClN_{5}O_{2}: 503.0 (MH^+).

4-[(4-(2-fluorophenyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{28}H_{28}FN_{3}O_{2}: 486.6 (MH^+).

4-[(4-(2-chlorophenyl)piperazin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{28}H_{28}ClN_{5}O_{2}: 503.0 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-[3-(methyloxy)phenyl)piperazin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{29}H_{31}N_{5}O_{3}: 498.6 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-[(4-pyrizin-2-yl)piperazin-1-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{28}H_{27}N_{7}O_{2}: 470.5 (MH^+).

7-(2-methyl-1H-benzimidazol-6-yl)-N-[(1r,3r,5R,7R-tricyclo[3.3.1.1^{3,7}]dec-2-yl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. MS (EI) for C_{28}H_{32}N_{4}O_{2}: 457.6 (MH^+).
7-(2-methyl-1H-benzimidazol-6-yl)-4-(4-[5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl)carbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{28}H_{32}N_{6}O_{2}: 537.6 (MH+).

ethyl N-{(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl \(-\)-N-(phenylmethyl)glycinate. MS (EI) for C_{29}H_{30}N_{4}O_{4}: 499.6 (MH+).

4-(4-{[2-chloro-6-fluorophenyl]methyl)piperazin-1-yl}carbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{29}H_{26}ClFN_{5}O_{2}: 535.0 (MH+).

N-methyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-[(3-methylphenyl)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. MS (EI) for C_{27}H_{28}N_{4}O_{2}: 441.5 (MH+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-{[(5-methyl-1,2,4-oxadiazol-3-yl)piperidin-1-yl]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{26}H_{28}N_{6}O_{3}: 473.5 (MH+).

4-{[(4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)piperidin-1-yl)carbonyl]-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{28}H_{30}N_{6}O_{3}: 499.6 (MH+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-{[(4-[(methylphenyl)oxy]methyl]morpholin-4-yl]carbonyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{30}H_{22}N_{4}O_{4}: 513.6 (MH+).

4-ethyl-9-{[(7-(2-methyl-1H-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl)carbonyl]-3,9-diazaspiro[5.5]undecan-2-one. MS (EI) for C_{29}H_{35}N_{5}O_{3}: 502.6 (MH+).

7-(2-methyl-1H-benzimidazol-6-yl)-N-(4-pentylphenyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. MS (EI) for C_{29}H_{32}N_{4}O_{2}: 469.6 (MH+).

N-methyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-(phenylethyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. MS (EI) for C_{26}H_{26}N_{4}O_{2}: 428 (MH+).

N-methyl-7-(2-methyl-1H-benzimidazol-6-yl)-N-(2-phenylethyl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxamide. MS (EI) for C_{27}H_{28}N_{4}O_{2}: 442 (MH+).

4-(3,4-dihydroisooquinolin-2(1H)-ylcarbonyl)-7-(2-methyl-1H-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{27}H_{26}N_{4}O_{2}: 440 (MH+).

7-(2-methyl-1H-benzimidazol-6-yl)-4-(octahydroisooquinolin-2(1H)-ylcarbonyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. MS (EI) for C_{27}H_{32}N_{4}O_{2}: 446 (MH+).
Biological Examples

Biological Example 1

mTOR/Gbl J Raptor (mTORCl) ELISA Assay

The measurement of mTORCl enzyme activity was performed in an ELISA assay format following the phosphorylation of 4E-BP1 protein. All experiments were performed in the 384-well format. Generally, 0.5 µL DMSO containing varying concentrations of the test compound was mixed with 15 µL enzyme solution. Kinase reactions were initiated with the addition of 15 µL of substrates-containing solution. The assay conditions were as follows; 0.2 nM mTORCl, 10 µM ATP and 50 nM NHis-tagged 4E-BP1 in 20 mM Hepes, pH 7.2, 1 mM DTT, 50 mM NaCl, 10 mM MnCl₂, 0.02 mg/mL BSA, 0.01% CHAPS, 50 mM β-glycerophosphate. Following an incubation of 120 minutes at ambient temperature, 20 µL of the reaction volume was transferred to a Ni-Chelate-coated 384-well plate. The binding step of the 4E-BP1 protein proceeded for 60 minutes, followed by washing 4 times each with 50 µL of Tris-buffered saline solution (TBS). Anti-phospho-4E-BP1 rabbit-IgG (20 µL, 1:5000) in 5% BSA-TBST (0.2% Tween-20 in TBS) was added and further incubated for 60 minutes. Incubation with a secondary HRP-tagged anti-IgG was similarly performed after washing off the primary antibody (4 washes of 50 µL). Following the final wash step with TBST, 20 µL of SuperSignal ELISA Femto (Pierce Biotechnology) was added and the luminescence measured using an EnVision plate reader.

In the above assay, Compounds 7, 20, 22, 23, 26-35, 36, 41-49, 53, 54, 55-62, 65, 66, 81, 73, 96, 109, 111, 114, 116, 118, 120, 123, 124, 125, 128-130, 142, and 179-181 have an IC₅₀ of less than or equal to 50 nM. Compounds 2, 11-16, 18, 19, 21, 25, 37-40, 51, 52, 63, 64, 69, 70, 72, 76, 83-85, 79, 90-92, 94, 95, 98, 102, 103, 105, 113, 121, 135, 136, 138-140, 143, 148, 156, 157, 170, and 176-178 have an IC₅₀ of greater than 50 nM but less than or equal to 250 nM. Compounds 5, 6, 8, 24, 50, 67, 68, 74, 80, 86, 88, 89, 97, 100, 104, 106-108, 110, 122, 127, 137, 141, 145-147, 152, 153, 155, 161, 162, 163, 171, 173, and 174 have an IC₅₀ of greater than 250 nM but less than or equal to 700 nM. Compounds 1, 3, 4, 10, 17, 75, 77, 93, 99, 117, 126, 131, 133, 134, 149, 154, 159, 160, 165-167, 172, and 175 have an IC₅₀ of greater than 700 nM but less than or equal to 2600 nM. Compounds 9, 71, 78, 82, 87, 101, 112, 115, 119, 132, 144, 150, 151, 158, 164, 168, and 169 were not active under the conditions the assay were run.
Biological Example 2

Immune-Complex mTORC2 Kinase (mTORC2 IP-Kinase) Assay

[00812] HeLa (ATCC) cells are grown in suspension culture and lysed in ice-cold lysis buffer containing 40 mM HEPES pH 7.5, 120 mM NaCl, 1 mM EDTA, 10 mM sodium pyrophosphate, 10 mM β-glycerophosphate, 10 mM NaF, 10 mM NaN₃, one tablet of protease inhibitors (Complete-Mini, EDTA-free, Roche), 0.3% chlamidopropylidemethylammoniopanesulfonate (CHAPS), 1 mM AEBSF, 0.5 mM benzamidine HCl, 20 µg/mL heparin, and 1.5 mM Na₃VO₄. The mTORC2 complex is immunoprecipitated with anti-RICTOR antibody for 2 h. The immune complexes are immobilized on Protein A sepharose (GE Healthcare, 17-5280-01), washed sequentially 3 times with wash buffer (40 mM HEPES pH 7.5, 120 mM NaCl, 10 mM β-glycerophosphate, 0.3% CHAPS, 1 mM AEBSF, 20 µg/mL heparin, 1.5 mM Na₃VO₄, and Complete-Mini, EDTA-free) and resuspended in kinase buffer (40 mM HEPES, pH 7.5, 120 mM NaCl, 0.3% CHAPS, 20 µg/mL heparin, 4 mM MgCl₂, 4 mM MnCl₂, 10% Glycerol, and 10 mM DTT). The immune complexes (equivalent to 1x10⁷ cells) are pre-incubated at 37 °C with a test compound or 0.6% DMSO for 5 min, and then subjected to a kinase reaction for 8 min in a final volume of 33 µL (including 5 µL bed volume) containing kinase buffer, 50 µM ATP, and 0.75 µg full length dephosphorylated AKT1. Kinase reactions are terminated by addition of 11 µL 4x SDS sample buffer containing 20% β-mercaptoethanol and resolved in a 10% Tris Glycine gels. The gels are transferred onto PVDF membrane at 50 V for 20 h at 4 °C. The membranes are blocked in 5% non-fat milk in TBST for 1 h and incubated overnight at 4 °C with 1/1000 dilution of rabbit anti-pAKT (S473) (Cell Signaling Technology, 4060) in 3% BSA/TBST. The membranes are washed 3 times in TBST and incubated for 1 h with a 1/10000 dilution of secondary goat anti-rabbit HRP antibody (Cell Signaling Technology, 2125) in 5% non-fat milk/TBST. The signal is detected using Amersham ECL-plus. The scanned data are analyzed using ImageQuant software. IC₅₀ for the test compound is determined relative to DMSO treated sample using XLfit4 software.

Biological Example 3

PI3K Biochemical Assays

[00813] PI3Ka activity is measured as the percent of ATP consumed following the kinase reaction using luciferase-luciferin-coupled chemiluminescence. Reactions were conducted in 384-well white, medium binding microtiter plates (Greiner). Kinase reactions were initiated by combining test compounds, ATP, substrate (PIP2), and kinase in a 20 µL volume in a
buffer solution. The standard PDKalpha assay buffer is composed 50 mM Tris, pH 7.5, 1 mM EGTA, 10 mM MgCl₂, 1 mM DTT and 0.03% CHAPS. The standard assay concentrations for enzyme, ATP, and substrate are 1.5 nM, 1 µM, and 10 µM, respectively. The reaction mixture was incubated at ambient temperature for approximately 2 h. Following the kinase reaction, a 10 µL aliquot of luciferase-luciferin mix (Promega Kinase-Glo) was added and the chemiluminescence signal measured using a Victor2 plate reader (Perkin Elmer). Total ATP consumption was limited to 40-60% and IC₅₀ values of control compounds correlate well with literature references. Substituting PI3Kα with PI3Kβ, PI3Kγ, or PI3K5, the inhibitory activity of the compounds for the other isoforms of I3K were measured.

All Compounds in Table 1 were tested in the assays described in Biological Examples 1 and 3. The Compounds demonstrated activity against PI3K, mTOR, or both. In the above assay, Compounds 7, 11, 12, 14, 16, 18, 20, 30, 32, 34-37, 39, 41, 42, 44-49, 53-56, 57, 59, 60, 66, 73, 81, 114, 130, 179, 179, and 181 have an IC₅₀ of less than or equal to 75 nM. Compounds 13, 17, 21, 23, 27-29, 38, 43, 58, 61, 62, 96, 109, 111, 116, 118, 121, 123-125, 128, 129, and 180 have an IC₅₀ of greater than 75 nM but less than or equal to 200 nM. Compounds 2, 15, 19, 22, 24, 25, 26, 31, 33, 40, 51, 52, 71, 72, 76, 84, 86, 88, 90, 91, 110, 112, 120, 127, 137, 140, 142, 143, 148, 156, 157, 161, 166, 172, 177, and 178 have an IC₅₀ of greater than 200 nM but less than or equal to 500 nM. Compounds 50, 63, 64, 71, 78, 79, 87, 89, 92, 95, 97-100, 102, 105, 107, 108, 113, 122, 132, 136, 138, 150, 169, and 174 have an IC₅₀ of greater than 500 nM but less than or equal to 1000 nM. Compounds 3, 5, 8, 9, 67-70, 74, 75, 80, 82, 83, 85, 93, 94, 101, 103, 106, 115, 119, 131, 134, 135, 139, 144, 145, 147, 151, 153, 154, 158, 162, 163, 164, 167, 170, 175, and 176 have an IC₅₀ of greater than 1000 nM but less than or equal to 3000 nM. Compounds 1, 4, 6, 10, 65, 77, 104, 117, 126, 133, 141, 146, 149, 152, 155, 159-160, 165, 171, and 173 were not active under the conditions the assay were run.

**Embodiments 1:** In one embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.5 µM or less and is inactive for mTOR (when tested at a concentration of 2.0 µM or greater) or is selective for PI3K-alpha over mTOR by about 5-fold or greater, about 7-fold or greater, or about 10-fold or greater. In another embodiment, the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.35 µM or less and is inactive for mTOR (when tested at a concentration of 2.0 µM or greater) or is selective for PI3K-alpha over mTOR by about 5-
fold or greater, about 7-fold or greater, or about 10-fold or greater. In another embodiment, the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.25 µM or less and is inactive for mTOR (when tested at a concentration of 2.0 µM or greater) or is selective for PI3K-alpha over mTOR by about 5-fold or greater, about 7-fold or greater, or about 10-fold or greater. In another embodiment the compounds of the invention have an PI3K-alpha-inhibitory activity of about 0.1 µM or less and is inactive for mTOR (when tested at a concentration of 2.0 µM or greater) or is selective for PI3K-alpha over mTOR by about 5-fold or greater, about 7-fold or greater, or about 10-fold or greater. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.05 µM or less and is selective for PI3K-alpha over mTOR by about 5-fold or greater, about 7-fold or greater, or about 10-fold or greater.

[00816] Embodiments 2: In one embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 2.0 µM or less and an mTOR-inhibitory activity of about 2.0 µM or less and the selectivity for one of the targets over the other does not exceed 3-fold. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 1.0 µM or less and an mTOR-inhibitory activity of about 1.0 µM or less and the selectivity for one of the targets over the other does not exceed 3-fold. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.5 µM or less and an mTOR-inhibitory activity of about 0.5 µM or less and the selectivity for one of the targets over the other does not exceed 3-fold. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.3 µM or less and an mTOR-inhibitory activity of about 0.3 µM or less and the selectivity for one of the targets over the other does not exceed 3-fold. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.2 µM or less and an mTOR-inhibitory activity of about 0.2 µM or less and the selectivity for one of the targets over the other does not exceed 2-fold. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.15 µM or less and an mTOR-inhibitory activity of about 0.15 µM or less and the selectivity for one of the targets over the other does not exceed 2-fold. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.1 µM or less and an mTOR-inhibitory activity of about 0.1 µM or less. In another embodiment the invention comprises a compound of the invention having a PI3K-alpha-inhibitory activity of about 0.05 µM or less.
and an mTOR-inhibitory activity of about 0.05 µM or less. In another embodiment the invention comprises a compound of the invention have a PI3K-alpha-inhibitory activity of about 0.02 µM or less and an mTOR-inhibitory activity of about 0.02 µM or less. In another embodiment the invention comprises a compound of the invention have a PI3K-alpha-inhibitory activity of about 0.01 µM or less and an mTOR-inhibitory activity of about 0.01 µM or less.

[00817] In some embodiments, a series of PI3K inhibitors with varying isozyme selectivity were profiled for inhibition of IGFl-mediated AKT(T308) phosphorylation in MCF-7 cells (PI3Ka-E545K mutant) and T-47D cells (PI3Ka-H1047R mutant) (Table 2).
### Table 3. Cell Line Seeding Densities for ELISA and Proliferation Assays

<table>
<thead>
<tr>
<th>Cell Line</th>
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<th>Proliferation Seeding Density cells/well</th>
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<td>12,000</td>
<td>IGF1</td>
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</tr>
</tbody>
</table>

N/A = not applicable

NEAA = 1% non-essential amino acids, P/S = 1% penicillin/streptomycin
IGF1 = 300 ng/mL long R3 IGF1 (Sigma, 11271) for 10 min (except HCT 116 for 20 min)
Herregulin = 100 ng/mL recombinant human HRGrI-beta EGF domain (R&D Systems #, 396-HB) for 15 min
EGF = 20 ng/mL EGF (US Biologicals, E3374-07A) for 10 min

### Biological Example 4

**pS6 (S240/244) ELISA Assay**

[00818] MCF-7 cells (ATCC) were seeded at 24000 cells per well in 96-well plates (Corning, 3904) in DMEM (Cellgro) containing 10% FBS (Cellgro), 1% NEAA (Cellgro) and 1% penicillin-streptomycin (Cellgro). Cells were incubated at 37°C, 5% CO₂ for 48 h, and the growth medium was replaced with serum-free DMEM or in medium containing 0.4% BSA. Serial dilutions of the test compound in 0.3% DMSO (vehicle) were added to the cells and incubated for 3h. To fix the cells, medium was removed and 100 µL/well of 4% formaldehyde (Sigma Aldrich, F8775) in TBS (20 mM Tris, 500 mM NaCl) was added to each well at RT for 30 min. Cells were washed 4 times with 200 µL TBS containing 0.1% Triton X-100 (Sigma, catalog # T9284). Plates were blocked with 100 µL Odyssey blocking buffer (Li-Cor Biosciences, 927-40000) for 1h at RT. Anti-pS6 (S240/244) antibody (Cell
Signaling Technology, 2215) and anti-total-S6 antibody (R&D systems, MAB5436) were diluted 1:400 in Odyssey blocking buffer, and 50 µL of the antibody solution containing both antibodies was added to one plate to detect pS6 and total S6. After incubation overnight at 4°C, plates were washed 4 times with 200 µL TBS containing 0.1% Tween20 (Bio-Rad, catalog # 170-6351) (TBST). Goat anti-rabbit and Goat anti-mouse secondary antibody (Li-Cor Biosciences, catalog # 926-32221 and 926-32210) conjugated to IRDye were diluted 1:400 in Odyssey blocking buffer containing 0.1% Tween20. 50 µL of antibody solution containing both antibodies was added to each well and incubated for 1 h at RT. Plates were washed 3 times with 200 µL TBST and 2 times with 200 µL TBS. Fluorescence was read on an Odyssey plate reader. IC50 values were determined based on the ratio of pS6 to total S6 signal for compound treated wells, normalized to the DMSO-treated control wells.

[00819] In one embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 1.0 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.5 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.25 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.2 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.15 µM or less.

[00820] In another embodiment, cells were seeded onto 96-well plates (Corning, 3904) in their respective growth media at the densities listed in Table 3. Cells were incubated at 37°C, 5% CO2 for 48 h. Compounds were serially diluted in DMSO and subsequently diluted in serum-free DMEM. Test compounds were added to cells in serum-free DMEM at a final concentration of 0.3% DMSO and incubated for 3 h. Cells were then stimulated with growth factors as listed in Table 3. To fix the cells, medium was removed and 50 µL well of 4% formaldehyde (Sigma, F8775) in high-salt TBS (20 mM Tris, pH 7.4; 500 mM NaCl) was added to each well at RT for 30 min. Cells were washed 3 times with 200 µL high salt TBST and blocked with Odyssey blocking agent (Li Cor Biosciences #, 927 40000) for 1 h. Anti-phospho-RPS6(S240/244) antibody (1:400 dilution factor, Cell Signaling Technology #, 2215L) and anti-total-RPS6 antibody (1:2000 dilution factor, Santa Cruz Biotech #, sc 74576) were diluted in Odyssey blocking solution and 50 µL added per well. After incubation overnight at 4°C, plates were washed 4 times with 200 µL high salt TBST. Goat anti-rabbit
IRDye 800CW- and goat anti-mouse IRDye 680-conjugated secondary antibodies (Li-Cor Biosciences #, 926 3221 1 and #, 926 32220, respectively) diluted 1:400 in Odyssey blocking buffer containing 0.1% Tween 20 were added to each well for 2 h at RT. Plates were washed 3 times with 200 µL high salt TBST and 3 times with 200 µL high salt TBS and then read on a Li-Cor Odyssey Infrared Imager with In-cell Western plug-in. Integrated intensities for phospho-RPS6(S240/244) were normalized to the signal for total RPS6 and IC50 values were determined relative to the DMSO treated control.

**Biological Example 5**

**pAKT (T308) ELISA Assay**

[00821] MCF-7 cells (ATCC) cells were seeded at 24000 cells per well in 96-well plates (Corning, 3904) in DMEM (Cellgro) containing 10% FBS (Cellgro), 1% NEAA (Cellgro) and 1% penicillin-streptomycin (Cellgro). Cells were incubated at 37°C, 5% CO2 for 48 h, and the growth medium was replaced with serum-free DMEM or in medium containing 0.4% BSA. Serial dilutions of the test compound in 0.3% DMSO (vehicle) were added to the cells and incubated for 3h. At the end of the incubation period, cells were stimulated for 10 minutes by the addition of L-IGF (Sigma, 1-1271) at a final concentration of 100ng/ml. Afterwards, media was discarded from cell plates and 110µl/well of cold lysis buffer (see table below) were added. Cell plates were incubated on ice and then put on shaker in 4°C cold room for 1h. Two capture plates (Thermo Scientific, Reacti-bind plate, 15042) were prepared for each cell plate by pre-coating with capture Akt antibody from the two sandwich ELISA antibody pairs used (Cell Signaling Technology 7142 and 7144). The Akt capture antibodies were diluted 1:100 in PBS and 100µl of diluted capture antibody was added per well. Capture plates were incubated at 4C overnight. Prior to use, capture plates were washed 3 times in TBS containing 0.1% Tween20 (Bio-Rad, 170-6351) (TBST) and blocked in blocking buffer (Thermo Scientific, Starting Block T20, 37543) for 1 - 2 h at room temperature. After 1h of cell lysis, 85µl of cell lysate/well was transferred to the capture plate for detection of pAkt(T308). 15µl of cell lysate was transferred from same well to the second capture plate for detection of total Aktl. After incubation overnight at 4°C, plates were washed 3 times with 200µL TBST. Primary antibodies, diluted 1:100 in blocking buffer, were added to the corresponding capture plates for pAkt(T308) (Cell Signaling Technology, 7144) and total Aktl (Cell Signaling Technology, 7142) detection and incubated at room temperature for 1h. Plates were washed 3 times with 200µL of TBST. Goat anti-mouse secondary antibody (Cell Signaling Technology, 7076) conjugated to HRP was diluted
1:1000 in blocking buffer and 100µL were added to each well and incubated for 30 minutes at room temperature. Plates were then washed 3 times with 200µL of TBST. 100µL of SuperSignal ELISA Femto stable peroxidase solution (Thermo Scientific, 37075) was added to each well. After 1 minute incubation, chemiluminescence was read on a Wallac Victor2 1420 multilabel counter. IC50 values were determined based on the ratio of pAkt(T308) to total Akt signal for compound treated wells, normalized to the DMSO-treated control wells.

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</tr>
</thead>
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<td></td>
</tr>
<tr>
<td>Complete Protease</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitors (Roche</td>
<td>1 x</td>
<td>1 x</td>
<td></td>
</tr>
<tr>
<td>1 836 170)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5x RIPA</td>
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<td>1 mM</td>
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<tr>
<td>B-glycerophosphate</td>
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</tr>
<tr>
<td>Phosphatase Inhibitor I (Sigma P2850)</td>
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<td>1x</td>
<td>100µL</td>
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<tr>
<td>Na orthovanadate</td>
<td>200 mM</td>
<td>1 mM</td>
<td>50µL</td>
</tr>
<tr>
<td>EDTA, pH 8</td>
<td>500 mM</td>
<td>1 mM</td>
<td>20µL</td>
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</table>

[00822] In one embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 1.5 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 1.0 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.75 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.5 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.25 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.2 µM or less. In another embodiment, the Compounds of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of about 0.15 µM or less.

[00823] In another embodiment, the pAKT ELISA Assay was performed by seeding cells onto 96-well plates (Corning, 3904) in their respective growth media at the densities listed in Table 3. Cells were incubated at 37°C, 5% CO2 for 48 h (except MDA-MB-453 cells which were cultured in the absence of CO2). Compounds were serially diluted in DMSO and subsequently diluted in serum-free DMEM. Test compounds were added to cells in serum-free DMEM at a final concentration of 0.3% DMSO and incubated for 3 h. Cells were
then stimulated with growth factors as listed in Table 3. Cells were lysed with 130 µL of ice-cold RIPA lysis buffer (50 mM Tris-HCl, pH 7.5; 0.5% sodium deoxycholic acid; 1% Triton X-100; 0.1% SDS; 150 mM NaCl) with protease and phosphatase inhibitors (1 mM EDTA, 1 mM NaF, 20 mM β-glycerophosphate, 1 mM Na-orthovanadate, Complete-Mini EDTA-free, Roche, 11836170001, and Phosphatase Inhibitor Cocktail I, Sigma, P2850), directly in 96-well plates. Cells were lysed on ice for 60-120 min at 4°C. The supernatants were added directly to capture ELISA plates previously pre-coated with rabbit anti-AKT capture antibody. ELISA assays for pAKT(T308) and total AKT were performed with the pAKT(T308) ELISA kit (Cell Signaling Technology, 7144) and AKT1 ELISA kit (Cell Signaling Technology, 7142). For the pAKT(T308) ELISA, 85 µL of cell lysate was added to each well. For the total AKT1 ELISA, 15 µL of cell lysate and 85 µL of Starting Block buffer (Pierce, 37543) were added to each well. The plates were incubated overnight at 4°C with gentle shaking, then washed 3 times with 200 µL of TBST (20 mM Tris, pH 7.4; 150 mM NaCl; 0.1% Tween 20) for 30 s each, and incubated for 1 h with 100 µL of detection antibody (mouse anti- pAKT(T308) antibody or mouse anti-AKT1 antibody). After 3 washes with TBST, the plates were incubated with a 1:1000 dilution of a horseradish peroxidase-labeled anti-mouse IgG (Cell Signaling Technology, 7076) in 100 µL of Starting Block buffer for 0.5 h. After 3 washes with TBST, 50 µL of SuperSignal ELISA Femto substrate solution (Thermo Scientific, 37075A) and 50 µL of SuperSignal ELISA enhancer solution mixture (Thermo Scientific, 37075B) were added to each well and the plates were incubated for approximately 2 min and protected from light. The wells were measured for luminescence using a Wallac plate reader at wavelength of 560 nm. After normalization of pAKT signal to total AKT1 signal, IC50 values were determined relative to the DMSO-treated control.

**Biological Example 6**

**PAKT (S473) ELISA Assay**

[00824] Cells were seeded onto 96-well plates (Corning, 3904) in their respective growth media at the densities listed in Table 3. Cells were incubated at 37°C, 5% CO2 for 48 h (except MDA-MB-453 cells which were cultured in the absence of CO2). Compounds were serially diluted in DMSO and subsequently diluted in serum-free DMEM. Test compounds were added to cells in serum-free DMEM at a final concentration of 0.3% DMSO and incubated for 3 h. Cells were then stimulated with growth factors as listed in Table 3. (For assays done in the presence of 10% FBS, compounds were added to cells at 10% FBS final concentration, cells were incubated for 3 hr, and no additional growth factors were added.)
To fix the cells, medium was removed and 50 µL/well of 4% formaldehyde (Sigma, F8775) in high-salt TBS (20 mM Tris, pH 7.4; 500 mM NaCl) was added to each well at RT for 30 min. Cells were washed 3 times with 200 µL high-salt TBST (20 mM Tris, pH 7.4; 500 mM NaCl; 0.1% Triton X-100) and blocked with Odyssey blocking agent (Li-cor Biosciences, 927-40000) for 1 h. Anti-pAKT(S473) antibody (1:400 dilution factor, Cell Signaling Technology, 4060) and anti-total-AKT antibody (1:600 dilution factor, R&D Systems, MAB2055) were diluted in Odyssey blocking solution. 50 µL of antibody solution was added per well. After incubation overnight at 4°C, plates were washed 4 times with 200 µL high-salt TBST. Goat anti-rabbit IRDye 800CW- and goat anti-mouse IRDye 680-conjugated secondary antibodies (Li-cor Biosciences, 926-32211 and, 926-32220, respectively) diluted 1:400 in Odyssey block containing 0.1% Tween-20 were added as 50 µL to each well for 2 h at RT. Plates were washed 3 times with 200 µL high-salt TBST and 3 times with 200 µL high-salt TBS and then read on a Li-Cor Odyssey Infrared Imager with In-cell Western plug-in. Integrated intensities for pAKT(S473) were normalized to the signal for total AKT and IC50 values were determined relative to the DMSO-treated control.

[00825] In order to determine if PI3Ka mutation status correlated with increased sensitivity of AKT(T308) to isozyme selective inhibitors, two representative PI3Ka /mTOR dual and two representative PI3Ka selective compounds are tested for inhibition of growth factor mediated AKT(T308) phosphorylation in a wild type PI3Ka line (SK-BR-3), an additional E545K line (NCI-H460), and three additional H1047R lines (BT-20, HCT 116, and MDA-MB-453). pAKT(T308) IC50 values for PI3Ka inhibitors are significantly lower in the four kinase domain mutant lines suggesting that the H1047R mutation may sensitize tumor cells to inhibition of PI3K signaling by PI3Ka-selective compounds.

Biological Example 7

Selectivity of PI3K-a mutations

[00826] In some embodiments, the ability of various classes of compounds to selectively profile distinct tumor cell genetic backgrounds was borne out using experiments described in Biological Examples 3, 5 and 6. The methods disclosed in these Biological Examples were performed using the following compounds:

PI3K-a selective inhibitors:
Using the above 3 PI3K-α selective inhibitors, 2 Dual PI3K-α/mTOR selective inhibitors and PI3K-β selective inhibitor in the Biological Examples 3, 5 and 6, it was found that PI3K-α selective inhibitors inhibit growth factor induced AKT phosphorylation with a 5 to 10-fold greater potency in PI3KCA (H1047R) mutated models. Furthermore, compared to PI3KCA (E545K) mutated models, a combination of a PI3K-α selective inhibitor and a PI3K-β selective inhibitor results in inhibition in an E545K cell model that is comparable to a PI3K-α selective alone in a H1047R model alone. See FIGs 1-4D. As shown in Table 4, Compounds 698, 696 and 699 (PI3Kα selective compounds) were shown to be specific for PI3Kα isoforms, but not PI3Kβ, PI3Kγ and mTOR. The dual PI3Kα/mTOR selective inhibitors (693 and 694) were similarly not active against PI3Kβ, PI3Kδ, PI3Kγ, but were
active in inhibiting the activity of mTOR. The PI3Kβ active compound TGX-221 was active against PI3Kβ mediated activity. See Table 3.

Table 4. PI3K biochemical IC_{50} values (nM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>PI3Kα</th>
<th>PI3Kα E545K</th>
<th>PI3Kα H1047R</th>
<th>PI3Kβ</th>
<th>PI3Kδ</th>
<th>PI3Kγ</th>
<th>mTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>698</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>1559</td>
<td>162</td>
<td>159</td>
<td>120</td>
</tr>
<tr>
<td>696</td>
<td>3</td>
<td>9</td>
<td>5</td>
<td>1314</td>
<td>149</td>
<td>1800</td>
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</tr>
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<td>6</td>
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<td>693</td>
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<td>575</td>
<td>1118</td>
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<td>694</td>
<td>4</td>
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<td>5</td>
<td>&gt;3000</td>
<td>831</td>
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<td>TGX-221</td>
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<td>nd</td>
<td>nd</td>
<td>16</td>
<td>142</td>
<td>1678</td>
<td>10856</td>
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</table>

PIP2 used as substrate for PI3K Class I isoforms
4EBP1 used as substrate for mTOR/Gbl/raptor kinase

[00828] In some embodiments, a series of PI3K inhibitors with varying isozyme selectivity were profiled for inhibition of IGFl-mediated AKT(T308) phosphorylation in MCF-7 cells (PI3Kα-E545K mutant) and T-47D cells (PI3Kα-H1047R mutant). Moreover, results of PI3Kα inhibitor activated vs. PTE-null cellular models are provided in Table 5. PI3K-a selective compounds inhibit IGFl-mediated AKT phosphorylation with similar potencies in MCF-7 (PI3K-αE545K) and PC3 (PTEN null) cellular models. Dual PI3K-a/mTOR selective inhibitors are more potent that PI3K-a-selective compounds in both models. PI3K-a selective compounds show 5 to 10 fold greater potency in inhibiting pAKT (T308) in H1048R-mutated vs. E545K-mutated cell lines. Results of PI3Kα inhibitor activated vs. PTE-null cellular models are provided in Table 5. PI3K-a selective compounds (698, 696 and 699) inhibit IGFl-mediated AKT phosphorylation with similar potencies in MCF-7 (PI3K-ot E545K) and PC3 (PTEN null) cellular models. Dual PI3K-cc/mTOR selective inhibitors (693 and 694) are more potent that PI3K-a-selective compounds in both models. PI3K-a selective compounds show 5 to 10 fold greater potency in inhibiting pAKT (T308) in H1048R-mutated vs. E545K-mutated cell lines.
In order to determine if PI3Kα mutation status correlated with increased sensitivity of AKT(T308) to isozyme selective inhibitors, a representative PI3Kα/mTOR dual and a representative PI3Kα selective compound were tested for inhibition of growth factor mediated AKT(T308) phosphorylation in an E545K line (MCF-7), and two additional H1047R lines (HCT 116, and T-47D). pAKT(T308) IC₅₀ values for PDKα inhibitors were significantly lower in the two kinase domain mutant lines suggesting that the H1047R mutation may sensitize tumor cells to inhibition of PI3K signaling by PI3Kα-selective compounds. IC₅₀ values for PDKα selective compounds were lowest in PI3K-H1047R/KRAS-wt lines T-47D, MDA-MB-453, HCT 116 (PI3K-H1047R/KRAS-G12D) and SK-OV-3, and highest in, (E545K) cell lines MCF-7 and, NCI-H460 (PDK-E545K/KRAS-Q61H), and PDKα wild-type SK-BR-3. See Table 6. The results suggest that the PI3K-H1047R mutation may sensitize cells to the phenotypic effects of PDKα selective compounds while PTEN loss or KRAS activation may desensitize cells to these inhibitors. In these cell assays, as would be expected TGX-221 PDKβ inhibitor has no effect on PDKα mediated activity in these cell models.

### Table 5. PDKα inhibitor activity in PI3K-activated vs. PTEN-null cellular models

<table>
<thead>
<tr>
<th>Compound</th>
<th>Biochemical IC₅₀ (nM)</th>
<th>pAKT (T308) IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MCF-7 PI3Kα E545K</td>
</tr>
<tr>
<td>698</td>
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<td>696</td>
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<td>TGX-221</td>
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<td>10856</td>
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</tbody>
</table>

In these cell assays, as would be expected TGX-221 PDKβ inhibitor has no effect on PDKα mediated activity in these cell models.
Table 6. Differential cellular activity in PI3Ka-mutated models

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cellular pAKT (T308) IC_{50} (nM)</th>
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<tbody>
<tr>
<td></td>
<td>PI3KaE545K</td>
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<tr>
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<td>MCF-7</td>
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<td>NCI-H460</td>
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</table>

Biological Example 8-16

Pharmacodynamic xenograft tumor models

[00830] Female and male athymic nude mice (NCr) 5-8 weeks of age and weighing approximately 20-25 g are used in the following models. Prior to initiation of a study, the animals are allowed to acclimate for a minimum of 48 h. During these studies, animals are provided food and water ad libitum and housed in a room conditioned at 70-75°F and 60% relative humidity. A 12 h light and 12 h dark cycle is maintained with automatic timers. All animals are examined daily for compound-induced or tumor-related deaths.

MCF-7 Breast adenocarcinoma model

[00831] MCF7 human mammary adenocarcinoma cells are cultured in vitro in DMEM (Cellgro) supplemented with 10% Fetal Bovine Serum (Cellgro), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO_{2} atmosphere. On day 0, cells are harvested by trypsinization, and 5 x 10^{6} cells in 100 μL of a solution made of 50% cold Hanks balanced salt solution with 50% growth factor reduced matrigel (Becton Dickinson) implanted subcutaneously into the hindflank of female nude mice. A transponder is implanted into each mouse for identification and data tracking, and animals are monitored daily for clinical symptoms and survival.

[00832] Tumors are established in female athymic nude mice and staged when the average tumor weight reached 100-200 mg. A Compound of the Invention is orally administered as a solution/fine suspension in water (with 1:1 molar ratio of 1 N HCL) once-daily (qd) or
twice-daily (bid) at 10, 25, 50 and 100 mg/kg for 14 days. During the dosing period of 14-19
days, tumor weights are determined twice-weekly and body weights are recorded daily.

Colo-205 colon model

[00833] Colo-205 human colorectal carcinoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO₂ atmosphere. On day 0, cells are harvested by trypsinization, and 3x10⁶ cells (passage 10-15, >95% viability) in 0.1 mL ice-cold Hank’s balanced salt solution are implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival.

[00834] Tumors are established in female athymic nude mice and staged when the average tumor weight reached 100-200 mg. A Compound of the Invention is orally administered as a solution/fine suspension in water (with 1:1 molar ratio of 1 N HCl) once-daily (qd) or twice-daily (bid) at 10, 25, 50 and 100 mg/kg for 14 days. During the dosing period of 14 days, tumor weights are determined twice-weekly and body weights are recorded daily.

PC-3 prostate adenocarcinoma model

[00835] PC-3 human prostate adenocarcinoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 20% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO₂ atmosphere. On day 0, cells are harvested by trypsinization and 3x10⁶ cells (passage 10-14, >95% viability) in 0.1 mL of ice-cold Hank’s balanced salt solution are implanted subcutaneously into the hindflank of 5-8 week old male nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival.

[00836] Tumors are established in male athymic nude mice and staged when the average tumor weight reached 100-200 mg. A Compound of the Invention is orally administered as a solution/fine suspension in water (with 1:1 molar ratio of 1 N HCl) once-daily (qd) or twice-daily (bid) at 10, 25, 50, or 100-mg/kg for 19 days. During the dosing period of 14-19 days, tumor weights are determined twice-weekly and body weights are recorded daily.

U-87 MG human glioblastoma model

[00837] U-87 MG human glioblastoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO₂ atmosphere. On day 0, cells are harvested by trypsinization and 2x10⁶ cells (passage 5, 96% viability) in 0.1 mL of ice-cold
Hank's balanced salt solution are implanted intradermally into the hindflank of 5-8 week old female nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

**A549 human lung carcinoma model**

[00838] A549 human lung carcinoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO₂ atmosphere. On day 0, cells are harvested by trypsinization and 10^5 cells (passage 12, 99% viability) in 0.1 mL of ice-cold Hank's balanced salt solution are implanted intradermally into the hindflank of 5-8 week old female nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

**A2058 human melanoma model**

[00839] A2058 human melanoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO₂ atmosphere. On day 0, cells are harvested by trypsinization and 3x10^6 cells (passage 3, 95% viability) in 0.1 mL ice-cold Hank's balanced salt solution are implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

**WM-266-4 human melanoma model**

[00840] WM-266-4 human melanoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO₂ atmosphere. On day 0, cells are harvested by trypsinization and 3x10^6 cells (passage 5, 99% viability) in 0.1 mL ice-cold Hank's balanced salt solution are implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

[00841] Tumor weight (TW) in the above models is determined by measuring perpendicular diameters with a caliper, using the following formula:

\[
\text{tumor weight (mg)} = \frac{[\text{tumor volume} \times \text{length (mm)} \times \text{width}^2 (\text{mm}^2)]}{2}
\]
These data were recorded and plotted on a tumor weight vs. days post-implantation line graph and presented graphically as an indication of tumor growth rates. Percent inhibition of tumor growth (TGI) is determined with the following formula:

\[
1 - \left( \frac{(X_t - X_0)}{(Y_t - X_0)} \right) \times 100
\]

where \( X_0 \) = average TW of all tumors on group day
\( X_t \) = TW of treated group on Day f
\( Y_t \) = TW of vehicle control group on Day f

If tumors regress below their starting sizes, then the percent tumor regression is determined with the following formula:

\[
\left( \frac{X_0 - X_r}{X_0} \right) \times 100
\]

Tumor size is calculated individually for each tumor to obtain a mean ± SEM value for each experimental group. Statistical significance is determined using the 2-tailed Student's t-test (significance defined as P<0.05).

**BrdU Cell Proliferation Assay**

Cells were seeded onto 96-well plates (Corning, 3904) in their respective growth media at the densities listed in Table 2. Cells were incubated at 37°C, 5% CO\(_2\) overnight (except MDA-MB-453 cells which were cultured in the absence of CO\(_2\)). Cells were then treated the next day with a serial dilution of compound in their respective growth medium (containing a final concentration of 0.3% DMSO). Triplicate wells were used for each compound concentration. The control wells received 0.3% DMSO in growth medium. The plates were incubated at 37°C, 5% CO\(_2\) for an additional 48 h. Cells were labeled with BrdU (Roche, 10280879001, 20 μM) for 2-4 h and then fixed with 70% EtOH + 0.1 M NaOH for 30 min at RT. Anti-BrdU-Peroxidase (Roche, 11585860001, 1/2000 in PBS + 1% BSA) conjugate was added to the cells, after which the plates were washed 3 times with 1x PBS. Chemiluminescent substrate solution (Pierce, 3707A and B) was added, and the plates were read for luminescence using the Wallac Victor plate reader for 0.1 sec. IC\(_{50}\) values were determined based on cell proliferation with compound treatment compared to the 0.3% DMSO vehicle control.

**Illustrative Embodiments**

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1. A method for treating a subject having a tumor comprising:
   (a) administering a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to the subject if said tumor comprises a mutation in a PI3K-a kinase domain; or
   (b) administering a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a PBK-β selective inhibitor, to said subject if said tumor comprises a mutation in a PI3K-a helical domain.

2. The method of embodiment 1, further comprising administering an additional chemotherapeutic agent in steps (a) or (b).

3. The method according to embodiment 2, wherein said additional chemotherapeutic agent comprises anti-microtubule agents; platinum coordination complexes; alkylating agents; antibiotic agents; topoisomerase II inhibitors; antimetabolites; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

4. The method of embodiment 2, wherein said additional therapeutic agent administered in step (b) further comprises a PI3K-5 selective inhibitor, a PI3K-γ selective inhibitor or a pan PI3K selective inhibitor.

5. The method according to embodiment 4, wherein said pan PI3K selective inhibitor comprises PI-103 or PIK-75.

6. The method according to embodiment 1, wherein the mutation in said kinase domain comprises a mutation at position 1047 of SEQ ED NO:1.

7. The method according to embodiment 6, wherein said mutation of said kinase domain is a substitution of H1047R in SEQ ID NO:1.

8. The method according to embodiment 1, wherein said mutation in said PI3K-a comprises a mutation in a helical domain.

9. The method according to embodiment 8, wherein said mutation in said helical domain comprises a mutation at position 545 in SEQ ID NO:1.

10. The method according to embodiment 9, wherein said mutation at position 545 comprises a substitution of E545K in SEQ ID NO:1.

11. The method according to embodiment 1, wherein said PI3K-a selective inhibitor comprises a PI3K-a selective inhibitor selected from Table 1.
12. The method according to embodiment 10, wherein said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or.

[Diagram of chemical structure]

13. The method according to embodiment 1, wherein said dual PBK-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor is a Compound of Formula I or a compound of Table 1.

14. The method according to claim 13, wherein said dual PI3K-a/mTOR selective inhibitor comprises one or more of

[Diagrams of chemical structures]

15. The method according to embodiment 1, wherein said combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor comprises a PI3K-α selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

16. The method according to embodiment 1, wherein said mutation in said helical domain comprises a PI3K-a having a substitution E545K in SEQ ID NO: 1.

17. The method according to embodiment 1, wherein administering a PI3K-a selective inhibitor comprises administering a PI3K-α selective inhibitor to the subject in an amount varying from about 0.001 mg/kg to about 100 mg/kg.
18. The method according to embodiment 1, wherein administering a PMK-β selective compound comprises administering a PKI3K-β selective inhibitor compound comprising TGX-221.

19. The method according to embodiment 18, wherein administering a PI3K-β selective inhibitor compound comprises administering the PI3K-β selective inhibitor compound to the subject in an amount ranging from about 0.001 mg/kg to about 100 mg/kg.

20. The method according to embodiment 1, wherein administering a dual PI3K-a/mTOR selective inhibitor comprises administering said dual PBK-a/mTOR selective inhibitor to the subject in an amount ranging from about 0.001 mg/kg to about 100 mg/kg.

21. The method according to embodiment 1, wherein administering a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor compound comprises administering said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to the subject, each inhibitor in an amount ranging from about 0.001 mg/kg to about 100 mg/kg.

22. The method according to any one of embodiments 1 to 21, wherein administering any one or more PI3K-a selective inhibitor, PI3K-β selective inhibitor, dual PI3K-a/mTOR selective inhibitor, combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor inhibitors or pharmaceutically acceptable salts thereof, each inhibitor or combination of inhibitors are administered in combination with a pharmaceutically acceptable carrier, excipient or diluent.

23. The method according to any one of embodiments 1 to 22, wherein said tumor is a breast cancer, a mantle cell lymphoma, a renal cell carcinoma, an acute myelogenous leukemia, a chronic myelogenous leukemia, a NPM/ALK-transformed anaplastic large cell lymphoma, a diffuse large B cell lymphoma, a rhabdomyosarcoma, an ovarian cancer, an endometrial cancer, a cervical cancer, a non-small cell lung carcinoma, a small-cell lung carcinoma, a melanoma, a pancreatic cancer, a prostate carcinoma, a thyroid carcinoma, an anaplastic large cell lymphoma, a hemangioma, a glioblastoma, or a head and neck cancer.

24. A method for identifying a selective inhibitor of a PI3K isozyme, the method comprising:

(a) contacting a first cell bearing a first mutation in a PI3K-a with a candidate inhibitor;

(b) contacting a second cell bearing a wild type PI3K-a, a PTEN null mutation, or a second mutation in said PI3K-a with the candidate inhibitor; and
(c) measuring AKT phosphorylation in said first and said second cells, wherein decreased AKT phosphorylation in said first cell when compared to said second cell identifies said candidate inhibitor as a selective PI3K-a inhibitor.

[00870] The method according to embodiment 24, wherein said first mutation in said PI3K-a comprises a mutation in a kinase domain of said PI3K-a.

[00871] 26. The method according to embodiment 25, wherein said mutation in said kinase domain comprises a substitution at amino acid 1047 of SEQ ID NO:1.

[00872] 27. The method according to embodiment 26, wherein said substituted amino acid at 1047 of SEQ ID NO:1 is arginine in place of histidine.

[00873] 28. The method according to embodiment 24, wherein said second mutation comprises a mutation in a helical domain of said PI3K-ot.

[00874] 29. The method according to embodiment 28, wherein said mutation in said helical domain comprises a substitution at amino acid 545 of SEQ ID NO:1.

[00875] 30. The method according to embodiment 29, wherein said substituted amino acid at 545 of SEQ ID NO:1 is lysine in place of glutamic acid.

[00876] 31. The method according to embodiment 24, wherein said first cell comprises a cell from a cell line comprising HCT-116, T-47D, MDA-MB-453, SIGOV-3, BT-20 or LS H74T.

[00877] 32. The method according to embodiment 24, wherein said second cell comprises a cell from a cell line comprising MCF-7, PC3 MCI-H460, SK-BR-3, PC-3, MDA-MB-468, SK-BR-3, MDA-MB-231T, or A549.

[00878] 33. The method according to embodiment 24, further comprising adding a growth factor to said first and said second cells.

[00879] 34. The method according to embodiment 33, wherein said growth factor comprises adding at least one of VEGF, IGF and heregulin to said first and said second cells.

[00880] 35. The method according to embodiment 24, wherein measuring AKT phosphorylation in said first cell and said second cell comprises measuring an amount of AKT phosphorylation at a residue of AKT comprising T308, S473, S240/244 or combinations thereof.

[00881] 36. The method according to embodiment 35, further comprising measuring the total amount of AKT present in said first and said second cells.

[00882] 37. The method according to embodiment 35, wherein measuring said amount of AKT phosphorylation comprises adding an anti-phosphorylated AKT antibody and
measuring said amount of phosphorylated AKT in the presence and absence of said candidate inhibitor.

38. The method according to embodiment 24, wherein measuring said AKT phosphorylation comprises determining an AKT phosphorylation IC50 concentration of said candidate inhibitor in said first and said second cells.

39. The method according to embodiment 38, wherein identifying said candidate inhibitor as a selective PI3K-a inhibitor comprises determining that said IC50 concentration of said candidate inhibitor is at least about 2 times lower in said first cell when compared to said second cell.

40. The method according to embodiment 38, wherein identifying said candidate inhibitor as a selective PI3K-a inhibitor comprises determining that said IC50 concentration of said candidate inhibitor is at least about 5 times lower in said first cell when compared to said second cell.

41. A method for determining a treatment regimen for a cancer patient having a tumor comprising a PI3K-a, the method comprising:

determining the presence or absence of a mutation in amino acids 1047 and/or 545 of said PI3K-a;

wherein if said PI3K-a has a mutation at position 1047, said method comprises administering to the cancer patient a therapeutically effective amount of a PI3K-a selective inhibitor compound or a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor; or

wherein if said PI3K-a has a mutation at position 545, said method comprises administering to the cancer patient a therapeutically effective amount of a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor.

42. The method according to embodiment 41, wherein determining the presence or absence of a mutation in amino acids 1047 and/or 545 of said PI3K-a comprises isolating a nucleic acid sample encoding said PI3K-a or isolating said PI3K-a or a fragment thereof from said tumor.

43. The method according to embodiment 42, wherein said tumor cell is obtained from a tumor or cancer comprising: breast cancer, mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B cell lymphoma,
rhabdomyosarcoma, ovarian cancer, endometrial cancer, cervical cancer, non-small cell lung
carcinoma, small cell lung carcinoma, adenocarcinoma, colon cancer, rectal cancer, gastric
carcinoma, hepatocellular carcinoma, melanoma, pancreatic cancer, prostate carcinoma,
thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, glioblastoma, or head and
neck cancer.

[00889] 44. The method according to embodiment 41, wherein said assay comprises whole
genome sequencing, partial genome sequencing, exome sequencing, nucleic acid probe
hybridization, restriction enzyme digestion analysis, direct sequencing, immunoprecipitation,
western blotting or combinations thereof.

[00890] 45. The method according to embodiment 41, wherein conducting an assay on
said cell to determine the presence or absence of a mutation in amino acids 1047 and/or 545
of SEQ ID NO: 1 comprises extracting a nucleic acid comprising genomic DNA, total RNA
or mRNA from said cell.

[00891] 46. The method according to embodiment 45, wherein genomic DNA is used in
said assay and said assay further comprises:

(a) amplifying a predetermined region of said genomic DNA;
(b) sequencing said amplified region to obtain a polynucleotide sequence of said
amplified region; and
(c) determining whether said amplified region contains either a genetic mutation
 corresponding to position 1047 of the amino acid sequence of SEQ ID NO: 1, or a genetic
 mutation corresponding to position 545 of the amino acid sequence of SEQ ID NO:1.

[00892] The method of embodiment 46, wherein amplifying a predetermined region of
said genomic DNA comprises amplifying said genomic DNA using a pair of nucleic acid
primers, a first primer capable of hybridizing stringently to a genomic DNA sequence
upstream of a DNA codon encoding the amino acid at either 1047 or 545 of SEQ ID NO: 1,
and second a nucleic acid primer operable to hybridize stringently to a genomic DNA
sequence downstream of a DNA codon encoding the amino acid at either amino acid at 1047
or 545 of SEQ ID NO: 1.

[00893] 48. The method according to embodiment 45, wherein said nucleic acid is an
RNA sample.

[00894] 49. The method according to embodiment 48, wherein said RNA sample is used in
said assay, and said assay further comprises:

(a) reverse transcribing said RNA sample into an equivalent cDNA;
(b) amplifying a predetermined region of said cDNA using a pair of nucleic acid probes directed to a predetermined region of the PI3K-a gene;

(c) sequencing said amplified cDNA region to obtain a polynucleotide sequence of said amplified cDNA region; and

(d) determining whether said amplified cDNA region contains a gene mutation corresponding to amino acid at position 1047 and or 545 of SEQ ID NO:1.

[00895] The method according to embodiment 49, wherein amplifying a predetermined region of the cDNA comprises amplifying said cDNA using a pair of nucleic acid primers, a first primer capable of hybridizing stringently to said cDNA upstream of a DNA codon encoding the amino acid at either 1047 or 545 of SEQ ID NO:1, and second a nucleic acid primer operable to hybridize stringently to said cDNA downstream of a DNA codon encoding the amino acid of either amino acid at 1047 or 545 of SEQ ID NO:1.

[00896] 51. The method according to embodiment 50, wherein determining whether the amplified cDNA region contains a gene mutation comprises determining the presence or absence of a polynucleotide substitution of at least one nucleotide at position 3296, 3297 and 3298 of SEQ ID NO:2, wherein said substitution in the codon does not result in the codon encoding histidine or the presence or absence of a polynucleotide substitution of at least one nucleotide at position 1790, 1791, and 1792 of SEQ ID NO:2, wherein the substitution in the codon does not result in the codon encoding glutamic acid.

[00897] 52. The method according to embodiment 51, wherein the mutation at said codon at positions 3296, 3297 and 3298 of SEQ ID NO:2 results in the substituted codon encoding arginine at position 1047 of SEQ ID NO:1.

[00898] 53. The method according to embodiment 51, wherein the mutation at codon at positions position 1790, 1791, and 1792 of SEQ ID NO:2 results in the substituted codon encoding lysine at position 545 of SEQ ID NO:2.

[00899] 54. The method according to embodiment 41, wherein said PI3K-a selective inhibitor comprises a PI3K-<x> selective inhibitor selected from Table 1.

[00900] 55. The method according to embodiment 41, wherein said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or.
[00901] 56. The method according to embodiment 41, wherein said dual PI3K-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor which is a Compound of Formula I or is selected from Table 1.

[00902] 57. The method according to embodiment 13, wherein said dual PBK-a/mTOR selective inhibitor is one or more of

[00903] The method according to embodiment 41, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PI3K-α selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

[00904] 59. The method according to embodiment 41, wherein said PI3K-β selective compound comprises TGX-221.

[00905] 60. A method for inhibiting AKT activity in a cancer cell, the method comprising administering a therapeutically effective amount of at least one of: a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, and a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to said cancer cell, wherein said cancer cell has a mutation in a kinase domain of PI3K-a.

[00906] 61. The method according to embodiment 1, wherein said PI3K-a selective inhibitor comprises a PI3K-a selective inhibitor selected from Table 1.
62. The method according to embodiment 61, wherein said PBK-a selective inhibitor wherein said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or

![Chemical Structure](image1)

63. The method according to embodiment 60, wherein said dual PI3K-a/mTOR selective inhibitor comprises a dual PBK-a/mTOR selective inhibitor selected from Table 1.

64. The method according to embodiment 63, wherein said dual PBK-a/mTOR selective inhibitor is one or more of

![Chemical Structures](image2)

65. The method according to embodiment 60, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PBK-a selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

66. The method according to any one of embodiments 60-65, wherein said mutation in said kinase domain comprises a mutation in said PBK-a having the substitution H1047R in SEQ ID NO:1.

67. A method for inhibiting proliferation of a cancer cell bearing a mutated PBK-a, the method comprising administering a therapeutically effective amount of at least one of: a PBK-a selective inhibitor, a dual PBK-a/mTOR selective inhibitor, and a combination of a PBK-a selective inhibitor and a mTOR selective inhibitor to said cancer cell, wherein said cancer cell has a mutation in a kinase domain of PBK-a.
[00913] 68. The method according to embodiment 67, wherein said PI3K-a selective inhibitor comprises a PI3K-a selective inhibitor selected from Table 1.

[00914] 69. The method according to embodiment 67, wherein said PI3K-a selective inhibitor wherein said PI3K-a selective inhibitor is a Compound of Formula 1, a compound as found in Table 1, or

![Chemical Structure]

[00915] The method according to embodiment 67, wherein said dual PBK-α/mTOR selective inhibitor comprises a dual PI3K-α/mTOR selective inhibitor selected from Table 1.

[00916] 71. The method according to embodiment 67, wherein said dual PI3K-α/mTOR selective inhibitor is one or more of

![Chemical Structures]

[00917] The method according to embodiment 67, wherein said combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor comprises a PI3K-α selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

[00918] 73. The method according to any one of embodiments 67-72, wherein said mutation in said kinase domain comprises a mutation in said PI3K-α having the substitution H1047R in SEQ ID NO:1.

[00919] 74. A method for inhibiting PI3K-α activity in a cancer cell bearing a mutated PI3K-α, the method comprising administering a therapeutically effective amount of at least one of: a PI3K-α selective inhibitor, a dual PI3K-α/mTOR selective inhibitor, and a
combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to said cancer cell, wherein said cancer cell has a mutation in a kinase domain of PI3K-α.

75. The method according to embodiment 74, wherein said PI3K-a selective inhibitor comprises a PI3K-a selective inhibitor selected from Table 1.

76. The method according to embodiment 74, wherein said PI3K-a selective inhibitor wherein said said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or

![Chemical Structure](image)

77. The method according to embodiment 74, wherein said dual PDK-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor selected from Table 1.

78. The method according to embodiment 74, wherein said dual PI3K-a/mTOR selective inhibitor is one or more of

![Chemical Structures](image)

79. The method according to embodiment 74, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PI3K-a selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

80. The method according to any one of embodiments 74-79 wherein said mutation in said kinase domain comprises a mutation in said PI3K-a having the substitution H1047R in SEQ ID NO:1.
A diagnostic kit for determining the suitability of administering a selective P3IK-CI inhibitor to a cancer patient, said kit comprising:

(a) a receptacle, operable to receive a patient sample;
(b) one or more PI3K-a amino acid sequence determining reagents; and
(c) a set of instructions to assist in sequencing of said PI3K-a in a patient's sample for determining the presence or absence of a mutation in said PI3K-a.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.
What is claimed is:

1. A method for treating a subject having a tumor comprising:
   (a) administering a PI3K-α selective inhibitor, a dual PI3K-α/mTOR selective inhibitor, or a combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor to the subject if said tumor comprises a mutation in a PI3K-α kinase domain; or
   (b) administering a combination of a PI3K-α selective inhibitor and a PI3K-β selective inhibitor, a dual PI3K-α/mTOR selective inhibitor, or a PI3K-β selective inhibitor, to said subject if said tumor comprises a mutation in a PI3K-α helical domain.

2. The method of claim 1, further comprising administering an additional chemotherapeutic agent in steps (a) or (b).

3. The method according to claim 2, wherein said additional chemotherapeutic agent comprises anti-microtubule agents; platinum coordination complexes; alkylating agents; antibiotic agents; topoisomerase II inhibitors; antimetabolites; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

4. The method of claim 2, wherein said additional therapeutic agent administered in step (b) further comprises a PI3K-8 selective inhibitor, a PI3K-γ selective inhibitor or a pan PI3K selective inhibitor.

5. The method according to claim 4, wherein said pan PI3K selective inhibitor comprises PI-103 or PIK-75.

6. The method according to claim 1, wherein the mutation in said kinase domain comprises a mutation at position 1047 of SEQ ID NO:1.

7. The method according to claim 6, wherein said mutation of said kinase domain is a substitution of H1047R in SEQ ID NO:1.
8. The method according to claim 1, wherein said mutation in said PI3K-a comprises a mutation in a helical domain.

9. The method according to claim 8, wherein said mutation in said helical domain comprises a mutation at position 542 or 545 in SEQ ID NO:1.

10. The method according to claim 9, wherein said mutation at position 545 comprises a substitution of E542K or E545K in SEQ ID NO: 1.

11. The method according to claim 1, wherein said PI3K-a selective inhibitor comprises a PI3K-a selective inhibitor selected from Table 1.

12. The method according to claim 10, wherein said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or

![Chemical Structure](image)

13. The method according to claim 1, wherein said dual PI3K-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor is a Compound of Formula I or is selected from Table 1.

14. The method according to claim 13, wherein said dual PI3K-a/mTOR selective inhibitor comprises one or more of

![Chemical Structures](image)
15. The method according to claim 1, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PI3K-a selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

16. The method according to claim 1, wherein said mutation in said helical domain comprises a PI3K-a having a substitution E545K in SEQ ID NO: 1.

17. The method according to claim 1, wherein administering a PI3K-ot selective inhibitor comprises administering a PI3K-a selective inhibitor to the subject in an amount varying from about 0.001 mg/kg to about 100 mg/kg.

18. The method according to claim 1, wherein administering a PK13K-β selective compound comprises administering a PKI3K-β selective inhibitor compound comprising TGX-221.

19. The method according to claim 18, wherein administering a PI3K-β selective inhibitor compound comprises administering the PI3K-β selective inhibitor compound to the subject in an amount ranging from about 0.001 mg/kg to about 100 mg/kg.

20. The method according to claim 1, wherein administering a dual PI3K-a/mTOR selective inhibitor comprises administering said dual PI3K-ct/mTOR selective inhibitor to the subject in an amount ranging from about 0.001 mg/kg to about 100 mg/kg.

21. The method according to claim 1, wherein administering a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor compound comprises administering said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to the subject, each inhibitor in an amount ranging from about 0.001 mg/kg to about 100 mg/kg.
22. The method according to any one of claims 1 to 21, wherein administering any one or more of a PI3K-α selective inhibitor, a PI3K-β selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises administering said inhibitors or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier, excipient or diluent.

23. The method according to any one of claims 1 to 22, wherein said tumor is a breast cancer, a mantle cell lymphoma, a renal cell carcinoma, an acute myelogenous leukemia, a chronic myelogenous leukemia, a NPM/ALK-transformed anaplastic large cell lymphoma, a diffuse large B cell lymphoma, a rhabdomyosarcoma, an ovarian cancer, an endometrial cancer, a cervical cancer, a non-small cell lung carcinoma, a small-cell lung carcinoma, a melanoma, a prostate carcinoma, a thyroid carcinoma, an anaplastic large cell lymphoma, a hemangioma, a glioblastoma, or a head and neck cancer.

24. A method for identifying a selective inhibitor of a PI3K isozyme, the method comprising:
   (a) contacting a first cell bearing a first mutation in a PI3K-a with a candidate inhibitor;
   (b) contacting a second cell bearing a wild type PI3K-a, a PTEN null mutation, or a second mutation in said PI3K-<x with the candidate inhibitor; and
   (c) measuring AKT phosphorylation in said first and said second cells, wherein decreased AKT phosphorylation in said first cell when compared to said second cell identifies said candidate inhibitor as a selective PI3K-a inhibitor.

25. The method according to claim 24, wherein said first mutation in said PI3K-a comprises a mutation in a kinase domain of said PI3K-a.

26. The method according to claim 25, wherein said mutation in said kinase domain comprises a substitution at amino acid 1047 of SEQ ID NO:1.

27. The method according to claim 26, wherein said substituted amino acid at 1047 of SEQ ID NO: 1 is arginine in place of histidine.
28. The method according to claim 24, wherein said second mutation comprises a mutation in a helical domain of said PI3K-a.

29. The method according to claim 28, wherein said mutation in said helical domain comprises a substitution at amino acid 542 or 545 of SEQ ID NO:1.

30. The method according to claim 29, wherein said substituted amino acid at 542 or 545 of SEQ ID NO:1 is lysine in place of glutamic acid.

31. The method according to claim 24, wherein said first cell comprises a cell from a cell line comprising HCT-116, T-47D, MDA-MB-453, SIGOV-3, BT-20 or LS H74T.

32. The method according to claim 24, wherein said second cell comprises a cell from a cell line comprising MCF-7, PC3 MCI-H460, SK-BR-3, PC-3, MDA-MB-468, SK-BR-3, MDA-MB-231T, or A549.

33. The method according to claim 24, further comprising adding a growth factor to said first and said second cells.

34. The method according to claim 33, wherein said growth factor comprises adding at least one of VEGF, IGF and heregulin to said first and said second cells.

35. The method according to claim 24, wherein measuring AKT phosphorylation in said first cell and said second cell comprises measuring an amount of AKT phosphorylation at a residue of AKT comprising T308, S473, S240/244 or combinations thereof.

36. The method according to claim 35, further comprising measuring the total amount of AKT present in said first and said second cells.

37. The method according to claim 35, wherein measuring said amount of AKT phosphorylation comprises adding an antibody specific for phosphorylated AKT and measuring binding of the antibody to AKT and determining said amount of phosphorylated AKT in the presence and absence of said candidate inhibitor.
38. The method according to claim 24, wherein measuring said AKT phosphorylation comprises determining an AKT phosphorylation IC$_{50}$ concentration of said candidate inhibitor in said first and said second cells.

39. The method according to claim 38, wherein identifying said candidate inhibitor as a selective PI3K-a inhibitor comprises determining that said IC$_{50}$ concentration of said candidate inhibitor is less than 50% of the IC$_{50}$ of the second cell.

40. The method according to claim 38, wherein identifying said candidate inhibitor as a selective PI3K-a inhibitor comprises determining that said IC$_{50}$ concentration of said candidate inhibitor is less than 20% of the IC$_{50}$ of the second cell.

41. A method for determining a treatment regimen for a cancer patient having a tumor comprising a PI3K-a, the method comprising:

determining the presence or absence of a mutation in amino acids 1047 and/or 545 of said PI3K-a;

wherein if said PI3K-α has a mutation at position 1047, said method comprises administering to the cancer patient a therapeutically effective amount of a PI3K-a selective inhibitor compound, or a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-α selective inhibitor and a mTOR selective inhibitor; or

wherein if said PI3K-a has a mutation at position 545, said method comprises administering to the cancer patient a therapeutically effective amount of a combination of a PI3K-a selective inhibitor and a PI3K-β selective inhibitor, or a dual PI3K-a/mTOR selective inhibitor, or a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor.

42. The method according to claim 41, wherein determining the presence or absence of a mutation in amino acids 1047 and/or 545 of said PI3K-a comprises isolating a nucleic acid sample encoding said PI3K-a or isolating said PI3K-a or a fragment thereof from said tumor.

43. The method according to claim 42, wherein said tumor cell is obtained from a tumor or cancer comprising: breast cancer, a mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, NPM/ALK-transformed anaplastic...

44. The method according to claim 41, wherein said assay comprises whole genome sequencing, partial genome sequencing, exome sequencing, nucleic acid probe hybridization, restriction enzyme digestion analysis, direct sequencing, immunoprecipitation, western blotting or combinations thereof.

45. The method according to claim 41, wherein conducting an assay on said cell to determine the presence or absence of a mutation in amino acids 1047 and/or 545 of SEQ ID NO:1 comprises extracting a nucleic acid comprising genomic DNA, total RNA or mRNA from said cell.

46. The method according to claim 45, wherein genomic DNA is used in said assay and said assay further comprises:

(a) amplifying a predetermined region of said genomic DNA;
(b) sequencing said amplified region to obtain a polynucleotide sequence of said amplified region; and
(c) determining whether said amplified region contains either a genetic mutation corresponding to position 1047 of the amino acid sequence of SEQ ID NO:1, or a genetic mutation corresponding to position 545 of the amino acid sequence of SEQ ID NO:1.

47. The method of claim 46, wherein amplifying a predetermined region of said genomic DNA comprises amplifying said genomic DNA using a pair of nucleic acid primers, a first primer capable of hybridizing stringently to a genomic DNA sequence upstream of a DNA codon encoding the amino acid at either 1047 or 545 of SEQ ID NO:1, and second a nucleic acid primer operable to hybridize stringently to a genomic DNA sequence downstream of a DNA codon encoding the amino acid of either amino acid at 1047 or 545 of SEQ ID NO:1.

48. The method according to claim 45, wherein said nucleic acid is an RNA sample.
49. The method according to claim 48, wherein said RNA sample is used in said assay, and said assay further comprises:
   (a) reverse transcribing said RNA sample into an equivalent cDNA;
   (b) amplifying a predetermined region of said cDNA using a pair of nucleic acid probes directed to a predetermined region of the PI3K-α gene;
   (c) sequencing said amplified cDNA region to obtain a polynucleotide sequence of said amplified cDNA region; and
   (d) determining whether said amplified cDNA region contains a gene mutation in a codon encoding the amino acid at either position 1047 and/or 545 of SEQ ID NO:1.

50. The method according to claim 49, wherein amplifying a predetermined region of the cDNA comprises amplifying said cDNA using a pair of nucleic acid primers, a first primer capable of hybridizing stringently to said cDNA upstream of a DNA codon encoding the amino acid at either amino acid 1047 or 545 of SEQ ID NO:1, and second a nucleic acid primer operable to hybridize stringently to said cDNA downstream of a DNA codon encoding the amino acid at either amino acid 1047 or 545 of SEQ ID NO:1.

51. The method according to claim 50, wherein determining whether the amplified cDNA region contains a gene mutation comprises determining the presence or absence of a polynucleotide substitution of at least one nucleotide at position 3296, 3297 and 3298 of SEQ ID NO:2, wherein said substitution in the codon does not result in the codon encoding histidine; or determining the presence or absence of a polynucleotide substitution of at least one nucleotide at position 1790, 1791, and 1792 of SEQ ID NO:2, wherein the substitution in the codon does not result in the codon encoding glutamic acid.

52. The method according to claim 51, wherein the mutation at said codon at positions 3296, 3297 and 3298 of SEQ ID NO:2 results in the substituted codon encoding arginine at position 1047 of SEQ ID NO:1.

53. The method according to claim 51, wherein the mutation at codon at positions position 1790, 1791, and 1792 of SEQ ID NO:2 results in the substituted codon encoding lysine at position 545 of SEQ ID NO:2.
54. The method according to claim 41, wherein said PI3K-a selective inhibitor comprises a PI3K-α selective inhibitor selected from Table 1.

55. The method according to claim 41, wherein said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or

56. The method according to claim 41, wherein said dual PI3K-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor selected from Table 1.

57. The method according to claim 13, wherein said dual PI3K-a/mTOR selective inhibitor comprises one or more of

58. The method according to claim 41, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PI3K-a selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

59. The method according to claim 41, wherein said PI3K-β selective compound comprises TGX-221.
60. A method for inhibiting AKT activity in a cancer cell, the method comprising administering a therapeutically effective amount of at least one of: a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, and a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to said cancer cell, wherein said cancer cell has a mutation in a kinase domain of PI3K-a.

61. The method according to claim 1, wherein said PI3K-a selective inhibitor comprises a PI3K-a selective inhibitor selected from Table 1.

62. The method according to claim 61, wherein said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or.

63. The method according to claim 60, wherein said dual PI3K-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor selected from Table 1.

64. The method according to claim 63, wherein said dual PI3K-a/mTOR selective inhibitor comprises one or more of
65. The method according to claim 60, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PI3K-a selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

66. The method according to any one of claims 60-65, wherein said mutation in said kinase domain comprises a mutation in said PI3K-a having the substitution H1047R in SEQ ID NO:1.

67. A method for inhibiting proliferation of a cancer cell bearing a mutated PI3K-a, the method comprising administering a therapeutically effective amount of at least one of: a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, and a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to said cancer cell, wherein said cancer cell has a mutation in a kinase domain of PI3K-a.

68. The method according to claim 67, wherein said PI3K-a selective inhibitor comprises a PI3K-a selective inhibitor selected from Table 1.

69. The method according to claim 67, wherein said PI3K-a selective inhibitor comprises

![Chemical Structure]

70. The method according to claim 67, wherein said dual PI3K-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor selected from Table 1.

71. The method according to claim 67, wherein said dual PI3K-a/mTOR selective inhibitor comprises one or more of

![Chemical Structures]
72. The method according to claim 67, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PI3K-a selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

73. The method according to any one of claims 67-72, wherein said mutation in said kinase domain comprises a mutation in said PI3K-a having the substitution H1047R in SEQ ID NO:1.

74. A method for inhibiting PI3K-a activity in a cancer cell bearing a mutated PI3K-a, the method comprising administering a therapeutically effective amount of at least one of: a PI3K-a selective inhibitor, a dual PI3K-a/mTOR selective inhibitor, and a combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor to said cancer cell, wherein said cancer cell has a mutation in a kinase domain of PI3K-a.

75. The method according to claim 74, wherein said PI3K-a selective inhibitor comprises a PI3K-0C selective inhibitor selected from Table 1.

76. The method according to claim 74, wherein said PI3K-a selective inhibitor is a Compound of Formula I, a compound as found in Table 1, or

77. The method according to claim 74, wherein said dual PI3K-a/mTOR selective inhibitor comprises a dual PI3K-a/mTOR selective inhibitor selected from Table 1.
78. The method according to claim 74, wherein said dual PI3K-a/mTOR selective inhibitor comprises one or more of

![Chemical structures](image1)

79. The method according to claim 74, wherein said combination of a PI3K-a selective inhibitor and a mTOR selective inhibitor comprises a PI3K-a selective inhibitor of Table 1 and a mTOR selective inhibitor of Table 1.

80. The method according to any one of claims 74-79 wherein said mutation in said kinase domain comprises a mutation in said PI3K-a having the substitution H1047R in SEQ ID NO:1.

81. A diagnostic kit for determining the suitability of administering a selective PI3K-a inhibitor to a cancer patient, said kit comprising:
   (a) a receptacle, operable to receive a patient sample;
   (b) one or more PI3K-a amino acid sequence determining reagents; and
   (c) a set of instructions to assist in sequencing of said PI3K-a in a patient's sample for determining the presence or absence of a mutation in said PI3K-a.
FIG. 1

PI3K pathway inhibition by PI3Kα-selective compounds in E545K vs. H1047R cell lines.

<table>
<thead>
<tr>
<th>MCF-7, IGF1 (PIK3CA-E545K)</th>
<th>Compound 899 (Table 4)</th>
<th>T-47D, IGF1 (PIK3CA-H1047R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMEO</td>
<td>PI-103</td>
<td>10000</td>
</tr>
<tr>
<td>pAKT(T308)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC₅₀ = 1736 nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pAKT(S473)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC₅₀ = 2398 nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC₅₀ = 1267 nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pPRAS40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC₅₀ = 8489 nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p4EBP1</td>
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<td></td>
</tr>
<tr>
<td>IC₅₀ = 5771 nM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tubulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIG. 2

PI3Kα-selectives, but not PI3Kα/mTOR duals, show preferential activity in PIK3CA H1047R models.
FIG. 3

Addition of PI3Kβ-selective inhibitor reduces PI3Kα-selective inhibitor IC₅₀s for select PI3k-activated models.

A  B  C

NCI-H460  A549  T-47D

Compound 899  Compound 899  Compound 699
(Table 4)  (Table 4)  (Table 4)

--- DMSO control  --- PI3Kβ TGX-221 (1µM)
**Fig. 4A**

**Compound 698 (± 1 μM TGX-221)**

(Table 4)

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>pAKT(S473)/IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCF-7</td>
<td>750</td>
</tr>
<tr>
<td>H660</td>
<td>1200</td>
</tr>
<tr>
<td>HCT116</td>
<td>1300</td>
</tr>
<tr>
<td>T-47D</td>
<td>1600</td>
</tr>
<tr>
<td>MDA-MB-453</td>
<td>1800</td>
</tr>
<tr>
<td>SK-OV-3</td>
<td>1900</td>
</tr>
<tr>
<td>A549</td>
<td>2100</td>
</tr>
<tr>
<td>SK-BR-3</td>
<td>2300</td>
</tr>
</tbody>
</table>

**Cell Lines**

- MCF-7: ES45K
- H660: ES45K
- HCT116: H1047R
- T-47D: H1047R
- MDA-MB-453: H1047R
- SK-OV-3: H1047R
- A549: wt PIK3Ca
- SK-BR-3: wt PIK3Ca

**Fig. 4B**

**Compound 696 (± 1 μM TGX-221)**

(Table 4)

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>pAKT(S473)/IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCF-7</td>
<td>750</td>
</tr>
<tr>
<td>H660</td>
<td>1200</td>
</tr>
<tr>
<td>HCT116</td>
<td>1300</td>
</tr>
<tr>
<td>T-47D</td>
<td>1600</td>
</tr>
<tr>
<td>MDA-MB-453</td>
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</tr>
<tr>
<td>SK-OV-3</td>
<td>1900</td>
</tr>
<tr>
<td>A549</td>
<td>2100</td>
</tr>
<tr>
<td>SK-BR-3</td>
<td>2300</td>
</tr>
</tbody>
</table>

**Cell Lines**

- MCF-7: ES45K
- H660: ES45K
- HCT116: H1047R
- T-47D: H1047R
- MDA-MB-453: H1047R
- SK-OV-3: H1047R
- A549: wt PIK3Ca
- SK-BR-3: wt PIK3Ca

**Fig. 4C**

**Compound 699 (± 1 μM TGX-221)**

(Table 4)

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>pAKT(S473)/IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCF-7</td>
<td>750</td>
</tr>
<tr>
<td>H660</td>
<td>1200</td>
</tr>
<tr>
<td>HCT116</td>
<td>1300</td>
</tr>
<tr>
<td>T-47D</td>
<td>1600</td>
</tr>
<tr>
<td>MDA-MB-453</td>
<td>1800</td>
</tr>
<tr>
<td>SK-OV-3</td>
<td>1900</td>
</tr>
<tr>
<td>A549</td>
<td>2100</td>
</tr>
<tr>
<td>SK-BR-3</td>
<td>2300</td>
</tr>
</tbody>
</table>

**Cell Lines**

- MCF-7: ES45K
- H660: ES45K
- HCT116: H1047R
- T-47D: H1047R
- MDA-MB-453: H1047R
- SK-OV-3: H1047R
- A549: wt PIK3Ca
- SK-BR-3: wt PIK3Ca
Fig. 4D