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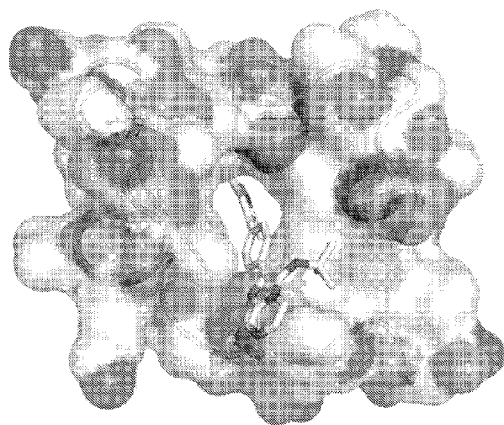
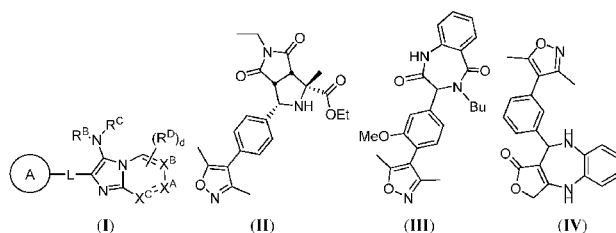


Figure 9



(57) Abstract: The present invention provides novel compounds of any one of Formulae (I) to (IV), and pharmaceutically compositions thereof. Compounds of any one of Formulae (I) to (IV) are believed to be inhibitors of bromodomain-containing proteins (e.g., bromo and extra terminal proteins (BETs)). Also provided are methods, uses, and kits using the inventive compounds and pharmaceutical compositions for inhibiting the activity of the bromodomain-containing proteins and for treating and/or preventing in a subject in need thereof diseases associated with bromodomain-containing proteins, such as proliferative diseases.



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INHIBITORS OF TRANSCRIPTION FACTORS AND USES THEREOF

Related Applications

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 61/858,521, filed July 25, 2013, which is incorporated herein by reference.

Government Support

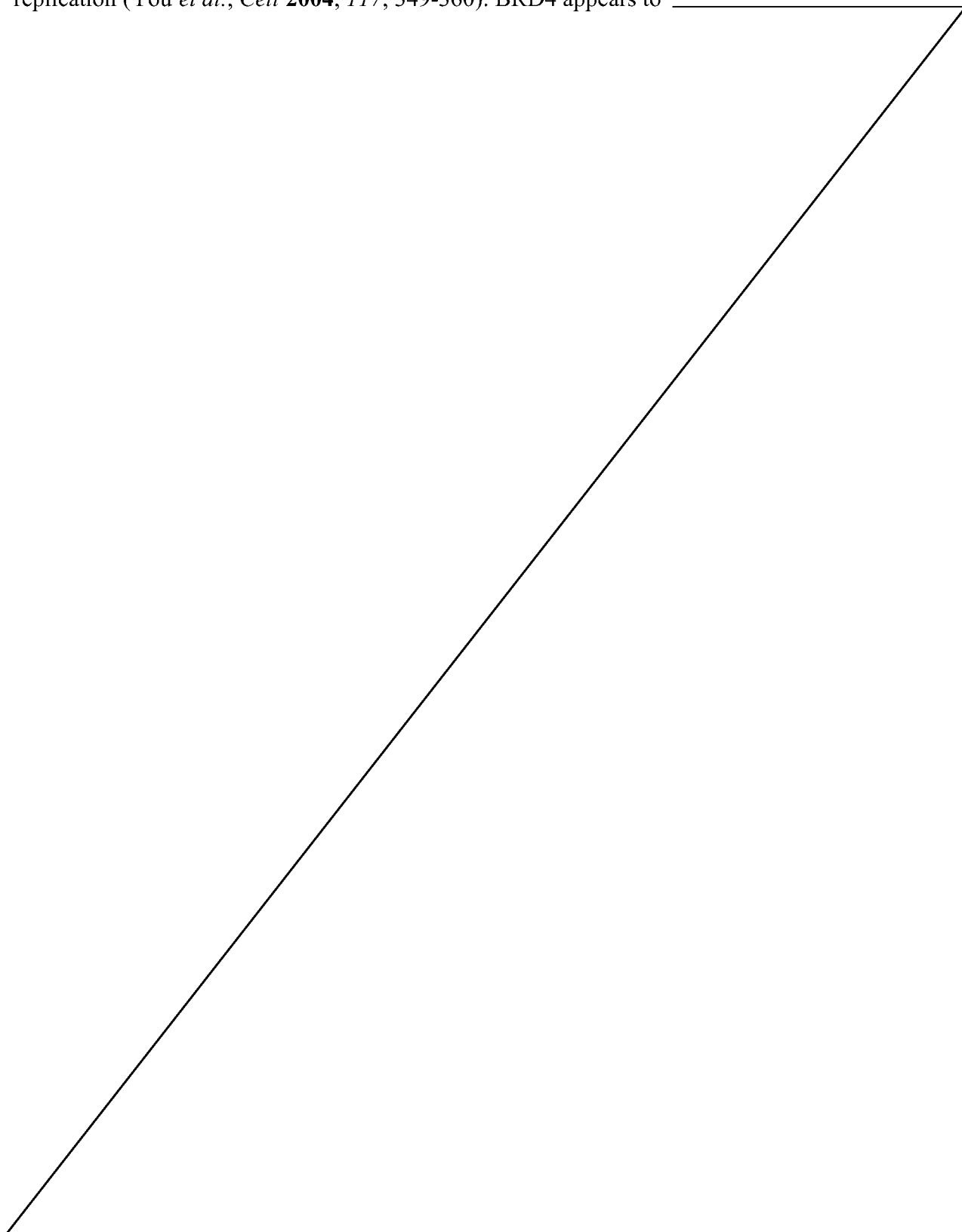
[0002] This invention was made with U.S. Government support under grants CA156732 and HD076508 awarded by the National Institutes of Health. The U.S. Government has certain rights in the invention.

Background of the Invention

[0002a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[0003] Bromodomain-containing proteins are of substantial biological interest, as components of transcription factor complexes and determinants of epigenetic memory. For example, the bromo and extra terminal protein (BET) family (*e.g.*, bromodomain-containing protein 2 (BRD2), bromodomain-containing protein 3 (BRD3), bromodomain-containing protein 4 (BRD4), and bromodomain testis-specific protein (BRDT)) shares a common domain architecture featuring two amino-terminal bromodomains that exhibit high levels of sequence conservation, and a more divergent carboxy-terminal recruitment domain (Filippakopoulos *et al.*, *Nature* **2010**, 468, 1067-1073). BRD2 and BRD3 are reported to associate with histones along actively transcribed genes and may be involved in facilitating transcriptional elongation (Leroy *et al.*, *Mol. Cell.* **2008**, 30, 51-60). It has also been reported that BRD4 or BRD3 may fuse with nuclear protein in testis (NUT), forming novel fusion oncogenes BRD4-NUT or BRD3-NUT, in a highly malignant form of epithelial neoplasia (French *et al.*, *Cancer Res.*, **2003**, 63, 304-307; French *et al.*, *J. Clin. Oncol.* **2004**, 22, 4135-4139). Data suggests that BRD-NUT fusion proteins contribute to carcinogenesis (French *et al.*, *Oncogene* **2008**, 27, 2237-2242). BRDT is uniquely expressed in the testes and ovary. All family members of BET have been reported to have some function in controlling or executing aspects of the cell cycle and have been shown to remain in complex with chromosomes during cell division, suggesting

a role in the maintenance of epigenetic memory. In addition, some viruses make use of BET proteins to tether their genomes to the host cell chromatin, as part of the process of viral replication (You *et al.*, *Cell* **2004**, *117*, 349-360). BRD4 appears to _____



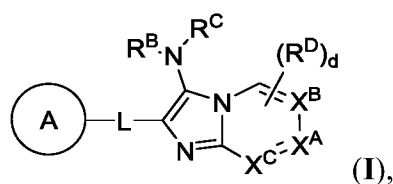
be involved in the recruitment of the pTEF-b complex to inducible genes, resulting in phosphorylation of RNA polymerase and increased transcriptional output (Hargreaves *et al.*, *Cell* **2009**, 138, 129-145). In humans, BRD2, BRD3, BRD4, and BRDT exhibit similar gene arrangements, domain organizations, and some functional properties (Wu *et al.*, *J. Biol. Chem.* **2007**, 282, 13141-13145).

[0004] Recently, some compounds have been reported to be bromodomain binding agents, *e.g.*, WO 2012/075383, WO 2011/054553, WO 2011/054841, WO 2011/054844, WO 2011/054845, WO 2011/054846, WO 2011/054848, WO 2011/143669, and WO 2011/161031. Moreover, Japanese patent application publication JP 2008/156311 discloses a benzimidazole derivative which is said to be a BRD2 bromodomain binding agent which has utility with respect to virus infection and/or proliferation. International PCT publication WO 2009/084693 discloses a series of thienotriazolodiazepine derivatives that are said to inhibit the binding between an acetylated histone and a bromodomain-containing protein which are said to be useful as anti-cancer agents. International PCT publication WO 2011/054843 suggests compounds which inhibit the binding of a bromodomain with its cognate acetylated proteins may have utility in the treatment of a range of autoimmune and inflammatory diseases or conditions.

[0005] BET proteins, however, are just one branch of the bromodomain containing protein family. There are dozens of undrugged bromodomains, and novel probe molecules against these targets would be invaluable tools both for improved biological studies and potential leads for drug development. Transcription initiation factor TFIID subunit 1 (TAF1) and TAF1L are two such proteins. As a part of the STAGA complex containing TRRAP, GCN5, TFIID, CBP/P300, mediator (Liu *et al.*, *Molecular Cell Biology* **2008**, 28, 108), and Sp1 (Schroder *et al.*, *J. Biol. Chem.* **2012**, 287, 1090), TAF1 is susceptible to oncogenic activation by MYC. Moreover, TAF1 has been shown to block p53 activity (Li *et al.*, *Molecular Cell*. **2004**, 13, 867), and inactivation of TAF1 triggers a DNA damage response (Buchmann *et al.*, *Molecular Cell Biology* **2004**, 24, 5332). In addition, the TFIID complex, of which TAF1 is a significant member, is vital to stem cell reprogramming (Pijnappel *et al.*, *Nature* **2013**, 495, 516). Inhibitors of TAF1 may help further elucidate its biological role and potentially be an inhibitor of cancer cell growth. With such promising studies related to drugging the epigenome, it is of the utmost importance to develop new chemistry capable of reaching these targets.

Summary of the Invention

[0005a] According to a first aspect, the present invention provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

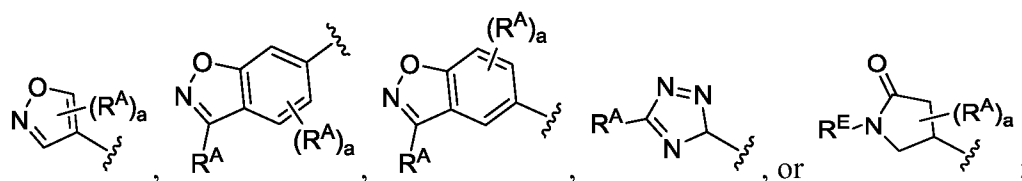
X^A is $C(R^D)$ or N;

X^B is $C(R^D)$ or N;

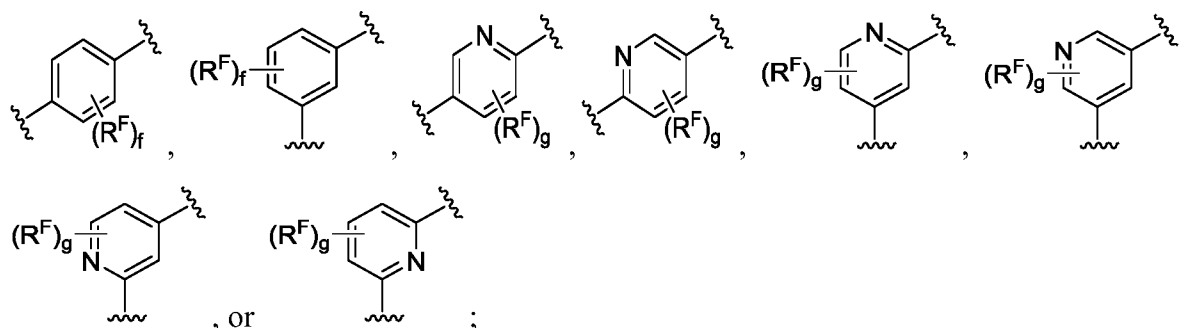
X^C is $C(R^D)$ or N;

wherein no more than two of X^A , X^B , and X^C can be N;

Ring A is of the formula:



L is a bond or of the formula:



each instance of R^A is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-CN$, $-SCN$, $-C(=NR^{A1})R^{A1}$, $-C(=NR^{A1})OR^{A1}$, $-C(=NR^{A1})N(R^{A1})_2$,

$-\text{C}(=\text{O})\text{R}^{\text{A1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{A1}})_2$, $-\text{NO}_2$, $-\text{NR}^{\text{A1}}\text{C}(=\text{O})\text{R}^{\text{A1}}$, $-\text{NR}^{\text{A1}}\text{C}(=\text{O})\text{OR}^{\text{A1}}$, $-\text{NR}^{\text{A1}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{A1}})_2$, $-\text{OC}(=\text{O})\text{R}^{\text{A1}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{A1}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{A1}})_2$, or two instances of R^{A} are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{A1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{A1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^{B} is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-\text{C}(=\text{O})\text{R}^{\text{B1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{B1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{B1}})_2$, or a nitrogen protecting group, or R^{B} and R^{C} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^{B1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{B1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^{C} is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-\text{C}(=\text{O})\text{R}^{\text{C1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{C1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{C1}})_2$, or a nitrogen protecting group, or R^{C} and R^{B} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^{C1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group

when attached to an oxygen atom, or two instances of R^{C1} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^D is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{D1}$, $-N(R^{D1})_2$, $-SR^{D1}$, $-CN$, $-SCN$, $-C(=NR^{D1})R^{D1}$, $-C(=NR^{D1})OR^{D1}$, $-C(=NR^{D1})N(R^{D1})_2$, $-C(=O)R^{D1}$, $-C(=O)OR^{D1}$, $-C(=O)N(R^{D1})_2$, $-NO_2$, $-NR^{D1}C(=O)R^{D1}$, $-NR^{D1}C(=O)OR^{D1}$, $-NR^{D1}C(=O)N(R^{D1})_2$, $-OC(=O)R^{D1}$, $-OC(=O)OR^{D1}$, or $-OC(=O)N(R^{D1})_2$, or two instances of R^D are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{D1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{D1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^E is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C(=O)R^{E1}$, $-C(=O)OR^{E1}$, $-C(=O)N(R^{E1})_2$, or a nitrogen protecting group;

each instance of R^{E1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{E1} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^F is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^{\text{F1}}$, $-\text{N}(\text{R}^{\text{F1}})_2$, $-\text{SR}^{\text{F1}}$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^{\text{F1}})\text{R}^{\text{F1}}$, $-\text{C}(=\text{NR}^{\text{F1}})\text{OR}^{\text{F1}}$, $-\text{C}(=\text{NR}^{\text{F1}})\text{N}(\text{R}^{\text{F1}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{F1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{F1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{F1}})_2$, $-\text{NO}_2$, $-\text{NR}^{\text{F1}}\text{C}(=\text{O})\text{R}^{\text{F1}}$, $-\text{NR}^{\text{F1}}\text{C}(=\text{O})\text{OR}^{\text{F1}}$, $-\text{NR}^{\text{F1}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{F1}})_2$, $-\text{OC}(=\text{O})\text{R}^{\text{F1}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{F1}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{F1}})_2$, or two instances of R^{F} are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{F1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{F1} are joined to form a substituted or unsubstituted heterocyclic ring;

a is 0, 1, 2, 3, 4, or 5;

d is 0, 1, or 2;

f is 0, 1, 2, 3 or 4; and

g is 0, 1, 2, or 3

[0005b] According to a third aspect, the present invention provides a pharmaceutical composition comprising a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0005c] According to a fourth aspect, the present invention provides a method of treating a disease associated with a bromodomain-containing protein in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect.

[0005d] According to a fifth aspect, the present invention provides a method of of reducing the risk of having a disease associated with a bromodomain-containing protein in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect.

[0005e] According to a sixth aspect, the present invention provides a method of screening a library of compounds, and pharmaceutically acceptable salts thereof, to identify a compound, or a pharmaceutically acceptable salt thereof, that is useful in the treatment of a disease associated with a bromodomain-containing protein in a subject, the method comprising:

providing at least two different compounds of the first aspect or the second aspect, or pharmaceutically acceptable salts thereof; and

performing at least one assay using the different compounds, or pharmaceutically acceptable salts thereof.

[0005f] According to a seventh aspect, the present invention provides a method of inhibiting the activity of a bromodomain-containing protein in a subject or cell, the method comprising:

administering to the subject or contacting the cell with a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect.

[0005g] According to an eighth aspect, the present invention provides a method of inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell, the method comprising:

administering to the subject or contacting the cell with a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect.

[0005h] According to a ninth aspect, the present invention provides a method of modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell, the method comprising:

administering to the subject or contacting the cell with a compound of first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect.

[0005i] According to a tenth aspect, the present invention provides a kit comprising:
a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect; and
instructions for using the kit.

[0005j] According to an eleventh aspect, the present invention provides use of a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect in the manufacture of a medicament for treating a disease associated with a bromodomain-containing protein.

[0005k] According to a twelfth aspect, the present invention provides use of a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect in the manufacture of a medicament for reducing the risk of having a disease associated with a bromodomain-containing protein.

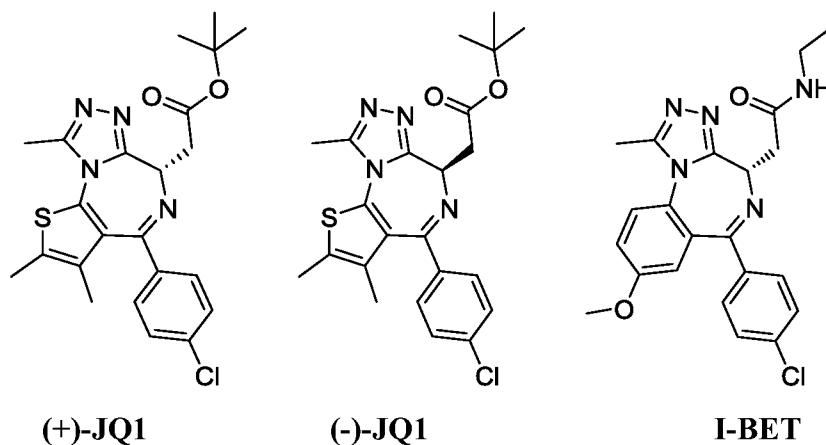
0005] According to a thirteenth aspect, the present invention provides use of a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect in the manufacture of a medicament for inhibiting the activity of a bromodomain-containing protein in a subject or cell.

[0005l] According to a fourteenth aspect, the present invention provides use of a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect in the manufacture of a medicament for inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell.

[0005m] According to a fifteenth aspect, the present invention provides use of a compound of the first aspect or the second aspect, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the third aspect in the manufacture of a medicament for modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell.

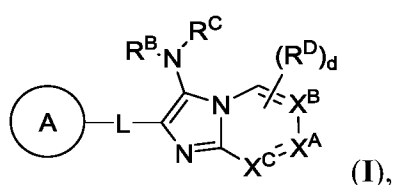
[0006] Compound **JQ1** (*e.g.*, (+)-**JQ1**, (-)-**JQ1**, or a mixture thereof; below) and certain compounds related to **JQ1** have been reported as inhibitors of bromodomain-containing proteins (*e.g.*, BET proteins). See, *e.g.*, international PCT patent application publication, WO 2011/143669. It has been demonstrated that **JQ1** may bind to the acetyl-lysine binding cavity of a bromodomain-containing protein (*e.g.*, BRD4). Binding of **JQ1** to the tandem bromodomains of BRD4 has been shown to be acetyl-lysine competitive and able to displace BRD4 from chromatin in human cells. It is expected that **JQ1** may be useful in treating a disease associated

with bromodomain-containing proteins, such as cancer (*e.g.*, human squamous cell carcinoma). Similar properties of compound **I-BET** (below), another bromodomain inhibitor, have also been reported (Nicodeme *et al.*, *Nature* **2010**, 468, 1119-1123).



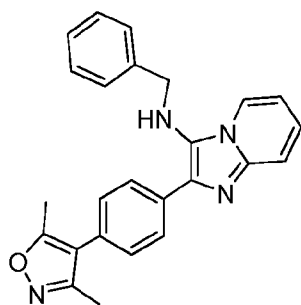
[0007] The present invention provides novel compounds of Formulae **(I)-(IV)**. The inventive compounds are thought to be inhibitors of transcription factors, such as bromodomain-containing proteins (*e.g.*, BET proteins) and may be useful in treating diseases associated with bromodomain-containing proteins, such as proliferative diseases (*e.g.*, cancers, benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases). Also provided in the present invention are pharmaceutical compositions, kits, methods, and uses involving a compound of the invention.

[0008] In one aspect, the present invention provides compounds of Formula **(I)**:

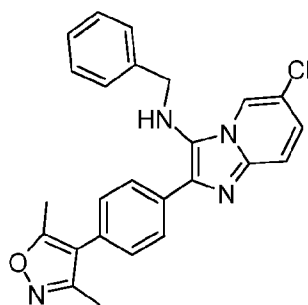


and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein X^A , X^B , X^C , Ring A, L, R^B , R^C , R^D , and d are as described herein.

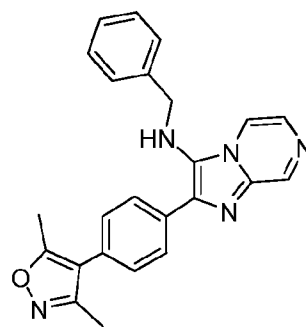
[0009] Exemplary compounds of Formula (I) include, but are not limited to:



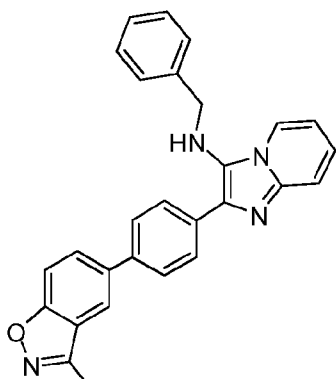
(UMB11)



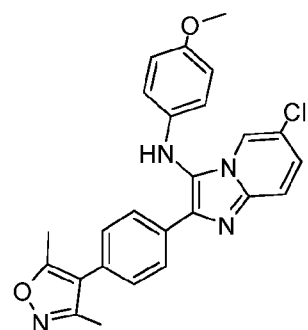
(UMB20)



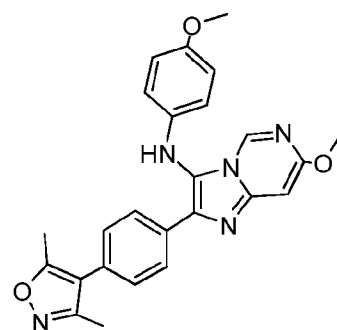
(UMB21)



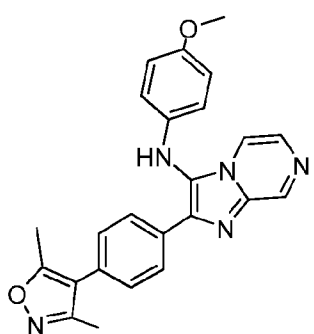
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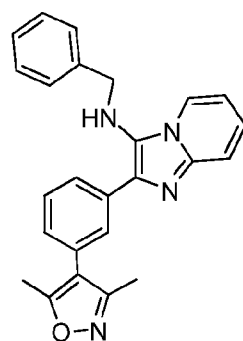
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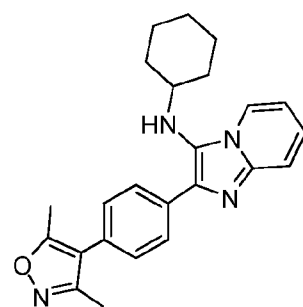
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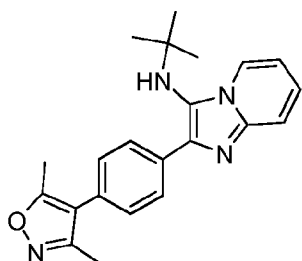
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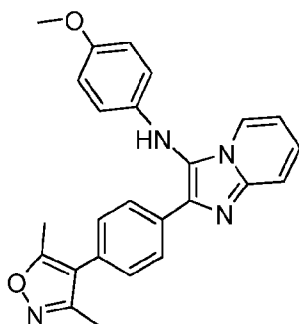
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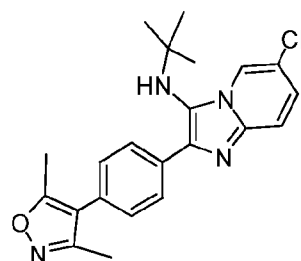
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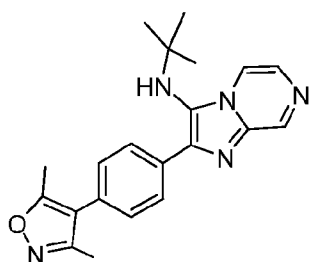
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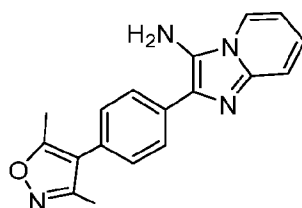
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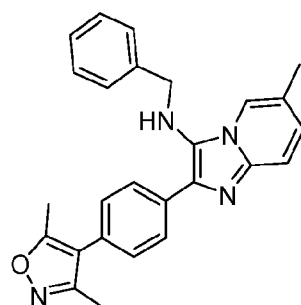
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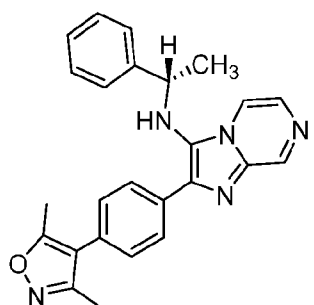
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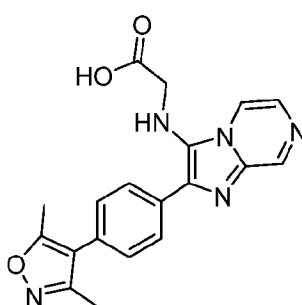
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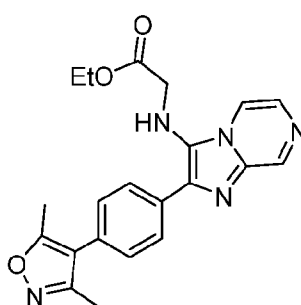
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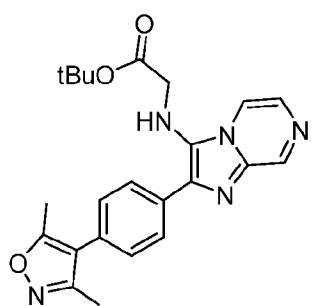
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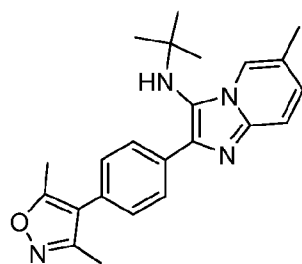
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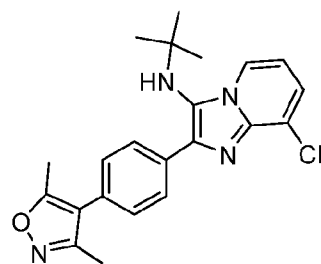
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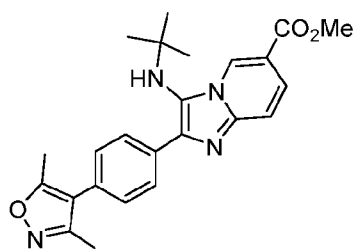
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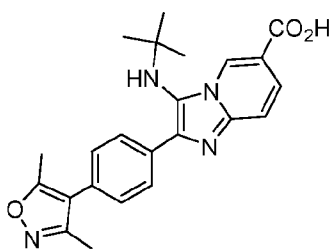
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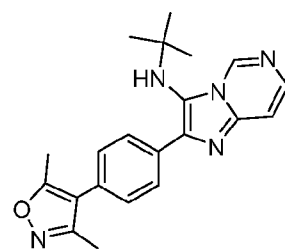
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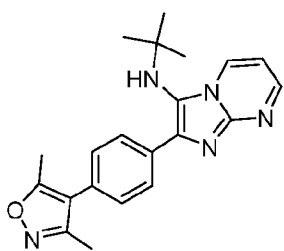
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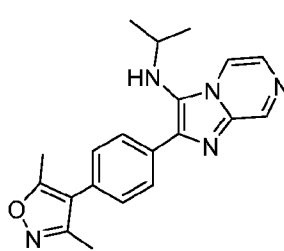
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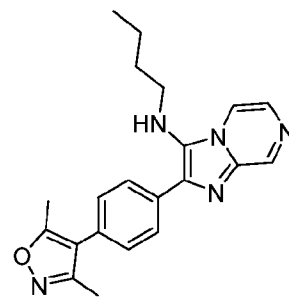
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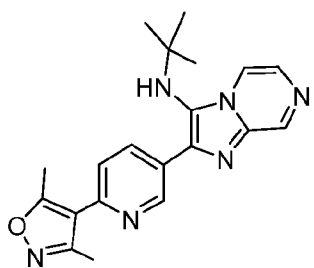
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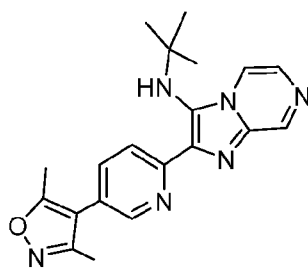
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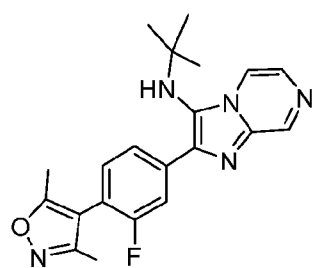
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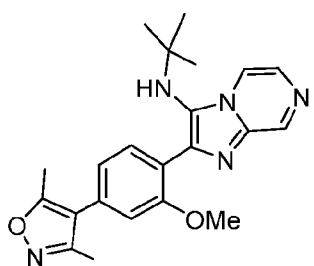
(UMB53)



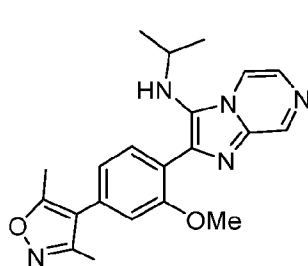
(UMB54)



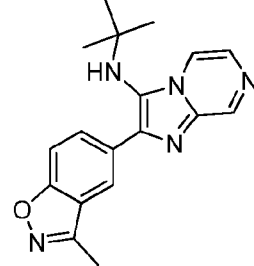
(UMB55)



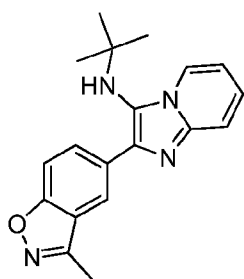
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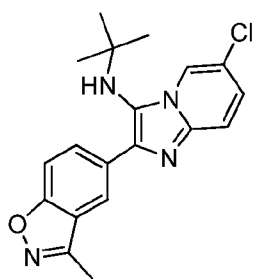
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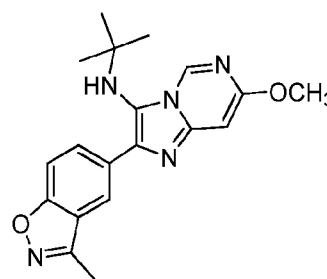
(UMB-33)



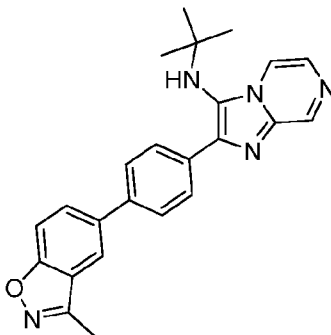
(UMB-34)



(UMB-35)



(UMB-36)

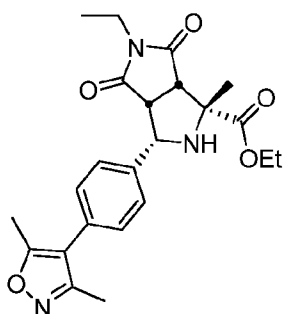


(UMB-42)

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof.

[0010] The compounds of the invention are thought to be able to bind bromodomain-containing proteins. In certain embodiments, the compounds of the invention bind to a bromodomain of the bromodomain-containing proteins. The compounds of the invention may inhibit the activity of the bromodomain-containing proteins. The compounds of the invention may also inhibit the function of a bromodomain of the bromodomain-containing proteins.

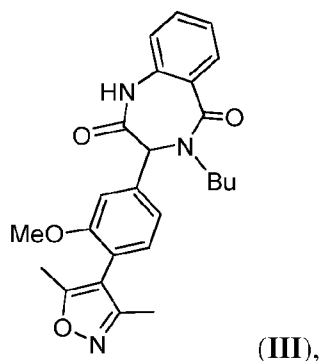
[0011] In another aspect, the present invention provides the compound of Formula (II):



(II),

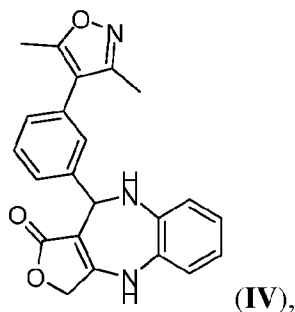
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. The compound of Formula (II) is also referred to as compound **UMB17**.

[0012] In yet another aspect, the present invention provides the compound of Formula (III):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. The compound of Formula (III) is also referred to as compound **UMB18**.

[0013] In still another aspect, the present invention provides the compound of Formula (IV):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. The compound of Formula (IV) is also referred to as compound **UMB27**.

[0014] In still another aspect, the present invention provides pharmaceutical compositions including a compound of the invention, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions described herein include a therapeutically or prophylactically effective amount of a compound of the invention. The pharmaceutical composition may be useful for treating and/or preventing a disease associated with a bromodomain-containing protein in a subject in need thereof. The pharmaceutical composition may also be useful in inhibiting the activity of a bromodomain-containing protein, in inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone, and/or in modulating (*e.g.*, down-regulating) the

transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell.

[0015] In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with the activity of the bromodomain-containing protein. In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with the function of a bromodomain of the bromodomain-containing protein. In certain embodiments, the disease associated with a bromodomain-containing protein is a proliferative disease (*e.g.*, cancer, benign neoplasm, angiogenesis, an inflammatory disease, or an autoimmune disease).

[0016] In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the cell is an *in vitro* cell.

[0017] Another aspect of the present invention relates to methods of treating a disease associated with a bromodomain-containing protein in a subject in need thereof. In another aspect, the present invention provides methods of preventing a disease associated with a bromodomain-containing protein in a subject in need thereof.

[0018] Another aspect of the present invention relates to methods of reducing the risk of having a disease associated with a bromodomain-containing protein in a subject in need thereof.

[0019] In another aspect, the present invention provides methods of inhibiting the activity of a bromodomain-containing protein in a subject or cell.

[0020] In yet another aspect, the present invention provides methods of inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell.

[0021] In still another aspect, the present invention provides methods of modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell. In certain embodiments, the methods of modulating the transcription of a gene are methods of down-regulating the transcription of the gene.

[0022] The methods of the present invention include administering to the subject an effective amount of a compound or pharmaceutical composition of the invention. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

[0023] Another aspect of the invention relates to methods of screening a library of compounds to identify a compound that is useful in the methods of the invention (*e.g.*, useful for inhibiting the activity of a bromodomain-containing protein).

[0024] Another aspect of the present invention relates to kits comprising a container with a compound or pharmaceutical composition of the invention. The kits of the invention may include a single dose or multiple doses of the inventive compound, or pharmaceutical compositions thereof. The provided kits may be useful in treating and/or preventing a disease associated with a bromodomain-containing protein in a subject in need thereof. The kits may also be useful in inhibiting the activity of a bromodomain-containing protein, in inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone, and/or in modulating (*e.g.*, down-regulating) the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell. In certain embodiments, the kit further includes instructions for administering the compound, or pharmaceutical composition, to the subject.

[0025] In yet another aspect, the present invention provides compounds and pharmaceutical compositions of the invention for use in the treatment of a disease associated with a bromodomain-containing protein in a subject in need thereof.

[0026] In still another aspect, the present invention provides compounds and pharmaceutical compositions of the invention for use in the prevention of a disease associated with a bromodomain-containing protein in a subject in need thereof.

[0027] In still another aspect, the present invention provides compounds and pharmaceutical compositions of the invention for use in reducing the risk of having a disease associated with a bromodomain-containing protein in a subject in need thereof.

[0028] The present application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

Definitions

[0029] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley &

Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0030] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0031] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example “C₁₋₆” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆.

[0032] The term “aliphatic” includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, acyclic, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, “aliphatic” is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties. Thus, the term “alkyl” includes straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as “alkenyl”, “alkynyl”, and the like. Furthermore, the terms “alkyl”, “alkenyl”, “alkynyl”, and the like encompass both substituted and unsubstituted groups. In certain embodiments, “lower alkyl” is used to indicate those alkyl groups (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-6 carbon atoms.

[0033] In certain embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention

contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the invention contain 1-4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -CH₂-cyclopropyl, vinyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH₂-cyclobutyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH₂-cyclopentyl, n-hexyl, sec-hexyl, cyclohexyl, -CH₂-cyclohexyl moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl, and the like.

[0034] “Alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds, and no triple bonds (“C₂₋₂₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents. In certain embodiments, the alkenyl group is unsubstituted C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is substituted C₂₋₁₀ alkenyl.

[0035] “Alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds, and optionally

one or more double bonds (“C₂₋₂₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkynyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octynyl (C₈), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is substituted C₂₋₁₀ alkynyl.

[0036] “Carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀),

octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or contain a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) and can be saturated or can be partially unsaturated. “Carbocyclyl” also includes ring systems wherein the carbocyclic ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclic ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₀ carbocyclyl. In certain embodiments, the carbocyclyl group is substituted C₃₋₁₀ carbocyclyl.

[0037] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C₃₋₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C₃₋₁₀ cycloalkyl.

[0038] “Heterocyclyl” or “heterocyclic” refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3-10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged, or spiro ring system, such as a bicyclic system (“bicyclic heterocyclyl”), and can be

saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclic ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclic ring, or ring systems wherein the heterocyclic ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclic ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclic ring system. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[0039] In some embodiments, a heterocyclyl group is a 5–10 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5–10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–8 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5–6 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heterocyclyl"). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0040] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenlyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny,

oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0041] “Aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 pi electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C_{6–14} aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6–14} aryl. In certain embodiments, the aryl group is substituted C_{6–14} aryl.

[0042] “Aralkyl” is a subset of alkyl and aryl and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group. In certain embodiments, the aralkyl is optionally substituted benzyl. In certain embodiments, the aralkyl is benzyl. In certain embodiments, the aralkyl is optionally substituted phenethyl. In certain embodiments, the aralkyl is phenethyl.

[0043] “Heteroaryl” refers to a radical of a 5–10 membered monocyclic or bicyclic $4n+2$ aromatic ring system (*e.g.*, having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[0044] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heteroaryl”). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with

one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

[0045] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0046] “Heteroaralkyl” is a subset of alkyl and heteroaryl and refers to an optionally substituted alkyl group substituted by an optionally substituted heteroaryl group.

[0047] “Unsaturated” or “partially unsaturated” refers to a group that includes at least one double or triple bond. A “partially unsaturated” ring system is further intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.*, aryl or heteroaryl groups) as herein defined. Likewise, “saturated” refers to a group that does not contain a double or triple bond, *i.e.*, contains all single bonds.

[0048] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, which are divalent bridging groups, are further referred to using the suffix –ene, *e.g.*, alkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene, and heteroarylene.

OP(=O)(R^{aa})₂, -OP(=O)(OR^{cc})₂, -P(=O)₂N(R^{bb})₂, -OP(=O)₂N(R^{bb})₂, -P(=O)(NR^{bb})₂, -OP(=O)(NR^{bb})₂, -NR^{bb}P(=O)(OR^{cc})₂, -NR^{bb}P(=O)(NR^{bb})₂, -P(R^{cc})₂, -P(R^{cc})₃, -OP(R^{cc})₂, -OP(R^{cc})₃, -B(R^{aa})₂, -B(OR^{cc})₂, -BR^{aa}(OR^{cc}), C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, =NN(R^{bb})₂, =NNR^{bb}C(=O)R^{aa}, =NNR^{bb}C(=O)OR^{aa}, =NNR^{bb}S(=O)₂R^{aa}, =NR^{bb}, or =NOR^{cc};

each instance of R^{aa} is, independently, selected from C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{cc} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{ee}, -ON(R^{ff})₂, -N(R^{ff})₂, -N(R^{ff})₃⁺X⁻, -N(OR^{ee})R^{ff}, -SH, -SR^{ee}, -SSR^{ee}, -C(=O)R^{ee}, -CO₂H, -CO₂R^{ee}, -OC(=O)R^{ee}, -OCO₂R^{ee}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{ee}, -NR^{ff}CO₂R^{ee}, -NR^{ff}C(=O)N(R^{ff})₂, -C(=NR^{ff})OR^{ee}, -OC(=NR^{ff})R^{ee}, -OC(=NR^{ff})OR^{ee}, -C(=NR^{ff})N(R^{ff})₂, -OC(=NR^{ff})N(R^{ff})₂, -

NR^{ff}C(=NR^{ff})N(R^{ff})₂, -NR^{ff}SO₂R^{ee}, -SO₂N(R^{ff})₂, -SO₂R^{ee}, -SO₂OR^{ee}, -OSO₂R^{ee}, -S(=O)R^{ee}, -Si(R^{ee})₃, -OSi(R^{ee})₃, -C(=S)N(R^{ff})₂, -C(=O)SR^{ee}, -C(=S)SR^{ee}, -SC(=S)SR^{ee}, -P(=O)₂R^{ee}, -P(=O)(R^{ee})₂, -OP(=O)(R^{ee})₂, -OP(=O)(OR^{ee})₂, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -ON(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₃⁺X⁻, -NH(C₁₋₆ alkyl)₂⁺X⁻, -NH₂(C₁₋₆ alkyl)⁺X⁻, -NH₃⁺X⁻, -N(OC₁₋₆ alkyl)(C₁₋₆ alkyl), -N(OH)(C₁₋₆ alkyl), -NH(OH), -SH, -SC₁₋₆ alkyl, -SS(C₁₋₆ alkyl), -C(=O)(C₁₋₆ alkyl), -CO₂H, -CO₂(C₁₋₆ alkyl), -OC(=O)(C₁₋₆ alkyl), -OCO₂(C₁₋₆ alkyl), -C(=O)NH₂, -C(=O)N(C₁₋₆ alkyl)₂, -OC(=O)NH(C₁₋₆ alkyl), -NHC(=O)(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), -NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -C(=NH)O(C₁₋₆ alkyl), -OC(=NH)(C₁₋₆ alkyl), -OC(=NH)OC₁₋₆ alkyl, -C(=NH)N(C₁₋₆ alkyl)₂, -C(=NH)NH(C₁₋₆ alkyl), -C(=NH)NH₂, -OC(=NH)N(C₁₋₆ alkyl)₂, -OC(NH)NH(C₁₋₆ alkyl), -OC(NH)NH₂, -NHC(NH)N(C₁₋₆ alkyl)₂, -NHC(=NH)NH₂, -NHCO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂OC₁₋₆ alkyl, -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, -Si(C₁₋₆ alkyl)₃, -OSi(C₁₋₆ alkyl)₃, -C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, -C(=O)S(C₁₋₆ alkyl), -C(=S)SC₁₋₆ alkyl, -SC(=S)SC₁₋₆ alkyl, -P(=O)₂(C₁₋₆ alkyl), -P(=O)(C₁₋₆ alkyl)₂, -OP(=O)(C₁₋₆ alkyl)₂, -OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, C₆₋₁₀ aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X⁻ is a counterion.

[0052] A “counterion” or “anionic counterion” is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.*, F⁻, Cl⁻, Br⁻, I⁻), NO₃⁻, ClO₄⁻, OH⁻, H₂PO₄⁻, HSO₄⁻, sulfonate ions (*e.g.*, methanesulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), and carboxylate ions (*e.g.*, acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0053] “Halo” or “halogen” refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[0054] “AcyI” refers to a moiety selected from the group consisting of -C(=O)R^{aa}, -CHO, -CO₂R^{aa}, -C(=O)N(R^{bb})₂, -C(=NR^{bb})R^{aa}, -C(=NR^{bb})OR^{aa}, -C(=NR^{bb})N(R^{bb})₂, -C(=O)NR^{bb}SO₂R^{aa}, -C(=S)N(R^{bb})₂, -C(=O)SR^{aa}, or -C(=S)SR^{aa}, wherein R^{aa} and R^{bb} are as defined herein.

[0055] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc}, and R^{dd} are as defined above.

[0056] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, -OH, -OR^{aa}, -N(R^{cc})₂, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, C₁₋₁₀ alkyl (*e.g.*, aralkyl, heteroaralkyl), C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1,

2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0057] For example, nitrogen protecting groups such as amide groups (*e.g.*, -C(=O)R^{aa}) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *o*-nitrophenoxycetamide, acetoacetamide, (*N*'-dithiobenzyloxyacylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivative, *o*-nitrobenzamide, and *o*-(benzoyloxymethyl)benzamide.

[0058] Nitrogen protecting groups such as carbamate groups (*e.g.*, -C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-*t*-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkylthio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-

methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacetylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p'*-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0059] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β -trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzyisulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0060] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, *N'*-*p*-toluenesulfonylaminoacyl derivative, *N'*-phenylaminothioacyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide,

N-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N'*,*N'*-dimethylaminomethylene)amine, *N,N'*-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

[0061] Exemplary oxygen atom substituents include, but are not limited to, $-R^{aa}$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, methyl, *t*-butyloxycarbonyl (BOC or Boc), methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl

(SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α -naphthyl diphenylmethyl, *p*-methoxyphenyl diphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodisulfuran-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate

(Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*-nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*-methoxybenzyl carbonate, alkyl 3,4-dimethoxybenzyl carbonate, alkyl *o*-nitrobenzyl carbonate, alkyl *p*-nitrobenzyl carbonate, alkyl *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenolate, *o*-(methoxyacyl)benzoate, α -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzyisulfonate, and tosylate (Ts).

[0062] Exemplary sulfur atom substituents include, but are not limited to, $-R^{aa}$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. In certain embodiments, the sulfur atom substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0063] The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other Definitions

[0064] The following definitions are more general terms used throughout the present application.

[0065] The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well

known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate, and aryl sulfonate.

[0066] The term “solvate” refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. “Solvate” encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0067] The term “hydrate” refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x H_2O$, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5 H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2 H_2O$) and hexahydrates ($R \cdot 6 H_2O$)).

[0068] The term “tautomers” or “tautomeric” refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or *vice versa*). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0069] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”.

[0070] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[0071] The term “polymorphs” refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof) in a particular crystal packing arrangement. All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical

and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0072] The term “prodrugs” refer to compounds, including derivatives of the compounds described herein, which have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, C₇-C₁₂ substituted aryl, and C₇-C₁₂ arylalkyl esters of the compounds described herein may be preferred.

[0073] The term “lipophilic” or “hydrophobic” refers to the ability of a compound to dissolve, or the ability of a moiety of a compound to assist the compound in dissolving in fats, oils, lipids, and/or non-polar solvents (*e.g.*, hexane or toluene). Lipophilic moieties include, but are not limited to, substituted or unsubstituted, branched or unbranched alkyl groups having 1 to 50 carbon atoms. In certain embodiments, the lipophilic moiety is an alkyl group including at least 1, at least 6, at least 12, at least 18, at least 24, at least 36, or at least 50 carbon atoms. In certain embodiments, the lipophilic moiety is an alkyl group including at most 50, at most 36, at most 24, at most 18, at most 12, or at most 6 carbon atoms. Combinations of the above-referenced ranges (*e.g.*, at least about 1 and at most about 24 carbon atoms) are also within the scope of the invention. In certain embodiments, the lipophilic moiety is unsubstituted alkyl. In certain embodiments, the lipophilic moiety is unsubstituted and unbranched alkyl. In certain embodiments, the lipophilic moiety is unsubstituted and unbranched C₁₋₂₄ alkyl. In certain embodiments, the lipophilic moiety is

unsubstituted and unbranched C₆₋₂₄ alkyl. In certain embodiments, the lipophilic moiety is unsubstituted and unbranched C₁₂₋₂₄ alkyl.

[0074] The term “small molecule” refers to molecules, whether naturally-occurring or artificially created (*e.g.*, via chemical synthesis) that have a relatively low molecular weight. Typically, a small molecule is an organic compound (*i.e.*, it contains carbon). The small molecule may contain multiple carbon-carbon bonds, stereocenters, and other functional groups (*e.g.*, amines, hydroxyl, carbonyls, and heterocyclic rings, *etc.*). In certain embodiments, the molecular weight of a small molecule is at most about 1,000 g/mol, at most about 900 g/mol, at most about 800 g/mol, at most about 700 g/mol, at most about 600 g/mol, at most about 500 g/mol, at most about 400 g/mol, at most about 300 g/mol, at most about 200 g/mol, or at most about 100 g/mol. In certain embodiments, the molecular weight of a small molecule is at least about 100 g/mol, at least about 200 g/mol, at least about 300 g/mol, at least about 400 g/mol, at least about 500 g/mol, at least about 600 g/mol, at least about 700 g/mol, at least about 800 g/mol, or at least about 900 g/mol, or at least about 1,000 g/mol. Combinations of the above ranges (*e.g.*, at least about 200 g/mol and at most about 500 g/mol) are also possible. In certain embodiments, the small molecule is a therapeutically active agent such as a drug (*e.g.*, a molecule approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (C.F.R.)). The small molecule may also be complexed with one or more metal atoms and/or metal ions. In this instance, the small molecule is also referred to as a “small organometallic molecule.” Preferred small molecules are biologically active in that they produce a biological effect in animals, preferably mammals, more preferably humans. Small molecules include, but are not limited to, radionuclides and imaging agents. In certain embodiments, the small molecule is a drug. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use in humans or animals by the appropriate governmental agency or regulatory body. For example, drugs approved for human use are listed by the FDA under 21 C.F.R. §§ 330.5, 331 through 361, and 440 through 460, incorporated herein by reference; drugs for veterinary use are listed by the FDA under 21 C.F.R. §§ 500 through 589, incorporated herein by reference. All listed drugs are considered acceptable for use in accordance with the present invention.

[0075] A “protein,” “peptide,” or “polypeptide” comprises a polymer of amino acid residues linked together by peptide bonds and refers to proteins, polypeptides, and peptides of any size, structure, or function. Typically, a protein will be at least three amino acids long. A protein may refer to an individual protein or a collection of proteins. Inventive proteins

preferably contain only natural amino acids, although non-natural amino acids (*i.e.*, compounds that do not occur in nature but that can be incorporated into a polypeptide chain) and/or amino acid analogs as are known in the art may alternatively be employed. Also, one or more of the amino acids in a protein may be modified, for example, by the addition of a chemical entity such as a carbohydrate group, a hydroxyl group, a phosphate group, a farnesyl group, an isofarnesyl group, a fatty acid group, a linker for conjugation or functionalization, or other modification. A protein may also be a single molecule or may be a multi-molecular complex. A protein may be a fragment of a naturally occurring protein or peptide. A protein may be naturally occurring, recombinant, synthetic, or any combination of these.

[0076] The term “gene” refers to a nucleic acid fragment that expresses a specific protein, including regulatory sequences preceding (5′ non-coding sequences) and following (3′ non-coding sequences) the coding sequence. “Native gene” refers to a gene as found in nature with its own regulatory sequences. “Chimeric gene” or “chimeric construct” refers to any gene or a construct, not a native gene, comprising regulatory and coding sequences that are not found together in nature. Accordingly, a chimeric gene or chimeric construct may comprise regulatory sequences and coding sequences that are derived from different sources, or regulatory sequences and coding sequences derived from the same source, but arranged in a manner different than that found in nature. “Endogenous gene” refers to a native gene in its natural location in the genome of an organism. A “foreign” gene refers to a gene not normally found in the host organism, but which is introduced into the host organism by gene transfer. Foreign genes can comprise native genes inserted into a non-native organism, or chimeric genes. A “transgene” is a gene that has been introduced into the genome by a transformation procedure.

[0077] The term “histone” refers to highly alkaline proteins found in eukaryotic cell nuclei that package and order the DNA into structural units called nucleosomes. They are the chief protein components of chromatin, acting as spools around which DNA winds, and play a role in gene regulation.

[0078] The term “bromodomain” refers to a protein domain that recognizes acetylated lysine residues such as those on the N-terminal tails of histones. In certain embodiments, a bromodomain of a BET protein comprises about 110 amino acids and shares a conserved fold comprising a left-handed bundle of four alpha helices linked by diverse loop regions that interact with chromatin.

[0079] The term “bromodomain-containing protein” or “bromodomain protein” refers to a protein, whether wild-type or mutant, natural or synthetic, truncated or complete, or a variant thereof, that possesses the minimum amino acid sequence sufficient for a functional bromodomain capable of mediating molecular recognition of acetyl-lysine of acetylated lysine residues on the tails of histones. Bromodomain-containing proteins include, for example, fusion proteins comprising a bromodomain and an additional portion having desired functionality (*e.g.*, a reporter portion).

[0080] The terms “composition” and “formulation” are used interchangeably.

[0081] A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) and/or other non-human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female at any stage of development. The animal may be a transgenic animal or genetically engineered animal. In certain embodiments, the subject is non-human animal. In certain embodiments, the animal is fish. A “patient” refers to a human subject in need of treatment of a disease. The subject may also be a plant. In certain embodiments, the plant is a land plant. In certain embodiments, the plant is a non-vascular land plant. In certain embodiments, the plant is a vascular land plant. In certain embodiments, the plant is a seed plant. In certain embodiments, the plant is a cultivated plant. In certain embodiments, the plant is a dicot. In certain embodiments, the plant is a monocot. In certain embodiments, the plant is a flowering plant. In some embodiments, the plant is a cereal plant, *e.g.*, maize, corn, wheat, rice, oat, barley, rye, or millet. In some embodiments, the plant is a legume, *e.g.*, a bean plant, *e.g.*, soybean plant. In some embodiments, the plant is a tree or shrub.

[0082] The terms “administer,” “administering,” or “administration” refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing an inventive compound, or a composition thereof, in or on a subject.

[0083] The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may

be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0084] The terms “condition,” “disease,” and “disorder” are used interchangeably.

[0085] An “effective amount” of a compound described herein refers to an amount sufficient to elicit the desired biological response, *i.e.*, treating the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0086] A “therapeutically effective amount” of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent.

[0087] A “prophylactically effective amount” of a compound described herein is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0088] A “proliferative disease” refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) the pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative

diseases include cancers (*i.e.*, “malignant neoplasms”), benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases.

[0089] The term “angiogenesis” refers to the physiological process through which new blood vessels form from pre-existing vessels. Angiogenesis is distinct from vasculogenesis, which is the *de novo* formation of endothelial cells from mesoderm cell precursors. The first vessels in a developing embryo form through vasculogenesis, after which angiogenesis is responsible for most blood vessel growth during normal or abnormal development. Angiogenesis is a vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, angiogenesis is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the use of angiogenesis inhibitors in the treatment of cancer. Angiogenesis may be chemically stimulated by angiogenic proteins, such as growth factors (*e.g.*, VEGF). “Pathological angiogenesis” refers to abnormal (*e.g.*, excessive or insufficient) angiogenesis that amounts to and/or is associated with a disease.

[0090] The terms “neoplasm” and “tumor” are used interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be “benign” or “malignant,” depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A “benign neoplasm” is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain “benign” tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor’s neoplastic cells, and these tumors are referred to as “pre-malignant neoplasms.” An exemplary pre-malignant neoplasm is a teratoma. In contrast, a “malignant neoplasm” is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites. The term “metastasis,” “metastatic,” or “metastasize” refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue and is typically identifiable by the presence of a “secondary tumor” or “secondary cell mass” of the tissue type of the primary or original

tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located. For example, a prostate cancer that has migrated to bone is said to be metastasized prostate cancer and includes cancerous prostate cancer cells growing in bone tissue.

[0091] The term “cancer” refers to a malignant neoplasm (*Stedman’s Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi’s sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett’s adenocarcinoma); Ewing’s sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familial hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström’s macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS)

lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*, bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[0092] The term “inflammatory disease” refers to a disease caused by, resulting from, or resulting in inflammation. The term “inflammatory disease” may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthroseitis, rheumatoid arthritis, inflammatory arthritis, Sjogren’s syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto’s thyroiditis, Graves’ disease, Goodpasture’s disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener’s granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis. An ocular inflammatory disease includes, but is not limited to, post-surgical inflammation.

[0093] An “autoimmune disease” refers to a disease arising from an inappropriate immune response of the body of a subject against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (*e.g.*, in autoimmune thyroiditis) or involve a particular tissue in different places (*e.g.*, Goodpasture’s disease which may affect the basement membrane in both the lung and kidney). The treatment of autoimmune diseases is typically with immunosuppression, *e.g.*, medications which decrease the immune response. Exemplary autoimmune diseases include, but are not limited to, glomerulonephritis, Goodspature’s syndrome, necrotizing vasculitis, lymphadenitis, peri-arteritis nodosa, systemic lupus erythematosus, rheumatoid, arthritis, psoriatic arthritis, systemic lupus erythematosus, psoriasis, ulcerative colitis, systemic sclerosis, dermatomyositis/polymyositis, anti-phospholipid antibody syndrome, scleroderma, perphigus vulgaris, ANCA-associated vasculitis (*e.g.*, Wegener’s granulomatosis, microscopic polyangiitis), urveitis, Sjogren’s syndrome, Crohn’s disease, Reiter’s syndrome, ankylosing spondylitis, Lyme disease, Guillain-Barre syndrome, Hashimoto’s thyroiditis, and cardiomyopathy.

Brief Description of the Drawings

[0094] *Figure 1* shows the dose-response curves of exemplary compounds of Formula (I) or (IV) for inhibiting BRD4(1). The response was measured in relative luminescence units (RLUs) and was normalized against DMSO.

[0095] *Figure 2* shows the dose-response curves of exemplary compounds of Formula (I) or (IV) for inhibiting the growth of cancer cell line 797, a nuclear protein in testis (NUT) midline carcinoma. The response was measured in relative luminescence units (RLUs) and was normalized against DMSO.

[0096] *Figures 3A-3B* show the selectivity of exemplary compounds of Formula (I) (*e.g.*, compounds **UMB11** and **UMB32**) for different bromodomain-containing proteins.

[0097] *Figure 4* shows existing BET bromodomain inhibitors with their biasing moieties highlighted by dashed circles.

[0098] *Figure 5* shows inhibitory curves and potency values for small fragment dimethylisoxazole inhibitors **1a-5a**.

[0099] *Figure 6A* shows the docking of compound **5a** into BRD4 crystal structure (PDB: 3MXF). *Figure 6B* shows the ligand interaction diagram of compound **5a** and BRD4.

[00100] *Figure 7* shows representative biochemical inhibitory curves (top) and 797 viability (bottom) for compounds **UMB11**, **UMB21**, and **UMB32**.

[00101] *Figure 8* shows the evaluation of compound **UMB32** selectivity against a panel of bromodomains.

[00102] *Figure 9* shows the crystal structure of **UMB32** in BRD4. Shaded areas are oxygen and nitrogen atoms.

[00103] *Figure 10* shows the ligand interaction diagram of **UMB32** in the BRD4 crystal.

[00104] *Figure 11* shows the crystal structure of **UMB32** overlaid on **JQ1** (top) and rotated 90° (bottom).

[00105] *Figure 12* shows isothermal titration calorimetry of **UMB-32** and BRD4 protein.

[00106] *Figure 13* shows the dose-response curves of exemplary compounds of Formula (I) or (IV) for inhibiting BRD4(1). The response was measured in relative luminescence units (RLUs) and was normalized against DMSO.

[00107] *Figure 14* shows the dose-response curves of exemplary compounds of Formula (I) or (IV) for inhibiting the growth of cancer cell line 797, a nuclear protein in testis (NUT) midline carcinoma. The response was measured in relative luminescence units (RLUs) and was normalized against DMSO.

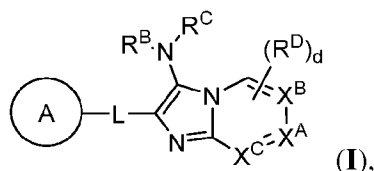
Detailed Description of Certain Embodiments of the Invention

[00108] Inhibitors (*e.g.*, **JQ1** and **I-BET**) of bromodomain-containing proteins (*e.g.*, BET proteins) are useful for treating diseases (such as cancer (*e.g.*, human squamous cell carcinoma)) associated with bromodomain-containing proteins.

[00109] The present invention provides compounds of Formulae (I)-(IV), which are novel inhibitors of bromodomain-containing proteins. The compounds of the invention may be able to bind to in a binding pocket of a bromodomain of a bromodomain-containing protein. In certain embodiments, the compounds of the invention bind to the binding pocket of the bromodomain by mimicking the contact between a histone acetyl-lysine residue and the binding pocket. In certain embodiments, the compounds of the invention bind to the apo binding pocket of the bromodomain. Also provided in the present invention are pharmaceutical compositions and kits useful in inhibiting the activity of a transcription factor (*e.g.*, a bromodomain-containing protein). The compounds, pharmaceutical compositions, and kits of the invention may be useful in treating diseases associated with a bromodomain-containing protein, such as proliferative diseases (*e.g.*, cancers, benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases).

Compounds

[00110] The present invention provides compounds of Formula (I):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof;

wherein:

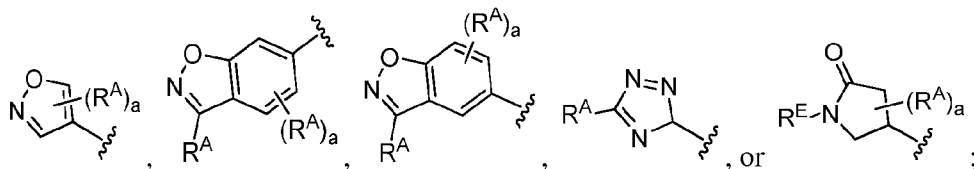
X^A is $C(R^D)$ or N;

X^B is $C(R^D)$ or N;

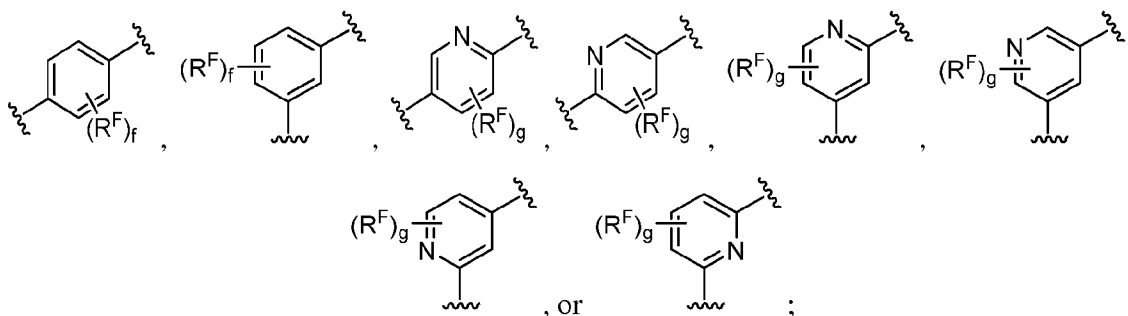
X^C is $C(R^D)$ or N;

wherein no more than two of X^A , X^B , and X^C can be N;

Ring A is of the formula:



L is a bond or of the formula:



each instance of R^A is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-CN$, $-SCN$, $-C(=NR^{A1})R^{A1}$, $-C(=NR^{A1})OR^{A1}$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, or $-OC(=O)N(R^{A1})_2$, or two instances of R^A are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{A1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{A1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, $-C(=O)N(R^{B1})_2$, or a nitrogen protecting group, or R^B and R^C are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^{B1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{B1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^C is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C(=O)R^{C1}$, $-C(=O)OR^{C1}$, $-C(=O)N(R^{C1})_2$, or a nitrogen protecting group, or R^C and R^B are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^{C1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{C1} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^D is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{D1}$, $-N(R^{D1})_2$, $-SR^{D1}$, $-CN$, $-SCN$, $-C(=NR^{D1})R^{D1}$, $-C(=NR^{D1})OR^{D1}$, $-C(=NR^{D1})N(R^{D1})_2$, $-C(=O)R^{D1}$, $-C(=O)OR^{D1}$, $-C(=O)N(R^{D1})_2$, $-NO_2$, $-NR^{D1}C(=O)R^{D1}$, $-NR^{D1}C(=O)OR^{D1}$, $-NR^{D1}C(=O)N(R^{D1})_2$, $-OC(=O)R^{D1}$, $-OC(=O)OR^{D1}$, or $-OC(=O)N(R^{D1})_2$, or two instances of R^D are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{D1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{D1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^E is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-C(=O)R^{E1}$, $-C(=O)OR^{E1}$, $-C(=O)N(R^{E1})_2$, or a nitrogen protecting group;

each instance of R^{E1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{E1} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^F is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{F1}$, $-N(R^{F1})_2$, $-SR^{F1}$, $-CN$, $-SCN$, $-C(=NR^{F1})R^{F1}$, $-C(=NR^{F1})OR^{F1}$, $-C(=NR^{F1})N(R^{F1})_2$, $-$

$C(=O)R^{F1}$, $-C(=O)OR^{F1}$, $-C(=O)N(R^{F1})_2$, $-NO_2$, $-NR^{F1}C(=O)R^{F1}$, $-NR^{F1}C(=O)OR^{F1}$, $-NR^{F1}C(=O)N(R^{F1})_2$, $-OC(=O)R^{F1}$, $-OC(=O)OR^{F1}$, or $-OC(=O)N(R^{F1})_2$, or two instances of R^F are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{F1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{F1} are joined to form a substituted or unsubstituted heterocyclic ring;

a is 0, 1, 2, 3, 4, or 5;

d is 0, 1, or 2;

f is 0, 1, 2, 3 or 4; and

g is 0, 1, 2, or 3.

[00111] In certain embodiments, the present invention provides compounds of Formula (I) and pharmaceutically acceptable salts thereof.

[00112] Compounds of Formula (I) include moiety X^A . In certain embodiments, X^A is $C(R^D)$. In certain embodiments, X^A is $=C(R^D)-$ or $-C(R^D)=$. In certain embodiments, X^A is CH. In certain embodiments, X^A is $=CH-$ or $-CH=$. In certain embodiments, X^A is N. In certain embodiments, X^A is $=N-$ or $-N=$.

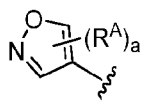
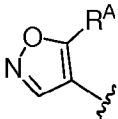
[00113] Compounds of Formula (I) include moiety X^B . In certain embodiments, X^B is $C(R^D)$. In certain embodiments, X^B is $=C(R^D)-$ or $-C(R^D)=$. In certain embodiments, X^B is CH. In certain embodiments, X^B is $=CH-$ or $-CH=$. In certain embodiments, X^B is N. In certain embodiments, X^B is $=N-$ or $-N=$.

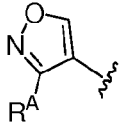
[00114] Compounds of Formula (I) include moiety X^C . In certain embodiments, X^C is $C(R^D)$. In certain embodiments, X^C is $=C(R^D)-$ or $-C(R^D)=$. In certain embodiments, X^C is CH. In certain embodiments, X^C is $=CH-$ or $-CH=$. In certain embodiments, X^C is N. In certain embodiments, X^C is $=N-$ or $-N=$.

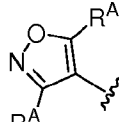
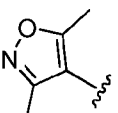
[00115] In certain embodiments, each one of X^A , X^B , and X^C is independently $C(R^D)$. In certain embodiments, each one of X^A , X^B , and X^C is CH. In certain embodiments, X^A and X^C are $C(R^D)$; and X^B is N. In certain embodiments, X^A and X^C are CH; and X^B is N. In certain embodiments, X^A and X^B are $C(R^D)$; and X^C is N. In certain embodiments, X^A and X^B are

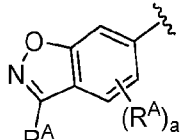
CH; and X^C is N. In certain embodiments, X^B and X^C are $C(R^D)$; and X^A is N. In certain embodiments, X^B and X^C are CH; and X^A is N. In certain embodiments, X^A and X^C are N; and X^B is $C(R^D)$. In certain embodiments, X^A and X^C are N; and X^B is CH. In certain embodiments, X^A and X^B are N; and X^C is $C(R^D)$. In certain embodiments, X^A and X^B are N; and X^C is CH. In certain embodiments, X^B and X^C are N; and X^A is $C(R^D)$. In certain embodiments, X^B and X^C are N; and X^A is CH. In certain embodiments, no more than two of X^A , X^B , and X^C are N. In certain embodiments, no more than one of X^A , X^B , and X^C are N. In certain embodiments, none of X^A , X^B , and X^C are N.

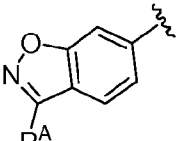
[00116] Compounds of Formula (I) include Ring A. In certain embodiments, Ring A is of

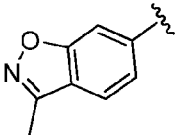
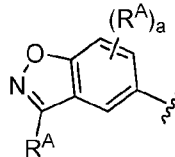
the formula: . In certain embodiments, Ring A is of the formula: . In

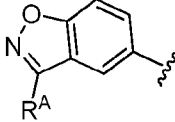
certain embodiments, Ring A is of the formula: . In certain embodiments, Ring A is

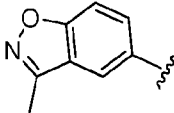
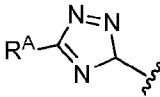
of the formula: . In certain embodiments, Ring A is of the formula: . In

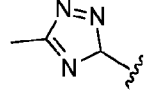
certain embodiments, Ring A is of the formula: . In certain embodiments, Ring

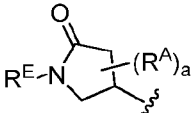
A is of the formula: . In certain embodiments, Ring A is of the formula:

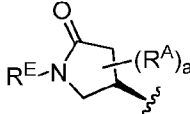
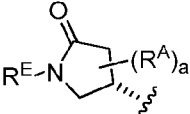
. In certain embodiments, Ring A is of the formula: . In certain

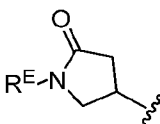
embodiments, Ring A is of the formula: . In certain embodiments, Ring A is of

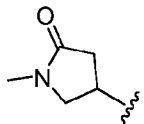
the formula: . In certain embodiments, Ring A is of the formula: 

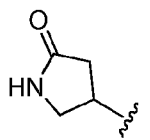
. In certain embodiments, Ring A is of the formula: . In certain embodiments,

Ring A is of the formula: . In certain embodiments, Ring A is of the formula:

. In certain embodiments, Ring A is of the formula: . In

certain embodiments, Ring A is of the formula: . In certain embodiments, Ring

A is of the formula: . In certain embodiments, Ring A is of the formula:



[00117] Ring A of Formula (I) may include one or more substituent R^A . In certain embodiments, at least one instance of R^A is H. In certain embodiments, at least one instance of R^A is halogen. In certain embodiments, at least one instance of R^A is F. In certain embodiments, at least one instance of R^A is Cl. In certain embodiments, at least one instance of R^A is Br. In certain embodiments, at least one instance of R^A is I (iodine). In certain embodiments, at least one instance of R^A is substituted acyl. In certain embodiments, at least one instance of R^A is unsubstituted acyl. In certain embodiments, at least one instance of R^A is substituted alkyl. In certain embodiments, at least one instance of R^A is unsubstituted alkyl. In certain embodiments, at least one instance of R^A is C_{1-12} alkyl. In certain embodiments, at least one instance of R^A is C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is unsubstituted methyl. In certain embodiments, at least one instance of R^A is substituted methyl. In certain embodiments, at least one instance of R^A is $-CH_2F$. In certain embodiments, at least one instance of R^A is $-CHF_2$. In certain embodiments, at least one

instance of R^A is $-\text{CF}_3$. In certain embodiments, at least one instance of R^A is Bn. In certain embodiments, at least one instance of R^A is unsubstituted ethyl. In certain embodiments, at least one instance of R^A is substituted ethyl. In certain embodiments, at least one instance of R^A is $-(\text{CH}_2)_2\text{Ph}$. In certain embodiments, at least one instance of R^A is propyl. In certain embodiments, at least one instance of R^A is butyl. In certain embodiments, at least one instance of R^A is pentyl. In certain embodiments, at least one instance of R^A is hexyl. In certain embodiments, at least one instance of R^A is substituted alkenyl. In certain embodiments, at least one instance of R^A is unsubstituted alkenyl. In certain embodiments, at least one instance of R^A is vinyl. In certain embodiments, at least one instance of R^A is substituted alkynyl. In certain embodiments, at least one instance of R^A is unsubstituted alkynyl. In certain embodiments, at least one instance of R^A is ethynyl. In certain embodiments, at least one instance of R^A is substituted carbocyclyl. In certain embodiments, at least one instance of R^A is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^A is saturated carbocyclyl. In certain embodiments, at least one instance of R^A is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^A is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^A is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^A is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^A is cyclopropyl. In certain embodiments, at least one instance of R^A is cyclobutyl. In certain embodiments, at least one instance of R^A is cyclopentyl. In certain embodiments, at least one instance of R^A is cyclohexyl. In certain embodiments, at least one instance of R^A is cycloheptyl. In certain embodiments, at least one instance of R^A is bicyclic carbocyclyl. In certain embodiments, at least one instance of R^A is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^A is substituted heterocyclyl. In certain embodiments, at least one instance of R^A is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^A is saturated heterocyclyl. In certain embodiments, at least one instance of R^A is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^A is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^A is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^A is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^A is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^A is bicyclic heterocyclyl. In certain embodiments, at least one instance

of R^A is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^A is substituted aryl. In certain embodiments, at least one instance of R^A is unsubstituted aryl. In certain embodiments, at least one instance of R^A is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^A is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^A is substituted phenyl. In certain embodiments, at least one instance of R^A is unsubstituted phenyl. In certain embodiments, at least one instance of R^A is substituted naphthyl. In certain embodiments, at least one instance of R^A is unsubstituted naphthyl. In certain embodiments, at least one instance of R^A is substituted heteroaryl. In certain embodiments, at least one instance of R^A is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^A is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^A is monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^A is pyridyl. In certain embodiments, at least one instance of R^A is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^A is 9-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^A is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^A is $-OR^{A1}$. In certain embodiments, at least one instance of R^A is $-OMe$. In certain embodiments, at least one instance of R^A is $-OEt$. In certain embodiments, at least one instance of R^A is $-OPr$. In certain embodiments, at least one instance of R^A is $-OBu$. In certain embodiments, at least one instance of R^A is $-O(pentyl)$. In certain embodiments, at least one instance of R^A is $-O(hexyl)$. In certain embodiments, at least one instance of R^A is $-OPh$. In certain embodiments, at least one instance of R^A is $-OBn$. In certain embodiments, at least one instance of R^A is $-O(CH_2)_2Ph$. In certain embodiments, at least one instance of R^A is $-OH$. In certain embodiments, at least one instance of R^A is $-SR^{A1}$. In certain embodiments, at least one instance of R^A is $-SMe$. In certain embodiments, at least one instance of R^A is $-SH$. In certain embodiments, at least one instance of R^A is $-N(R^{A1})_2$. In certain embodiments, at least one instance of R^A is $-NMe_2$. In certain embodiments, at least one instance of R^A is $-NH_2$. In certain embodiments, at least one instance of R^A is $-CN$. In certain embodiments, at least one instance of R^A is $-SCN$. In certain embodiments, at least one instance of R^A is $-C(=NR^{A1})R^{A1}$, $-C(=NR^{A1})OR^{A1}$, or $-C(=NR^{A1})N(R^{A1})_2$. In certain embodiments, at least one instance of R^A is $-C(=O)R^{A1}$, $-$

$C(=O)OR^{A1}$, or $-C(=O)N(R^{A1})_2$. In certain embodiments, at least one instance of R^A is $-NO_2$. In certain embodiments, at least one instance of R^A is $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, or $-NR^{A1}C(=O)N(R^{A1})_2$. In certain embodiments, at least one instance of R^A is $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, or $-OC(=O)N(R^{A1})_2$.

[00118] In compounds of Formula (I), two R^A groups may be joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a saturated or unsaturated carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a carbocyclic ring including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a 3- to 7-membered, monocyclic carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a 3-membered carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a 4-membered carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a 5-membered carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a 6-membered carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a 7-membered carbocyclic ring. In certain embodiments, two instances of R^A are joined to form a 5- to 13-membered, bicyclic carbocyclic ring.

[00119] In certain embodiments, two instances of R^A are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^A are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^A are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^A are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^A are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^A are joined to form a 5- to 13-membered, bicyclic heterocyclic ring.

[00120] In certain embodiments, two instances of R^A are joined to form a substituted or unsubstituted aryl ring. In certain embodiments, two instances of R^A are joined to form a 6- to 14-membered aryl ring. In certain embodiments, two instances of R^A are joined to form a 6- to 10-membered aryl ring. In certain embodiments, two instances of R^A are joined to form a monocyclic aryl ring. In certain embodiments, two instances of R^A are joined to form a phenyl. In certain embodiments, two instances of R^A are joined to form a bicyclic aryl ring. In certain embodiments, two instances of R^A are joined to form a naphthyl.

[00121] In certain embodiments, two instances of R^A are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments, two instances of R^A are joined to form a monocyclic heteroaryl ring, wherein one, two, or three atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^A are joined to form a 5-membered, monocyclic heteroaryl ring. In certain embodiments, two instances of R^A are joined to form a 6-membered, monocyclic heteroaryl ring. In certain embodiments, two instances of R^A are joined to form a pyridyl. In certain embodiments, two instances of R^A are joined to form a bicyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^A are joined to form a 9-membered, bicyclic heteroaryl ring. In certain embodiments, two instances of R^A are joined to form a 10-membered, bicyclic heteroaryl ring.

[00122] In certain embodiments, at least one instance of R^A is halogen or substituted or unsubstituted alkyl. In certain embodiments, at least one instance of R^A is halogen or unsubstituted alkyl. In certain embodiments, at least one instance of R^A is halogen or unsubstituted C_{1-6} alkyl.

[00123] In certain embodiments, at least one instance of R^{A1} is H. In certain embodiments, at least one instance of R^{A1} is substituted acyl. In certain embodiments, at least one instance of R^{A1} is unsubstituted acyl. In certain embodiments, at least one instance of R^{A1} is acetyl. In certain embodiments, at least one instance of R^{A1} is substituted alkyl. In certain embodiments, at least one instance of R^{A1} is unsubstituted alkyl. In certain embodiments, at least one instance of R^{A1} is C_{1-12} alkyl. In certain embodiments, at least one instance of R^{A1} is C_{1-6} alkyl. In certain embodiments, at least one instance of R^{A1} is methyl. In certain embodiments, at least one instance of R^{A1} is ethyl. In certain embodiments, at least one instance of R^{A1} is propyl. In certain embodiments, at least one instance of R^{A1} is butyl. In certain embodiments, at least one instance of R^{A1} is pentyl. In certain embodiments, at least one instance of R^{A1} is hexyl. In certain embodiments, at least one instance of R^{A1} is substituted alkenyl. In certain embodiments, at least one instance of R^{A1} is unsubstituted alkenyl. In certain embodiments, at least one instance of R^{A1} is vinyl. In certain embodiments, at least one instance of R^{A1} is substituted alkynyl. In certain embodiments, at least one instance of R^{A1} is unsubstituted alkynyl. In certain embodiments, at least one instance of R^{A1} is ethynyl. In certain embodiments, at least one instance of R^{A1} is substituted carbocyclyl. In certain embodiments, at least one instance of R^{A1} is unsubstituted carbocyclyl.

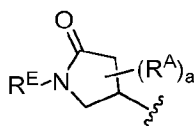
In certain embodiments, at least one instance of R^{A1} is saturated carbocyclyl. In certain embodiments, at least one instance of R^{A1} is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^{A1} is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^{A1} is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^{A1} is cyclopropyl. In certain embodiments, at least one instance of R^{A1} is cyclobutyl. In certain embodiments, at least one instance of R^{A1} is cyclopentyl. In certain embodiments, at least one instance of R^{A1} is cyclohexyl. In certain embodiments, at least one instance of R^{A1} is cycloheptyl. In certain embodiments, at least one instance of R^{A1} is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^{A1} is substituted heterocyclyl. In certain embodiments, at least one instance of R^{A1} is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^{A1} is saturated heterocyclyl. In certain embodiments, at least one instance of R^{A1} is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^{A1} is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^{A1} is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{A1} is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^{A1} is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted aryl. In certain embodiments, at least one instance of R^{A1} is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^{A1} is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^{A1} is monocyclic aryl. In certain embodiments, at least one instance of R^{A1} is phenyl. In certain embodiments, at least one instance of R^{A1} is bicyclic aryl. In certain embodiments, at least one instance of R^{A1} is naphthyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^{A1} is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{A1} is monocyclic heteroaryl. In certain embodiments, at least one instance of R^{A1} is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{A1} is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{A1} is pyridyl. In certain embodiments, at least one instance of R^{A1} is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^{A1} is 9-membered, bicyclic

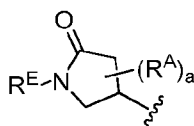
heteroaryl. In certain embodiments, at least one instance of R^{A1} is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{A1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^{A1} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{A1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{A1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^{A1} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^{A1} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulphenyl, 2-pyridine-sulphenyl, or triphenylmethyl when attached to a sulfur atom.

[00124] In certain embodiments, two instances of R^{A1} are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^{A1} are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^{A1} are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^{A1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^{A1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^{A1} are joined to form a 5- to 13-membered, bicyclic heterocyclic ring.

[00125] In certain embodiments, *a* is 0. In certain embodiments, *a* is 1. In certain embodiments, *a* is 2. In certain embodiments, *a* is 3. In certain embodiments, *a* is 4. In certain embodiments, *a* is 5.

[00126] In certain embodiments, at least one instance of R^A is halogen or substituted or unsubstituted alkyl; and *a* is 1 or 2. In certain embodiments, at least one instance of R^A is halogen or unsubstituted alkyl; and *a* is 1 or 2. In certain embodiments, at least one instance of R^A is halogen or unsubstituted C_{1-6} alkyl; and *a* is 1 or 2. In certain embodiments, at least one instance of R^A is halogen or methyl; and *a* is 1 or 2. In certain embodiments, at least one instance of R^A is substituted or unsubstituted alkyl; and *a* is 1 or 2. In certain embodiments, at least one instance of R^A is unsubstituted alkyl; and *a* is 1 or 2. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl; and *a* is 1 or 2. In certain embodiments, at least one instance of R^A is methyl; and *a* is 1 or 2.



[00127] When Ring A is of the formula: , compounds of Formula (I) include substituent R^E . In certain embodiments, R^E is H. In certain embodiments, R^E is substituted acyl. In certain embodiments, R^E is unsubstituted acyl. In certain embodiments, R^E is substituted alkyl. In certain embodiments, R^E is unsubstituted alkyl. In certain embodiments, R^E is C_{1-12} alkyl. In certain embodiments, R^E is C_{1-6} alkyl. In certain embodiments, R^E is unsubstituted methyl. In certain embodiments, R^E is substituted methyl. In certain embodiments, R^E is $-CH_2F$. In certain embodiments, R^E is $-CHF_2$. In certain embodiments, R^E is $-CF_3$. In certain embodiments, R^E is Bn. In certain embodiments, R^E is unsubstituted ethyl. In certain embodiments, R^E is substituted ethyl. In certain embodiments, R^E is $-(CH_2)_2Ph$. In certain embodiments, R^E is propyl. In certain embodiments, R^E is butyl. In certain embodiments, R^E is pentyl. In certain embodiments, R^E is hexyl. In certain embodiments, R^E is substituted alkenyl. In certain embodiments, R^E is unsubstituted alkenyl. In certain embodiments, R^E is vinyl. In certain embodiments, R^E is substituted alkynyl. In certain embodiments, R^E is unsubstituted alkynyl. In certain embodiments, R^E is ethynyl. In certain embodiments, R^E is substituted carbocyclyl. In certain embodiments, R^E is unsubstituted carbocyclyl. In certain embodiments, R^E is saturated carbocyclyl. In certain embodiments, R^E is unsaturated carbocyclyl. In certain embodiments, R^E is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, R^E is monocyclic carbocyclyl. In certain embodiments, R^E is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, R^E is cyclopropyl. In certain embodiments, R^E is cyclobutyl. In certain embodiments, R^E is cyclopentyl. In certain embodiments, R^E is cyclohexyl. In certain embodiments, R^E is cycloheptyl. In certain embodiments, R^E is bicyclic carbocyclyl. In certain embodiments, R^E is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, R^E is substituted heterocyclyl. In certain embodiments, R^E is unsubstituted heterocyclyl. In certain embodiments, R^E is saturated heterocyclyl. In certain embodiments, R^E is unsaturated heterocyclyl. In certain embodiments, R^E is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, R^E is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^E is monocyclic heterocyclyl. In certain embodiments, R^E is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, R^E is bicyclic heterocyclyl. In certain embodiments, R^E is 5- to 13-membered, bicyclic heterocyclyl. In certain

embodiments, R^E is substituted aryl. In certain embodiments, R^E is unsubstituted aryl. In certain embodiments, R^E is 6- to 14-membered aryl. In certain embodiments, R^E is 6- to 10-membered aryl. In certain embodiments, R^E is substituted phenyl. In certain embodiments, R^E is unsubstituted phenyl. In certain embodiments, R^E is substituted naphthyl. In certain embodiments, R^E is unsubstituted naphthyl. In certain embodiments, R^E is substituted heteroaryl. In certain embodiments, R^E is unsubstituted heteroaryl. In certain embodiments, R^E is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^E is monocyclic heteroaryl. In certain embodiments, R^E is 5-membered, monocyclic heteroaryl. In certain embodiments, R^E is 6-membered, monocyclic heteroaryl. In certain embodiments, R^E is pyridyl. In certain embodiments, R^E is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, R^E is 9-membered, bicyclic heteroaryl. In certain embodiments, R^E is 10-membered, bicyclic heteroaryl. In certain embodiments, R^E is $-C(=O)R^{E1}$. In certain embodiments, R^E is $-C(=O)OR^{E1}$. In certain embodiments, R^E is $-C(=O)N(R^{E1})_2$. In certain embodiments, R^E is a nitrogen protecting group. In certain embodiments, R^E is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00128] In certain embodiments, R^E is hydrogen or substituted or unsubstituted alkyl. In certain embodiments, R^E is hydrogen or unsubstituted alkyl. In certain embodiments, R^E is hydrogen or unsubstituted C_{1-6} alkyl.

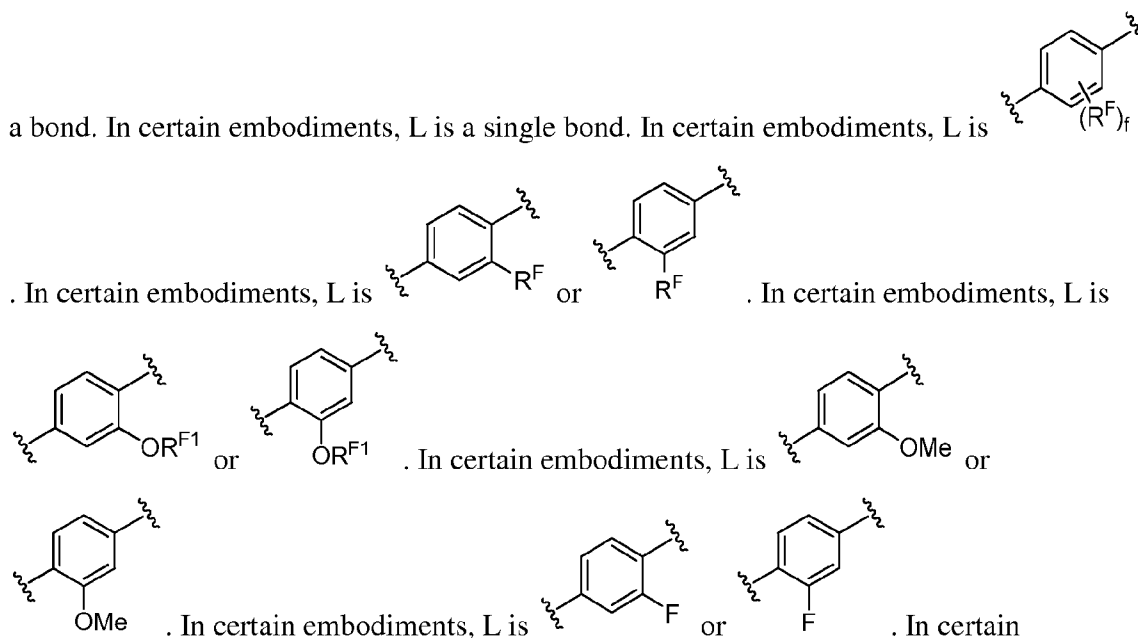
[00129] In certain embodiments, at least one instance of R^{E1} is H. In certain embodiments, at least one instance of R^{E1} is substituted acyl. In certain embodiments, at least one instance of R^{E1} is unsubstituted acyl. In certain embodiments, at least one instance of R^{E1} is acetyl. In certain embodiments, at least one instance of R^{E1} is substituted alkyl. In certain embodiments, at least one instance of R^{E1} is unsubstituted alkyl. In certain embodiments, at least one instance of R^{E1} is C_{1-12} alkyl. In certain embodiments, at least one instance of R^{E1} is C_{1-6} alkyl. In certain embodiments, at least one instance of R^{E1} is methyl. In certain embodiments, at least one instance of R^{E1} is ethyl. In certain embodiments, at least one instance of R^{E1} is propyl. In certain embodiments, at least one instance of R^{E1} is butyl. In certain embodiments, at least one instance of R^{E1} is pentyl. In certain embodiments, at least one instance of R^{E1} is hexyl. In certain embodiments, at least one instance of R^{E1} is substituted alkenyl. In certain embodiments, at least one instance of R^{E1} is unsubstituted alkenyl. In certain embodiments, at least one instance of R^{E1} is vinyl. In certain embodiments, at least one instance of R^{E1} is substituted alkynyl. In certain embodiments, at least one instance of R^{E1} is unsubstituted

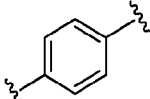
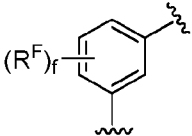
alkynyl. In certain embodiments, at least one instance of R^{E1} is ethynyl. In certain embodiments, at least one instance of R^{E1} is substituted carbocyclyl. In certain embodiments, at least one instance of R^{E1} is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^{E1} is saturated carbocyclyl. In certain embodiments, at least one instance of R^{E1} is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^{E1} is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^{E1} is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^{E1} is cyclopropyl. In certain embodiments, at least one instance of R^{E1} is cyclobutyl. In certain embodiments, at least one instance of R^{E1} is cyclopentyl. In certain embodiments, at least one instance of R^{E1} is cyclohexyl. In certain embodiments, at least one instance of R^{E1} is cycloheptyl. In certain embodiments, at least one instance of R^{E1} is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^{E1} is substituted heterocyclyl. In certain embodiments, at least one instance of R^{E1} is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^{E1} is saturated heterocyclyl. In certain embodiments, at least one instance of R^{E1} is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^{E1} is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^{E1} is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{E1} is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^{E1} is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^{E1} is substituted or unsubstituted aryl. In certain embodiments, at least one instance of R^{E1} is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^{E1} is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^{E1} is monocyclic aryl. In certain embodiments, at least one instance of R^{E1} is phenyl. In certain embodiments, at least one instance of R^{E1} is bicyclic aryl. In certain embodiments, at least one instance of R^{E1} is naphthyl. In certain embodiments, at least one instance of R^{E1} is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^{E1} is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{E1} is monocyclic heteroaryl. In certain embodiments, at least one instance of R^{E1} is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{E1} is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{E1} is pyridyl. In certain embodiments, at least one

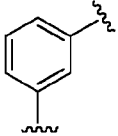
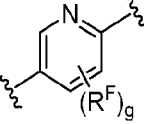
instance of R^{E1} is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^{E1} is 9-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{E1} is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{E1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^{E1} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{E1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{E1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom.

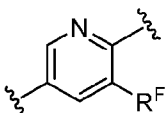
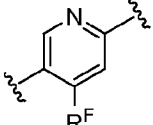
[00130] In certain embodiments, two instances of R^{E1} are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^{E1} are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^{E1} are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^{E1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^{E1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^{E1} are joined to form a 5- to 13-membered, bicyclic heterocyclic ring.

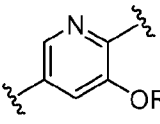
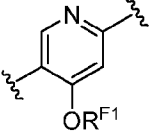
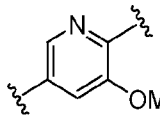
[00131] Compounds of Formula (I) includes linker moiety L. In certain embodiments, L is

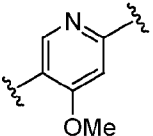
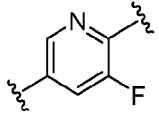
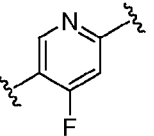


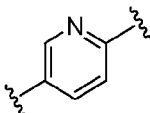
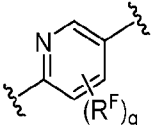
embodiments, L is . In certain embodiments, L is . In certain

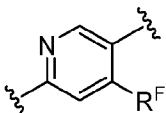
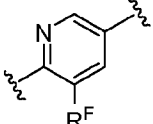
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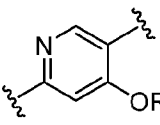
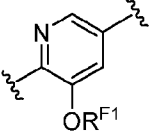
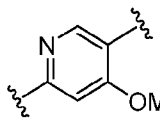
embodiments, L is  or . In certain embodiments, L is

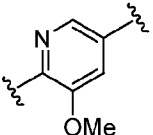
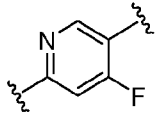
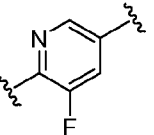
 or . In certain embodiments, L is  or

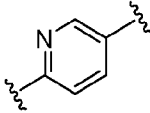
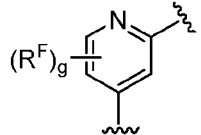
. In certain embodiments, L is  or . In certain

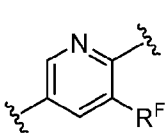
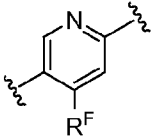
embodiments, L is . In certain embodiments, L is . In certain

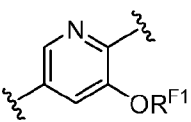
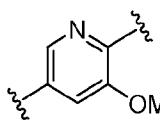
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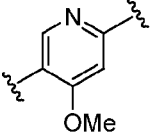
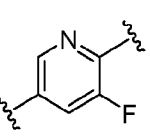
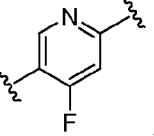
 or . In certain embodiments, L is  or

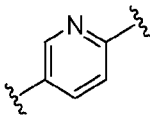
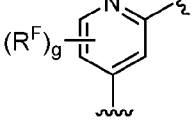
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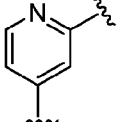
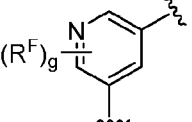
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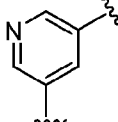
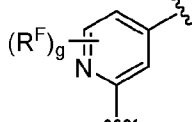
embodiments, L is  or . In certain embodiments, L is

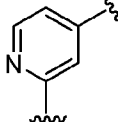
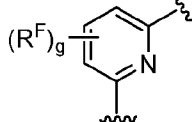
 or . In certain embodiments, L is  or

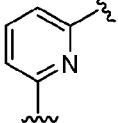
. In certain embodiments, L is  or . In certain

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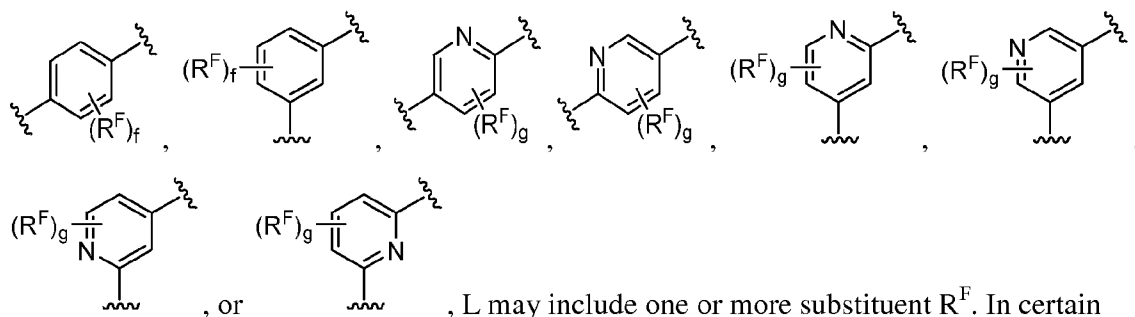
embodiments, L is . In certain embodiments, L is . In certain

embodiments, L is . In certain embodiments, L is . In certain

embodiments, L is . In certain embodiments, L is . In certain

embodiments, L is .

[00132] When linker moiety L of compounds of Formula (I) is of the formula:



embodiments, at least one instance of R^F is H. In certain embodiments, at least one instance

of R^F is halogen. In certain embodiments, at least one instance of R^F is F. In certain embodiments, at least one instance of R^F is Cl. In certain embodiments, at least one instance of R^F is Br. In certain embodiments, at least one instance of R^F is I (iodine). In certain embodiments, at least one instance of R^F is substituted acyl. In certain embodiments, at least one instance of R^F is unsubstituted acyl. In certain embodiments, at least one instance of R^F is substituted alkyl. In certain embodiments, at least one instance of R^F is unsubstituted alkyl. In certain embodiments, at least one instance of R^F is C_{1-12} alkyl. In certain embodiments, at least one instance of R^F is C_{1-6} alkyl. In certain embodiments, at least one instance of R^F is unsubstituted methyl. In certain embodiments, at least one instance of R^F is substituted methyl. In certain embodiments, at least one instance of R^F is $-CH_2F$. In certain embodiments, at least one instance of R^F is $-CHF_2$. In certain embodiments, at least one instance of R^F is $-CF_3$. In certain embodiments, at least one instance of R^F is Bn. In certain embodiments, at least one instance of R^F is unsubstituted ethyl. In certain embodiments, at least one instance of R^F is substituted ethyl. In certain embodiments, at least one instance of R^F is $-(CH_2)_2Ph$. In certain embodiments, at least one instance of R^F is propyl. In certain embodiments, at least one instance of R^F is butyl. In certain embodiments, at least one instance of R^F is pentyl. In certain embodiments, at least one instance of R^F is hexyl. In certain embodiments, at least one instance of R^F is substituted alkenyl. In certain embodiments, at least one instance of R^F is unsubstituted alkenyl. In certain embodiments, at least one instance of R^F is vinyl. In certain embodiments, at least one instance of R^F is substituted alkynyl. In certain embodiments, at least one instance of R^F is unsubstituted alkynyl. In certain embodiments, at least one instance of R^F is ethynyl. In certain embodiments, at least one instance of R^F is substituted carbocyclyl. In certain embodiments, at least one instance of R^F is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^F is saturated carbocyclyl. In certain embodiments, at least one instance of R^F is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^F is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^F is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^F is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^F is cyclopropyl. In certain embodiments, at least one instance of R^F is cyclobutyl. In certain embodiments, at least one instance of R^F is cyclopentyl. In certain embodiments, at least one instance of R^F is cyclohexyl. In certain embodiments, at least one instance of R^F is cycloheptyl. In certain embodiments, at least one instance of R^F is bicyclic carbocyclyl. In certain embodiments, at least one instance of R^F is 5- to 13-membered,

bicyclic carbocyclyl. In certain embodiments, at least one instance of R^F is substituted heterocyclyl. In certain embodiments, at least one instance of R^F is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^F is saturated heterocyclyl. In certain embodiments, at least one instance of R^F is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^F is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^F is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^F is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^F is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^F is bicyclic heterocyclyl. In certain embodiments, at least one instance of R^F is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^F is substituted aryl. In certain embodiments, at least one instance of R^F is unsubstituted aryl. In certain embodiments, at least one instance of R^F is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^F is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^F is substituted phenyl. In certain embodiments, at least one instance of R^F is unsubstituted phenyl. In certain embodiments, at least one instance of R^F is substituted naphthyl. In certain embodiments, at least one instance of R^F is unsubstituted naphthyl. In certain embodiments, at least one instance of R^F is substituted heteroaryl. In certain embodiments, at least one instance of R^F is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^F is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^F is monocyclic heteroaryl. In certain embodiments, at least one instance of R^F is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^F is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^F is pyridyl. In certain embodiments, at least one instance of R^F is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^F is 9-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^F is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^F is $-OR^{F1}$. In certain embodiments, at least one instance of R^F is $-OMe$. In certain embodiments, at least one instance of R^F is $-OEt$. In certain embodiments, at least one instance of R^F is $-OPr$. In certain embodiments, at least one instance of R^F is $-OBu$. In certain embodiments, at least one instance of R^F is $-O(pentyl)$. In

certain embodiments, at least one instance of R^F is $-O(\text{hexyl})$. In certain embodiments, at least one instance of R^F is $-O\text{Ph}$. In certain embodiments, at least one instance of R^F is $-OBn$. In certain embodiments, at least one instance of R^F is $-O(\text{CH}_2)_2\text{Ph}$. In certain embodiments, at least one instance of R^F is $-OH$. In certain embodiments, at least one instance of R^F is $-SR^{F1}$. In certain embodiments, at least one instance of R^F is $-SMe$. In certain embodiments, at least one instance of R^F is $-SH$. In certain embodiments, at least one instance of R^F is $-N(R^{F1})_2$. In certain embodiments, at least one instance of R^F is $-NMe_2$. In certain embodiments, at least one instance of R^F is $-NH_2$. In certain embodiments, at least one instance of R^F is $-CN$. In certain embodiments, at least one instance of R^F is $-SCN$. In certain embodiments, at least one instance of R^F is $-C(=NR^{F1})R^{F1}$, $-C(=NR^{F1})OR^{F1}$, or $-C(=NR^{F1})N(R^{F1})_2$. In certain embodiments, at least one instance of R^F is $-C(=O)R^{F1}$, $-C(=O)OR^{F1}$, or $-C(=O)N(R^{F1})_2$. In certain embodiments, at least one instance of R^F is $-NO_2$. In certain embodiments, at least one instance of R^F is $-NR^{F1}C(=O)R^{F1}$, $-NR^{F1}C(=O)OR^{F1}$, or $-NR^{F1}C(=O)N(R^{F1})_2$. In certain embodiments, at least one instance of R^F is $-OC(=O)R^{F1}$, $-OC(=O)OR^{F1}$, or $-OC(=O)N(R^{F1})_2$.

[00133] In compounds of Formula (I), two R^F groups may be joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a saturated or unsaturated carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a carbocyclic ring including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a 3- to 7-membered, monocyclic carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a 3-membered carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a 4-membered carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a 5-membered carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a 6-membered carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a 7-membered carbocyclic ring. In certain embodiments, two instances of R^F are joined to form a 5- to 13-membered, bicyclic carbocyclic ring.

[00134] In certain embodiments, two instances of R^F are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^F are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^F are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^F are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments,

two instances of R^F are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^F are joined to form a 5- to 13-membered, bicyclic heterocyclic ring.

[00135] In certain embodiments, two instances of R^F are joined to form a substituted or unsubstituted aryl ring. In certain embodiments, two instances of R^F are joined to form a 6- to 14-membered aryl ring. In certain embodiments, two instances of R^F are joined to form a 6- to 10-membered aryl ring. In certain embodiments, two instances of R^F are joined to form a monocyclic aryl ring. In certain embodiments, two instances of R^F are joined to form a phenyl. In certain embodiments, two instances of R^F are joined to form a bicyclic aryl ring. In certain embodiments, two instances of R^F are joined to form a naphthyl.

[00136] In certain embodiments, two instances of R^F are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments, two instances of R^F are joined to form a monocyclic heteroaryl ring, wherein one, two, or three atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^F are joined to form a 5-membered, monocyclic heteroaryl ring. In certain embodiments, two instances of R^F are joined to form a 6-membered, monocyclic heteroaryl ring. In certain embodiments, two instances of R^F are joined to form a pyridyl. In certain embodiments, two instances of R^F are joined to form a bicyclic heteroaryl ring system, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^F are joined to form a 9-membered, bicyclic heteroaryl ring system. In certain embodiments, two instances of R^F are joined to form a 10-membered, bicyclic heteroaryl ring system.

[00137] In certain embodiments, at least one instance of R^F is halogen, substituted or unsubstituted alkyl, or $-OR^{F1}$. In certain embodiments, at least one instance of R^F is halogen, unsubstituted alkyl, or $-O-(\text{unsubstituted alkyl})$. In certain embodiments, at least one instance of R^F is halogen, unsubstituted C_{1-6} alkyl, or $-O-(\text{unsubstituted } C_{1-6} \text{ alkyl})$.

[00138] In certain embodiments, at least one instance of R^{F1} is H. In certain embodiments, at least one instance of R^{F1} is substituted acyl. In certain embodiments, at least one instance of R^{F1} is unsubstituted acyl. In certain embodiments, at least one instance of R^{F1} is acetyl. In certain embodiments, at least one instance of R^{F1} is substituted alkyl. In certain embodiments, at least one instance of R^{F1} is unsubstituted alkyl. In certain embodiments, at least one instance of R^{F1} is C_{1-12} alkyl. In certain embodiments, at least one instance of R^{F1} is C_{1-6} alkyl. In certain embodiments, at least one instance of R^{F1} is methyl. In certain embodiments,

at least one instance of R^{F1} is ethyl. In certain embodiments, at least one instance of R^{F1} is propyl. In certain embodiments, at least one instance of R^{F1} is butyl. In certain embodiments, at least one instance of R^{F1} is pentyl. In certain embodiments, at least one instance of R^{F1} is hexyl. In certain embodiments, at least one instance of R^{F1} is substituted alkenyl. In certain embodiments, at least one instance of R^{F1} is unsubstituted alkenyl. In certain embodiments, at least one instance of R^{F1} is vinyl. In certain embodiments, at least one instance of R^{F1} is substituted alkynyl. In certain embodiments, at least one instance of R^{F1} is unsubstituted alkynyl. In certain embodiments, at least one instance of R^{F1} is ethynyl. In certain embodiments, at least one instance of R^{F1} is substituted carbocyclyl. In certain embodiments, at least one instance of R^{F1} is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^{F1} is saturated carbocyclyl. In certain embodiments, at least one instance of R^{F1} is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^{F1} is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^{F1} is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^{F1} is cyclopropyl. In certain embodiments, at least one instance of R^{F1} is cyclobutyl. In certain embodiments, at least one instance of R^{F1} is cyclopentyl. In certain embodiments, at least one instance of R^{F1} is cyclohexyl. In certain embodiments, at least one instance of R^{F1} is cycloheptyl. In certain embodiments, at least one instance of R^{F1} is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^{F1} is substituted heterocyclyl. In certain embodiments, at least one instance of R^{F1} is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^{F1} is saturated heterocyclyl. In certain embodiments, at least one instance of R^{F1} is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^{F1} is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^{F1} is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{F1} is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^{F1} is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^{F1} is substituted or unsubstituted aryl. In certain embodiments, at least one instance of R^{F1} is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^{F1} is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^{F1} is monocyclic aryl. In certain embodiments, at least one instance of R^{F1} is phenyl. In certain embodiments, at least one instance of R^{F1} is bicyclic aryl. In certain embodiments, at least one instance of R^{F1} is naphthyl. In certain embodiments, at least

one instance of R^{F1} is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^{F1} is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{F1} is monocyclic heteroaryl. In certain embodiments, at least one instance of R^{F1} is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{F1} is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{F1} is pyridyl. In certain embodiments, at least one instance of R^{F1} is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^{F1} is 9-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{F1} is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{F1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^{F1} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{F1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{F1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^{F1} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^{F1} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom.

[00139] In certain embodiments, two instances of R^{F1} are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^{F1} are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^{F1} are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^{F1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^{F1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^{F1} are joined to form a 5- to 13-membered, bicyclic heterocyclic ring.

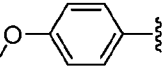
[00140] In certain embodiments, *f* is 0. In certain embodiments, *f* is 1. In certain embodiments, *f* is 2. In certain embodiments, *f* is 3. In certain embodiments, *f* is 4.

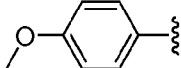
[00141] In certain embodiments, *g* is 0. In certain embodiments, *g* is 1. In certain embodiments, *g* is 2. In certain embodiments, *g* is 3.

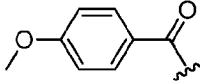
[00142] In certain embodiments, R^F is halogen, substituted or unsubstituted alkyl, or $-OR^{F1}$; and f or g is 1. In certain embodiments, R^F is halogen, unsubstituted alkyl, or $-O-$ (unsubstituted alkyl); and f or g is 1. In certain embodiments, R^F is halogen, unsubstituted C_{1-6} alkyl, or $-O-$ (unsubstituted C_{1-6} alkyl); and f or g is 1. In certain embodiments, R^F is $-OR^{F1}$; and f or g is 1. In certain embodiments, R^F is $-O-$ (unsubstituted alkyl); and f or g is 1. In certain embodiments, R^F is $-O-$ (unsubstituted C_{1-6} alkyl); and f or g is 1. In certain embodiments, R^F is $-OMe$; and f or g is 1.

[00143] Compounds of Formula (I) include substituent R^B on the amino moiety. In certain embodiments, R^B is H. In certain embodiments, R^B is substituted acyl. In certain embodiments, R^B is unsubstituted acyl. In certain embodiments, R^B is substituted alkyl. In certain embodiments, R^B is unsubstituted alkyl. In certain embodiments, R^B is C_{1-12} alkyl. In certain embodiments, R^B is C_{1-6} alkyl. In certain embodiments, R^B is unsubstituted methyl. In certain embodiments, R^B is substituted methyl. In certain embodiments, R^B is $-CH_2F$. In certain embodiments, R^B is $-CHF_2$. In certain embodiments, R^B is $-CF_3$. In certain embodiments, R^B is Bn. In certain embodiments, R^B is unsubstituted ethyl. In certain embodiments, R^B is substituted ethyl. In certain embodiments, R^B is $-(CH_2)_2Ph$. In certain embodiments, R^B is propyl. In certain embodiments, R^B is *n*-propyl. In certain embodiments, R^B is *iso*-propyl. In certain embodiments, R^B is butyl. In certain embodiments, R^B is *n*-butyl. In certain embodiments, R^B is *iso*-butyl. In certain embodiments, R^B is *t*-butyl. In certain embodiments, R^B is pentyl. In certain embodiments, R^B is hexyl. In certain embodiments, R^B is substituted alkenyl. In certain embodiments, R^B is unsubstituted alkenyl. In certain embodiments, R^B is vinyl. In certain embodiments, R^B is substituted alkynyl. In certain embodiments, R^B is unsubstituted alkynyl. In certain embodiments, R^B is ethynyl. In certain embodiments, R^B is substituted carbocyclyl. In certain embodiments, R^B is unsubstituted carbocyclyl. In certain embodiments, R^B is saturated carbocyclyl. In certain embodiments, R^B is unsaturated carbocyclyl. In certain embodiments, R^B is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, R^B is monocyclic carbocyclyl. In certain embodiments, R^B is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, R^B is cyclopropyl. In certain embodiments, R^B is cyclobutyl. In certain embodiments, R^B is cyclopentyl. In certain embodiments, R^B is cyclohexyl. In certain embodiments, R^B is cycloheptyl. In certain embodiments, R^B is bicyclic carbocyclyl. In certain embodiments, R^B is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, R^B is substituted heterocyclyl. In certain embodiments, R^B is unsubstituted heterocyclyl. In certain embodiments, R^B is saturated heterocyclyl. In certain embodiments, R^B is unsaturated

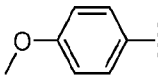
heterocyclyl. In certain embodiments, R^B is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, R^B is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^B is monocyclic heterocyclyl. In certain embodiments, R^B is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, R^B is bicyclic heterocyclyl. In certain embodiments, R^B is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, R^B is substituted aryl. In certain embodiments, R^B is unsubstituted aryl. In certain embodiments, R^B is 6- to 14-membered aryl. In certain embodiments, R^B is 6- to 10-membered aryl. In certain embodiments, R^B is substituted phenyl. In certain embodiments, R^B is *para*-substituted phenyl. In certain embodiments, R^B is

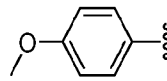
of the formula: (unsubstituted C_{1-6} alkyl) . In certain embodiments, R^B is of the

formula: . In certain embodiments, R^B is unsubstituted phenyl. In certain embodiments, R^B is substituted naphthyl. In certain embodiments, R^B is unsubstituted naphthyl. In certain embodiments, R^B is substituted heteroaryl. In certain embodiments, R^B is unsubstituted heteroaryl. In certain embodiments, R^B is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^B is monocyclic heteroaryl. In certain embodiments, R^B is 5-membered, monocyclic heteroaryl. In certain embodiments, R^B is 6-membered, monocyclic heteroaryl. In certain embodiments, R^B is pyridyl. In certain embodiments, R^B is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, R^B is 9-membered, bicyclic heteroaryl. In certain embodiments, R^B is 10-membered, bicyclic heteroaryl. In certain embodiments, R^B is $-C(=O)R^{B1}$. In certain embodiments, R^B is $-C(=O)-(substituted\ or\ unsubstituted\ alkyl)$. In certain embodiments, R^B is $-C(=O)-(unsubstituted\ C_{1-6}\ alkyl)$. In certain embodiments, R^B is $-C(=O)-(t-Bu)$. In certain embodiments, R^B is $-C(=O)-(substituted\ or\ unsubstituted\ phenyl)$. In certain embodiments,

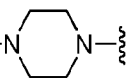
R^B is $-C(=O)Ph$. In certain embodiments, R^B is of the formula: . In certain embodiments, R^B is $-C(=O)OR^{B1}$. In certain embodiments, R^B is $-C(=O)N(R^{B1})_2$. In certain embodiments, R^B is a nitrogen protecting group. In certain embodiments, R^B is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

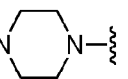
[00144] In certain embodiments, R^B is substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, or $-C(=O)N(R^{B1})_2$. In certain embodiments, R^B is substituted or unsubstituted alkyl, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl, substituted or unsubstituted phenyl, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, or $-C(=O)N(R^{B1})_2$. In certain embodiments, R^B is substituted or unsubstituted C_{1-6} alkyl, unsubstituted, 3- to 7-membered, monocyclic carbocyclyl, substituted or unsubstituted phenyl, or $-C(=O)R^{B1}$. In certain

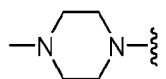
embodiments, R^B is *t*-Bu, benzyl, cyclohexyl, , $-C(=O)(t\text{-Bu})$, or $-C(=O)Ph$. In

certain embodiments, R^B is *t*-Bu, benzyl, cyclohexyl, or .

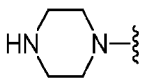
[00145] In certain embodiments, R^B and R^C are joined to form a substituted heterocyclic ring. In certain embodiments, R^B and R^C are joined to form an unsubstituted heterocyclic ring. In certain embodiments, R^B and R^C are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, R^B and R^C are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, R^B and R^C are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^B and R^C are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, R^B and R^C are joined to form a 5- or 6-membered, monocyclic heterocyclic ring wherein one or two atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen or oxygen. In certain embodiments, R^B and R^C are joined to form a heterocyclic ring of the formula:

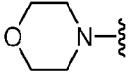
(substituted or unsubstituted alkyl)-. In certain embodiments, R^B and R^C are joined to

form a heterocyclic ring of the formula: (unsubstituted C_{1-6} alkyl)-. In certain

embodiments, R^B and R^C are joined to form a heterocyclic ring of the formula: .

In certain embodiments, R^B and R^C are joined to form a heterocyclic ring of the formula:

. In certain embodiments, R^B and R^C are joined to form a heterocyclic ring of the

formula: . In certain embodiments, R^B and R^C are joined to form a 5- to 13-membered, bicyclic heterocyclic ring system.

[00146] In certain embodiments, at least one instance of R^{B1} is H. In certain embodiments, at least one instance of R^{B1} is substituted acyl. In certain embodiments, at least one instance of R^{B1} is unsubstituted acyl. In certain embodiments, at least one instance of R^{B1} is acetyl. In certain embodiments, at least one instance of R^{B1} is substituted alkyl. In certain embodiments, at least one instance of R^{B1} is unsubstituted alkyl. In certain embodiments, at least one instance of R^{B1} is C₁₋₁₂ alkyl. In certain embodiments, at least one instance of R^{B1} is C₁₋₆ alkyl. In certain embodiments, at least one instance of R^{B1} is methyl. In certain embodiments, at least one instance of R^{B1} is ethyl. In certain embodiments, at least one instance of R^{B1} is propyl. In certain embodiments, at least one instance of R^{B1} is butyl. In certain embodiments, at least one instance of R^{B1} is pentyl. In certain embodiments, at least one instance of R^{B1} is hexyl. In certain embodiments, at least one instance of R^{B1} is substituted alkenyl. In certain embodiments, at least one instance of R^{B1} is unsubstituted alkenyl. In certain embodiments, at least one instance of R^{B1} is vinyl. In certain embodiments, at least one instance of R^{B1} is substituted alkynyl. In certain embodiments, at least one instance of R^{B1} is unsubstituted alkynyl. In certain embodiments, at least one instance of R^{B1} is ethynyl. In certain embodiments, at least one instance of R^{B1} is substituted carbocyclyl. In certain embodiments, at least one instance of R^{B1} is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^{B1} is saturated carbocyclyl. In certain embodiments, at least one instance of R^{B1} is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^{B1} is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^{B1} is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^{B1} is cyclopropyl. In certain embodiments, at least one instance of R^{B1} is cyclobutyl. In certain embodiments, at least one instance of R^{B1} is cyclopentyl. In certain embodiments, at least one instance of R^{B1} is cyclohexyl. In certain embodiments, at least one instance of R^{B1} is cycloheptyl. In certain embodiments, at least one instance of R^{B1} is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^{B1} is substituted heterocyclyl. In certain embodiments, at least one instance of R^{B1} is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^{B1} is saturated heterocyclyl. In certain embodiments, at least one instance of R^{B1} is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^{B1} is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one

instance of R^{B1} is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{B1} is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^{B1} is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted aryl. In certain embodiments, at least one instance of R^{B1} is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^{B1} is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^{B1} is monocyclic aryl. In certain embodiments, at least one instance of R^{B1} is phenyl. In certain embodiments, at least one instance of R^{B1} is bicyclic aryl. In certain embodiments, at least one instance of R^{B1} is naphthyl. In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^{B1} is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{B1} is monocyclic heteroaryl. In certain embodiments, at least one instance of R^{B1} is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{B1} is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{B1} is pyridyl. In certain embodiments, at least one instance of R^{B1} is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^{B1} is 9-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{B1} is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{B1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^{B1} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{B1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{B1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom.

[00147] In certain embodiments, two instances of R^{B1} are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^{B1} are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^{B1} are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^{B1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments,

two instances of R^{B1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^{B1} are joined to form a 5- to 13-membered, bicyclic heterocyclic ring.

[00148] Compounds of Formula (I) include substituent R^C on the amino moiety. In certain embodiments, R^C is H. In certain embodiments, R^C is substituted acyl. In certain embodiments, R^C is unsubstituted acyl. In certain embodiments, R^C is substituted alkyl. In certain embodiments, R^C is unsubstituted alkyl. In certain embodiments, R^C is C_{1-12} alkyl. In certain embodiments, R^C is C_{1-6} alkyl. In certain embodiments, R^C is unsubstituted methyl. In certain embodiments, R^C is substituted methyl. In certain embodiments, R^C is $-CH_2F$. In certain embodiments, R^C is $-CHF_2$. In certain embodiments, R^C is $-CF_3$. In certain embodiments, R^C is Bn. In certain embodiments, R^C is unsubstituted ethyl. In certain embodiments, R^C is substituted ethyl. In certain embodiments, R^C is $-(CH_2)_2Ph$. In certain embodiments, R^C is propyl. In certain embodiments, R^C is butyl. In certain embodiments, R^C is *t*-butyl. In certain embodiments, R^C is pentyl. In certain embodiments, R^C is hexyl. In certain embodiments, R^C is substituted alkenyl. In certain embodiments, R^C is unsubstituted alkenyl. In certain embodiments, R^C is vinyl. In certain embodiments, R^C is substituted alkynyl. In certain embodiments, R^C is unsubstituted alkynyl. In certain embodiments, R^C is ethynyl. In certain embodiments, R^C is substituted carbocyclyl. In certain embodiments, R^C is unsubstituted carbocyclyl. In certain embodiments, R^C is saturated carbocyclyl. In certain embodiments, R^C is unsaturated carbocyclyl. In certain embodiments, R^C is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, R^C is monocyclic carbocyclyl. In certain embodiments, R^C is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, R^C is cyclopropyl. In certain embodiments, R^C is cyclobutyl. In certain embodiments, R^C is cyclopentyl. In certain embodiments, R^C is cyclohexyl. In certain embodiments, R^C is cycloheptyl. In certain embodiments, R^C is bicyclic carbocyclyl. In certain embodiments, R^C is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, R^C is substituted heterocyclyl. In certain embodiments, R^C is unsubstituted heterocyclyl. In certain embodiments, R^C is saturated heterocyclyl. In certain embodiments, R^C is unsaturated heterocyclyl. In certain embodiments, R^C is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, R^C is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^C is monocyclic heterocyclyl. In certain embodiments, R^C is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, R^C is bicyclic heterocyclyl. In

certain embodiments, R^C is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, R^C is substituted aryl. In certain embodiments, R^C is unsubstituted aryl. In certain embodiments, R^C is 6- to 14-membered aryl. In certain embodiments, R^C is 6- to 10-membered aryl. In certain embodiments, R^C is substituted phenyl. In certain embodiments, R^C is unsubstituted phenyl. In certain embodiments, R^C is substituted naphthyl. In certain embodiments, R^C is unsubstituted naphthyl. In certain embodiments, R^C is substituted heteroaryl. In certain embodiments, R^C is unsubstituted heteroaryl. In certain embodiments, R^C is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^C is monocyclic heteroaryl. In certain embodiments, R^C is 5-membered, monocyclic heteroaryl. In certain embodiments, R^C is 6-membered, monocyclic heteroaryl. In certain embodiments, R^C is pyridyl. In certain embodiments, R^C is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, R^C is 9-membered, bicyclic heteroaryl. In certain embodiments, R^C is 10-membered, bicyclic heteroaryl. In certain embodiments, R^C is $-C(=O)R^{C1}$. In certain embodiments, R^C is $-C(=O)OR^{C1}$. In certain embodiments, R^C is $-C(=O)N(R^{C1})_2$. In certain embodiments, R^C is a nitrogen protecting group. In certain embodiments, R^C is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00149] In certain embodiments, R^C is substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-C(=O)R^{C1}$, $-C(=O)OR^{C1}$, or $-C(=O)N(R^{C1})_2$. In certain embodiments, R^C is substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, or $-C(=O)R^{C1}$. In certain embodiments, R^C is unsubstituted C_{1-6} alkyl, unsubstituted 3- to 7-membered monocyclic carbocyclyl, substituted or unsubstituted phenyl, or $-C(=O)R^{C1}$.

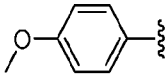
[00150] In certain embodiments, at least one instance of R^{C1} is H. In certain embodiments, at least one instance of R^{C1} is substituted acyl. In certain embodiments, at least one instance of R^{C1} is unsubstituted acyl. In certain embodiments, at least one instance of R^{C1} is acetyl. In certain embodiments, at least one instance of R^{C1} is substituted alkyl. In certain embodiments, at least one instance of R^{C1} is unsubstituted alkyl. In certain embodiments, at least one instance of R^{C1} is C_{1-12} alkyl. In certain embodiments, at least one instance of R^{C1} is C_{1-6} alkyl. In certain embodiments, at least one instance of R^{C1} is methyl. In certain embodiments, at least one instance of R^{C1} is ethyl. In certain embodiments, at least one instance of R^{C1} is propyl. In certain embodiments, at least one instance of R^{C1} is butyl. In certain embodiments, at least one instance of R^{C1} is pentyl. In certain embodiments, at least one instance of R^{C1} is

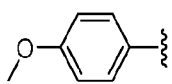
hexyl. In certain embodiments, at least one instance of R^{C1} is substituted alkenyl. In certain embodiments, at least one instance of R^{C1} is unsubstituted alkenyl. In certain embodiments, at least one instance of R^{C1} is vinyl. In certain embodiments, at least one instance of R^{C1} is substituted alkynyl. In certain embodiments, at least one instance of R^{C1} is unsubstituted alkynyl. In certain embodiments, at least one instance of R^{C1} is ethynyl. In certain embodiments, at least one instance of R^{C1} is substituted carbocyclyl. In certain embodiments, at least one instance of R^{C1} is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^{C1} is saturated carbocyclyl. In certain embodiments, at least one instance of R^{C1} is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^{C1} is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^{C1} is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^{C1} is cyclopropyl. In certain embodiments, at least one instance of R^{C1} is cyclobutyl. In certain embodiments, at least one instance of R^{C1} is cyclopentyl. In certain embodiments, at least one instance of R^{C1} is cyclohexyl. In certain embodiments, at least one instance of R^{C1} is cycloheptyl. In certain embodiments, at least one instance of R^{C1} is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^{C1} is substituted heterocyclyl. In certain embodiments, at least one instance of R^{C1} is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^{C1} is saturated heterocyclyl. In certain embodiments, at least one instance of R^{C1} is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^{C1} is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^{C1} is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{C1} is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^{C1} is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted aryl. In certain embodiments, at least one instance of R^{C1} is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^{C1} is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^{C1} is monocyclic aryl. In certain embodiments, at least one instance of R^{C1} is phenyl. In certain embodiments, at least one instance of R^{C1} is bicyclic aryl. In certain embodiments, at least one instance of R^{C1} is naphthyl. In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^{C1} is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In

certain embodiments, at least one instance of R^{C1} is monocyclic heteroaryl. In certain embodiments, at least one instance of R^{C1} is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{C1} is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{C1} is pyridyl. In certain embodiments, at least one instance of R^{C1} is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^{C1} is 9-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{C1} is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{C1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^{C1} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{C1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{C1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom.

[00151] In certain embodiments, two instances of R^{C1} are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^{C1} are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^{C1} are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^{C1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^{C1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^{C1} are joined to form a 5- to 13-membered, bicyclic heterocyclic ring.

[00152] In certain embodiments, R^B is substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, or $-C(=O)N(R^{B1})_2$; and R^C is hydrogen. In certain embodiments, R^B is substituted or unsubstituted alkyl, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl, substituted or unsubstituted phenyl, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, or $-C(=O)N(R^{B1})_2$; and R^C is hydrogen. In certain embodiments, R^B is substituted or unsubstituted C_{1-6} alkyl, unsubstituted, 3- to 7-membered, monocyclic carbocyclyl, substituted or unsubstituted phenyl, or $-C(=O)R^{B1}$; and R^C is hydrogen. In certain

embodiments, R^B is *t*-Bu, benzyl, cyclohexyl, , $-C(=O)(t\text{-Bu})$, or $-C(=O)Ph$; ;

and R^C is hydrogen. In certain embodiments, R^B is *t*-Bu, benzyl, cyclohexyl, or ; and R^C is hydrogen.

[00153] Compounds of Formula (I) may include one or more substituent R^D . In certain embodiments, at least one instance of R^D is H. In certain embodiments, at least one instance of R^D is halogen. In certain embodiments, at least one instance of R^D is F. In certain embodiments, at least one instance of R^D is Cl. In certain embodiments, at least one instance of R^D is Br. In certain embodiments, at least one instance of R^D is I (iodine). In certain embodiments, at least one instance of R^D is substituted acyl. In certain embodiments, at least one instance of R^D is unsubstituted acyl. In certain embodiments, at least one instance of R^D is substituted alkyl. In certain embodiments, at least one instance of R^D is unsubstituted alkyl. In certain embodiments, at least one instance of R^D is C_{1-12} alkyl. In certain embodiments, at least one instance of R^D is C_{1-6} alkyl. In certain embodiments, at least one instance of R^D is unsubstituted methyl. In certain embodiments, at least one instance of R^D is substituted methyl. In certain embodiments, at least one instance of R^D is $-CH_2F$. In certain embodiments, at least one instance of R^D is $-CHF_2$. In certain embodiments, at least one instance of R^D is $-CF_3$. In certain embodiments, at least one instance of R^D is Bn. In certain embodiments, at least one instance of R^D is unsubstituted ethyl. In certain embodiments, at least one instance of R^D is substituted ethyl. In certain embodiments, at least one instance of R^D is $-(CH_2)_2Ph$. In certain embodiments, at least one instance of R^D is propyl. In certain embodiments, at least one instance of R^D is butyl. In certain embodiments, at least one instance of R^D is pentyl. In certain embodiments, at least one instance of R^D is hexyl. In certain embodiments, at least one instance of R^D is substituted alkenyl. In certain embodiments, at least one instance of R^D is unsubstituted alkenyl. In certain embodiments, at least one instance of R^D is vinyl. In certain embodiments, at least one instance of R^D is substituted alkynyl. In certain embodiments, at least one instance of R^D is unsubstituted alkynyl. In certain embodiments, at least one instance of R^D is ethynyl. In certain embodiments, at least one instance of R^D is substituted carbocyclyl. In certain embodiments, at least one instance of R^D is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^D is saturated carbocyclyl. In certain embodiments, at least one instance of R^D is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^D is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^D is monocyclic carbocyclyl. In certain embodiments, at least one instance of R^D is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least

one instance of R^D is cyclopropyl. In certain embodiments, at least one instance of R^D is cyclobutyl. In certain embodiments, at least one instance of R^D is cyclopentyl. In certain embodiments, at least one instance of R^D is cyclohexyl. In certain embodiments, at least one instance of R^D is cycloheptyl. In certain embodiments, at least one instance of R^D is bicyclic carbocyclyl. In certain embodiments, at least one instance of R^D is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^D is substituted heterocyclyl. In certain embodiments, at least one instance of R^D is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^D is saturated heterocyclyl. In certain embodiments, at least one instance of R^D is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^D is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^D is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^D is monocyclic heterocyclyl. In certain embodiments, at least one instance of R^D is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^D is bicyclic heterocyclyl. In certain embodiments, at least one instance of R^D is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^D is substituted aryl. In certain embodiments, at least one instance of R^D is unsubstituted aryl. In certain embodiments, at least one instance of R^D is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^D is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^D is substituted phenyl. In certain embodiments, at least one instance of R^D is unsubstituted phenyl. In certain embodiments, at least one instance of R^D is substituted naphthyl. In certain embodiments, at least one instance of R^D is unsubstituted naphthyl. In certain embodiments, at least one instance of R^D is substituted heteroaryl. In certain embodiments, at least one instance of R^D is unsubstituted heteroaryl. In certain embodiments, at least one instance of R^D is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^D is monocyclic heteroaryl. In certain embodiments, at least one instance of R^D is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^D is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^D is pyridyl. In certain embodiments, at least one instance of R^D is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^D is 9-membered, bicyclic heteroaryl. In

certain embodiments, at least one instance of R^D is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^D is $-OR^{D1}$. In certain embodiments, at least one instance of R^D is $-O-(\text{substituted or unsubstituted alkyl})$. In certain embodiments, at least one instance of R^D is $-O-(\text{unsubstituted } C_{1-6} \text{ alkyl})$. In certain embodiments, at least one instance of R^D is $-OMe$. In certain embodiments, at least one instance of R^D is $-OEt$. In certain embodiments, at least one instance of R^D is $-OPr$. In certain embodiments, at least one instance of R^D is $-OBu$. In certain embodiments, at least one instance of R^D is $-O(\text{pentyl})$. In certain embodiments, at least one instance of R^D is $-O(\text{hexyl})$. In certain embodiments, at least one instance of R^D is $-OPh$. In certain embodiments, at least one instance of R^D is $-OBn$. In certain embodiments, at least one instance of R^D is $-O(CH_2)_2Ph$. In certain embodiments, at least one instance of R^D is $-OH$. In certain embodiments, at least one instance of R^D is $-SR^{D1}$. In certain embodiments, at least one instance of R^D is $-SMe$. In certain embodiments, at least one instance of R^D is $-SH$. In certain embodiments, at least one instance of R^D is $-N(R^{D1})_2$. In certain embodiments, at least one instance of R^D is $-NMe_2$. In certain embodiments, at least one instance of R^D is $-NH_2$. In certain embodiments, at least one instance of R^D is $-CN$. In certain embodiments, at least one instance of R^D is $-SCN$. In certain embodiments, at least one instance of R^D is $-C(=NR^{D1})R^{D1}$, $-C(=NR^{D1})OR^{D1}$, or $-C(=NR^{D1})N(R^{D1})_2$. In certain embodiments, at least one instance of R^D is $-C(=O)R^{D1}$, $-C(=O)OR^{D1}$, or $-C(=O)N(R^{D1})_2$. In certain embodiments, at least one instance of R^D is $-NO_2$. In certain embodiments, at least one instance of R^D is $-NR^{D1}C(=O)R^{D1}$, $-NR^{D1}C(=O)OR^{D1}$, or $-NR^{D1}C(=O)N(R^{D1})_2$. In certain embodiments, at least one instance of R^D is $-OC(=O)R^{D1}$, $-OC(=O)OR^{D1}$, or $-OC(=O)N(R^{D1})_2$.

[00154] In compounds of Formula (I), two R^D groups may be joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a saturated or unsaturated carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a carbocyclic ring including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a 3- to 7-membered, monocyclic carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a 3-membered carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a 4-membered carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a 5-membered carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a 6-membered carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a 7-membered carbocyclic ring. In certain embodiments, two instances of R^D are joined to form a 5- to 13-membered, bicyclic carbocyclic ring system.

[00155] In certain embodiments, two instances of R^D are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^D are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^D are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^D are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^D are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^D are joined to form a 5- to 13-membered, bicyclic heterocyclic ring system.

[00156] In certain embodiments, two instances of R^D are joined to form a substituted or unsubstituted aryl ring. In certain embodiments, two instances of R^D are joined to form a 6- to 14-membered aryl ring. In certain embodiments, two instances of R^D are joined to form a 6- to 10-membered aryl ring. In certain embodiments, two instances of R^D are joined to form a monocyclic aryl ring. In certain embodiments, two instances of R^D are joined to form a phenyl. In certain embodiments, two instances of R^D are joined to form a bicyclic aryl ring system. In certain embodiments, two instances of R^D are joined to form a naphthyl.

[00157] In certain embodiments, two instances of R^D are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments, two instances of R^D are joined to form a monocyclic heteroaryl ring, wherein one, two, or three atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^D are joined to form a 5-membered, monocyclic heteroaryl ring. In certain embodiments, two instances of R^D are joined to form a 6-membered, monocyclic heteroaryl ring. In certain embodiments, two instances of R^D are joined to form a pyridyl ring. In certain embodiments, two instances of R^D are joined to form a bicyclic heteroaryl ring system, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^D are joined to form a 9-membered, bicyclic heteroaryl ring system. In certain embodiments, two instances of R^D are joined to form a 10-membered, bicyclic heteroaryl ring system.

[00158] In certain embodiments, at least one instance of R^D is halogen, substituted or unsubstituted alkyl, or $-OR^{D1}$. In certain embodiments, at least one instance of R^D is halogen, unsubstituted alkyl, or $-O-(\text{unsubstituted alkyl})$. In certain embodiments, at least one instance of R^D is halogen, unsubstituted C_{1-6} alkyl, or $-O-(\text{unsubstituted } C_{1-6} \text{ alkyl})$. In certain

embodiments, at least one instance of R^D is Cl or $-OMe$. In certain embodiments, all instances of R^D are hydrogen.

[00159] In certain embodiments, at least one instance of R^{D1} is H. In certain embodiments, at least one instance of R^{D1} is substituted acyl. In certain embodiments, at least one instance of R^{D1} is unsubstituted acyl. In certain embodiments, at least one instance of R^{D1} is acetyl. In certain embodiments, at least one instance of R^{D1} is substituted alkyl. In certain embodiments, at least one instance of R^{D1} is unsubstituted alkyl. In certain embodiments, at least one instance of R^{D1} is C_{1-12} alkyl. In certain embodiments, at least one instance of R^{D1} is C_{1-6} alkyl. In certain embodiments, at least one instance of R^{D1} is methyl. In certain embodiments, at least one instance of R^{D1} is ethyl. In certain embodiments, at least one instance of R^{D1} is propyl. In certain embodiments, at least one instance of R^{D1} is butyl. In certain embodiments, at least one instance of R^{D1} is pentyl. In certain embodiments, at least one instance of R^{D1} is hexyl. In certain embodiments, at least one instance of R^{D1} is substituted alkenyl. In certain embodiments, at least one instance of R^{D1} is unsubstituted alkenyl. In certain embodiments, at least one instance of R^{D1} is vinyl. In certain embodiments, at least one instance of R^{D1} is substituted alkynyl. In certain embodiments, at least one instance of R^{D1} is unsubstituted alkynyl. In certain embodiments, at least one instance of R^{D1} is ethynyl. In certain embodiments, at least one instance of R^{D1} is substituted carbocyclyl. In certain embodiments, at least one instance of R^{D1} is unsubstituted carbocyclyl. In certain embodiments, at least one instance of R^{D1} is saturated carbocyclyl. In certain embodiments, at least one instance of R^{D1} is unsaturated carbocyclyl. In certain embodiments, at least one instance of R^{D1} is carbocyclyl including one, two, or three double bonds in the carbocyclic ring. In certain embodiments, at least one instance of R^{D1} is 3- to 7-membered, monocyclic carbocyclyl. In certain embodiments, at least one instance of R^{D1} is cyclopropyl. In certain embodiments, at least one instance of R^{D1} is cyclobutyl. In certain embodiments, at least one instance of R^{D1} is cyclopentyl. In certain embodiments, at least one instance of R^{D1} is cyclohexyl. In certain embodiments, at least one instance of R^{D1} is cycloheptyl. In certain embodiments, at least one instance of R^{D1} is 5- to 13-membered, bicyclic carbocyclyl. In certain embodiments, at least one instance of R^{D1} is substituted heterocyclyl. In certain embodiments, at least one instance of R^{D1} is unsubstituted heterocyclyl. In certain embodiments, at least one instance of R^{D1} is saturated heterocyclyl. In certain embodiments, at least one instance of R^{D1} is unsaturated heterocyclyl. In certain embodiments, at least one instance of R^{D1} is heterocyclyl including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, at least one instance of R^{D1} is heterocyclyl, wherein one, two,

or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{D1} is 3- to 7-membered, monocyclic heterocyclyl. In certain embodiments, at least one instance of R^{D1} is 5- to 13-membered, bicyclic heterocyclyl. In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted aryl. In certain embodiments, at least one instance of R^{D1} is 6- to 14-membered aryl. In certain embodiments, at least one instance of R^{D1} is 6- to 10-membered aryl. In certain embodiments, at least one instance of R^{D1} is monocyclic aryl. In certain embodiments, at least one instance of R^{D1} is phenyl. In certain embodiments, at least one instance of R^{D1} is bicyclic aryl. In certain embodiments, at least one instance of R^{D1} is naphthyl. In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of R^{D1} is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, at least one instance of R^{D1} is monocyclic heteroaryl. In certain embodiments, at least one instance of R^{D1} is 5-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{D1} is 6-membered, monocyclic heteroaryl. In certain embodiments, at least one instance of R^{D1} is pyridyl. In certain embodiments, at least one instance of R^{D1} is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl ring system, as valency permits. In certain embodiments, at least one instance of R^{D1} is 9-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{D1} is 10-membered, bicyclic heteroaryl. In certain embodiments, at least one instance of R^{D1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one instance of R^{D1} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{D1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{D1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^{D1} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^{D1} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom.

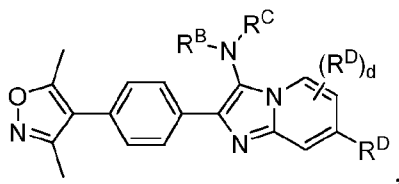
[00160] In certain embodiments, two instances of R^{D1} are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of R^{D1} are joined to form a saturated or unsaturated heterocyclic ring. In certain embodiments, two instances of R^{D1} are joined to form a heterocyclic ring including one, two, or three double bonds in the heterocyclic ring. In certain embodiments, two instances of R^{D1} are joined to form a

heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, two instances of R^{D1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring. In certain embodiments, two instances of R^{D1} are joined to form a 5- to 13-membered, bicyclic heterocyclic ring system.

[00161] In certain embodiments, d is 0. In certain embodiments, d is 1. In certain embodiments, d is 2.

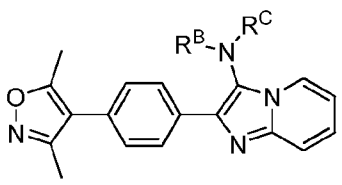
[00162] In certain embodiments, R^D is halogen, substituted or unsubstituted alkyl, or $-OR^{D1}$; and d is 1. In certain embodiments, R^D is halogen, unsubstituted alkyl, or $-O-$ (unsubstituted alkyl); and d is 1. In certain embodiments, R^D is halogen, unsubstituted C_{1-6} alkyl, or $-O-$ (unsubstituted C_{1-6} alkyl); and d is 1. In certain embodiments, R^D is halogen; and d is 1. In certain embodiments, R^D is Cl; and d is 1. In certain embodiments, R^D is $-OR^{D1}$; and d is 1. In certain embodiments, R^D is $-OMe$; and d is 1.

[00163] In certain embodiments, the compound of Formula (I) is of the formula:



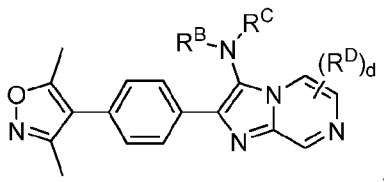
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00164] In certain embodiments, the compound of Formula (I) is of the formula:



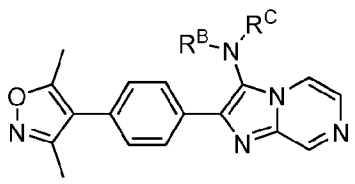
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00165] In certain embodiments, the compound of Formula (I) is of the formula:



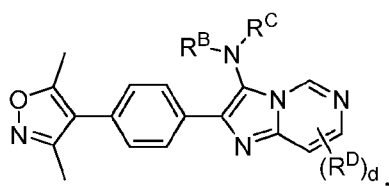
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00166] In certain embodiments, the compound of Formula (I) is of the formula:



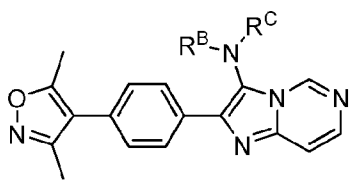
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00167] In certain embodiments, the compound of Formula (I) is of the formula:



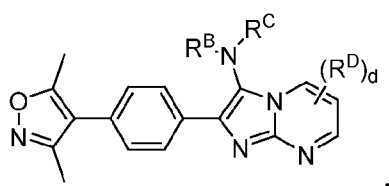
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00168] In certain embodiments, the compound of Formula (I) is of the formula:



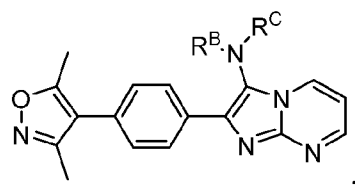
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00169] In certain embodiments, the compound of Formula (I) is of the formula:



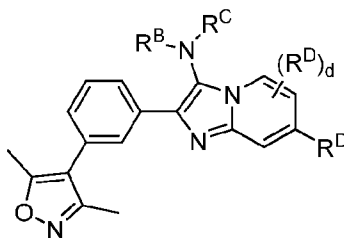
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00170] In certain embodiments, the compound of Formula (I) is of the formula:



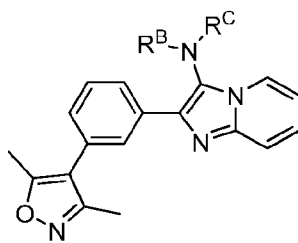
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00171] In certain embodiments, the compound of Formula (I) is of the formula:



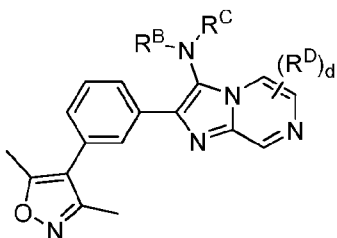
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00172] In certain embodiments, the compound of Formula (I) is of the formula:



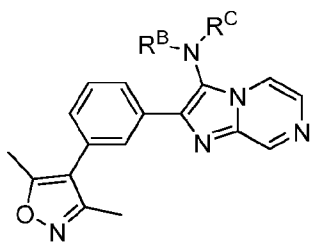
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00173] In certain embodiments, the compound of Formula (I) is of the formula:



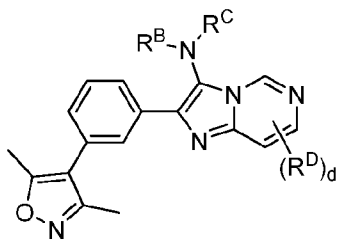
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00174] In certain embodiments, the compound of Formula (I) is of the formula:



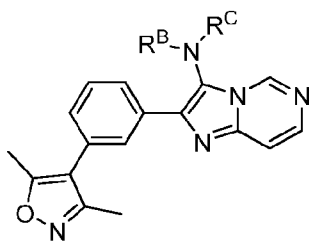
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00175] In certain embodiments, the compound of Formula (I) is of the formula:



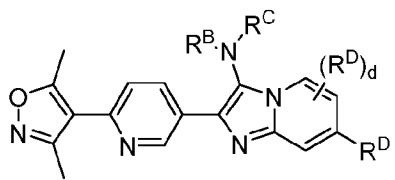
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00176] In certain embodiments, the compound of Formula (I) is of the formula:



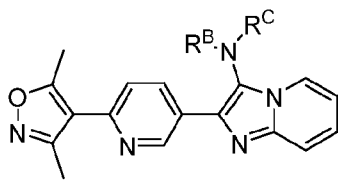
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00177] In certain embodiments, the compound of Formula (I) is of the formula:



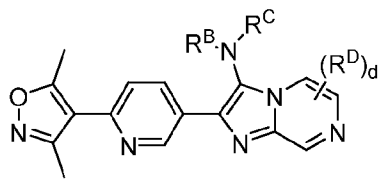
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00178] In certain embodiments, the compound of Formula (I) is of the formula:



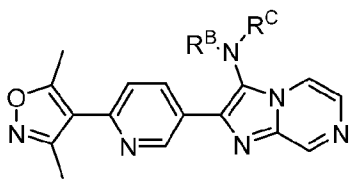
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00179] In certain embodiments, the compound of Formula (I) is of the formula:



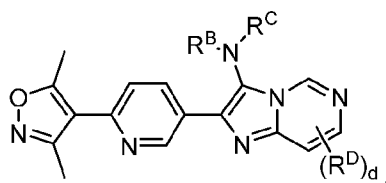
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00180] In certain embodiments, the compound of Formula (I) is of the formula:



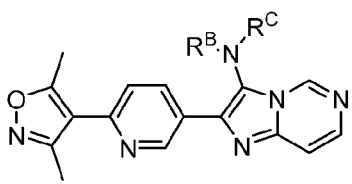
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00181] In certain embodiments, the compound of Formula (I) is of the formula:



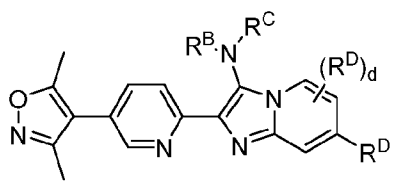
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00182] In certain embodiments, the compound of Formula (I) is of the formula:



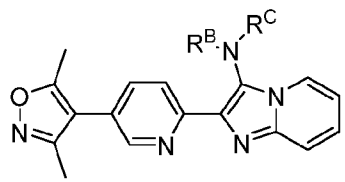
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00183] In certain embodiments, the compound of Formula (I) is of the formula:



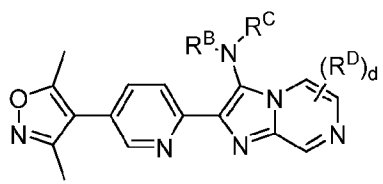
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00184] In certain embodiments, the compound of Formula (I) is of the formula:



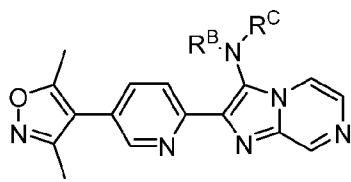
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00185] In certain embodiments, the compound of Formula (I) is of the formula:



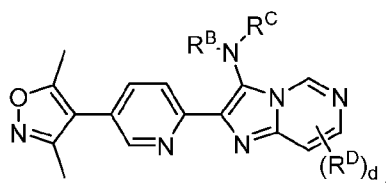
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00186] In certain embodiments, the compound of Formula (I) is of the formula:



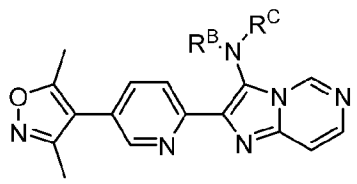
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00187] In certain embodiments, the compound of Formula (I) is of the formula:



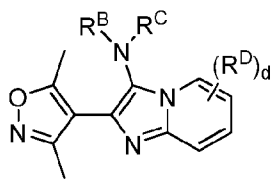
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00188] In certain embodiments, the compound of Formula (I) is of the formula:



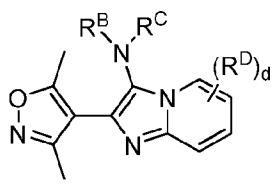
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00189] In certain embodiments, the compound of Formula (I) is of the formula:



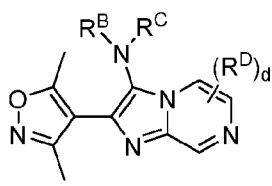
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00190] In certain embodiments, the compound of Formula (I) is of the formula:



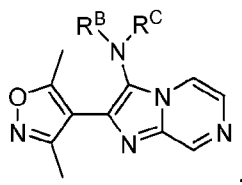
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00191] In certain embodiments, the compound of Formula (I) is of the formula:



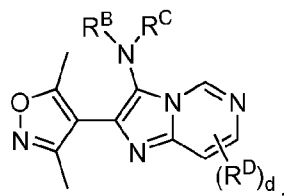
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00192] In certain embodiments, the compound of Formula (I) is of the formula:



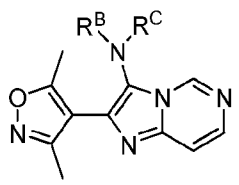
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00193] In certain embodiments, the compound of Formula (I) is of the formula:



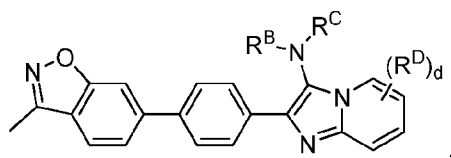
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00194] In certain embodiments, the compound of Formula (I) is of the formula:



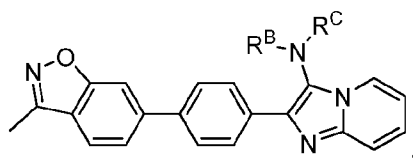
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00195] In certain embodiments, the compound of Formula (I) is of the formula:



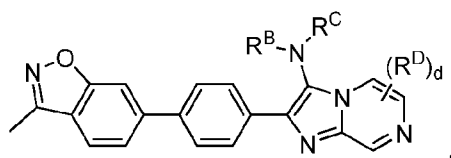
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00196] In certain embodiments, the compound of Formula (I) is of the formula:



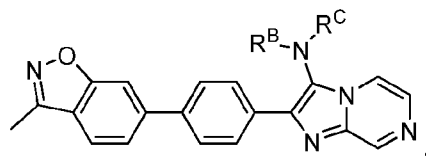
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00197] In certain embodiments, the compound of Formula (I) is of the formula:



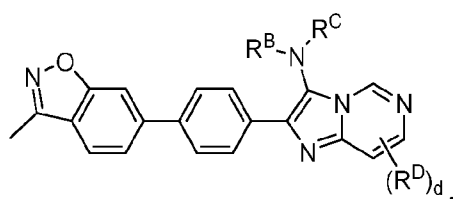
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00198] In certain embodiments, the compound of Formula (I) is of the formula:



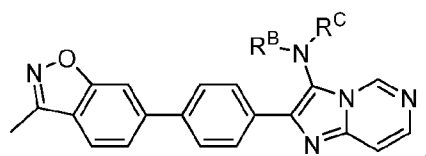
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00199] In certain embodiments, the compound of Formula (I) is of the formula:



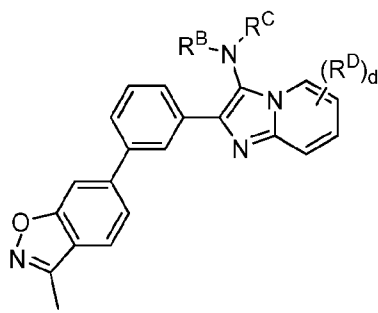
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00200] In certain embodiments, the compound of Formula (I) is of the formula:



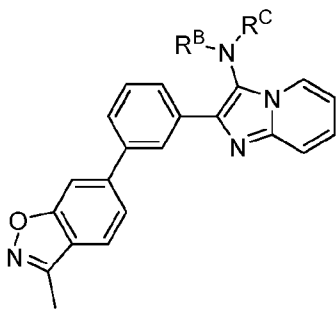
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00201] In certain embodiments, the compound of Formula (I) is of the formula:



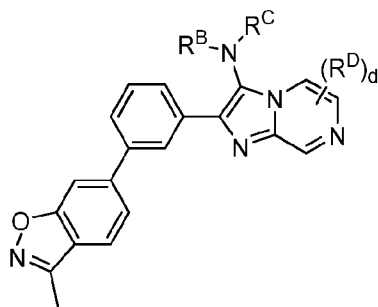
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00202] In certain embodiments, the compound of Formula (I) is of the formula:



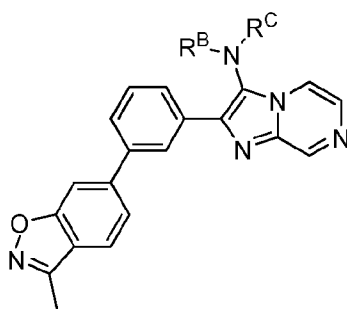
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00203] In certain embodiments, the compound of Formula (I) is of the formula:



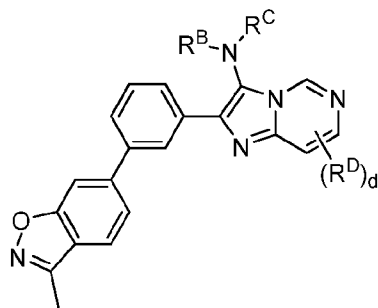
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00204] In certain embodiments, the compound of Formula (I) is of the formula:



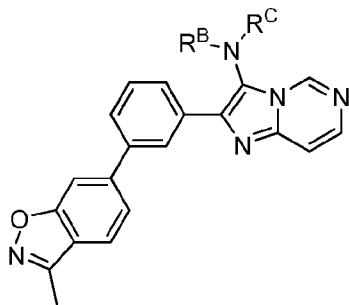
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00205] In certain embodiments, the compound of Formula (I) is of the formula:



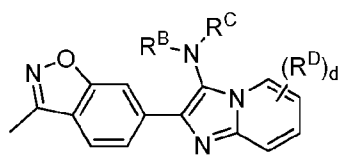
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00206] In certain embodiments, the compound of Formula (I) is of the formula:



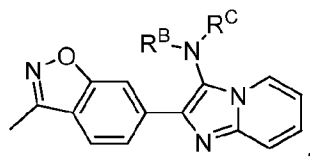
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00207] In certain embodiments, the compound of Formula (I) is of the formula:



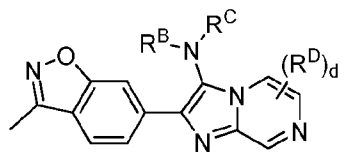
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00208] In certain embodiments, the compound of Formula (I) is of the formula:



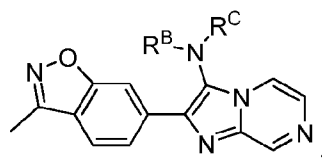
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00209] In certain embodiments, the compound of Formula (I) is of the formula:



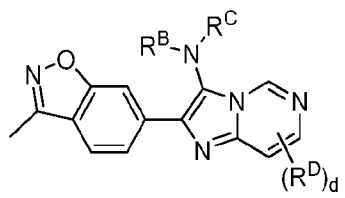
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00210] In certain embodiments, the compound of Formula (I) is of the formula:



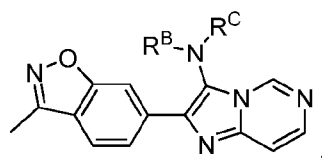
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00211] In certain embodiments, the compound of Formula (I) is of the formula:



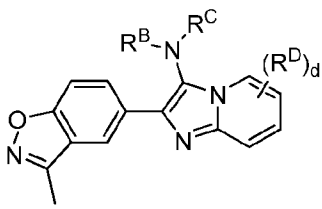
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00212] In certain embodiments, the compound of Formula (I) is of the formula:



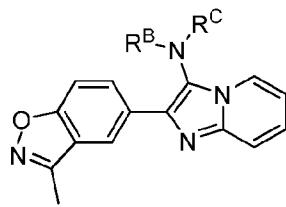
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00213] In certain embodiments, the compound of Formula (I) is of the formula:



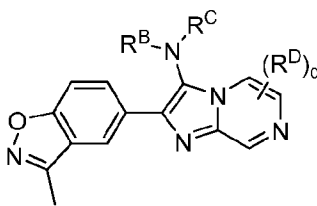
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00214] In certain embodiments, the compound of Formula (I) is of the formula:



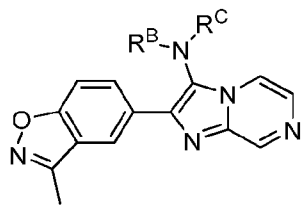
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00215] In certain embodiments, the compound of Formula (I) is of the formula:



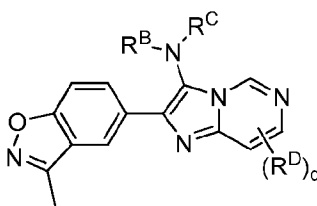
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00216] In certain embodiments, the compound of Formula (I) is of the formula:



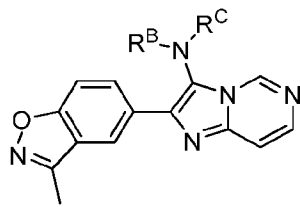
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00217] In certain embodiments, the compound of Formula (I) is of the formula:



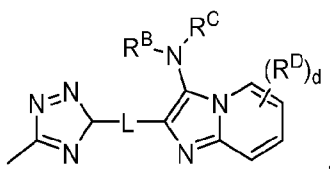
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00218] In certain embodiments, the compound of Formula (I) is of the formula:



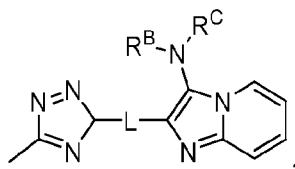
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00219] In certain embodiments, the compound of Formula (I) is of the formula:



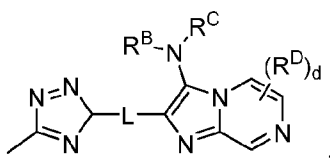
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00220] In certain embodiments, the compound of Formula (I) is of the formula:



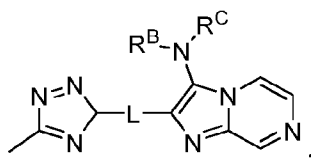
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00221] In certain embodiments, the compound of Formula (I) is of the formula:



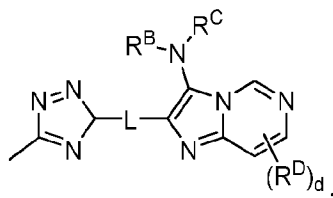
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00222] In certain embodiments, the compound of Formula (I) is of the formula:



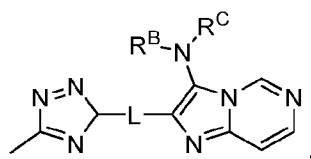
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00223] In certain embodiments, the compound of Formula (I) is of the formula:



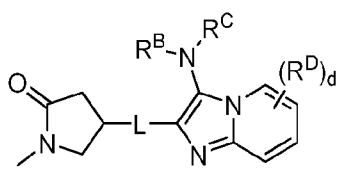
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00224] In certain embodiments, the compound of Formula (I) is of the formula:



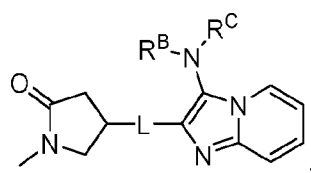
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00225] In certain embodiments, the compound of Formula (I) is of the formula:



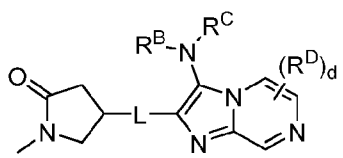
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00226] In certain embodiments, the compound of Formula (I) is of the formula:



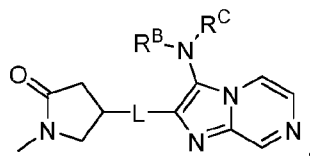
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00227] In certain embodiments, the compound of Formula (I) is of the formula:



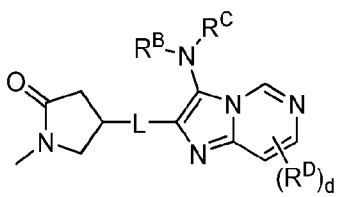
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00228] In certain embodiments, the compound of Formula (I) is of the formula:



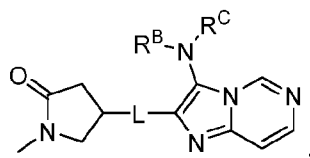
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00229] In certain embodiments, the compound of Formula (I) is of the formula:



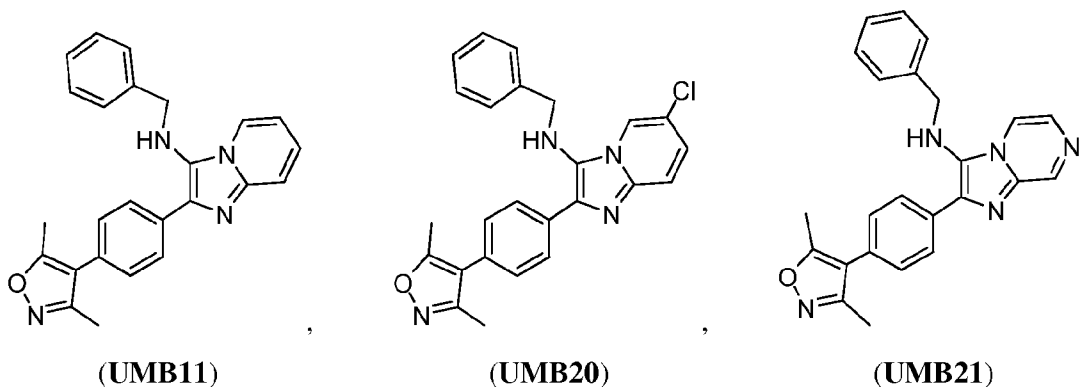
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

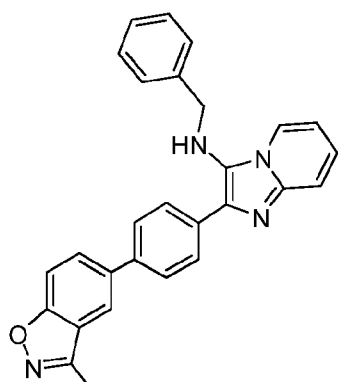
[00230] In certain embodiments, the compound of Formula (I) is of the formula:



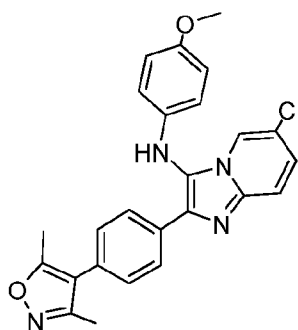
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00231] In certain embodiments, the compound of Formula (I) is of the formula:

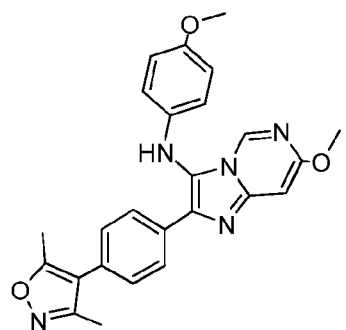




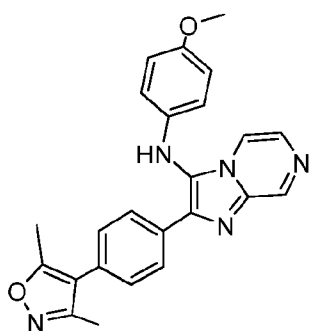
(UMB22)



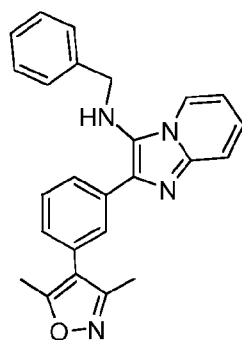
(UMB23)



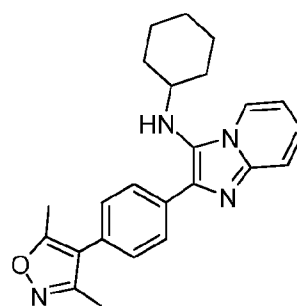
(UMB24)



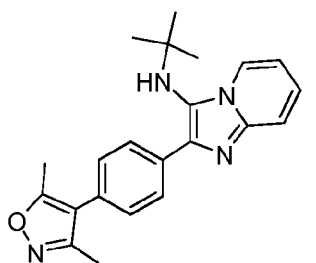
(UMB25)



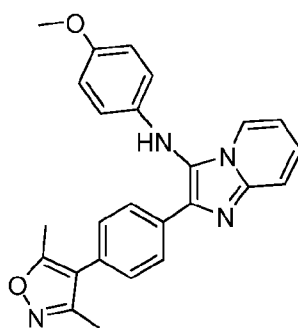
(UMB26)



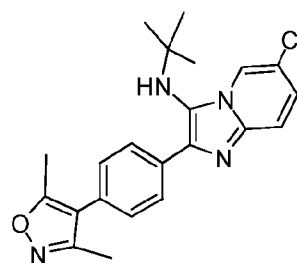
(UMB28)



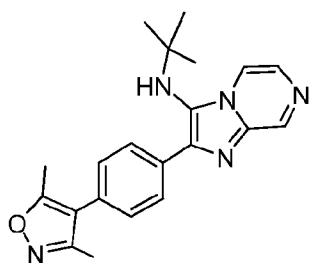
(UMB29)



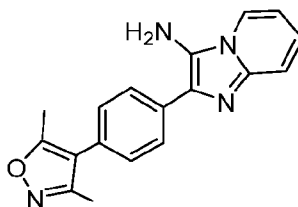
(UMB30)



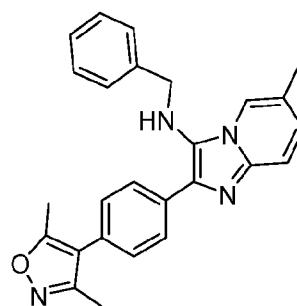
(UMB31)



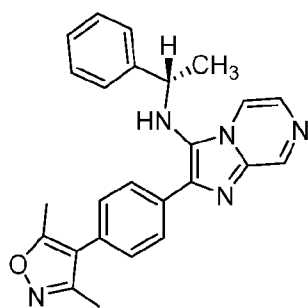
(UMB32)



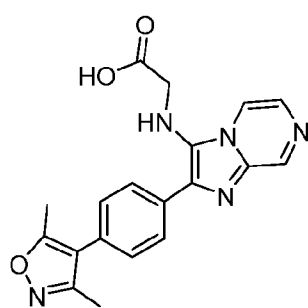
(12a)



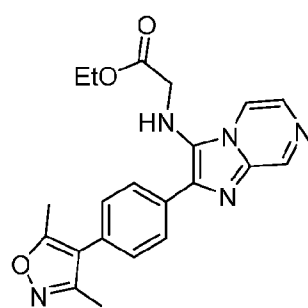
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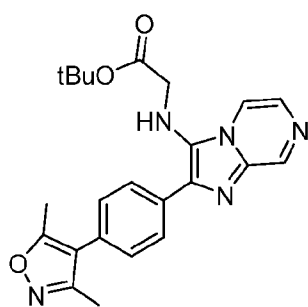
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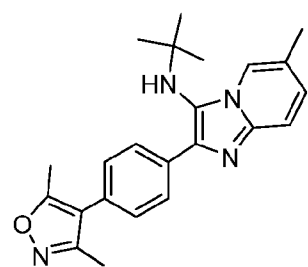
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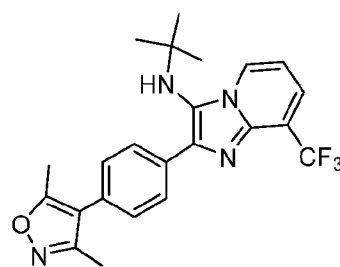
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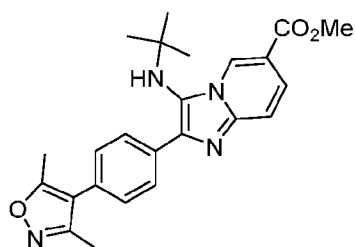
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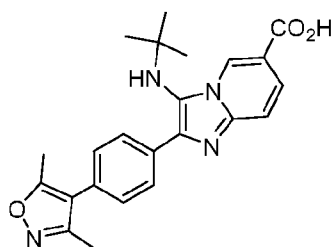
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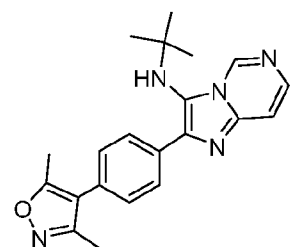
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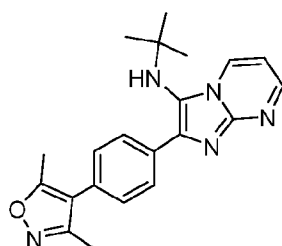
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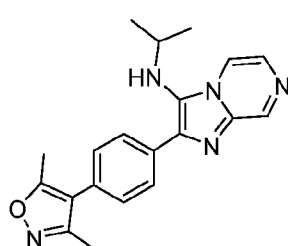
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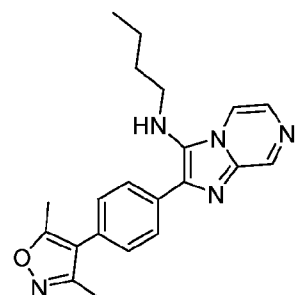
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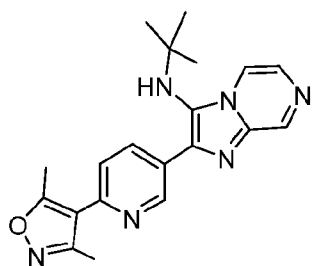
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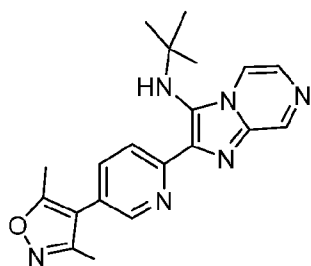
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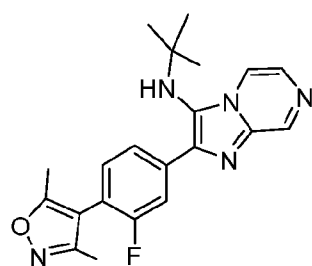
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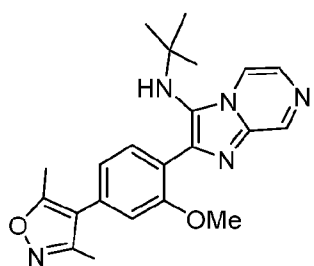
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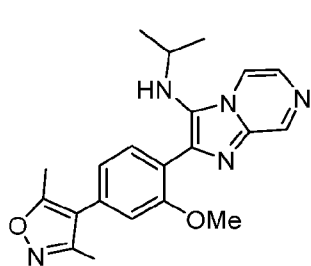
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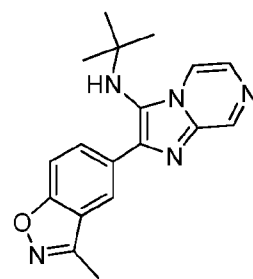
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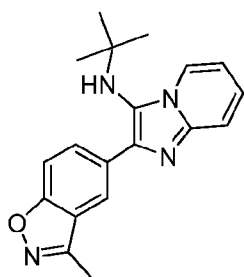
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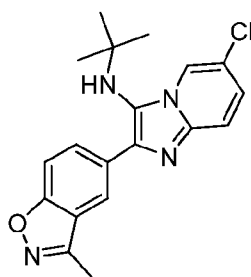
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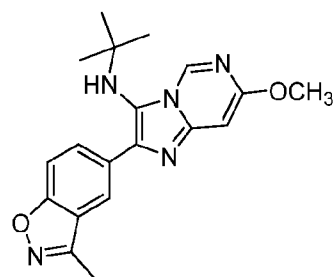
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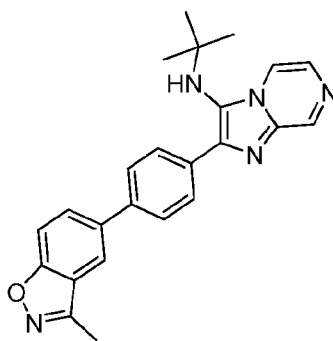
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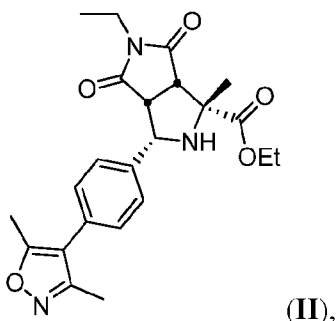
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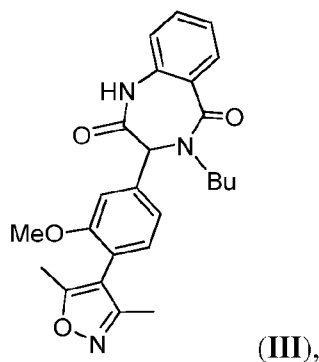
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00232] The present invention also provides the compound of Formula (II):



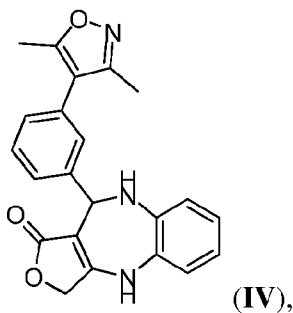
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, the present invention provides the compound of Formula (II), and pharmaceutically acceptable salts thereof.

[00233] The present invention also provides the compound of Formula (III):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, the present invention provides the compound of Formula (III), and pharmaceutically acceptable salts thereof.

[00234] The present invention also provides the compound of Formula (IV):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments,

the present invention provides the compound of Formula (IV), and pharmaceutically acceptable salts thereof.

[00235] In certain embodiments, compounds of the invention are compounds described herein, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, compounds of the invention are compounds described herein, and pharmaceutically acceptable salts thereof. In certain embodiments, compounds of the invention are compounds of any one of Formulae (I) to (IV), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, compounds of the invention are compounds of any one of Formulae (I) to (IV), and pharmaceutically acceptable salts thereof. In certain embodiments, compounds of the invention are compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, compounds of the invention are compounds of Formula (I), and pharmaceutically acceptable salts thereof.

[00236] Compounds of the invention are inhibitors of bromodomain-containing proteins. In certain embodiments, the compounds of the invention bind to a bromodomain-containing protein. Without wishing to be bound by any particular theory, the compounds of the invention are thought to bind in a binding pocket of a bromodomain of a bromodomain-containing protein. In certain embodiments, the compounds of the invention bind to the binding pocket of the bromodomain by mimicking the contact between a histone acetyl-lysine residue and the binding pocket. In certain embodiments, the compounds of the invention bind to the apo binding pocket of the bromodomain. In certain embodiments, the compounds of the invention covalently bind to the bromodomain-containing protein. In certain embodiments, the compounds of the invention non-covalently bind to the bromodomain-containing protein. In certain embodiments, the compounds of the invention reversibly bind to the bromodomain-containing protein. In certain embodiments, the compounds of the invention non-reversibly bind to the bromodomain-containing protein. In certain embodiments, the compounds of the invention inhibit the activity of a bromodomain-containing protein. In certain embodiments, the compounds of the invention inhibit the activity of a bromodomain-containing protein because of the binding of the compound to the bromodomain-containing protein. In certain embodiments, the compounds of the invention inhibit the activity of a bromodomain-containing protein because of the binding of the

compounds to a bromodomain of the bromodomain-containing protein. In certain embodiments, the inventive compounds specifically bind to a bromodomain-containing protein. In certain embodiments, the inventive compounds specifically bind to a bromodomain of a bromodomain-containing protein. In certain embodiments, the inventive compounds that specifically bind to a bromodomain-containing protein show a greater binding affinity to the bromodomain-containing protein than to one or more other proteins or one or more other bromodomain-containing proteins. In certain embodiments, the inventive compounds non-specifically bind to a bromodomain-containing protein. In certain embodiments, the inventive compounds non-specifically bind to a bromodomain of a bromodomain-containing protein. In certain embodiments, the compounds of the invention reduce transcriptional elongation. In certain embodiments, the compounds of the invention disrupt the subcellular localization of a bromodomain-containing protein. In certain embodiments, the compounds of the invention reduce chromatin binding. In certain embodiments, the compounds of the invention inhibit the binding of Histone H4 Kac peptide to a bromodomain of a bromodomain-containing protein. In certain embodiments, the compounds of the invention form one or more hydrogen bonds with an evolutionarily conserved asparagine in a bromodomain of a bromodomain-containing protein. In certain embodiments, the bromodomain-containing protein is BRD4 or BRD2; and the asparagine is Asn140 in BRD4(1) and Asn429 in BRD2(2). In certain embodiments, the compounds of the invention bind competitively with chromatin in a cellular environment. It is thus expected that the compounds of the invention may be useful in the treatment of a disease associated with the activity a bromodomain-containing protein (*e.g.*, a proliferative disease).

[00237] The bromodomain-containing proteins that may be bound, and whose activity may be inhibited, by the inventive compounds include, but are not limited to, the bromodomain-containing proteins described herein. In certain embodiments, the bromodomain-containing protein is a bromo and extra terminal protein (BET). In certain embodiments, the bromodomain-containing protein is BRD2. In certain embodiments, the bromodomain-containing protein is BRD2(1). In certain embodiments, the bromodomain-containing protein is BRD2(2). In certain embodiments, the bromodomain-containing protein is BRD3. In certain embodiments, the bromodomain-containing protein is BRD3(1). In certain embodiments, the bromodomain-containing protein is BRD3(2). In certain embodiments, the bromodomain-containing protein is BRD4. In certain embodiments, the bromodomain-containing protein is BRD4(1). In certain embodiments, the bromodomain-containing protein is BRD4(2). In certain embodiments, the bromodomain-containing protein is BRDT. In

certain embodiments, the bromodomain-containing protein is BRDT(1). In certain embodiments, the bromodomain-containing protein is BRDT(2). In certain embodiments, the bromodomain-containing protein is a TBP (TATA box binding protein)-associated factor protein (TAF). In certain embodiments, the bromodomain-containing protein is TAF1. In certain embodiments, the bromodomain-containing protein is TAF1L. In certain embodiments, the bromodomain-containing protein is CREB-binding protein (CBP). In certain embodiments, the bromodomain-containing protein is E1A binding protein p300 (EP300).

[00238] The binding affinity of a compound of the invention to a bromodomain-containing protein may be measured by the dissociation constant (K_d) value of an adduct of the compound of the invention and the bromodomain-containing protein using methods known in the art (*e.g.*, isothermal titration calorimetry (ITC)). In certain embodiments, the adduct comprises the compound of the invention and the bromodomain-containing protein, which are bound (*e.g.*, covalently or non-covalently) to each other. In certain embodiments, the K_d value of the adduct is at most about 100 μM , at most about 30 μM , at most about 10 μM , at most about 3 μM , at most about 1 μM , at most about 300 nM, at most about 100 nM, at most about 30 nM, at most about 10 nM, at most about 3 nM, or at most about 1 nM. In certain embodiments, the K_d value of the adduct is at least about 1 nM, at least about 10 nM, at least about 100 nM, at least about 1 μM , at least about 10 μM , or at least about 100 μM . Combinations of the above-referenced ranges (*e.g.*, at most about 10 μM and at least about 1 nM) are also within the scope of the invention. Other ranges are also possible. In certain embodiments, the K_d value of the adduct is at most about 10 μM . In certain embodiments, the K_d value of the adduct is at most about 300 nM. In certain embodiments, the K_d value of the adduct is at most about 100 nM.

[00239] In certain embodiments, the activity of the bromodomain-containing proteins described herein is inhibited by the inventive compounds. The inhibition of the activity of a bromodomain-containing protein by an inventive compound may be measured by the half maximal inhibitory concentration (IC_{50}) value of a compound of the invention when the inventive compound, or a pharmaceutical composition thereof, is contacted, directly or indirectly, with the bromodomain-containing protein. The IC_{50} values may be obtained using methods known in the art, *e.g.*, by competing the PEG-biotinylated **JQ1** off from a BRD protein in an alpha assay. In certain embodiments, the IC_{50} value of a compound of the invention is at most about 1 mM, at most about 300 μM , at most about 100 μM , at most about

30 μM , at most about 10 μM , at most about 3 μM , at most about 1 μM , at most about 300 nM, at most about 100 nM, at most about 30 nM, at most about 10 nM, at most about 3 nM, or at most about 1 nM. In certain embodiments, the IC_{50} value of a compound of the invention is at least about 1 nM, at least about 3 nM, at least about 10 nM, at least about 30 nM, at least about 100 nM, at least about 300 nM, at least about 1 μM , at least about 3 μM , at least about 10 μM , at least about 30 μM , at least about 100 μM , at least about 300 μM , or at least 1 mM. Combinations of the above-referenced ranges (*e.g.*, at most about 300 μM and at least about 1 μM) are also within the scope of the invention. Other ranges are also possible. In certain embodiments, the IC_{50} value of a compound of the invention is at most about 300 μM . In certain embodiments, the IC_{50} value of a compound of the invention is at most about 30 μM . In certain embodiments, the IC_{50} value of a compound of the invention is at most about 10 μM .

[00240] The compounds of the invention may selectively inhibit the activity of a bromodomain-containing protein. In certain embodiments, the inventive compounds that selectively inhibit the activity of a bromodomain-containing protein show a greater inhibitory activity against the bromodomain-containing protein than against one or more other proteins or one or more other bromodomain-containing proteins.

[00241] The selectivity of an inventive compound for a bromodomain-containing protein over another protein (*e.g.*, another bromodomain-containing protein) may be measured by the quotient of the IC_{50} value of the inventive compound in inhibiting the activity of the another protein over the IC_{50} value of the inventive compound in inhibiting the activity of the bromodomain-containing protein. The selectivity of an inventive compound for a bromodomain-containing protein over another protein (*e.g.*, another bromodomain-containing protein) may also be measured by the quotient of the K_d value of an adduct of the inventive compound and the another protein over the K_d value of an adduct of the inventive compound and the bromodomain-containing protein. In certain embodiments, the selectivity is at least about 1-fold, at least about 2-fold, at least about 5-fold, at least about 10-fold, at least about 30-fold, at least about 100-fold, at least about 300-fold, at least about 1,000-fold, at least about 3,000-fold, at least about 10,000-fold, at least about 30,000-fold, or at least about 100,000-fold. In certain embodiments, the selectivity is at most about 100,000-fold, at most about 10,000-fold, at most about 1,000-fold, at most about 100-fold, at most about 10-fold, or at most about 1-fold. Combinations of the above-referenced ranges (*e.g.*, and at least about 2-fold and at most about 10,000-fold) are also within the scope of the invention. Other ranges

are also possible. In certain embodiments, the selectivity is at least about 2-fold. In certain embodiments, the selectivity is at least about 10-fold. In certain embodiments, the selectivity is at least about 100-fold. In certain embodiments, the compounds of the invention selectively inhibit a bromodomain-containing protein described herein. In certain embodiments, the compounds of the invention selectively inhibit a BET protein. In certain embodiments, the compounds of the invention selectively inhibit BRD2. In certain embodiments, the compounds of the invention selectively inhibit BRD3. In certain embodiments, the compounds of the invention selectively inhibit BRD4. In certain embodiments, the compounds of the invention selectively inhibit BRDT. In certain embodiments, the compounds of the invention selectively inhibit a TAF protein (*e.g.*, TAF1 or TAF1L), CBP, and/or EP300. In certain embodiments, the compound of the inventions are non-selective inhibitors of two or more bromodomain-containing proteins.

[00242] It is known in the art that a bromodomain-containing protein is implicated in a wide range of diseases. For example, BRD3 and BRD4 are related to BRD3 NUT midline carcinoma and BRD4 NUT midline carcinoma, respectively, BRDT is related to sperm formation, and CBP is related to mixed-lineage leukemia (MLL). Therefore, the inventive compounds are expected to be useful in treating and/or preventing diseases associated with bromodomain-containing proteins or as a male contraceptive drug.

Pharmaceutical Compositions, Kits, and Administration

[00243] The present invention provides pharmaceutical compositions comprising a compound of the invention (*e.g.*, a compound of any one of Formulae (I)-(IV), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof), and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises the compound of Formula (II), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises the compound of Formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In

certain embodiments, the pharmaceutical composition of the invention comprises the compound of Formula (III), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises the compound of Formula (III), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises the compound of Formula (IV), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises the compound of Formula (IV), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00244] In certain embodiments, the compound of the invention is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective for treating and/or preventing a disease (*e.g.*, a disease described herein). In certain embodiments, the effective amount is an amount effective for treating a disease. In certain embodiments, the effective amount is an amount effective for treating and/or preventing a disease associated with a bromodomain-containing protein. In certain embodiments, the effective amount is an amount effective for treating a disease associated with a bromodomain-containing protein. In certain embodiments, the effective amount is an amount effective for treating and/or preventing a proliferative disease (*e.g.*, a proliferative disease described herein). In certain embodiments, the effective amount is an amount effective for treating a proliferative disease. In certain embodiments, the effective amount is an amount effective for treating and/or preventing cancer (*e.g.*, a cancer described herein). In certain embodiments, the effective amount is an amount effective for treating cancer. In certain embodiments, the effective amount is an amount effective for treating and/or preventing lung cancer (*e.g.*, small-cell lung cancer or non-small-cell lung cancer). In certain embodiments, the effective amount is an amount effective for treating lung cancer. In certain embodiments, the effective amount is an amount effective for treating and/or preventing a benign neoplasm (*e.g.*, a benign neoplasm described herein). In certain embodiments, the effective amount is an amount effective for treating a benign neoplasm. In certain embodiments, the effective amount is an amount effective for treating and/or preventing a diseases or process associated with angiogenesis. In certain embodiments, the effective amount is an amount effective for treating a disease or process associated angiogenesis. In certain embodiments, the effective

amount is an amount effective for treating and/or preventing an inflammatory disease (*e.g.*, an inflammatory disease described herein). In certain embodiments, the effective amount is an amount effective for treating an inflammatory disease. In certain embodiments, the effective amount is an amount effective for treating and/or preventing an autoimmune disease (*e.g.*, an autoimmune disease described herein). In certain embodiments, the effective amount is an amount effective for treating an autoimmune disease. In certain embodiments, the effective amount is an amount effective for treating and/or preventing diabetes (*e.g.*, type 1 diabetes, type 2 diabetes, and gestational diabetes), obesity, fatty liver (NASH or otherwise), multiple myeloma, neuroblastoma, medullo, atherosclerosis, arterial stent occlusion, heart failure, cachexia, graft versus host disease, an infection disease associated with a bromodomain-containing protein, an infection disease caused by a parasite, malaria, trypanosomes, an inflammatory disease, or male fertility.

[00245] An effective amount of a compound may vary from about 0.001 mg/kg to about 1000 mg/kg in one or more dose administrations for one or several days (depending on the mode of administration). In certain embodiments, the effective amount per dose varies from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 0.1 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, and from about 10.0 mg/kg to about 150 mg/kg.

[00246] An effective amount of a compound of the invention may be an amount effective for inhibiting the activity of a bromodomain-containing protein in a subject or cell. An effective amount of a compound of the invention may also be an amount effective for inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell. An effective amount of a compound of the invention may further be an amount effective for modulating (*e.g.*, down-regulating) the expression (*e.g.*, transcription) of a gene that is regulated by a bromodomain-containing protein in a subject or cell. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a bromodomain-containing protein, the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone, and/or the transcription of a gene that is regulated by a bromodomain-containing protein by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a bromodomain-containing protein, the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone, and/or the transcription of a gene

that is regulated by a bromodomain-containing protein by at most about 90%, at most about 80%, at most about 70%, at most about 60%, at most about 50%, at most about 40%, at most about 30%, at most about 20%, or at most about 10%. Combinations of the ranges described herein (*e.g.*, at least about 20% and at most about 50%) are also within the scope of the invention. In certain embodiments, the activity of a bromodomain-containing protein, the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone, and/or the transcription of a gene that is regulated by a bromodomain-containing protein are inhibited by a percentage or a range of percentage described herein by an effective amount of a compound of the invention.

[00247] In certain embodiments, the gene regulated by a bromodomain-containing protein is a gene regulated by a bromo and extra terminal protein (*BET*). In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD2*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD2(1)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD2(2)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD3*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD3(1)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD3(2)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD4*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD4(1)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRD4(2)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRDT*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRDT(1)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *BRDT(2)*. In certain embodiments, the gene regulated by a bromodomain-containing protein is a gene regulated by a TBP (TATA box binding protein)-associated factor protein (*TAF*). In certain embodiments, the gene regulated by a bromodomain-containing protein is *TAF1*. In certain embodiments, the gene regulated by a bromodomain-containing protein is *TAF1L*. In certain embodiments, the gene regulated by a bromodomain-containing protein is a gene regulated by a CREB-binding protein (*CBP*). In certain embodiments, the gene regulated by a bromodomain-containing protein is a gene regulated by an E1A binding protein p300 (*EP300*).

[00248] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound described herein (*i.e.*, the “active ingredient”) into association with a

carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[00249] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[00250] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. The composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00251] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00252] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00253] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00254] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan monolaurate (Tween[®] 20), polyoxyethylene sorbitan (Tween[®] 60), polyoxyethylene sorbitan monooleate (Tween[®] 80), sorbitan monopalmitate (Span[®] 40), sorbitan monostearate (Span[®] 60), sorbitan tristearate (Span[®] 65), glyceryl monooleate, sorbitan monooleate (Span[®] 80), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate (Myrj[®] 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol[®]), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor[®]), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether (Brij[®] 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic[®] F-68, Poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00255] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum[®]), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00256] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[00257] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00258] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00259] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00260] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00261] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00262] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant[®] Plus, Phenonip[®], methylparaben, Germall[®] 115, Germaben[®] II, Neolone[®], Kathon[®], and Euxyl[®].

[00263] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate,

potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00264] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00265] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00266] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor[®], alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00267] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00268] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00269] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle.

[00270] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00271] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as

paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[00272] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00273] The active ingredient can be in a micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating agents which can be used include polymeric substances and waxes.

[00274] Dosage forms for topical and/or transdermal administration of a compound of this invention may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of

transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00275] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration. Jet injection devices which deliver liquid vaccines to the dermis *via* a liquid jet injector and/or *via* a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate the compound in powder form through the outer layers of the skin to the dermis are suitable.

[00276] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and/or water-in-oil emulsions such as creams, ointments, and/or pastes, and/or solutions and/or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00277] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration *via* the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of

propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00278] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00279] Pharmaceutical compositions of the invention formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00280] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition of the invention. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00281] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition of

the invention can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00282] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier or excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are also contemplated as being within the scope of this invention.

[00283] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00284] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight,

general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00285] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration). In certain embodiments, the compound or pharmaceutical composition of the invention is suitable for topical administration to the eye of a subject.

[00286] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00287] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[00288] In certain embodiments, the compounds described herein may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to

about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic and/or prophylactic effect.

[00289] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00290] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease associated with a bromodomain-containing protein in a subject in need thereof, in preventing a disease associated with a bromodomain-containing protein in a subject in need thereof, in reducing the risk to have a disease associated with a bromodomain-containing protein in a subject in need thereof, in inhibiting the activity of a bromodomain-containing protein in a subject or cell, in inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell, in modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell), bioavailability, and/or safety, reduce drug resistance, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body of a subject. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, an inventive pharmaceutical composition including a compound of the invention and an additional pharmaceutical agent shows a synergistic effect that is absent in a pharmaceutical composition including one of the compound and the additional pharmaceutical agent, but not both.

[00291] The compound or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved for

human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a disease described herein. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00292] The additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-angiogenesis agents, anti-inflammatory agents, immunosuppressants, anti-bacterial agents, anti-viral agents, anti-diabetic agents, anti-allergic agents, and pain-relieving agents. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a bromodomain-containing protein. In certain embodiments, the additional pharmaceutical agent is selected from the group consisting of (+)-**JQ1**, (-)-**JQ1**, **I-BET**, and **PFI-1**. See, *e.g.*, international PCT patent application publication, WO 2011/143669. In certain embodiments, the additional pharmaceutical agent is selected from the group consisting of epigenetic or transcriptional modulators (*e.g.*, DNA methyltransferase inhibitors, histone deacetylase inhibitors (HDAC inhibitors), lysine methyltransferase inhibitors), antimitotic drugs (*e.g.*, taxanes and vinca alkaloids), hormone receptor modulators (*e.g.*, estrogen receptor modulators and androgen receptor modulators), cell signaling pathway inhibitors (*e.g.*, tyrosine kinase inhibitors), modulators of protein stability (*e.g.*, proteasome inhibitors), Hsp90 inhibitors, glucocorticoids, all-*trans* retinoic acids, and other agents that promote differentiation. In certain embodiments, the inventive compounds or pharmaceutical compositions can be administered in combination with an anti-cancer therapy including, but not limited to, surgery, radiation therapy, and chemotherapy.

[00293] Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the first container and the second container are combined to form one unit dosage form.

[00294] Thus, in one aspect, provided are kits including a first container comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits are useful for treating and/or preventing a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits are useful for treating a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits are useful for preventing a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits are useful for reducing the risk of having a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits are useful for inhibiting the activity of a bromodomain-containing protein in a subject or cell. In certain embodiments, the kits are useful for inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell. In certain embodiments, the kits are useful for modulating (*e.g.*, down-regulating) the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell. In certain embodiments, the kits are useful for screening a library of compounds to identify a compound that is useful in the methods of the invention (*e.g.*, useful for inhibiting the activity of a bromodomain-containing protein). In certain embodiments, the kits further include instructions for administering the compound or pharmaceutical composition of the invention. The kits may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating

and/or preventing a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits and instructions provide for treating a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits and instructions provide for reducing the risk of having a disease described herein (*e.g.*, a disease associated with bromodomain-containing proteins, such as a proliferative disease) in a subject in need thereof. In certain embodiments, the kits and instructions provide for inhibiting the activity of a bromodomain-containing protein in a subject or cell. In certain embodiments, the kits and instructions provide for inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell. In certain embodiments, the kits and instructions provide for modulating (*e.g.*, down-regulating) the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell. In certain embodiments, the kits and instructions provide for screening a library of compounds to identify a compound that is useful in the methods of the invention (*e.g.*, useful for inhibiting the activity of a bromodomain-containing protein). The kit of the invention may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods of Treatment and Uses

[00295] The present invention provides methods that are useful for the treatment of a disease associated with a bromodomain-containing protein, such as a proliferative disease. The invention also provides methods of inhibiting the activity of a bromodomain-containing protein, methods of inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone, and methods of modulating the expression (*e.g.*, transcription) of a gene that is regulated by a bromodomain-containing protein.

[00296] It has been reported that compound **JQ1** is a cell-permeable, potent, small-molecule bromodomain inhibitor with biochemical selectivity for the BET family of bromodomain-containing proteins and that compounds related to **JQ1** are capable of regulating bromodomain-containing proteins. See, *e.g.*, international PCT patent application publication, WO 2011/143669. Lysine acetylation has emerged as a signaling modification of broad relevance to cellular and disease biology. Targeting the enzymes which reversibly

mediate side-chain acetylation has been an active area of drug discovery for many years. To date, successful efforts have been limited to the “writers” (acetyl transferases) and “erasers” (histone deacetylases) of covalent modifications arising in the context of nuclear chromatin. Inhibitors of acetyl-lysine recognition modules, or bromodomains, are less studied. The recent characterization of a co-crystal structure of **JQ1**-BRD4 revealed excellent shape complementarity of **JQ1** with the acetyl-lysine binding cavity of BRD4. Binding of **JQ1** to the tandem bromodomains of BRD4 is acetyl-lysine competitive and displaces BRD4 from chromatin in human cells. Recurrent translocation of BRD4 has been observed in an incurable, genetically-defined subtype of human squamous cell carcinoma. Competitive binding of **JQ1** to the BRD4 fusion oncoprotein has resulted in immediate squamous differentiation and specific anti-proliferative effects in patient-derived cell lines and in a murine model of BRD4-dependent carcinoma. Similar properties of compound **I-BET**, another bromodomain inhibitor, have also been reported (Nicodeme *et al.*, *Nature* **2010**, 468, 1119-1123). These data have established the feasibility of targeting protein-protein interactions of epigenetic “readers” and have suggested a versatile chemical scaffold for the development of chemical probes more broadly throughout the bromodomain protein family.

[00297] Gene regulation is fundamentally governed by reversible, non-covalent assembly of macromolecules. Signal transduction to RNA polymerase requires higher-ordered protein complexes, spatially regulated by assembly factors capable of interpreting the post-translational modification states of chromatin. Epigenetic readers are structurally diverse proteins, and each of the epigenetic readers possesses one or more evolutionarily conserved effector modules, which recognize covalent modifications of histone proteins or DNA. The ϵ -N-acetylation of lysine residues (Kac) on histone tails is associated with an open chromatin architecture and transcriptional activation. Context-specific molecular recognition of acetyl-lysine is principally mediated by bromodomains.

[00298] Bromodomain-containing proteins are of substantial biological interest, as components of transcription factor complexes (*e.g.*, TBP (TATA box binding protein)-associated factor 1 (TAF1), CREB-binding protein (CBP or CREBBP), P300/CBP-associated factor (PCAF), and Gcn5) and determinants of epigenetic memory. There are 41 human proteins containing a total of 57 diverse bromodomains. Despite large sequence variations, all bromodomains share a conserved fold comprising a left-handed bundle of four alpha helices (α_Z , α_A , α_B , and α_C), linked by diverse loop regions (ZA and BC loops) that determine substrate specificity. Co-crystal structures with peptidic substrates showed that the acetyl-

lysine is recognized by a central hydrophobic cavity and is anchored by a hydrogen bond with an asparagine residue present in most bromodomains. The bromo and extra-terminal (BET) family (*e.g.*, BRD2, BRD3, BRD4 and BRDT) shares a common domain architecture comprising two N-terminal bromodomains that exhibit high level of sequence conservation, and a more divergent C-terminal recruitment domain.

[00299] Recent research has established a compelling rationale for targeting BRD4 in cancer. BRD4 functions to facilitate cell cycle progression and knock-down in cultured cancer cell lines prompts G1 arrest. BRD4 is an important mediator of transcriptional elongation, functioning to recruit the positive transcription elongation factor complex (P-TEFb). Cyclin dependent kinase-9, a core component of P-TEFb, is a validated target in chronic lymphocytic leukemia, and has recently been linked to c-Myc dependent transcription. Bromodomains present in BRD4 recruit P-TEFb to mitotic chromosomes resulting in increased expression of growth promoting genes. BRD4 remains bound to transcriptional start sites of genes expressed during M/G1 but has not been found present at start sites that are expressed later in the cell cycle. Knockdown of BRD4 in proliferating cells has been shown to lead to G1 arrest and apoptosis by decreasing expression levels of genes important for mitotic progression and survival.

[00300] Importantly, BRD4 has recently been identified as a component of a recurrent t(15;19) chromosomal translocation in an aggressive form of human squamous cell carcinoma. Such translocations express the tandem N-terminal bromodomains of BRD4 as an in-frame chimera with the nuclear protein in testis (NUT) protein, genetically defining the NUT midline carcinoma (NMC). Functional studies in patient-derived NMC cell lines have validated the essential role of the BRD4-NUT oncoprotein in maintaining the characteristic proliferation advantage and differentiation block of this malignancy. Notably, RNA silencing of BRD4-NUT gene expression arrests proliferation and prompts squamous differentiation with a marked increase in cytokeratin expression. A bromodomain may also down-regulates Myc and other transcriptional factors, such as interleukin 7 receptor (IL7R). These observations underscore the utility and therapeutic potential of an inhibitor of bromodomain-containing proteins.

[00301] In one aspect, the present invention provides methods of inhibiting the activity of a bromodomain-containing protein in a subject or cell. In certain embodiments, the bromodomain-containing protein is a bromodomain-containing protein described herein (*e.g.*, a BET protein, such as BRD2, BRD3, BRD4, or BRDT). In certain embodiments, the activity of a bromodomain-containing protein in a subject or cell is inhibited by the inventive

methods. In certain embodiments, the activity of a bromodomain-containing protein in a subject or cell is inhibited by the inventive methods by at least about 1%, at least about 3%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%. In certain embodiments, the activity of a bromodomain-containing protein in a subject or cell is inhibited by the inventive methods by at most about 90%, at most about 80%, at most about 70%, at most about 60%, at most about 50%, at most about 40%, at most about 30%, at most about 20%, at most about 10%, at most about 3%, or at most about 1%. Combinations of the above-referenced ranges (*e.g.*, at least about 10% and at most about 50%) are also within the scope of the invention. Other ranges are also possible. In some embodiments, the activity of a bromodomain-containing protein in a subject or cell is selectively inhibited by the inventive methods. In other embodiments, the activity of a bromodomain-containing protein in a subject or cell is non-selectively inhibited by the inventive methods. In certain embodiments, the cytokine level and/or histamine release are reduced by the inventive methods.

[00302] In certain embodiments, the subject described herein is a human. In certain embodiments, the subject is a human diagnosed as having a disease associated with a bromodomain-containing protein. In certain embodiments, the subject is a human diagnosed as being at a higher-than-normal risk to have a disease associated with a bromodomain-containing protein. In certain embodiments, the subject is a human suspected of having a disease associated with a bromodomain-containing protein. In certain embodiments, the subject is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject is a fish. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a human or non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal.

[00303] In certain embodiments, the cell is *in vitro*. In certain embodiments, the cell is *ex vivo*. In certain embodiments, the cell is *in vivo*.

[00304] In certain embodiments, the methods of the invention include administering to a subject in need thereof an effective amount of a compound or pharmaceutical composition of the invention. In certain embodiments, the methods of the invention include administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutical composition of the invention. In certain embodiments, the methods of the invention include administering to a subject in need thereof an effective amount of a pharmaceutical composition of the invention. In certain embodiments, the methods of the invention include administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention. In certain embodiments, the methods of the invention include contacting a cell with an effective amount of a compound or pharmaceutical composition of the invention. In certain embodiments, the methods of the invention include contacting a cell with an effective amount of a pharmaceutical composition of the invention.

[00305] In certain embodiments, the inventive methods are *in vitro* methods. In certain embodiments, the inventive methods are *ex vivo* methods. In certain embodiments, the inventive methods are *in vivo* methods.

[00306] Another aspect of the present invention relates to methods of inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell. In certain embodiments, the histone is selected from the group consisting of H1, H2A, H2B, H3, H4, and H5. In certain embodiments, the binding of a bromodomain of the bromodomain-containing protein to an acetyl-lysine residue of the histone is inhibited by the inventive methods.

[00307] In another aspect, the present invention provides methods of modulating the transcription of a gene (*e.g.*, a gene described herein) that is regulated by a bromodomain-containing protein in a subject or cell. In certain embodiments, the present invention provides methods of down-regulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell. Without wishing to be bound by any particular theory, the inventive compounds and pharmaceutical compositions may be able to interfere with the binding of a bromodomain-containing protein to a transcriptional start site of the gene. In certain embodiments, the inventive compounds and pharmaceutical compositions interfere with the acetyl-lysine recognition during the transcription of the gene. In certain embodiments, the inventive compounds and pharmaceutical compositions interfere with the acetyl-lysine anchoring during the transcription of the gene. In certain embodiments, the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or

cell is modulated by the inventive methods. In certain embodiments, the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell is down-regulated by the inventive methods. In certain embodiments, the gene that is regulated by a bromodomain-containing protein is an oncogene.

[00308] Another aspect of the present invention relates to methods of treating a disease associated with a bromodomain-containing protein in a subject in need thereof. In certain embodiments, the disease associated with a bromodomain-containing protein is treated by the inventive methods.

[00309] In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with the activity of the bromodomain-containing protein. In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with the function of a bromodomain of the bromodomain-containing protein. In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with a bromodomain of the bromodomain-containing protein. In certain embodiments, the disease associated with a bromodomain-containing protein is driven by a transcriptional activator. In certain embodiments, the transcriptional activator is Myc. In certain embodiments, the disease associated with a bromodomain-containing protein is associated with a NUT rearrangement. In certain embodiments, the disease associated with a bromodomain-containing protein is a proliferative disease (*e.g.*, a proliferative disease described herein). In certain embodiments, the disease associated with a bromodomain-containing protein is cancer (*e.g.*, a cancer described herein). In certain embodiments, the disease associated with a bromodomain-containing protein is lung cancer, multiple myeloma, neuroblastoma, colon cancer, or ovary cancer. In certain embodiments, the disease associated with a bromodomain-containing protein is lung cancer (*e.g.*, small-cell lung cancer or non-small-cell lung cancer). In certain embodiments, the disease associated with a bromodomain-containing protein is selected from the group consisting of Burkitt's lymphoma, breast cancer, colon cancer, neuroblastoma, glial blastoma multiforme, MLL-driven leukemia, chronic lymphocytic leukemia, NUT midline carcinoma, and squamous cell carcinoma. In certain embodiments, the disease associated with a bromodomain-containing protein is a benign neoplasm (*e.g.*, a benign neoplasm described herein). In certain embodiments, the disease associated with a bromodomain-containing protein is an inflammatory disease (*e.g.*, an inflammatory disease described herein). In certain embodiments, the disease associated with a bromodomain-containing protein is a disease that involves an inflammatory response to an infection with a bacterium, virus, fungus, parasite, and/or protozoon. In certain

embodiments, the disease associated with a bromodomain-containing protein is selected from the group consisting of osteoarthritis, acute gout, multiple sclerosis, an inflammatory bowel disease (*e.g.*, Crohn's disease and ulcerative colitis), neuroinflammation, asthma, a chronic obstructive airways disease, pneumonitis, myocarditis, pericarditis, myositis, eczema, dermatitis, acne, cellulitis, an occlusive disease, a cardiac valvular disease, stenosis, restenosis, in-stent-stenosis, a coronary arterial disease, congestive heart failure, angina pectoris, myocardial ischemia, thrombosis, alopecia, nephritis, vasculitis, atherosclerosis, retinitis, uveitis, scleritis, sclerosing cholangitis, hypophysitis, thyroiditis, sepsis, sepsis syndrome, septic shock, systemic inflammatory response syndrome (SIRS), toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, hepatitis (*e.g.*, fulminant hepatitis), burns, pancreatitis (*e.g.*, acute pancreatitis), post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, malaria, and SIRS associated with viral infections (such as influenza, herpes zoster, herpes simplex, and coronavirus). In certain embodiments, the disease associated with a bromodomain-containing protein is acute or chronic pancreatitis. In certain embodiments, the disease associated with a bromodomain-containing protein is burns. In certain embodiments, the disease associated with a bromodomain-containing protein is an inflammatory bowel disease. In certain embodiments, the disease associated with a bromodomain-containing protein is neuroinflammation. In certain embodiments, the disease associated with a bromodomain-containing protein is an autoimmune disease (*e.g.*, an autoimmune disease described herein). In certain embodiments, the disease associated with a bromodomain-containing protein is rheumatoid arthritis. In certain embodiments, the disease associated with a bromodomain-containing protein is selected from the group consisting of psoriasis, systemic lupus erythematosus, vitiligo, a bullous skin disease, hepatic cirrhosis, biliary cirrhosis, Addison's disease, acute rejection of transplanted organs, endotoxemia, and multi-organ dysfunction syndrome. In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with ischemia-reperfusion injury. In certain embodiments, the disease associated with a bromodomain-containing protein is selected from the group consisting of myocardial infarction, cerebrovascular ischemia (stroke), acute coronary syndromes, renal reperfusion injury, organ transplantation, coronary artery bypass grafting, a cardio-pulmonary bypass procedure, or pulmonary, renal, hepatic, gastro-intestinal, or peripheral limb embolism. In certain embodiments, the disease associated with a bromodomain-containing protein is a disorder of lipid metabolism via the regulation of apolipoprotein A1 (APOA1). In certain embodiments, the disease associated with a

bromodomain-containing protein is selected from the group consisting of hypercholesterolemia, atherosclerosis, and Alzheimer's disease. In certain embodiments, the disease associated with a bromodomain-containing protein is a viral infection. In certain embodiments, the disease associated with a bromodomain-containing protein is selected from the group consisting of infectious diseases caused by herpes virus, human papilloma virus, adenovirus, and/or poxvirus. In certain embodiments, the disease associated with a bromodomain-containing protein is a fibrotic condition. In certain embodiments, the disease associated with a bromodomain-containing protein is selected from the group consisting of idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma, and cardiac fibrosis. In certain embodiments, the disease associated with a bromodomain-containing protein is selected from the group consisting of diabetes (*e.g.*, type 1 diabetes, type 2 diabetes, and gestational diabetes), obesity, fatty liver (NASH or otherwise), atherosclerosis, arterial stent occlusion, heart failure, cachexia, graft versus host disease, an infection disease associated with a bromodomain-containing protein, an infection disease caused by a parasite, malaria, trypanosomes, an inflammatory disease, and male fertility. In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with aberrant Myc function. In certain embodiments, the disease associated with a bromodomain-containing protein is a disease associated with interleukin 7 receptor (IL7R).

[00310] In yet another aspect, the present invention provides methods of reducing the risk to have a disease associated with a bromodomain-containing protein in a subject in need thereof. In certain embodiments, the risk to have the disease associated with a bromodomain-containing protein is reduced by the inventive methods.

[00311] Another aspect of the invention relates to methods of inhibiting the interaction between a bromodomain-containing protein and an immunoglobulin (Ig) regulatory element in a subject or cell.

[00312] Another aspect of the invention relates to methods of screening a library of compounds, and pharmaceutical acceptable salts thereof, to identify a compound, or a pharmaceutical acceptable salt thereof, that is useful in the methods of the invention. In certain embodiments, the compound identified is useful for treating and/or preventing a disease associated with a bromodomain-containing protein in a subject in need thereof. In certain embodiments, the compound identified is useful for treating a disease associated with a bromodomain-containing protein in a subject in need thereof. In certain embodiments, the compound identified is useful for treating a proliferative disease in a subject in need thereof.

In certain embodiments, the compound identified is useful for treating cancer in a subject in need thereof. In certain embodiments, the compound identified is useful for treating a benign neoplasm in a subject in need thereof. In certain embodiments, the compound identified is useful for treating pathological angiogenesis in a subject in need thereof. In certain embodiments, the compound identified is useful for treating an inflammatory disease in a subject in need thereof. In certain embodiments, the compound identified is useful for treating an autoimmune disease in a subject in need thereof. In certain embodiments, the compound identified is useful for reducing the risk to have a disease associated with a bromodomain-containing protein in a subject in need thereof. In certain embodiments, the compound identified is useful for inhibiting the activity of a bromodomain-containing protein in a subject or cell. In certain embodiments, the compound identified is useful for inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell. In certain embodiments, the compound identified is useful for modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell. In certain embodiments, the library of compounds is a library of the compounds of the invention. In certain embodiments, the methods of screening a library include obtaining at least two different compounds of the invention; and performing at least one assay using the different compounds of the invention. In certain embodiments, at least one assay is useful in identifying a compound that is useful in the inventive methods.

[00313] Typically, the methods of screening a library of compounds involve at least one assay. In certain embodiments, the assay is performed to detect one or more characteristics associated with the treatment and/or prevention of a disease described herein, with the inhibition of the activity of a bromodomain-containing protein, with the inhibition of the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone, and/or with the modulation the transcription of a gene that is regulated by a bromodomain-containing protein. The characteristics may be desired characteristics (*e.g.*, a disease having been treated, a disease having been prevented, the risk to have a disease having been reduced, the activity of a bromodomain-containing protein having been inhibited, the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone having been inhibited, or the transcription of a gene that is regulated by a bromodomain-containing protein having been modulated). The characteristics may be undesired characteristics (*e.g.*, a disease not having been treated, a disease not having been prevented, the risk to have a disease not having been reduced, the activity of a bromodomain-containing protein not having been inhibited, the binding of a bromodomain of

a bromodomain-containing protein to an acetyl-lysine residue of a histone not having been inhibited, or the transcription of a gene that is regulated by a bromodomain-containing protein not having been modulated). The assay may be an immunoassay, such as a sandwich-type assay, competitive binding assay, one-step direct test, two-step test, or blot assay. The step of performing at least one assay may be performed robotically or manually. In certain embodiments, the assay comprises (a) contacting a library of compounds with a bromodomain-containing protein; and (b) detecting the binding of the library of compounds to the bromodomain-containing protein. In certain embodiments, the assay comprises detecting the specific binding of the library of compounds to the bromodomain-containing protein. In certain embodiments, the assay comprises detecting the specific binding of the library of compounds to a bromodomain of the bromodomain-containing protein. In certain embodiments, the detected binding of the library of compounds to the bromodomain-containing protein is useful in identifying the compound that is useful in the methods of the invention. In certain embodiments, the step of detecting the binding comprises using differential scanning fluorimetry (DSF), isothermal titration calorimetry (ITC), and/or an amplified luminescence proximity homogeneous assay (ALPHA). The step of performing at least one assay may be performed in a cell (*e.g.*, a cancer cell) *in vitro*, *ex vivo*, or *in vivo*. In certain embodiments, the step of performing at least one assay is performed in a cell (*e.g.*, a cancer cell) *in vitro*. In certain embodiments, the assay comprises (a) contacting a library of compounds with a cell; and (b) detecting a decrease in cell proliferation, an increase in cell death, and/or an increase in cell differentiation. In certain embodiments, the cell death is apoptotic cell death. In certain embodiments, the cell differentiation is identified by detecting an increase in cytokeratin expression. In certain embodiments, the step of performing at least one assay further comprises detecting a reduction in transcriptional elongation.

[00314] In another aspect, the present invention provides uses of the inventive compounds and pharmaceutical compositions in treating and/or preventing a disease described herein in a subject in need thereof. In certain embodiments, the invention provides uses of the inventive compounds and pharmaceutical compositions in treating a disease described herein in a subject in need thereof.

[00315] Another aspect of the present invention relates to uses of the inventive compounds and pharmaceutical compositions in reducing the risk to have a disease described herein in a subject in need thereof.

[00316] In yet another aspect, the present invention provides uses of the inventive compounds and pharmaceutical compositions in inhibiting the activity of a bromodomain-containing protein in a subject or cell.

[00317] Another aspect of the present invention relates to uses of the inventive compounds and pharmaceutical compositions in inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell.

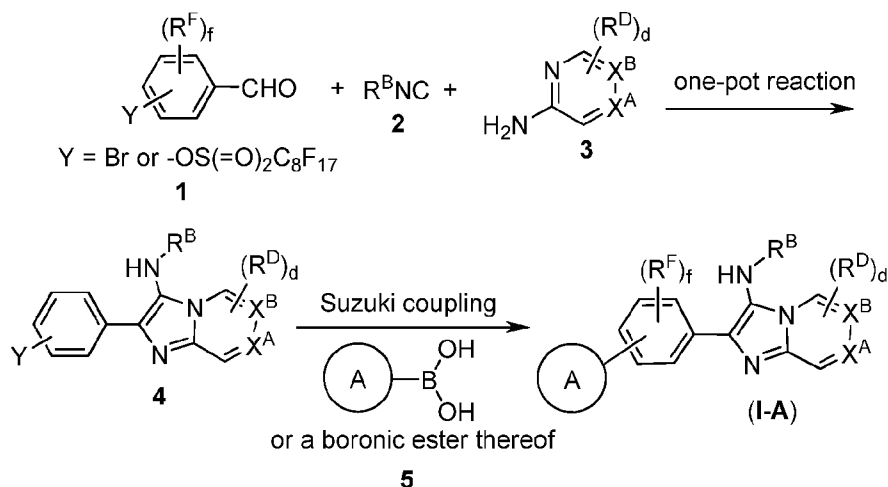
[00318] In still another aspect, the present invention provides uses of the inventive compounds and pharmaceutical compositions in modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell.

Examples

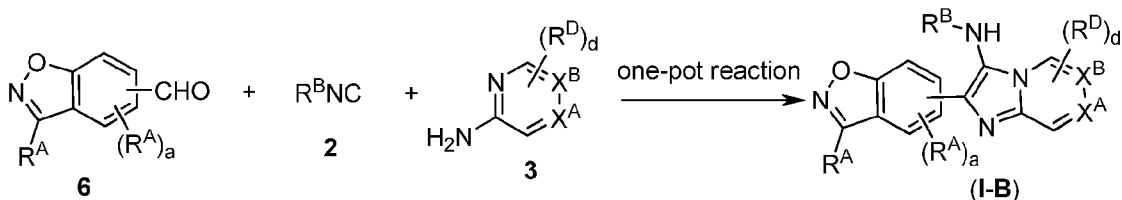
[00319] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Example 1. Preparation of Compounds

[00320] Compounds of Formula (I) (*e.g.*, compounds of Formula (I-A)), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, may be prepared by methods similar to the one reported in Lu *et al.*, *QSAR Comb. Sci.* **2004**, 23, 827-835, such as the synthetic sequence outlined below in *Scheme 1*, wherein X^A, X^B, Ring A, R^B, R^D, R^F, d, and f are as defined herein. The compounds of Formula (I) (*e.g.*, compounds of Formula (I-B)), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, may also be synthesized according to the method shown in *Scheme 2*. Alternatively, compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, may be prepared by other methods described herein or known in the art.

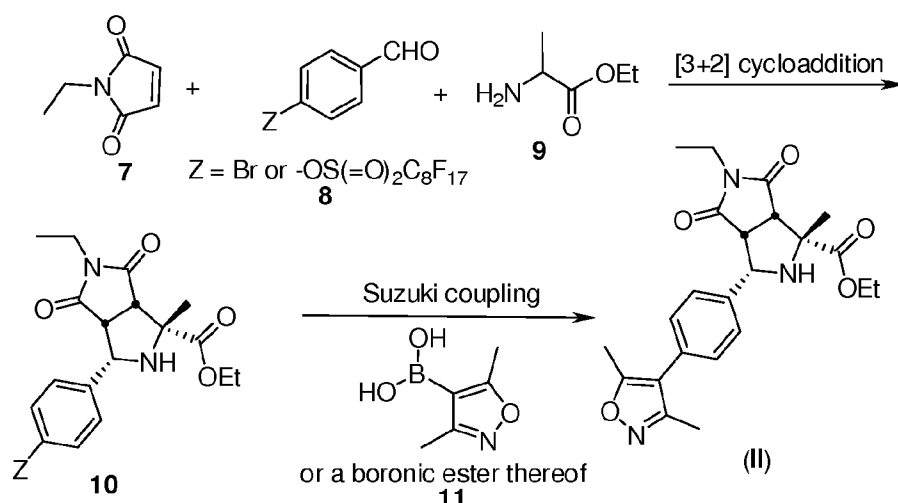


Scheme 1. Exemplary synthesis of compounds of Formula (I).



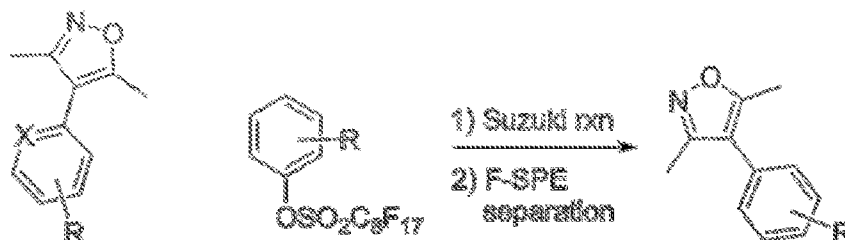
Scheme 2. Exemplary synthesis of compounds of Formula (I).

[00321] The compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, may be prepared by methods similar to the one reported in Zhang *et al.*, *Tetrahedron Lett.* **2005**, 46, 1807-1810, such as the synthetic sequence outlined below in Scheme 3. Alternatively, the compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, may be prepared by other methods described herein or known in the art.



Scheme 3. Exemplary synthesis of the compound of Formula (II).

[00322] Isoxazole probe compounds were prepared using Suzuki-type coupling reactions followed by purification of reaction intermediates using fluorosolid phase extraction (F-SPE). In this case, aryl perfluorooctylsulfonates ($\text{ArOSO}_2(\text{CF}_2)_7\text{CF}_3$) were reacted with 3,5-dimethylisoxazole-4-boronic acid pinacol esters to produce a low-molecular weight chemical series. The resulting compounds were purified using F-SPE. Initial compounds included positional isomers of carbonyl functionalities around the phenyl ring system.



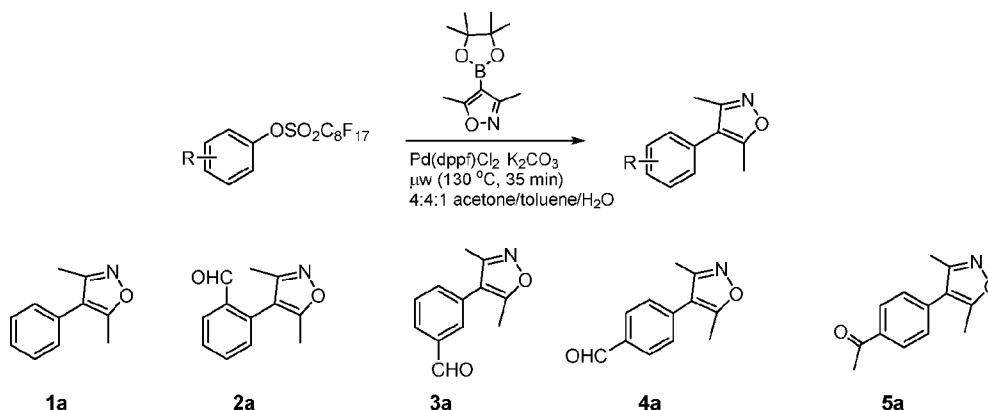
Scheme 4. Exemplary synthesis of isoxazole probe compounds.

General methods

[00323] All chemical reagents (including solvents) were purchased from commercial suppliers and used as received. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian NMR spectrometer. LC-MS were performed on an Agilent 2100 system with a C_{18} LC column (5.0 μm , 6.0 $\times$ 50 mm). The mobile phase was a mixture of MeOH (containing 0.05% trifluoroacetic acid) and water (containing 0.05% trifluoroacetic acid). A linear gradient was started from 75:25 MeOH- H_2O to 100% MeOH in 5.0 min at a flow rate of 0.7 mL/min. The chromatograms were recorded at UV 210 nm, 254 nm, and 365 nm. Low resolution mass spectra (LRMS) were recorded in APCI (atmospheric pressure chemical

ionization). Flash chromatography separations were performed on a YAMAZEN AI-580 system with Agela silica gel (12 g or 20 g, 230-400 μm) cartridges. The microwave reactions were performed on a Biotage Initiator 8 system.

Procedures for the synthesis of compounds 1a-5a.



[00324] These compounds were prepared by direct Suzuki coupling of fluororous arylsulfonates with the boronic ester. The Suzuki coupling reactions were carried out following the general procedure as shown.

[00325] 3,5-Dimethyl-4-phenylisoxazole (**1a**). Yellow oily compound, 58% yield, ^1H NMR (300 MHz, CDCl_3) δ 7.15–7.62 (m, 5H), 2.41 (s, 3H), 2.25 (s, 3H); MS(APCI) m/z 174.1 ($\text{M}^+ + 1$).

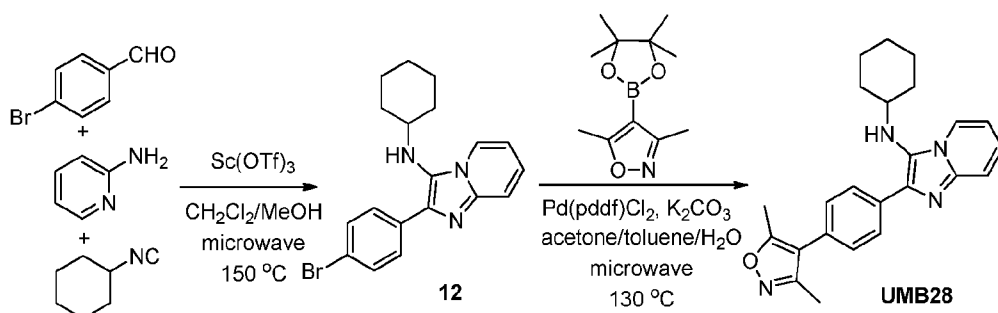
[00326] 2-(3,5-Dimethylisoxazol-4-yl)benzaldehydes (**2a**). Yellow oily compound, 17% yield, ^1H NMR (300 MHz, CDCl_3) δ 9.92 (s, 1H), 8.06 (d, $J=7.2\text{Hz}$, 1H), 7.69 (m, 1H), 7.54 (m, 2H), 2.28 (s, 3H), 2.16 (s, 3H); MS(APCI) m/z 202.1 ($\text{M}^+ + 1$).

[00327] 3-(3,5-Dimethylisoxazol-4-yl)benzaldehydes (**3a**). Yellow oily compound, 63%, yield, ^1H NMR (300 MHz, CDCl_3) δ 10.3 (s, 1H), 7.91 (d, 1H), 7.78 (s, 1H), 7.71 (d, 1H), 7.64 (t, 1H), 2.42 (s, 3H), 2.27 (s, 3H). MS (APCI) m/z 202.2 ($\text{M}^+ + 1$).

[00328] 4-(3,5-dimethylisoxazol-4-yl)benzaldehyde (**4a**). Yellow oily compound, 35% yield; ^1H NMR (300 MHz, CDCl_3) δ 10.07 (s, 1H), 7.99 (m, 2H), 7.46 (d, $J=6.6\text{Hz}$, 2H), 2.47 (s, 3H), 2.31 (s, 3H); MS(APCI) m/z 202.1 ($\text{M}^+ + 1$).

[00329] 1-(4-(3,5-Dimethylisoxazol-4-yl)phenyl)ethanone (**5a**). Yellow oily compound, 60% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.05 (d, $J = 8.7\text{Hz}$, 2H), 7.38 (d, $J = 8.7\text{Hz}$, 2H), 2.64 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H). MS(APCI) m/z 216.2 ($\text{M}^+ + 1$).

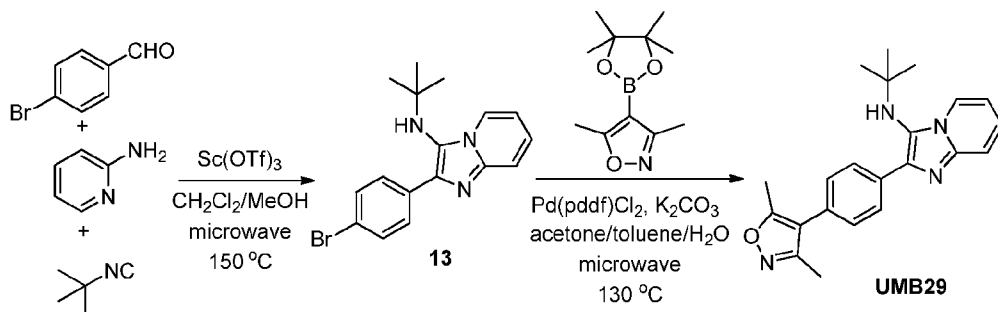
***N*-cyclohexyl-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-a]pyridin-3-amine (UMB28)**



[00330] A mixture of 4-bromobenzaldehyde (37 mg, 0.4 mmol), 2-aminopyridine (24 mg, 0.5 mmol), cyclohexyl isocyanide (32 μ L, 0.5 mmol), and catalyst Sc(OTf)₃ (10 mg, 0.04 mmol) in 2 mL of 3:1 CH₂Cl₂:H₂O was heated under microwave at 150 °C for 60 min. See, *e.g.*, Lu *et al.*, *QSAR Comb. Sci.* **2004**, 23, 827-835. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The concentrated filtrate was purified by flash chromatography (7:3 hexanes:EtOAc) to afford intermediate **12** (88 mg, 60% yield). MS (APCI) *m/z*: 371.1 (M+1)⁺.

[00331] A mixture of intermediate **12** (37 mg, 0.1 mmol), 3,5-dimethylisoxazole-4-boronic acid pinacol ester (33.6 mg, 0.15 mmol), catalyst Pd(pddf)Cl₂ (8.2 mg, 0.01 mmol), and base K₂CO₃ (27.6 mg, 0.2 mmol) in 2 mL of a solvent of 4:4:1 acetone:toluene:H₂O was heated under microwave at 130 °C for 60 min. See, *e.g.*, Lu *et al.*, *QSAR Comb. Sci.* **2004**, 23, 827-835. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The concentrated filtrate was purified by flash chromatography (5:5 hexanes:EtOAc) to afford compound **UMB28** (25 mg, 65% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.18 (m, 4 H), 7.58 (d, *J* = 6.0 Hz, 1 H), 7.38 (m, 2 H), 7.16 (m, 1 H), 2.24 (s, 3 H), 2.36 (s, 3 H), 1.6 (m, 6 H), 1.2 (m, 5 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 195.2, 165.1, 152.8, 129.2, 128.4, 124.0, 122.8, 116.6, 112.0, 57.6, 34.0, 25.2, 7.4 ppm. MS (APCI) *m/z*: 387.2 (M+1)⁺.

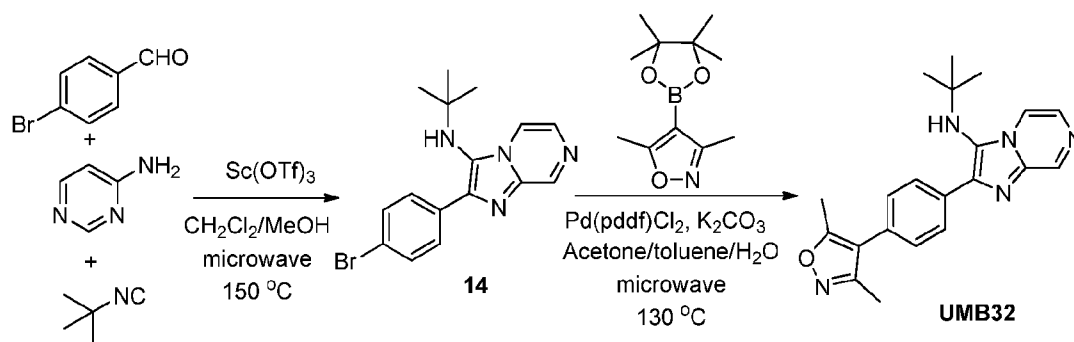
***N*-(*tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyridin-3-amine (UMB29)**



[00332] A mixture of 4-bromobenzaldehyde (37 mg, 0.4 mmol), 2-aminopyridine (45.2 mg, 0.48 mmol), *tert*-butyl isocyanide (54.3 μL , 0.48 mmol), and catalyst $\text{Sc}(\text{OTf})_3$ (10 mg, 0.04 mmol) in 2 mL of 3:1 $\text{CH}_2\text{Cl}_2:\text{H}_2\text{O}$ was heated under microwave at 150°C for 60 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The concentrated filtrate was purified by flash chromatography (7:3 hexanes:EtOAc) to afford intermediate **13** (110 mg, 79% yield). MS (APCI) m/z : 345.1 ($\text{M}+1$)⁺.

[00333] A mixture of intermediate **13** (30 mg, 0.09 mmol), 3,5-dimethylisoxazole-4-boric acid pinacol ester (30 mg, 0.135 mmol), catalyst $\text{Pd}(\text{pddf})\text{Cl}_2$ (5.7 mg, 0.007 mmol), and base K_2CO_3 (25 mg, 0.18 mmol) in 2 mL of 4:4:1 acetone:toluene: H_2O was heated under microwave at 130°C for 60 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The concentrated filtrate was purified by flash chromatography (7:3 hexanes:EtOAc) to afford compound UMB29 (18.2 mg, 56% yield). ^1H NMR (300 MHz, CDCl_3) δ 8.18 (m, 1 H), 7.96 (m, 2 H), 7.47 (m, 1 H), 7.26 (m, 2 H), 7.12 (m, 1 H), 6.75 (m, 1 H), 2.39 (s, 3 H), 2.25 (s, 3 H), 1.00 (s, 9 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ 215.9, 201.1, 200.7, 177.8, 128.9, 128.4, 123.4, 118.2, 30.4, 24.5, 11.7, 7.7 ppm. MS (APCI) m/z : 361.2 ($\text{M}+1$)⁺.

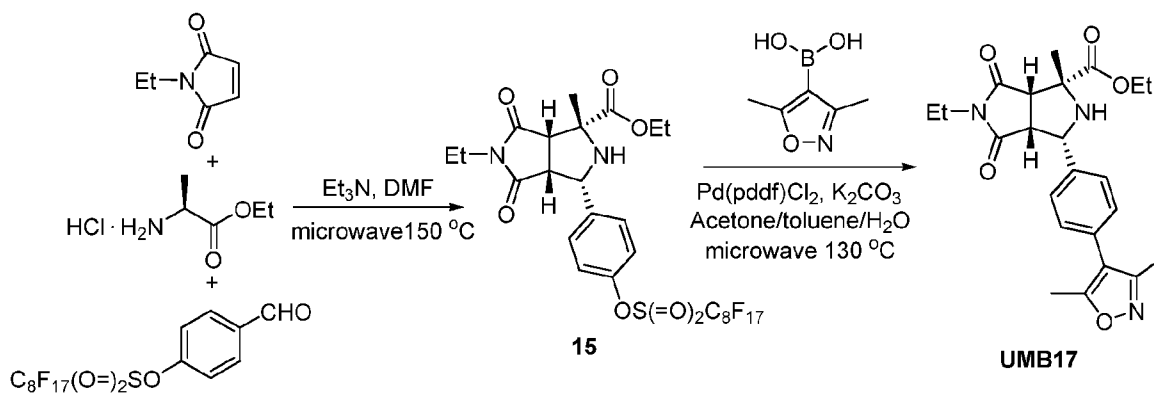
***N*-(*tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyrazin-3-amine (UMB32)**



[00334] A mixture of 4-bromobenzaldehyde (37 mg, 0.4 mmol), 4-aminopyrimidine (45.6 mg, 0.48 mmol), *tert*-butyl isocyanide (54.3 μ L, 0.48 mmol), and catalyst Sc(OTf)₃ (10 mg, 0.04 mmol) in 2 mL of 3:1 CH₂Cl₂:H₂O was heated under microwave at 150 °C for 60 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The concentrated filtrate was purified by flash chromatography (7:3 hexanes:EtOAc) to afford intermediate **14** (96 mg, 72% yield). MS (APCI) *m/z*: 346.1 (M+1)⁺.

[00335] A mixture of intermediate **14** (30 mg, 0.09 mmol), 3,5-dimethylisoxazole-4-boronic acid pinacol ester (30 mg, 0.135 mmol), catalyst Pd(pddf)Cl₂ (5.7 mg, 0.007 mmol), and base K₂CO₃ (25 mg, 0.18 mmol) in 2 mL of 4:4:1 acetone:toluene:H₂O was heated under microwave at 130 °C for 60 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The concentrated filtrate was purified by flash chromatography (7:3 hexanes:EtOAc) to afford compound **UMB32** (16.3 mg, 50% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.93 (s, 1 H), 8.10 (d, *J* = 6.0 Hz, 1 H), 7.95-8.08 (m, 2 H), 7.80 (d, *J* = 6.6 Hz, 1 H), 7.28 (d, *J* = 6.6 Hz, 2 H), 2.38 (s, 3 H), 2.24 (s, 3 H), 1.00 (s, 9 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 216.1, 201.2, 164.1, 129.2, 128.7, 118.2, 116.5, 30.6, 11.10, 7.81 ppm. MS (APCI) *m/z*: 362.2 (M+1)⁺.

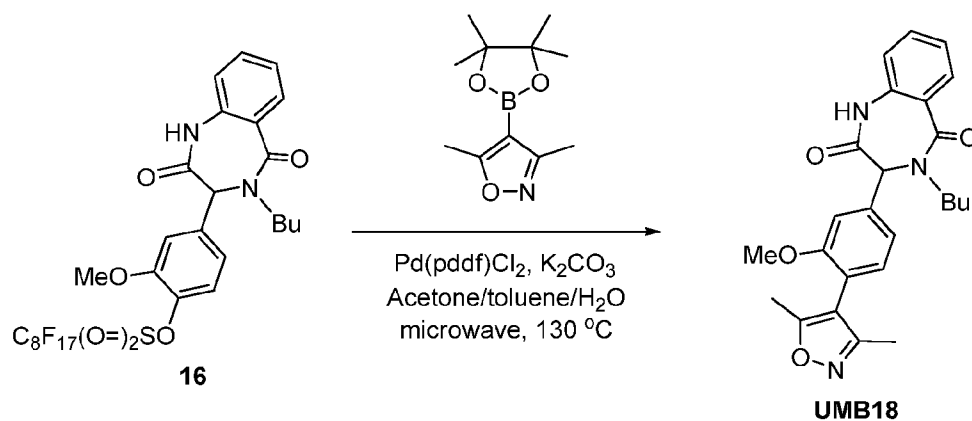
(1*R*,3*S*,3*aR*,6*aS*)-ethyl 3-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-5-ethyl-1-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (UMB17)



[00336] A mixture of *N*-ethylmaleimide (37.5 mg, 0.3 mmol), L-alanine ethyl ester hydrochloride (37 mg, 0.24 mmol), fluorous benzaldehyde (120.5 mg, 0.2 mmol), and triethylamine (69 μ L, 0.48 mmol) in 2 mL DMF was heated under microwave at 150 °C for 15 min. After aqueous workup, the concentrated crude product was purified by flash chromatography (8:2 hexanes:EtOAc) to give the perfluorooctylsulfate intermediate **15** (124.3 mg, 75% yield).

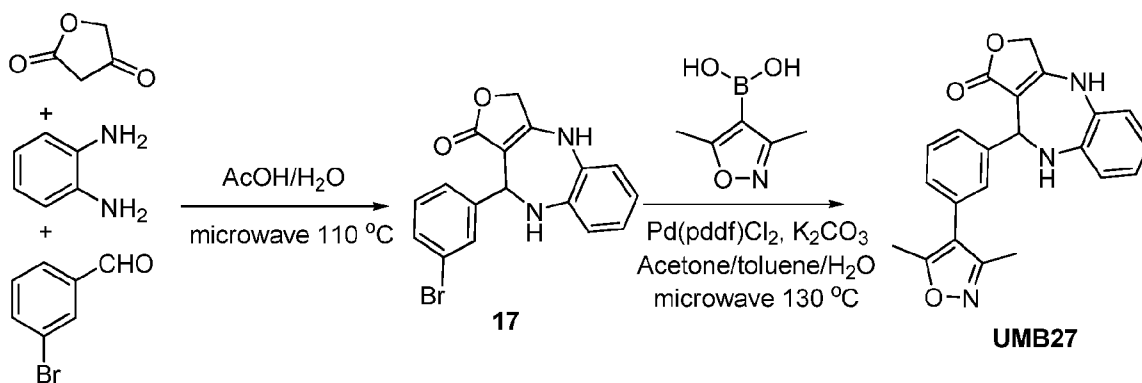
[00337] The perfluorooctylsulfate intermediate **15** (82.8 mg, 0.1 mmol), 3,5-dimethylisoxazole-4-yl boronic acid (21.1 mg, 0.15 mmol), Pd(pddf)Cl₂ (a catalyst, 65.1 mg, 0.08 mmol), and K₂CO₃ (a base, 27.6 mg, 0.2 mmol) in 2 mL of 4:4:1 acetone:toluene:H₂O was heated under microwave at 130 °C for 30 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by flash chromatography (7:3 hexanes: EtOAc) to afford compound **UMB17**. MS (APCI) *m/z*: 426.5 (M+1)⁺.

2-Butyl-3-(4-(3,5-dimethylisoxazol-4-yl)-3-methoxyphenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepine-1,4(5H)-dione (UMB18)



[00338] The fluorous sulfonate starting material **16** was synthesized following a procedure reported in Zhou *et al.*, *J. Comb. Chem.* **2010**, 12, 206-214. A mixture of fluorous sulfonate **16** (167.3 mg, 0.2 mmol), 3,5-dimethylisoxazole-4-boronic acid pinacol ester (67.2 mg, 0.3 mmol), Pd(pddf)Cl_2 (a catalyst, 16.4 mg, 0.02 mmol), and K_2CO_3 (a base, 55.2 mg, 0.4 mmol) in 2 mL of 4:4:1 acetone:toluene: H_2O was heated under microwave at $130\text{ }^\circ\text{C}$ for 60 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by flash chromatography (7:3 hexanes:EtOAc) to afford compound **UMB18**. MS (APCI) m/z : 434.2 ($\text{M}+1$)⁺.

10-(3-(3,5-Dimethylisoxazol-4-yl)phenyl)-3,4,9,10-tetrahydro-1H-benzo[b]furo[3,4-e][1,4]diazepin-1-one (UMB27)

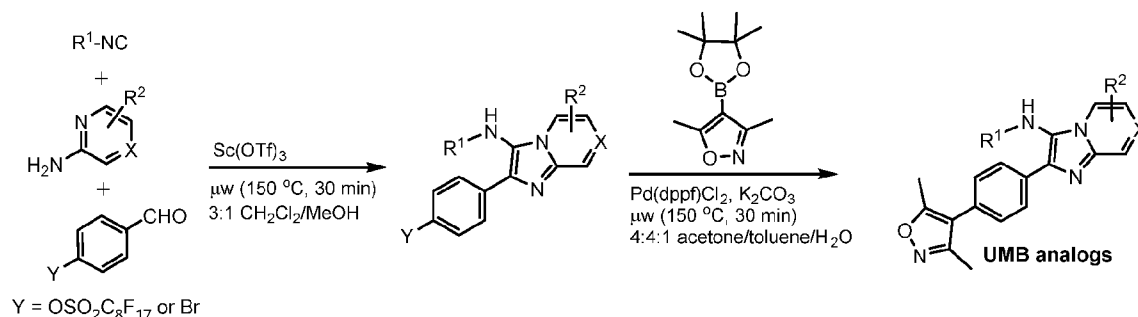


[00339] A mixture of benzene-1,2-diamine (54 mg, 0.5 mmol), tetronic acid (53.5 mg, 0.5 mmol), and acetic acid (3 μL , 0.05 mmol) in 1 mL of H_2O was stirred at room temperature for 30 min. Then 3-bromobenzaldehyde (92.5 mg, 0.5 mmol) was added. The reaction

mixture was heated under microwave at 110 °C for 10 min. See, *e.g.*, Wang *et al.*, *Tetrahedron* **2011**, 25, 4485-4493. The reaction mixture was filtered, and the residue was washed with 1 mL of 50% ethanol. The solid obtained was purified by flash chromatography (6:4 EtOAc:hexanes) to afford intermediate **17** (87 mg, 49% yield). MS (APCI) m/z : 357.2 (M+1)⁺.

[00340] A mixture of the intermediate **17** (32 mg, 0.09 mmol), 3,5-dimethylisoxazole-4-yl boronic acid (19 mg, 0.135 mmol), Pd(dppf)Cl₂ (a catalyst, 5.7 mg, 0.007 mmol), and K₂CO₃ (a base, 25 mg, 0.18 mmol) in 2 mL of 4:4:1 acetone:toluene:H₂O was heated under microwave at 130 °C for 30 min. The reaction mixture was filtered, and the residue was washed with ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by flash chromatography (6:4 EtOAc:hexanes) to afford compound **UMB27** (18 mg, 54% yield). MS (APCI) m/z : 374.1 (M+1)⁺.

Additional UMB Analog Synthesis and Characterization



product	X	R ¹	R ²
UMB11	CH4	PhCH ₂	H
12a	CH	H	H
13a	CH	PhCH ₂	Me
UMB20	CH	PhCH ₂	Cl
UMB21	7-N	PhCH ₂	H
UMB28	CH4	<i>c</i> -C ₆ H ₁₁	H
UMB30	CH	<i>p</i> -EtC ₆ H ₄	H
UMB23	CH	<i>p</i> -MeOC ₆ H ₄	Cl
UMB24	6-N	<i>p</i> -MeOC ₆ H ₄	7-OMe
UMB25	7-N	<i>p</i> -MeOC ₆ H ₄	H
21a	7-N	(S)-1-PhEt	H
24a	7-N	-CH ₂ CO ₂ tBu	H
UMB29	CH	<i>t</i> -Bu	H
UMB31	CH	<i>t</i> -Bu	Cl
27a	CH	<i>t</i> -Bu	6-Me
28a	CH	<i>t</i> -Bu	8-CF ₃
29a	CH	<i>t</i> -Bu	6-CO ₂ CH ₂
30a	CH	<i>t</i> -Bu	6-COOH
UMB56	6-N	<i>t</i> -Bu	H
UMB32	7-N	<i>t</i> -Bu	H
33a	8-N	<i>t</i> -Bu	H
UMB57	7-N	<i>i</i> -Pr	H
35a	7-N	<i>n</i> -Bu	H

[00341] *N*-Benzyl-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2- α]pyridin-3-amine (**UMB11**). Yellowish brown solid, 52% yield, ¹H NMR (300 MHz, CDCl₃) δ 8.24 (d, 1H), 7.72 (d, 2H), 7.66 (d, 1H), 7.58 (d, 2H), 7.53 (t, 1H), 7.42 (t, 1H), 7.22 (m, 5H), 4.21 (s, 2H), 3.15 (s, 1H), 2.42 (s, 3H), 2.37 (s, 3H); MS(APCI) *m/z* 395.2 (*M*⁺ + 1).

[00342] 2-(4-(3,5-Dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyridin-3-amine (**12a**). 36% yield, ¹H-NMR (300MHz, CDCl₃) δ 8.06 (m, 3H), 7.55 (m, 2H), 7.36 (d, *J*=6.3Hz, 2H), 7.15 (m, 1H), 6.83 (m, 1H), 3.45 (2, 2H), 2.44 (s, 3H), 2.31 (s, 3H). MS (APCI) *m/z* 305.1 (*M*⁺ + 1).

[00343] *N*-Benzyl-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-6-methylimidazo[1,2- α]pyridine-3-amine (**13a**). Yellow solid, 45% yield, ¹H NMR (300 MHz, CDCl₃) δ 7.99(d, 1H), 7.96 (d, 1H), 7.62 (s, 1H), 7.39 (d, 2H), 7.27 (m, 5H), 6.97 (d, 2H), 4.14 (s, 2H), 3.42 (s, 1H), 2.44 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H). MS(APCI) *m/z* 409.2 (*M*⁺ + 1).

[00344] *N*-Benzyl-6-chloro-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2- α]pyridin-3-amine (**UMB20**). 15% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.85 (s, 1H), 8.12 (d, 2H), 8.05 (d, 1H), 8.02 (d, 1H), 7.96 (d, 2H), 7.34 (m, 5H) 4.22 (s, 2H), 3.51 (s, 1H), 2.42 (s, 3H), 2.37 (s, 3H); MS(APCI) m/z 429.1 ($\text{M}^+ + 1$).

[00345] *N*-Benzyl-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2- α]-pyrazin-3-amine (**UMB21**). 16% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.11 (d, 1H), 8.05 (d, 1H), 8.01 (s, 1H), 7.92 (d, 2H), 7.52 (d, 2H), 7.42 (t, 1H), 7.28 (m, 5H), 4.22 (s, 2H), 3.51 (s, 1H), 2.43 (s, 3H), 2.37 (s, 3H); MS(APCI) m/z 396.2 ($\text{M}^+ + 1$).

[00346] *N*-Cyclohexyl-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2- α]pyridin-3-amine (**UMB28**). 19% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.11 (d, 1H), 8.05 (d, 2H), 7.57 (d, 1H), 7.35 (d, 2H), 7.08 (t, 1H), 6.81 (t, 1H), 3.01 (s, 1H), 2.42 (s, 3H), 2.27 (s, 3H), 1.12 (m, 11H); MS(APCI) m/z 387.2 ($\text{M}^+ + 1$).

[00347] 2-(4-(3,5-Dimethylisoxazol-4-yl)phenyl)-*N*-(4-methoxyphenyl)imidazo-[1,2- α]pyridin-3-amine (**UMB30**). 20% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.03 (d, $J = 8.4\text{Hz}$, 2H), 7.80 (d, $J = 6.6\text{Hz}$, 1H), 7.59 (d, $J = 9\text{Hz}$, 1H), 7.21 (d, $J = 8.4\text{Hz}$, 2H), 7.17 (t, 1H), 6.75 (d, $J = 6.6\text{Hz}$, 2H), 6.73 (t, 1H), 6.50 (d, $J = 6.6\text{Hz}$, 2H), 5.43 (s, 1H), 3.68 (s, 3H), 2.33 (s, 3H), 2.20 (s, 3H), 1.01 (s, 9H); MS(APCI) m/z 411.2 ($\text{M}^+ + 1$).

[00348] 6-Chloro-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-*N*-(4-methoxy-phenyl)imidazo[1,2- α]pyridine-3-amine (**UMB23**). 15% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.07 (s, 1H), 8.02 (d, 1H), 7.62 (d, 1H), 7.40 (d, 2H), 7.38 (d, 2H), 7.30 (d, 2H), 7.23 (d, 2H), 3.77 (s, 3H), 2.42 (s, 3H), 2.28 (s, 3H); MS(APCI) m/z 445.9 ($\text{M}^+ + 1$).

[00349] 2-(4-(3,5-Dimethylisoxazol-4-yl)phenyl)-7-methoxy-*N*-(4-methoxy-phenyl)imidazo[1,2- c]pyrimidin-3-amine (**UMB24**). 11% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.51 (s, 1H), 8.09 (d, $J = 8.4\text{Hz}$, 2H), 7.31 (d, $J = 8.4\text{Hz}$, 2H), 6.85 (d, $J = 8.7\text{Hz}$, 2H), 6.78 (s, 1H), 6.65 (d, $J = 8.7\text{Hz}$, 2H), 5.38 (s, 1H), 3.97 (s, 3H), 3.76 (s, 3H), 2.42 (s, 3H), 2.29 (s, 3H); MS(APCI) m/z 442.4 ($\text{M}^+ + 1$).

[00350] 2-(4-(3,5-Dimethylisoxazol-4-yl)phenyl)-*N*-(4-methoxyphenyl)imidazo[1,2- α]pyrazin-3-amine (**UMB25**). 42% yield, ^1H NMR (400 MHz, CD_3OD) δ 9.07 (s, 1H), 8.14 (m, 2H), 8.09 (d, 1H), 7.92 (d, 1H), 7.42 (m, 2H), 6.80 (m, 6.80), 6.57 (m, 2H), 3.70 (s, 3H), 2.42 (s, 3H), 2.26 (s, 3H); MS(APCI) m/z 412.2 ($\text{M}^+ + 1$).

[00351] (*S*)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-*N*-(1-phenylethyl)imidazo[1,2- α]pyrazin-3-amine (**21a**). 24% yield, ^1H -NMR (300MHz, CDCl_3) δ 8.96 (s, 1H), 8.05 (m,

2H), 7.78 (d, J=9.6Hz, 2H), 7.36 (d, J=2.1Hz, 2H), 7.27 (m, 5H), 4.38 (m, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 1.51 (s, 3H). MS (APCI) m/z 410.2 ($M^+ + 1$).

[00352] *Tert*-butyl 2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-a]pyrazin-3-ylglycinate (**24a**). 19% yield, ^1H -NMR (300MHz, CDCl_3) δ 9.01 (s, 1H), 8.19 (m, 3H), 7.89 (d, J=4.5Hz, 1H), 7.38 (d, J=7.2Hz, 2H), 3.77 (s, 2H), 2.46 (s, 3H), 2.33(s, 3H), 1.47(s, 9H). MS (APCI) m/z 420.2 ($M^+ + 1$).

[00353] *N*-(*t*-Butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2- α]pyridin-3-amine (**UMB29**). 20% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.15 (d, 1H), 7.99 (d, 2H), 7.45 (d, 1H), 7.22 (d, 2H), 7.03 (t, 1H), 6.71 (t, 1H), 3.01 (s, 1H), 2.40 (s, 3H), 2.25 (s, 3H), 1.01 (s, 9H); MS(APCI) m/z 361.2 ($M^+ + 1$).

[00354] *N*-(*t*-Butyl)-6-chloro-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-imidazo-[1,2- α]pyridin-3-amine (**UMB31**). 18% yield, ^1H NMR (300 MHz, CDCl_3) δ 8.19 (s, 1H), 7.93 (d, J = 6.6Hz, 2H), 7.44 (d, J = 9.6 Hz, 1H), 7.27 (d, J = 6.6 Hz, 2H), 7.07 (d, J = 9.6 Hz, 1H), 3.03 (s, 1H), 2.35 (s, 3H), 2.25(s, 3H), 1.01(s, 9H); MS(APCI) m/z 395.2 ($M^+ + 1$).

[00355] *N*-(*tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-6-methylimidazo[1,2-a]pyridin-3-amine (**27a**). 33% yield, ^1H -NMR (300MHz, CDCl_3) δ 8.06 (m, 3H), 7.55 (m, 2H), 7.36 (d, J=6.3Hz, 2H), 7.15 (m, 1H), 6.83 (m, 1H), 3.45 (2, 2H), 2.44 (s, 3H), 2.31 (s, 3H). MS (APCI) m/z 305.1 ($M^+ + 1$).

[00356] *N*-(*tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-8-(trifluoromethyl)imidazo[1,2-a]pyridin-3-amine (**28a**). 32 % yield, ^1H -NMR (400 MHz, CD_3OD) δ 8.67 (d, 1H), 8.12 (m, 2H), 7.67 (d, 1H), 7.45 (d, 2H), 7.03 (m, 1H), 2.46 (s, 3H), 2.30 (s, 3H), 1.04 (s, 9H). MS (APCI) m/z 429.2 ($M^+ + 1$).

[00357] Methyl 3-(*tert*-butylamino)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-a]pyridine-6-carboxylate (**29a**). 35 % yield, ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.08 (s, 1H), 8.35 (d, 2H), 7.59 (m, 2H), 7.45 (d, 2H), 4.96 (s, 1H), 3.92 (s, 3H), 2.45 (s, 3H), 2.27 (s, 3H), 1.06 (s, 9H). MS (APCI) m/z 419.2 ($M^+ + 1$).

[00358] 3-(*Tert*-butylamino)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-a]pyridine-6-carboxylic acid (**30a**). 30% yield, ^1H -NMR (400 MHz, CD_3OD) δ 9.03 (s, 1H), 8.13 (d, 2H), 7.82 (m, 1H), 7.42 (m, 3H), 2.46 (s, 3H), 2.30 (s, 3H), 1.07 (s, 9H). MS (APCI) m/z 405.1 ($M^+ + 1$).

[00359] *N*-(*Tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-c]pyrimidin-3-amine (**UMB56**). 18% yield, ^1H -NMR (400 MHz, CD_3OD) δ 9.05 (s, 1H), 7.87 (d, 1H),

7.71 (m, 2H), 7.59 (m, 2H), 7.40 (d, 1H), 2.48 (s, 3H), 2.33 (s, 3H), 1.45 (s, 9H). MS (APCI) m/z 361.9 ($M^+ + 1$).

[00360] *N*-(*Tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyrimidin-3-amine (**33a**). 15% yield, $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ 8.83 (d, 1H), 8.53 (d, 1H), 8.18 (m, 2H), 7.43 (m, 3H), 7.06 (m, 1H), 2.45 (s, 3H), 2.30 (s, 3H), 1.07 (s, 9H). MS (APCI) m/z 361.4 ($M^+ + 1$).

[00361] 2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)-*N*-isopropylimidazo[1,2-*a*]pyrazin-3-amine (**UMB57**). 19% yield, $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ 8.88 (d, 1H), 8.37 (d, 1H), 8.25 (m, 2H), 7.88 (d, 1H), 7.49 (m, 2H), 3.42 (m, 1H), 2.47 (s, 3H), 2.31 (s, 3H), 1.13, (d, 6H). MS (APCI) m/z 347.9 ($M^+ + 1$).

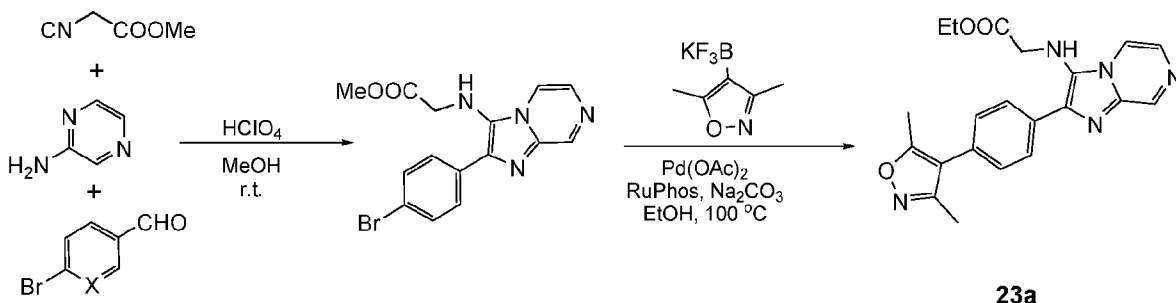
[00362] *N*-butyl-2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyrazin-3-amine (**35a**). 27% yield, $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 9.02 (s, 1H), 8.07 (d, $J=8.4\text{Hz}$, 2H), 7.98 (d, $J=4.2\text{Hz}$, 1H), 7.89 (d, $J=7.8\text{Hz}$, 1H), 7.39 (d, $J=8.1\text{Hz}$, 2H), 3.15 (s, 2H), 2.46 (s, 3H), 2.34 (s, 3H), 1.64 (m, 2H), 1.48 (m, 2H), 0.95 (t, 3H). MS (APCI) m/z 362.2 ($M^+ + 1$).

2-((2-(4-(3,5-Dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetic acid (22a**)**

[00363] Compound **24a** (0.284 g, 0.677 mmol, 1 eq) was dissolved in DCM (2.7 mL) and TFA (2.7 mL) and stirred at room temperature. After 12 hours, the mixture was concentrated, and purified by preparative HPLC (5 to 95% MeCN/water with 0.1%TFA) and lyophilized to yield the product as an orange powder (187 mg, 0.515 mmol, 76%).

[00364] $^1\text{H NMR}$ (400 MHz, MeOD) δ 9.08 (s, 1H), 8.69 (d, $J = 5.3\text{ Hz}$, 1H), 8.16 (d, $J = 8.2\text{ Hz}$, 2H), 7.94 (d, $J = 5.1\text{ Hz}$, 1H), 7.66 – 7.46 (m, 2H), 3.99 (s, 2H), 2.48 (s, 3H), 2.32 (s, 3H). MS (ESI) 364.76 ($M+H$).

Ethyl 2-((2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (23a**)**



Methyl 2-((2-(4-bromophenyl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate

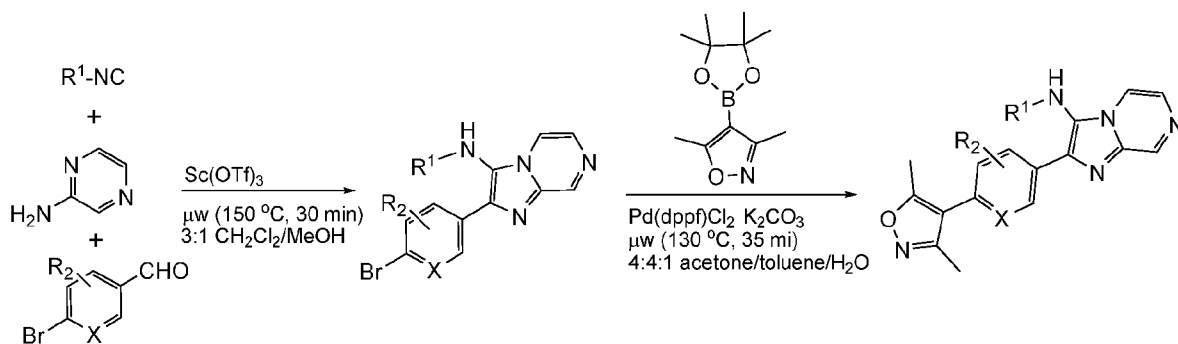
[00365] Aminopyrazine (95.2 mg, 1.00 mmol, 1 eq), 4-bromobenzaldehyde (278 mg, 1.50 mmol, 1.5 eq) and methyl isocyanoacetate (0.105 mL, 1.15 mmol, 1.15 eq) were dissolved in methanol (2 mL). A 1M solution of perchloric acid in methanol (0.20 mL, 0.10 eq) was added and the solution was stirred for 12 hours at room temperature. The mixture was then diluted with EtOAc and washed with saturated sodium bicarbonate, water and brine. The crude material was purified by automated column chromatography (50 to 100% EtOAc/hexanes) to yield a cream colored solid (0.21 g, 0.581 mmol, 58%).

[00366] ¹H NMR (400 MHz, CDCl₃) δ 8.99 (d, *J* = 1.5 Hz, 1H), 8.18 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.02 – 7.93 (m, 2H), 7.90 (d, *J* = 4.6 Hz, 1H), 7.68 – 7.51 (m, 2H), 3.83 (d, *J* = 5.6 Hz, 2H), 3.74 (s, 3H). MS (ESI) 361.69 (M+H).

Ethyl 2-((2-(4-(3,5-dimethylisoxazol-4-yl)phenyl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (23a)

[00367] Methyl 2-((2-(4-bromophenyl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (147 mg, 0.408 mmol, 1 eq), potassium 3,5-dimethylisoxazole-4-trifluoroborate (108 mg, 0.530 mmol, 1.3 eq), palladium (II) acetate (4.5 mg, 0.020 mmol, 5 mol %) RuPhos (19.1 mg, 0.041 mmol, 10 mol %) and sodium carbonate (86.5 mg, 0.816 mmol, 2 eq) were dissolved in ethanol (2.1 mL) and degassed with nitrogen for roughly 1 minute. The mixture was placed in a heat block at 100 °C. After 16 hours, the mixture was filtered through a silica plug and concentrated. The crude mixture was purified by automated column chromatography (30 to 100% EtOAc/hexanes) to yield the ethyl ester (as a result of trans-esterification during the course of the cross-coupling) as a brown solid (88.9 mg, 0.227 mmol, 56%).

[00368] ¹H NMR (400 MHz, CDCl₃) δ 8.96 (d, *J* = 1.3 Hz, 1H), 8.21 (dd, *J* = 4.6, 1.4 Hz, 1H), 8.18 – 8.10 (m, 2H), 7.85 (d, *J* = 4.6 Hz, 1H), 7.39 – 7.31 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.05 (t, *J* = 5.7 Hz, 1H), 3.86 (d, *J* = 5.7 Hz, 2H), 2.43 (s, 3H), 2.29 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). MS (ESI) 392.90 (M+H).



Compound	R ¹	R ²	X
UMB53	t-Bu	H	2-N
UMB54	t-Bu	H	3-N
UMB55	t-Bu	2-F	CH
39a	t-Bu	3-OMe	CH
40a	i-Pr	3-OMe	CH

[00369] *N*-(*tert*-butyl)-2-(6-(3,5-dimethylisoxazol-4-yl)pyridin-3-yl)imidazo[1,2-*a*]pyrazin-3-amine (**UMB53**). 25% yield, ¹H-NMR (300 MHz, CDCl₃) δ 8.92 (s, 1H), 8.84 (d, J=2.1Hz, 1H), 7.87 (m, 1H), 7.52 (d, J=8.1Hz, 1H), 7.35 (d, J=4.8Hz, 1H), 2.65 (s, 3H), 2.50 (s, 3H), 1.46 (s, 9H); MS (APCI) *m/z* 363.1 (M⁺ + 1).

[00370] *N*-(*tert*-butyl)-2-(5-(3,5-dimethylisoxazol-4-yl)pyridin-2-yl)imidazo[1,2-*a*]pyrazin-3-amine (**UMB54**). 31% yield, ¹H-NMR (300 MHz, CDCl₃) δ 9.54 (s, 1H), 8.55 (s, 1H), 7.93 (d, J=6.3Hz, 1H), 7.65 (m, 2H), 7.35 (d, J=4.5Hz, 1H), 2.48 (s, 3H), 2.34 (s, 3H), 1.25 (s, 9H); MS (APCI) *m/z* 363.1 (M⁺ + 1).

[00371] *N*-(*tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)-3-fluorophenyl)imidazo[1,2-*a*]pyrazin-3-amine (**UMB55**). 20% yield, ¹H-NMR (300 MHz, CDCl₃) δ 9.04 (s, 1H), 7.88 (d, J=5.4Hz, 1H), 7.36 (m, 4H), 2.43 (s, 3H), 2.31 (s, 3H), 1.51 (s, 9H); MS (APCI) *m/z* 380.1 (M⁺ + 1).

[00372] *N*-(*tert*-butyl)-2-(4-(3,5-dimethylisoxazol-4-yl)-2-methoxyphenyl)imidazo[1,2-*a*]pyrazin-3-amine (**39a**). 21% yield, ¹H-NMR (300 MHz, CDCl₃) δ 9.00 (s, 1H), 8.22 (d, J=4.5Hz, 1H), 7.88 (m, 2H), 7.05 (d, J=7.8Hz, 1H), 6.89 (s, 1H), 3.94 (s, 3H), 3.82 (s, 1H), 2.47 (s, 3H), 2.33 (s, 3H), 1.01 (s, 9H); MS (APCI) *m/z* 392.2 (M⁺ + 1).

[00373] 2-(4-(3,5-dimethylisoxazol-4-yl)-2-methoxyphenyl)-*N*-isopropylimidazo[1,2-*a*]pyrazin-3-amine (**40a**). 19% yield, ¹H-NMR (300 MHz, CDCl₃) δ 9.00 (s, 1H), 8.05 (m, 1H), 7.89 (m, 2H), 7.05 (d, J=6.6Hz, 1H), 6.91 (s, 1H), 7.05 (d, J=7.8Hz, 1H), 3.94 (s, 3H), 3.15 (m, 1H), 2.48 (s, 3H), 2.34 (s, 3H), 1.03 (d, 6H); MS (APCI) *m/z* 378.1 (M⁺ + 1).

*Example 2. Biochemical and Cellular Assays of the Compounds****In vitro* AlphaScreen[®] protein binding assay**

[00374] Assays were performed with minor modifications from the manufacturer's protocol (PerkinElmer, USA). All reagents were diluted in 50 mM HEPES, 150 mM NaCl, 0.1% w/v BSA, and 0.01% w/v Tween[®] 20 at pH 7.5 and allowed to equilibrate to room temperature prior to addition to plates. After addition of Alpha beads to master solutions, all subsequent steps were performed in low light conditions. A 2x solution of components with final concentrations of a BRD protein (*e.g.*, BRD4) at 40 nM, Ni-coated Acceptor Bead at 25 µg/ml, and 20 nM biotinylated **JQ1** was added in 10 µL to 384-well plates (AlphaPlate - 384, PerkinElmer, USA). Biotinylated **JQ1** was synthesized as described herein or according to methods known in the art. After a 1000-rpm spin-down for 1 minute, 100 nL of the solutions of compounds of the invention in DMSO from stock plates were added by pin transfer using a Janus Workstation (PerkinElmer, USA). The streptavidin-coated donor beads (25 µg/ml final) were added as with previous solution in a 2x, 10 µL volume. Following this addition, the plates were sealed with foil to block light exposure and to prevent evaporation. The plates were spun down again at 1000 rpm for 1 minute. Next, the plates were incubated in the room with the plate reader (for temperature equilibration) for 1 hour prior to reading the assay. Signal is stable for up to 3 hours after donor bead addition. AlphaScreen[®] measurements were performed on an Envision 2104 (PerkinElmer, USA) utilizing the manufacturer's protocol.

Acetyl-histone binding assay

[00375] Assays were performed with minor modifications from the manufacturer's protocol (PerkinElmer, USA). All reagents were diluted in 50 mM HEPES, 150 mM NaCl, 0.1% w/v BSA, and 0.01% w/v Tween[®] 20 at pH 7.5 and allowed to equilibrate to room temperature prior to addition to plates. After addition of Alpha beads to master solutions, all subsequent steps were performed in low light conditions. A 2x solution of components with final concentrations of BRD4.1 at 80 nM, Ni-coated Acceptor Bead at 25 µg/ml, and 80 nM biotinylated H4-tetra acetyl was added in 10 µL to 384-well plates (AlphaPlate - 384, PerkinElmer, USA). Biotinylated peptide for BRD4.1 was synthesized in-house on a CEM Liberty 9008005 microwave peptide synthesizer: H4-tetra acetyl, biotin-PEG2-SGRGKacGGKacGLGKacGGAKacRHRK-COOH. Addition to wells was performed with either a multichannel pipet (for optimization experiments) or a Biotek EL406 liquid handler. After a 1000-rpm spin-down for 1 minute, 100 nL of the solutions of the compounds of the

invention from stock plates were added by pin transfer using a Janus Workstation (PerkinElmer, USA). The streptavidin-coated donor beads (25 µg/ml final) were added as with previous solution in a 2x, 10 µL volume. Following this addition, the plates were sealed with foil to block light exposure and to prevent evaporation. The plates were spun down again at 1000 rpm for 1 minute. Next, the plates were incubated in the room with the plate reader (for temperature equilibration) for 1.5 hour prior to reading the assay. AlphaScreen[®] measurements were performed on an Envision 2104 (PerkinElmer, USA) utilizing the manufacturer's protocol.

Cellular assay

[00376] The compounds of the invention are also evaluated in the BRD4 dependant cell line for the cellular activity to generate cellular IC₅₀ values.

[00377] Cells (*e.g.*, BRD4 dependant cells) were counted and adjusted to 60,000 cells/mL. Using a Biotek EL406, 50 µL of the cells in media were distributed into 384 well white plates from Thermo. Immediately after plating, compounds of the invention in DMSO were distributed to plates. For large plate sets, cells were returned to a 37 °C incubator while not in use. The compounds were added to plates using a 100 nL 384 well pin transfer manifold on a Janus workstation. Stocks were arrayed in 10 point quadruplicate dose response in DMSO stock in 384-well Greiner compound plates. After addition of the compounds, plates were incubated for three days in a 37 °C incubator. Cell viability was read out using ATPlite from Perkin Elmer. Plates were removed from the incubator and brought to room temperature prior to use. Lyophilized powder was resuspended in lysis buffer and diluted 1:2 with DI water. 25µL of this solution was added to each well using the Biotek liquid handler. Plates were sealed with adherent aluminum seals prior to vortexing and spinning down at 1000 g for 1 minute. Plates were incubated for 15 minutes at room temperature before signal was read on an Envision Plate Reader.

Biologic and Biochemical Compound Evaluation Reagents

[00378] Endogenous BRD4-NUT-expressing midline carcinoma cell lines, 797 was described previously (Toretsky *et al.*, *Am. J. Clin. Oncol.* **2003**, 26, 300). Media, trypsin, and antibiotics for tissue culture were purchased from MediatechCloning. cDNA encoding human BRD2, BRD3, BRD4, BRDT, CREBBP and WDR9 (NCBI accession number NP 005095, NP 031397.1, NP 055114.1, NP 001717.2, NP 004371.1, NP 061836.2) were obtained from different sources (BRD2: Synthetic, BRD3: Origene, BRD4: FivePrime, BRDT: IMAGE

collection, CREBBP: Synthetic, WDR9: synthetic) and used as templates to amplify the bromodomain regions of the above proteins, using the polymerase chain reaction (PCR) in the presence of Platinum® Pfx DNA polymerase (Invitrogen™, UK). PCR products were purified (QIAquick PCR Purification Kit, Qiagen Ltd. UK) and further sub-cloned into a pET28 derived expression vector, pNIC28-Bsa4, using ligation independent cloning (Stols *et al.*, *Protein Expr. Purif.* **2002**, 25, 8). The constructs were transformed into competent Mach1™ cells (Invitrogen™, UK) to yield the final plasmid DNA. This vector includes sites for ligation-independent cloning and a Tobacco Etch Virus (TEV)-cleavable N-terminal His₆-tag (extension MHHHHHHSSGVDLGTENLYFQ*SM-) After digestion with TEV protease, the protein retains an additional serine and methionine on the N-terminus.

Protein Expression and Purification

[00379] The first bromodomain of Brd4 (Brd4-BD1, residues 42-168) was subcloned into a modified pET-15b(+) vector with an N-terminal His₆ tag followed by a Tobacco Etch Virus cleavage site. The encoded protein was expressed in the *E. coli* BL21(DE3) strain. *E. coli* cells transformed with the vector were grown 4 hours at 37 °C to an OD₆₀₀ of 1.0, in 1 liter LB media containing ampicillin (0.1 mg/ml). After 0.1 mM IPTG induction at 20 °C, cells were cultured overnight, and collected by centrifugation at 4,000 g. The pellet was suspended in 40 ml lysis buffer containing 50 mM HEPES, pH 7.4, 500 mM NaCl, 5 mM β-mercaptoethanol, and 1 mM PMSF. Cells were lysed on ice by sonication and cell debris was precipitated by centrifugation at 15,000 g for 30 minutes. Brd4-BD1 was purified by affinity chromatography on an Ni-NTA agarose column (Qiagen), using an elution buffer of 50 mM HEPES, pH 7.4, 500 mM NaCl, 5 mM β-mercaptoethanol, and 50 mM of imidazole. After overnight TEV cleavage of the His₆-tag, the cleaved tag was captured on affinity resin, and Brd4-BD1 was then purified to homogeneity by gel filtration before concentration to roughly 12 mg/ml in storage buffer (20mM HEPES, pH 7.4, and 150 mM NaCl). Samples for isothermal calorimetry were dialysed over night at 4 °C in a D-Tube™ Dialyser Midi, MWCO 3.5 kDa to a final buffer of 50 mM HEPES, pH 7.4 (at 25 °C), 150 mM NaCl. Protein handling was carried out on ice or in a cold room in all the above steps.

Isothermal Titration Calorimetry (ITC)

[00380] Experiments were carried out on a VP-ITC titration microcalorimeter from MicroCal™, LLC (Northampton, MA). All experiments were carried out at 15 °C while stirring at 295 rpm, in ITC buffer (50 mM HEPES pH 7.4 at 25 °C, 150 mM NaCl). The

microsyringe (250 μ L) was loaded with a solution of the protein sample (300 μ M protein for the BETs, 950 μ M protein for CREBBP and 600 μ M for WDR9(2), in ITC buffer). All titrations were conducted using an initial control injection of 2 μ l followed by 34 identical injections of 8 μ l with a duration of 16 sec (per injection) and a spacing of 250 sec between injections. The heat of dilution was determined by independent titrations (protein into buffer) and was subtracted from the experimental data. The collected data were implicated in the MicroCal™ Origin software supplied with the instrument to yield enthalpies of binding (ΔH) and binding constants (K_B) as previously described by Wiseman and co-workers (Wiseman *et al.*, *Anal. Biochem.* **1989**, 179, 131). Thermodynamic parameters were calculated ($\Delta G = \Delta H - T\Delta S = -RT\ln K_B$, where ΔG , ΔH and ΔS are the changes in free energy, enthalpy and entropy of binding respectively). In all cases a single binding site model was employed.

Results

[00381] Shown in *Table 1* are *in vitro* IC_{50} values, obtained through AlphaScreen®, of exemplary compounds of Formula (I) or (IV) in inhibiting the activity of BRD4. All compounds in *Table 1* inhibit the activity of BRD4.

Table 1. In vitro IC_{50} values of exemplary compounds of Formula (I) or (IV) in inhibiting the activity of BRD4.

Compound	IC_{50} (M)	Compound	IC_{50} (M)
UMB11	1.10E-05	UMB26	5.10E-06
UMB20	1.18E-05	UMB27	2.05E-06
UMB21	1.88E-05	UMB28	9.04E-07
UMB22	6.83E-05	UMB29	4.79E-07
UMB23	3.15E-05	UMB30	2.76E-06
UMB24	2.89E-06	UMB31	1.17E-06
UMB25	7.86E-06	UMB32	2.56E-07

[00382] *Table 2* shows *in vitro* IC_{50} values, obtained through AlphaScreen®, of exemplary compounds of Formula (I) or (II) in inhibiting BRD and CBP, and cellular IC_{50} values of the compounds in lung carcinoma cell line H2171. Compound UMB11 shows good selectivity toward BRD4 over CBP. Compounds UMB11 and UMB17 show cellular activity in H2171.

Table 2. In vitro IC₅₀ values of exemplary compounds of Formula (I) or (II) in inhibiting BRD and CBP, and cellular IC₅₀ values of the compounds in lung carcinoma cell line H2171.

Compound	BRD4 IC ₅₀ (μ M)	CBP IC ₅₀ (μ M)	H2171 IC ₅₀ (μ M)
UMB11	0.51	11	0.76
UMB17	122	30	55

[00383] Table 3 shows the *in vitro* IC₅₀ value, obtained through AlphaScreen[®], of an exemplary compound of Formula (I) in inhibiting the activity of BRD4. Also shown in Table 3 is the compound's cellular EC₅₀ value obtained from a cellular assay where a BRD4 dependant cell line was treated with the compound. Compound UMB32 is active in inhibiting the activity of BRD4 *in vitro* and also shows cellular activity in the BRD4 dependant cell line.

Table 3. In vitro IC₅₀ value of an exemplary compound of Formula (I) in inhibiting the activity of BRD4, and cellular EC₅₀ value of the compound in a BRD4 dependant cell line.

Compound	BRD4 IC ₅₀ (μ M)	BRD4 EC ₅₀ (μ M)
UMB32	0.26	1.1

[00384] Shown in Table 4 are cellular EC₅₀ values obtained from a cellular assay where a BRD4 (site 1) dependant cell line was treated with exemplary compounds of Formula (I) or (IV). All compounds tested show cellular activity in the BRD4 dependant cell line.

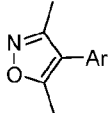
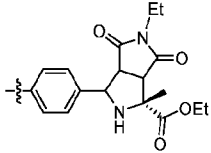
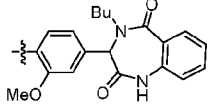
Table 4. Cellular EC₅₀ values of exemplary compounds of Formula (I) or (IV) in a BRD4 dependant cell line.

Compound	EC ₅₀ (M)	Compound	EC ₅₀ (M)
UMB11	1.41E-05	UMB26	2.02E-05
UMB20	1.84E-05	UMB27	2.07E-04
UMB21	4.91E-05	UMB28	5.07E-06
UMB22	1.24E-05	UMB29	2.04E-06
UMB23	2.07E-05	UMB30	7.36E-06

UMB24	1.18E-05	UMB31	2.19E-06
UMB25	3.28E-05	UMB32	1.13E-06

[00385] A diverse set of molecules was synthesized using reactions previously developed around fluororous-tagged multicomponent reactions. These reactions created structural diversity by changing the substituent groups on each fractional component, allowing generation of diverse small-molecule libraries around a biasing element. The perfluoroalkyl tags can substituted with a binding motif of choice *via* Suzuki coupling. Synthesized compounds included tertiary amines, pyrimidines and fused heterocyclic ring systems in order to explore the optimal shape for exploiting protein-inhibitor contour interactions. In addition to biochemical IC₅₀, these compounds were selectively evaluated in a BRD4-dependent cell viability study (see *Table 5*). The EC₅₀s were collected by assessing viability using PerkinElmer ATPlite kits against the BRD4-dependent Nut-Midline Carcinoma line 797. The use of a fluororous-tagged Groebke-Blackburn-Bienayme multi-component reaction was used to develop the para-imidazo[1,2-a]pyridine scaffold (**UMB11**), which was found have biochemical and cellular inhibitory values of 11.0 μ M and 14.1 μ M, respectively. In addition, the **UMB11** scaffold is accessible at a variety of positions for diversification to drive potency and develop understanding of SAR.

Table 5. Exploration of Compound Scaffold Region.

			
Compound	Ar	BRD4--IC ₅₀ (μ M)	797--EC ₅₀ (μ M)
II		>100	9.42
III		13.0	9.91

IV		2.05	>100
UMB11		11.0	14.1

[00386] Further analogs were synthesized to explore the functional role of both sterics and electronics of the fused bicyclic scaffold on inhibitor function (see *Table 6*). Variations of R^B from the benzyl group to bulky, non-aromatic groups like cyclohexane and *t*-Bu improved potency. Ring-nitrogens at the 7 and 8 position resulted in little biochemical potency change. Cellular potency, however, modestly improved upon substitution of a 7-N.

Table 6. Exploration of Compound Scaffold Region.

Compound	R^B	R^D	X	BRD4--IC ₅₀ (μM)	797--EC ₅₀ (μM)
12a	H	H	CH	3.89	
13a	Bn	6-Me	CH	>100	
UMB20	Bn	6-Cl	CH	11.8	18.4
UMB21	Bn	H	7-N	18.8	49.1
UMB28	cyclohexane	H	CH	0.904	5.07
UMB30	4-(OMe)Ph	H	CH	2.76	7.36
UMB23	4-(OMe)Ph	6-Cl	CH	31.5	20.7
UMB24	4-(OMe)Ph	7-OMe	6-N	2.89	11.8
UMB25	4-(OMe)Ph	H	7-N	7.86	32.8
21a	(S)-1-PhEt	H	7-N	2.86	
22a	-CH ₂ CO ₂ H	H	7-N	>100	
23a	-CH ₂ CO ₂ Et	H	7-N	4.53	
24a	-CH ₂ CO ₂ <i>t</i> Bu	H	7-N	4.96	
UMB29	<i>t</i> -Bu	H	CH	0.479	2.04
UMB31	<i>t</i> -Bu	6-Cl	CH	1.17	2.19
27a	<i>t</i> -Bu	6-Me	CH	3.17	

28a	<i>t</i> -Bu	8-CF ₃	CH	11.9	
29a	<i>t</i> -Bu	6-CO ₂ CH ₂	CH	1.62	
30a	<i>t</i> -Bu	6-COOH	CH	0.968	
UMB56	<i>t</i> -Bu	H	6-N	20.7	2.06
UMB32	<i>t</i> -Bu	H	7-N	0.637	0.724
33a	<i>t</i> -Bu	H	8-N	0.860	
UMB57	<i>i</i> -Pr	H	7-N	0.807	0.494
35a	<i>n</i> -Bu	H	7-N	1.66	

[00387] Limited structural study around the linking phenyl ring is shown below (see *Table 7*). Electron-donating methoxy substituents appear to be mildly beneficial in biochemical assays. Additional work regarding this linking region of the molecule will be a focus of continued medicinal chemistry.

Table 7. Variations to UMB-32 linker.

Compound **R^B** **R^F** **X** **BRD4--IC₅₀ (μM)** **797--EC₅₀ (μM)**

UMB53	<i>t</i> -Bu	H	2-N	51.9	>100
UMB54	<i>t</i> -Bu	H	3-N	12.9	8.29
UMB55	<i>t</i> -Bu	2-F	CH	13.0	12.8
39a	<i>t</i> -Bu	3-OMe	CH	0.562	
40a	<i>i</i> -Pr	3-OMe	CH	0.474	

Example 3. Selectivity of the Compounds for Different Bromodomain-Containing Proteins

[00388] The compounds of the invention (*e.g.*, **UMB11** and **UMB32**) were profiled with a panel of bromodomain-containing proteins for selectivity and were also fully characterized by isothermal titration calorimetry (ITC) (*Figure 12*). The results show that the compounds of the invention are active against bromodomain-containing proteins such as TAF1 and TAF1L, which may be validated targets for cancer therapy (*Tables 8 and 9 and Figures 3A-3B*).

Table 8. Selectivity of exemplary compounds of Formula (I) for different bromodomain-containing proteins measured by dissociation constant (K_d) values.

Bromodomain-containing protein	K_d (nM)			
	JQ1	I-BET	UMB32	UMB11
ATAD2A	40000	40000	40000	40000
ATAD2B	40000	40000	40000	40000
BAZ2A	40000	40000	40000	40000
BAZ2B	40000	40000	40000	40000
BRD1	40000	40000	40000	40000
BRD2(1)	27	79	94	2400
BRD2(2)	18	23	95	5800
BRD3(1)	14	34	35	1300
BRD3(2)	19	27	38	1800
BRD4(1)	14	59	80	2500
BRD4(2)	8	11	31	3500
BRD9	40000	40000	40000	40000
BRDT(1)	47	160	110	6000
BRDT(2)	35	45	75	40000
BRPF1	40000	40000	40000	40000
BRPF3	40000	40000	40000	40000
CBP	24000	76000	4500	6800
EP300	51000	71000	4500	5800
FALZ	40000	40000	40000	40000
PBRM1(2)	40000	40000	40000	40000
TAF1(2)	40000	40000	560	9700
TAF1L(2)	40000	40000	1300	40000
TRIM24(PHD Bromo.)	40000	40000	40000	40000
TRIM33(PHD Bromo.)	40000	40000	40000	40000
WDR9(2)	40000	40000	40000	40000

Table 9. BromoScan selectivity profile (K_d , nM) of compounds **UMB11** and **UMB32**.

	Compound UMB11	Compound UMB32
ATAD2A	40000	40000
ATAD2B	40000	40000
BAZ2A	40000	40000
BAZ2B	40000	40000
BRD1	40000	40000
BRD2(1)	2400	94
BRD2(2)	5800	95
BRD3(1)	1300	35
BRD3(2)	1800	38
BRD4(1)	2500	80
BRD4(2)	3500	31
BRD9	40000	40000
BRDT(1)	6000	110
BRDT(2)	40000	75
BRPF1	40000	40000
BRDF3	40000	40000
CREBBP	6800	4500
EP300	5800	4500
FALZ	40000	40000
PBRM1(2)	40000	40000
TAF1(2)	9700	560
TAF1L(2)	40000	1300
TRIM24(PHD,Bromo.)	40000	40000
TRIM33(PHD,Bromo.)	40000	40000
WDR9(2)	40000	40000

*Example 4. Computational Methods***Computational Methods**

[00389] All computational work was performed in Schrodinger Suite (Schrodinger, LLC). Conformational analysis of lead compounds was performed using Schrodinger's Conformational Search function. Possible poses were prepared for docking by Ligprep. In both cases, default settings were used (OPLS2005 force field, water solvent). Docking was conducted using Glide. The co-crystal of BRD4 and **JQ1** (PDB: 3MXF) was used to define the ligand receptor grid. Water molecules outside the binding pocket were excluded, and hydrogen bonding interactions were optimized prior to docking.

Results

[00390] Computational modeling was performed to better understand the modality of binding and inform further medicinal chemistry. Using previously published crystal structures of both **JQ1** and **iBET151**, fragments were docked into the structure. As is the case

with **iBET151**, compound **5a** is thought to bind through a conserved hydrogen bond with **N-140** through the ring oxygen, while the ring nitrogen coordinates through a structured water interacting with the hydroxyl group of **Y-97**. Based on this interaction, further analogs were built off the 4-position of the phenyl ring to improve potency by optimizing protein surface interactions near the BC loop region.

Example 5. X-ray Crystallography

Crystallization and Diffraction Data Collection

[00391] Crystallization was conducted using the sitting drop vapor diffusion method at 22°C. Crystals of inhibitor-free BRD4-BD1 were first obtained in a drop with equal volumes of BD1 at 12 mg/ml and a precipitant solution containing 100mM sodium nitrate, 5% ethylene glycol, and 18% (w/v) PEG3350, as precipitant. Rod-like crystals were typically grown in 10 days reaching a maximal size of 0.05x0.05x0.4 mm³. Then, native crystals were transferred and soaked in 1 mM UMB32 in the same crystallization buffer for 7 days. For data collection, a single crystal was flash frozen with a precipitant solution containing 20% (v/v) glycerol. Diffraction data for BD1-UMB32 complex were collected from a flash-cooled crystal at 100°K using the 24ID-E beam lines at the NE-CAT, Argonne National Laboratory and were processed, integrated, and scaled together with HKL2000 (Otwinowski *et al.*, *Methods Enzymol* **1997**, 276, 307).

Structure Determination and Refinement

[00392] The structure of the BD1-UMB32 complex was solved by molecular replacement (MR) as implemented in Phenix⁵ using the previous BD1-JQ1 structure (PDB 3MXF) as the search model. Structure refinement was carried out using conjugate-gradient energy minimization, torsion-constrained molecular dynamics simulated annealing, group B factor refinement, and individual B factor refinement protocols in Phenix⁵ with 5% of the reflections omitted for free R factor calculation. Electron density peaks in difference Fourier maps at a height of above 3 σ were assigned as water molecules in later refinement stages if they had reasonable geometry in relation to hydrogen bond donors or acceptors and their B-factors did not rise above 50 Å² during subsequent refinement. Model building was performed in Coot⁶ guided by σ_A -weighted 2Fo-Fc and Fo-Fc maps and composite omit maps.

Data collection and refinement statistics

Beam line	X19
Wavelength (Å)	0.9792
Resolution range (Å)	35.45 - 1.56 (1.616 - 1.56)
Space group	P212121
Unit cell	43.562 49.21 60.991 90 90 90
Unique reflections	19177 (1862)
Redundancy	3.9(3.9)
Completeness (%)	99.58 (100)
Mean I/sigma(I)	9.88 (1.8)
R-work	0.1697 (0.2587)
R-free	0.201 (0.2661)
Number of non-hydrogen atoms	1248
macromolecules	1047
ligands	47
water	154
Protein residues	127
RMS(bonds)	0.007
RMS(angles)	1.32
Ramachandran favored (%)	99
Ramachandran allowed (%)	1
Ramachandran outliers (%)	0
Clashscore	0.92
Average B-factor	19.6
macromolecules	17.5
ligands	22.5
solvent	32.9

Equivalents and Scope

[00393] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments, described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00394] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[00395] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is

present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, *etc.*, from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Furthermore, where the claims recite a composition, it is to be understood that methods of using the composition for any of the purposes disclosed herein are included, and methods of making the composition according to any of the methods of making disclosed herein or other methods known in the art are included, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise.

[00396] Where elements are presented as lists, *e.g.*, in Markush group format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, *etc.*, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, *etc.* For purposes of simplicity those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the term “comprising” is intended to be open and permits the inclusion of additional elements or steps.

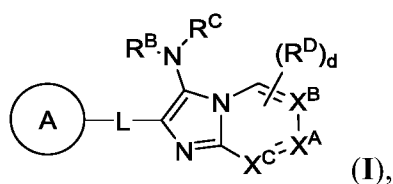
[00397] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00398] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (*e.g.*, any supercharged protein; any nucleic acid; any method of production; any method of use; *etc.*) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[00399] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

Claims

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

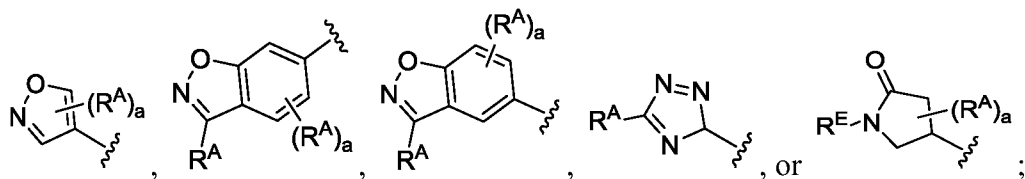
X^A is $C(R^D)$ or N;

X^B is $C(R^D)$ or N;

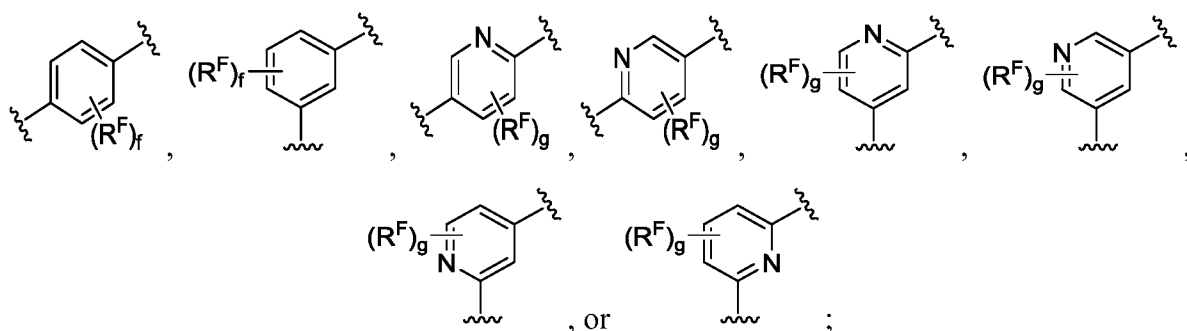
X^C is $C(R^D)$ or N;

wherein no more than two of X^A , X^B , and X^C can be N;

Ring A is of the formula:



L is a bond or of the formula:



each instance of R^A is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-CN$, $-SCN$, $-C(=NR^{A1})R^{A1}$, $-C(=NR^{A1})OR^{A1}$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, or $-OC(=O)N(R^{A1})_2$, or two instances of R^A are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{A1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{A1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^B is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, $-C(=O)N(R^{B1})_2$, or a nitrogen protecting group, or R^B and R^C are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^{B1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{B1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^C is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-C(=O)R^{C1}$, $-C(=O)OR^{C1}$, $-C(=O)N(R^{C1})_2$, or a nitrogen protecting group, or R^C and R^B are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^{C1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{C1} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^D is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^{\text{D1}}$, $-\text{N}(\text{R}^{\text{D1}})_2$, $-\text{SR}^{\text{D1}}$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^{\text{D1}})\text{R}^{\text{D1}}$, $-\text{C}(=\text{NR}^{\text{D1}})\text{OR}^{\text{D1}}$, $-\text{C}(=\text{NR}^{\text{D1}})\text{N}(\text{R}^{\text{D1}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{D1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{D1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{D1}})_2$, $-\text{NO}_2$, $-\text{NR}^{\text{D1}}\text{C}(=\text{O})\text{R}^{\text{D1}}$, $-\text{NR}^{\text{D1}}\text{C}(=\text{O})\text{OR}^{\text{D1}}$, $-\text{NR}^{\text{D1}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{D1}})_2$, $-\text{OC}(=\text{O})\text{R}^{\text{D1}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{D1}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{D1}})_2$, or two instances of R^{D} are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{D1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{D1} are joined to form a substituted or unsubstituted heterocyclic ring;

R^{E} is hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{C}(=\text{O})\text{R}^{\text{E1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{E1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{E1}})_2$, or a nitrogen protecting group;

each instance of R^{E1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or two instances of R^{E1} are joined to form a substituted or unsubstituted heterocyclic ring;

each instance of R^{F} is independently hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^{\text{F1}}$, $-\text{N}(\text{R}^{\text{F1}})_2$, $-\text{SR}^{\text{F1}}$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^{\text{F1}})\text{R}^{\text{F1}}$, $-\text{C}(=\text{NR}^{\text{F1}})\text{OR}^{\text{F1}}$, $-\text{C}(=\text{NR}^{\text{F1}})\text{N}(\text{R}^{\text{F1}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{F1}}$, $-\text{C}(=\text{O})\text{OR}^{\text{F1}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{F1}})_2$, $-\text{NO}_2$, $-\text{NR}^{\text{F1}}\text{C}(=\text{O})\text{R}^{\text{F1}}$, $-\text{NR}^{\text{F1}}\text{C}(=\text{O})\text{OR}^{\text{F1}}$, $-\text{NR}^{\text{F1}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{F1}})_2$, $-\text{OC}(=\text{O})\text{R}^{\text{F1}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{F1}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{F1}})_2$, or two instances of

R^F are joined to form a substituted or unsubstituted carbocyclic, substituted or unsubstituted heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl ring;

each instance of R^{F1} is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^{F1} are joined to form a substituted or unsubstituted heterocyclic ring;

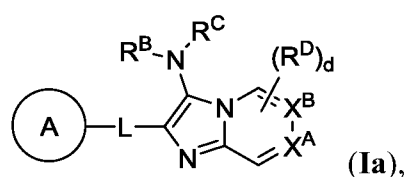
a is 0, 1, 2, 3, 4, or 5;

d is 0, 1, or 2;

f is 0, 1, 2, 3 or 4; and

g is 0, 1, 2, or 3.

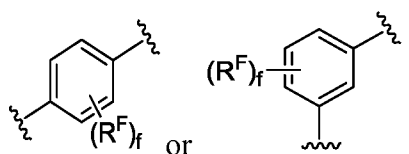
2. The compound of claim 1 of Formula (Ia):



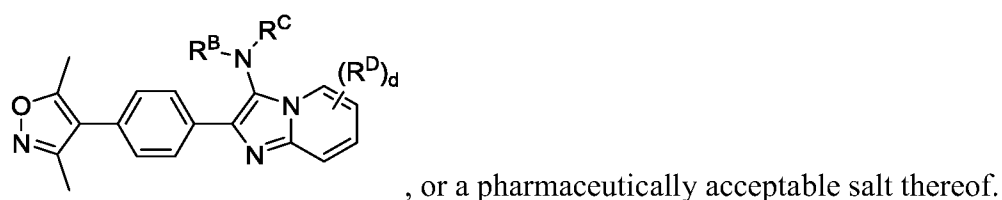
or a pharmaceutically acceptable salt thereof;

wherein:

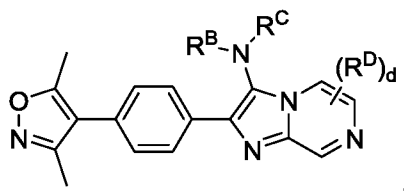
L is a bond or of the formula:



3. The compound of claim 1 or claim 2, wherein the compound is of the formula:

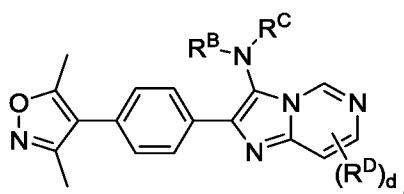


4. The compound of claim 1 or claim 2 wherein the compound is of the formula:



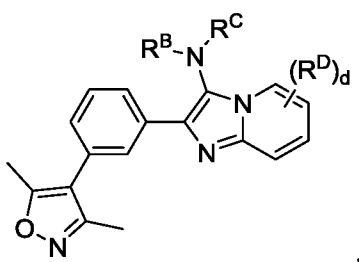
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 or claim 2, wherein the compound is of the formula:



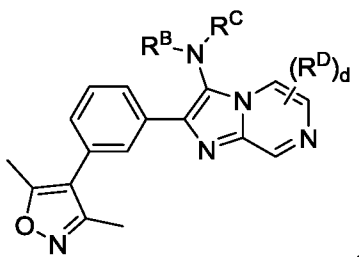
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 or claim 2, wherein the compound is of the formula:



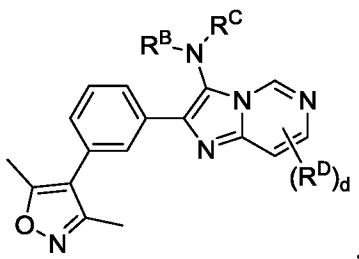
or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 or claim 2, wherein the compound is of the formula:



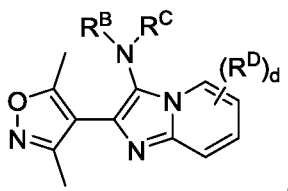
or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1 or claim 2, wherein the compound is of the formula:



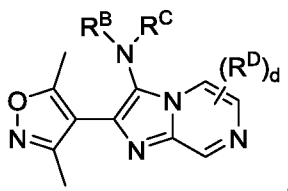
or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1 or claim 2, wherein the compound is of the formula:



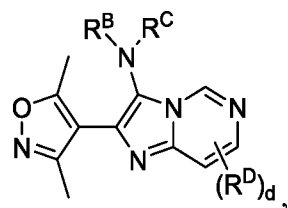
or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1 or claim 2, wherein the compound is of the formula:



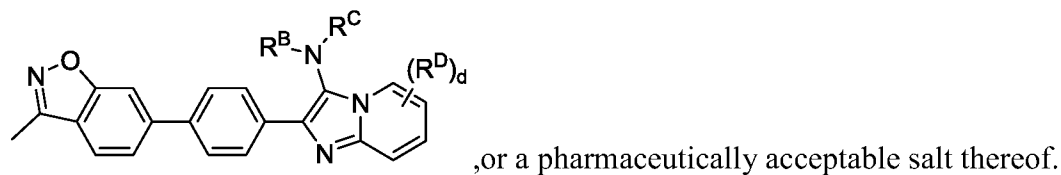
or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 or claim 2, wherein the compound is of the formula:

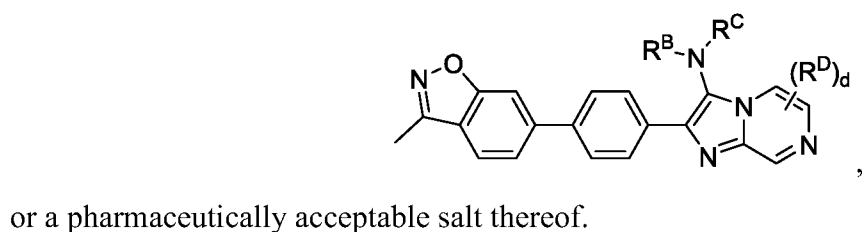


or a pharmaceutically acceptable salt thereof.

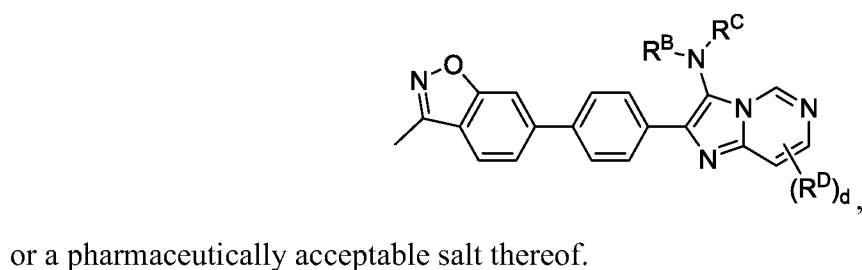
12. The compound of claim 1 or claim 2, wherein the compound is of the formula:



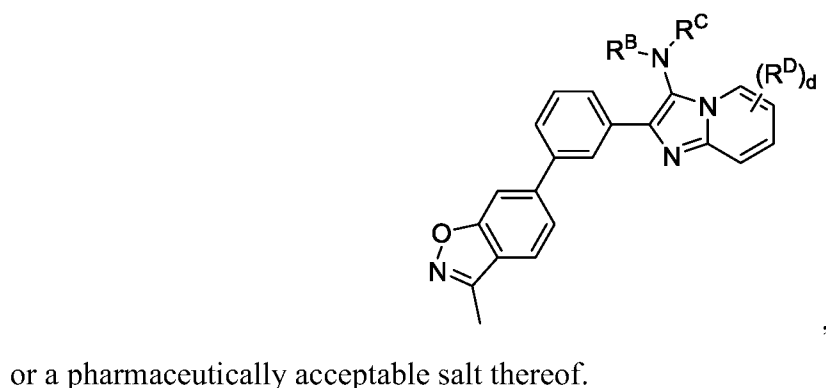
13. The compound of claim 1 or claim 2, wherein the compound is of the formula:



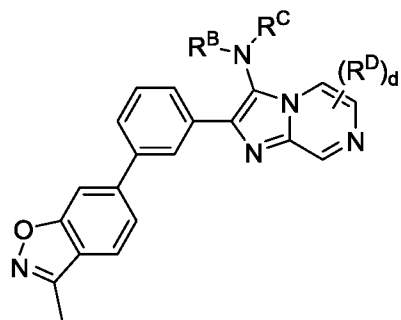
14. The compound of claim 1 or claim 2, wherein the compound is of the formula:



15. The compound of claim 1 or claim 2, wherein the compound is of the formula:

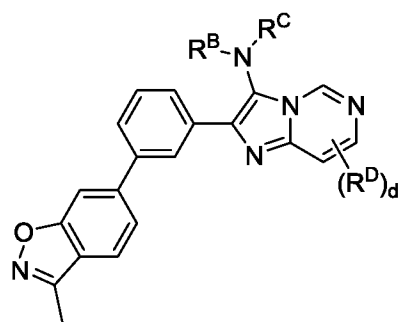


16. The compound of claim 1 or claim 2, wherein the compound is of the formula:



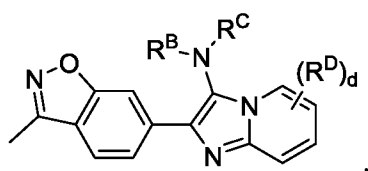
or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1 or claim 2, wherein the compound is of the formula:



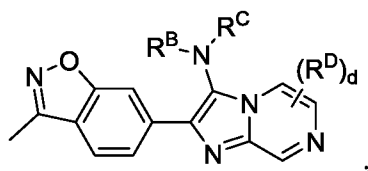
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1 or claim 2, wherein the compound is of the formula:



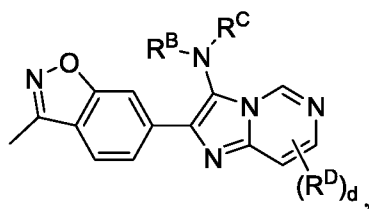
or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1 or claim 2, wherein the compound is of the formula:



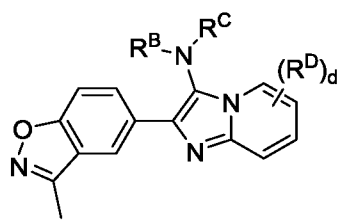
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1 or claim 2, wherein the compound is of the formula:



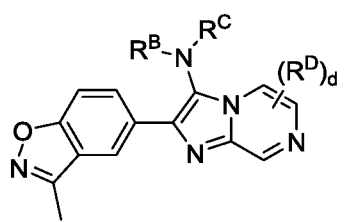
or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 or claim 2, wherein the compound is of the formula:



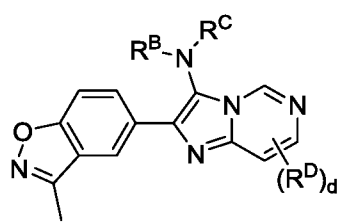
or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1 or claim 2, wherein the compound is of the formula:



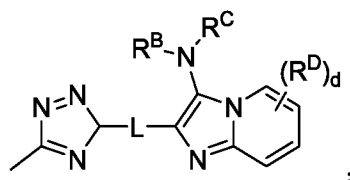
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1 or claim 2, wherein the compound is of the formula:



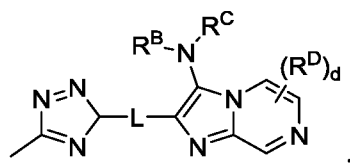
or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1 or claim 2, wherein the compound is of the formula:



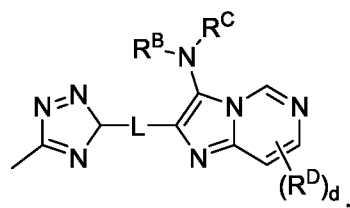
or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1 or claim 2, wherein the compound is of the formula:



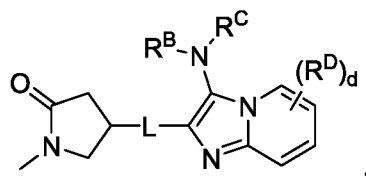
or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1 or claim 2, wherein the compound is of the formula:



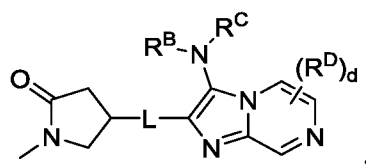
or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1 or claim 2, wherein the compound is of the formula:



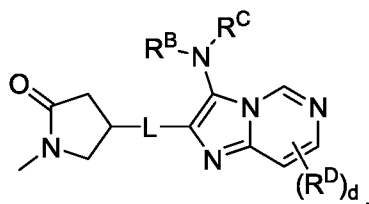
or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1 or claim 2, wherein the compound is of the formula:



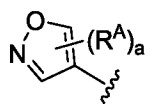
or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1 or claim 2, wherein the compound is of the formula:

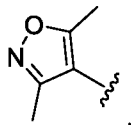


or a pharmaceutically acceptable salt thereof.

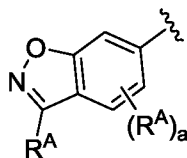
30. The compound of claim 1 or claim 2, wherein X^A is C(R^D).
31. The compound of claim 1 or claim 2, wherein X^A is CH.
32. The compound of claim 1 or claim 2, wherein X^A is N.
33. The compound of any one of claims 1, 2, or 30 to 32, wherein X^B is C(R^D).
34. The compound of any one of claims 1, 2, or 30 to 32, wherein X^B is CH.
35. The compound of any one of claims 1, 2, or 30 to 32, wherein X^B is N.
36. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



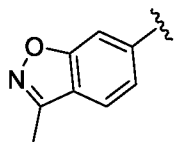
37. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



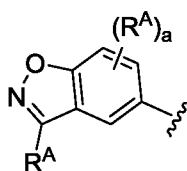
38. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



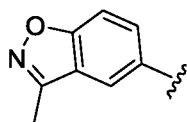
39. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



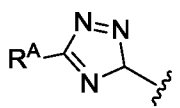
40. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



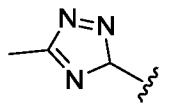
41. The compound any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



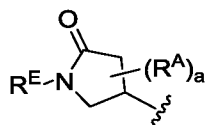
42. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



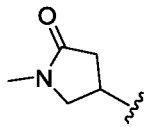
43. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



44. The compound of any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



45. The compound any one of claims 1, 2, or 30 to 35, wherein Ring A is of the formula:



46. The compound of any one of claims 1, 2, 30 to 36, 38, 40, 42 or 44, wherein at least one instance of R^A is substituted or unsubstituted alkyl or halogen.

47. The compound of any one of claims 1, 2, 30 to 36, 38, 40, 42 or 44, wherein at least one instance of R^A is substituted or unsubstituted C_{1-6} alkyl.

48. The compound of any one of claims 1, 2, 30 to 36, 38, 40, 42 or 44, wherein at least one instance of R^A is methyl.

49. The compound of any one of claims 1, 2, 30 to 36, 38, 40, 44 or 46 to 48, wherein a is 0.

50. The compound of any one of claims 1, 2, 30 to 36, 38, 40, 44 or 46 to 48, wherein a is 1.

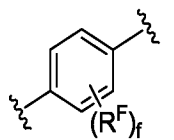
51. The compound of any one of claims 1, 2, 30 to 36, 38, 40, 44 or 46 to 48, wherein a is 2.

52. The compound of any one of claims 1, 2 or 30 to 51, wherein at least one instance of R^E is substituted or unsubstituted alkyl.

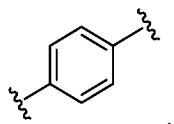
53. The compound of any one of claims 1, 2 or 30 to 51, wherein at least one instance of R^E is methyl.

54. The compound of any one of claims 1, 2 or 24 to 53, wherein L is a bond.

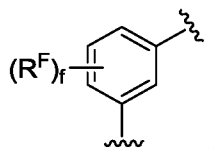
55. The compound of any one of claims 1, 2 or 24 to 53, wherein L is of the formula:



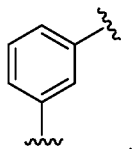
56. The compound of any one of claims 1, 2 or 24 to 53, wherein L is of the formula:



57. The compound of any one of claims 1, 2 or 24 to 53, wherein L is of the formula:



58. The compound of any one of claims 1, 2 or 24 to 53, wherein L is of the formula:



59. The compound of any one of claims 1, 2, 24 to 55 or 57, wherein at least one instance of R^F is halogen, substituted or unsubstituted alkyl, or $-OR^{F1}$.

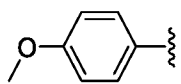
60. The compound of any one of claims 1, 2, 24 to 55 or 57, wherein f is 0.

61. The compound of any one of claims 1 to 60, wherein R^B is substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted aryl, $-C(=O)R^{B1}$, $-C(=O)OR^{B1}$, or $-C(=O)N(R^{B1})_2$.

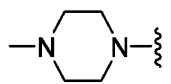
62. The compound of any one of claims 1 to 60, wherein R^B is substituted or unsubstituted C_{1-6} alkyl.

63. The compound of any one of claims 1 to 60, wherein R^B is *t*-Bu.

64. The compound of any one of claims 1 to 60, wherein R^B is benzyl.
65. The compound of any one of claims 1 to 60, wherein R^B is substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl.
66. The compound of any one of claims 1 to 60, wherein R^B is cyclohexyl.
67. The compound of any one of claims 1 to 60, wherein R^B is substituted or unsubstituted phenyl.
68. The compound of any one of claims 1 to 60, wherein R^B is of the formula:

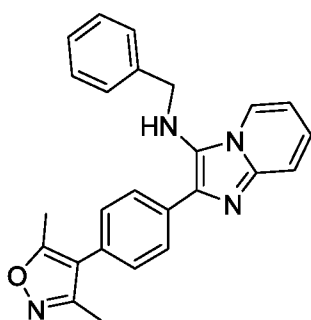


69. The compound of any one of claims 1 to 60, wherein R^B is $-C(=O)R^{B1}$.
70. The compound of any one of claims 1 to 60, wherein R^B and R^C are joined to form a substituted or unsubstituted heterocyclic ring.
71. The compound of any one of claims 1 to 60, wherein R^B and R^C are joined to form a substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring are independently selected from the group consisting of nitrogen, oxygen, and sulfur.
72. The compound of any one of claims 1 to 60, wherein R^B and R^C are joined to form a heterocyclic ring of the formula:

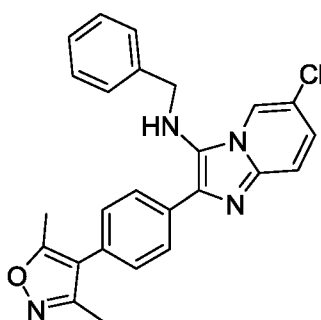


73. The compound of any one of claims 1 to 72, wherein R^C is hydrogen.
74. The compound of any one of claims 1 to 72, wherein R^C is substituted or unsubstituted alkyl.

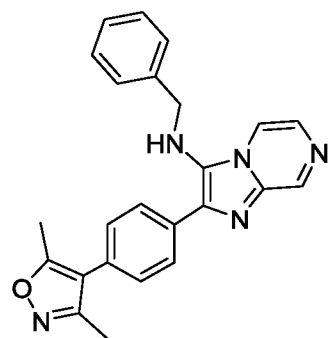
75. The compound of any one of claims 1 to 72, wherein R^C is methyl.
76. The compound of any one of claims 1 to 75, wherein at least one instance of R^D is halogen, substituted or unsubstituted alkyl, or $-OR^{D1}$.
77. The compound of any one of claims 1 to 75, wherein at least one instance of R^D is Cl or $-OMe$.
78. The compound of any one of claims 1 to 75, wherein all instances of R^D are hydrogen.
79. The compound of any one of claims 1 to 78, wherein d is 0.
80. The compound of any one of claims 1 to 78, wherein d is 1.
81. The compound of claim 1, wherein the compound is of the formula:



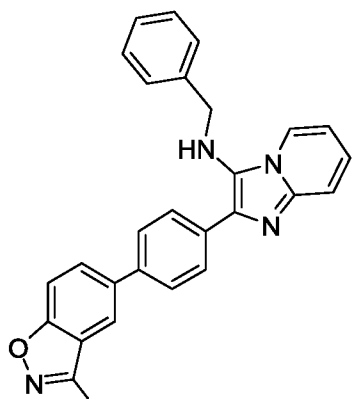
(UMB11)



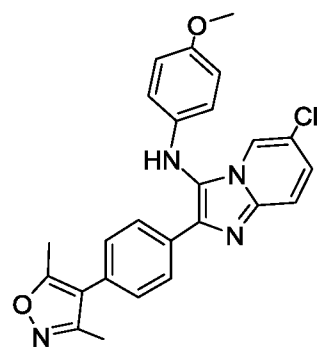
(UMB20)



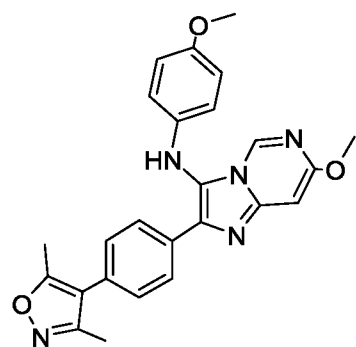
(UMB21)



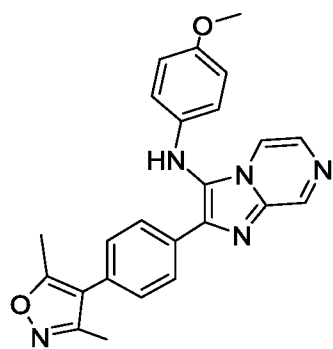
(UMB22)



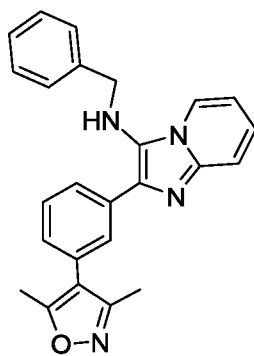
(UMB23)



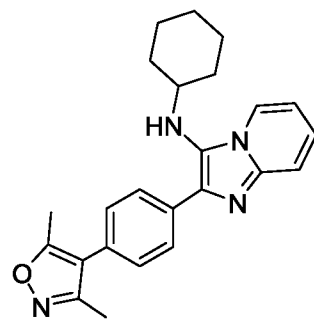
(UMB24)



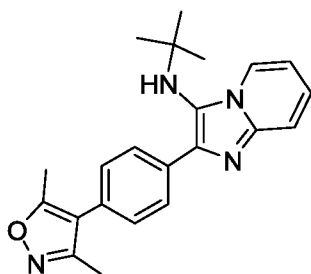
(UMB25)



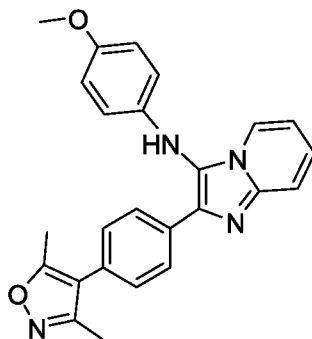
(UMB26)



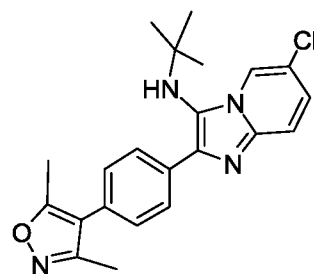
(UMB28)



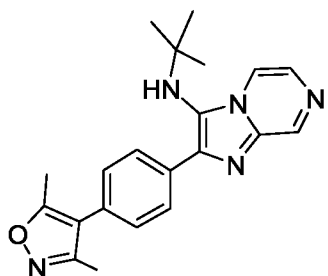
(UMB29)



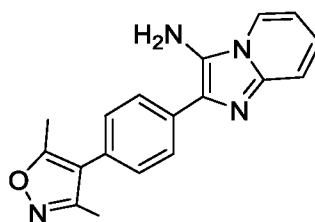
(UMB30)



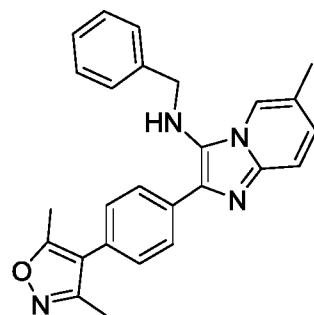
(UMB31)



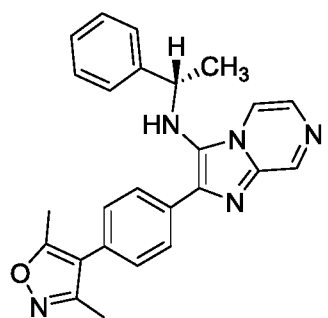
(UMB32)



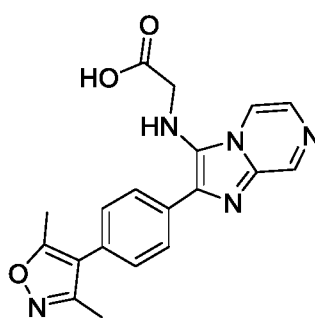
(12a)



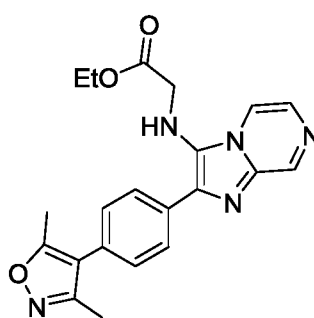
(13a)



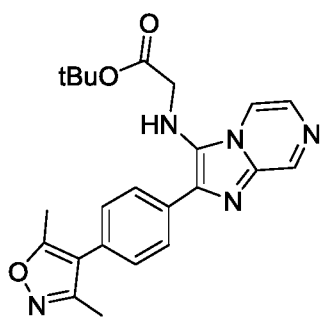
(21a)



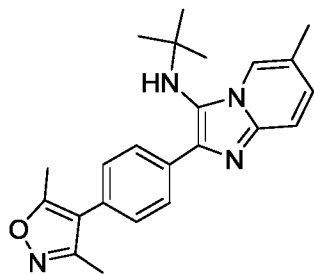
(22a)



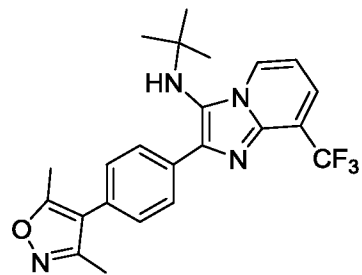
(23a)



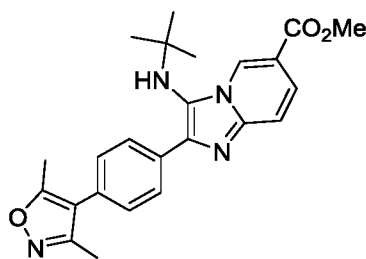
(24a)



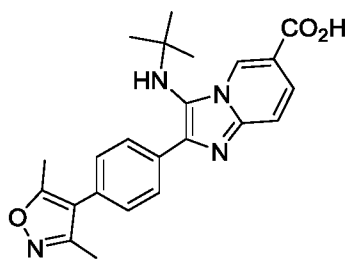
(27a)



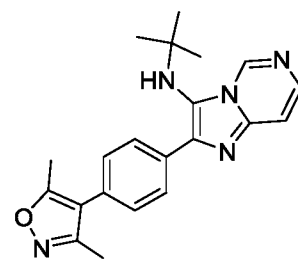
(28a)



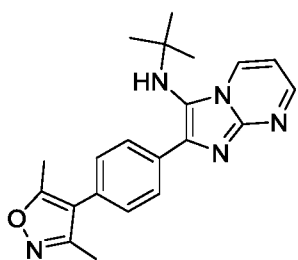
(29a)



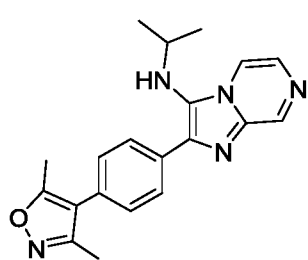
(30a)



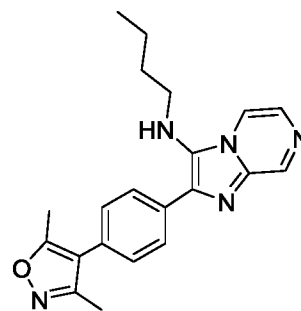
(UMB56)



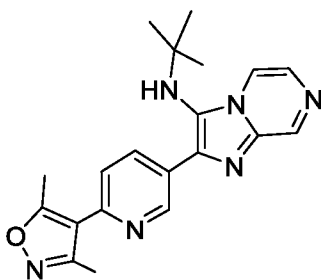
(33a)



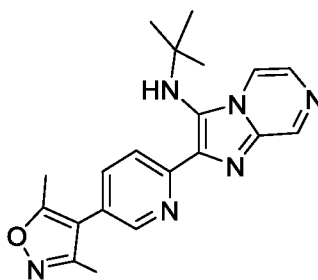
(UMB57)



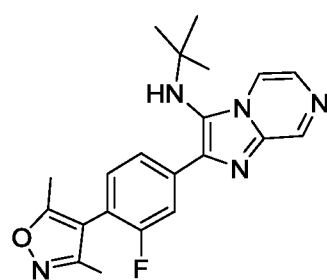
(35a)



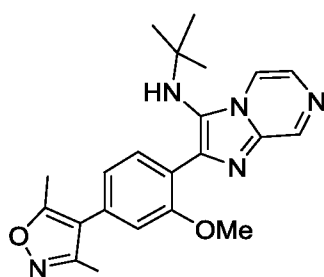
(UMB53)



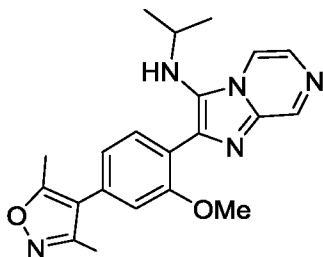
(UMB54)



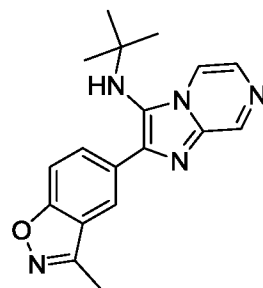
(UMB55)



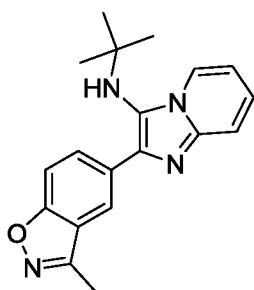
(39a)



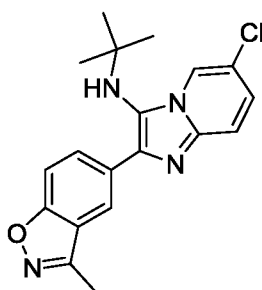
(40a)



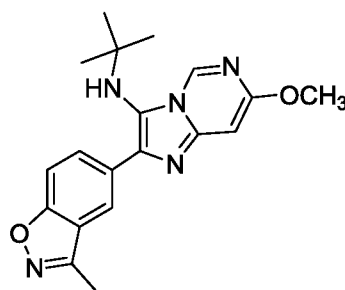
(UMB-33)



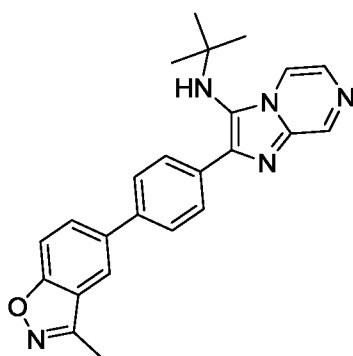
(UMB-34)



(UMB-35)



(UMB-36)



(UMB-42)

or a pharmaceutically acceptable salt thereof.

82. A pharmaceutical composition comprising a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

83. The pharmaceutical composition of claim 82, wherein the pharmaceutical composition is useful in treating a disease associated with a bromodomain-containing protein in a subject in need thereof and comprises a therapeutically effective amount of the compound or pharmaceutically acceptable salt.

84. A method of treating a disease associated with a bromodomain-containing protein in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83.

85. A method of reducing the risk of having a disease associated with a bromodomain-containing protein in a subject in need thereof, the method comprising:

administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83.

86. A method of screening a library of compounds, and pharmaceutically acceptable salts thereof, to identify a compound, or a pharmaceutically acceptable salt thereof, that is useful in the treatment of a disease associated with a bromodomain-containing protein in a subject, the method comprising:

providing at least two different compounds of any one of claims 1 to 81, or pharmaceutically acceptable salts thereof; and

performing at least one assay using the different compounds, or pharmaceutically acceptable salts thereof.

87. A method of inhibiting the activity of a bromodomain-containing protein in a subject or cell, the method comprising:

administering to the subject or contacting the cell with a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83.

88. A method of inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell, the method comprising:

administering to the subject or contacting the cell with a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83.

89. A method of modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell, the method comprising:

administering to the subject or contacting the cell with a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83.

90. A kit comprising:

a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83; and
instructions for using the kit.

91. The kit of claim 90, wherein the kit is useful in treating a disease associated with a bromodomain-containing protein in a subject in need thereof and comprises a therapeutically effective amount of the compound, pharmaceutically acceptable salt, or pharmaceutical composition.

92. The pharmaceutical composition of claim 83, the method of any one of claims 84 to 89, or the kit of claim 91, wherein the bromodomain-containing protein is a bromo and extra terminal protein (BET).

93. The pharmaceutical composition of claim 83, the method of any one of claims 84 to 89, or the kit of claim 91, wherein the bromodomain-containing protein is bromodomain-containing protein 2 (BRD2), bromodomain-containing protein 3 (BRD3), or bromodomain-containing protein 4 (BRD4).

94. The pharmaceutical composition of claim 83, the method of any one of claims 84 to 89, or the kit of claim 91, wherein the bromodomain-containing protein is a TBP (TATA box binding protein)-associated factor protein (TAF).

95. The pharmaceutical composition of claim 83, the method of any one of claims 84 to 89, or the kit of claim 91, wherein the bromodomain-containing protein is TAF1 or TAF1L.

96. The pharmaceutical composition of claim 83, the method of any one of claims 84 to 89, or the kit of claim 91, wherein the bromodomain-containing protein is CREB-binding protein (CBP).

97. The pharmaceutical composition of claim 83, the method of any one of claims 84 to 89, or the kit of claim 91, wherein the bromodomain-containing protein is E1A binding protein p300 (EP300).

98. The pharmaceutical composition of any one of claims 83 or 92 to 97, the method of any one of claims 84 to 86 or 92 to 97, or the kit of any one of claims 91 to 97, wherein the disease associated with a bromodomain-containing protein is a proliferative disease.

99. The pharmaceutical composition of any one of claims 83 or 92 to 97, the method of any one of claims 84 to 86 or 92 to 97, or the kit of any one of claims 91 to 97, wherein the disease associated with a bromodomain-containing protein is cancer.

100. The pharmaceutical composition of any one of claims 83 or 92 to 97, the method of any one of claims 84 to 86 or 92 to 97, or the kit of any one of claims 91 to 97, wherein the disease associated with a bromodomain-containing protein is lung cancer, multiple myeloma, neuroblastoma, colon cancer, or ovary cancer.

101. The pharmaceutical composition of any one of claims 83 or 92 to 97, the method of any one of claims 84 to 86 or 92 to 97, or the kit of any one of claims 91 to 97, wherein the disease associated with a bromodomain-containing protein is a benign neoplasm.

102. The pharmaceutical composition of any one of claims 83 or 92 to 97, the method of any one of claims 84 to 86 or 92 to 97, or the kit of any one of claims 91 to 97, wherein the disease associated with a bromodomain-containing protein is pathological angiogenesis.

103. The pharmaceutical composition of any one of claims 83 or 92 to 97, the method of any one of claims 83 to 86 or 92 to 97, or the kit of any one of claims 91 to 97, wherein the disease associated with a bromodomain-containing protein is an inflammatory disease.

104. The pharmaceutical composition of any one of claims 83 or 92 to 97, the method of any one of claims 83 to 86 or 92 to 97, or the kit of any one of claims 91 to 97, wherein the disease associated with a bromodomain-containing protein is an autoimmune disease.

105. The pharmaceutical composition of any one of claims 83 or 92 to 101, the method of any one of claims 84 to 89 or 92 to 101, or the kit of any one of claims 91 to 101, wherein the subject is a human.

106. Use of a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83 in the manufacture of a medicament for treating a disease associated with a bromodomain-containing protein.

107. Use of a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83 in the manufacture of a medicament for reducing the risk of having a disease associated with a bromodomain-containing protein.

108. Use of a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83 in the manufacture of a medicament for inhibiting the activity of a bromodomain-containing protein in a subject or cell.

109. Use of a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83 in the manufacture of a medicament for inhibiting the binding of a bromodomain of a bromodomain-containing protein to an acetyl-lysine residue of a histone in a subject or cell.

110. Use of a compound of any one of claims 1 to 81, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 82 or claim 83 in the manufacture of a medicament for modulating the transcription of a gene that is regulated by a bromodomain-containing protein in a subject or cell.

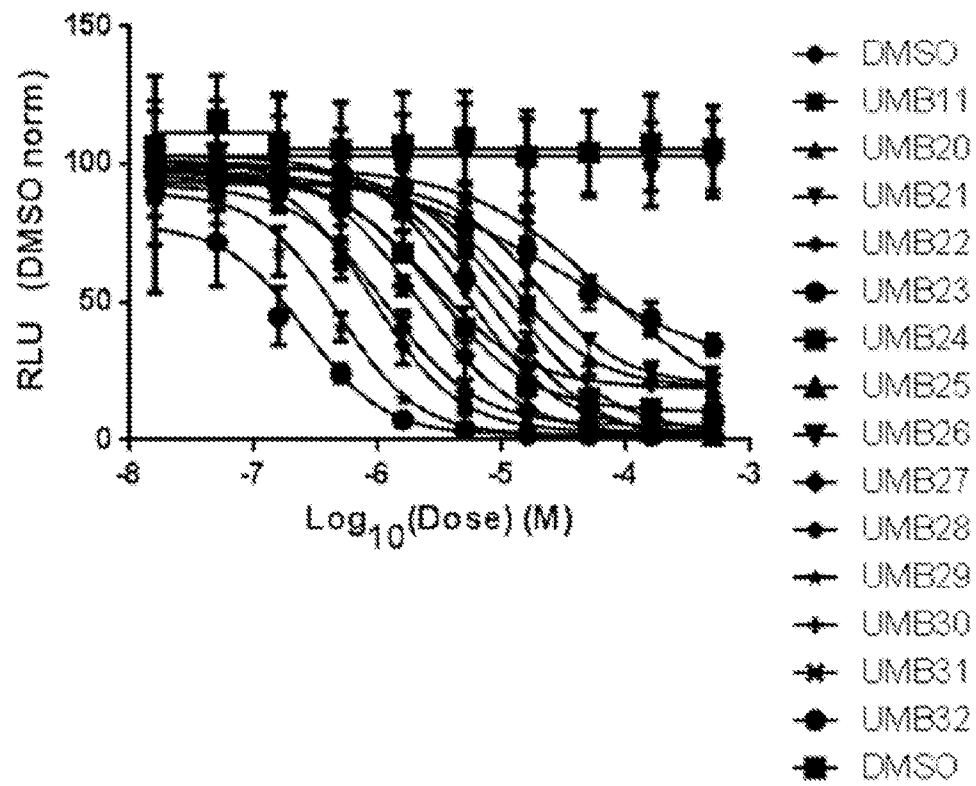
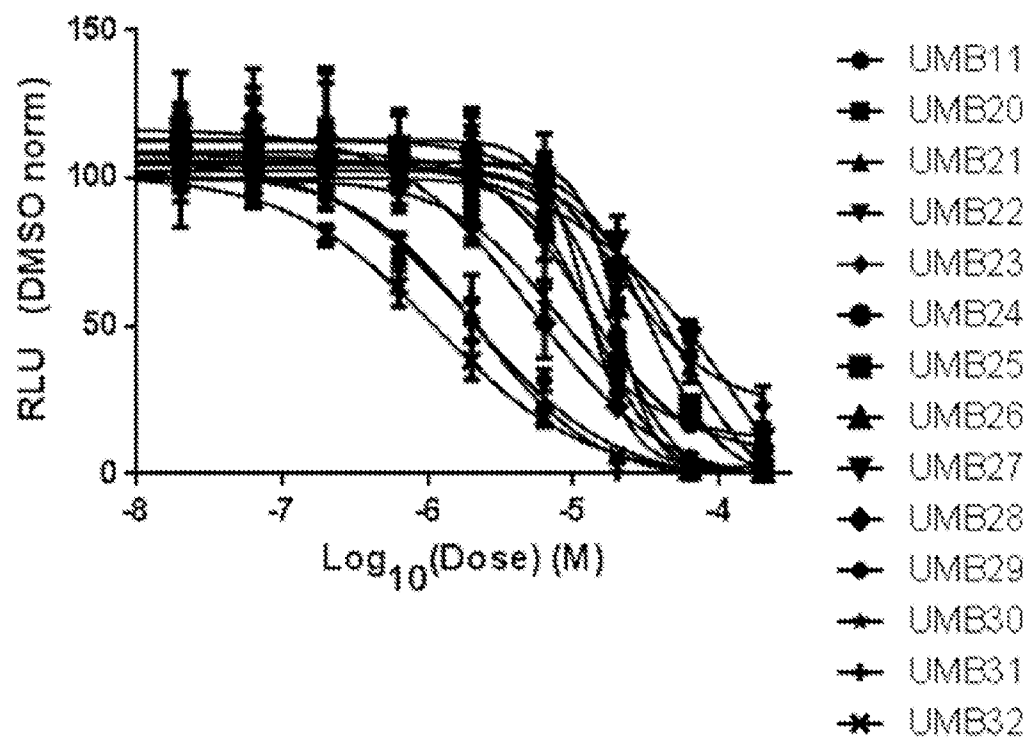


Figure 1

**Figure 2**

UMB32

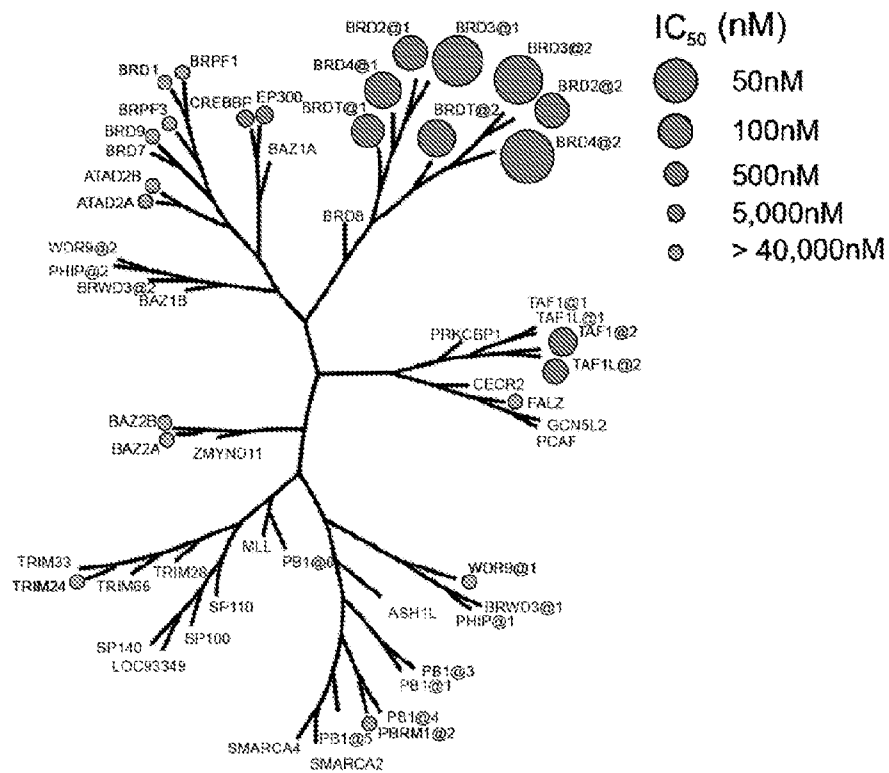


Figure 3A

UMB11

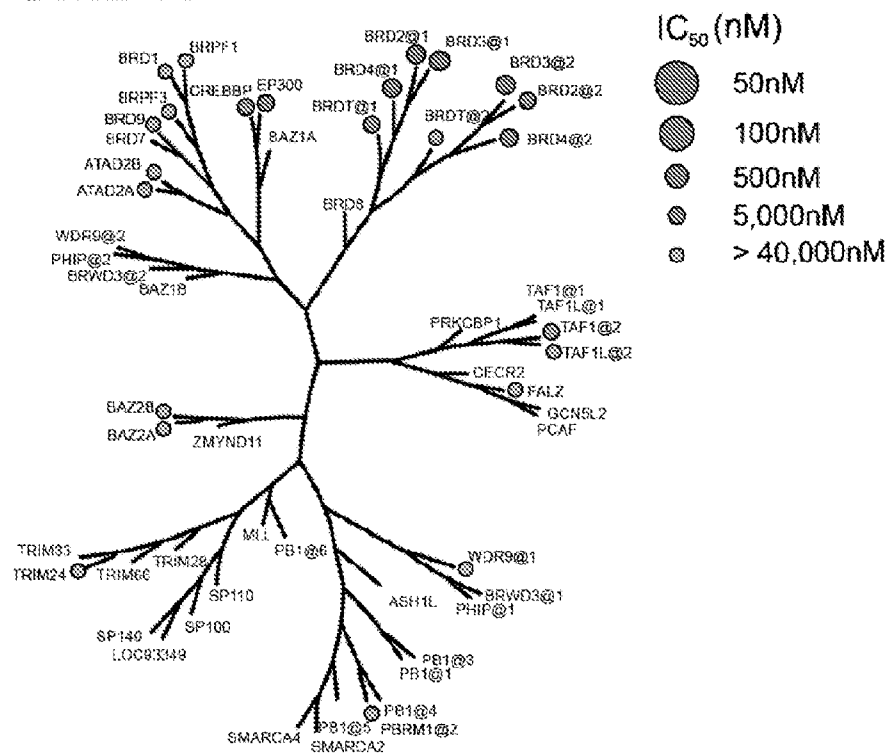
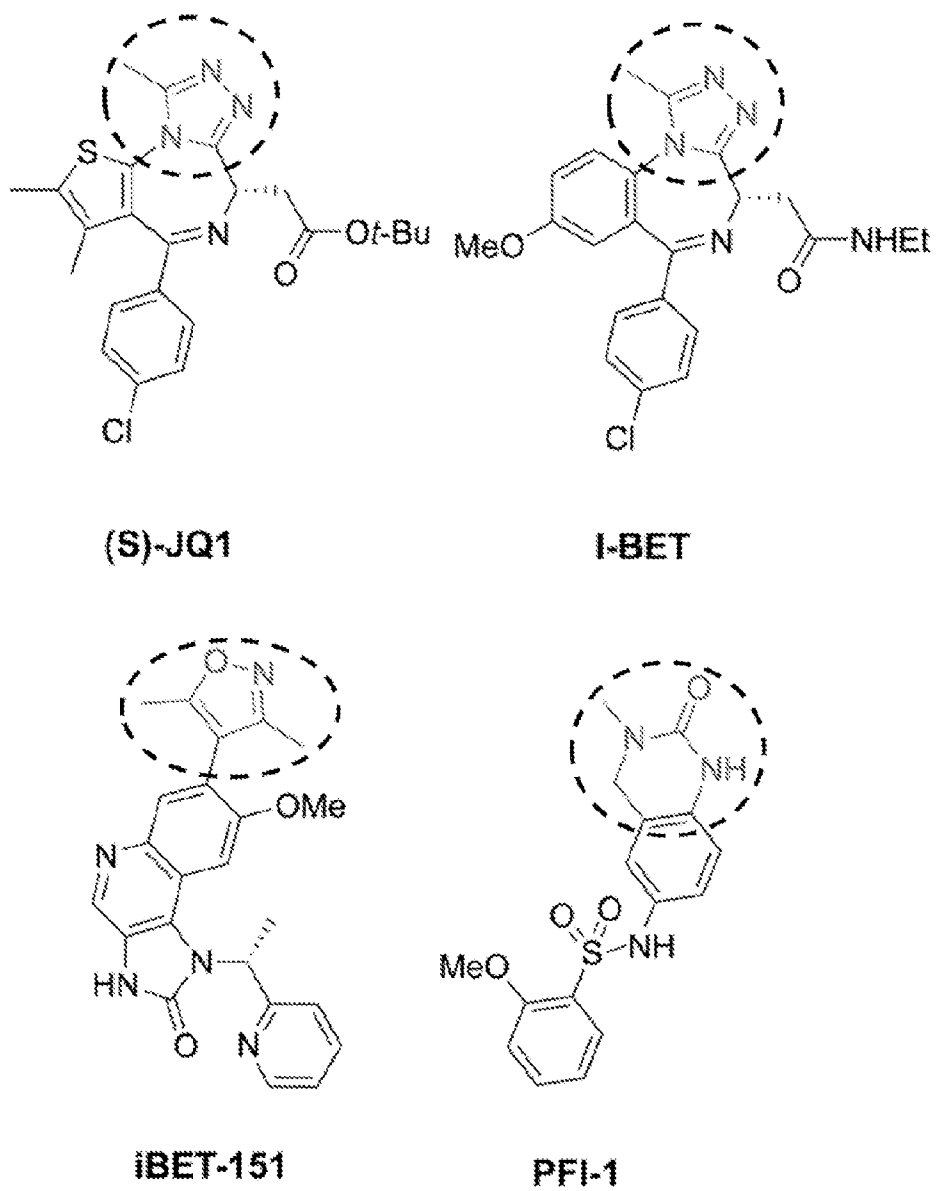
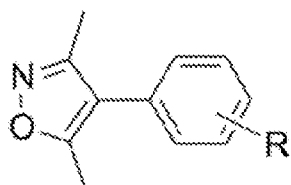
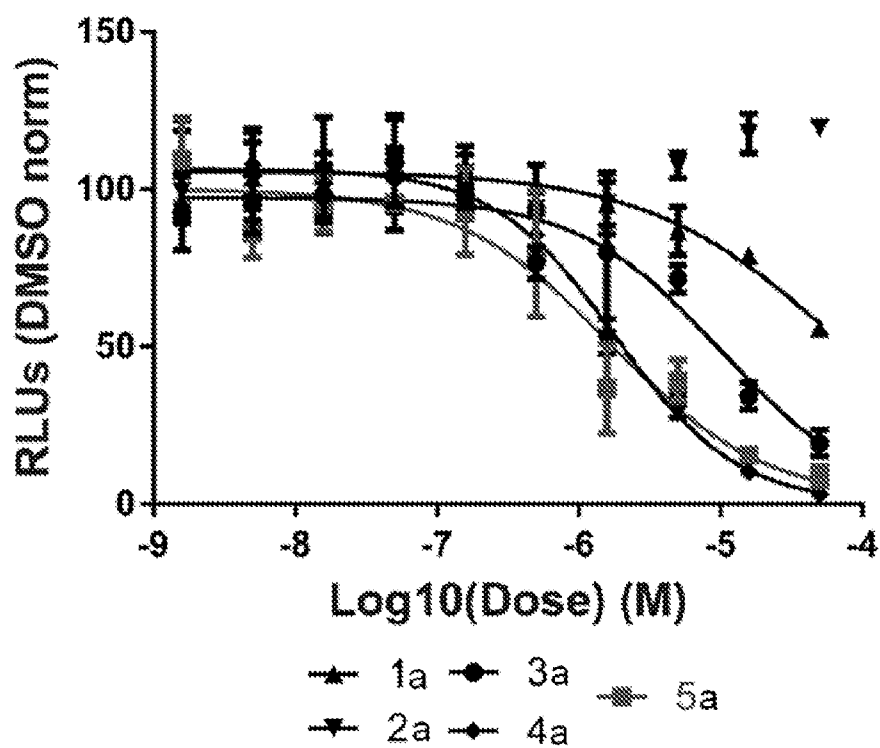


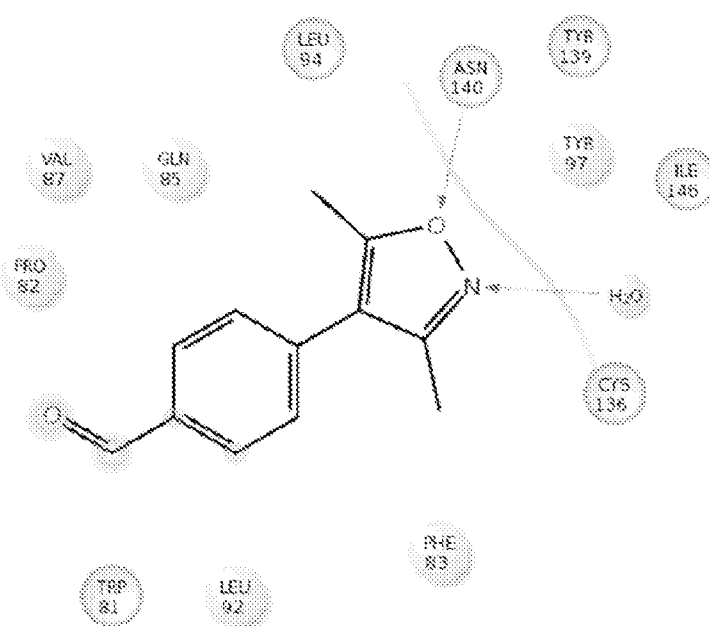
Figure 3B

**Figure 4**



Compound	R	BRD4--IC ₅₀ (μM)
1a	H	>100
2a	2-CHO	>100
3a	3-CHO	79.4
4a	4-CHO	1.89
5a	4-Ac	16.1

Figure 5

**Figure 6A****Figure 6B**

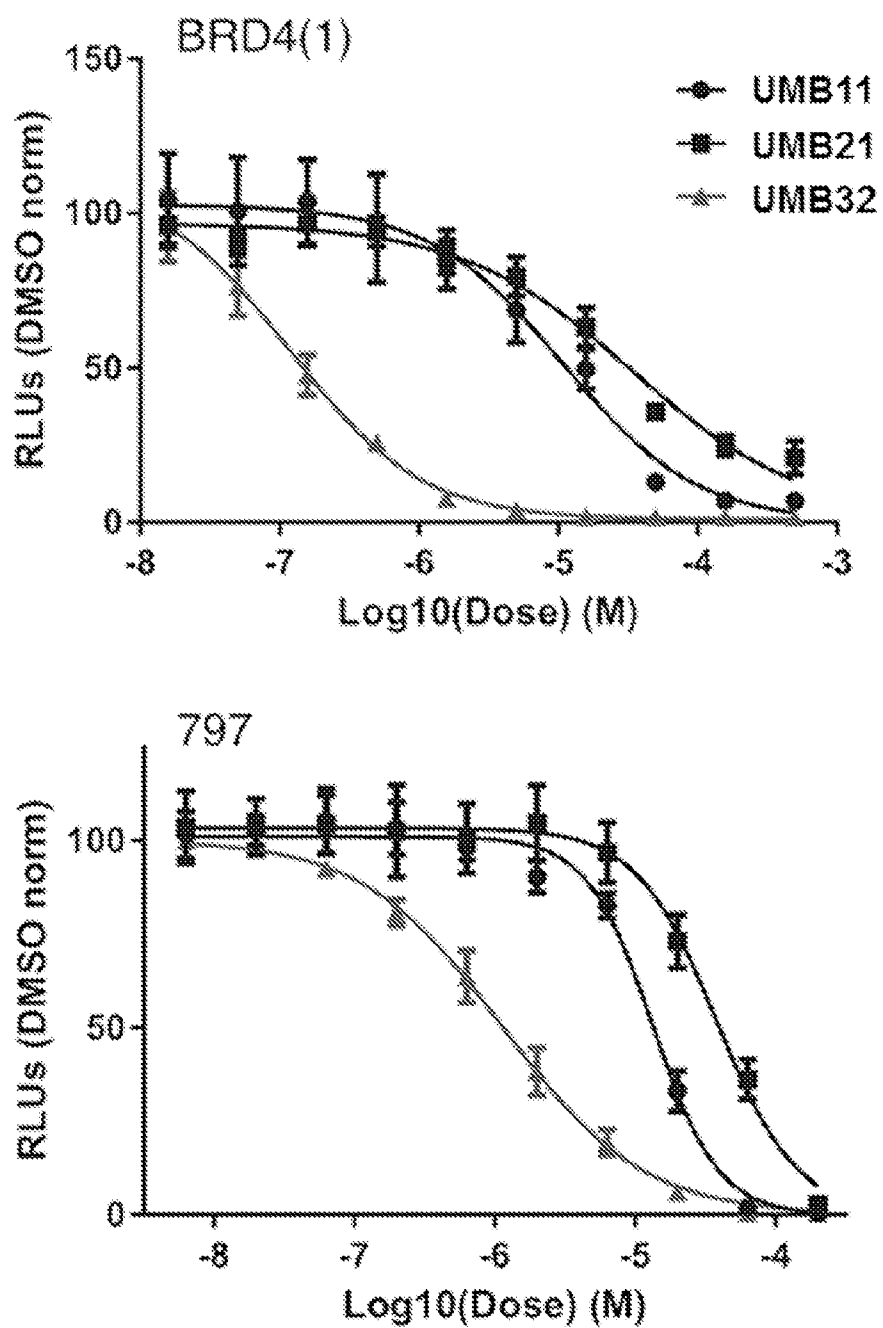


Figure 7

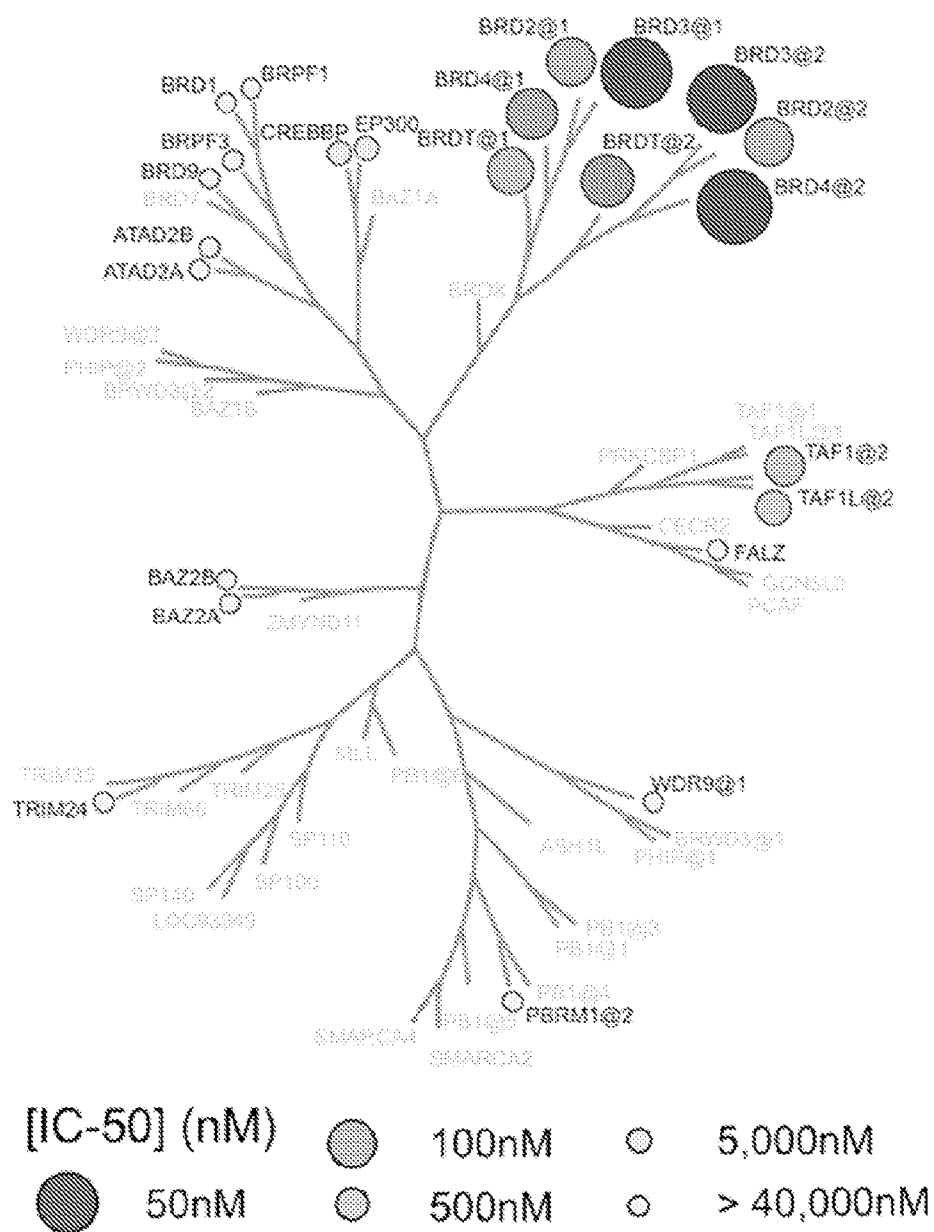


Figure 8

10/15

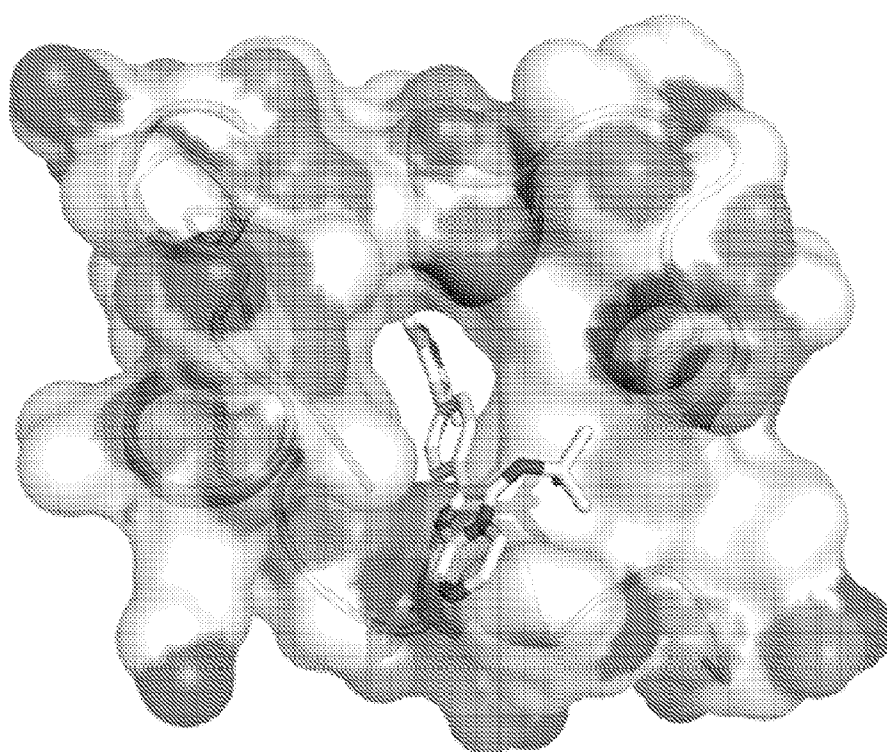
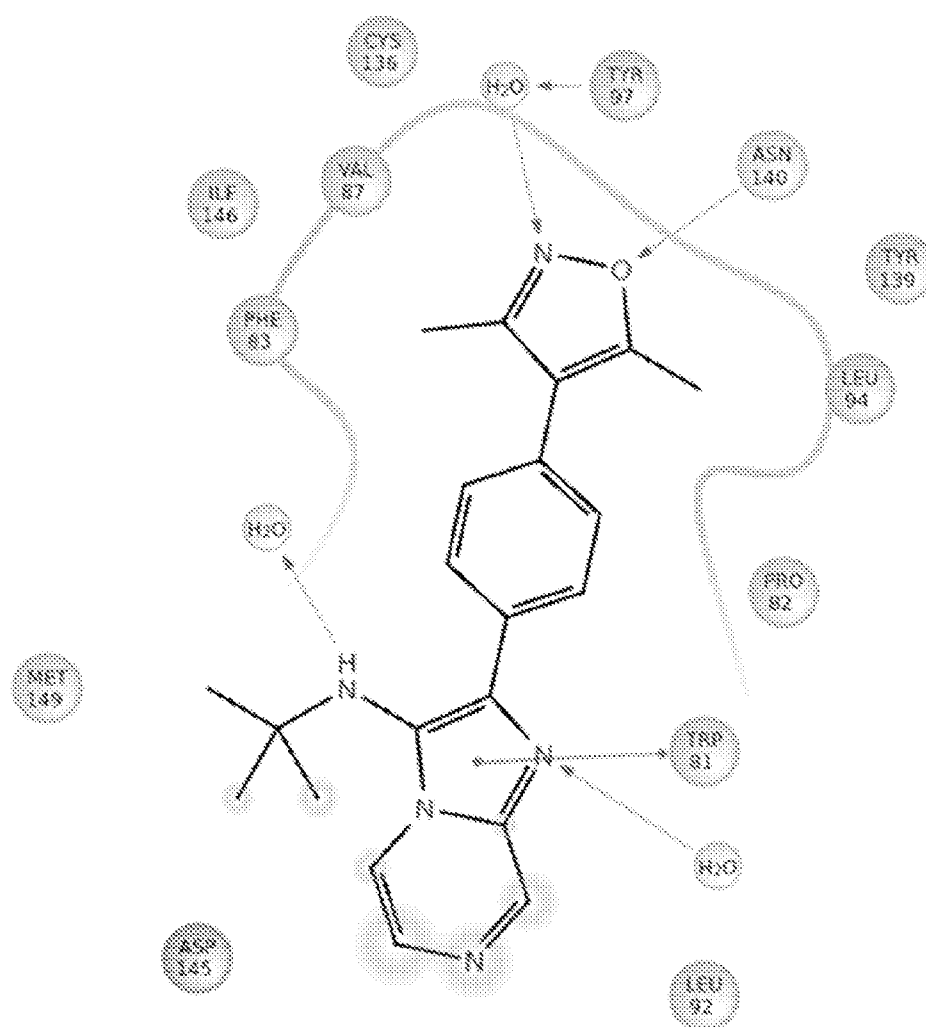
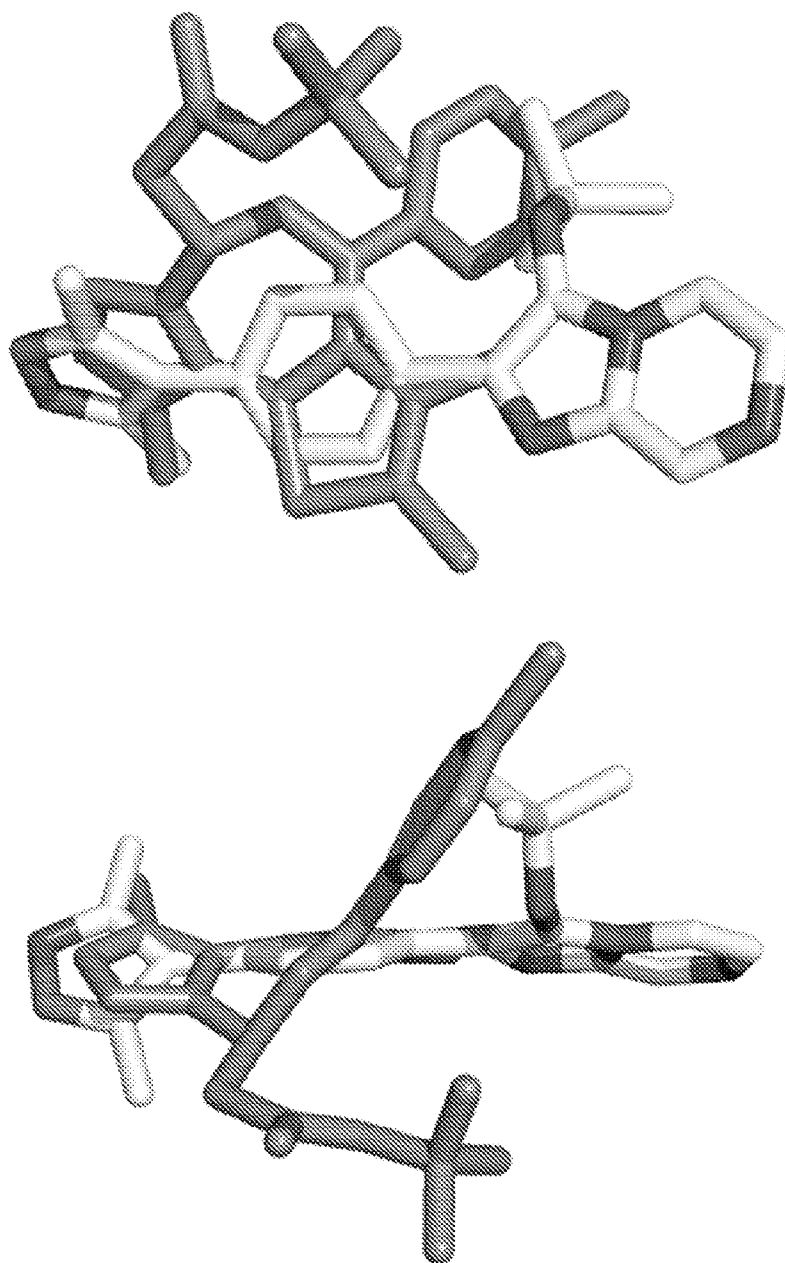
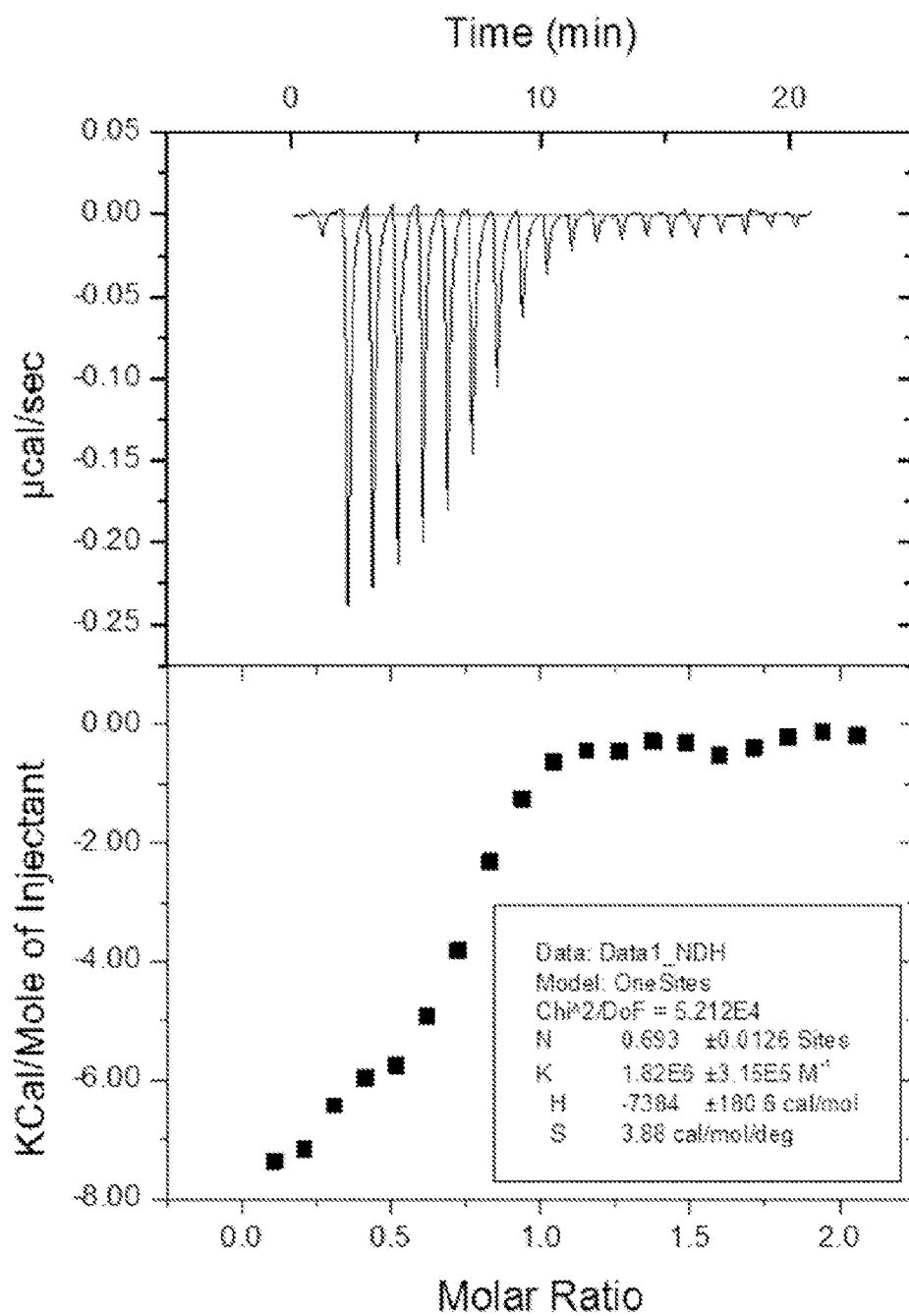
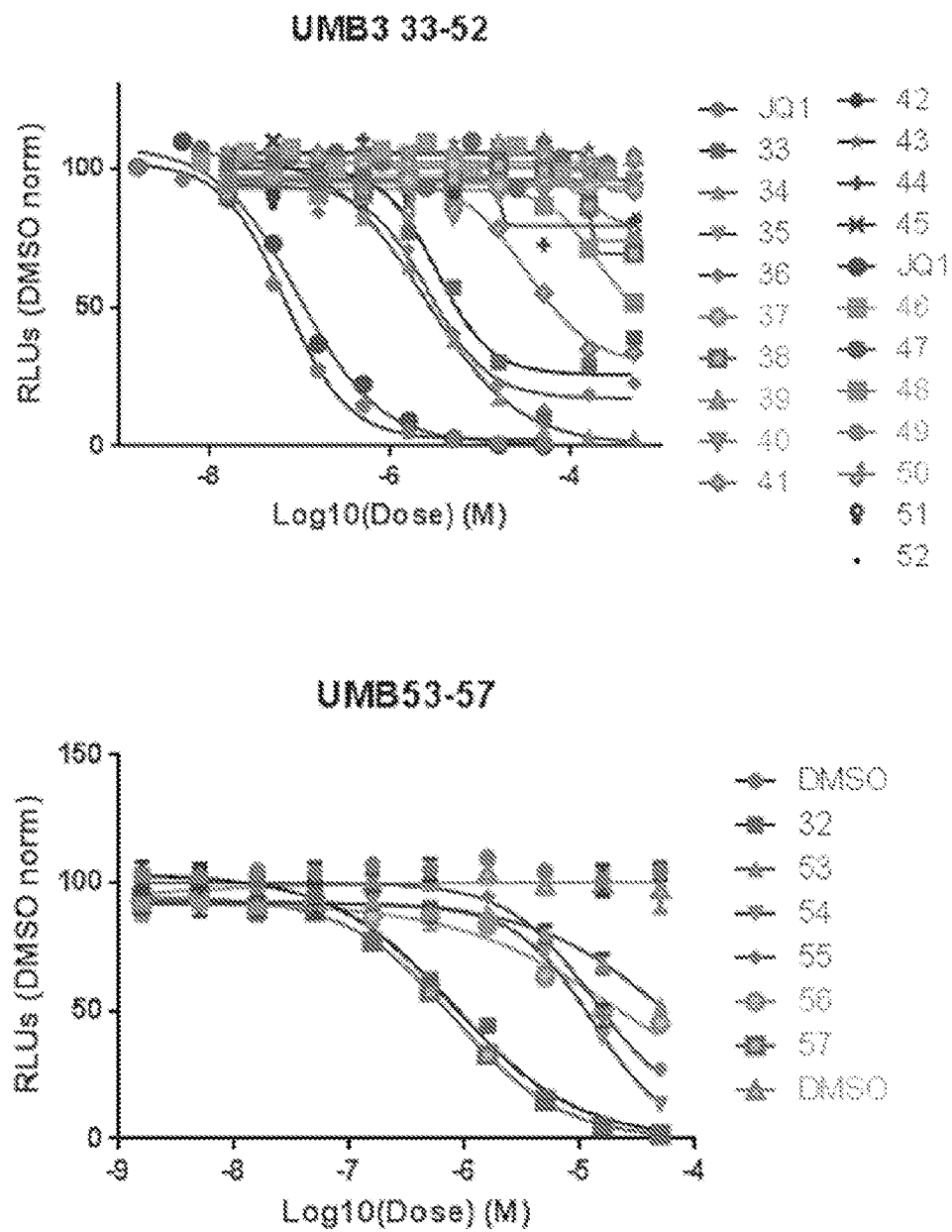


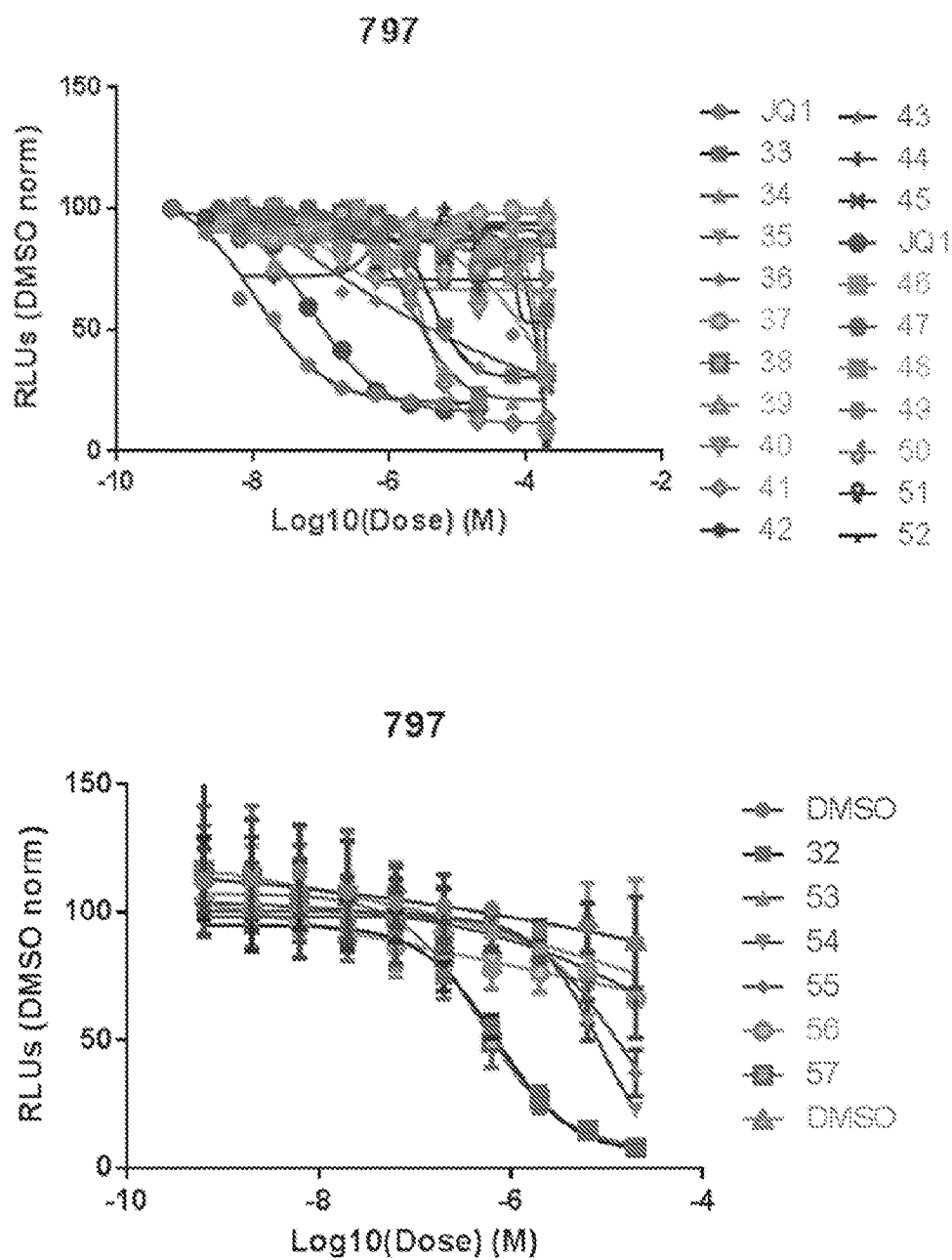
Figure 9

**Figure 10**

**Figure 11**

**Figure 12**

**Figure 13**

**Figure 14**