(51) International Patent Classification:
C07D 513/04 (2006.01) A61P 35/00 (2006.01)
A61K 31/5377 (2006.01)

(21) International Application Number:
PCT/US2010/055042

(22) International Filing Date:
2 November 2010 (02.11.2010)

(25) Filing Language:
English

(26) Publication Language:
English

(30) Priority Data:
61/258,526 5 November 2009 (05.1.2009) US


(72) Inventor; and
(75) Inventor/Applicant (for US only): BHAGWAT, Shripad, S. [US/US]; 5015 Ashley Falls Court, San Diego, CA 92130 (US).


Published:
with international search report (Art. 21(3))

(54) Title: ISOTOPICALLY ENRICHED OR FLUORINATED IMIDAZO[2,1-B][1,3]BENZOTHIAZOLES

(57) Abstract: Provided herein are isotopically enriched or fluorinated imidazo[2,1-b][1,3]benzothiazoles, for example, of Formula (I). Also provided are pharmaceutical compositions comprising such compounds, and methods of their use for the treatment of a proliferative disease.
ISOTOPICALLY ENRICHED OR FLUORINATED IMIDAZO[2,1-b][1,3]BENZOTHIAZOLES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/258,526, filed November 5, 2009, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are isotopically enriched and/or fluorinated imidazo[2,1-b][1,3]benzothiazoles. Also provided are pharmaceutical compositions comprising such compounds, and methods of their use for the treatment of a proliferative disease.

BACKGROUND

[0003] Protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine, and/or threonine residues of proteins. Protein kinases, in particular, the receptor protein tyrosine kinases (RPTKs), act primarily as growth factor receptors and play a central role in signal transduction pathways regulating cellular functions, such as cell cycle, cell growth, cell differentiation, and cell death. Aberrant or excessive activity or the disregulation of activity of RPTKs has been observed in many disease states, including benign and malignant proliferative disorders as well as inflammatory disorders and immune system disorders that result from inappropriate activation of the immune system to cause, for example, autoimmune diseases.

[0004] Additionally, inhibitors of certain kinases may have utility in the treatment of diseases when the kinases are not misregulated, but are nonetheless essential for maintenance of the disease state. In such cases, inhibition of the kinase activity would act either as a cure or palliative for these diseases. For example, many viruses, such as human papilloma virus, disrupt the cell cycle and drive cells into the S-phase of the cell cycle (Vousden, FASEBJ. 1993, 7, 872-879). Preventing cells from entering DNA synthesis after viral infection by inhibition of essential S-phase initiating activities via kinase inhibition may disrupt the virus life cycle by preventing virus replication. This same principle may be used to protect normal cell cycles.

In view of the large number of protein kinase inhibitors and the multitude of PK-mediated proliferative, inflammatory, and immune function diseases, there is an ever-existing need to provide compounds that are useful as PK inhibitors, and thus useful for treating PK-mediated diseases.

SUMMARY OF THE DISCLOSURE

Provided herein is a compound of Formula I:

![Diagram](image)

(I)

or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof;

wherein:

R₁, R₂, and R₃ are each independently hydrogen, deuterium, fluoro, or methyl, where the methyl is optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro; or R₂ and R₃ together with the carbon to which they are attached form C₃₋₇ cycloalkylene, optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro;

R⁴, R⁷, R⁸, R⁹, R¹₀, R¹¹, R¹₂, R¹₃, R¹₄, R¹₅, R¹₆, R¹₇, R¹₈, R², R³, R⁴, R⁵, R⁶, and R⁷ are each independently hydrogen, deuterium, or fluoro;

R⁵ and R⁶ are each independently hydrogen or deuterium; and

X is O and Y is N; or X is N and Y is O;

with the proviso that at least one of R¹, R², and R³ is deuterium, fluoro, or methyl substituted with at least one deuterium or fluoro; or at least one of R⁴, R⁷, R⁸, R⁹, R¹₀, R¹¹, R¹₂, R¹₃, R¹₄, R¹₅, R¹₆, R¹₇, R¹₈, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ is deuterium or fluoro; or at least one of R⁵ and R⁶ is deuterium.
Also provided herein are pharmaceutical compositions comprising a compound provided herein, e.g., a compound of Formula I, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; in combination with one or more pharmaceutically acceptable excipients or carriers.

Further provided herein is a method for treating a proliferative disease in a subject, which comprises administering to the subject a therapeutically effective amount of a compound provided herein, e.g., a compound of Formula I, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In one embodiment, the proliferative disease is cancer. In another embodiment, the proliferative disease is a solid tumor. In yet another embodiment, the proliferative disease is a blood-borne tumor. In yet another embodiment, the proliferative disease is a leukemia. In one embodiment, the leukemia is acute myeloid leukemia. In another embodiment, the leukemia is acute lymphocytic leukemia. In still another embodiment, the leukemia is a drug resistant leukemia.

In one embodiment, the drug resistant leukemia is drug resistant acute myeloid leukemia. In another embodiment, the drug resistant acute myeloid leukemia has an activating mutant FLT3. In another embodiment, the drug resistant acute myeloid leukemia is Philadelphia positive.

In another embodiment, the drug resistant leukemia is drug resistant acute lymphocytic leukemia. In one embodiment, the drug resistant acute myeloid leukemia has an activating mutant FLT3. In another embodiment, the drug resistant acute myeloid leukemia is Philadelphia positive.

Each method provided herein may further comprise administering a second therapeutic agent. In one embodiment, the second therapeutic agent is an anticancer agent. The second therapeutic agent is, in one embodiment, a protein kinase inhibitor; in another embodiment, a tyrosine kinase inhibitor; and in yet another embodiment, a second FLT3 kinase inhibitor.
DETAILED DESCRIPTION

[0013] Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0014] The term "subject" refers to an animal, including, but not limited to, a primate (e.g., human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in one embodiment, a human.

[0015] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[0016] The terms "prevent," "preventing," and "prevention" are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or its attendant symptoms; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject's risk of acquiring a disorder, disease, or condition.

[0017] The term "therapeutically effective amount" are meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (e.g., a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0018] The term "IC50" or "EC50" refers an amount, concentration, or dosage of a compound that is required for 50% inhibition of a maximal response in an assay that measures such response.
The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, Remington: The Science and Practice of Pharmacy, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; Handbook of Pharmaceutical Excipients, 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; Handbook of Pharmaceutical Additives, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; Pharmaceutical Preformulation and Formulation, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term "cycloalkylene" refers to a cyclic divalent hydrocarbon radical, which may be optionally substituted with one or more substituents Q as described herein. In one embodiment, cycloalkyl groups may be saturated or unsaturated but non-aromatic, and/or bridged, and/or non-bridged, and/or fused bicyclic groups. In certain embodiments, the cycloalkylene has from 3 to 20 (C3.20), from 3 to 15 (C3-15), from 3 to 10 (C3-10), or from 3 to 7 (C3.7) carbon atoms. Examples of cycloalkylene groups include, but are not limited to, cyclopropylene (e.g., 1,1-cyclopropylene and 1,2-cyclopropylene), cyclobutylene (e.g., 1,1-cyclobutylene, 1,2-cyclobutylene, or 1,3-cyclobutylene), cyclopentylene (e.g., 1,1-cyclopentylene, 1,2-cyclopentylene, or 1,3-cyclopentylene), cyclohexylene (e.g., 1,1-cyclohexylene, 1,2-cyclohexylene, 1,3-cyclohexylene, or 1,4-cyclohexylene), cycloheptylene (e.g., 1,1-cycloheptylene, 1,2-cycloheptylene, 1,3-cycloheptylene, or 1,4-cycloheptylene), decalinylene, and adamantylene.

The term "optionally substituted" is intended to mean that a group or substituent, such as a cycloalkylene group, may be substituted with one or more substituents Q, each of which is independently selected from, e.g., (a) C 1-6 alkyl, C 2-6 alkenyl, C 2-6 alkynyl, C 3-7 cycloalkyl, C 6-14 aryl, C 7-is aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q²; and (b) halo, cyano (-CN), nitro (-NO₂), -C(O)R, -C(O)OR, and/or...
-C(O)NR \textsuperscript{b}R\textsuperscript{c}, -C(NR \textsuperscript{a})NR \textsuperscript{b}R\textsuperscript{c}, -OR, -OC(O)R \textsuperscript{a}, -OC(O)OR \textsuperscript{a}, -OC(O)NR \textsuperscript{b}R\textsuperscript{c}, -OC(=NR \textsuperscript{a})NR \textsuperscript{b}R\textsuperscript{c}, -OS(O)R \textsuperscript{a}, -OS(O)NR \textsuperscript{b}R\textsuperscript{c}, -OS(O)\textsuperscript{2}NR \textsuperscript{b}R\textsuperscript{c}, -NR \textsuperscript{b}R\textsuperscript{c}, -NR \textsuperscript{c}(=NR \textsuperscript{d})NR \textsuperscript{b}R\textsuperscript{c}, -NR \textsuperscript{a}(S)R\textsuperscript{d}, -NR \textsuperscript{a}S(O)\textsuperscript{2}R\textsuperscript{d}, -NR \textsuperscript{a}S(O)NR \textsuperscript{b}R\textsuperscript{c}, -NR \textsuperscript{a}S(O)\textsuperscript{2}NR \textsuperscript{b}R\textsuperscript{c}, -SR \textsuperscript{a}, -S(O)R \textsuperscript{a}, -S(O)\textsuperscript{2}R\textsuperscript{a}, -S(O)NR \textsuperscript{b}R\textsuperscript{c}, -S(O)\textsuperscript{2}NR \textsuperscript{b}R\textsuperscript{c}, wherein each R\textsuperscript{a}, R\textsuperscript{b}, R\textsuperscript{c}, and R\textsuperscript{d} is independently (i) hydrogen; (ii) C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, c\textsubscript{3-7} cycloalkyl, C\textsubscript{6-14} aryl, C\textsubscript{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q\textsuperscript{a}; or (iii) R\textsuperscript{b} and R\textsuperscript{c} together with the N atom to which they are attached form heteroaryl or heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q\textsuperscript{a}. As used herein, all groups that can be substituted are "optionally substituted," unless otherwise specified.

In one embodiment, each Q\textsuperscript{a} is independently selected from the group consisting of (a) cyano, halo, and nitro; and (b) C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{3-7} cycloalkyl, C\textsubscript{6-14} aryl, C\textsubscript{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) -C(O)R \textsuperscript{e}, -C(O)OR \textsuperscript{e}, -C(O)NR \textsuperscript{e}R\textsuperscript{f}, -C(O)NR \textsuperscript{e}R\textsuperscript{f}\textsuperscript{g}, -C(O)NR \textsuperscript{e}R\textsuperscript{f}R\textsuperscript{g}, -OR \textsuperscript{e}, -OC(O)R \textsuperscript{e}, -OC(O)OR \textsuperscript{e}, -OC(O)NR \textsuperscript{e}R\textsuperscript{f}, -OC(O)NR \textsuperscript{e}R\textsuperscript{f}\textsuperscript{g}, -OC(O)NR \textsuperscript{e}R\textsuperscript{f}R\textsuperscript{g}, -OC(=O)NR \textsuperscript{e}R\textsuperscript{f}, -OC(=O)NR \textsuperscript{e}R\textsuperscript{f}\textsuperscript{g}, -OC(=O)NR \textsuperscript{e}R\textsuperscript{f}R\textsuperscript{g}, -S(O)NR \textsuperscript{e}R\textsuperscript{f}, -S(O)NR \textsuperscript{e}R\textsuperscript{f}\textsuperscript{g}, -S(O)NR \textsuperscript{e}R\textsuperscript{f}R\textsuperscript{g}, -S(O)NR \textsuperscript{e}R\textsuperscript{f}R\textsuperscript{g}\textsuperscript{h}, -S(O)NR \textsuperscript{e}R\textsuperscript{f}R\textsuperscript{g}\textsuperscript{i}, -S(O)NR \textsuperscript{e}R\textsuperscript{f}R\textsuperscript{g}\textsuperscript{j}, where each R\textsuperscript{e}, R\textsuperscript{f}, R\textsuperscript{g}, and R\textsuperscript{h} is independently (i) hydrogen; (ii) C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{3-7} cycloalkyl, C\textsubscript{6-14} aryl, C\textsubscript{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R\textsuperscript{f} and R\textsuperscript{g} together with the N atom to which they are attached form heteroaryl or heterocyclyl.

The term "hydrogen" or the symbol "H" refers to the composition of naturally occurring hydrogen isotopes, which include protium (\textsuperscript{1}H), deuterium (\textsuperscript{2}H or D), and tritium (\textsuperscript{3}H). In their natural abundances, protium is the most common hydrogen isotope having a natural abundance of more than 99.98%. Deuterium is a less prevalent hydrogen isotope having a natural abundance of about 0.0156%.

The term "isotopic enrichment" refers to the percentage of incorporation of a less prevalent isotope (e.g., D for hydrogen) of an element at a given position in a molecule in the place of a more prevalent isotope (e.g., \textsuperscript{1}H for hydrogen) of the element. As used herein, when an atom at a particular position in a molecule is designated as a particular less prevalent...
isotope, it is understood that the abundance of that isotope at that position is substantially greater than its natural abundance.

[0025] The term "isotopic enrichment factor" refers the ratio between the isotopic abundance in an isotopically enriched compound and the natural abundance of a specific isotope.

[0026] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156% on average, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156% on average. As used herein, when a particular position in an isotopically enriched compound is designated as having deuterium, it is understood that the abundance of deuterium at that position in the compound is substantially greater than its natural abundance (0.0156%).

[0027] The terms "substantially pure" and "substantially homogeneous" mean sufficiently homogeneous to appear free of readily detectable impurities as determined by standard analytical methods used by one of ordinary skill in the art, including, but not limited to, thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), gas chromatography (GC), nuclear magnetic resonance (NMR), and mass spectrometry (MS); or sufficiently pure such that further purification would not detectably alter the physical, chemical, biological, and/or pharmacological properties, such as enzymatic and biological activities, of the substance. In certain embodiments, "substantially pure" or "substantially homogeneous" refers to a collection of molecules, wherein at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% by weight of the molecules are a single compound, including a single enantiomer, a racemic mixture, a mixture of enantiomers, or a diastereomeric mixture thereof, as determined by standard analytical methods. As used herein, when an atom at a particular position in an isotopically enriched molecule is designated as a particular less prevalent isotope, a molecule that contains other than the designated isotope at the specified position is an impurity with respect to the isotopically enriched compound. Thus, for a deuterated compound that has an atom at a
particular position designated as deuterium, a compound that contains a protium at the same position is an impurity.

[0028] The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0029] The terms "active ingredient" and "active substance" refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition. As used herein, "active ingredient" and "active substance" may be an optically active isomer.

[0030] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition.

[0031] In certain embodiments, "optically active" and "enantiomerically active" refer to a collection of molecules, which has an enantiomeric excess of no less than about 50%, no less than about 60%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%.

[0032] In describing an optically active compound, the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The (+) and (-) are used to denote the optical rotation of a optically active compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (-) prefix indicates that a compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or counterclockwise. The (+) prefix indicates that a compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or
clockwise. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of a molecule, R and S.

[0033] The term "solvate" refers to a complex or aggregate formed by one or more molecules of a solute, e.g., a compound provided herein, and one or more molecules of a solvent, which present in stoichiometric or non-stoichiometric amount. Suitable solvents include, but are not limited to, water, methanol, ethanol, w-propanol, isopropanol, and acetic acid. In certain embodiments, the solvent is pharmaceutically acceptable. In one embodiment, the complex or aggregate is in a crystalline form. In another embodiment, the complex or aggregate is in a noncrystalline form. Where the solvent is water, the solvate is a hydrate. Examples of hydrates include, but are not limited to, a hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and pentahydrate.

[0034] The term "proliferative disorder or disease" refers to unwanted cell proliferation of one or more subset of cells in a multicellular organism resulting in harm (i.e., discomfort or decreased life expectancy) to the multicellular organisms. A proliferative disorder or disease can occur in different types of animals and humans. For example, as used herein, "proliferative disorder or disease" includes neoplastic disorders and other proliferative disorders.

[0035] The term "neoplastic disorder or disease" or "cancer" refers to a tumor resulting from abnormal or uncontrolled cellular growth. Examples of neoplastic disorders include, but are not limited to, hematopoietic disorders, such as the myeloproliferative disorders, thrombocythemia, essential thrombocytosis (ET), angiogenic myeloid metaplasia, myelofibrosis (MF), myelofibrosis with myeloid metaplasia (MMM), chronic idiopathic myelofibrosis (IMF), polycythemia vera (PV), the cytopenias, and pre-malignant myelodysplastic syndromes; cancers, such as glioma cancers, lung cancers, breast cancers, colorectal cancers, prostate cancers, gastric cancers, esophageal cancers, colon cancers, pancreatic cancers, ovarian cancers, and hematologic malignancies.

[0036] The term "hematologic malignancy" refers to cancer of the body's blood-forming and immune system-the bone marrow and lymphatic tissue. Examples of hematological malignancies include, for instance, myelodysplasia, lymphomas, leukemias, lymphomas (non-IodgkhVs lymphoma), Hodgkirsch disease (also called Hodgkin's lymphoma), and myeloma, such as acute lymphocytic leukemia (ALL), acute myeloid
leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocyte leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplasia syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma, (MM).

[0037] The term "leukemia" refers to malignant neoplasms of the blood-forming tissues, including, but not limited to, chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myeloid leukemia and acute myeloblasts leukemia. The leukemia can be relapsed, refractory, or resistant to conventional therapy.

[0038] The term "promyelocytic leukemia" or "acute promyelocytic leukemia" refers to a malignancy of the bone marrow in which there is a deficiency of mature blood cells in the myeloid line of cells and an excess of immature cells called promyelocytes. It is usually marked by an exchange of parts of chromosomes 15 and 17.

[0039] The term "acute lymphocytic leukemia," "acute lymphoblastic leukemia," or "ALL" refers to a malignant disease caused by the abnormal growth and development of early nongranular white blood cell or lymphocytes.

[0040] The term "T-cell leukemia" refers to a disease in which certain cells of the lymphoid system called T lymphocytes or T cells are malignant. T cells are white blood cells that normally can attack virus-infected cells, foreign cells, and cancer cells; and produce substances that regulate the immune response.

[0041] The term "relapsed" refers to a situation where a subject or a mammal, who has had a remission of cancer after therapy has a return of cancer cells.

[0042] The term "refractory or resistant" refers to a circumstance where a subject or a mammal, even after intensive treatment, has residual cancer cells in his body.

[0043] The term "drug resistance" refers to the condition when a disease does not respond to the treatment of a drug or drugs. Drug resistance can be either intrinsic, which means the disease has never been responsive to the drug or drugs, or it can be acquired, which means the disease ceases responding to a drug or drugs that the disease had previously
responded to. In certain embodiments, drug resistance is intrinsic. In certain embodiments, the drug resistance is acquired. As used herein, the term "drug resistance" is meant to include imatinib-resistance, dasatinib-resistance, and/or nilotinib-resistance.

[0044] The phrase "a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof" has the same meaning as the phrase "a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers of the compound referenced therein; or a pharmaceutically acceptable salt, solvate, or prodrug of the compound referenced therein, or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers of the compound referenced therein."

The Compound

[0045] In one embodiment, provided herein is a compound of Formula I:

![Formula I](image)

or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof;

wherein:

R', R', and R' are each independently hydrogen, deuterium, fluoro, or methyl, where the methyl is optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro; or R' and R' together with the carbon to which they are attached form cycloalkylene, optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro;


R' and R' are each independently hydrogen or deuterium; and

X is O and Y is N; or X is N and Y is O;

with the proviso that at least one of R', R', and R' is deuterium, fluoro, or...
methyl substituted with at least one deuterium or fluoro; or at least one of \( R^4, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^a, R^b, R^c, R^d, R^e, R^f, R^g, \) and \( R^h \) is deuterium or fluoro; or at least one of \( R^5 \) and \( R^6 \) is deuterium.

[0046] In one embodiment, provided herein is a compound of Formula I or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein \( R^1, R^2, \) and \( R^3 \) are each independently hydrogen, deuterium, fluoro, or methyl, where the methyl is optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro; and \( R^4, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^a, R^b, R^c, R^d, R^e, R^f, R^g, \) and \( R^h \) are each as defined herein.

[0047] In another embodiment, provided herein is a compound of Formula II:

\[
\text{(II)}
\]

or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein \( R^1, R^2, R^3, R^{15}, R^{16}, R^{17}, R^a, R^b, R^c, R^d, R^e, R^f, R^g, X, \) and \( Y \) are each as defined herein; with the proviso that at least one of \( R^1, R^2, \) and \( R^3 \) is deuterium, fluoro, or methyl substituted with at least one deuterium or fluoro; or at least one of \( R^{15}, R^{16}, R^{17}, R^{18}, R^a, R^b, R^c, R^d, R^e, R^f, R^g, \) and \( R^h \) is deuterium or fluoro.
In another embodiment, provided herein is a compound of Formula III:

![Chemical Structure III](image)

or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; wherein $R_1$, $R_2$, $R_3$, $R_a$, $R_b$, $R_c$, $R_d$, $R_e$, $R_f$, $R_g$, and $R_h$ are each as defined herein; with the proviso that at least one of $R_1$, $R_2$, and $R_3$ is deuterium, fluoro, or methyl substituted with at least one deuterium or fluoro; or at least one of $R_a$, $R_b$, $R_c$, $R_d$, $R_e$, $R_f$, $R_g$, and $R_h$ is deuterium or fluoro.

In yet another embodiment, provided herein is a compound of Formula IV:

![Chemical Structure IV](image)

or a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof;

wherein:

- $R_1$, $R_2$, and $R_3$ are each independently hydrogen, deuterium, fluoro, CH$_3$, CDH$_2$, CD$_2$H, CD$_3$, CFH$_2$, CFDH, CFD$_2$, CF$_2$H, CF$_2$D, or CF$_3$; or $R_2$ and $R_3$ together with the carbon to which they are attached form cyclopropylene or cyclobutylene; and
- $X$ is O and $Y$ is N; or $X$ is N and $Y$ is O;
- with the proviso that at least one of $R_1$, $R_2$, and $R_3$ is deuterium, fluoro, CDH$_2$, CD$_2$H, CD$_3$, CFH$_2$, CFDH, CFD$_2$, CF$_2$H, CF$_2$D, or CF$_3$.

In one embodiment, in Formula I, II, III, or IV, $R_1$ is fluoro, $R_2$ and $R_3$ are each independently CH$_3$, CDH$_2$, CD$_2$H, CD$_3$, CFH$_2$, CFDH, CFD$_2$, CF$_2$H, CF$_2$D, or CF$_3$. 

- 13 -
In another embodiment, in Formula I, II, III, or IV, \( R^1 \) is fluoro, \( R^2 \) and \( R^3 \) are each independently CH, CDH, CDH₂, CD₂H, or CD₃.

In yet another embodiment, in Formula I, II, III, or IV, \( R^1 \) is CH₃, \( R^2 \) and \( R^3 \) are each independently CFH₂, CFDH, or CFD₂.

In yet another embodiment, in Formula I, II, III, or IV, \( R^1 \), \( R^2 \), and \( R^3 \) are each independently hydrogen, deuterium, fluoro, CH₃, CDH₂, CD₂H, CD₃, CFH₂, CFDH, CFD₂, CF₂H, CF₂D, or CF₃.

In still another embodiment, in Formula I, II, III, or IV, \( R^1 \) is deuterium or fluoro; and \( R^2 \) and \( R^3 \) together with the carbon to which they are attached form cyclopropylene or cyclobutylene.

The groups, \( R^1 \), \( R^2 \), \( R^3 \), \( R^4 \), \( R^5 \), \( R^6 \), \( R^7 \), \( R^8 \), \( R^9 \), \( R^{10} \), \( R^{11} \), \( R^{12} \), \( R^{13} \), \( R^{14} \), \( R^{15} \), \( R^{16} \), \( R^{17} \), \( R^{18} \), \( R^a \), \( R^b \), \( R^c \), \( R^d \), \( R^e \), \( R^f \), \( R^g \), \( R^h \), X, and Y in Formulae provided herein, e.g., Formula I, II, III, or IV, are further defined herein. All combinations of the embodiments provided herein for such groups are within the scope of this disclosure.

In certain embodiments, \( R^1 \) is hydrogen. In certain embodiments, \( R^1 \) is deuterium. In certain embodiments, \( R^1 \) is methyl, optionally substituted with one, two, or three groups, each independently selected from deuterium and fluoro. In certain embodiments, \( R^1 \) is CH₃. In certain embodiments, \( R^1 \) is CDH₂. In certain embodiments, \( R^1 \) is CD₂H. In certain embodiments, \( R^1 \) is CD₃. In certain embodiments, \( R^1 \) is CFH₂. In certain embodiments, \( R^1 \) is CFDH. In certain embodiments, \( R^1 \) is CFD₂. In certain embodiments, \( R^1 \) is CF₂H. In certain embodiments, \( R^1 \) is CF₂D. In certain embodiments, \( R^1 \) is CF₃.

In certain embodiments, \( R^2 \) is hydrogen. In certain embodiments, \( R^2 \) is deuterium. In certain embodiments, \( R^2 \) is methyl, optionally substituted with one, two, or three groups, each independently selected from deuterium and fluoro. In certain embodiments, \( R^2 \) is CH₃. In certain embodiments, \( R^2 \) is CDH₂. In certain embodiments, \( R^2 \) is CD₂H. In certain embodiments, \( R^2 \) is CD₃. In certain embodiments, \( R^2 \) is CFH₂. In certain embodiments, \( R^2 \) is CFDH. In certain embodiments, \( R^2 \) is CFD₂. In certain embodiments, \( R^2 \) is CF₂H. In certain embodiments, \( R^2 \) is CF₂D. In certain embodiments, \( R^2 \) is CF₃.
[0058] In certain embodiments, R³ is hydrogen. In certain embodiments, R³ is deuterium. In certain embodiments, R¹ is fluoro. In certain embodiments, R³ is methyl, optionally substituted with one, two, or three groups, each independently selected from deuterium and fluoro. In certain embodiments, R³ is CH₃. In certain embodiments, R³ is CDH₃. In certain embodiments, R³ is CD₂H. In certain embodiments, R³ is CD₃. In certain embodiments, R³ is CF₂H. In certain embodiments, R³ is CF₂D. In certain embodiments, R³ is CF₃.

[0059] In certain embodiments, R² and R³ together with the carbon to which they are attached form C₃H₃ cycloalkylene, optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro. In certain embodiments, R² and R³ together with the carbon to which they are attached form cyclopropylene, optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro. In certain embodiments, R² and R³ together with the carbon to which they are attached form cyclobutylene, optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro.

[0060] In certain embodiments, R¹ is deuterium or fluoro; and R² and R³ together with the carbon to which they are attached form cyclopropylene. In certain embodiments, R¹ is deuterium or fluoro; and R² and R³ together with the carbon to which they are attached form cyclobutylene.

[0061] In certain embodiments, R⁴ is hydrogen. In certain embodiments, R⁴ is deuterium. In certain embodiments, R⁴ is fluoro.

[0062] In certain embodiments, R³ is hydrogen. In certain embodiments, R⁵ is deuterium.

[0063] In certain embodiments, R⁶ is hydrogen. In certain embodiments, R⁶ is deuterium.

[0064] In certain embodiments, R⁷ is hydrogen. In certain embodiments, R⁷ is deuterium. In certain embodiments, R⁷ is fluoro.

[0065] In certain embodiments, R⁸ is hydrogen. In certain embodiments, R⁸ is
deuterium. In certain embodiments, R\textsuperscript{8} is fluoro.

[0066] In certain embodiments, R\textsuperscript{9} is hydrogen. In certain embodiments, R\textsuperscript{9} is deuterium. In certain embodiments, R\textsuperscript{9} is fluoro.

[0067] In certain embodiments, R\textsuperscript{10} is hydrogen. In certain embodiments, R\textsuperscript{10} is deuterium. In certain embodiments, R\textsuperscript{10} is fluoro.

[0068] In certain embodiments, R\textsuperscript{7}, R\textsuperscript{8}, R\textsuperscript{9}, and R\textsuperscript{10} are hydrogen. In certain embodiments, at least one of R\textsuperscript{7}, R\textsuperscript{8}, R\textsuperscript{9}, and R\textsuperscript{10} is deuterium. In certain embodiments, R\textsuperscript{7}, R\textsuperscript{8}, R\textsuperscript{9}, and R\textsuperscript{10} are deuterium. In certain embodiments, at least one of R\textsuperscript{7}, R\textsuperscript{8}, R\textsuperscript{9}, and R\textsuperscript{10} is fluoro. In certain embodiments, R\textsuperscript{7}, R\textsuperscript{8}, R\textsuperscript{9}, and R\textsuperscript{10} are fluoro.

[0069] In certain embodiments, R\textsuperscript{11} is hydrogen. In certain embodiments, R\textsuperscript{11} is deuterium. In certain embodiments, R\textsuperscript{11} is fluoro.

[0070] In certain embodiments, R\textsuperscript{12} is hydrogen. In certain embodiments, R\textsuperscript{12} is deuterium. In certain embodiments, R\textsuperscript{12} is fluoro.

[0071] In certain embodiments, R\textsuperscript{13} is hydrogen. In certain embodiments, R\textsuperscript{13} is deuterium. In certain embodiments, R\textsuperscript{13} is fluoro.

[0072] In certain embodiments, R\textsuperscript{14} is hydrogen. In certain embodiments, R\textsuperscript{14} is deuterium. In certain embodiments, R\textsuperscript{14} is fluoro.

[0073] In certain embodiments, R\textsuperscript{12}, R\textsuperscript{13}, and R\textsuperscript{14} are hydrogen. In certain embodiments, at least one of R\textsuperscript{12}, R\textsuperscript{13}, and R\textsuperscript{14} is deuterium. In certain embodiments, R\textsuperscript{12}, R\textsuperscript{13}, and R\textsuperscript{14} are deuterium. In certain embodiments, at least one of R\textsuperscript{12}, R\textsuperscript{13}, and R\textsuperscript{14} is fluoro. In certain embodiments, R\textsuperscript{12}, R\textsuperscript{13}, and R\textsuperscript{14} are fluoro.

[0074] In certain embodiments, R\textsuperscript{15} is hydrogen. In certain embodiments, R\textsuperscript{15} is deuterium. In certain embodiments, R\textsuperscript{15} is fluoro.

[0075] In certain embodiments, R\textsuperscript{16} is hydrogen. In certain embodiments, R\textsuperscript{16} is deuterium. In certain embodiments, R\textsuperscript{16} is fluoro.

[0076] In certain embodiments, R\textsuperscript{17} is hydrogen. In certain embodiments, R\textsuperscript{17} is deuterium. In certain embodiments, R\textsuperscript{17} is fluoro.
In certain embodiments, R18 is hydrogen. In certain embodiments, R18 is deuterium. In certain embodiments, R18 is fluoro.

In certain embodiments, R15 and R16 are hydrogen. In certain embodiments, R15 and R16 are deuterium. In certain embodiments, R15 and R16 are fluoro.

In certain embodiments, R17 and R18 are hydrogen. In certain embodiments, R17 and R18 are deuterium. In certain embodiments, R17 and R18 are fluoro.

In certain embodiments, R15, R16, R17, and R18 are hydrogen. In certain embodiments, at least one of R15, R16, R17, and R18 is deuterium. In certain embodiments, R15, R16, R17, and R18 are deuterium. In certain embodiments, at least one of R15, R16, R17, and R18 is fluoro. In certain embodiments, R15, R16, R17, and R18 are fluoro.

In certain embodiments, R15 and R16 are hydrogen, and R17 and R18 are deuterium. In certain embodiments, R15 and R16 are deuterium, and R17 and R18 are hydrogen. In certain embodiments, R15 and R16 are hydrogen, and R17 and R18 are fluoro. In certain embodiments, R15 and R16 are fluoro, and R17 and R18 are hydrogen. In certain embodiments, R15 and R16 are deuterium, and R17 and R18 are fluoro. In certain embodiments, R15 and R16 are fluoro, and R17 and R18 are deuterium.

In certain embodiments, Ra is hydrogen. In certain embodiments, Ra is deuterium. In certain embodiments, Ra is fluoro.

In certain embodiments, Rb is hydrogen. In certain embodiments, Rb is deuterium. In certain embodiments, Rb is fluoro.

In certain embodiments, Rc is hydrogen. In certain embodiments, Rc is deuterium. In certain embodiments, Rc is fluoro.

In certain embodiments, Rd is hydrogen. In certain embodiments, Rd is deuterium. In certain embodiments, Rd is fluoro.

In certain embodiments, Re is hydrogen. In certain embodiments, Re is deuterium. In certain embodiments, Re is fluoro.

In certain embodiments, Rf is hydrogen. In certain embodiments, Rf is...
deuterium. In certain embodiments, $R_f$ is fluoro.

[0088] In certain embodiments, $R_g$ is hydrogen. In certain embodiments, $R_f$ is deuterium. In certain embodiments, $R_g$ is fluoro.

[0089] In certain embodiments, $R_h$ is hydrogen. In certain embodiments, $R_f$ is deuterium. In certain embodiments, $R_h$ is fluoro.

[0090] In certain embodiments, $R_a$, $R_b$, $R_c$, and $R_d$ are hydrogen. In certain embodiments, $R_a$, $R_b$, $R_c$, and $R_d$ are deuterium. In certain embodiments, $R_a$, $R_b$, $R_c$, and $R_d$ are fluoro.

[0091] In certain embodiments, $R_e$, $R_f$, $R_g$, and $R_h$ are hydrogen. In certain embodiments, $R_e$, $R_f$, $R_g$, and $R_h$ are deuterium. In certain embodiments, $R_e$, $R_f$, $R_g$, and $R_h$ are fluoro.

[0092] In certain embodiments, $R_a$, $R_b$, $R_c$, and $R_f$ are hydrogen. In certain embodiments, $R_a$, $R_b$, $R_c$, and $R_f$ are deuterium. In certain embodiments, $R_a$, $R_b$, $R_c$, and $R_f$ are fluoro.

[0093] In certain embodiments, $R_d$, $R_e$, $R_g$, and $R_h$ are hydrogen. In certain embodiments, $R_d$, $R_e$, $R_g$, and $R_h$ are deuterium. In certain embodiments, $R_d$, $R_e$, $R_g$, and $R_h$ are fluoro.

[0094] In certain embodiments, $R_a$, $R_b$, $R_c$, $R_d$, $R_e$, $R_f$, $R_g$, and $R_h$ are hydrogen. In certain embodiments, at least one of $R_a$, $R_b$, $R_c$, $R_d$, $R_e$, $R_f$, $R_g$, and $R_h$ is deuterium. In certain embodiments, at least one of $R_a$, $R_b$, $R_c$, $R_d$, $R_e$, $R_f$, $R_g$, and $R_h$ is deuterium. In certain embodiments, at least one of $R_a$, $R_b$, $R_c$, $R_d$, $R_e$, $R_f$, $R_g$, and $R_h$ is fluoro. In certain embodiments, $R_a$, $R_b$, $R_c$, $R_d$, $R_e$, $R_f$, $R_g$, and $R_h$ are fluoro.
In one embodiment, provided here is a compound selected from:

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>R⁶</th>
<th>R⁷</th>
<th>R⁸</th>
<th>R⁹</th>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>9</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>10</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>11</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>12</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>17</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>18</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>19</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>20</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>21</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>22</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>23</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>---</td>
<td>------</td>
<td>------</td>
<td>-----</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>24</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>25</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>26</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>27</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td></td>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>28</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td></td>
<td></td>
<td>H</td>
<td>D</td>
<td>G</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>29</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>30</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td></td>
<td></td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>31</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>32</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>33</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>34</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>35</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>36</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>37</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>38</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>39</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>42</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td></td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>43</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>44</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>45</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>46</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>47</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td></td>
<td></td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>56</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>57</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>58</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>59</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>60</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>61</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>62</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>63</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>64</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>65</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>66</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>67</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>68</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
</tr>
<tr>
<td>69</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>70</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
</tr>
<tr>
<td>71</td>
<td>CF₃</td>
<td>Cyclopropylene</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>72</td>
<td>CF₃</td>
<td>Cyclopropylene</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>73</td>
<td>CF₃</td>
<td>Cyclopropylene</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>74</td>
<td>CF₃</td>
<td>Cyclopropylene</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>75</td>
<td>CF₃</td>
<td>Cyclobutylene</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>76</td>
<td>CF₃</td>
<td>Cyclobutylene</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>77</td>
<td>CF₃</td>
<td>Cyclobutylene</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>78</td>
<td>CF₃</td>
<td>Cyclobutylene</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>O</td>
</tr>
</tbody>
</table>

and enantiomers, mixtures of enantiomers, and mixtures of diastereomers thereof; and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

[0096] In certain embodiments, the compound provided herein has an isotopic enrichment factor of no less than about 64 (about 1% deuterium incorporation), no less than about 130 (about 2% deuterium incorporation), no less than about 320 (about 5% deuterium incorporation), no less than about 640 (about 10% deuterium incorporation), no less than about 1,300 (about 20% deuterium incorporation), no less than about 3,200 (about 50% deuterium incorporation), no less than about 4,800 (about 75% deuterium incorporation), no less than about 5,130 (about 80% deuterium incorporation), no less than about 5,450 (about
85% deuterium incorporation), no less than about 5,770 (about 90% deuterium incorporation), no less than about 6,090 (about 95% deuterium incorporation), no less than about 6,220 (about 97% deuterium incorporation), no less than about 6,280 (about 98% deuterium incorporation), no less than about 6,350 (about 99% deuterium incorporation), or no less than about 6,380 (about 99.5% deuterium incorporation). The deuterium enrichment can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0097] In certain embodiments, the compound provided herein is isolated or purified. In certain embodiments, the compound provided herein has a purity of at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% by weight.

[0098] In certain embodiments, the compound provided herein contains one or more less prevalent isotopes for other elements, including, but not limited to, \(^{13}\text{C}\) or \(^{14}\text{C}\) for carbon; \(^{15}\text{N}\) for nitrogen; \(^{17}\text{O}\) or \(^{18}\text{O}\) for oxygen, and \(^{33}\text{S}\), \(^{34}\text{S}\), or \(^{36}\text{S}\) for sulfur.

[0099] In one embodiment, the compounds provided herein are active against a protein kinase. In another embodiment, the compounds provided herein are active against a kinase of the platelet derived growth factor receptor (PDGFR) subfamily, including, but not limited to, PDGFR \(\alpha\), PDGFR \(\beta\), CSF-1R, c-kit, and FLT3. In yet another embodiment, the compounds provided herein are active against a kinase of the fetus liver kinase ("Flk") receptor subfamily, including, but not limited to, kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), Flk-1R, Flk-4, and Fms-like tyrosine kinase 1 (Flt-1). In yet another embodiment, the compounds provided herein are active against a kinase of the "HER" receptor tyrosine kinase subfamily, including, but not limited to, HER1 (also known as epithelial growth factor receptor (EGFR)), HER2, HER3, and HER4. In yet another embodiment, the compounds provided herein are active against a kinase of the insulin receptor (IR) subfamily, including, but not limited to, insulin-like growth factor I receptor (IGF-1R). In yet another embodiment, the compounds provided herein are active against a kinase of the vascular endothelial growth factor ("VEGF") receptor subgroup. In yet another embodiment, the compounds provided herein are active against a kinase of the fibroblast growth factor ("FGF") receptor subgroup, including, but not limited to, the receptors FGFR1, FGFR 2, FGFR3, and FGFR4, and the ligands, FGF1, FGF2, FGF3, FGF4, FGF5, FGF6, and
FGF7. In yet another embodiment, the compounds provided herein are active against a kinase of the c-Met receptor family. In yet another embodiment, the compounds provided herein are active against a kinase of the Abl protein tyrosine family. In yet another embodiment, the compounds provided herein are active against a kinase of the Fms-like tyrosine kinase 3 receptor kinase (FLT3 kinase). In yet another embodiment, the compounds provided herein are active against a kinase of the Src subfamily, including, but not limited to, Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and York. In still another embodiment, the compounds provided herein are active against one or more kinases selected from the group consisting of sterile 20, sterile 11, sterile, the camk subfamily (calmodulin regulated kinases and related kinases), the AGC subfamily (protein kinase A, protein kinase G and protein kinase C), the CMGC subfamily (cdk, map kinase, glycogen synthetase kinase and elk), the sterile 20 sub family, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack, and their respective subfamilies.

[00100] The compounds provided herein are intended to encompass all possible stereoisomers, unless a particular stereochemistry is specified. Where the compound provided herein contains an alkenyl or alkenylene group, the compound may exist as one or mixture of geometric cistrans (or Z/E) isomers. Where structural isomers are interconvertible via a low energy barrier, the compound may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in a compound that contains, for example, an imino, keto, or oxime group; or so-called valence tautomerism in a compound that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[00101] The compounds provided herein may be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a racemic mixture or a diastereomeric mixture. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for the compound that undergoes epimerization in vivo, to administration of the compound in its (S) form. Conventional techniques for the preparation/isolation of individual enantiomers include synthesis from a suitable optically pure precursor, asymmetric synthesis from achiral starting materials, or resolution of an enantiomeric mixture, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.
When the compound provided herein contains a basic moiety, it may also be provided as a pharmaceutically acceptable salt (See, Berge et al., J. Pharm. Sci. 1977, 66, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stahl and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002).

Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(15)-camphor-10-sulfonic acid, capric acid, caprylic acid, cinnamic acid, citric acid, cyclamatic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ephanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, a-oxoglutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (−)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyrogallic acid, saccharic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluensulfonic acid, undecylenic acid, and valeric acid.

In one embodiment, the compound provided herein is a free base of a compound provided herein, e.g., a compound of Formula I, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof. In one embodiment, the free base is a solid. In another embodiment, the free base is a solid in an amorphous form. In yet another embodiment, the free base is a solid in a crystalline form. The free base in solid forms can be prepared according to the method described in U.S. Pat. Appl. Publ. No. 2009/0131426, the disclosure of which is incorporated herein by reference in its entirety.

In another embodiment, the free base is a pharmaceutically acceptable solvate. In one embodiment, the free base is a hydrate. In another embodiment, the pharmaceutically acceptable solvent is a methanol solvate. The methanol solvate of a compound provided herein can be prepared according to the method described in U.S. Pat. Appl. Publ. No.
2009/0131426, the disclosure of which is incorporated herein by reference in its entirety.

[00106] In yet another embodiment, the compound provided herein is a pharmaceutically acceptable salt of a compound provided herein, which includes, but is not limited to, acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, 1,2-ethanedisulfonate (edisylate), ethanesulfonate (esylate), formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate (mesylate), 2-naphthalenesulfonate (napsylate), nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate salts.

[00107] In one embodiment, the pharmaceutically acceptable salt is a hydrochloride, hydrobromide, sulfate, mesylate, esylate, edisylate, besylate, tosylate, or napsylate salt of a compound provided herein. In another embodiment, the pharmaceutically acceptable salt is a hydrochloride salt of a compound provided herein. In yet another embodiment, the pharmaceutically acceptable salt is a hydrobromide of a compound provided herein. In yet another embodiment, the pharmaceutically acceptable salt is a sulfate of a compound provided herein. In yet another embodiment, the pharmaceutically acceptable salt is a mesylate of a compound provided herein. In yet another embodiment, the pharmaceutically acceptable salt is an esylate of a compound provided herein. In yet another embodiment, the pharmaceutically acceptable salt is an edisylate of a compound provided herein. In yet another embodiment, the pharmaceutically acceptable salt is a besylate of a compound provided herein. In yet another embodiment, the pharmaceutically acceptable salt is a tosylate of a compound provided herein. In still another embodiment, the pharmaceutically acceptable salt is a napsylate of a compound provided herein. The pharmaceutically acceptable salt of a compound provided herein can be prepared according to the method described in U.S. Pat. Appl. Publ. No. 2009/0131426, the disclosure of which is incorporated herein by reference in its entirety.

[00108] The compound provided herein may also be provided as a prodrug, which is a functional derivative of a compound, for example, of Formula I and is readily convertible into

Methods of Synthesis

[00109] The compounds provided herein can be prepared, isolated, or obtained by any method known to one of skill in the art. For an example, a compound of Formula I can be prepared according to the methods described in U.S. Pub. No. 2007/0232604, the disclosure of which is incorporated herein by reference in its entirety.
In one embodiment, an isotope or fluoro is introduced into a compound
provided herein by synthetic techniques that employ suitable isotopically enriched or
fluorinated reagents, whereby incorporation rates are pre-determined. In another
embodiment, an isotope is introduced into a compound provided herein by exchange
techniques, wherein incorporation rates are determined by equilibrium conditions, which may
be highly variable depending on the reaction conditions. In yet another embodiment,
deuterium or fluoro is introduced into a compound provided herein by direct deuteration or
fluorination.

In certain embodiments, deuterium and fluoro are incorporated synthetically into different positions of a compound of Formula I, according to the synthetic procedures as shown in Scheme 1, using appropriate deuterated or fluorinated starting materials or intermediates. In one embodiment, to introduce deuterium or fluoro at one or more positions or groups of R1, R2, R3, and R4, compound F with the corresponding deuterium or fluoro substitutions is coupled with compound E, for example, in a suitable dry solvent such as THF, dioxane, EtOAc, DMF, NMP or DCM, optionally in the presence of a base such as DIEA, TEA or an alkali metal carbonate, and optionally in the presence of DMAP, with moderate heating as necessary to complete the reaction, to form a deuterated or fluorinated compound of compound G. In another embodiment, to introduce deuterium or fluoro at one or more positions selected from R7, R8, R9, R10, and R11, nitrobenzene C with the corresponding deuterium or fluoro substitutions is coupled with benzothiazole B to form deuterated or fluorinated compound D. In yet another embodiment, to introduce deuterium or fluoro at one or more positions selected from R12, R13, and R14, aniline A with the corresponding deuterium or fluoro substitutions is treated with ammonium thiocyanate to form deuterated or fluorinated benzothiazole B. In still another embodiment, to introduce deuterium or fluoro at one or more positions selected from R15, R16, R17, R18, R19, R20, R21, R22, R23, 4-morpholinylethane H with the corresponding deuterium or fluoro substitutions is coupled with compound G to form a deuterated or fluorinated compound of Formula I. The deuterated or fluorinated starting materials and intermediates used herein are either commercially available, or can be prepared by methods known to one of skill in the art or following procedures similar to those described herein in the Example section and routine modifications thereof.

In certain embodiments, deuterium is also incorporated to various positions of
a compound of Formula I, which has an exchangeable proton, such as amine or amide N-H and hydroxyl O-H, via proton-deuterium equilibrium exchange. In one embodiment, to introduce deuterium at R⁵ or R⁶, the protons can be replaced with deuterium selectively or non-selectively through a proton-deuterium exchange method known in the art.

Scheme 1

In certain embodiments, deuterium and fluoro are incorporated synthetically into different positions of a compound of Formula I, according to the synthetic procedures as shown in Scheme 2 and 3, using appropriate deuterated or fluorinated starting materials or intermediates. In one embodiment, to introduce deuterium or fluoro at one or more positions or groups of R¹, R², and R³, compound J with the corresponding deuterium or fluoro
substitutions is first coupled with R^4CH₂CN to form compound K, followed by the reaction with hydroxyamine to form deuterated or fluorinated compound L. In another embodiment, to introduce deuterium or fluoro at the position of R^4, R^4CH₂CN with the corresponding a deuterium or fluoro substitution is first coupled with compound J to form compound K, followed by the reaction with hydroxyamine to form deuterated or fluorinated compound L. Compound L is converted into into compound M, which can be coupled with compound O, for example, in a suitable dry solvent such as THF, dioxane, EtOAc, DMF, NMP or DCM, optionally in the presence of a base such as DIEA, TEA or an alkali metal carbonate, and optionally in the presence of DMAP, with moderate heating as necessary to complete the reaction, to form a deuterated or fluorinated compound of Formula Ia.

Pharmaceutical Compositions

[00114] In one embodiment, provided herein are pharmaceutical compositions comprising a compound provided herein, e.g., a compound of Formula I, as an active ingredient, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.
Suitable excipients are well known to those skilled in the art, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art, including, but not limited to, the method of administration. For example, oral dosage forms such as tablets may contain excipients not
suited for use in parenteral dosage forms. The suitability of a particular excipient may also
depend on the specific active ingredients in the dosage form. For example, the
decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary
amines are particularly susceptible to such accelerated decomposition. Consequently,
provided herein are pharmaceutical compositions and dosage forms that contain little, if any,
lactose other mono- or di-saccharides. As used herein, the term "lactose- free" means that the
amount of lactose present, if any, is insufficient to substantially increase the degradation rate
of an active ingredient. In one embodiment, lactose-free compositions comprise an active
ingredient provided herein, a binder/filler, and a lubricant. In another embodiment, lactose-
free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized
starch, and magnesium stearate.

[00116] The compound provided herein may be administered alone, or in combination
with one or more other compounds provided herein. The pharmaceutical compositions that
comprise a compound provided herein, e.g., a compound of Formula I, including an
enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a
pharmacologically acceptable salt, solvate, or prodrug thereof, can be formulated in various
dosage forms for oral, parenteral, and topical administration. The pharmaceutical
compositions can also be formulated as modified release dosage forms, including delayed-,
extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-
programmed-release, and gastric retention dosage forms. These dosage forms can be
prepared according to conventional methods and techniques known to those skilled in the art
(see, Remington: The Science and Practice of Pharmacy, supra; Modified-Release Drug
Delivery Technology, 2nd ed.; Rathbone et al., Eds.; Marcel Dekker, Inc.: New York, NY,
2008).

[00117] In one embodiment, the pharmaceutical compositions are provided in a dosage
form for oral administration, which comprise a compound provided herein, e.g., a compound
of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of
diastereomers thereof; or a pharmacologically acceptable salt, solvate, or prodrug thereof; and
one or more pharmacologically acceptable excipients or carriers.

[00118] In another embodiment, the pharmaceutical compositions are provided in a
dosage form for parenteral administration, which comprise a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00119] In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00120] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. For example, a 100 mg unit dose contains about 100 mg of an active ingredient in a packaged tablet or capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[00121] The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.
A. Oral Administration

[00122] The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[00123] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; cellulosics, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline cellulosics, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.
Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

Suitable disintegrants include, but are not limited to, agar; bentonite; cellulosics, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked cellulosics, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; t alc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents
include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monoooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine olate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaureate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[00128] It should be understood that many carriers and excipients may serve a plurality of functions, even within the same formulation.

[00129] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a
sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00130] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00131] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propylparabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00132] The pharmaceutical compositions provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or
solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

[00133] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or polyalkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanoiamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00134] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00135] The pharmaceutical compositions provided herein for oral administration can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00136] Coloring and flavoring agents can be used in all of the above dosage forms.
The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (see, Remington: The Science and Practice of Pharmacy, supra).

The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection. Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil,
and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, N-methyl-2-pyrrolidone, N,N-dimethylacetamide, and dimethyl sulfoxide.

[00142] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether -P-cyclodextrin, and sulfobutylether 7-p-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00143] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00144] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are
provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In
still another embodiment, the pharmaceutical compositions are provided as ready-to-use
sterile emulsions.

[00145] The pharmaceutical compositions provided herein for parenteral
administration can be formulated as immediate or modified release dosage forms, including
delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00146] The pharmaceutical compositions provided herein for parenteral
administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for
administration as an implanted depot. In one embodiment, the pharmaceutical compositions
provided herein are dispersed in a solid inner matrix, which is surrounded by an outer
polymeric membrane that is insoluble in body fluids but allows the active ingredient in the
pharmaceutical compositions diffuse through.

[00147] Suitable inner matrixes include, but are not limited to,
polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized
polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber,
polysoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate
copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers,
hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen,
cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00148] Suitable outer polymeric membranes include but are not limited to,
polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate
copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes,
neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with
vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene
terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer,
ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinylxyethanol copolymer.

C. Topical Administration

[00149] The pharmaceutical compositions provided herein can be administered
topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes
(intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal,
nasal, vaginal, urethral, respiratory, and rectal administration.

[00150] The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, and dermal patches. The topical formulation of the pharmaceutical compositions provided herein can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00151] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00152] The pharmaceutical compositions can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00153] The pharmaceutical compositions provided herein can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (see, Remington: The Science and Practice of Pharmacy, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00154] Suitable cream base can be oil-in-water or water-in-oil. Suitable cream
vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00155] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include, but are not limited to, crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, and CARBOPOL®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulose polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00156] The pharmaceutical compositions provided herein can be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in Remington: The Science and Practice of Pharmacy, supra.

[00157] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di-
and triglycerides of fatty acids, and hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, and polyacrylic acid. Combinations of the various vehicles can also be used. Rectal and vaginal suppositories may be prepared by compressing or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00158] The pharmaceutical compositions provided herein can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00159] The pharmaceutical compositions provided herein can be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions can also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00160] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein; a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00161] The pharmaceutical compositions provided herein can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00162] Capsules, blisters, and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of
the monohydrate. Other suitable excipients or carriers include, but are not limited to, dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration can further comprise a suitable flavor, such as menthol and levomenthol; and/or sweeteners, such as saccharin and saccharin sodium.

[00163] The pharmaceutical compositions provided herein for topical administration can be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

D. Modified Release

[00164] The pharmaceutical compositions provided herein can be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include, but are not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphism of the active ingredient(s).

[00165] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,958,458; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,270,798; 6,375,987; 6,376,461; 6,419,961; 6,589,548; 6,613,358; 6,623,756; 6,699,500; 6,793,936; 6,827,947; 6,902,742; 6,958,161; 7,255,876; 7,416,738; 7,427,414; 7,485,322; Bussemer et al., Crit. Rev. Ther. Drug Carrier Syst. 2001, 18, 433-458; Kfodified-Release Drug Delivery Technology, 2nd ed.; Rathbone et al., Eds.; Marcel Dekker AG: 2005; Maroni et al, Expert.

1. Matrix Controlled Release Devices

[00166] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using a matrix controlled release device known to those skilled in the art. See, Takada et al. in Encyclopedia of Controlled Drug Delivery; Mathiowitz Ed.; Wiley: 1999; Vol. 2.

[00167] In certain embodiments, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is waterswellable, erodible, or soluble polymers, including, but not limited to, synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00168] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; cellulosics, such as ethyl cellulose (EC), methylcellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxy-propyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethyl hydroxyethyl cellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate);
polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-
glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid
derivatives, such as homopolymers and copolymers of butylmethacrylate, methyl
methacrylate, ethyl methacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and
(trimethylaminoethyl)methacrylate chloride.

[00169] In certain embodiments, the pharmaceutical compositions provided herein are
formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or
dispersed in an inert matrix and is released primarily by diffusion through the inert matrix
once administered. Materials suitable for use as a non-erodible matrix device include, but are
not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene,
polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated
polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-
v vinyl acetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate
copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and
propylene, ionomer polyethylene terephthalate, butyl rubbers, epichlorohydrin rubbers,
ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer,
ethylene/vinylxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized
polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, and
silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose
acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty
compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00170] In a matrix controlled release system, the desired release kinetics can be
controlled, for example, via the polymer type employed, the polymer viscosity, the particle
sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus
the polymer, and other excipients or carriers in the compositions.

[00171] The pharmaceutical compositions provided herein in a modified release
dosage form can be prepared by methods known to those skilled in the art, including direct
compression, dry or wet granulation followed by compression, and melt-granulation followed
by compression.
2. Osmotic Controlled Release Devices

[00172] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using an osmotic controlled release device, including, but not limited to, one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) a core which contains an active ingredient; and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00173] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents is water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels." Suitable water-swellable hydrophilic polymers as osmotic agents include, but are not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium crosclarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00174] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfate, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic
acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid,
edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00175] Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANNOGEM™ EZ (SP1 Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00176] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00177] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxy lated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, IIIEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00178] Semipermeable membrane can also be a hydrophobic microporous membrane,
wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polycrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00179] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports can be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00180] The total amount of the active ingredient(s) released and the release rate can substantially by modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00181] The pharmaceutical compositions in an osmotic controlled-release dosage form can further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00182] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art. See, Remington: The Science and Practice of Pharmacy, supra; Santus and Baker, J. Controlled Release 1995, 35, 1-21; Verma et al., Drug Development and Industrial Pharmacy 2000, 26, 695-708; and Verma et al., J. Controlled Release 2002, 79, 7-27.

[00183] In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. See, U.S. Pat. No. 5,612,059 and International Pat. Appl. Publ. No. WO 2002/I 791 8. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including
direct compression, dry granulation, wet granulation, and a dip-coating method.

[00184] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticulate Controlled Release Devices

[00185] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated as a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 µm to about 3 mm, about 50 µm to about 2.5 mm, or from about 100 µm to about 1 mm in diameter. Such multiparticulates can be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spherization, roller-compaction, melt-congealing, and by spray-coating seed cores. See, for example, *Multiparticulate Oral Drug Delivery; Gebre-Sellassie Ed.: Marcel Dekker: 1994*; and *Pharmaceutical Pelletization Technology; Gebre-Sellassie Ed.: Marcel Dekker: 1989*.

[00186] Other excipients or carriers as described herein can be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00187] The pharmaceutical compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, those disclosed in U.S. Pat. Nos. 5,709,874; 5,759,542; 5,840,674; 5,900,252; 5,972,366; 5,985,307; 6,004,534; 6,039,975; 6,048,736; 6,060,082; 6,071,495; 6,120,751; 6,131,570; 6,139,865; 6,253,872; 6,271,359; 6,274,552; 6,316,652; and 7,169,410.
Methods of Use

[00188] In one embodiment, provided herein is a method for treating a proliferative disease in a subject, which comprises administering to the subject a therapeutically effective amount of a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00189] In certain embodiments, the therapeutically effective amount is ranging from about 0.01 to about 5 mg/kg/day, from about 0.05 to about 5 mg/kg/day, from about 0.05 to about 4 mg/kg/day, from about 0.1 to about 3 mg/kg/day, from about 0.1 to about 2 mg/kg/day, or from about 0.1 to about 1 mg/kg/day. In one embodiment, the therapeutically effective amount is ranging from about 0.01 to about 5 mg/kg/day. In another embodiment, the therapeutically effective amount is ranging from about 0.05 to about 5 mg/kg/day. In yet another embodiment, the therapeutically effective amount is ranging from about 0.05 to about 4 mg/kg/day. In yet another embodiment, the therapeutically effective amount is ranging from about 0.1 to about 3 mg/kg/day. In yet another embodiment, the therapeutically effective amount is ranging from about 0.1 to about 2 mg/kg/day. In still another embodiment, the therapeutically effective amount is ranging from about 0.1 to about 1 mg/kg/day.

[00190] It is understood that the administered dose can also be expressed in units other than as mg/kg/day. For example, doses for parenteral administration can be expressed as mg/m²/day. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to mg/m²/day to given either the height or weight of a subject or both (see, www.fda.gov/cder/cancer/animalframe.htm). For example, a dose of 1 mg/m²/day for a 65 kg human is approximately equal to 38 mg/m²/day.

[00191] In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human.

[00192] In certain embodiments, the proliferative disease is a carcinoma, including, but not limited to, Kit-mediated carcinomas, adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, teratocarcinoma, head and neck cancer, brain cancer, intracranial carcinoma, glioblastoma (including PDGFR-mediated glioblastoma), glioblastoma
multiforme (including PDGFR-mediated glioblastoma multiforme), neuroblastoma, cancer of the larynx, multiple endocrine neoplasias 2A and 2B (MENS 2A and MENS 2B) (including RET-mediated MENS), thyroid cancer (including sporadic and familial medullary thyroid carcinoma), papillary thyroid carcinoma, parathyroid carcinoma (including any RET-mediated thyroid carcinoma), follicular thyroid cancer, anaplastic thyroid cancer, bronchial carcinoid, oat cell carcinoma, lung cancer, small-cell lung cancer (including FLT3 and/or Kit-mediated small cell lung cancer), stomach/gastric cancer, gastrointestinal cancer, gastrointestinal stromal tumors (GIST) (including Kit-mediated GIST and PDGFR a-mediated GIST), colon cancer, colorectal cancer, pancreatic cancer, islet cell carcinoma, hepatic/liver cancer, metastases to the liver, bladder cancer, renal cell cancer (including PDGFR-mediated renal cell cancer), cancers of the genitourinary tract, ovarian cancer (including Kit-mediated and/or PDGFR-mediated ovarian cancer), endometrial cancer (including CSF-lR-mediated endometrial cancer), cervical cancer, breast cancer (including FLT3-mediated and/or PDGFR-mediated breast cancer), prostate cancer (including Kit-mediated prostate cancer), germ cell tumors (including Kit-mediated germ cell tumors), seminomas (including Kit-mediated seminomas), dysgerminomas (including Kit-mediated dysgerminomas), melanoma (including PDGFR-mediated melanoma), metastases to the bone (including CSF-lR-mediated bone metastases), metastatic tumors (including VEGFR-mediated tumors), stromal tumors, neuroendocrine tumors, tumor angiogenesis (including VEGFR-mediated tumor angiogenesis), and mixed mesodermal tumors.

[00193] In certain embodiments, the proliferative disease is sarcomas, including, but not limited to, PDGFR-mediated sarcomas, osteosarcoma, osteogenic sarcoma, bone cancer, glioma (including PDGFR-mediated and/or CSF-lR-mediated glioma), astrocytoma, vascular tumors (including VEGFR-mediated vascular tumors), Kaposi’s sarcoma, carcinosarcoma, hemangiosarcomas (including VEGFR3-mediated hemangiosarcomas), and lymphangiosarconia (including VEGFR3-mediated lymphangiosarcoma).

[00194] In certain embodiments, the proliferative disease is myeloma, leukemia, myeloproliferative diseases, acute myeloid leukemia (AML) (including FLT3 mediated and/or KIT-mediated and/or CSFR-mediated acute myeloid leukemia), chronic myeloid leukemias (CML) (including FLT3-mediated and/or PDGFR-mediated chronic myeloid leukemia), myelodysplasia leukemias (including FLT3-mediated myelodysplastic leukemia), myelodysplasia syndrome (including FLT3 mediated and/or Kit-mediated myelodysplastic
syndrome), idiopathic hypereosinophilic syndrome (HES) (including PDGFR-mediated HES), chronic eosinophilic leukemia (CEL) (including PDGFR-mediated CEL), chronic myelomonocytic leukemia (CMML), mast cell leukemia (including Kit-mediated mast cell leukemia), or systemic mastocytosis (including Kit-mediated systemic mastocytosis).

[00195] In certain embodiments, the proliferative disease is lymphoma, lymphoproliferative diseases, acute lymphoblastic leukemia (ALL), B-cell acute lymphoblastic leukemias, T-cell acute lymphoblastic leukemias, natural killer (NK) cell leukemia, B-cell lymphoma, T-cell lymphoma, or natural killer (NK) cell lymphoma, any of which may be FLT3 mediated and/or PDGFR-mediated.

[00196] In certain embodiments, the proliferative disease is Langerhans cell histiocytosis (including CSF-lR-mediated and/or FLT3-mediated Langerhans cell histiocytosis), mast cell tumors, or mastocytosis.

[00197] In certain embodiments, the proliferative disease is a nonmalignant proliferation disease, including, but not limited to, atherosclerosis (including PDGFR-mediated atherosclerosis), restenosis following vascular angioplasty (including PDGFR-mediated restenosis), and fibroproliferative disorders (including obliterator bronchiolitis and idiopathic myelofibrosis, both of which may be PDGFR-mediated).

[00198] In certain embodiments, the proliferative disease is an inflammatory disease or disorder related to immune dysfunction, immunodeficiency, or immunomodulation, including, but not limited to, autoimmune diseases, tissue transplant rejection, graft-versus-host disease, wound healing, kidney disease, multiple sclerosis, thyroiditis, type 1 diabetes, sarcoidosis, allergic rhinitis, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis (UC)), systemic lupus erythematosus (SLE), arthritis, osteoarthritis, rheumatoid arthritis, osteoporosis, asthma, and chronic obstructive pulmonary disease (COPD), any of which may FLT3-mediated and/or CSF-lR-mediated.

[00199] In certain embodiments, the proliferative disease is an infectious disease mediated either via viral or bacterial pathogens and sepsis, including KIT-mediated sepsis.

[00200] In certain embodiments, the proliferative disease is cancer, including, but not limited to, head and neck cancer (originating lip, oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, nasal cavity, paranasal sinuses, or salivary glands), lung cancer
(including small cell lung cancer and non-small cell lung cancer), gastrointestinal tract cancers (including esophageal cancer), gastric cancer, colorectal cancer, anal cancer, pancreatic cancer, liver cancer, gallbladder cancer, extrahepatic bile duct cancer, cancer of the ampulla of vater, breast cancer, gynecologic cancers (including cancer of uterine cervix), cancer of the uterine body, vaginal cancer, vulvar cancer, ovarian cancer, gestational trophoblastic cancer, testicular cancer, urinary tract cancers (including renal cancer), urinary bladder cancer, prostate cancer, penile cancer, urethral cancer, neurologic tumors, endocrine neoplasms (including carcinoid and islet cell tumors), pheochromocytoma, adrenal cortical carcinoma, parathyroid carcinoma and metastases to endocrine glands.

[00201] Further examples of cancers are basal cell carcinoma, squamous cell carcinoma, chondrosarcoma (a cancer arising in cartilage cells), mesenchymal-chondrosarcoma, soft tissue sarcomas (including malignant tumors that may arise in any of the mesodermal tissues (muscles, tendons, vessels that carry blood or lymph, joints and fat)), soft tissue sarcomas (include alveolar soft-part sarcoma), angiosarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, hemangiopericytoma, mesenchymoma, schwannoma, peripheral neuroectodermal tumours, rhabdomyosarcoma, synovial sarcoma, gestational trophoblastic tumor (malignancy in which the tissues formed in the uterus following conception become cancerous), Hodgkin's lymphoma, and laryngeal cancer.

[00202] In certain embodiments, the cancer is a leukemia. In one embodiment, the leukemia is chronic lymphocytic leukemia, chronic myelocytic leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, and acute myeloblastic leukemia.

[00203] In another embodiment, the leukemia is acute leukemia. In one embodiment, the acute leukemia is acute myeloid leukemia (AML). In one embodiment, acute myeloid leukemia is undifferentiated AML (M0), myeloblastic leukemia (M1), myeloblastic leukemia (M2), promyelocytic leukemia (M3 or M3 variant [M3V]), myelomonocytic leukemia (M4 or M4 variant with eosinophilia [M4E]), monocytic leukemia (M5), erythroleukemia (M6), or megakaryoblastic leukemia (M7). In another embodiment, the acute myeloid leukemia is undifferentiated AML (M0). In yet another embodiment, the acute myeloid leukemia is myeloblastic leukemia (M1). In yet another embodiment, the acute myeloid leukemia is myeloblastic leukemia (M2). In yet another embodiment, the acute myeloid leukemia is
promyelocyte leukemia (M3 or M3 variant [M3V]). In yet another embodiment, the acute myeloid leukemia is myelomonocytic leukemia (M4 or M4 variant with eosinophilia [M4E]). In yet another embodiment, the acute myeloid leukemia is monocytic leukemia (M5). In yet another embodiment, the acute myeloid leukemia is erythroleukemia (M6). In yet another embodiment, the acute myeloid leukemia is megakaryoblastic leukemia (M7). In yet another embodiment, the acute myeloid leukemia is promyelocytic leukemia. In yet another embodiment, the leukemia is attributable to a FLT3 internal tandem duplication (ITD) mutation. In yet another embodiment, the leukemia is attributable to a FLT3 point mutation. In still another embodiment, the FLT3 point mutation is a point mutation at amino acid D835.

[00204] In another embodiment, the acute leukemia is acute lymphocytic leukemia (ALL). In one embodiment, the acute lymphocytic leukemia is leukemia that originates in the blast cells of the bone marrow (B-cells), thymus (T-cells), or lymph nodes. The acute lymphocytic leukemia is categorized according to the French-American-British (FAB) Morphological Classification Scheme as L1 - Mature-appearing lymphoblasts (T-cells or pre-B-cells), L2 - Immature and pleomorphic (variously shaped) lymphoblasts (T-cells or pre-B-cells), and L3 - Lymphoblasts (B-cells; Burkitt's cells). In another embodiment, the acute lymphocytic leukemia originates in the blast cells of the bone marrow (B-cells). In yet another embodiment, the acute lymphocytic leukemia originates in the thymus (T-cells). In yet another embodiment, the acute lymphocytic leukemia originates in the lymph nodes. In yet another embodiment, the acute lymphocytic leukemia is L1 type characterized by mature-appearing lymphoblasts (T-cells or pre-B-cells). In yet another embodiment, the acute lymphocytic leukemia is L2 type characterized by immature and pleomorphic (variously shaped) lymphoblasts (T-cells or pre-B-cells). In yet another embodiment, the acute lymphocytic leukemia is L3 type characterized by lymphoblasts (B-cells; Burkitt's cells).

[00205] In yet another embodiment, the leukemia is T-cell leukemia. In one embodiment, the T-cell leukemia is peripheral T-cell leukemia, T-cell lymphoblastic leukemia, cutaneous T-cell leukemia, and adult T-cell leukemia. In another embodiment, the T-cell leukemia is peripheral T-cell leukemia. In yet another embodiment, the T-cell leukemia is T-cell lymphoblastic leukemia. In yet another embodiment, the T-cell leukemia is cutaneous T-cell leukemia. In still another embodiment, the T-cell leukemia is adult T-cell leukemia.
In yet another embodiment, the leukemia is Philadelphia positive. In one embodiment, the Philadelphia positive leukemia is Philadelphia positive AML, including, but not limited to, undifferentiated AML (MO), myeloblasts leukemia (MI), myeloblastic leukemia (M2), promyelocyte leukemia (M3 or M3 variant [M3VI]), myelomonocytic leukemia (M4 or M4 variant with eosinophilia [M4E]), monocytic leukemia (M5), erythroleukemia (M6), or megakaryoblastic leukemia (M7). In another embodiment, the Philadelphia positive leukemia is Philadelphia positive ALL.

In still another embodiment, the leukemia is drug resistant. In one embodiment, the subject has developed drug resistance to the anticancer therapy. In another embodiment, the subject has developed drug resistance to a FLT3 kinase inhibitor. In yet another embodiment, the subject has been treated with PKC 412, MLN 578, CEP-701, CT 53518, CT-53608, CT-52923, D-64406, D-65476, AGL-2033, AG1295, AG1296, KN-1022, PKC-412, SU5416, SU5614, SU1 1248, L-00021649, or CHIR-258. In still another embodiment, the subject has a constitutively activating FLT3 mutant.

In certain embodiments, the cancer that can be treated with the methods provided herein includes, but is not limited to, bladder cancer, breast cancer, cervical cancer, colon cancer (e.g., colorectal cancer), esophageal cancer, head and neck cancer, liver cancer, lung cancer (e.g., small cell and non-small cell lung cancers), melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma (e.g., osteosarcoma), skin cancer (e.g., squamous cell carcinoma), stomach cancer, testicular cancer, thyroid cancer, and uterine cancer.

In certain embodiments, the cancer is a metastatic cancer, including, but not limited to, bladder cancer, breast cancer, cervical cancer, colon cancer (e.g., colorectal cancer), esophageal cancer, head and neck cancer, liver cancer, lung cancer (e.g., small cell and non-small cell lung cancers), melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma (e.g., osteosarcoma), skin cancer (e.g., squamous cell carcinoma), stomach cancer, testicular cancer, thyroid cancer, and uterine cancer. In one embodiment, the metastatic cancer is breast or prostate cancer. In another embodiment, the metastatic cancer is breast cancer. In yet another embodiment, the metastatic cancer is prostate cancer.

In certain embodiments, the subject to be treated with one of the methods
provided herein has not been treated with anticancer therapy prior to the administration of a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In certain embodiments, the subject to be treated with one of the methods provided herein has been treated with anticancer therapy prior to the administration of a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In certain embodiments, the subject to be treated with one of the methods provided herein has been treated with a FLT3 kinase inhibitor. In certain embodiments, the subject to be treated with one of the methods provided herein has been treated with PKC 412, MLN 578, CEP-701, CT 53518, CT-53608, CT-52923, D-64406, D-65476, AGL-2033, AG1295, AG1296, KN-1022, PKC-412, SU5416, SU5614, SUI 1248, L-00021649, CHIR-258, or others known or approved therapeutic agents for treating AML or ALL. In certain embodiments, the subject to be treated with one of the methods provided herein has developed drug resistance to the anticancer therapy. In certain embodiments, the subject to be treated with one of the methods provided herein has developed drug resistance to a FLT3 kinase inhibitor. In certain embodiments, the subject to be treated with the methods provided herein has a constitutively activating FLT3 mutant.

[00211] The methods provided herein encompass treating a subject regardless of patient's age, although some diseases or disorders are more common in certain age groups. Further provided is a method for treating a subject who has undergone surgery in an attempt to treat the disease or condition at issue, as well as the one who have not. Because the subjects with cancer have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a particular subject may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation, specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual subject with cancer.

[00212] Depending on the disease to be treated and the subject's condition, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, CIV, intracistemal injection or infusion.
subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration. A compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants and vehicles, appropriate for each route of administration. In one embodiment, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered orally. In another embodiment, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered parenterally. In yet another embodiment, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered intravenously.

[00213] A compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof can be delivered as a single dose such as, e.g., a single bolus injection, or oral tablets or pills; or over time such as, e.g., continuous infusion over time or divided bolus doses over time. The compound can be administered repetitively if necessary, for example, until the patient experiences stable disease or regression, or until the patient experiences disease progression or unacceptable toxicity. For example, stable disease for solid tumors generally means that the perpendicular diameter of measurable lesions has not increased by 25% or more from the last measurement. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, *Journal of the National Cancer Institute* 92(3): 205-216 (2000). Stable disease or lack thereof is determined by methods known in the art such as evaluation of patient symptoms, physical examination, visualization of the tumor that has been imaged using X-ray, CAT, PET, or MRI scan and other commonly accepted evaluation modalities.

[00214] A compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, can be administered once daily
(QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). In addition, the administration can be continuous, i.e., every day, or intermittently. The term "intermittent" or "intermittently" as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administration for one to six days per week, administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days.

[00215] In certain embodiments, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[00216] In another embodiment, provided are methods of modulating the activity or subcellular distribution of a kinase, which comprising contacting the kinase with a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00217] In certain embodiments, the kinase is a kinase of the platelet derived growth factor receptor (PDGFR) subfamily, including PDGFR α, PDGFR β, CSF-1R, Kit, and FLT3. In certain embodiments, the kinase is a kinase of the vascular endothelial growth factor (VEGF) receptor subfamily, including VEGFR1 (Flt1), VEGFR2 (KDR or Flk1), and VEGFR3 (Flt4). In certain embodiments, the kinase is a kinase of the insulin receptor (IR) subfamily, including insulin-like growth factor I receptor (IGF-IR). In certain embodiments, the kinase is Ret. In certain embodiments, the kinase is a kinase of the HER (EGFR) subfamily. In certain embodiments, the kinase is a kinase of the FGFR subfamily. In certain embodiments, the kinase is a kinase of the HGFR (Met) subfamily. In certain embodiments,
the kinase is a kinase of the Abl protein tyrosine subfamily. In certain embodiments, the kinase is a kinase of the Src subfamily, including Src, Yesl, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. In certain embodiments, the kinase is a kinase of Frk, Btk, Csk, Abl, Syk, Fes, Fps, Fak, Jak, or Ack. In certain embodiments, the kinase is a kinase of selected form the group consisting of prostate-derived sterile, 20, sterile 11, and sterile 7. In certain embodiments, the kinase is a kinase of the cam kinase subfamily (calmodulin regulated kinases and related kinases). In certain embodiments, the kinase is a kinase of the AGC subfamily. In certain embodiments, the kinase is a kinase of the CMGC sub family (cdk, map kinase, glycogen synthetase kinase, and elk).

[00218] A compound provided herein, e.g., a compound of Formula 1, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, can also be combined or used in combination with other therapeutic agents useful in the treatment and/or prevention of a disease described herein.

[00219] As used herein, the term "in combination" includes the use of more than one therapy (e.g., one or more prophylactic and/or therapeutic agents). However, the use of the term "in combination" does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject with a disease or disorder. A first therapy (e.g., a prophylactic or therapeutic agent such as a compound provided herein) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent) to the subject. Triple therapy is also contemplated herein.

[00220] The route of administration of a compound provided herein, e.g., a compound of Formula 1, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is independent of the route of administration of a second therapy. In one embodiment, a compound provided herein, e.g., a compound of Formula 1, including an enantiomer, a
mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered orally. In another embodiment, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered intravenously. Thus, in accordance with these embodiments, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered orally or intravenously, and the second therapy can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intradiposally, intraarticularly, intrathecally, or in a slow release dosage form. In one embodiment, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a second therapy are administered by the same mode of administration, orally or by IV. In another embodiment, a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, is administered by one mode of administration, e.g., by IV, whereas the second agent (an anticancer agent) is administered by another mode of administration, e.g., orally.

[00221] In certain embodiments, each method provided herein may independently, further comprise the step of administering a second therapeutic agent. In one embodiment, the second therapeutic agent is an anticancer agent. In another embodiment, the anticancer agent is an antimetabolite, including, but not limited to, 5-fluoro uracil, methotrexate, cytarabine (also known as cytosine arabinoside or Ara-C), and HDAC (high dose cytarabine) and fludarabine. In yet another embodiment, the anticancer agent is an antimicrotubule agent, including, but not limited to, vinca alkaloids (e.g., vincristine and vinblastine) and taxanes (e.g., paclitaxel and docetaxel). In yet another embodiment, the anticancer agent is an alkylating agent, including, but not limited to, cyclophosphamide, melphalan, carmustine, and nitrosoureas (e.g., bischloroethyl nitrosourea and hydroxyurea). In yet another embodiment, the anticancer agent is a platinum agent, including, but not limited to, cisplatin,
carboplatin, oxaliplatin, satraplatin (JM-216), and CI-973. In yet another embodiment, the anticancer agent is an anthracycline, including, but not limited to, doxorubicin and daunorubicin. In yet another embodiment, the anticancer agent is an antitumor antibiotic, including, but not limited to, mitomycin, idarubicin, adriamycin, and daunomycin (also known as daunorubicin). In yet another embodiment, the anticancer agent is a topoisomerase inhibitor, e.g., etoposide and camptothecins. In yet another embodiment, the anticancer agent is selected from the group consisting of adriamycin, busulfan, cytarabine, cyclophosphamide, dexamethasone, fludarabine, fluorouracil, hydroxyurea, interferons, oblimersen, platinum derivatives, taxol, topotecan, and vincristine.

[00222] In another embodiment, the anticancer agent is a Bcr-Abl kinase inhibitor. In one embodiment, the Bcr-Abl kinase inhibitor is selected from the group consisting of imatinib, BMS354825 (dasatinib), AMN107 (nilotinib), AP23464, AZD0530, CGP76030, ON012380, INN-0406 (NS-187), SKI-606 (bosutinib), VX-680, and pyrrolo[2,3-d]pyrimidines including PD166326, PD173955 and PD180970. In another embodiment, the Bcr-Abl kinase inhibitor is imatinib. In yet another embodiment, the Bcr-Abl kinase inhibitor is dasatinib. In yet another embodiment, the Bcr-Abl kinase inhibitor is nilotinib. In yet another embodiment, the Bcr-Abl kinase inhibitor is AP23464. In yet another embodiment, the Bcr-Abl kinase inhibitor is AZD0530. In yet another embodiment, the Bcr-Abl kinase inhibitor is CGP76030. In yet another embodiment, the Bcr-Abl kinase inhibitor is SKI-606. In yet another embodiment, the Bcr-Abl kinase inhibitor is ON012380. In yet another embodiment, the Bcr-Abl kinase inhibitor is INN-0406 (NS-187). In yet another embodiment, the Bcr-Abl kinase inhibitor is a pyrrolo[2,3-d]pyrimidine. In another embodiment, the Bcr-Abl kinase inhibitor is VX-680. In another embodiment, the Bcr-Abl kinase inhibitor is PD166326. In yet another embodiment, the Bcr-Abl kinase inhibitor is PD173955. In still another embodiment, the Bcr-Abl kinase inhibitor is PD180970.

[00223] In still another embodiment, the anticancer agent is a FLT3 kinase inhibitor. In one embodiment, the FLT3 kinase inhibitor is selected from the group consisting of PKC 412, MLN 578, CEP-701, CT 53518, CT-53608, CT-52923, D-64406, D-65476, AGL-2033, AG1295, AG1296, KN-1022, PKC-412, SU5416, SU5614, SU1 1248, L-00021649, and CHIR-258. In another embodiment, the FLT3 kinase inhibitor is PKC 412. In another embodiment, the FLT3 kinase inhibitor is MLN 578. In still another embodiment, the FLT3 kinase inhibitor is CEP-701. In still another embodiment, the FLT3 kinase inhibitor is CT.
53518. In yet another embodiment, the FLT3 kinase inhibitor is CT-53608. In yet another embodiment, the FLT3 kinase inhibitor is CT-52923. In yet another embodiment, the FLT3 kinase inhibitor is D-64406. In yet another embodiment, the FLT3 kinase inhibitor is D-65476. In yet another embodiment, the FLT3 kinase inhibitor is AGL-2033. In yet another embodiment, the FLT3 kinase inhibitor is AG1295. In yet another embodiment, the FLT3 kinase inhibitor is AG1296. In yet another embodiment, the FLT3 kinase inhibitor is KN-1022. In yet another embodiment, the FLT3 kinase inhibitor is KN-1022. In yet another embodiment, the FLT3 kinase inhibitor is SU5416. In yet another embodiment, the FLT3 kinase inhibitor is SU5614. In yet another embodiment, the FLT3 kinase inhibitor is SU1 1248. In yet another embodiment, the FLT3 kinase inhibitor is L-00021649. In still another embodiment, the FLT3 kinase inhibitor is CHIR-258.

[00224] Other therapies or anticancer agents that may be used in combination with a compound provided herein, e.g., a compound of Formula I, including an enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, biologic response modifiers (e.g., interferons, interleukins, and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, cyclophosphamide, melphalan, and ifosfamide), antimetabolites (cytarabine (also known as cytosine arabinoside or Ara-C), HDAC (high dose cytarabine), and methotrexate), purine antagonists and pyrimidine antagonists (6-mercaptopurine, 5-fluorouracil, cytarbine, and gemcitabine), spindle poisons (vinblastine, vincristine, vinorelbine, and paclitaxel), podophyllotoxins (etoposide, irinotecan, and topotecan), antibiotics (daunorubicin, doxorubicin, bleomycin, and mitomycin), nitrosoureas (carmustine and lomustine), inorganic ions (cisplatin and carboplatin), enzymes (asparaginase), and hormones (tamoxifen, leuprolide, flutamide, and megestrol), imatinib, adriamycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies see, http://www.cancer.gov/nci/ftp/agents/agentlistframe.htm, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.
Biological Evaluation of Compounds

[00225] Standard physiological, pharmacological, and biochemical procedures are available for testing compounds provided herein to identify those that possess biological activities and/or selectively modulate the activity of kinases.

[00226] Such assays include, for example, biochemical assays such as binding assays, radioactivity incorporation assays, fluorescence polarization assays, and fluorescence resonance energy transfer (FRET) based assays (see generally Glickman et al, J. Biomolecular Screening 2002, 7, 3-10), as well as a variety of cell based assays.

[00227] In one embodiment, inhibition is determined in vitro. In certain embodiments, inhibition is assessed by phosphorylation assays. Any suitable phosphorylation assay can be employed. For example, membrane autophosphorylation assays, receptor autophosphorylation assays in intact cells, and ELISA’s can be employed. See, Gazit, et al, J. Med. Chem. 1996, 39, 2170-2177).

[00228] In addition, a variety of cell based assay methodologies can be successfully used in screening assays to identify and profile the specificity of compounds provided herein. Cells useful in such assays include cells with wild type or mutated forms. In one embodiment, the wild type is a kinase that is not constitutively active, but is activated with upon dimenization. For example, the mutant FLT3 kinase is constitutively active via internal tandem duplication mutations or point mutations in the activation domain. Suitable cells include those derived through cell culture from patient samples as well as cells derived using routine molecular biology techniques, e.g., retroviral transduction, transfection, mutagenesis, etc. Exemplary cells include Ba/F3 or 32Decl3 cells transduced with, e.g., MSCV retroviral constructs FLT3-ITD (Kelly et al., 2002); Molm-13 and MolI-14 cell line (Fujisaki Cell Center, Okayama, Japan); HL60 (AML-M3), AML193 (AML-M5), KG-1, KG-la, CRL-1873, CRL-9591, and THP-1 (American Tissue Culture Collection, Bethesda, MD); or any suitable cell line derived from a patient with a hematopoietic malignancy.

[00229] In some embodiments, the compounds described herein significantly inhibit receptor tyrosine kinases. A significant inhibition of a receptor tyrosine kinase activity refers to an IC₅₀ of no greater than about 100 µM. In certain embodiments, the compound provided herein has an IC₅₀ of no greater than about 50 µM, no greater than about 10 µM, no greater
than about 1 µM, no greater than about 100 nM, or no greater than about 50 nM. Lower IC₅₀'s are preferred because the IC₅₀ provides an indication as to the *in vivo* effectiveness of the compound. Other factors known in the art, such as compound half-life, biodistribution, and toxicity should also be considered for therapeutic uses. Such factors may enable a compound with a lower IC₅₀ to have greater *in vivo* efficacy than a compound having a higher IC₅₀. In one embodiment, a compound that inhibits activity is administered at a dose where the effective tyrosine phosphorylation, i.e., IC₅₀, is less than its cytotoxic effects, LD₅₀.

[00230] Compound binding may also be determined using phage display of fusion proteins exposed on the outer surface of the phage head, for example, using an affinity based phage display screening system as described in Fabian et al., (Nat Biotechnol. 2005 23(3):329-36). This approach employs a competition binding assay to determine the relative affinity of a compound of interest to a protein expressed as a fusion protein on the surface of the T7 bacteriophage. The assay uses phage tagged with a kinase of interest and an immobilized bait which are combined with the compound to be tested. A test compound which binds to the kinase directly or indirectly competes with the immobilized bait and prevents the binding of the phage-tagged kinase to the solid support. If the compound does not bind to the kinase, the tagged phage can bind to the solid support through the interaction between the kinase and the immobilized bait. The results can be read out by quantifying the amount of fusion protein bound to the solid support, which can be accomplished by either traditional plaque assays or by quantitative PCR (QPCR) using the phage genome as a template.

**EXAMPLES**

**Example 1**

Preparation of \(N-(3-(2\text{-fluoropropan-2-yl})\text{isoxazol-5-yl})\text{-N'}-\{4-[7-(2\text{-methoxy})\text{imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}\text{urea} \)

![Chemical Structure](image)

5
Compound 5 was synthesized as shown in Scheme E1.

**Scheme E1**

Step 1: To a stirred suspension of 60% NaH/mineral oil (12.48 g, 0.31 mol) in dry THF at 75 °C was added dropwise methyl 2-fluoro-2-methylpropanoate (24 g, 0.2 mol) in dry acetonitrile (16 mL, 0.31 mol) over the course of 45 min. The resulting pale yellow suspension was heated at 70 °C overnight, whereupon analysis by TLC indicated a single new product. After cooling to rt, the mixture was poured into water, acidified to pH~2 with 2N HCl, and extracted with diethyl ether (1 L). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-30% EtOAc in petroleum ether to afford 4-fluoro-4-methyl-3-oxopentanenitrile D1 as a colorless oil (18 g, 72% yield). LC-MS (ESI) m/z 128 (M - H)$^+$. 

Step 2: To a stirred solution of 4-fluoro-4-methyl-3-oxopentanenitrile D1 (12.9 g, 0.1 mol) and sodium hydroxide (8.20 g, 0.11 mol) in 1:1 water/EtOH (184 mL) was added hydroxylamine sulfate (17.23 g, 0.11 mol). The mixture was adjusted to pH 7.5 with IN NaOH, then heated at 80 °C for 15 hrs. After cooling to room temperature, the mixture was concentrated to dryness under reduced pressure. The resulting solid was partitioned between water and dichloromethane, and the separated organic layer was washed with brine, dried
over MgSC\textsubscript{4}, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-10% EtOAc in petroleum ether to afford 3-(2-fluoropropan-2-yl)isoxazol-5-amine D2 as a yellow solid (5 g, 35%). LC-MS (ESI) \textit{m/z} 145 (M + H)+.

**Step 3:** To a mixture of 3-(2-fluoropropan-2-yl)isoxazol-5-amine D2 (4.32 g, 0.03 mol) and K\textsubscript{2}C\textsubscript{3}O\textsubscript{4} (8.28 g, 0.06 mol) in THF (100 mL) at 0 °C was added dropwise a solution of phenyl carbonochloridate (6 mL, 0.045 mol) in THF (50 mL). The mixture was stirred at 0 °C for 1 hr, then at 40 °C for 20 hrs. Analysis by LC-MS and TLC indicated that the starting material was almost completely consumed and a new product had formed. The mixture was poured into water (150 mL) and the resulting mixture was extracted with EtOAc (100 mL). The organic layer was dried over Na\textsubscript{2}S\textsubscript{2}O\textsubscript{4} and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-4% EtOAc in petroleum ether to afford phenyl 3-(2-fluoropropan-2-yl)isoxazol-5-ylcarbamate D3 as a white solid (6 g, 76%).

**Step 4:** To a stirred solution of phenyl 3-(2-fluoropropan-2-yl)isoxazol-5-ylcarbamate D3 (66 mg, 0.22 mmol) in THF (2 mL) were added 7-(2-morpholin-4-yl-ethoxy)-2-(4-aminophenyl)imidazo[2,1-b]benzothiazole D4 (80 mg, 0.20 mmol) and a catalytic amount of DMAP (3 mg, 0.020 mmol). The solution was stirred at rt for 24 hrs. LC-MS indicated that the reaction was mostly complete. The precipitate was collected by filtration washing with THF (2 x 1 mL), MeOH (1 x 0.5 mL), ether (1 x 1 mL), and dried under reduced pressure to give N-(3-(2-fluoropropan-2-yl)isoxazol-5-yl)-N'-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea 5 (30 mg, 27%). LC-MS (ESI) \textit{m/z} 565 (M + H)+. \textit{\textsuperscript{1}}H NMR (300 MHz, DMSO-d\textsubscript{6}) \textit{δ} 10.35 (br. s., 1H), 8.94 (s, 1H), 8.61 (s, 1H), 7.87 (d, \textit{J} = 8.85 Hz, 1H), 7.79 (d, \textit{J} = 8.67 Hz, 2H), 7.68 (d, \textit{J} = 2.45 Hz, III), 7.53 (d, \textit{J} = 8.67 Hz, 2H), 7.09-7.26 (m, 1H), 6.18 (s, 1H), 4.04-4.29 (m, 2H), 3.46-3.73 (m, 4H), 2.63-2.81 (in, 2H), 2.53-2.58 (m, 4H), 1.72 (s, 3H), 1.65 (s, 3H).

**Example 2**

Preparation of N-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)-N'-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea 67
Step 1: Phenyl 5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-ylcarbamate D5 was prepared using procedures analogous to those described in Steps 1-3 of Example 1, substituting methyl 3,3,3-trifluoro-2,2-dimethylpropanoate for methyl 2-fluoro-2-methylpropanoate used in Example 1.

Step 2: N-(5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)-N'N'-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea 67 (84 mg, 68%) was prepared using a procedure analogous to that described in Step 4 of Example 1, substituting phenyl 5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-ylcarbamate D5 from Step 1 above for phenyl 3-(2-fluoropropan-2-yl)isoxazol-5-ylcarbamate D3 used in Example 1.

LC-MS (ESI) m/z 615 (M + H)+. 1H NMR (300 MHz, DMSO-d6) δ 9.70 (s, 1H), 8.89 (s, 1H), 8.60 (s, 1H), 7.86 (d, J = 8.85 Hz, 1H), 7.79 (d, J = 8.67 Hz, 2H), 7.67 (d, J = 2.45 Hz, 1H), 7.52 (d, J = 8.67 Hz, 2H), 7.15 (dd, J = 2.54, 8.95 Hz, 1H), 6.93 (s, 1H), 4.08-4.25 (m, 2H), 3.52-3.68 (m, 4H), 2.65-2.82 (m, 2H), 2.45-2.58 (m, 4H), 1.57 (s, 6H).

Example 3
Preparation of N-(5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-yl)-N'N'-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea 71
Step 1: Phenyl 5-(1-(trifluoromethyl)cyclopropyl)isoxazol-3-ylcarbamate D6 was prepared using procedures analogous to those described in Steps 1-3 of Example 1, substituting methyl 1-(trifluoromethyl)cyclopropanecarboxylate for the methyl 2-fluoro-2-methylpropanoate used in Example 1.

Step 2: N-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-N’-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea 71 (88 mg, 72%) was prepared using a procedure analogous to that described in Step 4 of Example 1, substituting phenyl 5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-ylcarbamate D6 from Step 1 above for phenyl 3-(2-fluoropropan-2-yl)isoxazol-5-ylcarbamate D3 used in Example 1.

LC-MS (ESI) m/z 613 (M +H)+. 1H NMR (300 MHz, DMSO-d6) δ 9.69 (s, 1H), 8.88 (s, 1H), 8.60 (s, 1H), 7.86 (d, J = 8.85 Hz, 1H), 7.79 (d, J = 8.67 Hz, 2H), 7.67 (d, J = 2.26 Hz, 1H), 7.54 (d, J = 8.67 Hz, 2H), 7.15 (dd, J = 2.35, 8.95 Hz, 1H), 6.91 (s, 1H), 4.16 (t, J = 5.65 Hz, 2H), 3.52-3.66 (m, 4H), 2.72 (t, j = 5.65 Hz, 2H), 2.41-2.53 (m, 4H), 1.40 - 1.61 (m, 4H).

Example 4

Preparation of N-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-N’-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea 59
Step 1: Phenyl 5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-ylcarbamate D7 was prepared using procedures analogous to those described in Steps 1-3 of Example 1, substituting methyl 3-fluoro-2-(fluoromethyl)-2-methylpropanoate for the methyl 2-fluoro-2-methylpropanoate used in Example 1.

Step 2: N-(5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-yl)-N’-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea 55 (38 mg, 32%) was prepared using a procedure analogous to that described in Step 4 of Example 1, substituting phenyl 5-(1,3-difluoro-2-methylpropan-2-yl)isoxazol-3-ylcarbamate D7 from Step 1 above for phenyl 3-(2-fluoropropan-2-yl)isoxazol-5-ylcarbamate D3 used in Example 1.

LC-MS (ESI) m/z 597 (M + H)+. 1H NMR (300 MHz, DMSO-d6) δ 9.65 (s, 1H), 8.89 (s, 1H), 8.59 (s, 1H), 7.85 (d, J = 8.85 Hz, 1H), 7.78 (d, J = 8.29 Hz, 2H), 7.66 (d, J = 2.07 Hz, 1H), 7.52 (d, J = 8.48 Hz, 2H), 7.14 (dd, J = 1.98, 8.76 Hz, 1H), 6.82 (s, 1H), 4.74 (s, 2H), 4.58 (s, 2H), 4.15 (t, J = 5.65 Hz, 2H), 3.53-3.64 (m, 4H), 2.71 (t, J = 5.46 Hz, 2H), 2.47 (d, J = 4.33 Hz, 4H), 1.35 (s, 3H).

Example 5
Preparation of N-(5-(1-ethyl-1-butyl-D9)isoxazol-3-yl)-N’-{4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2, 1-b][1,3]benzothiazol-2-yl]phenyl}urea 55
Compound 55 was synthesized as shown in Scheme E2.

Scheme E2

**Step 1:** To a stirred suspension of 60% NaH/mineral oil (1.5 molar equivalents) in dry THF at 75 °C is added dropwise methyl trimethyl-D9-acetate E1 (commercially available from CDN) (1.0 molar equivalent) in dry acetonitrile (1.5 molar equivalents) over the course of 45 min. The resulting mixture is then heated at 70 °C overnight, whereupon analysis by TLC shows significant formation a single new product.
After cooling to room temperature, the mixture is poured into water, acidified to pH~2 with 2N HCl, and extracted with diethyl ether. The organic layer is dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue is purified by silica gel chromatography afford 4-tert-butyl-D9-3-oxopentanenitrile E2.

Step 2: A solution of hydroxylamine hydrochloride (1.5 molar equivalents) in water (one volume) is added dropwise over a 10-minute period to a stirred, refluxing mixture of 4-tert-butyl-D9-3-oxopentanenitrile E2 (1.0 molar equivalent) in a mixture of water (4 volumes) and ethanol (3 volumes). The mixture is heated at reflux for 5 to 10 hrs, and the pH of the mixture is periodically adjusted to 6.5 by the addition of either aq. hydrogen chloride or aq. sodium hydroxide, as required. Then the mixture is concentrated under reduced pressure, and the residual liquid is dried over MgSO$_4$, dissolved in 200 mL of hexane and chilled. Filtration affords 3-amino-5-(1,1-dimethylethyl-D9)-isoxazole E3 as a yellow solid.

Step 3: To a mixture of 3-amino-5-(1,1-dimethylethyl-D9)-isoxazole E3 (1.0 molar equivalent) and K$_2$CO$_3$ (2.0 molar equivalents) in THF (2 volumes) at 0 °C is added dropwise a solution of phenyl carbonochloridate (1.5 molar equivalents) in THF (1 volume). The mixture is stirred at 0 °C for 1 hr, then at 40 °C for 20 hrs. The mixture is poured into water (3 volumes) and the resulting mixture is extracted with EtOAc (2 volumes). The organic layer is dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue is purified by silica gel chromatography to afford phenyl 5-(1,1-dimethylethyl-D9)isoxazol-3-ylcarbamate E4.

Step 4: To a stirred solution of phenyl 5-(1,1-dimethylethyl-D9)isoxazol-3-ylcarbamate E4 (1.1 molar equivalents) in THF are added 7-(2-morpholin-4-yl-ethoxy)-2-(4-aminophenyl)imidazo[2,1-b]benzothiazole E6 (1.0 molar equivalent), DIET (1.5 molar equivalents), and a catalytic amount of DMAP (0.05 molar equivalent). The solution is stirred at 65 °C for 2 hrs. The mixture is concentrated under reduced pressure and the residue is purified by reverse phase HPLC to give N-(5-(tert-butyl-D9)isoxazol-3-yi)-N’-[4-[7-(2-morpholin-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl]urea 55.

Alternatively, to a stirred solution of phenyl 5-(1,1-dimethylethyl-D9)isoxazol-3-ylcarbamate E4 (1.1 molar equivalents) from Step 3 of this Example in DCM are added 7-(2-morpholin-4-yl-ethoxy)-2-(4-aminophenyl) imidazo [2,1-b]benzothiazole E6 (1.0 molar equivalent), and a catalytic amount of DMAP (0.06 molar equivalent). Upon
mixing, triethylamine (TEA, 0.15 equiv) is added, optionally followed by additional DCM. The reaction is heated to reflux (~ 40 °C) and agitated for 2 - 20 hrs. Upon complete dissolution, crystallization of compound 55 may be observed from the solution after ~ 30 min.

Example 6
Preparation of \(N-(5\text{-}t\text{-}\text{butylisoxazol}-3\text{-}y\text{l})\text{-}N\text{'-}[4\text{-}[7\text{-}(2\text{-}morpholin-D8\text{-}4\text{-}y\text{l}-ethoxy)imidazo[2, 1-b][1,3]benzothiazol-2\text{-}y\text{l}]phenyl \text{]}\) urea 53

[00248] Compound 53 was synthesized as shown in Scheme E3.

[00249] **Step 1:** Morpholine-D8 (1.0 molar equivalent) and chloracetaldehyde (1.0 molar equivalent) are mixed in 1,2-dichloroethane and then treated with sodium triacetoxyborohydride (1.4 molar equivalents) and AcOH (1.0 molar equivalent). The mixture is stirred at room temperature under \(N_2\) for 24 hrs until the reactants are consumed as determined by LC-MS. The reaction mixture is quenched by adding sat. NaHCO\(_3\), and the product is extracted with EtOAc. The organic layer is washed with brine, dried over MgSO\(_4\), and evaporated under reduced pressure to give 4-(2-chloroethyl)morpholine-D8 E7.

[00250] **Step 2:** To a round bottom flask is charged with 2-(4-nitrophenyl) imidazo[2,1-\text{b\text{-}}]benzothiazol-7-ol E8 (1.0 mol equivalent), which is made according to WO 2009/38757, DMF, 4-(2-chloroethyl)morpholine-D8 E7 (1.5 mol equivalents), potassium carbonate (2.0 mol equivalents), and tetrabutylammonium iodide (0.05 mol equivalent) with stirring. The resulting suspension is heated to 90 °C to 95 °C, maintaining the temperature for approximately 5 hrs. The reaction is monitored by TLC until no starting material is
observed. The reaction mixture is cooled to ~10 °C, and the yellow solids are collected by filtration. The solids are slurried in water (2 x 5 L) and filtered. The crude wet product is slurried in acetone (5 L), filtered, and the solids rinsed with acetone (2 x 1.5 L). The solids are dried in a vacuum oven at 45 °C to give 7-(2-morpholin-D8-4-yl-ethoxy)-2-(4-nitrophenyl) imidazo [2,1-b]benzothiazole E9.

Scheme E3

[00251] **Step 3:** To a Parr shaker, 7-(2-morpholin-D8-4-yl-ethoxy)-2-(4-nitrophenyl) imidazo [2,1-b]benzothiazole E9 (1.0 molar equivalent), THF (1 volume), methanol (1 volume), and Raney nickel catalyst (1.0 molar equivalent) are added. The reaction vessel is purged with nitrogen and hydrogen with stirring briefly under pressure and then venting. The
reaction vessel is pressurized with hydrogen (150 psi). The resulting mixture is stirred and the hydrogen pressure is maintained at 150 psi for over 24 hrs with repressurization as necessary. The reaction progress is monitored by TLC. Reaction is complete when the TLC indicates no starting material present, typically after 24 hrs of stirring at 150 psi. The reaction mixture is filtered through a Buchner funnel. The filtrate is concentrated under reduced pressure, and the residue is triturated with methyl tert-butyl ether. The resultant solids are collected by filtration, washed with methyl tert-butyl ether, and dried in a vacuum oven at 25 °C to give 7-(2-Morpholin-D8-4-yl-ethoxy)-2-(4-aminophenyl) imidazo [2,1-b]benzothiazole E10.

[00252] Step 4: To a stirred solution of phenyl 5-(1,1-dimethylethyl)isoxazol-3-ylcarbamate E11 (1.1 molar equivalents) in THF are added 7-(2-morpholin-D8-4-yl-ethoxy)-2-(4-aminophenyl) imidazo [2,1-b]benzothiazole E10 (1.0 molar equivalent), DIEA (1.5 molar equivalents), and a catalytic amount of DMAP (0.05 molar equivalent). The solution is stirred at 65 °C for 2 hrs. The mixture is concentrated under reduced pressure and the residue is purified by reverse phase HPLC to give N-(5-err-butylisoxazol-3-yl)-N'-[4-[7-(2-morpholin-D8-4-yl-ethoxy)imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl]urea 53.

[00253] Alternatively, to a stirred solution of phenyl 5-(1,1-dimethylethyl)isoxazol-3-ylcarbamate E11 (1.1 molar equivalents) in DCM are added 7-(2-morpholin-D8-4-yl-ethoxy)-2-(4-aminophenyl) imidazo [2,1-b]benzothiazole E10 (1.0 molar equivalent), and a catalytic amount of DMAP (0.06 molar equivalent). Upon mixing, triethylamine (TEA, 0.15 equiv) is added, optionally followed by additional DCM. The reaction is heated to reflux (~40 °C) and agitated for 2 - 20 hrs. Upon complete dissolution, crystallization of compound 53 may be observed from the solution after ~ 30 min.

Example 7

Binding constant (K_d) measurements for a small-molecule to a kinase

[00254] Competition binding assays used herein were developed, validated and performed as described in Fabian et al, Nature Biotechnology 2005, 23, 329-336. Kinases were produced as fusions to 17 phage (See, Fabian et al. or WO 04/01 5142) or alternatively, the kinases were expressed in HEK-293 cells and subsequently tagged with DNA for PGR detection (See, WO 08/005310). For the binding assays, streptavidin-coated magnetic beads were treated with biotinylated affinity ligands for 30 min at room temperature to generate
affinity resins. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinase, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17x PBS, 0.05% Tween 20, 6 mM DTT). Test compounds were prepared as 100x stocks in DMSO and rapidly diluted into the aqueous environment. DMSO was added to control assays lacking a test compound. Primary screen interactions were performed in polypropylene 384-well plates in a final volume of 34 µL, while Kd determinations were performed in polystyrene 96-well plates in a final volume of 135 µL. The assay plates were incubated at room temperature with shaking for 1 hour, long enough for binding reactions to reach equilibrium, and the affinity beads were washed extensively with wash buffer (1x PBS, 0.05% Tween 20) to remove unbound protein. The beads were then resuspended in elution buffer (1x PBS, 0.05% Tween 20, 2 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 min. The kinase concentration in the eluates was measured by quantitative PCR. Each kinase was tested individually against each compound. Kd's were determined using eleven serial threefold dilutions.

[00255] The biological results are summarized in Table 1, wherein A represents a value smaller than 100 nM, and B represents a value between 100 nM to 1 µM, C represents a value between 1 µM to 50 µM and D represents a value greater than 50 µM.

[00256] In certain embodiments, the compounds provided herein were found to have a Kd of less than 100 nM. In certain embodiments, the compounds provided herein were found to have a Kd of less than 10 nM. In certain embodiments, the compounds provided herein were found to have a Kd of less than 2 nM. In certain embodiments, the compounds provided herein were found to have a Kd of less than 1 nM.

**TABLE 1**

<table>
<thead>
<tr>
<th>Cmpd #</th>
<th>FLT3 Kd</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td>59</td>
<td>A</td>
</tr>
<tr>
<td>67</td>
<td>A</td>
</tr>
<tr>
<td>71</td>
<td>A</td>
</tr>
</tbody>
</table>

- 76 -
Example 8

MV4-1 1 cellular proliferation assay

[00257] Cancer cell viability and proliferation was measured using a fluorimetric assay that measures reduction of a resazurin-containing dye CTB, (Cell Titer Blue®, Promega #G8081), into the highly fluorescent resorufin by various redox enzymes, where metabolic activity is taken as a measure of cell viability.

[00258] MV4;1 1 is a well-characterized FLT3 -dependent human cell line that contains the internal tandem duplication mutation (ITD mutation) found in a certain subset of patients with acute myeloid leukemia and which expresses constitutively active FLT3 receptors (Yee et al. Blood 2002 100(8), 2941-2949). This cell line was used to determine the ability of Compound I-1 to inhibit FLT3 receptors having the ITD mutation. RS4;1 1 is a cell line expressing wild type FLT3 established from the bone marrow of an acute leukemia patient having the t(4;1 1) chromosomal abnormality. This cell line was used to determine the ability of Compound I-1 to inhibit wild type FLT3.

[00259] MV4; 11 and RS4;1 11 cells were obtained from ATCC (Manassas, VA) and cultured in Iscove's media with 10% FBS and RPMI complete with 10% FBS, respectively. Cells were cultured overnight in low serum media with 0.5% FBS. The following day, cells were seeded on to a 96-well plate at 40,000 cells per well at a volume of 100 μL per well. The compound plate containing Compound I-1 or positive control (Compound 1A) was set up to achieve a final working concentration of 185 nM down to 0.03 nM by serially diluting three-fold with DMSO. DMSO was used as a negative control. 100 μL of compound was added to 100 μL of cells and incubated at 37°C in 5% CO₂ for 72 hrs for MV4;1 1 cells and 48 hours for RS4; 11 cells.

[00260] CTB reagent was thawed in a 37°C water bath. 40 μL of CTB reagent was added to the plate containing the cells, and the cells were incubated with the reagent at 37°C in 5% CO₂ for 3 hours. The absorbance was measured at 560 nm(excitation)/ 590 nm (emission) using Spectramax Plus 384 Absorbance Microplate Reader by Molecular Devices.

[00261] Cellular proliferation values were measured in terms of concentration of compounds that achieves 50% inhibition of MV4;1 1 cellular proliferation compared to control (EC₅₀). The biological results are summarized in Table 2, wherein A represents a
value smaller than 100 nM, and B represents a value between 100 nM to 1 µM, C represents a value between 1 µM to 50 µM and D represents a value greater than 50 µM.

[00262] In certain embodiments, the compounds provided herein were found to have an EC50 of less than 100 nM. In certain embodiments, the compounds provided herein were found to have an EC50 of less than 10 nM. In certain embodiments, the compounds provided herein were found to have an EC50 of less than 1 nM. In certain embodiments, the compounds provided herein were found to have an EC50 of less than 0.5 nM.

### TABLE 2

<table>
<thead>
<tr>
<th>Cmpd #</th>
<th>FLT3 Kd</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>A</td>
</tr>
<tr>
<td>59</td>
<td>A</td>
</tr>
<tr>
<td>67</td>
<td>A</td>
</tr>
<tr>
<td>71</td>
<td>A</td>
</tr>
</tbody>
</table>

Example 9
Pharmacokinetic studies with compound 59

Study Design

[00263] Rats were dosed either intravenously at 1 mg/kg dose or orally at 10 mg/kg dose with compound 59. Blood samples were collected over a 24 hr time-course. The plasma was analyzed for compound 59 and the pharmacokinetic parameters were determined.

Study Procedures And Methods

[00264] Pre-catheterized (jugular vein), male Sprague-Dawley rats (230-300 g) obtained from Charles River, Hollister, CA, were acclimated at the vivarium of Rabbit and Rodent Diagnostic Associates (San Diego, CA) for at least three days following delivery and prior to entering a study. Rats were fasted overnight before intravenous or oral dosing. For intravenous dosing, compound 59 was dissolved in a 22% hydroxypropyl-beta-cyclodextrin (HPBCD) solution and administered at a dose of 1 mg/kg. For oral dosing, compound 59 was dissolved in Pharmatek #6 solution and administered at a dose of 10 mg/kg. Blood was collected at 5 (IV only), 15, 30 min, 1, 2, 4, 6, and 24 hrs postdose using K3EDTA as
anticoagulant and plasma was harvested for the analysis of compound 59.

Plasma samples, calibration standards, and quality control samples (20 µL) were extracted with six volumes of acetonitrile containing an internal standard (25 ng/mL) and analyzed using LC-MS/MS analysis (API 3200). Sample separation was achieved on a Zorbax SB C8 column (5 µm, 4.6 x 50 mm) at a flow rate of 1.6 mL/min. The gradient program was from 5-95% acetonitrile in 0.05% formic acid over one minute. The mass transition from m/z 577.18 to 421.10 was monitored for compound 59. The internal standard mass transitions monitored were 483.0 to 317.2.

Data Analysis And Results

Pharmacokinetic parameters of compound 59 were calculated based on the plasma concentration-time profiles of each animal using an internally developed modelling program. Results are summarized in Table 3.

### TABLE 3. Summary of Compound 59 Oral and Intravenous Pharmacokinetic Parameters in Rats

<table>
<thead>
<tr>
<th></th>
<th>Oral (mg/kg)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µM)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (hr)</th>
<th>AUC&lt;sub&gt;0-&lt;infty&gt;&lt;/sub&gt; (µM hr)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</th>
<th>F&lt;sub&gt;I&lt;/sub&gt; (%)</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.55</td>
<td>3.3</td>
<td>24</td>
<td>7.5</td>
<td>29.0</td>
<td>22% HPBCD</td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>1</td>
<td>3.39</td>
<td>1.46</td>
<td>8.27</td>
<td>7.0</td>
<td>22% HPBCD</td>
<td></td>
</tr>
</tbody>
</table>

1. F% was calculated with the dose normalized AUC<sub>0-<infty></sub> IV data.
2. n = 3 for PO; and n=2 for IV.

Example 10

*In vitro* metabolic disposition of compounds in human liver microsomal fractions

Metabolic stability of compounds was measured in human microsomes.

Microsomal Stability:

Test compound (1 µM) was incubated with pooled liver microsomes. Aliquots were taken at 0, 5, 15, 30, and 60 min and quenched immediately with two-volumes
of ACN containing an internal standard (IS). The samples were extracted and analyzed by LC-MS/MS.

Experimental Procedure:

Reagents

[00269] 0.5 M K$_2$HP0$_4$, pH 7.4 (19 mL 1 M monobasic (Sigma P8709) + 81 mL 1 M dibasic (Sigma P8584) + 100 mL H$_2$O); 0.065 M MgCl$_2$$\cdot$6H$_2$O (Sigma M-0250); 10 mM NADPH; tetrasodium salt (Sigma N7785).

Materials

[00270] Pooled human liver microsomes (male and female) were purchased from (CellzDirect lot HMMC-PL020). Microsomes were stored at -80°C prior to use.

[00271] Microsomes and test compound were pre-mixed prior to the addition of NADPH (final concentration = 1 mM) to initiate the reaction for a final concentration of 0.5mg/mL microsome and 1 µM compound in 0.1M phosphate buffer pH 7.4, 6.5 mM MgCl$_2$ and 0.5 % DMSO. The final incubation volume with NADPH was 600 µL. A control incubation was included for each compound tested where water was added instead of NADPH (minus NADPH). Testosterone was included with each incubation as a positive control. All incubations were performed in duplicate for each test compound.

[00272] Samples were incubated at 37 °C and 50 µL aliquots were taken from each incubation at 0, 5, 15, 30, and 60 min, and added to 200 µL ACN containing internal standard to quench the reaction. The samples were then diluted with 100 µL 50/50 ACN/water, and the incubation plates were vortexed and centrifuged at 3600 rpm for 10 min at 4 °C to precipitate the protein. Following protein precipitation, the sample supernatants were analyzed by LC-MS/MS.

Data Analysis:

[00273] The peak area ratio (compound peak area/ internal standard peak area) was normalized to 100 % using the time = 0 min data and the natural log (In) of the percent compound remaining was plotted against time. The slope of the line was determined using a linear fit and the elimination rate constant was calculated.
The elimination rate constant \( (k) = (-\text{slope}) \)

From the above, half-life and intrinsic clearance was calculated using the following equations.

\[
\text{Half life (} t_{1/2} \text{) (min)} = \frac{0.693}{k}
\]

\[
\text{Intrinsic Clearance (CL}_{\text{tr}} \text{) (} \mu \text{i/min/mg protein)} = \frac{V \times 0.693}{t_{1/2}} \quad \text{where V is a volume term expressed as } \mu \text{L/mg protein.}
\]

One to two control compounds were included in the assay to verify the enzymes were active. If the control compounds were not sufficiently turned over the results were rejected. Results are shown in Table 4.

TABLE 4. Microsomal stability in human liver microsome for select compounds.

<table>
<thead>
<tr>
<th>Compound #</th>
<th>Half-life (min)</th>
<th>Intrinsic Clearance (( \mu \text{i/min/mg} ))</th>
<th>Percent compound remaining at assay end</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&gt;60</td>
<td>&lt;23</td>
<td>100</td>
</tr>
<tr>
<td>59</td>
<td>&gt;60</td>
<td>&lt;23</td>
<td>94.5</td>
</tr>
<tr>
<td>67</td>
<td>&gt;60</td>
<td>&lt;23</td>
<td>100</td>
</tr>
<tr>
<td>71</td>
<td>&gt;60</td>
<td>&lt;23</td>
<td>100</td>
</tr>
</tbody>
</table>

Limit of calculation for intrinsic clearance is 23 pL/min/mg at 60 min.

* * * * *

The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.
What is claimed is:

1. A compound of Formula I:

   \[
   \begin{align*}
   &R^1, R^2, \text{ and } R^3 \text{ are each independently hydrogen, deuterium, fluoro, or methyl,} \\
   &\text{where the methyl is optionally substituted with one, two, or three groups, which are each} \\
   &\text{independently deuterium or fluoro; or } R^2 \text{ and } R^3 \text{ together with the carbon to which they are} \\
   &\text{attached form } c_3, c_7 \text{ cycloalkylene, optionally substituted with one, two, or three groups, which} \\
   &\text{are each independently deuterium or fluoro;} \\
   &R^4, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^3, R^9, R^c, R^d, R^e, R^f, \\
   &R^8, \text{ and } R^h \text{ are each independently hydrogen, deuterium, or fluoro;} \\
   &R^5 \text{ and } R^6 \text{ are each independently hydrogen or deuterium; and} \\
   &X \text{ is } O \text{ and } Y \text{ is } N; \text{ or } X \text{ is } N \text{ and } Y \text{ is } O; \\
   &\text{with the proviso that at least one of } R^1, R^2, \text{ and } R^3 \text{ is deuterium, fluoro, or} \\
   &\text{methyl substituted with at least one deuterium or fluoro; or at least one of } R^4, R^7, R^8, R^9, R^{10}, \\
   &R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^b, R^l, R^s, R^3, R^b, R^c, R^d, R^e, R^f, R^g, \text{ and } R^h \text{ is deuterium or fluoro;} \\
   &\text{or at least one of } R^5 \text{ and } R^6 \text{ is deuterium; and when the compound comprises deuterium but} \\
   &\text{not fluoro, the compound has an isotopic enrichment factor of no less than about 64 or a} \\
   &\text{purity of no less than about 50%}. \\
   
   \end{align*}
   \]

2. The compound of claim 1, wherein at least one of R^7, R^8, R^9, and R^{10} is deuterium or fluoro.

3. The compound of claim 1 or 2, wherein R^{11} is deuterium or fluoro.
4. The compound of any of claims 1 to 3, wherein at least one of R\textsubscript{12}, R\textsubscript{13}, and R\textsubscript{14} is deuterium or fluoro.

5. The compound of claim 1 having the structure of Formula II:

![Formula II](image)

6. The compound of any of claims 1 to 5, wherein at least one of R\textsubscript{15}, R\textsubscript{16}, R\textsubscript{17}, and R\textsubscript{18} is deuterium or fluoro.

7. The compound of claim 1 having the structure of Formula III:

![Formula III](image)

8. The compound of any of claims 1 to 7, wherein at least one of R\textsubscript{a}, R\textsubscript{b}, R\textsubscript{c}, R\textsubscript{d}, R\textsubscript{e}, R\textsubscript{f}, R\textsubscript{g}, and R\textsubscript{h} is deuterium or fluoro.

9. The compound of claim 8, wherein at least one of R\textsubscript{a}, R\textsubscript{b}, R\textsubscript{c}, and R\textsubscript{f} is deuterium or fluoro.

10. The compound of claim 8, wherein at least one of R\textsubscript{c}, R\textsubscript{d}, R\textsubscript{g}, and R\textsubscript{h} is deuterium or fluoro.

11. The compound of claim 8, wherein at least one of R\textsubscript{a}, R\textsubscript{b}, R\textsubscript{c}, and R\textsubscript{d} is deuterium or fluoro.
12. The compound of claim 8, wherein at least one of R<sub>e</sub>, R<sub>f</sub>, R<sub>h</sub>, and R<sub>i</sub> is deuterium or fluoro.

13. The compound of claim 1 having the structure of Formula III:

![Formula](image)

(IV)

14. The compound of any of claims 1 to 13, wherein at least one of R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> comprises deuterium or fluoro.

15. The compound of claim 14, wherein R<sup>1</sup> is fluoro.

16. The compound of claim 14, wherein R<sup>1</sup> is CH<sub>3</sub>, CDH<sub>2</sub>, CD<sub>2</sub>H, CD<sub>3</sub>, CFH<sub>2</sub>, CFDH, CFD<sub>2</sub>, CF<sub>2</sub>H, CF<sub>2</sub>D, or CF<sub>3</sub>.

17. The compound of any of claims 14 to 16, wherein R<sup>2</sup> is CH<sub>3</sub>, CDH<sub>2</sub>, CD<sub>2</sub>H, CD<sub>3</sub>, CFH<sub>2</sub>, CFDH, CFD<sub>2</sub>, CF<sub>2</sub>H, CF<sub>2</sub>D, or CF<sub>3</sub>.

18. The compound of any of claims 14 to 16, wherein R<sup>2</sup> is CH<sub>3</sub> or CFH<sub>2</sub>.

19. The compound of any of claims 14 to 18, wherein R<sup>3</sup> is CH<sub>3</sub>, CDH<sub>2</sub>, CD<sub>2</sub>H, CD<sub>3</sub>, CFH<sub>2</sub>, CFDH, CFD<sub>2</sub>, CF<sub>2</sub>H, CF<sub>2</sub>D, or CF<sub>3</sub>.

20. The compound of any of claims 14 to 18, wherein R<sup>3</sup> is CH<sub>3</sub> or CFH<sub>2</sub>.

21. The compound of any of claims 1 to 16, wherein R<sup>2</sup> and R<sup>3</sup> together with the carbon to which they are attached form C<sub>3-7</sub> cycloalkylene, optionally substituted with one, two, or three groups, which are each independently deuterium or fluoro.

22. The compound of claim 21, wherein R<sup>2</sup> and R<sup>3</sup> together with the carbon to which they are attached form cyclopropyl or cyclobutyl.

23. The compound of any of claims 1 to 22, wherein X is O and Y is N.
24. The compound of any of claims 1 to 22, wherein X is N and Y is O.

25. The compound of claim 1 selected from the group consisting of:

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>R^I</th>
<th>R^C</th>
<th>R^J</th>
<th>R^B</th>
<th>R^C</th>
<th>R^D</th>
<th>R^E</th>
<th>R^F</th>
<th>R^G</th>
<th>R^H</th>
<th>X</th>
<th>Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>10</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>11</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>12</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>18</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>19</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>20</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>21</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>22</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>23</td>
<td>CD₃</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>II</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>24</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
<td>O</td>
</tr>
<tr>
<td>25</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>26</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>27</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>28</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>29</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>30</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>31</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>CFH₂</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>32</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>33</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>34</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>N</td>
</tr>
<tr>
<td>35</td>
<td>CF₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>36</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>37</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>38</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>39</td>
<td>D</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>42</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>44</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>45</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>46</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>47</td>
<td>D</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>49</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>50</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>CD₃</td>
<td>CD₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>52</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>D</td>
<td>H</td>
<td>O</td>
</tr>
<tr>
<td>53</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>O</td>
</tr>
<tr>
<td>54</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>F</td>
<td>H</td>
<td>O</td>
</tr>
</tbody>
</table>
and enantiomers, mixtures of enantiomers, and mixtures of diastereomers thereof; and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

26. A pharmaceutical composition comprising the compound of any of claims 1 to 25, and one or more pharmaceutically acceptable excipients.

27. The pharmaceutical composition of claim 26, wherein the composition is formulated for single dose administration.
28. The pharmaceutical composition of claim 26 or 27, wherein the composition is formulated as oral, parenteral, or intravenous dosage form.

29. The pharmaceutical composition of any of claims 26 to 28, further comprising a second agent selected from a chemotherapeutic agent, an antiproliferative agent, an anti-inflammatory agent, an immunomodulatory agent, an immunosuppressive agent, or an antiemetic agent.

30. A method of treating a proliferative disease, which comprises administering the compound of any of claims 1 to 25 or the pharmaceutical composition of any of claims 26 to 29.

31. The method of claim 30, wherein the proliferative disease is cancer.

32. The method of claim 31, wherein the cancer is a leukemia.

33. The method of claim 32, wherein the leukemia is an acute leukemia.

34. The method of claim 32, wherein the leukemia is acute myeloblastic leukemia.

35. The method of claim 32, wherein the leukemia is promyelocyte leukemia.

36. The method of claim 32, wherein the leukemia is acute lymphoblastic leukemia.

37. The method of any of claims 32 to 36, wherein the leukemia is Philadelphia positive.

38. The method of any of claims 32 to 37, wherein the leukemia is relapsed or refractory.

39. The method of any of claims 32 to 38, wherein the leukemia is a drug-resistant leukemia.

40. The method of claim 39, wherein the drug-resistant leukemia is resistant to a FLT3 kinase inhibitor.

41. The method of claim 39, wherein the drug-resistant leukemia is resistant to PKC 412, MLN 578, CEP-701, CT 53518, CT-53608, CT-52923, D-64406, D-65476, AGL-
2033, AG1295, AG1296, KN-1022, PKC-412, SU5416, SU5614, SU1 1248, L-00021649, or CHIR-258.

42. The method of any of claims 39 to 41, wherein the drug-resistant leukemia has a constitutively activating FLT3 mutant.

43. The method of any of claims 30 to 42, further comprising administering a second therapeutic agent.

44. The method of claim 43, wherein the second therapeutic agent is an anticancer agent.

45. The method of claim 44, wherein the anticancer agent is selected from the group consisting of adriamycin, busulfan, cytarabine, cyclophosphamide, dexamethasone, fludarabine, fluorouracil, hydroxyurea, interferons, oblimersen, platinum derivatives, taxol, topotecan, and vincristine.

46. The method of claim 45, wherein the anticancer agent is a FLT3 kinase inhibitor selected from the group consisting of PKC-412, MLN 578, CEP-701, CT 53518, CT-53608, CT-52923, D-64406, D-65476, AGL-2033, AG1295, AG1296, KN-1022, PKC-412, SU5416, SU5614, SU1 1248, L-00021649, and CHIR-258.

47. The method of claim 31, wherein the cancer is a solid tumor.

48. The method of claim 31, wherein the cancer is a bladder cancer, breast cancer, cervical cancer, CNS cancer, colon cancer, esophageal cancer, head and neck cancer, liver cancer, lung cancer, nasopharyngeal cancer, neuroendocrine cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, salivary gland cancer, small cell lung cancer, skin cancer, stomach cancer, testicular cancer, thyroid cancer, uterine cancer, or hematologic malignancy.

49. The method of any of claims 30 to 48, wherein the administration is oral.

50. The method of any of claims 30 to 48, wherein the administration is parenteral.

51. The method of any of claims 30 to 47, wherein the administration is
intravenous.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/US201Q/055042

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D513/04 A61K31/5377 A61P35/00

**ADD.**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, BEI LSTEIN Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

* Special categories of cited documents:

- **"A"** document defining the general state of the art which is not considered to be of particular relevance
- **"E"** earlier document but published on or after the international filing date
- **"L"** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **"O"** document referring to an oral disclosure, use, exhibition or other means
- **"P"** document published prior to the international filing date but later than the priority date claimed

- **"T"** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **"X"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **"Y"** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **"Z"** document member of the same patent family

**Date of the actual completion of the international search**

19 January 2011

**Date of mailing of the international search report**

31/01/2011

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Mini ejew, Catherine
### DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>wo 95/26325 A2 (ISOTECHNIKA INC [CA]) 5 October 1995 (1995-10-05) claim 1 page 1, line 9 - line 15 page 19, line 8 - page 20, line 7</td>
<td>1-51</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2646437 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101448843 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2001892 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2009530300 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20080108548 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2008141169 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2007232604 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2010298313 A1</td>
</tr>
<tr>
<td>W0 9526325 A2</td>
<td>05-10-1995</td>
<td>AT 372966 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 707748 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 1944195 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 9507200 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2186371 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1148843 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69535592 T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0751926 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2293638 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 3696684 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 9510717 T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5846514 A</td>
</tr>
</tbody>
</table>