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- (71) Applicants: WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH [US/US]; Nine Cambridge Center, Cambridge, MA 02142 (US). DANA-FARBER CANCER INSTITUTE, INC. [US/US]; 450 Brookline Avenue, Boston, MA 02215 (US).
- (72) Inventors: THEUNISSEN, Thorold, W.; 50 Follen Street, Apt. 506, Cambridge, MA 02138 (US). GRAY, Nathanael; 26 Greenview Avenue, Boston, MA 02130 (US). JAENISCH, Rudolf; 111 Seaver Street, Brookline, MA 02445 (US).
- (74) Agent: BAKER, C., Hunter; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (US).
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(54) Title: USES OF KINASE INHIBITORS FOR INDUCING AND MAINTAINING PLURIPOTENCY

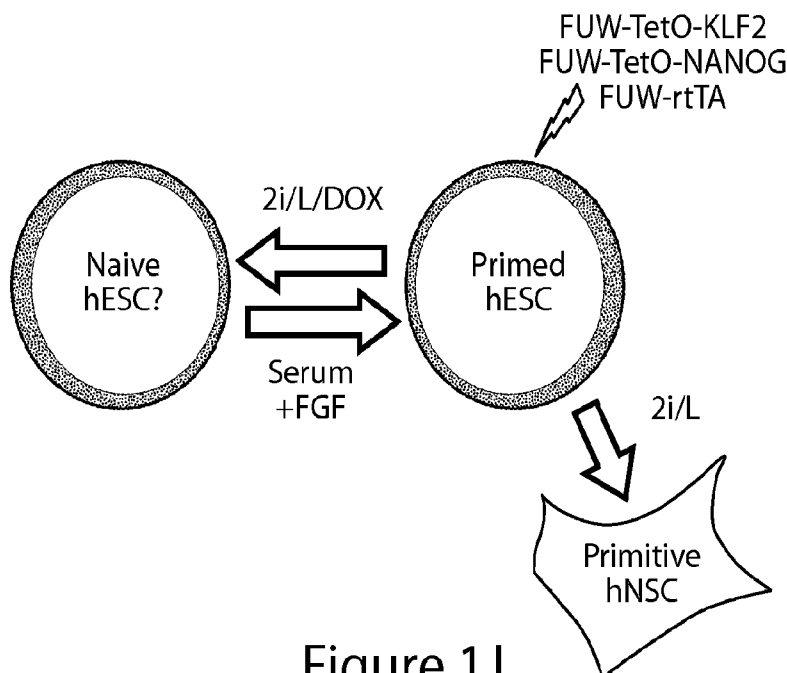


Figure 1J

(57) Abstract: The present disclosure provides compounds of any one of Formulae (A) to (L). The present disclosure also provides compositions, uses, and methods that include or involve a compound described herein, a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, a fibroblast growth factor receptor 1 (FGFR1) inhibitor, or a combination thereof. The compounds, compositions, uses, and methods are useful in changing the pluripotency state of a vertebrate cell to a more naive state.



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USES OF KINASE INHIBITORS FOR INDUCING AND MAINTAINING PLURIPOTENCY

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. provisional applications, U.S.S.N. 62/014,674, filed June 19, 2014, and U.S.S.N. 62/045,337, filed September 3, 2014, each of which is incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] This invention was made with U.S. Government support under grant number RO1-CA084198 awarded by the National Institutes of Health. The U.S. Government has certain rights in the invention.

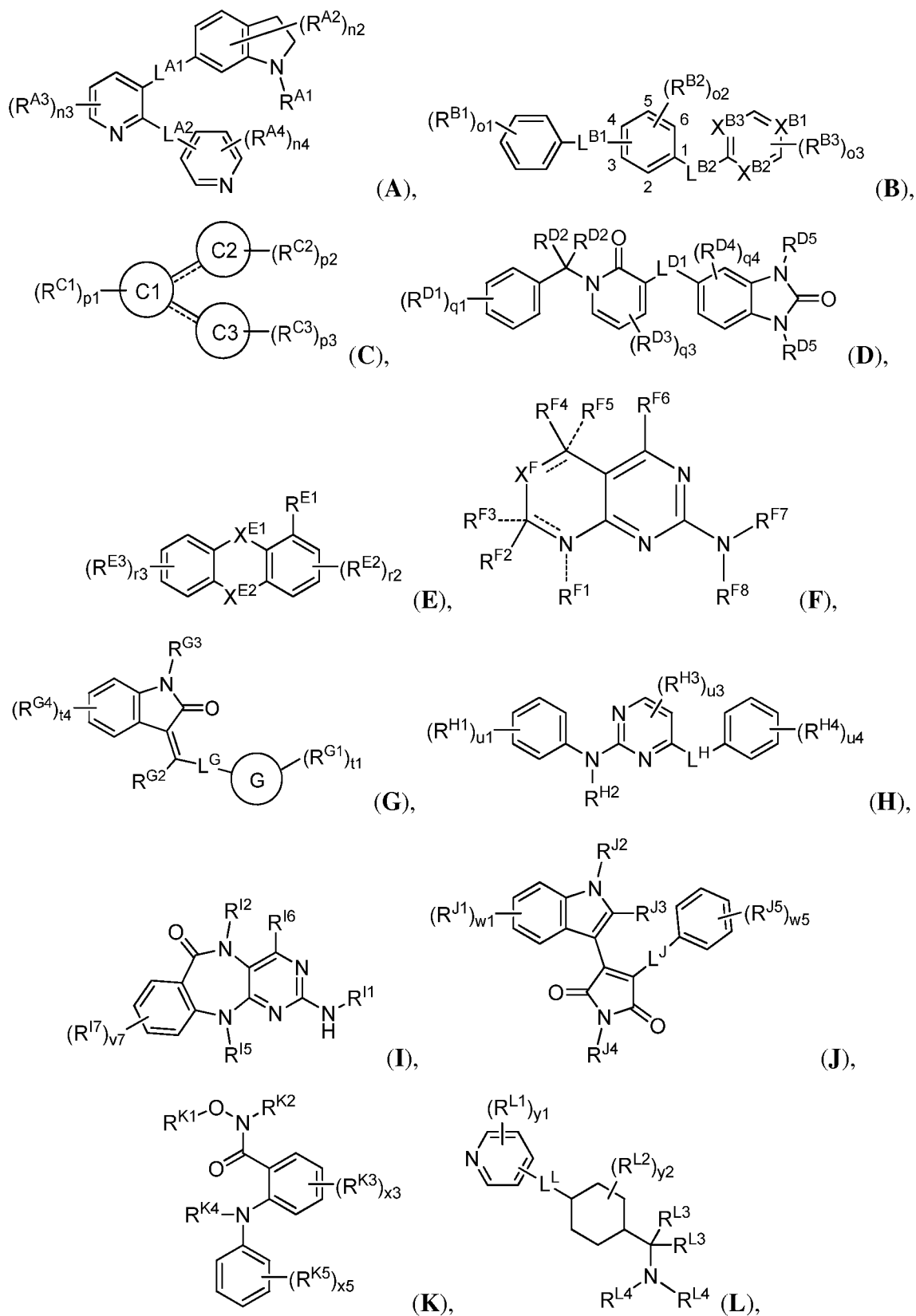
BACKGROUND OF THE INVENTION

[0003] Human pluripotent stem cells, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), hold great promise for regenerative medicine and disease modeling (Hanna *et al.*, 2010b). Full realization of their potential is currently constrained by laborious culture requirements and inconsistencies in developmental potential between lines (Melichar *et al.*, 2011; Osafune *et al.*, 2008). Researchers have had a relatively easy time genetically manipulating and preventing differentiation in mouse ES and iPS cells. However, human ES cells can be more technically demanding to culture and exhibit properties such as slow growth and poor tolerance to passaging as single cells. Thus, there is a need for more effective techniques to isolate and culture human pluripotent stem cells.

SUMMARY OF THE INVENTION

[0004] One aspect of the disclosure provides methods for changing the pluripotency state of a vertebrate cell to a more naïve state, the methods comprising: culturing a pluripotent vertebrate cell in the presence of a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor; and maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of culturing step.

[0005] Another aspect of the disclosure provides methods for changing the pluripotency state of a vertebrate cell to a more naïve state, the method comprising: culturing a pluripotent vertebrate cell in the presence of a compound of any one of Formulae (A) to (L):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof; and maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of culturing step. In some embodiments, the time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state is at least about 5 days (*e.g.*, about 10 days).

[0006] Exemplary compounds useful in a system, composition, kit, or method described herein include, but are not limited to, AMG706, AMN-107, AZ-628, BAY 73-4506, BAY-439006, GDC-0879, KIN001-260, SB590885, CHIR99021, KIN001-244, KU55933, SP600125, PD0332991, PD173074, WZ-7043, BIBF-1120, PHA-665752, SU11248, SU11274, KIN001-220, WH-4-023, WH-4-025, XMD 8-92, XMD11-50, XMD 8-85, IM12, PD0325901, and Y-27632.

[0007] Another aspect of the disclosure provides compositions comprising naïve pluripotent vertebrate cells produced by a method described herein.

[0008] Another aspect of the disclosure provides naïve pluripotent vertebrate cells, wherein the cells have a global gene expression profile which clusters with naïve mouse ESCs as opposed to stem cell lines derived from mouse epiblast (EpiSCs) and/or less naïve human ESCs.

[0009] Yet another aspect of the disclosure relates to naïve pluripotent vertebrate cells, wherein the cells have a global gene expression profile which clusters with naïve mouse ESCs as opposed to stem cell lines derived from mouse epiblast (EpiSCs) and/or less naïve human ESCs.

[0010] Another aspect of the disclosure provides kits for changing the pluripotency state of a vertebrate cell to a more naïve state, the kits comprising a pluripotent vertebrate cell; and cell culture medium comprising a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor.

[0011] In yet another aspect, the present disclosure provides compounds, compositions, and kits described herein for use in a method of the present disclosure.

[0012] The details of particular embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

DEFINITIONS

[0013] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0014] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The disclosure additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0015] In a formula, --- is absent or a single bond, and === or == is a single or double bond.

[0016] The term "heteroatom" refers to an atom that is not hydrogen or carbon. In certain embodiments, the heteroatom is nitrogen. In certain embodiments, the heteroatom is oxygen. In certain embodiments, the heteroatom is sulfur.

[0017] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example "C₁₋₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0018] The term “aliphatic” refers to alkyl, alkenyl, alkynyl, and carbocyclic groups.

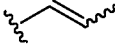
Likewise, the term “heteroaliphatic” refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[0019] The term “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms (“C₁₋₁₀ alkyl”). In some embodiments, an alkyl group has 1 to 9 carbon atoms (“C₁₋₉ alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C₁₋₈ alkyl”). In some embodiments, an alkyl group has 1 to 7 carbon atoms (“C₁₋₇ alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C₂₋₆ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), iso-butyl (C₄), n-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and n-hexyl (C₆). Additional examples of alkyl groups include n-heptyl (C₇), n-octyl (C₈) and the like. Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents. In certain embodiments, the alkyl group is an unsubstituted C₁₋₁₀ alkyl (*e.g.*, -CH₃). In certain embodiments, the alkyl group is a substituted C₁₋₁₀ alkyl.

[0020] The term “haloalkyl” is a substituted alkyl group, wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. “Perhaloalkyl” is a subset of haloalkyl, and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms (“C₁₋₈ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms (“C₁₋₆ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms (“C₁₋₄ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms (“C₁₋₃ haloalkyl”). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms (“C₁₋₂ haloalkyl”). In some embodiments, all of the haloalkyl hydrogen atoms are replaced with fluoro to provide a perfluoroalkyl group. In some embodiments, all of the haloalkyl hydrogen atoms are replaced with chloro to provide a “perchloroalkyl” group. Examples of haloalkyl groups include -CF₃, -CF₂CF₃, -CF₂CF₂CF₃, -CCl₃, -CFCl₂, -CF₂Cl, and the like.

[0021] The term “heteroalkyl” refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₁₀ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₉ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₈ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₇ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₆ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₁₋₅ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₁₋₄ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₃ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₂ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“heteroC₁ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₆ alkyl”). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC₁₋₁₀ alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC₁₋₁₀ alkyl.

[0022] The term “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some

embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), and the like. Unless otherwise specified, each instance of an alkenyl group is independently unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is a substituted C₂₋₁₀ alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is unspecified (*e.g.*, –CH=CHCH₃ or ) may be an (*E*)- or (*Z*)-double bond.

[0023] The term “heteroalkenyl” refers to an alkenyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₀ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₉ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₈ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₇ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₅ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₄ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1

heteroatom within the parent chain (“heteroC₂₋₃ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₆ alkenyl”). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an “unsubstituted heteroalkenyl”) or substituted (a “substituted heteroalkenyl”) with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC₂₋₁₀ alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC₂₋₁₀ alkenyl.

[0024] The term “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) (“C₂₋₁₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptyne (C₇), octynyl (C₈), and the like. Unless otherwise specified, each instance of an alkynyl group is independently unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is a substituted C₂₋₁₀ alkynyl.

[0025] The term “heteroalkynyl” refers to an alkynyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₀ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₉ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 8 carbon

atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₈ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₇ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₅ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₄ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain (“heteroC₂₋₃ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₆ alkynyl”). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an “unsubstituted heteroalkynyl”) or substituted (a “substituted heteroalkynyl”) with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC₂₋₁₀ alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC₂₋₁₀ alkynyl.

[0026] The term “carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms (“C₃₋₇ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms (“C₄₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms (“C₅₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the

aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) or tricyclic system (“tricyclic carbocyclyl”)) and can be saturated or can contain one or more carbon-carbon double or triple bonds. “Carbocyclyl” also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C₃₋₁₄ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₄ carbocyclyl. In some embodiments, carbocyclyl is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms (“C₄₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C₃₋₁₄ cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C₃₋₁₄ cycloalkyl.

[0027] The term “heterocyclyl” or “heterocyclic” refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“3-14

membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”) or tricyclic system (“tricyclic heterocyclyl”)), and can be saturated or can contain one or more carbon–carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl.

[0028] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–8 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–6 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heterocyclyl”). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0029] Exemplary 3–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidiny, oxetanyl, and thietanyl. Exemplary 5–membered heterocyclyl groups containing 1 heteroatom include,

without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5-membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolanyl, oxadiazolanyl, and thiadiazolanyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholanyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing 2 heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolanyl, isoindolanyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolanyl, tetrahydroisoquinolanyl, decahydroquinolanyl, decahydroisoquinolanyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2-b]pyrrole, indolanyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e][1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo[3,2-b]pyranyl, 5,7-dihydro-4H-thieno[2,3-c]pyranyl, 2,3-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 2,3-dihydrofuro[2,3-b]pyridinyl, 4,5,6,7-tetrahydro-1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0030] The term “aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) $4n+2$ aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C_{6–14} aryl”). In some embodiments, an aryl group has 6 ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in

the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C₆₋₁₄ aryl. In certain embodiments, the aryl group is a substituted C₆₋₁₄ aryl.

[0031] “Aralkyl” is a subset of “alkyl” and refers to an alkyl group substituted by an aryl group, wherein the point of attachment is on the alkyl moiety.

[0032] The term “heteroaryl” refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–14 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[0033] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heteroaryl”). In some embodiments, the

5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5–14 membered heteroaryl.

[0034] Exemplary 5–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5–membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing 1 heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6–bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl and phenazinyl.

[0035] “Heteroaralkyl” is a subset of “alkyl” and refers to an alkyl group substituted by a heteroaryl group, wherein the point of attachment is on the alkyl moiety.

[0036] The term “unsaturated bond” refers to a double or triple bond.

[0037] The term “unsaturated” or “partially unsaturated” refers to a moiety that includes at least one double or triple bond.

[0038] The term “saturated” refers to a moiety that does not contain a double or triple bond, *i.e.*, the moiety only contains single bonds.

[0039] Affixing the suffix “-ene” to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0040] A group is optionally substituted unless expressly provided otherwise. In certain embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted. “Optionally substituted” refers to a group which may be substituted or unsubstituted (*e.g.*, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” heteroalkyl, “substituted” or “unsubstituted” heteroalkenyl, “substituted” or “unsubstituted” heteroalkynyl, “substituted” or “unsubstituted” carbocyclyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted” means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, and includes any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0041] Exemplary carbon atom substituents include, but are not limited to, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{aa}, -ON(R^{bb})₂, -N(R^{bb})₂, -N(R^{bb})₃⁺X⁻, -N(OR^{cc})R^{bb}, -SH, -SR^{aa}, -SSR^{cc}, -C(=O)R^{aa}, -CO₂H, -CHO, -C(OR^{cc})₂, -CO₂R^{aa}, -OC(=O)R^{aa},

$-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$,
 $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$,
 $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$,
 $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$,
 $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$,
 $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$,
 $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$,
 $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{OR}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$,
 $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{R}^{\text{cc}})_4$, $-\text{P}(\text{OR}^{\text{cc}})_4$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(\text{OR}^{\text{cc}})_2$, $-\text{OP}(\text{OR}^{\text{cc}})_3^+\text{X}^-$,
 $-\text{OP}(\text{R}^{\text{cc}})_4$, $-\text{OP}(\text{OR}^{\text{cc}})_4$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl,
 C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10}
carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein
each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl,
heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd}
groups; wherein X^- is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group $=\text{O}$, $=\text{S}$,
 $=\text{NN}(\text{R}^{\text{bb}})_2$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{OR}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{S}(=\text{O})_2\text{R}^{\text{aa}}$, $=\text{NR}^{\text{bb}}$, or $=\text{NOR}^{\text{cc}}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl,
 C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10}
carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two
 R^{aa} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl
ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl,
carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4,
or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-\text{OH}$, $-\text{OR}^{\text{aa}}$,
 $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CN}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$,
 $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$,
 $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{cc}})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl,
 C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10}
carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two
 R^{bb} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl
ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl,
carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4,
or 5 R^{dd} groups; wherein X^- is a counterion;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hetero C_{1-6} alkyl, hetero C_{2-6} alkenyl, hetero C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form $=O$ or $=S$; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hetero C_{1-6} alkyl, hetero C_{2-6} alkenyl, hetero C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hetero C_{1-6} alkyl, hetero C_{2-6} alkenyl, hetero C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–10 membered heterocyclyl or 5–10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6} \text{ alkyl})_2$, $-N(C_{1-6} \text{ alkyl})_2$, $-N(C_{1-6} \text{ alkyl})_3^+X^-$, $-NH(C_{1-6} \text{ alkyl})_2^+X^-$, $-NH_2(C_{1-6} \text{ alkyl})^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6} \text{ alkyl})(C_{1-6} \text{ alkyl})$, $-N(OH)(C_{1-6} \text{ alkyl})$, $-NH(OH)$, $-SH$, $-SC_{1-6} \text{ alkyl}$, $-SS(C_{1-6} \text{ alkyl})$, $-C(=O)(C_{1-6} \text{ alkyl})$, $-CO_2H$, $-CO_2(C_{1-6} \text{ alkyl})$, $-OC(=O)(C_{1-6} \text{ alkyl})$, $-OCO_2(C_{1-6} \text{ alkyl})$, $-C(=O)NH_2$, $-C(=O)N(C_{1-6} \text{ alkyl})_2$, $-OC(=O)NH(C_{1-6} \text{ alkyl})$, $-NHC(=O)(C_{1-6} \text{ alkyl})$, $-N(C_{1-6} \text{ alkyl})C(=O)(C_{1-6} \text{ alkyl})$, $-NHCO_2(C_{1-6} \text{ alkyl})$, $-NHC(=O)N(C_{1-6} \text{ alkyl})_2$, $-NHC(=O)NH(C_{1-6} \text{ alkyl})$, $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6} \text{ alkyl})$, $-OC(=NH)(C_{1-6} \text{ alkyl})$, $-OC(=NH)OC_{1-6} \text{ alkyl}$, $-C(=NH)N(C_{1-6} \text{ alkyl})_2$, $-C(=NH)NH(C_{1-6} \text{ alkyl})$, $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6} \text{ alkyl})_2$, $-OC(NH)NH(C_{1-6} \text{ alkyl})$, $-OC(NH)NH_2$, $-NHC(NH)N(C_{1-6} \text{ alkyl})_2$, $-NHC(=NH)NH_2$, $-NHOSO_2(C_{1-6} \text{ alkyl})$, $-SO_2N(C_{1-6} \text{ alkyl})_2$, $-SO_2NH(C_{1-6} \text{ alkyl})$, $-SO_2NH_2$, $-SO_2C_{1-6} \text{ alkyl}$, $-SO_2OC_{1-6} \text{ alkyl}$, $-OSO_2C_{1-6} \text{ alkyl}$, $-SOC_{1-6} \text{ alkyl}$, $-Si(C_{1-6} \text{ alkyl})_3$, $-OSi(C_{1-6} \text{ alkyl})_3$, $-C(=S)N(C_{1-6} \text{ alkyl})_2$, $C(=S)NH(C_{1-6} \text{ alkyl})$, $C(=S)NH_2$, $-C(=O)S(C_{1-6} \text{ alkyl})$, $-C(=S)SC_{1-6} \text{ alkyl}$, $-SC(=S)SC_{1-6} \text{ alkyl}$, $-P(=O)(OC_{1-6} \text{ alkyl})_2$, $-P(=O)(C_{1-6} \text{ alkyl})_2$, $-OP(=O)(C_{1-6} \text{ alkyl})_2$, $-OP(=O)(OC_{1-6} \text{ alkyl})_2$, $C_{1-6} \text{ alkyl}$, $C_{1-6} \text{ perhaloalkyl}$, $C_{2-6} \text{ alkenyl}$, $C_{2-6} \text{ alkynyl}$, $\text{hetero}C_{1-6} \text{ alkyl}$, $\text{hetero}C_{2-6} \text{ alkenyl}$, $\text{hetero}C_{2-6} \text{ alkynyl}$, $C_{3-10} \text{ carbocyclyl}$, $C_{6-10} \text{ aryl}$, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form $=O$ or $=S$; wherein X^- is a counterion.

[0042] The term “halo” or “halogen” refers to fluorine (fluoro, $-F$), chlorine (chloro, $-Cl$), bromine (bromo, $-Br$), or iodine (iodo, $-I$).

[0043] The term “hydroxyl” or “hydroxy” refers to the group $-OH$. The term “substituted hydroxyl” or “substituted hydroxyl,” by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-OR^{aa}$, $-ON(R^{bb})_2$, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3^+X^-$, $-OP(OR^{cc})_2$, $-OP(OR^{cc})_3^+X^-$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, and $-OP(=O)(N(R^{bb}))_2$, wherein X^- , R^{aa} , R^{bb} , and R^{cc} are as defined herein.

[0044] The term “thiol” or “thio” refers to the group $-SH$. The term “substituted thiol” or “substituted thio,” by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-SR^{aa}$, $-S=SR^{cc}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, and $-SC(=O)R^{aa}$, wherein R^{aa} and R^{cc} are as defined herein.

[0045] The term “amino” refers to the group -NH_2 . The term “substituted amino,” by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino. In certain embodiments, the “substituted amino” is a monosubstituted amino or a disubstituted amino group.

[0046] The term “monosubstituted amino” refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $\text{-NH(R}^{\text{bb}}\text{)}$, $\text{-NHC(=O)R}^{\text{aa}}$, $\text{-NHCO}_2\text{R}^{\text{aa}}$, $\text{-NHC(=O)N(R}^{\text{bb}}\text{)}_2$, $\text{-NHC(=NR}^{\text{bb}}\text{)N(R}^{\text{bb}}\text{)}_2$, $\text{-NHSO}_2\text{R}^{\text{aa}}$, $\text{-NHP(=O)(OR}^{\text{cc}}\text{)}_2$, and $\text{-NHP(=O)(N(R}^{\text{bb}}\text{)}_2)_2$, wherein R^{aa} , R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $\text{-NH(R}^{\text{bb}}\text{)}$ is not hydrogen.

[0047] The term “disubstituted amino” refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $\text{-N(R}^{\text{bb}}\text{)}_2$, $\text{-NR}^{\text{bb}}\text{C(=O)R}^{\text{aa}}$, $\text{-NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $\text{-NR}^{\text{bb}}\text{C(=O)N(R}^{\text{bb}}\text{)}_2$, $\text{-NR}^{\text{bb}}\text{C(=NR}^{\text{bb}}\text{)N(R}^{\text{bb}}\text{)}_2$, $\text{-NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $\text{-NR}^{\text{bb}}\text{P(=O)(OR}^{\text{cc}}\text{)}_2$, and $\text{-NR}^{\text{bb}}\text{P(=O)(N(R}^{\text{bb}}\text{)}_2)_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0048] The term “trisubstituted amino” refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $\text{-N(R}^{\text{bb}}\text{)}_3$ and $\text{-N(R}^{\text{bb}}\text{)}_3^+\text{X}^-$, wherein R^{bb} and X^- are as defined herein.

[0049] The term “carbonyl” refers a group wherein the carbon directly attached to the parent molecule is sp^2 hybridized, and is substituted with an oxygen, nitrogen or sulfur atom, *e.g.*, a group selected from ketones ($\text{-C(=O)R}^{\text{aa}}$), carboxylic acids ($\text{-CO}_2\text{H}$), aldehydes (-CHO), esters ($\text{-CO}_2\text{R}^{\text{aa}}$, $\text{-C(=O)SR}^{\text{aa}}$, $\text{-C(=S)SR}^{\text{aa}}$), amides ($\text{-C(=O)N(R}^{\text{bb}}\text{)}_2$, $\text{-C(=O)NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $\text{-C(=S)N(R}^{\text{bb}}\text{)}_2$), and imines ($\text{-C(=NR}^{\text{bb}}\text{)R}^{\text{aa}}$, $\text{-C(=NR}^{\text{bb}}\text{)OR}^{\text{aa}}$, $\text{-C(=NR}^{\text{bb}}\text{)N(R}^{\text{bb}}\text{)}_2$), wherein R^{aa} and R^{bb} are as defined herein.

[0050] The term “silyl” refers to the group $\text{-Si(R}^{\text{aa}}\text{)}_3$, wherein R^{aa} is as defined herein.

[0051] The term “oxo” refers to the group =O , and the term “thiooxo” refers to the group =S .

[0052] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH , -OR^{aa} , $\text{-N(R}^{\text{cc}}\text{)}_2$, -CN , $\text{-C(=O)R}^{\text{aa}}$, $\text{-C(=O)N(R}^{\text{cc}}\text{)}_2$, $\text{-CO}_2\text{R}^{\text{aa}}$, $\text{-SO}_2\text{R}^{\text{aa}}$, $\text{-C(=NR}^{\text{bb}}\text{)R}^{\text{aa}}$, $\text{-C(=NR}^{\text{cc}}\text{)OR}^{\text{aa}}$, $\text{-C(=NR}^{\text{cc}}\text{)N(R}^{\text{cc}}\text{)}_2$, $\text{-SO}_2\text{N(R}^{\text{cc}}\text{)}_2$, $\text{-SO}_2\text{R}^{\text{cc}}$, $\text{-SO}_2\text{OR}^{\text{cc}}$, -SOR^{aa} , $\text{-C(=S)N(R}^{\text{cc}}\text{)}_2$, $\text{-C(=O)SR}^{\text{cc}}$, $\text{-C(=S)SR}^{\text{cc}}$, $\text{-P(=O)(OR}^{\text{cc}}\text{)}_2$, $\text{-P(=O)(R}^{\text{aa}}\text{)}_2$, $\text{-P(=O)(N(R}^{\text{cc}}\text{)}_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10}

carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0053] In certain embodiments, the substituent present on the nitrogen atom is an nitrogen protecting group (also referred to herein as an “amino protecting group”). Nitrogen protecting groups include, but are not limited to, –OH, –OR^{aa}, –N(R^{cc})₂, –C(=O)R^{aa}, –C(=O)N(R^{cc})₂, –CO₂R^{aa}, –SO₂R^{aa}, –C(=NR^{cc})R^{aa}, –C(=NR^{cc})OR^{aa}, –C(=NR^{cc})N(R^{cc})₂, –SO₂N(R^{cc})₂, –SO₂R^{cc}, –SO₂OR^{cc}, –SOR^{aa}, –C(=S)N(R^{cc})₂, –C(=O)SR^{cc}, –C(=S)SR^{cc}, C₁₋₁₀ alkyl (*e.g.*, aralkyl, heteroaralkyl), C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, heteroC₁₋₁₀ alkyl, heteroC₂₋₁₀ alkenyl, heteroC₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3–14 membered heterocyclyl, C₆₋₁₄ aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0054] For example, nitrogen protecting groups such as amide groups (*e.g.*, –C(=O)R^{aa}) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N*'-dithiobenzylxyacylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivative, *o*-nitrobenzamide and *o*-(benzoyloxymethyl)benzamide.

[0055] Nitrogen protecting groups such as carbamate groups (*e.g.*, –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-

methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-*t*-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC or Boc), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonyl ethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p*'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0056] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, -S(=O)₂R^{aa}) include, but are not limited to, *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-

dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β -trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0057] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, *N'*-*p*-toluenesulfonylaminoacyl derivative, *N'*-phenylaminothioacyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N'*,*N'*-dimethylaminomethylene)amine, *N,N'*-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

[0058] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an “hydroxyl protecting group”). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein X^- , R^{aa} , R^{bb} , and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

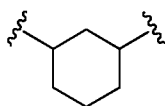
[0059] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α -naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl

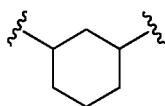
(TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *t*-butyl carbonate (BOC or Boc), *p*-nitrophenyl carbonate, benzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, *o*-nitrobenzyl carbonate, *p*-nitrobenzyl carbonate, *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenate, *o*-(methoxyacyl)benzoate, α -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0060] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a “thiol protecting group”). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3^+X^-$, $-P(OR^{cc})_2$, $-P(OR^{cc})_3^+X^-$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, and $-P(=O)(N(R^{bb})_2)_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in Protecting Groups in Organic Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

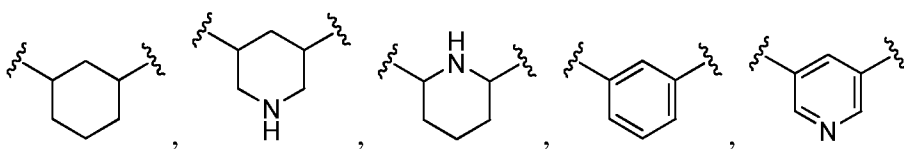
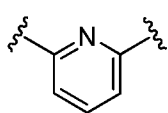
[0061] A “counterion” or “anionic counterion” is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (i.e., including one formal negative charge). An anionic counterion may also be multivalent (i.e., including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^- , Cl^- , Br^- , I^-), NO_3^- , ClO_4^- , OH^- , $H_2PO_4^-$, HCO_3^- , HSO_4^- , sulfonate ions (*e.g.*, methanesulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^- , PF_4^- , PF_6^- , AsF_6^- , SbF_6^- , $B[3,5-(CF_3)_2C_6H_3]_4^-$, $B(C_6F_5)_4^-$, BPh_4^- , $Al(OC(CF_3)_3)_4^-$, and carborane anions (*e.g.*, $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-} , HPO_4^{2-} , PO_4^{3-} , $B_4O_7^{2-}$, SO_4^{2-} , $S_2O_3^{2-}$, carboxylate anions (*e.g.*, tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

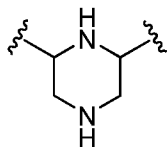
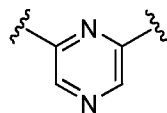
[0062] An “aliphatic chain” refers to a substituted or unsubstituted divalent alkyl, alkenyl, or alkynyl group. An aliphatic chain includes (1) one or more chains of carbon atoms immediately between the two radicals of the aliphatic chain; (2) optionally one or more hydrogen atoms on the chain(s) of carbon atoms; and (3) optionally one or more substituents (“non-chain substituents,” which are not hydrogen) on the chain(s) of carbon atoms. A chain of carbon atoms consists of consecutively connected carbon atoms (“chain atoms”) and does not include hydrogen atoms or heteroatoms. However, a non-chain substituent of an aliphatic chain may include any atoms, including hydrogen atoms, carbon atoms, and heteroatoms. For example, aliphatic chain $-C^A H(C^B H_2 C^C H_3)-$ includes one chain atom C^A , one hydrogen atom on C^A , and non-chain substituent $-(C^B H_2 C^C H_3)$. The term “ C_x aliphatic chain,” wherein x is a positive integer, refers to an aliphatic chain that includes x number of chain atom(s) between the two radicals of the aliphatic chain. If there is more than one possible value of x , the smallest possible value of x is used for the definition of the aliphatic chain. For example,



$-CH(C_2H_5)-$ is a C_1 aliphatic chain, and  is a C_3 aliphatic chain. When a range of values is used, the meaning of the range is as described herein. For example, a C_{3-10} aliphatic chain refers to an aliphatic chain where the number of chain atoms of the shortest chain of carbon atoms immediately between the two radicals of the aliphatic chain is 3, 4, 5,

6, 7, 8, 9, or 10. An aliphatic chain may be saturated (*e.g.*, $-(\text{CH}_2)_4-$). An aliphatic chain may also be unsaturated and include one or more $\text{C}=\text{C}$ and/or $\text{C}\equiv\text{C}$ bonds anywhere in the aliphatic chain. For instance, $-\text{CH}=\text{CH}-(\text{CH}_2)_2-$, $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-$, and $-\text{C}\equiv\text{C}-\text{CH}=\text{CH}-$ are all examples of a unsubstituted and unsaturated aliphatic chain. In certain embodiments, the aliphatic chain is unsubstituted (*e.g.*, $-\text{C}\equiv\text{C}-$ or $-(\text{CH}_2)_4-$). In certain embodiments, the aliphatic chain is substituted (*e.g.*, $-\text{CH}(\text{C}_2\text{H}_5)-$ and $-\text{CF}_2-$). Any two substituents on the aliphatic chain may be joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring.

For instance, , and  are all examples of an aliphatic chain. In contrast, in certain embodiments,

 and  are not within the scope of the aliphatic chains described

herein. A “heteroaliphatic chain” is an aliphatic chain where at least one chain atom of each chain of the aliphatic chain is independently replaced with a heteroatom. In certain embodiments, an aliphatic chain described herein is a C_{1-4} aliphatic chain, a C_{1-6} aliphatic chain, a C_{3-7} aliphatic chain, a C_2 aliphatic chain, a C_3 aliphatic chain, or a C_5 aliphatic chain. In certain embodiments, one, two, or three chain atoms of an aliphatic chain described herein are independently replaced with $-\text{O}-$, $-\text{S}-$, $-\text{NR}^1-$, $-\text{N}=\text{}$, or $=\text{N}-$, wherein each instance of R^1 is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, one, two, or three chain atoms of an aliphatic chain described herein are independently replaced with $-\text{O}-$, $-\text{S}-$, or $-\text{NR}^1-$. In certain embodiments, the molecular weight of an aliphatic or heteroaliphatic chain is not more than about 300 g/mol, not more than about 200 g/mol, not more than about 150 g/mol, not more than about 100 g/mol, not more than about 70 g/mol, not more than about 50 g/mol, or not more than 30 g/mol. In certain embodiments, an aliphatic or heteroaliphatic chain consists of not more than about 70 atoms, not more than about 50 atoms, not more than about 30 atoms, not more than about 20 atoms, not more than about 15 atoms, or not more than 10 atoms. In certain embodiments, an aliphatic or heteroaliphatic chain does not include unsaturated bonds in the shortest chain. In certain embodiments, an aliphatic or heteroaliphatic chain consists of one

or two unsaturated bonds in the shortest chain. In certain embodiments, an aliphatic or heteroaliphatic chain includes at least one instance of =O as a non-chain substituent on a chain atom (*e.g.*, carbon or sulfur atom).

[0063] The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0064] The term “solvate” refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline

form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0065] The term "hydrate" refers to a compound that is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x H_2O$, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5 H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2 H_2O$) and hexahydrates ($R \cdot 6 H_2O$)).

[0066] The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or *vice versa*). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[0067] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

[0068] Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A

chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[0069] The term “polymorphs” refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof) in a particular crystal packing arrangement. All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0070] The term “prodrugs” refer to compounds which have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds described herein are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, C₇-C₁₂ substituted aryl, and C₇-C₁₂ arylalkyl esters of the compounds described herein may be preferred.

[0071] The “molecular weight” of a monovalent moiety –R is calculated by subtracting 1 from the molecular weight of the compound R–H. The “molecular weight” of a divalent moiety –L– is calculated by subtracting 2 from the molecular weight of the compound H–L–H.

[0072] The terms “composition” and “formulation” are used interchangeably.

[0073] A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) and/or

other non-human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs); and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female at any stage of development. The animal may be a transgenic animal or genetically engineered animal. In certain embodiments, the subject is a non-human animal. In certain embodiments, the animal is a fish or reptile.

[0074] The term “administer,” “administering,” or “administration” refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound or cell described herein or generated as described herein, or a composition thereof, in or on a subject.

[0075] The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen and/or in light of detecting that the subject has a genotype associated with the disease). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0076] The terms “condition,” “disease,” and “disorder” are used interchangeably.

[0077] A “kinase” is a type of enzyme that transfers phosphate groups from high energy donor molecules, such as ATP, to specific substrates, referred to as phosphorylation. Kinases are part of the larger family of phosphotransferases. One of the largest groups of kinases are protein kinases, which act on and modify the activity of specific proteins. Kinases are used extensively to transmit signals and control complex processes in cells. Various other kinases act on small molecules such as lipids, carbohydrates, amino acids, and nucleotides, either for signaling or to prime them for metabolic pathways. Kinases are often named after their substrates. More than 500 different protein kinases have been identified in humans. These exemplary human protein kinases include, but are not limited to, AAK1, ABL, ACK, ACTR2, ACTR2B, AKT1, AKT2, AKT3, ALK, ALK1, ALK2, ALK4, ALK7, AMPKa1, AMPKa2, ANKRD3, ANPa, ANPb, ARAF, ARAFps, ARG, AurA, AurAps1, AurAps2, AurB, AurBps1, AurC, AXL, BARK1, BARK2, BIKE, BLK, BMPR1A, BMPR1Aps1, BMPR1Aps2, BMPR1B, BMPR2, BMX, BRAF, BRAFps, BRK, BRSK1, BRSK2, BTK,

BUB1, BUBR1, CaMK1a, CaMK1b, CaMK1d, CaMK1g, CaMK2a, CaMK2b, CaMK2d, CaMK2g, CaMK4, CaMKK1, CaMKK2, caMLCK, CASK, CCK4, CCRK, CDC2, CDC7, CDK10, CDK11, CDK2, CDK3, CDK4, CDK4ps, CDK5, CDK5ps, CDK6, CDK7, CDK7ps, CDK8, CDK8ps, CDK9, CDKL1, CDKL2, CDKL3, CDKL4, CDKL5, CGDps, CHED, CHK1, CHK2, CHK2ps1, CHK2ps2, CK1a, CK1a2, CK1aps1, CK1aps2, CK1aps3, CK1d, CK1e, CK1g1, CK1g2, CK1g2ps, CK1g3, CK2a1, CK2a1-rs, CK2a2, CLIK1, CLIK1L, CLK1, CLK2, CLK2ps, CLK3, CLK3ps, CLK4, COT, CRIK, CRK7, CSK, CTK, CYGD, CYGF, DAPK1, DAPK2, DAPK3, DCAMKL1, DCAMKL2, DCAMKL3, DDR1, DDR2, DLK, DMPK1, DMPK2, DRAK1, DRAK2, DYRK1A, DYRK1B, DYRK2, DYRK3, DYRK4, EGFR, EphA1, EphA10, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphB1, EphB2, EphB3, EphB4, EphB6, Erk1, Erk2, Erk3, Erk3ps1, Erk3ps2, Erk3ps3, Erk3ps4, Erk4, Erk5, Erk7, FAK, FER, FERps, FES, FGFR1, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT1ps, FLT3, FLT4, FMS, FRK, Fused, FYN, GAK, GCK, GCN2, GCN22, GPRK4, GPRK5, GPRK6, GPRK6ps, GPRK7, GSK3A, GSK3B, Haspin, HCK, HER2/ErbB2, HER3/ErbB3, HER4/ErbB4, HH498, HIPK1, HIPK2, HIPK3, HIPK4, HPK1, HRI, HRIps, HSER, HUNK, ICK, IGF1R, IKKa, IKKb, IKKe, ILK, INSR, IRAK1, IRAK2, IRAK3, IRAK4, IRE1, IRE2, IRR, ITK, JAK1, JAK2, JAK3, JNK1, JNK2, JNK3, KDR, KHS1, KHS2, KIS, KIT, KSGCps, KSR1, KSR2, LATS1, LATS2, LCK, LIMK1, LIMK2, LIMK2ps, LKB1, LMR1, LMR2, LMR3, LOK, LRRK1, LRRK2, LTK, LYN, LZK, MAK, MAP2K1, MAP2K1ps, MAP2K2, MAP2K2ps, MAP2K3, MAP2K4, MAP2K5, MAP2K6, MAP2K7, MAP3K1, MAP3K2, MAP3K3, MAP3K4, MAP3K5, MAP3K6, MAP3K7, MAP3K8, MAPKAPK2, MAPKAPK3, MAPKAPK5, MAPKAPKps1, MARK1, MARK2, MARK3, MARK4, MARKps01, MARKps02, MARKps03, MARKps04, MARKps05, MARKps07, MARKps08, MARKps09, MARKps10, MARKps11, MARKps12, MARKps13, MARKps15, MARKps16, MARKps17, MARKps18, MARKps19, MARKps20, MARKps21, MARKps22, MARKps23, MARKps24, MARKps25, MARKps26, MARKps27, MARKps28, MARKps29, MARKps30, MAST1, MAST2, MAST3, MAST4, MASTL, MELK, MER, MET, MISR2, MLK1, MLK2, MLK3, MLK4, MLKL, MNK1, MNK1ps, MNK2, MOK, MOS, MPSK1, MPSK1ps, MRCKa, MRCKb, MRCKps, MSK1, MSK12, MSK2, MSK22, MSSK1, MST1, MST2, MST3, MST3ps, MST4, MUSK, MYO3A, MYO3B, MYT1, NDR1, NDR2, NEK1, NEK10, NEK11, NEK2, NEK2ps1, NEK2ps2, NEK2ps3, NEK3, NEK4, NEK4ps, NEK5, NEK6, NEK7, NEK8, NEK9, NIK, NIM1, NLK, NRBP1, NRBP2, NuaK1, NuaK2, Obscn, Obscn2, OSR1, p38a, p38b, p38d, p38g, p70S6K, p70S6Kb, p70S6Kps1, p70S6Kps2, PAK1, PAK2, PAK2ps, PAK3, PAK4, PAK5, PAK6, PASK, PBK, PCTAIRE1,

PCTAIRE2, PCTAIRE3, PDGFRa, PDGFRb, PDK1, PEK, PFTAIRE1, PFTAIRE2, PHKg1, PHKg1ps1, PHKg1ps2, PHKg1ps3, PHKg2, PIK3R4, PIM1, PIM2, PIM3, PINK1, PITSLRE, PKACa, PKACb, PKACg, PKCa, PKCb, PKCd, PKCe, PKCg, PKCh, PKCi, PKCips, PKCt, PKCz, PKD1, PKD2, PKD3, PKG1, PKG2, PKN1, PKN2, PKN3, PKR, PLK1, PLK1ps1, PLK1ps2, PLK2, PLK3, PLK4, PRKX, PRKXps, PRKY, PRP4, PRP4ps, PRPK, PSKH1, PSKH1ps, PSKH2, PYK2, QIK, QSK, RAF1, RAF1ps, RET, RHOK, RIPK1, RIPK2, RIPK3, RNaseL, ROCK1, ROCK2, RON, ROR1, ROR2, ROS, RSK1, RSK12, RSK2, RSK22, RSK3, RSK32, RSK4, RSK42, RSKL1, RSKL2, RYK, RYKps, SAKps, SBK, SCYL1, SCYL2, SCYL2ps, SCYL3, SGK, SgK050ps, SgK069, SgK071, SgK085, SgK110, SgK196, SGK2, SgK223, SgK269, SgK288, SGK3, SgK307, SgK384ps, SgK396, SgK424, SgK493, SgK494, SgK495, SgK496, SIK (*e.g.*, SIK1, SIK2), skMLCK, SLK, Slob, smMLCK, SNRK, SPEG, SPEG2, SRC, SRM, SRPK1, SRPK2, SRPK2ps, SSTK, STK33, STK33ps, STLK3, STLK5, STLK6, STLK6ps1, STLK6-rs, SuRTK106, SYK, TAK1, TAO1, TAO2, TAO3, TBCK, TBK1, TEC, TESK1, TESK2, TGFbR1, TGFbR2, TIE1, TIE2, TLK1, TLK1ps, TLK2, TLK2ps1, TLK2ps2, TNK1, Trad, Trb1, Trb2, Trb3, Trio, TRKA, TRKB, TRKC, TSSK1, TSSK2, TSSK3, TSSK4, TSSKps1, TSSKps2, TTBK1, TTBK2, TTK, TTN, TXK, TYK2, TYK22, TYRO3, TYRO3ps, ULK1, ULK2, ULK3, ULK4, VACAMKL, VRK1, VRK2, VRK3, VRK3ps, Wee1, Wee1B, Wee1Bps, Wee1ps1, Wee1ps2, Wnk1, Wnk2, Wnk3, Wnk4, YANK1, YANK2, YANK3, YES, YESps, YSK1, ZAK, ZAP70, ZC1/HGK, ZC2/TNIK, ZC3/MINK, and ZC4/NRK.

[0078] The term “inhibition”, “inhibiting”, “inhibit,” or “inhibitor” refer to the ability of a compound to reduce, slow, halt, or prevent activity of a particular biological process (*e.g.*, kinase activity) in a cell relative to vehicle.

[0079] By “pluripotency” and pluripotent stem cells it is meant that such cells have the ability under appropriate conditions to differentiate into cells that are derivatives of all three embryonic germ layers (endoderm, mesoderm and ectoderm). A pluripotent cell line or cell culture is often characterized in that the cells can differentiate into a wide variety of cell types *in vitro* and *in vivo*. Cells that are able to form teratomas containing cells having characteristics of endoderm, mesoderm, and ectoderm when injected into SCID mice are considered pluripotent. In addition, cells that possess the ability to participate in the formation of chimeras (upon injection into a blastocyst of the same species that is transferred to a suitable foster mother of the same species) that survive to term are considered pluripotent. Pluripotent cell types as used in the present invention may be provided in the

form of human embryonic stem cells, or human induced pluripotent cell (iPS cell), or may be derived from a human embryonic stem cell line.

[0080] The term “stem cell” refers to a vertebrate cell that has the ability both to self-renew, and to generate differentiated progeny. The ability to generate differentiated progeny may be described as pluripotent (see Morrison *et al.* (1997) Cell 88:287-298). “Embryonic stem cells” (ES cells) are pluripotent stem cells derived from the inner cell mass of a blastocyst, an early-stage preimplantation embryo. Pluripotency distinguishes embryonic stem cells from adult stem cells found in adults; while embryonic stem cells can generate all cell types in the body, adult stem cells are multipotent and can produce only a limited number of cell types.

[0081] “Induced pluripotent stem cells”, abbreviated as iPS cells, are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing expression of certain genes (*e.g.*, injection of an expression construct). Induced pluripotent stem cells are identical in many respects to natural pluripotent stem cells, such as embryonic stem (ES) cells (*e.g.*, in their physical properties). They may be the same in their expressions of certain stem cell genes and proteins, chromatin methylation patterns, doubling time, embryoid body formation, teratoma formation, viable chimera formation, and potency and differentiability. The term “induced pluripotent stem cell” encompasses pluripotent cells, that, like embryonic stem (ES) cells, can be cultured over a long period of time while maintaining the ability to differentiate into all types of cells in an organism. However, unlike ES cells (which are typically derived from the inner cell mass of blastocysts), iPS cells are derived from differentiated somatic cells, that is, cells that have a narrower, more defined potential.

[0082] By “culturing” the cell means growing the cells in an artificial, *in vitro* environment. By “maintaining” means continuing to grow the cells in culture under suitable conditions until the pluripotency state of the cell is converted to a more naïve state.

[0083] A “cell culture medium” (also referred to herein as a “culture medium” or “medium”) is a medium for culturing cells containing nutrients that maintain cell viability and support proliferation. The cell culture medium may contain any of the following nutrients in appropriate amounts and combinations: salt(s), buffer(s), amino acids, glucose or other sugar(s), antibiotics, serum or serum replacement, and other components such as, but not limited to, peptide growth factors, cofactors, and trace elements. Cell culture media ordinarily used for particular cell types are known to those skilled in the art. For example, cell culture media of use for culturing and maintaining pluripotent cells are known in the art.

[0084] In some embodiments, the cell culture medium is chemically defined medium. In some embodiments, cell culture medium is serum-free medium, *e.g.*, mTeSR1™ medium (StemCell Technologies, Vancouver, BC). In some embodiments, the culture medium comprises one or more supplements, such as, but not limited to N2 and B27. In some embodiments, the cell culture medium comprises a serum replacement composition. In some embodiments, the cell culture medium comprises low amount, such as less than 1% or less than 0.5%, of knock-out serum replacement medium. In some embodiments, the cell culture medium does not comprise a serum replacement composition. In some embodiments, the cell culture medium comprises an activator of STAT3 pathways, for example but not limited to leukemia inhibitory factor (LIF). In some embodiments, the cell culture comprises serum free recombinant human LIF.

[0085] In some embodiments, the cell culture medium comprises a basal medium to which one or more supplements are added, such as : DMEM/F12, Neurobasal, N2 supplement, 10 mL B27 supplement, human LIF, glutamine, nonessential amino acids, β -mercaptoethanol, penicillin-streptomycin, and/or BSA (Sigma). In some embodiments, the supplemented basal cell culture medium further comprises fibroblast growth factor 2 (FGF2) and 1%, 0.8%, 0.6%, 0.4%, 0.2%, or 0.1% KSR.

[0086] In some embodiments, the cell culture medium is free or essentially free of components of non-human origin. In some embodiments, the cell culture medium is free or essentially free of components isolated from humans or non-human animals. In some embodiments, the cell culture medium uses recombinant human proteins (*e.g.*, recombinant human albumin).

[0087] “Cell line” refers to a population of largely or substantially identical cells, wherein the cells have often been derived from a single ancestor cell or from a defined and/or substantially identical population of ancestor cells. For example, a cell line may consist of descendants of a single cell. A cell line may have been or may be capable of being maintained in culture for an extended period (*e.g.*, months, years, for an unlimited period of time). It will be appreciated that cells may acquire mutations and possibly epigenetic changes over time such that some individual cells of a cell line may differ with respect to each other. In some embodiments, at least 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the cells of a cell line or cell culture are at least 95%, 96%, 97%, 98%, or 99% genetically identical. In some embodiments, at least 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the cells of a cell line or cell culture express the same set of cell surface markers. The

set of markers could be markers indicative of ground state (naïve) pluripotency or cell-type specific markers.

[0088] A “clone” refers to a cell derived from a single cell without change. It will be understood that if cells of a clone are subjected to different culture conditions or if some of the cells are subjected to genetic modification, the resulting cells may be considered distinct clones.

BRIEF DESCRIPTION OF THE DRAWINGS

[0089] Figure 1 shows a reporter system for naïve human pluripotency based on endogenous *OCT4* distal enhancer activity. In Figure 1A, the proximal enhancer (PE) targeting strategy in human ESCs containing a 2A-GFP sequence in frame with the 3′ UTR of *OCT4* is shown. Figure 1B is a Southern blot analysis confirming disruption of the PE in *OCT4*-GFP ESCs. NdeI-digested genomic DNA was hybridized with 5′ and 3′ external probes. Expected fragment size: WT (wild type) = 5.6 kb, T (targeted) = 6.4 kb. Figure 1C shows the images of *OCT4*-GFP human ESCs before (left) and after TALEN-mediated deletion of the PE (right). Figure 1D shows the single molecule RNA FISH analysis for *OCT4* and GFP transcripts in *OCT4*-GFP human ESCs before and after TALEN-mediated disruption of the PE. Figure 1E shows the flow cytometric analysis of the proportion of *OCT4*-ΔPE-GFP+ cells obtained after DOX induction of lentiviral KLF2, NANOG or KLF2+NANOG. Following primary infection WIBR3 human ESCs containing the *OCT4*-ΔPE-GFP reporter allele were trypsinized and treated with hESM, 2i/L, or 2i/L/DOX for one week. Figure 1F are phase and fluorescence images and flow cytometric analysis of the proportion of *OCT4*-ΔPE-GFP+ cells of a clonal line of 38 hESCs derived in 2i/L/DOX (left). Phase and fluorescence images and flow cytometric analysis after replating in the absence of DOX for one week (right). Figure 1G shows the quantitative gene expression analysis for FUW-KLF2, FUW-NANOG, endogenous *OCT4*, and endogenous KLF4 in WIBR3 hESCs cultured in hESM and clonal *OCT4*-ΔPE-GFP+ derivatives generated in 2i/L/DOX. Figure 1H are phase and fluorescence images of primitive neural stem cells (pNSCs) derived by treating WIBR3 hESCs containing the *OCT4*-ΔPE-GFP allele with 2i/L for three passages. Figure 1I shows immunofluorescence staining for NANOG and NESTIN in a clonal line of *OCT4*-ΔPE-GFP-positive cells derived in 2i/L/DOX, and a clonal line of *OCT4*-ΔPE-GFP-negative pNSCs derived in 2i/L. Figure 1J is a model representing the distinct phenotypic responses of hESCs to treatment with 2i/L and 2i/L/DOX. *OCT4*-ΔPE-GFP+ cells generated in 2i/L/DOX do not maintain reporter activity upon transgene withdrawal. *OCT4*-ΔPE-GFP+

cells can revert back to the conventional 'primed' hESC state by re-exposure to serum and FGF.

[0090] Figure 2 shows the identification of small molecules that maintain OCT4- Δ PE-GFP activity after transgene withdrawal. Figure 2A shows the strategy for screening a kinase inhibitor library to identify compounds that maintain OCT4- Δ PE-GFP reporter activity upon withdrawal of DOX-dependent KLF2 and NANOG expression. Figure 2B is the raw data obtained from high-throughput flow cytometric analysis of the proportion of OCT4- Δ PE-GFP+ cells in 96 wells supplemented with a kinase inhibitor library (n=2). Figure 2C shows the hit compounds from a maintenance screen using a clonal line of WIBR3 OCT4- Δ PE-GFP+ ESCs established in 2i/L/DOX. Figure 2D are the phase images (top) and flow cytometric analysis of the proportion of OCT4- Δ PE-GFP+ cells (bottom) in a clonal line of OCT4- Δ PE-GFP+ cells derived in 2i/L/DOX and maintained for 10 passages without DOX in the presence of each candidate compound. Figure 2E is the quantitative gene expression analysis for FUW-KLF2, FUW-NANOG, endogenous OCT4, and EGFP in a clonal line of OCT4- Δ PE-GFP+ cells maintained in 2i/L/DOX or for five passages without DOX in the presence of each candidate compound. Figure 2F is the chemical structure of the BRAF inhibitor, SB590885. Figure 2G shows phase images of a clonal line of WIBR3 human ESCs established in 2i/L/DOX and maintained for 8 passages without DOX in 2i/L/SB590885 (1 μ M). Figure 2H is the quantitative gene expression analysis for FUW-KLF2, FUW-NANOG, and endogenous OCT4 in two clonal lines of WIBR3 human ESCs maintained for 8 passages without DOX in 2i/L/SB590885 (1 μ M).

[0091] Figure 3 shows the optimization of medium for maintaining viable OCT4- Δ PE-GFP+ cells.

[0092] Figure 3A shows the flow cytometric analyses of the proportion of OCT4- Δ PE-GFP+ cells in a 96 well one week after culture in 2i/L/DOX, 2i/L alone or 2i/L/SB590885 (1 μ M). Top panel shows quantification of OCT4- Δ PE-GFP+ cells without including live/dead discrimination. Bottom panel shows quantification of OCT4- Δ PE-GFP+ cells after gating out DAPI+ cells. Figure 3B shows the strategy for screening a kinase inhibitor library to identify compounds that improve the fraction of viable (DAPI-) OCT4- Δ PE-GFP+ cells maintained without DOX for 2 passages in 2i/L/SB590995 (1 μ M). Figure 3C is the raw data obtained from high-throughput flow cytometric analysis of the proportion of DAPI-/OCT4- Δ PE-GFP+ cells in 96 wells supplemented with one plate of a kinase inhibitor library (n=2). Hit compound WH-4-023 is indicated with chemical structure. Figures 3D-3E show high-throughput flow cytometric quantification of the proportion of DAPI-/OCT4- Δ PE-GFP+ cells

in 96 wells cultured for one passage (Figure 3D) or two passages (Figure 3E) in 64 different concentrations of PD0325901, CHIR99021, and SB590885. All the legends in Figure 3E also apply in Figure 3D. Asterisk denotes rank of the standard concentration of the three inhibitors used in the preceding experiments (1 μ M PD0325901, 0.3 μ M CHIR99021 and 0.5 μ M SB590885). Figure 3F are the phase and fluorescence images (top) and flow cytometric analysis of the proportion of OCT4- Δ PE-GFP+ cells (bottom) in a clonal line of OCT4- Δ PE-GFP+ cells derived in 2i/L/DOX and maintained for 2 passages without DOX in 2i/L/SB590885^{opt}/Y-27632 or 2i/L/SB590885^{opt}/Y-27632/WH-4-023. Opt = optimized concentrations of PD0325901, CHIR99021, and SB590885 (see Figure 4E). Figure 3G are the phase and fluorescence images of a clonal line of WIBR3 OCT4- Δ PE-GFP+ cells (left) and a clonal line of wild-type WIBR3 human ESCs generated in 2i/L/DOX (right) and maintained for 3 passages in PD0325901/IM12/SB590885/Y-27632/WH-4-023 (5i) and hLIF. Figure 3H shows the teratoma generated from wild-type WIBR3 human ESCs maintained in PD0325901/IM12/SB590885/Y-27632/WH-4-023 (5i) and hLIF after transgene withdrawal. Representative tissues of the three germ layers are indicated.

[0093] Figure 4 shows the direct conversion of conventional human ESCs to naïve pluripotency in 5i/L. Figure 4A shows the strategy for assessing direct conversion of primed human ESCs into OCT4- Δ PE-GFP+ cells under optimized chemical conditions. Figure 4B shows phase and fluorescence images of emerging naïve colony and expanded cells from WIBR3 OCT4- Δ PE-GFP human ESCs treated with 5i/L for 10 days. Figure 4C are the phase and fluorescence images and flow cytometric analyses of the proportion of GFP+ cells during conversion experiments in 5i/L supplemented with FGF and/or Activin A (FA). Figure 4D are the phase images of wild-type naïve WIBR2 human ES cells converted in 5i/L supplemented with FGF and/or Activin A (FA).

Figure 4E shows the phase image of a primary human ESC line derived in 5i/L/FA conditions from an explanted human blastocyst. Cell line is called Whitehead Institute Naïve Human ESC (WIN)-1. Figure 4F is the flow cytometric analysis of the proportion of OCT4- Δ PE-GFP+ cells three passages after withdrawal of individual inhibitors and growth factors. Figure 4G is the quantitative gene expression analysis for OCT4, NANOG, KLF4, KLF2, SOX2, and REX1 three passages after withdrawal of individual inhibitors and growth factors.

[0094] Figure 5 shows the evaluation of alternative culture conditions for naïve human pluripotency. Figure 5A is a table comparing the components of four recent protocols for capturing naïve-like human ESCs with 5i/L/A medium. Figure 5B show the phase and fluorescence images and flow cytometric analyses showing the response of OCT4- Δ PE-GFP-

negative primed cells to recently reported protocols for naïve human pluripotency (see Figure 5A) and 5i/L/A. Figure 5C shows the quantification of the proportion of GFP-positive cells in WIBR3 OCT4-GFP and OCT4-ΔPE-GFP human ESCs upon removal of DOX-inducible KLF2 and NANOG expression in primed medium (PM) and four alternative conditions for naïve human pluripotency. Figure 5D shows the flow cytometric analysis of the proportion of OCT4-ΔPE-GFP⁺ cells in 5i/L/A and the JNK inhibitor SP600125 (6i/L/A) in serum-free N2B27 basal medium vs. 20% KSR basal medium. Figure 5E is the quantitative gene expression analysis for OCT4, SOX2, KLF2 and NANOG in human ESCs cultured in 6i/L/A and supplemented with 1-10% FBS or KSR. Figure 5F are the phase and fluorescence images of induction of OCT4-ΔPE-GFP activity from the primed state in 6i/L/A, and 6i/L/A supplemented with 0.5-1% KSR.

[0095] Figure 6 shows the transcriptional profiling of naïve human ESCs in 5i/L/A. Figure 6A shows the cross-species hierarchical clustering of naïve and primed pluripotent cells from mice and humans, as performed previously by Gafni *et al.* (2013). Affymetrix expression data were normalized using RNA spike-in. Two groups of human ESC samples are included: WIBR2, WIBR3 and WIN1 human ESCs derived in the optimized naïve medium (5i/L/A or 6i/L/A, as indicated), and parental WIBR2 and WIBR3 human ESCs in primed human ESC medium. Correlation matrix of gene expression was clustered using Pearson correlation coefficients (PCCs). The average linkage hierarchical clustering of the Pearson correlation is shown in the heatmap. mEpiSCs, mouse EpiSCs; mESC, mouse ESC; miPSC, mouse iPSC.

[0096] Figure 6B shows the gene ontology (GO) analysis showing up- and down-regulated gene categories with most significant p values between the naïve human conditions and primed human ESCs. Figure 6C is a volcano plot showing fold change (x axis) between the naïve human ESC samples and primed human ESCs on all genes (left); volcano plot showing previously published fold change (x axis) between the naïve human ESC samples of Gafni *et al.* (2013) and primed human ESCs on all genes (right). The open circles are those that are log₂ fold change > 1 and < -1 & meet a p<0.05. Figure 6D shows the fold changes in expression of naïve pluripotency-associated transcripts in the naïve human ESC samples vs. primed hESCs (blue or black), and the naïve human samples published by Gafni *et al.* (2013) vs. primed human ESCs (red or grey). Figure 6E shows, for comparison with (Figure 6D), fold changes in expression of naïve pluripotency-associated transcripts in naïve mouse ESCs vs. primed mouse EpiSCs were curated from a previously published study (Najm *et al.*, 2011). Figure 6F shows the quantitative gene expression analysis for *NANOG* and *STELLA* in human ESCs cultured in parallel in primed medium, the medium of Gafni *et al.* (2013) and

5i/L/FA. Figure 6G shows single molecule (sm) RNA FISH analysis using *OCT4* and *NANOG* probes in WIBR2 human ESCs cultured in primed medium, the medium of Gafni *et al.* (2013) or 5i/L/A. Figure 6H shows single molecule (sm) RNA FISH analysis using *OCT4*, *NANOG*, *KLF4* and *REX1* probes in human ESCs cultured in primed medium, the medium of Gafni *et al.* (2013) or 5i/L/A.

[0097] Figure 7 shows the chromatin landscape of naïve human pluripotency. Figure 7A-7E show the ChIP-Seq tracks for H3K4me3 and H3K27me3 at four classes of genes: (Figure 7A) developmental genes that are bivalent in the primed state and exhibit loss of H3K27me3 in the naïve state; (Figure 7B) naïve pluripotency genes that are bivalent in the primed state and exhibit loss of H3K27me3 in the naïve state; (Figure 7C) naïve pluripotency genes that acquire H3K4me3 in the naïve state; (Figure 7D) master transcription factors that have a signal for H3K4me3, but not H3K27me3, in both naïve and primed states; (Figure 7E) ChIP-Seq tracks for H3K4me3 and H3K27me3 at the *DUSP6* and *SOX11* loci in WIBR2 human ESCs cultured under primed (red or grey) or naïve 6i/L/A (blue or black) conditions. Figure 7F shows the ChIP-Seq analysis for H3K4me3 and H3K27me3 at Polycomb target genes in WIBR2 human ESCs cultured in primed medium (left) or naïve 6i/L/A medium (right). Figure 7G shows average H3K4me3 and H3K27me3 signal at Polycomb target genes in WIBR2 human ESCs cultured in primed medium (red or grey) or naïve 6i/L/A medium (blue or black).

[0098] Figure 8 shows a reporter system for naïve human pluripotency based on endogenous *OCT4* distal enhancer activity (associated with Figure 1). Figure 8A: southern blot analysis confirming deletion of the PE in *OCT4*-GFP ESCs and the removal of floxed PGK-puro cassette. NdeI-digested genomic DNA was hybridized with 5' and 3' external probes. Expected fragment size: WT (wild type) = 5.6 kb, T (targeted) = 6.4 kb, PEKO (targeted allele after PGK-puro removal) = 4.6 kb. Figure 8B: phase and GFP images of *OCT4*-ΔPE-GFP+ cells obtained after DOX induction of lentiviral *KLF2*+*NANOG*. Following primary infection, WIBR3 human ESCs containing the *OCT4*-ΔPE-GFP reporter allele were trypsinized and treated with hESM, 2i/L or 2i/L/DOX for one week. Figure 8C: immunofluorescence staining for *OCT4* in a clonal line of *OCT4*-ΔPE-GFP-positive cells derived in 2i/L/DOX, and a clonal line of *OCT4*-ΔPE-GFP-negative pNSCs derived in 2i/L. Figure 8D: quantitative gene expression analysis for EGFP, *SOX2*, *PRMD14* and *PAX6* in clonal *OCT4*-ΔPE-GFP+ human ESC lines generated in 2i/L/DOX, secondary primed cells generated by withdrawal of DOX and expansion in conventional hESM, and clonal lines of *OCT4*-ΔPE-GFP-negative pNSCs derived in 2i/L.

[0099] Figure 9 shows the identification of small molecules that maintain OCT4- Δ PE-GFP activity after transgene withdrawal (associated with Figure 2). Figure 9A: raw data obtained from high-throughput flow cytometric analysis of the proportion of OCT4- Δ PE-GFP+ cells in 96 wells supplemented with a kinase inhibitor library (n=2). Figure 9B: quantitative gene expression analysis for STELLA, KLF4, PRDM14 and SOX2 in a clonal line of OCT4- Δ PE-GFP+ cells maintained in 2i/L/DOX or for five passages without DOX in the presence of each candidate compound. Figure 9C: flow cytometric analyses of the proportion of viable (DAPI-negative) and OCT4- Δ PE-GFP+ cells in 2i/L/DOX or two passages after DOX withdrawal in 2i/L/SB590885 (1 μ M).

[00100] Figure 10 shows the optimization of medium for maintaining viable OCT4- Δ PE-GFP+ cells (associated with Figure 3). Figure 10A: raw data obtained from high-throughput flow cytometric analysis of the proportion of DAPI-/OCT4- Δ PE-GFP+ cells in 96 wells supplemented with three plates of a kinase inhibitor library in the presence of the primary hit compound SB590885 (n=2). Figure 10B: hit compounds from a viability screen using a clonal line of WIBR3 OCT4- Δ PE-GFP+ ESCs established in 2i/L/DOX. Figure 10C: phase images and flow cytometric analyses of OCT4- Δ PE-GFP+ cells maintained in 2i/L/SB590885 (0.5 μ M) $\pm$ ROCK inhibitor Y-27632 (10 μ M) for two passages. Figure 10D: phase and GFP images of OCT4- Δ PE-GFP+ cells maintained for four passages in 2i/L/DOX, 2i/L/SB590885 (0.5 μ M) + ROCK inhibitor Y-27632 (10 μ M) or the same medium in which CHIR99021 was replaced with an alternative GSK3 inhibitor, IM-12 (1.0 μ M).

[00101] Figure 11 shows the direct conversion of conventional human ESCs to naïve pluripotency in 5i/L [associated with Figure 4]. Figure 11A: karyotype analysis of naïve human ESCs WIBR2 (P8 in 5i/L/A). Cytogenetic analysis was performed on 20 metaphase cells. Figure 11B: karyotype analysis of naïve human ESCs WIN1 (P7 in 5i/L/FA). Cytogenetic analysis was performed on 20 metaphase cells. Figure 11C: phase images of OCT4- Δ PE-GFP+ cells three passages after withdrawal of individual inhibitors and growth factors.

[00102] Figure 12 shows the evaluation of alternative culture conditions for naïve human pluripotency [associated with Figure 5]. Figure 12A: phase and fluorescence images (Top) and flow cytometric analysis of the proportion of OCT4- Δ PE-GFP+ cells (Bottom) in OCT4- Δ PE-GFP+ cells derived in 5i/L/FA and maintained for three passages in the presence of additional media additives, as indicated. Figure 12B: quantitative gene expression analysis for KLF2 and KLF4 in OCT4- Δ PE-GFP-positive naïve human ESCs cultured in 5i/L/A and supplemented with various components of the medium of Gafni *et al.* (2013). Figure 12C:

phase and fluorescence images (Top) and flow cytometric analysis of the proportion of OCT4-ΔPE-GFP+ cells (Bottom) in OCT4-ΔPE-GFP+ cells derived in 5i/L/FA and maintained for three passages in 20% KSR basal medium supplemented with the media additives described in (Figure 12A).

[00103] Figure 13 shows the transcriptional profiling of naïve human ESCs in 5i/L/A and 6i/L/A [associated with Figure 6]. Figure 13A: quantitative gene expression analysis for KLF4 and REX1 in human ESCs cultured in parallel in primed medium, 5i/L/FA and the medium of Gafni *et al.* (2013). Figure 13B: expression profile of transcripts upregulated in 6i/L/A during human embryonic development. For each gene, the normalized expression values in human ESCs cultured in 6i/L/A vs. primed human ESCs are indicated (Left). An unpaired two-tailed t test was performed to establish the degree of significance. Expression of the corresponding transcript is shown at nine stages of human pre-implantation development, as detected by single cell RNA-Seq profiling (Yan *et al.*, 2013) (Right). This comparison indicates that naïve-associated transcripts upregulated in 6i/L/A are enriched at the morula/epiblast stage of human development when compared to human ESCs at passage 0 or passage 10. Figure 13C: variability in NANOG expression compared between single human ESCs cultured in primed medium, 5i/L/A or the medium of Gafni *et al.* (2013).

[00104] Figure 14 shows the developmental potential of naïve human ESCs in 5i/L/A. Figure 14A: teratomas generated from WIBR3 OCT4-ΔPE-GFP-positive human ESCs derived and maintained in 5i/L±FA and WIBR3 AAVS1-tdTomato human ESCs in 5i/L/FA. Representative tissues of the three germ layers are indicated. Figure 14B: immunofluorescence staining for AFP and HNF4a following 20d of hepatic differentiation in naïve WIBR2 human ESCs derived and maintained in 5i/L/A. Figure 14C: table summarizing injections of human ESCs maintained in 5i/L/FA (top) or the medium of Gafni *et al.* (2013) (bottom) in mouse embryos. C1-AAVS1-GFP human ESCs in the medium of Gafni *et al.* (2013) were cultured on MEFs, gelatin/vitronectin or matrigel prior to injection. (*) E10.5 embryos injected with human ESCs cultured in 5i/L/FA and the medium of Gafni *et al.* (2013) were mixed during collection, but none were identified as positive. (**) 30 injected embryos were lost during transfer.

[00105] Figure 15 shows that the proliferation of naïve human embryonic stem cells is enhanced by reduction or removal of GSK3 inhibition. Figure 15A: transgene-dependent naïve human embryonic stem (ES) cell line used to titrate the concentrations of inhibitors in 5i/L/A (see Theunissen *et al.*, Cell Stem Cell, 2014). This subclone of WIBR3 is dependent on Doxycycline (DOX) to maintain expression of two lentiviral transgenes, KLF2 and

NANOG. Left, phase image shows colony morphology in 2i/L/DOX. Middle, flow cytometric quantification shows the proportion of cells positive for the OCT4-ΔPE-GFP reporter in 2i/L/DOX. Right, this cell line has a normal (46,XX) karyotype. Figure 15B: titration assay to attain optimal concentrations of small molecule inhibitors for maintenance of naïve human ES cells. Top, phase images showing colony morphology after sequential passaging by single cell dissociation at low density (1:10) in four different conditions: 2i/L, 5i/L/A, t5i/L/A (0.2 μM GSK3 inhibitor IM12) and 4i/L/A (removal of GSK3 inhibitor IM12). Bottom, flow cytometric quantification shows the proportion of cells positive for the OCT4-ΔPE-GFP reporter in each condition. Figure 15C: quantitative RT-PCR (qRT-PCR) analysis confirming the downregulation of exogenous KLF2 and NANOG transgenes and primed marker VIMENTIN and upregulation of naïve markers KLF4, REX1 and STELLA in t5i/L/A and 4i/L/A. Error bars indicate one standard deviation.

[00106] Figure 16 shows the quantification of the proliferation of naïve human cells in presence of different Wnt signal modulators. Quantification of cell number in naïve culture conditions supplemented with distinct Wnt signal modulators after withdrawal of DOX from transgene-dependent naïve human ES cells (see Figure 15A). 1x10⁵ cells were seeded per individual well of a 6 well plate and cells were dissociated and re-seeded at 1:5 density for three successive passages. Cell numbers at successive passages were recorded in six conditions (n=2): 2i/L/DOX (control), 2i/L, 5i/L/A, 4i/L/A (removal of GSK3 inhibitor IM12), 4i/L/A+CHIR99021 (1 μM), and 4i/L/A+IWR1 (2.5 μM). At passages 2 and 3 the proliferation was significantly elevated in 4i/L/A compared to 5i/L/A. Replacing IM12 with alternative GSK3 inhibitor CHIR99021 or addition of the Wnt inhibitor IWR1 did not further stimulate the proliferation of naïve human cells.

[00107] Figure 17 shows the induction of naïve human pluripotency in 5i/L/A or 4i/L/A is associated with X chromosome reactivation. Figure 17A: a reporter system for X chromosome status of human ES cells was engineered by TALEN-mediated targeting of both alleles of the X-linked MECP2 gene with fluorescent reporters. Figure 17B: starting from a single color (GFP-positive) primed line, conversion to the naïve state in 5i/L/A or 4i/L/A (-IM12) results in activation of the tdTomato-labelled allele while GFP activity is maintained. Figure 17C: starting from a single color (tdTomato-positive) primed line, conversion to the naïve state in 5i/L/A or 4i/L/A (-IM12) results in activation of the GFP-labelled allele while tdTomato activity is maintained. These results indicate that induction of naïve human pluripotency is accompanied by a switch towards biallelic expression of X-linked genes, which is confirmed by RNA FISH data (not shown).

DETAILED DESCRIPTION OF THE INVENTION

[00108] The present disclosure, in one aspect, is based on the identification of compounds (*e.g.*, compounds of any one of Formulae (A) to (L), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof) that support self-renewal of naïve human ESCs. In particular, iterative chemical screening identified kinase inhibitors that induce and maintain OCT4 distal enhancer activity, a molecular signature of ground state pluripotency, when applied directly to conventional human ESCs. These inhibitors generate a homogeneous population of human pluripotent stem cells in which transcription factors associated with the ground state of pluripotency are highly upregulated. Comparison with previously reported naïve human ESCs indicates that the procedures defined herein capture a novel pluripotent state in humans that closely resembles mouse ESCs. Accordingly, aspects of the disclosure provide methods for converting the pluripotency state of a vertebrate (*e.g.*, human) cell to a more naïve state. Also provided are naïve pluripotent vertebrate cells (*e.g.*, human) and cell lines produced by the methods described herein. Some aspects of the invention also involve kits for converting the pluripotency state of a vertebrate (*e.g.*, human) cell to a more naïve state.

[00109] Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have attracted much attention because of their potential to mature into virtually any cell type in the body. However, mouse ESCs and iPSCs have different growth factor requirements and provide a more reliable vehicle for directed differentiation as compared to human ESCs and iPSCs. It was thought for many years that these differences reflected variation between species. In 2007, however, two groups reported that novel stem cell lines derived from the post-implantation epiblast of mouse embryos, called EpiSCs, have properties similar to human ESCs (Brons *et al.*, 2007; Tesar *et al.*, 2007). These include a flat morphology, dependence on bFGF and activin signaling, and use of the OCT4 proximal enhancer element. The inner cell mass (ICM)-like state of mouse ESCs was described as “naïve,” whereas EpiSCs and human ESCs were designated as “primed” (Nichols and Smith, 2009); the implication is that the primed state is prone to differentiate, whereas the naïve condition corresponds to the more immature “ground state” of pluripotency.

[00110] The present disclosure relates to the discovery that conventional human ESCs can be converted into a more immature/less restricted state (*i.e.*, a more “naïve” pluripotent state) that extensively shares defining features with pluripotent mouse ESCs. Described

herein are optimized conditions that enable the interconversion between conventional and naïve human ESCs in the absence of reprogramming factors, as well as the direct isolation of genetically unmodified naïve ESCs from human blastocysts. The methods described herein capture a distinct and novel state of human pluripotency that shares defining features with mouse ESCs.

[00111] Accordingly, some aspects of the disclosure provide a method for changing the pluripotency state of a vertebrate cell to a more naïve state. The method comprises (a) culturing a pluripotent vertebrate cell in the presence of a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor; and (b) maintaining the cell in culture under conditions suitable and a time sufficient to changing the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the original vertebrate cell of step (a).

[00112] The kinase inhibitor(s) used herein may be a small molecule, antibodies/antibody fragments (at least for those kinases that have an extracellular domain), short interfering RNA, and/or aptamers. A “small molecule,” (M) as used herein, refers to an alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclic, or heterocyclic moiety, as defined herein, comprising carbon and hydrogen, and optionally comprising one or more heteroatoms as a part of the molecule (in the case of heteroaryl and heterocyclic groups) and/or attached to the molecule selected from oxygen, nitrogen, sulfur, phosphorus, boron, silicon, and selenium. In certain embodiments, the specificity of the inhibitors is given by the IC₅₀ value. The IC₅₀ value is defined as the concentration of inhibitor required to inhibit 50% of the kinase activity. In certain embodiments, the compounds of Formula (I) or (II) may exhibit IC₅₀ values < 100 µM. In certain other embodiments, the compounds exhibit IC₅₀ values < 50 µM. In certain other embodiments, the compounds exhibit IC₅₀ values < 40 µM. In certain other embodiments, the compounds exhibit IC₅₀ values < 30 µM. In certain other embodiments, the compounds exhibit IC₅₀ values < 20 µM. In certain other embodiments, the compounds exhibit IC₅₀ values < 10 µM. In certain other embodiments, the compounds exhibit IC₅₀ values < 7.5 µM. In certain embodiments, the compounds exhibit IC₅₀ values < 5 µM. In certain other embodiments, the compounds exhibit IC₅₀ values < 2.5 µM. In certain embodiments, the compounds exhibit IC₅₀ values < 1 µM. In certain embodiments, the compounds exhibit IC₅₀ values < 0.75 µM. In certain embodiments, the compounds exhibit IC₅₀ values < 0.5 µM. In certain embodiments, the compounds exhibit IC₅₀ values < 0.25 µM. In certain embodiments, the compounds exhibit IC₅₀ values < 0.1 µM. In certain

other embodiments, the compounds exhibit IC₅₀ values < 75 nM. In certain other embodiments, the compounds exhibit IC₅₀ values < 50 nM. In certain other embodiments, the compounds exhibit IC₅₀ values < 25 nM. In certain other embodiments, the compounds exhibit IC₅₀ values < 10 nM. In other embodiments, the compounds exhibit IC₅₀ values < 7.5 nM. In other embodiments, the compounds exhibit IC₅₀ values < 5 nM.

[00113] In certain embodiments, the BRAF inhibitor is a compound of Formula (B) (*e.g.*, AZ-628 or BAY-439006) or Formula (C) (*e.g.*, GDC-0879 or SB590885). In certain embodiments, the BRAF inhibitor is sorafenib; PLX4720; PLX-3603; GSK2118436; *N*-(3-(5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2;4-difluorophenyl)propane-1-sulfonamide; vemurafenib (also known as Zelobraf[®] and PLX-4032); GSK 2118436; RAF265 (Novartis); XL281; ARQ736; a compound described in international PCT application publication, WO 2007/002325, WO 2007/002433, WO 2009/111278, WO 2009/111279, WO 2009/111277, WO 2009/111280, or WO 2011/025927; or a compound described in U.S. Patent No. 7,491,829 or 7,482,367. In certain embodiments, the VEGFR1 inhibitor is a compound of Formula (A) (*e.g.*, AMG706), Formula (B) (*e.g.*, BAY 73-4506), or Formula (G) (*e.g.*, BIBF-1120 or SU11248). In certain embodiments, the VEGFR1 inhibitor is SU5416 or a compound described in U.S. patent application publication, US 2006/0030000. In certain embodiments, the FGFR1 inhibitor is a compound of Formula (F) (*e.g.*, PD173074). In certain embodiments, the FGFR1 inhibitor is cediranib; brivanib; TSU-68; BIBF1120; dovitinib; Ki23057; MK-2461; E7080; SU5402; BGJ398; E-3810; AZD4547; PLX052; or a compound described in U.S. Patent No., US 8,709,718. In certain embodiments, the MEK inhibitor is a compound of Formula (K) (*e.g.*, PD0325901). In certain embodiments, the MEK inhibitor is a compound described in international PCT application publication, WO 2010/138377, WO 2009/153554, WO 2009/093009, WO 2009/013462, WO 2009/093013, WO 2008/020206, WO 2008/078086, WO 2008/120004, WO 2008/125820, WO 2009/093008, WO 2009/074827, WO 2009/093009, WO 2010/108652, WO 2010/105110, WO 2010/105082, WO 2009/129246, WO 2009/018238, WO 2009/018233, WO 2008/089459, WO 2008/124085, WO 2008/076415, WO 2008/021389, WO 2010/051935, WO 2010/051933, WO 2009/129938, WO 2009/021887, WO 2008/101840, WO 2008/055236, WO 2010/003025, WO 2010/003022, WO 2007/096259, WO 2008/067481, WO 2008/024724, WO 2008/024725, or WO 2010/0145197; or a compound described in U.S. patent application publication, US 2008/0255133, US 2008/0058340, US 2009/0275606, or US 2009/0246198. In certain embodiments, the GSK3 inhibitor is a compound of Formula (C) (*e.g.*, CHIR99021) or

Formula (J) (*e.g.*, IM12). In certain embodiments, the GSK3 inhibitor is CHIR98014; CHIR98023; BIO-acetoxime; BIO; LiCl; SB 216763; SB 415286; AR-A014418; 1-azakenpaullone; bis-7- indolylmaleimide; kenpaullone; CT 99021; CT 20026; SB216763; SB 415286; TDZD-8; TIBPO (2-thio(3-iodobenzyl)-5-(1-pyridyl)-[1,3,4]-oxadiazole); a compound described in U.S. patent application publication, US 2013/0059385, US 2001/0034051, US 2002/0156087, US 2004/0092535, US 2004/0209878, US 2004/0138273, US 2004/0077707, US 2005/0054663, US or 2006/0089369; a compound described in U.S. Patent No. US 6,057,117; US 6,608,063; US 6,417,185; US 6,489,344; or US 6,153,618; or a compound described in international PCT application publication, WO/2003/049739; WO/2002/085909; WO/2003/011287, WO/2005/039485, or WO/2006/091737. In certain embodiments, the ROCK inhibitor is a compound of Formula (L) (*e.g.*, Y-27632). In certain embodiments, the ROCK inhibitor is fasudil (HA-1077); thiazovivin; AMA0076; AR-12286; AMA0076; AR-12286; AR-13324; ATS907; DE-104; INS-115644; INS-117548; K-115; PG324; Y-39983; RKI-983; SNJ-1656; a compound described in international PCT application publication, WO 2014/068035, WO 2013/030216, WO 2013/030367, WO 2013/030366, WO 2013/030365, WO 2011/107608, WO 2012/146724, WO 2006/137368, or WO 2005/035506; or a compound described in U.S. patent application publication, US 2013/196437. In certain embodiments, the Src inhibitor is a compound of Formula (H) (*e.g.*, WH-4-023). In certain embodiments; the Src inhibitor is SKI606 (bosutinib); dasatinib (SPYRCEL); saracatenib (AZD-0530); PPI; PP2; PD173955; AGL1872; PD162531; radicicol R2146; geldanamycin; or a compound described in U.S. patent application publication, US 2006/258686, US 2009/0227608, US 2010/0249152, or US 2013/0040972.

[00114] ESCs are pluripotent cells. ESCs have been derived from vertebrate animals such as mice, primates (including humans), and some other species. ESCs are often derived from cells obtained from the inner cell mass (ICM) of a vertebrate blastocyst but can also be derived from single blastomeres (*e.g.*, removed from a morula). Pluripotent cells can also be obtained using parthenogenesis, *e.g.*, from germ cells, *e.g.*, oocytes. Other pluripotent cells include embryonic carcinoma (EC) and embryonic germ (EG) cells. See, *e.g.*, Yu J, Thomson J A, *Genes Dev.* Pluripotent stem cell lines. 22(15):1987-97, 2008.

[00115] Standard techniques for preparing deriving human ES cells typically involve the use of a MEF or human cell feeder layer and serum or, if cultured in serum-free medium, compounds such as bFGF. For example, the ICM of a human blastocyst is removed by immunosurgery, dissociated in Ca^{2+} - Mg^{2+} -free medium, and plated over mouse embryonic fibroblasts or human feeder cells (Thomson *et al.*, Science 282, 1145 (1998). The mouse

cells are irradiated to suppress their proliferation. See, *e.g.*, B. E. Reubinoff *et al.*, *Nature Biotechnol.* 18, 399, 2000; Mitalipova M & Palmarini G. Isolation and characterization of human embryonic stem cells. *Methods Mol. Biol.* 331:55-76, 2006; Ilic D, *et al.*, Derivation of hESC from intact blastocysts. *Curr Protoc Stem Cell Biol.*, Chapter 1:Unit 1A.2, 2007; Ludwig T, Thomson J., Defined, feeder-independent medium for human embryonic stem cell culture. *Curr Protoc Stem Cell Biol.* Chapter 1:Unit 1C.2, 2007. It will be understood that culture conditions can be feeder layer free. It will also be understood that the culture conditions can include the use of matrices such as laminin, Matrigel™, and the like. In some embodiments, methods described in Chen A E, *et al.*, Optimal timing of inner cell mass isolation increases the efficiency of human embryonic stem cell derivation and allows generation of sibling cell lines. *Cell Stem Cell.* 4(2): 103-6, 2009, are used. In some embodiments, mitomycin C-inactivated mouse embryonic fibroblast feeder cells are used for culturing human embryonic stem cells. It will be understood that in some embodiments other methods of inactivating feeder cells may be used such as other compounds or gamma irradiation.

[00116] A pluripotent vertebrate cell can be converted to a more naïve state by culturing the cell in the presence of a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor; and maintaining the cell in culture under conditions suitable and a time sufficient to change the pluripotency state of the vertebrate cell to a more naïve state.

[00117] The cell is cultured and maintained in a culture medium under suitable conditions until the pluripotency state of the cell is converted to a more naïve state. Conditions suitable for conversion of the pluripotent state of the cell to a more naïve state include the presence of one or more kinase inhibitors in the culture medium. Thus, in some embodiments, the culture medium contains a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor. In some embodiments, the culture medium further contains a mitogen-activated protein kinase kinase (MEK) inhibitor. In some embodiments, the culture medium further contains a ROCK inhibitor and/or an Src inhibitor. In some embodiments, the culture medium further contains a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK

inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the culture medium further contains fibroblast growth factor and/or Activin A. In some embodiments, the culture medium contains one or more of the compounds described herein. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the culture medium does not contain a GSK3 inhibitor.

[00118] The concentration of the kinase inhibitors used in the culture medium will depend on the amount of culture medium being generated. In some embodiments, 0.1 μM , 0.2 μM , 0.3 μM , 0.4 μM , 0.5 μM , 1 μM , 1.5 μM , 2.0 μM , 2.5 μM , 3.0 μM , 3.5 μM , 4.0 μM , 4.5 μM , 5.0 μM , 5.5 μM , 6.0 μM , 6.5 μM , 7.0 μM , 8.0 μM , 8.5 μM , 9.0 μM , 9.5 μM , 10.5 μM , 11.0 μM , 12.0 μM , 13.0 μM , 14.0 μM , or 15.0 μM of one or more kinase inhibitors are included in about 500 mL of culture medium. In some embodiments, 0.1-1.0 μM of BRAF inhibitor is used in about 500 ml of culture medium. In some embodiments, 0.5-1.5 μM of MEK inhibitor is used in about 500 ml of culture medium. In some embodiments, 0.5-1.5 μM of Src inhibitor is used in about 500 ml of culture medium. In some embodiments, 5.0-15 μM of ROCK inhibitor is used in about 500 ml of culture medium. In some embodiments, 1.0-5.0 μM of GSK3 inhibitor is used in about 500 ml of culture medium.

[00119] In some embodiments, the concentration of GSK3 inhibitor is 1 nM to 10 nM. In some embodiments, the concentration of GSK3 inhibitor is 10 nM to 0.1 μM . In some embodiments, the concentration of GSK3 inhibitor is 0.1 μM to 0.2 μM . In some embodiments, the concentration of GSK3 inhibitor is 0.2 μM to 0.5 μM . In some embodiments, the concentration of GSK3 inhibitor is 0.5 μM to 1 μM . In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor, and further contains a GSK3 inhibitor in concentration range listed above in this paragraph.

[00120] In some embodiments, if a different kinase inhibitor that targets the same kinase is used, such kinase inhibitor may be used at a concentration that provides an approximately equivalent effect.

[00121] In some embodiments, conditions suitable for conversion of the pluripotent state of the cell to a more naïve state include, in addition to the one or more kinase inhibitors described herein, the addition of one or more of the following components to the culture medium: N2 supplement, B27 supplement, human LIF, glutamine, nonessential amino acids, β -mercaptoethanol, penicillin-streptomycin, and/or albumin (*e.g.*, BSA or human albumin). In some embodiments, the culture media comprise DMEM/F12 or Neurobasal. In some

embodiments, the culture media comprise DMEM/F12 and Neurobasal in a suitable ratio (*e.g.*, 10:90 to 90:10 (*e.g.*, 25:75, 50:50, and 75:25) DMEM/F12 : Neurobasal). In some embodiments, the culture media comprising DMEM/F12 and/or Neurobasal further comprise N2 supplement, B27 supplement, human LIF, glutamine, nonessential amino acids, β -mercaptoethanol, penicillin-streptomycin, and/or albumin (*e.g.*, BSA or human albumin). In some embodiments, the culture medium further comprises fibroblast growth factor 2 (FGF2) and 1%, 0.8%, 0.6%, 0.4%, 0.2%, or 0.1% KSR. In some embodiment, the cells are maintained on mitomycin C-inactivated mouse embryonic fibroblast feeder cells. In some embodiments, conditions suitable for conversion of the pluripotent state of the cell to a more naïve state include growing the cells under physiological oxygen conditions, *i.e.*, about 5% O₂. In some embodiments, the cells are grown under between about 1% O₂ and about 5% O₂. In some embodiments, the cells are grown under between about 2% O₂ and about 5% O₂. In some embodiments, the cells are grown under between about 5% O₂ and about 10% O₂. In some embodiments, the cells are grown under between about 10% O₂ and about 20% O₂. In some embodiments, the cells are grown under 1% O₂, 2% O₂, 3% O₂, 4% O₂, 5% O₂, 6% O₂, 7% O₂, 8% O₂, 9% O₂, 10% O₂, 11% O₂, 12% O₂, 13% O₂, 14% O₂, 15% O₂, 16% O₂, 17% O₂, 18% O₂, 19% O₂, 20% O₂, 21% O₂, 22% O₂, 23% O₂, 24% O₂, or 25% O₂.

[00122] Some aspects of the invention relate to a cell culture medium comprising: a basal medium; and a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor. In some embodiments, the cell culture medium further comprises mitogen-activated protein kinase kinase (MEK) inhibitor. In some embodiments, the cell culture medium further comprises a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor. In some embodiments, the culture medium further contains a ROCK inhibitor and/or an Src inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the culture medium contains an inhibitor of a receptor tyrosine kinase, a MEK inhibitor, and a GSK3 inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and an Src inhibitor. In some embodiments, any of the culture media contains a VEGFR1 inhibitor, an

EGFR inhibitor, a FGFR1 inhibitor, or a combination thereof, instead of, or in addition to, a BRAF inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor and a MEK inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, and a ROCK inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the culture medium contains an inhibitor of a receptor tyrosine kinase and a MEK inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, and an Src inhibitor. In some embodiments, the culture medium does not contain a GSK3 inhibitor.

[00123] In some embodiments, the concentration of GSK3 inhibitor is 1 nM to 10 nM. In some embodiments, the concentration of GSK3 inhibitor is 10 nM to 0.1 μ M. In some embodiments, the concentration of GSK3 inhibitor is 0.1 μ M to 0.2 μ M. In some embodiments, the concentration of GSK3 inhibitor is 0.2 μ M to 0.5 μ M. In some embodiments, the concentration of GSK3 inhibitor is 0.5 μ M to 1 μ M. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor, and further contains a GSK3 inhibitor in concentration range listed above in this paragraph. In some embodiments, the culture medium contains a BRAF inhibitor and a MEK inhibitor, and further contains a GSK3 inhibitor in concentration range listed above in this paragraph. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, and a ROCK inhibitor and further contains a GSK3 inhibitor in concentration range listed above in this paragraph. In some embodiments, the culture medium contains a receptor tyrosine kinase and a MEK inhibitor, and further contains a GSK3 inhibitor in concentration range listed above in this paragraph. In some embodiments, the culture medium contains BRAF inhibitor, a MEK inhibitor, and an Src inhibitor, and further contains a GSK3 inhibitor in concentration range listed above in this paragraph.

[00124] As used herein, a “basal medium” is typically an unsupplemented medium (*e.g.*, Eagle's minimal essential medium (EMEM); Dulbecco's modified Eagle's medium (DMEM)). As will be appreciated by those of skill in the art, a basal medium can comprises a variety of components such as one or more amino acids (*e.g.*, non-essential amino acids, essential amino acids), salts (*e.g.*, calcium chloride, potassium chloride, magnesium sulfate, sodium chloride, and monosodium phosphate), sugars (*e.g.*, glucose), and vitamins (*e.g.*, folic acid, nicotinamide, riboflavin, B12), iron and pH indicators (*e.g.*, phenol red). The basal medium can further comprise proteins (*e.g.*, albumin), hormones (*e.g.*, insulin), glycoproteins

(*e.g.*, transferrin), minerals (*e.g.*, selenium), serum (*e.g.*, fetal bovine serum), antibiotics, antimycotics and glycosaminoglycans.

[00125] In some embodiments, the basal medium is serum-free medium. In some embodiments, the basal medium comprises one or more supplements, such as, but not limited to, supplements such as B27 and/or N2. In some embodiments, the basal medium is supplemented with one or more of the following: DMEM/F12, Neurobasal, N2 supplement, 10 mL B27 supplement, human LIF, glutamine, nonessential amino acids, β -mercaptoethanol, penicillin-streptomycin, and/or BSA (Sigma). In some embodiments, the supplemented basal cell culture medium further comprises fibroblast growth factor 2 (FGF2) and 1%, 0.8%, 0.6%, 0.4%, 0.2%, or 0.1% KSR.

[00126] The pluripotent vertebrate cell is maintained in culture for a time sufficient to change the pluripotency state of the cell to a more naïve state. In some embodiments, time sufficient to change the pluripotency state of the cell to a more naïve state is at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, at least 7 days, at least 8 days, at least 9 days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least 14 days, at least 15 days, at least 16 days, at least 17 days, at least 18 days, at least 19 days, or at least 20 days. In some embodiments, time sufficient to change the pluripotency state of the cell to a more naïve state is between 1-5 days, 1-10 days, 1-15 days, 1-20 days, 5-10 days, 5-15 days, 5-20 days, 10-15 days, 10-20 days, or 15-20 days. In some embodiments, time sufficient to change the pluripotency state of the cell to a more naïve state is at least about 5 days (*e.g.*, about 10 days). In some embodiments, the culture medium is replenished as required during this time. In some embodiments, the cell is maintained in culture until the cell has at least one property which is similar to the corresponding property of mouse embryonic stem cells. In some embodiments, the at least one property which is similar to the corresponding property of mouse embryonic stem cells is the utilization of the distal OCT4 enhancer element. An important molecular signature of naïve pluripotency in the mouse system is the use of the distal enhancer (DE) of *OCT4*. Thus, in some embodiments, the cell is maintained in culture until the cell uses the distal Oct4 enhancer element for OCT4 expression. In some embodiments, the cell is maintained in culture until the cell uses the endogenous distal Oct4 enhancer element for OCT4 expression. In some embodiments, the cell is maintained in culture until the cell has enhanced utilization of the distal Oct4 enhancer element for OCT4 expression as compared to the cell prior to the culturing/maintenance period. In some embodiments, the cell is maintained in culture until the cell has enhanced utilization of the endogenous distal Oct4 enhancer element for OCT4 expression as compared

to the cell prior to the culturing/maintenance period. The utilization of the distal OCT4 enhancer element can be tested using the OCT4-ΔPE-GFP reporter system described in the Examples below.

[00127] In some embodiments, the at least one property which is similar to the corresponding property of mouse embryonic stem cells is colony morphology. Naïve pluripotent cells that correspond to the more immature “ground state” of pluripotency, exhibit a dome-like colony morphology. Thus, in certain embodiments, the cell is maintained in culture until it exhibits a dome-like colony morphology.

[00128] In some embodiments, the at least one property which is similar to the corresponding property of mouse embryonic stem cells is gene expression profile. The cell is maintained in culture until it has a global gene expression profile which clusters with naïve mouse ESCs as opposed to mouse EpiSCs and/or less naïve human ESCs. In some embodiments, the gene expression profile includes markers of ground state pluripotency, such as, but not limited to, *NANOG*, *OCT4*, *DPPA5*, *DPPA3* (also known as *STELLA*), *KLF4*, *KLF5*, *TFCP2L1*, and/or *REX1*. In some embodiments, the cell is maintained in culture until it exhibits a gene expression profile similar to that shown in Fig. 6.

[00129] Some aspects of the invention relate to a method for culturing vertebrate cells, the method comprising growing vertebrate cells in a cell culture medium comprising a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor. The vertebrate cells can be naïve pluripotent cells, human pluripotent cells, or naïve human pluripotent cells. In some embodiments, the cell culture medium further comprises mitogen-activated protein kinase kinase (MEK) inhibitor. In some embodiments, the cell culture medium further comprises a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor. In some embodiments, the culture medium further contains a ROCK inhibitor and/or an Src inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor and a MEK inhibitor. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, and a ROCK inhibitor. In some embodiments, the culture medium contains

a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the culture medium does not contain a GSK3 inhibitor.

[00130] In some embodiments, the concentration of GSK3 inhibitor is 1 nM to 10 nM. In some embodiments, the concentration of GSK3 inhibitor is 10 nM to 0.1 μ M. In some embodiments, the concentration of GSK3 inhibitor is 0.1 μ M to 0.2 μ M. In some embodiments, the concentration of GSK3 inhibitor is 0.2 μ M to 0.5 μ M. In some embodiments, the concentration of GSK3 inhibitor is 0.5 μ M to 1 μ M. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor, and further contains a GSK3 inhibitor in concentration range listed above in this paragraph. In some embodiments, the culture medium contains a BRAF inhibitor and a MEK inhibitor, and further contains a GSK3 inhibitor in concentration range listed above in this paragraph. In some embodiments, the culture medium contains a BRAF inhibitor, a MEK inhibitor, and a ROCK inhibitor and further contains a GSK3 inhibitor in concentration range listed above in this paragraph.

[00131] The cell culture medium may be a basal medium. As used herein, a “basal medium” is typically an unsupplemented medium (*e.g.*, Eagle’s minimal essential medium (EMEM); Dulbecco's modified Eagle's medium (DMEM)). As will be appreciated by those of skill in the art, a basal medium can comprises a variety of components such as one or more amino acids (*e.g.*, non-essential amino acids, essential amino acids), salts (*e.g.*, calcium chloride, potassium chloride, magnesium sulfate, sodium chloride, and monosodium phosphate), sugars (*e.g.*, glucose), and vitamins (*e.g.*, folic acid, nicotinamide, riboflavin, B12), iron and pH indicators (*e.g.*, phenol red). The basal medium can further comprise proteins (*e.g.*, albumin), hormones (*e.g.*, insulin), glycoproteins (*e.g.*, transferrin), minerals (*e.g.*, selenium), serum (*e.g.*, fetal bovine serum), antibiotics, antimycotics and glycosaminoglycans.

[00132] In some embodiments, the basal medium is serum-free medium. In some embodiments, the basal medium is supplemented with one or more of the following: DMEM/F12, Neurobasal, N2 supplement, 10 mL B27 supplement, human LIF, glutamine, nonessential amino acids, β -mercaptoethanol, penicillin-streptomycin, and/or BSA (Sigma). In some embodiments, the supplemented basal medium further comprises fibroblast growth factor 2 (FGF2) and 1%, 0.8%, 0.6%, 0.4%, 0.2%, or 0.1% KSR.

[00133] Some aspects of the disclosure relate to naïve pluripotent vertebrate cells produced by the methods described herein. Some aspects of the disclosure relate to compositions comprising the naïve pluripotent vertebrate cells produced by the methods

described herein. The disclosure provides pluripotent cells, cell lines, and cell clones derived or cultured using the methods and/or compositions described herein. The invention further provides cell cultures, wherein at least some of the cells in the cell culture are derived or cultured using the methods and/or compositions described herein. Some aspects of the invention relate to a naïve pluripotent vertebrate cell line, *e.g.*, a naïve pluripotent human cell line, produced by the methods described herein. In some aspects, a naïve pluripotent vertebrate cell is provided, wherein the cell uses the distal Oct4 enhancer element for OCT4 expression. In some embodiments, the cell primarily uses the endogenous distal OCT4 enhancer element, *e.g.*, the ratio of the cell's use of endogenous distal OCT4 enhancer to the cell's use of endogenous proximal OCT4 enhancer is at least about 1:1 (*e.g.*, about 2:1, about 3:1, about 5:1, or about 10:1). In some aspects, a naïve pluripotent vertebrate cell, *e.g.*, a naïve pluripotent human cell, is provided, wherein the cell has a global gene expression profile which clusters with naïve mouse ESCs as opposed to stem cell lines derived from mouse epiblast (EpiSCs) and/or less naïve human ESCs. In some embodiments, these cells are produced by methods described herein. In some aspects, provided herein are conventional pluripotent vertebrate cells (*e.g.*, conventional pluripotent human cells) with a deletion of the proximal OCT4 enhancer element (or other disabling mutation). In some aspects, provided herein are methods of using the conventional pluripotent vertebrate cells (*e.g.*, conventional pluripotent human cells) with a deletion of the proximal OCT4 enhancer element (or other disabling mutation), examples of such methods including methods of identifying compounds that induce a naïve pluripotent state.

[00134] In some embodiments, at least 80% or at least 90% of the pluripotent stem cells of a colony, cell line, or cell culture express one or more marker(s), *e.g.*, a set of markers, indicative of pluripotency, *e.g.*, a ground state of pluripotency. In some embodiments at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or more of the cells of a colony, cell line, or cell culture express the marker(s).

[00135] Some aspects of the invention provide a kit for culturing vertebrate cells. The kit comprises a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor. In some embodiments, the kit also comprises instructions for culturing vertebrate cells.

[00136] In some embodiments, the kit further comprises mitogen-activated protein kinase kinase (MEK) inhibitor. In some embodiments, the kit further comprises a glycogen

synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor. In some embodiments, the kit further comprises a ROCK inhibitor and/or an Src inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the kit comprises a BRAF inhibitor and a MEK inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, and a ROCK inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the kit does not comprise a GSK inhibitor. In some embodiments, the kit further comprises cell culture medium. The vertebrate cells can be naïve pluripotent cells, human pluripotent cells, or naïve human pluripotent cells. The compositions or contents of the kits can be provided in one or more containers (*e.g.*, compounds that are compatible can be provided together in the same container). The components of the kit may be sterile.

[00137] Some aspects of the invention relate to a kit for preparing a cell culture medium. The kit comprises a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor; and instructions for preparing a cell culture medium. In some embodiments, the kit further comprises mitogen-activated protein kinase kinase (MEK) inhibitor. In some embodiments, the kit further comprises a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor. In some embodiments, the kit further comprises a ROCK inhibitor and/or an Src inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the kit comprises a BRAF inhibitor and a MEK inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, and a ROCK inhibitor. In some embodiments, the kit comprises a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the kit does not comprise a GSK3 inhibitor.

[00138] In some embodiments, the kit further comprises a basal medium. As used herein, a “basal medium” is typically an unsupplemented medium (*e.g.*, Eagle's minimal essential medium (EMEM); Dulbecco's modified Eagle's medium (DMEM)). As will be appreciated by those of skill in the art, a basal medium can comprises a variety of components such as one or more amino acids (*e.g.*, non-essential amino acids, essential amino acids), salts (*e.g.*, calcium chloride, potassium chloride, magnesium sulfate, sodium chloride, and monosodium phosphate), sugars (*e.g.*, glucose), and vitamins (*e.g.*, folic acid, nicotinamide, riboflavin, B12), iron and pH indicators (*e.g.*, phenol red). The basal medium can further comprise proteins (*e.g.*, albumin), hormones (*e.g.*, insulin), glycoproteins (*e.g.*, transferrin), minerals (*e.g.*, selenium), serum (*e.g.*, fetal bovine serum), antibiotics, antimycotics and glycosaminoglycans.

[00139] In some embodiments, the basal medium is serum-free medium. In some embodiments, the basal medium comprises one or more supplements, such as, but not limited to, supplements such as B27 and/or N2. In some embodiments, the basal medium is supplemented with one or more of the following: DMEM/F12, Neurobasal, N2 supplement, 10 mL B27 supplement, human LIF, glutamine, nonessential amino acids, β -mercaptoethanol, penicillin-streptomycin, and/or BSA (Sigma). In some embodiments, the supplemented basal cell culture medium further comprises fibroblast growth factor 2 (FGF2) and 1%, 0.8%, 0.6%, 0.4%, 0.2%, or 0.1% KSR.

[00140] Some aspects of the invention provide a kit for changing the pluripotency state of a vertebrate cell to a more naïve state. The kit comprises a pluripotent vertebrate cell; and cell culture medium comprising a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor. In some embodiments, the cell culture medium further comprises mitogen-activated protein kinase kinase (MEK) inhibitor. In some embodiments, the cell culture medium further comprises a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor. In some embodiments, the cell culture medium further comprises a ROCK inhibitor and/or an Src inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the cell

culture medium comprises a BRAF inhibitor and a MEK inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, and a ROCK inhibitor. In some embodiments, the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor. In some embodiments, the cell culture medium does not comprise a GSK3 inhibitor.

[00141] Gene expression profiling may be used to assess the pluripotency state of a cell or population of cells. Primed or conventional pluripotent cells, such as embryonic stem cells, and multipotent cells (*i.e.*, adult stem cells) exhibit a distinct pattern of global gene expression as compared to more naïve pluripotent cells (*i.e.*, the more immature “ground state” of pluripotency). Thus, one may assess DNA methylation, gene expression, and/or epigenetic state of cellular DNA, and/or developmental potential of the cells, *e.g.*, as described in Wernig *et al.*, Nature, 448:318-24, 2007. Other methods of assessing pluripotency state include epigenetic analysis, *e.g.*, analysis of DNA methylation state (Nazor *et al.* *Cell Stem Cell*. 2012 May 4;10(5):620-34).

[00142] In some embodiments a pluripotent cell described herein is used to prepare a composition for cell therapy to be administered to a vertebrate subject, *e.g.*, a non-human animal, or a human. In some embodiments, a pluripotent cell derived or cultured according to the systems and methods described herein is used to prepare a composition for cell therapy to be administered to a vertebrate subject, *e.g.*, a non-human animal, or a human. In some embodiments, the composition comprises autologous cells. In other embodiments, the composition comprises non-autologous cells. In some embodiments, the cells are genetically matched to an individual.

[00143] The naïve pluripotent vertebrate stem cells may be used to treat a number of life-threatening diseases and disorders. Examples include, but are not limited to, cancers (such as, but not limited to, acute leukemia, chronic leukemia, high-risk solid tumors, Hodgkin & Non-Hodgkin Lymphoma, myelodysplastic syndromes), blood disorders (such as, but not limited to, aplastic anemia, beta thalassemia, Diamond-Blackfan Anemia, Fanconi Anemia, Sickle Cell Disease), immune disorders (such as, but not limited to, chronic granulomatous disease, histiocytic disorders, leukocyte adhesion deficiency, severe combined immunodeficiency diseases, Wiskott-Aldrich Syndrome), and metabolic disorders (such as, but not limited to, Krabbe Disease, Hurler Syndrome, Metachromatic Leukodystrophy, and Sanfilippo Syndrome). The naïve pluripotent vertebrate stem cells produced by the methods described herein are administered to a subject having or suspected of having a disease or disorder that can be treated using stem cell therapy. Several

approaches may be used for the introduction of the naïve pluripotent vertebrate stem cells stem cells into the subject, including but not limited to, catheter-mediated delivery I.V. (*e.g.*, endovascular catheter), direct injection into a target site, intravenous injection, intraperitoneal injection, parenteral injection, subcutaneous injection, intramuscular injection, and/or intracardiac injection.

[00144] The compositions and methods of the disclosure may be applied to derive or culture naïve pluripotent cells from non-human animals including but not limited to, dogs, cats, horses, sheep, goats, cows, and/or rodents (such as rats, rabbits, hamsters, guinea pigs). The disclosure may be applied to derive or culture naïve pluripotent cells from primates, *e.g.*, non-human primates, or humans. In many embodiments, the vertebrate is a mammal. In some embodiments the mammal is a bovine, ovine, caprine, equine, canine, or feline. It is also envisioned that compositions and methods of the invention may be used to derive naïve pluripotent cells, *e.g.*, ES cells or iPS cells from non-mammalian vertebrates, *e.g.*, zebrafish or other non-mammalian organisms of interest such as birds. In some embodiments, if the species is one from which ES or iPS cells have not heretofore been derived, techniques and culture conditions can be adapted from standard techniques used in other species, *e.g.*, related species.

[00145] Systems, compositions, and methods of the invention can be applied in the derivation or culture of naïve pluripotent cells derived from cells obtained from any of a variety of sources. For example, cells obtained from the inner cell mass (ICM) or epiblast can be used to derive naïve ES cells. In some embodiments, the systems, compositions, and methods are applied to derive naïve pluripotent stem cells from blastomeres, *e.g.*, blastomeres isolated from a morula or from a 4-8 cell stage embryo. In some embodiments, the compositions and methods are applied to derive naïve pluripotent stem cells from germ cells. In some embodiments the compositions and methods are used to derive naïve pluripotent cells using parthenogenesis or SCNT. In some embodiments the methods are applied to derive or culture naïve induced pluripotent stem (iPS) cells. Methods for generating iPS cells are well-known in the art (see, for example, WO2013159103, WO 2013177133, and US8748179). iPSCs are typically derived by introducing a specific set of pluripotency-associated genes, or “reprogramming factors”, into a given cell type. The original set of reprogramming factors are the genes Oct4 (Pou5f1), Sox2, cMyc, and Klf4. While this combination is most conventional in producing iPSCs, each of the factors can be functionally replaced by related transcription factors, miRNAs, small molecules, or even non-related genes such as lineage specifiers. In some embodiments, somatic cells used to generate iPS

cells include, but are not limited to, fibroblasts, keratinocytes, immune system cells, and epithelial cells. In some embodiments, iPS cells are generated without genomic modification. In some embodiments, iPS cells are free of exogenously introduced DNA. For example, they may be generated using synthetic modified mRNA, small molecules, or a combination thereof. For example, iPS cells may be generated using the methods described in Mandal, PK & Rossi, DJ, Nature Protocols 8, 568–582 (2013). In some embodiments, iPS cells are generated using episomal expression of one or more of the reprogramming factors. After the iPS cells are generated, the episome(s) may be lost resulting in cells free of exogenously introduced DNA.

[00146] The invention contemplates a variety of uses for the pluripotent cells, cell lines derived, cultured, or generated as described herein. In general, pluripotent cells may be used for any purpose contemplated in the art for use of pluripotent cells, *e.g.*, ES or iPS cells. See, *e.g.*, international PCT applications, no. PCT/US2013/050077 (WO 2014/011881) and PCT/US2001/006912 (WO 2001/066697).

[00147] In some embodiments a pluripotent cell derived or cultured according to the invention is used to produce one or more differentiated cells. Such cells are considered to be an aspect of the disclosure. The cells could be, *e.g.*, multipotent stem cells or fully differentiated cells. The cells may be, *e.g.*, hematopoietic cells (*e.g.*, of the myeloid or erythroid lineage), neural cells (*e.g.*, neural precursors, neurons or glial cells), myoblasts, myocytes, cardiomyocytes, melanoblasts, keratinocytes, chondroblasts, chondrocytes, osteoblasts, osteoclasts, pancreatic beta cells, retinal cells, endothelial cells, *etc.* Protocols known in the art for differentiating cells into cells of a desired type may be used (see, for example, US 20130273651). In some embodiments a pluripotent cell may be differentiated to a cell type of interest *ex vivo*, *e.g.*, before being administered to a subject. For example, a pluripotent cell may be differentiated to produce cells of a cell type that is affected by a disease or that may be useful in treating a disease for which the subject is in need of treatment. In some embodiments cells are used to generate a tissue or organ *in vitro* or to supplement a tissue or organ *in vivo*.

[00148] The disclosure also provides methods of producing non-human vertebrates, *e.g.*, non-human mammals, which can be genetically modified or non-genetically modified, using the pluripotent cells of the disclosure. Such non-human vertebrates are aspects of the disclosure. In some embodiments the non-human vertebrates are mice. In some embodiments, non-human mammals are produced using methods known in the art for producing non-human mammals from ES or iPS cells (see, for example, WO 2010124290).

For example, ES or iPS cells are introduced into a blastocyst of the same species which is transferred to a suitable foster mother (*e.g.*, a pseudopregnant female of the same species) under conditions suitable for production of live offspring. If a diploid blastocyst is used, chimeric offspring may be produced, which are typically derived in part from the ES cell or iPS cell and in part from the blastocyst into which the cell was introduced. Chimeric offspring may be interbred to generate homozygous animals if the chimeric offspring contain ES-derived contribution to the germ line as known in the art. In some embodiments, the mice are produced using methods that do not require production of chimera or chimeric offspring. In some embodiments, pluripotent ES cells are introduced into tetraploid blastocysts of the same vertebrate species under conditions that result in production of an embryo (at least one/one or more embryos) and the resulting embryo(s) transferred into an appropriate foster mother, such as a pseudopregnant female of the same vertebrate species. The resulting female is maintained under conditions that result in development of live offspring, thereby producing a non-human mammal derived from the introduced ES cells. See, *e.g.*, U.S. Pat. No. 6,784,336. In some embodiments, the mouse is produced by a method that involves laser-assisted injection or piezo-injection of ES cells of the invention into four- or eight-cell embryos. In some embodiments the mouse is produced without need to generate a chimera, *e.g.*, using methods described in international PCT application, no. PCT/EP2003/002180 (WO 2003/073843). Another embodiment of the present invention is a method of producing a non-human mammalian strain, such as a mouse strain, *e.g.*, a genetically engineered mouse strain, that is derived from a given (single) iPS or ES cell clone of the present disclosure without outcrossing with a wild type partner. See, *e.g.*, U.S. Pat. No. 6,784,336. In some embodiments the mice are genetically modified, *e.g.*, they are derived from an ES or iPS cell that is genetically modified. The invention contemplates interbreeding non-human vertebrates, *e.g.*, mice, derived from the ES cells or iPS cells with mice of any strain of interest, the resulting strains being considered other aspects of the invention.

[00149] A naïve pluripotent cell can be derived from a cell, *e.g.*, a somatic cell, obtained from an individual of interest. The individual can be, *e.g.*, a human suffering from a disease or condition. In some embodiments the individual is immunocompatible with an individual suffering from a disease or condition. In some embodiments the disease is a neurodegenerative disease, *e.g.*, Parkinson's disease, Alzheimer's disease, or amyotrophic lateral sclerosis. In some embodiments the individual suffers from diabetes. In some embodiments the individual suffers from heart failure or a muscle disorder or an enzyme deficiency, sickle cell anemia, hemophilia, a glycogen storage disorder, or cystic fibrosis. In

some embodiments the disease is a heritable disease. In some embodiments the disease is a monogenic disorder. In some embodiments the disease has an autosomal dominant inheritance pattern. In some embodiments the disease has an autosomal recessive inheritance pattern. In some embodiments the disease is sporadic, *i.e.*, there is no evident pattern of inheritance. In some embodiments the individual has suffered an injury, *e.g.*, traumatic brain injury, spinal cord injury. In some embodiments the individual is in need of cell therapy.

[00150] In some embodiments a naïve pluripotent cell, *e.g.*, a naïve pluripotent human cell, is derived from a cell (*e.g.*, a somatic cell) obtained from an individual who harbors a mutation or genetic variation that is known to cause or suspected of causing a disease (or an immunocompatible donor). The mutation or genetic variation is corrected *ex vivo*. Resulting cells or cells derived therefrom are administered to the subject.

[00151] In some embodiments, a naïve pluripotent cell, *e.g.*, a naïve pluripotent human cell, may be used to generate a model of a disease, *e.g.*, an animal model or a cellular model of a disease, *e.g.*, any of the diseases mentioned herein or other diseases of interest. In some embodiments the naïve pluripotent cell is derived from a cell, *e.g.*, a somatic cell, obtained from an individual who has the disease. In some embodiments the naïve pluripotent cell is genetically engineered to harbor a mutation or genetic variation that is known to cause or suspected of causing the disease. In some embodiments the naïve pluripotent cell may be differentiated to a cell of a cell type that is affected by the disease.

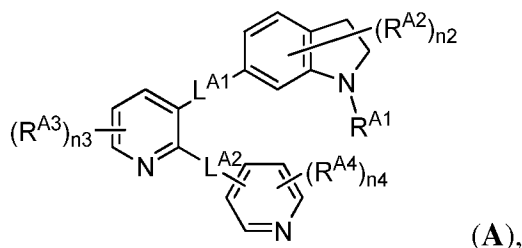
[00152] In some embodiments, a naïve pluripotent cell is not genetically modified. In some embodiments, the naïve pluripotent cell is devoid of DNA or genetic alterations (*e.g.*, insertions, substitutions, deletions) introduced by the hand of man. In some embodiments, a naïve pluripotent cell may be genetically modified after it is derived. Any of a variety of different methods may be employed to genetically modify a naïve pluripotent cell or a cell derived therefrom, *e.g.*, a differentiated cell. Examples of such methods include, but are not limited to, homologous recombination and transfection (see, for example, WO 2013042731, and US 8637311). In some embodiments, genome editing technologies such as, but not limited to zinc fingers, TALENs, CRISPR/Cas systems are used to genetically modify the naïve pluripotent cell.

Compounds

[00153] Exemplary compounds that are useful in a composition, system, kit, or method described herein are provided below.

Compounds of Formula (A)

[00154] In one aspect, the present disclosure provides compounds of Formula (A):



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

L^{A1} is a substituted or unsubstituted, saturated or unsaturated, C_{1-4} aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{A5}-$, $-N=$, or $=N-$, wherein each instance of R^{A5} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

L^{A2} is a substituted or unsubstituted, saturated or unsaturated, C_{1-6} aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{A6}-$, $-N=$, or $=N-$, wherein each instance of R^{A6} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

R^{A1} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{A2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

atom, or two instances of R^a are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

n_2 is 0, 1, 2, 3, 4, 5, 6, or 7;

each instance of R^{A3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

n_3 is 0, 1, 2, or 3;

each instance of R^{A4} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

n_4 is 0, 1, 2, 3, or 4.

[00155] In certain embodiments, L^{A1} is a substituted or unsubstituted, saturated or unsaturated, C_2 aliphatic chain, optionally wherein one chain atom of the aliphatic chain is replaced with $-O-$, $-S-$, $-NR^{A5}-$ (*e.g.*, $-NH-$), $-N=$, or $=N-$. In certain embodiments, L^{A1} is $-C(=O)NR^{A5}-$ (*e.g.*, $-C(=O)NH-$) or $-NR^{A5}C(=O)-$ (*e.g.*, $-NHC(=O)-$). In certain embodiments, L^{A1} is a substituted or unsubstituted, saturated or unsaturated, C_1 , C_3 , or C_4 aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{A5}-$ (*e.g.*, $-NH-$), $-N=$, or $=N-$.

[00156] In certain embodiments, all instances of R^{A5} are the same. In certain embodiments, two instances of R^{A5} are different from each other. In certain embodiments, at least one instance of R^{A5} is hydrogen. In certain embodiments, all instances of R^{A5} are hydrogen. In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{A5} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00157] In certain embodiments, L^{A2} is a substituted or unsubstituted, saturated or unsaturated, C_2 aliphatic chain, optionally wherein one chain atom of the aliphatic chain is replaced with $-O-$, $-S-$, $-NR^{A6}-$ (*e.g.*, $-NH-$), $-N=$, or $=N-$. In certain embodiments, L^{A2} is $-CH_2NR^{A6}-$ (*e.g.*, $-CH_2NH-$) or $-NR^{A6}CH_2-$ (*e.g.*, $-NHCH_2-$). In certain embodiments, L^{A2} is a substituted or unsubstituted, saturated or unsaturated, C_1 , C_3 , or C_4 aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{A6}-$ (*e.g.*, $-NH-$), $-N=$, or $=N-$.

[00158] In certain embodiments, all instances of R^{A6} are the same. In certain embodiments, two instances of R^{A6} are different from each other. In certain embodiments, at least one instance of R^{A6} is hydrogen. In certain embodiments, all instances of R^{A6} are hydrogen. In certain embodiments, at least one instance of R^{A6} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{A6} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00159] In certain embodiments, R^{A1} is hydrogen. In certain embodiments, R^{A1} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{A1} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00160] In certain embodiments, two instances of R^{A2} are the same. In certain embodiments, two instances of R^{A2} are different from each other. In certain embodiments, at least one instance of R^{A2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{A2} is $-CH_3$. In certain embodiments, at least one instance of R^{A2} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or

three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{A2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A2} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{A2} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{A2} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{A2} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{A2} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{A2} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{A2} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{A2} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00161] Each of Formulae (A) to (L) may independently include one or more substituents R^a . In certain embodiments, all instances of R^a are the same. In certain embodiments, two instances of R^a are different from each other. In certain embodiments, at least one instance of R^a is H. In certain embodiments, at least one instance of R^a is substituted or unsubstituted acyl (*e.g.*, acetyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^a is $-CH_3$. In certain embodiments, at least one instance of R^a is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted,

monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^a is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^a is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts) when attached to a nitrogen atom. In certain embodiments, R^a is an oxygen protecting group (*e.g.*, silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl) when attached to an oxygen atom. In certain embodiments, R^a is a sulfur protecting group (*e.g.*, acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heterocyclic ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heteroaryl ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00162] In certain embodiments, n_2 is 0. In certain embodiments, n_2 is 1. In certain embodiments, n_2 is 2. In certain embodiments, n_2 is 3. In certain embodiments, n_2 is 4. In certain embodiments, n_2 is 5. In certain embodiments, n_2 is 6. In certain embodiments, n_2 is 7.

[00163] In certain embodiments, all instances of R^{A3} are the same. In certain embodiments, two instances of R^{A3} are different from each other. In certain embodiments, at least one instance of R^{A3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{A3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{A3} is $-CH_3$. In certain embodiments, at least one instance of R^{A3} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain

embodiments, at least one instance of R^{A3} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{A3} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{A3} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{A3} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A3} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{A3} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{A3} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A3} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{A3} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{A3} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{A3} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{A3} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{A3} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{A3} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{A3} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

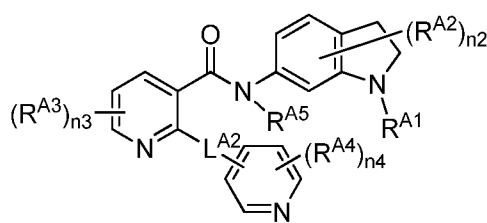
[00164] In certain embodiments, n_3 is 0. In certain embodiments, n_3 is 1. In certain embodiments, n_3 is 2. In certain embodiments, n_3 is 3.

[00165] In certain embodiments, all instances of R^{A4} are the same. In certain embodiments, two instances of R^{A4} are different from each other. In certain embodiments, at least one instance of R^{A4} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6}

alkyl). In certain embodiments, at least one instance of R^{A4} is $-CH_3$. In certain embodiments, at least one instance of R^{A4} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{A4} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A4} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{A4} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{A4} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{A4} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{A4} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{A4} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{A4} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{A4} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

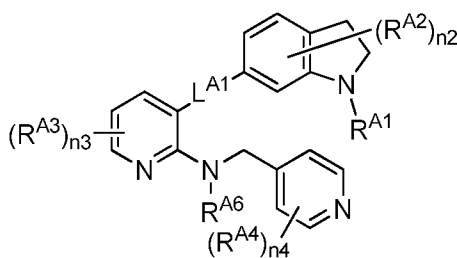
[00166] In certain embodiments, n_4 is 0. In certain embodiments, n_4 is 1. In certain embodiments, n_4 is 2. In certain embodiments, n_4 is 3. In certain embodiments, n_4 is 4.

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



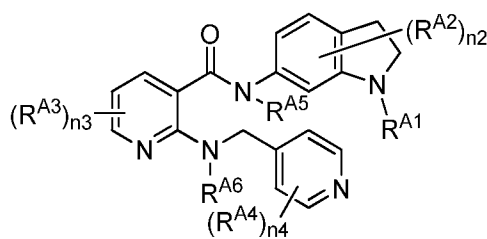
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



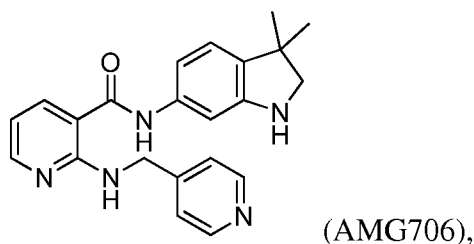
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



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

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



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

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

each instance of R^{B1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

o1 is 0, 1, 2, 3, 4, or 5;

each instance of R^{B2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

o2 is 0, 1, 2, 3, or 4;

each instance of R^{B3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$, or an instance of R^{B3} and an instance of R^{B7} are joined to form a substituted or unsubstituted heterocyclic ring; and

o3 is 0, 1, or 2.

[00174] In certain embodiments, L^{B1} is $-N(R^{B4})C(=O)-$ (*e.g.*, $-NHC(=O)-$) or $-C(=O)N(R^{B4})-$ (*e.g.*, $-C(=O)NH-$). In certain embodiments, L^{B1} is $-N(R^{B4})C(=O)N(R^{B4})-$ (*e.g.*, $-NHC(=O)NH-$).

[00175] In certain embodiments, all instances of R^{B4} are the same. In certain embodiments, two instances of R^{B4} are different from each other. In certain embodiments, at least one instance of R^{B4} is hydrogen. In certain embodiments, at least one instance of R^{B4} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{B4} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00176] In certain embodiments, L^{B2} is $-O-$ or $-S-$. In certain embodiments, L^{B2} is $-NR^{B5}-$ (*e.g.*, $-NH-$). In certain embodiments, L^{B2} is $-C(R^{B6})_2-$ (*e.g.*, $-CH_2-$).

[00177] In certain embodiments, R^{B5} is hydrogen. In certain embodiments, R^{B5} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{B5} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00178] In certain embodiments, all instances of R^{B6} are the same. In certain embodiments, two instances of R^{B6} are different from each other. In certain embodiments, at least one instance of R^{B6} is hydrogen. In certain embodiments, at least one instance of R^{B6} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B6} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl).

[00179] In certain embodiments, X^{B1} , X^{B2} , and X^{B3} are CR^{B7} (*e.g.*, CH), N, and N, respectively. In certain embodiments, each of X^{B1} , X^{B2} , and X^{B3} is CR^{B7} (*e.g.*, CH). In certain embodiments, X^{B1} , X^{B2} , and X^{B3} are N, CR^{B7} (*e.g.*, CH), and CR^{B7} (*e.g.*, CH), respectively.

[00180] In certain embodiments, all instances of R^{B7} are the same. In certain embodiments, two instances of R^{B7} are different from each other. In certain embodiments, at least one instance of R^{B7} is hydrogen. In certain embodiments, at least one instance of R^{B7} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{B7} is $-CH_3$. In certain embodiments, at least one instance of R^{B7} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl,

perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B7} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{B7} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{B7} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{B7} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{B7} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{B7} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{B7} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{B7} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00181] In certain embodiments, all instances of R^{B1} are the same. In certain embodiments, two instances of R^{B1} are different from each other. In certain embodiments, at least one instance of R^{B1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{B1} is $-CF_3$ or $-C(Me)_2CN$. In

certain embodiments, at least one instance of R^{B1} is $-CH_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted imidazolyl (*e.g.*, substituted or unsubstituted 1-imidazolyl). In certain embodiments, at least one instance of R^{B1} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{B1} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{B1} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{B1} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{B1} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{B1} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{B1} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{B1} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00182] In certain embodiments, at least one instance of R^{B1} is halogen, substituted or unsubstituted alkyl, or substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl,

wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

[00183] In certain embodiments, o1 is 0. In certain embodiments, o1 is 1. In certain embodiments, o1 is 2. In certain embodiments, o1 is 3. In certain embodiments, o1 is 4. In certain embodiments, o1 is 5.

[00184] In certain embodiments, all instances of R^{B2} are the same. In certain embodiments, two instances of R^{B2} are different from each other. In certain embodiments, at least one instance of R^{B2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{B2} is $-CH_3$. In certain embodiments, at least one instance of R^{B2} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{B2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B2} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{B2} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{B2} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{B2} is $-CN$, $-SCN$, or

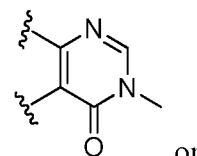
$-\text{NO}_2$. In certain embodiments, at least one instance of $\text{R}^{\text{B}2}$ is $-\text{C}(=\text{NR}^{\text{a}})\text{R}^{\text{a}}$, $-\text{C}(=\text{NR}^{\text{a}})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{NR}^{\text{a}})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{B}2}$ is $-\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHMe}$, or $-\text{C}(=\text{O})\text{NMe}_2$). In certain embodiments, at least one instance of $\text{R}^{\text{B}2}$ is $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{B}2}$ is $-\text{OC}(=\text{O})\text{R}^{\text{a}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$.

[00185] In certain embodiments, o2 is 0. In certain embodiments, o2 is 1. In certain embodiments, o2 is 2. In certain embodiments, o2 is 3. In certain embodiments, o2 is 4.

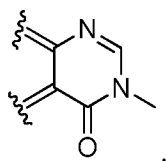
[00186] In certain embodiments, all instances of $\text{R}^{\text{B}3}$ are the same. In certain embodiments, two instances of $\text{R}^{\text{B}3}$ are different from each other. In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{CH}_3$. In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{CF}_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted pyridyl (*e.g.*, 3-pyridyl). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{OR}^{\text{a}}$ (*e.g.*, $-\text{OH}$, $-\text{O}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{OMe}$, $-\text{OEt}$, $-\text{OPr}$, $-\text{OBu}$, or $-\text{OBn}$), or $-\text{O}(\text{substituted or unsubstituted phenyl})$ (*e.g.*, $-\text{OPh}$)). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{SR}^{\text{a}}$ (*e.g.*, $-\text{SH}$, $-\text{S}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{SMe}$, $-\text{SEt}$, or $-\text{SPh}$)).

SEt, $-\text{SPr}$, $-\text{SBu}$, or $-\text{SBn}$), or $-\text{S}(\text{substituted or unsubstituted phenyl})$ (*e.g.*, $-\text{SPh}$)). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{NH}_2$, $-\text{NH}(\text{substituted or unsubstituted C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{NHMe}$), or $-\text{N}(\text{substituted or unsubstituted C}_{1-6} \text{ alkyl})-(\text{substituted or unsubstituted C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{NMe}_2$)). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{CN}$, $-\text{SCN}$, or $-\text{NO}_2$. In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHMe}$, or $-\text{C}(=\text{O})\text{NMe}_2$). In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is $-\text{OC}(=\text{O})\text{R}^{\text{a}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, an instance of $\text{R}^{\text{B}3}$ and an instance of $\text{R}^{\text{B}7}$ are joined to form a substituted or unsubstituted heterocyclic ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain

embodiments, an instance of $\text{R}^{\text{B}3}$ and an instance of $\text{R}^{\text{B}7}$ are joined to form



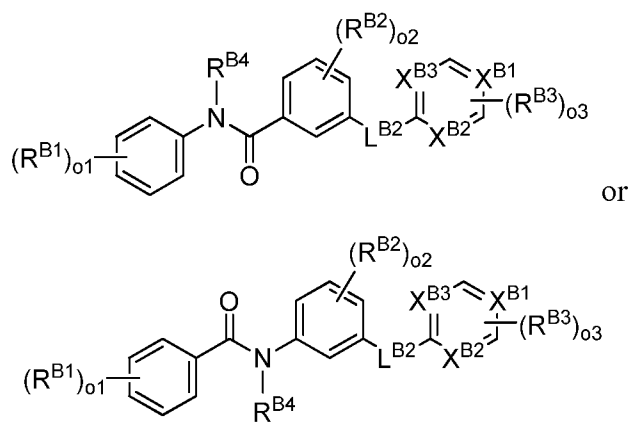
or



[00187] In certain embodiments, at least one instance of $\text{R}^{\text{B}3}$ is substituted or unsubstituted heteroaryl or $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$, or an instance of $\text{R}^{\text{B}3}$ and an instance of $\text{R}^{\text{B}7}$ are joined to form a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

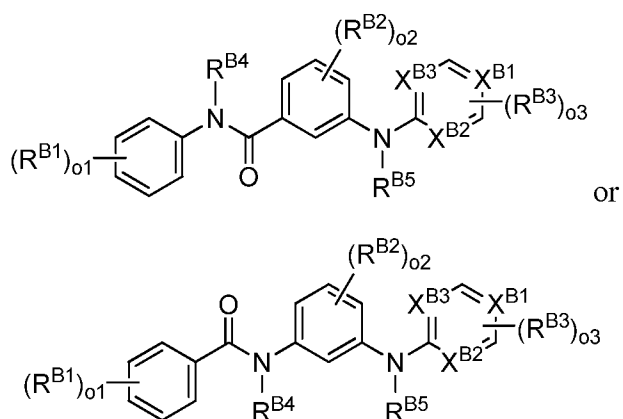
[00188] In certain embodiments, o3 is 0. In certain embodiments, o3 is 1. In certain embodiments, o3 is 2.

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



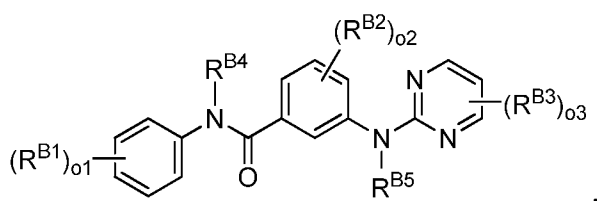
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



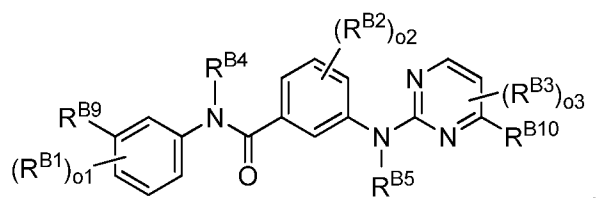
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



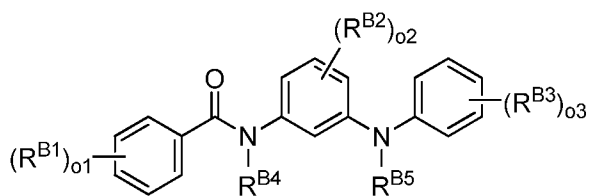
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



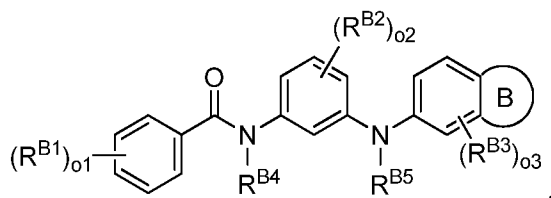
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein each of R^{B9} and R^{B10} is independently substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, R^{B9} is substituted or unsubstituted imidazolyl (*e.g.*, substituted or unsubstituted 1-imidazolyl). In certain embodiments, R^{B10} is substituted or unsubstituted pyridyl (*e.g.*, substituted or unsubstituted 3-pyridyl).

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



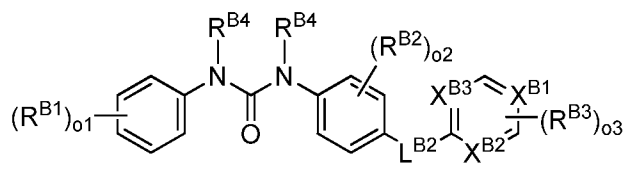
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



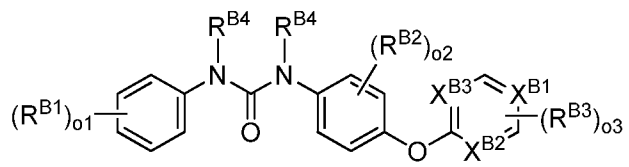
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Ring B is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

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



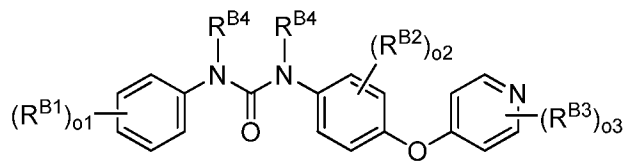
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



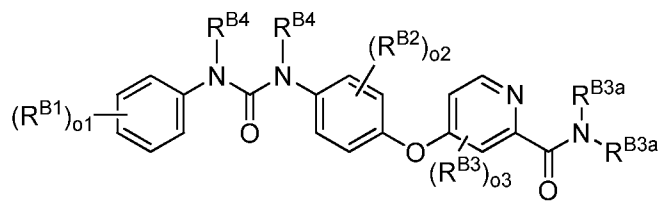
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



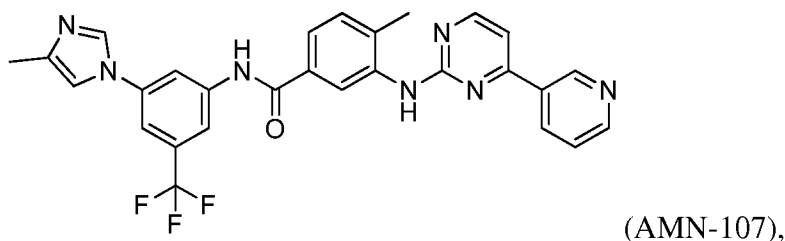
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

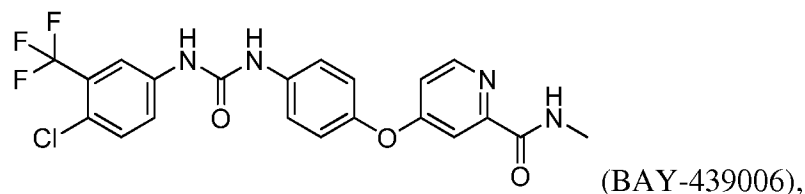
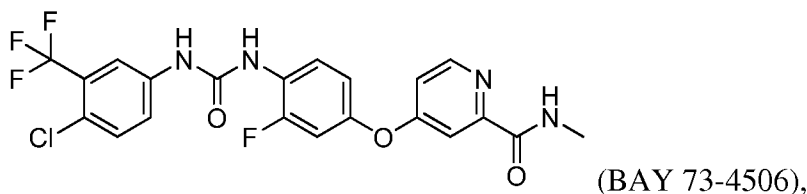
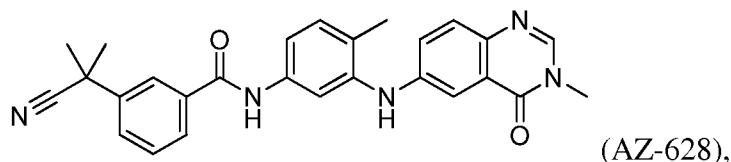
[00198] In certain embodiments, the compound of Formula (B) is of the formula:



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

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





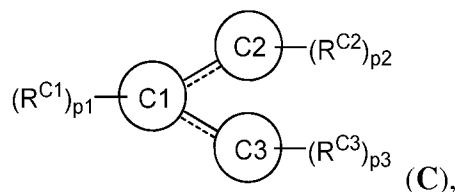
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00200] In certain embodiments, a compound of Formula (B) is not AMN-107, AZ-628, BAY 73-4506, BAY-439006, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00201] It is believed that compounds of Formula (B), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are ANL inhibitors (*e.g.*, AMN-107), BRAF inhibitors (*e.g.*, AZ-628 and BAY-439006), VEGFR inhibitors (*e.g.*, VEGFR2 inhibitors, such as BAY 73-4506), and/or TIE2 inhibitors (*e.g.*, BAY 73-4506).

Compounds of Formula (C)

[00202] In another aspect, the present disclosure provides compounds of Formula (C):



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

Ring C1 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heterocyclic or heteroaryl ring system are nitrogen;

Ring C2 is a substituted or unsubstituted, monocyclic, 6-membered carbocyclic ring or a substituted or unsubstituted phenyl ring;

Ring C3 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heterocyclic or heteroaryl ring system are nitrogen;

each instance of R^{C1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

p1 is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

each instance of R^{C2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$, or two instances of R^{C2} are joined to form a substituted or unsubstituted carbocyclic ring;

p2 is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

each instance of R^{C3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$,

$-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$; and

p_3 is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

[00203] In certain embodiments, Ring C1 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two atoms in the heterocyclic ring system are nitrogen. In certain embodiments, Ring C1 is a substituted or unsubstituted 1,2-dihydropyridinyl ring. In certain embodiments, Ring C1 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heteroaryl ring system are nitrogen. In certain embodiments, Ring C1 is a substituted or unsubstituted pyrazolyl ring, substituted or unsubstituted imidazolyl ring, substituted or unsubstituted pyridyl ring, or substituted or unsubstituted pyrimidinyl ring.

[00204] In certain embodiments, Ring C2 is a substituted or unsubstituted, monocyclic, 6-membered carbocyclic ring. In certain embodiments, Ring C2 is a cyclohexa-2,4-dienone ring or cyclohexa-1,4-diene ring. In certain embodiments, Ring C2 is a substituted or unsubstituted phenyl ring.

[00205] In certain embodiments, Ring C3 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one or two atoms in the heterocyclic ring system are nitrogen. In certain embodiments, Ring C3 is a substituted or unsubstituted piperidinyl ring (*e.g.*, substituted or unsubstituted 4-piperidinyl ring) or substituted or unsubstituted 1,4-dihydropyridinyl ring (*e.g.*, substituted or unsubstituted 1,4-dihydropyridin-4-yl ring). In certain embodiments, Ring C3 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heteroaryl ring system are nitrogen. In certain embodiments, Ring C3 is a substituted or unsubstituted pyridinyl ring (*e.g.*, substituted or unsubstituted 4-pyridinyl ring) or substituted or unsubstituted imidazolyl ring (*e.g.*, substituted or unsubstituted 2-imidazolyl ring).

[00206] In certain embodiments, all instances of $\text{R}^{\text{C}1}$ are the same. In certain embodiments, two instances of $\text{R}^{\text{C}1}$ are different from each other. In certain embodiments, at least one instance of $\text{R}^{\text{C}1}$ is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of $\text{R}^{\text{C}1}$ is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of $\text{R}^{\text{C}1}$ is $-\text{CH}_2\text{CH}_2\text{OH}$. In certain embodiments, at least one instance of $\text{R}^{\text{C}1}$ is $-\text{CH}_3$, $-\text{CF}_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of $\text{R}^{\text{C}1}$ is substituted or unsubstituted alkenyl (*e.g.*,

substituted or unsubstituted C₁₋₆ alkenyl). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkynyl). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C1} is -OR^a (*e.g.*, -OH, -O(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, -OMe, -OEt, -OPr, -OBu, or -OBn), or -O(substituted or unsubstituted phenyl) (*e.g.*, -OPh)). In certain embodiments, at least one instance of R^{C1} is -OCH₂CH₂N(Me)₂. In certain embodiments, at least one instance of R^{C1} is -SR^a (*e.g.*, -SH, -S(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, -SMe, -SEt, -SPr, -SBu, or -SBn), or -S(substituted or unsubstituted phenyl) (*e.g.*, -SPh)). In certain embodiments, at least one instance of R^{C1} is -N(R^a)₂ (*e.g.*, -NH(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, -NHMe) or -N(substituted or unsubstituted C₁₋₆ alkyl)-(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, -NMe₂)). In certain embodiments, at least one instance of R^{C1} is -NH₂. In certain embodiments, at least one instance of R^{C1} is -CN, -SCN, or -NO₂. In certain embodiments, at least one instance of R^{C1} is -C(=NR^a)R^a, -C(=NR^a)OR^a, or -C(=NR^a)N(R^a)₂. In certain embodiments, at least one instance of R^{C1} is -C(=O)R^a, -C(=O)OR^a, or -C(=O)N(R^a)₂ (*e.g.*, -C(=O)NH₂, -C(=O)NHMe, or -C(=O)NMe₂). In certain embodiments, at least one instance of R^{C1} is -NR^aC(=O)R^a, -NR^aC(=O)OR^a, or -NR^aC(=O)N(R^a)₂. In certain embodiments, at least one instance of R^{C1} is -OC(=O)R^a, -OC(=O)OR^a, or -OC(=O)N(R^a)₂.

[00207] In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkyl, -OR^a, -N(R^a)₂, or -CN.

[00208] In certain embodiments, p1 is 0. In certain embodiments, p1 is 1. In certain embodiments, p1 is 2. In certain embodiments, p1 is 3. In certain embodiments, p1 is 4. In certain embodiments, p1 is 5. In certain embodiments, p1 is 6. In certain embodiments, p1 is 7. In certain embodiments, p1 is 8. In certain embodiments, p1 is 9.

[00209] In certain embodiments, all instances of R^{C2} are the same. In certain embodiments, two instances of R^{C2} are different from each other. In certain embodiments, at least one instance of R^{C2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{C2} is $-CH_3$. In certain embodiments, at least one instance of R^{C2} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C2} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{C2} is $-OCH_2$ (unsubstituted cyclopropyl). In certain embodiments, at least one instance of R^{C2} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{C2} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{C2} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{C2} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{C2} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{C2} is $-NR^aC(=O)R^a$, $-$

$\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{C}2}$ is $-\text{OC}(=\text{O})\text{R}^{\text{a}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, two instances of $\text{R}^{\text{C}2}$ are joined to form a substituted or unsubstituted carbocyclic ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered carbocyclic ring). In certain embodiments, two instances of $\text{R}^{\text{C}2}$ are joined to form a substituted or unsubstituted cyclopentyl ring or substituted or unsubstituted cyclopentenyl ring.

[00210] In certain embodiments, at least one instance of $\text{R}^{\text{C}2}$ is halogen or $-\text{OR}^{\text{a}}$.

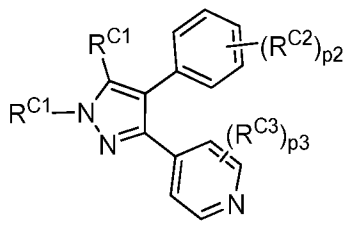
[00211] In certain embodiments, p2 is 0. In certain embodiments, p2 is 1. In certain embodiments, p2 is 2. In certain embodiments, p2 is 3. In certain embodiments, p2 is 4. In certain embodiments, p2 is 5. In certain embodiments, p2 is 6. In certain embodiments, p2 is 7. In certain embodiments, p2 is 8. In certain embodiments, p2 is 9. In certain embodiments, p2 is 10. In certain embodiments, p2 is 11.

[00212] In certain embodiments, all instances of $\text{R}^{\text{C}3}$ are the same. In certain embodiments, two instances of $\text{R}^{\text{C}3}$ are different from each other. In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is $-\text{CH}_3$. In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is $-\text{CF}_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of $\text{R}^{\text{C}3}$ is $-\text{OR}^{\text{a}}$ (*e.g.*, $-\text{OH}$, $-\text{O}(\text{substituted or unsubstituted})$).

C₁₋₆ alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{C3} is –SR^a (*e.g.*, –SH, –S(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{C3} is –N(R^a)₂ (*e.g.*, –NH₂, –NH(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C₁₋₆ alkyl)–(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, –NMe₂)). In certain embodiments, at least one instance of R^{C3} is –CN, –SCN, or –NO₂. In certain embodiments, at least one instance of R^{C3} is –C(=NR^a)R^a, –C(=NR^a)OR^a, or –C(=NR^a)N(R^a)₂. In certain embodiments, at least one instance of R^{C3} is –C(=O)R^a, –C(=O)OR^a, or –C(=O)N(R^a)₂ (*e.g.*, –C(=O)NH₂, –C(=O)NHMe, or –C(=O)NMe₂). In certain embodiments, at least one instance of R^{C3} is –NR^aC(=O)R^a, –NR^aC(=O)OR^a, or –NR^aC(=O)N(R^a)₂. In certain embodiments, at least one instance of R^{C3} is –OC(=O)R^a, –OC(=O)OR^a, or –OC(=O)N(R^a)₂.

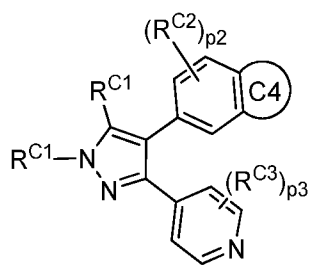
[00213] In certain embodiments, p3 is 0. In certain embodiments, p3 is 1. In certain embodiments, p3 is 2. In certain embodiments, p3 is 3. In certain embodiments, p3 is 4. In certain embodiments, p3 is 5. In certain embodiments, p3 is 6. In certain embodiments, p3 is 7. In certain embodiments, p3 is 8. In certain embodiments, p3 is 9. In certain embodiments, p3 is 10.

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



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

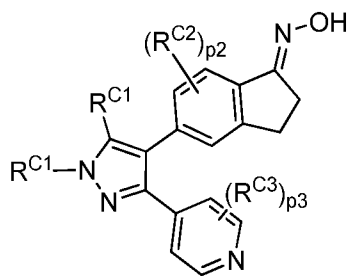
[00215] In certain embodiments, the compound of Formula (C) is of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Ring C4 is a

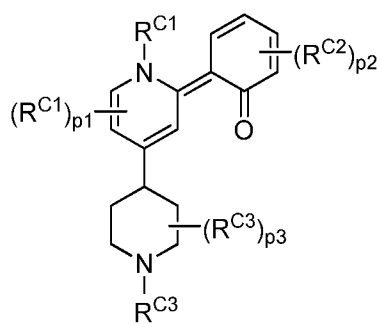
substituted or unsubstituted, monocyclic, 5- to 6-membered carbocyclic ring (*e.g.*, substituted or unsubstituted cyclopentyl ring or substituted or unsubstituted cyclopentenyl ring).

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



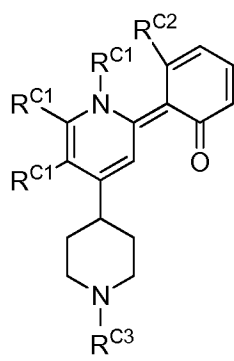
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



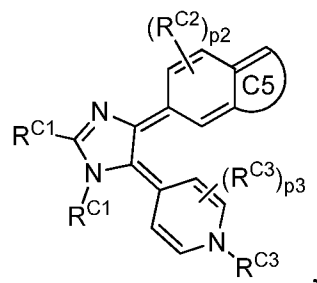
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



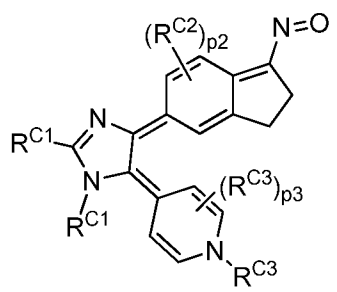
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



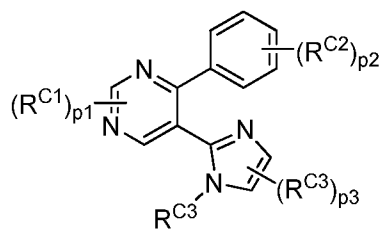
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Ring C5 is a substituted or unsubstituted, monocyclic, 5- to 6-membered carbocyclic ring (*e.g.*, substituted or unsubstituted cyclopentenyl ring).

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



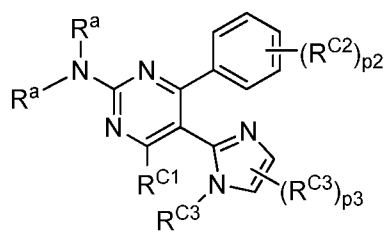
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



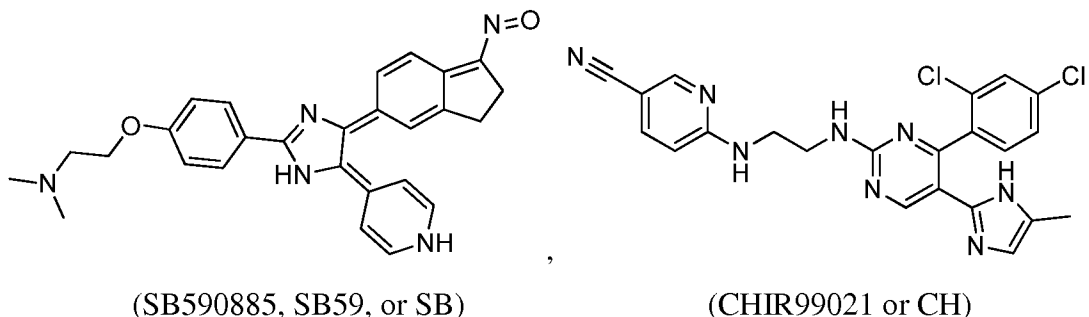
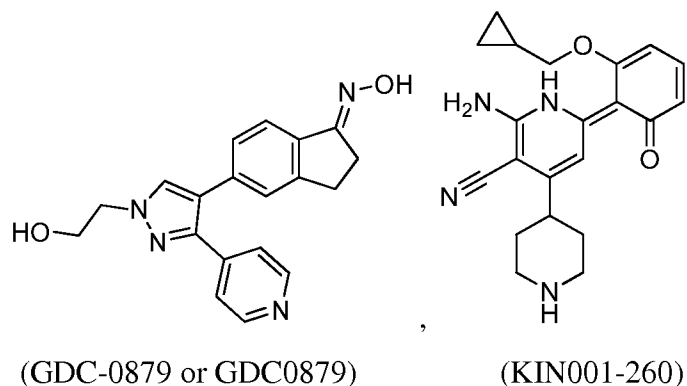
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

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



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

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



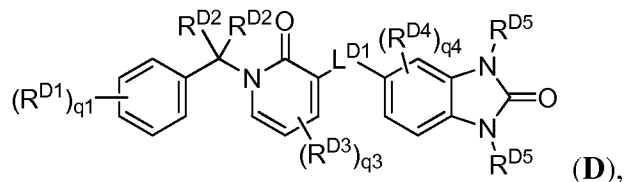
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00224] In certain embodiments, a compound of Formula (C) is not GDC-0879, KIN001-260, SB590885, CHIR99021, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00225] It is believed that compounds of Formula (C), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are BRAF inhibitors (*e.g.*, GDC-0879 and SB590885), IKK inhibitors (*e.g.*, IKK β inhibitors, such as KIN001-260), and/or GSK3 inhibitors (*e.g.*, GSK3B inhibitors, such as CHIR99021).

Compounds of Formula (D)

[00226] In another aspect, the present disclosure provides compounds of Formula (D):



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

L^{D1} is a substituted or unsubstituted, saturated or unsaturated, C_{3-7} aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{D6}-$, $-N=$, or $=N-$, wherein each instance of R^{D6} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{D1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

$q1$ is 0, 1, 2, 3, 4, or 5;

each instance of R^{D2} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

each instance of R^{D3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or

unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

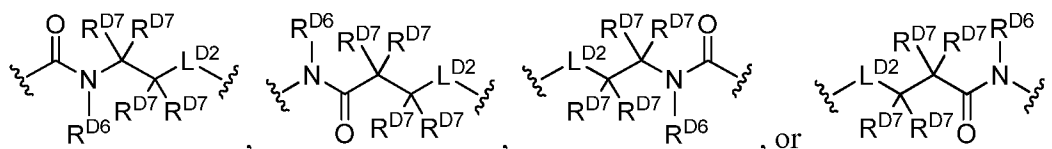
q3 is 0, 1, 2, or 3;

each instance of R^{D4} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

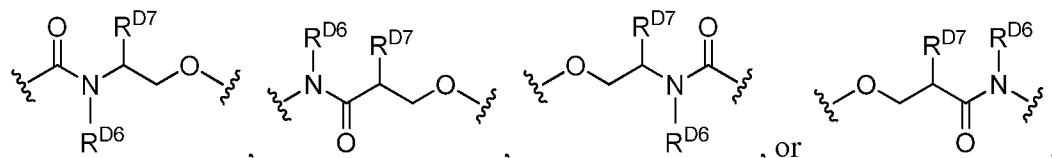
q4 is 0, 1, 2, or 3; and

each instance of R^{D5} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group.

[00227] In certain embodiments, L^{D1} is a substituted or unsubstituted, saturated or unsaturated, C_5 aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-\text{O}-$, $-\text{S}-$, $-\text{NR}^{\text{D6}}-$ (e.g., $-\text{NH}-$), $-\text{N}=\text{}$, or $=\text{N}-$. In certain embodiments, L^{D1} is of the formula:



wherein each instance of R^{D7} is independently hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted phenyl; and L^{D2} is $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{\text{D8}})-$, or $-\text{C}(\text{R}^{\text{D9}})_2-$, wherein R^{D8} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group, and each instance of R^{D9} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, L^{D1} is of the formula:



wherein R^{D7} is substituted or unsubstituted phenyl. In certain embodiments, L^{D1} is a substituted or unsubstituted, saturated or unsaturated, C_3 , C_4 , C_6 , or C_7 aliphatic chain,

optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{D6}-$ (*e.g.*, $-NH-$), $-N=$, or $=N-$.

[00228] In certain embodiments, all instances of R^{D6} are the same. In certain embodiments, two instances of R^{D6} are different from each other. In certain embodiments, at least one instance of R^{D6} is hydrogen. In certain embodiments, at least one instance of R^{D6} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{D6} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00229] In certain embodiments, all instances of R^{D1} are the same. In certain embodiments, two instances of R^{D1} are different from each other. In certain embodiments, at least one instance of R^{D1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{D1} is $-CH_3$. In certain embodiments, at least one instance of R^{D1} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{D1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{D1} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{D1} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-$

S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{D1} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{D1} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{D1} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{D1} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{D1} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{D1} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00230] In certain embodiments, $q1$ is 0. In certain embodiments, $q1$ is 1. In certain embodiments, $q1$ is 2. In certain embodiments, $q1$ is 3. In certain embodiments, $q1$ is 4. In certain embodiments, $q1$ is 5.

[00231] In certain embodiments, both instances of R^{D2} are the same. In certain embodiments, two instances of R^{D2} are different from each other. In certain embodiments, at least one instance of R^{D2} is hydrogen. In certain embodiments, each instance of R^{D2} is hydrogen. In certain embodiments, at least one instance of R^{D2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{D2} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl).

[00232] In certain embodiments, all instances of R^{D3} are the same. In certain embodiments, two instances of R^{D3} are different from each other. In certain embodiments, at least one instance of R^{D3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{D3} is $-CH_3$. In certain embodiments, at least one instance of R^{D3} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or

three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{D3} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{D3} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{D3} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{D3} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-Nme_2$)). In certain embodiments, at least one instance of R^{D3} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{D3} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{D3} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)Nme_2$). In certain embodiments, at least one instance of R^{D3} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{D3} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00233] In certain embodiments, $q3$ is 0. In certain embodiments, $q3$ is 1. In certain embodiments, $q3$ is 2. In certain embodiments, $q3$ is 3.

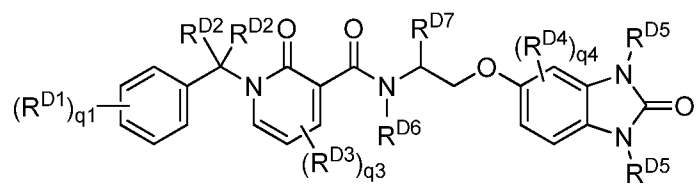
[00234] In certain embodiments, all instances of R^{D4} are the same. In certain embodiments, two instances of R^{D4} are different from each other. In certain embodiments, at least one instance of R^{D4} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{D4} is $-CH_3$. In certain embodiments, at least one instance of R^{D4} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted carbocycl

(*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{D4} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{D4} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{D4} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{D4} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-Nme_2$)). In certain embodiments, at least one instance of R^{D4} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{D4} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{D4} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)Nme_2$). In certain embodiments, at least one instance of R^{D4} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{D4} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00235] In certain embodiments, $q4$ is 0. In certain embodiments, $q4$ is 1. In certain embodiments, $q4$ is 2. In certain embodiments, $q4$ is 3.

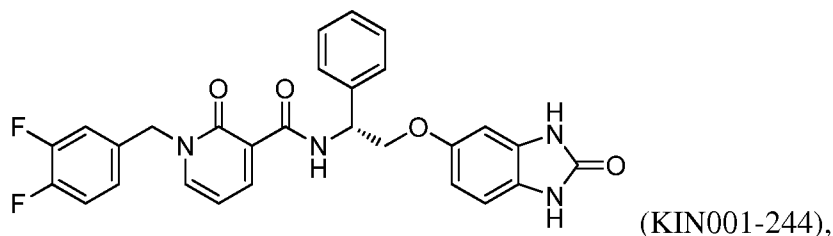
[00236] In certain embodiments, both instances of R^{D5} are the same. In certain embodiments, two instances of R^{D5} are different from each other. In certain embodiments, at least one instance of R^{D5} is hydrogen. In certain embodiments, each instance of R^{D5} is hydrogen. In certain embodiments, at least one instance of R^{D5} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{D5} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00237] In certain embodiments, the compound of Formula (D) is of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^{D7} is substituted or unsubstituted phenyl.

[00238] In certain embodiments, the compound of Formula (D) is of the formula:



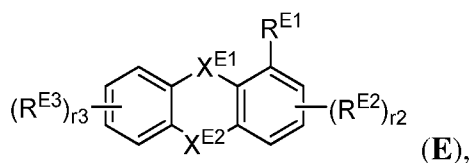
or a solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00239] In certain embodiments, a compound of Formula (D) is not KIN001-244, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00240] It is believed that compounds of Formula (D), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are PDK inhibitors.

Compounds of Formula (E)

[00241] In another aspect, the present disclosure provides compounds of Formula (E):



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

X^{E1} is $-O-$, $-S-$, $-C(=O)-$, $-C(=S)-$, or $-C(=NR^{E4})-$, wherein R^{E4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

X^{E2} is $-O-$, $-S-$, $-C(=O)-$, or $-C(=S)-$;

R^{E1} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$, or R^{E1} and R^{E4} are joined to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

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

each instance of R^{E2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

r_2 is 0, 1, 2, or 3;

each instance of R^{E3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

r_3 is 0, 1, 2, 3, or 4.

[00242] In certain embodiments, X^{E1} is $-S-$. In certain embodiments, X^{E1} is $-C(=NR^{E4})-$. In certain embodiments, X^{E1} is $-O-$, $-C(=O)-$, or $-C(=S)-$.

[00243] In certain embodiments, R^{E4} is hydrogen. In certain embodiments, R^{E4} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{E4} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00244] In certain embodiments, X^{E2} is $-S-$. In certain embodiments, X^{E2} is $-C(=O)-$. In certain embodiments, X^{E2} is $-O-$ or $-C(=S)-$.

[00245] In certain embodiments, R^{E1} is hydrogen. In certain embodiments, R^{E1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{E1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{E1} is $-CH_3$. In certain embodiments, R^{E1} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{E1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{E1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{E1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{E1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{E1} is a substituted or unsubstituted 4H-pyran-4-one moiety. In certain embodiments, R^{E1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{E1} is substituted or unsubstituted phenyl. In certain embodiments, R^{E1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{E1} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, R^{E1} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, R^{E1} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, R^{E1} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, R^{E1} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, R^{E1} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$.

(*e.g.*, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHMe}$, or $-\text{C}(=\text{O})\text{NMe}_2$). In certain embodiments, R^{E1} is $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, R^{E1} is $-\text{OC}(=\text{O})\text{R}^{\text{a}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, R^{E1} and R^{E4} are joined to form a substituted or unsubstituted heterocyclic ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur) or a substituted or unsubstituted heteroaryl ring (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00246] In certain embodiments, all instances of R^{E2} are the same. In certain embodiments, two instances of R^{E2} are different from each other. In certain embodiments, at least one instance of R^{E2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{E2} is $-\text{CH}_3$. In certain embodiments, at least one instance of R^{E2} is $-\text{CF}_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{E2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{E2} is $-\text{OR}^{\text{a}}$ (*e.g.*, $-\text{OH}$, $-\text{O}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{OMe}$, $-\text{OEt}$, $-\text{OPr}$, $-\text{OBu}$, or $-\text{OBn}$), or $-\text{O}(\text{substituted or unsubstituted phenyl})$ (*e.g.*, $-\text{OPh}$)). In certain embodiments, at least one instance of R^{E2} is $-\text{SR}^{\text{a}}$ (*e.g.*, $-\text{SH}$, $-\text{S}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{SMe}$, $-\text{SEt}$, $-\text{SPr}$, $-\text{SBu}$, or $-\text{SBn}$), or $-\text{S}(\text{substituted or$

unsubstituted phenyl) (*e.g.*, $-\text{SPh}$). In certain embodiments, at least one instance of $\text{R}^{\text{E}2}$ is $-\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{NH}_2$, $-\text{NH}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{NHMe}$), or $-\text{N}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})-(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{NMe}_2$). In certain embodiments, at least one instance of $\text{R}^{\text{E}2}$ is $-\text{CN}$, $-\text{SCN}$, or $-\text{NO}_2$. In certain embodiments, at least one instance of $\text{R}^{\text{E}2}$ is $-\text{C}(=\text{NR}^{\text{a}})\text{R}^{\text{a}}$, $-\text{C}(=\text{NR}^{\text{a}})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{NR}^{\text{a}})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{E}2}$ is $-\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHMe}$, or $-\text{C}(=\text{O})\text{NMe}_2$). In certain embodiments, at least one instance of $\text{R}^{\text{E}2}$ is $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{E}2}$ is $-\text{OC}(=\text{O})\text{R}^{\text{a}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$.

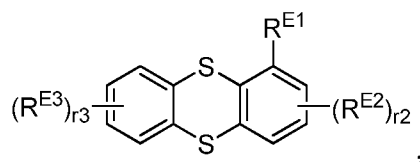
[00247] In certain embodiments, r_2 is 0. In certain embodiments, r_2 is 1. In certain embodiments, r_2 is 2. In certain embodiments, r_2 is 3.

[00248] In certain embodiments, all instances of $\text{R}^{\text{E}3}$ are the same. In certain embodiments, two instances of $\text{R}^{\text{E}3}$ are different from each other. In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is $-\text{CH}_3$. In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is $-\text{CF}_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of $\text{R}^{\text{E}3}$ is $-\text{OR}^{\text{a}}$ (*e.g.*, $-\text{OH}$, $-\text{O}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{OMe}$, $-\text{OEt}$, $-\text{OPh}$), or $-\text{O}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})_2$ (*e.g.*, $-\text{OEt}_2$, $-\text{OPh}_2$)).

OEt, -OPr, -OBu, or -OBn), or -O(substituted or unsubstituted phenyl) (*e.g.*, -OPh)). In certain embodiments, at least one instance of R^{E3} is $-SR^a$ (*e.g.*, -SH, -S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, -SMe, -SEt, -SPr, -SBu, or -SBn), or -S(substituted or unsubstituted phenyl) (*e.g.*, -SPh)). In certain embodiments, at least one instance of R^{E3} is $-N(R^a)_2$ (*e.g.*, -NH₂, -NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, -NHMe), or -N(substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, -NMe₂)). In certain embodiments, at least one instance of R^{E3} is -CN, -SCN, or -NO₂. In certain embodiments, at least one instance of R^{E3} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{E3} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{E3} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{E3} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

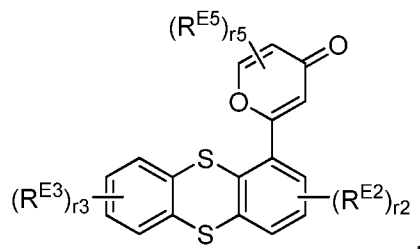
[00249] In certain embodiments, $r3$ is 0. In certain embodiments, $r3$ is 1. In certain embodiments, $r3$ is 2. In certain embodiments, $r3$ is 3. In certain embodiments, $r3$ is 4.

[00250] In certain embodiments, the compound of Formula (E) is of the formula:



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

[00251] In certain embodiments, the compound of Formula (E) is of the formula:



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

each instance of R^{E5} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, -CN, -SCN,

$-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$; and

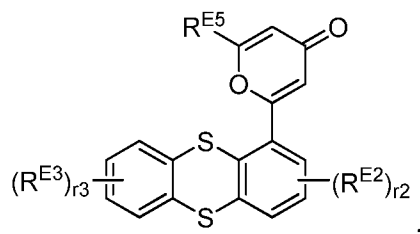
r_5 is 0, 1, 2, or 3.

[00252] In certain embodiments, all instances of R^{E5} are the same. In certain embodiments, two instances of R^{E5} are different from each other. In certain embodiments, at least one instance of R^{E5} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{E5} is $-\text{CH}_3$. In certain embodiments, at least one instance of R^{E5} is $-\text{CF}_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted morpholinyl (*e.g.*, substituted or unsubstituted *N*-morpholinyl). In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{E5} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{E5} is $-\text{OR}^a$ (*e.g.*, $-\text{OH}$, $-\text{O}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{OMe}$, $-\text{OEt}$, $-\text{OPr}$, $-\text{OBu}$, or $-\text{OBn}$), or $-\text{O}(\text{substituted or unsubstituted phenyl})$ (*e.g.*, $-\text{OPh}$)). In certain embodiments, at least one instance of R^{E5} is $-\text{SR}^a$ (*e.g.*, $-\text{SH}$, $-\text{S}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{SMe}$, $-\text{SEt}$, $-\text{SPr}$, $-\text{SBu}$, or $-\text{SBn}$), or $-\text{S}(\text{substituted or unsubstituted phenyl})$ (*e.g.*, $-\text{SPh}$)). In certain embodiments, at least one instance of R^{E5} is $-\text{N}(\text{R}^a)_2$ (*e.g.*, $-\text{NH}_2$, $-\text{NH}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (*e.g.*, $-\text{NHMe}$), or $-\text{N}(\text{substituted or unsubstituted } \text{C}_{1-6} \text{ alkyl})$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-\text{NMe}_2$)). In certain embodiments, at least one

instance of R^{E5} is $-\text{CN}$, $-\text{SCN}$, or $-\text{NO}_2$. In certain embodiments, at least one instance of R^{E5} is $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, or $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$. In certain embodiments, at least one instance of R^{E5} is $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, or $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ (e.g., $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHMe}$, or $-\text{C}(=\text{O})\text{NMe}_2$). In certain embodiments, at least one instance of R^{E5} is $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, or $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$. In certain embodiments, at least one instance of R^{E5} is $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$.

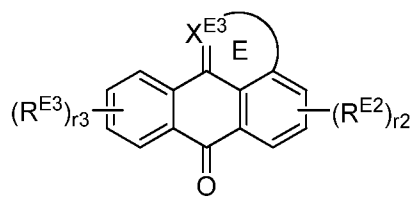
[00253] In certain embodiments, $r5$ is 0. In certain embodiments, $r5$ is 1. In certain embodiments, $r5$ is 2. In certain embodiments, $r5$ is 3.

[00254] In certain embodiments, the compound of Formula (E) is of the formula:



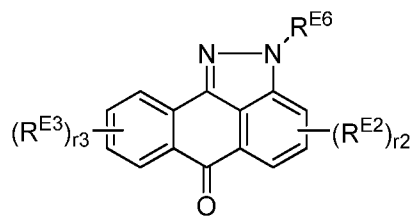
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00255] In certain embodiments, the compound of Formula (E) is of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein X^{E3} is C or N, and Ring E is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, or three atoms in the heterocyclic or heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

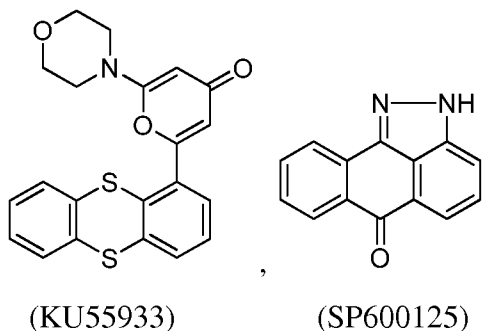
[00256] In certain embodiments, the compound of Formula (E) is of the formula:



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^{E6} is hydrogen,

substituted or unsubstituted C₁₋₆ alkyl (*e.g.*, CH₃, –CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl), or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00257] In certain embodiments, the compound of Formula (E) is of the formula:



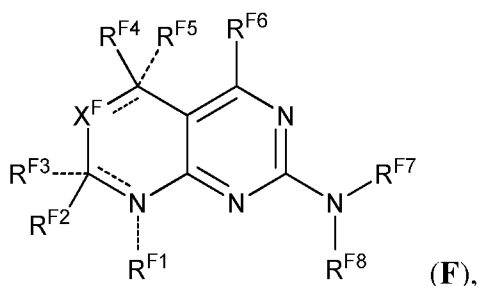
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00258] In certain embodiments, a compound of Formula (E) is not KU55933, SP600125, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00259] It is believed that compounds of Formula (E), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are ATM inhibitors (*e.g.*, KU55933) and/or JNK inhibitors (*e.g.*, SP600125).

Compounds of Formula (F)

[00260] In another aspect, the present disclosure provides compounds of Formula (F):



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

X^F is $-N(R^{F9})-$, $=N-$, $-C(R^{F10})_2-$, or $=C(R^{F10})-$, wherein:

R^{F9} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl,

substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group; and

each instance of R^{F10} is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

R^{F1} is absent, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

R^{F2} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

R^{F3} is absent, hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl, or R^{F3} and R^{F2} are joined to form $=O$;

R^{F4} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-$

$C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

R^{F5} is absent, hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

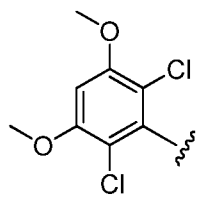
R^{F6} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

R^{F7} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group; and

R^{F8} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group.

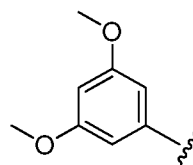
[00261] In certain embodiments, X^F is $-N(R^{F9})-$ or $=N-$. In certain embodiments, X^F is $-C(R^{F10})_2-$ or $=C(R^{F10})-$.

[00262] In certain embodiments, R^{F9} is hydrogen. In certain embodiments, R^{F9} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{F9} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{F9} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{F9} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{F9} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F9} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{F9} is substituted or unsubstituted phenyl (*e.g.*,



). In certain embodiments, R^{F9} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F9} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00263] In certain embodiments, two instances of R^{F10} are the same. In certain embodiments, two instances of R^{F10} are different from each other. In certain embodiments, at least one instance of R^{F10} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkyl). In certain embodiments, at least one instance of R^{F10} is -CH₃. In certain embodiments, at least one instance of R^{F10} is -CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkenyl). In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkynyl). In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one



instance of R^{F10} is substituted or unsubstituted phenyl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{F10} is -OR^a (*e.g.*, -OH, -O(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, -OMe, -OEt, -OPr, -OBu, or -OBn), or -O(substituted or

unsubstituted phenyl) (*e.g.*, $-\text{OPh}$). In certain embodiments, at least one instance of R^{F10} is $-\text{SR}^{\text{a}}$ (*e.g.*, $-\text{SH}$, $-\text{S}$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-\text{SMe}$, $-\text{SEt}$, $-\text{SPr}$, $-\text{SBu}$, or $-\text{SBn}$), or $-\text{S}$ (substituted or unsubstituted phenyl) (*e.g.*, $-\text{SPh}$). In certain embodiments, at least one instance of R^{F10} is $-\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{NH}_2$, $-\text{NH}$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-\text{NHMe}$), or $-\text{N}$ (substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-\text{NMe}_2$). In certain embodiments, at least one instance of R^{F10} is $-\text{CN}$, $-\text{SCN}$, or $-\text{NO}_2$. In certain embodiments, at least one instance of R^{F10} is $-\text{C}(=\text{NR}^{\text{a}})\text{R}^{\text{a}}$, $-\text{C}(=\text{NR}^{\text{a}})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{NR}^{\text{a}})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of R^{F10} is $-\text{C}(=\text{O})\text{R}^{\text{a}}$ (*e.g.*, $-\text{C}(=\text{O})\text{Me}$), $-\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHMe}$, or $-\text{C}(=\text{O})\text{NMe}_2$). In certain embodiments, at least one instance of R^{F10} is $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of R^{F10} is $-\text{OC}(=\text{O})\text{R}^{\text{a}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$.

[00264] In certain embodiments, at least one instance of R^{F10} is substituted or unsubstituted phenyl, or $-\text{C}(=\text{O})\text{R}^{\text{a}}$.

[00265] In certain embodiments, R^{F1} is absent. In certain embodiments, R^{F1} is hydrogen. In certain embodiments, R^{F1} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-\text{CH}_3$, $-\text{CF}_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{F1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{F1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{F1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{F1} is substituted or unsubstituted cyclopentyl. In certain embodiments, R^{F1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{F1} is substituted or unsubstituted phenyl. In certain embodiments, R^{F1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F1} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, R^{F1} is absent, substituted or unsubstituted alky, or substituted or unsubstituted, monocyclic, 5- to 6-membered carbocyclyl.

[00266] In certain embodiments, R^{F2} is hydrogen. In certain embodiments, R^{F2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{F2} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{F2} is $-CH_3$. In certain embodiments, R^{F2} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{F2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{F2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{F2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{F2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{F2} is substituted or unsubstituted phenyl. In certain embodiments, R^{F2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F2} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, R^{F2} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, R^{F2} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, R^{F2} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, R^{F2} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, R^{F2} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, R^{F2} is $-NR^aC(=O)R^a$ or $-NR^aC(=O)OR^a$. In certain embodiments, R^{F2} is $-NR^aC(=O)N(R^a)_2$ (*e.g.*, $-NHC(=O)NH$ (substituted or unsubstituted C_{1-6} alkyl), such as $-NHC(=O)NH(t-Bu)$). In certain embodiments, R^{F2} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00267] In certain embodiments, R^{F3} is absent. In certain embodiments, R^{F3} is hydrogen. In certain embodiments, R^{F3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{F3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{F3} is $-CH_3$. In certain embodiments, R^{F3} is $-CF_3$,

unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{F3} and R^{F2} are joined to form $=O$.

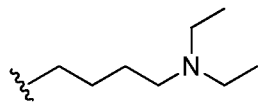
[00268] In certain embodiments, R^{F4} is hydrogen. In certain embodiments, R^{F4} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{F4} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{F4} is $-CH_3$. In certain embodiments, R^{F4} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{F4} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{F4} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{F4} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{F4} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F4} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{F4} is substituted or unsubstituted phenyl. In certain embodiments, R^{F4} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F4} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, R^{F4} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, R^{F4} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, R^{F4} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, R^{F4} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, R^{F4} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, R^{F4} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, R^{F4} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$. In certain embodiments, R^{F4} is hydrogen or substituted or unsubstituted alkyl.

[00269] In certain embodiments, R^{F5} is absent. In certain embodiments, R^{F5} is hydrogen. In certain embodiments, R^{F5} is halogen (*e.g.*, F, Cl, Br, or I). In certain

embodiments, R^{F5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{F5} is $-CH_3$. In certain embodiments, R^{F5} is $-CF_5$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl.

[00270] In certain embodiments, R^{F6} is hydrogen. In certain embodiments, R^{F6} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{F6} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{F6} is $-CH_3$. In certain embodiments, R^{F6} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{F6} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{F6} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{F6} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{F6} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F6} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{F6} is substituted or unsubstituted phenyl. In certain embodiments, R^{F6} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F6} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, R^{F6} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, R^{F6} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, R^{F6} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, R^{F6} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, R^{F6} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, R^{F6} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, R^{F6} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

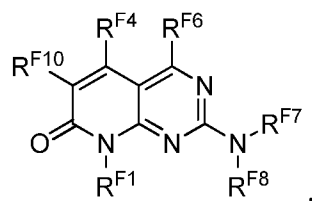
[00271] In certain embodiments, R^{F7} is hydrogen. In certain embodiments, R^{F7} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{F7} is of the formula:



. In certain embodiments, R^{F7} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{F7} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{F7} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{F7} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F7} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{F7} is substituted or unsubstituted phenyl. In certain embodiments, R^{F7} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{F7} is substituted or unsubstituted pyridyl (*e.g.*, substituted or unsubstituted 2-pyridyl). In certain embodiments, R^{F7} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, R^{F7} is substituted or unsubstituted alkyl or substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

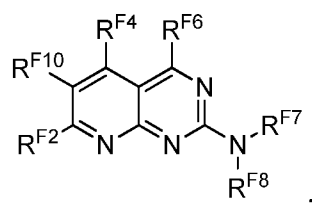
[00272] In certain embodiments, R^{F8} is hydrogen. In certain embodiments, R^{F8} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{F8} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00273] In certain embodiments, the compound of Formula (F) is of the formula:



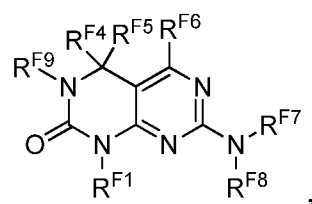
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00274] In certain embodiments, the compound of Formula (F) is of the formula:



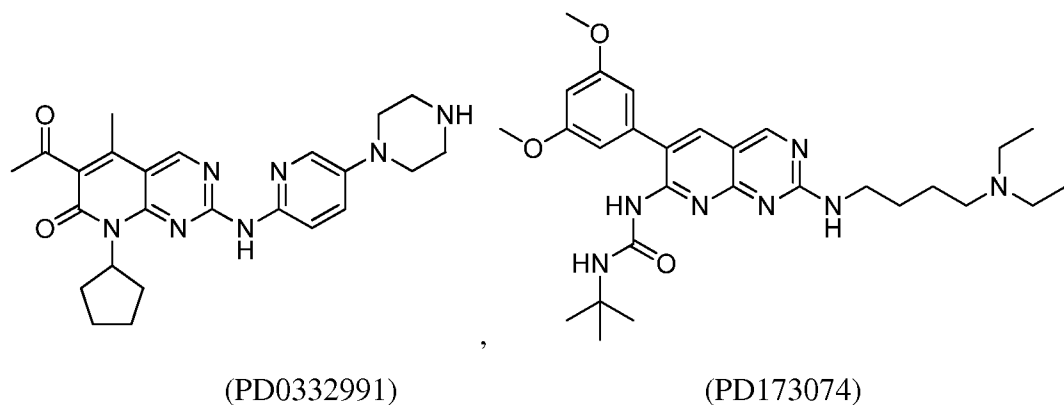
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

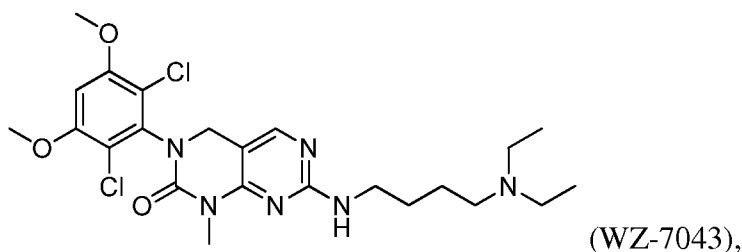
[00275] In certain embodiments, the compound of Formula (F) is of the formula:



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

[00276] In certain embodiments, the compound of Formula (F) is of the formula:





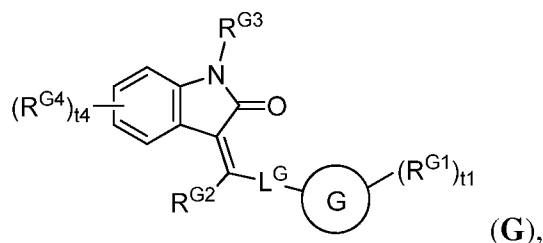
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00277] In certain embodiments, a compound of Formula (F) is not PD0332991, PD173074, WZ-7043, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00278] It is believed that compounds of Formula (F), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are CDK inhibitors (*e.g.*, CDK4 inhibitors, such as PD0332991), FGFR inhibitors (*e.g.*, FGFR1 inhibitors, such as PD173074), and/or CSF1R inhibitors (*e.g.*, WZ-7043).

Compounds of Formula (G)

[00279] In another aspect, the present disclosure provides compounds of Formula (G):



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

Ring G is a substituted or unsubstituted phenyl ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur;

each instance of R^{G1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-$

NO_2 , $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

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

t_1 is 0, 1, 2, 3, 4, or 5;

L^G is a bond, $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^{G5})-$, or $-\text{C}(\text{R}^{G6})_2-$, wherein R^{G5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group; and each instance of R^{G6} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

R^{G2} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{G3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

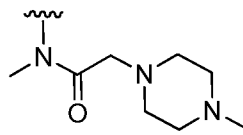
each instance of R^{G4} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^a$, or $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)_2$; and

t_4 is 0, 1, 2, 3, or 4.

[00280] In certain embodiments, Ring G is a substituted or unsubstituted phenyl ring. In certain embodiments, Ring G is a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments, Ring G is substituted or unsubstituted pyrrolyl ring.

[00281] In certain embodiments, all instances of R^{G1} are the same. In certain embodiments, two instances of R^{G1} are different from each other. In certain embodiments, at least one instance of R^{G1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{G1} is $-CH_3$. In certain embodiments, at least one instance of R^{G1} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{G1} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{G1} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{G1} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{G1} is $-CN$, $-SCN$, or

–NO₂. In certain embodiments, at least one instance of R^{G1} is –C(=NR^a)R^a, –C(=NR^a)OR^a, or –C(=NR^a)N(R^a)₂. In certain embodiments, at least one instance of R^{G1} is –C(=O)R^a or –C(=O)OR^a. In certain embodiments, at least one instance of R^{G1} is –C(=O)N(R^a)₂ (e.g., –C(=O)NH₂, –C(=O)NHMe, –C(=O)NMe₂, –C(=O)NHCH₂CH₂N(Et)₂, –C(=O)–(substituted or unsubstituted *N*-pyrrolidiny), or –C(=O)–(substituted or unsubstituted *N*-piperaziny)). In certain embodiments, at least one instance of R^{G1} is –NR^aC(=O)R^a (e.g., –N(substituted or unsubstituted C₁₋₆ alkyl)–C(=O)(substituted or unsubstituted C₁₋₆ alkyl), such as



(. In certain embodiments, at least one instance of R^{G1} is –NR^aC(=O)OR^a or –NR^aC(=O)N(R^a)₂. In certain embodiments, at least one instance of R^{G1} is –OC(=O)R^a, –OC(=O)OR^a, or –OC(=O)N(R^a)₂.

[00282] In certain embodiments, at least one instance of R^{G1} is substituted or unsubstituted alkyl, –C(=O)N(R^a)₂, or –N(R^a)C(=O)R^a.

[00283] In certain embodiments, t1 is 0. In certain embodiments, t1 is 1. In certain embodiments, t1 is 2. In certain embodiments, t1 is 3. In certain embodiments, t1 is 4. In certain embodiments, t1 is 5.

[00284] In certain embodiments, L^G is a bond. In certain embodiments, L^G is –O–, –S–, or –C(R^{G6})₂– (e.g., –CH₂–). In certain embodiments, L^G is –N(R^{G5})– (e.g., –NH–).

[00285] In certain embodiments, R^{G5} is hydrogen. In certain embodiments, R^{G5} is substituted or unsubstituted C₁₋₆ alkyl (e.g., –CH₃, –CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{G5} is a nitrogen protecting group (e.g., Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00286] In certain embodiments, both instances of R^{G6} are the same. In certain embodiments, two instances of R^{G6} are different from each other. In certain embodiments, at least one instance of R^{G6} is hydrogen. In certain embodiments, each instance of R^{G6} is hydrogen. In certain embodiments, at least one instance of R^{G6} is halogen (e.g., F, Cl, Br, or I). In certain embodiments, at least one instance of R^{G6} is substituted or unsubstituted C₁₋₆ alkyl (e.g., –CH₃, –CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl).

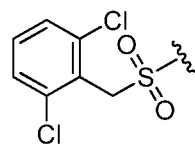
[00287] In certain embodiments, R^{G2} is hydrogen. In certain embodiments, R^{G2} is halogen (e.g., F, Cl, Br, or I). In certain embodiments, R^{G2} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C₁₋₆ alkyl (e.g., –CH₃, –CF₃, unsubstituted ethyl,

perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{G2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{G2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{G2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{G2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{G2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{G2} is substituted or unsubstituted phenyl. In certain embodiments, R^{G2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

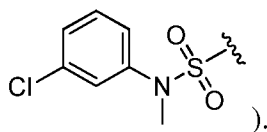
[00288] In certain embodiments, R^{G3} is hydrogen. In certain embodiments, R^{G3} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{G3} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00289] In certain embodiments, all instances of R^{G4} are the same. In certain embodiments, two instances of R^{G4} are different from each other. In certain embodiments, at least one instance of R^{G4} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{G4} is $-CH_3$. In certain embodiments, at least one instance of R^{G4} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In

certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{G4} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{G4} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{G4} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{G4} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{G4} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{G4} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{G4} is $-C(=O)R^a$, $-C(=O)OR^a$ (*e.g.*, $-C(=O)O$ (substituted or unsubstituted C_{1-6} alkyl), such as $-C(=O)OMe$), or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{G4} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{G4} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{G4} is $-S(=O)_2R^a$ (*e.g.*, $-S(=O)_2$ (substituted or unsubstituted C_{1-6} alkyl), such as



$-S(=O)_2$ (substituted or unsubstituted C_{1-6} alkyl), such as $-S(=O)_2N(R^a)_2$ (*e.g.*, $-S(=O)_2N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or

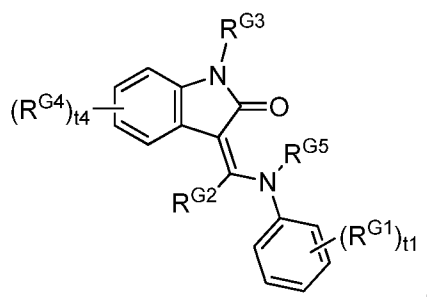


unsubstituted phenyl), such as

[00290] In certain embodiments, at least one instance of R^{G4} is halogen, $-C(=O)OR^a$, $-S(=O)_2R^a$, or $-S(=O)_2N(R^a)_2$.

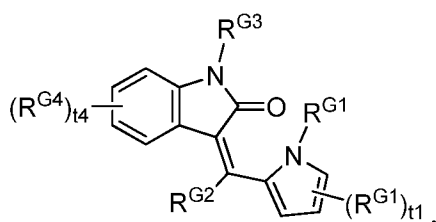
[00291] In certain embodiments, t_4 is 0. In certain embodiments, t_4 is 1. In certain embodiments, t_4 is 2. In certain embodiments, t_4 is 3. In certain embodiments, t_4 is 4.

[00292] In certain embodiments, the compound of Formula (G) is of the formula:



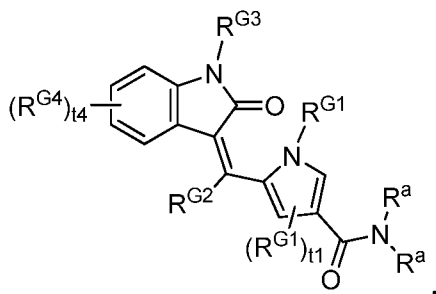
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00293] In certain embodiments, the compound of Formula (G) is of the formula:



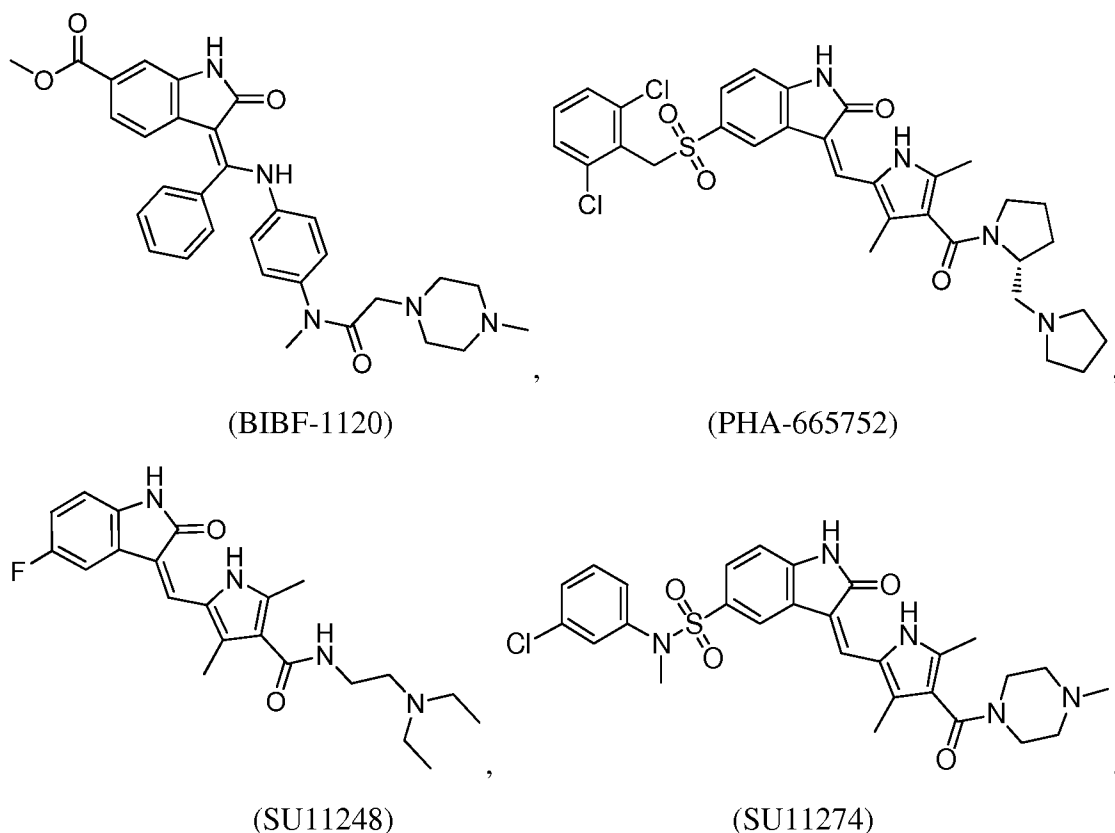
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00294] In certain embodiments, the compound of Formula (G) is of the formula:



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

[00295] In certain embodiments, the compound of Formula (G) is of the formula:



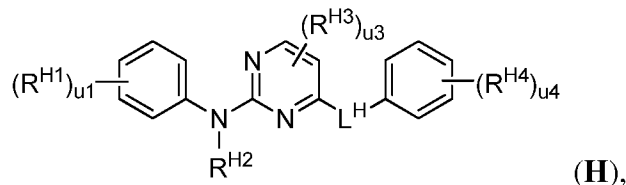
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00296] In certain embodiments, a compound of Formula (G) is not BIBF-1120, PHA-665752, SU11248, SU11274, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00297] It is believed that compounds of Formula (G), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are VEGFR inhibitors (*e.g.*, SU11248 (a VEGFR1 inhibitor) and BIBF-1120), PDGFR inhibitors (*e.g.*, BIBF-1120 and SU11248), FGFR inhibitors (*e.g.*, BIBF-1120), MET inhibitors (*e.g.*, PHA-665752 and SU11274), KIT inhibitors (*e.g.*, SU11248), and/or FLT inhibitors (*e.g.*, FLT3 inhibitors, such as SU11248).

Compounds of Formula (H)

[00298] In another aspect, the present disclosure provides compounds of Formula (H):



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

L^H is a substituted or unsubstituted, saturated or unsaturated, C_{1-4} aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{H5}-$, $-N=$, or $=N-$, wherein each instance of R^{H5} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

each instance of R^{H1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

$u1$ is 0, 1, 2, 3, 4, or 5;

R^{H2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{H3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

$u3$ is 0, 1, or 2;

each instance of R^{H4} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

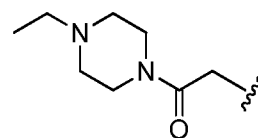
$u4$ is 0, 1, 2, 3, 4, or 5.

[00299] In certain embodiments, L^H is a substituted or unsubstituted C_1 aliphatic chain. In certain embodiments, L^H is $-O-$ or $-S-$. In certain embodiments, L^H is $-NR^{H5}-$ (*e.g.*, $-NH-$). In certain embodiments, L^H is a substituted or unsubstituted, saturated or unsaturated, C_3 aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{H5}-$ (*e.g.*, $-NH-$), $=N-$, or $=N-$. In certain embodiments, L^H is $-NR^{H5}C(=O)O-$ (*e.g.*, $-NHC(=O)O-$ or $-N(\text{substituted or unsubstituted phenyl})C(=O)O-$) or $-OC(=O)NR^{H5}-$ (*e.g.*, $-OC(=O)NH-$ or $-OC(=O)N(\text{substituted or unsubstituted phenyl})-$). In certain embodiments, L^H is $-NR^{H5}C(=O)NR^{H5}-$ (*e.g.*, $-NHC(=O)NH-$). In certain embodiments, L^H is a substituted or unsubstituted, saturated or unsaturated, C_2 or C_4 aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{H5}-$ (*e.g.*, $-NH-$), $=N-$, or $=N-$.

[00300] In certain embodiments, all instances of R^{H5} are the same. In certain embodiments, two instances of R^{H5} are different from each other. In certain embodiments, at least one instance of R^{H5} is hydrogen. In certain embodiments, at least one instance of R^{H5} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{H5}

is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkenyl). In certain embodiments, at least one instance of R^{H5} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkynyl). In certain embodiments, at least one instance of R^{H5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{H5} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H5} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{H5} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{H5} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H5} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, at least one instance of R^{H5} is hydrogen or substituted or unsubstituted phenyl.

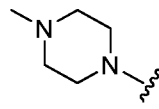
[00301] In certain embodiments, all instances of R^{H1} are the same. In certain embodiments, two instances of R^{H1} are different from each other. In certain embodiments, at least one instance of R^{H1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkyl). In certain embodiments, at least one instance of R^{H1} is -CH₃. In certain embodiments, at least one instance of R^{H1} is -CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain



embodiments, at least one instance of R^{H1} is of the formula: . In certain

embodiments, at least one instance of R^{H1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkenyl). In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkynyl). In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or

three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted piperazinyl



(*e.g.*, substituted or unsubstituted *N*-piperazinyl, such as R^{H1}). In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H1} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{H1} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{H1} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{H1} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{H1} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{H1} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{H1} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{H1} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00302] In certain embodiments, at least one instance of R^{H1} is substituted or unsubstituted alkyl or substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

[00303] In certain embodiments, $u1$ is 0. In certain embodiments, $u1$ is 1. In certain embodiments, $u1$ is 2. In certain embodiments, $u1$ is 3. In certain embodiments, $u1$ is 4. In certain embodiments, $u1$ is 5.

[00304] In certain embodiments, R^{H2} is hydrogen. In certain embodiments, R^{H2} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl,

unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{H2} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00305] In certain embodiments, all instances of R^{H3} are the same. In certain embodiments, two instances of R^{H3} are different from each other. In certain embodiments, at least one instance of R^{H3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{H3} is $-CH_3$. In certain embodiments, at least one instance of R^{H3} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{H3} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H3} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{H3} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{H3} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{H3} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{H3} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{H3} is $-C(=O)R^a$, $-$

$C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{H3} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{H3} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00306] In certain embodiments, $u3$ is 0. In certain embodiments, $u3$ is 1. In certain embodiments, $u3$ is 2. In certain embodiments, $u3$ is 3.

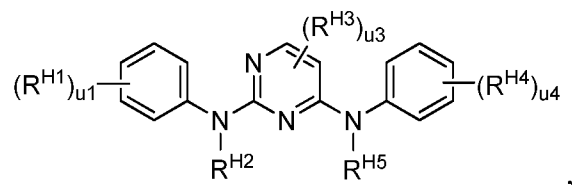
[00307] In certain embodiments, all instances of R^{H4} are the same. In certain embodiments, two instances of R^{H4} are different from each other. In certain embodiments, at least one instance of R^{H4} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{H4} is $-CH_3$. In certain embodiments, at least one instance of R^{H4} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{H4} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{H4} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{H4} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{H4} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6}

alkyl) (*e.g.*, $-\text{NMe}_2$). In certain embodiments, at least one instance of $\text{R}^{\text{H}4}$ is $-\text{CN}$, $-\text{SCN}$, or $-\text{NO}_2$. In certain embodiments, at least one instance of $\text{R}^{\text{H}4}$ is $-\text{C}(=\text{NR}^{\text{a}})\text{R}^{\text{a}}$, $-\text{C}(=\text{NR}^{\text{a}})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{NR}^{\text{a}})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{H}4}$ is $-\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ (*e.g.*, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{NHMe}$, $-\text{C}(=\text{O})\text{NH}(\text{substituted or unsubstituted phenyl})$ (*e.g.*, $-\text{C}(=\text{O})\text{NH}-(2\text{-chlorophenyl})$), or $-\text{C}(=\text{O})\text{NMe}_2$). In certain embodiments, at least one instance of $\text{R}^{\text{H}4}$ is $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$, $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$. In certain embodiments, at least one instance of $\text{R}^{\text{H}4}$ is $-\text{OC}(=\text{O})\text{R}^{\text{a}}$, $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$.

[00308] In certain embodiments, at least one instance of $\text{R}^{\text{H}4}$ is substituted or unsubstituted alkyl, or $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$.

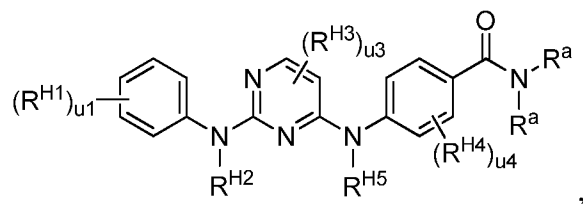
[00309] In certain embodiments, u_4 is 0. In certain embodiments, u_4 is 1. In certain embodiments, u_4 is 2. In certain embodiments, u_4 is 3. In certain embodiments, u_4 is 4. In certain embodiments, u_4 is 5.

[00310] In certain embodiments, the compound of Formula (H) is of the formula:



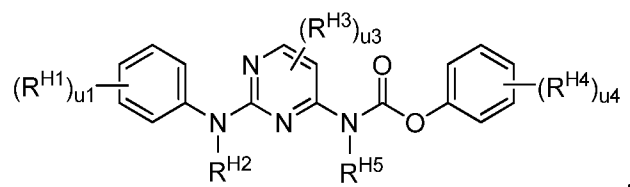
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00311] In certain embodiments, the compound of Formula (H) is of the formula:



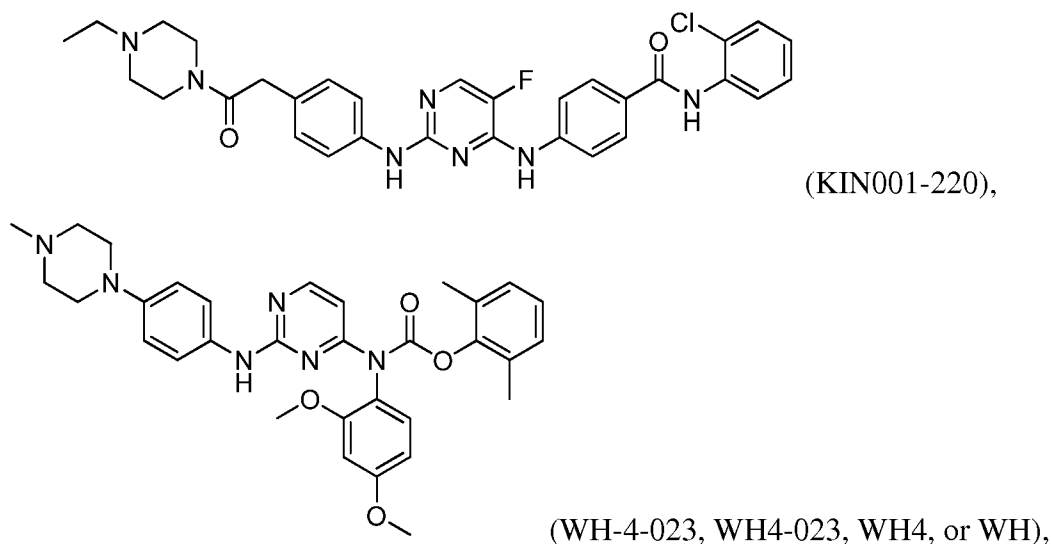
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00312] In certain embodiments, the compound of Formula (H) is of the formula:



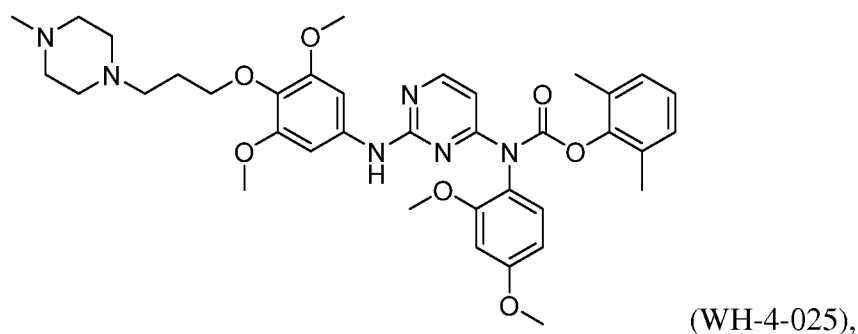
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00313] In certain embodiments, the compound of Formula (H) is of the formula:



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

[00314] In certain embodiments, the compound of Formula (H) is of the formula:



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

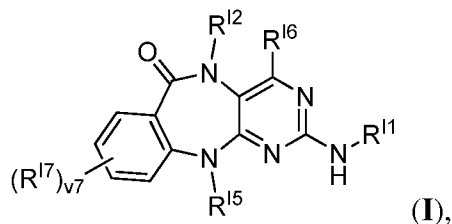
[00315] Compounds WH-4-023 and WH-4-025 are disclosed in U.S. Patent Application Publication, US 2005/0026914, published February 3, 2005, which is incorporated herein by reference. In certain embodiments, a compound of Formula (H) is not KIN001-220, WH-4-023, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof. In certain embodiments, a compound of Formula (H) is not WH-4-025, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00316] It is believed that compounds of Formula (H), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers,

isotopically labeled derivatives, and prodrugs thereof, are aurora kinase inhibitors (*e.g.*, KIN001-220) and/or SRC inhibitors (*e.g.*, WH-4-023).

Compounds of Formula (I)

[00317] In another aspect, the present disclosure provides compounds of Formula (I):



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

R^{11} is substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{12} is hydrogen or substituted or unsubstituted alkyl;

R^{15} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted carbocyclyl;

R^{16} is hydrogen or substituted or unsubstituted alkyl;

each instance of R^{17} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-O-$ (substituted or unsubstituted alkyl), $-NH-$ (substituted or unsubstituted alkyl), $-NH-$ (substituted or unsubstituted aryl), $-N$ (substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), $-N$ (substituted or unsubstituted alkyl)–(substituted or unsubstituted aryl), $-NO_2$, or $-CN$; and

$v7$ is 0, 1, 2, 3, or 4.

[00318] In certain embodiments, R^{11} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{11} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{11} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are

independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{II} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{II} is substituted or unsubstituted phenyl. In certain embodiments, R^{II} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00319] In certain embodiments, R^{I2} is hydrogen. In certain embodiments, R^{I2} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl).

[00320] In certain embodiments, R^{I5} is hydrogen. In certain embodiments, R^{I5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{I5} is $-CH_3$. In certain embodiments, R^{I5} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{I5} is substituted or unsubstituted aralkyl (*e.g.*, Bn). In certain embodiments, R^{I5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered carbocyclyl).

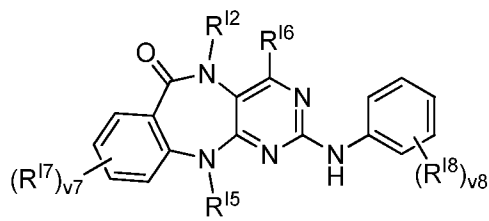
[00321] In certain embodiments, R^{I6} is hydrogen. In certain embodiments, R^{I6} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl).

[00322] In certain embodiments, all instances of R^{I7} are the same. In certain embodiments, two instances of R^{I7} are different from each other. In certain embodiments, at least one instance of R^{I7} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{I7} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{I7} is $-CH_3$. In certain embodiments, at least one instance of R^{I7} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{I7} is substituted or unsubstituted aralkyl (*e.g.*, Bn). In certain embodiments, at least one instance of R^{I7} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{I7} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{I7} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered

heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{17} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{17} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{17} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{17} is $-O-$ (substituted or unsubstituted alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, or $-OBu$). In certain embodiments, at least one instance of R^{17} is $-NH-$ (substituted or unsubstituted alkyl) (*e.g.*, $-NHMe$), $-NH-$ (substituted or unsubstituted aryl) (*e.g.*, $-NHPh$), $-N$ (substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl) (*e.g.*, $-NMe_2$), or $-N$ (substituted or unsubstituted alkyl)–(substituted or unsubstituted aryl). In certain embodiments, at least one instance of R^{17} is $-NO_2$ or $-CN$.

[00323] In certain embodiments, v_7 is 0. In certain embodiments, v_7 is 1. In certain embodiments, v_7 is 2. In certain embodiments, v_7 is 3. In certain embodiments, v_7 is 4.

[00324] In certain embodiments, the compound of Formula (I) is of the formula:



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

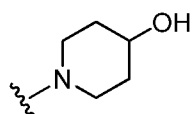
each instance of R^{18} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

v_8 is 0, 1, 2, 3, 4, or 5.

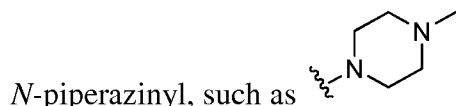
[00325] In certain embodiments, all instances of R^{18} are the same. In certain embodiments, two instances of R^{18} are different from each other. In certain embodiments, at

least one instance of R^{18} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{18} is $-CH_3$. In certain embodiments, at least one instance of R^{18} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur).

[00326] In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted piperidinyl (*e.g.*, substituted or unsubstituted *N*-piperidinyl, such as

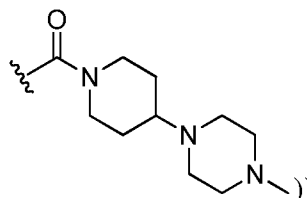


) or substituted or unsubstituted piperazinyl (*e.g.*, substituted or unsubstituted



N-piperazinyl, such as)). In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{18} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{18} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{18} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{18} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl) (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{18} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{18}

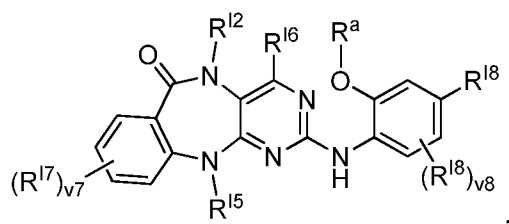
is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{18} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (e.g., $-C(=O)NH_2$, $-C(=O)NHMe$, $-C(=O)NMe_2$, or $-C(=O)-(substituted \text{ or } unsubstituted \text{ } N\text{-piperidinyl})$ (e.g.,



$NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{18} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

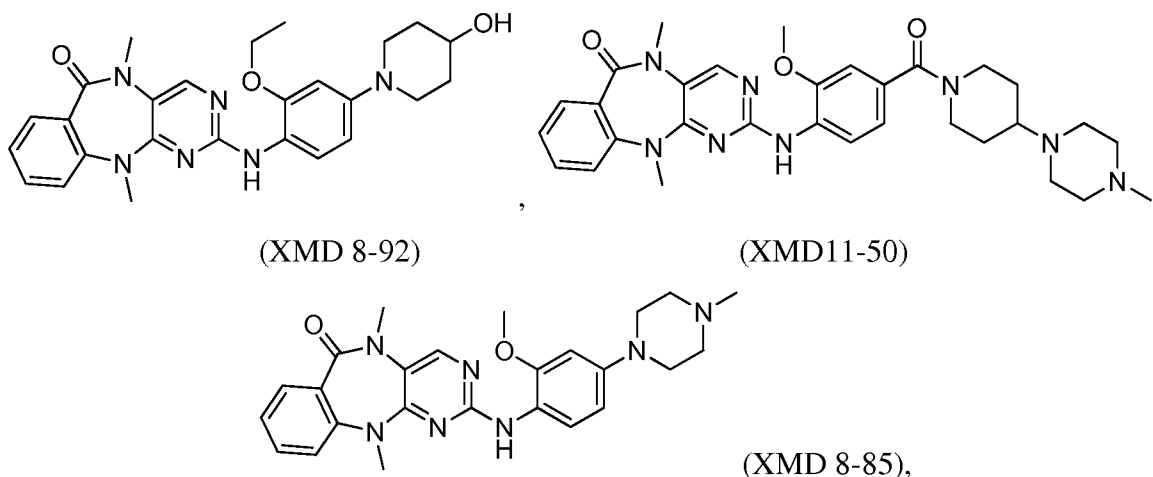
[00327] In certain embodiments, v_8 is 0. In certain embodiments, v_8 is 1. In certain embodiments, v_8 is 2. In certain embodiments, v_8 is 3. In certain embodiments, v_8 is 4. In certain embodiments, v_8 is 5.

[00328] In certain embodiments, the compound of Formula (I) is of the formula:



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

[00329] In certain embodiments, the compound of Formula (I) is of the formula:



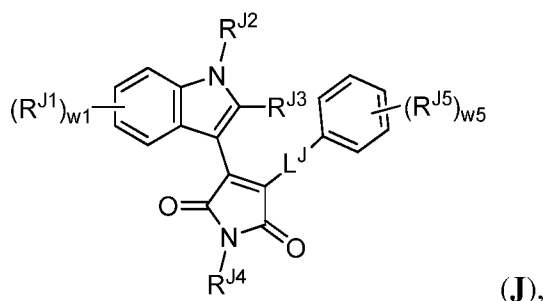
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00330] In certain embodiments, a compound of Formula (I) is not XMD 8-92, XMD11-50, XMD 8-85, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00331] It is believed that compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are ERK inhibitors (*e.g.*, ERK5 inhibitors, such as XMD 8-92, XMD11-50, and XMD 8-85) and/or LRRK inhibitors (*e.g.*, LRRK2 inhibitors, such as XMD11-50).

Compounds of Formula (J)

[00332] In another aspect, the present disclosure provides compounds of Formula (J):



(J),

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

L^J is a substituted or unsubstituted, saturated or unsaturated, C₁₋₆ aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with -O-, -S-, -NR^{J6}-, -N=, or =N-, wherein each instance of R^{J6} is independently hydrogen, substituted or unsubstituted C₁₋₆ alkyl, or a nitrogen protecting group;

each instance of R^{J1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR^a, -N(R^a)₂, -SR^a, -CN, -SCN, -C(=NR^a)R^a, -C(=NR^a)OR^a, -C(=NR^a)N(R^a)₂, -C(=O)R^a, -C(=O)OR^a, -C(=O)N(R^a)₂, -NO₂, -NR^aC(=O)R^a, -NR^aC(=O)OR^a, -NR^aC(=O)N(R^a)₂, -OC(=O)R^a, -OC(=O)OR^a, or -OC(=O)N(R^a)₂;

each instance of R^a is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a

nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^a are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

w_1 is 0, 1, 2, 3, or 4;

R^{J2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

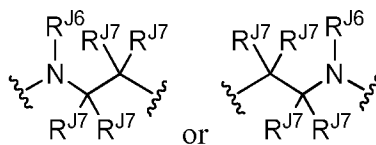
R^{J3} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

R^{J4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{J5} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

w_5 is 0, 1, 2, 3, 4, or 5.

[00333] In certain embodiments, L^J is a substituted or unsubstituted, saturated or unsaturated, C_3 aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{J6}-$ (e.g., $-NH-$), $-N=$, or $=N-$. In



certain embodiments, L^J is of the formula: R^{J6} R^{J7} R^{J7} R^{J7} R^{J7} or R^{J7} R^{J7} R^{J6} R^{J7} R^{J7} , wherein each instance of R^{J7} is independently hydrogen, halogen (e.g., F, Cl, Br, or I), or substituted or unsubstituted C_{1-6} alkyl (e.g., $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, all instances of R^{J7} are the same. In certain embodiments, two instances of R^{J7} are different from each other. In certain embodiments, each instance of R^{J7} is hydrogen.

[00334] In certain embodiments, all instances of R^{J6} are the same. In certain embodiments, two instances of R^{J6} are different from each other. In certain embodiments, at least one instance of R^{J6} is hydrogen. In certain embodiments, at least one instance of R^{J6} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{J6} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00335] In certain embodiments, all instances of R^{J1} are the same. In certain embodiments, two instances of R^{J1} are different from each other. In certain embodiments, at least one instance of R^{J1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{J1} is $-CH_3$. In certain embodiments, at least one instance of R^{J1} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{J1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{J1} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{J1} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{J1} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or

unsubstituted C₁₋₆ alkyl)–(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, –NMe₂). In certain embodiments, at least one instance of R^{J1} is –CN, –SCN, or –NO₂. In certain embodiments, at least one instance of R^{J1} is –C(=NR^a)R^a, –C(=NR^a)OR^a, or –C(=NR^a)N(R^a)₂. In certain embodiments, at least one instance of R^{J1} is –C(=O)R^a, –C(=O)OR^a, or –C(=O)N(R^a)₂ (*e.g.*, –C(=O)NH₂, –C(=O)NHMe, or –C(=O)NMe₂). In certain embodiments, at least one instance of R^{J1} is –NR^aC(=O)R^a, –NR^aC(=O)OR^a, or –NR^aC(=O)N(R^a)₂. In certain embodiments, at least one instance of R^{J1} is –OC(=O)R^a, –OC(=O)OR^a, or –OC(=O)N(R^a)₂.

[00336] In certain embodiments, w₁ is 0. In certain embodiments, w₁ is 1. In certain embodiments, w₁ is 2. In certain embodiments, w₁ is 3. In certain embodiments, w₁ is 4.

[00337] In certain embodiments, R^{J2} is hydrogen. In certain embodiments, R^{J2} is substituted or unsubstituted C₁₋₆ alkyl (*e.g.*, –CH₃, –CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{J2} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00338] In certain embodiments, R^{J3} is hydrogen. In certain embodiments, R^{J3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{J3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkyl). In certain embodiments, R^{J3} is –CH₃. In certain embodiments, R^{J3} is –CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{J3} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkenyl). In certain embodiments, R^{J3} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkynyl). In certain embodiments, R^{J3} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{J3} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{J3} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{J3} is substituted or unsubstituted phenyl. In certain embodiments, R^{J3} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{J3} is –OR^a (*e.g.*, –OH, –O(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, R^{J3} is –SR^a (*e.g.*, –SH, –S(substituted or unsubstituted C₁₋₆

alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, R^{J3} is $-N(R^a)_2$ (*e.g.*, –NH₂, –NH(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C₁₋₆ alkyl)–(substituted or unsubstituted C₁₋₆ alkyl) (*e.g.*, –NMe₂)). In certain embodiments, R^{J3} is –CN, –SCN, or –NO₂. In certain embodiments, R^{J3} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, R^{J3} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, R^{J3} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, R^{J3} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

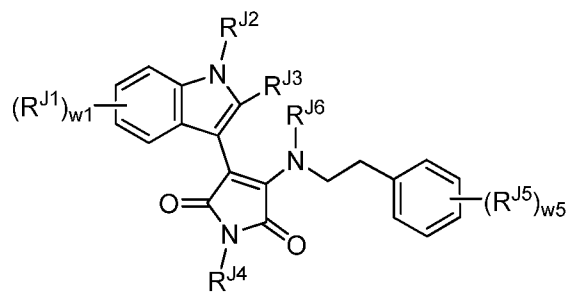
[00339] In certain embodiments, R^{J4} is hydrogen. In certain embodiments, R^{J4} is substituted or unsubstituted C₁₋₆ alkyl (*e.g.*, –CH₃, –CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{J4} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00340] In certain embodiments, all instances of R^{J5} are the same. In certain embodiments, two instances of R^{J5} are different from each other. In certain embodiments, at least one instance of R^{J5} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkyl). In certain embodiments, at least one instance of R^{J5} is –CH₃. In certain embodiments, at least one instance of R^{J5} is –CF₃, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkenyl). In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkynyl). In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{J5} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are

independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{J5} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{J5} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{J5} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{J5} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{J5} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{J5} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{J5} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{J5} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

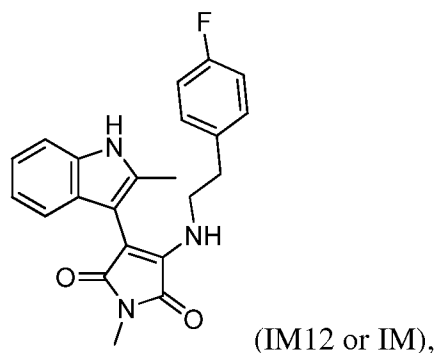
[00341] In certain embodiments, $w5$ is 0. In certain embodiments, $w5$ is 1. In certain embodiments, $w5$ is 2. In certain embodiments, $w5$ is 3. In certain embodiments, $w5$ is 4. In certain embodiments, $w5$ is 5.

[00342] In certain embodiments, the compound of Formula (J) is of the formula:



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

[00343] In certain embodiments, the compound of Formula (J) is of the formula:



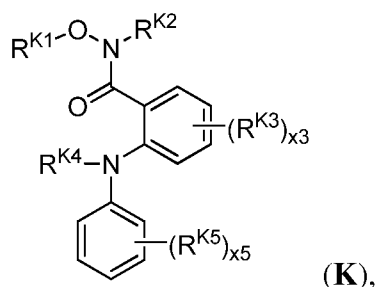
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00344] In certain embodiments, a compound of Formula (J) is not IM12, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00345] It is believed that compounds of Formula (J), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are GSK inhibitors (*e.g.*, GSK3 inhibitors).

Compounds of Formula (K)

[00346] In another aspect, the present disclosure provides compounds of Formula (K):



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

R^{K1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{K2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{K3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^a are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

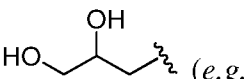
x_3 is 0, 1, 2, 3, or 4;

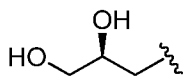
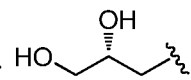
R^{K4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{K5} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

x_5 is 0, 1, 2, 3, 4, or 5.

[00347] In certain embodiments, R^{K1} is hydrogen. In certain embodiments, R^{K1} is substituted or unsubstituted alkyl, such as substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{K1} is C_{1-6} alkyl substituted

with at least one $-OH$. In certain embodiments, R^{K1} is of the formula:  (*e.g.*,

 or ). In certain embodiments, R^{K1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, R^{K1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{K1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, R^{K1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{K1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{K1} is substituted or unsubstituted phenyl. In certain embodiments, R^{K1} is

substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00348] In certain embodiments, R^{K2} is hydrogen. In certain embodiments, R^{K2} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{K2} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00349] In certain embodiments, all instances of R^{K3} are the same. In certain embodiments, two instances of R^{K3} are different from each other. In certain embodiments, at least one instance of R^{K3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{K3} is $-CH_3$. In certain embodiments, at least one instance of R^{K3} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{K3} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{K3} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{K3} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one

instance of R^{K3} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{K3} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{K3} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{K3} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{K3} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{K3} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00350] In certain embodiments, x_3 is 0. In certain embodiments, x_3 is 1. In certain embodiments, x_3 is 2. In certain embodiments, x_3 is 3. In certain embodiments, x_3 is 4.

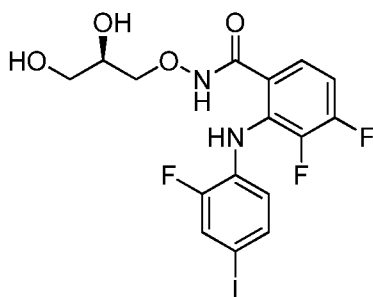
[00351] In certain embodiments, R^{K4} is hydrogen. In certain embodiments, R^{K4} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{K4} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00352] In certain embodiments, all instances of R^{K5} are the same. In certain embodiments, two instances of R^{K5} are different from each other. In certain embodiments, at least one instance of R^{K5} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{K5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{K5} is $-CH_3$. In certain embodiments, at least one instance of R^{K5} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{K5} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{K5} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{K5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{K5} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{K5} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{K5} is substituted or unsubstituted phenyl. In certain embodiments, at least one

instance of R^{K5} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{K5} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{K5} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{K5} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{K5} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{K5} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{K5} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{K5} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{K5} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00353] In certain embodiments, x_5 is 0. In certain embodiments, x_5 is 1. In certain embodiments, x_5 is 2. In certain embodiments, x_5 is 3. In certain embodiments, x_5 is 4. In certain embodiments, x_5 is 5.

[00354] In certain embodiments, the compound of Formula (K) is of the formula:



(PD0325901, PD03, or PD),

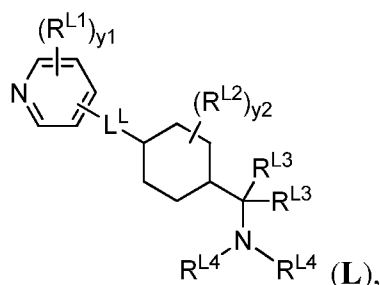
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00355] In certain embodiments, a compound of Formula (K) is not PD0325901, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00356] It is believed that compounds of Formula (K), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are MEK inhibitors.

Compounds of Formula (L)

[00357] In another aspect, the present disclosure provides compounds of Formula (L):



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

L^L is a substituted or unsubstituted, saturated or unsaturated, C_{1-4} aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{L5}-$, $-N=$, or $=N-$, wherein each instance of R^{L5} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{L1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

y_1 is 0, 1, 2, 3, or 4;

each instance of R^{L2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

y_2 is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

each instance of R^{L3} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl; and

each instance of R^{L4} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group.

[00358] In certain embodiments, L^L is a substituted or unsubstituted, saturated or unsaturated, C_2 aliphatic chain, optionally wherein one chain atom of the aliphatic chain is replaced with $-O-$, $-S-$, $-NR^{L5}-$ (*e.g.*, $-NH-$), $-N=$, or $=N-$. In certain embodiments, L^L is $-C(=O)NR^{L5}-$ (*e.g.*, $-C(=O)NH-$) or $-NR^{L5}C(=O)-$ (*e.g.*, $-NHC(=O)-$). In certain embodiments, L^L is a substituted or unsubstituted, saturated or unsaturated, C_1 , C_3 , or C_4 aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{L5}-$ (*e.g.*, $-NH-$), $-N=$, or $=N-$.

[00359] In certain embodiments, all instances of R^{L5} are the same. In certain embodiments, two instances of R^{L5} are different from each other. In certain embodiments, at least one instance of R^{L5} is hydrogen. In certain embodiments, at least one instance of R^{L5} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{L5} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00360] In certain embodiments, all instances of R^{L1} are the same. In certain embodiments, two instances of R^{L1} are different from each other. In certain embodiments, at least one instance of R^{L1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{L1} is $-CH_3$. In certain embodiments, at least one instance of R^{L1} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6}

alkenyl). In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{L1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{L1} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{L1} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{L1} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{L1} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{L1} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{L1} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{L1} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{L1} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

[00361] In certain embodiments, $y1$ is 0. In certain embodiments, $y1$ is 1. In certain embodiments, $y1$ is 2. In certain embodiments, $y1$ is 3. In certain embodiments, $y1$ is 4.

[00362] In certain embodiments, all instances of R^{L2} are the same. In certain embodiments, two instances of R^{L2} are different from each other. In certain embodiments, at least one instance of R^{L2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{L2} is $-CH_3$. In certain embodiments,

at least one instance of R^{L2} is $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{1-6} alkenyl). In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 3- to 7-membered carbocyclyl). In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{L2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{L2} is $-OR^a$ (*e.g.*, $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-OMe$, $-OEt$, $-OPr$, $-OBu$, or $-OBn$), or $-O$ (substituted or unsubstituted phenyl) (*e.g.*, $-OPh$)). In certain embodiments, at least one instance of R^{L2} is $-SR^a$ (*e.g.*, $-SH$, $-S$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-SMe$, $-SEt$, $-SPr$, $-SBu$, or $-SBn$), or $-S$ (substituted or unsubstituted phenyl) (*e.g.*, $-SPh$)). In certain embodiments, at least one instance of R^{L2} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, $-NH$ (substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NHMe$), or $-N$ (substituted or unsubstituted C_{1-6} alkyl)-(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{L2} is $-CN$, $-SCN$, or $-NO_2$. In certain embodiments, at least one instance of R^{L2} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{L2} is $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, $-C(=O)NHMe$, or $-C(=O)NMe_2$). In certain embodiments, at least one instance of R^{L2} is $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, or $-NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{L2} is $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$.

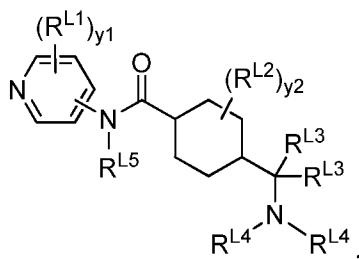
[00363] In certain embodiments, y_2 is 0. In certain embodiments, y_2 is 1. In certain embodiments, y_2 is 2. In certain embodiments, y_2 is 3. In certain embodiments, y_2 is 4. In certain embodiments, y_2 is 5. In certain embodiments, y_2 is 6. In certain embodiments, y_2 is

7. In certain embodiments, y2 is 8. In certain embodiments, y2 is 9. In certain embodiments, y2 is 10.

[00364] In certain embodiments, both instances of R^{L3} are the same. In certain embodiments, two instances of R^{L3} are different from each other. In certain embodiments, at least one instance of R^{L3} is hydrogen. In certain embodiments, each instance of R^{L3} is hydrogen. In certain embodiments, at least one instance of R^{L3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{L3} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, each instance of R^{L3} is independently hydrogen or substituted or unsubstituted alkyl.

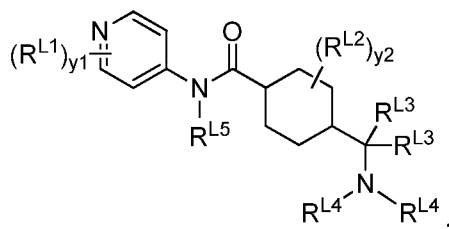
[00365] In certain embodiments, both instances of R^{L4} are the same. In certain embodiments, two instances of R^{L4} are different from each other. In certain embodiments, at least one instance of R^{L4} is hydrogen. In certain embodiments, each instance of R^{L4} is hydrogen. In certain embodiments, at least one instance of R^{L4} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, at least one instance of R^{L4} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00366] In certain embodiments, the compound of Formula (L) is of the formula:



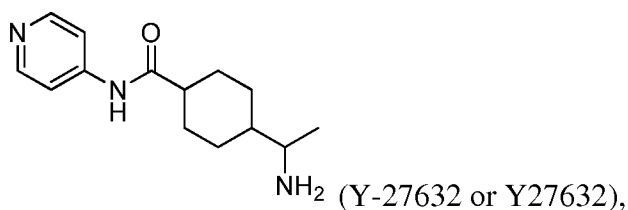
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00367] In certain embodiments, the compound of Formula (L) is of the formula:



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

[00368] In certain embodiments, the compound of Formula (L) is of the formula:



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

[00369] In certain embodiments, a compound of Formula (L) is not Y-27632, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof.

[00370] It is believed that compounds of Formula (L), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, are ROCK inhibitors.

[00371] In another aspect, the present disclosure provides a mixture of compounds described herein. In certain embodiments, the mixture of compounds include two or more compounds of any one of Formula (A) to (L), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein any two compounds of the mixture of compounds are of the same or different Formula (*e.g.*, any one of Formula (A) to (L)).

EXAMPLES

Materials and Methods

Culture conditions

[00372] Conventional (primed) human iPSC line C1 (Whitehead Institute Center for Human Stem Cell Research, Cambridge, MA) (Hockemeyer *et al.*, 2008) and human ESC lines WIBR2 and WIBR3 (Whitehead Institute Center for Human Stem Cell Research, Cambridge, MA) (Lengner *et al.*, 2010) (Lengner *et al.*, 2010) were maintained on mitomycin C inactivated mouse embryonic fibroblast (MEF) feeder layers and passaged using Collagenase (1 mg/mL) or manual methods. Primed human ESCs and human iPSCs were cultured in human ESC medium [DMEM/F12 (Invitrogen) supplemented with 15% fetal bovine serum (FBS) (Hyclone), 5% KnockOut Serum Replacement (Invitrogen), 1 mM glutamine (Invitrogen), 1% nonessential amino acids (Invitrogen), 0.1 mM β-mercaptoethanol (Sigma) and 4 ng/ml FGF2 (R&D systems)]. Naïve human ESCs/hiPSCs

were kept on mitomycin C-inactivated mouse embryonic fibroblast feeder cells, and were passaged by brief single-cell dissociation using Accutase (Gibco) every 5–10 days. Naïve human pluripotent cells were derived and maintained in serum-free N2B27-based media. 500 mL of medium was generated by including: 240 mL DMEM/F12 (Invitrogen; 11320), 240 mL Neurobasal (Invitrogen; 21103), 5 mL N2 supplement (Invitrogen; 17502048), 10 mL B27 supplement (Invitrogen; 17504044), 10 µg recombinant human LIF (made in-house), 1 mM glutamine (Invitrogen), 1% nonessential amino acids (Invitrogen), 0.1 mM β-mercaptoethanol (Sigma), penicillin-streptomycin (Invitrogen), 5 mg/mL BSA (Sigma), and the following small molecules and cytokines: PD0325901 (Stemgent, 1 µM), IM-12 (Enzo, 1 µM), SB590885 (R&D systems, 0.5 µM), WH4-023 (A Chemtek, 1 µM), Y-27632 (Stemgent, 10 µM) and Activin A (Peprotech, 20 ng/mL). To accelerate the kinetics of naïve cell induction FGF2 (R&D systems, 8 ng/mL) and 0.5% KSR (Gibco) were also included. Additional inhibitors described in this work include: CHIR99021 (Stemgent, 3 µM), SP600125 (R&D systems, 1 µM), PD173074 (Stemgent, 0.1 µM), SB431542 (Tocris, 5 µM) and BIRB796 (Axon Medchem, 2 µM). Tissue culture media were filtered using a low protein-binding binding 0.22 µm filter (Corning). Alternative formulations for naïve human ESC culture were followed as described previously (Chan *et al.*, 2013; Gafni *et al.*, 2013; Valamehr *et al.*, 2014; Ware *et al.*, 2014).

Gene targeting

[00373] Human ESCs and iPSCs were cultured in ROCK-inhibitor Y-27632 24 hours prior to electroporation. Cells were harvested using 0.25% trypsin/EDTA solution (Invitrogen) and 1×10^7 cells resuspended in phosphate buffered saline (PBS) were electroporated if not otherwise indicated with 40 µg of donor plasmids and 5 µg of each Talen encoding plasmid (Gene Pulser Xcell System, Bio-Rad; 250 V, 500 µF, 0.4 cm cuvettes (Costa *et al.*, 2007)). Cells were subsequently plated on MEF feeder layers (DR4 MEFs for puromycin selection) in human ESC medium supplemented with ROCK-inhibitor for the first 24 hours. Individual colonies were picked and expanded after puromycin selection (0.5 µg/ml) 10 to 14 days after electroporation. Correctly targeted clones were confirmed by southern blot (NdeI digested) and used for the removal of floxed PGK-puro cassette. Cells were harvested using 0.25% trypsin/EDTA solution (Invitrogen) and 1×10^7 cells resuspended in PBS were electroporated with pTurbo-Cre (40 µg; GenBank accession number AF334827) (Gene Pulser Xcell System, Bio-Rad; 250 V, 500 µF, 0.4-cm cuvettes). Cells were subsequently plated on MEF feeder layers at a low density in human ESC medium

supplemented with ROCK inhibitor. Individual colonies were picked 10–14 d after electroporation. The excision of PGK-puro was confirmed by Southern blot analysis.

Lentiviral infection

[00374] VSVG coated lentiviruses were generated in HEK-293 cells as described previously (Brambrink *et al.*, 2008; Soldner *et al.*, 2009; Soldner *et al.*, 2011). Briefly, culture medium was changed 12 hr post-transfection and virus-containing supernatant was collected 48 to 72 hr post transfection. Viral supernatant was filtered through a 0.45 mm filter. Virus-containing supernatants of the 2 reprogramming viruses (FUW-tetO-lox-hKLF2 and FUW-tetO-lox-hNANOG) were pooled and supplemented with the FUW-lox-M2rtTA virus and an equal volume of fresh culture medium. 1×10^6 human ESCs were seeded 24 hr before transduction in T75 flasks on matrigel in mTesr1 medium (STEMCELL Technologies). Two consecutive infections in the presence of 2 mg/ml of polybrene were performed over a period of 24 hr. Culture medium was changed 12 hr after the last infection. Five days after transduction, human ESCs were passaged using 0.25% trypsin/EDTA solution (Invitrogen) and re-plated on mitomycin C inactivated mouse embryonic fibroblast (MEF) feeder layers in conventional human ESC medium. To induce conversion to the naïve state, human ESCs were trypsinized and seeded at a density of 1×10^5 cells per 6 individual well on a MEF feeder layer in presence of ROCK inhibitor Y-27632. Medium was replaced 24 hr later with N2B27 basal medium supplemented with PD0325901 (Stemgent, 1 μ M), CHIR99021 (Stemgent, 3 μ M), 20 ng/mL hLIF (2i/L) and doxycycline (DOX) (Sigma-Aldrich; 2 mg/ml). OCT4- Δ PE-GFP+ human ESC colonies were picked manually within 10 days after DOX induction and passaged using Accutase (Gibco) on a MEF feeder layer. Upon the addition of 2i/L/DOX, latent OCT4- Δ PE-GFP-negative cells could be removed almost entirely by additional treatment with 0.1 μ M PD173074 and 5 μ M SB431542, which effectively inhibit the signaling pathways on which primed human ESCs are reliant. These additional inhibitors also facilitated the isolation of transgene-dependent naïve human ESCs from wild-type WIBR3 human ESCs.

Chemical screening

[00375] To screen for small molecules that support naïve human pluripotency, doxycycline was withdrawn from a clonal line of WIBR3 OCT4- Δ PE-GFP+ human ESCs derived in 2i/L/DOX. 24h after Dox withdrawal, cells were dissociated in 0.25% trypsin/EDTA solution (Invitrogen) and seeded at a density of 5000 cells per individual well

in 96 well plates on a MEF feeder layer in 2i/L supplemented with the ROCK-inhibitor Y-27632. After an additional 24h, 2i/L medium in each individual 96 well was supplemented with a kinase inhibitor from the LINCS inhibitor library (Gray Laboratory, Dana Farber Cancer Institute, Boston, MA) at a final concentration of 1 μ M. To improve experimental consistency the small molecule library was applied using the Caliper RapidPlate 96 well Liquid Handling System (Zymark, Westborough, MA). Briefly, a master plate containing 10 mM stock solution of the library in DMSO was first diluted to 100 μ M in HEPES aqueous solution (daughter plate), and subsequently to 10 μ M in N2B27 basal medium supplemented with 2i/L (granddaughter plate). This granddaughter plate was then diluted a further 10X in 2i/L medium, the final medium was pre-mixed and applied slowly to the 96 well assay plate. Following two medium changes during a seven day period the proportion of OCT4- Δ PE-GFP+ human ESCs in each well was assessed using the High-Throughput System on the LSRFortessa (Beckton-Dickinson, San Jose, CA). To screen for small molecules that improve the proportion of viable OCT4- Δ PE-GFP+ cells, this assay was modified by the addition of 1.0 μ M SB590885 to each well and inclusion of a 10 minute DAPI (Life Technologies) staining prior to high-throughput FACS analysis. Viable cells were gated from the DAPI-negative fraction and subsequently assessed for GFP status.

Immunostaining

[00376] Immunostaining was performed according to standard protocols using the following primary antibodies: Oct-3/4 (mouse monoclonal, Santa Cruz Biotechnology); hNANOG (Cat. No. AF1997, goat polyclonal, R&D Systems); AFP (Cat. No. A8452, mouse monoclonal, Sigma); HNF4a (goat polyclonal, Santa Cruz); Nestin (Cat. No. AB5922, mouse monoclonal, Milipore); Pax6 (Cat. No. PRB-278P, rabbit polyclonal, Covance); appropriate Alexa Fluor dye conjugated secondary antibodies (Invitrogen) were used. Nuclei were stained with DAPI (Life Technologies) and analyzed (LSM710, Zeiss; Eclipse Ti - Nikon). Images were taken using LSM710 confocal microscope (Zeiss) or Inverted microscope (Eclipse Ti - Nikon).

RNA FISH and imaging

[00377] RNA FISH was performed as outlined in (Faddah *et al.*, 2013; Raj *et al.*, 2010; Raj *et al.*, 2008). All hybridizations were performed in solution using probes coupled to either tetramethylrhodamine (TMR) (Invitrogen), Alexa 594 (Invitrogen) or Cy5 (GE Amersham). TMR was used for the probes against human Klf4 mRNA, Alexa 594 for the

probes against human Oct4, Rex1, and Nanog mRNA, and Cy5 for the probes against human Oct4 mRNA. Optimal probe concentrations during hybridization were determined empirically. Imaging involved taking stacks of images spaced 0.4 μm apart using filters appropriate for DAPI, TMR, Alexa 594 and Cy5. All images were taken with a Nikon Ti-E inverted fluorescence microscope equipped with a 100X oil-immersion objective and a Photometrics Pixis 1024 CCD camera using MetaMorph software (Molecular Devices, Downingtown, PA). During imaging, photobleaching was minimized through the use of an oxygen-scavenging solution using glucose oxidase. The cells were segmented manually and counted the number of fluorescent spots, each of which corresponds to an individual mRNA, using a combination of a semi-automated method described in (Itzkovitz *et al.*, 2011; Raj *et al.*, 2008) and custom software written in MATLAB (Mathworks).

RNA Extraction and Synthetic RNA Spike-In

[00378] Total RNA and sample preparation was performed as previously described (Loven *et al.*, 2012). Briefly, 1 million naïve or primed human ESCs were trypsinized and separated from GFP-labeled MEFs using the FACS Aria (Beckton-Dickinson) prior to lysis and RNA extraction. Biological duplicates were subsequently collected and homogenized in 1 ml of TRIzol Reagent (Life Technologies, 15596-026), purified using the mirVANA miRNA isolation kit (Ambion, AM1560) following the manufacturer's instructions and re-suspended in 100 μl nuclease-free water (Ambion, AM9938). Total RNA was spiked-in with ERCC RNA Spike-In Mix (Ambion, 4456740), treated with DNA-freeTM DNase I (Ambion, AM1906) and analyzed on Agilent 2100 Bioanalyzer for integrity. RNA with the RNA Integrity Number (RIN) above 9.8 was hybridized to GeneChip PrimeView Human Gene Expression Arrays (Affymetrix).

Microarray Sample Preparation and Analysis

[00379] For microarray analysis, total RNA samples were used for microarray expression analysis. 100 ng of total RNA was used to prepare biotinylated cRNA (cRNA) according to the manufacturer's protocol (30 IVT Express Kit, Affymetrix 901228). GeneChip arrays (Primeview, Affymetrix 901837) were hybridized and scanned according to standard Affymetrix protocols. The raw data was obtained by using Affymetrix Gene Chip Operating Software using default settings. A Primeview CDF provided by Affymetrix was used to generate .CEL files. The CEL files were processed with the *expresso* command to convert the raw probe intensities to probeset expression values with MAS5 normalization

using the standard tools available within the affy package in R. The probesets of the same gene were next collapsed into a single value to represent the gene by taking the mean value. Differential gene expression was determined using moderated t-statistic in the “limma” package (<http://bioinf.wehi.edu.au/limma/>) from Bioconductor (www.bioconductor.org) (Smyth, 2004). A gene was considered differentially expressed if it met the following criteria: 1) absolute log₂ fold- change ≥ 1 between the mean expression of the two condition, 2) adjusted p-value less than 0.1 by a moderated t-test within the limma package with BH multiple hypothesis testing correction.

[00380] The previously published expression profiles from the naïve human ES cells were also processed (GSM1139484 and GSM1139494) and primed ES cells (GSM1139488 and GSM1139495) from Gafni *et al.*, 2013. The Affymetric CDF file (version V1.r3) was used to generate .CEL files. The CEL files were processed with RMA normalization using the standard tools variable within the affy package in R. The p-values for differential gene expression analysis were determined using moderated t-statistic in the “limma” package (<http://bioinf.wehi.edu.au/limma/>) from Bioconductor (www.bioconductor.org) (Smyth, 2004).

Cross-Species Gene Expression Analysis

[00381] Cross-species gene expression analysis was performed as previously described (Gafni *et al.*, 2013) with some modifications. Previously published mouse ES cell and EpiSC cell gene expression datasets on an Agilent 4 X 44k array platform (GSE15603). Probeset mapping between the Agilent 4 X 44k array platform and Affymetric Primeview platform of human-mouse homologous genes was downloaded from Ensembl biomart (www.ensembl.org/biomart). The probesets of the same gene in human or mouse were next collapsed into a single value to represent the gene independently in each species by taking the mean value. The relative expression values from mouse and human were next calculated independently by dividing the expression values of the samples by the mean of expression values within the same genes across samples in the same species. Pair-wise comparisons were performed on the relative expression values from the human and mouse expression profiles using Pearson correlation coefficients (PCCs). The average linkage hierarchical clustering of the Pearson correlation was shown in the heatmap.

Chromatin Immunoprecipitation (ChIP)

[00382] Cells were crosslinked for 10 minutes at room temperature by the addition of one-tenth of the volume of 11% formaldehyde solution (11% formaldehyde, 50mMHEPES pH 7.3, 100mMNaCl, 1mMEDTA pH 8.0, 0.5mMEGTA pH 8.0) to the growth media followed by quenching with 100 mM glycine. Cells were washed twice with PBS, then the supernatant was aspirated and the cell pellet was flash frozen in liquid nitrogen. Frozen crosslinked cells were stored at -80C. 20 ul of Dynal magnetic beads (Sigma) were blocked with 0.5% BSA (w/v) in PBS. Magnetic beads were bound with 2ug of the indicated antibody. The antibodies used were as follows: H3K4me3 (Abcam ab8580) and H3K27me3 (Millipore 07-449). Crosslinked cells were lysed with lysis buffer 1 (50mMHEPES pH 7.3, 140mMNaCl, 1mMEDTA, 10% glycerol, 0.5% NP-40, and 0.25% Triton X-100) and resuspended and sonicated in sonication buffer (50 mM Tris-HCl [pH 7.5], 140mMNaCl, 1mMEDTA, 1% Triton X-100, 0.1% Na-deoxycholate, 0.1% SDS). Cells were sonicated at 4C with a Bioruptor (Diagenode) at high power for 25 cycles for 30 s with 30 s between cycles. Sonicated lysates were cleared and incubated overnight at 4_C with magnetic beads bound with antibody to enrich for DNA fragments bound by the indicated factor. Beads were washed two times with sonication buffer, one time with sonication buffer with 500 mM NaCl, one time with LiCl wash buffer (20 mM Tris pH 8.0, 1 mM EDTA, 250 mM LiCl, 0.5% NP-40, 0.5% Na-deoxycholate) and one time with TE with 50 mM NaCl. DNA was eluted in elution buffer (50 mM Tris-HCL pH 8.0, 10 mM EDTA, 1% SDS). Cross-links were reversed overnight. RNA and protein were digested using RNase A and Proteinase K, respectively and DNA was purified with phenol chloroform extraction and ethanol precipitation.

Illumina Sequencing and Library Generation

[00383] Purified ChIP DNA was used to prepare Illumina multiplexed sequencing libraries. Libraries for Illumina sequencing were prepared following the Illumina TruSeq DNA Sample Preparation v2 kit protocol with the following exceptions. After end-repair and A-tailing, Immunoprecipitated DNA (_10-50 ng) or Whole Cell Extract DNA (50 ng) was ligated to a 1:50 dilution of Illumina Adaptor Oligo Mix assigning one of 24 unique indexes in the kit to each sample. Following ligation, libraries were amplified by 18 cycles of PCR using the HiFi NGS Library Amplification kit from KAPA Biosystems. Amplified libraries were then size-selected using a 2% gel cassette in the Pippin Prep system from Sage Science set to capture fragments between 200 and 400 bp. Libraries were quantified by qPCR using

the KAPA Biosystems Illumina Library Quantification kit according to kit protocols. Libraries with distinct TruSeq indexes were multiplexed by mixing at equimolar ratios and running together in a lane on the Illumina HiSeq 2000 for 40 bases in single read mode.

Gene Sets and Annotations

[00384] All analysis was performed using RefSeq (NCBI37/HG19) (Pruitt *et al.*, 2007) human gene annotations.

ChIP-Seq Data Processing

[00385] All ChIP-Seq datasets were aligned using Bowtie (version 0.12.9) (Langmead *et al.*, 2009) to build version NCBI37/HG19 of the human genome using $-n2$, $-e70$, $-m2$, $-k2$, $--best$. The MACS version 1.4.1 (Model based analysis of ChIP-Seq) was used (Zhang *et al.*, 2008) peak finding algorithm to identify regions of ChIP-Seq enrichment over background. A p-value threshold of enrichment of $1e-9$ was used for all datasets.

Heatmap representation of read density profiles.

[00386] A gene was defined as Polycomb-associated if an enriched region for H3K27me3 (representing polycomb complexes) was located within ± 1 kb of the TSS. H3K27me3 is a histone modification associated with Polycomb complexes (Boyer *et al.*, 2006). The annotated TSS of Polycomb-associated genes were aligned at the center in the composite view of signal density profile. The average ChIP-seq read density (r.p.m./bp) around 5 kb centered on the centers in 50 bp bin was calculated.

Meta Representations of ChIP-Seq Occupancy

[00387] Genome-wide average “meta” representations of ChIP-seq occupancy of different factors were created by mapping ChIP-seq read density to Polycomb-associated genes. Three sets of regions were created: upstream, gene body and downstream. 80 equally-sized bins divided the -2000 to 0 promoter region, 200 equally-sized bins divided the length of the gene body, and 80 equally-sized bins divided the 0 to +2kb downstream region. The average ChIP-Seq factor density in each bin was calculated to create a meta genome-wide average in units of rpm/bp.

Differentiation assays

Teratoma formation

[00388] Single cell dissociations of naïve human ESCs were resuspended in 250 µl of medium and co-injected subcutaneously with 250 µl of matrigel in the flank of NOD/SCID mice. Tumors generally developed within 8 to 12 weeks and animals were sacrificed before tumor size exceeded 3 cm in diameter. Teratomas were isolated after sacrificing the mice and fixed in formalin. After sectioning, teratomas were diagnosed based on hematoxylin and eosin staining.

Directed differentiation into hepatocytes

[00389] Differentiation of naïve human ESCs into hepatocytes was obtained as described previously in conventional human ESCs (Si-Tayeb *et al.*, 2010). Single cells were cultivated on Matrigel coated plates (2 mg/ml) under low oxygen conditions. Differentiation was initiated by cultivating cells for 5 days in Activin A (100 ng/ml) containing RPMI/B27 medium under ambient oxygen, followed by 5 days in BMP4 (20 ng/ml)/ FGF-2 (10 ng/ml) containing RPMI/B27 and 5 days in HGF (20 ng/ml) containing RPMI/B27 under 5% oxygen. Finally cells were cultured for 5 days in Hepatocyte Culture Medium supplemented with Oncostatin-M (20 ng/ml) under ambient oxygen conditions. Generated hepatocytes were identified by expression of AFP, HNF4a and human Albumin.

Morula and blastocyst injection

[00390] Six to eight weeks old B6D2F1 females were superovulated with 7.5 I.U. of Pregnant Mare Serum (PMS) each given by intraperitoneal (IP) injections followed by an IP injection of 7.5 I.U. of Human Chorionic Gonadotropin (HCG) 46 to 48 hours later. They were then mated with B6D2F1 stud males and checked for copulatory plugs the following day. One-cell fertilized embryos were harvested and incubated at 37°C, 5% O₂ for 2-3 days in KSOM medium (Zenith Biotech). At the 8-cell, morula, and blastocyst stage, embryos were injected with 10-15 naïve human ESCs using a 16 µm piezo needle (Humagen). During injection, the human cells were kept continuously in drops of their own culture medium, whereas the embryos were kept in M2+ROCKi drops. After injection, the injected embryos were cultured in KSOM+ROCKi for 3-4 hours, then washed in 5 individual drops of KSOM and cultured overnight to the blastocyst stage. When the injected embryos reached the blastocyst stage, 20 embryos were transferred into each E2.5 p.c pseudopregnant female by uterine transfer. Seven to eight days later, the post-op females were sacrificed by CO₂ asphyxiation and embryos were harvested at E9.5-E10.5 p.c for analysis.

qRT-PCR

[00391] Total RNA was isolated using the Rneasy Kit (QIAGEN) and reversed transcribed using the Superscript III First Strand Synthesis kit (Invitrogen). Quantitative RT-PCR analysis was performed in triplicate using the ABI 7900 HT system with FAST SYBR Green Master Mix (Applied Biosystems). Gene expression was normalized to GAPDH. Error bars represent the standard deviation (SD) of the mean of triplicate reactions. Primer sequences are included in Table 1.

[00392] **Table 1. Primers used in this study**

Gene	Primer sequence (5'- 3')	Application	SEQ ID NO:
NANOG-F	GCAGAAGGCCTCAGCACCTA	RT-PCR	1
NANOG-R	AGGTTCCCAGTCGGGTTC		2
OCT4-F	GCTCGAGAAGGATGTGGTCC	RT-PCR	3
OCT4-R	CGTTGTGCATAGTCGCTGCT		4
SOX2-F	CACTGCCCCTCTCACACATG	RT-PCR	5
SOX2-R	TCCCATTTCCCTCGTTTTTCT		6
STELLA-F	GTTACTGGGCGGAGTTCGTA	RT-PCR	7
STELLA-R	TGAAGTGGCTTGGTGTCTTG		8
KLF4-F	GATGGGGTCTGTGACTGGAT	RT-PCR	9
KLF4-R	CCCCCAACTCACGGATATAA		10
GAPDH-F	CGAGATCCCTCCAAAATCAA	RT-PCR	11
GAPDH-R	ATCCACAGTCTTCTGGGTGG		12
REX1-F	GGAATGTGGGAAAGCGTTCGT	RT-PCR	13
REX1-R	CCGTGTGGATGCGCACGT		14
PRDM14-F	TGAGCCTTCAGGTCACAGAG	RT-PCR	15
PRDM14-R	ATTCCTATCGCCCTTGTCC		16
EGFP-F	AGAACGGCATCAAGGTGAAC	RT-PCR	17
EGFP-R	TGCTCAGGTAGTGGTTGTCG		18
FUW-KLF2-F	GATTTTGCTGGGTGTTT		19

Gene	Primer sequence (5' - 3')	Application	SEQ ID NO:
FUW-KLF2-R	CCACATAGCGTAAAAGGAGCA	RT-PCR	20
FUW-NANOG-F	GCTGGGGAAGGCCTTAATGT	RT-PCR	21
FUW-NANOG-R	CCACATAGCGTAAAAGGAGCA		22
PAX6-F	CTTTGCTTGGGAAATCCGAG	RT-PCR	23
PAX6-R	AGCCAGGTTGCGAAGAAGCTC		24

RESULTS

A reporter system for naïve human pluripotency based on *OCT4* distal enhancer activity

[00393] An important molecular signature of naïve pluripotency in the mouse system is the use of the distal enhancer (DE) of *OCT4*. This element controls *Oct4* expression in naïve mouse ESCs, pre-implantation mouse embryos and germ cells (Yeom *et al.*, 1996). In contrast, expression of *Oct4* in primed EpiSCs and the mouse post-implantation embryo is under control of the proximal enhancer (PE) element (Tesar *et al.*, 2007). To detect rare naïve human ESCs in a large population of primed cells, a reporter system for OCT4 DE activity was engineered using TALENs. The PE element was deleted in an OCT4-GFP allele that was previously established in WIBR3 primed human ESCs (Hockemeyer *et al.*, 2011) (Figure 1A and Figure 8A). TALENs were designed to cleave in the 5' end of the PE, together with a donor vector containing LoxP sites bordering a selectable marker and gene sequences homologous to those flanking the PE. After targeting the allele harbors an approximately 1Kb deletion of the PE sequence. Successful integration of this PE targeting vector (Figure 1B), and subsequent removal of the selection cassette (Figure 8A) were confirmed. As expected, deletion of the PE resulted in substantial attenuation of the OCT4-GFP signal (Figure 1C). Single molecule RNA FISH analysis in individual cells showed that GFP expression was diminished, while OCT4 expression was reduced approximately by 50%, following PE removal (Figure 1D). These changes in OCT4 and GFP expression demonstrate that OCT4 expression in primed human ESCs is primarily dependent on the PE, rather than the DE, as observed in mouse EpiSCs.

[00394] It was investigated whether overexpression of transcription factors specific to naïve pluripotency together with the application of serum-free 2i/L culture conditions would result in augmented OCT4-ΔPE-GFP activity. For this reason the transcription factors KLF2

and NANOG were overexpressed using doxycycline (DOX) inducible lentiviral expression vectors. Compared to its family members Klf4 and Klf5, Klf2 has enhanced capability to induce naïve pluripotency in mouse EpiSCs (Hall *et al.*, 2009). In addition, the homeodomain transcription factor Nanog is critical for the establishment of naïve pluripotency (Silva *et al.*, 2009) and can revert EpiSCs to the naïve state in the absence of kinase inhibition (Theunissen *et al.*, 2011). Consistent with the potent effects of these factors in the mouse system, combined overexpression of KLF2 and NANOG in primed human ESCs resulted in increased OCT4-ΔPE-GFP reporter levels in a fraction of cells (Figure 1E and Figure 8B). The appearance of high OCT4-ΔPE-GFP⁺ cells was strictly dependent on the expression of both factors, and could only be observed in presence of 2i/L/DOX. GFP⁺ colonies were clonally expanded on a mouse embryonic fibroblast (MEF) feeder layers in the presence of 2i/L/DOX, while retaining a dome-like colony morphology and pluripotency gene expression (Figure 1F and Figure 1G). Strikingly, withdrawal of DOX-dependent KLF2 and NANOG expression resulted in the rapid loss of colony morphology, appearance of differentiated cells and shutdown of OCT4-ΔPE-GFP reporter activity within 7 days (Figure 1F, *Right*). Thus, 2i/L culture conditions are insufficient to maintain the self-renewal of OCT4-ΔPE-GFP⁺ cells after withdrawal of exogenous factor expression. The rapid downregulation of naïve reporter activity provides a defined time window in which to screen for small molecules that support the maintenance of a putative naïve human pluripotent state.

[00395] The inability to maintain OCT4-ΔPE-GFP activity in 2i/L led us to further investigate the consequences of these culture conditions when applied directly to conventional human ESCs in the absence of transgene expression. In the mouse system dual MEK and GSK3 inhibition is thought to consolidate the ground state and eliminate EpiSCs and other differentiated phenotypes that cannot survive under these minimal conditions (Silva and Smith, 2008). In contrast, rapid expansion in serum-free 2i/L was observed of initially dome-shaped human ESC colonies that assumed a neural morphology upon further passaging (Figure 1H). Flow cytometric analysis revealed that weak levels of OCT4-ΔPE-GFP detected in primed human ESCs completely disappeared in 2i/L alone (Figure 1E). Consistent with the morphological change, the loss of OCT4 and NANOG expression and upregulation of NESTIN and PAX6 expression in primed human ESCs expanded in serum-free 2i/L medium was observed (Figure 1I and Figure 8C-D). These observations are in agreement with a report that 2i/L treatment induces differentiation of human ESCs into primitive neural stem cells (Hirano *et al.*, 2012). We conclude that 2i/L conditions do not interfere with expansion of differentiated cell types in human cells to the same extent as in the mouse system and are

consequently insufficient for stabilizing naïve human pluripotency (Figure 1J).

Identification of compounds that maintain naïve reporter activity upon transgene withdrawal

[00396] To identify compounds that sustain OCT4-ΔPE-GFP activity in the absence of KLF2 and NANOG expression, a kinase inhibitor library was screened in the presence of 2i/L for a period of 7 days after DOX withdrawal in 96 well format (Figure 2A). This screen identified 10 different hit compounds that partially rescued the proportion of GFP+ cells when assayed by high-throughput FACS analysis (Figure 2B-C and Figure 9A). Notable among these hits were four separate inhibitors of BRAF and four inhibitors of upstream receptor tyrosine kinases (RTKs), including DDR1, VEGFR1 and FGFR1. A validation experiment was then performed in 6 well format by withdrawing DOX and culturing the cells in 2i/L supplemented with each hit compound for up to 10 passages (Figure 2D). Nearly all hit compounds maintained a proportion of GFP+ cells similar to that observed with DOX. However, the BRAF inhibitor SB590885 preserved the best colony morphology and proliferation. In contrast, treatment with the FGF receptor inhibitor PD173074 or pan-RTK inhibitor WZ-4-145 resulted in maintenance of OCT4-ΔPE-GFP activity in colonies with a disorganized morphology. Gene expression analysis 5 passages after DOX withdrawal confirmed the absence of KLF2 and NANOG transgene expression and retention of endogenous OCT4 and GFP transcripts (Figure 2E and Figure 9B). To validate these findings in an independent system DOX-inducible KLF2 and NANOG transgenes were introduced in a line of wild-type WIBR3 human ESCs. Upon application of DOX and 2i/L, dome-shaped colonies appeared that could be expanded clonally. After DOX withdrawal these lines were maintained in 2i/L/SB590885 while retaining both colony morphology and the expression of endogenous *OCT4* (Figure 2F-H). Thus, high-throughput chemical screening identified a number of kinase inhibitors, most notably the BRAF inhibitor SB590885, that synergize with 2i/L to maintain OCT4-ΔPE-GFP reporter activity and pluripotency gene expression in human ESCs after removal of exogenous KLF2 and NANOG expression.

[00397] Using a FACS-based live/dead discrimination assay it was determined that cells maintained in 2i/L/SB590885 had reduced viability (Figure 9C). This led us to consider whether other small molecules could cooperate with 2i/L/SB590885 to improve the fraction of viable GFP+ cells. Inclusion of a live/dead assay enhanced the resolution of the 96 well high-throughput FACS analysis, allowing for more sensitive discrimination between the

proportion of viable OCT4-ΔPE-GFP+ cells cultured in 2i/L/DOX vs. 2i/L/SB590885 (Figure 3A). This viability assay was included in a modified screen in which GFP+ cells were cultured for two passages after DOX withdrawal in 2i/L/SB590885 supplemented with the kinase inhibitor library (Figure 3B-C and Figure 10A). This screen identified several hit compounds that improved the fraction of viable GFP+ cells, including the LCK/SRC inhibitor WH-4-023 (Figure 10B). A titration of the concentrations of PD0325901, CHIR99021 and SB590885 was also performed during two passages after DOX withdrawal followed by high-throughput FACS analysis (Figure 3D). A significant improvement was observed in the proportion of viable GFP+ cells using a concentration of 1 μM PD0325901, 0.3 μM CHIR99021 and 0.5 μM SB590885. Notably, lower concentrations of CHIR99021 improved the proportion of viable GFP+ cells, whereas higher concentrations of CHIR99021 had an opposite effect. This is reminiscent of recent evidence that lowered GSK3 inhibition reduces differentiation and enhances the self-renewal of rat ESCs (Meek *et al.*, 2013).

[00398] The proportion of viable OCT4-ΔPE-GFP+ cells after DOX withdrawal was further improved by combining optimized concentrations of PD0325901, CHIR99021 and SB590885 with 1 μM WH-4-023 (Figure 3F). The ROCK inhibitor Y-27632, which improved the proportion of viable GFP+ cells, was also included (Figure 10C). Finally, improved morphology upon long-term culture was observed without DOX by replacing CHIR99021 with an alternative GSK3 inhibitor, IM12 (Figure 3G and Figure 10D). Pluripotency of putative naïve human ESCs maintained under these conditions was confirmed by generation of high-grade teratomas including tissues representing all three germ layers after subcutaneous injection in NOD/SCID mice (Figure 3H). In summary, a combination of five compounds have been provided, including inhibitors of MEK, GSK3, BRAF, ROCK and SRC, that supports the expansion of viable OCT4-ΔPE-GFP+ human pluripotent cells after removal of exogenous transcription factor expression.

Derivation of genetically unmodified naïve human ESCs in 5i/L

[00399] The consequences of applying the optimized 5i/L medium to conventional human ESCs was investigated in the absence of ectopic factor expression. Not surprisingly, this highly selective inhibitor cocktail generated widespread cell death within 2 days of treatment. However, the emergence of a small number of dome-shaped colonies was observed within 10 days that were positive for the OCT4-ΔPE-GFP reporter allele (Figure 4B). In addition, these colonies were efficiently isolated and clonally expanded after dissociation in trypsin (Figure 4B). The appearance of these OCT4-ΔPE-GFP+ cells using the optimized chemical conditions suggested that genetic manipulation, such as

overexpression of KLF2 and NANOG, may be dispensable for driving primed human ESCs to the naïve state. However, the slow and inefficient kinetics of this chemical conversion event led us to consider whether providing additional growth factor support might boost the efficiency of naïve cell induction. Provision of 5i/L supplemented with FGF and Activin A (5i/L/FA) enhanced the kinetics of OCT4-ΔPE-GFP induction (Figure 4C), and enabled conversion of wild-type WIBR2 primed human ESCs into a cell state with identical morphology and normal karyotype (Figure 4D and Figure 11A). Given the selective nature of the 5i culture regimen, it is speculated that additional growth factor support prolongs the time window during which primed human ESCs are amenable to convert to the naïve state. Consideration was taken toward culture conditions and if they would support the direct derivation of novel ESC lines from human blastocysts. Application of 5i/L/FA to human blastocyst outgrowths resulted in the establishment of a human ESC line with a similar dome-shaped colony morphology and normal karyotype (Figure 4E and Figure 11B). Hence, 5i/L/FA promotes induction of OCT4-ΔPE-GFP activity in the absence of reprogramming transgenes, and the derivation of putative naïve human ESCs directly from blastocysts.

[00400] To investigate the relative contribution of individual components in 5i/L/FA medium, single kinase inhibitors or growth factors were removed from a clonal line of OCT4-ΔPE-GFP⁺ cells derived in the absence of transgenes. Withdrawal of the MEK inhibitor PD0325901 or BRAF inhibitor SB590885 resulted in the rapid and widespread loss of colony morphology (Figure 11C), OCT4-ΔPE-GFP reporter activity (Figure 4F) and pluripotency gene expression (Figure 4G). Withdrawal of the SRC inhibitor WH-4-023 caused a change in morphology (Figure 11C) and slight reduction in OCT4-ΔPE-GFP reporter activity (Figure 4F). In addition, withdrawal of the ROCK inhibitor Y-27632 caused a significant reduction in proliferation (Figure 11C). On the other hand, withdrawal of FGF had no apparent effect by any of the parameters examined, which is consistent with this growth factor being involved in the maintenance of primed pluripotency. Similarly, withdrawal of Activin A did not cause a reduction in OCT4-ΔPE-GFP activity (Figure 4F). However, more differentiation and reduced expression was observed of pluripotency genes when FGF and Activin A were removed together (Figure 4G and Figure 11C). Surprisingly, reporter activity and pluripotency gene expression were unaffected by the removal of either GSK3 inhibition or hLIF (Figure 4F-G). Therefore, the maintenance of OCT4-ΔPE-GFP reporter activity is dependent primarily on MEK inhibition and BRAF inhibition, while robust proliferation of GFP⁺ cells requires ROCK inhibition. Recombinant FGF enhances the induction of naïve reporter activity, but can be omitted in established GFP⁺ cells.

Evaluation of alternative culture systems for naïve human pluripotency

[00401] Recently, several groups reported alternative conditions for inducing a naïve pluripotent state in conventional human ESCs (Chan *et al.*, 2013; Gafni *et al.*, 2013; Valamehr *et al.*, 2014; Ware *et al.*, 2014). Comparison of the culture components in these studies with the media shows both commonalities and differences (Figure 5A). All previously published protocols for naïve human pluripotency include 2i. Another ubiquitous component is FGF, which is added either as a recombinant protein (Gafni *et al.*, 2013; Valamehr *et al.*, 2014; Ware *et al.*, 2014) or present at high levels in mTesp basal medium (Chan *et al.*, 2013). However, the use of additional FGF-Raf-Erk inhibitors, the primary hits from the kinase inhibitor screen, was not previously reported. Furthermore, while these studies considered various criteria for defining naïve human pluripotency, endogenous *OCT4* distal enhancer activity was not assessed. Therefore, it was examined whether previously published culture conditions for naïve human pluripotency could activate the reporter system. Remarkably, increased levels of OCT4-ΔPE-GFP activity were exclusively observed upon application of 5i/L/A (Figure 5B). Whereas the naïve conditions described in Gafni *et al.* (2013) were capable of maintaining regular OCT4-GFP reporter activity after removal of KLF2 and NANOG expression, these conditions did not maintain OCT4-ΔPE-GFP activity (Figure 5C). This result is consistent with the observation that none of six JNK inhibitors and seven p38 MAP kinase inhibitors present in the kinase inhibitor library showed ability to maintain OCT4-ΔPE-GFP activity after withdrawal of KLF2 and NANOG expression (Figure 2B and Figure 9A). These findings suggest that the combination of kinase inhibitors induces a novel and distinct state of human pluripotency.

[00402] The kinase inhibitors reported by Hanna and colleagues may have an additive effect in combination with the 5i/L/A medium. Inclusion of the JNK inhibitor SP600125 and/or p38 MAP kinase inhibitor BIRB796 did not affect the proportion of OCT4-ΔPE-GFP+ cells (Figure 12A). However, an increase in expression of *KLF4* and *KLF2* was observed upon addition of SP600125 (Figure 12B). A beneficial effect was not observed when adding insulin (Figure 12A and Figure 5C). Another difference between the naïve human studies reported to date is the use of 20% knock-out serum replacement (KSR) or Albumax-containing medium (Gafni *et al.*, 2013; Valamehr *et al.*, 2014; Ware *et al.*, 2014) vs. serum-free N2B27 medium (this study). The consequences of applying the inhibitor cocktail in the presence of 20% KSR was therefore investigated. Remarkably, this switch in basal medium resulted in the rapid attenuation of OCT4-ΔPE-GFP signal concomitant with morphological

changes (Figure 5D and Figure 12C). Hence, a high concentration of KSR appears to be detrimental to naïve reporter activity, independent of additional kinase inhibition. In fact, a reduction in pluripotency gene expression was observed upon provision of KSR or FBS at concentrations >5% (Figure 5E). However, including 0.5-1% KSR in combination with 5i/L, JNKi and Activin A (6i/L/A) enhanced the efficiency of OCT4-ΔPE-GFP induction from the primed state (Figure 5F). It is concluded that the induction and maintenance of OCT4-ΔPE-GFP⁺ human ESCs is highly sensitive to the choice of basal medium.

Molecular characterization of naïve human pluripotency

[00403] To characterize the gene expression profile of naïve human ESCs derived under the conditions, RNA was collected from WIBR2 and WIBR3 human ESCs cultured in primed medium or 6i/L/A, and embryo-derived naïve WIN1 cells cultured in 5i/L/A or 6i/L/A. Expression analysis on Affymetrix arrays were then performed using RNA spike-in normalization (Loven *et al.*, 2012). Cross-species gene expression comparison demonstrated that primed WIBR2 and WIBR3 human ESCs clustered with primed mouse EpiSCs, while naïve human ESCs cultured in 5i/L/A or 6i/L/A clustered with naïve mouse ESCs (Figure 6A). The naïve human ESC samples clustered together closely, and addition of the JNK inhibitor had little impact on overall gene expression in the naïve state (Figure 6A). The most upregulated gene ontology (GO) categories in the naïve state were associated with transcriptional control, while the most down-regulated categories were implicated in neural differentiation and cell adhesion (Figure 6B). Comparison with the gene expression data published by Gafni *et al.* (2013) indicated that the conditions for naïve human pluripotency induce greater transcriptional differences with the primed state (Figure 6C). In particular, 3238 differentially expressed genes (DEGs) were observed compared to primed human ESCs, whereas Gafni *et al.* reported 831 DEGs (where log₂fold change > 1 and < -1 & p<0.05). Intriguingly, the naïve human ESCs exhibited marked downregulation of the transcription factors *OTX2* and *ZIC2/3*, which were recently shown to direct Oct4 to primed state-specific enhancer sites in mouse EpiSCs (Buecker *et al.*, 2014). In contrast, these transcription factors were slightly upregulated in the naïve human ESCs reported by Gafni *et al.* (2013). The list of differentially expressed genes was examined for presence of bona fide markers of naïve pluripotency. A number of transcription factors typically associated with the self-renewal and pluripotency of mouse ESCs ranked among the most highly upregulated genes in 5i/L/A or 6i/L/A, including *DPPA5*, *DPPA3* (also known as *STELLA*), *DPPA2*, *REX1*, *KLF4*, *KLF5*, *TFCP2L1*, and *NANOG* (Figure 6D-E). Expression of these factors was largely unaffected in

the conditions for naïve human pluripotency described by Gafni *et al.* (2013) (Figure 6D). Upregulation of transcripts specific to naïve pluripotency under the conditions was confirmed by qRT-PCR (Figure 6F and Figure 13A). A recent single cell RNA-Seq analysis revealed that these markers of naïve pluripotency were highly upregulated at the morula and epiblast stages of human pre-implantation development compared to conventional (primed) human ESCs (Yan *et al.*, 2013) (Figure 13B). This suggests that 5i/L/A culture re-establishes an early pre-implantation epiblast-specific gene expression signature that is lost during derivation of human ESCs under conventional conditions. Hence, the conditions induce a unique transcriptional profile in human ESCs, characterized by upregulation of naïve-specific transcription factors and suppression of neural differentiation genes.

[00404] A defining feature of ground state pluripotency in the mouse system is that transcriptional regulators such as *Nanog* are expressed homogeneously (Wray *et al.*, 2010). In contrast, human ESCs under conventional conditions are known to exhibit significant variability in gene expression at the single cell level (Hough *et al.*, 2009). It was therefore investigated whether human ESCs cultured under the conditions are more homogeneous with respect to expression of *NANOG* by single molecule (sm) RNA FISH analysis. The mean number of *OCT4* mRNAs per cell was approximately similar between WIBR2 human ESCs in primed medium, the naïve medium of Gafni *et al.* (2013), and 5i/L/A (Figure 6G). As expected from array and qRT-PCR analyses (Figure 6D and Figure 6F), the mean number of *NANOG* mRNAs per cell was significantly higher in 5i/L/A (Figure 6G-H). Intriguingly, 5i/L/A culture also resulted in reduced cell-to-cell variability in *NANOG* expression (Figure 13C). Thus, the increased expression level of *NANOG* in 5i/L/A does not arise from a subset of cells, but is uniform across the population. It was also confirmed by RNA FISH that single cells cultured in 5i/L/A express significantly higher numbers of *KLF4* and *REX1* mRNAs (Figure 6H).

[00405] Chromatin immunoprecipitation was performed followed by DNA sequencing (ChIP-Seq) analysis to determine the genome-wide distribution of the activation-associated marker, trimethylation of histone 3 lysine 4 (H3K4me3) and the transcriptional-silencing-associated marker, trimethylation of histone 3 lysine 27 (H3K27me3). Developmental genes with bivalent domains marked by the presence of both H3K4me3 and H3K27me3 in the primed state, such as *HOXA9*, *FOXA2*, *GATA6* and *NKX2.5*, exhibited a reduced H3K27me3 signal in the naïve state (Figure 7A). The histone methylation profile at loci encoding naïve-specific pluripotency regulators was then examined. *KLF2*, *KLF4* and *KLF5* were bivalent in the primed state, but almost entirely lost the H3K27me3 mark in the naïve state (Figure 7B).

Other markers of ground state pluripotency that are highly upregulated in the system, such as *DPPA5*, *DPPA3* and *REX1*, acquired H3K4me3 signal during conversion from primed to naïve pluripotency (Figure 7C). The core pluripotency determinants *OCT4*, *SOX2* and *NANOG* were marked exclusively by H3K4me3 in naïve and primed human ESCs (Figure 7D). However, a slightly higher H3K4me3 signal was observed at the *NANOG* promoter in the naïve state, consistent with increased transcription (Figure 6A). Finally, while H3K27me3 was generally depleted from promoter regions in the naïve state, some genes that were strongly down-regulated acquired H3K27me3 signal (Figure 7E). Consistent with observations in naïve pluripotent mouse ESCs (Marks *et al.*, 2012), H3K27me3 was strongly reduced at the transcriptional start site (TSS) of Polycomb group target genes in human ESCs cultured in 6i/L/A (Figure 7F-G). It is concluded that the conversion from primed to naïve human pluripotency is accompanied by the dynamic rearrangement of activating and repressive histone modifications. In particular, transcriptional upregulation of specific regulators of ground state pluripotency is associated with the gain of H3K4me3 or loss of H3K27me3 in a locus-specific manner.

Developmental potential of human ESCs in 5i/L/A

[00406] The classical assay for pluripotency of human ESCs and iPSCs is to examine teratomas formed after subcutaneous injection in NOD/SCID mice. Naïve human ESCs converted under the optimized conditions contributed to high-grade teratomas containing tissues representing all three germ layers, regardless of the presence of FGF and Activin in the medium (Figure 14A). As the practical utility of human pluripotent stem cells resides mainly in the capacity to differentiate into defined lineages *in vitro*, the suitability of naïve human ESCs in directed differentiation was also investigated. For this purpose human ESCs derived from WIBR2 and WIBR3 primed cells in 5i/L/A were subjected to a five-step protocol for hepatic differentiation (Si-Tayeb *et al.*, 2010). Hepatocytes positive for the mature markers AFP and HNF4a were generated from both lines of naïve ESCs (Figure 14B).

[00407] In the mouse system, naïve ESCs are functionally distinguished by the capability to colonize the embryo and contribute to chimeric animals. In contrast, primed EpiSCs contribute only very inefficiently to chimeras (Brons *et al.*, 2007; Tesar *et al.*, 2007). Hanna and colleagues reported that human ESCs cultured in the presence of 2i, hLIF, JNK inhibition, p38 inhibition, FGF and TGFβ contributed robustly to interspecies chimeric embryos after injection into mouse morulae (Gafni *et al.*, 2013). This assay would provide a defining functional read-out for naïve human pluripotency. Therefore, a reproduction this

experiment was attempted using human ESCs containing constitutive GFP and tdTomato transgenes in the AAVS1 locus. In total, 860 embryos (8-cell, morula and blastocyst stages) were injected with GFP and tdTomato-labeled human ESCs cultured in 5i/L/A. 436 embryos were also injected with C1-AAVS1-GFP cells provided by the Hanna laboratory, which were cultured using the conditions reported by Gafni *et al.* (2013). Only a fraction of embryos (43-45%) were recovered from both experimental groups at E10.5, suggesting that the majority of embryos had been reabsorbed. No fluorescent signal was detected by microscopy in any embryos recovered at E10.5 (Figure 14C). Thus, contribution of human ESCs in 5i/L/A or the medium of Gafni *et al.* (2013) to interspecies chimeras is currently too inefficient for detection by standard visual inspection. The development of novel optical clearing methods may facilitate the investigation of low-contribution interspecies chimerism in the future.

[00408] The proliferation of naïve human embryonic stem cells was found to be enhanced by the reduction or removal of GSK3 inhibition. A transgene-dependent naïve human embryonic stem (ES) cell line, a subclone of WIBR3, was used to titrate different concentrations of inhibitors in 5i/L/A (see Theunissen *et al.*, Cell Stem Cell, 2014). The cell line used is dependent on Doxycycline (DOX) to maintain the expression of two lentiviral transgenes, KLF2 and NANOG. Flow cytometry revealed that proportion of cells positive for the OCT4-ΔPE-GFP reporter in 2i/L/DOX was approximately 60% (Figure 15A). The cell line was karyotyped, and showed a normal (46, XX) karyotype. A titration assay was performed to determine the optimal concentrations of small molecule inhibitors to maintain naïve human DES cells. The cells were subject to sequential passaging by single cell dissociation at low density (1:10) under four conditions: 2i/L, 5i/L/A, t5i/L/A (0.2 μM GSK3 inhibitor IM12) and 4i/L/A (removal of GSK3 inhibitor IM12). Flow cytometry demonstrated that the two latter conditions showed higher proportions of cells positive for the OCT4-ΔPE-GFP reporter (Figure 15B). Quantitative RT-PCR was performed, and it confirmed the downregulation of exogenous KLF2 and NANOG transgenes and the primed marker VIMENTIN, as well as the upregulation of naïve markers, including KLF4, REX1 and STELLA in t5i/L/A and 4i/L/A (Figure 15C).

[00409] The proliferation of naïve human ES cells in the presence of different Wnt signal modulators was quantified after the withdrawal of DOX from the transgene-dependent cell line described above. In a six-well plate, 1×10^5 cells were seeded per well and cells were dissociated and re-seeded at a 1:5 density for three successive passages. Cell numbers at successive passages were recorded under six conditions (n=2 per group): 2i/L/DOX (control), 2i/L, 5i/L/A, 4i/L/A (removal of GSK3 inhibitor IM12), 4i/L/A+CHIR99021 (1 μM), and

4i/L/A+IWR1 (2.5 μ M). The proliferation was significantly elevated in 4i/L/A compared to 5i/L/A at passages 2 and 3 (Figure 16). Replacing IM12 with an alternative GSK3 inhibitor, CHIR99021, or addition of the Wnt inhibitor, IWR1, did not further stimulate the proliferation of naïve human cells, demonstrating that the reduction or removal of GSK3 inhibitors further enhances human ES cell proliferation.

[00410] The induction of naïve human pluripotency in 5i/L/A or 4i/L/A is associated with X chromosome reactivation. Using TALEN-mediated targeting of both alleles of the X-linked MECP2 gene, a fluorescent reporter system for the X chromosome status of human ES cells was established (Figure 17A). Conversion of the naïve state in 5i/L/A or 4i/L/A (-IM12) results in activation of the tdTomato-labeled allele and GFP activity is maintained, regardless of whether the starting color is tdTomato-positive (Figure 17C) or GFP-positive (Figure 17B). Therefore, the induction of naïve human pluripotency results from a switch toward biallelic expression of X-linked genes.

DISCUSSION

[00411] The morphological, molecular and functional similarity between human ESCs and mouse post-implantation epiblast-derived EpiSCs has prompted widespread interest in capturing the equivalent of a naïve pluripotent stem cell in humans. At the outset of this study, it was considered that the identification of putative naïve human ESCs would be greatly facilitated by the availability of a selective reporter system. In the mouse, enhancer-specific regulation of *Oct4* expression is a defining molecular distinction between ESCs and EpiSCs *in vitro* (Brons *et al.*, 2007; Tesar *et al.*, 2007), and between the ICM and post-implantation epiblast *in vivo* (Yeom *et al.*, 1996). The primed-specific PE from an *OCT4-GFP* allele were deleted using TALEN-mediated genome editing in human ESCs (Hockemeyer *et al.*, 2011). The observation that OCT4-GFP expression was down-regulated following PE removal demonstrated that this reporter behaves as expected in the primed state. Conversely, OCT4- Δ PE-GFP activity was strongly induced by combined overexpression of KLF2 and NANOG. A systematic approach was then taken to screen a diverse collection of 230 kinase inhibitors for the capacity to maintain OCT4- Δ PE-GFP activity after removal of ectopic KLF2 and NANOG expression. Through iterative screening a combination of five kinase inhibitors were identified that maintained viable GFP-positive cells upon transgene withdrawal. Moreover, this kinase inhibitor cocktail was capable of inducing OCT4- Δ PE-GFP activity when applied directly to conventional (primed) human ESCs in the complete absence of reprogramming factors.

[00412] Previous studies describing the isolation of naïve human ESCs also reported transgene-free interconversion from primed to naïve pluripotency (Chan *et al.*, 2013; Gafni *et al.*, 2013; Valamehr *et al.*, 2014; Ware *et al.*, 2014). However, these published protocols did not induce OCT4-ΔPE-GFP activity. This finding was surprising given that Gafni *et al.* (2013) reported activation of luciferase and BAC reporter constructs under the control of the DE of human *OCT4*, while Ware *et al.* (2014) observed increased DNaseI hypersensitivity at the DE in human ESCs derived in 2i and FGF. Thus, the activation of the DE of endogenous *OCT4* may represent a more stringent criterion for the naïve pluripotent state. A difference in the kinetics of conversion was noticed using previously reported protocols: whereas the emergence of naïve colonies under the conditions is a relatively protracted process (ca. 10 days) that occurs after widespread cell death, the application of previously described naïve conditions was accompanied with little cell death and rapid expansion in primed human ESCs. The slow kinetics of conversion observed in 5i/L/A are consistent with a reprogramming event towards a novel cellular state, rather than adaptation to an identity closer to conventional (primed) human ESCs. Thus, the observations suggest that the chemical screens used in this study have identified a distinct and novel state of human pluripotency.

[00413] There are several important differences in the selection of inhibitors, growth factors and basal medium between this protocol and previously reported protocols for capturing naïve human pluripotency. First, the primary screen for maintenance of OCT4-ΔPE-GFP activity identified a number of inhibitors of BRAF and upstream RTKs, including VEGFR1/2, FGFR1 and EGFR. These targets were not previously implicated in the establishment of naïve human pluripotency. The requirement for further inhibition of FGF-Ras-MEK signaling contrasts with the dependence on FGF signaling reported in the published protocols. In the mouse system, independence of FGF signaling is considered to be a hallmark of ground state pluripotent cells, which are primed for commitment by auto-inductive Fgf4/Erk signaling (Silva and Smith, 2008). While recombinant FGF facilitated the conversion of primed human ESCs into OCT4-ΔPE-GFP-positive cells, the removal of FGF did not affect reporter activity or pluripotency gene expression in established OCT4-ΔPE-GFP-positive cells.

[00414] Unlike previous approaches for capturing transgene-independent naïve human ESCs, the protocol uses serum-free N2B27 basal medium. This basal medium was originally used in neural differentiation, but was subsequently adapted by the Smith laboratory to develop fully defined conditions for self-renewal of mouse ESCs in combination with LIF

and BMP4 (Ying *et al.*, 2003) or 2i (Ying *et al.*, 2008). Maintenance of OCT4-ΔPE-GFP activity is highly sensitive to the choice of basal medium: addition of as little as 5% FBS or KSR resulted in attenuation of the GFP signal concomitant with a reduction in pluripotency gene expression. However, a low percentage (<1%) of KSR improved the kinetics of inducing GFP-positive cells from the primed state. Thus, previously proposed basal media for naïve human ESCs do not appear to support the maintenance of OCT4-ΔPE-GFP reporter activity.

[00415] Transcriptional profiling of human ESCs cultured in 5i/L/A and primed human ESCs indicated that the conditions induce a dramatic upregulation in the expression of transcription factors typically associated with naïve pluripotency, suggesting that induction of endogenous OCT4-ΔPE-GFP activity correlates with a broader expression signature of the naïve state. Intriguingly, many of the top-ranked differentially expressed genes were also enriched during human pre-implantation development, specifically at the morula and epiblast stages, in comparison to conventional human ESCs (Yan *et al.*, 2013). These transcripts include several factors that possess the capability to instate the naïve pluripotent program in mouse EpiSCs, such as *KLF4* (Guo *et al.*, 2009), *NANOG* (Silva *et al.*, 2009), and *TFCP2L1* (Martello *et al.*, 2013; Ye *et al.*, 2013). The latter gene is of particular interest as it was identified as the main effector downstream of LIF-STAT3 signaling in naïve mouse ESCs. Induction of *TFCP2L1* provides a rationale for the surprising observation that withdrawal of hLIF does not affect OCT4-ΔPE-GFP activity or pluripotency gene expression in the naïve human ESCs. Strong upregulation of *REX1* and *STELLA* were also observed, both of which are used as reporters of ground state pluripotency in the mouse system (Hayashi *et al.*, 2008; Marks *et al.*, 2012). Of further interest is that the conditions for naïve human pluripotency induced significant downregulation of *OTX2* and *ZIC2/3*, which drive primed-specific enhancer binding of Oct4 in mouse EpiSCs (Buecker *et al.*, 2013). In contrast, these transcription factors were upregulated in the naïve human ESCs reported by Gafni *et al.* (2013), while typical markers of naïve pluripotency such as *NANOG*, *KLF2*, *KLF4*, *STELLA*, *REX1* and *TFCP2L1* were not induced.

[00416] Human ESCs can be expanded in the presence of 2i and various additional inhibitors and growth factors while maintaining a dome-shaped morphology and expression of some pluripotency genes (Gafni *et al.*, 2013; Valamehr *et al.*, 2014; Ware *et al.*, 2014). These protocols offer practical advantages, including enhanced proliferation and single cell cloning, which benefit applications such as gene targeting. As such, these studies facilitate the application of human iPSCs in disease modeling and regenerative medicine. The state of

pluripotency defined here is based on activation of the endogenous OCT4-ΔPE-GFP allele along with a transcriptional and epigenomic profile that closely resembles naïve mouse pluripotency, and is distinct from previously reported naïve human ESCs.

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EQUIVALENTS AND SCOPE

- [00463] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.
- [00464] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that

is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00465] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00466] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

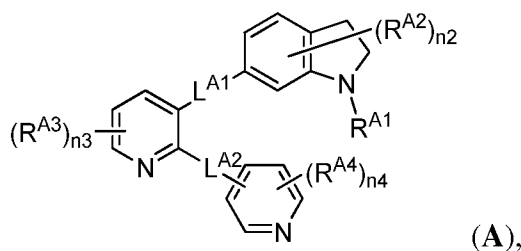
CLAIMS

What is claimed is:

1. A method for changing the pluripotency state of a vertebrate cell to a more naïve state, the method comprising:
culturing a pluripotent vertebrate cell in the presence of a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor; and
maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of culturing step.
2. The method of claim 1, wherein the cell is cultured and maintained in the presence of a mitogen-activated protein kinase kinase (MEK) inhibitor.
3. The method of claims 1 or 2, wherein the cell is cultured and maintained in the presence of a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor.
4. The method of any one of claims 1-3, wherein the cell is cultured and maintained in the presence of a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor.
5. The method of any one of claims 1-3, wherein the cell is cultured and maintained in the presence of a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor.
6. The method of any one of claims 1-3, wherein the cell is cultured and maintained in the presence of a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor.
7. The method any one of claims 1-3, wherein the cell is cultured and maintained in the presence of a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor.

8. A method for changing the pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (A):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of culturing step;

wherein:

L^{A1} is a substituted or unsubstituted, saturated or unsaturated, C_{1-4} aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{A5}-$, $-N=$, or $=N-$, wherein each instance of R^{A5} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

L^{A2} is a substituted or unsubstituted, saturated or unsaturated, C_{1-6} aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{A6}-$, $-N=$, or $=N-$, wherein each instance of R^{A6} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

R^{A1} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{A2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^a are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

n_2 is 0, 1, 2, 3, 4, 5, 6, or 7;

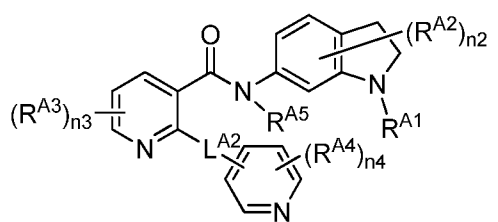
each instance of R^{A3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

n_3 is 0, 1, 2, or 3;

each instance of R^{A4} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

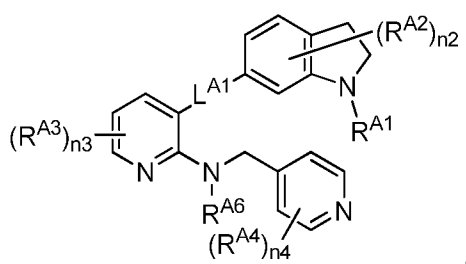
n_4 is 0, 1, 2, 3, or 4.

9. The method of claim 8, wherein the compound is of the formula:



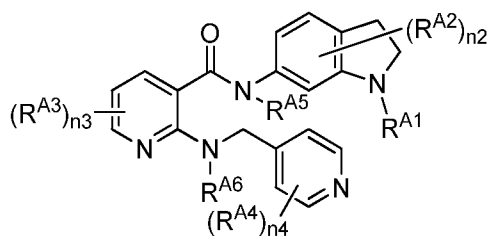
or a pharmaceutically acceptable salt thereof.

10. The method of claim 8, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

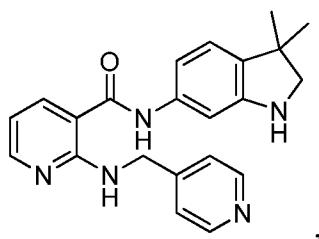
11. The method of claim 8, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

12. The method of any one of any one of claims 8-11, wherein R^{A1} is hydrogen.
13. The method of any one of claims 8-12, wherein at least one instance of R^{A2} is substituted or unsubstituted alkyl.
14. The method of any one of claims 8-13, wherein $n3$ is 0.
15. The method of any one of claims 8-14, wherein $n4$ is 0.
16. The method of any one of claims 8-15, wherein at least one instance of R^{A5} is hydrogen.
17. The method of any one of claims 8-16, wherein at least one instance of R^{A6} is hydrogen.

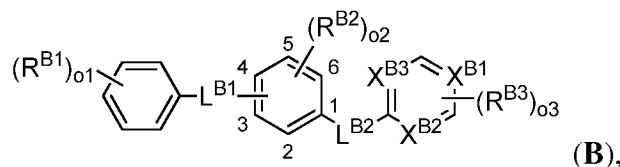
18. The method of claim 8, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

19. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (B):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing; wherein:

L^{B1} is $-N(R^{B4})C(=O)-$, $-C(=O)N(R^{B4})-$, or $-N(R^{B4})C(=O)N(R^{B4})-$, wherein each instance of R^{B4} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

when L^{B1} is $-N(R^{B4})C(=O)-$ or $-C(=O)N(R^{B4})-$, L^{B1} is directly attached to the carbon atom labeled with 3 or 5;

when L^{B1} is $-N(R^{B4})C(=O)N(R^{B4})-$, L^{B1} is directly attached to the carbon atom labeled with 4;

L^{B2} is $-O-$, $-S-$, $-NR^{B5}-$, or $-C(R^{B6})_2-$, wherein R^{B5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group; and each instance of R^{B6} is independently hydrogen, halogen, or substituted or unsubstituted alkyl;

each of X^{B1} , X^{B2} , and X^{B3} is independently N or CR^{B7} , wherein each instance of R^{B7} is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl,

substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

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

each instance of $\text{R}^{\text{B}1}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

$o1$ is 0, 1, 2, 3, 4, or 5;

each instance of $\text{R}^{\text{B}2}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

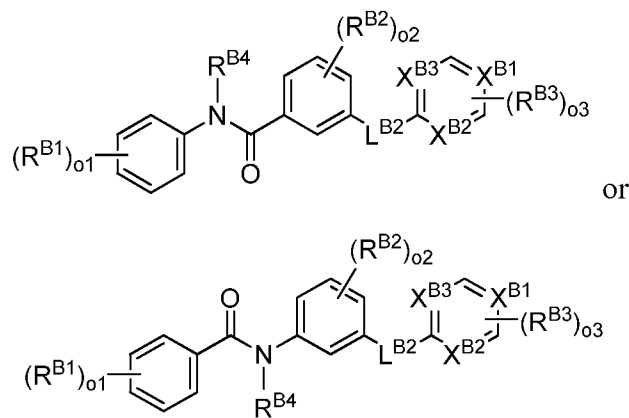
$o2$ is 0, 1, 2, 3, or 4;

each instance of $\text{R}^{\text{B}3}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

OC(=O)OR^a, or -OC(=O)N(R^a)₂, or an instance of R^{B3} and an instance of R^{B7} are joined to form a substituted or unsubstituted heterocyclic ring; and

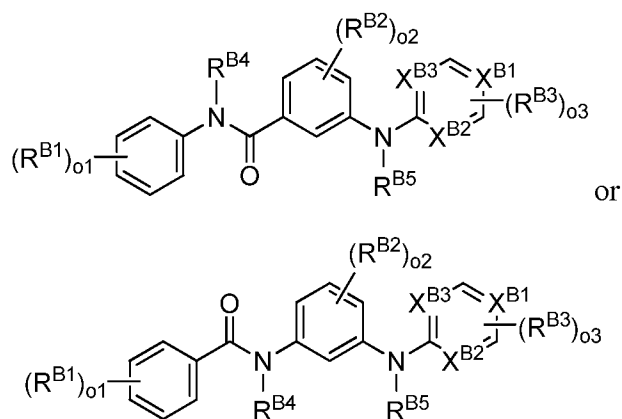
o3 is 0, 1, or 2.

20. The method of claim 19, wherein the compound is of the formula:



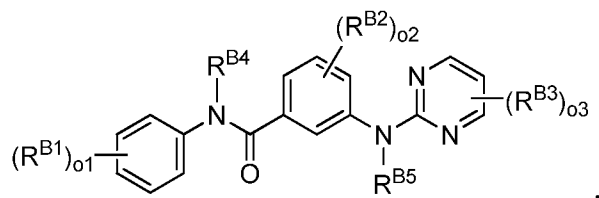
or a pharmaceutically acceptable salt thereof.

21. The method of claim 19, wherein the compound is of the formula:



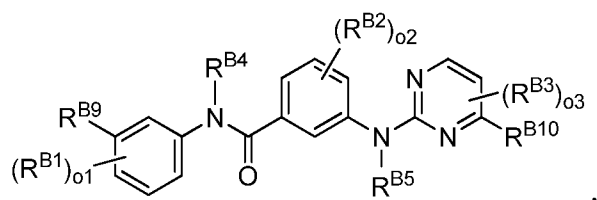
or a pharmaceutically acceptable salt thereof.

22. The method of claim 19, wherein the compound is of the formula:



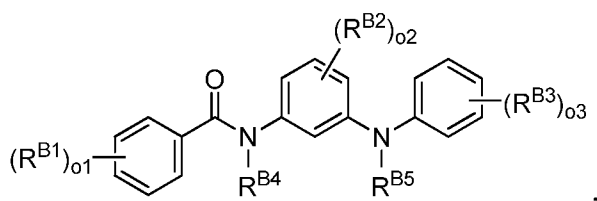
or a pharmaceutically acceptable salt thereof.

23. The method of claim 19, wherein the compound is of the formula:



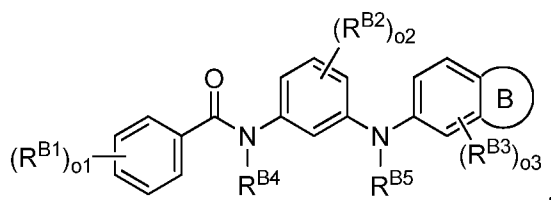
or a pharmaceutically acceptable salt thereof, wherein each of R^{B9} and R^{B10} is independently substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

24. The method of claim 19, wherein the compound is of the formula:



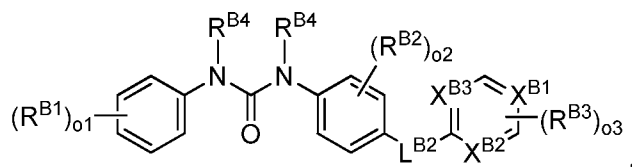
or a pharmaceutically acceptable salt thereof.

25. The method of claim 19, wherein the compound is of the formula:



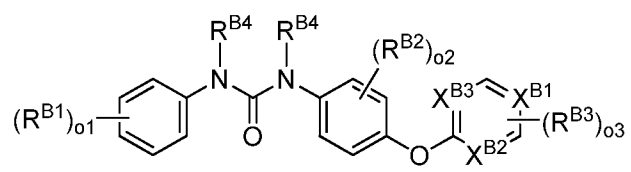
or a pharmaceutically acceptable salt thereof, wherein Ring B is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

26. The method of claim 19, wherein the compound is of the formula:



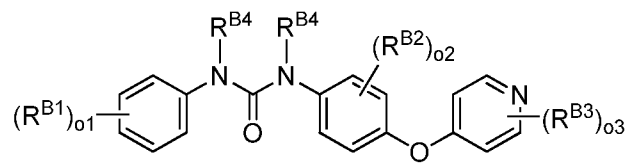
or a pharmaceutically acceptable salt thereof.

27. The method of claim 19, wherein the compound is of the formula:



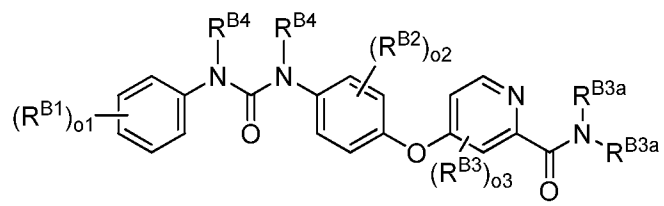
or a pharmaceutically acceptable salt thereof.

28. The method of claim 19, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

29. The method of claim 19, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

30. The method of any one of claims 19-29, wherein at least one instance of R^{B1} is halogen, substituted or unsubstituted alkyl, or substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

31. The method of any one of claims 19-30, wherein at least one instance of R^{B2} is halogen or substituted or unsubstituted alkyl.

32. The method of any one of claims 19-31, wherein o_2 is 0.

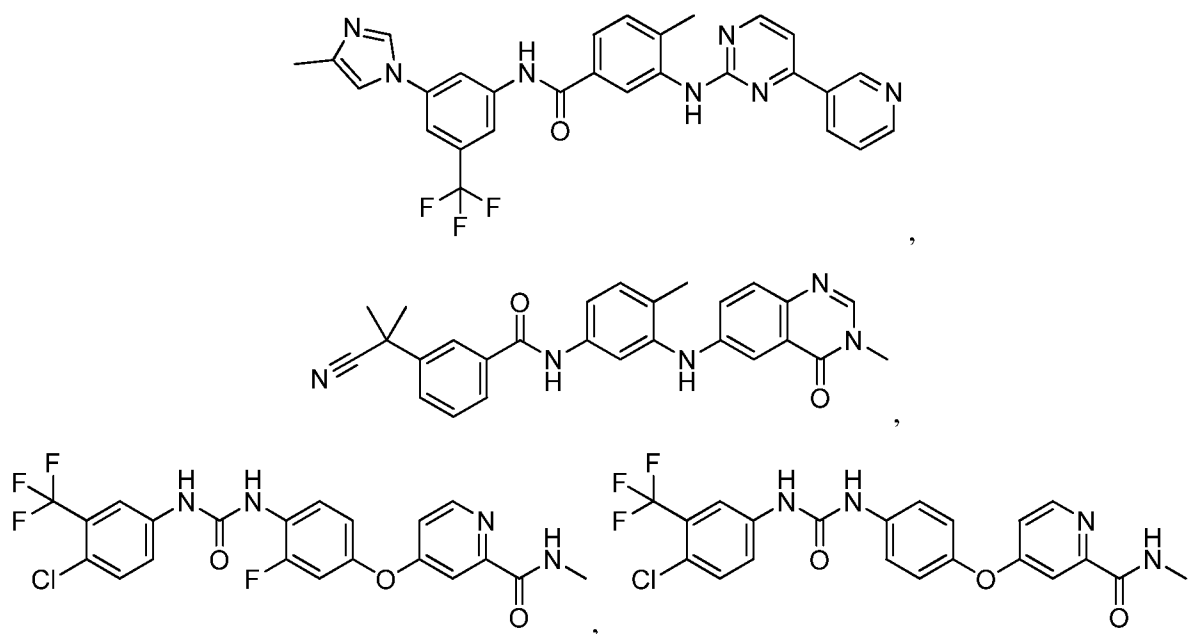
33. The method of any one of claims 19-32, wherein at least one instance of R^{B3} is substituted or unsubstituted heteroaryl or $-C(=O)N(R^a)_2$, or an instance of R^{B3} and an instance of R^{B7} are joined to form a substituted or unsubstituted, monocyclic, 5- to 6-membered

heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

34. The method of any one of claims 19-33, wherein each instance of R^{B4} is hydrogen.

35. The method of any one of claims 19-34, wherein R^{B5} is hydrogen.

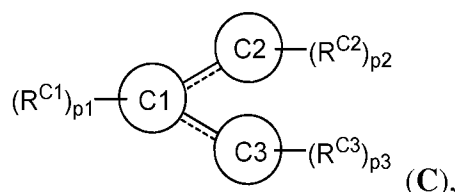
36. The method of claim 19, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

37. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (C):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing;
wherein:

Ring C1 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heterocyclic or heteroaryl ring system are nitrogen;

Ring C2 is a substituted or unsubstituted, monocyclic, 6-membered carbocyclic ring or a substituted or unsubstituted phenyl ring;

Ring C3 is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heterocyclic or heteroaryl ring system are nitrogen;

each instance of R^{C1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

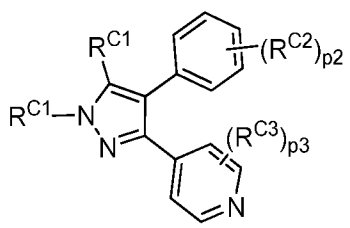
p1 is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

each instance of R^{C2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$, or two instances of R^{C2} are joined to form a substituted or unsubstituted carbocyclic ring;

p2 is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11;

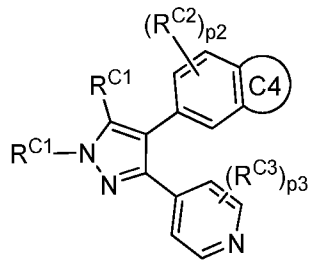
each instance of R^{C3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and $p3$ is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

38. The method of claim 37, wherein the compound is of the formula:



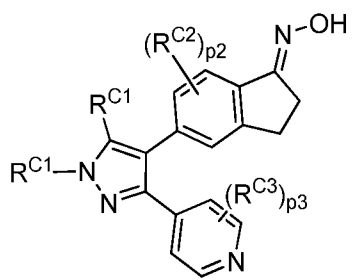
or a pharmaceutically acceptable salt thereof.

39. The method of claim 37, wherein the compound is of the formula:



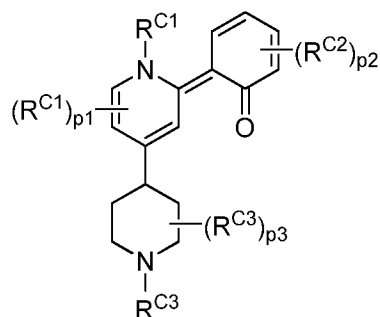
or a pharmaceutically acceptable salt thereof, wherein Ring C4 is a substituted or unsubstituted, monocyclic, 5- to 6-membered carbocyclic ring.

40. The method of claim 37, wherein the compound is of the formula:



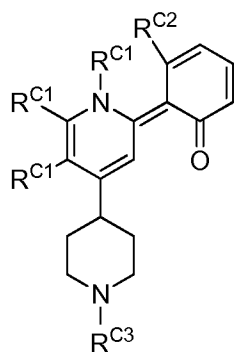
or a pharmaceutically acceptable salt thereof.

41. The method of claim 37, wherein the compound is of the formula:



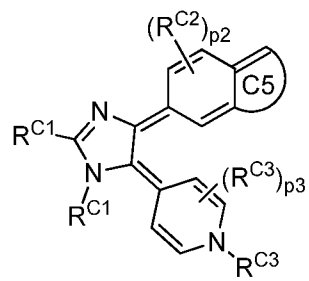
or a pharmaceutically acceptable salt thereof.

42. The method of claim 37, wherein the compound is of the formula:



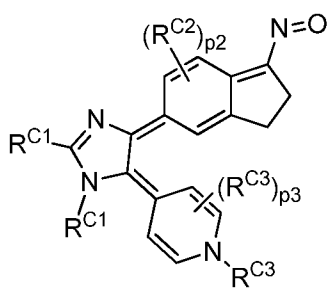
or a pharmaceutically acceptable salt thereof.

43. The method of claim 37, wherein the compound is of the formula:



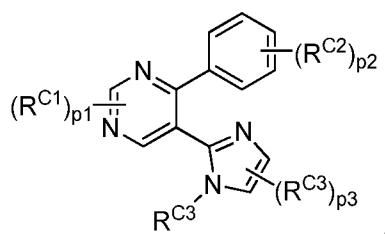
or a pharmaceutically acceptable salt thereof, wherein Ring C5 is a substituted or unsubstituted, monocyclic, 5- to 6-membered carbocyclic ring.

44. The method of claim 37, wherein the compound is of the formula:



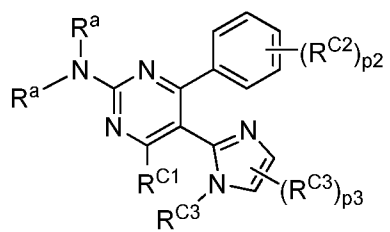
or a pharmaceutically acceptable salt thereof.

45. The method of claim 37, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

46. The method of claim 37, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

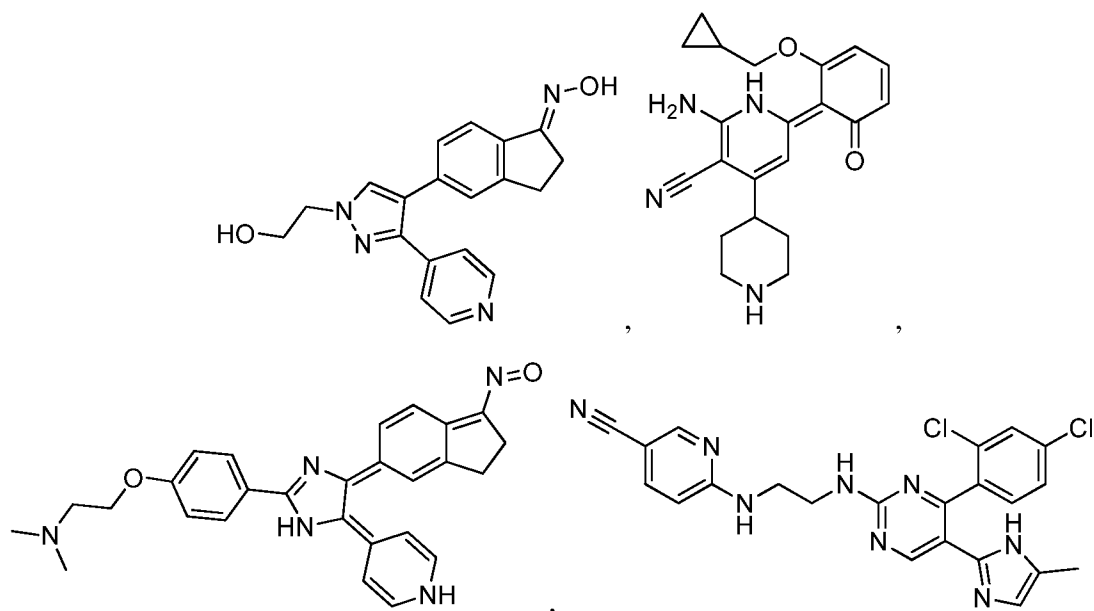
47. The method of any one of claims 37-46, wherein at least one instance of R^{C1} is substituted or unsubstituted alkyl, $-OR^a$, $-N(R^a)_2$, or $-CN$.

48. The method of any one of claims 37-47, wherein at least one instance of R^{C2} is halogen or $-OR^a$.

49. The method of any one of claims 37-48, wherein at least one instance of R^{C3} is substituted or unsubstituted alkyl.

50. The method of any one of claims 37-49, wherein p_3 is 0.

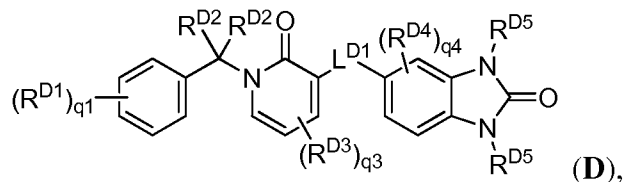
51. The method of claim 37, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

52. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (D):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing;

wherein:

L^{D1} is a substituted or unsubstituted, saturated or unsaturated, C_{3-7} aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{D6}-$, $-N=$, or $=N-$, wherein each instance of R^{D6} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{D1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

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

q_1 is 0, 1, 2, 3, 4, or 5;

each instance of $\text{R}^{\text{D}2}$ is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

each instance of $\text{R}^{\text{D}3}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

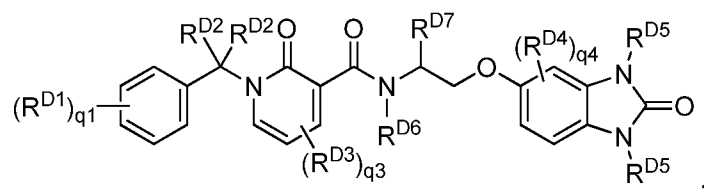
q_3 is 0, 1, 2, or 3;

each instance of $\text{R}^{\text{D}4}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

q_4 is 0, 1, 2, or 3; and

each instance of $\text{R}^{\text{D}5}$ is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group.

53. The method of claim 52, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof, wherein R^{D7} is substituted or unsubstituted phenyl.

54. The method of any one of claims 52-53, wherein L^{D1} is a substituted or unsubstituted, saturated or unsaturated, C_5 aliphatic chain, optionally wherein one, two, or three chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{D6}-$, $=N-$, or $-N=$.

55. The method of any one of claims 52-54, wherein at least one instance of R^{D1} is halogen.

56. The method of any one of claims 52-55, wherein each instance of R^{D2} is hydrogen.

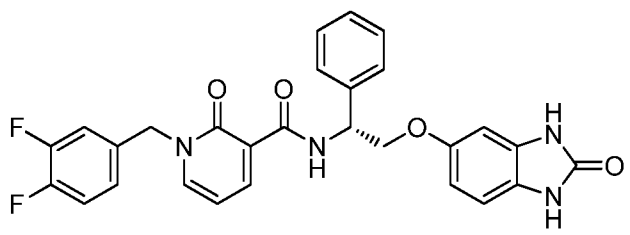
57. The method of any one of claims 52-56, wherein q_3 is 0.

58. The method of any one of claims 52-57, wherein q_4 is 0.

59. The method of any one of claims 52-58, wherein each instance of R^{D5} is hydrogen.

60. The method of any one of claims 52-59, wherein at least one instance of R^{D6} is hydrogen.

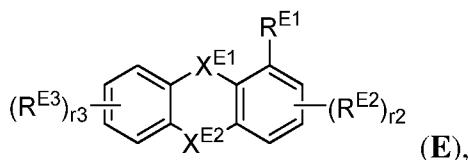
61. The method of claim 52, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

62. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (E):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of culturing step;

wherein:

X^{E1} is $-O-$, $-S-$, $-C(=O)-$, $-C(=S)-$, or $-C(=NR^{E4})-$, wherein R^{E4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

X^{E2} is $-O-$, $-S-$, $-C(=O)-$, or $-C(=S)-$;

R^{E1} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$, or R^{E1} and R^{E4} are joined to form a substituted or unsubstituted heterocyclic ring or a substituted or unsubstituted heteroaryl ring;

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

each instance of R^{E2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or

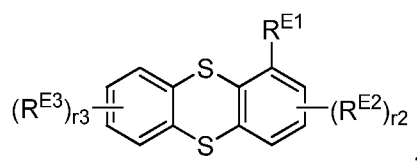
unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

r_2 is 0, 1, 2, or 3;

each instance of $\text{R}^{\text{E}3}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$; and

r_3 is 0, 1, 2, 3, or 4.

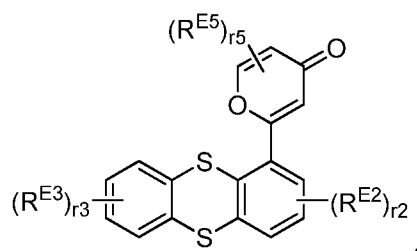
63. The method of claim 62, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

64. The method of any one of claims 62-63, wherein $\text{R}^{\text{E}1}$ is substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

65. The method of claim 62, wherein the compound is of the formula:

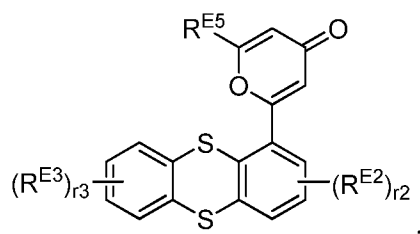


or a pharmaceutically acceptable salt thereof, wherein:

each instance of $\text{R}^{\text{E}5}$ is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

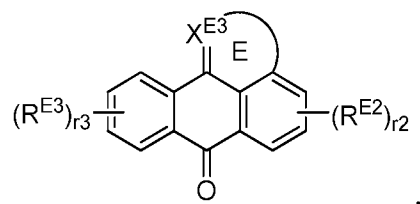
unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$; and r_5 is 0, 1, 2, or 3.

66. The method of claim 62, wherein the compound is of the formula:



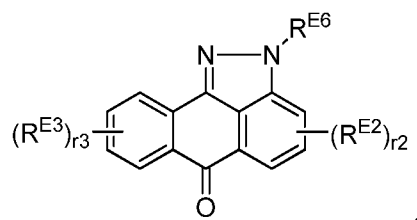
67. The method of any one of claims 65-66, wherein at least one instance of $\text{R}^{\text{E}5}$ is substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

68. The method of claim 62, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof, wherein $\text{X}^{\text{E}3}$ is C or N, and Ring E is a substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclic ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one, two, or three atoms in the heterocyclic or heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

69. The method of claim 62, wherein the compound is of the formula:



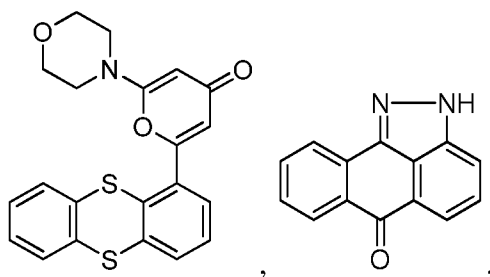
or a pharmaceutically acceptable salt thereof, wherein R^{E6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group.

70. The method of claim 69, wherein R^{E6} is hydrogen.

71. The method of any one of claims 62-70, wherein r_2 is 0.

72. The method of any one of claims 62-71, wherein r_3 is 0.

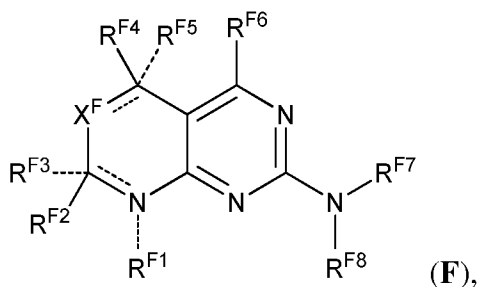
73. The method of claim 62, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

74. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (F):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing;

wherein:

X^F is $-N(R^{F9})-$, $=N-$, $-C(R^{F10})_2-$, or $=C(R^{F10})-$, wherein:

R^{F9} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group; and

each instance of R^{F10} is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

R^{F1} is absent, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

R^{F2} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-$

$\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

$\text{R}^{\text{F}3}$ is absent, hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl, or $\text{R}^{\text{F}3}$ and $\text{R}^{\text{F}2}$ are joined to form $=\text{O}$;

$\text{R}^{\text{F}4}$ is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

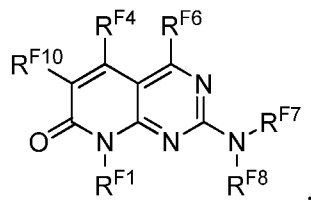
$\text{R}^{\text{F}5}$ is absent, hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

$\text{R}^{\text{F}6}$ is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, or $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$;

$\text{R}^{\text{F}7}$ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group; and

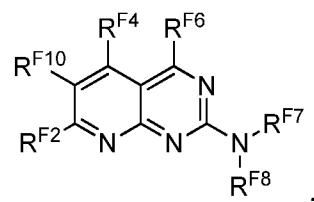
$\text{R}^{\text{F}8}$ is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group.

75. The method of claim 74, wherein the compound is of the formula:



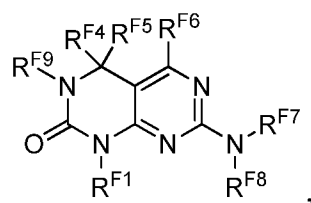
or a pharmaceutically acceptable salt thereof.

76. The method of claim 74, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

77. The method of claim 74, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

78. The method of any one of claims 74-77, wherein R^{F1} is absent, substituted or unsubstituted alkyl, or substituted or unsubstituted, monocyclic, 5- to 6-membered carbocycl.

79. The method of any one of claims 74-78, wherein R^{F2} is $-NR^aC(=O)N(R^a)_2$.

80. The method of any one of claims 74-78, wherein R^{F2} and R^{F3} are joined to form $=O$.

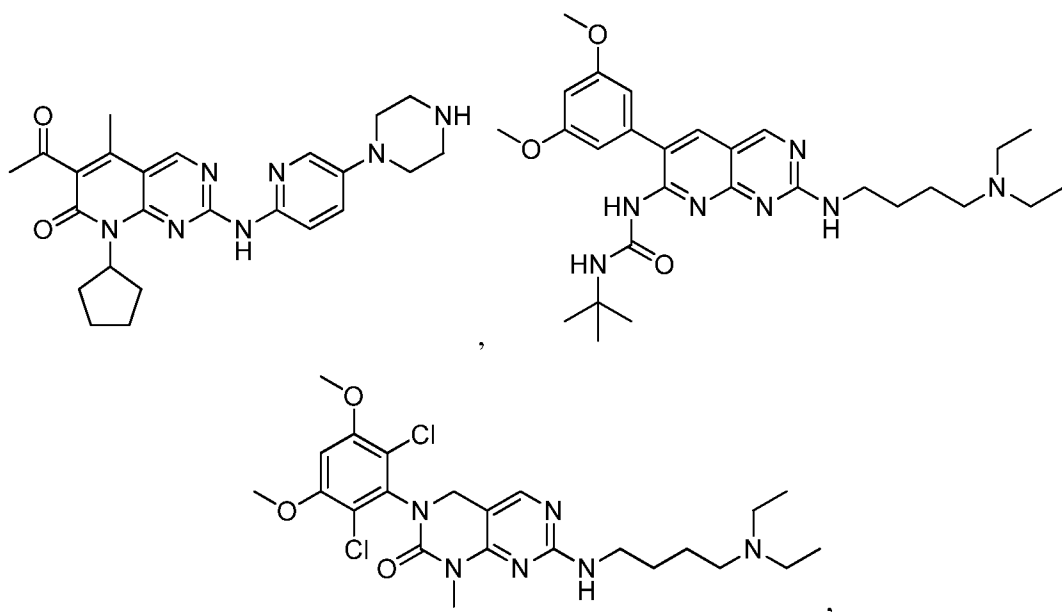
81. The method of any one of claims 74-80, wherein R^{F4} is hydrogen or substituted or unsubstituted alkyl.

82. The method of any one of claims 74-81, wherein R^{F5} is absent or hydrogen.

83. The method of any one of claims 74-82, wherein R^{F6} is hydrogen.

84. The method of any one of claims 74-83, wherein R^{F7} is substituted or unsubstituted alkyl or substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

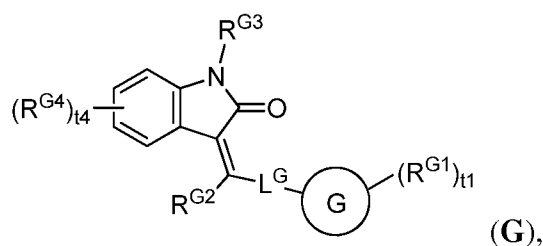
85. The method of any one of claims 74-84, wherein R^{F8} is hydrogen.
86. The method of any one of claims 74-85, wherein R^{F9} is substituted or unsubstituted phenyl.
87. The method of any one of claims 74-86, wherein at least one instance of R^{F10} is substituted or unsubstituted phenyl, or $-C(=O)R^a$.
88. The method of claim 74, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

89. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (G):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of culturing step; wherein:

Ring G is a substituted or unsubstituted phenyl ring or a substituted or unsubstituted, monocyclic, 5- to 6-membered heteroaryl ring, wherein one or two atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur;

each instance of R^{G1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

$t1$ is 0, 1, 2, 3, 4, or 5;

L^G is a bond, $-O-$, $-S-$, $-N(R^{G5})-$, or $-C(R^{G6})_2-$, wherein R^{G5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group; and each instance of R^{G6} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

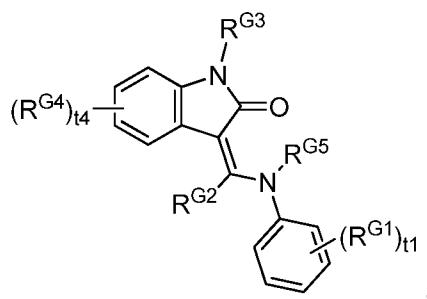
R^{G2} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{G3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{G4} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

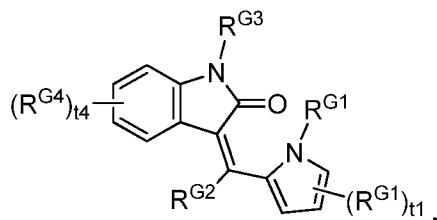
unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-\text{OR}^a$, $-\text{N}(\text{R}^a)_2$, $-\text{SR}^a$, $-\text{CN}$, $-\text{SCN}$, $-\text{C}(=\text{NR}^a)\text{R}^a$, $-\text{C}(=\text{NR}^a)\text{OR}^a$, $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^a$, $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{NO}_2$, $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$, $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^a$, $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^a$, or $-\text{S}(=\text{O})_2\text{N}(\text{R}^a)_2$; and t_4 is 0, 1, 2, 3, or 4.

90. The method of claim 89, wherein the compound is of the formula:



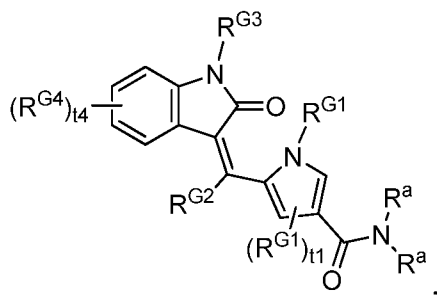
or a pharmaceutically acceptable salt thereof.

91. The method of claim 89, wherein the compound is of the formula:



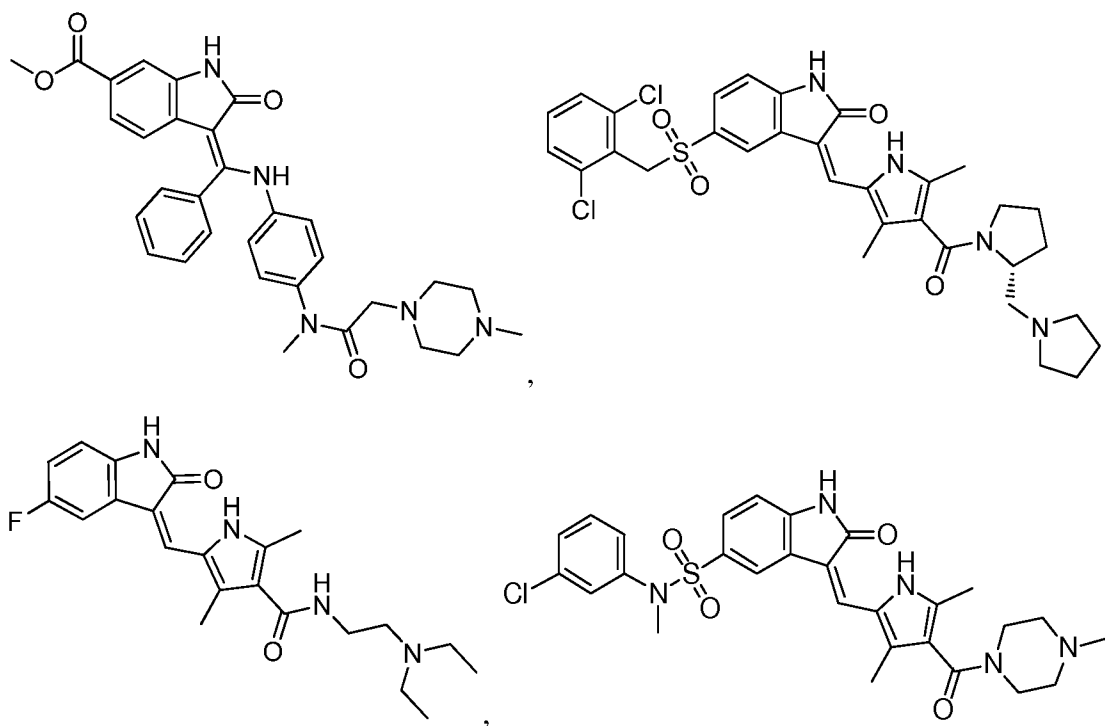
or a pharmaceutically acceptable salt thereof.

92. The method of claim 89, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

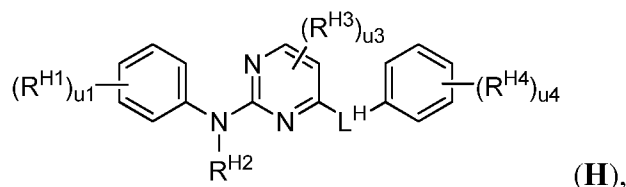
93. The method of any one of claims 89-92, wherein at least one instance of R^{G1} is substituted or unsubstituted alkyl, $-C(=O)N(R^a)_2$, or $-N(R^a)C(=O)R^a$.
94. The method of any one of claims 89-93, wherein R^{G2} is substituted or unsubstituted phenyl.
95. The method of any one of claims 89-94, wherein R^{G3} is hydrogen.
96. The method of any one of claims 89-95, wherein at least one instance of R^{G4} is halogen, $-C(=O)OR^a$, $-S(=O)_2R^a$, or $-S(=O)_2N(R^a)_2$.
97. The method of any one of claims 89-96, wherein R^{G5} is hydrogen.
98. The method of claim 89, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

99. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (H):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing;

wherein:

L^H is a substituted or unsubstituted, saturated or unsaturated, C_{1-4} aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{H5}-$, $-N=$, or $=N-$, wherein each instance of R^{H5} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

each instance of R^{H1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

u_1 is 0, 1, 2, 3, 4, or 5;

R^{H2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

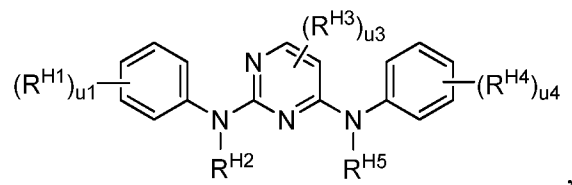
each instance of R^{H3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

u_3 is 0, 1, or 2;

each instance of R^{H4} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

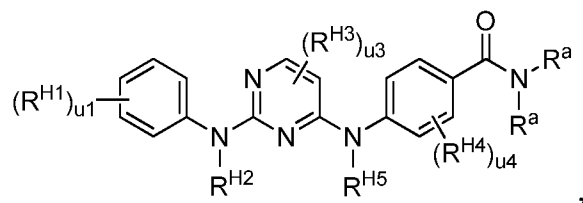
u_4 is 0, 1, 2, 3, 4, or 5.

100. The method of claim 99, wherein the compound is of the formula:



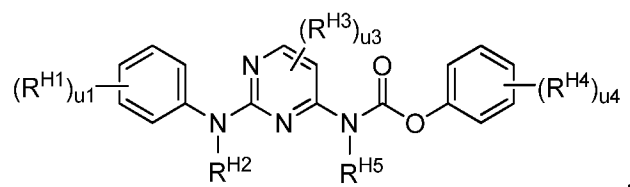
or a pharmaceutically acceptable salt thereof.

101. The method of claim 99, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

102. The method of claim 99, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

103. The method of any one of claims 99-102, wherein at least one instance of R^{H1} is substituted or unsubstituted alkyl or substituted or unsubstituted, monocyclic, 5- to 6-membered heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

104. The method of any one of claims 99-103, wherein R^{H2} is hydrogen.

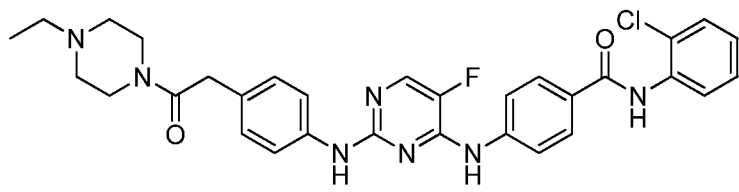
105. The method of any one of claims 99-104, wherein at least one instance of R^{H3} is halogen.

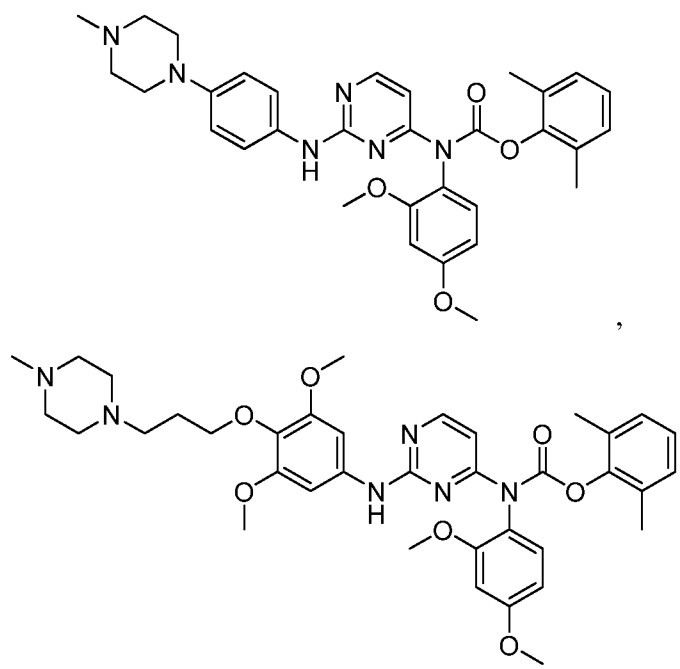
106. The method of any one of claims 99-105, wherein $u3$ is 0.

107. The method of any one of claims 99-106, wherein at least one instance of R^{H4} is substituted or unsubstituted alkyl, or $-C(=O)N(R^a)_2$.

108. The method of any one of claims 99-107, wherein at least one instance of R^{H5} is hydrogen or substituted or unsubstituted phenyl.

109. The method of claim 99, wherein the compound is of the formula:

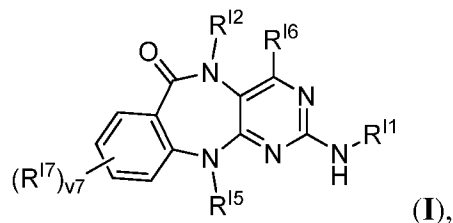




or a pharmaceutically acceptable salt thereof.

110. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (I):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing;
wherein:

R^{11} is substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{12} is hydrogen or substituted or unsubstituted alkyl;

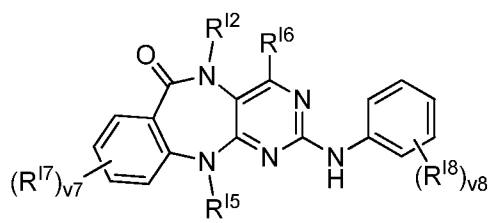
R^{15} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, or substituted or unsubstituted carbocyclyl;

R^{16} is hydrogen or substituted or unsubstituted alkyl;

each instance of R^{17} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-O-$ (substituted or unsubstituted alkyl), $-NH-$ (substituted or unsubstituted alkyl), $-NH-$ (substituted or unsubstituted aryl), $-N$ (substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), $-N$ (substituted or unsubstituted alkyl)–(substituted or unsubstituted aryl), $-NO_2$, or $-CN$; and

v_7 is 0, 1, 2, 3, or 4.

111. The method of claim 110, wherein the compound is of the formula:



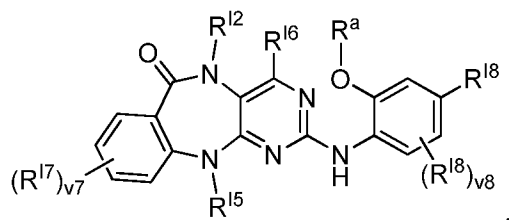
or a pharmaceutically acceptable salt thereof, wherein:

each instance of R^{18} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

v_8 is 0, 1, 2, 3, 4, or 5.

112. The method of claim 111, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

113. The method of any one of claims 110-112, wherein R^{12} is substituted or unsubstituted alkyl.

114. The method of any one of claims 110-113, wherein R^{15} is substituted or unsubstituted alkyl.

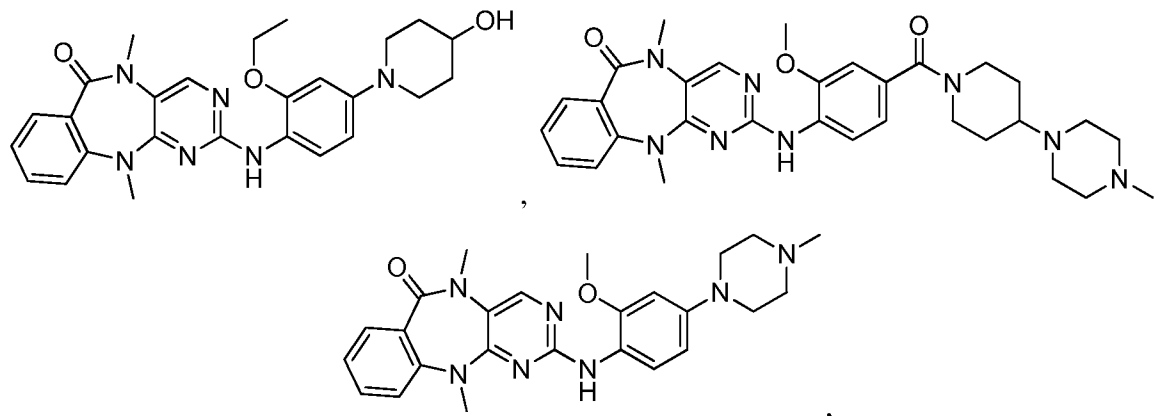
115. The method of any one of claims 110-114, wherein R^{16} is hydrogen.

116. The method of any one of claims 110-115, wherein v_7 is 0.

117. The method of any one of claims 111-116, wherein v_8 is 0.

118. The method of any one of claims 111-117, wherein R^a is substituted or unsubstituted C_{1-6} alkyl.

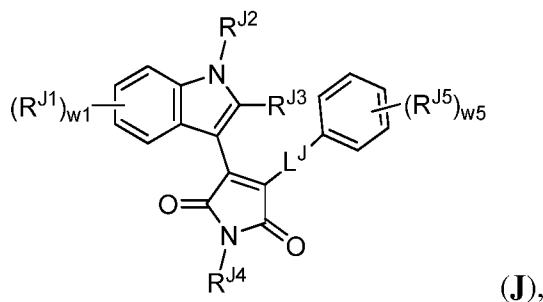
119. The method of claim 110, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

120. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (J):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing;

wherein:

L^J is a substituted or unsubstituted, saturated or unsaturated, C_{1-6} aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{J6}-$, $-N=$, or $=N-$, wherein each instance of R^{J6} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{J1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

$w1$ is 0, 1, 2, 3, or 4;

R^{J2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

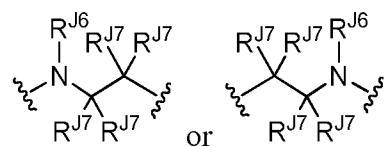
R^{J3} is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

R^{J4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{J5} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

w5 is 0, 1, 2, 3, 4, or 5.

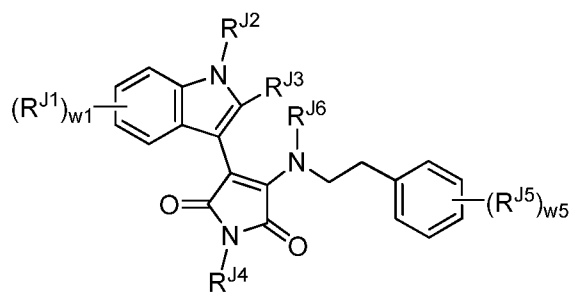
121. The method of claim 120, wherein L^J is a substituted or unsubstituted, saturated or unsaturated, C_3 aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{J6}-$, $-N=$, or $=N-$.



122. The method of claim 120, wherein L^J is of the formula:

wherein each instance of R^{J7} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl.

123. The method of claim 120, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

124. The method of any one of claims 120-123, wherein w_1 is 0.

125. The method of any one of claims 120-124, wherein R^{J2} is hydrogen.

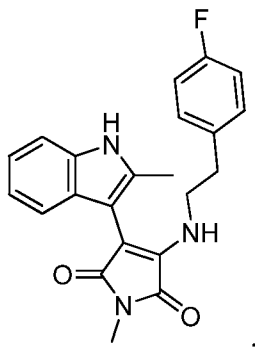
126. The method of any one of claims 120-125, wherein R^{J3} is substituted or unsubstituted alkyl.

127. The method of any one of claims 120-126, wherein R^{J4} is substituted or unsubstituted alkyl.

128. The method of any one of claims 120-127, wherein at least one instance of R^{J5} is halogen.

129. The method of any one of claims 120-128, wherein at least one instance of R^{J6} is hydrogen.

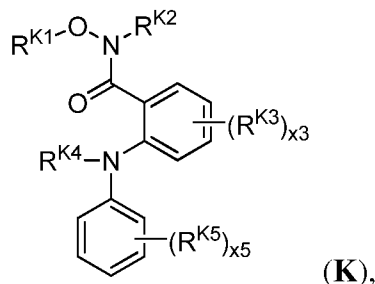
130. The method of claim 120, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

131. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (K):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing; wherein:

R^{K1} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{K2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{K3} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

atom, or two instances of R^a are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

x_3 is 0, 1, 2, 3, or 4;

R^{K4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{K5} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$; and

x_5 is 0, 1, 2, 3, 4, or 5.

132. The method of claim 131, wherein R^{K1} is substituted or unsubstituted alkyl.

133. The method of claim 131, wherein R^{K1} is C_{1-6} alkyl substituted with at least one $-OH$.

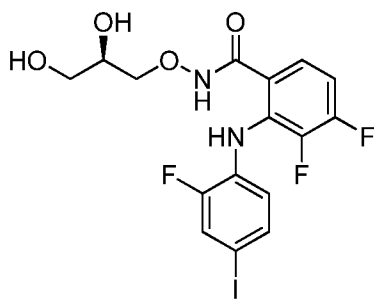
134. The method of any one of claims 131-133, wherein R^{K2} is hydrogen.

135. The method of any one of claims 131-134, wherein at least one instance of R^{K3} is halogen.

136. The method of any one of claims 131-135, wherein R^{K4} is hydrogen.

137. The method of any one of claims 131-136, wherein at least one instance of R^{K5} is halogen.

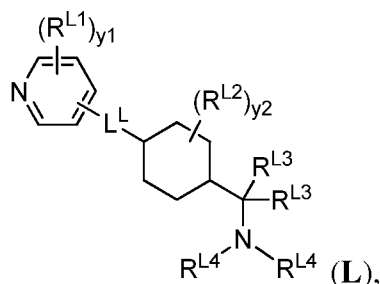
138. The method of claim 131, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

139. A method for converting pluripotency state of a vertebrate cell to a more naïve state, the method comprising:

culturing a pluripotent vertebrate cell in the presence of a compound of Formula (L):



or a pharmaceutically acceptable salt thereof; and

maintaining the cell in culture under conditions suitable and a time sufficient to convert the pluripotency state of the vertebrate cell to a more naïve state than the pluripotency state of the vertebrate cell of the step of culturing; wherein:

L^L is a substituted or unsubstituted, saturated or unsaturated, C_{1-4} aliphatic chain, optionally wherein one or two chain atoms of the aliphatic chain are independently replaced with $-O-$, $-S-$, $-NR^{L5}-$, $-N=$, or $=N-$, wherein each instance of R^{L5} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{L1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

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

y_1 is 0, 1, 2, 3, or 4;

each instance of R^{L2} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $-OR^a$, $-N(R^a)_2$, $-SR^a$, $-CN$, $-SCN$, $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, $-C(=NR^a)N(R^a)_2$, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

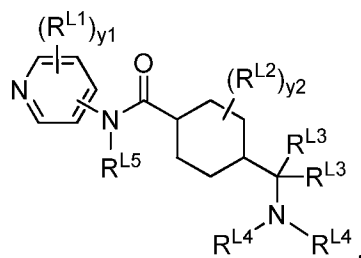
y_2 is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

each instance of R^{L3} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl; and

each instance of R^{L4} is independently hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group.

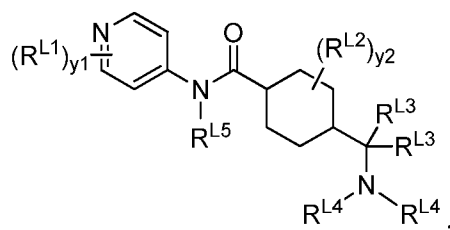
140. The method of claim 139, wherein L^L is a substituted or unsubstituted, saturated or unsaturated, C_2 aliphatic chain, optionally wherein one chain atom of the aliphatic chain is replaced with $-O-$, $-S-$, $-NR^{L5}-$, $=N-$, or $-N=$.

141. The method of claim 139, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

142. The method of claim 139, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

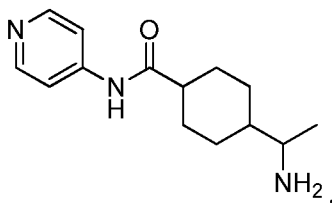
143. The method of any one of claims 139-142, wherein y_1 is 0.

144. The method of any one of claims 139-143, wherein y_2 is 0.

145. The method of any one of claims 139-144, wherein each instance of R^{L3} is independently hydrogen or substituted or unsubstituted alkyl.

146. The method of any one of claims 139-145, wherein each instance of R^{L4} is hydrogen.

147. The method of claim 139, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

148. The method of any one of claims 1-147, wherein the culture comprises fibroblast growth factor and/or Activin A.

149. The method of any one of claims 1-148, wherein the vertebrate cell is a human stem cell.

150. The method of claim 149, wherein the human stem cell is a human embryonic stem cell.

151. The method of any one of claims 1-148, wherein the vertebrate cell is a human induced pluripotent cell (iPS cell).
152. The method of any one of claims 1-148, wherein the vertebrate cell is derived from a human embryonic stem cell line.
153. The method of any one of claims 1-148, wherein the vertebrate cell is derived from an embryo.
154. The method of any one of claims 1-153, wherein the more naïve pluripotent vertebrate cell of the step of maintaining uses the distal Oct4 enhancer element for OCT4 expression.
155. The method of any one of claims 1-154, wherein the more naïve pluripotent vertebrate cell of the step of maintaining has a global gene expression profile which clusters with naïve mouse ESCs as opposed to stem cell lines derived from mouse epiblast (EpiSCs) and/or less naïve human ESCs.
156. A composition comprising naïve pluripotent vertebrate cells produced by the methods of any one of claims 1-155.
157. A naïve pluripotent vertebrate cell line produced by the methods of any one of claims 1-155.
158. A naïve pluripotent vertebrate cell, wherein the cell uses the distal Oct4 enhancer element for OCT4 expression.
159. The naïve pluripotent vertebrate cell of claim 158, wherein the cell is a primate cell and wherein the cell uses the endogenous distal OCT4 enhancer element for Oct4 expression.
160. The naïve pluripotent vertebrate cell of claim 158, wherein the cell is a human cell and wherein the cell uses the endogenous distal OCT4 enhancer element for Oct4 expression.

161. A naïve pluripotent vertebrate cell, wherein the cell has a global gene expression profile which clusters with naïve mouse ESCs as opposed to stem cell lines derived from mouse epiblast (EpiSCs) and/or less naïve human ESCs.
162. The naïve pluripotent vertebrate cell of claim 161, wherein the cell is a primate cell.
163. The naïve pluripotent vertebrate cell of claim 161, wherein the cell is a human cell.
164. The naïve pluripotent vertebrate cell of any one of claims 158 to 163, wherein the cell is produced by the methods of any one of claims 1-155.
165. A kit for culturing vertebrate cells, the kit comprising:
a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor; and
instructions for culturing vertebrate cells.
166. The kit of claim 165, wherein the kit further comprises mitogen-activated protein kinase kinase (MEK) inhibitor.
167. The kit of claims 165 or 166, wherein the kit further comprises a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor.
168. The kit of any one of claims 165-167, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor.
169. The kit of any one of claims 165-167, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor.
170. The kit of any one of claims 165-167, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor.

171. The kit of any one of claims 165-167, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor.

172. The kit of any one of claims 165-171, wherein the kit further comprises cell culture medium.

173. The kit of any one of claims 165-172, wherein the vertebrate cells are naïve pluripotent cells, human pluripotent cells, or naïve human pluripotent cells.

174. A kit for preparing a cell culture medium, the kit comprising:
a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor; and
instructions for preparing a cell culture medium.

175. The kit of claim 174, wherein the kit further comprises mitogen-activated protein kinase kinase (MEK) inhibitor.

176. The kit of claims 174 or 175, wherein the kit further comprises a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor.

177. The kit of any one of claims 174-176, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor.

178. The kit of any one of claims 174-176, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor.

179. The kit of any one of claims 174-176, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor.

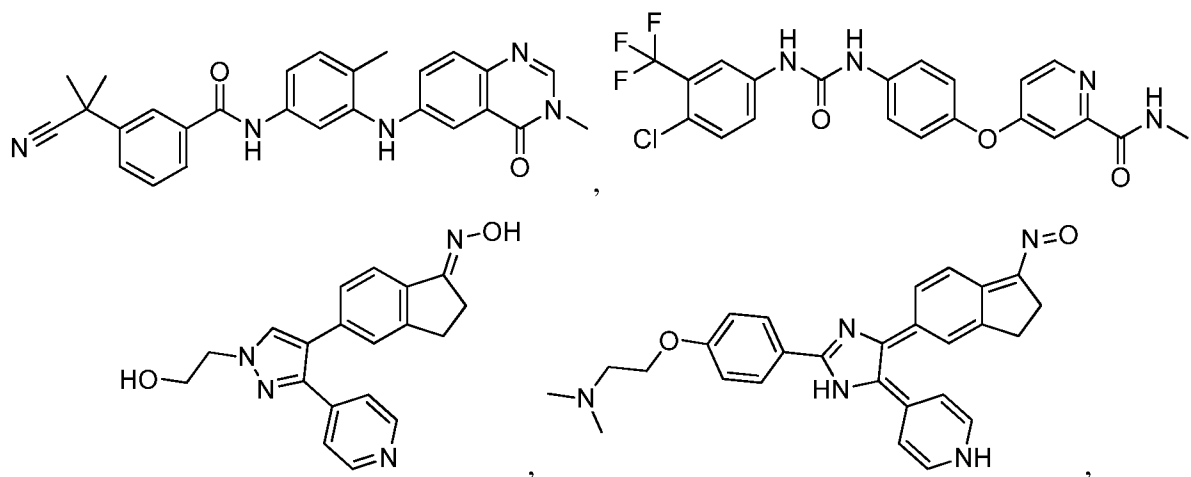
180. The kit of any one of claims 174-176, wherein the kit comprises a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor.

181. The kit of any one of claims 174-180, wherein the kit further comprises a basal medium.

182. The kit of any one of claims 174-181, wherein the basal medium is a serum-free medium.

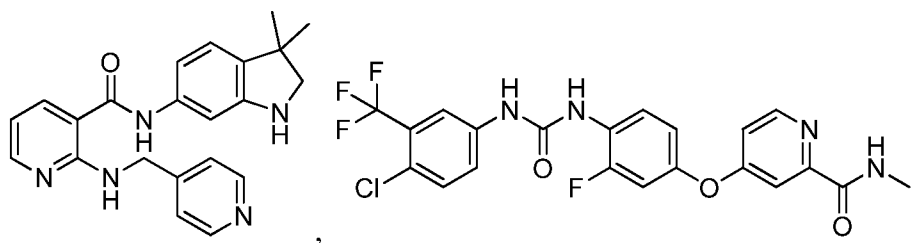
183. The kit of any one of claims 174-182, wherein the basal medium comprises one or more supplements.

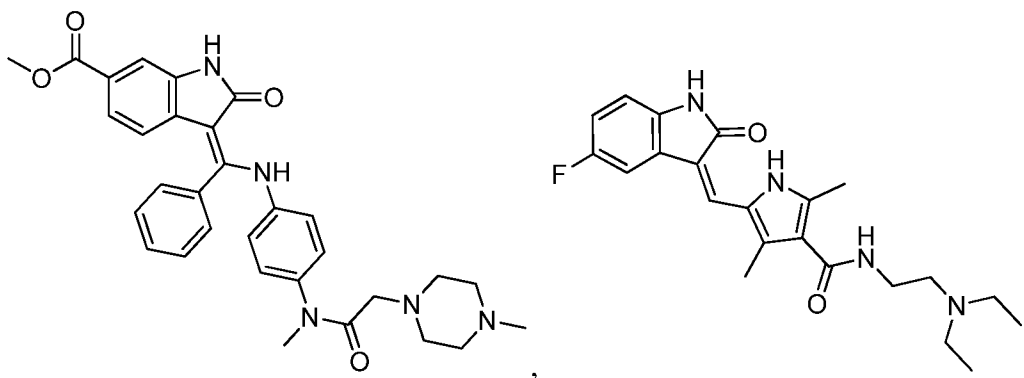
184. The method of any one of claims 1-155 or the kit of any one of claims 165-183, wherein the BRAF inhibitor is of the formula:



or a pharmaceutically acceptable salt thereof.

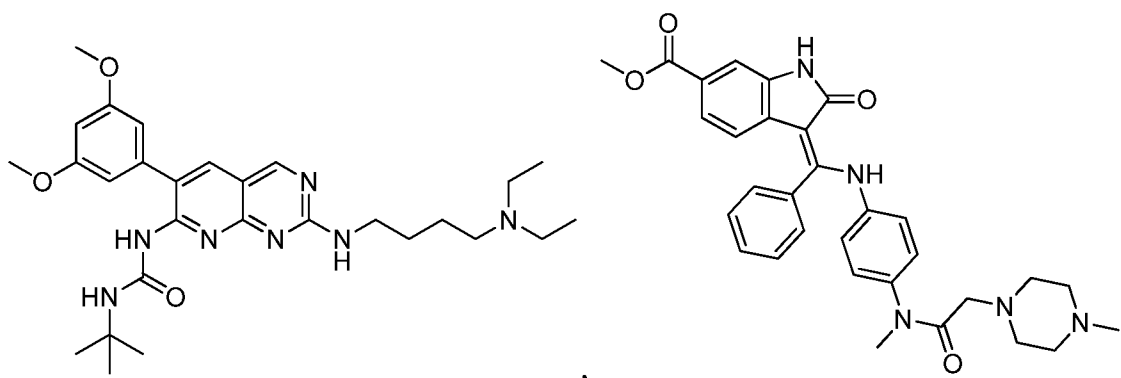
185. The method of any one of claims 1-155 or the kit of any one of claims 165-183, wherein the VEGFR1 inhibitor is of the formula:





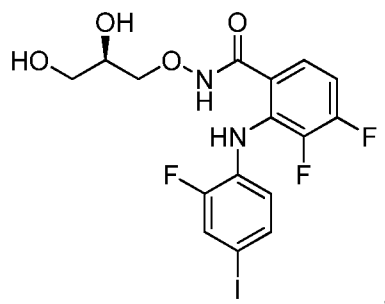
or a pharmaceutically acceptable salt thereof.

186. The method of any one of claims 1-155 or the kit of any one of claims 165-183, wherein the FGFR1 inhibitor is of the formula:



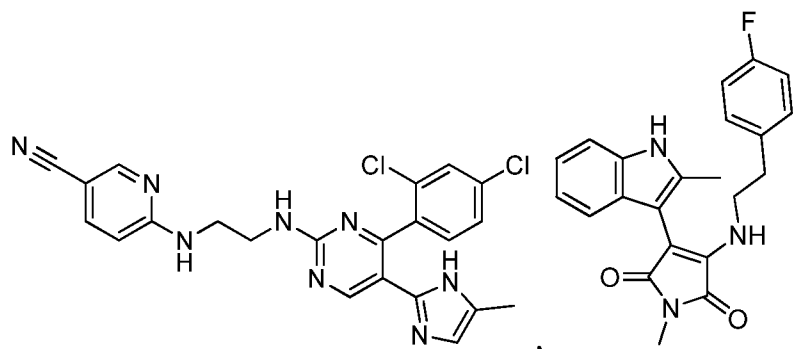
or a pharmaceutically acceptable salt thereof.

187. The method of any one of claims 1-155 or the kit of any one of claims 165-183, wherein the MEK inhibitor is of the formula:



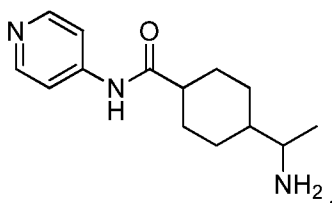
or a pharmaceutically acceptable salt thereof.

188. The method of any one of claims 1-155 or the kit of any one of claims 165-183, wherein the GSK3 inhibitor is of the formula:



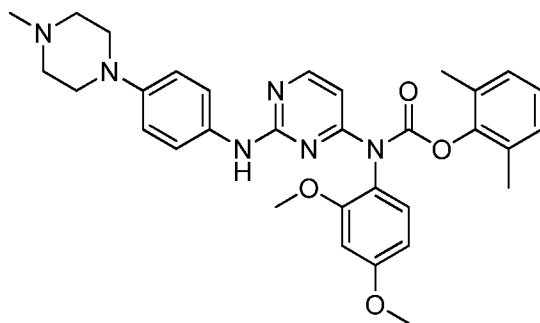
or a pharmaceutically acceptable salt thereof.

189. The method of any one of claims 1-155 or the kit of any one of claims 165-183, wherein the ROCK inhibitor is of the formula:



or a pharmaceutically acceptable salt thereof.

190. The method of any one of claims 1-155 or the kit of any one of claims 165-183, wherein the Src inhibitor is of the formula:



or a pharmaceutically acceptable salt thereof.

191. A cell culture medium comprising:

a basal medium; and

a serine/threonine-protein kinase B-Raf (BRAF) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a vascular endothelial growth factor 1 (VEGFR1) inhibitor, or a fibroblast growth factor receptor 1 (FGFR1) inhibitor.

192. The cell culture medium of claim 191, wherein the cell culture medium further comprises mitogen-activated protein kinase kinase (MEK) inhibitor.

193. The cell culture medium of claim 191 or 192, wherein the cell culture medium further comprises a glycogen synthase kinase 3 (GSK3) inhibitor, a rho-associated protein kinase (ROCK) inhibitor, and/or a proto-oncogene tyrosine-protein kinase (Src) inhibitor.

194. The cell culture medium of any one of claims 191-193, wherein the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, and a GSK3 inhibitor.

195. The cell culture medium of any one of claims 191-193, wherein the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, and a ROCK inhibitor.

196. The cell culture medium of any one of claims 191-193, wherein the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a GSK3 inhibitor, a ROCK inhibitor, and an Src inhibitor.

197. The cell culture medium of any one of claims 191-193, wherein the cell culture medium comprises a BRAF inhibitor, a MEK inhibitor, a ROCK inhibitor, and an Src inhibitor.

198. The cell culture medium of any one of claims 191-197, wherein the basal medium is a serum-free medium.

199. The cell culture medium of any one of claims 191-198, wherein the basal medium comprises one or more supplements.

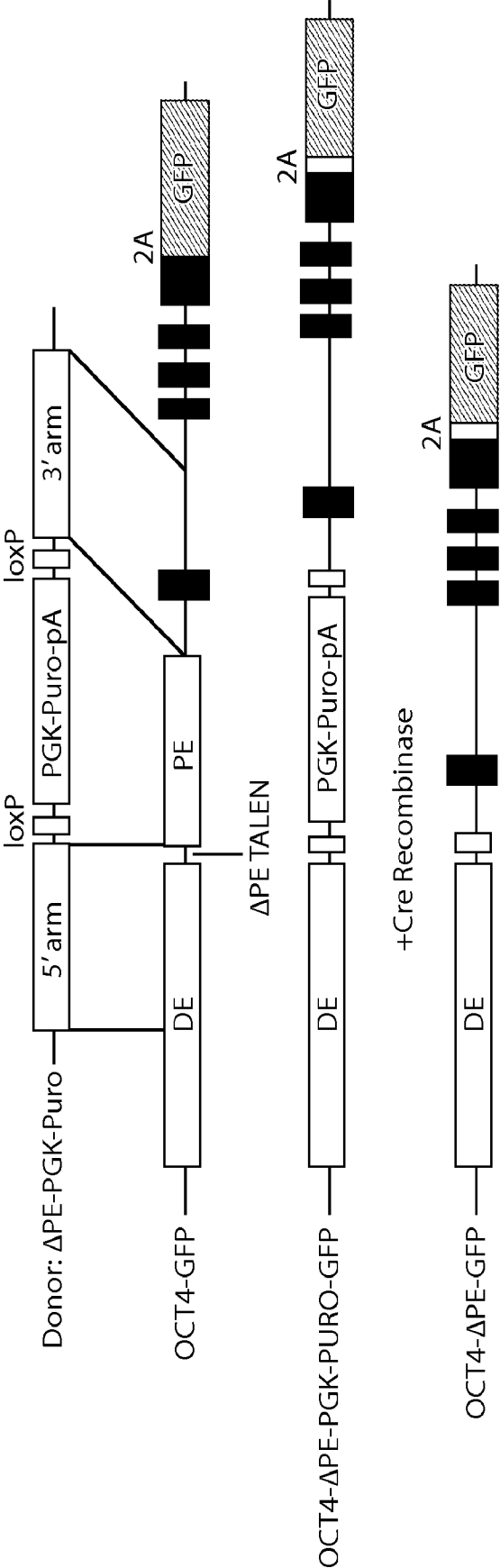


Figure 1A

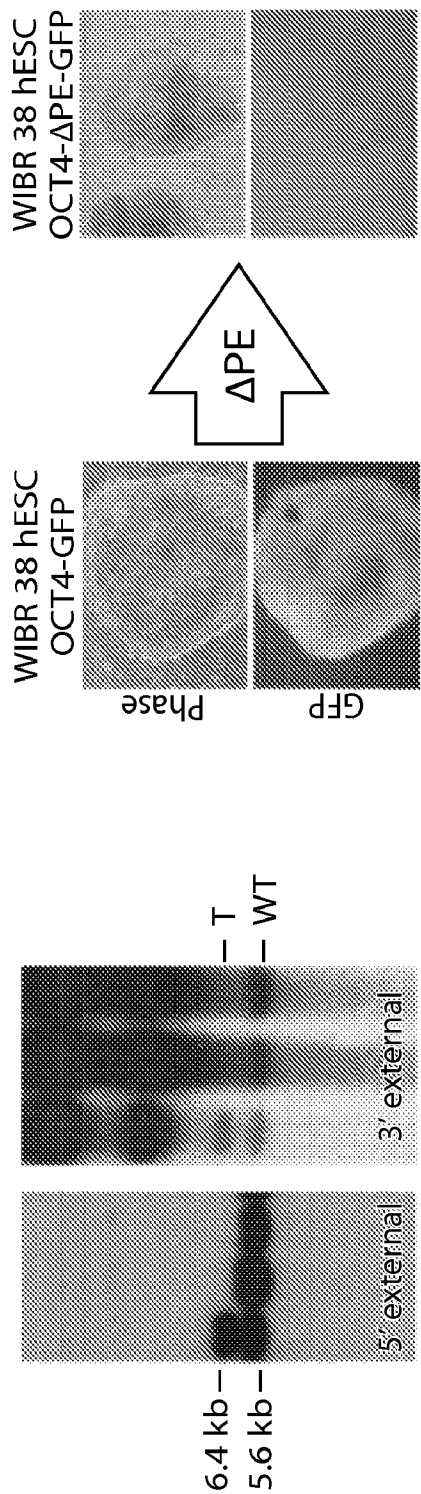


Figure 1B

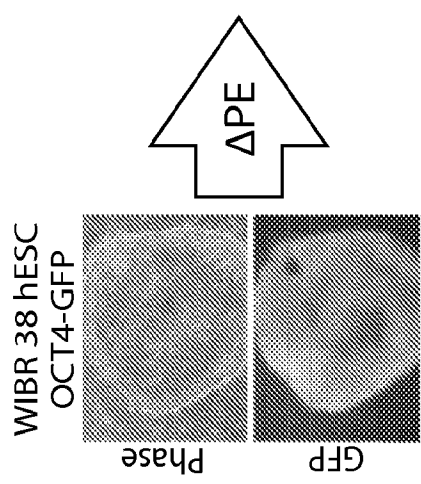


Figure 1C

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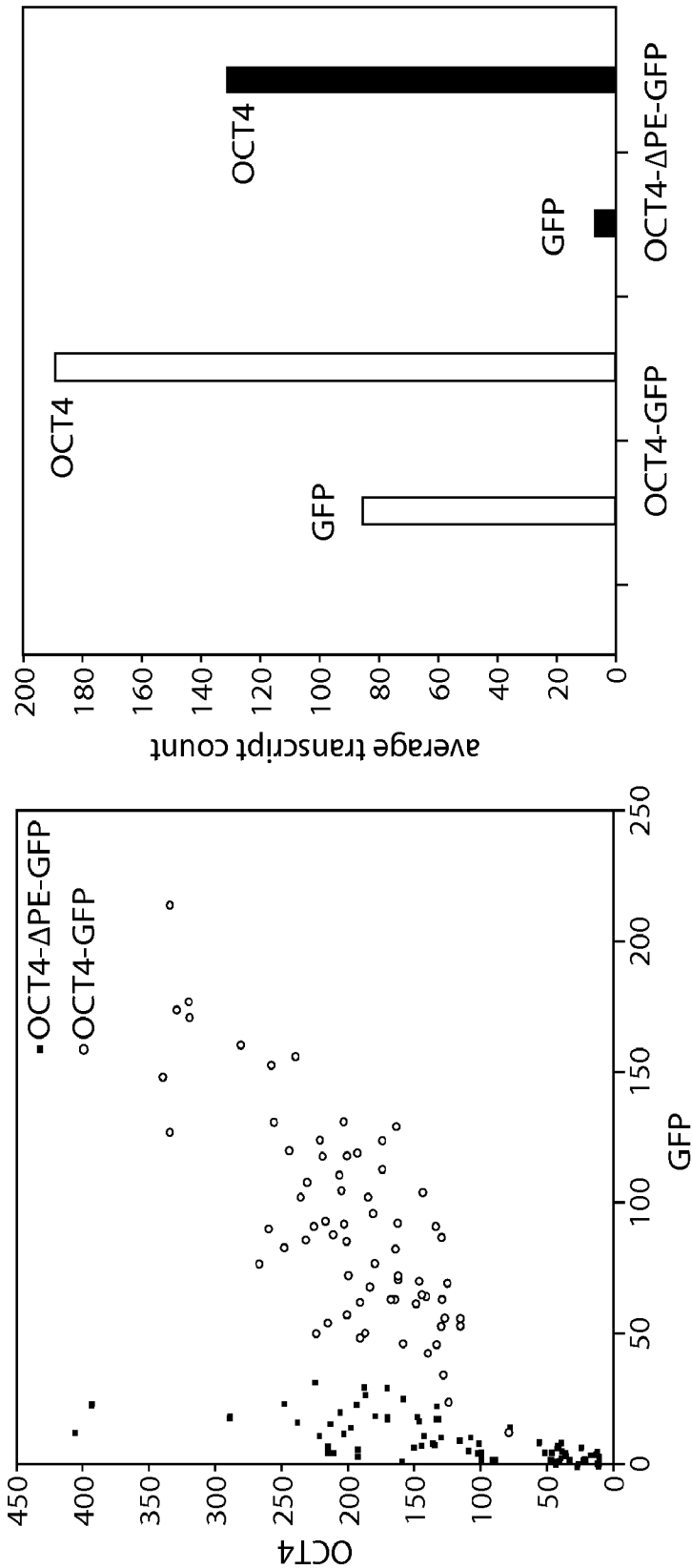


Figure 1D

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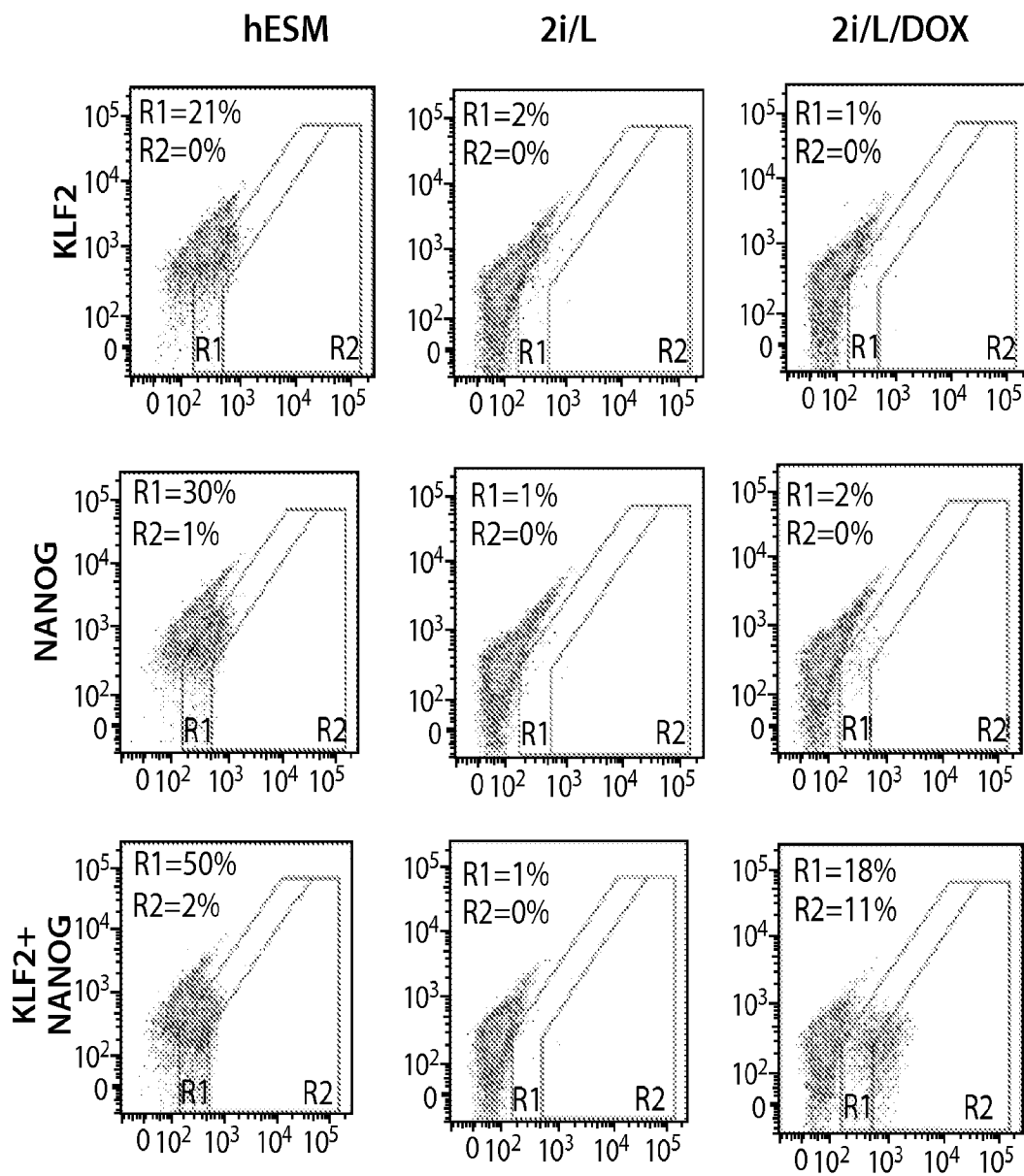


Figure 1E

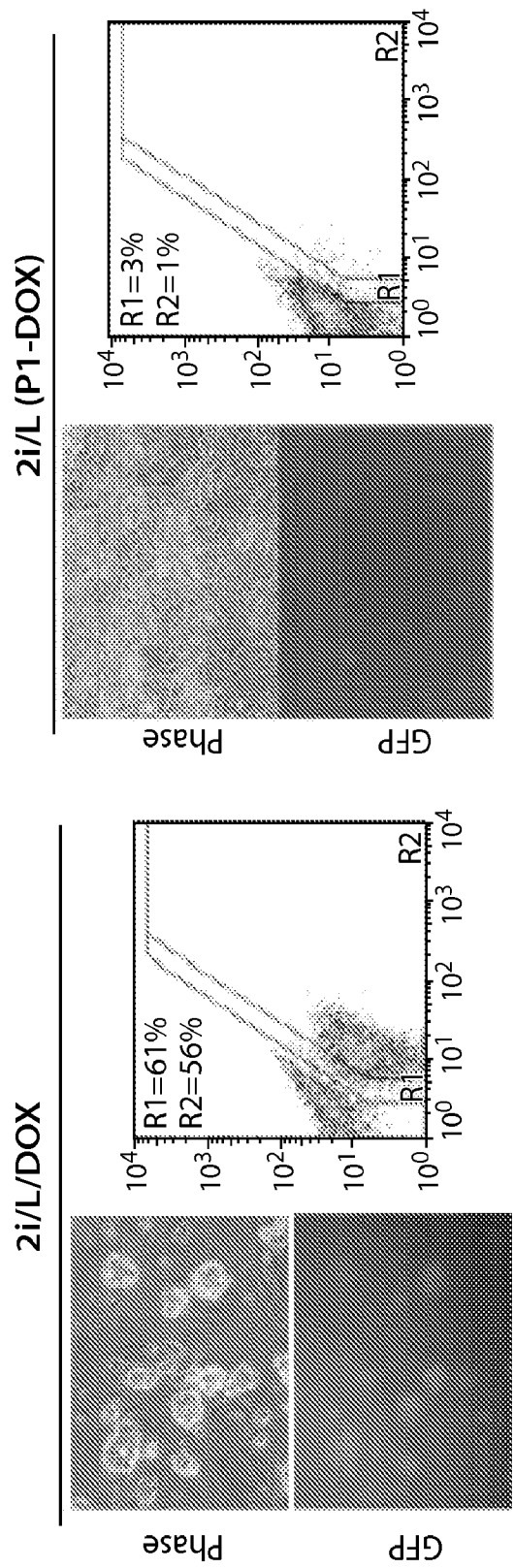


Figure 1F

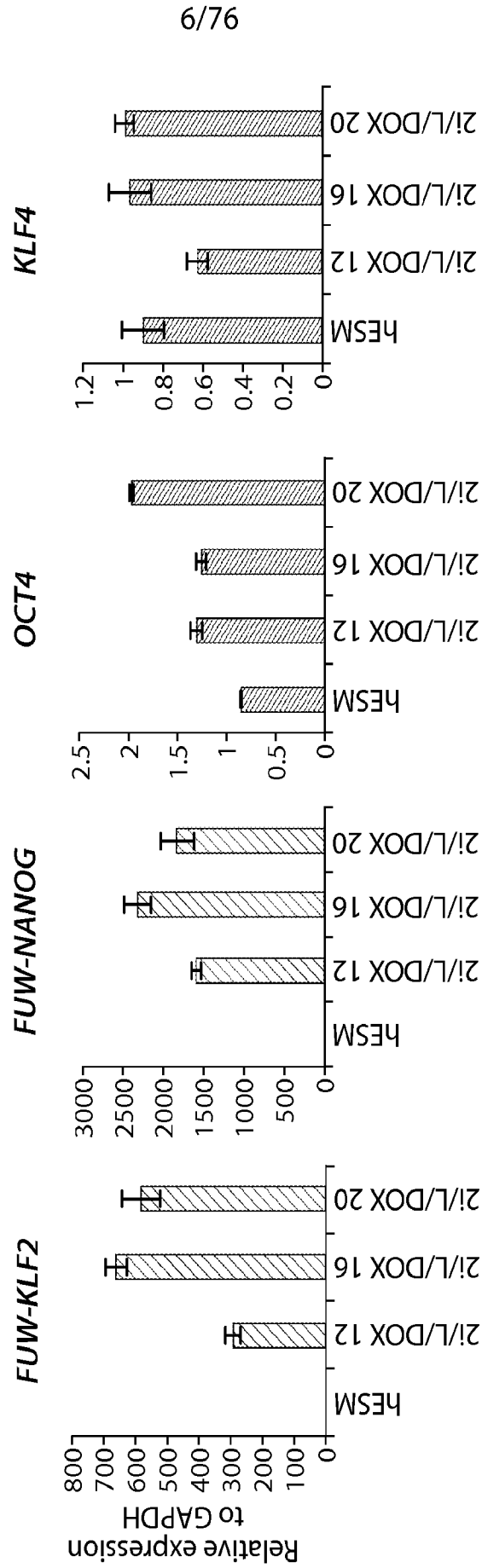


Figure 1G

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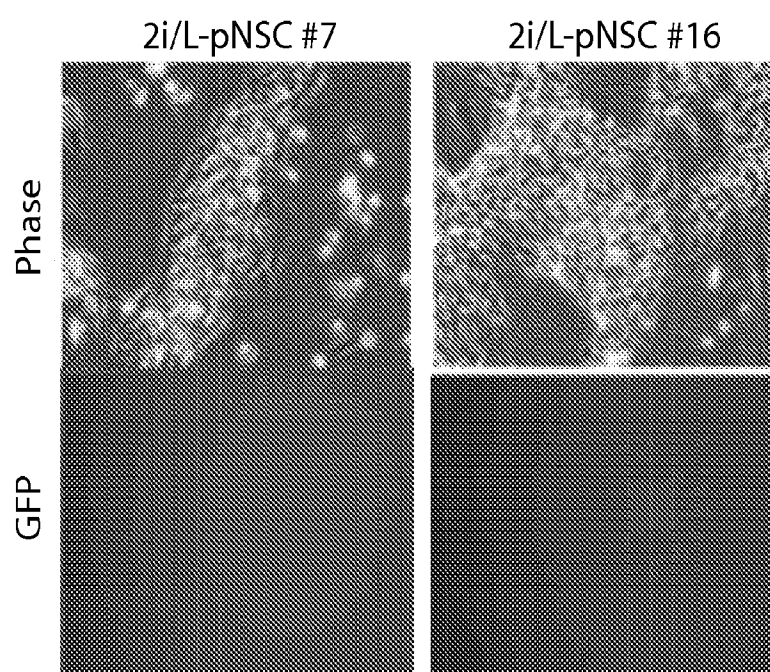


Figure 1H

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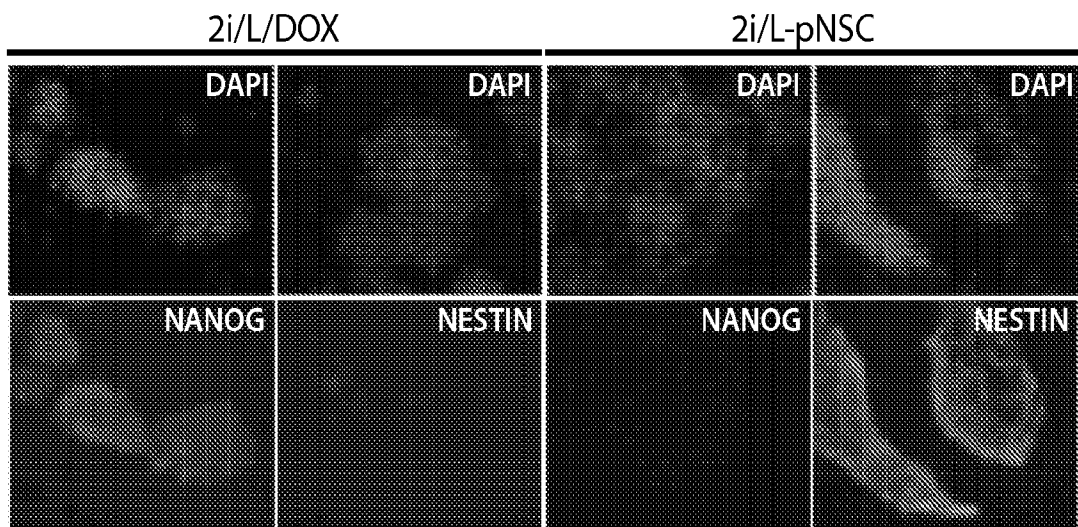


Figure 1I

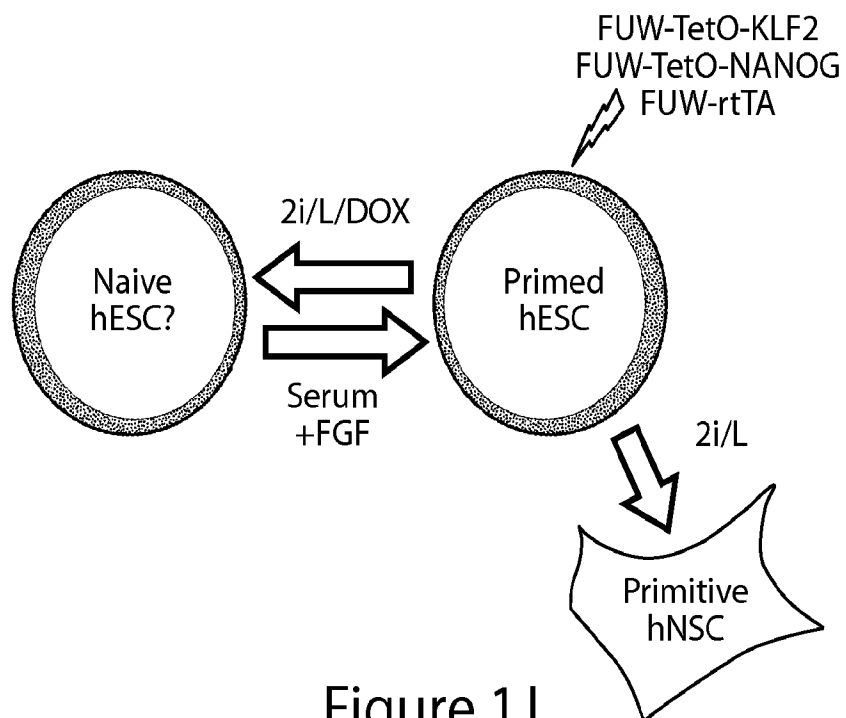
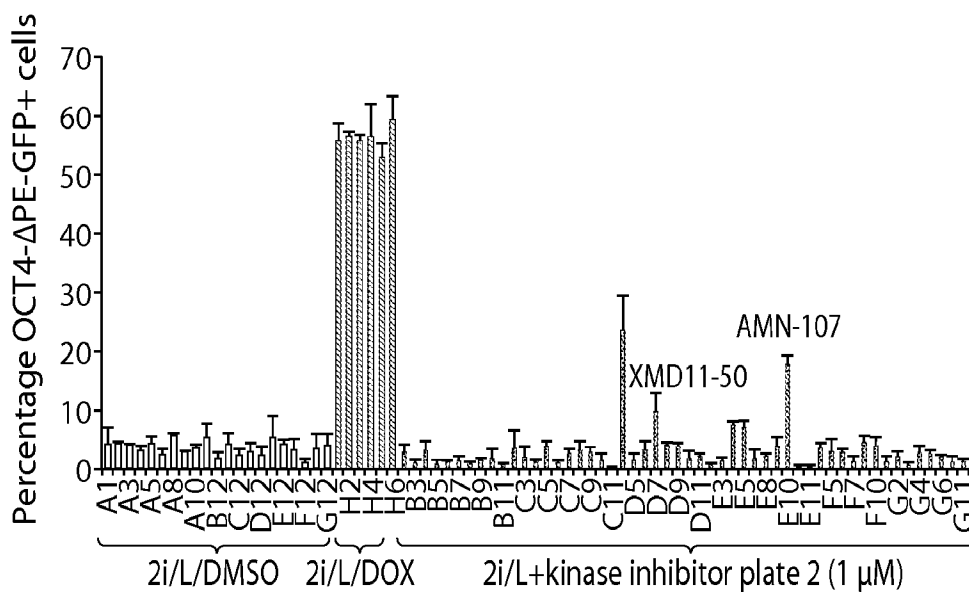
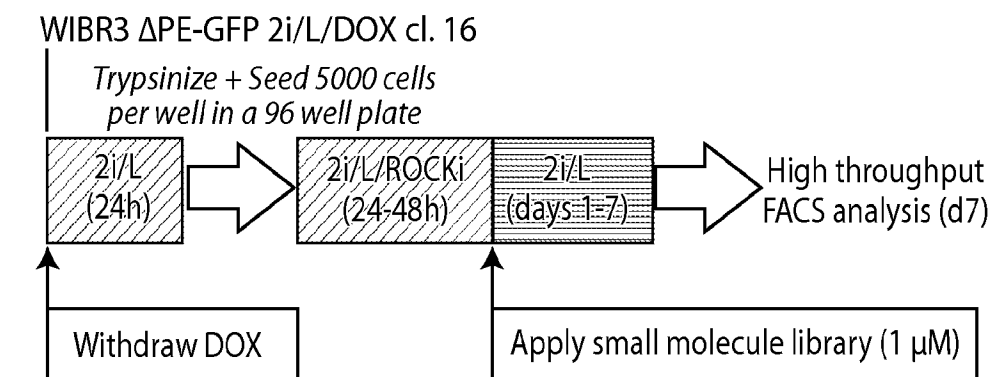


Figure 1J

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Maintenance Screen**Figure 2A**

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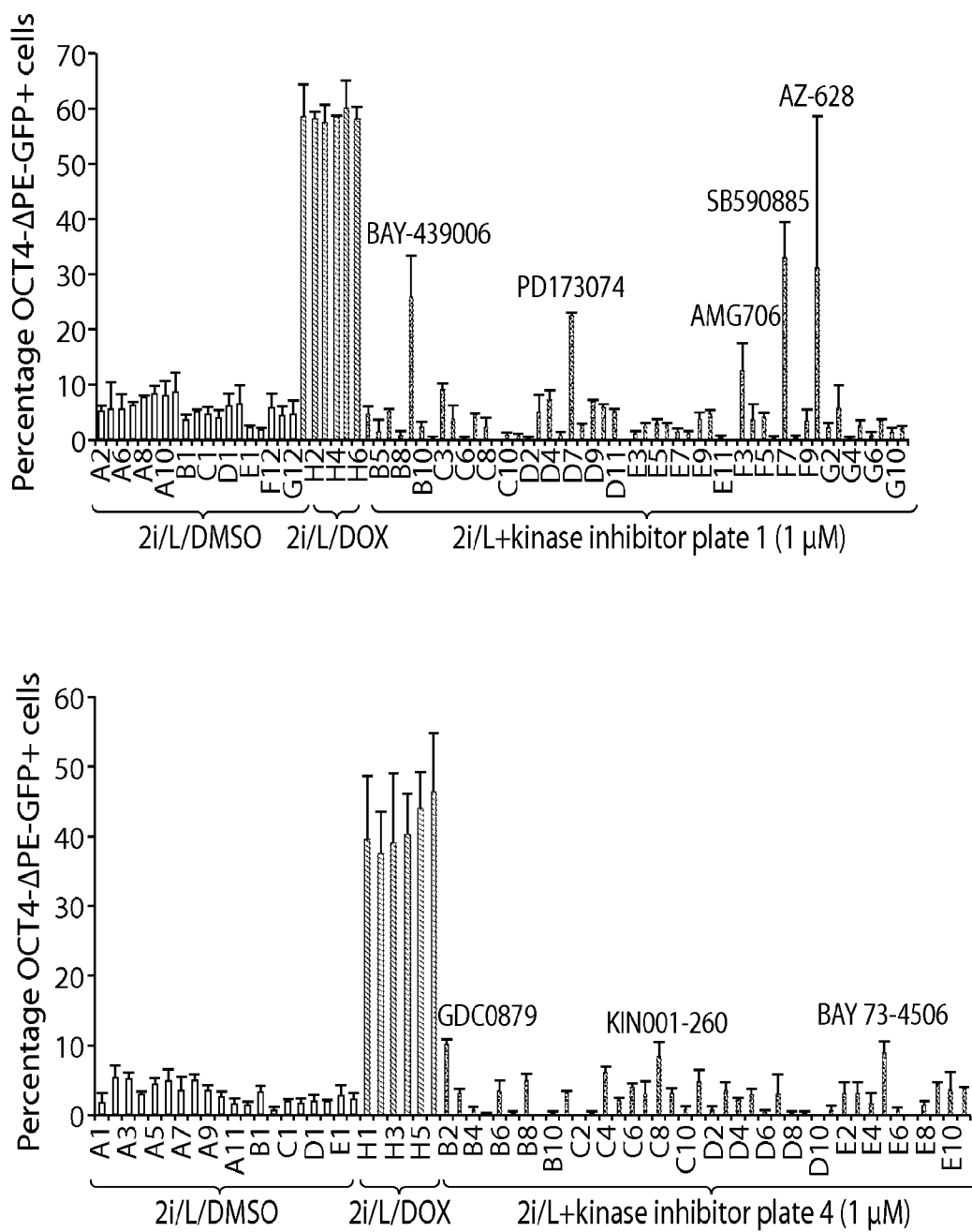


Figure 2B

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Compound	Target(s)
AMG706	VEGFR1
AMN-107	ANL
AZ-628	BRAF
BAY-439006	BRAF
BAY 73-4506	VEGFR2-TIE2
GDC-0879	BRAF
KIN001-260	IKK β
PD173074	FGFR1
SB590885	BRAF
XMD11-50	LRRK2/ERK5

Figure 2C

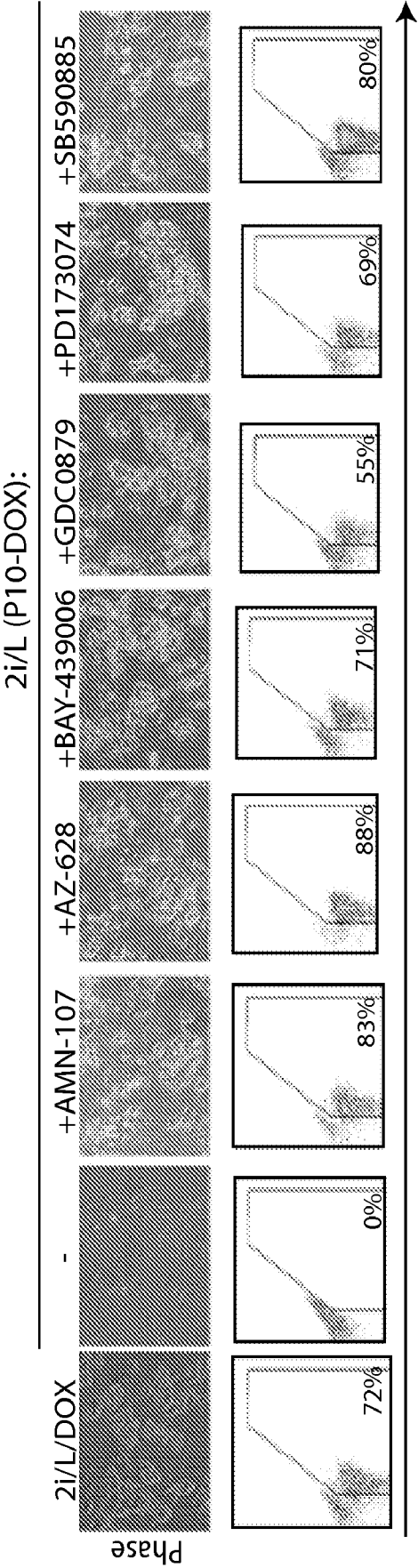


Figure 2D

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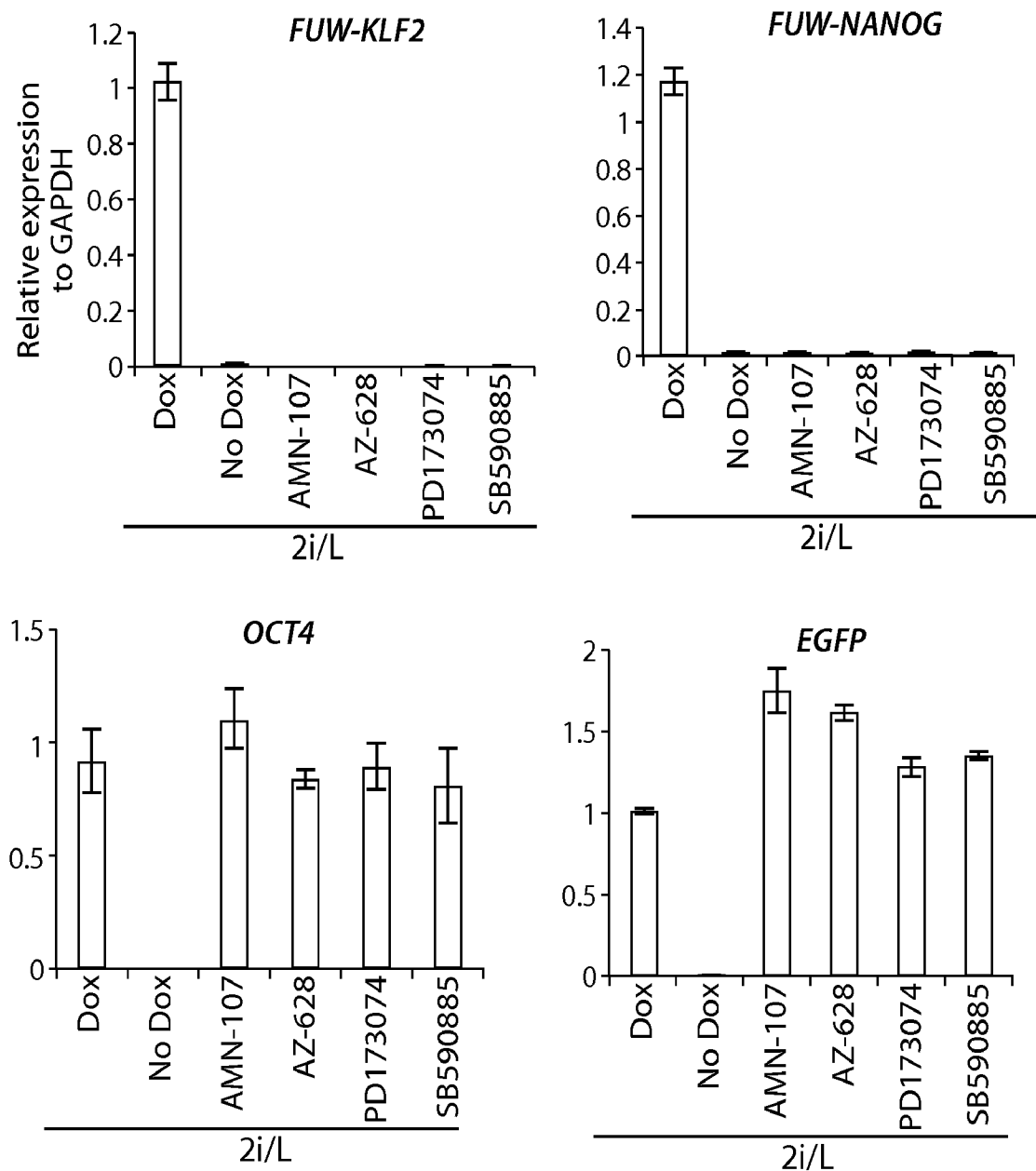
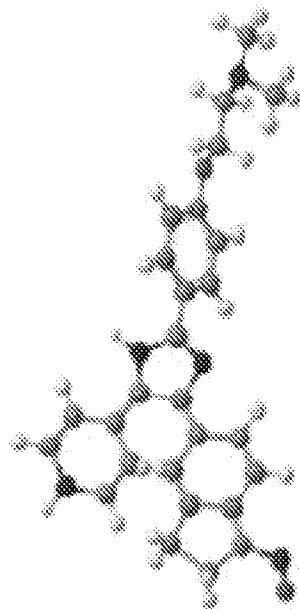


Figure 2E

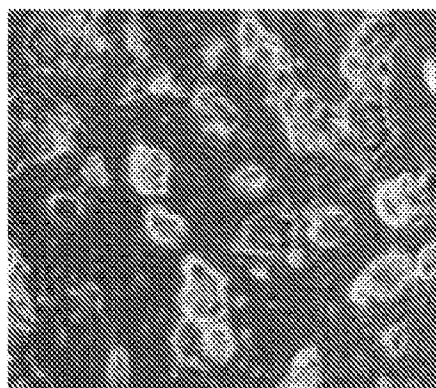
14/76



SB590885

Figure 2F

2i/L/DOX



2i/L/SB59
(P8-DOX)

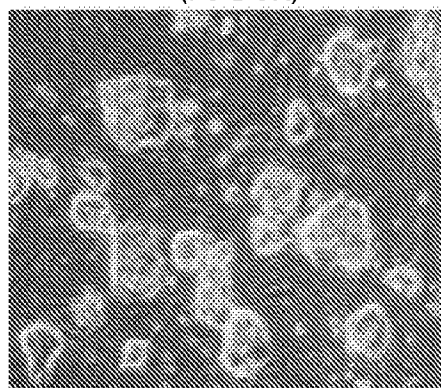


Figure 2G

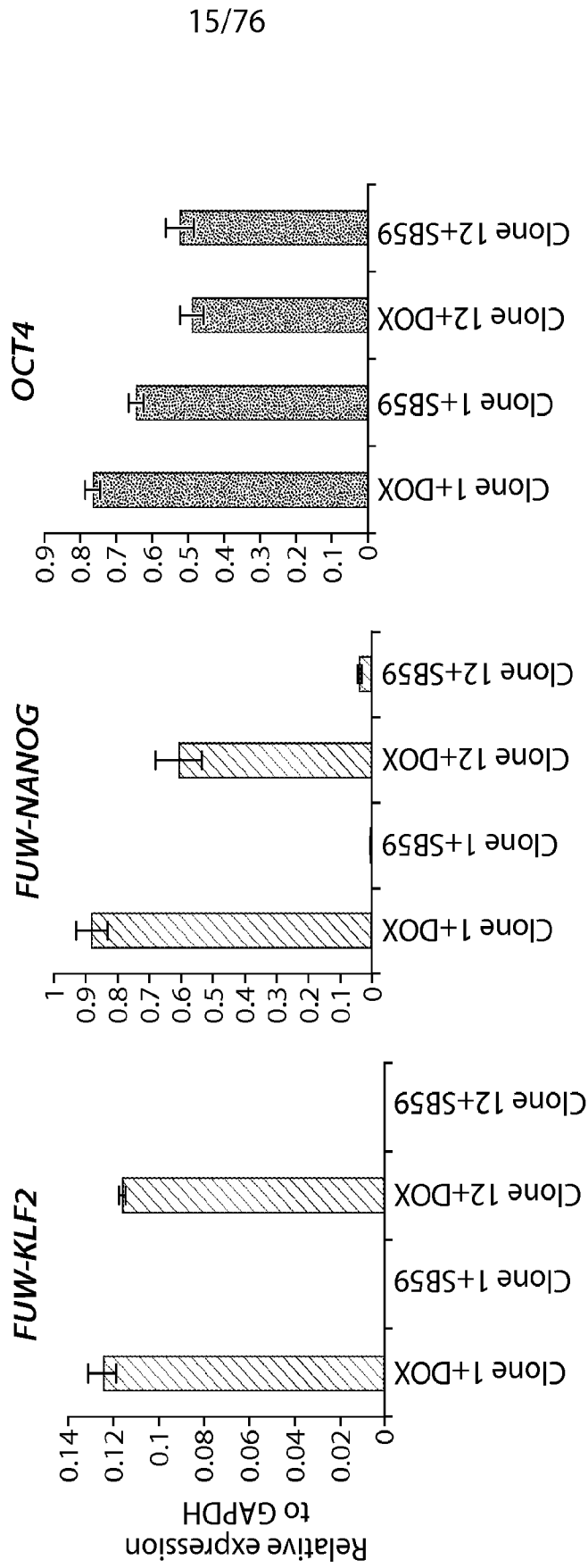


Figure 2H

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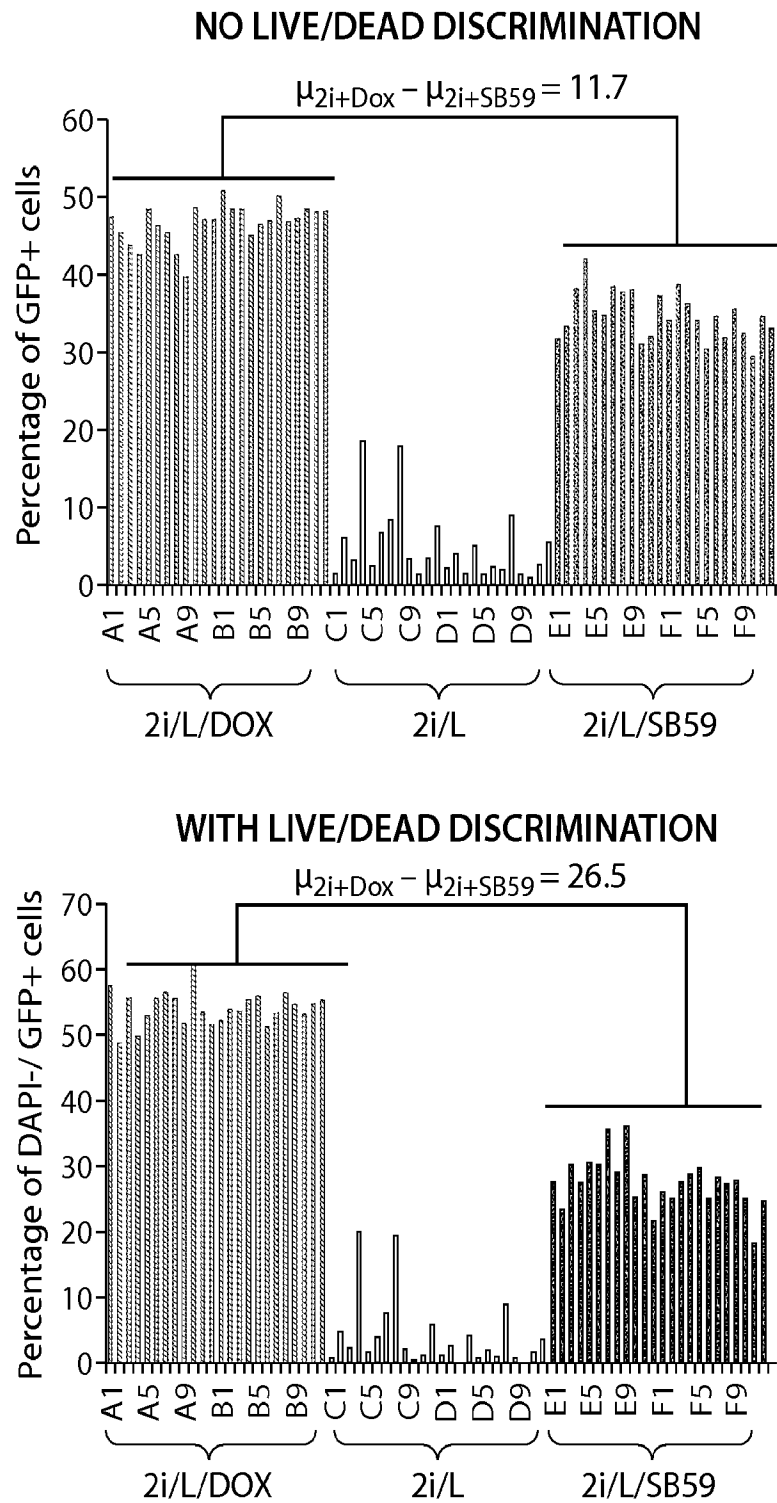


Figure 3A

17/76

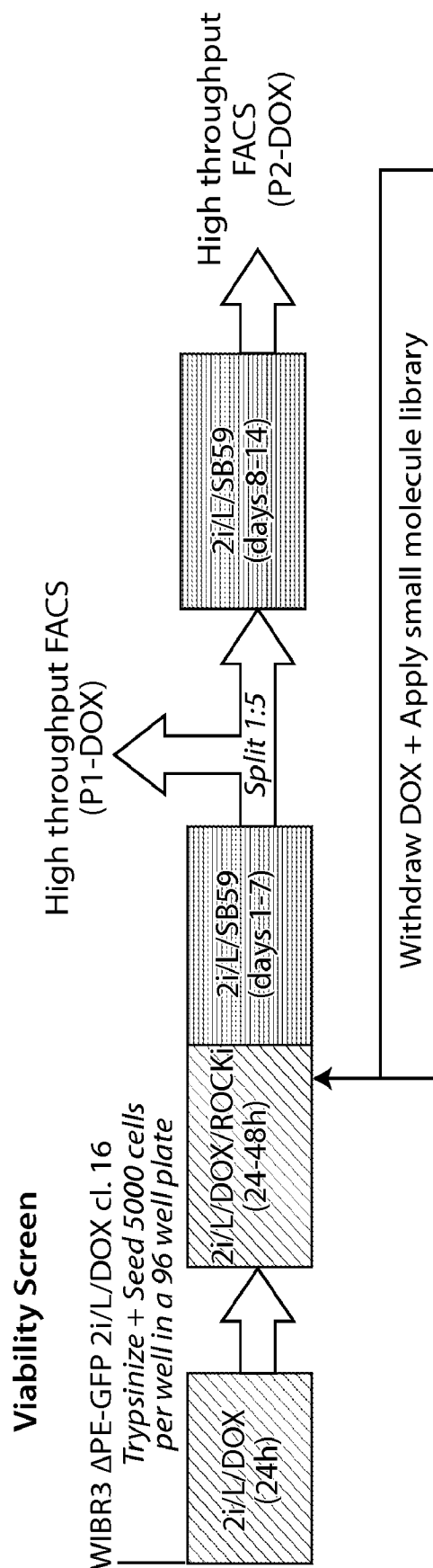


Figure 3B

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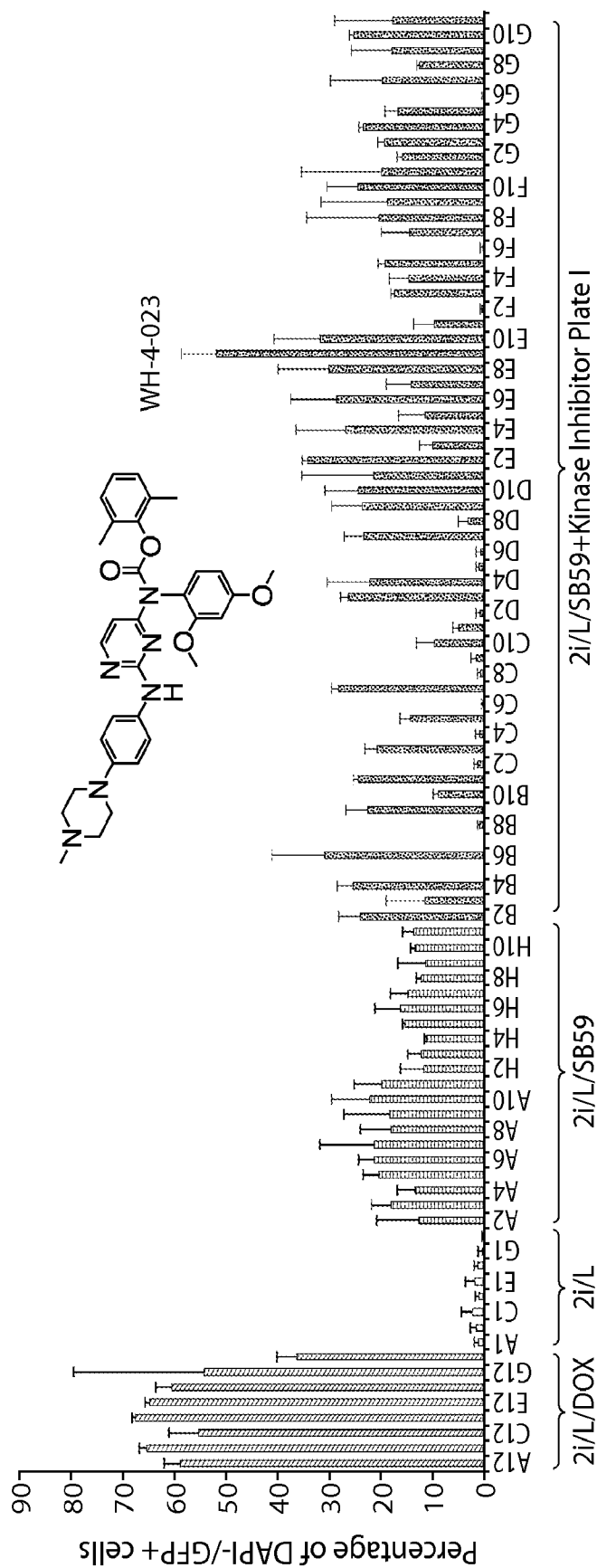


Figure 3C

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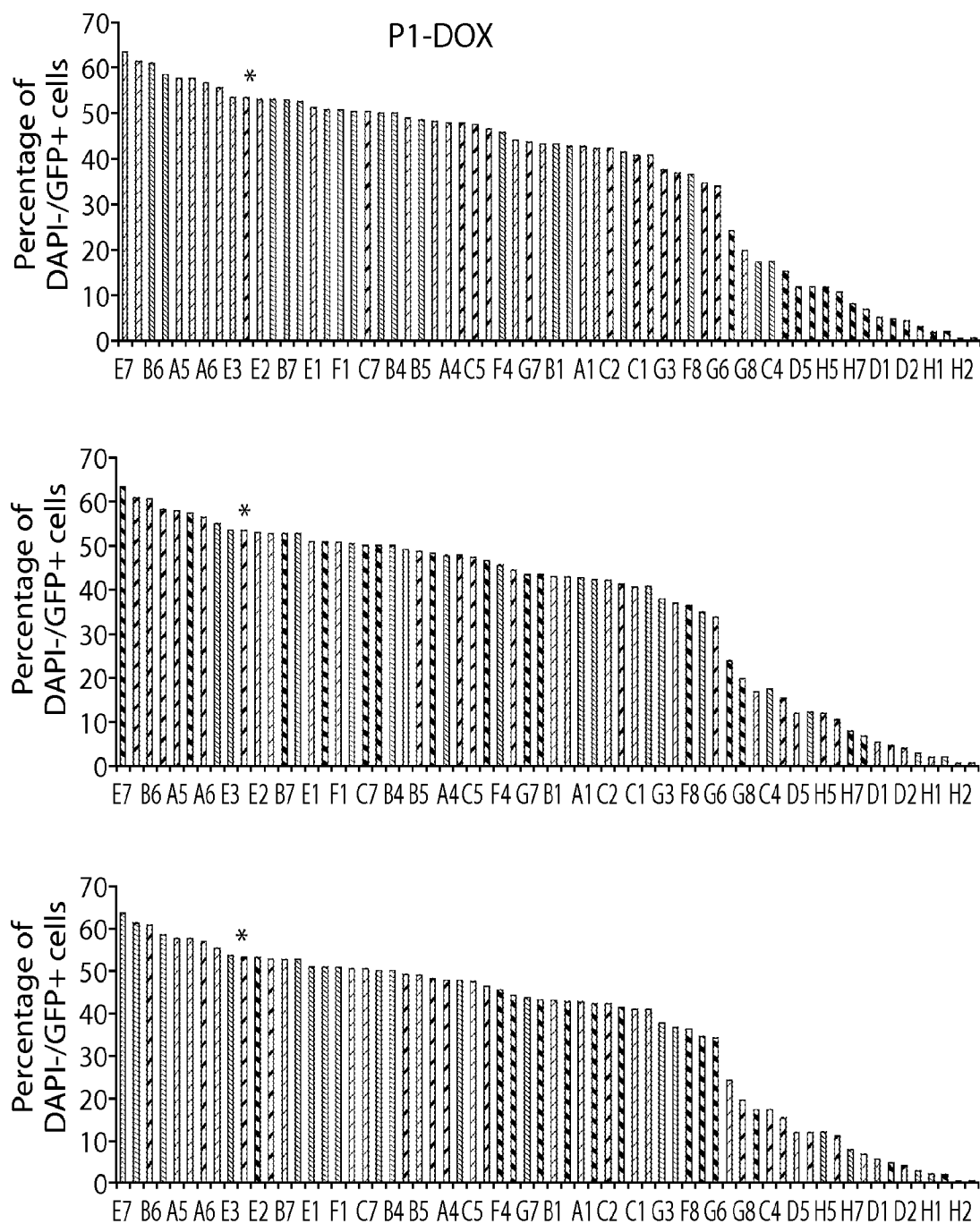


Figure 3D

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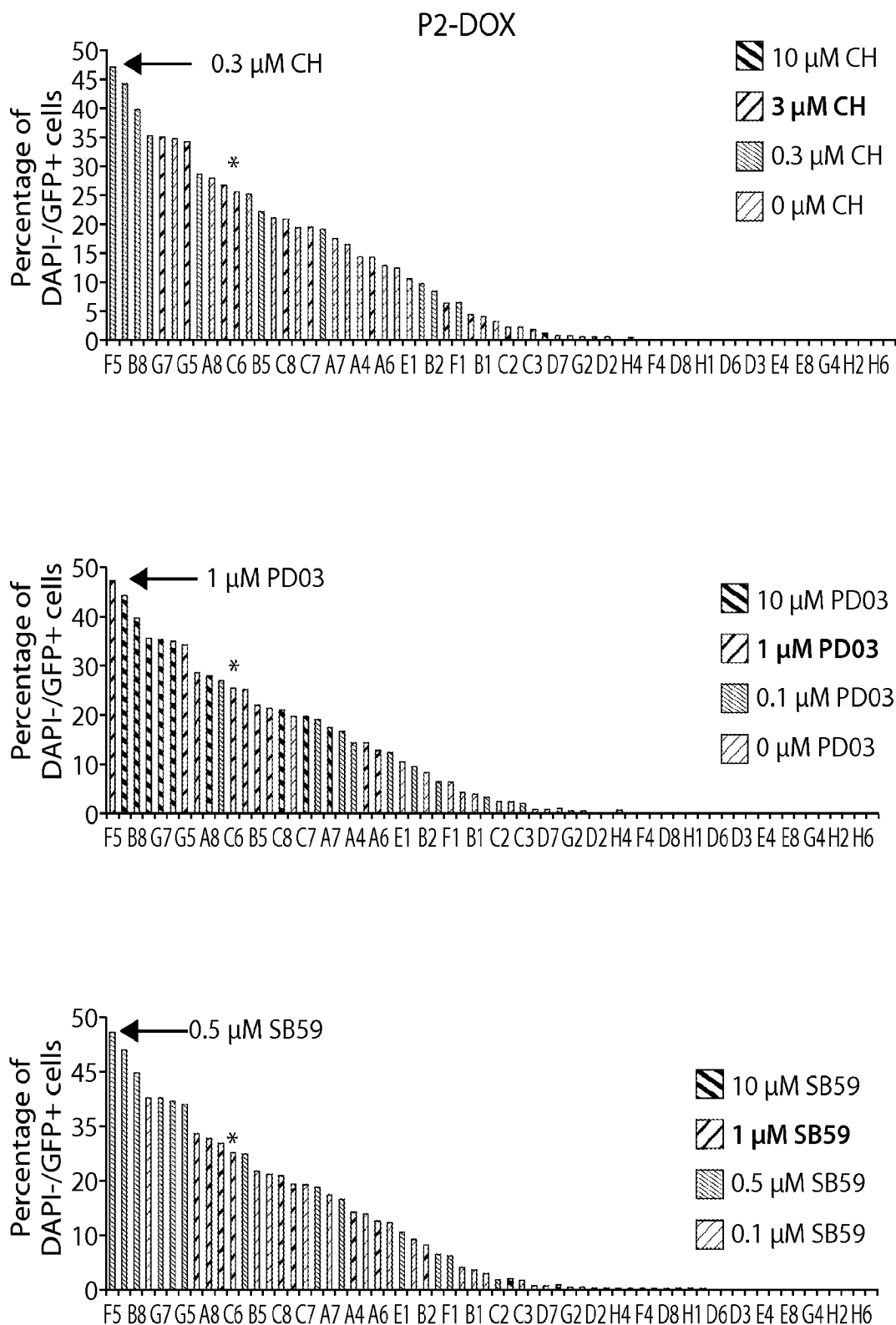


Figure 3E

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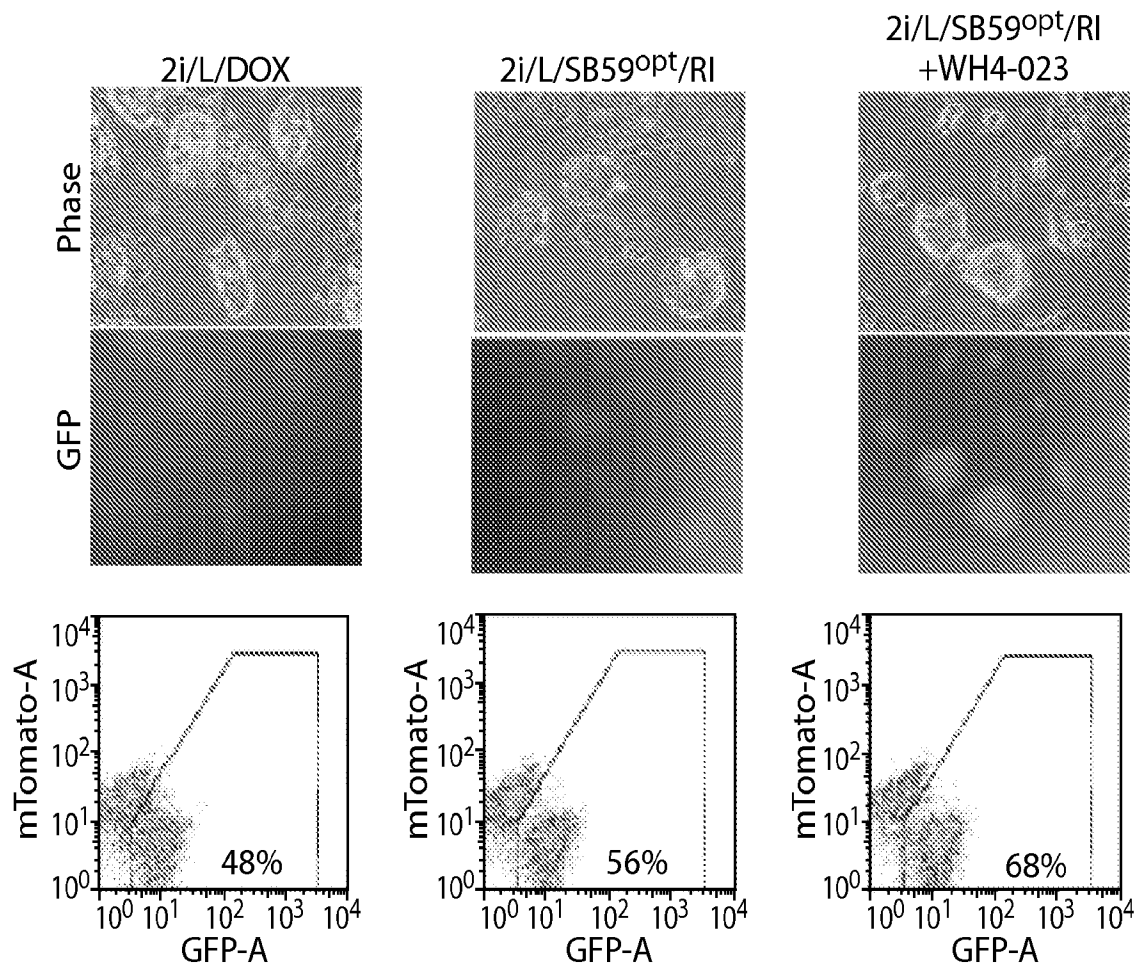


Figure 3F

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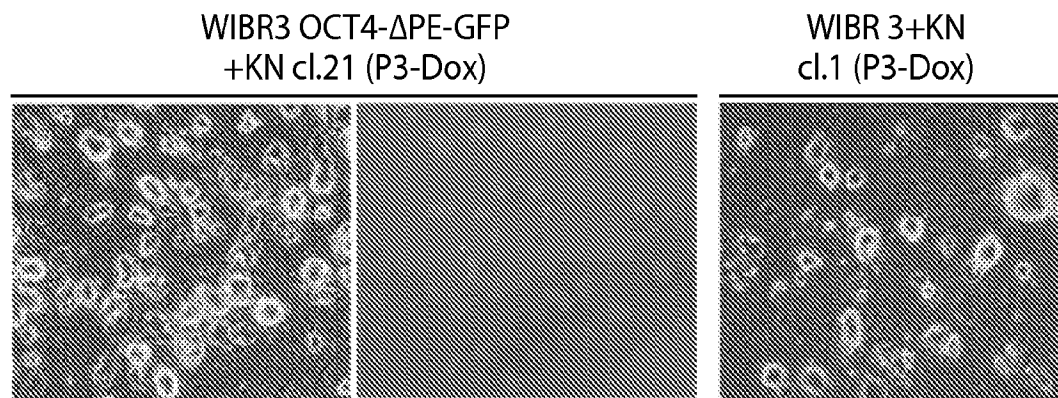


Figure 3G

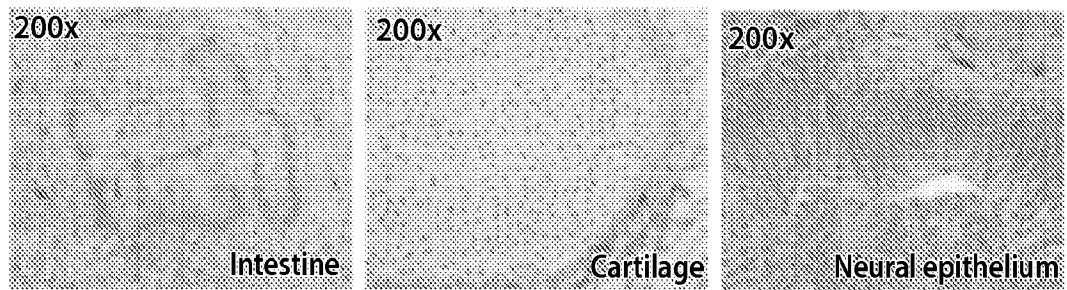
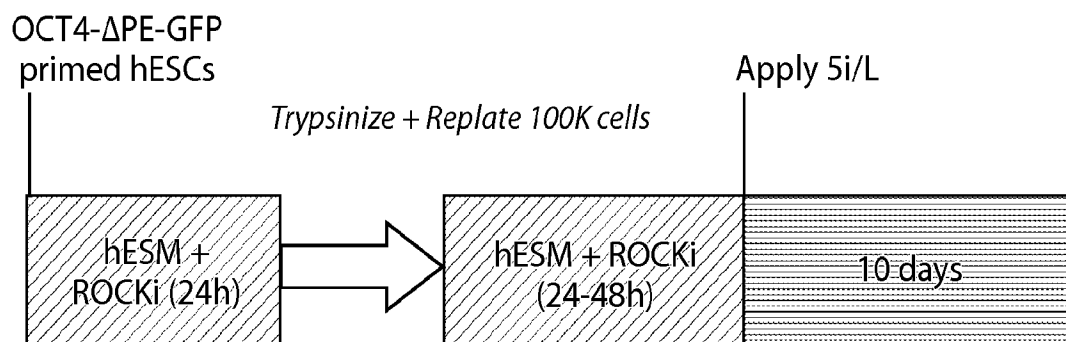
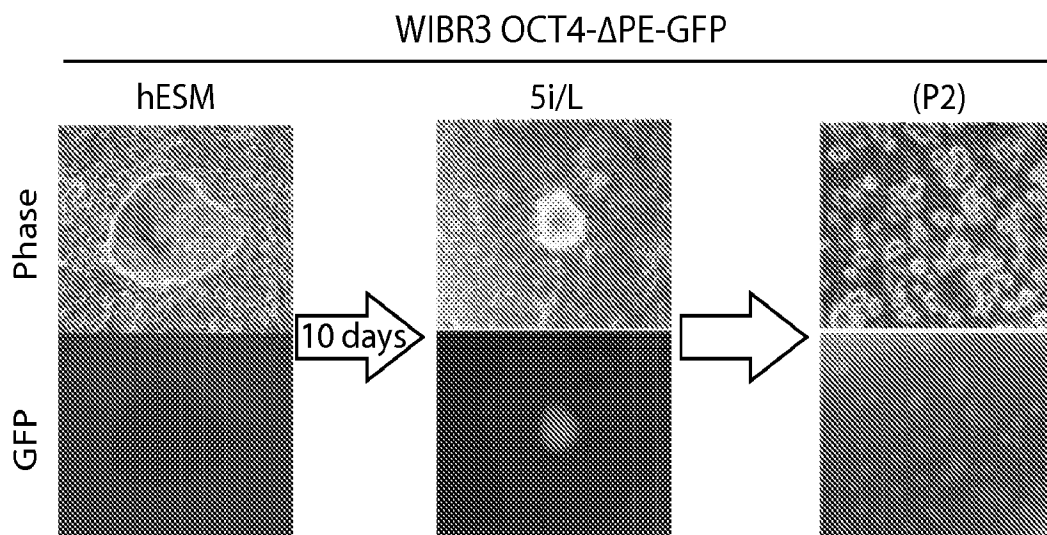


Figure 3H

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Transgene-free conversion**Figure 4A****Figure 4B**

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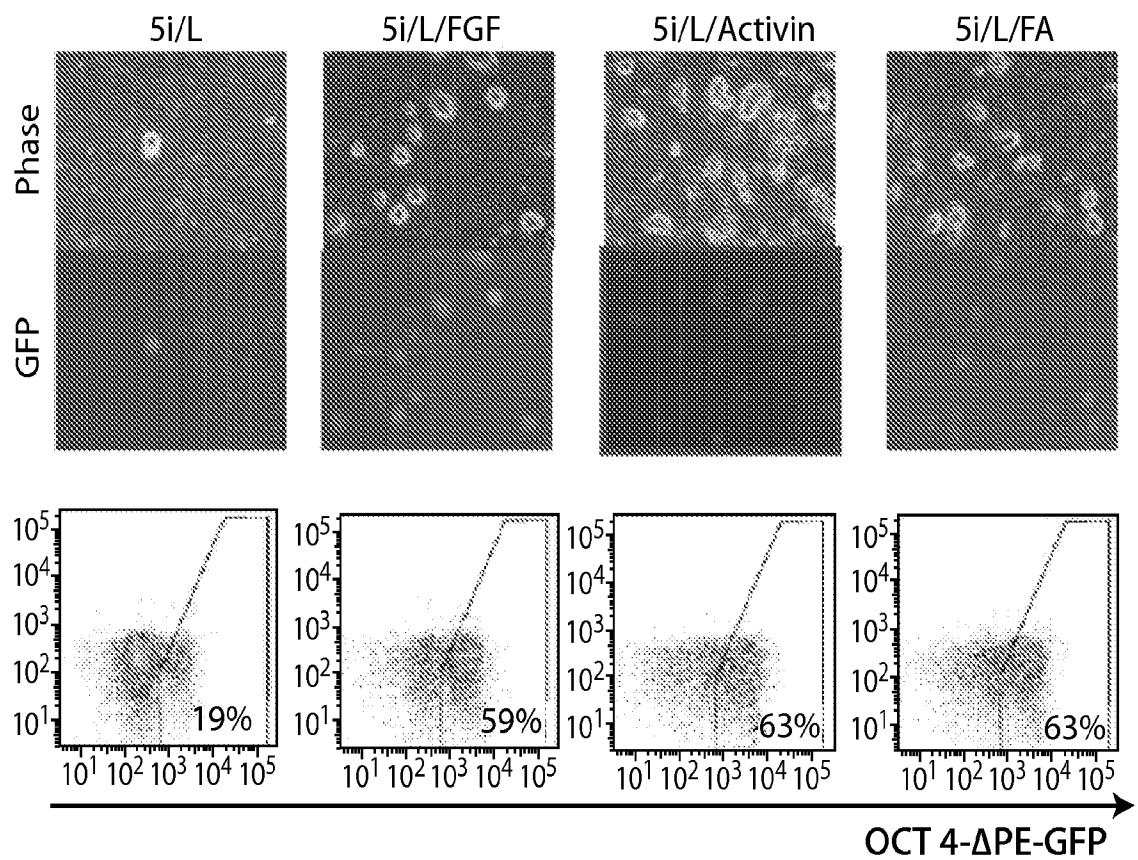


Figure 4C

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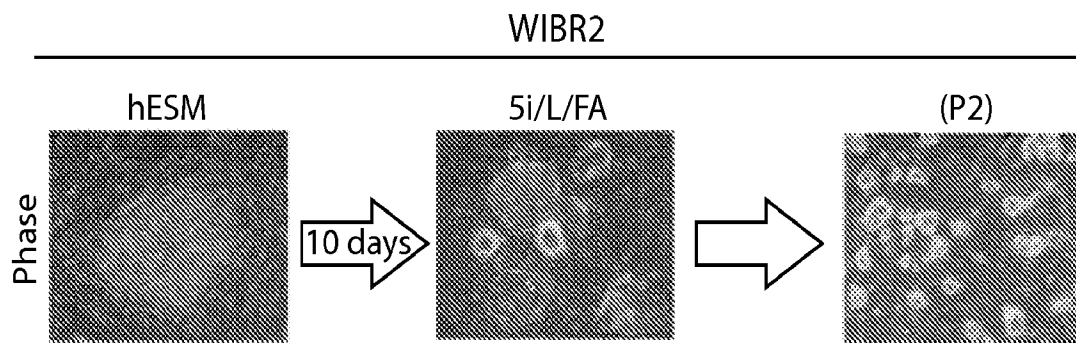


Figure 4D

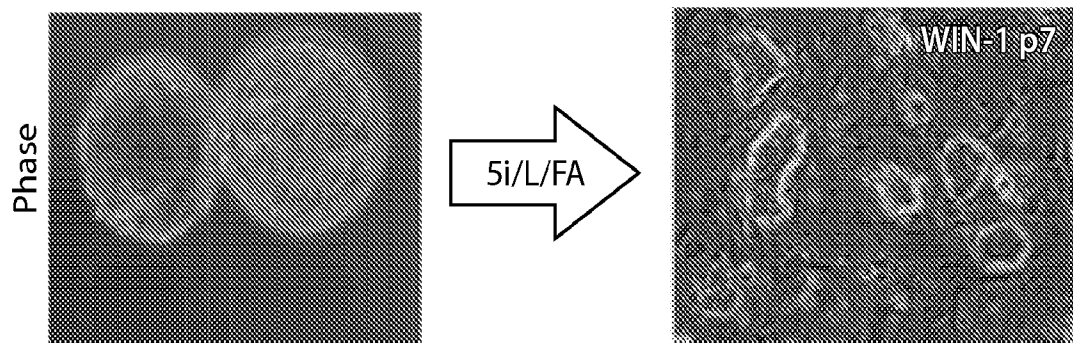


Figure 4E

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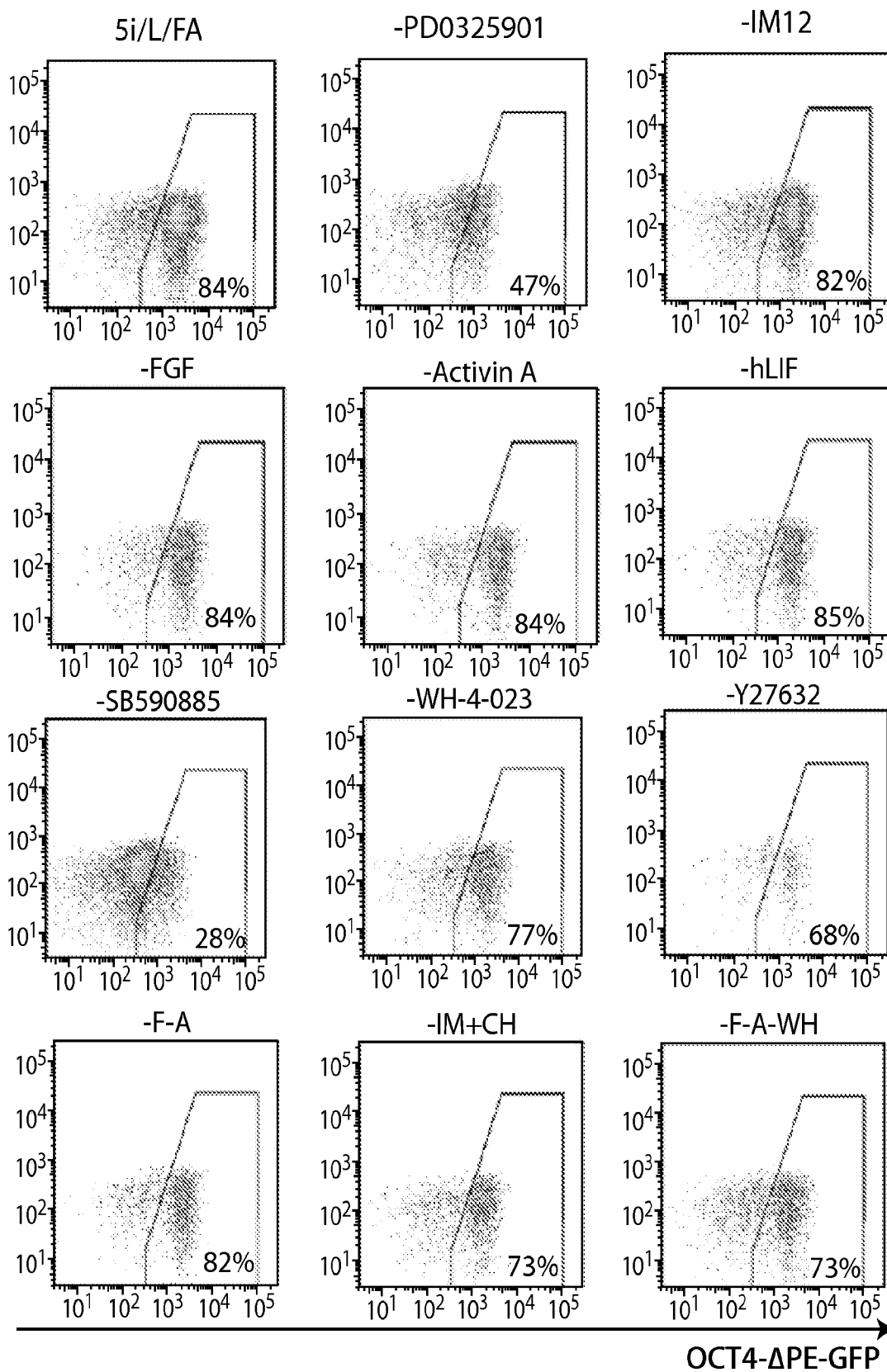


Figure 4F

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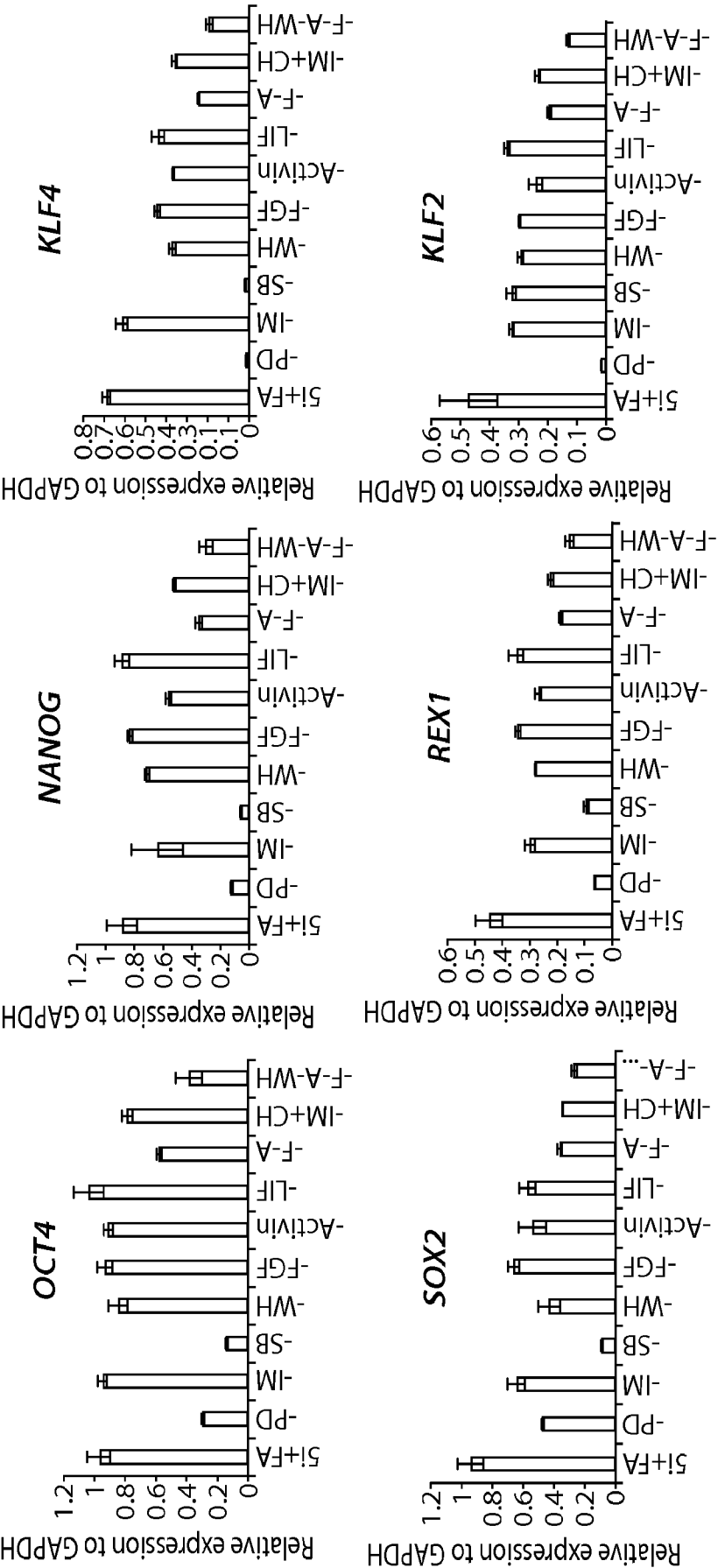


Figure 4G

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	Gafni (2013)	Chan (2013)	Valamehr (2014)	Ware (2014)	5i/L/A
Inhibitors	MEKi	MEKi	MEKi	MEKi	MEKi
	GSK3i	GSK3i	GSK3i	GSK3i	GSK3i
	JNKi				
	P38i				
	PKCi				
	ROCKi		ROCKi		ROCKi
		BMPi			
					BRAFi
					SRCi
Growth factors	bFGF		bFGF	bFGF	
	TGF β				Activin
	hLIF	hLIF	hLIF		hLIF
Base	Albumax+N2 or 20% KSR	mTsr1 (bFGF+TGF β)	20% KSR	20% KSR	N2B27

Figure 5A

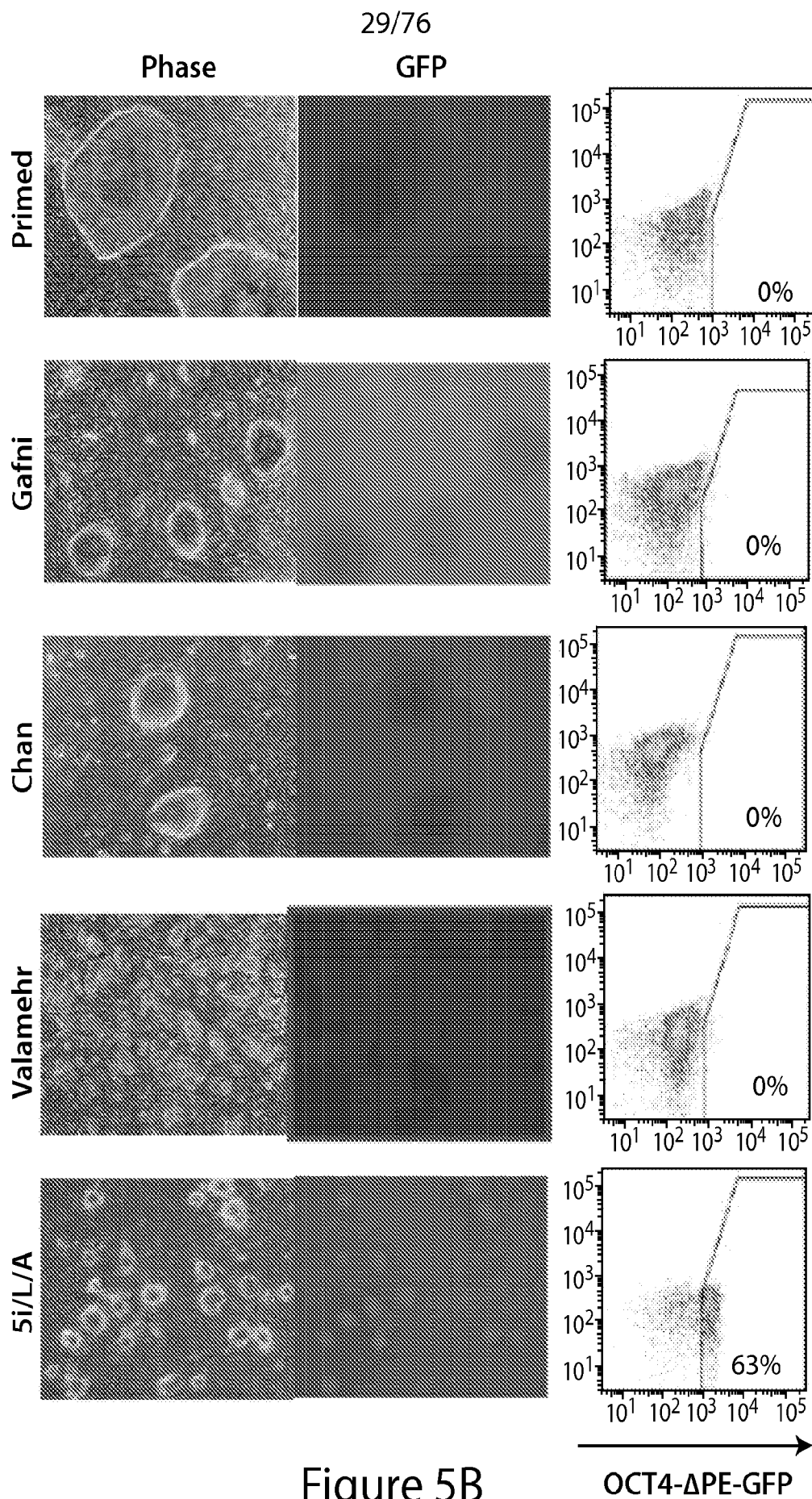


Figure 5B

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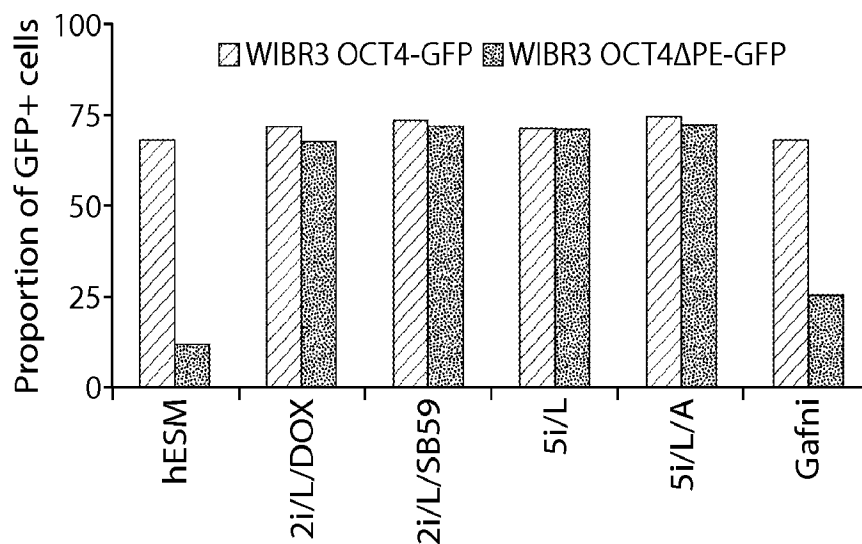


Figure 5C

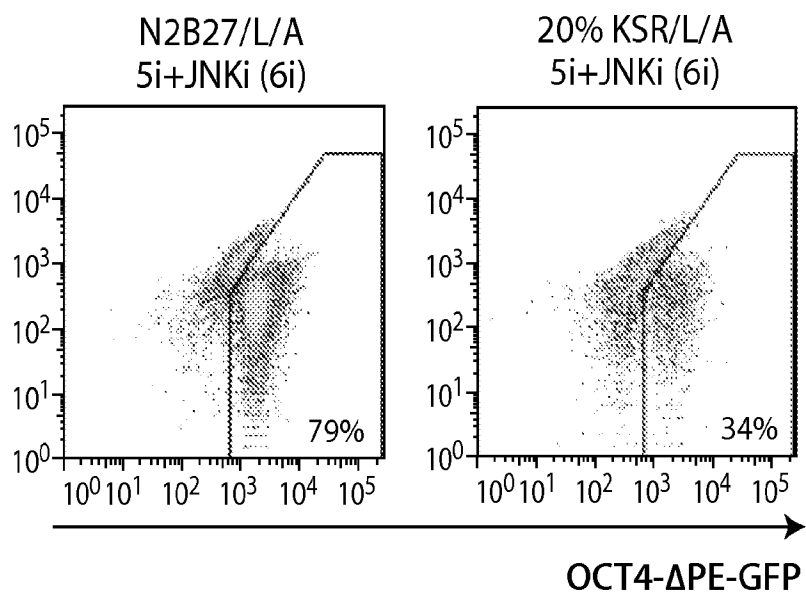


Figure 5D

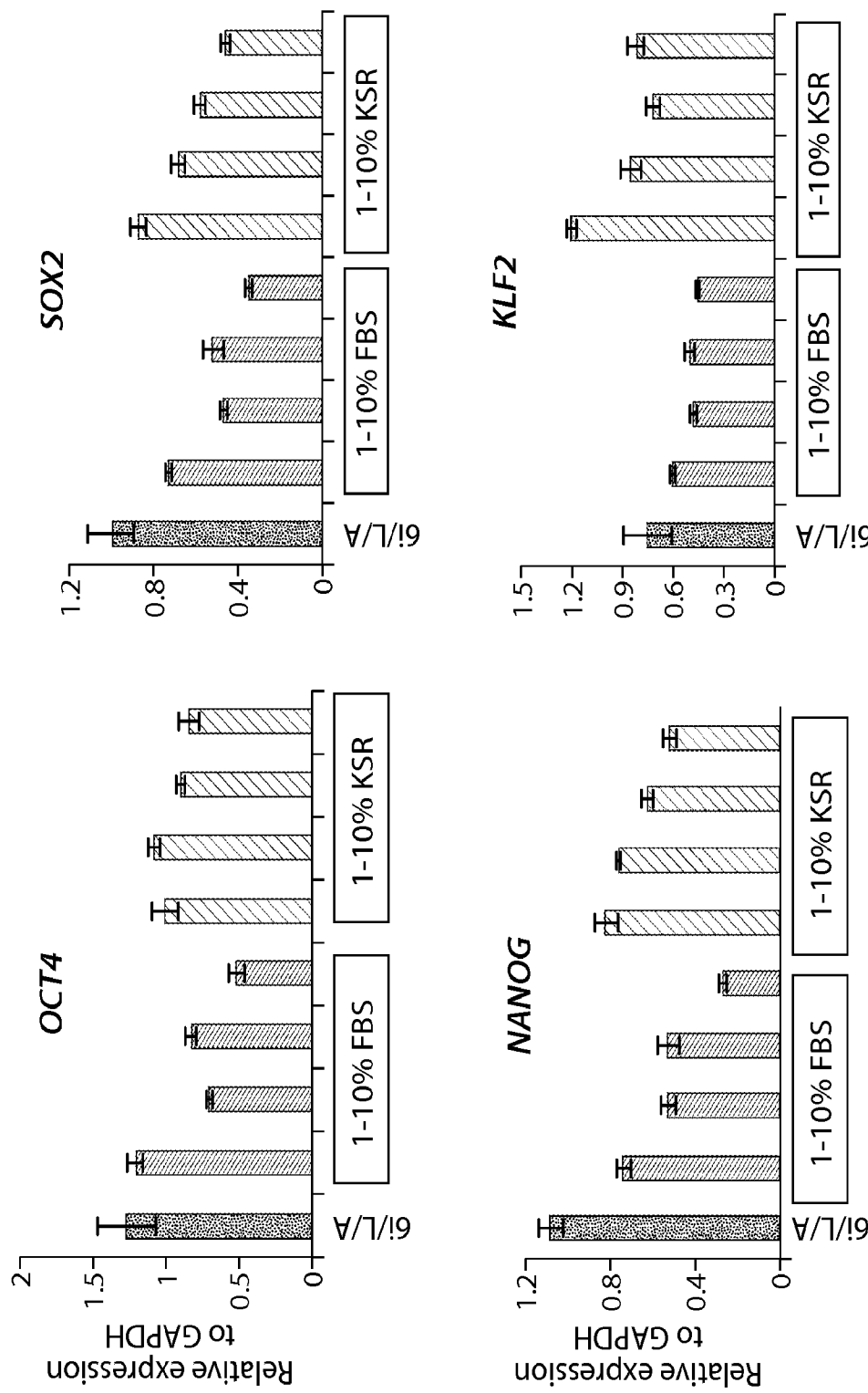


Figure 5E

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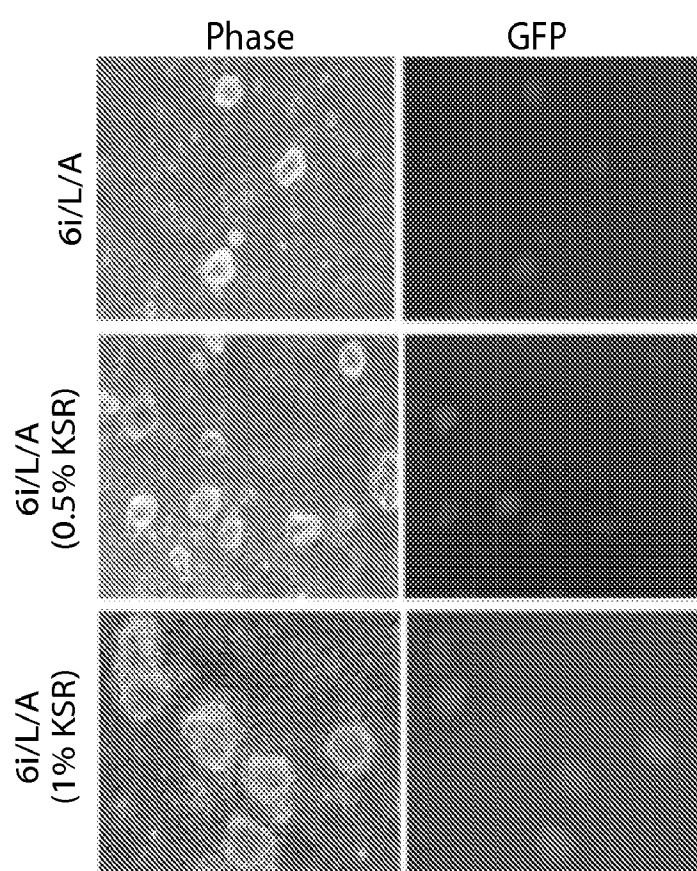


Figure 5F

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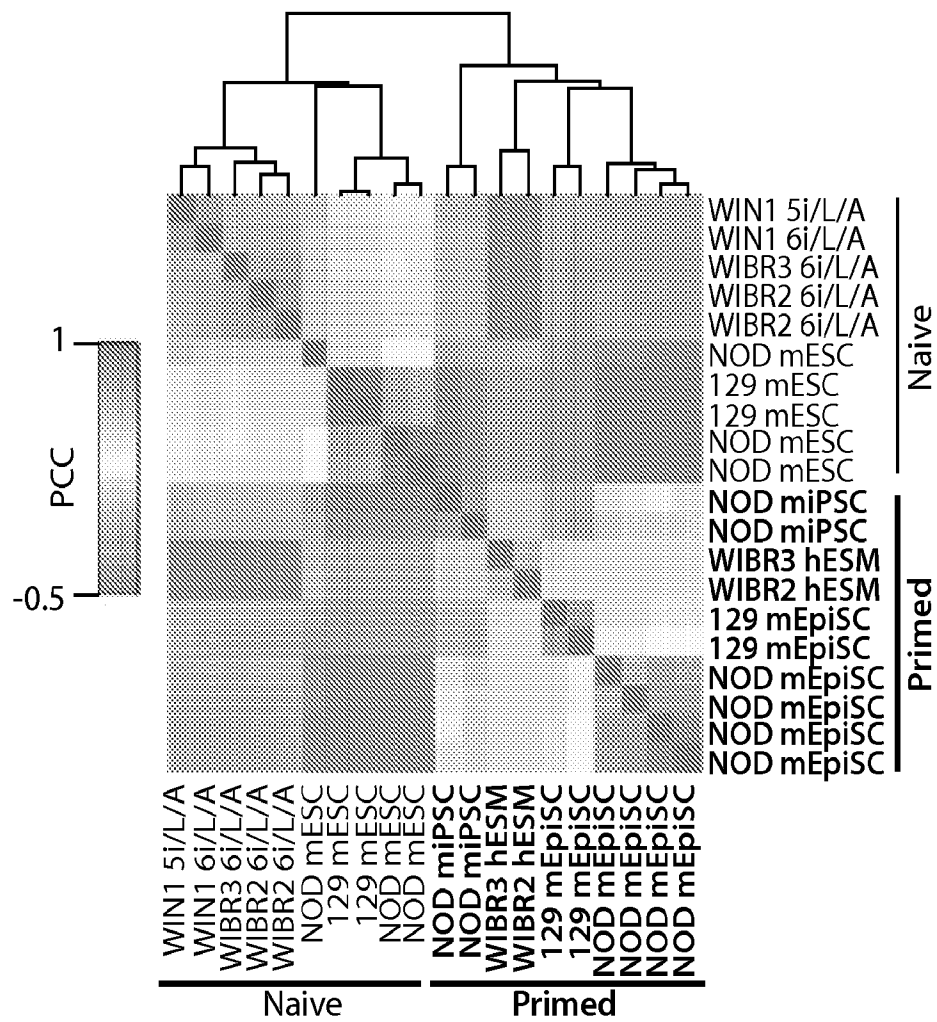
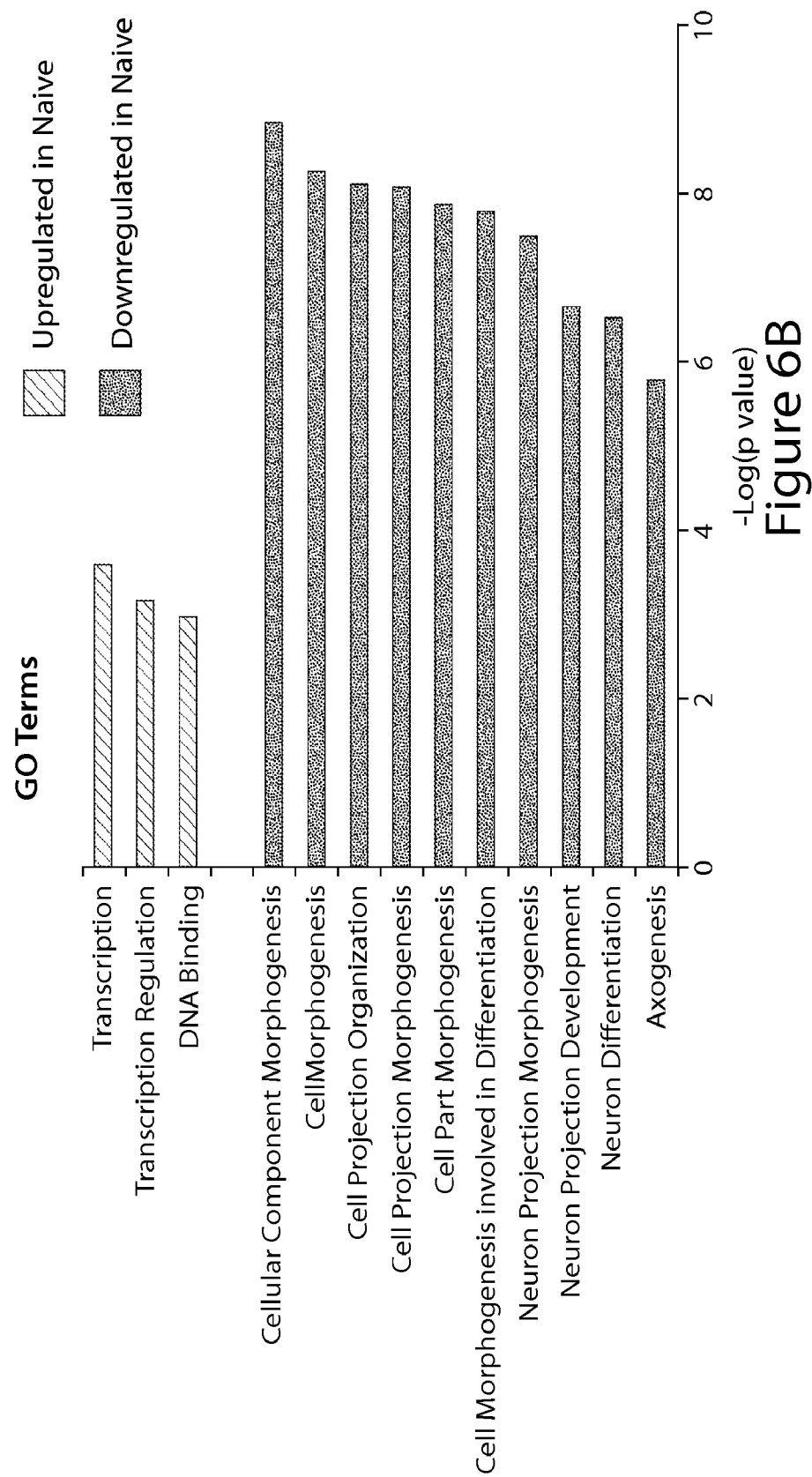


Figure 6A



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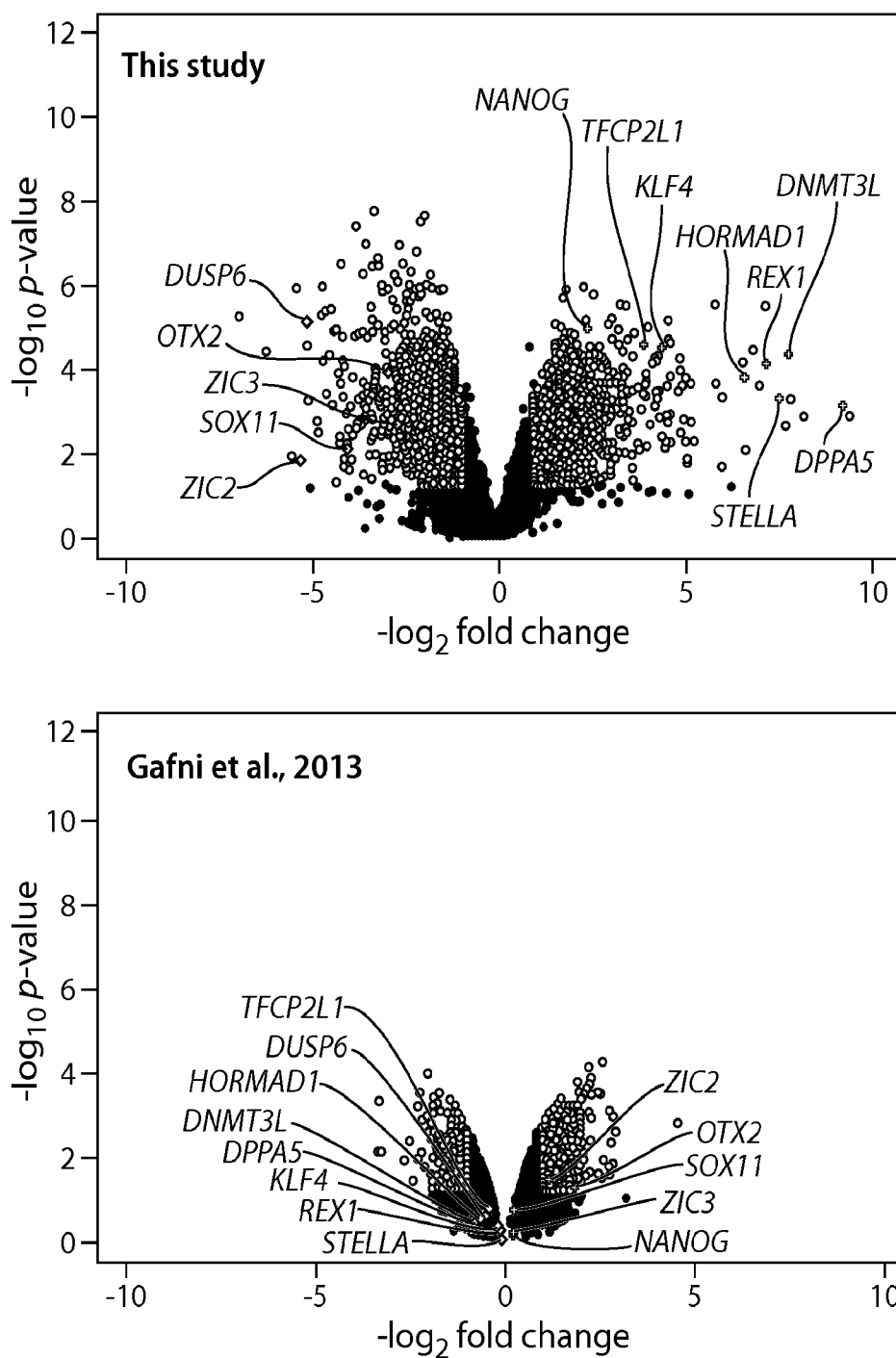


Figure 6C

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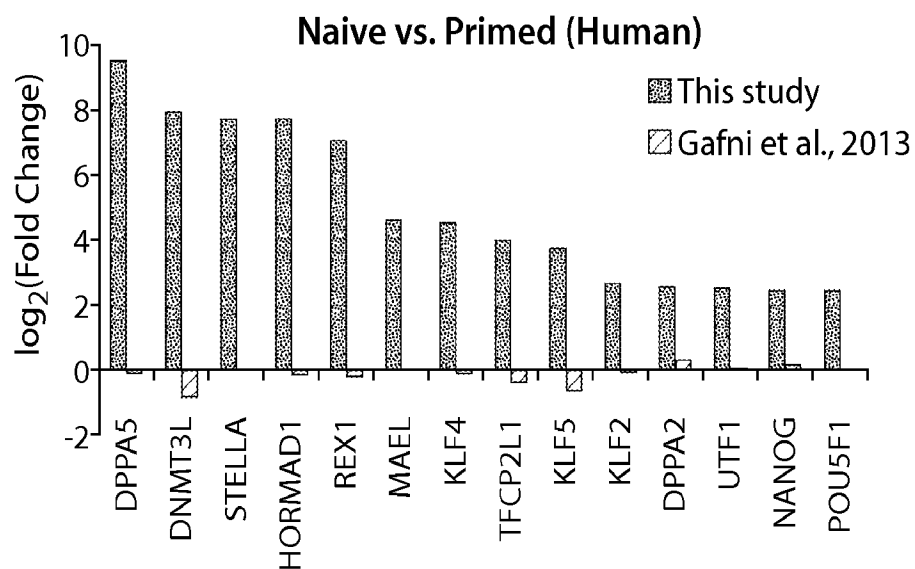


Figure 6D

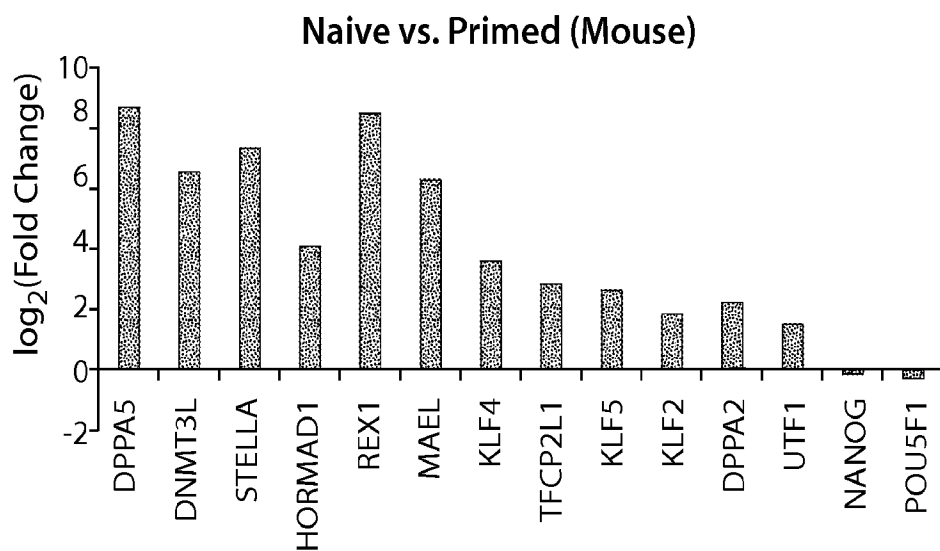


Figure 6E

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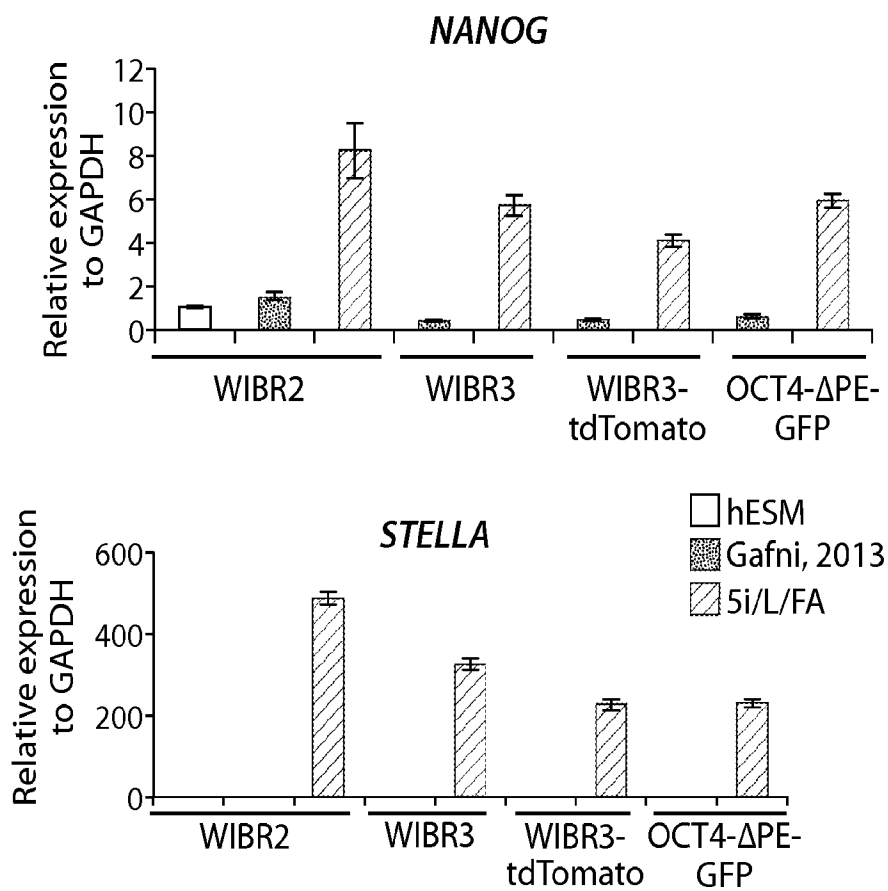


Figure 6F

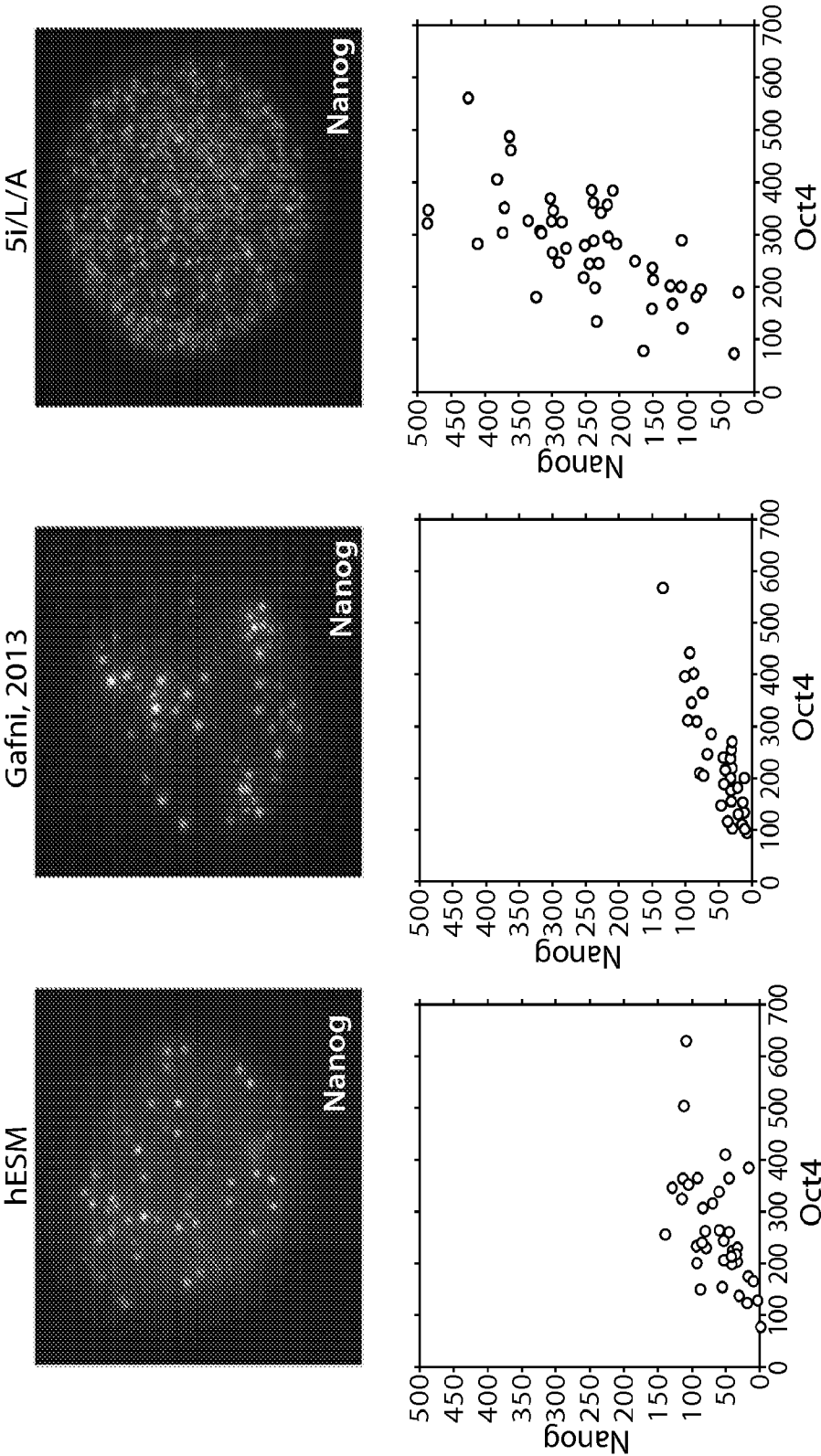


Figure 6G

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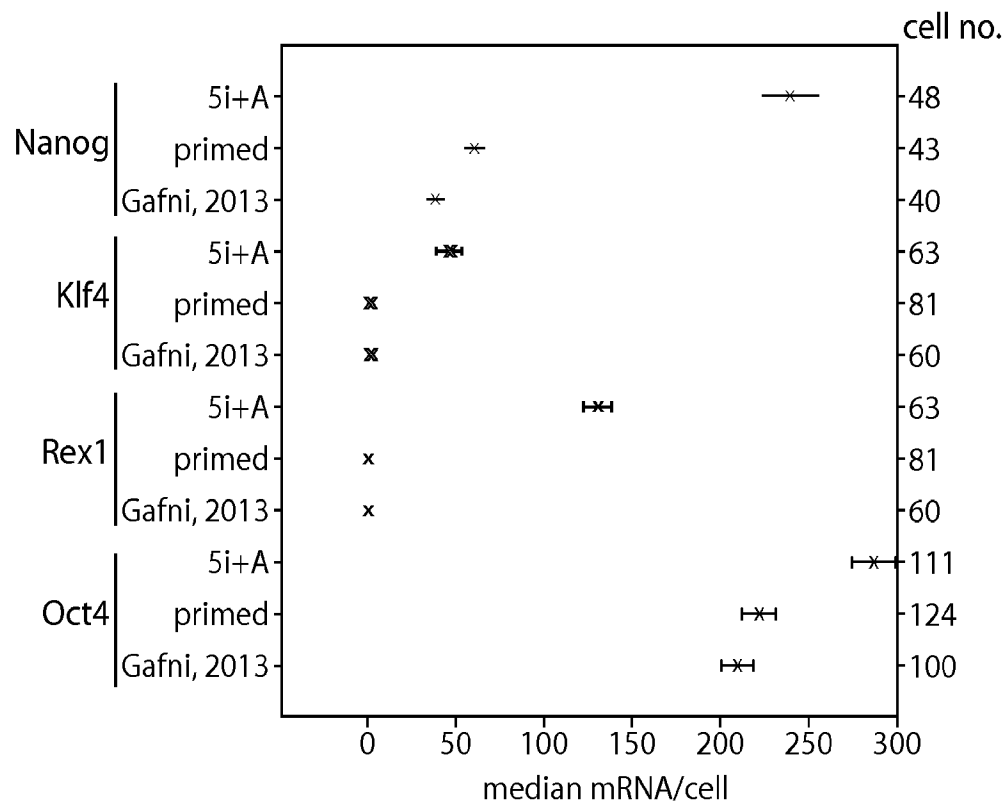


Figure 6H

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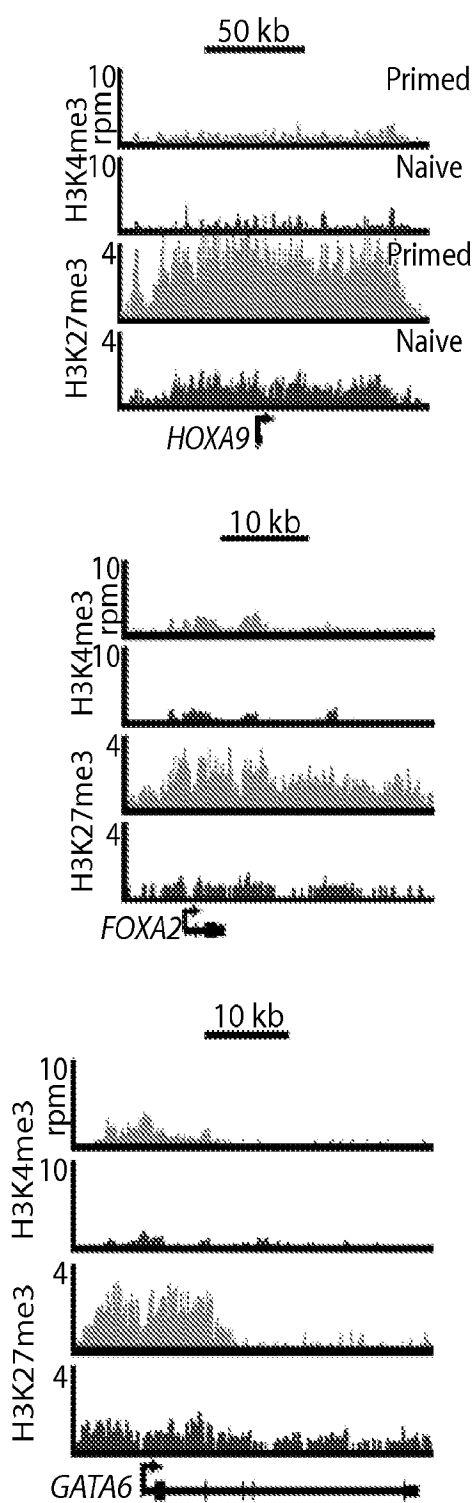


Figure 7A

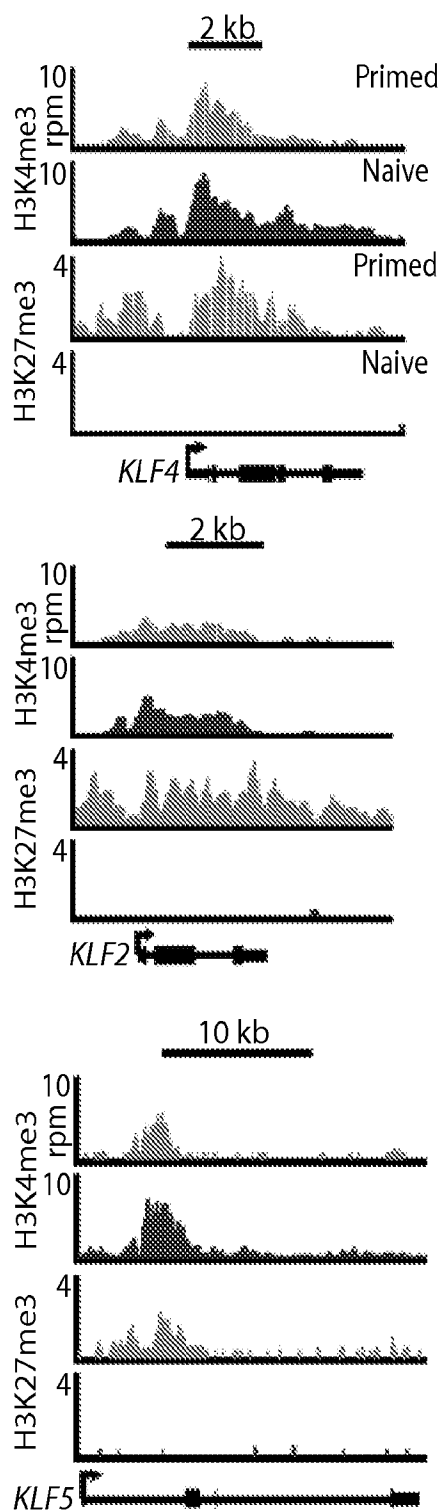


Figure 7B

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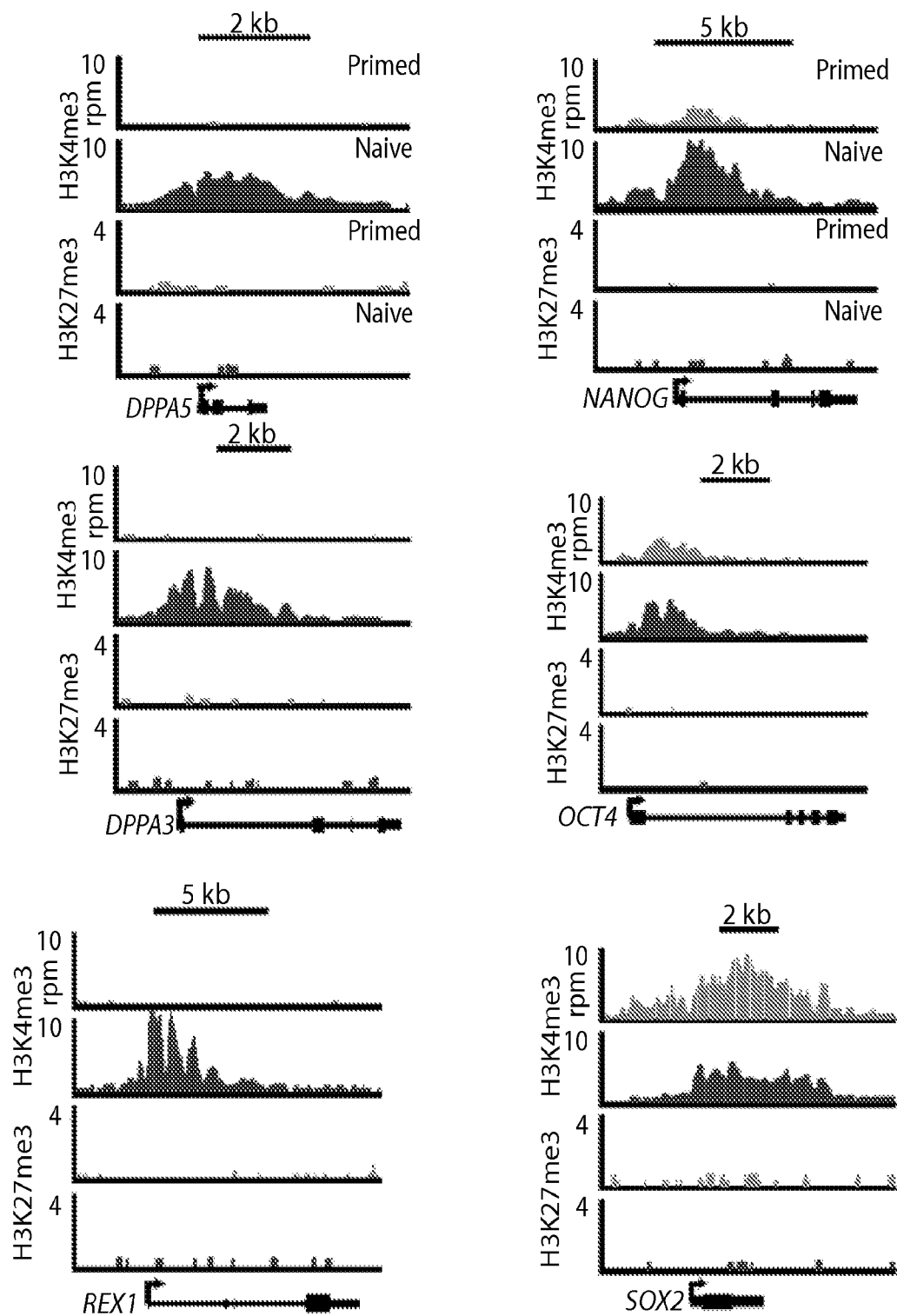


Figure 7C

Figure 7D

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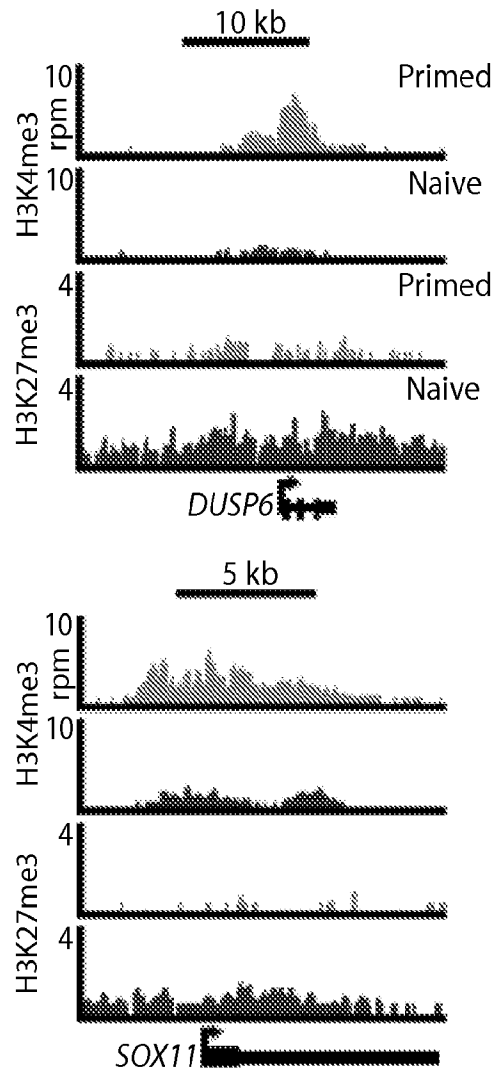


Figure 7E

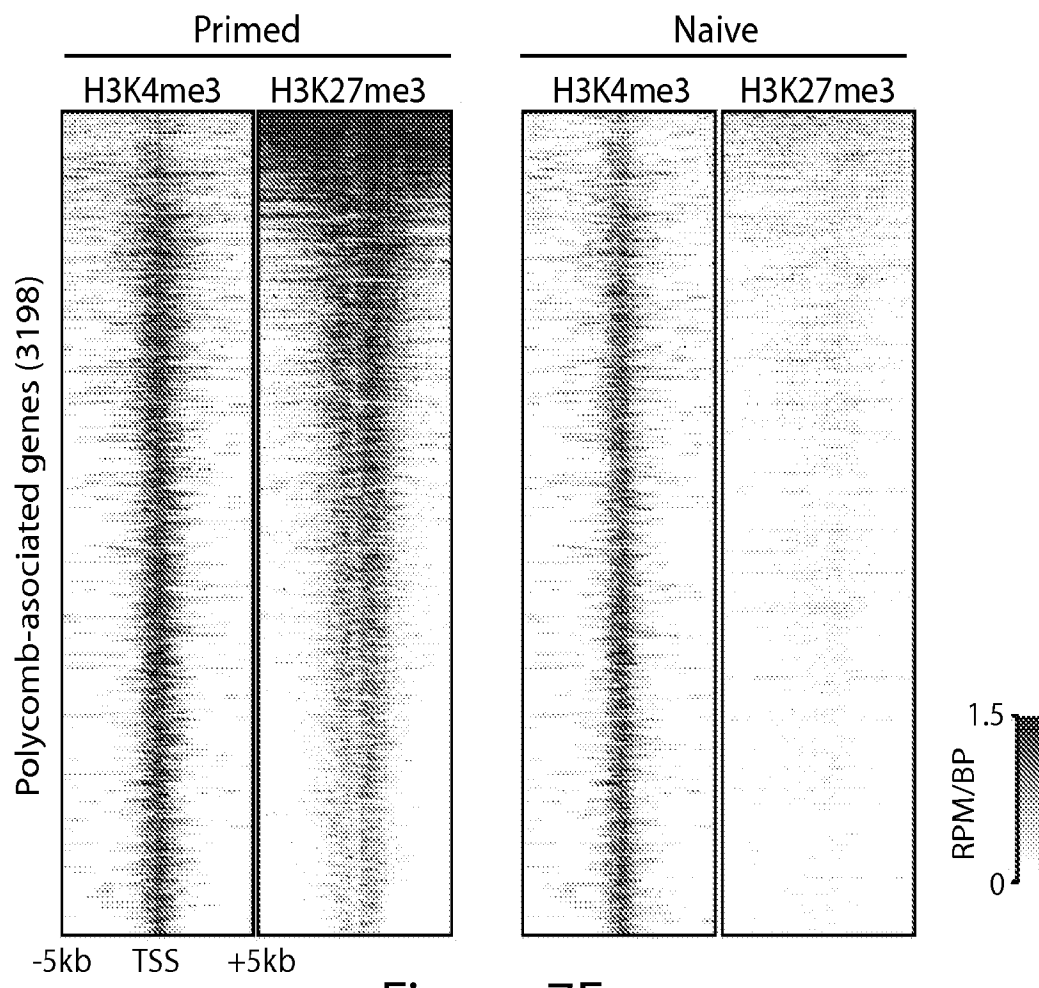


Figure 7F

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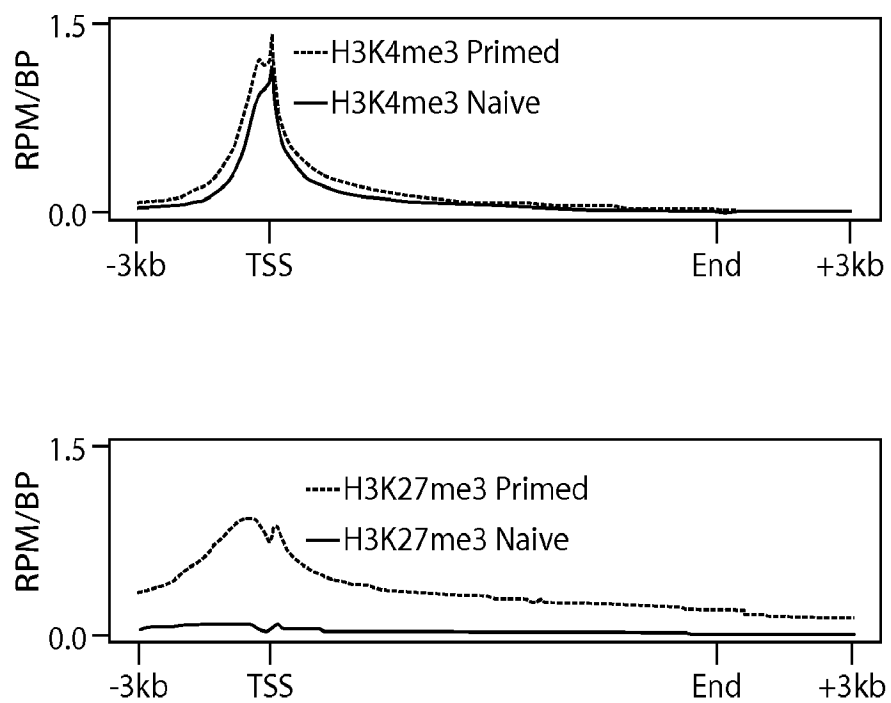


Figure 7G

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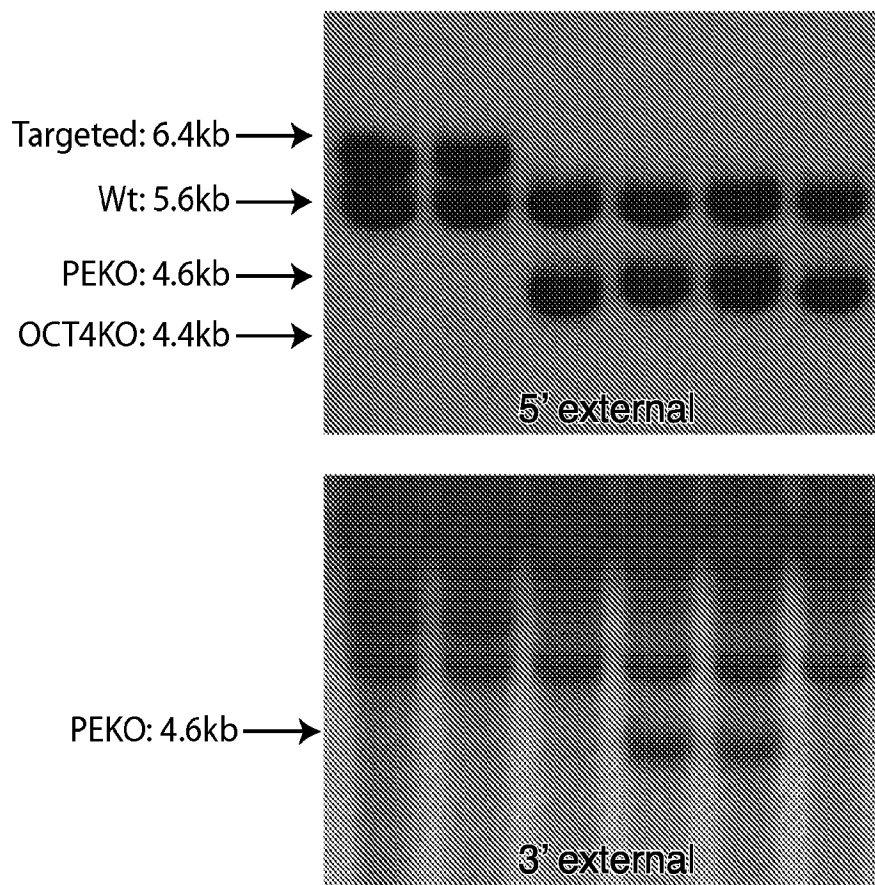


Figure 8A

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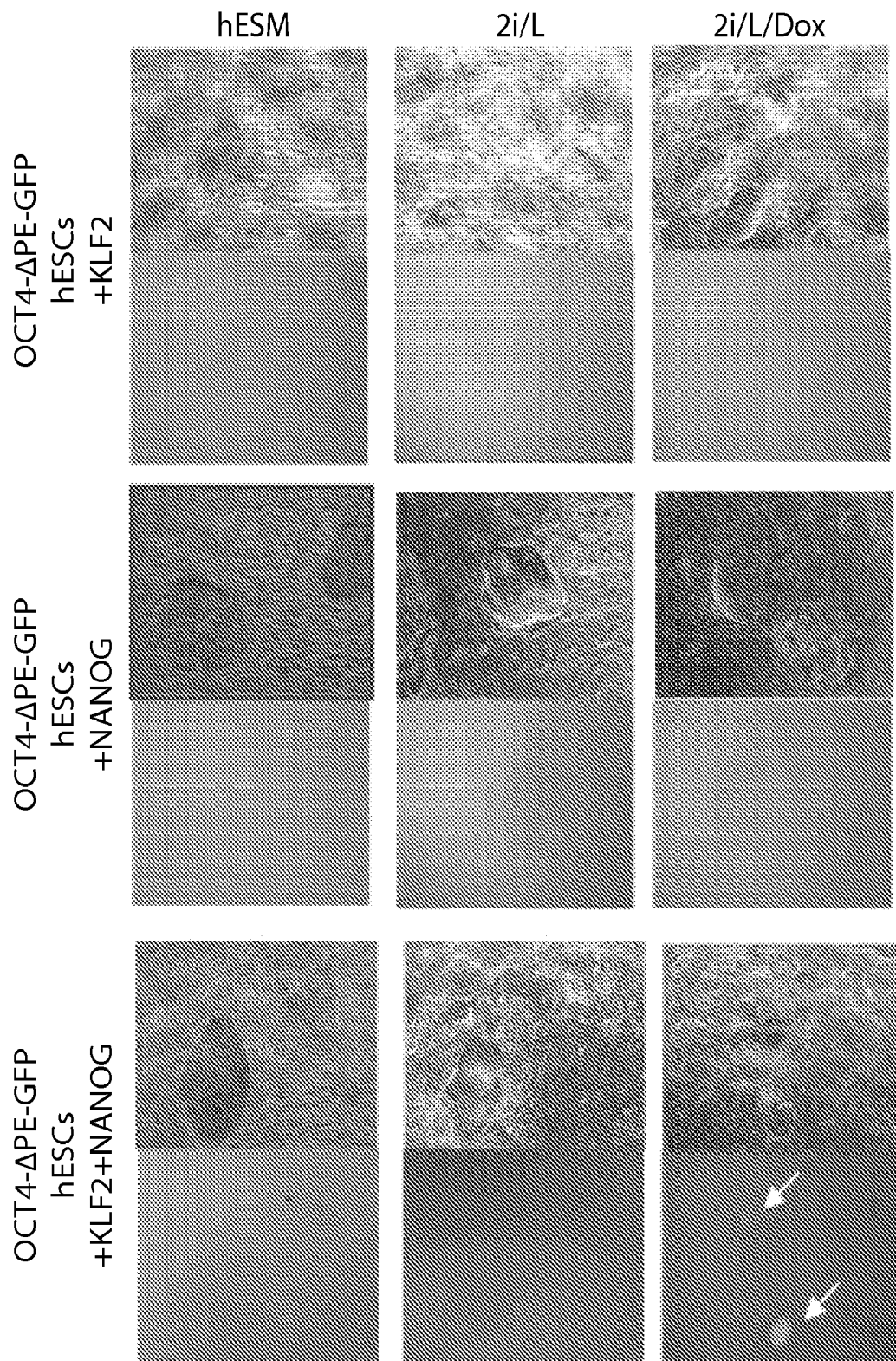


Figure 8B

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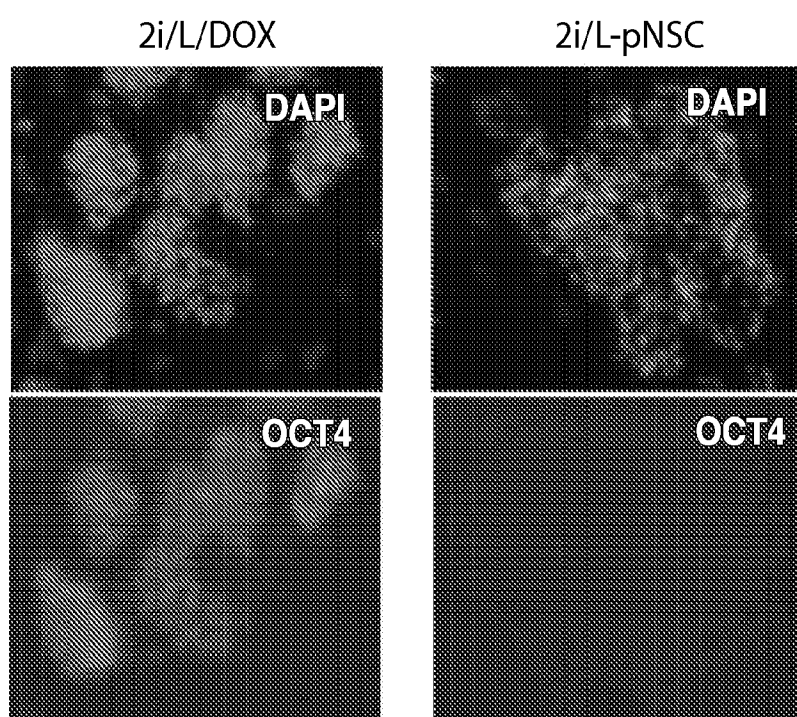


Figure 8C

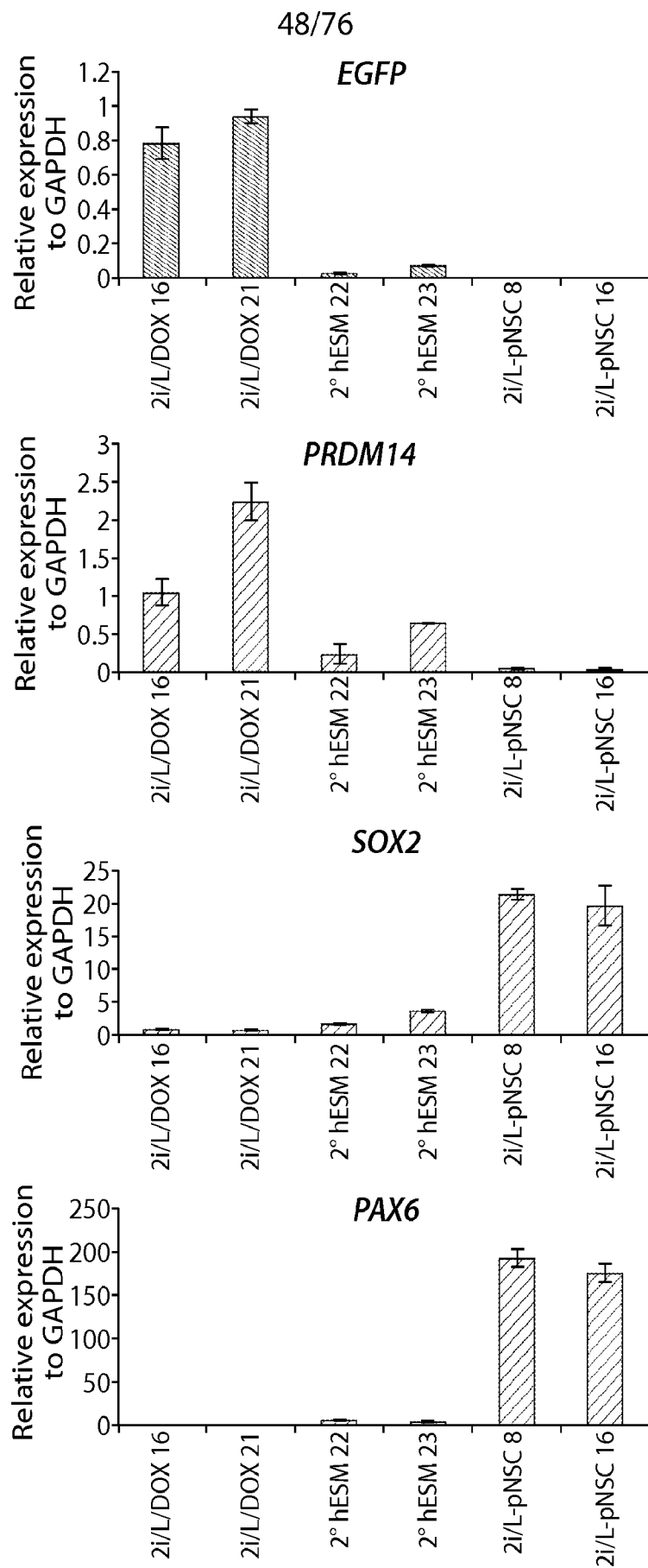


Figure 8D

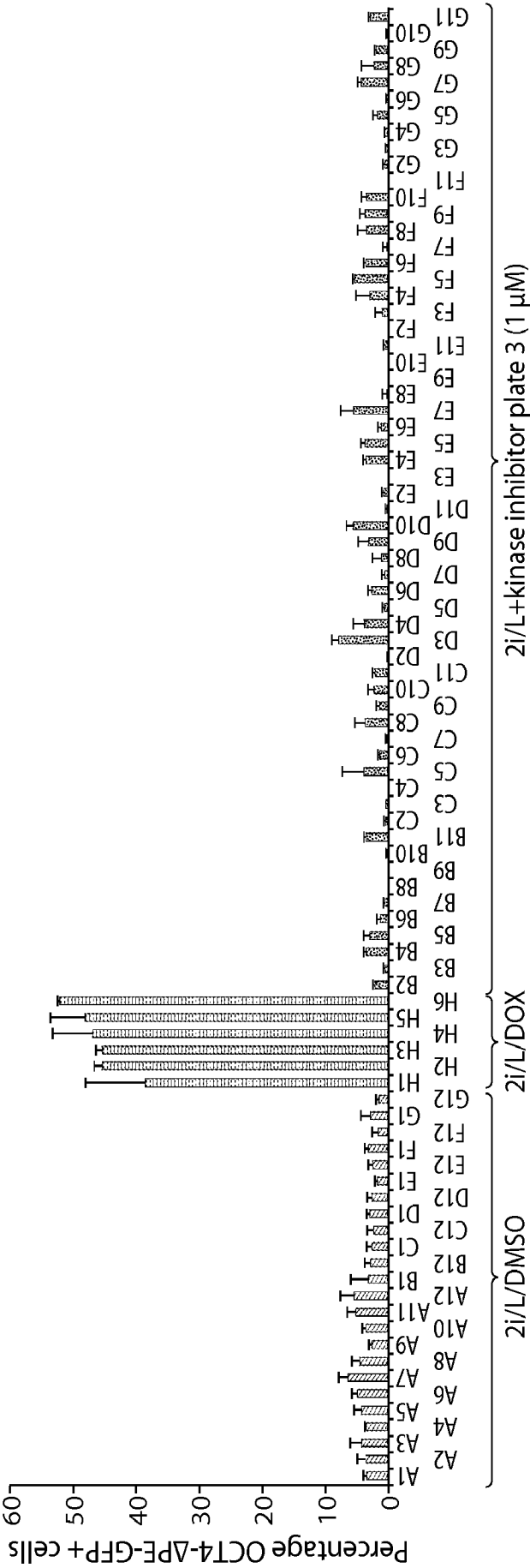


Figure 9A

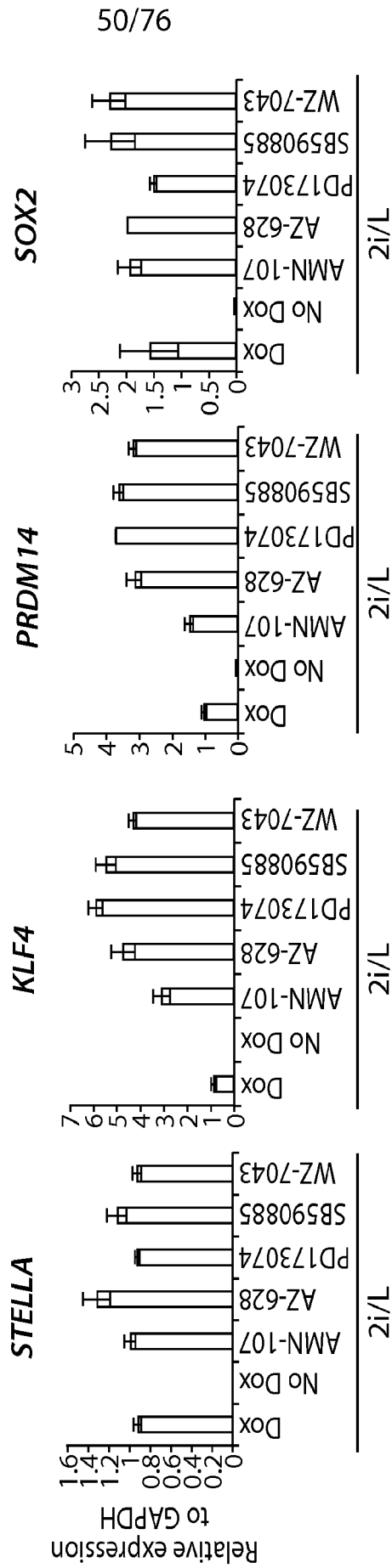


Figure 9B

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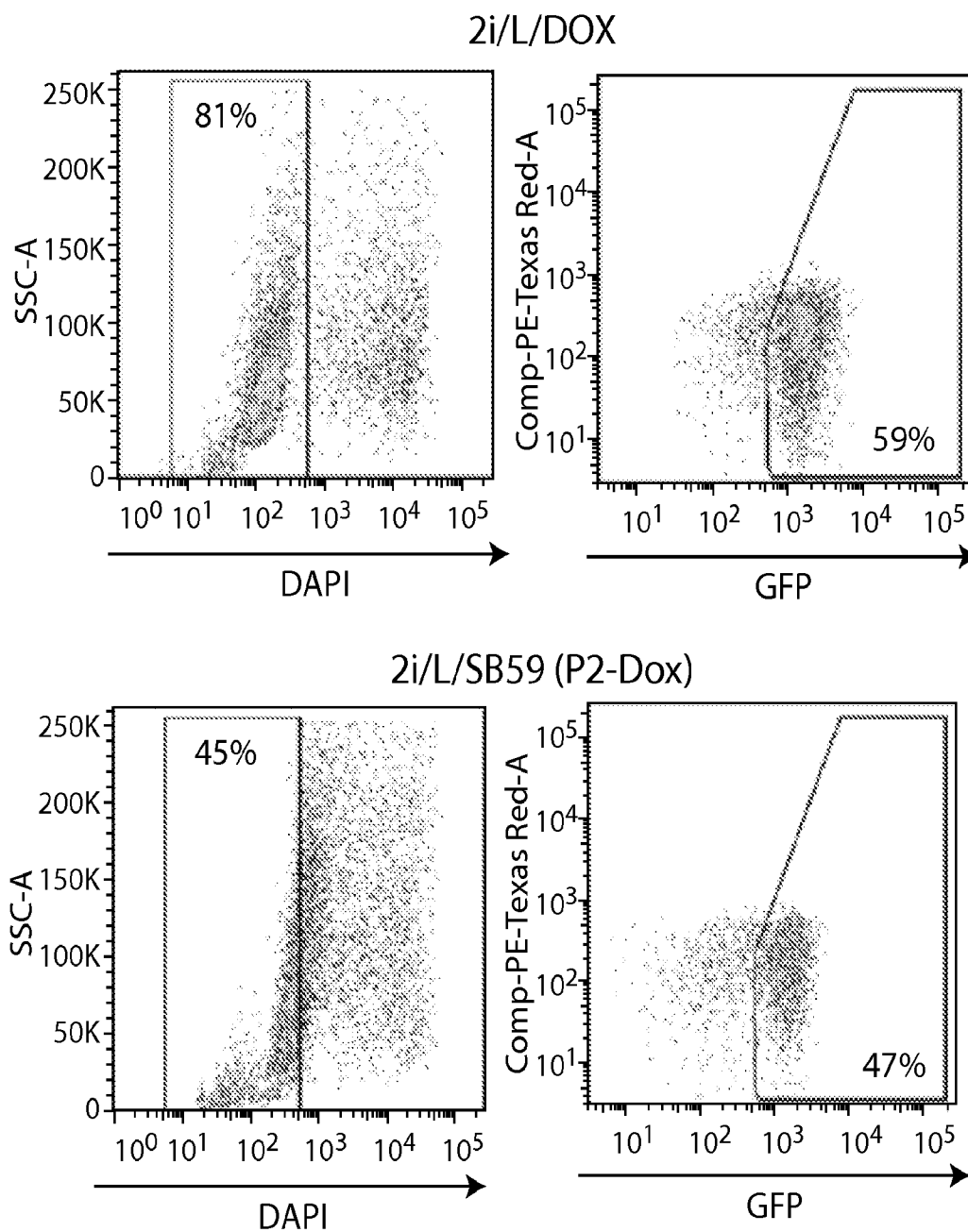


Figure 9C

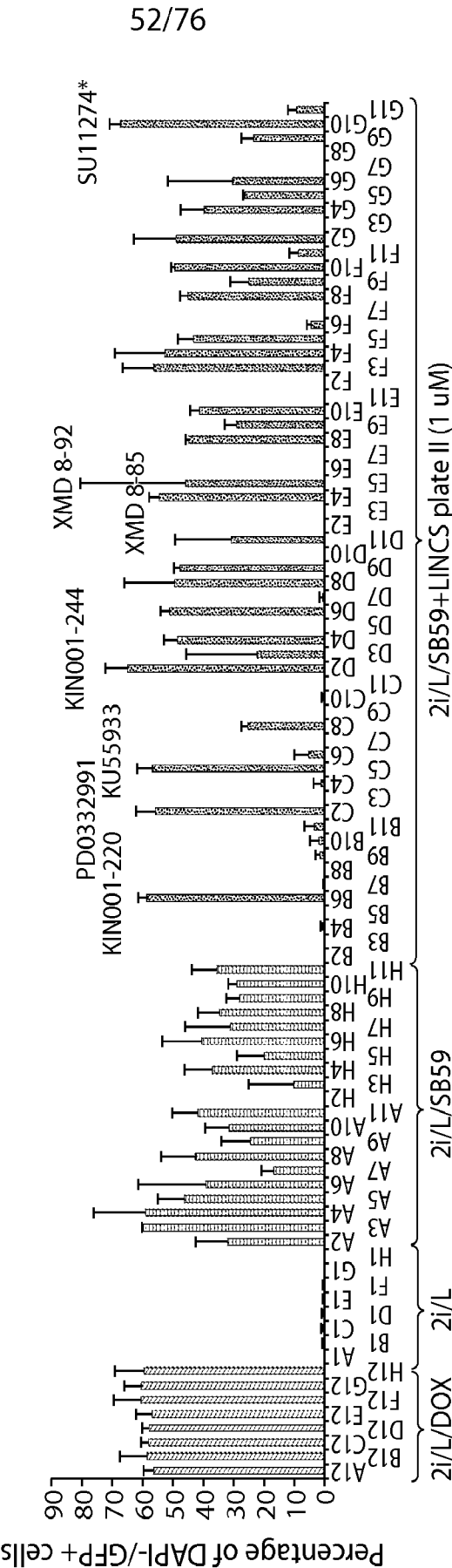


Figure 10A-1

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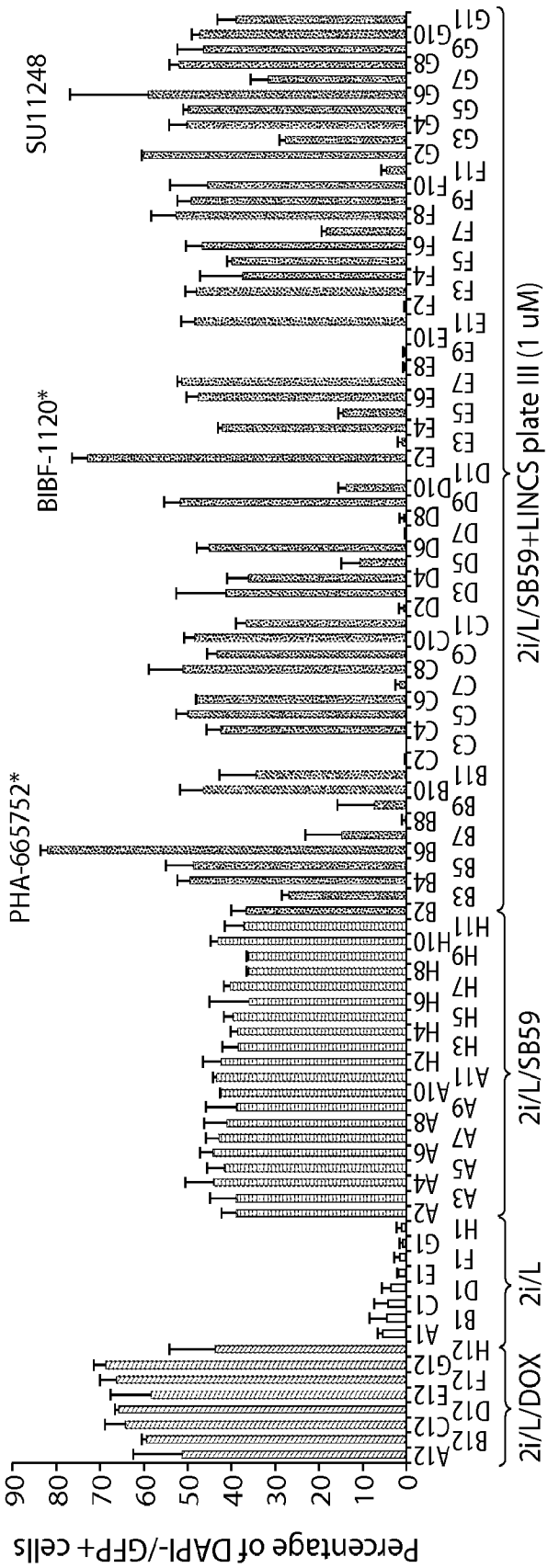


Figure 10A-2

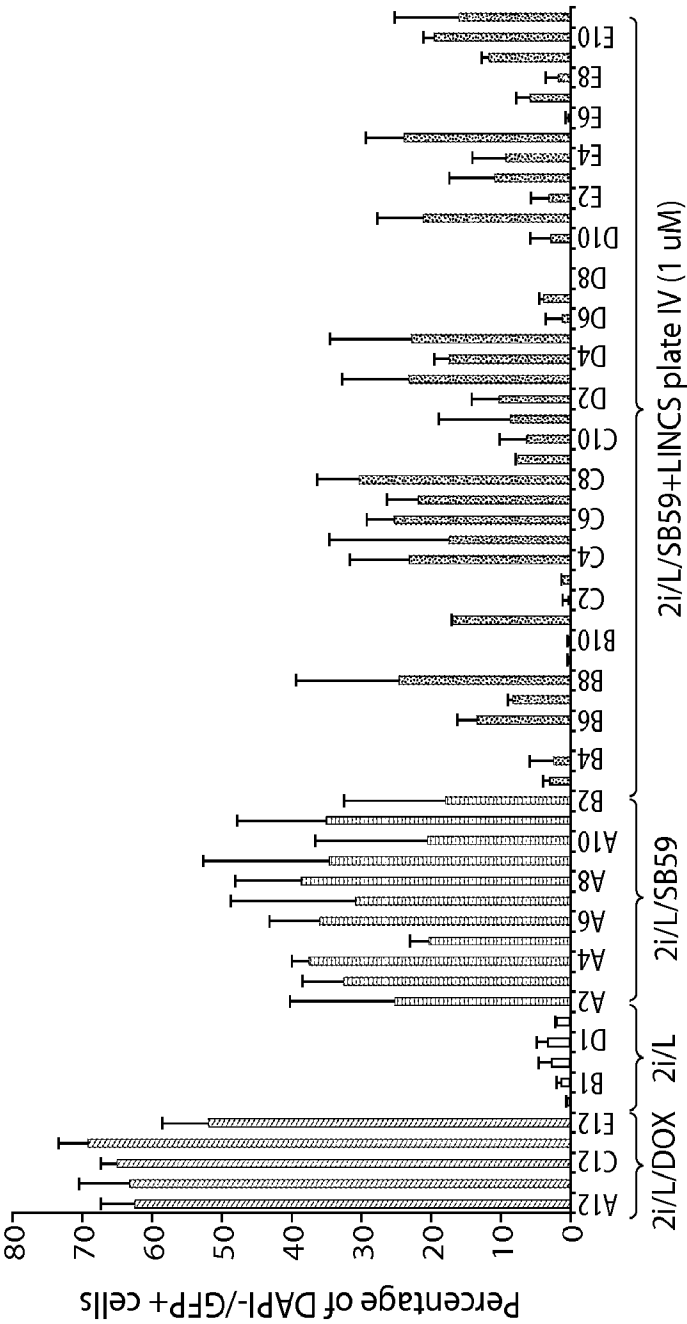


Figure 10A-3

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Compound	Target(s)
WH-4-023	SRC
KIN001-220	Aurora kinase
PD0332991	CDK4
KU55933	ATM
KIN001-244	PKC
XMD 8-85	ERK5
XMD 8-92	ERK5
SU11274*	MET
PHA-665752*	MET
BIBF-1120*	VEGFR, PDGFR, FGFR
SU11248	VEGFR1, PDGFR, KIT, FLT3

Figure 10B

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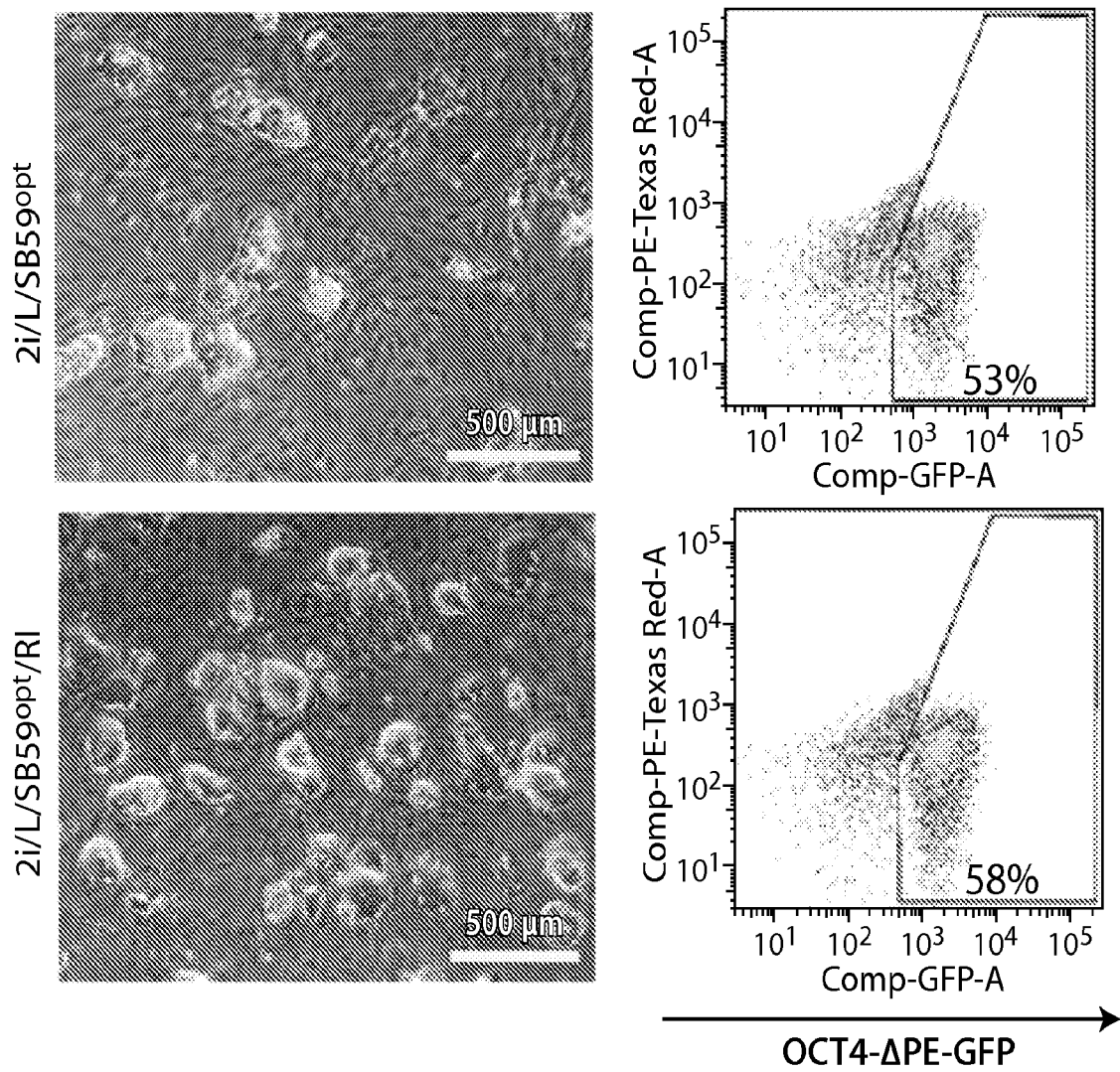


Figure 10C

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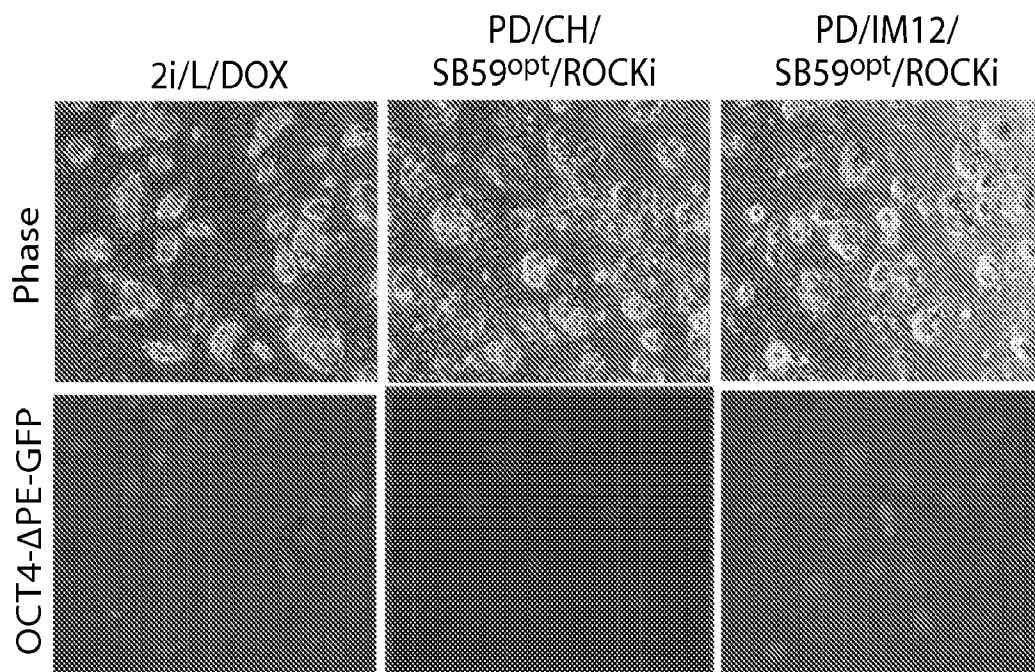


Figure 10D

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WIBR2 in 5i/L/A (P8)

(46,XX)

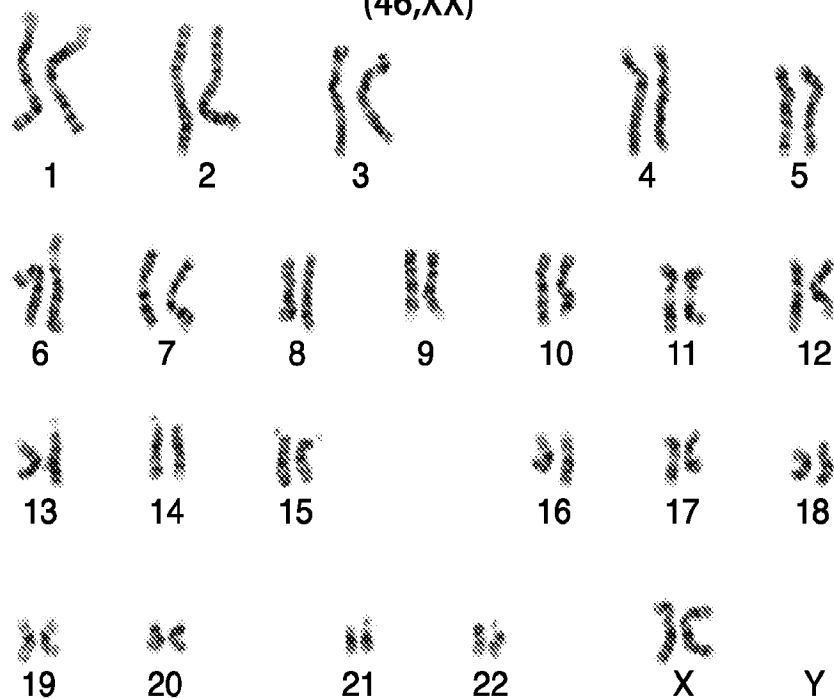


Figure 11A

WIN1 in 5i/L/FA (P7)

(46,XY)

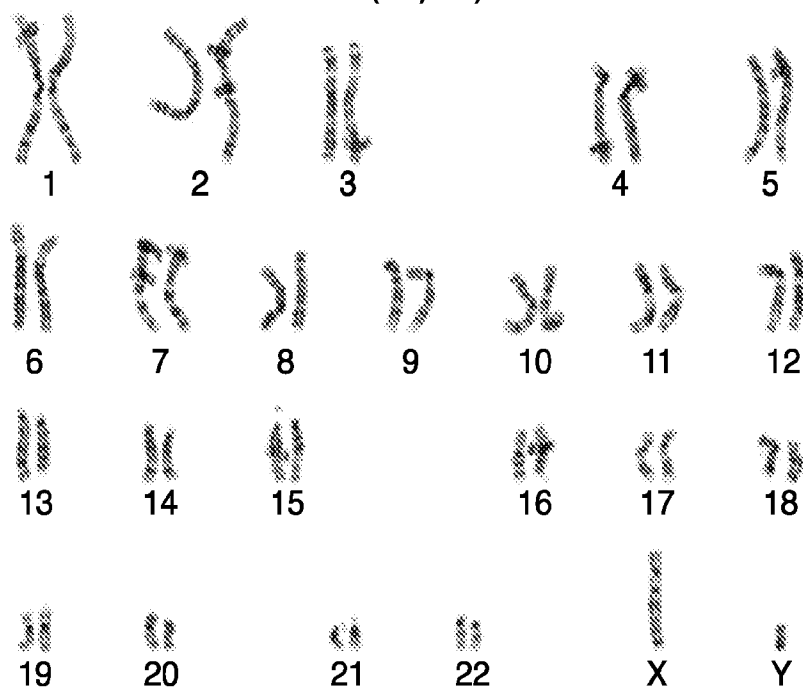


Figure 11B

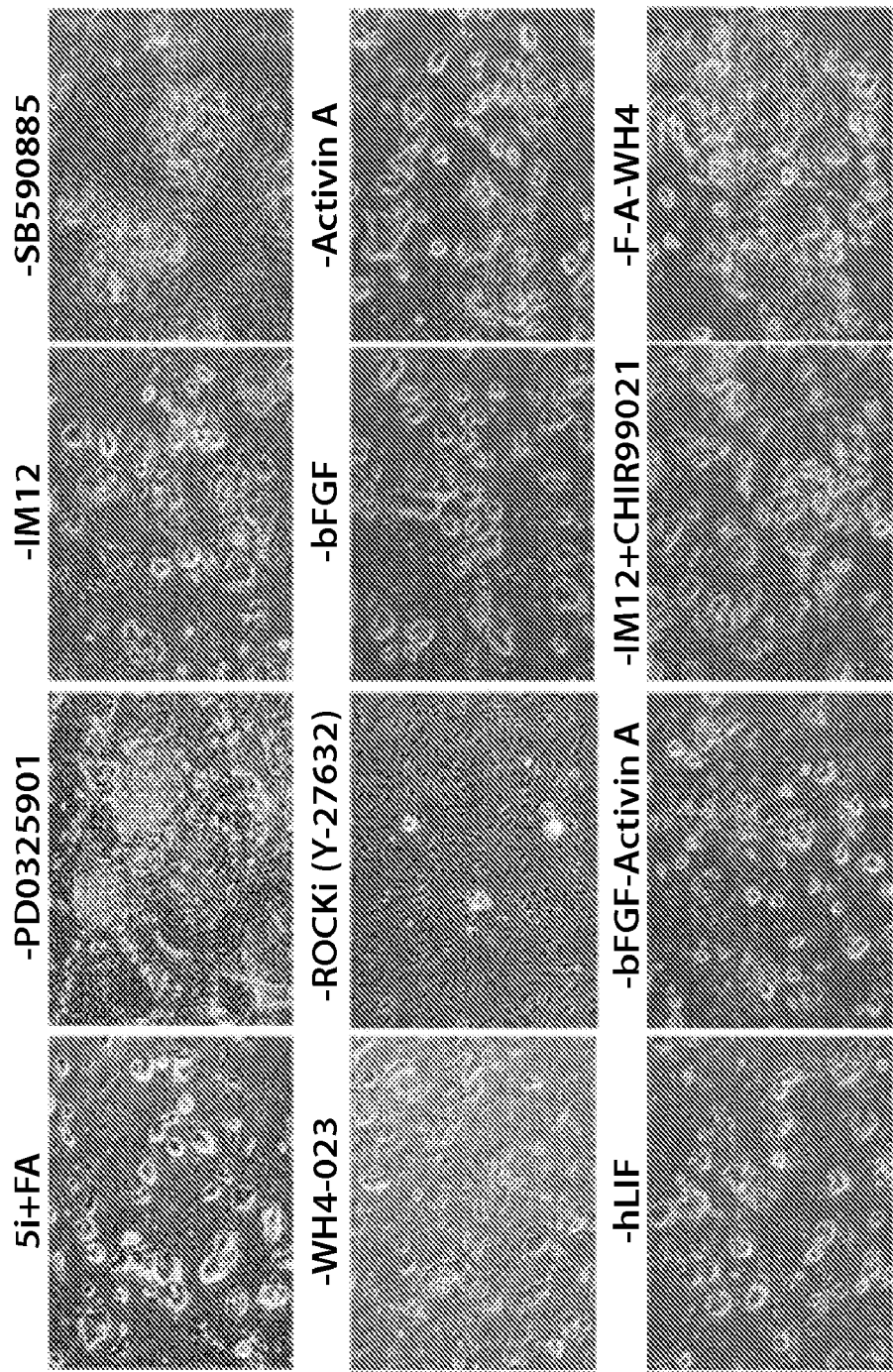


Figure 11C

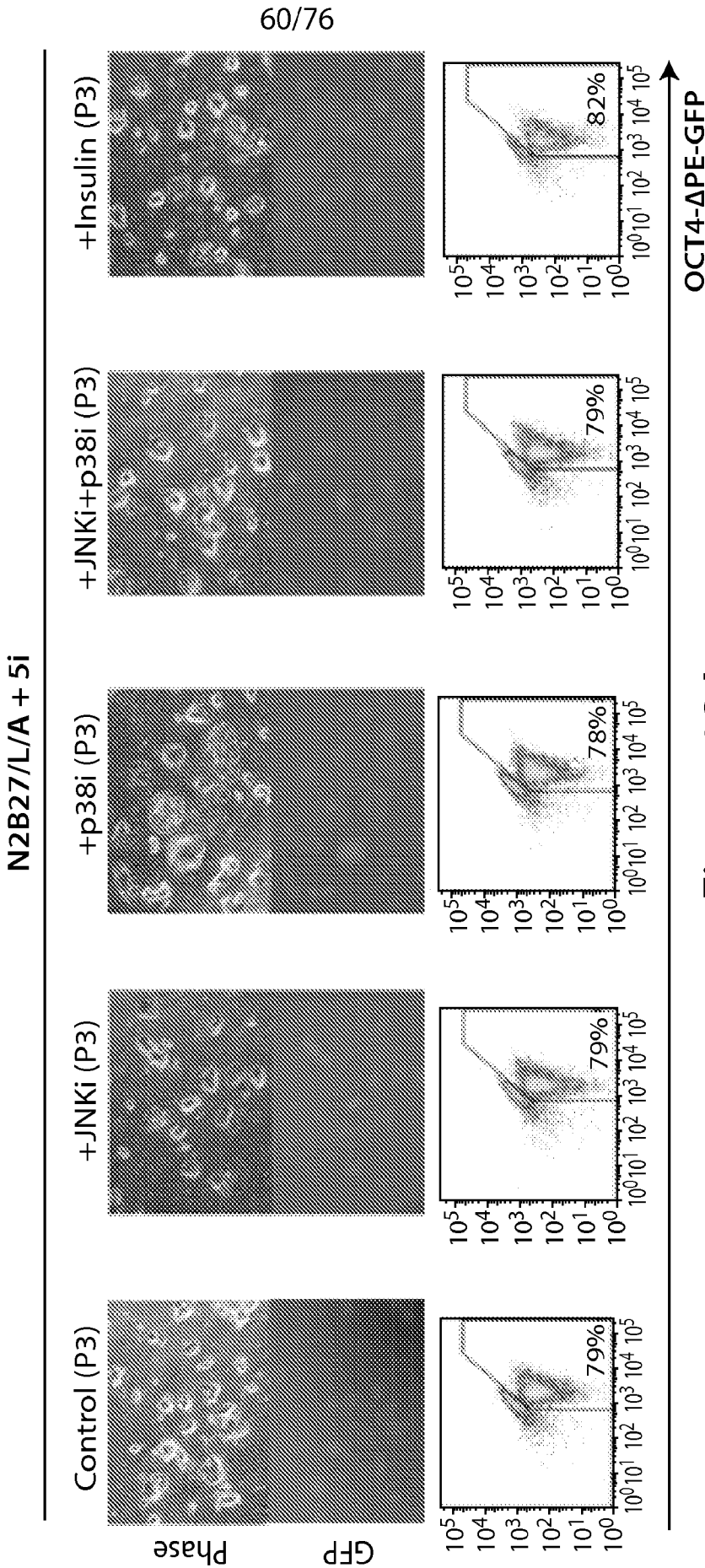


Figure 12A

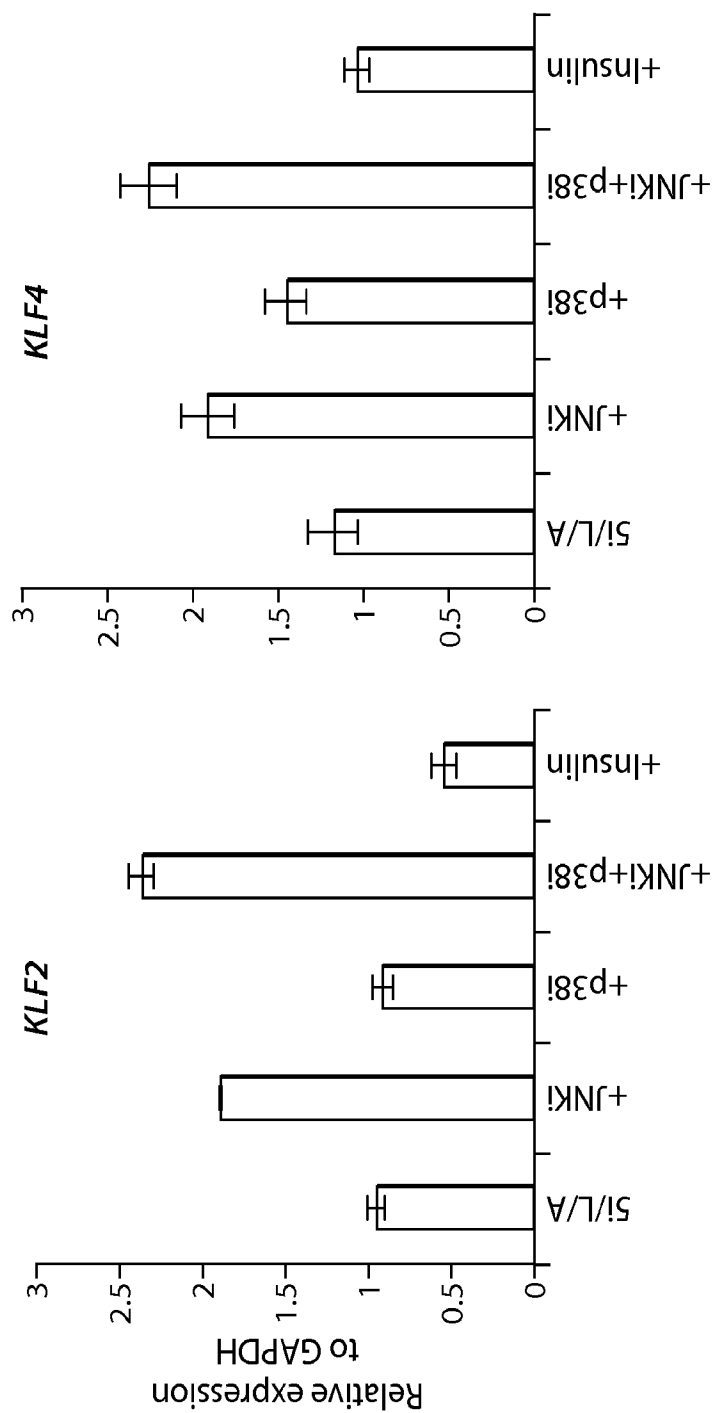


Figure 12B

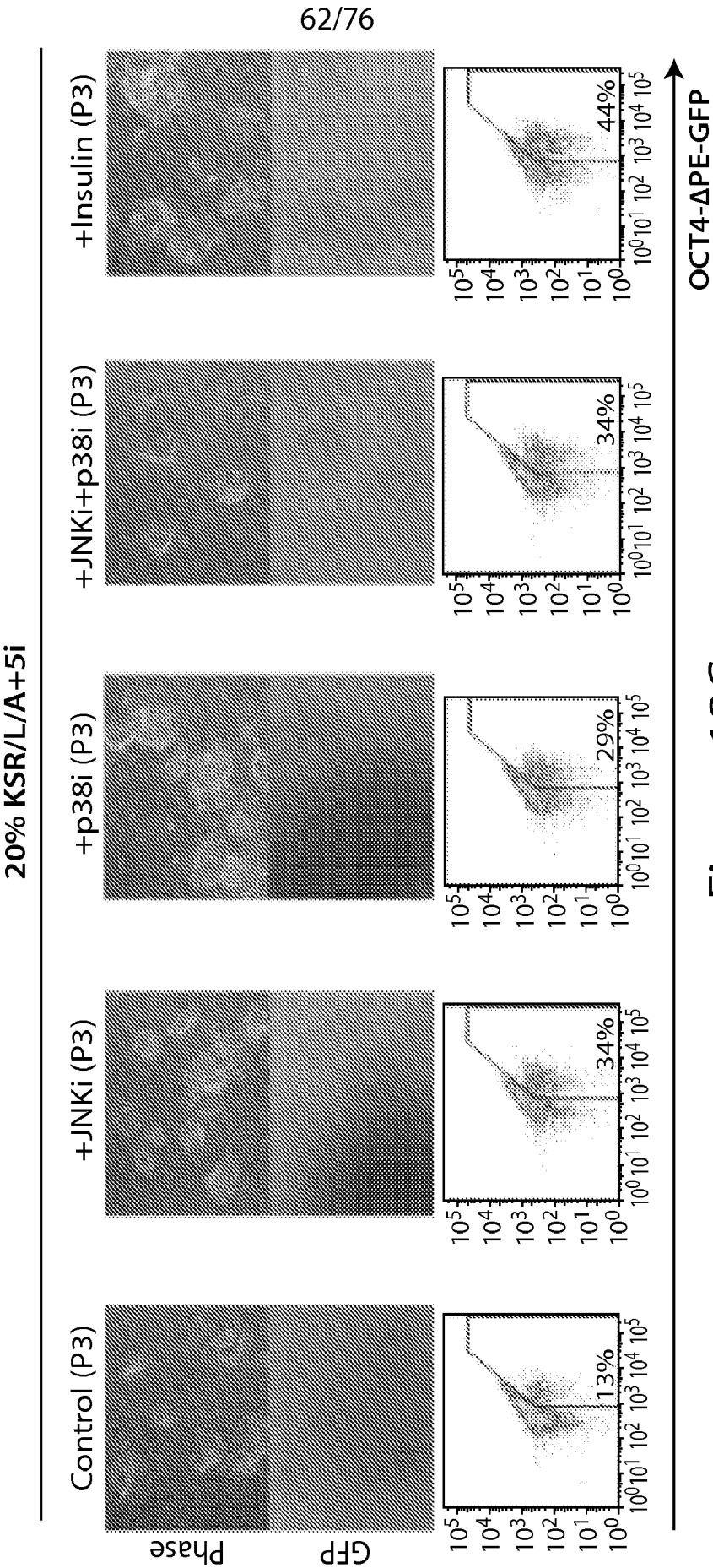


Figure 12C

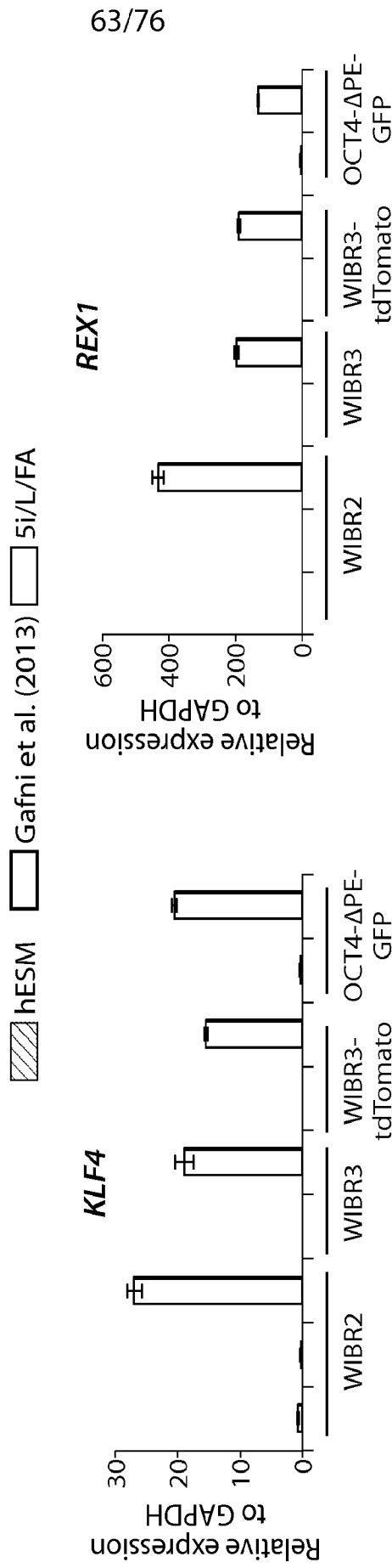


Figure 13A

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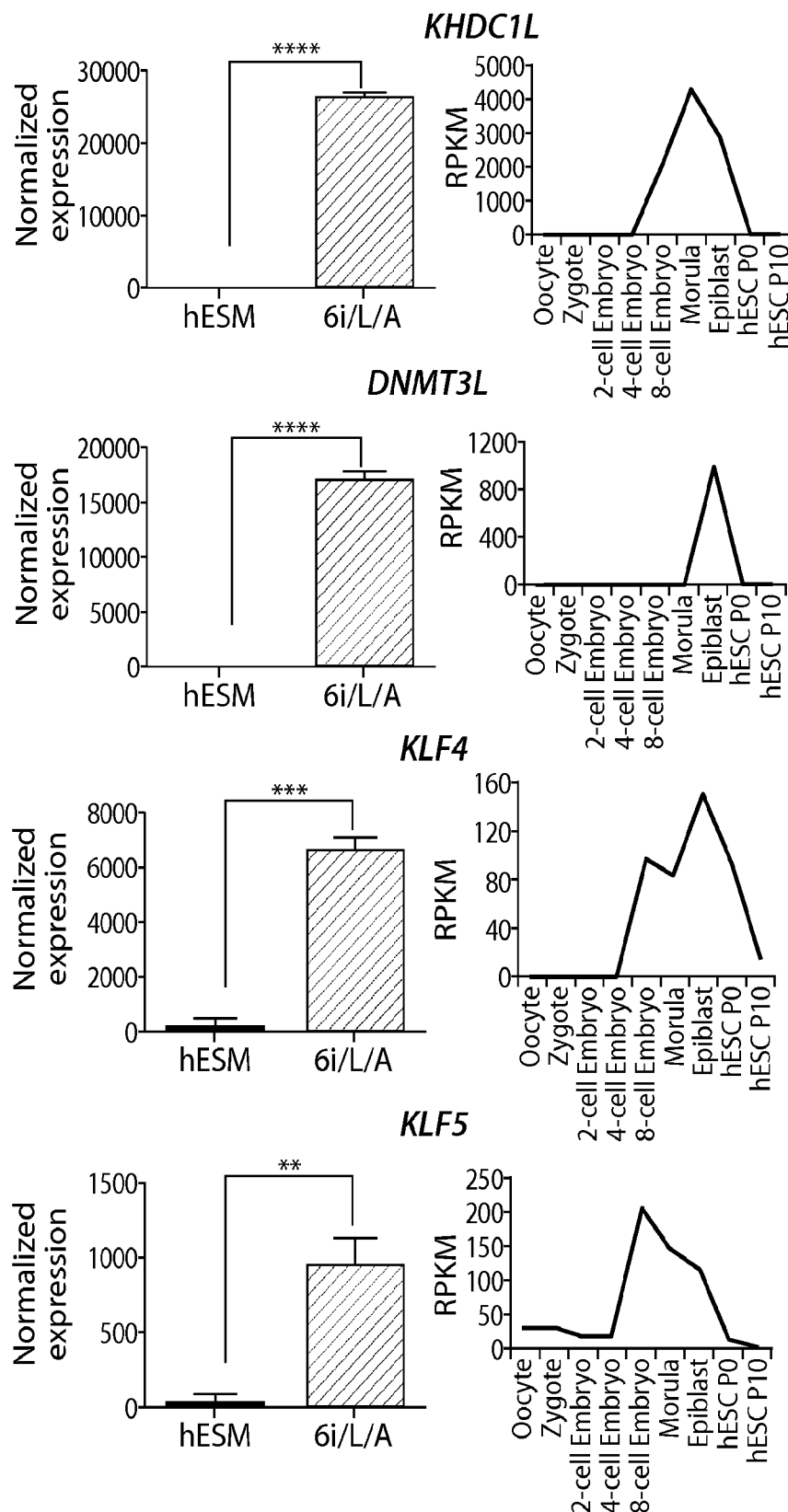


Figure 13B

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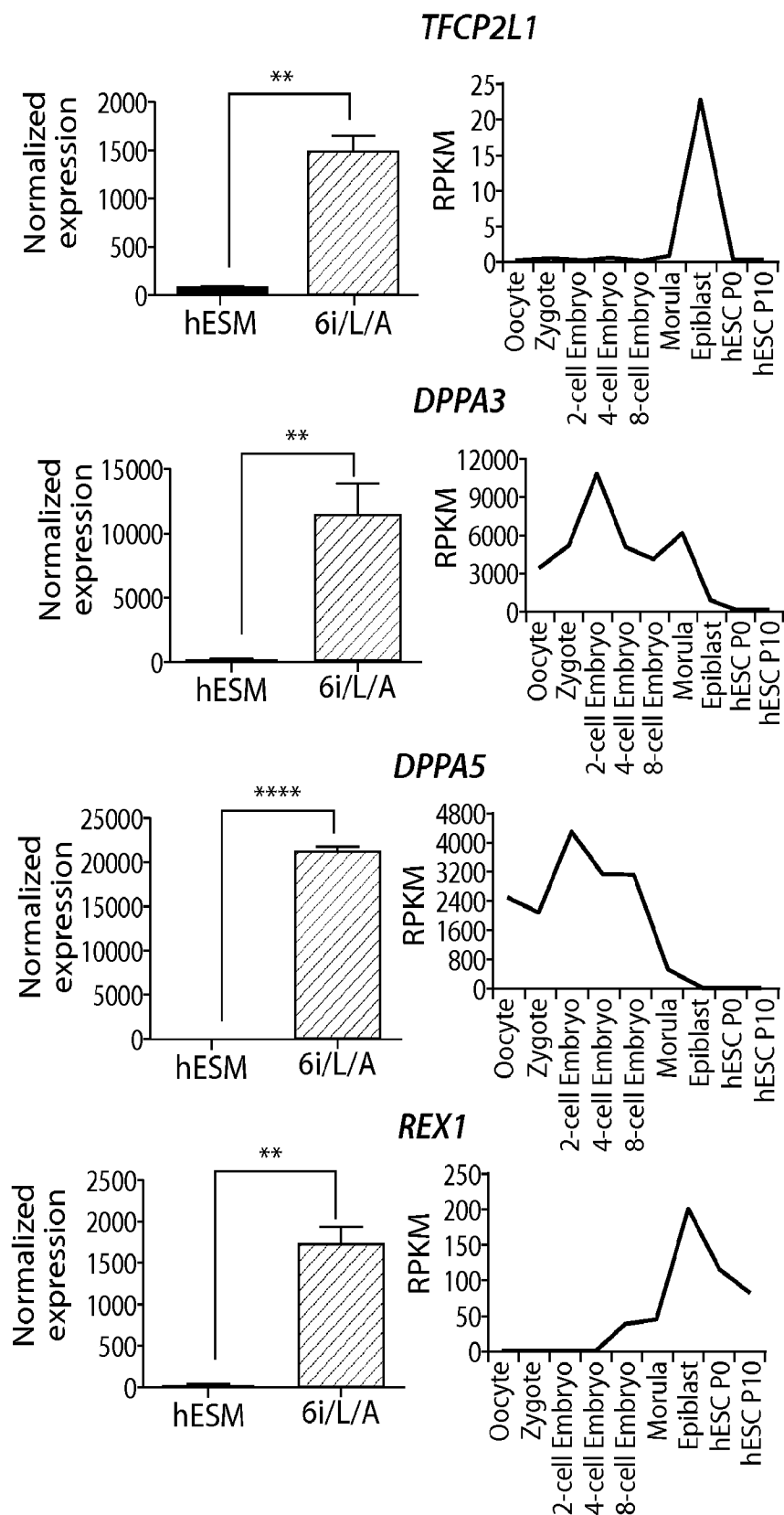


Figure 13B
Continued

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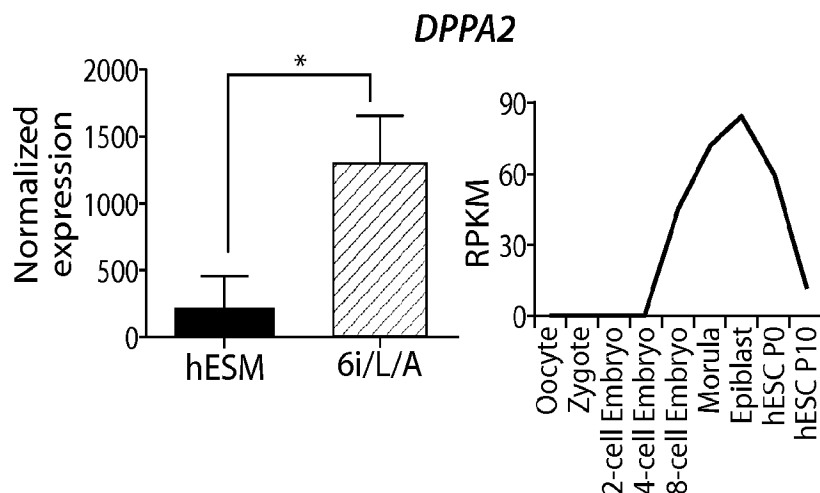


Figure 13B
Continued

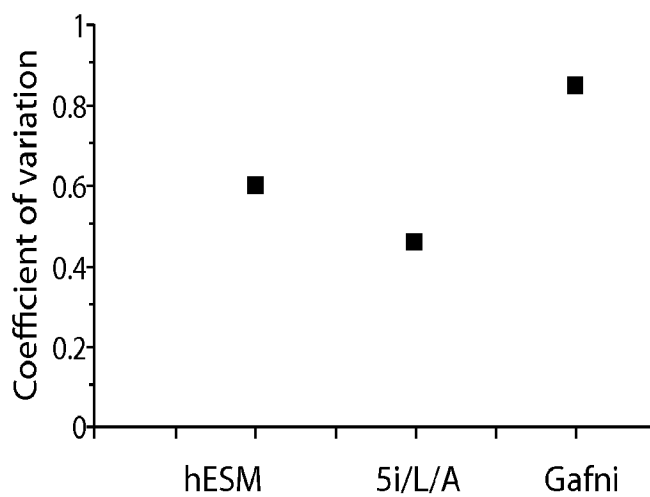


Figure 13C

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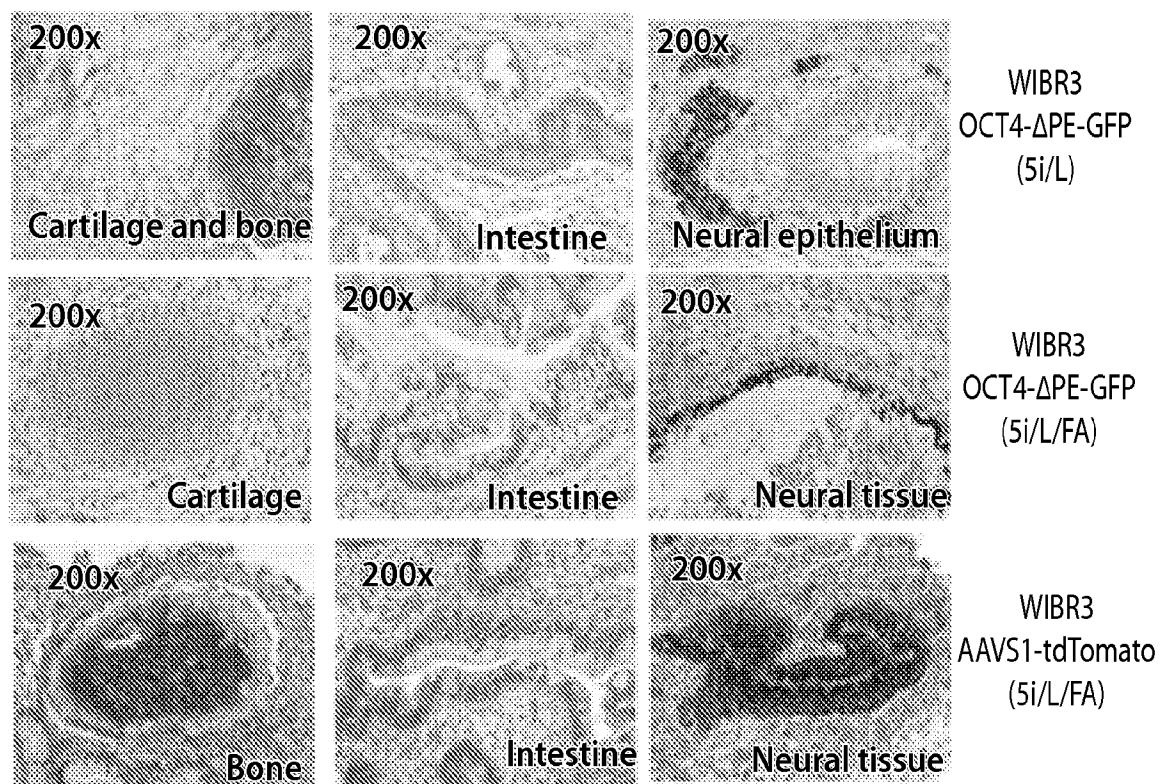


Figure 14A

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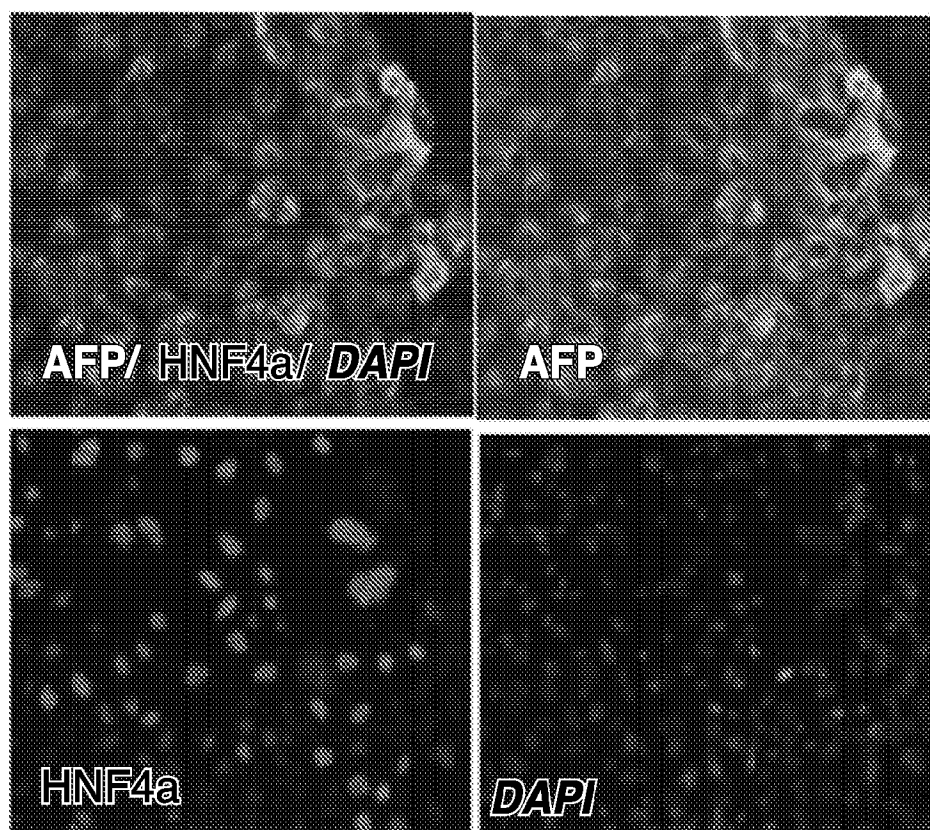


Figure 14B

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5i/L/FA medium Human-Mouse injections							
Dev. Stage	8-cell	8-cell	Morula	Morula	Blastocyst	Blastocyst	Total
Cell line	WIBR3 AAVS1-tdTomato	WIBR3 AAVS1-GFP	WIBR3 AAVS1-tdTomato	WIBR3 AAVS1-GFP	WIBR3 AAVS1-tdTomato	WIBR3 AAVS1-GFP	-
Injected embryos	245	363	92	60	50	50	860
Embryos recovered at E10.5	92	164*	47	28	11	26	368
Positive embryos	0	0	0	0	0	0	0
Gafni et al. (2013) medium Human-Mouse injections							
Dev. Stage	8-cell	8-cell	8-cell	Morula	Morula	Blastocyst	Total
Cell line	C1 AAVS1-GFP on MEFs	C1 AAVS1-GFP on gel/vit	C1 AAVS1-GFP on matrigel	C1 AAVS1-GFP on MEFs	C1 AAVS1-GFP on gel/vit	C1 AAVS1-GFP on matrigel	-
Injected embryos	140	100	40	40	40	76	436
Embryos recovered at E10.5	96*	28	12	24	7**	28	195
Positive embryos	0	0	0	0	0	0	0

Figure 14C

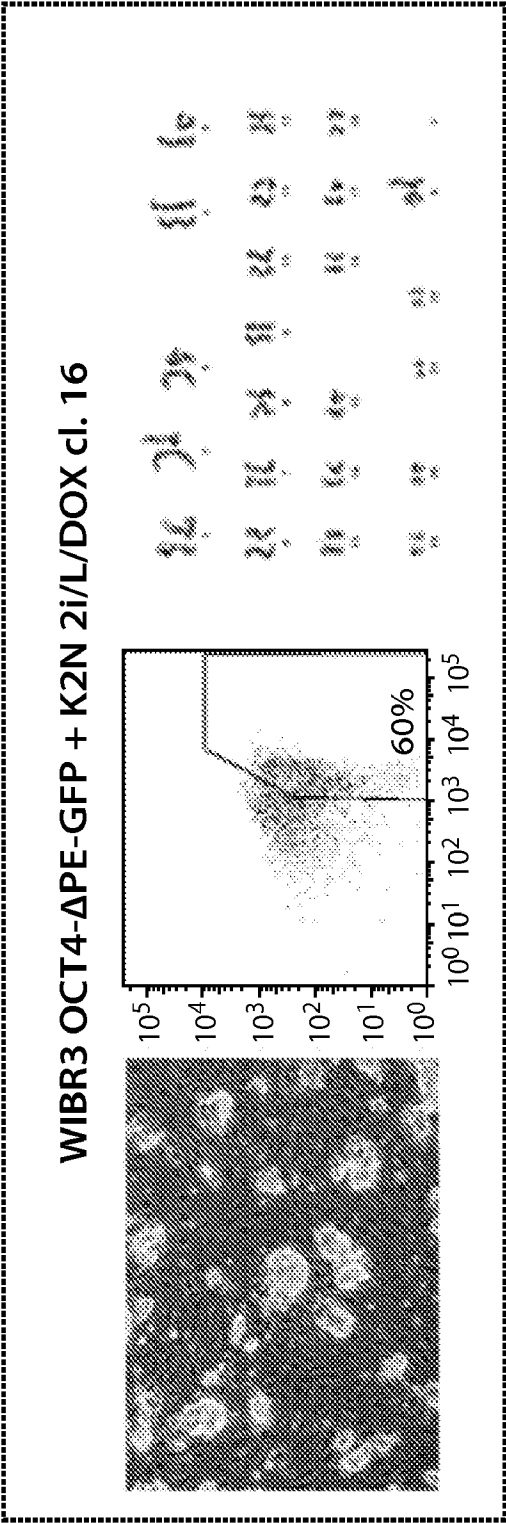


Figure 15A

3 passages after DOX withdrawal (1:10 density splitting):

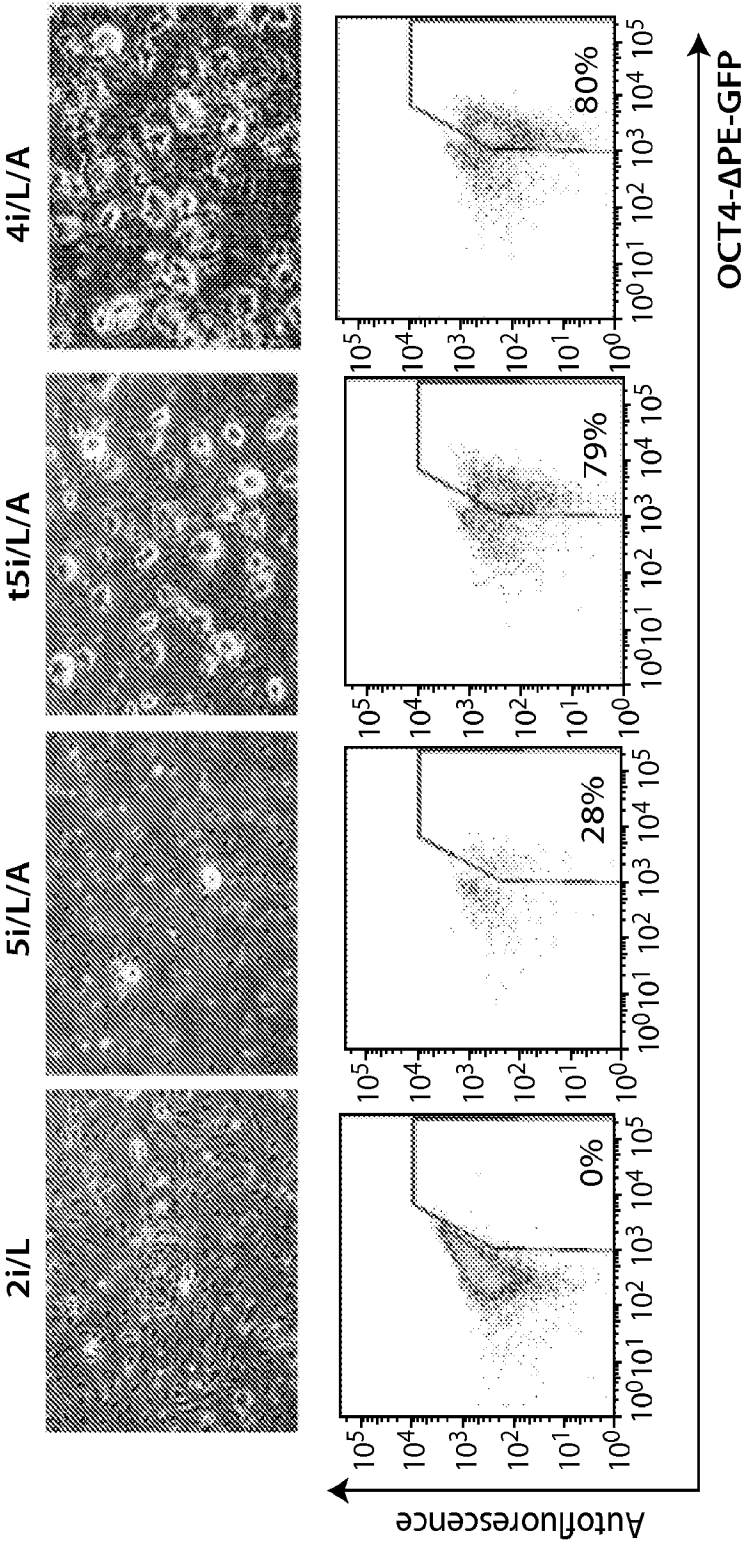


Figure 15B

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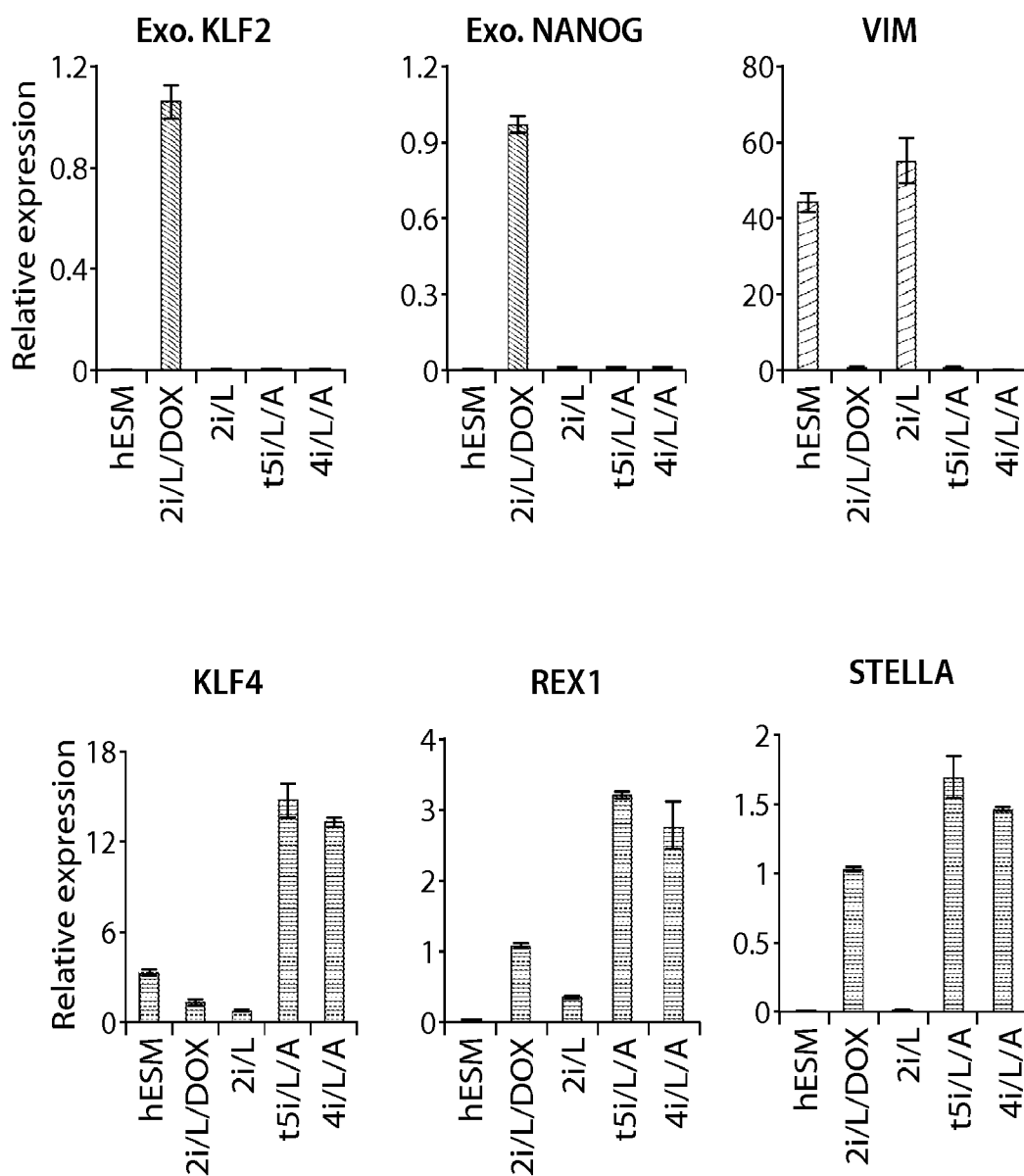


Figure 15C

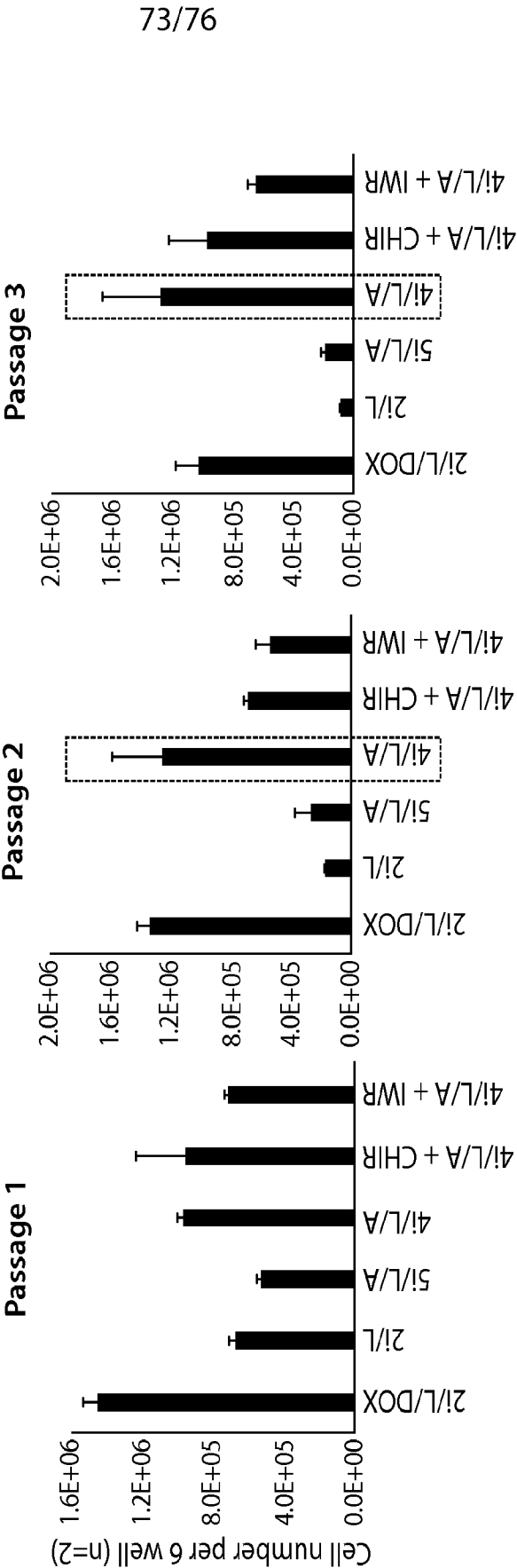


Figure 16

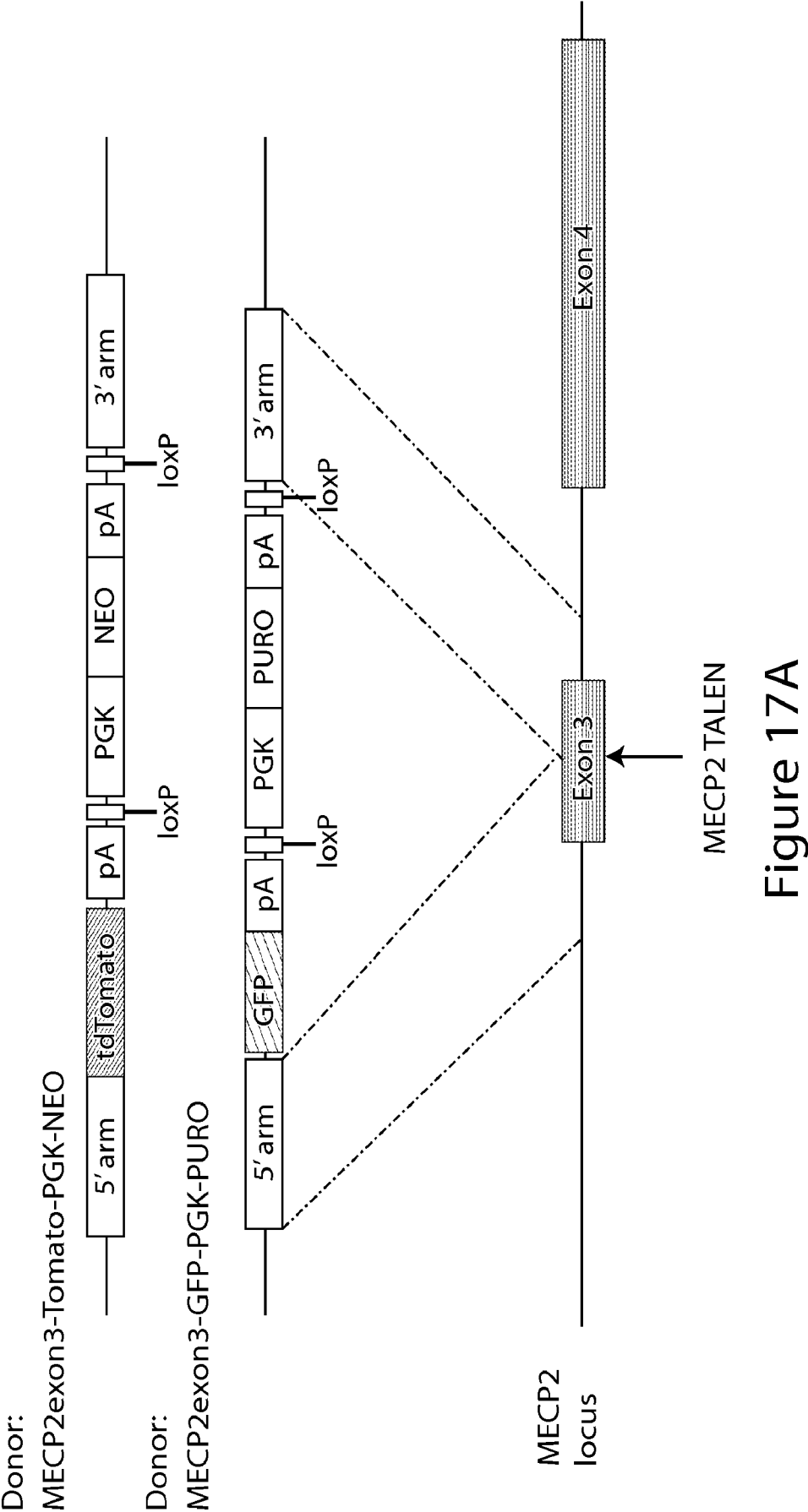


Figure 17A

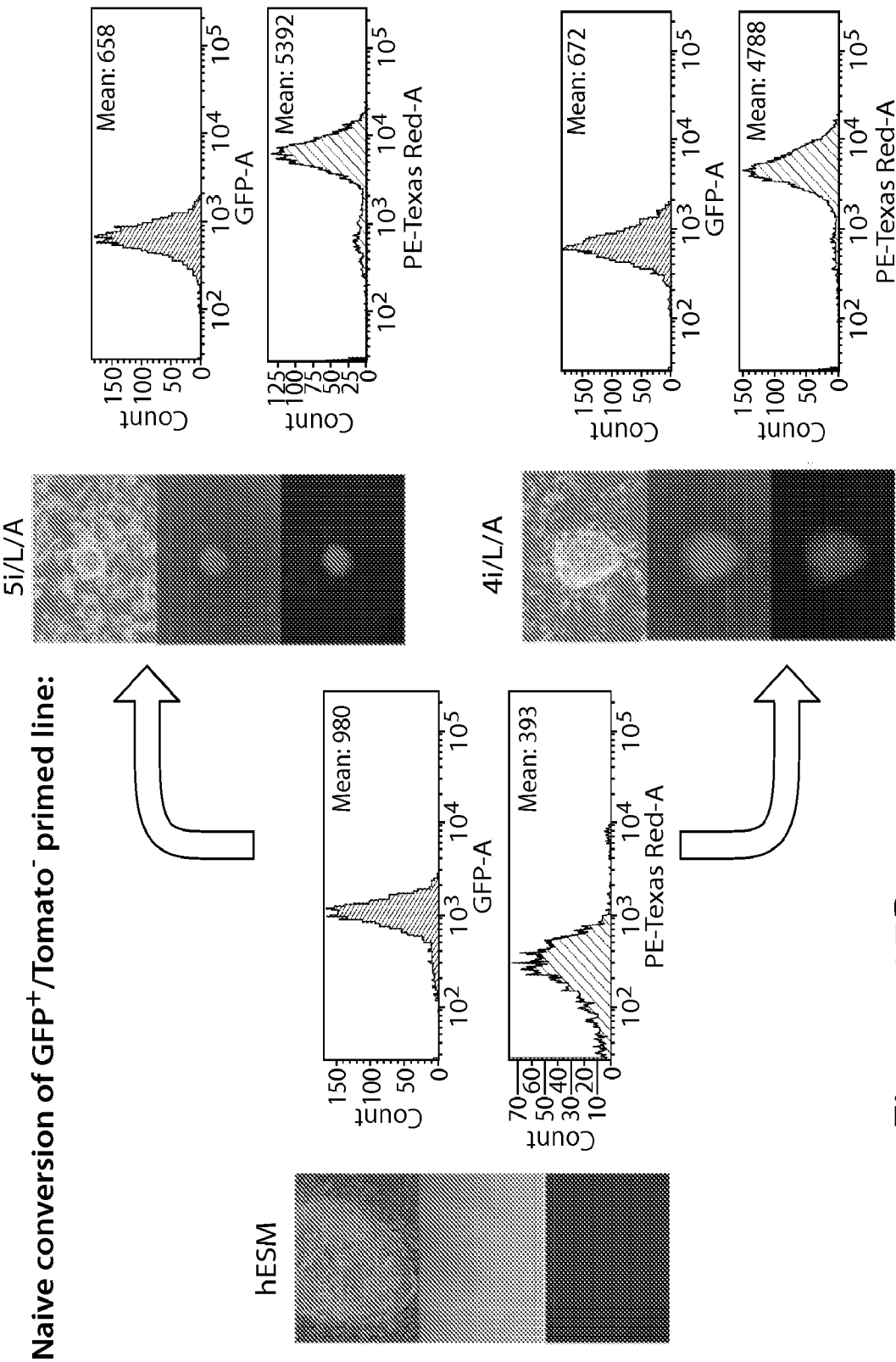


Figure 17B

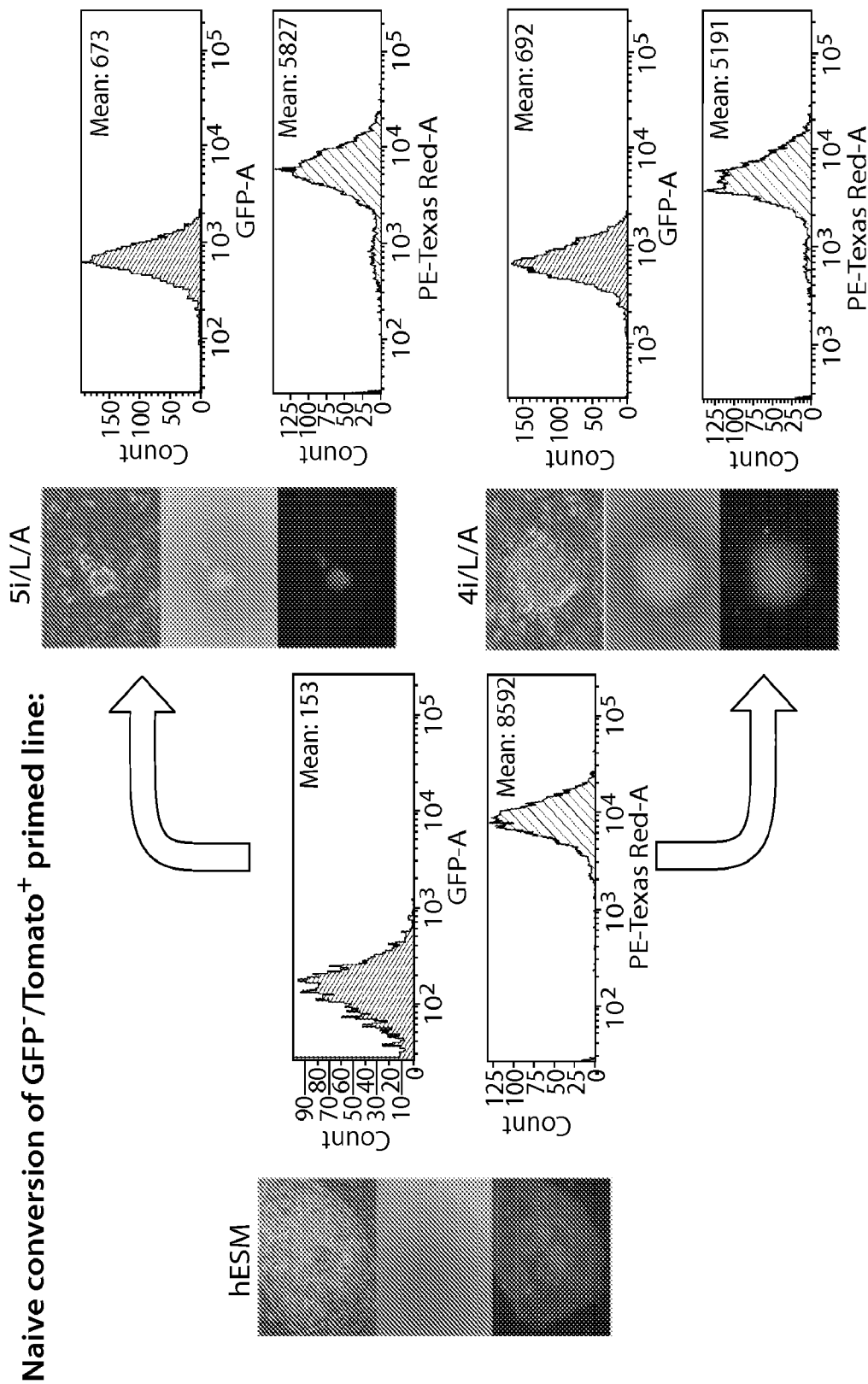


Figure 17C