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(54) Title: NOVEL SUICIDAL LSD1 INHIBITORS TARGETING SOX2-EXPRESSING CANCER CELLS

(57) Abstract: Disclosed are inhibitors of lysine-specific demethylase I (LSD1); synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of treating cancers characterized by the presence of Sox2 using the compounds and compositions Also disclosed are methods of treating cancers characterized by the presence of Sox2 using inhibitors of LSD 1 and/or histone deacetylation I (HDAC1). This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

NOVEL SUICIDAL LSD1 INHIBITORS TARGETING SOX2-EXPRESSING CANCER CELLS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims the benefit of U.S. Provisional Application No. 61/828,749, filed on May 30, 2013, and U.S. Provisional Application No. 61/937,394, filed on February 7, 2014, which are incorporated herein by reference in their entireties.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with U.S. Government support under grant number R01CA989550, awarded by the National Institute of Health (NIH). The U.S. government has certain rights in the invention.

REFERENCE TO SEQUENCE LISTING

[0003] The Sequence Listing submitted May 30, 2014 as a text file named "37474_0004P1_Sequence_Listing.txt," created on May 30, 2014, and having a size of 82,916 bytes is hereby incorporated by reference pursuant to 37 C.F.R. § 1.52(e)(5).

BACKGROUND

[0004] The official name and symbol of the Sox2 gene are "SRY (sex determining region Y)-box 2" and *SOX2*, respectively. The *SOX2* gene provides instructions for making a protein that plays a critical role in the formation of many different tissues and organs during embryonic development. This protein regulates the activity of other genes by attaching (binding) to specific regions of DNA in order to turn other genes on or off. On the basis of this action, the SOX2 protein is referred to as a transcription factor. The SOX2 protein is especially important for the development of the eyes. At least 33 mutations in the *SOX2* gene have been found to cause the SOX2 anophthalmia syndrome or the anophthalmia-esophageal-genital (AEG) syndrome. Some of these mutations prevent the gene from making any SOX2 protein, while others result in the production of an abnormally short, nonfunctional version of the protein. A few mutations change single protein building blocks (amino acids) in the SOX2 protein. All of these mutations disrupt the protein's ability to regulate genes essential for normal development of the eyes and other parts of the body. Abnormal development of these structures causes the signs and symptoms of *SOX2* anophthalmia syndrome or anophthalmia-esophageal-genital (AEG) syndrome.

[0005] In lung development, Sox2 controls the branching morphogenesis of the bronchial tree and differentiation of the epithelium of airways. Over-expression causes an increase in neuroendocrine, gastric/intestinal, and basal cells. Under normal conditions, Sox2 is critical

for maintaining self-renewal and the appropriate proportion of basal cells in adult tracheal epithelium. However, its over-expression gives rise to extensive epithelial hyperplasia and eventually carcinoma in both developing and adult mouse lungs.

[0006] In squamous cell carcinoma, gene amplifications frequently target the 3q26.3 region. The gene for Sox2 lies within this region, which effectively characterizes Sox2 as an oncogene. Sox2 is a key upregulated factor in lung squamous cell carcinoma, directing many genes involved in tumor progression. Its over-expression also activates cellular migration and anchorage-independent growth. The ectopic expression of SOX2 may be related to abnormal differentiation of colorectal cancer cells.

[0007] Lung cancer is the most frequent cause of cancer death in the United States. Squamous cell carcinoma of the lung is a major form of frequent and aggressive lung cancer. Recent studies show that the gene amplification of *Sox2* that encodes a high mobility group domain-containing transcription factor is the most frequent and common event in squamous cell carcinomas of the lung, esophagus, and oral cavity at 3q22.33 (Bass, A.J., et al. (2009) *Nat. Genet.* **41**, 1238-1242). Sox2 is a master regulator of pluripotent embryonic stem cells (ESCs) and adult neural stem cells. It can reprogram somatic cells into the induced pluripotent stem cells (iPSCs) with Oct4, Klf4, and Myc, or with Oct4, Lin 28, and Nanog. Sox2 also plays an essential role in the morphogenesis and homeostasis of the esophageal, tracheo-bronchial and bronchiolar epithelia. Sox2 acts as a lineage-survival oncogene for the expression of pluripotent stem cell signatures and for the lineage-specific gene expression of squamous cells in lung squamous cell
carcinomas. Ectopic expression of Sox2 causes the oncogenic transformation of normal tracheobronchial epithelial cells. The *Sox2* gene is also amplified in a fraction of small-cell lung carcinomas (Rudin et al. (2012) *Nat. Genet.* **44**, 1111-1116). Sox2 is expressed in lung adenocarcinomas whose expression is associated with poor prognosis. Sox2 is frequently expressed in other types of poorly differentiated and aggressive human cancers. Sox2 is expressed in a subpopulation of stem cell-like ovarian cancer cells with other pluripotent stem cell proteins such as Oct4 or Lin28. In breast carcinomas, expression of Sox2 is associated with basal-like phenotypes and is required for mammosphere formation in culture, which is considered as part of stem cell-like properties.

[0008] Histone methylation is a major covalent modification of histones that provides the structural and functional characteristics of chromatin to epigenetically define gene expression patterns in a cell. LSD1 (lysine-specific demethylase 1), also known as KDM1, AOF2, or BHC110, is a highly conserved flavin adenine dinucleotide (FAD)-dependent lysine-specific

demethylase that belongs to the monoamine oxidase family and specifically removes monomethyl- and dimethyl- groups from histone H3 at lysine 4 (H3K4), and in certain cells lysine-9 (H3K9). LSD1 is highly expressed in undifferentiated ESCs but progressively downregulated during differentiation. Loss of LSD1 in the mouse causes early embryonic lethality. Recent studies indicate that LSD1 is an essential epigenetic regulator of pluripotency in ESCs. It has been previously shown that the levels of LSD1 are elevated in pluripotent teratocarcinoma, embryonic carcinoma, and seminoma cells (Wang, J. et al. (2011) *Cancer Research* **71**, 7238-7249).

[0009] Elevated levels of Sox2 in cancers also correlate with the presence of lymphnode and distant metastases colon cancers (Neumann, J., et al. (2011) *BMC Cancer* **11**, 518). The over-expression and gene amplification of *Sox2* were also found in a fraction of glioblastoma multiforme (GBM) (Alonso, M.M., et al. (2011) *PLoS One* **6**, e26740) the most aggressive primary brain tumor. Lengerke et al. discloses that SOX2 expression was detected in 28% of invasive breast carcinoma as well as in 44% of ductal carcinoma in situ (DCIS) lesions (see Lengerke, C., et al. (2011) *BMC Cancer* **11**:42). A score of SOX2 expression (score 0 to 3) was defined in order to distinguish SOX2 negative (score 0) from SOX2 positive samples (score 1-3) and among latter subgroup of SOX2 high expressors (score 3 > 50% positive cells). Overall, the incidence of SOX2 expression (score 1-3) was higher than previously reported in a cohort of lymph node negative patients (28% versus 16.7%). SOX2 expression was detected across different breast cancer subtypes and did not correlate with tumor grading. However, high SOX2 expression (score 3) was associated with larger tumor size ($p = 0.047$) and positive lymph node status (0.018). Corresponding metastatic lymph nodes showed higher SOX2 expression and were significantly more often SOX2 positive than primary tumors ($p = 0.0432$). It has further been shown that the embryonic stem cell factor SOX2 is expressed in a variety of early stage postmenopausal breast carcinomas and metastatic lymph nodes. These data suggest that SOX2 plays an early role in breast carcinogenesis and that high expression of SOX2 may promote metastatic potential. Further studies are needed to explore whether SOX2 can predict metastatic potential at an early tumor stage.

[0010] Histone acetylation is another post-transcription modification of histones controlled by two opposing enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs) through adding and removing acetyl groups from lysine residues. In mammals, 18 HDACs have been identified, which catalyze deacetylation of histones and many other non-histone proteins. Histone deacetylase 1 (HDAC1) belongs to the Class I HDACs, which also include HDAC2, HDAC3, and HDAC8 and are mostly localized to the

nucleus. HDAC1 and HDAC2 share substantial amino acid sequence homologies and are often found to co-exist in repressive transcriptional complexes. Both HDAC1 and HDAC2 can remove the acetyl group from the acetylated histone H3 at lysine 56 (H3K56) (Miller, K.M., et al. (2010) *Nature Struct. Mol. Biol.* **17**, 1144-1151). However, HDAC1 and HDAC2 may have distinct functions because germ-line deletion of HDAC1 causes mouse embryo lethality before embryonic day 10.5 while HDAC2 specifically regulates synaptic plasticity and memory formation. HDAC1 is highly expressed in pancreatic ductal adenocarcinoma, colon cancer, ovarian cancer and lung cancer. A group of HDAC inhibitors are currently being tested in clinical applications. Most of these HDAC inhibitors, which usually belong to either aliphatic acids (i.e., butyrate and valproic acid), hydroxamates (i.e., tricostatin A and SAHA), benzamides (i.e., MS-275 and MGCD0103), cyclic peptides (i.e., FK228/resminostat), or electrophilic ketone hybrid molecules (i.e., trapoxin B or CHAP31) (Khan, O. and La Thangue, N. B. (2012) *Immunology and Cell Biology* **90**, 85-94), interfere with the enzymatic activities of multiple members of class I HDACs or other HDACs. These HDAC inhibitors also usually induce histone H3 or H4 hyperacetylation, which correlate with broad cytotoxicities in different cancer cells.

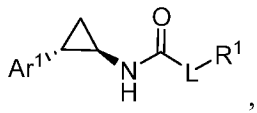
[0011] Despite the knowledge that Sox2 is frequently over-expressed in variety of human cancers and acts as an oncogene to confer certain stem cell properties to carcinoma cells, compounds and compositions capable of selectively targeting Sox2-expressing cancer cells have remained elusive. Thus, there remains a need for selective inhibitors that target cancer cells that exhibit cancer stem cell properties and methods of making and using same.

SUMMARY

[0012] The present invention relates to the field of cancer treatments and especially the treatment of cancers in which *Sox2* expression is involved in cancer propagation or metastasis. LSD1 was identified as a unique and selective epigenetic target for a wide variety of human carcinoma cells that express Sox2. In addition, one mechanism by which LSD1 suppresses the growth of cancer cells that express Sox2 is via modulation of the activity of histone deacetylase 1 (HDAC1) through the control of acetylation of histone H4 at lysine 16 (H4K16). LSD1 and HDAC1 form a protein complex in Sox2-expressing carcinoma cells to coordinately regulate histone methylation and acetylation. Indeed, the levels of both LSD1 and HDAC1 are elevated in these cells. The present technology employs the inactivation of LSD1 and/or HDAC1 to selectively suppress or inhibit growth of cells that express Sox2. The inhibition of these two enzymes selectively suppresses or inhibits the growth and/or

replication of cancer cells that express Sox2.

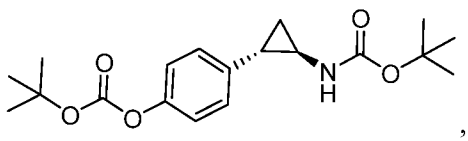
[0013] In one aspect, the invention relates to compound having a structure represented by a formula:



wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, –

$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[0014] Also disclosed are compounds having a structure selected from:



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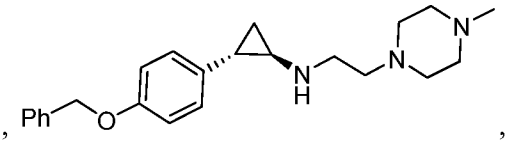

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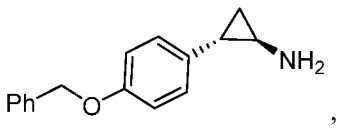
and



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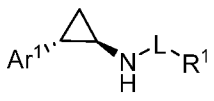
or a pharmaceutically acceptable salt thereof.

[0015] Also disclosed are pharmaceutical composition comprising a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, and a pharmaceutically acceptable carrier.

[0016] Also disclosed are methods of modulating at least one histone methylation event in at least one cell, the method comprising contacting the cell with an effective amount of at least one compound having a structure represented by a formula:



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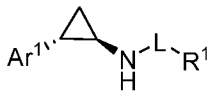
wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8

polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3

monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[0017] Also disclosed are methods of inhibiting LSD1 (lysine-specific demethylase I) in at least one cell, the method comprising the method comprising contacting the cell with an effective amount of at least one compound represented by a formula:



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wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-

C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[0018] Also disclosed are methods of treating a cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor.

[0019] Also disclosed are methods of treating a cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

[0020] Also disclosed are methods of inhibiting the proliferation of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor.

[0021] Also disclosed are methods of inhibiting the proliferation of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

[0022] Also disclosed are methods of inhibiting the proliferation of at least one cancer cell, the method comprising contacting the at least one cell with an effective amount of at least one LSD1 inhibitor.

[0023] Also disclosed are methods of inhibiting the proliferation of at least one cancer cell, the method comprising contacting the at least one cell with an effective amount of at least one HDAC1 inhibitor.

[0024] Also disclosed are methods of inhibiting the survival of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor.

[0025] Also disclosed are methods of inhibiting the survival of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

[0026] Also disclosed are methods of inhibiting the survival of at least one cancer cell, the method comprising contacting the at least one cell with an effective amount of at least one LSD1 inhibitor.

[0027] Also disclosed are methods of inhibiting the survival of at least one cancer cell, the method comprising contacting the at least one cell with an effective amount of at least one HDAC1 inhibitor.

[0028] Also disclosed are methods for the manufacture of a medicament for treatment of cancer in a mammal, the method comprising the step of combining an effective amount of at least one LSD1 inhibitor.

[0029] Also disclosed are methods for the manufacture of a medicament for treatment of cancer in a mammal, the method comprising the step of combining an effective amount of at least one HDAC1 inhibitor.

[0030] Also disclosed are kits comprising at least one disclosed compound or a pharmaceutically acceptable salt thereof, and one or more of: a) at least one agent known to inhibit LSD1; b) at least one agent known to inhibit HDAC1; c) at least one anticancer therapeutic agent; d) instructions for detecting cancer; and e) instructions for treating cancer.

BRIEF DESCRIPTION OF THE FIGURES

[0031] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0032] **FIG. 1** shows representative spectral data for CBB3001 (Compound 10). Specifically, ^{1}H NMR (**1A**), ^{13}C NMR (**1B**), HRMS (**1C**), and HPLC (**1D**) spectra are shown.

[0033] **FIG. 2** shows representative data pertaining to the potency of representative compounds 1-10. Specifically, **FIG. 2A** quantifies the enzyme activity in the presence of 100 μM compound. **FIG. 2B** shows concentration effect curves for compounds 1, 2 (CBB3002), 3 (CBB3003), and 10 (CBB3001).

[0034] **FIG. 3** shows representative data pertaining to the potency of compound 10 (CBB3001) in ES-2 (**3A**), PA-1 (**3B**), and T47D (**3C**) cells.

[0035] **FIG. 4A-C** show representative data pertaining to the expression of Sox2 in lung SCCs.

[0036] **FIG. 5A-C** show representative data illustrating that lung carcinoma cells expressing Sox2 are selectively sensitive to LSD1 inactivation.

[0037] **FIG. 6A-C** show representative data pertaining to the sensitivity of a panel of breast, ovarian, and other human carcinoma cells to LSD1 inhibitors and LSD1 siRNA-mediated ablation.

[0038] **FIG. 7A** and **7B** show representative data pertaining to the effects of LSD1 inhibitor CBB1007 and siRNAs on the growth of a panel of ovarian and breast carcinoma cells.

[0039] **FIG. 8A-C** show representative data demonstrating that loss of LSD1 activity causes growth inhibition in ovarian A2780, and breast T47D cells.

[0040] **FIG. 9A-C** show representative data pertaining to the ablation of LSD1 by specific siRNAs.

[0041] **FIG. 10A-C** show representative data pertaining to the expression of Oct 4, Sox2, Nano, Lin28, Sall4, and other proteins in lung, breast, ovarian, teratocarcinoma, embryonic carcinoma, and other carcinoma cells.

[0042] **FIG. 11A-C** show representative data pertaining to the regulation of Sox2 expression by LSD1.

[0043] **FIG. 12A** and **12B** show representative data demonstrating that LSD1 regulates Sox2 expression by modulating bivalent H3K9 and H3K4 methylations.

[0044] **FIG. 13A-C** show representative data pertaining to the presence of LSD1, H3K4me1/2, H3K9me2, and H3K27Me3 on either the Sox2 gene, the FoxA2 gene, the CyclinA gene, or SAT2 in A549 (**13A-C**) or A2780 (**13C**) cells.

[0045] **FIG. 14** shows representative data pertaining to the presence of LSD1, H3K4Me1 and H3K4Me2 on the CyclinA gene in A549 cells.

[0046] **FIG. 15A** and **15B** show representative data demonstrating that LSD1 deficiency suppresses the expression of Sox2-regulated lineage-specific genes.

[0047] **FIG. 16A-C** show representative data demonstrating that inactivation of Sox2 causes G_1 cell-cycle arrest and inhibits the cell growth of Sox2-expressing carcinoma cells.

[0048] **FIG. 17A** shows representative data pertaining to the effect of G_1 cell cycle arrest on Sox2 in expression. **FIG. 17B** shows representative data pertaining to the effect of ablation of Sox2 on cells that are sensitive to LSD1 inhibitors.

[0049] **FIG. 18A** and **18B** show representative data pertaining to the effects of Sox2 inactivation on cell cycles (**18A**) and the induction of differentiation genes (**18B**).

[0050] **FIG. 19A-C** show representative data demonstrating that Sox2 is a target of LSD1 inactivation in Sox2-expressing carcinoma cells.

[0051] **FIG. 20A-E** show representative data demonstrating that LSD1 binds to CoREST and loss of CoREST phenocopies the selective growth inhibition of LSD1 inactivation in Sox2-expressing cancer cells.

[0052] **FIG 21A-D** show representative data demonstrating that inactivation of LSD1 induces the expression of differentiation genes.

[0053] **FIG. 22** shows representative data demonstrating that inactivation of LSD1 induces the expression of differentiation genes by increased methylation of H3K4, but not methylated H3K9, and suppression of the Cyclin A Gene by Increased H3K4me1/2 and H3K9me2.

[0054] **FIG. 23A** and **23B** shows representative data demonstrating that LSD1 inhibitors CBB1003 and CBB1007 selectively block the growth of squamous carcinoma cells containing Sox2 gene amplification.

[0055] **FIG. 24A** and **24B** show representative data pertaining to the design of LSD1 inhibitors using a crystal structure of LSD1 and a pseudo-substrate.

[0056] **FIG. 25** shows a representative schematic illustrating that histone methylation at lysine 4 (H3K4) is dynamically regulated by MLL-WDR5-RBBP5 methyltransferases and LSD1/2 and JARIAD1A-1D demthylases.

[0057] **FIG. 26** shows a representative schematic illustrating the removal of H3K4 in histone 3 by an FAD-dependent oxidation catalyzed by LSD1.

[0058] **FIG. 27A-F** show representative data pertaining to the effects of inactivation of HDAC1 in ES/EC cells.

[0059] **FIG. 28A-D** show representative data demonstrating that inactivation of LSD1 or HDAC1 causes similar changes of histone methylation and acetylation in ES/EC cells.

[0060] **FIG. 29A-G** show representative data pertaining to the regulation of LSD1 and HDAC1 by mutual activities in the LSD1-CoREST-HDAC1 complex.

[0061] **FIG. 30A-C** show representative data pertaining to the regulation of LSD1 and HDAC1 activities by substrate modification.

[0062] **FIG. 31A-E** show representative data pertaining to the regulation of H4K16 acetylation by elevated HDAC1 and LSD1 levels in ES/EC cells.

[0063] **FIG. 32A** and **32B** show representative data demonstrating that HDAC1 is required for the expression of Oct4 and Sox2 by directly binding to the regulatory regions.

[0064] **FIG. 33A** and **33B** show representative data demonstrating that loss of HDAC1 or LSD1 induces the expression of genes for differentiation.

[0065] **FIG. 34A** and **34B** show representative data demonstrating that LSD1 or HDAC1 inactivation induces elevated levels of H3K4me2 and H4K16ac on the regulatory regions of differentiation genes.

[0066] **FIG. 35A** and **35B** show representative data demonstrating that loss of LSD1 or HDAC1 induces G_1 cell cycle arrest in F9 and PA-1 cells.

[0067] **FIG. 36A-D** show representative data demonstrating that HDAC1 and Sirt1 regulate the expression of different sets of genes.

[0068] **FIG. 37A-C** show representative data demonstrating that inactivation of MOF reverses the effects of LSD1 inactivation on increased acetylation of H4K16 and gene expression in ES/EC cells.

[0069] **FIG. 38A-F** show representative data pertaining to the restoration of LSD1, HDAC1, and MOF siRNA ablation effects by reexpression of cognate cDNAs.

[0070] **FIG. 39** shows a representative schematic summarizing LSD1- or HDAC1-regulated pluripotency of mES or EC cells through HDAC1-mediated H4K16 acetylation.

[0071] **FIG. 40** shows the cytogenic location of the *Sox2* configuration in the human genome.

[0072] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION

[0073] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0074] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0075] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

[0076] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein may be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

[0077] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog rules for stereochemistry can be employed to designate stereochemical priority, *E/Z* specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as CHEMDRAW™ (Cambridgesoft Corporation, U.S.A.).

[0078] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a functional group," "an alkyl," or "a residue" includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0079] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0080] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0081] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the

component is included.

[0082] As used herein, the terms "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0083] As used herein, the term "subject" can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more disorders prior to the administering step. In various aspects, the one or more disorders are a disorder of cellular proliferation.

[0084] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0085] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0086] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of a disorder of cellular proliferation prior to the administering step. As used herein, the phrase "identified to be in need of treatment for a disorder," or the like, refers to selection of a subject based upon need for treatment of the disorder. It is contemplated that the identification can, in one aspect, be performed by a person different from the person making the diagnosis. It is also contemplated, in a further aspect, that the administration can be performed by one who subsequently performed the administration.

[0087] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0088] The term "contacting" as used herein refers to bringing a disclosed compound and a cell, target histamine receptor, or other biological entity together in such a manner that the compound can affect the activity of the target (e.g., receptor, cell, etc.), either directly; i.e., by interacting with the target itself, or indirectly; i.e., by interacting with another molecule, co-factor, factor, or protein on which the activity of the target is dependent.

[0089] As used herein, the terms "effective amount" and "amount effective" refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is

sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[0090] As used herein, "EC_{50}," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC_{50} can refer to the concentration of a substance that is required for 50% agonism *in vivo*, as further defined elsewhere herein. In a further aspect, EC_{50} refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response.

[0091] As used herein, "IC_{50}," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an IC_{50} can refer to the concentration of a substance that is required for 50% inhibition *in vivo*, as further defined elsewhere herein. In a further aspect, IC_{50} refers to the half maximal (50%) inhibitory concentration (IC) of a substance.

[0092] The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of

undesirable biological effects or interacting in a deleterious manner.

[0093] As used herein, the term "derivative" refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0094] The term "leaving group" refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include sulfonate esters, including triflate, mesylate, tosylate, brosylate, and halides.

[0095] A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $-OCH_2CH_2O-$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more $-CO(CH_2)_8CO-$ moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

[0096] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by

rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0097] In defining various terms, "A^1," "A^2," "A^3," and "A^4" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0098] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *s*-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can also be substituted or unsubstituted. The alkyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms.

[0099] Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" specifically refers to an alkyl group that is substituted with one or more halide, *e.g.*, fluorine, chlorine, bromine, or iodine. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "alkylamino" specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When "alkyl" is used in one instance and a specific term such as "alkylalcohol" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "alkylalcohol" and the like.

[00100] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, *e.g.*, an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, *e.g.*, a "halogenated alkoxy," a particular substituted alkenyl can be, *e.g.*, an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is

not meant to imply that the general term does not also include the specific term.

[00101] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term "heterocycloalkyl" is a type of cycloalkyl group as defined above, and is included within the meaning of the term "cycloalkyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[00102] The term "polyalkylene group" as used herein is a group having two or more CH_2 groups linked to one another. The polyalkylene group can be represented by the formula —$(CH_2)_a$—, where "a" is an integer of from 2 to 500.

[00103] The terms "alkoxy" and "alkoxyl" as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an "alkoxy" group can be defined as —OA^1 where A^1 is alkyl or cycloalkyl as defined above. "Alkoxy" also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as —OA^1—OA^2 or —OA^1—$(OA^2)_a$—OA^3, where "a" is an integer of from 1 to 200 and A^1, A^2, and A^3 are alkyl and/or cycloalkyl groups.

[00104] The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(A^1A^2)C=C(A^3A^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[00105] The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bound, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term "heterocycloalkenyl" is a type of

cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkenyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[00106] The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[00107] The term "cycloalkynyl" as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bound. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononynyl, and the like. The term "heterocycloalkynyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkynyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[00108] The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term "aryl" also includes "heteroaryl," which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term "non-heteroaryl," which is also included in the term "aryl," defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be

substituted with one or more groups including, but not limited to, optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of "aryl." Biaryl refers to two aryl groups that are bound together *via* a fused ring structure, as in naphthalene, or are attached *via* one or more carbon-carbon bonds, as in biphenyl.

[00109] The term "aldehyde" as used herein is represented by the formula —C(O)H. Throughout this specification "C(O)" is a short hand notation for a carbonyl group, *i.e.*, C=O.

[00110] The terms "amine" or "amino" as used herein are represented by the formula —NA^1A^2, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[00111] The term "alkylamino" as used herein is represented by the formula —NH(-alkyl) where alkyl is a described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[00112] The term "dialkylamino" as used herein is represented by the formula —N(-alkyl)$_2$ where alkyl is a described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

[00113] The term "carboxylic acid" as used herein is represented by the formula —C(O)OH.

[00114] The term "ester" as used herein is represented by the formula —$OC(O)A^1$ or —$C(O)OA^1$, where A^1 can be an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "polyester" as used herein is represented by the formula —$(A^1O(O)C\text{-}A^2\text{-}C(O)O)_a$— or —$(A^1O(O)C\text{-}A^2\text{-}OC(O))_a$—, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer from 1 to 500. "Polyester" is as the term used to describe a group

that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[00115] The term "ether" as used herein is represented by the formula A^1OA^2, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term "polyether" as used herein is represented by the formula $—(A^1O\text{-}A^2O)_a—$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[00116] The term "halide" as used herein refers to the halogens fluorine, chlorine, bromine, and iodine.

[00117] The term "heterocycle," as used herein refers to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Heterocycle includes pyridinde, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole,thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like.

[00118] The term "hydroxyl" as used herein is represented by the formula —OH.

[00119] The term "ketone" as used herein is represented by the formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[00120] The term "azide" as used herein is represented by the formula $—N_3$.

[00121] The term "nitro" as used herein is represented by the formula $—NO_2$.

[00122] The term "nitrile" as used herein is represented by the formula —CN.

[00123] The term "silyl" as used herein is represented by the formula $—SiA^1A^2A^3$, where A^1, A^2, and A^3 can be, independently, hydrogen or an optionally substituted alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[00124] The term "sulfo-oxo" as used herein is represented by the formulas $—S(O)A^1$, $—S(O)_2A^1$, $—OS(O)_2A^1$, or $—OS(O)_2OA^1$, where A^1 can be hydrogen or an optionally

substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S=O. The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula —$S(O)_2A^1$, where A^1 can be hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by the formula $A^1S(O)_2A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by the formula $A^1S(O)A^2$, where A^1 and A^2 can be, independently, an optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[00125] The term "thiol" as used herein is represented by the formula —SH.

[00126] "R^1," "R^2," "R^3," "R^n," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

[00127] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. In is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[00128] The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[00129] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[00130] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or

more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[00131] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

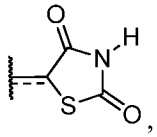
[00132] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00133] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00134] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, –$R^{\bullet}$, -(halo$R^{\bullet}$), –OH, –$OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, –C(O)$OR^{\bullet}$, –NH_2, –$NHR^{\bullet}$, –$NR^{\bullet}_2$, or -NO_2, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, –CH_2Ph, –$O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00135] The term "organic residue" defines a carbon containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms

[00136] A very close synonym of the term "residue" is the term "radical," which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure:



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more "substituent radicals." The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[00137] "Organic radicals," as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals

often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[00138] "Inorganic radicals," as the term is defined and used herein, contain no carbon atoms and therefore comprise only atoms other than carbon. Inorganic radicals comprise bonded combinations of atoms selected from hydrogen, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and halogens such as fluorine, chlorine, bromine, and iodine, which can be present individually or bonded together in their chemically stable combinations. Inorganic radicals have 10 or fewer, or preferably one to six or one to four inorganic atoms as listed above bonded together. Examples of inorganic radicals include, but not limited to, amino, hydroxy, halogens, nitro, thiol, sulfate, phosphate, and like commonly known inorganic radicals. The inorganic radicals do not have bonded therein the metallic elements of the periodic table (such as the alkali metals, alkaline earth metals, transition metals, lanthanide metals, or actinide metals), although such metal ions can sometimes serve as a pharmaceutically acceptable cation for anionic inorganic radicals such as a sulfate, phosphate, or like anionic inorganic radical. Inorganic radicals do not comprise metalloids elements such as boron, aluminum, gallium, germanium, arsenic, tin, lead, or tellurium, or the noble gas elements, unless otherwise specifically indicated elsewhere herein.

[00139] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[00140] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each

enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[00141] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Inglod-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

[00142] When the disclosed compounds contain one chiral center, the compounds exist in two enantiomeric forms. Unless specifically stated to the contrary, a disclosed compound includes both enantiomers and mixtures of enantiomers, such as the specific 50:50 mixture referred to as a racemic mixture. The enantiomers can be resolved by methods known to those skilled in the art, such as formation of diastereoisomeric salts which may be separated,

for example, by crystallization (see, CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation by David Kozma (CRC Press, 2001)); formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step can liberate the desired enantiomeric form. Alternatively, specific enantiomers can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[00143] Designation of a specific absolute configuration at a chiral carbon in a disclosed compound is understood to mean that the designated enantiomeric form of the compounds can be provided in enantiomeric excess (*e.e.*). Enantiomeric excess, as used herein, is the presence of a particular enantiomer at greater than 50%, for example, greater than 60%, greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. In one aspect, the designated enantiomer is substantially free from the other enantiomer. For example, the "R" forms of the compounds can be substantially free from the "S" forms of the compounds and are, thus, in enantiomeric excess of the "S" forms. Conversely, "S" forms of the compounds can be substantially free of "R" forms of the compounds and are, thus, in enantiomeric excess of the "R" forms.

[00144] When a disclosed compound has two or more chiral carbons, it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to four optical isomers and two pairs of enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers that are not mirror-images (e.g., (S,S) and (R,S)) are diastereomers. The diastereoisomeric pairs can be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Unless otherwise specifically excluded, a disclosed compound includes each diastereoisomer of such compounds and mixtures thereof.

[00145] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labeled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labeled reagent for a non- isotopically labeled reagent.

[00146] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvate or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[00147] The term "co-crystal" means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrates or solvates, see e.g. "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almarasson, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-

toluenesulfonic acid and benzenesulfonic acid.

[00148] It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[00149] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00150] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

[00151] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and

described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[00152] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. LSD1 INHIBITORS

[00153] In one aspect, the invention relates to inhibitors of lysine-specific demethylase I (LSD1) useful in the treatment of cancers. In various aspects, LSD1 inhibitors can be useful in the treatment or control of carcinomas, such as squamous cell carcinomas.

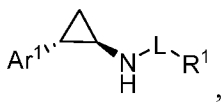
[00154] LSD1 is a gene which codes a flavin-dependent monoamine oxidase, which can demethylate mono- and di-methylated lysines, specifically histone 3, lysines 4 and 9 (H3K4 and H3K9). LSD1 is also involved in histone methylation. LSD1, also known as KDM1, is the first of several protein lysine demethylases discovered. Through a FAD-dependent oxidative reaction, LSD1 specifically removes histone H3K4me2 to H3K4me1 or H3K4me0. When forming a complex with androgen receptor (and possibly other nuclear hormone receptors), LSD1 changes its substrates to H3K9me2. It's now known that the LSD1 complex mediates a coordinated histone modification switch through enzymatic activities as well as histone modification readers in the complex.

[00155] LSD1 is co-expressed with Sox2 in lung squamous cell carcinomas with high frequency. Although the roles of Sox2 in carcinogenesis of many human cancers remains largely unclear, recent studies have shown that the gene amplification of *Sox2* is the most frequent and common event in squamous cell carcinomas of lung, esophagus, and oral cavity at 3q22.33, as well as in a fraction of small cell lung carcinoma and glioblastoma multiforme. In lung squamous cell carcinomas, Sox2 acts as a lineage-survival oncogene for the expression of pluripotent stem cell signatures and genes for lineage-specific squamous cell differentiation.

[00156] Most LSD1 inhibitors bind to the active demethylation site to block LSD1 demethylase activity. Examples of LSD1 inhibitors include inhibitors of monoamine oxidases (i.e., derivatives of parnate (2-phenylcyclopropylamine/2-PCPA or derivatives of tranylcypromine) that form a covalent bond with FAD in LSD1, and derivatives of bisguanidine polyamine analogues, which may mimic the binding of the methylated H3K4 peptide substrate to LSD1 (Yang et al. (2007) *Biochemistry* **46**, 8058-8065; Dawn, M. Z., et al. (2007) *Biochemistry* **46**, 4408-4416; Harris, W. J., et al. (2012) *Cancer Cell* **21**, 473-487); Huang, Y., et al. (2007) *PNAS* **104**, 8023-8028). Recent studies also indicate that LSD1 is essential for maintaining the oncogenic potential of MLL-AF9 leukemia stem cells and acute myeloid leukemia. While LSD1 is essential for ESCs and related teratocarcinomas/embryonic carcinomas or leukemia cells, the mechanism by which LSD1 regulates the pluripotency of ESCs, teratocarcinomas/embryonic carcinomas, cancer stem cells or cancer cells has thus far remained unclear.

[00157] In a further aspect, the LSD1 inhibitor mimics the binding of methylated H3K4 peptide substrate to LSD1 in a non-covalent manner.

[00158] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



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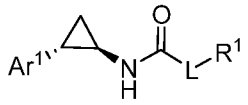
wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8

polyhaloalkyl, C1-C8 hydroxyalkyl, $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $-(CR^{2a}R^{2b})_n-$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-NO_2$, –CN, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-

C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00159] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



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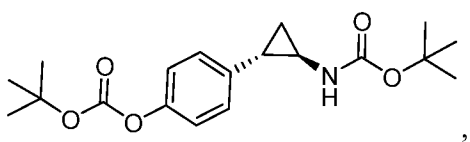
wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and

wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00160] In a further aspect, the LSD1 inhibitor is selected from: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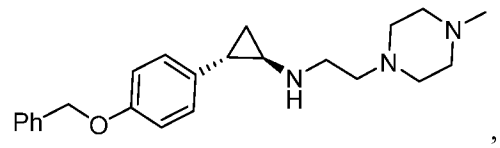
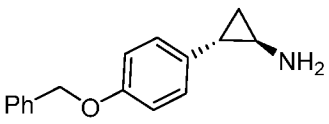
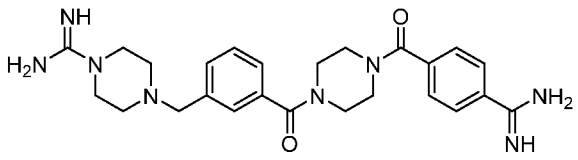

,
and

,

or a pharmaceutically acceptable salt thereof.

[00161] In a further aspect, the LSD1 inhibitor is selected from: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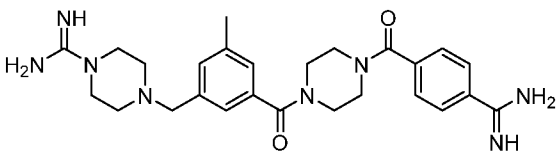
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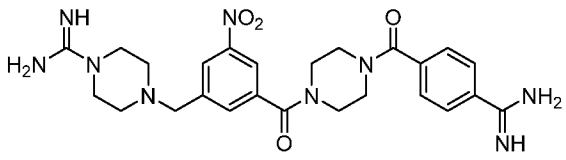
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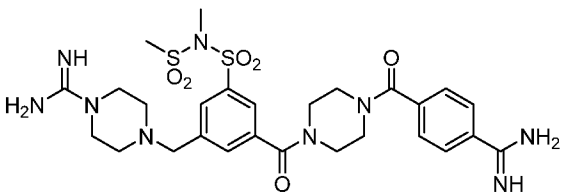
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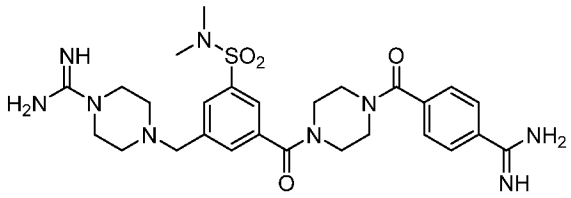

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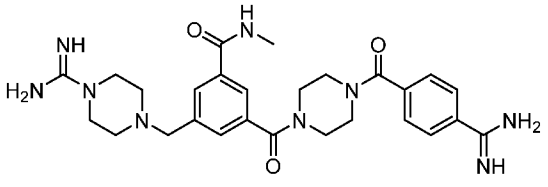

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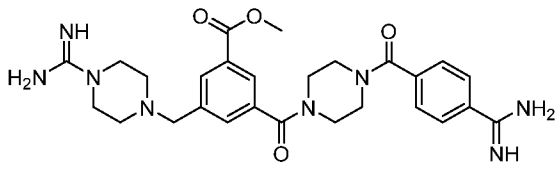

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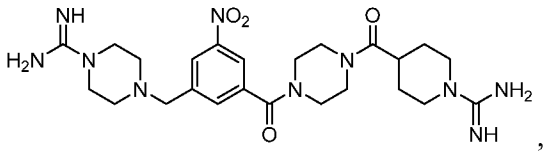

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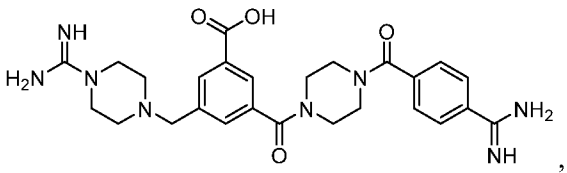
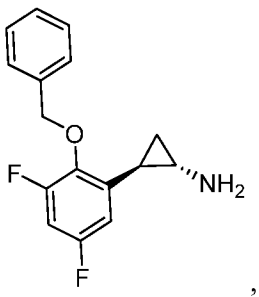
and



,

or a pharmaceutically acceptable salt thereof.

[00162] In a further aspect, the LSD1 inhibitor is selected from:



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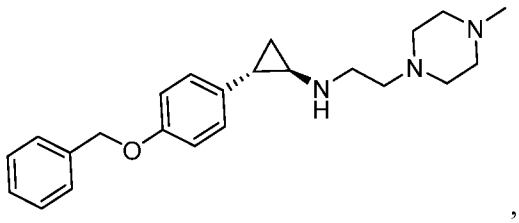
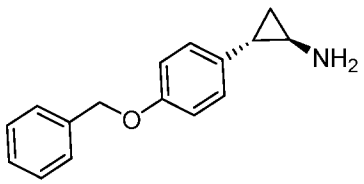


,



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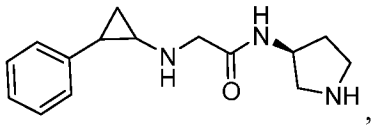

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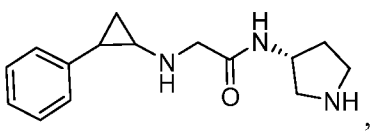

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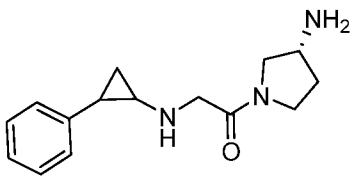

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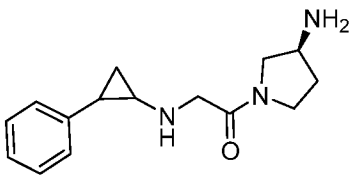

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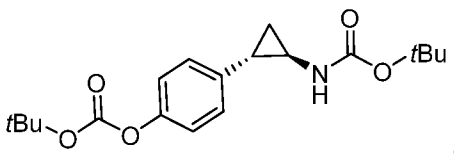

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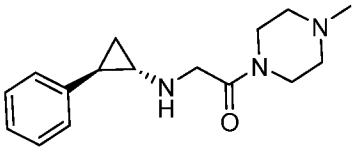
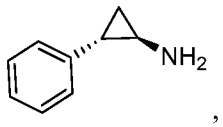
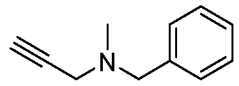




or a pharmaceutically acceptable salt thereof.

[00163] In a further aspect, the LSD1 inhibitor is selected from parnate 2-phenylcyclopropylamine (2-PCPA), tranylcypromine, and derivatives thereof. In a still further aspect, the LSD1 inhibitor is a bisguanidine polyamine.

C. HDAC1 INHIBITORS

[00164] In one aspect, the invention relates to inhibitors of histone deacetylase I (HDAC1) useful in the treatment of cancers. In various aspects, HDAC1 inhibitors can be useful in the treatment or control of carcinomas, such as squamous cell carcinomas.

[00165] HDAC1 is an enzyme that in humans is encoded by the *HDAC1* gene. Histone acetylation and deacetylation, catalyzed by multi-subunit complexes, play a key role in the regulation of eukaryotic gene expression. The protein encoded by this gene belongs to the histone deacetylase/acuc/apha family and is a component of the histone deacetylase complex. It also interacts with retinoblastoma tumor-suppressor protein and this complex is a key element in the control of cell proliferation and differentiation. In addition to histones, HDAC1 also deacetylates non-histone proteins. Together with metastasis-associated protein-2 MTA2, it deacetylates p53 and modulates its effect on cell growth and apoptosis.

[00166] Examples of HDAC inhibitors include, but are not limited to, aliphatic acids, hyroxamate, benzamide, cyclic peptide, and electrophilic ketone hybrid molecules. Additional examples can include butyrate acid, Valproate (valproic acid), Tricostatin A (TSA), Vorinostat (SAHA), Entinostat (MS-275, SNDX-275), MGCD-0103, Romidepsin (FK-228/resminostate), trapoxin B, CHAP31, Panobinostate (Belinostat, PXD101), M344 (PCI-34051), CI994 (Tacedinaline), Tubastatin A hydrochloride, AR-42 (HDAC-42), SB939 (Pracinostat), ITF2357, Givinostat, CUDC-101, LAQ824 (NVP-LAQ824, Dacinostat), PCI-24781 (CRA-024781), APHA compound 8, BATCP, MOCPAC, PTACH, and PP.

[00167] In various aspects, HDAC1 forms a unique complex with LSD1 and CoREST in stem cells or Sox2-expressing cancer cells. In the LSD1-CoREST-HDAC1 complex, the LSD1 activity is dependent on the presence of an active HDAC1. So in Sox2-expressing

cancer cells, HDAC1 inhibitors, such as MS-275, not only inhibited the activity of HDAC1, but also reduced the activity of LSD1, thereby producing the same growth inhibitory effects on Sox2-expressing cancer cells or cancer stem cells as that of LSD1 inhibitors.

D. COMPOUNDS

[00168] In one aspect, the invention relates to compounds useful in treating or controlling oncological disorders, such as cancer. The compounds and pharmaceutical compositions containing the compounds can be useful in the treatment or control of carcinomas, such as squamous cell carcinomas.

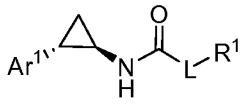
[00169] In one aspect, the disclosed compounds exhibit inhibition of LSD1.

[00170] In one aspect, the compounds of the invention are useful in the treatment of cancers characterized by the presence of Sox2, as described herein.

[00171] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. STRUCTURE

[00172] In one aspect, the invention relates to compounds having a structure represented by a formula:

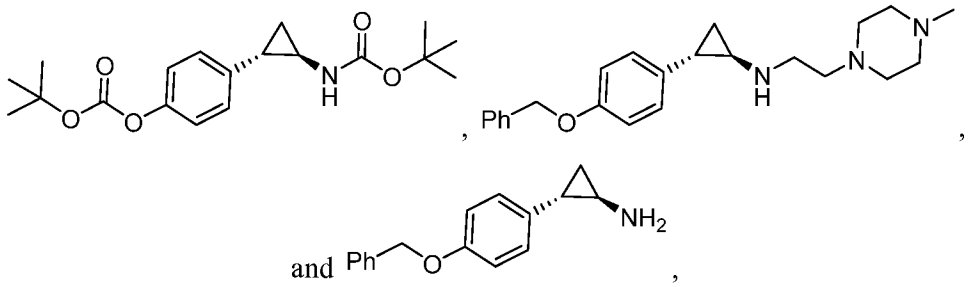


,

wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2,

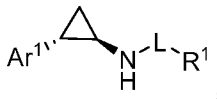
or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and –CO_2R^{21}; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00173] In one aspect, the invention relates to compounds having a structure selected from:



or a pharmaceutically acceptable salt thereof.

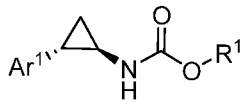
[00174] In a further aspect, the compound has a structure represented by a formula:



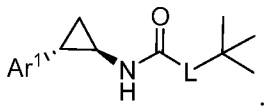
wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –C(O)SR^8, –SO_2R^9, –$CONR^{10a}R^{10b}$, –$SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups

independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –NO_2, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and –CO_2R^{21}; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

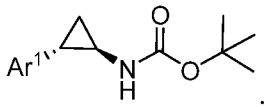
[00175] In a further aspect, the compound has a structure represented by a formula:



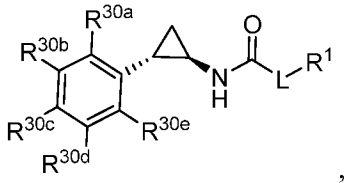
[00176] In a still further aspect, the compound has a structure represented by a formula:



[00177] In yet a further aspect, the compound has a structure represented by a formula:



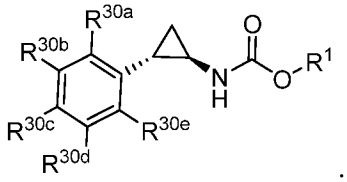
[00178] In a further aspect, the compound has a structure represented by a formula:



,

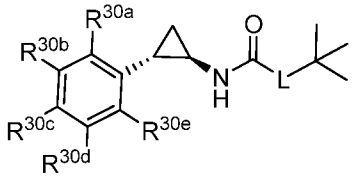
wherein each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00179] In a still further aspect, the compound has a structure represented by a formula:



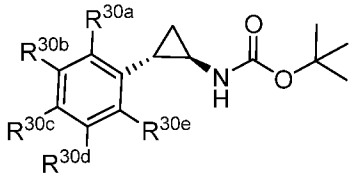
.

[00180] In yet a further aspect, the compound has a structure represented by a formula:



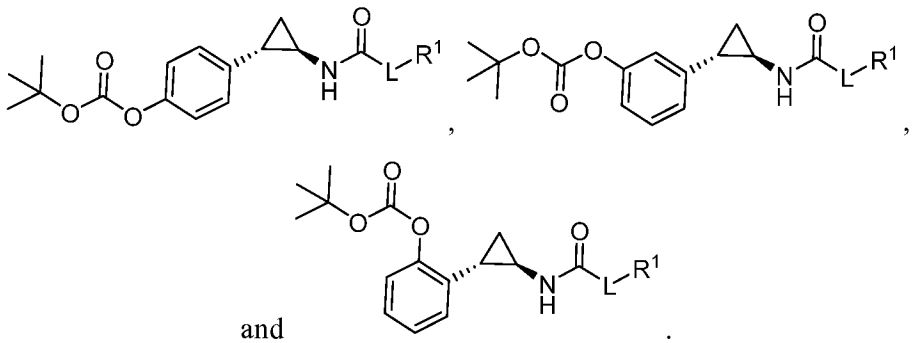
.

[00181] In an even further aspect, the compound has a structure represented by a formula:



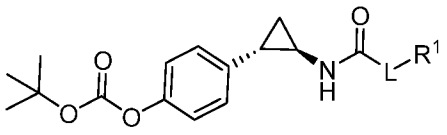
.

[00182] In a still further aspect, the compound has a structure represented by a formula selected from:



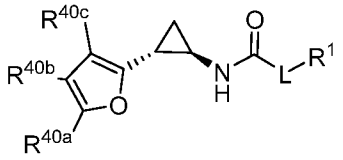
and .

[00183] In yet a further aspect, the compound has a structure represented by a formula:

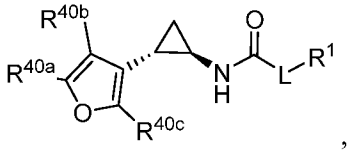


.

[00184] In a further aspect, the compound has a structure represented by a formula selected from:



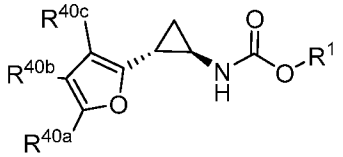
and



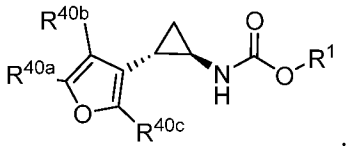
,

wherein each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, halogen, $-NO_2$, $-CN$, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00185] In a still further aspect, the compound has a structure represented by a formula selected from:

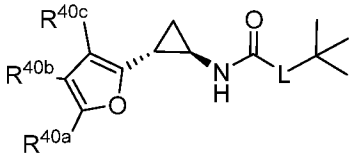


and

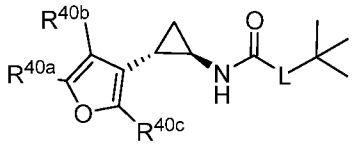


.

[00186] In yet a further aspect, the compound has a structure represented by a formula selected from:

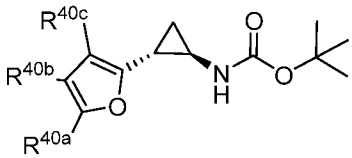


and

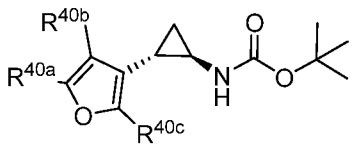


.

[00187] In an even further aspect, the compound has a structure represented by a formula selected from:

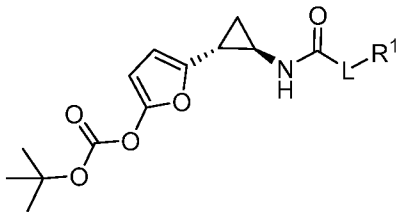
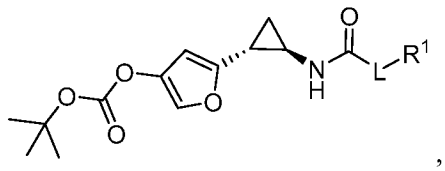
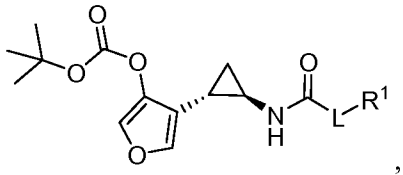
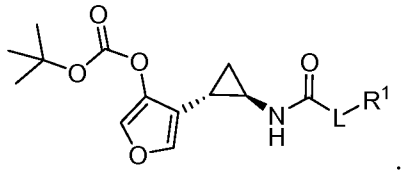


and

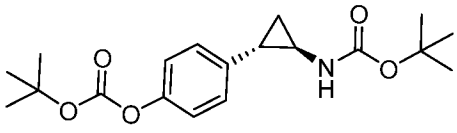
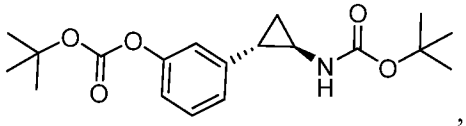
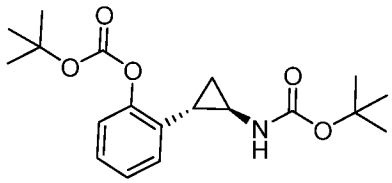


.

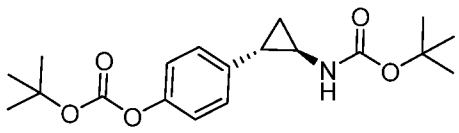
[00188] In a still further aspect, the compound has a structure represented by a formula selected from:


,

,

, and

.

[00189] In a further aspect, the compound is selected from:


,

,

and .

[00190] In a further aspect, the compound is:


.

[00191] In a further aspect, n is an integer selected from 1 and 2. In a still further aspect, n is 1. In yet a further aspect, n is 2.

a. L GROUPS

[00192] In one aspect, L is a moiety selected from –O– and $-(CR^{2a}R^{2b})_n-$. In a further aspect, L is –O–. In a still further aspect, L is $-(CR^{2a}R^{2b})_n-$.

[00193] In one aspect, L is a moiety selected from –C(O)–, $-CO_2-$, and $-(CR^{2a}R^{2b})_n-$. In a further aspect, L is a moiety selected from –C(O)– and $-CO_2-$. In a still further aspect, L is –C(O)–. In yet a further aspect, L is $-CO_2-$. In an even further aspect, L is $-(CR^{2a}R^{2b})_n-$.

b. R^1 GROUPS

[00194] In one aspect, R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$. In a further aspect, R^1 is selected from hydrogen, C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$.

[00195] In one aspect, R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$. In a further aspect, R^1 is selected from hydrogen, C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$.

[00196] In a further aspect, R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 and L is –O–. In a still further aspect, R^1 is selected from hydrogen, C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, Ar^2, and Cy^1 and L is –O–. In yet a further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, *t*-butyl, ethene, propene, but-2-ene, but-1-ene, ethyne, prop-1-yne, but-1-yne, but-2-yne, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, Ar^2, and Cy^1 and L is –O–. In an even further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, ethene, propene, ethyne, prop-1-yne, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$,

—CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, Ar^2, and Cy^1 and L is –O–. In a still further aspect, R^1 is selected from hydrogen, methyl, ethyl, ethene, ethyne, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, Ar^2, and Cy^1 and L is –O–. In yet a further aspect, R^1 is selected from hydrogen, methyl, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —OCH_3, Ar^2, and Cy^1 and L is –O–.

[00197] In a further aspect, R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, and C1-C8 alkynyl and L is –O–. In a still further aspect, R^1 is selected from hydrogen, C1-C4 alkyl, C1-C4 alkenyl, and C1-C4 alkynyl and L is –O–. In yet a further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, *t*-butyl, ethene, propene, but-2-ene, but-1-ene, ethyne, prop-1-yne, but-1-yne, and but-2-yne and L is –O–. In an even further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, ethene, propene, ethyne, and prop-1-yne and L is –O–. In a still further aspect, R^1 is selected from hydrogen, methyl, ethyl, ethene, and ethyne and L is –O–. In yet a further aspect, R^1 is selected from hydrogen and methyl and L is –O–. In an even further aspect, R^1 is hydrogen and L is –O–. In

[00198] In a further aspect, R^1 is C1-C8 alkyl and L is –O–. In a still further aspect, R^1 is C1-C4 alkyl and L is –O–. In yet a further aspect, R^1 is selected from methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, and *t*-butyl and L is –O–. In an even further aspect, R^1 is selected from methyl, ethyl, *i*-propyl, and *n*-propyl and L is –O–. In a still further aspect, R^1 is selected from methyl and ethyl and L is –O–. In yet a further aspect, R^1 is methyl and L is –O–. In an even further aspect, R^1 is ethyl and L is –O–. In a still further aspect, R^1 is *i*-propyl and L is –O–. In yet a further aspect, R^1 is *n*-propyl and L is –O–. In an even further aspect, R^1 is *i*-butyl and L is –O–. In a still further aspect, R^1 is *n*-butyl and L is –O–. In yet a further aspect, R^1 is *s*-butyl and L is –O–. In an even further aspect, R^1 is *t*-butyl and L is –O–.

[00199] In a further aspect, R^1 is selected from hydrogen, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is –O–. In a still further aspect, R^1 is selected from hydrogen, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C4 hydroxyalkyl and L is –O–. In yet a further aspect, R^1 is selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, and —OCH_2CH_3 and L is –O–. In an even further aspect, R^1 is selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, and —OCH_3 and L is –O–

.

[00200] In a further aspect, R^1 is selected from hydrogen, Ar^2, and Cy^1 and L is –O–. In a still further aspect, R^1 is selected from hydrogen and Ar^2 and L is –O–. In yet a further aspect, R^1 is Ar^2 and L is –O–. In an even further aspect, R^1 is Cy^1 and L is –O–.

[00201] In a further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ and L is $–(CR^{2a}R^{2b})_n–$. In a still further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ and L is $–(CR^{2a}R^{2b})_n–$. In yet a further aspect, R^1 is selected from $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ and L is $–(CR^{2a}R^{2b})_n–$. In an even further aspect, R^1 is selected from –OH, –SH, $–NH_2$, $–CO_2H$, –C(O)SH, $–SO_2H$, $–CONH_2$, and $–SO_2NH_2$ and L is $–(CR^{2a}R^{2b})_n–$.

[00202] In a further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ and L is $–(CH_2)_n–$. In a still further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ and L is $–(CR^{2a}R^{2b})_n–$. In yet a further aspect, R^1 is selected from $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ and L is $–(CH_2)_n–$. In an even further aspect, R^1 is selected from –OH, –SH, $–NH_2$, $–CO_2H$, –C(O)SH, $–SO_2H$, $–CONH_2$, and $–SO_2NH_2$ and L is $–(CH_2)_n–$.

[00203] In a further aspect, R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 and L is $–CO_2–$. In a still further aspect, R^1 is selected from hydrogen, C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, Ar^2, and Cy^1 and L is $–CO_2–$. In yet a further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, *t*-butyl, ethene, propene, but-2-ene, but-1-ene, ethyne, prop-1-yne, but-1-yne, and but-2-yne and L is $–CO_2–$. In an even further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, ethene, propene, ethyne, and prop-1-yne and L is $–CO_2–$. In a still further aspect, R^1 is selected from hydrogen, methyl, ethyl, ethene, and ethyne and L is $–CO_2–$. In yet a further aspect, R^1 is selected from hydrogen and methyl and L is $–CO_2–$. In an even further aspect, R^1 is hydrogen and L is $–CO_2–$.

[00204] In a further aspect, R^1 is C1-C8 alkyl and L is $–CO_2–$. In a still further aspect, R^1 is C1-C4 alkyl and L is $–CO_2–$. In yet a further aspect, R^1 is selected from methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, and *t*-butyl and L is $–CO_2–$. In an even further

aspect, R^1 is selected from methyl, ethyl, *i*-propyl, and *n*-propyl and L is $-CO_2-$. In a still further aspect, R^1 is selected from methyl and ethyl and L is $-CO_2-$. In yet a further aspect, R^1 is methyl and L is $-CO_2-$. In an even further aspect, R^1 is ethyl and L is $-CO_2-$. In a still further aspect, R^1 is *i*-propyl and L is $-CO_2-$. In yet a further aspect, R^1 is *n*-propyl and L is $-CO_2-$. In an even further aspect, R^1 is *i*-butyl and L is $-CO_2-$. In a still further aspect, R^1 is *n*-butyl and L is $-CO_2-$. In yet a further aspect, R^1 is *s*-butyl and L is $-CO_2-$. In an even further aspect, R^1 is *t*-butyl and L is $-CO_2-$.

[00205] In a further aspect, R^1 is selected from hydrogen, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is $-CO_2-$. In a still further aspect, R^1 is selected from hydrogen, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C4 hydroxyalkyl and L is $-CO_2-$. In yet a further aspect, R^1 is selected from hydrogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2Cl$, $-CH_2CHCl_2$, $-CH_2CCl_3$, $-OCH_3$, and $-OCH_2CH_3$ and L is $-CO_2-$. In an even further aspect, R^1 is selected from hydrogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, and $-OCH_3$ and L is $-CO_2-$.

[00206] In a further aspect, R^1 is selected from hydrogen, Ar^2, and Cy^1 and L is $-CO_2-$. In a still further aspect, R^1 is selected from hydrogen and Ar^2 and L is $-CO_2-$. In yet a further aspect, R^1 is Ar^2 and L is $-CO_2-$. In an even further aspect, R^1 is Cy^1 and L is $-CO_2-$.

[00207] In a further aspect, R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $-NO_2$, $-CN$, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is selected from $-C(O)-$ and $-(CR^{2a}R^{2b})_n-$. In a still further aspect, R^1 is selected from C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-NO_2$, $-CN$, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is selected from $-C(O)-$ and $-(CR^{2a}R^{2b})_n-$.

[00208] In a further aspect, R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is selected from $-C(O)-$ and $-(CR^{2a}R^{2b})_n-$. In a still further aspect, R^1 is selected from C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is selected from $-C(O)-$ and $-(CR^{2a}R^{2b})_n-$. In yet a further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, *t*-butyl, ethene, propene, but-2-ene, but-1-ene, ethyne, prop-1-yne, but-1-yne, and but-2-yne and L is selected from $-C(O)-$ and $-(CR^{2a}R^{2b})_n-$. In an even further aspect, R^1 is selected from

hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, ethene, propene, ethyne, and prop-1-yne and L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$. In a still further aspect, R^1 is selected from hydrogen, methyl, ethyl, ethene, and ethyne and L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$. In yet a further aspect, R^1 is selected from hydrogen and methyl and L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$. In an even further aspect, R^1 is hydrogen and L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$.

[00209] In a further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$. In a still further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$. In yet a further aspect, R^1 is selected from $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$.

[00210] In a further aspect, R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is –C(O)–. In a still further aspect, R^1 is selected from C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is –C(O)–.

[00211] In a further aspect, R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is –C(O)–. In a still further aspect, R^1 is selected from C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is –C(O)–. In yet a further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, *t*-butyl, ethene, propene, but-2-ene, but-1-ene, ethyne, prop-1-yne, but-1-yne, and but-2-yne and L is –C(O)–. In an even further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, ethene, propene, ethyne, and prop-1-yne and L is –C(O)–. In a still further aspect, R^1 is selected from hydrogen, methyl, ethyl, ethene, and ethyne and L is –C(O)–. In yet a further aspect, R^1 is selected from hydrogen and methyl and L is $–CO_2–$. In an even further aspect, R^1 is hydrogen and L is –C(O)–.

[00212] In a further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is –C(O)–. In a still further aspect, R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$,

$-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is –C(O)–. In yet a further aspect, R^1 is selected from $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is –C(O)–.

[00213] In a further aspect, R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CR^{2a}R^{2b})_n-$. In a still further aspect, R^1 is selected from C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CR^{2a}R^{2b})_n-$.

[00214] In a further aspect, R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is $-(CR^{2a}R^{2b})_n-$. In a still further aspect, R^1 is selected from C1-C4 alkyl, C1-C4 alkenyl, C1-C4 alkynyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C8 hydroxyalkyl and L is $-(CR^{2a}R^{2b})_n-$. In yet a further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *s*-butyl, *t*-butyl, ethene, propene, but-2-ene, but-1-ene, ethyne, prop-1-yne, but-1-yne, and but-2-yne and L is $-(CR^{2a}R^{2b})_n-$. In an even further aspect, R^1 is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, ethene, propene, ethyne, and prop-1-yne and L is $-(CR^{2a}R^{2b})_n-$. In a still further aspect, R^1 is selected from hydrogen, methyl, ethyl, ethene, and ethyne and L is $-(CR^{2a}R^{2b})_n-$. In yet a further aspect, R^1 is selected from hydrogen and methyl and L is $-(CR^{2a}R^{2b})_n-$. In an even further aspect, R^1 is hydrogen and L is $-(CR^{2a}R^{2b})_n-$.

[00215] In a further aspect, R^1 is selected from $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CR^{2a}R^{2b})_n-$. In a still further aspect, R^1 is selected from $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CR^{2a}R^{2b})_n-$. In yet a further aspect, R^1 is selected from $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CR^{2a}R^{2b})_n-$.

[00216] In a further aspect, R^1 is selected from $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CH_2)_n-$. In a still further aspect, R^1 is selected from $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CH_2)_n-$. In yet a further aspect, R^1 is selected from $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-CO_2R^7$, –

$C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 and L is $-(CH_2)_n-$.

c. R^{2A} AND R^{2B} GROUPS

[00217] In one aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $-NH_2$, $-NO_2$, –CN, and $-N_3$. In a further aspect, each of R^{2a} and R^{2b}, when present, is hydrogen.

[00218] In a further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, –OH, $-NH_2$, $-NO_2$, –CN, and $-N_3$. In a still further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, –OH, $-NH_2$, $-NO_2$, and –CN. In yet a further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, –OH, $-NH_2$, and $-NO_2$. In an even further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, –OH, and $-NH_2$. In a still further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and –OH. In yet a further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and $-NH_2$. In an even further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and $-NO_2$. In a still further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and –CN. In yet a further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and $-N_3$.

[00219] In a further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and halogen. In a still further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, –F, –Cl, and –Br. In yet a further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, –F, and –Cl. In an even further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and –F. In a still further aspect, each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen and –Cl.

d. R^3, R^4, R^{5A}, R^{5B}, R^6, R^7, R^8, R^9, R^{10A}, R^{10B}, R^{11A}, AND R^{11B} GROUPS

[00220] In one aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2. In a further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is hydrogen.

[00221] In a further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present,

is independently selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, methyl, and ethyl. In an even further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen and methyl. In a still further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen and ethyl.

[00222] In a further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl. In a still further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2Cl$, $-CH_2CHCl_2$, and $-CH_2CCl_3$. In yet a further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, and $-CCl_3$. In an even further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, $-CH_2F$, $-CHF_2$, and $-CF_3$.

[00223] In a further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, Ar^3, and Cy^2. In a still further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen and Ar^3. In yet a further aspect, each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen and Cy^2.

e. R^{12} GROUPS

[00224] In one aspect, R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$. In a further aspect, R^{12}, when present, is hydrogen.

[00225] In a further aspect, R^{12}, when present, is selected from hydrogen and CO_2R^{21}. In a still further aspect, R^{12}, when present, is $-CO_2R^{21}$.

[00226] In a further aspect, R^{12}, when present, is selected from hydrogen, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl. In a still further aspect, R^{12}, when present, is selected from hydrogen, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2Cl$, $-CH_2CHCl_2$, and $-CH_2CCl_3$. In yet a further aspect,

R^{12}, when present, is selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, and —CCl_3. In an even further aspect, R^{12}, when present, is selected from hydrogen, —CH_2F, —CHF_2, and —CF_3.

[00227] In a further aspect, R^{12}, when present, is selected from hydrogen and C1-C4 alkyl. In a still further aspect, R^{12}, when present, is selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, R^{12}, when present, is selected from hydrogen, methyl, and ethyl. In an even further aspect, R^{12}, when present, is selected from hydrogen and methyl. In a still further aspect, R^{12}, when present, is selected from hydrogen and ethyl.

f. R^{13}, R^{14A}, R^{14B}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20A}, AND R^{20B} GROUPS

[00228] In one aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl. In a further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is hydrogen.

[00229] In a further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, methyl, and ethyl. In an even further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen and methyl. In a still further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen and ethyl.

[00230] In a further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl. In a still further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, and —CH_2CCl_3. In yet a further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, and —CCl_3. In an even further aspect, each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, —CH_2F, —CHF_2, and —CF_3.

g. R^{21} GROUPS

[00231] In one aspect, R^{21}, when present, is selected from hydrogen and C1-C4 alkyl. In a further aspect, R^{21}, when present, is hydrogen.

[00232] In a further aspect, R^{21}, when present, is selected from hydrogen, methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *t*-butyl, and *s*-butyl. In a still further aspect, R^{21}, when present, is selected from methyl, ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *t*-butyl, and *s*-butyl. In yet a further aspect, R^{21}, when present, is selected from ethyl, *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *t*-butyl, and *s*-butyl. In an even further aspect, R^{21}, when present, is selected from *i*-propyl, *n*-propyl, *i*-butyl, *n*-butyl, *t*-butyl, and *s*-butyl. In a still further aspect, R^{21}, when present, is selected from *i*-butyl, *n*-butyl, *t*-butyl, and *s*-butyl. In yet a further aspect, R^{21}, when present, is selected from *i*-butyl, *n*-butyl, and *t*-butyl. In an even further aspect, R^{21}, when present, is selected from *i*-butyl and *t*-butyl. In a still further aspect, R^{21}, when present, is methyl. In yet a further aspect, R^{21}, when present, is ethyl. In an even further aspect, R^{21}, when present, is i-propyl. In a still further aspect, R^{21}, when present, is *n*-propyl. In yet a further aspect, R^{21}, when present, is i-butyl. In an even further aspect, R^{21}, when present, is *n*-butyl. In a still further aspect, R^{21}, when present, is *s*-butyl. In yet a further aspect, R^{21}, when present, is *t*-butyl.

h. R^{30A}, R^{30B}, R^{30C}, R^{30D}, AND R^{30E} GROUPS

[00233] In one aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is hydrogen.

[00234] In a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, —F, —Cl, –CN, $–N_3$, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—CH_2OH$, $—CH_2CH_2OH$, OR^{12}, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, —F, —Cl, –CN, $–N_3$, $—CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2OH$, OR^{12}, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00235] In a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and halogen. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, —F, —Cl, and —Br. In yet a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, —F and —Cl. In an even further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and —F. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and —Cl.

[00236] In a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, methyl, and ethyl. In an even further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and methyl. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and ethyl.

[00237] In a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C4 hydroxyalkyl. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —CH_2OH, and —CH_2CH_2OH. In yet a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, and —CH_2OH.

[00238] In a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen,–CN, $–N_3$,–OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00239] In a further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, –OR^{12}, –SR^{13}, and –$NR^{14a}R^{14b}$. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, –OR^{12} and –SR^{13}. In yet a

further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and $-NR^{14a}R^{14b}$. In an even further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and $-SR^{13}$. In a still further aspect, each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen and $-OR^{12}$.

i. R^{40A}, R^{40B}, AND R^{40C} GROUPS

[00240] In one aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, halogen, –CN, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is hydrogen.

[00241] In a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, —F, —Cl, –CN, $-N_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2Cl$, $-CH_2CHCl_2$, $-CH_2CCl_3$, $-CH_2OH$, $-CH_2CH_2OH$, OR^{12}, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, —F, —Cl, –CN, $-N_3$, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2OH$, OR^{12}, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00242] In a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and halogen. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, —F, —Cl, and —Br. In yet a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, —F and —Cl. In an even further aspect, each of each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and —F. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and —Cl.

[00243] In a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, each of each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, methyl, and ethyl. In an even further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and methyl. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and ethyl.

[00244] In a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C4 hydroxyalkyl. In a still

further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —CH_2OH, and —CH_2CH_2OH. In yet a further aspect, each of each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, and —CH_2OH.

[00245] In a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen,–CN, $–N_3$,–OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00246] In a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, –OR^{12}, –SR^{13}, and –$NR^{14a}R^{14b}$. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen, –OR^{12} and –SR^{13}. In yet a further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and –$NR^{14a}R^{14b}$. In an even further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and –SR^{13}. In a still further aspect, each of R^{40a}, R^{40b}, and R^{40c} is independently selected from hydrogen and –OR^{12}.

j. Ar^1 Groups

[00247] In one aspect, Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00248] In one aspect, Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00249] In a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is phenyl with 0, 1, or 2 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, Ar^1 is phenyl with 0 or 1 group selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, Ar^1 is phenyl monosubstituted with a group selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is unsubstituted phenyl.

[00250] In a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, –CN, $–N_3$, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—CH_2OH$, $—CH_2CH_2OH$, OR^{12}, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, –CN, $–N_3$, $—CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2OH$, OR^{12}, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00251] In a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 halogen groups. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, and —Br. In yet a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F and —Cl. In an even further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 fluoro groups. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 chloro groups.

[00252] In a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 C1-C4 alkyl groups. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from methyl, and ethyl. In an

even further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 methyl groups. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 ethyl groups.

[00253] In a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C4 hydroxyalkyl. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2Cl$, $-CH_2CHCl_2$, $-CH_2CCl_3$, $-CH_2OH$, and $-CH_2CH_2OH$. In yet a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, and $-CH_2OH$.

[00254] In a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from –CN, $–N_3$,$–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00255] In a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from $–OR^{12}$, $–SR^{13}$, and $–NR^{14a}R^{14b}$. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 groups independently selected from $–OR^{12}$ and $–SR^{13}$. In yet a further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 $–NR^{14a}R^{14b}$ groups. In an even further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 $–SR^{13}$ groups. In a still further aspect, Ar^1 is phenyl substituted with 0, 1, 2, or 3 $–OR^{12}$ groups.

[00256] In a further aspect, Ar^1 is heteroaryl with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is heteroaryl with 0, 1, or 2 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, Ar^1 is heteroaryl with 0 or 1 group selected from halogen, –CN, $–N_3$, C1-C4

alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, Ar^1 is heteroaryl monosubstituted with a group selected from halogen, –CN, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is unsubstituted heteroaryl.

[00257] In a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, –CN, $-N_3$, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—CH_2OH$, $—CH_2CH_2OH$, OR^{12}, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, –CN, $-N_3$, $—CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2OH$, OR^{12}, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00258] In a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 halogen groups. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, and —Br. In yet a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F and —Cl. In an even further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 fluoro groups. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 chloro groups.

[00259] In a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 C1-C4 alkyl groups. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from methyl, and ethyl. In an even further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 methyl groups. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 ethyl groups.

[00260] In a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C4 hydroxyalkyl. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—CH_2OH$, and $—CH_2CH_2OH$. In yet a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups

independently selected from —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, and —CH_2OH.

[00261] In a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from –CN, –N_3,–OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00262] In a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from –OR^{12}, –SR^{13}, and –$NR^{14a}R^{14b}$. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from –OR^{12} and –SR^{13}. In yet a further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 –$NR^{14a}R^{14b}$ groups. In an even further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 –SR^{13} groups. In a still further aspect, Ar^1 is heteroaryl substituted with 0, 1, 2, or 3 –OR^{12} groups.

[00263] In a further aspect, Ar^1 is selected from phenyl, furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyridazine, and pyrazine.

[00264] In a further aspect, Ar^1 is furan with 0, 1, 2, or 3 groups independently selected from halogen, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is furan with 0, 1, or 2 groups independently selected from halogen, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, Ar^1 is furan with 0 or 1 group selected from halogen, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, Ar^1 is furan monosubstituted with a group selected from halogen, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –

$CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is unsubstituted furan.

[00265] In a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, –CN, $-N_3$, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—CH_2OH$, $—CH_2CH_2OH$, OR^{12}, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, –CN, $-N_3$, $—CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2OH$, OR^{12}, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00266] In a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 halogen groups. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, and —Br. In yet a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from —F and —Cl. In an even further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 fluoro groups. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 chloro groups.

[00267] In a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 C1-C4 alkyl groups. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from methyl, ethyl, *i*-propyl, and *n*-propyl. In yet a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from methyl, and ethyl. In an even further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 methyl groups. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 ethyl groups.

[00268] In a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and C1-C4 hydroxyalkyl. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—CH_2OH$, and $—CH_2CH_2OH$. In yet a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, and $—CH_2OH$.

[00269] In a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from –CN, $-N_3$,$-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, –

$P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In yet a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4. In an even further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

[00270] In a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from $-OR^{12}$, $-SR^{13}$, and $-NR^{14a}R^{14b}$. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 groups independently selected from $-OR^{12}$ and $-SR^{13}$. In yet a further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 $-NR^{14a}R^{14b}$ groups. In an even further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 $-SR^{13}$ groups. In a still further aspect, Ar^1 is furan substituted with 0, 1, 2, or 3 $-OR^{12}$ groups.

k. Ar^2 Groups

[00271] In one aspect, Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a further aspect, Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0 or 1 group selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is monosubstituted with a group selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is unsubstituted.

[00272] In a further aspect, Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $-NH_2$, —CN, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$,

—$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00273] In a further aspect, Ar^2, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is aryl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^2, when present, is aryl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^2, when present, is aryl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is unsubstituted aryl.

[00274] In a further aspect, Ar^2, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^2, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00275] In a further aspect, Ar^2, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is

phenyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^2, when present, is phenyl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^2, when present, is phenyl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is unsubstituted phenyl.

[00276] In a further aspect, Ar^2, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^2, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00277] In a further aspect, Ar^2, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is heteroaryl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^2, when present, is heteroaryl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^2, when present, is heteroaryl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is unsubstituted heteroaryl.

[00278] In a further aspect, Ar^2, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^2, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00279] In a further aspect, Ar^2, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^2, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^2, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^2, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^2, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^2, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^2, when present is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^2, when present, is unsubstituted.

[00280] In a further aspect, Ar^2, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^2, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

l. Ar^3 Groups

[00281] In one aspect, Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a further aspect, Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is unsubstituted.

[00282] In a further aspect, Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected

from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00283] In a further aspect, Ar^3, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is aryl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^3, when present, is aryl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^3, when present, is aryl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted aryl.

[00284] In a further aspect, Ar^3, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^3, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00285] In a further aspect, Ar^3, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3

monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is phenyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^3, when present, is phenyl substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^3, when present, is phenyl monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted phenyl.

[00286] In a further aspect, Ar^3, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OH$, $—CH_2CH_2OH$, $—CH(CH_3)_2$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, $—N(CH_3)_2$, $—N(CH_3)CH_2CH_3$, and $—N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^3, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CF_3$, $—CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—OCF_3$, $—OCH_2CF_3$, $—CH_2OCF_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, and $—N(CH_3)_2$.

[00287] In a further aspect, Ar^3, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is heteroaryl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^3, when present, is heteroaryl substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^3, when present, is heteroaryl monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted heteroaryl.

[00288] In a further aspect, Ar^3, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^3, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00289] In a further aspect, Ar^3, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^3, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^3, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^3, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^3, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^3, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^3, when present is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^3, when present, is unsubstituted.

[00290] In a further aspect, Ar^3, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^3, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

m. Ar^4 Groups

[00291] In one aspect, Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^4, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a further aspect, Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^4, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^4, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^4, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^4, when present, is unsubstituted.

[00292] In a further aspect, Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^4, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^4, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00293] In a further aspect, Ar^4, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is aryl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^4, when present, is aryl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^4, when present, is aryl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is unsubstituted aryl.

[00294] In a further aspect, Ar^4, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^4, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00295] In a further aspect, Ar^4, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is phenyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^4, when present, is phenyl substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^4, when present, is phenyl monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is unsubstituted phenyl.

[00296] In a further aspect, Ar^4, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OH$, $—CH_2CH_2OH$, $—CH(CH_3)_2$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, $—N(CH_3)_2$, $—N(CH_3)CH_2CH_3$, and $—N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^4, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CF_3$, $—CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—OCF_3$, $—OCH_2CF_3$, $—CH_2OCF_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, and $—N(CH_3)_2$.

[00297] In a further aspect, Ar^4, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is heteroaryl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^4, when present, is heteroaryl substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^4, when present, is heteroaryl monosubstituted with a group selected from halogen, –OH, –

NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is unsubstituted heteroaryl.

[00298] In a further aspect, Ar^4, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^4, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00299] In a further aspect, Ar^4, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^4, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^4, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Ar^4, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^4, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Ar^4, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^4, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Ar^4, when present is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine,

pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^4, when present, is unsubstituted.

[00300] In a further aspect, Ar^4, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^4, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Ar^4, when present, is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, oxazole, pyridine, pyridazine, pyrazine, indole, quinoline, and isoquinoline and wherein Ar^4, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

n. Cy^1 Groups

[00301] In one aspect, Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino.

[00302] In a further aspect, Cy^1, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is C3-C6 cycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^1, when present, is C3-C6 cycloalkyl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^1, when present, is C3-C6 cycloalkyl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3

polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is unsubstituted C3-C6 cycloalkyl.

[00303] In a further aspect, Cy^1, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^1, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00304] In a further aspect, Cy^1, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^1, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^1, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^1, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^1, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^1, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^1, when present, is unsubstituted.

[00305] In a further aspect, Cy^1, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl,

—CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^1, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00306] In a further aspect, Cy^1, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^1, when present, is C2-C5 heterocycloalkyl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^1, when present, is C2-C5 heterocycloalkyl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is unsubstituted C2-C5 heterocycloalkyl.

[00307] In a further aspect, Cy^1, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^1, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00308] In a further aspect, Cy^1, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^1, when present, is substituted

with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^1, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^1, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^1, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^1, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^1, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^1, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^1, when present, is unsubstituted.

[00309] In a further aspect, Cy^1, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^1, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3,

—OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

o. Cy^2 Groups

[00310] In one aspect, Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino.

[00311] In a further aspect, Cy^2, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is C3-C6 cycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^2, when present, is C3-C6 cycloalkyl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^2, when present, is C3-C6 cycloalkyl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is unsubstituted C3-C6 cycloalkyl.

[00312] In a further aspect, Cy^2, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^2, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00313] In a further aspect, Cy^2, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups

independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^2, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^2, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^2, when present, is substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^2, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^2, when present, is monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^2, when present, is unsubstituted.

[00314] In a further aspect, Cy^2, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OH$, $—CH_2CH_2OH$, $—CH(CH_3)_2$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, $—N(CH_3)_2$, $—N(CH_3)CH_2CH_3$, and $—N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^2, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CF_3$, $—CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—OCF_3$, $—OCH_2CF_3$, $—CH_2OCF_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, and $—N(CH_3)_2$.

[00315] In a further aspect, Cy^2, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-

C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^2, when present, is C2-C5 heterocycloalkyl substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^2, when present, is C2-C5 heterocycloalkyl monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is unsubstituted C2-C5 heterocycloalkyl.

[00316] In a further aspect, Cy^2, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OH$, $—CH_2CH_2OH$, $—CH(CH_3)_2$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, $—N(CH_3)_2$, $—N(CH_3)CH_2CH_3$, and $—N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^2, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CF_3$, $—CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—OCF_3$, $—OCH_2CF_3$, $—CH_2OCF_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, and $—N(CH_3)_2$.

[00317] In a further aspect, Cy^2, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^2, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^2, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^2, when present, is substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-

C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^2, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^2, when present, is monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^2, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^2, when present, is unsubstituted.

[00318] In a further aspect, Cy^2, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OH$, $—CH_2CH_2OH$, $—CH(CH_3)_2$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, $—N(CH_3)_2$, $—N(CH_3)CH_2CH_3$, and $—N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^2, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CF_3$, $—CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—OCF_3$, $—OCH_2CF_3$, $—CH_2OCF_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, and $—N(CH_3)_2$.

p. Cy^3 Groups

[00319] In one aspect, Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino.

[00320] In a further aspect, Cy^3, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is

C3-C6 cycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^3, when present, is C3-C6 cycloalkyl substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^3, when present, is C3-C6 cycloalkyl monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is unsubstituted C3-C6 cycloalkyl.

[00321] In a further aspect, Cy^3, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CH_2CH_3$, $—CH_2F$, $—CHF_2$, $—CF_3$, $—CH_2Cl$, $—CHCl_2$, $—CCl_3$, $—CH_2CH_2F$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CH_2Cl$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OH$, $—CH_2CH_2OH$, $—CH(CH_3)_2$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, $—N(CH_3)_2$, $—N(CH_3)CH_2CH_3$, and $—N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^3, when present, is C3-C6 cycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, $—NH_2$, —CN, $—CH_3$, $—CF_3$, $—CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—CH_2OCH_3$, $—OCF_3$, $—OCH_2CF_3$, $—CH_2OCF_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—NHCH(CH_3)_2$, and $—N(CH_3)_2$.

[00322] In a further aspect, Cy^3, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^3, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^3, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^3, when present, is substituted with 0 or 1 group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^3, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^3, when present, is monosubstituted with a group selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3

monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^3, when present, is unsubstituted.

[00323] In a further aspect, Cy^3, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^3, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

[00324] In a further aspect, Cy^3, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^3, when present, is C2-C5 heterocycloalkyl substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^3, when present, is C2-C5 heterocycloalkyl monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is unsubstituted C2-C5 heterocycloalkyl.

[00325] In a further aspect, Cy^3, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH,

—CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^3, when present, is C2-C5 heterocycloalkyl substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

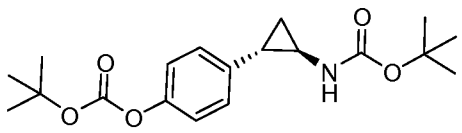
[00326] In a further aspect, Cy^3, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^3, when present, is substituted with 0, 1, or 2 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In yet a further aspect, Cy^3, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^3, when present, is substituted with 0 or 1 group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In an even further aspect, Cy^3, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^3, when present, is monosubstituted with a group selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino. In a still further aspect, Cy^3, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^3, when present, is unsubstituted.

[00327] In a further aspect, Cy^3, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3,

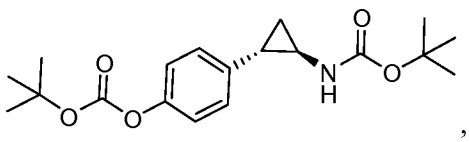
—CH_2CH_3, —CH_2F, —CHF_2, —CF_3, —CH_2Cl, —$CHCl_2$, —CCl_3, —CH_2CH_2F, —CH_2CHF_2, —CH_2CF_3, —CH_2CH_2Cl, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)_2$, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, —$N(CH_3)_2$, —$N(CH_3)CH_2CH_3$, and —$N(CH_3)CH(CH_3)_2$. In a still further aspect, Cy^3, when present, is selected from aziridine, oxirane, thiirane, azetidine, oxetane, thietane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydro-*2H*-pyran, tetrahydro-2*H*-thiopyran, and piperidine and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from —F, —Cl, —OH, —NH_2, —CN, —CH_3, —CF_3, —CCl_3, —OCH_3, —OCH_2CH_3, —CH_2OCH_3, —OCF_3, —OCH_2CF_3, —CH_2OCF_3, —$NHCH_3$, —$NHCH_2CH_3$, —$NHCH(CH_3)_2$, and —$N(CH_3)_2$.

2. Example Compounds

[00328] In one aspect, a compound can be present as the following structure:



[00329] In one aspect, the invention relates to compounds having a structure selected from:



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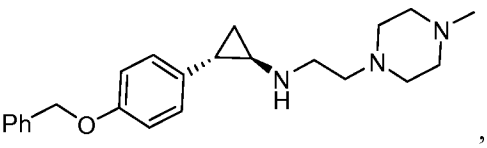

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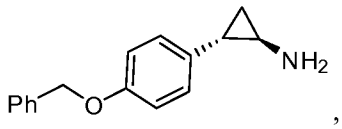
and



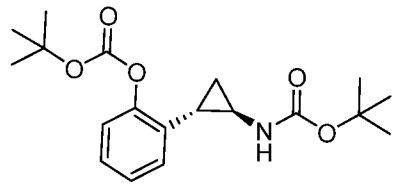
,

or a pharmaceutically acceptable salt thereof.

3. Prophetic Compound Examples

[00330] The following compound examples are prophetic, and can be prepared using the synthesis methods described herein above and other general methods as needed as would be known to one skilled in the art. It is anticipated that the prophetic compounds would be active as inhibitors of LSD1, and such activity can be determined using the assay methods described herein.

[00331] In one aspect, a compound can be selected from: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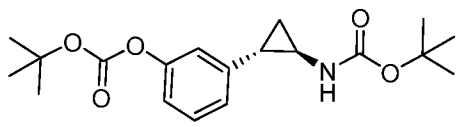
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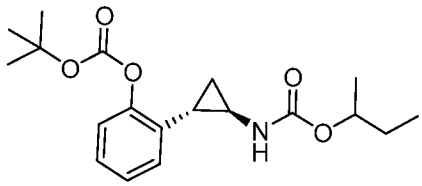
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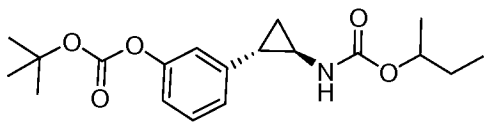
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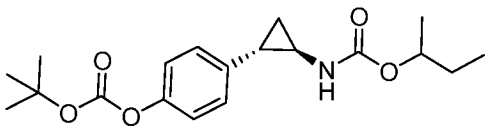
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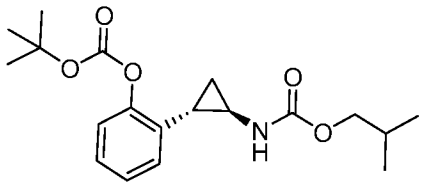
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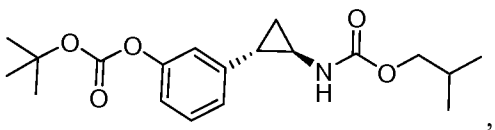
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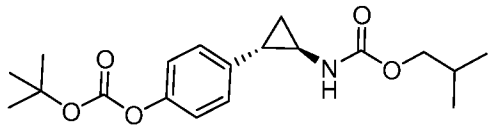
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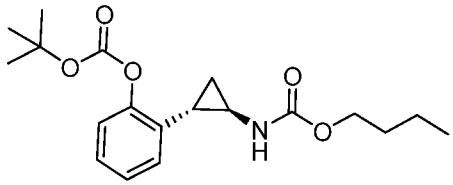
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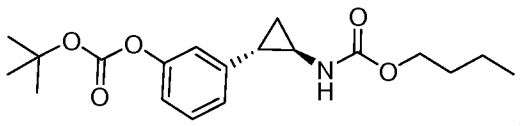
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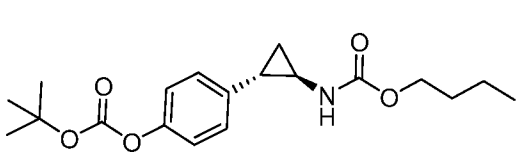
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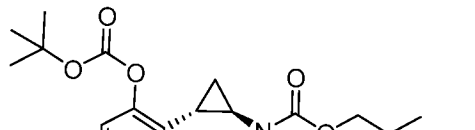
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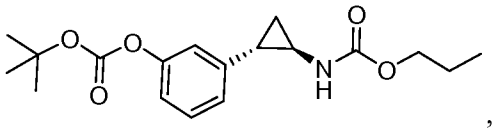
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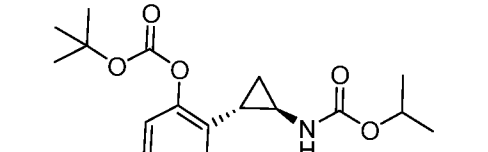
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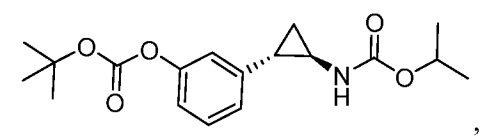
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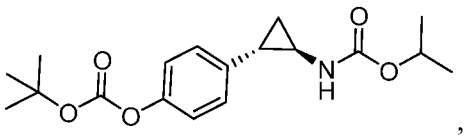
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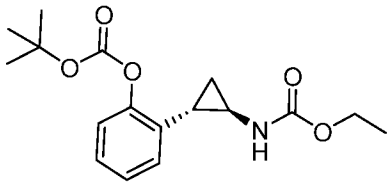
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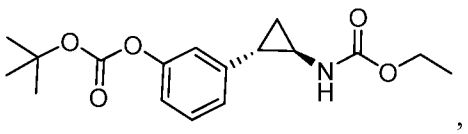
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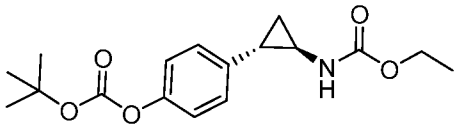
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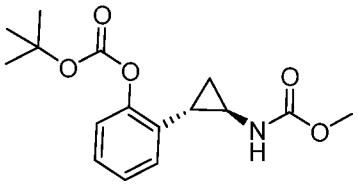
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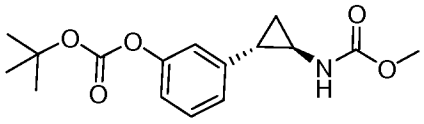
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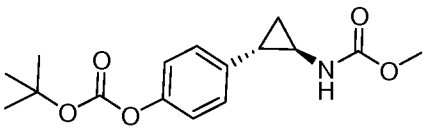
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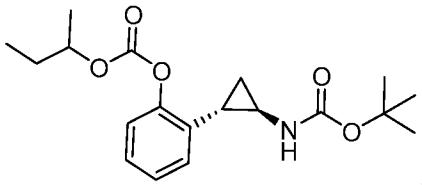
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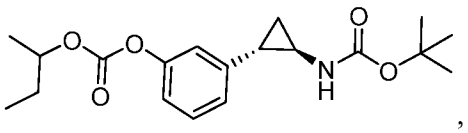
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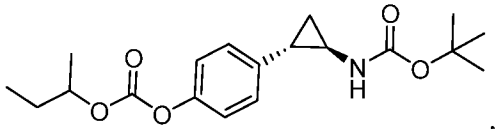
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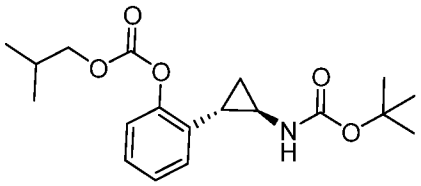
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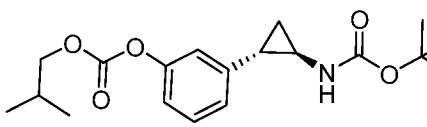
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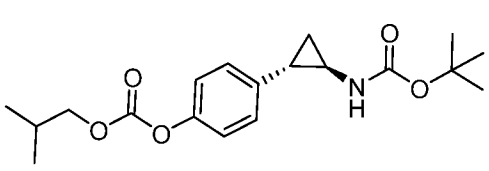
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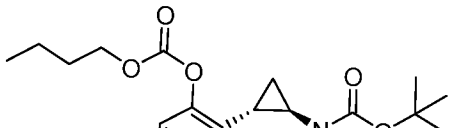
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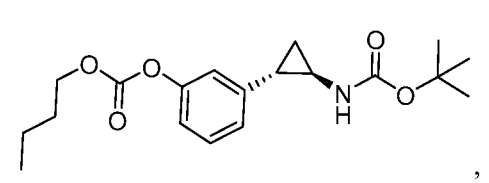
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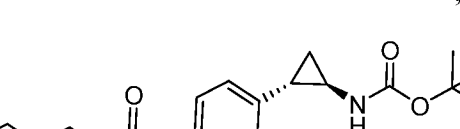
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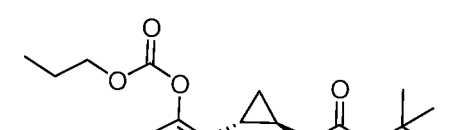
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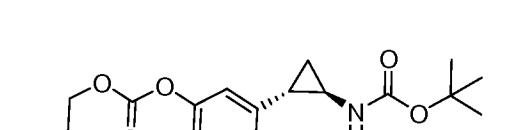
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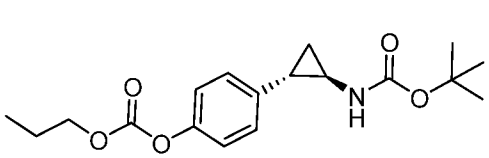
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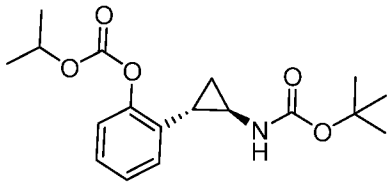
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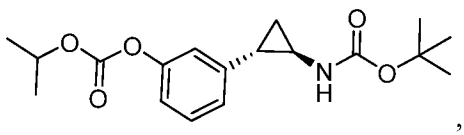
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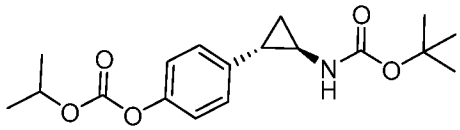
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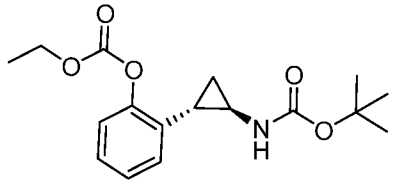
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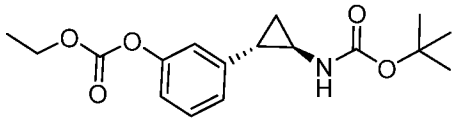
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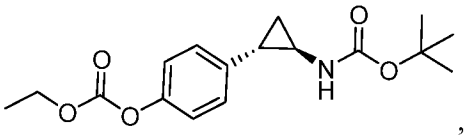
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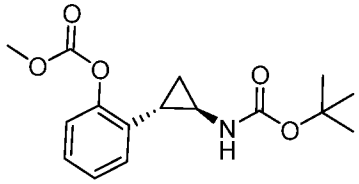
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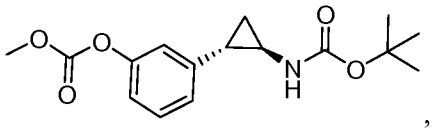
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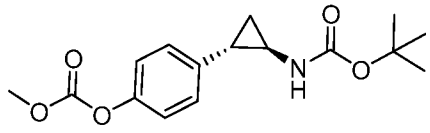
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[00332] It is contemplated that one or more compounds can optionally be omitted from the disclosed invention.

[00333] It is understood that the disclosed compounds can be used in connection with the disclosed methods, compositions, kits, and uses.

[00334] It is understood that pharmaceutically acceptable derivatives of the disclosed compounds can be used also in connection with the disclosed methods, compositions, kits, and uses. The pharmaceutical acceptable derivatives of the compounds can include any suitable derivative, such as pharmaceutically acceptable salts as discussed below, isomers, radiolabeled analogs, tautomers, and the like.

E. PHARMACEUTICAL COMPOSITIONS

[00335] In one aspect, the invention relates to pharmaceutical compositions comprising at least one disclosed compound and a pharmaceutically acceptable carrier. In a further aspect, a pharmaceutical composition can be provided comprising a therapeutically effective amount of at least one disclosed compound. In a still further aspect, a pharmaceutical composition

can be provided comprising a prophylactically effective amount of at least one disclosed compound. In yet a further aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound, wherein the compound is present in an effective amount.

[00336] In one aspect, the invention relates to pharmaceutical compositions comprising a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt, solvate, or polymorph thereof; and a pharmaceutically acceptable carrier.

[00337] Pharmaceutically acceptable salts of the compounds are conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Exemplary acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Example base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. Chemical modification of a pharmaceutical compound into a salt is a known technique to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, *e.g.*, H. Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 196 and 1456-1457.

[00338] The pharmaceutical compositions comprise the compounds in a pharmaceutically acceptable carrier. A pharmaceutically acceptable carrier refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. The compounds can be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, Pa., 1995.

[00339] In a further aspect, the pharmaceutical composition is administered to a mammal. In a still further aspect, the mammal is a human. In an even further aspect, the human is a patient.

[00340] In a further aspect, the pharmaceutical composition is administered following identification of the mammal in need of treatment of a cancer. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step.

[00341] In various aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00342] In various aspects, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[00343] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[00344] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed.

Optionally, tablets can be coated by standard aqueous or nonaqueous techniques

[00345] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[00346] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00347] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[00348] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00349] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[00350] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[00351] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

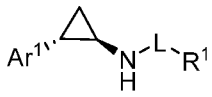
[00352] In a further aspect, the composition further comprises at least one agent anticancer therapeutic agent. In a still further aspect, the anticancer therapeutic agent is selected from: a) a hormone therapy therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; b) an alkylating therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; c) an antineoplastic antimetabolite therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; d) a mitotic inhibitor therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; e) an antineoplastic antibiotic therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; or f) other chemotherapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof.

[00353] In a further aspect, the composition further comprises at least one agent known to have a side effect of increasing the risk of cancer.

[00354] It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

F. METHODS OF MAKING THE COMPOUNDS

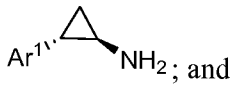
[00355] In various aspects, the invention relates to methods of making compounds useful to treat cancer. Thus, in one aspect, the invention relates to methods of making a compound having a structure represented by a formula:



wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –C(O)SR^8, –SO_2R^9, –$CONR^{10a}R^{10b}$, –$SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5

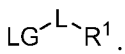
heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $—NH_2$, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

(a) providing a compound having a structure represented by a formula:



; and

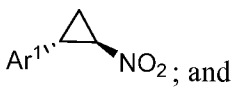
(b) reacting with a compound having a structure represented by a formula:



.

[00356] In a further aspect, providing comprises the steps of:

(a) providing a compound having a structure represented by a formula:



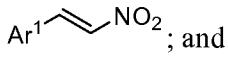
; and

(b) reacting with a reducing agent.

[00357] In a further aspect, the reducing agent is Zn/HCl.

[00358] In a further aspect, providing comprises the steps of:

(a) providing a compound having a structure represented by a formula:



; and

(b) reacting with a cyclizing agent.

[00359] In a further aspect, the cyclizing agent comprises trimethylsulfoxonium iodide and potassium *tert*-butoxide.

[00360] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

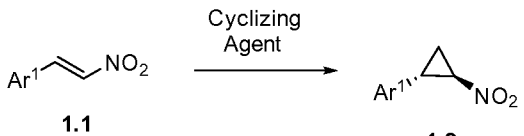
[00361] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, as described and exemplified below. In certain specific examples, the disclosed compounds can be prepared by Route I and Route II, as described and exemplified below. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

[00362] In one aspect, the disclosed compounds comprise the products of the synthetic methods described herein. In a further aspect, the disclosed compounds comprise a compound produced by a synthetic method described herein. In a still further aspect, the invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising combining at least one compound of any of disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

1. ROUTE I

[00363] In one aspect, substituted trans-cyclopropanes can be prepared as shown below.

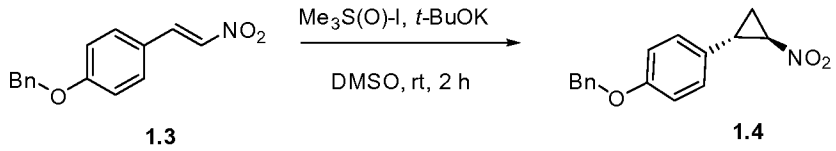
SCHEME 1A.



1.1 1.2

[00364] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 1B.

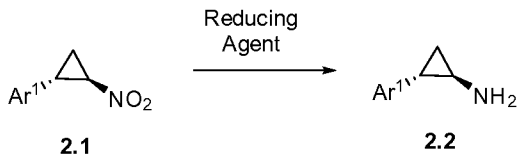


[00365] In one aspect, compounds of type **1.2**, and similar compounds, can be prepared according to reaction **Scheme 1B** above. Thus, compounds of type **1.4** can be prepared by cyclization of an appropriate alkene, e.g., **1.3** as shown above. Appropriate alkenes are commercially available or prepared by methods known to one skilled in the art. The cyclization is carried out in the presence of an appropriate cyclizing agent, e.g., trimethylsulfoxonium iodide and potassium *tert*-butoxide, in an appropriate solvent, e.g., dimethylsulfoxide (DMSO), at an appropriate temperature, e.g., room temperature, for a sufficient period of time, e.g., 2 hours. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **1.1**), can be substituted in the reaction to provide substituted trans-cyclopropanes similar to Formula **1.2**.

2. ROUTE II

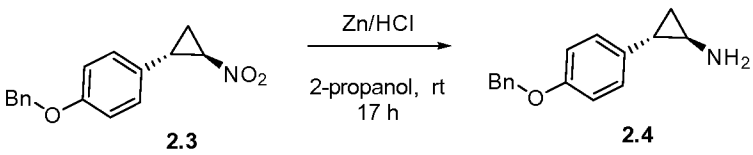
[00366] In one aspect, substituted trans-cyclopropanes can be prepared as shown below.

SCHEME 2A.



[00367] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 2B.

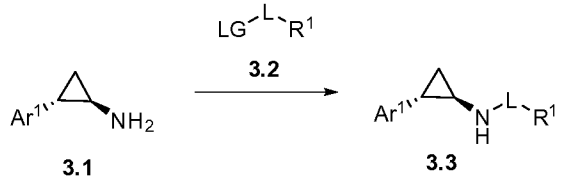


[00368] In one aspect, compounds of type **2.2**, and similar compounds, can be prepared according to reaction **Scheme 2B** above. Thus, compounds of type **2.4** can be prepared by reduction of an appropriate nitrocycloalkane, e.g., **2.3** as shown above. Appropriate nitrocycloalkanes are commercially available or prepared by methods known to one skilled in the art. The reduction is carried out in the presence of an appropriate reducing agent, e.g., Zn/HCl, in an appropriate solvent, e.g., 2-propanol, at an appropriate temperature, e.g., room temperature, for a sufficient period of time, e.g., 17 hours. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **2.1**), can be substituted in the reaction to provide substituted trans-cyclopropanes similar to Formula **2.2**.

3. ROUTE III

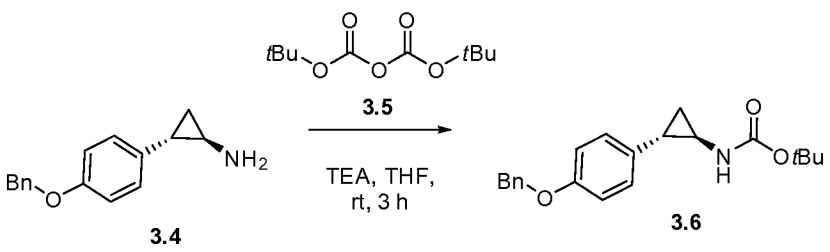
[00369] In one aspect, substituted trans-cyclopropanes can be prepared as shown below.

SCHEME 3A.



[00370] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 3B.



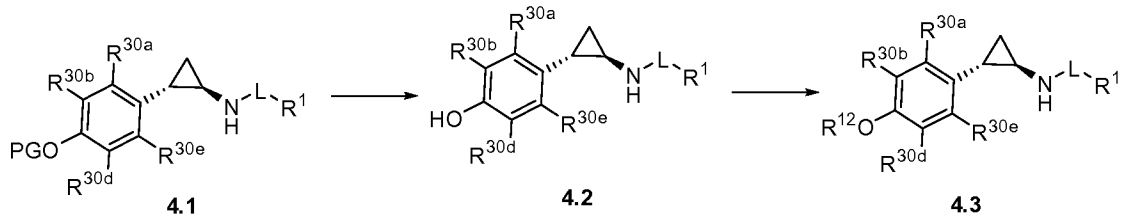
[00371] In one aspect, compounds of type **3.3**, and similar compounds, can be prepared according to reaction **Scheme 3B** above. Thus, compounds of type **3.6** can be prepared by acylation (or alkylation) of an appropriate amine, e.g., **3.4** as shown above. Appropriate amines are commercially available or prepared by methods known to one skilled in the art. The reduction is carried out in the presence of an appropriate acylating agent (or alkylating agent), e.g., di-*tert*-butyl dicarbonate, in the presence of an appropriate base, e.g.,

triethylamine (TEA), at an appropriate temperature, e.g., room temperature, for a sufficient period of time, e.g., 3 hours. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **3.1** and **3.2**), can be substituted in the reaction to provide substituted trans-cyclopropanes similar to Formula **3.3**.

4. ROUTE IV

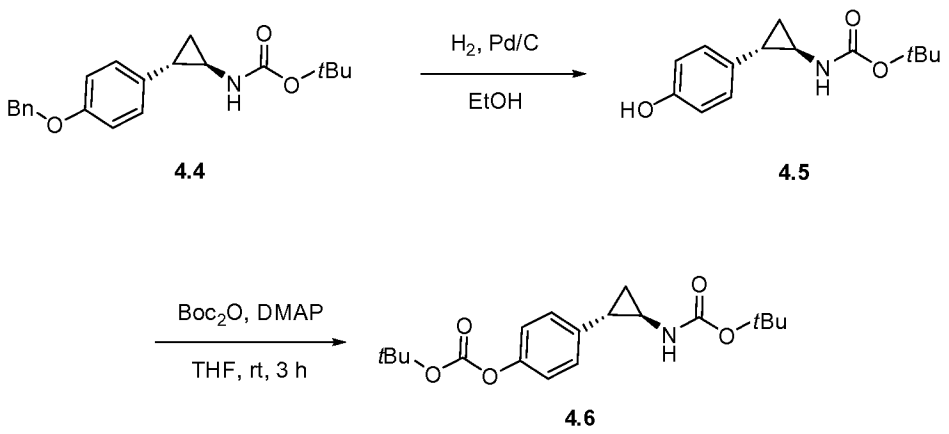
[00372] In one aspect, substituted trans-cyclopropanes can be prepared as shown below.

SCHEME 4A.



[00373] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 4B.

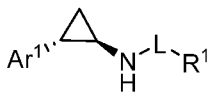


[00374] In one aspect, compounds of type **4.3**, and similar compounds, can be prepared according to reaction **Scheme 4B** above. Thus, compounds of type **4.5** can be prepared by deprotection of an appropriate cyclopropane, e.g., **4.4** as shown above. The deprotection is carried out in the presence of an appropriate deprotecting agent, e.g., hydrogen gas and palladium on carbon, and an appropriate solvent, e.g., ethanol (EtOH). Compounds of type **4.6** can be prepared by acylation (or alkylation) of an appropriate phenol, e.g., **4.5** as shown

above. The acylation (or alkylation) is carried out in the presence of an appropriate acylating agent (or alkylating agent), e.g., di-*tert*-butyl dicarbonate, in the presence of an appropriate activating agent, e.g., 4-dimethylaminopyridine (DMAP), in an appropriate solvent, e.g., tetrahydrofuran (THF), at an appropriate temperature, e.g., room temperature, for a sufficient period of time, e.g., 3 hours. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type **4.1** and **4.2**), can be substituted in the reaction to provide substituted trans-cyclopropanes similar to Formula **4.3**.

G. Methods of Modulating a Histone Methylation Event in Cells

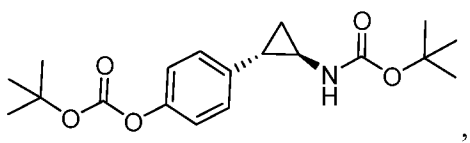
[00375] In one aspect, the invention relates to a method of modulating at least one histone methylation event in at least one cell, the method comprising contacting the cell with an effective amount of at least one compound having a structure represented by a formula:



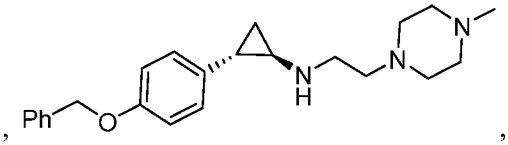
wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –C(O)SR^8, –SO_2R^9, –$CONR^{10a}R^{10b}$, –$SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-

C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

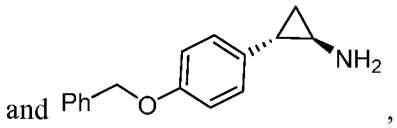
[00376] In one aspect, the invention relates to a method of modulating a histone methylation event in at least one cell, the method comprising contacting the cell with an effective amount of at least one compound selected from:



,



,

and  ,

or a pharmaceutically acceptable salt thereof.

[00377] In a further aspect, modulating is inhibiting.

[00378] In a further aspect, the histone methylation event occurs on histone H3.

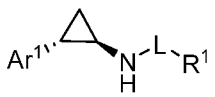
[00379] In a further aspect, the cell is selected from a cancer stem cell and a cancer-initiating cell. In a still further aspect, the cell expresses at least one *Sox2* stem cell marker. In yet a further aspect, the cancer stem cell is an embryonic cancer stem cell with germ tumor cell properties.

[00380] In a further aspect, contacting is via administration to a mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need of treatment of a cancer.

[00381] In a further aspect, the compound exhibits an IC_{50} of less than about 100 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 90 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 80 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 70 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 60 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 50 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 40 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 30 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 20 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 10 mM.

H. METHODS OF INHIBITING LSD1 IN CELLS

[00382] In one aspect, the invention relates to a method of inhibiting LSD1 (lysine-specific demethylase I) in at least one cell, the method comprising the method comprising contacting the cell with an effective amount of at least one compound having a structure represented by a formula:

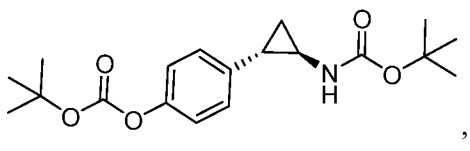
 ,

wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently

selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups

independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00383] In one aspect, the invention relates to a method of inhibiting LSD1 in at least one cell, the method comprising contacting the at least one cell with an effective amount of at least one compound selected from: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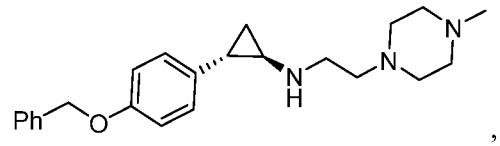
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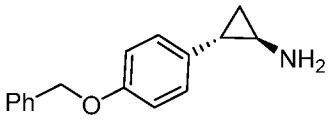
and

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or a pharmaceutically acceptable salt thereof.

[00384] In a further aspect, the cell is selected from a cancer stem cell and a cancer-initiating cell. In a still further aspect, the cell expresses at least one *Sox2* stem cell marker. In yet a further aspect, the cancer stem cell is an embryonic cancer stem cell with germ tumor cell properties.

[00385] In a further aspect, contacting is via administration to a mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need of treatment of a cancer.

[00386] In a further aspect, the compound exhibits an IC_{50} of less than about 100 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 90 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 80 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 70 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 60 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 50 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 40 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 30 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 20 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 10

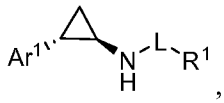
mM.

I. METHODS OF INHIBITING CANCER CELL PROLIFERATION

1. VIA ADMINISTRATION OF A LSD1 INHIBITOR

[00387] In one aspect, the invention relates to a method of inhibiting the proliferation of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor.

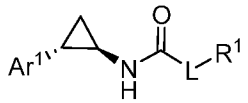
[00388] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-

C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00389] the LSD1 inhibitor is a compound having a structure represented by a formula:

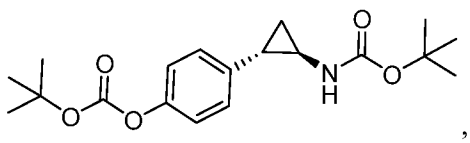


,

wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is

selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00390] In a further aspect, the LSD1 inhibitor is selected from: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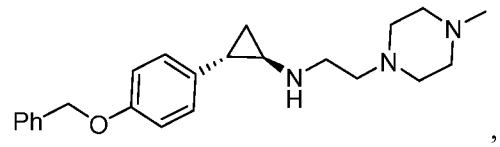
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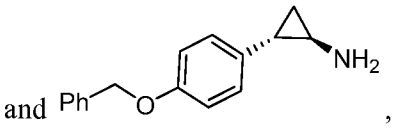
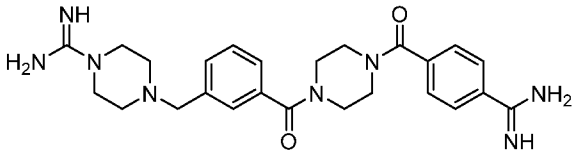

and ,

or a pharmaceutically acceptable salt thereof.

[00391] In a further aspect, the LSD1 inhibitor is selected from: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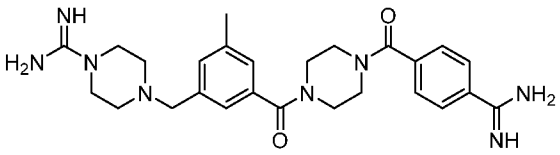
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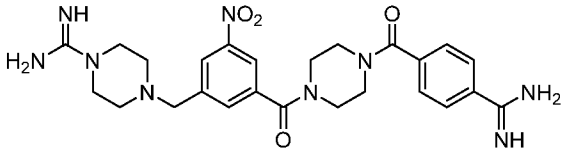
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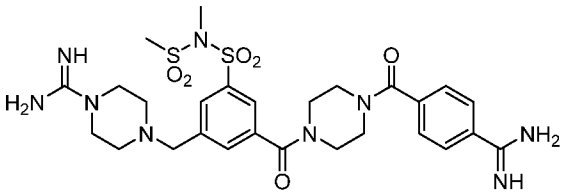
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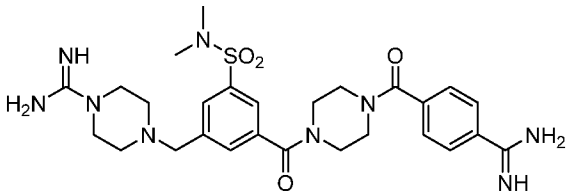
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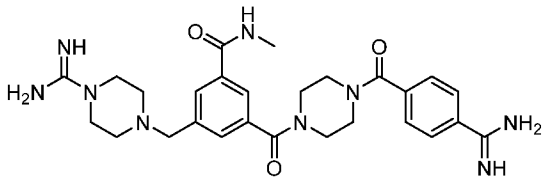
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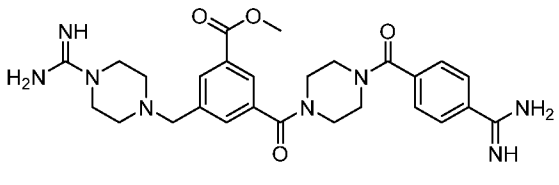
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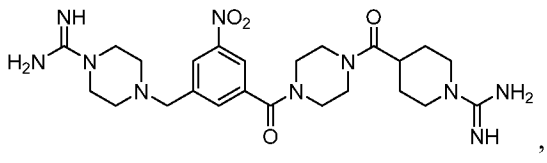
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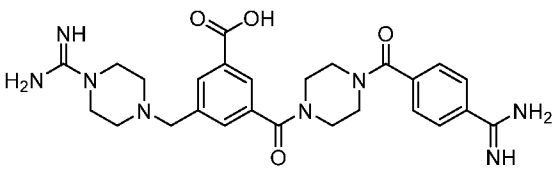
and 
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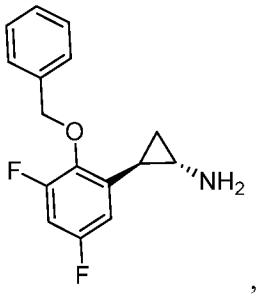
or a pharmaceutically acceptable salt thereof.

[00392] In a further aspect, the LSD1 inhibitor is selected from:



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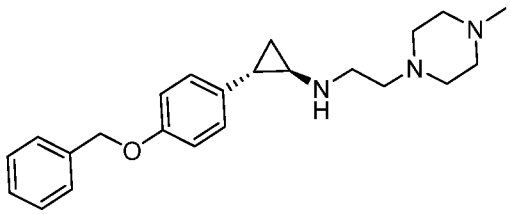

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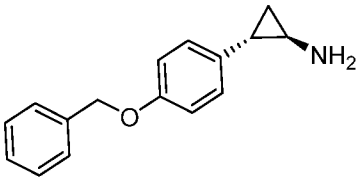

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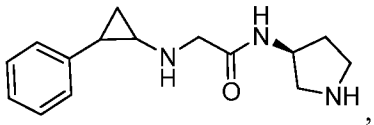

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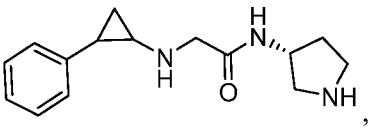

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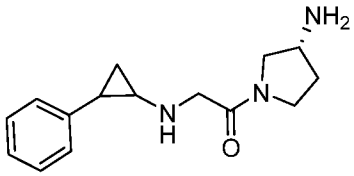

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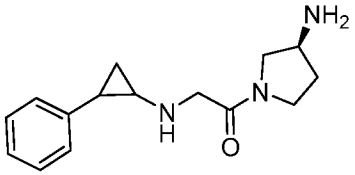

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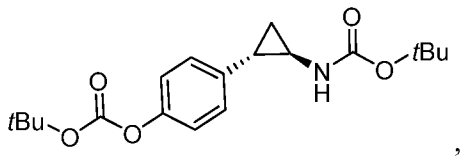

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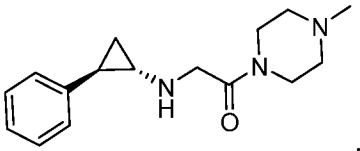

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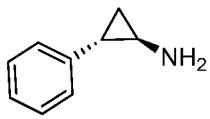

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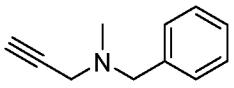
and 

,

or a pharmaceutically acceptable salt thereof.

[00393] In a further aspect, the LSD1 inhibitor is selected from parnate 2-phenylcyclopropylamine (2-PCPA), tranylcypromine, and derivatives thereof. In a still further aspect, the LSD1 inhibitor is a bisguanidine polyamine.

[00394] In a further aspect, the cancer comprises cells expressing at least one *Sox2* stem cell marker.

[00395] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need

of treatment of a cancer.

[00396] In a further aspect, the cancer is selected from a lymphoma, sarcoma, and a carcinoma. In a still further aspect, the carcinoma is a squamous cell carcinoma.

[00397] In a further aspect, the cancer is characterized by the presence of Sox2. In a still further aspect, the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00398] In a further aspect, the cancer is associated with gene amplification of *Sox2*. In a still further aspect, the gene amplification occurs at 3q22.33.

2. Via Administration of an HDAC1 Inhibitor

[00399] In one aspect, the invention relates to a method of inhibiting the proliferation of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

[00400] In a further aspect, the HDAC1 inhibitor is selected from aliphatic acids, hyroxamate, benzamide, cyclic peptide, and electrophilic ketone hybrid molecules. In a still further aspect, the HDAC1 inhibitor is selected from butyrate acid, Valproate (valproic acid), Tricostatin A (TSA), Vorinostat (SAHA), Entinostat (MS-275, SNDX-275), MGCD-0103, Romidepsin (FK-228/resminostate), trapoxin B, CHAP31, Panobinostate (Belinostat, PXD101), M344 (PCI-34051), CI994 (Tacedinaline), Tubastatin A hydrochloride, AR-42 (HDAC-42), SB939 (Pracinostat), ITF2357, Givinostat, CUDC-101, LAQ824 (NVP-LAQ824, Dacinostat), PCI-24781 (CRA-024781), APHA compound 8, BATCP, MOCPAC, PTACH, and PP.

[00401] In a further aspect, the cancer comprises cells expressing at least one *Sox2* stem cell marker.

[00402] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need of treatment of a cancer.

[00403] In a further aspect, the cancer is selected from a lymphoma, sarcoma, and a carcinoma. In a still further aspect, the carcinoma is a squamous cell carcinoma.

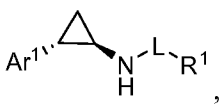
[00404] In a further aspect, the cancer is characterized by the presence of Sox2. In a still further aspect, the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00405] In a further aspect, the cancer is associated with gene amplification of *Sox2*. In a still further aspect, the gene amplification occurs at 3q22.33.

3. VIA CONTACTING AT LEAST ONE CELL WITH A LSD1 INHIBITOR

[00406] In one aspect, the invention relates to a method of inhibiting the survival of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor.

[00407] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



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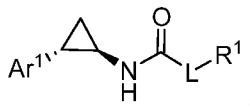
wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –C(O)SR^8, –SO_2R^9, –$CONR^{10a}R^{10b}$, –$SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –NO_2, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –C(O)SR^{17}, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and –CO_2R^{21}; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4

monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00408] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



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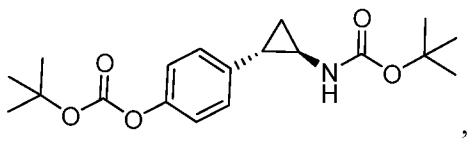
wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from –NO_2, –CN, –N_3, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-

C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00409] In a further aspect, the LSD1 inhibitor is selected from:



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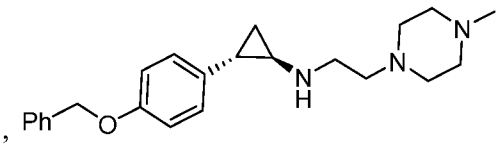

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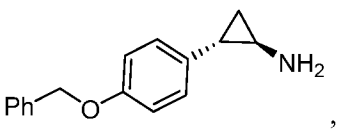

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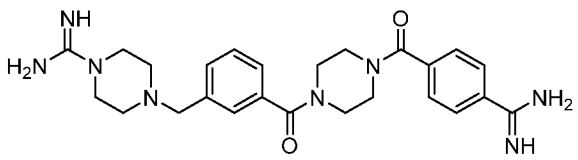
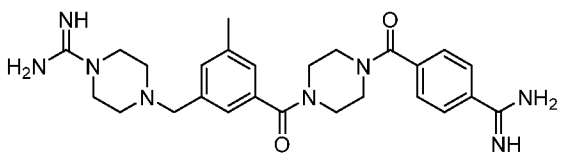
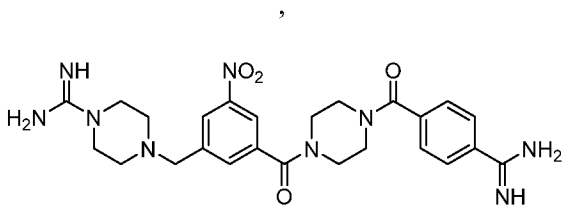
or a pharmaceutically acceptable salt thereof.

[00410] In a further aspect, the LSD1 inhibitor is selected from:



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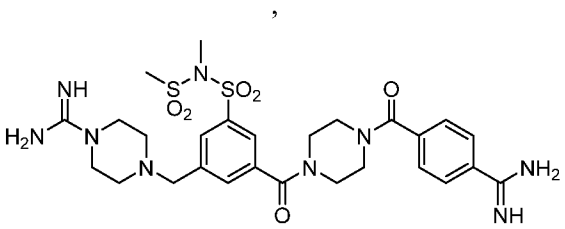
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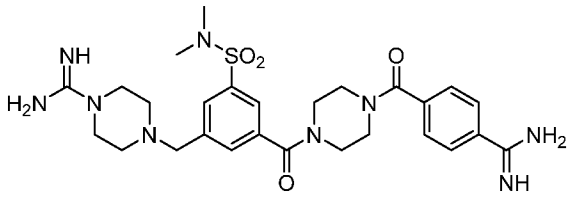
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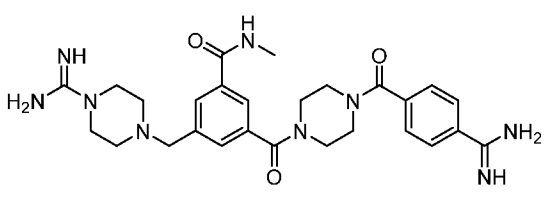
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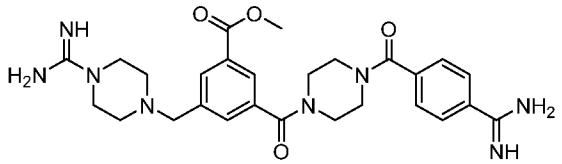
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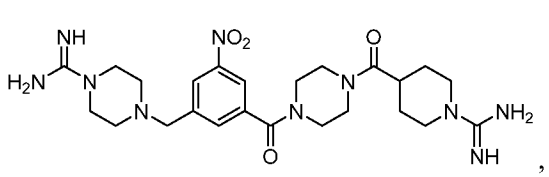
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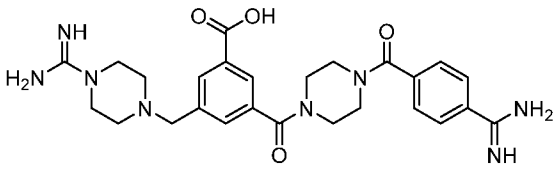
and 
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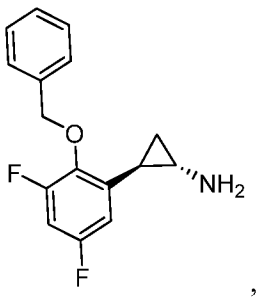
or a pharmaceutically acceptable salt thereof.

[00411] In a further aspect, the LSD1 inhibitor is selected from: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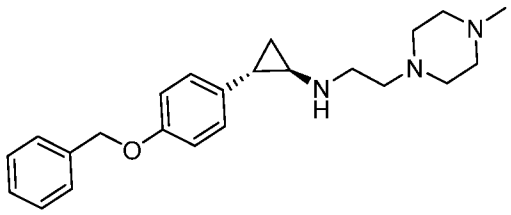
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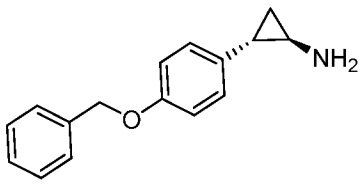
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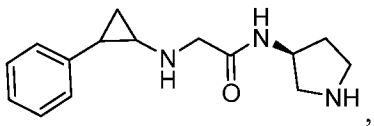
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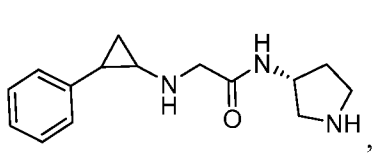
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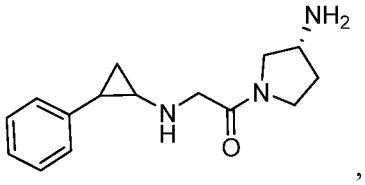
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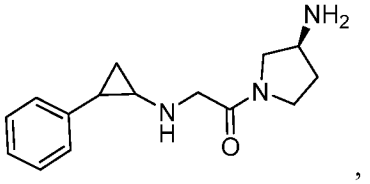
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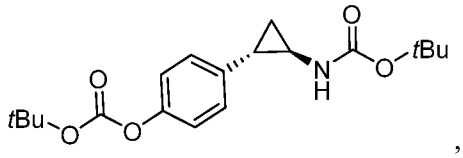
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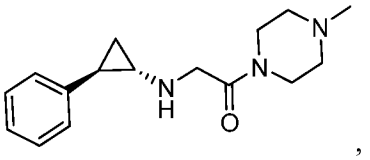
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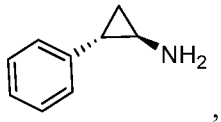
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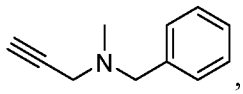
and 
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or a pharmaceutically acceptable salt thereof.

[00412] In a further aspect, the LSD1 inhibitor is selected from parnate 2-phenylcyclopropylamine (2-PCPA), tranylcypromine, and derivatives thereof. In a still further aspect, the LSD1 inhibitor is a bisguanidine polyamine.

[00413] In a further aspect, the cell is selected from a cancer stem cell and a cancer-initiating cell. In a still further aspect, the cell expresses at least one *Sox2* stem cell marker. In yet a further aspect, the cancer stem cell is an embryonic cancer stem cell with germ tumor cell properties.

[00414] In a further aspect, contacting is via administration to a mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need of treatment of a cancer.

[00415] In a further aspect, the compound exhibits an IC_{50} of less than about 100 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 90 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 80 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 70 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 60 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 50 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 40 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 30 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than

about 20 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 10 mM.

4. Via Contacting at Least One Cell with a HDAC1 Inhibitor

[00416] In one aspect, the invention relates to a method of inhibiting the survival of cancer cells in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

[00417] In a further aspect, the HDAC1 inhibitor is selected from aliphatic acids, hyroxamate, benzamide, cyclic peptide, and electrophilic ketone hybrid molecules. In a still further aspect, the HDAC1 inhibitor is selected from butyrate acid, Valproate (valproic acid), Tricostatin A (TSA), Vorinostat (SAHA), Entinostat (MS-275, SNDX-275), MGCD-0103, Romidepsin (FK-228/resminostate), trapoxin B, CHAP31, Panobinostate (Belinostat, PXD101), M344 (PCI-34051), CI994 (Tacedinaline), Tubastatin A hydrochloride, AR-42 (HDAC-42), SB939 (Pracinostat), ITF2357, Givinostat, CUDC-101, LAQ824 (NVP-LAQ824, Dacinostat), PCI-24781 (CRA-024781), APHA compound 8, BATCP, MOCPAC, PTACH, and PP.

[00418] In a further aspect, the cell is selected from a cancer stem cell and a cancer-initiating cell. In a still further aspect, the cell expresses at least one *Sox2* stem cell marker. In yet a further aspect, the cancer stem cell is an embryonic cancer stem cell with germ tumor cell properties.

[00419] In a further aspect, contacting is via administration to a mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need of treatment of a cancer.

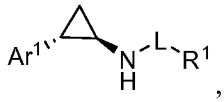
[00420] In a further aspect, the compound exhibits an IC_{50} of less than about 100 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 90 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 80 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 70 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 60 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 50 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 40 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 30 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 20 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 10 mM.

J. METHODS OF INHIBITING SURVIVAL OF CANCER CELLS

1. VIA CONTACTING AT LEAST ONE CELL WITH A LSD1 INHIBITOR

[00421] In one aspect, the invention relates to a method of inhibiting the survival of at least one cancer cell, the method comprising contacting the at least one cell with an effective amount of at least one LSD1 inhibitor.

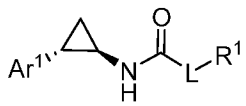
[00422] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups

independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –NO_2, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and –CO_2R^{21}; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00423] the LSD1 inhibitor is a compound having a structure represented by a formula:



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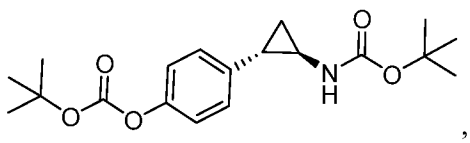
wherein L is a moiety selected from –O– and –$(CR^{2a}R^{2b})_n$–; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –$C(O)SR^8$, –SO_2R^9, –$CONR^{10a}R^{10b}$, and –$SO_2NR^{11a}R^{11b}$ when L is –$(CR^{2a}R^{2b})_n$–; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3

monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00424] In a further aspect, the LSD1 inhibitor is selected from: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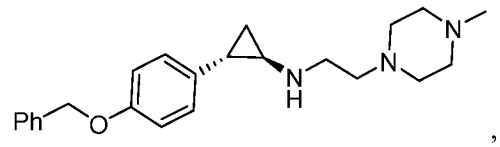
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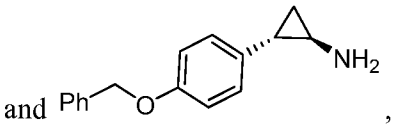
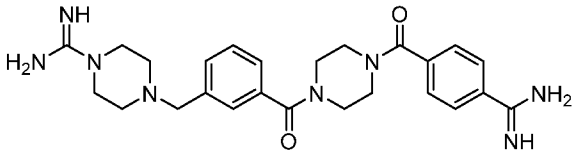

and ,

or a pharmaceutically acceptable salt thereof.

[00425] In a further aspect, the LSD1 inhibitor is selected from: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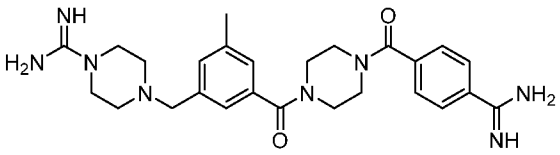
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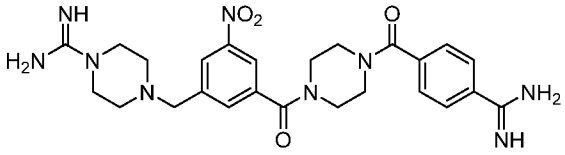
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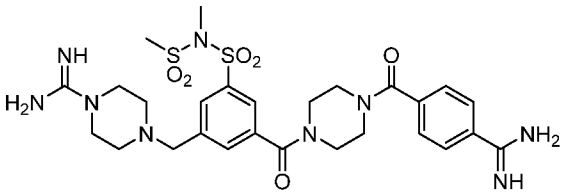
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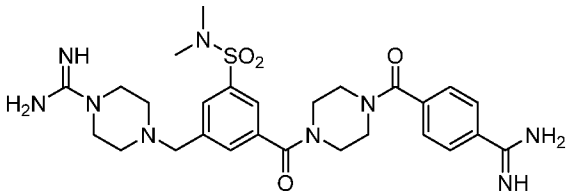
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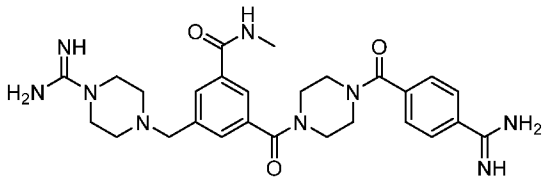
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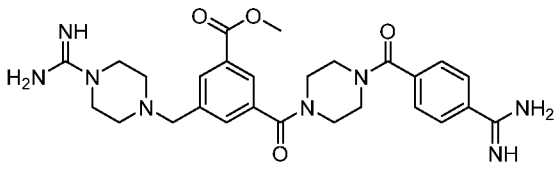
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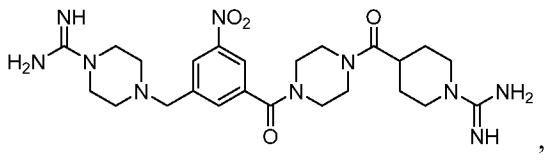
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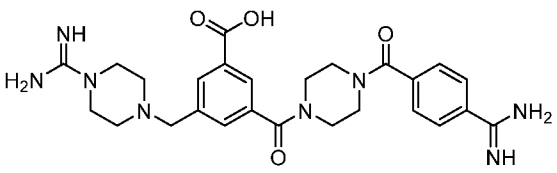
and 
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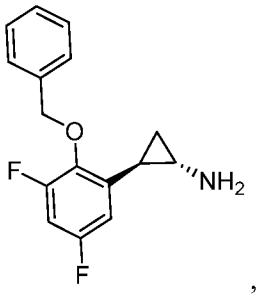
or a pharmaceutically acceptable salt thereof.

[00426] In a further aspect, the LSD1 inhibitor is selected from:



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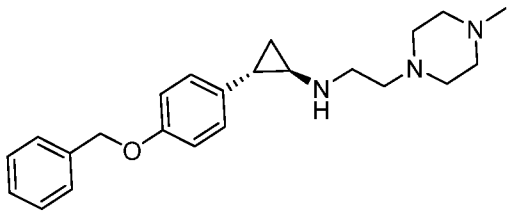

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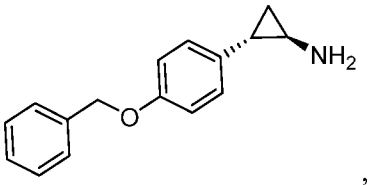

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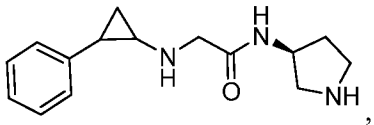

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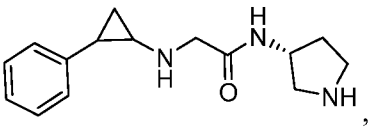

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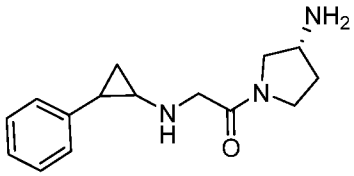

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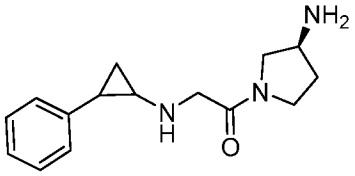

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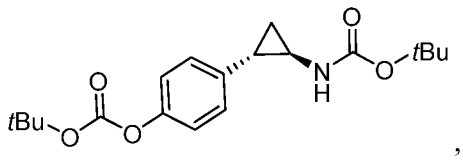

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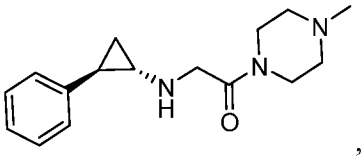

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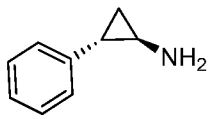

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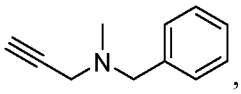
and 

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or a pharmaceutically acceptable salt thereof.

[00427] In a further aspect, the LSD1 inhibitor is selected from parnate 2-phenylcyclopropylamine (2-PCPA), tranylcypromine, and derivatives thereof. In a still further aspect, the LSD1 inhibitor is a bisguanidine polyamine.

[00428] In a further aspect, the cell is selected from a cancer stem cell and a cancer-initiating cell. In a still further aspect, the cell expresses at least one *Sox2* stem cell marker. In yet a further aspect, the cancer stem cell is an embryonic cancer stem cell with germ tumor cell properties.

[00429] In a further aspect, contacting is via administration to a mammal. In a still further

aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need of treatment of a cancer.

[00430] In a further aspect, the compound exhibits an IC_{50} of less than about 100 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 90 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 80 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 70 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 60 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 50 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 40 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 30 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 20 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 10 mM.

2. Via Contacting at Least One Cell with a HDAC1 Inhibitor

[00431] In one aspect, the invention relates to a method of inhibiting the survival of at least one cancer cell, the method comprising contacting the at least one cell with an effective amount of at least one HDAC1 inhibitor.

[00432] In a further aspect, the HDAC1 inhibitor is selected from aliphatic acids, hyroxamate, benzamide, cyclic peptide, and electrophilic ketone hybrid molecules. In a still further aspect, the HDAC1 inhibitor is selected from butyrate acid, Valproate (valproic acid), Tricostatin A (TSA), Vorinostat (SAHA), Entinostat (MS-275, SNDX-275), MGCD-0103, Romidepsin (FK-228/resminostate), trapoxin B, CHAP31, Panobinostate (Belinostat, PXD101), M344 (PCI-34051), CI994 (Tacedinaline), Tubastatin A hydrochloride, AR-42 (HDAC-42), SB939 (Pracinostat), ITF2357, Givinostat, CUDC-101, LAQ824 (NVP-LAQ824, Dacinostat), PCI-24781 (CRA-024781), APHA compound 8, BATCP, MOCPAC, PTACH, and PP.

[00433] In a further aspect, the cell is selected from a cancer stem cell and a cancer-initiating cell. In a still further aspect, the cell expresses at least one *Sox2* stem cell marker. In yet a further aspect, the cancer stem cell is an embryonic cancer stem cell with germ tumor cell properties.

[00434] In a further aspect, contacting is via administration to a mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of

identifying a mammal in need of treatment of a cancer.

[00435] In a further aspect, the compound exhibits an IC_{50} of less than about 100 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 90 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 80 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 70 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 60 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 50 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 40 mM. In a still further aspect, the compound exhibits an IC_{50} of less than about 30 mM. In yet a further aspect, the compound exhibits an IC_{50} of less than about 20 mM. In an even further aspect, the compound exhibits an IC_{50} of less than about 10 mM.

K. Methods of Using the Compounds

[00436] The compounds and pharmaceutical compositions of the invention are useful in treating or controlling oncological disorders, such as cancer. The compounds and pharmaceutical compositions containing the compounds can be useful in the treatment or control of squamous cell carcinomas by action of inhibiting LSD1 and/or HDAC.

[00437] Examples of cancers for which the compounds and compositions can be useful in treating, include, but are not limited to, glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00438] To treat or control the oncological disorder, the compounds and pharmaceutical compositions comprising the compounds are administered to a subject in need thereof, such as a vertebrate, *e.g.*, a mammal, a fish, a bird, a reptile, or an amphibian. The subject can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or

rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. The subject is preferably a mammal, such as a human. Prior to administering the compounds or compositions, the subject can be diagnosed with a need for treatment of an oncological disorder, such as cancer.

[00439] The compounds or compositions can be administered to the subject according to any method. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. A preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. A preparation can also be administered prophylactically; that is, administered for prevention of a disease or condition, such as cancer.

[00440] The therapeutically effective amount or dosage of the compound can vary within wide limits. Such a dosage is adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg or more, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, as a continuous infusion. Single dose compositions can contain such amounts or submultiples thereof of the compound or composition to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days.

1. TREATMENT METHODS

[00441] The compounds disclosed herein are useful for treating or preventing an oncological disorder, such as cancer. Thus, provided are methods comprising administering a therapeutically effective amount of at least one LSD1 inhibitor and/or HDAC1 inhibitor. In one aspect, the method can be a method for treating an oncological disorder. In yet another aspect, the method can be a method for treating a cancer. In a still further aspect, the method

can be a method for inhibiting LSD1 and/or HDAC1.

a. TREATING A CANCER VIA ADMINISTRATION OF A LSD1 INHIBITOR

[00442] The present invention relates to methods and compositions and procedures for the treatment of a cancer, at least by suppression of cancer cell growth. A method for treating a cancer in which *Sox2* stem cell markers are present in the expression of cancer cells may include steps such as: a) identifying the existence of *Sox2* stem cell markers in the cancer within a patient; and b) introducing LSD1 inhibitors or reagents that interfere with LSD1 activity into or onto the patient to suppress gene expression by the cancer cells having *Sox2* stem cell markers.

[00443] Thus, in one aspect, the invention relates to a method of treating a cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor.

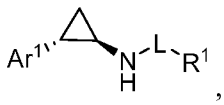
[00444] The LSD1 inhibitor may be introduced into the patient by infusion, perfusion, transdermal application, implanted delivery system, ingestion or intravenous introduction. One method includes the LSD1 inhibitors being introduced onto the patient by application of a liquid or gel. The term "onto" includes either conventional transdermal application on the outer layers of the skin, or direct application of the liquid or gel to an organ or tissue. In one embodiment, the liquid or gel further contains a transdermal carrier.

[00445] The rate of delivery and final amount of delivery of the various inhibitors will depend upon the treatment parameters defined by the condition of the patient, the extent and location of the cancer and the aggressiveness of the treatment desired. The rate of delivery is generally lowest with transdermal delivery, as is the amount delivered during any transdermal treatment. In general, a useful range requires at least 0.1 milligrams during a 24 hour period and other treatments may use 500 milligrams or more in a 24 hour treatment period. So one range would be 0.1 to 500 milligrams inhibitor/24 hour period. Other useful ranges of treatment could include least 20 grams in 24 hours and at least 50 grams in 24 hour, a rate selected from the group consisting of at least 5 grams in 24 hours and at least 10 grams in 24 hours, a rate selected from the group consisting of at least 200 milligrams in 24 hours, at least 0.5 grams in 24 hours and at least 1 gram in 24 hours, a rate selected from the group consisting of between 50 milligrams in 24 hours and 5 grams in 24 hours, a rate selected from the group consisting of between 5 milligrams in 24 hours and 1 gram in 24 hours.

[00446] Particularly in transdermal or gel/liquid applications, the range of concentration of the inhibitors as compared to the total weight of the liquid or gel composition (including the

inhibitor) might be about 0.1 milligrams inhibitor to 200 milligrams to milliliter of liquid or gel. Ranges for compositions might include any minimum amount of 0.1, 0.5, 1.0, 2.5, 5, 10, 50, 100 or 200 milligrams inhibitor to each milliliter of total volume with the liquid or gel.

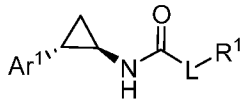
[00447] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, $–SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-

C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $—NH_2$, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00448] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



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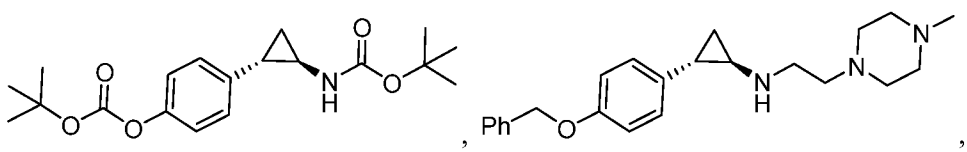
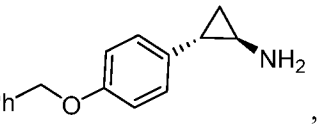
wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3

monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

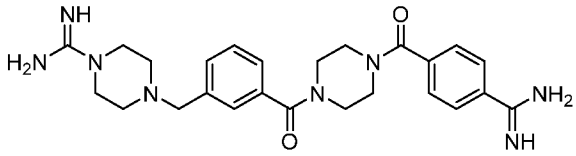
[00449] In a further aspect, the LSD1 inhibitor is selected from:

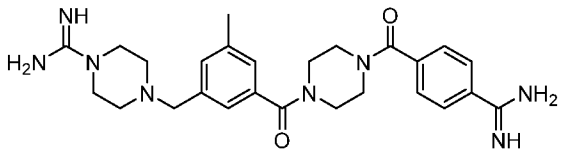


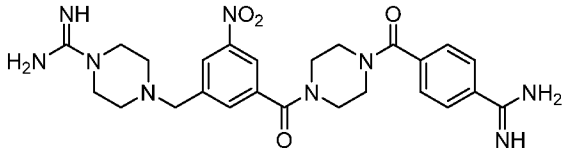
and  ,

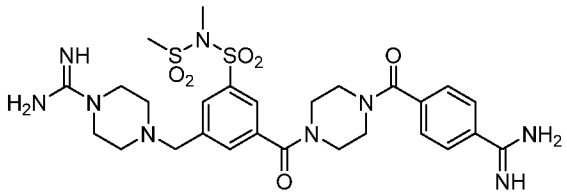
or a pharmaceutically acceptable salt thereof.

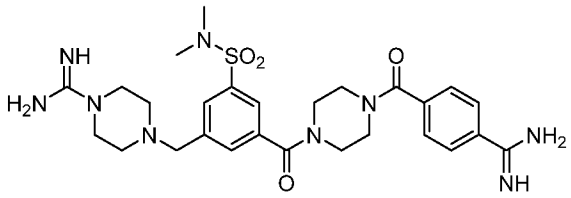
[00450] In a further aspect, the LSD1 inhibitor is selected from:

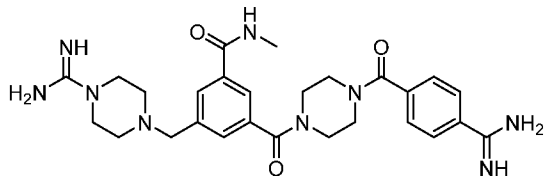
 ,

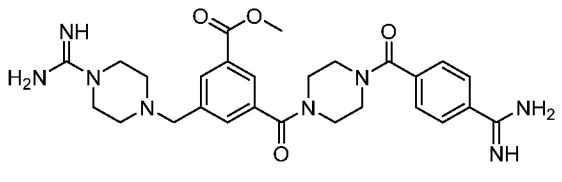
 ,

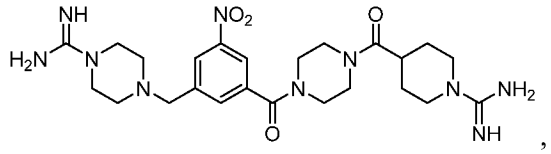
 ,

 ,

 ,

 ,

 ,

 ,

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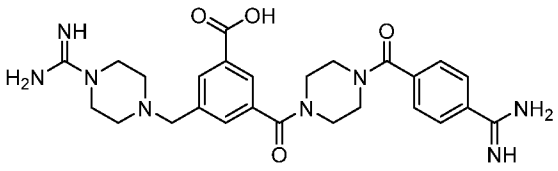
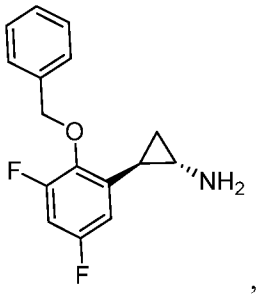
and  ,

or a pharmaceutically acceptable salt thereof.

[00451] In a further aspect, the LSD1 inhibitor is selected from:



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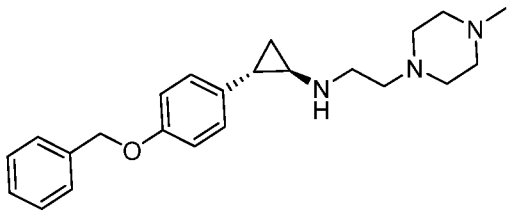

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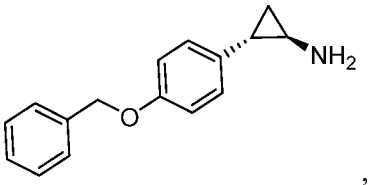

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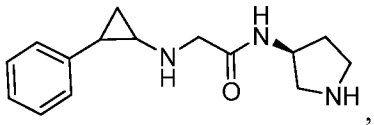

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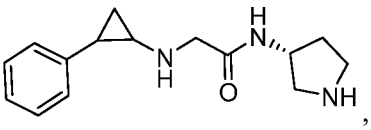

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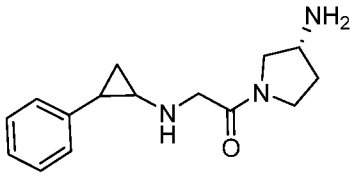

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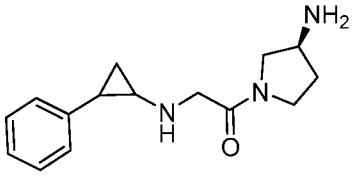

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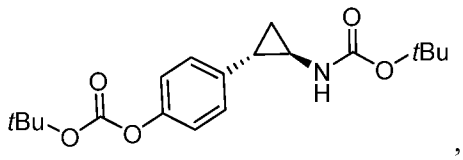

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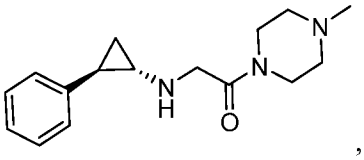

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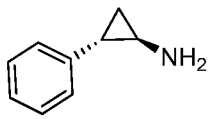

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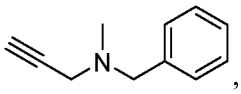
and 

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or a pharmaceutically acceptable salt thereof.

[00452] In a further aspect, the LSD1 inhibitor is selected from parnate 2-phenylcyclopropylamine (2-PCPA), tranylcypromine, and derivatives thereof. In a still further aspect, the LSD1 inhibitor is a bisguanidine polyamine.

[00453] In a further aspect, the cancer comprises cells expressing at least one *Sox2* stem cell marker.

[00454] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need

of treatment of a cancer.

[00455] In a further aspect, the cancer is selected from a lymphoma, sarcoma, and a carcinoma. In a still further aspect, the carcinoma is a squamous cell carcinoma.

[00456] In a further aspect, the cancer is characterized by the presence of Sox2. In a still further aspect, the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00457] In a further aspect, the cancer is associated with gene amplification of *Sox2*. In a still further aspect, the gene amplification occurs at 3q22.33.

b. TREATING A CANCER VIA ADMINISTRATION OF AN HDAC1 INHIBITOR

[00458] The present invention relates to methods and compositions and procedures for the treatment of a cancer, at least by suppression of cancer cell growth. A method for treating a cancer in which *Sox2* stem cell markers are present in the expression of cancer cells may include steps such as: a) identifying the existence of *Sox2* stem cell markers in the cancer within a patient; and b) introducing HDAC1 inhibitors or reagents that interfere with HDAC1 activity to suppress gene expression by the cancer cells having *Sox2* stem cell markers.

[00459] Thus, in one aspect, the invention relates to a method of treating a cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

[00460] The HDAC1 inhibitors may be introduced into the patient by infusion, perfusion, transdermal application, implanted delivery system, ingestion or intravenous introduction. One method includes the HDAC1 inhibitors being introduced onto the patient by application of a liquid or gel. The term "onto" includes either conventional transdermal application on

the outer layers of the skin, or direct application of the liquid or gel to an organ or tissue. In one embodiment, the liquid or gel further contains a transdermal carrier.

[00461] The rate of delivery and final amount of delivery of the various inhibitors will depend upon the treatment parameters defined by the condition of the patient, the extent and location of the cancer and the aggressiveness of the treatment desired. The rate of delivery is generally lowest with transdermal delivery, as is the amount delivered during any transdermal treatment. In general, a useful range requires at least 0.1 milligrams during a 24 hour period and other treatments may use 500 milligrams or more in a 24 hour treatment period. So one range would be 0.1 to 500 milligrams inhibitor/24 hour period. Other useful ranges of treatment could include least 20 grams in 24 hours and at least 50 grams in 24 hour, a rate selected from the group consisting of at least 5 grams in 24 hours and at least 10 grams in 24 hours, a rate selected from the group consisting of at least 200 milligrams in 24 hours, at least 0.5 grams in 24 hours and at least 1 gram in 24 hours, a rate selected from the group consisting of between 50 milligrams in 24 hours and 5 grams in 24 hours, a rate selected from the group consisting of between 5 milligrams in 24 hours and 1 gram in 24 hours.

[00462] Particularly in transdermal or gel/liquid applications, the range of concentration of the inhibitors as compared to the total weight of the liquid or gel composition (including the inhibitor) might be about 0.1 milligrams inhibitor to 200 milligrams to milliliter of liquid or gel. Ranges for compositions might include any minimum amount of 0.1, 0.5, 1.0, 2.5, 5, 10, 50, 100 or 200 milligrams inhibitor to each milliliter of total volume with the liquid or gel.

[00463] In a further aspect, the HDAC1 inhibitor is selected from aliphatic acids, hyroxamate, benzamide, cyclic peptide, and electrophilic ketone hybrid molecules. In a still further aspect, the HDAC1 inhibitor is selected from butyrate acid, Valproate (valproic acid), Tricostatin A (TSA), Vorinostat (SAHA), Entinostat (MS-275, SNDX-275), MGCD-0103, Romidepsin (FK-228/resminostate), trapoxin B, CHAP31, Panobinostate (Belinostat, PXD101), M344 (PCI-34051), CI994 (Tacedinaline), Tubastatin A hydrochloride, AR-42 (HDAC-42), SB939 (Pracinostat), ITF2357, Givinostat, CUDC-101, LAQ824 (NVP-LAQ824, Dacinostat), PCI-24781 (CRA-024781), APHA compound 8, BATCP, MOCPAC, PTACH, and PP.

[00464] In a further aspect, the cancer comprises cells expressing at least one *Sox2* stem cell marker.

[00465] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need

of treatment of a cancer.

[00466] In a further aspect, the cancer is selected from a lymphoma, sarcoma, and a carcinoma. In a still further aspect, the carcinoma is a squamous cell carcinoma.

[00467] In a further aspect, the cancer is characterized by the presence of Sox2. In a still further aspect, the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00468] In a further aspect, the cancer is associated with gene amplification of *Sox2*. In a still further aspect, the gene amplification occurs at 3q22.33.

2. USE OF COMPOUNDS

[00469] In one aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method. In a further aspect, a use relates to the manufacture of a medicament for the treatment of a cancer in a mammal. In a further aspect, a use relates to treatment of a cancer in a mammal.

[00470] Also provided are the uses of the disclosed compounds and products. In one aspect, the invention relates to use of at least one disclosed compound; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. In a further aspect, the compound used is a product of a disclosed method of making.

[00471] In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, for use as a medicament.

[00472] In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of the compound or the product of a disclosed method of making.

[00473] In various aspects, the use relates to a treatment of a cancer in a mammal. Also disclosed is the use of a compound for inhibition of LSD1 and/or HDAC1. In one aspect, the use is characterized in that the mammal is a human. In one aspect, the use is characterized in that the disorder is a cancer characterized by the presence of Sox2. In one aspect, the cancer characterized by the presence of Sox2 is treated by inhibition of LSD1 and/or HDAC1 activity in a mammal.

[00474] In a further aspect, the use relates to the manufacture of a medicament for the treatment of a cancer characterized by the presence of Sox2 in a mammal. In a further aspect, the medicament is used in the treatment of a cancer characterized by the presence of Sox2 in a mammal.

[00475] In a further aspect, the use relates to inhibition of LSD1 and/or HDAC1 activity in a mammal. In a further aspect, the use relates to modulating LSD1 and/or HDAC1 activity in a mammal. In a still further aspect, the use relates to modulating LSD1 and/or HDAC1 activity in a cell. In yet a further aspect, the mammal is a human.

[00476] In one aspect, the use is associated with the treatment of a cancer characterized by the presence of Sox2. In a further aspect, the use is associated with a cancer selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00477] It is understood that the disclosed uses can be employed in connection with the disclosed compounds, products of disclosed methods of making, methods, compositions, and kits. In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product in the manufacture of a medicament for the treatment of a cancer associated with gene amplification of *Sox2*. In a still further aspect, the gene amplification occurs at 3q22.33.

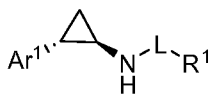
3. MANUFACTURE OF A MEDICAMENT

[00478] In one aspect, the invention relates to a method for the manufacture of a medicament for treatment of cancer in a mammal, the method comprising the step of combining an effective amount of at least one LSD1 inhibitor.

[00479] In one aspect, the invention relates to a method for the manufacture of a medicament for treatment of cancer in a mammal, the method comprising the step of combining an effective amount of at least one HDAC1 inhibitor.

[00480] In a further aspect, the HDAC1 inhibitor is selected from aliphatic acids, hyroxamate, benzamide, cyclic peptide, and electrophilic ketone hybrid molecules. In a still further aspect, the HDAC1 inhibitor is selected from butyrate acid, Valproate (valproic acid), Tricostatin A (TSA), Vorinostat (SAHA), Entinostat (MS-275, SNDX-275), MGCD-0103, Romidepsin (FK-228/resminostate), trapoxin B, CHAP31, Panobinostate (Belinostat, PXD101), M344 (PCI-34051), CI994 (Tacedinaline), Tubastatin A hydrochloride, AR-42 (HDAC-42), SB939 (Pracinostat), ITF2357, Givinostat, CUDC-101, LAQ824 (NVP-LAQ824, Dacinostat), PCI-24781 (CRA-024781), APHA compound 8, BATCP, MOCPAC, PTACH, and PP.

[00481] In a further aspect, the LSD1 inhibitor is a compound having a structure represented by a formula:



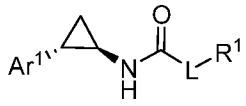
,

wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8

polyhaloalkyl, C1-C8 hydroxyalkyl, $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and $-(CR^{2a}R^{2b})_n-$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-NO_2$, –CN, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-

C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00482] the LSD1 inhibitor is a compound having a structure represented by a formula:

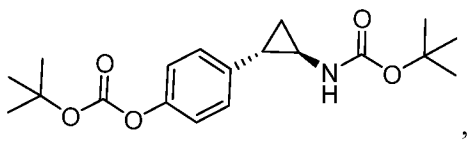


,

wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –

CN, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof.

[00483] In a further aspect, the LSD1 inhibitor is selected from: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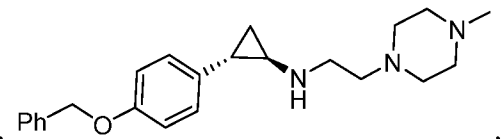
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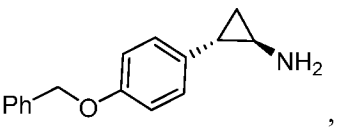
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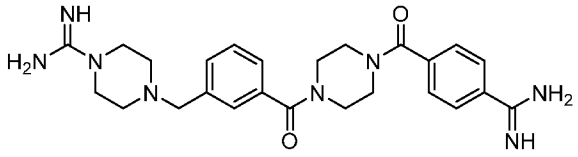
or a pharmaceutically acceptable salt thereof.

[00484] In a further aspect, the LSD1 inhibitor is selected from: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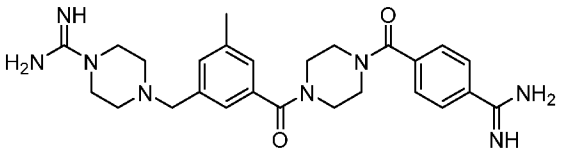
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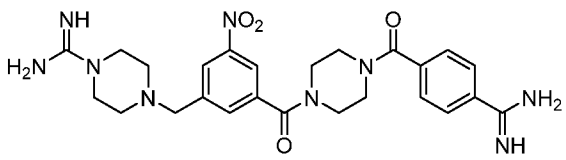
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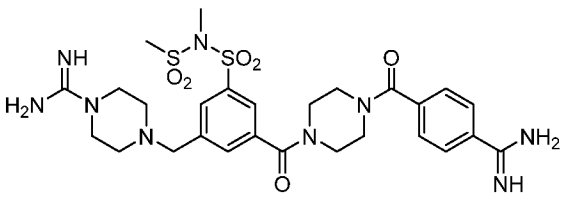
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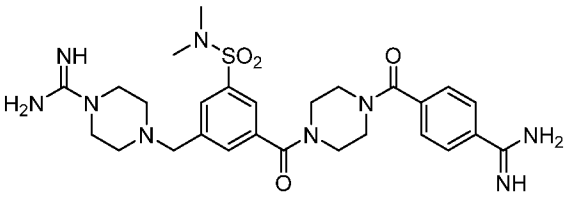
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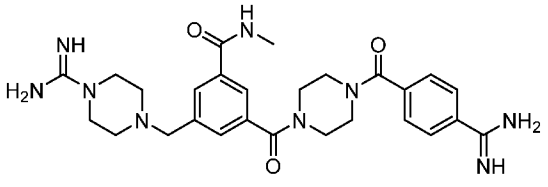
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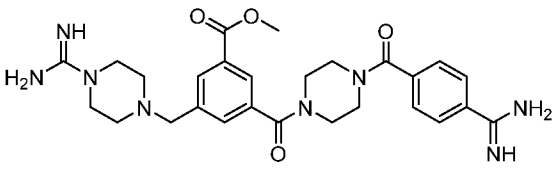
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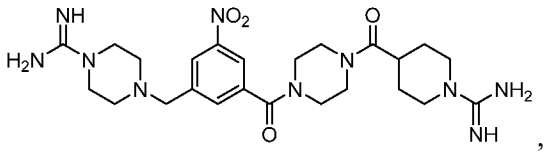
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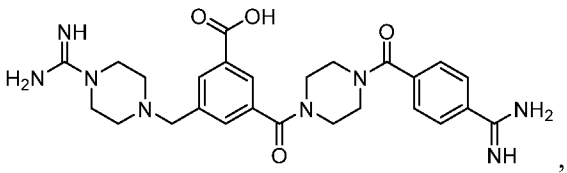
and 
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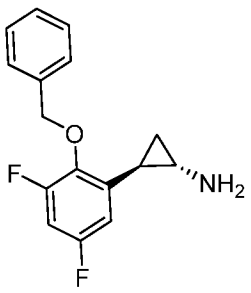
or a pharmaceutically acceptable salt thereof.

[00485] In a further aspect, the LSD1 inhibitor is selected from: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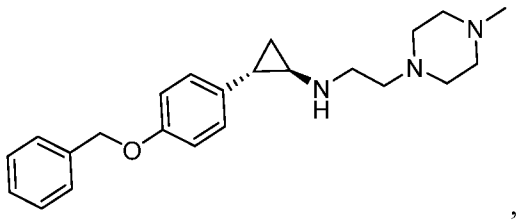
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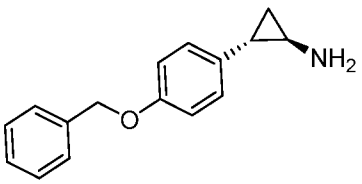
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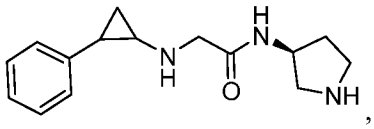
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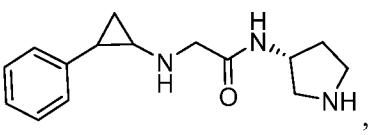
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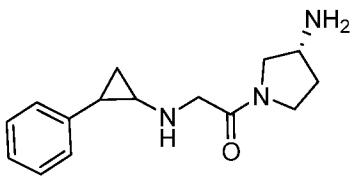
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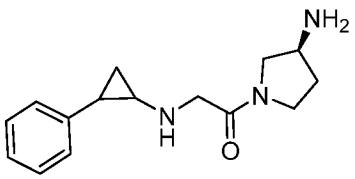
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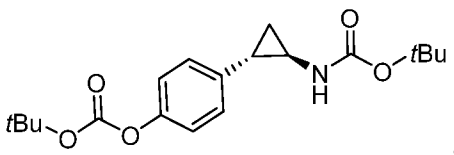
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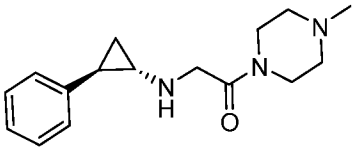
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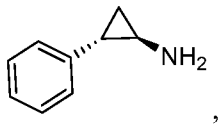
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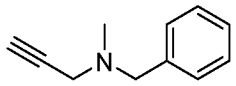
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or a pharmaceutically acceptable salt thereof.

[00486] In a further aspect, the LSD1 inhibitor is selected from parnate 2-phenylcyclopropylamine (2-PCPA), tranylcypromine, and derivatives thereof. In a still further aspect, the LSD1 inhibitor is a bisguanidine polyamine.

[00487] In a further aspect, the cancer comprises cells expressing at least one *Sox2* stem cell marker.

[00488] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for treatment of a cancer prior to the administering step. In yet a further aspect, the method further comprises the step of identifying a mammal in need of treatment of a cancer.

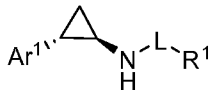
[00489] In a further aspect, the cancer is selected from a lymphoma, sarcoma, and a carcinoma. In a still further aspect, the carcinoma is a squamous cell carcinoma.

[00490] In a further aspect, the cancer is characterized by the presence of Sox2. In a still further aspect, the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00491] In a further aspect, the cancer is associated with gene amplification of *Sox2*. In a still further aspect, the gene amplification occurs at 3q22.33.

4. KITS

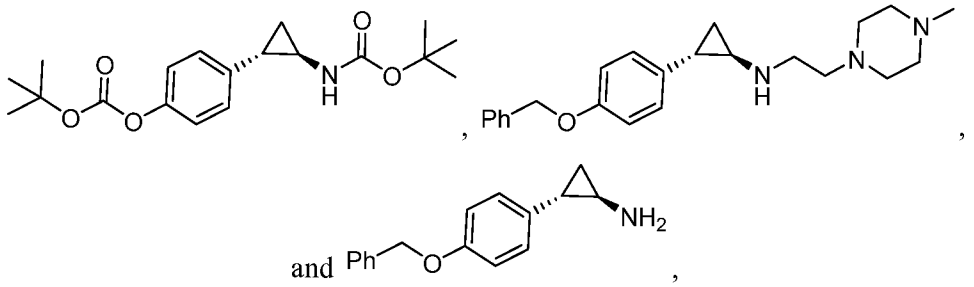
[00492] In one aspect, the invention relates to kits comprising at least one compound having a structure represented by a formula:



wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–; wherein n is an integer selected from 1, and 2; wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3; wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –C(O)SR^8, –SO_2R^9, –$CONR^{10a}R^{10b}$, –$SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–; wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2; wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –NO_2, –CN, –N_3,

C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4; wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$; wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl; wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl; wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt thereof, and one or more of: a) at least one agent known to inhibit LSD1; b) at least one agent known to inhibit HDAC1; c) at least one anticancer therapeutic agent; d) instructions for detecting a cancer; and e) instructions for treating a cancer.

[00493] In one aspect, the invention relates to a kit comprising at least one compound selected from:



or a pharmaceutically acceptable salt thereof, and one or more of: a) at least one agent known to inhibit LSD1; b) at least one agent known to inhibit HDAC1; c) at least one agent know to treat a cancer; d) instructions for detecting a cancer; and e) instructions for treating a cancer.

[00494] In a further aspect, the compound and the agent are co-formulated. In a still further aspect, the compound and the agent are co-packaged.

[00495] In a further aspect, the kit further comprises a plurality of dosage forms, the plurality comprising one or more doses; wherein each dose comprises an effective amount of the compound and the agent known to inhibit LSD1. In a still further aspect, the effective

amount is a therapeutically effective amount. In yet a further aspect, the effective amount is a prophylactically effective amount.

[00496] In a further aspect, each dose of the compound and the agent known to inhibit LSD1 are co-formulated. In a still further aspect, each dose of the compound and the agent known to inhibit LSD1 are co-packaged.

[00497] In a further aspect, the dosage form for the compound is formulated for oral administration and the dosage form for the agent known to inhibit LSD1 is formulated for intravenous administration. In a still further aspect, the dosage form for the compound is formulated for intravenous administration and the dosage form for the agent known to inhibit LSD1 is formulated for oral administration.

[00498] In a further aspect, the kit further comprises a plurality of dosage forms, the plurality comprising one or more doses; wherein each dose comprises an effective amount of the compound and the agent known to inhibit HDAC1. In a still further aspect, the effective amount is a therapeutically effective amount. In yet a further aspect, the effective amount is a prophylactically effective amount.

[00499] In a further aspect, each dose of the compound and the agent known to inhibit HDAC1 are co-formulated. In a still further aspect, each dose of the compound and the agent known to inhibit HDAC1 are co-packaged.

[00500] In a further aspect, the dosage form for the compound is formulated for oral administration and the dosage form for the agent known to inhibit HDAC1 is formulated for intravenous administration. In a still further aspect, the dosage form for the compound is formulated for intravenous administration and the dosage form for the agent known to inhibit HDAC1 is formulated for oral administration.

[00501] In a further aspect, the kit further comprises a plurality of dosage forms, the plurality comprising one or more doses; wherein each dose comprises an effective amount of the compound and the anticancer therapeutic agent. In a still further aspect, the effective amount is a therapeutically effective amount. In yet a further aspect, the effective amount is a prophylactically effective amount.

[00502] In a further aspect, each dose of the compound and the anticancer therapeutic are co-formulated. In a still further aspect, each dose of the compound and the anticancer therapeutic agent are co-packaged.

[00503] In a further aspect, the dosage form for the compound is formulated for oral administration and the dosage form for the anticancer therapeutic agent is formulated for intravenous administration. In a still further aspect, the dosage form for the compound is

formulated for intravenous administration and the dosage form for the anticancer therapeutic agent is formulated for oral administration.

[00504] In a further aspect, the dosage forms are formulated for oral and/or intravenous administration. In a still further aspect, the dosage forms are formulated for oral administration. In yet a further aspect, the dosage forms are formulated for intravenous administration.

[00505] In a further aspect, the agent known to inhibit LSD1 is a monoamine oxidase inhibitor. In a still further aspect, the monoamine oxidase inhibitor is selected from a MAO-A inhibitor and a MOA-B inhibitor. In yet a further aspect, the monoamine oxidase inhibitor is selected from pargyline and phenelzine. In an even further aspect, the monoamine oxidase is a trans-2-phenylcyclopropylamine. In a still further aspect, the trans-2-phenylcyclopropylamine is selected from tranylcypromine, 2-PCPA, parnate, tranylcypromine (TCP), S2101, and RN-1.

[00506] In a further aspect, the anticancer therapeutic agent is selected from: a) a hormone therapy therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; b) an alkylating therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; c) an antineoplastic antimetabolite therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; d) a mitotic inhibitor therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; e) an antineoplastic antibiotic therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; or f) other chemotherapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof.

[00507] In a further aspect, the hormone therapy agent is selected from one or more of the group consisting of leuprolide, tamoxifen, raloxifene, megestrol, fulvestrant, triptorelin, medroxyprogesterone, letrozole, anastrozole, exemestane, bicalutamide, goserelin, histrelin, fluoxymesterone, estramustine, flutamide, toremifene, degarelix, nilutamide, abarelix, and testolactone, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00508] In a further aspect, the alkylating agent is selected from one or more of the group consisting of carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00509] In a further aspect, the antineoplastic antimetabolite agent is selected from one or more of the group consisting of gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea,

mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00510] In a further aspect, the mitotic inhibitor agent is selected from one or more of the group consisting of irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etopside, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00511] In a further aspect, the antineoplastic antibiotic agent is selected from one or more of the group consisting of doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plicamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00512] In a further aspect, the cancer is selected from a lymphoma, sarcoma, and a carcinoma. In a still further aspect, the carcinoma is a squamous cell carcinoma.

[00513] In a further aspect, the cancer is characterized by the presence of Sox2. In a still further aspect, the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

[00514] In a further aspect, the cancer is associated with gene amplification of *Sox2*. In a still further aspect, the gene amplification occurs at 3q22.33.

L. EXAMPLES

[00515] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely

exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[00516] Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein. The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. The Examples are typically depicted in free base form, according to the IUPAC naming convention. Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way.

1. EXPERIMENTAL PROCEDURES

a. CELL LINES AND CELL CULTURE

[00517] Lung, breast, ovarian, and other carcinoma cells were either obtained from American Type Culture Collection (ATCC) or from the DTP and DCTD Tumor Repository of National Cancer Institute (the NCI-60 cancer cell line panel), operated by Charles River Laboratory, Inc., as listed in Table 1. They were cultured according to instructions and treated with various concentrations of LSD1 inhibitors for 30-36 hours for mRNA analysis by quantitative real time RT-PCR or for 30-48 hours for protein analysis and the cell viability assays using Western blotting or microscopy and MTT assays as described previously (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249).

TABLE 1.

Cell Lines	Sources	Cancer Types	Oct4	Lin28	Sox2	Sensitivity to LSD1 inhibitors
F9*	ATCC	Murine teratocarcinoma	Yes	Yes	Yes	Yes
PA-1**	ATCC	Ovarian teratocarcinoma	Yes	Yes	Yes	Yes
NTERA-2**	ATCC	Embryonal carcinoma	Yes	Yes	Yes	Yes
HS38.T	ATCC	Ovarian teratoma (fibroblast-like)	No	No	No	No
HeLa	ATCC	Cervical adenocarcinoma	No	No	No	No
IGROV-1	NCI-60	Ovarian adenocarcinoma	Yes	Yes	Yes	Yes
A2780**	NCI-60	Ovarian carcinoma	No	Yes	Yes	Yes
SKOV-3	NCI-60	Ovarian adenocarcinoma	No	No	Yes	Yes

Cell Lines	Sources	Cancer Types	Oct4	Lin28	Sox2	Sensitivity to LSD1 inhibitors
OVCAR-3	NCI-60	Ovarian adenocarcinoma	No	No	Yes	Yes
OVCAR-8	NCI-60	Ovarian carcinoma	No	No	No	No
ES-2	ATCC	Ovarian carcinoma	No	No	No	No
MCF7	NCI-60	Breast adenocarcinoma	No	No	Yes	Yes
T47D	NCI-60	Breast ductal carcinoma	No	Yes	Yes	Yes
MDA-MB-453	ATCC	Breast carcinoma	No	No	Yes	Yes
MDA-MB-468	NCI-60	Breast adenocarcinoma	No	No	Yes	Yes
MDA-MB-231	NCI-60	Breast adenocarcinoma	No	No	No	No
MDA-MB-361	ATCC	Breast adenocarcinoma	No	No	Yes	Yes
SK-BR-3	ATCC	Breast adenocarcinoma	No	No	No	No
BT-549	ATCC	Breast ductal carcinoma	No	No	No	No
NCI-H520	ATCC	Lung squamous cell carcinoma	No	No	Yes	Yes
NCI-H1437	ATCC	Lung adenocarcinoma	No	No	No	No
A549	NCI-60	Lung carcinoma	No	No	Yes	Yes
H1299	ATCC	Lung carcinoma	No	No	No	No
G401**	ATCC	Kidney rhabdoid tumor	No	Yes	Yes	Yes
MDA-MB-435s	NCI-60	Melanoma	No	No	No	No
K562	NCI-60	Myelogenous leukemia	No	No	Yes	Yes

* Also expresses Nanog and Sall4; ** Also express Sall4

[00518] Cell culture was conducted as described earlier (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). PA-1 and MCF7 were maintained in Eagle's Minimum Essential Medium; Hs38.T, F9, HeLa and 293 cells were in Dulbecco's Modified Eagle's Medium; IGROV-1 cells were in RPMI Medium 1640 without folic acid; SKOV-3, ES-2, SK-BR-3 and G401 cells were in McCoy's 5a Medium; A2780, OVCAR-3, OVCAR-8, T47D, BT-549, and H1299 cells were in RPMI-1640 Medium; MDA-MB-231, MDA-MB-468, MDA-MB-453, MDAMB-435s and MDA-MB-361 cells were in Leibovitz's L-15 Medium; A549 cells were maintained in F-12K Medium and K562 cells were maintained in Iscove's Modified Dulbecco's Medium. All media were supplemented with 10% FBS, whereas OVCAR-3 cells were cultured with 20% FBS. The media for OVCAR-3 and MCF7 cells were supplemented with 0.01 mg/mL bovine insulin, while the medium for BT-549 cells was with 0.023 IU/mL insulin.

[00519] Mouse ES cells, F9 teratocarcinoma cells, immortalized NIH 3T3 cells, and PA-1 human ovarian teratocarcinoma, HeLa cervical carcinoma, and HCT116 colorectal carcinoma

cells were purchased from the American Type Culture Collection (ATCC). The mouse normal liver cell line NCTC1469 was from the Cell Center of Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences. The cells were cultured as previously described (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). For mouse ES cells, they were cultured in knockout Dulbecco modified Eagle medium supplemented with 15% knockout serum replacement, 0.1mM2-mercaptoethanol, 200 mM L-glutamine, 1/100 (vol/vol) nonessential amino acids, and 1/100 (vol/vol) penicillin-streptomycin (all from Gibco) and 1/1,000 (vol/vol) leukemia inhibitory factor (Millipore). The ES cells were maintained on a feeder layer of mitomycin C-treated primary mouse embryonic fibroblasts (MEFs).

b. Western Blot, Immunohistochemistry, and Antibodies

[00520] Log-phase growing cancer cells were directly lysed in a buffer containing 0.5% SDS. Proteins in the lysates were equalized and analyzed by Western blotting using antibodies against Sox2, LSD1, H3K4Me1, H3K4Me2, Oct4, and other proteins as described previously or in the figure descriptions (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). For immunohistochemical staining, rabbit monoclonal anti-LSD1 (clone C69G12, cat. #2184) and anti-Sox2 (clone D6D9, cat. #3579) antibodies were obtained from Cell Signaling. Rabbit anti-Sox2 polyclonal antibodies were raised using the purified GST-Sox2 fusion protein as the antigen.

[00521] Immunohistochemical staining was performed as described previously (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). Briefly, tumor tissues from clinic patients were fixed in 10% neutral buffered formalin and then embedded in paraffin. Serial section was carried out to produce 5 microns slices. Slides were deparaffinized, rehydrated, and immersed in 3% H_2O_2 to inactivate the endogenous peroxidase. Antigens were retrieved and immunostained with anti- LSD1 and anti-Sox2 antibodies. The slides were then incubated with the Rabbit-Probe Streptavidin-Peroxidase polymer detection system, developed with 3, 3'-diaminobenzidine (DAB) substrate, counterstained with hematoxylin, dehydrated, and then mounted with Neutral balsam. Images were captured on a Zeiss fluorescence microscope (Axio Observer) coupled with a cooled charge-coupled device camera (AxioCam MRM, Zeiss) and processed by using AxioVision program.

[00522] Protein detection using Western blotting was conducted as previously described (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). The rabbit polyclonal anti-LSD1, Sall4, Nanog, H3K4Me1, H3K4Me2, and Histone 3 antibodies were purchased from Abcam;

anti-Lin28 and anti-Klf4 antibodies were from Proteintech Group; anti-H3K4Me3 antibody was from Millipore; anti-FoxA2 antibodies were from Sigma; and anti-Sox2 antibodies were from Bethyl Laboratory. The goat anti-mouse IgG-HRP and goat anti-rabbit IgG-HRP and mouse monoclonal anti-Oct4 antibodies were purchased from Santa Cruz Biotechnologies.

[00523] Antibodies against HDAC1, HDAC2, HDAC3, HDAC6, Sox2, and CoREST were obtained from Bethyl Laboratories; anti-histone H4 peptide with acetylated lysine 16 (anti-H4K16ac; catalog no. 07-329), anti-histone H4 peptide with acetylated lysine 12 (anti-H4K12ac; catalog no. 04719), and histone H3 peptide with trimethylated lysine 4 (anti-H3K4me3) antibodies were from Millipore; anti-histone H3 peptide with acetylated lysine 56 (H3K56ac) antibodies (catalog no. 39281) were from Active Motif; anti-histone H3 peptide with dimethylated lysine 4 (H3K4me2; ab32356), histone H3 peptide with methylated lysine 4 (H3K4me1; ab8895), histone H3 (ab1791), histone H3 peptide with acetylated lysine 14 (H3K14ac; ab52946), histone H3 peptide with acetylated lysine 9 (H3K9ac; ab4441), histone H3 peptide with acetylated lysine 27 (H3K27ac; ab4279), Sall4, Nanog, and LSD1 (ab17721) antibodies were from Abcam; and Lin28 and Klf4 antibodies were from Proteintech Group. Goat anti-mouse IgG–horseradish peroxidase (HRP), goat anti-rabbit IgG–HRP, and mouse monoclonal anti-Oct4 antibodies were from Santa Cruz Biotechnologies. MS-275, valproic acid (VPA), all-*trans*-retinoic acid (RA), and trichostatin A (TSA) were from Sigma. CBB1003 and CBB1007 were synthesized as described previously (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249).

[00524] For immunoaffinity purification, cells were lysed in ice-cold lysis buffer (50 mM Tris-HCl, pH 7.5, 120 mM NaCl, 0.5% Nonidet P-40, 10% glycerol, protease inhibitors) and centrifuged at 13,000 rpm for 15 min, and the supernatant was incubated with anti-LSD1 or anti-HDAC1 antibodies and rabbit IgG (normal rabbit serum [NRS]) overnight at 4 °C. The immunocomplexes were captured by protein A-Sepharose. Isolated LSD1-protein A or HDAC1-protein A complexes were verified by Western blotting with LSD1 andHDAC1antibodies. For purification of the 3_Flag-3_ hemagglutinin (HA)-LSD1 complexes, human LSD1 cDNA was cloned into the 3_ Flag-3_ HA-pMSCV retroviral vector. The recombinant virus was packaged in 293 cells and used to transfect F9 cells (Jin, J., et a. (2006) *Mol. Cell* **23**, 709-721). Stable 3_Flag-3_HA-LSD1-expressing F9 cells were selected under puromycin selection, and the expression of tagged LSD1 was confirmed by Western blotting. For the isolation of 3_ Flag-3_ HA-LSD1 complexes, 30 dishes (15 cm) of F9 cells were harvested and the tagged LSD1 complexes were first immunoprecipitated using anti-Flag M2 affinity gel (Sigma) and eluted with the 3_ Flag peptide. The eluted complex

was further purified by anti-HA affinity Sepharose (Roche). The proteins in the 3_ Flag-3_ HA-LSD1 complexes were separated on an SDS-polyacrylamide gel, excised, trypsinized, and identified using an ESI LTQ Orbitrap XL mass spectrometer (Thermo Scientific) coupled with an Eksigent nano-liquid chromatograph. The presence of CoREST and HDAC1 in the LSD1 complex was confirmed independently by immunoprecipitation and Western blotting.

c. SMALL RNA INTERFERENCE

[00525] Cells were transfected with 50-100 nM siRNAs using the DharmaFECT reagent 1(Dharmacon) for 30-36 hours for mRNA analysis using quantitative real-time RT-PCR or for 48-60 hours for Western blotting as described previously (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). The siRNA sequences are: human LSD1: GGAAGAAGAUAGUGAAAAC (SEQ ID NO:1) and human Sox2: CGCUCAUGAAGAAGGAUAA (SEQ ID NO:2).

[00526] For the small interfering RNA (siRNA) assay, cells were seeded at a density of 30% confluence at 20 h before transfection and transfected with 50 nM the indicated siRNAs using the DharmaFECT transfection reagent (Thermo Scientific) for F9, NCTC1469, PA-1, and HCT116 cells, while Oligofectamine (Invitrogen) was used for HeLa and NIH 3T3 cells. Cells were harvested at 48 h after transfection. To optimize transfection efficiency in mouse ES (mES) cells, mES cells were passaged twice on plates coated with 0.1% gelatin and supplemented with ES cell complete medium recovered from MEFs. Mouse ES cells were cultured for 24 h prior to transfection and were transfected with 50 nM the indicated siRNAs using the DharmaFECT transfection reagent. The medium was replaced with fresh ES complete medium at 24 h after transfection, and samples were harvested 48 h later. The siRNAs used are listed in Table 2. To prevent potential off-target effects of siRNAs, at least two independent siRNAs against each target were designed and used. All of the siRNA experiments were repeated at least three times to ensure consistent results.

TABLE 2.

siRNA Name	Sequence (5'-3')	SEQ. ID NO.
Mouse-HDAC1	GCAAGCAGATGCAGAGATT	3
Human-HDAC1	GCAAGCAGATGCAGAGATT	4
Mouse-HDAC2	CCAGAACACTCCAGAATAT	5
Human-HDAC2	AGACTGATATGGCTGTTAA	6
Mouse-HDAC3	GCATTGATGACCAGAGTTA	7
Human-HDAC3	AAAGCGATGTGGAGATTTA	8
Mouse-HDAC6	GGATGTTCATCATGGTAAT	9
Human-HDAC6	TGACCAAAATATGATGAAT	10

siRNA Name	Sequence (5'-3')	SEQ. ID NO.
Mouse-Sirt1	CCATGAAGTATGACAAAGA	11
Human-Sirt1	CCTCAAAGTAAGACCAGTA	12
Mouse-LSD1	AAGGAAAGCUAGAAGAAAA	13
Human-LSD1	AAGGAAAGCUAGAAGAAAA	14
Mouse-MOF	GATCCAGTCTCGAGTGAAC	15
Human-MOF	GATCCAGTCTCGAGTGAAC	16
Mouse-HDAC1 5'-UTR	GCAAGAUGGCGCAGACUCA	17
Human-HDAC1 3'-UTR	AAGACAAACUCCUGAAAUG	18
Mouse-LSD1 3'-UTR	AAGCAAGTGGTGTGAGATA	19
Human-LSD1 3'-UTR	GGGAGGAACUUGUCCAUUA	20
Mouse-MOF 3'-UTR	TCTGGGTTTCCTGGCCTCT	21
Human-MOF 3'-UTR	GGGAAGGGGAGGCCAAGAA	22
Mouse-Tip60	GACGGAGUAUGACUGCAAA	23
Human-Tip60	CUCCAGGCAAUGAGAUUUA	24

d. Chromatin Immunoprecipitation (ChIP) Assays

[00527] The ChIP assays were carried out according to the Abcam protocol and other published protocols (Whyte, W. A., et al. (2012) *Nature* **482**, 221-225). After cross-linking the chromatin proteins, chromatin DNA was sonicated to average 500-1,000 base pairs and used for immunoprecipitation by specific antibodies. DNA was isolated for quantitative real time PCR after reversing the cross-linking on immunoprecipitated chromatin fragments. The real-time PCR primers are shown in Tables 3 and 4. The ChIP grade anti-H3K4Me2 (Ab32356), anti-H3K4Me1 (Ab8895), and anti-LSD1 (Ab17721) antibodies were from Abcam.

Table 3.

Chromatin Immunoprecipitation (ChIP) qPCR Analysis		
Gene	**Primer sequence (5'-3')**	**SEQ. ID NO.**
SOX2_ human (-4000)-F	AATACTGGTGGTCGTCAAAC	25
SOX2_ human (-4000)-R	TGAGAACTAGCCAAGCATCT	26
SOX2_ human (-3000)-F	TGCTGGATTGAAATAGAGTG	27
SOX2_ human (-3000)-R	TAAGCCTGCTGTACTTATCG	28
SOX2_ human (-2000)-F	CTTAGACGAGGCTTTGTTTG	29
SOX2_ human(-2000)-R	GGGTTAGAGGAGGATGAGAT	30
SOX2_ human (-1000)-F	TTTGGGTCTCCTAACTTCTA	31
SOX2_ human (-1000)-R	GTCATTGTTCTCCCGCTCAT	32
SOX2_ human (0)-F	CAGGAGTTGTCAAGGCAGAG	33
SOX2_ human (0)-R	GGAAAATCAGGCGAAGAATA	34
SOX2_ human (+1000)-F	CATCACCCACAGCAAATGAC	35
SOX2_ human (+1000)-R	TTCCTGCAAAGCTCCTACCG	36
SOX2_ human (+2000)-F	TACTGTGCTCAGCCAAGAAA	37

Chromatin Immunoprecipitation (ChIP) qPCR Analysis		
Gene	**Primer sequence (5'-3')**	**SEQ. ID NO.**
SOX2_ human (+2000)-R	GCAACAAGTGGCATAAATCA	38
SOX2_ human (+4000)-F	TCCCGGAATTTGAGGCAGTC	39
SOX2_ human (+4000)-R	TTGGCTCGGCGATATGAAGG	40
FOXA2_human (-4000)-F	CAACCTTCGGCACAACGATC	41
FOXA2_human (-4000)-R	GAAGCCACCATACAAACTGA	42
FOXA2_human (-2500)-F	AATAGTGCTGTGGTGGAGGT	43
FOXA2_human (-2500)-R	TTTGTGAGCTTATGTGGGTG	44
FOXA2_human (-1500)-F	CCTGTGCCTACTGCTACCTC	45
FOXA2_human (-1500)-R	GTTAGCCTGTGAGCCCAGAT	46
FOXA2_human (-1000)-F	GCTTCTCCCGAGGCCGTTCC	47
FOXA2_human (-1000)-R	ACTCGCCCGCTGCTGCTCCT	48
FOXA2_human (0)-F	CCGCCCACTTCCAACTACCG	49
FOXA2_human (0)-R	GTCAGCCAAAGCACCGTCCC	50
FOXA2_human (+1000)-F	GGTGTACTCCCGGCCCATTA	51
FOXA2_human (+1000)-R	ATTTCTTCTCCCTTGCGTCT	52
FOXA2_human (+2000)-F	CCAGGTCTCGGGTCCGATTA	53
FOXA2_human (+2000)-R	CCCTCCCTCCTTCTTGAAAT	54
Lin28A_human(-4000)-F	GGGTGGATCACGAGGTCA	55
Lin28A_human (-4000)-R	CCAGGTTCAAGCCATTCT	56
Lin28A_human (-3000)-F	TTGCAGCGAGCCAAGATC	57
Lin28A_human (-3000)-R	TGTAAAGGGTTAGGAAAGAA	58
Lin28A_human (-1500)-F	TAAATGGGTTGTAGTGGTGG	59
Lin28A_human (-1500)-R	TACTGCCCTGGTCGGAGA	60
Lin28A_human (-1000)-F	AGGCAGACATTCAGATGTAGT	61
Lin28A_human (-1000)-R	GTGCTTAGATAGACCTGGAGT (	62
Lin28A_human (0)-F	AAAGGGAGGGGAAAGGAGA	63
Lin28A_human (0)-R	GCACAATAGCGGTGGGAG	64
Lin28A_human (+500)-F	TGCGCCAAGGCGGCAGAAGA	65
Lin28A_human (+500)-R	TGGACAGGAAGCCGAACCC	66
Lin28A_human (+1000)-F	GGGGCGTAAAGCCGAGAA	67
Lin28A_human (+1000)-R	ACGGGAACTGGACAGCAAAG	68
Lin28A_human (+3000)-F	ATGGCATGATCTCCACTCA	69
Lin28A_human (+3000)-R	CCTGTAATCCCAGCACTTT	70
KLF4_human (-4000)-F	GAGCCAAGATCACGCCACT	71
KLF4_human (-4000)-R	TGCCGCAGGACTCAAGAA	72
KLF4_human (-2500)-F	GATCTTAGAGGGATTCCTGG	73
KLF4_human (-2500)-R	TGTTTGAACCCTGCGATT	74
KLF4_human (-1500)-F	TGGCGCACGCCTGTAATC	75
KLF4_human (-1500)-R	CATCTCGAAGCCCTTTCC	76
KLF4_human (-1000)-F	GGAGATGGAGGGCTGGATG	77
KLF4_human (-1000)-R	GCGAAGACTGGTGGGGTCA	78
KLF4_human (0)-F	ACGCTGCTGAGTGGAAGA	79
KLF4_human (0)-R	AATTGGCCGAGATCCTTC	80
KLF4_human (+500)-F	TGTATGCCCGTGGTGCGA	81
KLF4_human (+500)-R	TCTGGCCCAGCCAGTGTC	82

Chromatin Immunoprecipitation (ChIP) qPCR Analysis		
Gene	**Primer sequence (5'-3')**	**SEQ. ID NO.**
KLF4_human (+1000)-F	GAGACCGAGGAGTTCAACGA	83
KLF4_human (+1000)-R	GCGACGACGAAGAGGAGG	84
KLF4_human (+3000)-F	GGTGTAGGTGGTGGTTGT	85
KLF4_human (+3000)-R	TGACCCTATCCTAAAGAAAT	86
BMP2_human (-2500)-F	CCCAGCGGGGAAATAAGAGG	87
BMP2_human (-2500)-R	CGCCTCCACTCCCTGCTC	88
BMP2_human (-1500)-F	TCCTAAGGAGGACGACAGCA	89
BMP2_human (-1500)-R	TCGGAGATGGCGAAGCAG	90
BMP2_human (-1000)-F	TCTTCCACCCCTCTTTCT	91
BMP2_human (-1000)-R	AGGGATTTCTTTGACCCA	92
BMP2_human (0)-F	GAGGGCAAATCCCAAATC	93
BMP2_human (0)-R	GGTAAGACCGACCGAAGC	94
BMP2_human (+500)-F	AGTAACTCCGCACCCTCT	95
BMP2_human (+500)-R	TTGCACGTTTAGCTGACTAG	96
BMP2_human (+1800)-F	ATAAAAGCGTTTGTAGCA	97
BMP2_human (+1800)-R	CAAGCAGAAATATCCCAC	98
BMP2_human (+3000)-F	CCAGGTGCTTCTTGTTCT	99
BMP2_human (+3000)-R	TTTGTGGAAAGAGGGTTA	100
TP63_human (-4000)-F	AGTGGCTACCACATCAGA	101
TP63_human (-4000)-R	CACATTAGACACCGAGTA	102
TP63_human (-2500)-F	GCTCATGCCTGTAATCCC	103
TP63_human (-2500)-R	TCTGCCTCAGCTTCCTGT	104
TP63_human (-1500)-F	TCTCGGGCTAAGTAAAGG	105
TP63_human (-1500)-R	AGTTCACATCTTCCCTTC	106
TP63_human (-1000)-F	TAAAGAATAGAGTGGAGCCG	107
TP63_human (-1000)-R	TTTGCCTGACCCGAATAA	108
TP63_human (0)-F	AAAATCAAGAAACGCTCCG	109
TP63_human (0)-R	GCAATAGGGTCAAATGCT	110
TP63_human (+500)-F	CAGCACCTACTCACTCAA	111
TP63_human (+500)-R	AATGACAAGCCACAATCT	112
TP63_human (+1000)-F	GGGGTCTCCAAGGTTTCA	113
TP63_human (+1000)-R	AACCCAATCCTCAACTGC	114
TP63_human (+3000)-F	GGGACTTCATCCTCTGTT	115
TP63_human (+3000)-R	GGTAATGTGATTTTATCCAACT	116
KRT6A_human (-4000)-F	CCTTCGTGCTTCTGTCTA	117
KRT6A_human (-4000)-R	TTCAGTGCCTAATCTTGC	118
KRT6A_human (-2500)-F	ACCACCTTTCCTTCCAAT	119
KRT6A_human (-2500)-R	CAGGCTTGTGCCACATTA	120
KRT6A_human (-1500)-F	CTTGCCAGACGCTGAGTT	121
KRT6A_human (-1500)-R	AGCAGTCCCATTTCTCCA	122
KRT6A_human (-1000)-F	TGGCAGAAGTCAGGTCTC	123
KRT6A_human (-1000)-R	CTTTACACTGTAGGAGCAAC	124
KRT6A_human (0)-F	GCTGGAAGGCAGGAGAAT	125
KRT6A_human (0)-R	GGTGAGCTTGCAGGTTGG	126
KRT6A_human (+500)-F	GAGGTCACCGTCAACCAG	127

Chromatin Immunoprecipitation (ChIP) qPCR Analysis		
Gene	**Primer sequence (5'-3')**	**SEQ. ID NO.**
KRT6A_human (+500)-R	CGATGAAGGAGGCAAACT	128
KRT6A_human (+1500)-F	TGTTCGAGCAGTACATCAA	129
KRT6A_human (+1500)-R	CCTGGTCACCCAATAGTC	130
KRT6A_human (+3000)-F	GAACTTATGCCCAAGTCAA	131
KRT6A_human (+3000)-R	CCTCATTATGGCACCACT	132
Sox17_human (-4000)-F	ACGCTGCTGATAAGGCTGTC	133
Sox17_human (-4000)-R	TGGGCTGTGGAACCTCATAC	134
Sox17_human (-3000)-F	CCAAGAACAAGGGCAAATAA	135
Sox17_human (-3000)-R	TCAAGCGATTCTCCTGTCTC	136
Sox17_human (-2000)-F	GGAGGCTGAGACAGGAGAAT	137
Sox17_human (-2000)-R	GGAGCCAAGAAGGTGGAGAA	138
Sox17_human (-1000)-F	TCTTTGCTAATGCTGGAGGG	139
Sox17_human (-1000)-R	AAATGTCCGAGTTTGTTTGG	140
Sox17_human (0)-F	CAGTGCCTCACTCCCCACCC	141
Sox17_human (0)-R	GCCTCGCCCTTCACCTTCAT	142
Sox17_human (+2000)-F	TTCCCATAGTTGGATTGTCA	143
Sox17_human (+2000)-R	GCATTTATGTTCACCCTTTT	144
Sox17_human (+4000)-F	TGTCCCAAGAGTTCCCAGTA	145
Sox17_human (+4000)-R	AACACCAATCCCTCCATCCA	146
CyclinA_human (-4000)-F	AGGGAAAGAAGGAGTGAG	147
CyclinA_human (-4000)-R	ACCTTGCAGAGCTATTGT	148
CyclinA_human (-3000)-F	ACCTCAGCCTCCCAAAGT	149
CyclinA_human (-3000)-R	TAGCAGCATCCAATAGCAAA	150
CyclinA_human (-2000)-F	TAGACCGCTTTATAGGCT	151
CyclinA_human (-2000)-R	CATACATAGTAACCAGGAC	152
CyclinA_human (-1000)-F	CAGTAGTTCAAGGTGCCA	153
CyclinA_human (-1000)-R	CTTAACATTTAGGCGTTTAT	154
CyclinA_human (0)-F	CCTGCTCAGTTTCCTTTGGT	155
CyclinA_human (0)-R	ATCCCGCGACTATTGAAATG	156
CyclinA_human (+500)-F	GTTCTCCCATATTAGCATCA	157
CyclinA_human (+500)-R	GAGCTGAGCGAAGACTACA	158
CyclinA_human (+1000)-F	CCTTTGTGGGAATGCCTGTG	159
CyclinA_human (+1000)-	RGGGTGTTGGCCTTTGCTT	160
CyclinA_human (+3000)-F	AGCCAGACATCACTAACA	161
CyclinA_human (+3000)-	RTGTAGTTCACAGCCAAAT	162
CyclinB_human (-4000)-F	CCGGTTGGAGTGCAGTAG	163
CyclinB_human (-4000)-R	CTGGGATTGGTGGTGTAT	164
CyclinB_human (-3000)-F	TCAGGAGTTTGAGGTTAC	165
CyclinB_human (-3000)-R	TCTGTTCAGGTATTTTGC	166
CyclinB_human (-2000)-F	GAAGGCAGGTGAAATGCT	167
CyclinB_human (-2000)-R	TGCGATTACAGGCGTGAG	168
CyclinB_human (-1000)-F	ATCTGAGTAAAGGGCATA	169
CyclinB_human (-1000)-R	GTTTTAGCTTTCTATTTGGA	170
CyclinB_human (0)-F	GAGTGAGTGCCACGAACAGG	171
CyclinB_human (0)-R	ACCCAGCAGAAACCAACAGC	172

Chromatin Immunoprecipitation (ChIP) qPCR Analysis		
Gene	**Primer sequence (5'-3')**	**SEQ. ID NO.**
CyclinB_human (+500)-F	AGAGGTCGGCGGAAACTG	173
CyclinB_human (+500)-R	AGGTGGGGCACAAGGAGA	174
CyclinB_human (+1000)-F	AAATGCCTATGAAGAAGG	175
CyclinB_human (+1000)-R	TTTTCCAGTAGCTGAAGG	176
CyclinB_human (+3000)-F	GGCTGGTCTCGAACTCCT	177
CyclinB_human (+3000)-R	CTTCATGGCATCCTCAAA	178
CyclinD_human (-4000)-F	GCAAGTTCCGGAGTGGGG	179
CyclinD_human (-4000)-R	GAGACGCAGGGCTTCGCT	180
CyclinD_human (-3000)-F	AACCCAAGCCCCGAGCCC	181
CyclinD_human (-3000)-R	GCGTGTTCGCCACCGTCC	182
CyclinD_human (-2000)-F	TCTGAGGCTTGGCTATGCG	183
CyclinD_human (-2000)-R	TGGGGAGCGATGGGTTGC	184
CyclinD_human (-1000)-F	AGGTAGGAAGGCAGCCCGAAGA	185
CyclinD_human (-1000)-R	AGCAGCAGCCCAAGATGG	186
CyclinD_human (0)-F	ACCCAGCCAGGACCCACA	187
CyclinD_human (0)-R	GGTTTCCACTTCGCAGCAC	188
CyclinD_human (+500)-F	CGTTTCTTTGCTACTCACCC	189
CyclinD_human (+500)-R	CCACCCCTTCCTCCTTCA	190
CyclinD_human (+1000)-F	TGAAAGTGCGGCGTGGTG	191
CyclinD_human (+1000)-	RCTCGGGCGACCCTTTACC	192
CyclinD_human (+3000)-F	GGATGGAGGGAGATTTGCT	193
CyclinD_human(+3000)-	RGAAGGACGAGGCCAGAGTAA	194
SAT2_human-F	AATCATCGAATGGTCTCGAT	195
SAT2_human-R	ATAATTCCATTCGATTCCAC	196
GAPDH_human-F	ACCACAGTCCATGCCATCA	197
GAPDH_human-R	CAGGGATGATGTTCTGGAGA	198

TABLE 4.

mRNA qPCR Analysis		
Gene	Primer Sequence (5'-3')	SEQ. ID NO.
SOX2 _human-F	GTGAGCGCCCTGCAGTACAA	199
SOX2 _human-R	GCGAGTAGGACATGCTGTAGGTG	200
LSD1_human-F	AGCGTCATGGTCTTATCAA	201
LSD1_human-R	GAAATGTGGCAACTCGTC	202
FOXA2_human-F	CCCCAACAAGATGCTGACGC	203
FOXA2 _human-R	GCGAGTGGCGGATGGAGTT	204
BMP2_human-F	ACAGCGGAAACGCCTTAA	205
BMP2 _human-R	GGGAGCCACAATCCAGTC	206
EOMES_human-F	CCCAGACCCAACCTTTCC	207

mRNA qPCR Analysis		
Gene	Primer Sequence (5'-3')	SEQ. ID NO.
EOMES _human-R	GAGCCAATTTCCTCTTTCACTT	208
SOX17_human-F	CTGCAGGCCAGAAGCAGTGTTA	209
SOX17_human-R	CCCAAACTGTTCAAGTGGCAGA	210
HNF4A_human-F	AGCTGCAGATCGATGACAATGAG	211
HNF4A _human-R	CATACTGGCGGTCGTTGATGTAG	212
TP63_human-F	CCTTACTTTGCTGAGGGTTTGAA	213
TP63 _human-R	CAAGGCCCTAGTGTTACCTGAATAG	214
KRT6A_human-F	GGCTGAGGAGCGTGAACAG	215
KRT6A _human-R	CAGGAACCGCACCTTGT	216
β-Actin _human-F	GGCCACGGCT GCTTC	217
β-Actin _human-R	GTTGGCGTACAGGTCTTTGC	218

[00528] Alternatively, 1×10^7 human A2780 cells were used for each immunoprecipitation. Cells were fixed in 0.75% formaldehyde, collected, resuspended in the FA lysis buffer (0.1% SDS, 0.1% sodium deoxycholate, 1mM EDTA, 1% Triton X-100, 140 mM NaCl and 50 mM HEPES-KOH, pH 7.5) and sonicated to generate DNA fragments of 500–1000 base pairs (bp). The sonicated chromatin was cleared and incubated with specific primary antibodies or normal rabbit IgG overnight followed by incubation with protein A Sepharose beads (pre-adsorbed with sonicated single-stranded herring sperm DNA and BSA) for 1 hour. After incubation, the immunocomplexes were washed sequentially with wash buffer (0.1% SDS, 1% Triton X-100, 2mM EDTA, 20mM Tris-HCl, at pH 8.0 and 150mM NaCl), final wash buffer (0.1% SDS, 1% Triton X-100, 2mM EDTA, 20mM Tris-HCl, at pH 8.0, and 500mM NaCl). Immunocomplexes were eluted in elution buffer (0.1% SDS and 0.1M NaHCO3) and the crosslinking was reversed overnight at 65 °C. DNA was extracted with phenol/chloroform and precipitated with ethanol. Purified DNA was quantified by real-time PCR.

[00529] Alternatively, chromatin immunoprecipitation (ChIP) assays were carried out according to previously described procedures (8, 9). Briefly, 1 x 10^7 to 5 x 10^7 cells were used for each sample. Proteins were cross-linked to DNA by addition of formaldehyde to a final concentration of 0.75%. After incubating with 125 mM glycine for 5 min, cells were harvested, resuspended in FA lysis buffer (50 mM HEPES-K^+, pH 7.5, 140 mM NaCl, 1 mM EDTA pH 8.0, 1% Triton X-100, 0.1% sodium deoxycholate, 0.1% SDS, protease inhibitors),

and sonicated to generate DNA fragments of 500 to 1,000 bp in average length. Soluble chromatin fragments were diluted (1:8) in radioimmunoprecipitation assay buffer (50 mM Tris-HCl, pH 8.0, 150 mM NaCl, 2 mM EDTA, 1% NP-40, 0.5% sodium deoxycholate, 0.1% SDS, protease inhibitors) and incubated with primary antibodies overnight. The immunocomplexes were incubated with protein A-Sepharose resins for 2 h, briefly centrifuged, and washed sequentially with the wash buffer (0.1% SDS, 1% Triton X-100, 2 mM EDTA, 150mMNaCl, 20mMTris-HCl, pH 8.0) and the final wash buffer (0.1% SDS, 1% Triton X-100, 2 mM EDTA, pH 8.0, 500 mM NaCl, 20 mM Tris-HCl, pH 8.0). Immunocomplexes were eluted, and the crosslinks were reversed in the elution buffer (1% SDS, 0.1 M NaHCO3) at 65 °C. Purified DNA was quantified by real-time qPCR using beta-actin as a control. The sequences of the primers used for ChIP assays are listed in Table 5.

TABLE 5.

Primer	Orientation	Position Relative to ATG	Sequence (5'-3')	SEQ. ID NO.
Human FoxA2	Forward	+ 4000	TCAGTGCCAAGTAGACAAAT	219
Human FoxA2	Reverse	+ 4000	TACGAAATTAACAGGATGTG	220
Human FoxA2	Forward	+ 2000	CCAGGTCTCGGGTCCGATTA	221
Human FoxA2	Reverse	+ 2000	CCCTCCCTCCTTCTTGAAAT	222
Human FoxA2	Forward	+ 1500	GGTGTACTCCCGGCCCATTA	223
Human FoxA2	Reverse	+ 1500	ATTTCTTCTCCCTTGCGTCT	224
Human FoxA2	Forward	0 (-1000)	CCGCCCACTTCCAACTACCG	225
Human FoxA2	Reverse	0 (-890)	GTCAGCCAAAGCACCGTCCC	226
Human FoxA2	Forward	-2000	TTTCAAGTCTGCGGTCATCC	227
Human FoxA2	Reverse	-2000	CAGCAACATCAGTGCCCTTT	228
Human FoxA2	Forward	-4000	CAACCTTCGGCACAACGATC	229
Human FoxA2	Reverse	-4000	GAAGCCACCATACAAACTGA	230
Human FoxA2	Forward	-6000	CAAGCCTCACATTTGAACCC	231
Human FoxA2	Reverse	-6000	CTGCGGAACCACTGACCACC	232
Mouse FoxA2	Forward	+ 4000	AACGCTGGCCGTCTGTATTG	233
Mouse FoxA2	Reverse	+ 4000	GCCTATGGACTCTGCCCTTC	234
Mouse FoxA2	Forward	+ 2000	AGGCTGAGTGGAGACTTTGG	235
Mouse FoxA2	Reverse	+ 2000	ATTTCCATTCCCTTCCCTAT	236

Primer	Orientation	Position Relative to ATG	Sequence (5'-3')	SEQ. ID NO.
Mouse FoxA2	Forward	+ 1500	GGACCTCTTCCCTTTCTACC	237
Mouse FoxA2	Reverse	+ 1500	GTCTTCTTGCCTCCGCTACT	238
Mouse FoxA2	Forward	0 (-900)	CCCACTCCCAGCTACTTCCC	239
Mouse FoxA2	Reverse	0 (-650)	CAGCCACAACAAACGACCAG	240
Mouse FoxA2	Forward	-2000	GCTCCAATGCTTACTCCTCT	241
Mouse FoxA2	Reverse	-2000	TTCTCCCACAAATTCAAGGT	242
Mouse FoxA2	Forward	-4000	CCCCATAGACAAGTGTTTCG	243
Mouse FoxA2	Reverse	-4000	TTCTTCCAGCCTTCCCTAAT	244
Mouse FoxA2	Forward	-6000	ATGGCTTTGCCTATTTGTCC	245
Mouse FoxA2	Reverse	-6000	GGTTTCCTGGCTGATGCTTA	246
Human Sox2	Forward	+ 4000	TTCTCCTGCCTCAGCCTCCT	247
Human Sox2	Reverse	+ 4000	GCCTATAATTCCAGCACTTT	248
Human Sox2	Forward	+ 2000	TGCTTCCTCCCTACTGTCTG	249
Human Sox2	Reverse	+ 2000	CTCACCGCAACCTCCATCTC	250
Human Sox2	Forward	+ 1000	CATCACCCACAGCAAATGAC	251
Human Sox2	Reverse	+ 1000	TTCCTGCAAAGCTCCTACCG	252
Human Sox2	Forward	0 (-400)	CAGGAGTTGTCAAGGCAGAG	253
Human Sox2	Reverse	0 (-400)	GGAAAATCAGGCGAAGAATA	254
Human Sox2	Forward	-1000	TTTGGGTCTCCTAACTTCTA	255
Human Sox2	Reverse	-1000	GTCATTGTTCTCCCGCTCAT	256
Human Sox2	Forward	-2000	GCATTCCGTTGGCTATTCTC	257
Human Sox2	Reverse	-2000	GATGTGCTTTGTTTAGTGGG	258
Human Sox2	Forward	-4000	AATACTGGTGGTCGTCAAAC	259
Human Sox2	Reverse	-4000	TGAGAACTAGCCAAGCATCT	260
Mouse Sox2	Forward	-4000	GGGCATAGACAAACAGAACC	261
Mouse Sox2	Reverse	-4000	ACCACAACCATAGCAGGAAT	262
Mouse Sox2	Forward	-2000	TCCAAGTCGCTGCCTTTATT	263
Mouse Sox2	Reverse	-2000	TTCCGTTTCCTCCACTCTGT	264
Mouse Sox2	Forward	-1000	GTGCTGGCGACAAGGTTGGA	265
Mouse Sox2	Reverse	-1000	ATGGGTGGTTCAGGGCGACT	266

Primer	Orientation	Position Relative to ATG	Sequence (5'-3')	SEQ. ID NO.
Mouse Sox2	Forward	0 (-300)	AAGACTAGGGCTGGGAGAAA	267
Mouse Sox2	Reverse	0 (-300)	ATCTGGCGGAGAATAGTTGG	268
Mouse Sox2	Forward	+ 1000	CTGGACTGCGAACTGGAGAA	269
Mouse Sox2	Reverse	+ 1000	ATTTGGATGGGATTGGTGGT	270
Mouse Sox2	Forward	+ 2000	GGACATTTGGCTACTTAGAG	271
Mouse Sox2	Reverse	+ 2000	GAAGATATTGAAACAGGGAC	272
Mouse Sox2	Forward	+ 4000	TCCCAACGAGAAGAGTATGA	273
Mouse Sox2	Reverse	+ 4000	AGAGCAGTGACGGGAACAGA	274
Human Oct4	Forward	-1000	TGTGCTTATGGCTGTTGATG	275
Human Oct4	Reverse	-1000	CCACTGTGCCCTGTTAGTTT	276
Human Oct4	Forward	-2000	GCATTCCGTTGGCTATTCTC	277
Human Oct4	Reverse	-2000	GATGTGCTTTGTTTAGTGGG	278
Human Oct4	Forward	-4000	GGATGTACGGCAGCTTGATA	279
Human Oct4	Reverse	-4000	GCTGGACACTGGAGGATAGA	280
Human Oct4	Forward	0 (-100)	GCCACCACCATTAGGCAAAC	281
Human Oct4	Reverse	0 (-100)	GCGAAGGGACTACTCAACCC	282
Human Oct4	Forward	+ 1000	AGAAAGCGAACCAGTATCGA	283
Human Oct4	Reverse	+ 1000	GCGCCGGTTACAGAACCACA	284
Human Oct4	Forward	+ 2000	TGCTTCCTCCCTACTGTCTG	285
Human Oct4	Reverse	+ 2000	CTCACCGCAACCTCCATCTC	286
Human Oct4	Forward	+ 4000	TTCTCCTGCCTCAGCCTCCT	287
Human Oct4	Reverse	+ 4000	GCCTATAATTCCAGCACTTT	288
Mouse Oct4	Forward	-1000	AGGCACTCTGAGGGCTATTC	289
Mouse Oct4	Reverse	-1000	GACACTAAGGAGACGGGATT	290
Mouse Oct4	Forward	-2000	TCCAAGTCGCTGCCTTTATT	291
Mouse Oct4	Reverse	-2000	TTCCGTTTCCTCCACTCTGT	292
Mouse Oct4	Forward	-4000	GCAGAAGGTCAGGTCCACTC	293
Mouse Oct4	Reverse	-4000	CATTCAAGATAACCAGCCAC	294
Mouse Oct4	Forward	0 (-100)	GGTCCCGTCCTAAGGGTTGT	295
Mouse Oct4	Reverse	0 (-100)	TGGGTGGGTGGAGGAGCAGA	296

Primer	Orientation	Position Relative to ATG	Sequence (5'-3')	SEQ. ID NO.
Mouse Oct4	Forward	+ 1000	TCCCAACGAGAAGAGTATGA	297
Mouse Oct4	Reverse	+ 1000	CCAGAGCAGTGACGGGAACA	298
Mouse Oct4	Forward	+ 2000	GGACATTTGGCTACTTAGAG	299
Mouse Oct4	Reverse	+ 2000	GAAGATATTGAAACAGGGAC	300
Mouse Oct4	Forward	+ 4000	TCCCAACGAGAAGAGTATGA	301
Mouse Oct4	Reverse	+ 4000	AGAGCAGTGACGGGAACAGA	302

e. Statistical Analyses

[00530] Statistical analysis was performed using the GraphPad Prism v4.0 software as described previously (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). Data are presented as mean ± SD. One-way ANOVA was used for comparisons.

f. RNA Extraction, Reverse Transcription, and Quantitative Real-Time RT-PCR/PCR

[00531] Total RNA was extracted using TRIZOL reagent (TaKaRa) and complementary DNA was generated according to instructions in the PrimeScript 1st strand cDNA Synthesis Kit (TaKaRa) as described previously (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). The cDNAs were diluted to 1/20 and 1 μL of each diluted sample was used as template for each sample. Real-time quantitative PCR was performed on an ABI Prism 7300 sequence detection system (Applied Biosystems) using SYBR Green (TaKaRa) according to the manufacturer's instructions. PCR amplification of the housekeeping gene *β-Actin* was performed as a control. Experiments for specific silencing or induction of gene expression were repeated at least three times. The real-time PCR primers of human genes are described in Table 3 above.

[00532] Alternatively, total RNA was extracted with the TRIzol reagent (Invitrogen), and cDNA was generated using a cloned avian myeloblastosis virus first-strand cDNA synthesis kit (TaKaRa). The mRNA levels of the target genes were quantified by realtime PCR using SYBR green (TaKaRa) in an ABI Prism 7300 real-time PCR system (Applied Biosystems). The sequences of the oligonucleotide primers used for quantitative PCR (qPCR) are listed in Table 6.

TABLE 6.

Primer Name	Orientation	Sequence (5'-3')	SEQ. ID NO.
Mouse Sox2	Forward	GTGAGCGCCCTGCAGTACAA	303
Mouse Sox2	Reverse	GCGAGTAGGACATGCTGTAGGTG	304
Human Sox2	Forward	GTGAGCGCCCTGCAGTACAA	305
Human Sox2	Reverse	GCGAGTAGGACATGCTGTAGGTG	306
Mouse Oct4	Forward	GATCACTCACATCGCCAATC	307
Mouse Oct4	Reverse	GGTGTCCCTGTAGCCTCATA	308
Human Oct4	Forward	TGAAGCTGGAGAAGGAGAAGCTG	309
Human Oct4	Reverse	GCAGATGGTCGTTTGGCTGA	310
Mouse HDAC1	Forward	TTGCTCGCTGCTGGACTTAC	311
Mouse HDAC1	Reverse	TGGCTTCTCCTCCTTGGTTT	312
Human HDAC1	Forward	GGGATCGGTTAGGTTGCTTC	313
Human HDAC1	Reverse	TTGTCAGGGTCGTCTTCGTC	314
Mouse HDAC2	Forward	GGACAGGCTTGGTTGTTTCA	315
Mouse HDAC2	Reverse	ATTCCTACGACCTCCTTCAC	316
Human HDAC2	Forward	AAGGCAAATACTATGCTGTC	317
Human HDAC2	Reverse	TTGGGAATCTCACAATCAAG	318
Mouse HDAC3	Forward	CCGAAATGTTGCCCGGTGTT	319
Mouse HDAC3	Reverse	GGGTGCTTCTGGCCTGCTGT	320
Human	Forward	GCACCATGCCAAGAAGTTTG	321

Primer Name	Orientation	Sequence (5'-3')	SEQ. ID NO.
HDAC3			
Human HDAC3	Reverse	CACCACCCAGCACGAGTAGA	322
Mouse HDAC6	Forward	AACCGCACTGGGCTGGTCTA	323
Mouse HDAC6	Reverse	TCAAAGTTGGCACCTTCACG	324
Human HDAC6	Forward	CAGCGAAGAAGTAGGCAGAA	325
Human HDAC6	Reverse	GCTGTCATCCCAGAGGCAAT	326
Mouse Sirt1	Forward	GGGAACCTTTGCCTCATCTA	327
Mouse Sirt1	Reverse	TACTGGAACCAACAGCCTTA	328
Human Sirt1	Forward	TCCTCATTGTTATTGGGTCT	329
Human Sirt1	Reverse	ATTACTCTTAGCTGCTTGGT	330
Mouse LSD1	Forward	TCTTATCAACTTCGGCATCT	331
Mouse LSD1	Reverse	TAGCAACTCGTCCACCTACT	332
Human LSD1	Forward	AGCGTCATGGTCTTATCAA	333
Human LSD1	Reverse	GAAATGTGGCAACTCGTC	334
Mouse HNF4A	Forward	GATGCTTCTCGGAGGGTCTG	335
Mouse HNF4A	Reverse	GCTGTGGAGTCTCGGGAGTG	336
Human HNF4A	Forward	AGCTGCAGATCGATGACAATGAG	337
Human HNF4A	Reverse	CATACTGGCGGTCGTTGATGTAG	338
Mouse FoxA2	Forward	AGAACTCCATCCGCCACTCT	339
Mouse	Reverse	GGTCTTCTTGCCTCCGCTAC	340

Primer Name	Orientation	Sequence (5'-3')	SEQ. ID NO.
FoxA2			
Human FoxA2	Forward	CCCCAACAAGATGCTGACGC	341
Human FoxA2	Reverse	GCGAGTGGCGGATGGAGTT	342
Mouse Sox17	Forward	GGGATACGCCAGTGACGACC	343
Mouse Sox17	Reverse	CCACCTCGCCTTTCACCTTT	344
Human Sox17	Forward	CTGCAGGCCAGAAGCAGTGTTA	345
Human Sox17	Reverse	CCCAAACTGTTCAAGTGGCAGA	346
Mouse BMP2	Forward	TGTGAGGATTAGCAGGTCTT	347
Mouse BMP2	Reverse	GTCCACATACAAAGGGTGTC	348
Human BMP2	Forward	ACAGCGGAAACGCCTTAA	349
Human BMP2	Reverse	GGGAGCCACAATCCAGTC	350
Human beta-Actin	Reverse	GAAGGTGGACAGTGAGGCCAGGAT	351
Mouse EOMES	Forward	CCCAACAGAGCGAAGAGGTG	352
Mouse EOMES	Reverse	GAAGGTCGGGTCAGGGTAAT	353
Human EOMES	Forward	CCCAGACCCAACCTTTCC	354
Human EOMES	Reverse	GAGCCAATTTCCTCTTTCACTT	355
Human beta-Actin	Forward	TCCAGCCTTCCTTCTTGGGTATG	356
Mouse beta-Actin	Forward	TGCGTGACATCAAAGAGAAG	357
Mouse beta-	Reverse	GATGCCACAGGATTCCATA	358

Primer Name	Orientation	Sequence (5'-3')	SEQ. ID NO.
Actin			
Human Hes1	Forward	ATAGCTCGCGGCATTCCAAG	359
Human Hes1	Reverse	GAAGCGGGTCACCTCGTTCA	360
Human DLL1	Forward	ACAGCAAGCGTGACACCAAG	361
Human DLL1	Reverse	TGAAGTTGAACAGCCCGAGT	362
Human Gadd45g	Forward	ACGCTGATCCAGGCTTTCTG	363
Human Gadd45g	Reverse	AACAGGCTGAGCTTCTCCAA	364
Mouse Hes1	Forward	GACGGCCAATTTGCCTTTCTCATC	365
Mouse Hes1	Reverse	TCAGTTCCGCCACGGTCTCCACA	366
Mouse DLL1	Forward	CAGATAACCCTGACGGAGGCTACA	367
Mouse DLL1	Reverse	GGAGGAGGCACAGTCATCCACATT	368
Mouse Gadd45g	Forward	CGTCTACGAGTCCGCCAAAGTCC	369
Mouse Gadd45g	Reverse	CAGAACGCCTGAATCAACGTGAAAT	370
Human Tip60	Forward	GATGGAATACCGTCAGCACC	371
Human Tip60	Reverse	TGAGGCAGAACTCGCACAGG	372
Mouse Tip60	Forward	GTGAAACGGAAGGTGGAGGT	373
Mouse Tip60	Reverse	CCAGTCATTCGTGGTGCTGA	374

g. Cell Cycle Analysis, Viability, Synchronization, and Differentiation

[00533] The fluorescence-activated cell sorting (FACS) and 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assays were conducted as described previously (Lan, R., et al. (2012) *Lab. Invest.* **92**, 1503-1514). To synchronize PA-1 and F9 cells at the G_1/S phase transition, cells were treated with 2.5 mM thymidine for 12 h, released into fresh medium for 6 h, and blocked again with 2.5 mM thymidine for an additional 12 h. The cell

cycle arrest was analyzed by FACS. For differentiation, F9 and PA-1 cells were seeded in 6-well plates at a density of 1 x 10^4 cells per well and supplemented with 5 μM RA for 3 days. Cells were then recultured in fresh medium without RA for another 2 days, and the cell cycle was analyzed on a BD FACSCalibur cell sorter using the CellQuest program (Becton, Dickinson, Mountain View, CA). The percentages of cells in G_1, S, and G_2/M phases were determined by the use of ModFit LT software.

[00534] Alternatively, cell viability assays were conducted as previously described (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). For the MTT assay, cells were seeded onto 96-well culture plates with a density of 2000-5000 cells/well, and incubated with CBB1003 or CBB1007 at various concentrations from 1 to 100 μM for 30-48 hours, depending cell growth rate. Dimethylsulfoxide (DMSO) was used as a solvent control. MTT was added to a final concentration of 0.5 mg/mL and cells were re-incubated for 4 hours. After removing the medium, 200 μL DMSO was added to dissolve formazan, followed by incubation for 10 minutes, and absorbance was measured at 490 nm by a Bio Red microplate reader. All assays were performed in triplicates for each concentration. The cell viability rate was calculated as the relative percentage of MTT absorption as follows: % cell viability = (mean experimental absorbance/mean control absorbance) × 100.

h. Peptide and Recombinant Proteins

[00535] H3K4me2 and H4K16ac were purchased from AnaSpec and Shanghai Science Peptide Biological Technology Co., Ltd., respectively. Human LSD1 and HDAC1 full-length cDNAs were obtained from Open Biosystems. Human CoREST cDNA was amplified by reverse transcription-PCR (RT-PCR) using mRNA isolated from HeLa cells. These cDNAs were fully sequenced and cloned into the pGEX-KG or pET28a vector and expressed as the glutathione *S*-transferase (GST)- or His-tagged fusion proteins in the *Escherichia coli* BL21 strain and affinity purified with glutathione or Ni-Sepharose (GE Healthcare, United Kingdom) resin. The GST tag of purified protein GSTHDAC1 or GST-LSD1 was removed by the use of PreScission protease at 4 °C for 16 h in the digestion buffer (20 mM Tris-HCl, pH 7.4, 200 mM NaCl, 1 mM dithiothreitol [DTT], protease and phosphatase inhibitors). The GST tag and uncut GST-HDAC1/GST-LSD1 proteins were depleted by glutathione-Sepharose. For the reconstitution reaction, recombinant GST-CoREST, His-LSD1, and recombinant HDAC1 (rHDAC1) (GST was removed by the use of PreScission protease) (10 μg) were assembled into the LSD1-CoREST-HDAC1 complex and then pulled down by GSTSepharose resins. Protein A-Sepharose was used as a negative-control resin.

i. PREPARATION OF NUCLEOSOMES

[00536] Nucleosomes were purified according to previously described procedures (Shi, Y. J., et al. (2005) *Mol. Cell* **19**, 857-864). Briefly, cells (1 x 10^6) were washed twice with ice-cold hypotonic buffer (20 mM potassium-HEPES, pH 7.8, 5 mM potassium acetate, 0.5 mM $MgCl_2$, 0.5 mM DTT), swelled, and disrupted with 25 strokes in a Dounce homogenizer using a tightfitting pestle. Nuclei were pelleted at 4,000 rpm for 5 min and resuspended in buffer A (20 mM HEPES, pH 7.9, 1.5 mM magnesium acetate, 50 mM potassium acetate, 10% glycerol, 0.5 mM DTT, 150 mM NaCl, protease and phosphatase inhibitors). After incubation on ice for 15 min, the nuclei were centrifuged for 10 min at 10,000 rpm. The chromatin pellet was resuspended in 0.5 mL buffer B (0.32 M sucrose, 50 mM Tris-HCl, pH 7.5, 4 mM MgCl2, 1 mM $CaCl_2$, 0.1 mM phenylmethylsulfonyl fluoride) and incubated with 30 units of micrococcal nuclease for 10 min at 37 °C. The digested samples were centrifuged at 8,000 x *g* for 10 min, and the supernatant, which contained oligonucleosomes, was recovered.

j. *IN VITRO* DEACETYLATION AND DEMETHYLATION ASSAYS

[00537] For a typical deacetylation assay, 1 μg rHDAC1 or 1 μg immunoprecipitated endogenous HDAC1-protein A complexes (from two 10-cm dishes) was incubated with 0.4 μg H4K16ac peptide in the presence or absence of 50 μM CBB1007 or 2 μM MS-275 at 30 °C for 1 h. The percentages of deacetylated products were analyzed by mass spectrometry, and the data were analyzed by GraphPad Prism (version 5) software. The reaction products were analyzed by mass spectrometry to separate the peptide substrate (H4K16ac) and the product (H4K16), as previously described (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). For a typical demethylation assay, 0.4 μg H3K4me2 substrate peptide was incubated individually with 1 μg recombinant LSD1 (rLSD1) or 1 μg immunoprecipitated LSD1-protein A complex in the presence or absence of 50 μM CBB1007 or 2 μM MS-275 at 30 °C for 1 h. The reaction products were analyzed by mass spectrometry to separate the products (H3K4me1 and H3K4) from the substrate (H3K4me2), as previously described (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249).

[00538] For reactions with nucleosomes, 2 μg nucleosomes was incubated with 1 μg rLSD1, rHDAC1, or the recombinant CoREST-LSD1-HDAC1 complex in the presence or absence of 50 μM CBB1007 or 2 μM MS-275 at 30 °C for 45 min. The reaction products (demethylated or deacetylated histones) were analyzed by Western blotting.

k. REEXPRESSION AND siRNA RESCUES

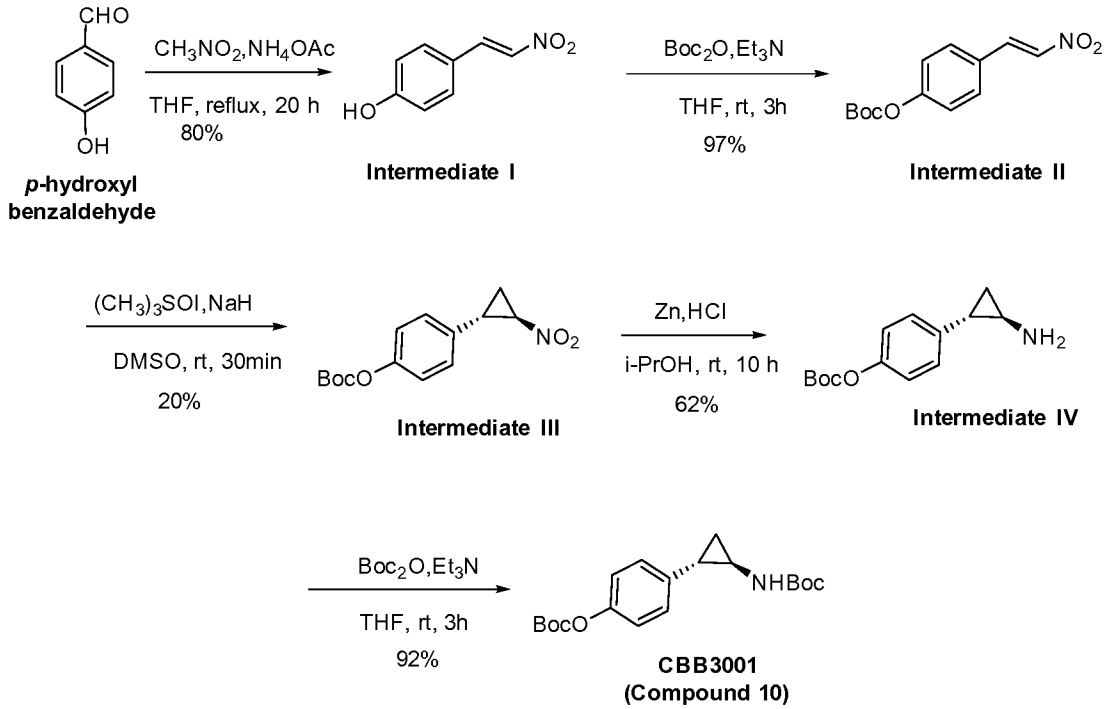
[00539] Wild-type pCMV10-3Flag-LSD1, pCMV10-3Flag-HDAC1, and pCMV10-3Flag-MOF plasmids were constructed by fusing the full-length cDNAs of human LSD1, HDAC1, or MOF with the Flag tag in the pCMV10-3Flag vector (Clontech). F9 and PA-1 cells were transfected with LSD1, HDAC1, and MOF siRNAs for the untranslated regions (UTRs) first by use of the DharmaFECT transfection reagent to silence the endogenous LSD1, HDAC1, and MOF proteins. Twenty-four hours later, these cells were transfected with 5 μg of each recombinant plasmid by use of Lipofectamine LTX and PLUS reagent (Invitrogen) for 24 to 36 h, and cells were harvested and analyzed. The green fluorescent protein (GFP) expression control vector was used in parallel to estimate the transfection efficiency in each experiment, which was about 50 to 60% of total cells. The efficacy of siRNAs and the expression of exogenous proteins were further confirmed by Western blotting or qPCR.

l. IMMUNOBLOTTING AND QUANTIFICATION

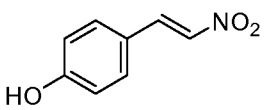
[00540] To quantify and compare the protein band densities in the Western blots shown in the figures, a titration by serial dilution of the siRNA protein samples for mES cell lysates was used as a reference. The concentration of titration samples was measured by use of a NanoDrop 2000 apparatus, and the protein concentration of all titration samples was adjusted to 1 μg/μL. The protein samples were loaded onto an SDS-polyacrylamide gel at levels ranging from 1 μg to 13 μg at 2-μg intervals and immune blotted with each antibody, including anti-LSD1, anti-HDAC1, and anti-histone H3 antibodies, with three independent loadings. The Western blots were developed with exposure times ranging from 30 s to 1 min. The exposure density of each band was scanned by Adobe Photoshop Elements (version 4.0) software using a CanonScan 8600F scanner (Canon, CA) and was subsequently quantified by use of the area density tool of Gel-Pro Analyzer (version 4.0) software (Media Cybernetics, Inc.) and plotted. The regression analysis of each signal was performed by use of the Microsoft Excel program's Analysis Tool Pak regression option. The titration data showed that the association between the amount of proteins loaded and protein band intensities after Western blotting was statistically significant and all of the values used for quantification fell within the linear range. Using the titration plots as references, all of the samples for the Western blots shown in the figures were loaded with 5 μg to 7 μg total proteins, and the exposure time was from 30 s to 3 min. The amount of the protein band in the Western blot shown in the figures was quantified by scanning, as described for the reference titration. The

band density of each protein in various samples was internally corrected by the use of loading controls, such as histone H3, which is assumed to be constant in each sample. The quantity of protein band densities between two protein samples was externally corrected by use of the reference plots. The internally and externally corrected protein band intensities were compared between duplicate or triplicate samples tested in parallel or independently and plotted. The statistical differences between the experimental and control groups were analyzed by one-way analysis of variance (ANOVA). All Western blotting results are representative of those from at least three independent experiments.

2. **PREPARATION OF TERT-BUTYL ((1R,2S)-2-(4-((TERT-BUTOXYCARBONYL)OXY)PHENYL)CYCLOPROPYL)CARBAMATE (CBB3001; COMPOUND 10)**



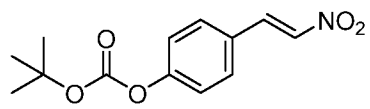
a. **SYNTHESIS OF (*E*)-1-HYDROXY-4-(2-NITROVINYL)BENZENE**



[00541] A mixture of *p*-hydroxyl benzaldehyde (2.5 g, 20 mmol) and NH_4OAc (2.0 g, 26 mmol) in dry THF (30 mL) and CH_3NO_2 was refluxed for 20 h, and the solvent was removed. Then the resulting was pour into water (30 mL), and extracted with EtOAc (25 mL ×3), the organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and

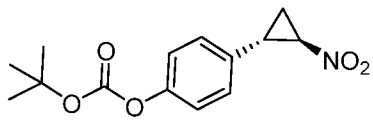
concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc 3/1) affording (*E*)-1-hydroxy-4- (2-nitrovinyl)benzene as a yellow solid (2.10 g, 80%).

b. SYNTHESIS OF (*E*)-TERT-BUTYL (4-(2-NITROVINYL)PHENYL) CARBONATE



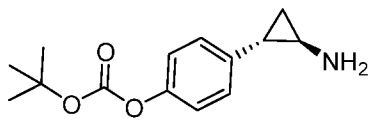
[00542] Boc_2O (3 mL, 20.2 mmol) was added to a solution of (*E*)-1-hydroxy -4-(2-nitrovinyl)benzene (1.7 g, 10.1 mmol) and NEt_3 (3 mL, 20.1 mmol) in THF (50 mL) and stirred for 3 h at rt.. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes/EtOAc 5/1) affording (*E*)-tert-butyl (4-(2-nitrovinyl) phenyl) carbonate as a yellow solid (2.68 g, 97%).

c. SYNTHESIS OF *TERT*-BUTYL (4-((TRANS)-2-NITROCYCLOPROPYL)PHENYL) CARBONATE



[00543] Trimethylsulfoxonium iodide (297 mg, 1.61 mmol) was added in small portions to a suspension of NaH (0.07 g, 1.61 mmol) in dry DMSO (5 mL). The mixture was stirred until gas evolution ceased and a clear solution was formed (45 min). Then a solution of (*E*)-tert-butyl (4-(2-nitrovinyl)phenyl) carbonate (312 mg, 1.52 mmol) in DMSO (2 mL) was transferred via cannula and the reaction was stirred for 30 min in an ice-bath. The mixture was poured into water (15 mL), and extracted with Et_2O (20 mL ×3).The organic layers were washed with brine (20 mL), dried and concentration. Then the residue was purified by column chromatography on silica gel (hexanes/EtOAc 10/1) affording *tert*-butyl (4-((trans)-2- nitrocyclopropyl)phenyl) carbonate as a white solid (62 mg, 20%).

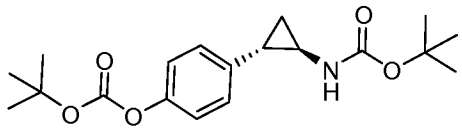
d. SYNTHESIS OF 4-((TRANS)-2-AMINOCYCLOPROPYL)PHENYL TERT-BUTYL CARBONATE



[00544] Zn dust (260 mg, 4 mmol) was added in small portions, over a period of 20 min, to a vigorously stirred solution of *tert*-butyl (4-((trans)-2-nitrocyclopropyl)phenyl) carbonate

(110 mg, 0.4 mmol) in *i*-PrOH (10 mL) and HCl (2 mL of 2 N aqueous solution, 4 mmol). After 10 h, the mixture was basified with NaOH (10% aqueous solution, 15 mL) and filtered through a pad of Celite. The mixture was extracted with EtOAc (20 mL ×3), the organic layers were dried and concentrated. Then the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 50:1) affording 4-((*trans*)-2-aminocyclopropyl) phenyl *tert*-butyl carbonate as a white solid (70 mg, 62%).

e. Synthesis of tert-butyl ((1R,2S)-2-(4-((tert-butoxycarbonyl)oxy)phenyl)cyclopropyl)carbamate (CBB3001)



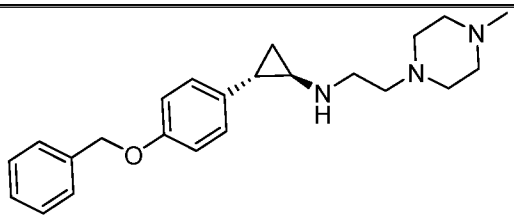
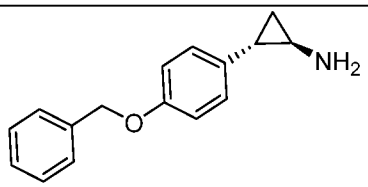
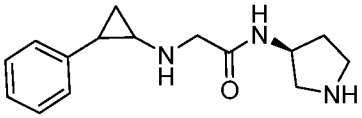
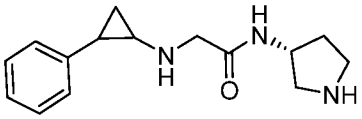
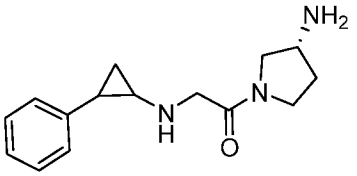
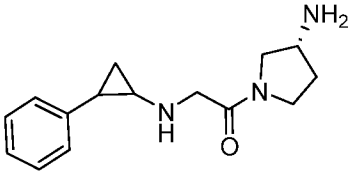
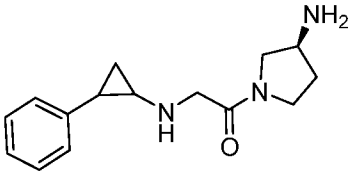
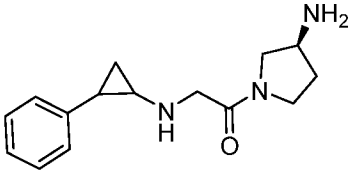
[00545] Boc_2O (0.15 mL, 1 mmol) was added to a solution of (*E*)-1-hydroxy -4-(2-nitrovinyl)benzene (125 mg, 0.5 mmol) and Et_3N (0.15 mL, 1 mmol) in THF (20 mL) and stirred for 3 h at rt. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes/EtOAc 15/1) affording a white solid (165 mg, 92%). ^{1}H-NMR ($CDCl_3$) δ (ppm) 7.14 (d, 2H), 7.05 (d, 2H), 4.84 (br, 1H), 2.69 (br, 1H), 2.01-2.05 (m, 1H), 1.55 (s, 9H), 1.45 (s, 9H), 1.13-1.26 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ (ppm) 155.6 (s), 151.9 (s), 149.3 (s), 138.2 (s), 127.5 (d×2), 121.0 (d ×2), 83.3 (s), 29.6 (d), 28.3 (q),28.0 (d) , 27.6 (q), 16.1 (t). HR-MS $[M+Na]^+$ 372.1780. (See FIG. 1A-1D).

3. Evaluation of Exemplary Compounds

[00546] Table 7 below lists specific compounds and LSD1 activity determined in a cell-based assay as described herein (see also FIG. 2A and 2B).

Table 7.

Compound No.	UNLV No.	Structure	LSD1 IC_{50} (μM)
1	-		33.15

Compound No.	UNLV No.	Structure	LSD1 IC_{50} (μM)
2	CBB3002		31.38
3	CBB3003		39.38
4	-		
5	-		
6	-		
7	-		
8	-		
9	-		

Compound No.	UNLV No.	Structure	LSD1 IC_{50} (μM)
10	CBB3001		21.25
11	-		
12	-		
13	-		

[00547] Table 8 below lists activity of CBB3001 (compound 10) in Sox2-negative (ES-2) and Sox2-expressing (PA-1 and T47D) cancer cells determined in a cell-based assay as described herein (see also FIG. 3A-C).

TABLE 8.

Compound No.	Cell Type	IC_{50} (μM)
10	ES-2	309.9
10	PA-1	15.16
10	T47D	22.1

4. LSD1 EXPRESSION IS ELEVATED IN HUMAN LUNG SCCS THAT OVEREXPRESS SOX2

[00548] Previous studies indicated that germ cell tumors such as teratocarcinomas and embryonic carcinoma cells expressed elevated levels of LSD1. They were also highly sensitive to the LSD1-specific inhibitors that noncovalently interact with LSD1 (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). Given that these cells usually express the PSC proteins Oct4, Sox2, and Lin28, which are also expressed in other human cancers (Leis, O., et al. (2012) *Oncogene* **31**, 1354-1365; Peng, S., et al. (2008) *Oncogene* **29**, 2153-2159; Zhong, X., et al. (2010) *J. Biol. Chem.* **285**, 41961-41971), LSD1 was examined in various human

cancer tissues that also co-express some of the PSC markers (only de-identified samples were used, which were acquired with the approval of the Ethics Committee of the First Affiliated Hospital, Shihezi University School of Medicine). In 13 independent cases of human lung SCC, highly elevated levels of Sox2 and LSD1 were observed in five poorly differentiated cases, moderate Sox2 and LSD1 increases in seven moderately differentiated cancer cases, and low LSD1 expression in a single Sox2-negative and moderately differentiated cancer (FIG. 4A and 4B; and Table 9). Statistical analysis revealed a significant correlation between Sox2 and LSD1 expression (Pearson's correlations: $R^2 = 0.4372$ and $p = 0.014$). In contrast, Sox2 expression was low or non-detectable in all 17 cases of lung adenocarcinoma carcinomas. In the lung adenocarcinoma samples, only two cases of poorly differentiated cancers had moderately increased levels of LSD1, and LSD1 was low in the remaining 15 moderately differentiated cancers. As a control, the surrounding normal lung tissues expressed undetectable levels of LSD1 and Sox2 proteins (FIG. 4A).

TABLE 9.

Type	Differentiation Degree	LSD1 expression	Sox2 expression	total
Lung Squamous Carcinomas (13 cases)	Poorly differentiated (5/13)	+++	+++	5
	Moderately differentiated (8/13)	+++	+++	1
		++	+++	3
		+	++	3
		+	-	1
Lung Adenocarcinoma Carcinomas (17 cases)	Poorly differentiated (2/1)	++/+++	-	2
	Moderately differentiated (15/17)	+/++	-	15

[00549] Referring to FIG. 4A, LSD1 and Sox2 expression are illustrated in lung SCCs. One example of serial tissue sections from clinical lung SCC patients (n = 13) immunostained with Sox2 or LSD1 antibodies. LSD1 and Sox2 were strongly stained in pathological tissues (right), but weakly stained or nondetectable in normal lung tissue (left) surrounding the pathological areas (scale bar = 100 μM; lower panels represent magnified images, 4x of upper panels, total magnification = 400x).

[00550] Referring to FIG. 4B, LSD1 and Sox2 expression are illustrated in human lung SCC (left panels, N = 13) and lung adenocarcinoma (right panel, N = 17) tissues. Serial

tissue sections from clinical patient samples were immunostained with anti-Sox2 or LSD1 antibodies. LSD1 and Sox2 were elevated in squamous cell carcinoma pathological tissues. Sox2 is non-detectable in all 17 adenocarcinoma cases and LSD1 is lower in lung adenocarcinoma cases (scale bar = 100 microns; lower panels represent magnified images, 4x).

[00551] Referring to FIG. 4C, statistical analysis of the correlation (Pearson's) between Sox2 an LSD1 expression in lung squamous cell carcinomas are shown.

[00552] The finding that the levels of LSD1 are significantly elevated in Sox2-expressing SCCs is consistent with previously reported studies. For example, in a search of publicly reported tumor microarray data from Oncomine (http://www.oncome.org), it was discovered that in 21 SCC cases reported by Bhattacharjee et al. (2001), Sox2 was overexpressed in 18 cases, whereas LSD1 was co-overexpressed in 16 cases. In another six small cell lung carcinoma cases with elevated LSD1, Sox2 was also over-expressed in four of them. In 17 cases of esophagus carcinomas (Hu, N., et al. (2010) *BMC Genomics* **11**, 576) with high LSD1 levels, Sox2 was overexpressed in 14 cases. The overexpression of Sox2 and LSD1 was also found in other cancers. For example, in 19 cases of large cell lung carcinomas (Hu, N., et al. (2010) *BMC Genomics* **11**, 576), 16 cases overexpressed LSD1 and 15 overexpressed Sox2. In a study of cervical SCCS (Scotto, L., et al. (2008) *Genes Chromosomes Cancer* **47**, 755-765), Sox2 was overexpressed in 50% of 84 cases and LSD1 was co-elevated in 48% of all cases. In 122 cases of ductal breast carcinomas (Sorlie, T., et al. (2003) *Proc. Natl. Acad. Sci. USA* **100**, 8418-8423), Sox2 was overexpressed in ~52% of them and LSD1 was co-overexpressed with Sox2 in ~49% of all cases. In a single undifferentiated breast carcinoma case, both Sox2 and LSD1 were overexpressed. Without wishing to be bound by theory, these data suggest that there is a significant correlation between Sox2 and LSD1 expression in a wide array of human cancers.

5. LUNG SCC CELLS THAT CONTAIN AMPLIFIED *SOX2* GENE OR OTHER LUNG CARCINOMA CELLS THAT EXPRESS SOX2 ARE PARTICULARLY SENSITIVE TO LSD1 INACTIVATION

[00553] The observation that LSD1 levels are elevated in Sox2-expressing lung SCCs prompted an investigation of the functional relationship between Sox2 and LSD1 in lung carcinomas. For this purpose, human SCC NCI-H520 cells that contain the *Sox2* gene amplification at 3q26.33, and human lung adenocarcinoma NCI-H1437 cells that do not express Sox2 were used (Bass, A. J., et al. (2009) *Nat. Genet.* **41**, 1238-1242; FIG. 5A). H520

and H1437 cells were treated with LSD1 inhibitors for 24-30 hr, and cell growth was analyzed. The LSD1 inhibitor CBB1007 was found to selectively and specifically inhibit the growth of H520 cells, but had no detectable effects on H1437 (FIG. 5B and 5C).

[00554] Referring to FIG. 5A, Sox2 and LSD1 expression are illustrated in human lung SCC NCI-H520, lung adenocarcinoma A549, and lung carcinoma NCI-H1437 and H1299 cells (CUL1 and histone H3 = loading control).

[00555] Referring to FIG. 5B, LSD1 inactivation specifically inhibited the growth of H520 and A549 cells, but not that of H1437 or H1299 cells. Actively growing lung cancer cells were treated with 50 μM LSD1 inhibitor CBB1007 for 30 hr or were transfected with 50 nM control luciferase (Luc) or LSD1 siRNAs for 60 hr. Cell growth was examined by microscopy.

[00556] Referring to FIG. 5C, the percent viability of cells treated with LSD1 inhibitors or siRNAs compared with control cells, as determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay is shown. Data are presented as mean ± SD. The statistical differences between inhibitor-treated and control groups were analyzed by one-way ANOVA (scale bar = 100 μM; **$p<0.01$).

[00557] To identify additional Sox2 or other PSC-specific gene-expression signatures in carcinoma cells, the microarray mRNA data of the Cancer Genome Anatomy Project database (http://cgap.nci.nih.gov/Microarray/GeneList) was search in 60 cancer cell lines collected by the National Cancer Institute. Using this approach, it was discovered that approximately one-third of these cancer cells express Sox2 or other PSC proteins. Treatment of A549, a Sox2-expressing human lung adenocarcinoma cell derived from adenocarcinomic alveolar basal epithelial cells, and H1299, a Sox2-negative human non-small cell lung carcinoma cell (FIG. 5A), with LSD1 inhibitors revealed that A549 cells are highly sensitive to LSD1 inhibitors, whereas H1299 cells are not (FIG. 5B and 5C). The expression of LSD1 was also ablated using specific siRNAs in both H520, H1437, A549, and H1299 cells, and these studies showed that ablation of LSD1 phenocopied the selective growth-inhibitory effects of LSD1 inhibitors on H520 and A549 cells, but not on H1437 and H1299 cells (FIG. 5B and 5C). Without wishing to be bound by theory, these data suggest that lung carcinoma cells that express Sox2 are particularly sensitive to LSD1 inactivation, whereas Sox2-negative cells are not. In addition, both Sox2-expressing H520 and A549 cells appeared to express higher levels of LSD1 (FIG. 5A).

6. Breast and Ovarian Carcinoma Cells Can Be Distinguished by their Sensitivity to LSD1 Inhibition

[00558] Although LSD1 inhibitors specifically target lung carcinoma cells that over-express Sox2, it remains unclear whether lung carcinoma cells are uniquely sensitive to LSD1 inhibition. Search of the Cancer Genome Anatomy Project database and published reports revealed that several breast and ovarian carcinoma cells may also express key pluripotent stem cell (PSC) proteins Oct4, Sox2, Lin28, Nanog, and Sall4 either alone or in combination (Leis, O., et al. (2012) *Oncogene* **31**, 1354-1365; Peng, S., et al. (2008) *Oncogene* **29**, 2153-2159; Zhong, X., et al. (2010) *J. Biol. Chem.* **285**, 41961-41971). Therefore, a panel of ovarian, breast, and other carcinoma cells were examined for their response to LSD1 inhibition (see Table 1 above). Although the growth of some cells was not inhibited by LSD1 inhibitors such as human ovarian carcinoma cells OVCAR8, Hs28.T, and ES-2, and breast carcinoma cells MDA-MB-231, BT549, and SK-BR-3, several of them were highly sensitive to LSD1 inhibitors such as ovarian carcinoma cells OVCAR3, A2780, SKOV-3, and IGROV-1; ovarian teratocarcinoma PA-1 cells; and breast carcinoma cells MDA-MB-468, T47D, and MCF-7 (FIG. 6A, 6B, 7A, 7B, and 8A-8C). The selective effects of LSD1 inhibitors were confirmed by ablation of LSD1 using LSD1 siRNAs (FIG. 9A and 9C). Analysis of the cell-cycle effects by fluorescence-activated cell sorting (FACS) revealed that loss of LSD1 induced significant G1 cell-cycle arrest in cancer cells that are sensitive to LSD1 inhibition, such as A549, T47D, and IGROV1, which was associated with decreased expression of the cell-cycle regulatory proteins c-Myc and various cyclins, whereas such an arrest was not observed in cancer cells that are not sensitive to LSD1 inhibitors, such as H1437 (FIG. 9A, 9B, and 9C).

[00559] Referring to FIG. 6A, the effects of LSD1 inhibitor CBB1007 and siRNAs on the growth of ovarian carcinoma OVCAR-8, OVCAR-3, and A2780 cells, and breast carcinoma MDA-MB-231, MDA-MB-468, and T47D cells are shown.

[00560] Referring to FIG. 6B and 6C, quantitative analyses of the sensitivity of a panel of breast, ovarian, and other human carcinoma cells to LSD1 inhibitors (6B) and LSD1 siRNA-mediated ablation (6C) are shown. The statistical differences between inhibitor-treated and control groups were analyzed by one-way ANOVA (*$p<0.05$, **$p<0.01$).

[00561] Referring to FIG. 7A, ovarian and breast cancer cells were treated with control (DMSO) or 50 μM LSD1 inhibitors CBB1003 and CBB1007 for 30 hours as indicated. Cell growth was monitored by microscopy (scale bar, 100 microns). While ovarian carcinoma Hs38.T and ES-2 and breast carcinoma BT549 and SK-BR-3 cells were not sensitive to

LSD1 inhibitors, breast carcinoma MCF7 and ovarian carcinoma IGROV-1 and SKOV-3 cells, as well as ovarian teratocarcinoma PA-1 cells were sensitive to LSD1 inhibition.

[00562] Referring to FIG. 7B, the indicated ovarian and breast cancer cells were transfected 50 nM luciferase (Luc) or LSD1 specific siRNAs for 60 hours and cell growth was monitored by microscopy and ablation efficiency by Western blotting.

[00563] Referring to FIG. 8A and 8B, ovarian A2780 and breast T47D carcinoma cells were treated with various concentrations of LSD1 inhibitors CBB1003 and CBB1007 for 30 hours as indicated. Cell growth was monitored (8A) and quantified by the MTT assay (8B). All error bars indicate mean ± SD. *: $p < 0.05$ and **: $p < 0.01$.

[00564] Referring to FIG. 8C, A2780 and T47D cells were transfected with 50 nM luciferase or LSD1 specific siRNAs for 60 hours. Cell growth inhibition was analyzed by MTT. The effects of LSD1 siRNAs on LSD1 and methylations on histone H3K4 proteins were monitored by Western blotting using specific antibodies (right). **: $p < 0.01$.

[00565] Referring to FIG. 9A, ablation of LSD1 by siRNAs induces G1 cell-cycle arrest in Sox2-expressing A549, T47D, and IGROV1 cells, but not in Sox2-negative H1437 carcinoma cells. The distributions of the cell cycle population were as follows: A549 cells, Luc siRNA: G0/G1: 54.64%, S: 28.42%, G2/M: 16.94%; and A549, LDS1 siRNA: G0/g1: 74.81%, S: 24.55%, G2/M: 0.65%. IGROV1 cells, Luc siRNA: G0/G1: 55.48%, S: 27.48%, G2/M: 17.04%; and IGROV1, LSD1 siRNA: G0/G1: 78.07%, S: 13.37%, G2/M: 8.56%. T47D cells, Luc: G0/G1: 65.87%, S: 17.91%, G2/M: 16.22%; and T47D, LSD1 siRNA: G0/G1: 76.34%, S: 11.49%, G2/M: 12.17%. H1437 cells, Luc siRNA: G0/G1: 39.53%, S: 23.30%, G2/M: 37.17%; and H1437 cells, LSD1 siRNA: G0/G1: 37.28%, S: 24.97%, G2/M: 37.75%.

[00566] Referring to FIG. 9B, the effects of LSD1 inactivation on the protein levels of c-Myc and cyclins are shown. The indicated cells were transfected with 50 nM Luc or LSD1 siRNAs, and histone methylation were analyzed.

[00567] Referring to FIG. 9C, Sox2-expressing A549, IGROV1, T47D and Sox2-negative H1437 cells were transfected with 50 nM luciferase (Luc) or LSD1 specific siRNAs for 60 hours and the cell cycle was analyzed by flow-cytometry (FACS). The Sox2-expressing cells were G1 cell cycle arrested by LSD1 inactivation but not Sox2-negative H1437 cells.

7. SOX2 IS THE ONLY PSC PROTEIN WHOSE EXPRESSION CORRELATES WITH SENSITIVITY TO LSD1 INACTIVATION IN CARCINOMA CELLS

[00568] Previous studies indicated that sensitivity to LSD1 inactivation is usually

associated with cells derived from germ cell tumors that express PSC proteins (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). As some of the breast and ovarian cancer cells in this collection were reported to express PSC proteins such as Oct4, Sox2, Lin28, Nanog, and/or Sall4 (Leis, O., et al. (2012) *Oncogene* **31**, 1354-1365; Peng, S., et al. (2008) *Oncogene* **29**, 2153-2159; Zhong, X., et al. (2010) *J. Biol. Chem.* **285**, 41961-41971), a direct correlation between the expression of these proteins and the sensitivity to LSD1 inactivation has not been established. To determine the mechanism by which various carcinoma cells are sensitive to LSD1 inactivation, the expression of known PSC proteins in the collected cell lines was analyzed and their expression correlated with the sensitivity to LSD1 inactivation, using teratocarcinoma/embryonic carcinoma F9 and NTERA-2 cells and cervical carcinoma HeLa cells as controls (FIG. 10A; see Table 1 above) (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249).

[00569] Referring to FIG. 10A, analysis of the expression of Oct4, Sox2, Nanog, Lin28, Sall4, and other proteins in lung, breast, ovarian, teratocarcinoma, embryonic carcinoma, and other carcinoma cells as indicated is shown. Cells that are sensitive to LSD1 inactivation are indicated by *. Among PSC proteins, only the expression of Sox2 correlates with the growth-inhibitory effects of LSD1 inactivation.

[00570] Several notable findings were revealed using this approach. First, it was determined that Oct4, Lin28, Sall4, and Nanog were each expressed in breast and ovarian carcinoma IGROV1, A2780, and T47D cells, and all teratocarcinoma/embryonic carcinoma F9, PA-1, and NTERA-2 cells (FIG. 10A). Not find a single cell line was found that expressed these PSC proteins independently of Sox2, suggesting the importance of Sox2. Second, Sox2 was the only PSC protein that was expressed alone and independently of other PSC proteins in SKOV-3, OVCAR-3, MCF-7, MDA-MB-361, MDA-MB-468, MDA-MB-453, NCI-H520, and A549 cells, again indicating that Sox2 is unique for these carcinoma cells. Third, and most importantly, these analyses revealed that all Sox2-expressing carcinoma cells were sensitive to LSD1 inactivation, whereas all Sox2-negative cancer cells were insensitive (FIG. 10A; Table 1). Consistently, it was also found that K562, a human myelogenous leukemia cell, and G401, a human rhabdoid-tumor-derived cell, also expressed Sox2, and both were sensitive to LSD1 inhibition, whereas MDA-MB-435S, a melanoma cell that does not express Sox2, was insensitive (FIG. 10A, 10B, and 10C; Table 1). Whereas K652 cells only express Sox2, G401 cells also express Lin28 and Sall4. Without wishing to be bound by theory, these data suggest that there is a strong correlation between Sox2 expression and sensitivity to LSD1 inactivation.

[00571] Referring to FIG. 10B, Sox2-expressing myelogenous leukemia and rhabdoid tumor cells were also sensitive to LSD1 inhibitors. The growth of human Sox2-expressing rhabdoid tumor G401 cells was inhibited after treatment of 50 μM CBB1007 or CBB1003 for 30 hours but not that of Sox2-negative melanoma MDA-MB-435s cells. The statistical differences between compound treated and control groups were analyzed by One-way ANOVA. *: $p < 0.05$ and **: $p < 0.01$.

[00572] Referring to FIG. 10C, human myelogenous leukemia K562 cells, which express Sox2, were treated with increasing concentrations of LSD1 inhibitor CBB1007 for 30 hours and relative cell viability of compound-treated and control groups was analyzed.

8. LDS1 Inactivation of LSD1 Suppresses Sox2 Expression and Increases the Mono- and Dimethylation of H3K9 and Trimethylation of H3K27 Only in Sox2-Expressing Carcinoma Cells

[00573] Analysis of the effects of LSD1 inactivation revealed that LSD1 inactivation consistently reduced the expression of Sox2 in H520, A2780, T47D (FIG. 11A and 11B), and other Sox2-expressing cancer cells (FIG. 11C). In contrast, LSD1 inactivation did not change the levels of Lin28, another PSC protein, which is often co-expressed with Sox2 in a fraction of carcinoma cells (FIG. 10A, 11A, and 11C). Without wishing to be bound by theory, these data suggest that LSD1 is required for the expression of Sox2 in these carcinoma cells.

[00574] Referring to FIG. 11A, inactivation of LSD1 by LSD1 inhibitors or siRNAs caused the downregulation of Sox2. The indicated carcinoma cells were treated with 50 mM of the LSD1 inhibitors CBB1007 and CBB1003 for 30 hr or with 50 nM of Luc or LSD1 siRNAs for 60 hr. The protein levels of LSD1, Sox2, Lin28, CUL1, and histone H3 were analyzed by western blotting.

[00575] Referring to FIG. 11B, the mRNA levels of Sox2 were analyzed by real-time quantitative RT-PCR. Data are presented as mean ± SD. **$p < 0.01$.

[00576] Referring to FIG. 11C, ovarian teratocarcinoma PA-1 cells were either treated with 50 μM CBB1007 for 30 hours, or transfected with luciferase (Luc) or LSD1 specific siRNAs for 48 hours. The protein levels of Sox2, Oct4, Lin28 and control proteins CUL1 and tublin were monitored by Western blotting analysis with specific antibodies.

[00577] As LSD1 is a histone demethylase that removes the mono- and dimethyl groups from methylated H3K4 (H3K4me1/me2) (Shi, Y., et al. (2004) *Cell* **119**, 941-953), LSD1 inactivation caused a dose dependent increase of H3K4me1/me2 in both Sox2-postive and -negative cells (FIG. 8C, 12A, and 12B), indicating that the inhibitors specifically blocked

LSD1 demethylase activity in all cancer cells.

[00578] Referring to FIG. 12A, T47D cells were treated with 50 mM CBB1007. They were subsequently harvested at various time points as indicated. The effects of the LSD1 inhibitor on H3K4, H3K9, and H3K27 methylations were examined.

[00579] Referring to FIG. 12B, the indicated cells were transfected with 50 nM Luc or LSD1 siRNAs, and histone methylations were analyzed as above.

[00580] Because LSD1 interacts with the androgen receptor to act as an H3K9-specific demethylase to remove the mono- and dimethyl groups from methylated H3K9 (H3K9me1/me2) in certain prostate cancer cells (Metzger, E., et al. (2005) *Nature*, **437**, 436-439), the effect of LSD1 inactivation on H3K9me1/me2 as well as the trimethylation of histone H3 at lysine 27 (H3K27me3), which is not a target of LSD1, was also examined. Strikingly, LSD1 inactivation induced global increases of both H3K9me1/me2 and H3K27me3 only in Sox2-expressing carcinoma cells, but not in Sox2-negative cancer cells such as H1299 or H1437 (FIG. 12A and 12B). A kinetic analysis of induction revealed that the increases of both H3K4me1/2 and H3K9me1/2 occurred early (<1 hr) and simultaneously, whereas H3K27me3 was induced much later (4–8 hr; FIG. 12A) after LSD1 inhibition, suggesting that the increases of H3K4me1/2- and H3K9me1/2 are likely a direct consequence of LSD1 inhibition, and H3K27me3 elevation may occur as a secondary event.

9. LSD1 Binds Directly to the Transcriptional Regulatory Region of *Sox2* to Regulate Bivalent H3K4 and H3K9 Methylation

[00581] Because LSD1 inactivation reduced Sox2 expression, in order to determine whether Sox2 is a direct target of LSD1, a chromatin immunoprecipitation (ChIP) assay (Whyte, W. A., et al. (2012) *Nature* **482**, 221-225) was used to determine whether LSD1 binds to the Sox2 gene. ChIP analysis revealed that LSD1 is enriched in the transcriptional regulatory region (_3.0 to _4.0 kb) of the Sox2 gene (FIG. 13A) a region that was reported to act as a distal enhancer for Sox2 expression in breast cancer cells (Leis, O., et al. (2012) *Oncogene* **31**, 1354-1365). This enrichment of LSD1 appears to be specific for Sox2, as no enrichment was observed on Lin28, Klf4, or the pericentromeric heterochromatin region (Dovey, O. M., et al. (2010) *Proc. Natl. Acad. Sci. USA* **107**, 8242-8247; FIG. 13B), which are not regulated by LSD1.

[00582] Referring to FIG. 13A, ChIP assays for the presence of LSD1, H3K4me1/2, and H3K9me2 on the Sox2 gene in A549 cells were performed. Chromatin-associated proteins were crosslinked to chromatin, sonicated (average 500–1,000 bp DNA), and

immunoprecipitated with control rabbit immunoglobulin G (IgG), LSD1, or H3K9me2 antibodies as indicated. The DNA fragments were purified and used for real-time quantitative PCR with various primers along the Sox2 promoter. Data are presented as mean ± SD. The statistical differences for increased H3K4 and H3K9 methylations along the Sox2 gene between inhibitor-treated and control groups were analyzed by one-way ANOVA. *$p < 0.05$, **$p < 0.01$.

[00583] Referring to FIG. 13B, ChIP assays for the presence of LSD1, H3K9me2, H3K4me1, and H3K4me2 on the pericentromeric heterochromatin region SAT2 and BMP2 genes after LSD1 inactivation in A549 cells. Chromatin fragments were immunoprecipitated with control rabbit IgG-, LSD1-, H3K9me2-, H3K4me1-, and H3K4me2-specific antibodies as indicated. The DNA fragments were purified and used for real-time quantitative PCR with various primers along the FOXA2 and cyclin A genes or the SAT2 and BMP2 regions. Data are presented as mean ± SD.

[00584] To determine whether LSD1 binding is associated with the demethylase activity on Sox2, the presence and changes of the characteristic H3K4me1/me2 and H3K9me1/me2 on Sox2 after LSD1 inactivation were examined. Repeated ChIP analyses in Sox2-expressng cells, such as A2780 and A549 cells, consistently revealed that H3K9me2 (ChIPgrade H3K9me1 antibodies were not good) and H3K4me1/me2 were present in the Sox2 regulatory region, and inhibition of LSD1 caused significantly increased levels of both H3K9me2 and H3K4m1/me2 on Sox2 (FIG. 13A). Reciprocal re-ChIP of H3K9me2 or H3K4me2-enriched chromatin fragments revealed that H3K9me2 and H3K4me2 coexisted on the same Sox2 regulatory fragment. Although H3K27me3 was also induced on Sox2, the major site was located farther down the gene within the coding region (+2.0; FIG. 13C). Thus, without wishing to be bound by theory, these data suggest that the Sox2 regulatory region is regulated directly by the bivalent H3K4 and H3K9 methylations by LSD1 demethylase. Sox2 downregulation after LSD1 inactivation is likely to be directly caused by increased repressive H3K9 methylations on the Sox2 gene, even though H3K4me1/2 also increased on Sox2 (see below).

[00585] Referring to FIG. 13C, Sox2-expressing lung carcinoma A549 and ovarian carcinoma A2780 cells were treated with 50 μM CBB1007 for 30 hours or transfected with luciferase or LSD1 siRNAs for 48 hours as indicated. The changes of H3K27me3 along the transcriptional regulatory regions of *Sox2, FOXA2,* and *cyclin A* genes after LSD1 inactivation were analyzed using the ChIP assays.

[00586] ChIP analysis also indicated that LSD1 also binds to the cyclin A, cyclin B, and cyclin D1 genes, and inactivation of LSD1 caused the increased levels of H3K4me1/me2, H3K9me2, and H3K27me3 on the cyclin promoters (FIG. 13C and 14). Thus, without wishing to be bound by theory, these data suggest that increased levels of H3K9me2 on the cyclin genes may also repress the expression of cyclins, which may contribute to the G1 cell-cycle arrest after LSD1 inactivation (FIG. 9A-C).

[00587] Referring to FIG. 14, ChIP assays for the presence of LSD1, H3K9me2, H3K4me1, and H3K4me2 on the *cyclin A* gene after LSD1 inactivation in A549 cells. Chromatin fragments were immunoprecipitated with control rabbit IgG-, LSD1-, H3K9me2-, H3K4me1-, and H3K4me2-specific antibodies as indicated. The DNA fragments were purified and used for real-time quantitative PCR with various primers along the FOXA2 and cyclin A genes or the SAT2 and BMP2 regions. Data are presented as mean ± SD.

10. Loss of LSD1 Suppresses Sox2-Dependent Lineage-Specific Gene Expression

[00588] In lung squamous cell carcinomas, Sox2 acts as a lineage-survival oncogene and is required for the expression of lineage-specific genes such as TP63 and KRT6A (Bass, A. J., et al. (2009) *Nat. Genet.* **41**, 1238-1242). To further analyze the functional correlation between LSD1 inhibition and Sox2 downregulation, the effects of LSD1 and Sox2 inactivation on the expression of lineage-specific TP63 and KRT6A genes in lung carcinoma cells were examined. It was found that loss of either LSD1 or Sox2 led to the downregulation of PT63 and KRT6A expression in Sox2-expressing NCI-H520 and A549 lung carcinoma cells but not in Sox2-negative H1299 lung carcinoma cells (FIG. 15A and 15B). As lineage-specific gene expression is regulated by Sox2 in Sox2-expressing lung carcinoma cells (Bass, A. J., et al. (2009) *Nat. Genet.* **41**, 1238-1242), these data suggest that LSD1 directly acts on a Sox2-dependent stem cell regulatory transcriptional program to promote the lineage-survival oncogene function of Sox2.

[00589] Referring to FIG. 15A and 15B, lineage-specific genes TP63 (15A) and KRT6A (15B) were down-regulated after the inactivation of LSD1 or Sox2. Left panels: lung carcinoma NCI-H520, A549, and H1299 cells were either treated with 50 μM CBB1003 for 30 hours or were transfected with Luc, LSD1, or Sox2 specific siRNAs for 48 hours as indicated. The mRNA levels of TP63 and KRT6A were down-regulated in Sox2-expressing H520 and A549 cells but not H1299 cells. The statistical differences between experimental and control groups were analyzed by one-way ANOVA (*: $p<0.05$ and **: $p<0.01$). Right

panels: the ablation efficiency of LSD1 and Sox2 siRNAs was examined.

11. Loss of Sox2 Phenocopies the Growth-Inhibitory Effects of LSD1 Inactivation on Carcinoma Cells

[00590] Although Sox2 acts as an amplified lineage-survival oncogene in lung SCCs (Bass, A. J., et al. (2009) *Nat. Genet.* **41**, 1238-1242), the role of Sox2 in other carcinoma cells remains largely uncharacterized. Because LSD1 inactivation reduced Sox2 expression, the role of Sox2 in regulating cancer cell growth was further investigated. Ablation of Sox2 expression using specific siRNAs consistently showed that it caused G1 cell-cycle arrest and growth inhibition in Sox2-expressing carcinoma cells that are sensitive to LSD1 inactivation, but not in Sox2-negative cancer cells (FIG. 16A-C, 17A, and 17B). Loss of Sox2 also downregulated c-Myc and cyclin A, cyclin B, and cyclin D1, and induced the expression of genes for differentiation, including FOXA2, HNF4A, BMP2, EOMES, and Sox17 (FIG. 18A and 18B). However, loss of Sox2 increased only the levels of trimethylated H3K27, and not those of H3K4 and H3K9 methylations; without wishing to be bound by theory, this may suggest that induction of H3K27 trimethylation after LSD1 inactivation might be an indirect consequence of Sox2 downregulation (FIG. 12A, 12B, and 18A). ChIP analysis revealed that Sox2 inactivation induced elevated H3K27me3 on Sox2 and cyclin promoters after Sox2 ablation, suggesting that increased H3K27me3 on these genes suppressed their expression. Thus, without wishing to be bound by theory, these data indicate that Sox2 serves as a primary and key direct target of LSD1 inactivation for growth inhibition and differentiation, because downregulation of Sox2 further amplifies and enhances the effects of LSD1 inactivation through the increased levels of H3K27me3. This observation is consistent with previous reports of critical thresholds and phenotypes associated with haploid insufficiency and hypomorphic mutations of Sox2 in animals and human diseases (Episkopou, V. (2005) *Trends Neurosci.* **28**, 219-221). Mutations of human Sox2 that compromise one allele of the Sox2 genes were shown to cause anophthalmia-esophageal-genital (AEG) syndrome and exhibited neurological phenotypes, including seizures (Fantes, J., et al. (2003) *Nat. Genet.* **33**, 461-463; Williamson, K. A., et al. (2006) *Hum. Mol. Genet.* **15**, 1413-1422), whereas hypomorphic deletion of the enhancer of the mouse Sox2 genes, which reduced Sox2 mRNA and protein levels by 20%–30% compared with wild type levels, exhibited lower birth frequency and neurological phenotypes in the mouse (Ferri, A. L., et al. (2004) *Development* **131**, 3805-3819).

[00591] Referring to FIG. 16A, A549, NCI-H1437, T47D, and IGROV1 cells were transfected with 50 nM luciferase or Sox2 siRNAs for 60 hr and the cell growth of control and Sox2-ablated cells was examined by microscopy.

[00592] Referring to FIG. 16B, cell cycles after Sox2 inactivation were analyzed by FACS. The cell-cycle distribution of cells was as follows: A549 cells, Luc siRNA: G0/G1: 54.68%, S: 30.52%, G2/M: 14.80%; and A549, Sox2 siRNA: G0/G1: 76.40%, S: 23.41%, G2/M: 0.19%. H1437 cells, Luc siRNA: G0/G1: 39.69%, S: 23.11%, G2/M: 37.20%; and H1437 cells, Sox2 siRNA: G0/G1: 39.39%, S: 25.10%, G2/M: 35.51%. IGROV1 cells, Luc siRNA: G0/G1: 57.29%, S: 27.32%, G2/M: 15.39%; IGROV1, Sox2 siRNA: G0/G1: 74.62%, S: 12.87%, G2/M: 12.52%. T47D cells, Luc: G0/G1: 66.02%, S: 17.27%, G2/M: 16.71%, T47D, Sox2 siRNA: G0/G1: 74.65%, S: 14.48%, G2/M: 10.86%.

[00593] Referring to FIG. 16C, the indicated lung, breast, ovarian, and other carcinoma cells were transfected with 50 nM luciferase or Sox2 siRNAs for 48 hr and cell growth was monitored by MTT assay. *$p < 0.05$, **$p < 0.01$.

[00594] Referring to FIG. 17A, Sox2-expressing A549, IGROV1, and T47D and Sox2-negative H1437 cells were transfected with luciferase and Sox2 specific siRNAs for 48 hours. The cell cycles of these cells after Sox2 ablation were analyzed by flow-cytometry.

[00595] Referring to FIG. 17B, ablation of Sox2 induced growth inhibition in cells that are sensitive to LSD1 inhibitors, but not in insensitive cells. Ovarian and breast cancer cells were transfected with luciferase (Luc) or Sox2 specific siRNAs for 60 hours as indicated. Cell growth was monitored by microscopy. Scale bar: 100 microns. The effects of Sox2 siRNA were analyzed by Western blotting as indicated.

[00596] Referring to FIG. 18A, the effects of Sox2 inactivation as above on c-Myc, cyclins, and methylated H3K4, H3K9, and H3K27 proteins were analyzed by western blotting.

[00597] Referring to FIG. 18B, induction of differentiation genes FOXA2, HNF4A, BMP2, EOMES, and Sox17 by Sox2 deficiency in A549, H520, A2780, and T47D cells, analyzed by western blotting and real-time quantitative RT-PCR is shown.

12. SOX2 IS INVOLVED IN MEDIATING THE GROWTH-INHIBITORY EFFECTS OF LSD1 INACTIVATION

[00598] To further determine whether reduced expression of Sox2 is responsible for the growth inhibition caused by LSD1 inactivation, Sox2 was ectopically expressed in Sox2-expressing carcinoma cells. In both Sox2-expressing ovarian A2780 and lung A549

carcinoma cells, stable and ectopic expression of Sox2 led to a significant resistance of these cells to LSD1 inhibition as compared with control cells (FIG. 19A). Co-inactivation of Sox2 and LSD1 in Sox2-expressing cancer cells by siRNAs or LSD1 inhibitors also did not reveal any additive or synergetic effects on growth inhibition induced by the loss of LSD1 or Sox2 alone (FIG. 19B and 19C), which may suggest that LSD1 and Sox2 act in the same pathway to control cell growth.

[00599] Referring to FIG. 19A, ectopic expression of Sox2 conferred resistance to LSD1 inhibitors. Human Sox2 cDNA was tagged with Flag epitope at the amino terminus and stably expressed in A2780 or A549 cells using the retroviral pMSCV vector. Control and Flag-Sox2-expressing cells were treated with various concentrations of CBB1007 for 30 hr, and cell viability was assayed and compared.

[00600] Referring to FIG. 19B, Sox2-expressing A549 carcinoma cells were separated by serial dilution into single cells. The single-cell clones were expanded and two representative clones are shown. The mRNA levels of Sox2 and LSD1 in the small and large clones were analyzed by real-time quantitative RT-PCR.

[00601] Referring to FIG. 19C, the responses of the single small and large clones of A549 carcinoma cells to various concentrations of CBB1007 were examined.

[00602] Referring to FIG. 19D, Sox2-expressing A549, T47D, or A2780 cells were treated with 50 mM CBB1007 for 30 hr and the effects on their growth were monitored and quantified.

[00603] LSD1 was shown to interact with several proteins, such as CoREST, in various cells (Shi, Y. J., et al. (2005) *Mol. Cell* **19**, 857-864). To confirm that the effects of LSD1 inactivation are mediated through its interaction with cellular proteins, the expression of CoREST was also ablated. Loss of CoREST caused the same selective growth-inhibitory effects and induction of H3K4, H3K9, and H3K27 methylations on Sox2-expressing cancer cells, but not Sox2-negative cancer cells, as LSD1 inactivation (FIG. 20A-E). It is likely that LSD1 acts through the CoREST complex to selectively regulate the growth of Sox2-expressing cancer cells, although loss of CoREST slightly reduced the level of LSD1 protein, possibly because of their *in vivo* association.

[00604] Referring to FIG. 20A-E, LSD1 binds to CoREST and loss of CoREST phenocopies the selective growth inhibition of LSD1 inactivation in Sox2-expressing cancer cells. LSD1 binds to CoREST in NCI-H520, A549, and H1299 cells (20A). The LSD1 protein complexes were immunoprecipitated from the lysates of H520, A549 and H1299 cells and the complexes were blotted with anti-LSD1 and CoREST antibodies. Ablation of

CoREST by specific siRNAs induced growth inhibition in Sox2-expressing H520 and A549 cells but not in Sox2-negative H1299 cells (20B). Indicated cells were transfected with luciferase (Luc) or CoREST specific siRNAs for 48 hours and cell growth were monitored by microscopy. Examination of ablation efficiency of CoREST and the effects of CoREST deficiency on LSD1 and Sox2 as above (20C). Quantitative analysis of cell growth inhibition in B by the MTT assay (20D). Association of CoREST and the changes of LSD1 binding and H3K4me1, H3K4me2, H3K9me2, and H3K27me3 with the transcriptional regulatory region of *Sox* in control (Luc) and CoREST ablated A549 cells by specific siRNAs were analyzed using the ChIP assays. CoREST inactivation phenocopied the effects of LSD1 inactivation on the methylations of H3K4, H3K9, and H3K27 on Sox2-expressing lung carcinoma NCI-H520 and A549 cells and Sox2-negative H1299 cells (20E).

13. Loss of LSD1 Suppresses Sox2-Dependent, Lineage-Specific Gene Expression and Reduces Sox2-Mediated Repression of Genes for Differentiation

[00605] In lung SCCs, Sox2 acts as a lineage-survival oncogene that is required for the expression of lineage-specific genes such as TP63 and KRT6A (Bass, A. J., et al. (2009) *Nat. Genet.* **41**, 1238-1242). These studies revealed that loss of either LSD1 or Sox2 led to the downregulation of TP63 and KRT6A expression in Sox2-expressing H520 and A549, but not in Sox2-negative H1299 lung carcinoma cells. Additionally, ChIP assays were used to determine whether LSD1 inactivation affects the ability of Sox2 to bind the promoters of TP63 and KRT6A. In H520 cells, Sox2 bound directly to the promoters of TP63 and KRT6A genes, and inhibition of LSD1 significantly reduced the binding of Sox2 to these lineage-specific genes.

[00606] These studies also revealed that ablation of Sox2 induced the expression of differentiation genes such as FOXA2 and Sox17 (FIG. 18B). ChIP assays indicated that Sox2 bound directly to these promoters and inactivation of LSD1 significantly decreased Sox2 binding to these promoters, suggesting that Sox2 normally acts as a repressor of these differentiation genes. Thus, without wishing to be bound by theory, these data suggest that LSD1 inactivation acts directly on a Sox2-dependent transcriptional program to reduce the lineage-survival oncogene function of Sox2 and to impair Sox2-mediated repression of differentiation genes.

14. Loss of LSD1 Induces the Expression of Genes for Differentiation by Selectively Increasing the Levels of Methylated H3K4, but not Methylated H3K9 or H3K27, on the Promoters

[00607] LSD1 inactivation in germ tumor cells or ESCs induced the expression of genes for differentiation (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). To determine whether the function of LSD1 is preserved in Sox2-expressing carcinoma cells, the effects of LSD1 inactivation on the expression of differentiation genes were analyzed. LSD1 inactivation led to the induction of differentiation genes such as FOXA2, HNF4A, BMP2, EOMES, and Sox17 only in Sox2-expressing cancer cells, and not in Sox2-negative cancer cells (FIG. 21A-D). Although loss of LSD1 caused G1 cell-cycle arrest (FIG. 9A and 9C), the induction of differentiation genes did not appear to be the consequence of LSD1 inactivation-induced G1 cell-cycle arrest, as arresting Sox2-expressing A549 cells in the G1/S border alone did not promote the induction of differentiation genes or the suppression of Sox2 expression.

[00608] Referring to FIG. 21A-C, A549, NCI-H520, H1437, A2780, and T47D cells were transfected with 50 nM luciferase or LSD1 siRNAs for 48 hr or treated with 50 mM LSD1 inhibitors CBB1003 and 1007 for 30 hr. The effects of LSD1 inactivation on the induction of FOXA2 (21A) or on various differentiation genes (FOXA2, HNF4A, BMP2, EOMES, and Sox17 [21B and 21C]) were analyzed by western blotting (21A) or real-time quantitative RT-PCR (21B and 21C).

[00609] Referring to FIG. 21D, the indicated lung, breast, ovarian, and other carcinoma cells were treated with 50 mM CBB1003 or CBB1007 for 30 hr, and induced expression of FOXA2 mRNAs was monitored, quantified, and compared between control and inhibitor-treated cells using real-time quantitative RT-PCR. *$p < 0.05$, **$p < 0.01$.

[00610] Because LSD1 inactivation promotes the primary global methylations of H3K4me1/2, H3K9me1/2, and H3K27me3 in Sox2-expressing cancer cells (FIG. 12A and 12B), and increased levels of these methylations on the promoters of Sox2 and cyclin genes (FIG. 13A, 13C, and 14A), these methylations were examined in the regulatory regions of differentiation genes. In sharp contrast to the increased H3K4, H3K9, and H3K27 methylations on the Sox2 or cyclin genes after LSD1 inactivation, LSD1 inhibition consistently increased the mono- and dimethylations of H3K4 in the regulatory regions of FOXA2, BMP2, and Sox17 genes, but not the H3K9 and H3K27 methylations in Sox2-expressing carcinoma cells (FIG. 22). Thus, without wishing to be bound by theory, these data suggest a mechanism by which LSD1 inactivation suppresses the expression of Sox2 and

cyclins by increased H3K9 and H3K27 methylations on their regulatory regions/promoters, whereas it causes the induction of differentiation genes by selectively elevating the levels of H3K4me1/me2 on differentiation genes, but not methylated H3K9 and H3K27. The effects of LSD1 inhibitors on differentiation may be enhanced by Sox2 downregulation, which de-represses Sox2-mediated suppression of differentiation genes and causes further cellular differentiation.

[00611] Referring to FIG. 22, ChIP assays for the presence of LSD1, H3K9me2, H3K4me1, and H3K4me2 in the regulatory regions of the differentiation gene FOXA2 with or without LSD1 inhibitors were performed for 30 hr.

15. LDS1 Forms a Complex with HDAC1, and Loss of HDAC1 Phenocopies the Selective Growth-Inhibitory Effects of LSD1 Inactivation in ES/EC cells

[00612] It was previously demonstrated that LSD1 inhibitors specifically block the growth of ES and EC cells and induce their differentiation but not that of nonpluripotent cells, such as HeLa, 293, or NIH 3T3 cells (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249). To investigate the mechanism by which LSD1 regulates the pluripotency of ES/EC cells, the proteins that interact with LSD1 in ES/EC cells were isolated, as LSD1 was reported to be a component of several repressor complexes (Shi, Y. J., et al. (2005) *Nature* 437, 432-435; Lee, M. G., et al. (2005) *Nature* 437, 432-435; Shi, Y., et al. (2003) *Nature* **422**, 735-738; Wang, Y., et al. (2009) *Cell* **138**, 660-672; Shi, Y. (2007) *Nat. Rev. Genet.* 8, 829-833). For this purpose, human LSD1 was epitope tagged with triple Flag and HA tags and stably expressed it in pluripotent mouse teratocarcinoma F9 cells. The LSD1 complexes were isolated by immunoprecipitation of anti-Flag and HA antibodies, and the associated proteins were identified by mass spectrometry analyses. This analysis revealed that LSD1 primarily associated with CoREST and HDAC1 in F9 cells (FIG. 27A). Independent immunocoprecipitation followed by Western blotting of LSD1 complexes confirmed that LSD1 forms a protein complex with HDAC1 and CoREST in F9 cells (FIG. 27B).

[00613] Referring to FIG. 27A, LSD1 formed a protein complex with CoREST and HDAC1. The 3XFlag/HA-tagged LSD1 protein complex was isolated by immunoprecipitation from F9 cells that stably expressed the tagged LSD1 using F9 cells as a control. LSD1, HDAC1, and CoREST were identified by mass spectrometry. Marker, molecular weight markers (in thousands).

[00614] Referring to FIG. 27B, the interactions among LSD1, HDAC1, and CoREST were confirmed by immunoprecipitation (IP), followed by Western blotting, as indicated. NRS, normal rabbit serum as a control.

[00615] To determine the significance of the association between LSD1 and HDAC1 (FIG. 27C), the expression of LSD1 or HDAC1 was ablated by the use of specific siRNAs in pluripotent mouse ES (mES) and F9 cells and nonpluripotent mouse NIH 3T3 cells (FIG. 27D and 27E). Consistent with previous findings (Wang, J., et al. (2011) *Cancer Research* **71**, 7238-7249), loss of LSD1 led to profound and selective growth inhibition only of the pluripotent mES and F9 cells (FIG. 27D and 27E), which expressed pluripotent stem cell proteins Sox2, Oct4, and Lin28 (Table 9), while LSD1 ablation had no significant effects on that of nonpluripotent NIH 3T3 cells (FIG. 27E). Notably, ablation of HDAC1 using specific siRNAs phenocopied the effects of LSD1 inactivation on the selective growth inhibition of pluripotent mES and F9 cells but not that of nonpluripotent NIH 3T3 cells (FIG. 27D and 27E). These effects were specific to the loss of LSD1 or HDAC1, as inactivation using independent siRNAs against LSD1 or HDAC1 produced the same selective effects (FIG. 27E). Further examination of the effects of LSD1 and HDAC1 ablation by their specific siRNAs in pluripotent PA-1 human ovarian teratocarcinoma cells and nonpluripotent NCTC1469 normal mouse liver, HeLa, and HCT116 human colorectal carcinoma cells confirmed that inactivation of LSD1 or HDAC1 impaired the growth only of pluripotent PA-1 cells and not that of nonpluripotent cells (FIG. 27F).

TABLE 9.

Cell Line	Protein Expression[a]					
	Oct4	**Sox2**	**Klf4**	**Lin28**	**Nanog**	**Sall4**
mES	√	√	√	√	√	√
F9	√	√	√	√	√	√
PA-1	√	√	√	√	X	√
NIH 3T3	X	X	√	X	X	X
NCTC1469	X	X	√	X	X	X
HeLa	X	X	√	X	X	X
HCT116	X	X	√	X	X	X

[a] √, expression of proteins, as confirmed by Western blotting; X, no detectable expression of proteins.

[00616] Referring to FIG. 27C, a schematic of the experimental design for the functional relationship between LSD1, CoREST, and HDAC1 is shown.

[00617] Referring to FIG. 27D, ablation of HDAC1 or LSD1 inhibits the proliferation of pluripotent mES cells. The mES cells were transfected with luciferase, HDAC1, or LSD1 siRNA (siLuc, siHDAC1, and siLSD1, respectively), and the growth of mES cells was examined under a microscope and quantified by the MTT assay. The efficacy of the siRNAs was determined by Western blotting and quantified by the use of Gel-Pro Analyzer (version 4.0) software.

[00618] Referring to FIG. 27E, inactivation of LSD1 or HDAC1 specifically inhibits the proliferation of pluripotent F9 cells but not that of nonpluripotent NIH 3T3 cells. Cells were transfected with two sets of independent LSD1 and HDAC1 siRNAs for 48 h. Only one set of cell images is shown. The rest were quantified by MTT assay, as described above for FIG. 27D.

[00619] Referring to FIG. 27F, loss of LSD1 or HDAC1 by siRNA-mediated ablation also caused growth inhibition of pluripotent human PA-1 teratoma cells but not that of nonpluripotent HeLa, HCT116, or mouse NCTC1469 cells. All experiments were performed in duplicate with consistent results each time and repeated at least three times. Error bars represent SEMs for duplicates of the data. The statistical differences between experimental and control groups were analyzed by one-way ANOVA. **, $P < 0.01$.

16. Inhibition of HDAC1 or LSD1 Increases Both H4K16 Acetylation and H3K4 Methylation in Cells Sensitive to LSD1 Inhibitors

[00620] The similarity between the inhibitory effects of LSD1 and HDAC1 inactivation on the proliferation of pluripotent ES/EC cells and the interaction between LSD1 and HDAC1 in these cells raised the possibility that LSD1-regulated H3K4 methylation cross talks with the HDAC1-mediated histone acetylation in pluripotent ES/EC cells. To identify the potential link between these two pathways in pluripotent ES/EC cells, the changes of epigenetic modifications of histones H3 and H4 in pluripotent mES and F9 cells were examined and compared (FIG. 28A and 28B). Inactivation of LSD1 by LSD1 inhibitors or specific siRNAs not only induced the accumulation of mono- and dimethylated H3K4 but also increased the levels of acetylated H4K16, H3K56, and H3K14 in these cells but not the level of trimethylated H3K4 (FIG. 28A and 28B). Notably, a loss of HDAC1 caused the same patterns of accumulation of mono- and dimethylated H3K4 and acetylated H4K16, H3K56, and H3K14 in these pluripotent cells (FIG. 28B). These observations are consistent with the

notion that LSD1 and HDAC1 may coordinate to regulate H3K4 methylation and histone acetylation in pluripotent cells.

[00621] Referring to FIG. 28A, F9 and NIH 3T3 cells were treated with the LSD1 inhibitors CBB1003 and CBB1007 for 24 h, and the acetylation and methylation of histones H3 and H4 were monitored by Western blotting and quantified by the use of Gel-Pro Analyzer (version 4.0) software using histone H3 as a loading control.

[00622] Referring to FIG. 28B, mES, F9, and NIH 3T3 cells were transfected with luciferase, LSD1, or HDAC1 siRNAs, and methylated and acetylated histones were analyzed and quantified as described for panel A.

[00623] As inactivation of both LSD1 and HDAC1 only selectively induced growth inhibition of pluripotent ES/EC cells and not that of nonpluripotent cells, the changes of histone methylation and acetylation between pluripotent and nonpluripotent cells were also compared. Strikingly, it was repeatedly observed that while inactivation of LSD1 or HDAC1 selectively caused the increased levels of acetylated H4K16 in pluripotent mES and F9 cells, such an increase in acetylated H4K16 did not happen in nonpluripotent NIH 3T3 cells (FIG. 28A and 28B). It is possible that the loss of LSD1 caused secondary changes in histone modification when the cells were treated with LSD1 inhibitors or siRNAs for an extended time. Therefore, the time course of changes in histone modifications after treatment of F9 cells with the LSD1 inhibitor CBB1007 were monitored (FIG. 28C and 28D). It was repeatedly found that the increases of acetylation at H4K16 and H3K56 and mono- and dimethylation at H3K4 occurred within 20 min after addition of CBB1007 in F9 cells, whereas the accumulation of H3K14 acetylation appeared to occur relatively late, at between 4 and 8 h. Without wishing to be bound by theory, these data suggest that the changes in histone modifications in H3K56ac, H4K16ac, and H3K4me1/me2 may be the primary effects of LSD1 inactivation.

[00624] Referring to FIG. 28C, time course analyses of the effects of 50 μM LSD1 inhibitor CBB1007 on histone modifications in F9 cells are shown.

[00625] Referring to FIG. 28D, time course analyses of the effects of 50 μM LSD1 inhibitor CBB1007 on histone modifications in F9 cells are shown, but with a shorter time course than above. The mean density of each band was quantified by the use of Gel-Pro Analyzer (version 4.0) software, and error bars represent SEMs for duplicate samples. All of the experiments were repeated more than three times, with similar results each time. The statistical differences were analyzed by one-way ANOVA. *, *P*_0.05; **, *P*_0.01.

17. ACETYLATED H4K16 IS A DIRECT SUBSTRATE OF HDAC1

[00626] As the effects of LSD1 and HDAC1 inactivation mirrored each other and affected both histone methylation and acetylation, it prompted further biochemical characterization of these effects *in vitro* using defined substrates and proteins. To determine whether acetylated H3K56, H4K16, and H3K14 are direct substrates of HDAC1, recombinant HDAC1 protein (FIG. 29A) was used to analyze its deacetylase activity against these acetylated bulk histones from F9 cells. GST-HDAC1 was found to remove the acetyl groups from the acetylated H3K56 and H4K16 but not the acetyl group of acetylated H3K14 (FIG. 29C). To further confirm that the acetylated H4K16 is a substrate of HDAC1, a synthetic H4K16ac that contains the acetylated H4K16 as a substrate was also used, and these studies showed that HDAC1 could deacetylate this peptide in a reaction that was inhibited by MS-275, an inhibitor of class I HDACs, which include HDAC1 (FIG. 29B). These observations, as well as the findings from the *in vivo* studies (FIG. 29C and 29D), suggest that acetylated H3K56 and H4K16 are indeed the specific and direct substrates of HDAC1, while acetylated H3K14 is not.

[00627] Referring to FIG. 29A, purified recombinant GST-LSD1, 6-histidine-tagged LSD1 (His-LSD1), GST-HDAC1, and GST-CoREST proteins are shown. Lanes M.W., molecular weight markers (in thousands).

[00628] Referring to FIG. 29B, analysis of the activities of recombinant HDAC1 and LSD1 proteins on peptide substrates. (Left) Concentration-dependent GST-HDAC1 (top) and GST-LSD1 (bottom) activities using H4K16ac and H3K4me2 peptides as the substrates. The products were analyzed by mass spectrometry and quantified by GraphPad Prism (version 5) software. (Right) Determination of the 50% inhibitory concentration (IC_{50}) of MS-275 toward HDAC1 and that of CBB1007 toward LSD1.

[00629] Referring to FIG. 29C, GST-HDAC1 deacetylates H4K16ac and H3K56ac in acid-extracted histones.

18. REGULATION OF LSD1 AND HDAC1 BY MUTUAL ACTIVITIES IN THE LSD1-COREST-HDAC1 COMPLEX

[00630] To investigate the relationship between LSD1 and HDAC1, the activities of recombinant LSD1 and HDAC1 proteins were compared with those of LSD1-HDAC1 complexes isolated from F9 cells. Additionally, the sensitivity of recombinant LSD1 or HDAC1 proteins and isolated LSD1 or HDAC1 protein complexes to LSD1 or HDAC1 inhibitors *in vitro* was evaluated (FIG. 29A and 29D). The LSD1-proteinA and HDAC1-

proteinA complexes, which also contain CoREST, from F9 cells using anti-LSD1 and HDAC1 antibodies were also immunoaffinity purified (FIG. 27A-B and 29E) to compare their activities with those of recombinant proteins. The substrate H4K16ac peptide was incubated with GST-HDAC1 and HDAC1-protein A. The substrate (acetylated H4K16) and product (nonacetylated H4K16) peptides were separated, resolved, and quantified by mass spectrometry (FIG. 29E, middle). Both GST-HDAC1 and HDAC1-protein A could remove the acetyl group from the H4K16ac peptide, and both were sensitive to MS-275, although the endogenous HDAC1 appeared to be more active, even though it consisted of about 2.5 times less protein (FIG. 29E, left and middle). Because H4K16ac in F9 cells is sensitive to LSD1 inhibitors (FIG. 28), the potential effects of LSD1 inhibitors in the HDAC1 assay were also evaluated *in vitro*. Strikingly, the LSD1 inhibitor CBB1007 was sufficient to inhibit the deacetylase activity of immuno affinity purified HDAC1 (HDAC1-protein A) but not that of GSTHDAC1 (FIG. 29E, middle) in the deacetylation reaction.

[00631] Referring to FIG. 29D, a schematic design to test whether inhibition of LSD1 blocks the activity of HDAC1 and vice versa is shown.

[00632] Referring to FIG. 29E, the activities of HDAC1 and LSD1 in the isolated endogenous protein complexes were sensitive to both MS-275 and CBB1007. (Left) Protein levels of recombinant HDAC1 and LSD1 (rHADC1 or rLSD1) and immunoaffinity-purified HDAC1 and LSD1 (HDAC1-protein A or LSD1-protein A complexes) from F9 cells. The GST tag of the GST-HDAC1 and GST-LSD1 proteins was removed prior to the reactions. (Middle) The endogenous HDAC1 in immunoprecipitated protein complexes was sensitive to both CBB1007 and MS-275, whereas rHDAC1 was sensitive only to MS-275. (Right) The activity of LSD1 in the isolated immunoprecipitated LSD1-protein A was inhibited by MS-275 and CBB1007, while the activity of rLSD1 was inhibited only by CBB1007.

[00633] As H3K4me1 and H3K4me2 were also sensitive to the inactivation of HDAC1 in pluripotent ES and EC cells (FIG. 28A and 28B), the effects of MS-275 on the *in vitro* activities of recombinant and endogenous LSD1 complexes isolated from F9 cells using a dimethylated H3K4 peptide as a substrate were also evaluated (FIG. 29E). While both GST-LSD1 and the immunoaffinity-isolated LSD1 complexes from F9 cells (LSD1-protein A) could remove the methyl groups from the dimethylated H3K4 peptide and convert it into mono- and nonmethylated H3K4 peptides in a reaction that was sensitive to CBB1007 (FIG. 29B and 29E, right), addition of HDAC inhibitor MS-275 in the demethylation reaction blocked the demethylation activity of immunoaffinity-purified LSD1 but not that of GST-LSD1 (FIG. 29E, right). Similar to the endogenous HDAC1, the immunoaffinity-purified

LSD1 protein from F9 cells seemed to be more active, as 4 times less LSD1 protein was present in the LSD1-protein A complex (FIG. 29E). Without wishing to be bound by theory, these results suggest that, different from the recombinant LSD1 or HDAC1 proteins, the activities of LSD1 and HDAC1 are mutually dependent on each other in the protein complexes isolated from F9 cells, which is consistent with our observation that loss of LSD1 or HDAC1 selectively inhibited cell growth and increased H3K4me1/me2, H4K16ac, and H3K56ac levels in ES/EC cells (FIG. 27 and 28).

[00634] Because LSD1 and HDAC1 were both associated with CoREST in F9 cells (FIG. 27A and 27B), it was hypothesized that the mutual requirements of LSD1 and HDAC1 activities may be due to their binding to the same CoREST complex. To validate this point, the recombinant proteins were used to reconstitute the LSD1-CoRESTHDAC1 protein complex (FIG. 29F, top left). The activities of the reconstituted complexes were then assayed using oligonucleosomal histones as the substrate which were extracted from F9 cells after micrococcal nuclease digestion, as recombinant LSD1 alone did not work on such a substrate (Shi, Y. J., et al. (2005) *Mol. Cell* **19**, 857-864; Lee, M. G., et al. (2005) *Nature* **437**, 432-435). These studies showed that the reconstituted LSD1-CoREST-HDAC1 complex could be assembled *in vitro* and the complex contained both demethylase and deacetylase activities toward the nucleosomal substrates (FIG. 29F, top right). Treatment of this complex with the LSD1 inhibitor CBB1007 not only inhibited the activity of LSD1 demethylase but also caused the partial inhibition of the HDAC1 deacetylase activity. Conversely, the HDAC inhibitor MS-275 could also partially inhibit the LSD1 demethylase activity by blocking the HDAC1 activity in the reconstituted LSD1-CoREST-HDAC1 complex (FIG. 29F, bottom). The formation of the LSD1 and HDAC1 complexes and the mutual sensitivities toward either LSD1 or HDAC1 inhibitors are dependent on CoREST. In the absence of CoREST, not only did the LSD1-HDAC1 complex not form but also the activity of LSD1 was independent of HDAC1 and vice versa for HDAC1 (FIG. 29F and 29G). Without wishing to be bound by theory, these studies suggest that the allosteric effects of LSD1 and HDAC1 through their trimeric complex formation with CoREST to regulate their demethylase and deacetylase activities.

[00635] Referring to FIG. 29F, both LSD1 and HDAC1 in the reconstituted recombinant LSD1-CoREST-HDAC1 complex were partially sensitive to LSD1 or HDAC1 inhibitors. (Top left) The indicated recombinant LSD1, HDAC1, and GST-CoREST proteins were mixed, and the protein complexes were isolated by GST beads. The components in the isolated reconstituted complexes were examined by Western blotting. Protein A beads were

used as a negative control. (Top right) The activity of the reconstituted LSD1-CoREST-HDAC1 complexes was measured using oligonucleosomes as the substrate either in the presence or in the absence of 50 μM CBB1007 or 2 μM MS-275. (Bottom) The protein levels in the top right panel were quantified using Gel-Pro Analyzer (version 4.0) software. The first lane in the top right panel contained oligonucleosomes only.

[00636] Referring to FIG. 29G, in the absence of CoREST, LSD1 was not sensitive to MS-275, while HDAC1 was not inhibited by CBB1007 using the H3K4me2 or H4K16ac peptide as the substrate. All experiments were conducted at least three times, and only the results of a representative experiment are shown. Error bars denote SEMs for duplicate samples. The statistical differences were analyzed by one-way ANOVA. **, $P<0.01$.

19. Regulation of LSD1 and HDAC1 Activities by Substrate Modification

[00637] Because the loss of LSD1 or HDAC1 in ES/EC cells induces hypermethylated HsK4 or hyperacetylated H4K16 or H3K56, respectively (FIG. 28), whether the hypermethylated or hyperacetylated nucleosomes serve as optimal substrates for HDAC1 or LSD1 was investigated (FIG. 30A). To isolate hypermethylated or hyperacetylated nucleosomes, F9 cells were treated with either the LSD1 inhibitor CBB1007 or the HDAC inhibitor MS-275, and oligonucleosomes were subsequently isolated (FIG. 30A and 30B, top, and C, left). The hypermethylated nucleosomes from CBB1007-treated cells were incubated with immunoaffinity-purified HDAC1 complex (HDAC1-protein A), and the efficiency of deacetylation was compared with that of dimethyl sulfoxide (DMSO)-treated nucleosomes (FIG. 30B). The HDAC1 complex could no longer efficiently deacetylate the H3K4 hypermethylated nucleosomes isolated from LSD1 inhibitor treated F9 cells (FIG. 30B, bottom). Conversely, when hyperacetylated nucleosomes isolated from MS-275-treated F9 cells were used as the substrates (FIG. 30C, left), the immunoaffinity-purified LSD1 complex (LSD1-protein A) could not utilize this substrate (FIG. 30C, right), consistent with the findings of previous TSA experiments (Shi, Y. J., et al. (2005) *Mol. Cell* **19**, 857-864). Thus, without wishing to be bound by theory these studies suggest not only that LSD1 and HDAC1 can mutually regulate their activities through an allosteric effect in the CoREST complex but also that their activities are controlled by the preference for the hypomethylated or hypoacetylated nucleosomal substrates, respectively.

[00638] Referring to FIG. 30A, a schematic outline for the experimental design is shown. The hyperacetylated or hypermethylated nucleosomes were isolated from cells treated with either MS-275 or LSD1 inhibitors. The hyperacetylated or hypermethylated nucleosomes, as

well as the control nucleosomes (DMSO treated), were subsequently used as the substrates for immunoaffinity-purified HDAC1 or LSD1 complexes to determine the substrate preferences.

[00639] Referring to FIG. 30B, HDAC1 was unable to use hypermethylated H3K4 oligonucleosomes as a substrate. (Top) Oligonucleosomes from CBB1007-treated F9 cells were hypermethylated on H3K4, and HDAC1 in the immunoprecipitated HDAC1-proteinA complexes could not efficiently use hypermethylated histones as a substrate; (bottom) the protein bands were quantified by the use of Gel-Pro Analyzer (version 4.0) software.

[00640] Referring to FIG. 30C, LSD1 preferred hypoacetylated oligonucleosomes as the substrate. Oligonucleosomes from MS-275-treated F9 cells were hyperacetylated on H4K16 (left), and they were resistant to the demethylase activity of LSD1 in the immunoprecipitated LSD1-protein A complex (right). Quantification was done as described in the legend to FIG. 27, and error bars denote SEMs for duplicate samples. Results are representative of those from three independent experiments. The statistical differences were analyzed by one-way ANOVA. **, $P < 0.01$.

20. Multiple HDACs Regulate the Acetylation of Histone H4K16 in Nonpluripotent Cells

[00641] These results indicated that the acetylated H4K16 is a substrate of HDAC1 (FIG. 28 and 29). However, the loss of HDAC1 could induce the accumulation of acetylated H4K16 only in pluripotent ES/EC cells and not in nonpluripotent NIH 3T3 or HeLa cells (FIG. 28A-B and 31A). HDAC1 belongs to the HDAC family, which has 18 members in the human genome. Because HDAC1 and HDAC2 were reported to play a redundant role in the proliferation of HeLa cells (Jurkin, J., et al. (2011) *Cell Cycle* **10**, 406-412; Haberland, M., et al. (2009) *Proc. Natl. Acad. Sci. USA* **106**, 7751-7755), it was hypothesized that acetylation of H4K16 may be regulated by multiple HDACs in nonpluripotent cells. To test this, HeLa cells were treated with various HDAC inhibitors, including valproic acid (VPA), trichostatin A (TSA), and MS-275 (FIG. 31B). It is known that MS-275 inhibits the activities of HDACs 1, 2, and 3 and VPA specifically targets HDACs 1, 2, 3, and 8, while TSA has a broader substrate specificity against class I and class II HDACs, including HDAC6 and HDAC10 (Witt, O., et al. (2009) *Cancer Lett.* **277**, 8-21). Indeed, these pan-HDAC inhibitors induced the accumulation of acetylated H4K16 in HeLa cells (FIG. 31B); without wishing to be bound by theory, this may suggest that the deacetylation of H4K16 in nonpluripotent cells may be regulated by multiple HDACs, in addition to HDAC1.

[00642] Referring to FIG. 31A, F9 and HeLa cells were transfected with the indicated siRNAs, and histone modifications were analyzed and quantified.

[00643] Referring to FIG. 31B, the acetylation of H4K16 is sensitive to pan-HDAC inhibitors in HeLa cells. F9 and HeLa cells were treated with the HDAC inhibitor VPA (1 μM) or MS-275 (2 μM) for 24 h or TSA (40 nM) for 16 h. Methylated and acetylated histones H3 and H4 were blotted by specific antibodies, as indicated, and quantified by the use of Gel-Pro Analyzer (version 4.0) software.

[00644] To determine whether additional HDACs are involved in the deacetylation of H4K16ac, the expression of HDACs 1 to 3 and 6 were individually ablated and their effects on the acetylation of H4K16 in nonpluripotent HeLa and pluripotent F9 cells was examined. Loss of HDAC3 or HDAC6 alone was sufficient to induce the accumulation of acetylated H4K16 in HeLa cells, even though the loss of HDAC1 could sometimes cause a slight increase of this acetylation (FIG. 31A). However, the loss of HDAC3 and HDAC6 in pluripotent EC cells, such as F9 cells, did not induce the accumulation of acetylated H4K16 and cause growth inhibition of EC cells, such as PA-1 and F9 cells (FIG. 31A and 31C), even though HDAC6 deficiency caused some growth inhibition in HeLa cells (FIG. 31C). Without wishing to be bound by theory, these studies suggest that HDAC1 is unique in regulating the acetylation of H4K16 in ES/EC cells (FIG. 27, 28, and 31).

[00645] Referring to FIG. 31C, only the loss of HDAC1 causes inhibition of F9 and PA-1 cell growth. The cell growth was analyzed by microscopy, and proteins were analyzed by Western blotting and quantified by the use of Gel-Pro Analyzer (version 4.0) software.

[00646] Referring to FIG 31D, total mRNAs were isolated from pluripotent PA-1, F9, and mES cells and nonpluriptoent HeLa, HCT116, NIH 3T3, and NCTC1469 cells. The expression levels of *LSD1*, *HDAC1*, *HDAC2*, *HDAC3*, and *HDAC6* were compared using quantitative real-time PCR (qPCR).

[00647] Referring to FIG. 31E, the levels of the HDAC1, HDAC2, HDAC3, and HDAC6, CoREST, and LSD1 proteins were compared between the various cell lines, as indicated. The RNA interference effects were confirmed in three independent experiments. The error bars denote SEMs for duplicate samples. The statistical differences were analyzed by one-way ANOVA. **, $P < 0.01$.

21. Levels of Both HDAC1 and LSD1 are Significantly Elevated in ES/EC Cells

[00648] To determine the mechanism by which HDAC1 or LSD1 inactivation causes the

accumulation of H4K16 acetylation only in pluripotent ES/EC cells (FIG. 28 and 27A), the mRNA and protein levels of HDACs 1 to 3 and HDAC6 were examined in pluripotent ES/EC cells and nonpluripotent cells. RNA levels of HDAC1 and LSD1 are significantly elevated in pluripotent mES, F9, and PA-1 cells compared with their levels in nonpluripotent cells, such as HeLa, HCT116, NIH 3T3, and NCTC1469 cells (FIG. 27D). Analysis of the levels of the HDAC1 and LSD1 proteins confirmed these observations (FIG. 27E). In contrast, the expression of HDAC2, HDAC3, and HDAC6, as well as that of CoREST, remained relatively constant in both pluripotent and nonpluripotent cells (FIG. 27D and 27E). Without wishing to be bound by theory, these studies suggest that the elevated expression of HDAC1 and LSD1 and the formation of a predominant LSD1-HDAC1 protein complex in pluripotent ES/EC cells may account for the enhanced sensitivity of H4K16 acetylation to the changes of HDAC1 or LSD1, which is required for the proliferation of ES/EC cells. However, because of the relatively low levels of LSD1 and HDAC1 in nonpluripotent cells, other HDACs, such as HDAC3 and HDAC6, may play a major role in the removal of acetylated H4K16.

22. HDAC1 IS REQUIRED FOR THE EXPRESSION OF OCT4 AND SOX2 AND FOR SUPPRESSING GENES FOR DIFFERENTIATION OF ES/EC CELLS

[00649] Previous studies revealed that inhibition of LSD1 in ES/EC cells caused the downregulation of pluripotent stem cell proteins Oct4 and Sox2 (Wang, J. et al. (2011) *Cancer Research* **71**, 7238-7249). Consistent with this observation, loss of HDAC1 in pluripotent F9 and PA-1 cells also reduced the expression of both Oct4 and Sox2 at the mRNA and protein levels (FIG. 32A and 32B). In addition, inactivation of LSD1 can induce the expression of differentiation-associated genes in ES/EC cells (Adamo, A., et al. (2011) *Nat. Cell Biol.* **13**, 652-659; Wang, J. et al. (2011) *Cancer Research* **71**, 7238-7249). Ablation of either HDAC1 or LSD1 by specific siRNAs also induced the expression of differentiation genes, such as *FOXA2*, *HNF4A*, *SOX17*, *BMP2*, and *EOMES*, in F9 and PA-1 cells (FIG. 33A), consistent with the notion that LSD1 and HDAC1 act through the same pathway to regulate the pluripotency of ES/EC cells.

[00650] Referring to FIG. 32A and 32B, inactivation of HDAC1 or LSD1 suppresses the expression of pluripotent stem cell proteins Oct4 and Sox2. F9 and PA-1 cells were transfected with siRNAs specific for HDAC1 or LSD1, and the effects of Oct4 and Sox2 on the protein (32A) and mRNA (32B) levels were analyzed by Western blotting and qPCR.

[00651] Referring to FIG. 33A, PA-1 and F9 cells were transfected with the indicated siRNAs. The mRNAs were isolated, and the levels of the differentiation genes *FOXA2*,

HNF4A, *SOX17*, *BMP2*, and *EOMES* were analyzed using qPCR.

[00652] To further determine the roles of HDAC1 and LSD1 in regulating the expression of Oct4 and Sox2 and the genes for differentiation, the chromatin immunoprecipitation (ChIP) assay was carried out using antibodies specific for HDAC1, LSD1, H3K4me2, and H4K16ac and IgG as a control. The ChIP analysis allowed for mapping of the binding sites of HDAC1 and LSD1 and the presence of histone methylation/acetylation on the transcriptional regulatory regions of the target genes in F9 and PA-1 cells. Without wishing to be bound by theory, these data suggest that both HDAC1 and LSD1, as well as H3K4me2 and H4K16ac, are enriched and colocalized on the *OCT4*, *SOX2*, and *FOXA2* upstream regulatory regions (FIG. 32B). Inactivation of LSD1 or HDAC1 activities by siRNAs or by LSD1 inhibitors reduced the binding of LSD1 or HDAC1 to the promoters of differentiation genes, such as the *FOXA2* promoter, and induced elevated levels of H3K4me2 and H4K16ac on the *FOXA2* regulatory region (FIG. 34A and 34B). Without wishing to be bound by theory, these analyses suggest that LSD1 and HDAC1 directly regulate the expression of these genes in pluripotent EC cells.

[00653] Referring to FIG. 33B, LSD1, HDAC1, H3K4me2, and H4K16ac colocalize to the regulatory regions of the differentiation gene *FOXA2*. The ChIP assay showed that LSD1, HDAC1, H3K4me2, and H4K16ac were enriched in the kb 0.0 to -2.0 upstream region of the *FOXA2* gene in F9 and PA-1 cells. All experiments were conducted in triplicate, and the results were confirmed at least three times. Error bars denote SEMs for triplicate experiments. The statistical differences were analyzed by one-way ANOVA. **, $P < 0.01$.

[00654] Referring to FIG. 34A and 34B, F9 and PA-1 cells were transfected with siRNAs for 48 h (34A) or treated with CBB1007 or MS-275 for 30 h (34B), as indicated. The ChIP assay was performed to analyze the association of LSD1, HDAC1, H3K4me2, and H4K16ac with the transcriptional regulatory regions of *FOXA2* in control and LSD1- or HDAC1-inactivated cells through qPCR in F9 and PA-1 cells. While the binding of LSD1 and HDAC1 was reduced when either LSD1 or HDAC1 was inactivated, the presence of H3K4me2 and H4K16ac was stimulated on the upstream regulatory region of the *FOXA2* gene. All experiments were confirmed at least three times. The error bars represent SEMs for triplicate experiments. The statistical differences were analyzed by one-way ANOVA. **, $P < 0.01$.

23. Loss of LSD1 or HDAC1 Causes G_1 Cell Cycle Arrest in Pluripotent EC Cells

[00655] The cell cycle effects of F9 and PA-1 cells after LSD1 or HDAC1 inactivation were examined, using fluorescence activated cell sorting (FACS) analyses. Inactivation of LSD1 or HDAC1 consistently caused a profound G_1 cell cycle arrest in these EC cells (FIG. 35A and 35B). Such a G_1 cell cycle arrest could also be induced by the treatment of these EC cells with retinoic acid (RA), a differentiation inducer. RA treatment also caused the reduction of pluripotent stem cell gene *OCT4* and *SOX2* levels and the induction of genes for differentiation, such as *FOXA2* and *BMP2*. However, synchronization of F9 and PA-1 cells in the G1/S border by the double-thymidine-block method was insufficient to cause the downregulation of *OCT4* and *SOX2* and the induction of genes for differentiation. Without wishing to be bound by theory, these data suggest that the effects induced by inactivation of LSD1 or HDAC1 on the expression of Oct4, Sox2, and differentiation genes are similar to those induced by the differentiation agent RA, while G1 cell cycle arrest alone was not sufficient to induce effects similar to those induced by LSD1 or HDAC1 inactivation on F9 and PA-1 cells.

[00656] Referring to FIG. 35A and 35B, F9 and PA-1 cells were transfected with the indicated siRNAs, and the cell cycle was analyzed by FACS. F9 and PA-1 cells were arrested in the G_1 cell cycle by LSD1 or HDAC1 inactivation.

24. HDAC1 is Unique in Coupling the Acetylation of H4K16 to the Methylation of H3K4 to Control the Proliferation of ES/EC Cells

[00657] It was reported that Sirt1, another HDAC, interacts with histone H1 and removes the acetyl group from the acetylated H4K16 and H3K9 (Vaquero, A., et al. (2004) *Mol. Cell* **16**, 93-105). Loss of Sirt1 did not cause growth inhibition of pluripotent F9 and PA-1 cells, even though the proliferation of NIH 3T3 cells was affected, indicating that Sirt1 deficiency did not have effects on pluripotent EC cells similar to those of HDAC1 inactivation. Examination of various chromatin modifications revealed that Sirt1 inactivation caused increased levels of acetylated H4K16 and H3K9 but not increased levels of H3K4me1/me2, while the loss of HDAC1 induced the accumulation of H4K16ac and H3K4me1/me2 but not that of acetylated H3K9. Without wishing to be bound by theory, these analyses suggest that Sirt1 inactivation induced patterns of histone modifications that are different from those induced by the loss of HDAC1 or LSD1, except for H4K16ac. Consistent with the differential histone modifications, the loss of Sirt1 also caused gene expression patterns in F9 and PA-1

cells different from those caused by HDAC1 inactivation. While the loss of HDAC1 caused the downregulation of *OCT4* and *SOX2* and induced the genes for differentiation, ablation of Sirt1 did not have similar effects on the expression of these genes. Rather, Sirt1 inactivation induced the expression of *HES1*, which was not regulated by HDAC1 in F9 and PA-1 cells. It is likely that Sirt1 and HDAC1 regulate distinct sets of target genes due to their differences in combinatorial chromatin modifications and, possibly, compositional differences in various protein complexes in F9 and PA-1 cells.

25. Loss of MOF Rescues Growth Inhibition of ES and EC Cells by LSD1 Inactivation

[00658] Loss of LSD1 or HDAC1 caused the unique increase of H4K16 acetylation in ES/EC cells (FIG. 28A). If increased acetylation of H4K16 plays a critical role in the selective growth-inhibitory effects after LSD1 inhibition in ES/EC cells, reduction or elimination of the increased level of H4K16 acetylation should diminish the effects of LSD1 inactivation. To test this possibility, the effects of ablation of MOF on growth inhibition was examined after LSD1 inactivation in pluripotent mES, F9, and PA-1 cells. MOF is an acetyltransferase that usually associates with H3K4-specific methyltransferase MLL complexes to specifically acetylate H4K16 (Dou, Y., et al. (2005) *Cell* **121**, 873-885). While the loss of LSD1 caused the marked growth inhibition of mES, F9, and PA-1 cells, coablation of LSD1 and MOF significantly rescued the growth inhibition caused by LSD1 deficiency in these ES/EC cells (FIG. 36A-C). However, the loss of MOF alone did not have discernible effects on the growth of ES/EC cells (FIG. 36A and 36B).

[00659] Referring to FIG. 36A-C, F9, PA-1, and mES cells were transfected with siRNAs specific for luciferase, LSD1, LSD1 plus MOF, and MOF for 48 h. Cell growth was examined by microscopy (36A) and quantified by MTT assays (36B). Proteins were analyzed by Western blotting and quantified by the use of Gel-Pro Analyzer (version 4.0) software (33C).

[00660] Examination of histone modifications showed that while the loss of LSD1 increased the levels of acetylated H4K16, coablation of LSD1 and MOF nearly restored the normal levels of acetylated H4K16 in LSD1-deficient cells (FIG. 37A). Interestingly, the loss of MOF did not appear to have significant effects on the global mono- and dimethylation of H3K4 or dimethylated H3K4 on the *FOXA2* gene, even though it caused decreased levels of H4K16ac on *FOXA2* (FIG. 36D and 37A), suggesting that MOF acts through H4K16 acetylation to rescue the growth inhibition in ES/EC cells. Importantly, ablation of MOF is

also sufficient to restore the down-regulated Oct4 and Sox2 levels in LSD1-deficient ES/EC cells (FIG. 37B) and partially suppressed the induction of differentiation genes *FOXA2*, *HNF4A*, *BMP2*, and *EOMES* in these cells (FIG. 37C). The rescuing effect is specific for MOF, as loss of another histone acetyltransferase, Tip60 (KAT5), could not rescue growth inhibition, the reduction of Oct4/Sox2, or the suppression of differentiation genes induced by LSD1 inactivation in F9 and PA-1 cells. Without wishing to be bound by theory, these studies suggest that LSD1 acts through the HDAC1- and MOF-mediated regulation of H4K16 acetylation to maintain the pluripotency of ES/EC cells.

[00661] Referring to FIG. 33D, the loss of MOF restored the levels of H4K16ac but not those of H3K4me2 on the *FOXA2* gene. F9 cells were transfected with siRNAs, as indicated, and the presence of H3K4me2 and H4K16ac on *FOXA2* was analyzed by ChIP using control IgG and anti-H3K4me2 and anti-H4K16ac antibodies. The results of the rescue experiments were independently confirmed three times. The error bars represent SEMs for duplicate samples. The statistical differences were analyzed by one-way ANOVA. **, $P < 0.01$.

[00662] Referring to FIG. 37A, F9, mES, and PA-1 cells were transfected with the indicated siRNAs. Histone modifications of H3 and H4 were monitored by Western blotting and quantified by the use of Gel-Pro Analyzer (version 4.0) software. MOF inactivation reversed the increase in H4K16ac in LSD1-deficient cells.

[00663] Referring to FIG. 37B and 37C, MOF inactivation restored the protein (12B) and mRNA (12C) levels of Oct4 and Sox2 and partially rescued the mRNA expression of differentiation genes *FOXA2*, *BMP2*, *EOMES*, and *HNF4A* in LSD1-deficient mES and F9 cells.

[00664] To eliminate the possibility of potential off-target effects of siRNAs, whether the effects of inactivation of LSD1, HDAC1, and MOF by siRNAs can be rescued by reexpression of LSD1, HDAC1, and MOF, respectively, were tested. While ablation of LSD1, HDAC1, or MOF expression using siRNAs specifically targeting the UTRs of their cognate mRNAs caused growth inhibition of F9 or PA-1 cells, re-expression of the coding cDNAs of LSD1, HDAC1, and MOF in these growth-inhibited cells restored their growth (FIG. 38). Without wishing to be bound by theory, these data suggest that LSD1, HDAC1, and MOF may indeed regulate pluripotency and cell cycle progression in these EC cells.

[00665] Referring to FIG. 38A-C, after they were transfected with siRNA specific for the LSD1 and HDAC1 5' or 3' UTR for 24 h, F9 and PA-1 cells were transfected with Flag-tagged LSD1 (LSD1re, where the suffix -re represents reexpression) or HDAC1 (HDAC1re) cDNA to express ectopic cDNAs for another 24 h. The transfection efficiency for re-

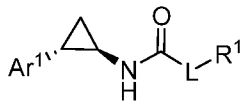
expression was about 50 to 60%, using parallel expression of GFP on the same vector as a control. Cell growth (38A), proteins (38B), and mRNAs (38C) were analyzed to determine the effects of expression of exogenous (exo.) proteins after target gene ablation. endo., endogenous.

[00666] Referring to FIG. 38D-F, the effects of re-expression of Flag-tagged MOF (MOFre) in LSD1- and MOF-ablated F9 and PA-1 cells are shown. siMOF, siRNA for MOF. Experiments were confirmed with three repeats. Error bars denote the SEMs for duplicate data. The statistical differences were analyzed by one-way ANOVA. **, $P < 0.01$.

CLAIMS

What is claimed is:

1. A compound having a structure represented by a formula:



,

wherein L is a moiety selected from –O– and $–(CR^{2a}R^{2b})_n–$;

wherein n is an integer selected from 1, and 2;

wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$;

wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $–NO_2$, –CN, $–N_3$, $–OR^3$, $–SR^4$, $–NR^{5a}R^{5b}$, $–P(R^6)_3$, $–CO_2R^7$, $–C(O)SR^8$, $–SO_2R^9$, $–CONR^{10a}R^{10b}$, and $–SO_2NR^{11a}R^{11b}$ when L is $–(CR^{2a}R^{2b})_n–$;

wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2;

wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected

from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4;

wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$;

wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl;

wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl;

wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

or a pharmaceutically acceptable salt thereof.

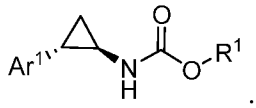
2. The compound of claim 1, wherein L is –O– and R^1 is C1-C4 alkyl.

3. The compound of claim 1, wherein Ar^1 is selected from phenyl, furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyridazine, and pyrazine.

4. The compound of claim 1, wherein Ar^1 is phenyl with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

5. The compound of claim 1, wherein each of R^{12}, R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen and C1-C4 alkyl.

6. The compound of claim 1, wherein the compound has a structure represented by a formula:



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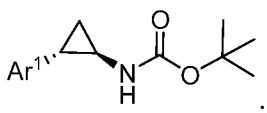
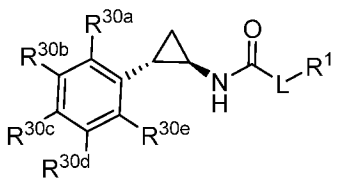
7. The compound of claim 1, wherein the compound has a structure represented by a formula:



.

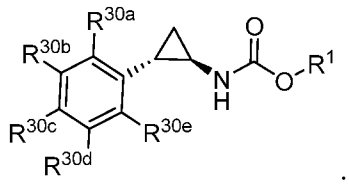
8. The compound of claim 1, wherein the compound has a structure represented by a formula:



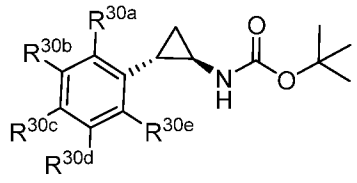
,

wherein each of R^{30a}, R^{30b}, R^{30c}, R^{30d}, and R^{30e} is independently selected from hydrogen, halogen, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

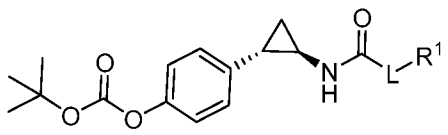
9. The compound of claim 8, wherein the compound has a structure represented by a formula:



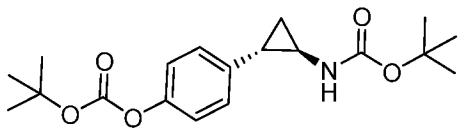
10. The compound of claim 8, wherein the compound has a structure represented by a formula:



11. The compound of claim 8, wherein the compound has a structure represented by a formula:

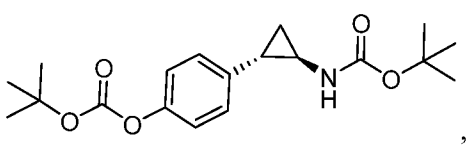
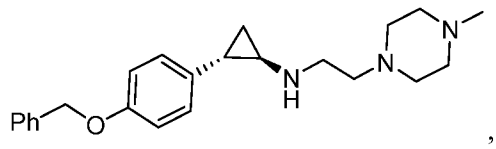


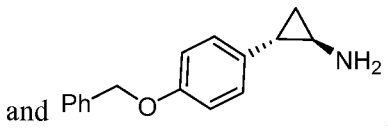
12. The compound of claim 1, wherein the compound is:



13. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of any of claims 1-12, or a pharmaceutically acceptable salt, solvate, or polymorph thereof; and a pharmaceutically acceptable carrier.

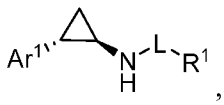
14. A compound having a structure selected from:

 ,  ,

and  ,

or a pharmaceutically acceptable salt thereof.

15. A method of inhibiting LSD1 (lysine-specific demethylase I) in at least one cell, the method comprising the method comprising contacting the cell with an effective amount of at least one compound having a structure represented by a formula:



wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–;

wherein n is an integer selected from 1, and 2;

wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3;

wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –$C(O)SR^8$, –SO_2R^9, –$CONR^{10a}R^{10b}$, –$SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–;

wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2;

wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4;

wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$;

wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl;

wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl;

wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-

C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

or a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein L is a moiety selected from –C(O)– and –CO_2–.

17. The method of claim 15, wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from–NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –$C(O)SR^8$, –SO_2R^9, –$CONR^{10a}R^{10b}$, and –$SO_2NR^{11a}R^{11b}$ when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–.

18. The method of claim 15, wherein L is –CO_2– and R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1.

19. The method of claim 15, wherein L is –CO_2– and R^1 is C1-C4 alkyl.

20. The method of claim 15, wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

21. The method of claim 15, wherein Ar^1 is selected from phenyl, furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyridazine, and pyrazine.

22. The method of claim 15, wherein Ar^1 is phenyl with 0, 1, 2, or 3 groups independently selected from halogen, –CN, –N_3, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, –OR^{12}, –SR^{13}, –$NR^{14a}R^{14b}$, –$P(R^{15})_3$, –CO_2R^{16}, –$C(O)SR^{17}$, –SO_2R^{18}, –$CONR^{19a}R^{19b}$, –$SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4.

23. The method of claim 15, wherein each of R^{12}, R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen and C1-C4 alkyl.

24. The method of claim 15, wherein the cell is selected from a cancer stem cell and a cancer-initiating cell.

25. The method of claim 15, wherein the cell expresses at least one *Sox2* stem cell marker.

26. The method of claim 24, wherein the cancer stem cell is an embryonic cancer stem cell with germ tumor cell properties.

27. The method of claim 15, wherein contacting is via administration to a mammal.

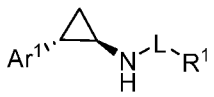
28. The method of claim 27, wherein the mammal has been diagnosed with a need for treatment of cancer prior to the administering step.

29. The method of claim 15, wherein the compound exhibits an IC_{50} of less than about 40 mM.

30. The method of claim 15, wherein the compound exhibits an IC_{50} of less than about 30 mM.

31. A method of treating a cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor.

32. The method of claim 31, wherein the LSD1 inhibitor is a compound having a structure represented by a formula:



,

wherein L is a moiety selected from –C(O)–, $–CO_2–$, and $–(CR^{2a}R^{2b})_n–$;

wherein n is an integer selected from 1, and 2;

wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $–NH_2$, $–NO_2$, –CN, and $–N_3$;

wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is $–CO_2–$; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, $–NO_2$, –CN, $–N_3$, –

OR^3, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$, $-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, $-SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from $-C(O)-$ and $-(CR^{2a}R^{2b})_n-$;

wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2;

wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-NO_2$, $-CN$, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4;

wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$;

wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl;

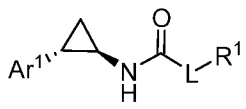
wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl;

wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $-NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

or a pharmaceutically acceptable salt thereof.

33. The method of claim 31, wherein the LSD1 inhibitor is a compound having a structure represented by a formula:



,

wherein L is a moiety selected from –O– and $-(CR^{2a}R^{2b})_n-$;

wherein n is an integer selected from 1, and 2;

wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, $-NH_2$, $-NO_2$, –CN, and $-N_3$;

wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –O–; or wherein R^1 is selected from $-NO_2$, –CN, $-N_3$, $-OR^3$, $-SR^4$, $-NR^{5a}R^{5b}$, $-P(R^6)_3$,

$-CO_2R^7$, $-C(O)SR^8$, $-SO_2R^9$, $-CONR^{10a}R^{10b}$, and $-SO_2NR^{11a}R^{11b}$ when L is $-(CR^{2a}R^{2b})_n-$;

wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2;

wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-OH$, $-NH_2$, $-CN$, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^1 is selected from phenyl and monocyclic heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $-CN$, $-N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $-OR^{12}$, $-SR^{13}$, $-NR^{14a}R^{14b}$, $-P(R^{15})_3$, $-CO_2R^{16}$, $-C(O)SR^{17}$, $-SO_2R^{18}$, $-CONR^{19a}R^{19b}$, $-SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4;

wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $-CO_2R^{21}$;

wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl;

wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl;

wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $—NH_2$, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

or a pharmaceutically acceptable salt thereof.

34. The method of claim 31, wherein the LSD1 inhibitor is selected from:

35. The method of claim 31, wherein the LSD1 inhibitor is selected from parnate 2-phenylcyclopropylamine (2-PCPA), tranylcypromine, and derivatives thereof.

36. The method of claim 31, wherein the LSD1 inhibitor is a bisguanidine polyamine.

37. The method of claim 31, wherein the cancer comprises cells expressing at least one *Sox2* stem cell marker.

38. The method of claim 31, wherein the mammal is a human.

39. The method of claim 31, wherein the mammal has been diagnosed with a need for treatment of cancer prior to the administering step.

40. The method of claim 31, further comprising the step of identifying a mammal in need of treatment of cancer.

41. The method of claim 31, wherein the cancer is selected from a lymphoma, sarcoma, and a carcinoma.

42. The method of claim 41, wherein the carcinoma is a squamous cell carcinoma.

43. The method of claim 31, wherein the cancer is characterized by the presence of Sox2.

44. The method of claim 43, wherein the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

45. The method of claim 31, wherein the cancer is associated with gene amplification of *Sox2*.

46. The method of claim 45, wherein the gene amplification occurs at 3q22.33.

47. A method of treating cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

48. The method of claim 47, wherein the HDAC1 inhibitor is selected from an aliphatic acid, a hyroxamate, a benzamide, a cyclic peptide, and an electrophilic ketone hybrid molecule.

49. The method of claim 47, wherein the HDAC1 inhibitor is selected from butyrate acid, Valproate (valproic acid), Tricostatin A (TSA), Vorinostat (SAHA), Entinostat (MS-275, SNDX-275), MGCD-0103, Romidepsin (FK-228/resminostate), trapoxin B, CHAP31, Panobinostate (Belinostat, PXD101), M344 (PCI-34051), CI994

(Tacedinaline), Tubastatin A hydrochloride, AR-42 (HDAC-42), SB939 (Pracinostat), ITF2357, Givinostat, CUDC-101, LAQ824 (NVP-LAQ824, Dacinostat), PCI-24781 (CRA-024781), APHA compound 8, BATCP, MOCPAC, PTACH, and PP.

50. The method of claim 47, wherein the cancer comprises cells expressing at least one *Sox2* stem cell marker.

51. The method of claim 47, wherein the mammal is a human.

52. The method of claim 47, wherein the mammal has been diagnosed with a need for treatment of cancer prior to the administering step.

53. The method of claim 47, further comprising the step of identifying a mammal in need of treatment of cancer.

54. The method of claim 47, wherein the cancer is selected from a lymphoma, sarcoma, and a carcinoma.

55. The method of claim 54, wherein the carcinoma is a squamous cell carcinoma.

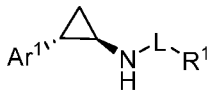
56. The method of claim 47, wherein the cancer is characterized by the presence of Sox2.

57. The method of claim 56, wherein the cancer is selected from glioblastoma multiforme, breast cancer, lung cancer, skin cancer, neuroblastoma, leukemia, lymphoma, prostate cancer, glioma, bladder cancer, colon and rectal cancer, gastric cancer, liver cancer, germ cell tumor, endometrial cancer, cervical cancer, retinoblastoma, medulloblastoma, medulloepithelioma, bronchial cancer, brain cancer, mesothelioma, kidney cancer, pancreatic cancer, lip and oral cancer, laryngeal and pharyngeal cancer, melanoma, pituitary cancer, penile cancer, parathyroid cancer, thyroid cancer, pheochromocytoma and paraganglioma, thymoma and thymic carcinoma, plasma cell neoplasms, myeloproliferative disorders, islet cell tumor, small intestine cancer, transitional cell cancer, pleuropulmonary blastoma, gestational trophoblastic cancer, esophageal cancer, central nervous system cancer, head and neck cancer, endocrine cancer, cardiovascular cancer, rhabdomyosarcoma, soft tissue carcinomas, carcinomas of bone, cartilage, fat, vascular, neural, and hematopoietic tissues and AIDS-related cancers, and ovarian cancer.

58. The method of claim 47, wherein the cancer is associated with gene amplification of *Sox2*.

59. The method of claim 58, wherein the gene amplification occurs at 3q22.33.

60. A kit comprising at least one compound having a structure represented by a formula:



wherein L is a moiety selected from –C(O)–, –CO_2–, and –$(CR^{2a}R^{2b})_n$–;

wherein n is an integer selected from 1, and 2;

wherein each of R^{2a} and R^{2b}, when present, is independently selected from hydrogen, halogen, –OH, –NH_2, –NO_2, –CN, and –N_3;

wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, Ar^2, and Cy^1 when L is –CO_2–; or wherein R^1 is selected from C1-C8 alkyl, C1-C8 alkenyl, C1-C8 alkynyl, C1-C8 monohaloalkyl, C1-C8 polyhaloalkyl, C1-C8 hydroxyalkyl, –NO_2, –CN, –N_3, –OR^3, –SR^4, –$NR^{5a}R^{5b}$, –$P(R^6)_3$, –CO_2R^7, –$C(O)SR^8$, –SO_2R^9, –$CONR^{10a}R^{10b}$, –$SO_2NR^{11a}R^{11b}$, Ar^2, and Cy^1 when L is selected from –C(O)– and –$(CR^{2a}R^{2b})_n$–;

wherein each of R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^8, R^9, R^{10a}, R^{10b}, R^{11a}, and R^{11b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, Ar^3, and Cy^2;

wherein Ar^3, when present, is selected from aryl and heteroaryl and wherein Ar^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^2, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, –NH_2, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^2, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^1, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^1, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Ar^1 is selected from phenyl and heteroaryl and wherein Ar^1 is substituted with 0, 1, 2, or 3 groups independently selected from halogen, $–NO_2$, –CN, $–N_3$, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 hydroxyalkyl, $–OR^{12}$, $–SR^{13}$, $–NR^{14a}R^{14b}$, $–P(R^{15})_3$, $–CO_2R^{16}$, $–C(O)SR^{17}$, $–SO_2R^{18}$, $–CONR^{19a}R^{19b}$, $–SO_2NR^{20a}R^{20b}$, Cy^3, and Ar^4;

wherein R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, and $–CO_2R^{21}$;

wherein R^{21}, when present, is selected from hydrogen and C1-C4 alkyl;

wherein each of R^{13}, R^{14a}, R^{14b}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20a}, and R^{20b}, when present, is independently selected from hydrogen, C1-C4 alkyl, C1-C4 monohaloalkyl, and C1-C4 polyhaloalkyl;

wherein Ar^4, when present, is selected from aryl and heteroaryl and wherein Ar^2, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

wherein Cy^3, when present, is selected from C3-C6 cycloalkyl and C2-C5 heterocycloalkyl and wherein Cy^3, when present, is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –OH, $–NH_2$, –CN, C1-C3 alkyl, C1-

C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 hydroxyalkyl, C1-C3 monoalkylamino, and C1-C3 dialkylamino;

or a pharmaceutically acceptable salt thereof, and one or more of:

a) at least one agent known to inhibit LSD1;

b) at least one agent known to inhibit HDAC1;

c) at least one anticancer therapeutic agent;

d) instructions for detecting a cancer; and

e) instructions for treating a cancer.

61. The kit of claim 60, wherein the compound and the agent are co-formulated.

62. The kit of claim 60, wherein the compound and the agent are co-packaged.

63. The kit of claim 60, wherein the agent known to inhibit LSD1 is a monoamine oxidase inhibitor.

64. The kit of claim 63, wherein the monoamine oxidase inhibitor is selected from a MAO-A inhibitor and a MOA-B inhibitor.

65. The kit of claim 63, wherein the monoamine oxidase inhibitor is selected from pargyline and phenelzine.

66. The kit of claim 63, wherein the monoamine oxidase is a trans-2-phenylcyclopropylamine.

67. The kit of claim 60, wherein the trans-2-phenylcyclopropylamine is selected from tranylcypromine, 2-PCPA, parnate, tranylcypromine (TCP), S2101, and RN-1.

68. The kit of claim 60, wherein the anticancer therapeutic agent is selected from:

a) a hormone therapy therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof;

b) an alkylating therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof;

c) an antineoplastic antimetabolite therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof;

d) a mitotic inhibitor therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof;

e) an antineoplastic antibiotic therapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof; or

f) other chemotherapeutic agent, or a pharmaceutically acceptable prodrug, salt, solvate, or polymorph thereof.

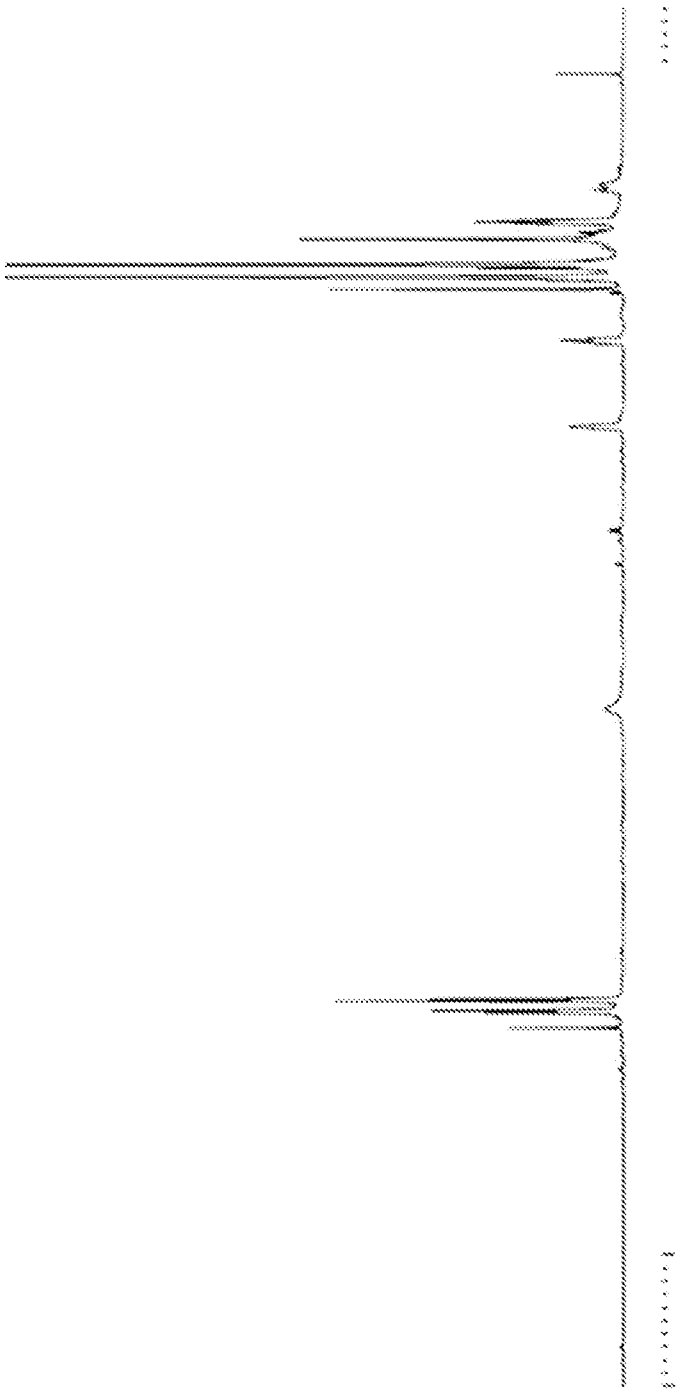


FIG. 1A

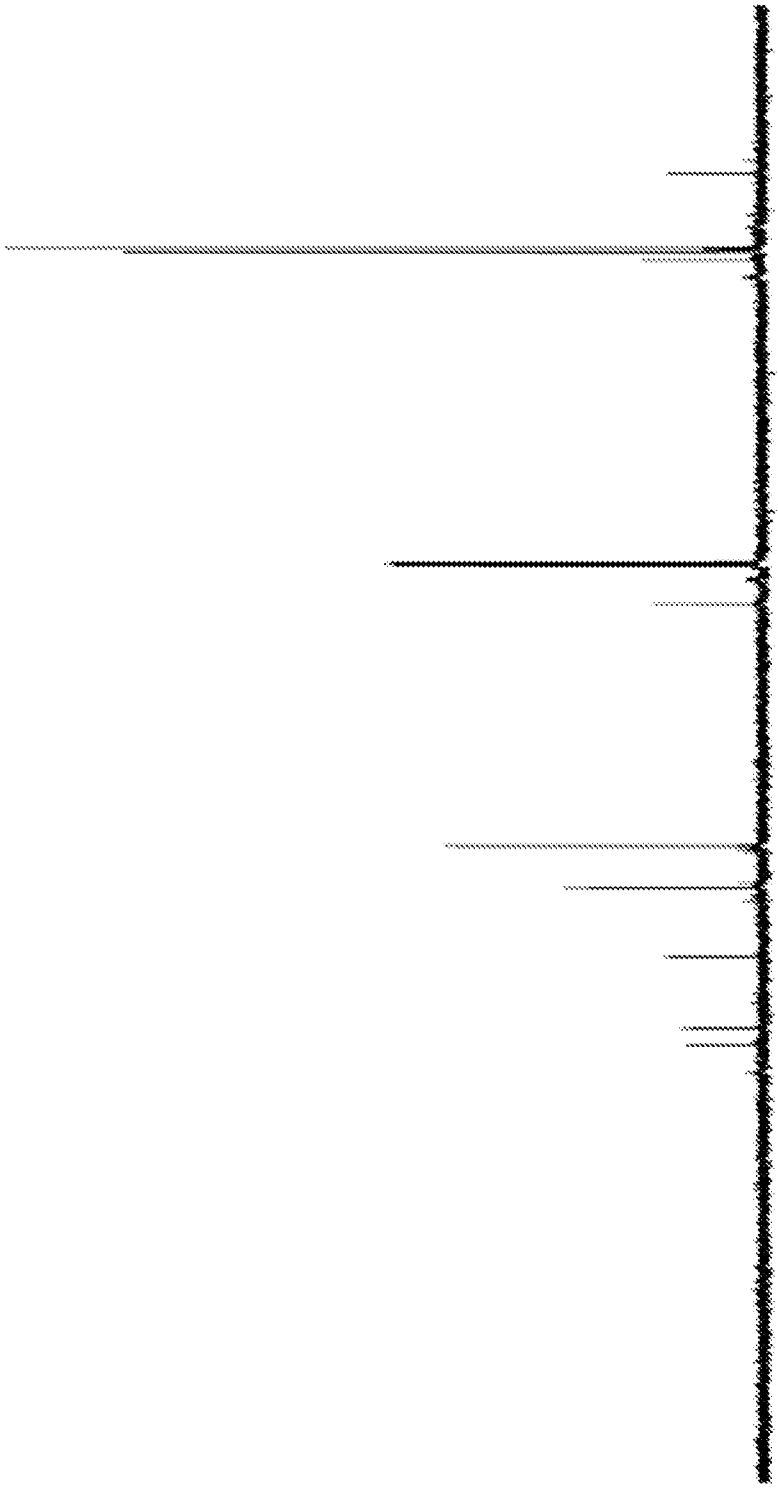


FIG. 1B

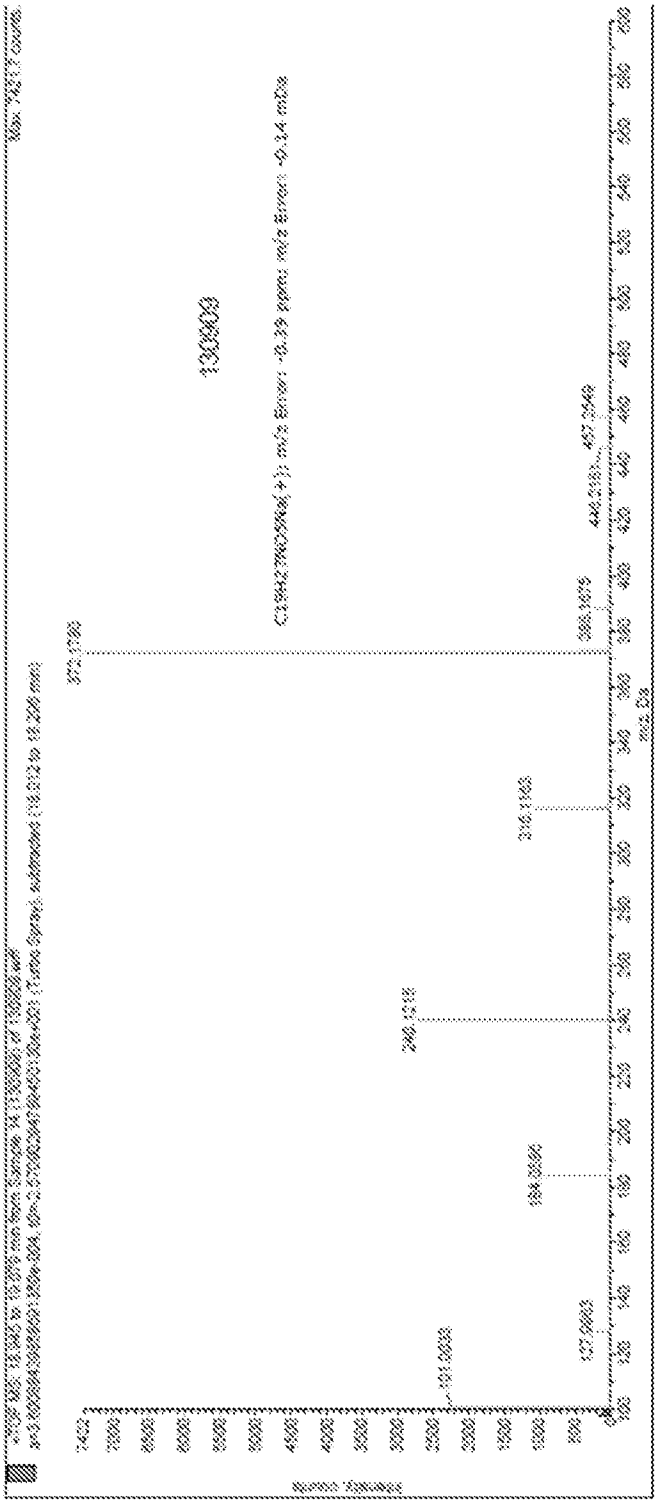


FIG. 1C

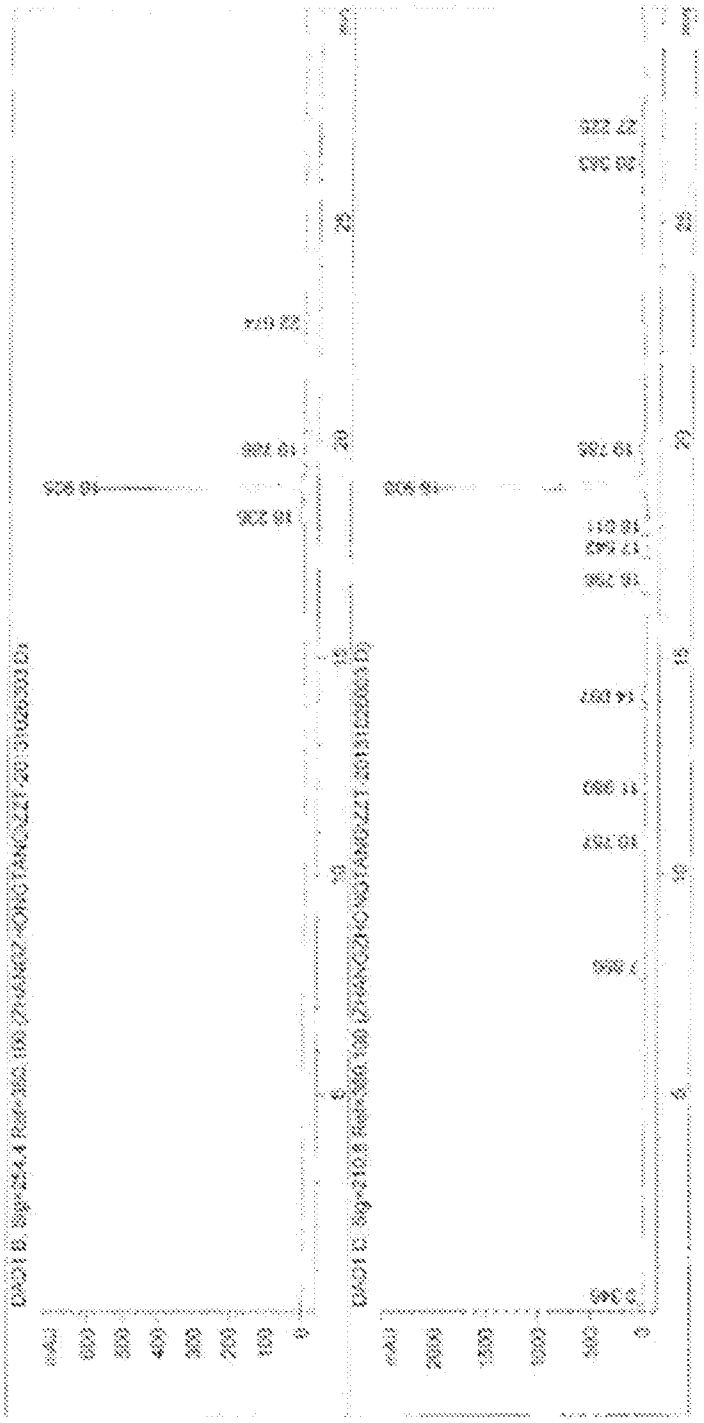


FIG. 1D

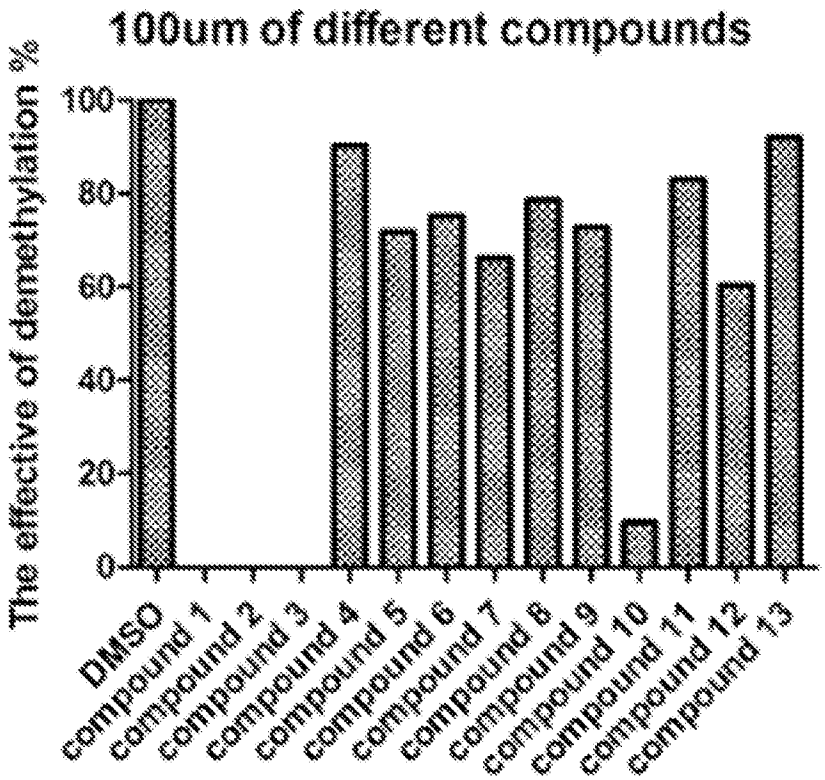

100um of different compounds
The effective of demethylation %
100
80
60
40
20
0
DMSO
compound 1
compound 2
compound 3
compound 4
compound 5
compound 6
compound 7
compound 8
compound 9
compound 10
compound 11
compound 12
compound 13

FIG. 2A

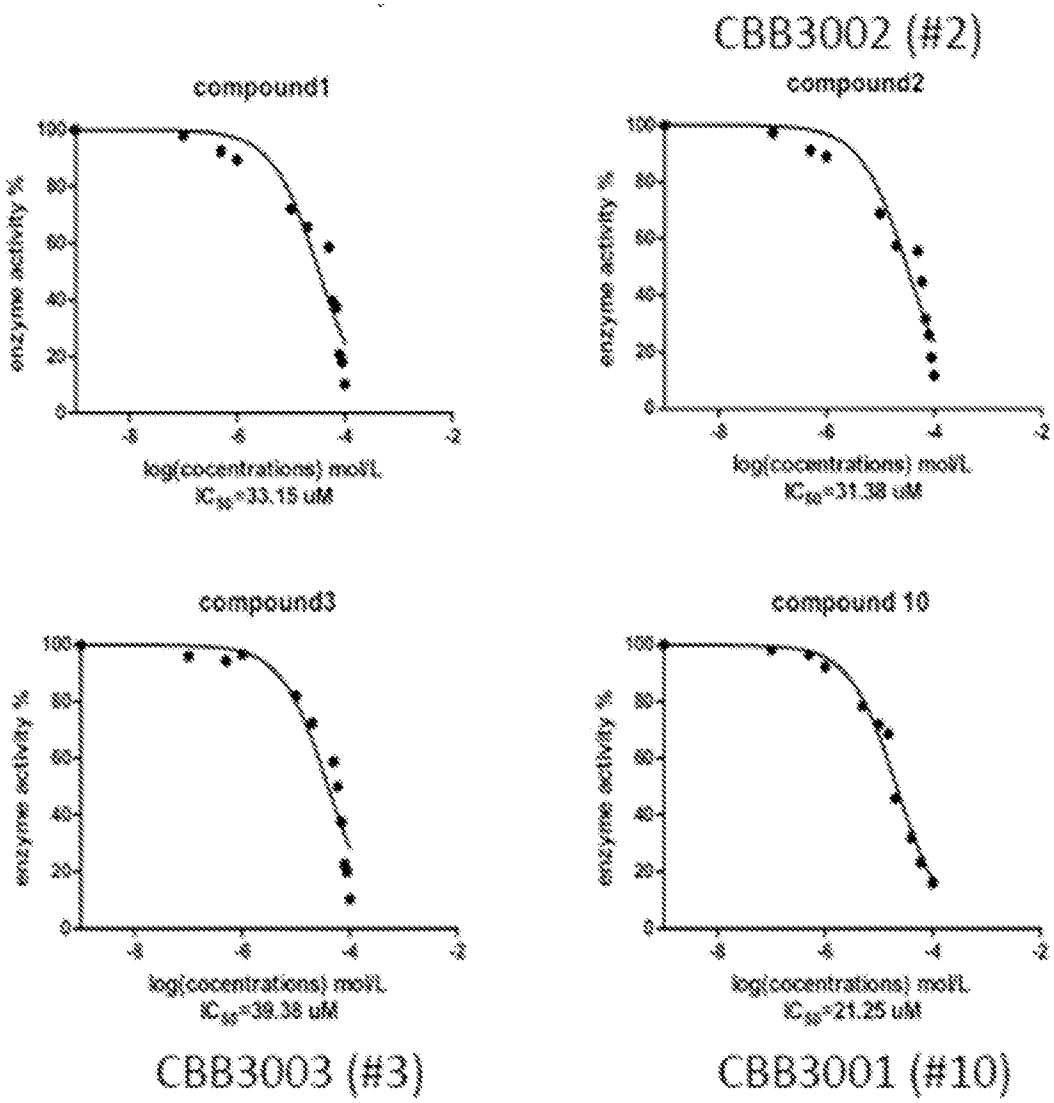

compound1
enzyme activity %
log(cocentrations) mol/L
IC50=33.15 uM
CBB3002 (#2)
compound2
enzyme activity %
log(cocentrations) mol/L
IC50=31.38 uM
compound3
enzyme activity %
log(cocentrations) mol/L
IC50=38.38 uM
CBB3003 (#3)
compound 10
enzyme activity %
log(cocentrations) mol/L
IC50=21.25 uM
CBB3001 (#10)

FIG. 2B

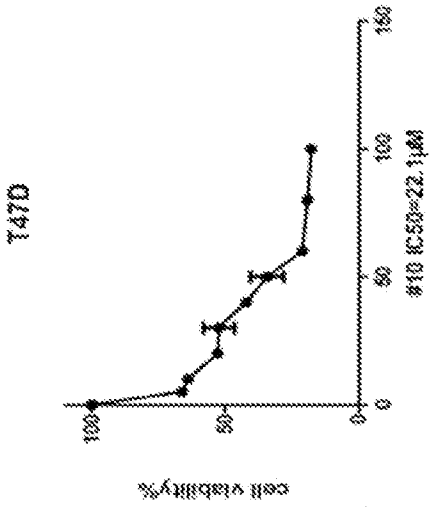


FIG. 3C

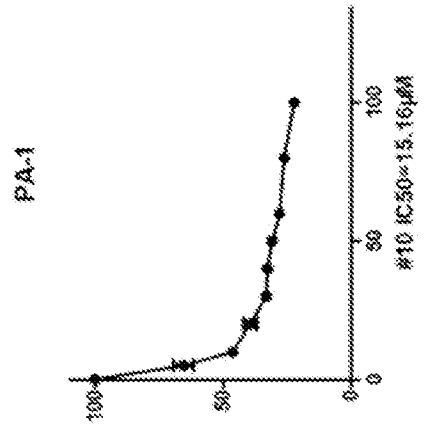


FIG. 3B

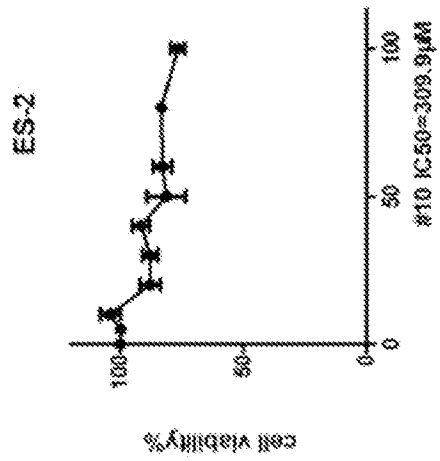


FIG. 3A

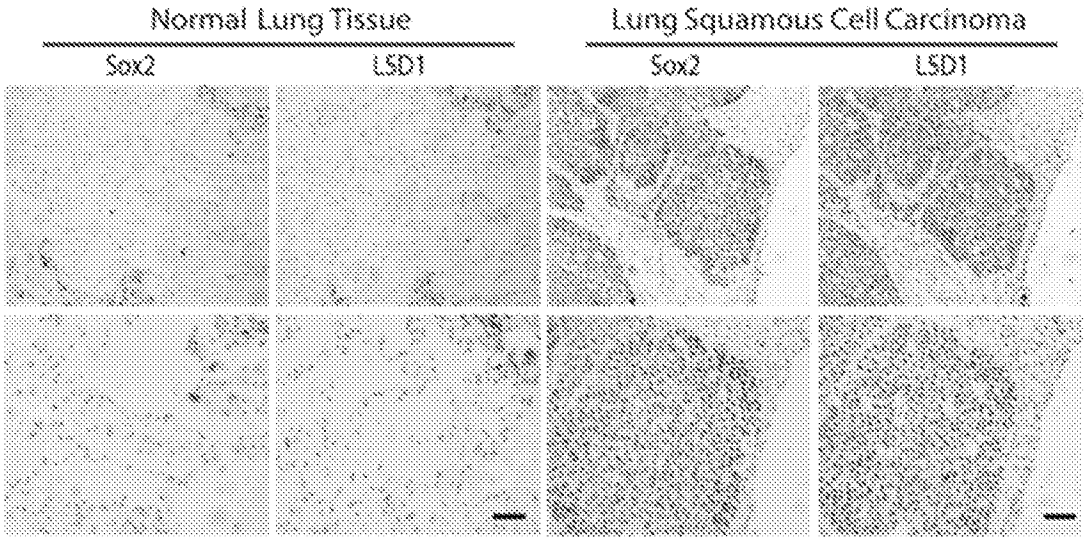

Normal Lung Tissue
Lung Squamous Cell Carcinoma
Sox2
LSD1
Sox2
LSD1

FIG. 4A

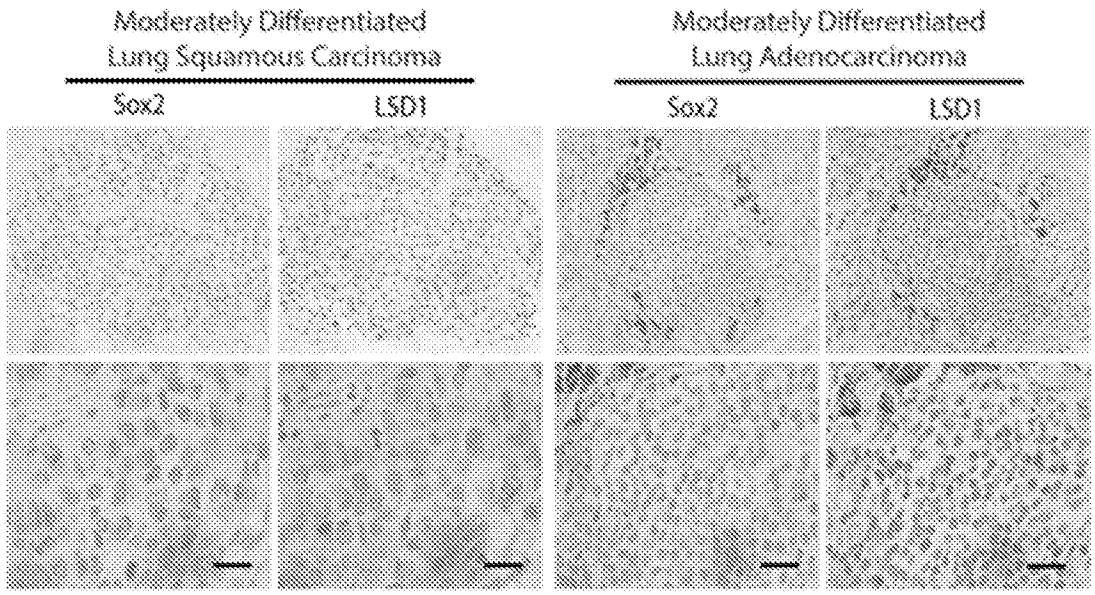

Moderately Differentiated
Lung Squamous Carcinoma
Moderately Differentiated
Lung Adenocarcinoma
Sox2
LSD1
Sox2
LSD1

FIG. 4B

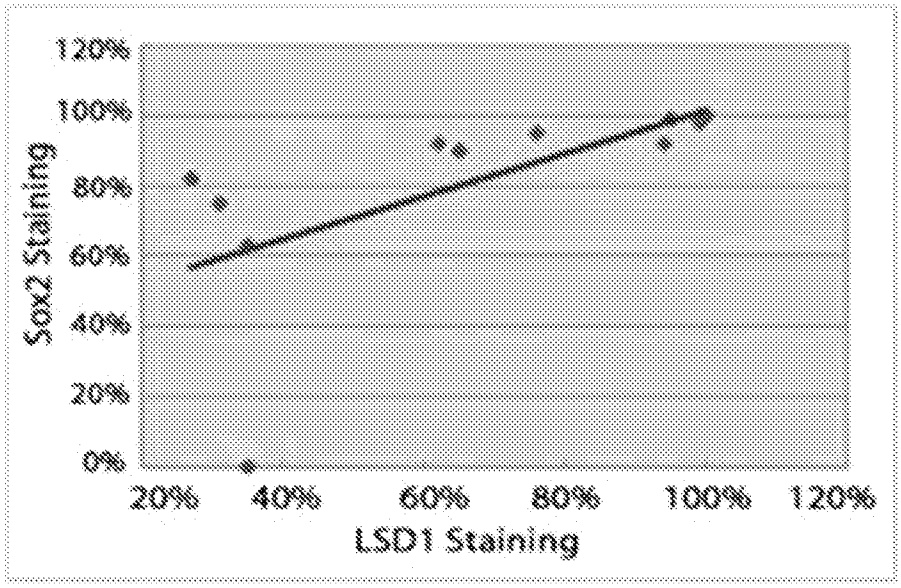

120%
100%
80%
60%
40%
20%
0%
Sox2 Staining
20%
40%
60%
80%
100%
120%
LSD1 Staining

FIG. 4C

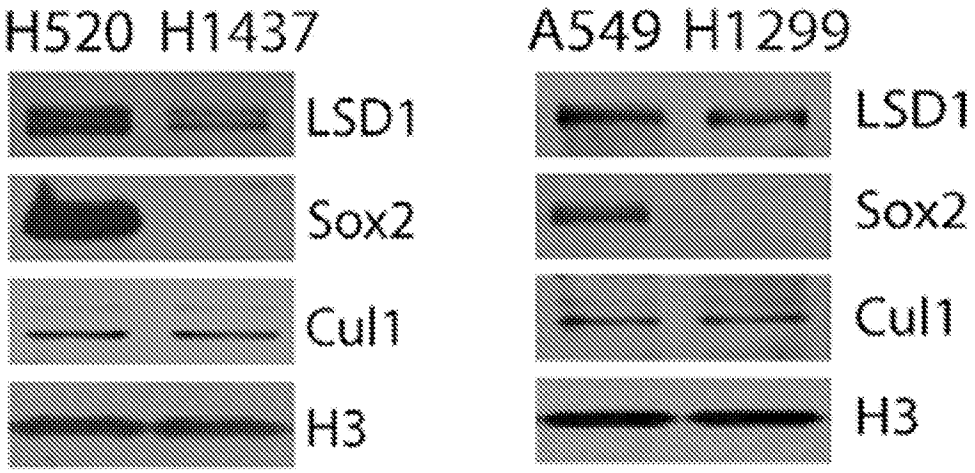

H520 H1437
A549 H1299
LSD1
Sox2
Cul1
H3
LSD1
Sox2
Cul1
H3

FIG. 5A

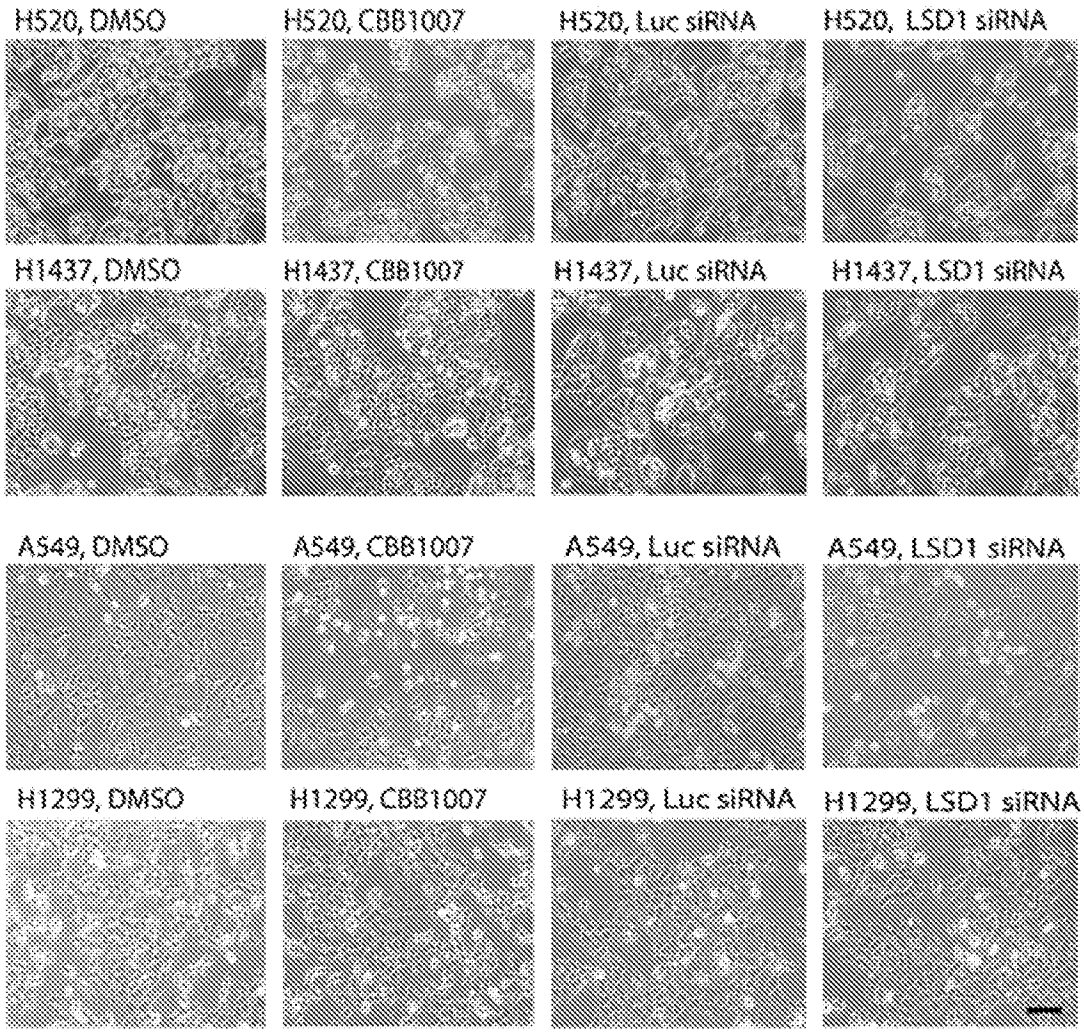

H520, DMSO
H520, CBB1007
H520, Luc siRNA
H520, LSD1 siRNA
H1437, DMSO
H1437, CBB1007
H1437, Luc siRNA
H1437, LSD1 siRNA
A549, DMSO
A549, CBB1007
A549, Luc siRNA
A549, LSD1 siRNA
H1299, DMSO
H1299, CBB1007
H1299, Luc siRNA
H1299, LSD1 siRNA

FIG. 5B

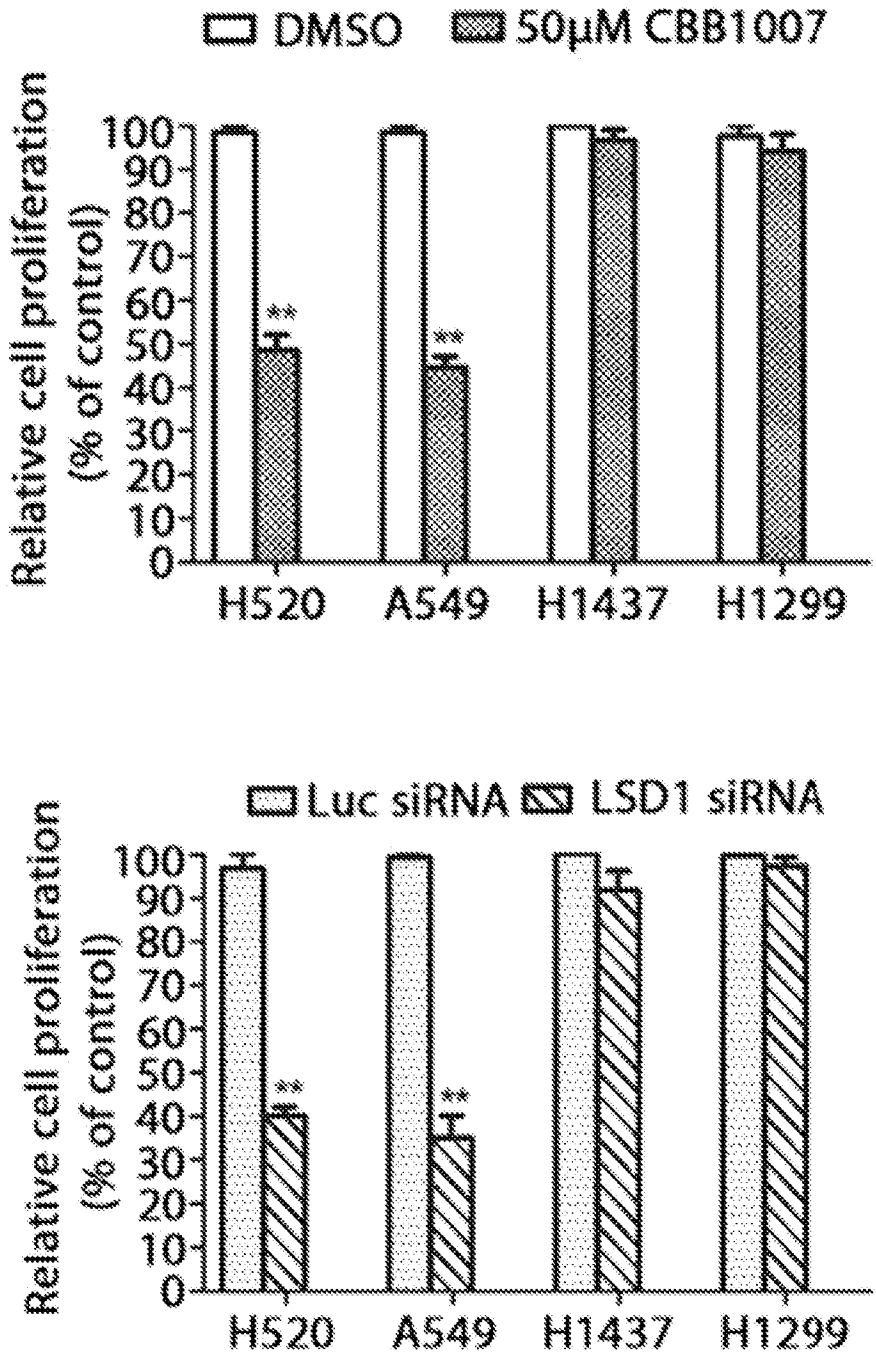

DMSO
50μM CBB1007
Relative cell proliferation
(% of control)
100
90
80
70
60
50
40
30
20
10
0
**
**
H520
A549
H1437
H1299
Luc siRNA
LSD1 siRNA
Relative cell proliferation
(% of control)
100
90
80
70
60
50
40
30
20
10
0
**
**
H520
A549
H1437
H1299

FIG. 5C

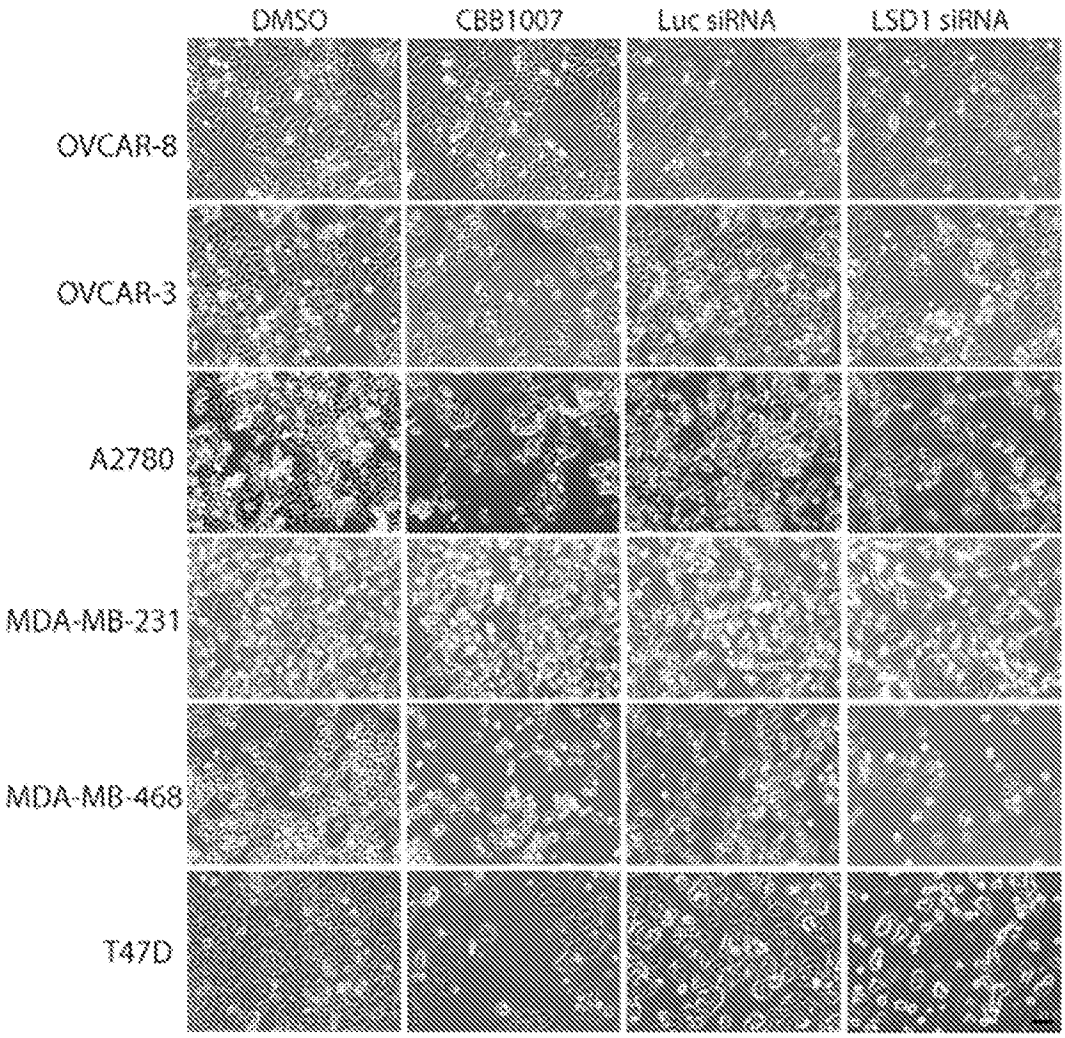

DMSO
CBB1007
Luc siRNA
LSD1 siRNA
OVCAR-8
OVCAR-3
A2780
MDA-MB-231
MDA-MB-468
T47D

FIG. 6A

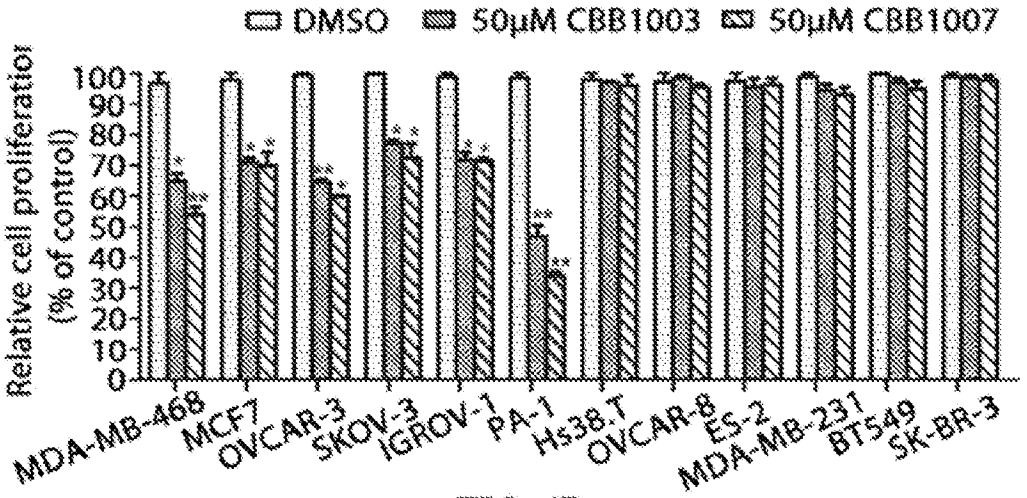

DMSO
50μM CBB1003
50μM CBB1007
Relative cell proliferation
(% of control)
100
90
80
70
60
50
40
30
20
10
0
MDA-MB-468
MCF7
OVCAR-3
SKOV-3
IGROV-1
PA-1
Hs38.T
OVCAR-8
ES-2
MDA-MB-231
BT549
SK-BR-3

FIG. 6B

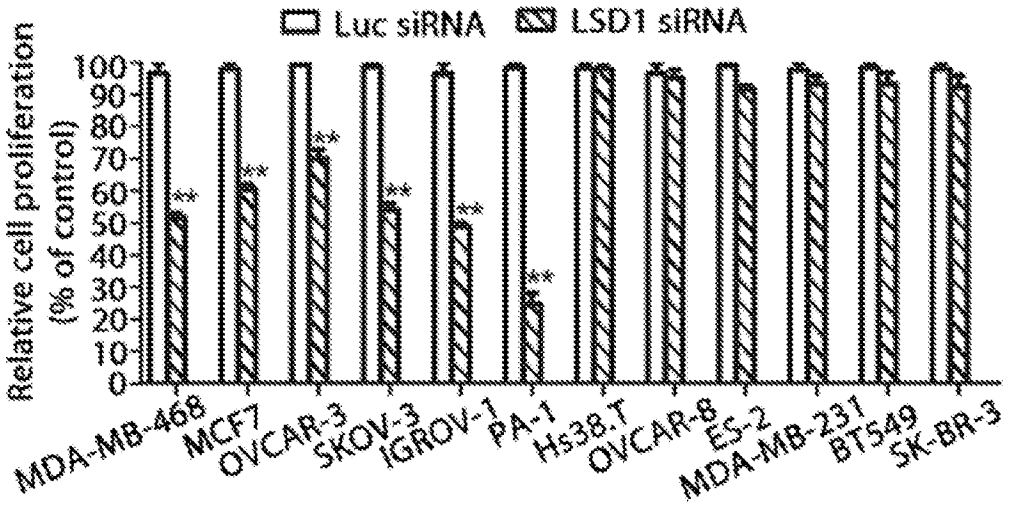

Luc siRNA
LSD1 siRNA
Relative cell proliferation
(% of control)
100
90
80
70
60
50
40
30
20
10
0
MDA-MB-468
MCF7
OVCAR-3
SKOV-3
IGROV-1
PA-1
Hs38.T
OVCAR-8
ES-2
MDA-MB-231
BT549
SK-BR-3

FIG. 6C

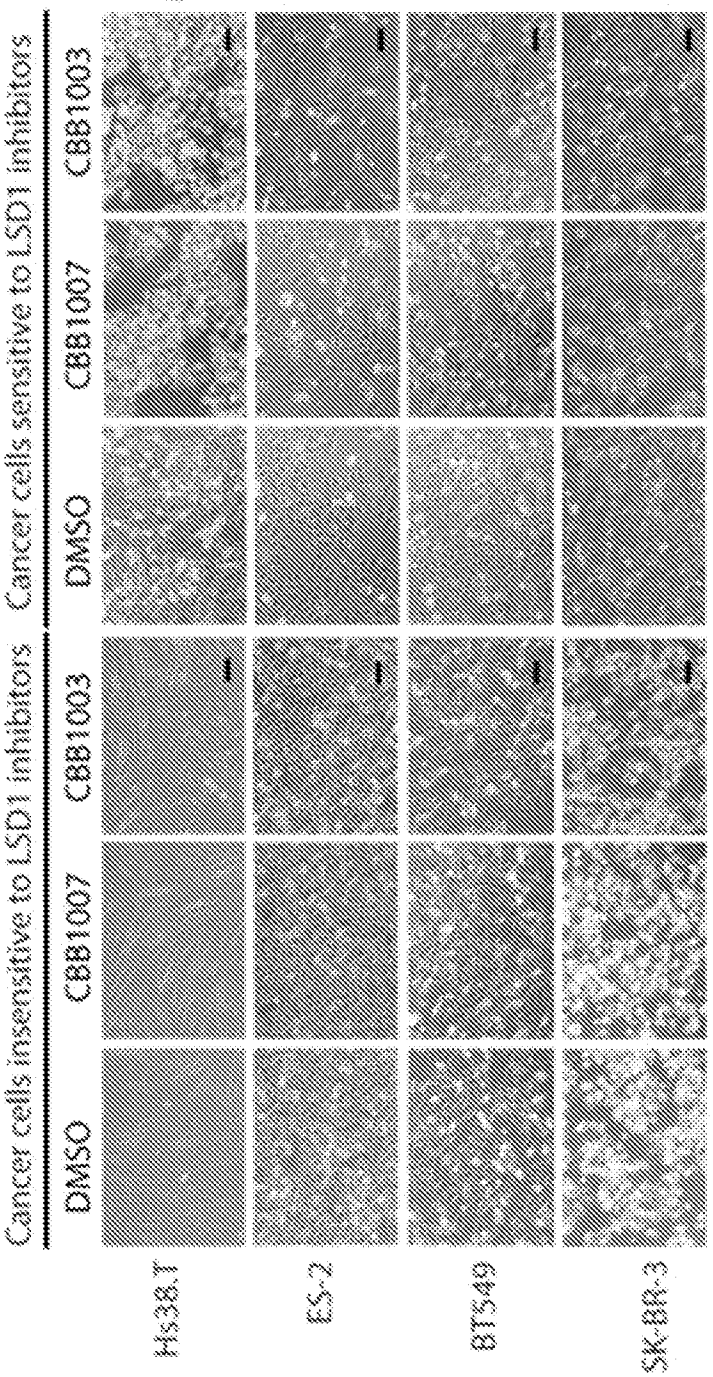

Cancer cells insensitive to LSD1 inhibitors
Cancer cells sensitive to LSD1 inhibitors
DMSO
CBB1007
CBB1003
DMSO
CBB1007
CBB1003
Hs38.T
ES-2
BT549
SK-BR-3
MCF7
SKOV-3
IGROV-1
PA-1

FIG. 7A

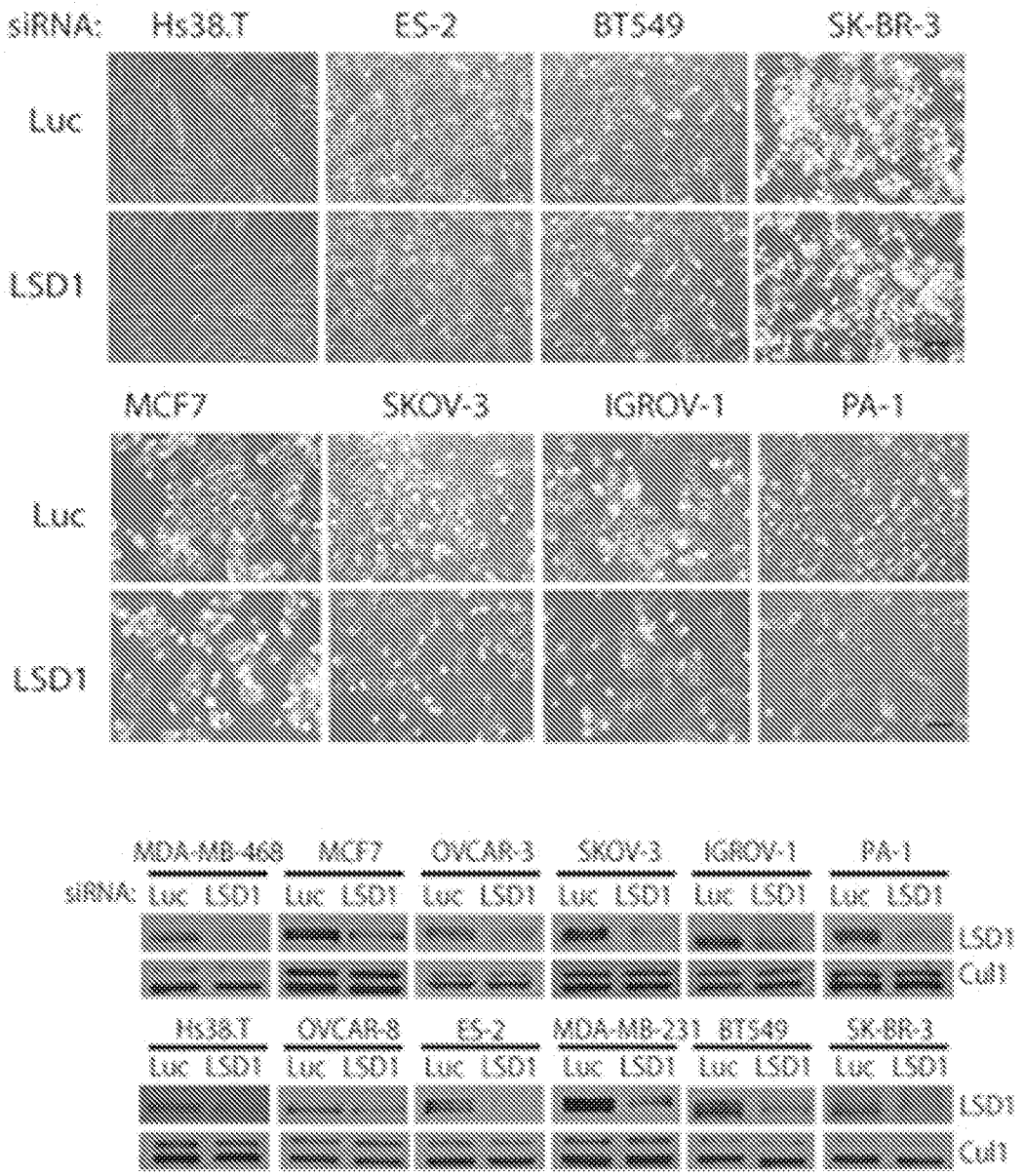

siRNA:
Hs38.T
ES-2
BT549
SK-BR-3
Luc
LSD1
MCF7
SKOV-3
IGROV-1
PA-1
Luc
LSD1
MDA-MB-468
MCF7
OVCAR-3
SKOV-3
IGROV-1
PA-1
siRNA: Luc LSD1 Luc LSD1 Luc LSD1 Luc LSD1 Luc LSD1 Luc LSD1
LSD1
Cul1
Hs38.T
OVCAR-8
ES-2
MDA-MB-231
BT549
SK-BR-3
Luc LSD1 Luc LSD1 Luc LSD1 Luc LSD1 Luc LSD1 Luc LSD1
LSD1
Cul1

FIG. 7B

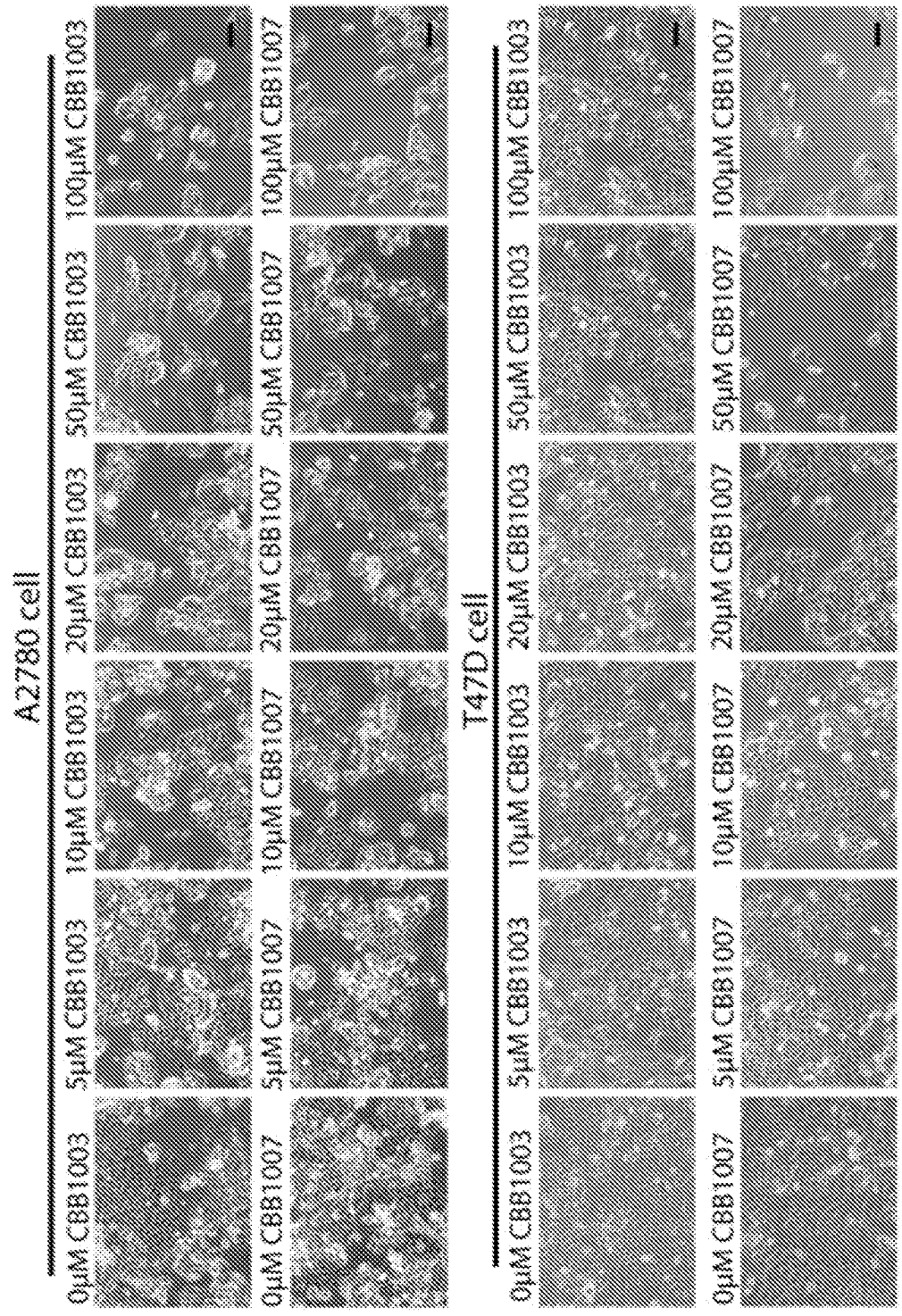

A2780 cell
0μM CBB1003
5μM CBB1003
10μM CBB1003
20μM CBB1003
50μM CBB1003
100μM CBB1003
0μM CBB1007
5μM CBB1007
10μM CBB1007
20μM CBB1007
50μM CBB1007
100μM CBB1007
T47D cell
0μM CBB1003
5μM CBB1003
10μM CBB1003
20μM CBB1003
50μM CBB1003
100μM CBB1003
0μM CBB1007
5μM CBB1007
10μM CBB1007
20μM CBB1007
50μM CBB1007
100μM CBB1007

FIG. 8A

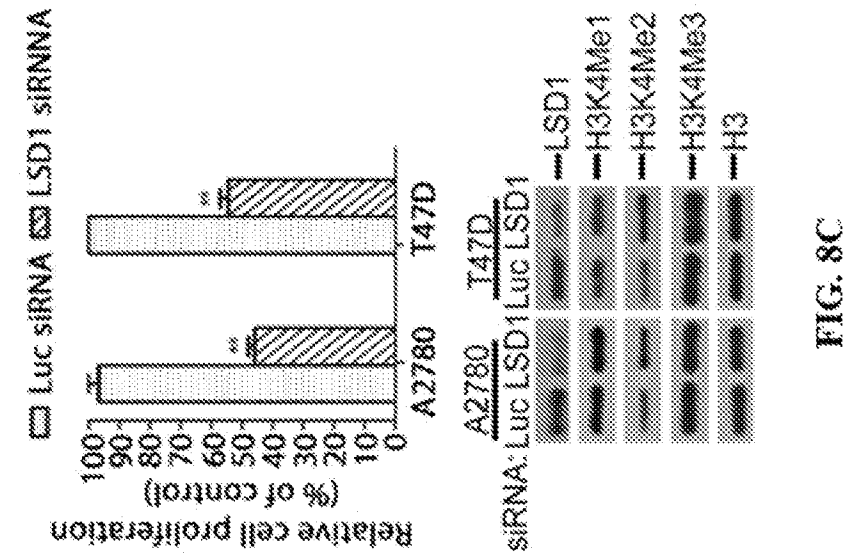

Luc siRNA
LSD1 siRNA
Relative cell proliferation
(% of control)
A2780
T47D
siRNA: Luc LSD1 Luc LSD1
LSD1
H3K4Me1
H3K4Me2
H3K4Me3
H3

FIG. 8C

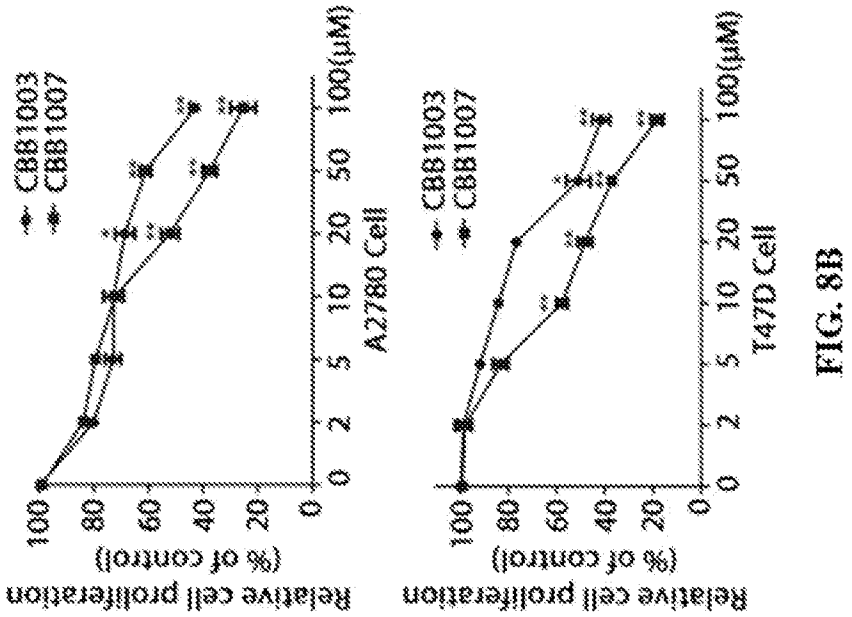

CBB1003
CBB1007
Relative cell proliferation
(% of control)
A2780 Cell
T47D Cell
100(μM)

FIG. 8B

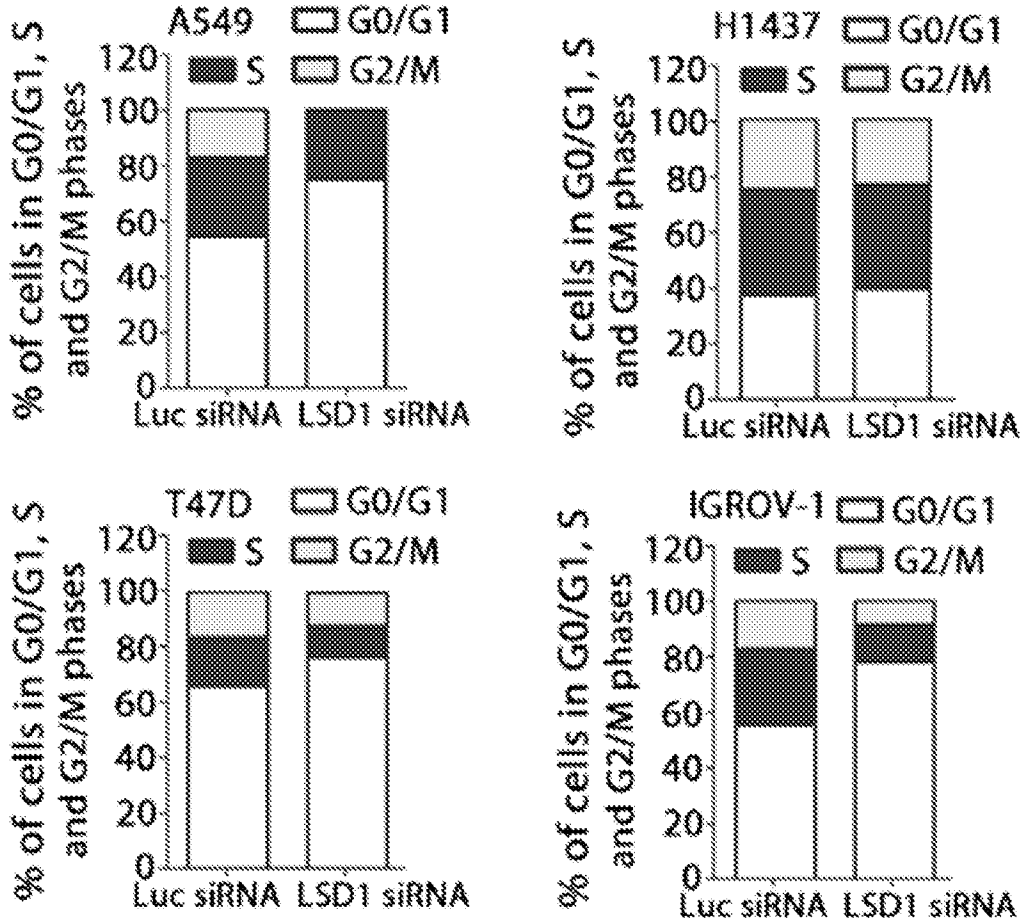

A549
H1437
T47D
IGROV-1
G0/G1
S
G2/M
% of cells in G0/G1, S and G2/M phases
120
100
80
60
40
20
0
Luc siRNA
LSD1 siRNA

FIG. 9A

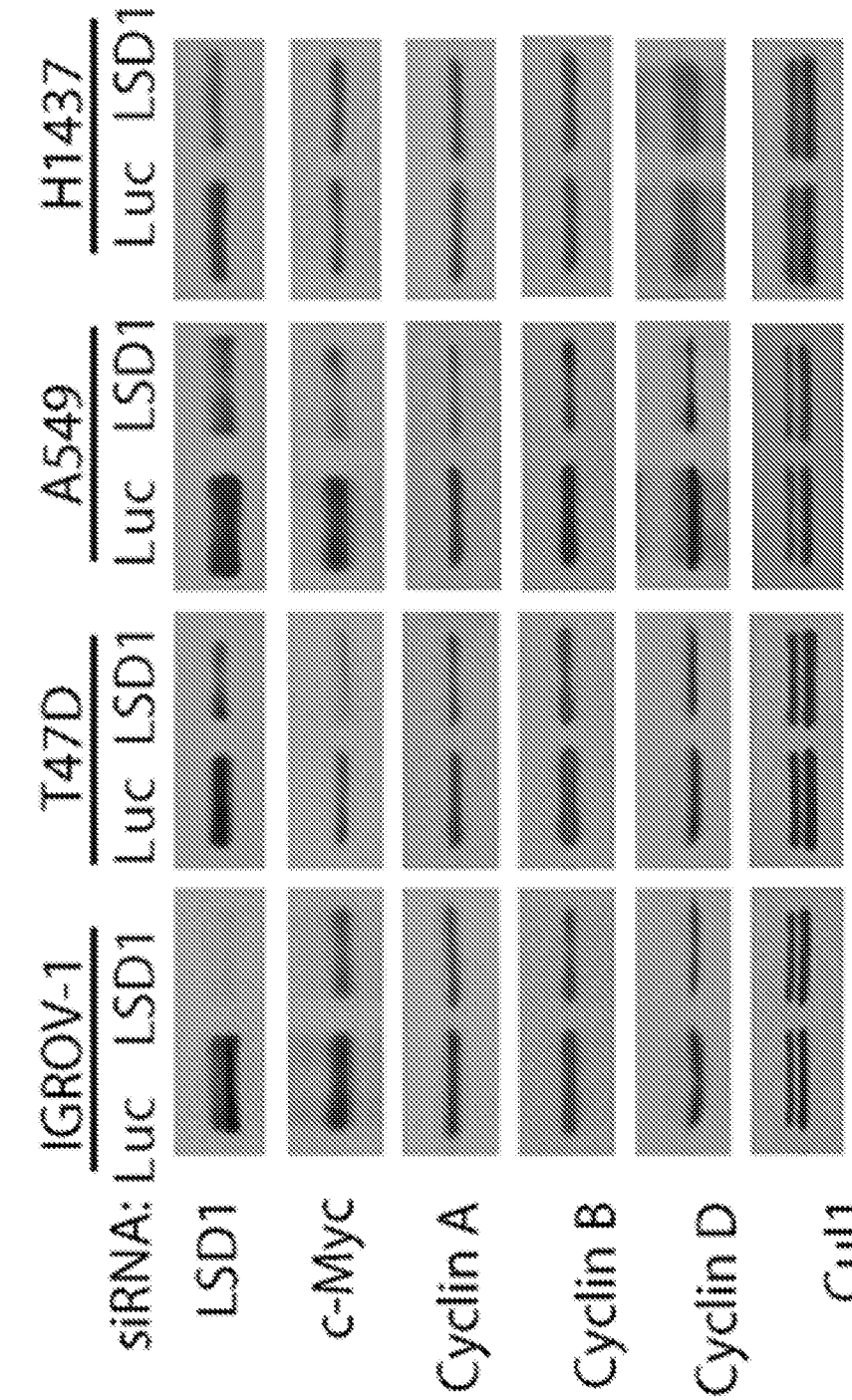

IGROV-1
T47D
A549
H1437
siRNA: Luc LSD1 Luc LSD1 Luc LSD1 Luc LSD1
LSD1
c-Myc
Cyclin A
Cyclin B
Cyclin D
Cul1

FIG. 9B

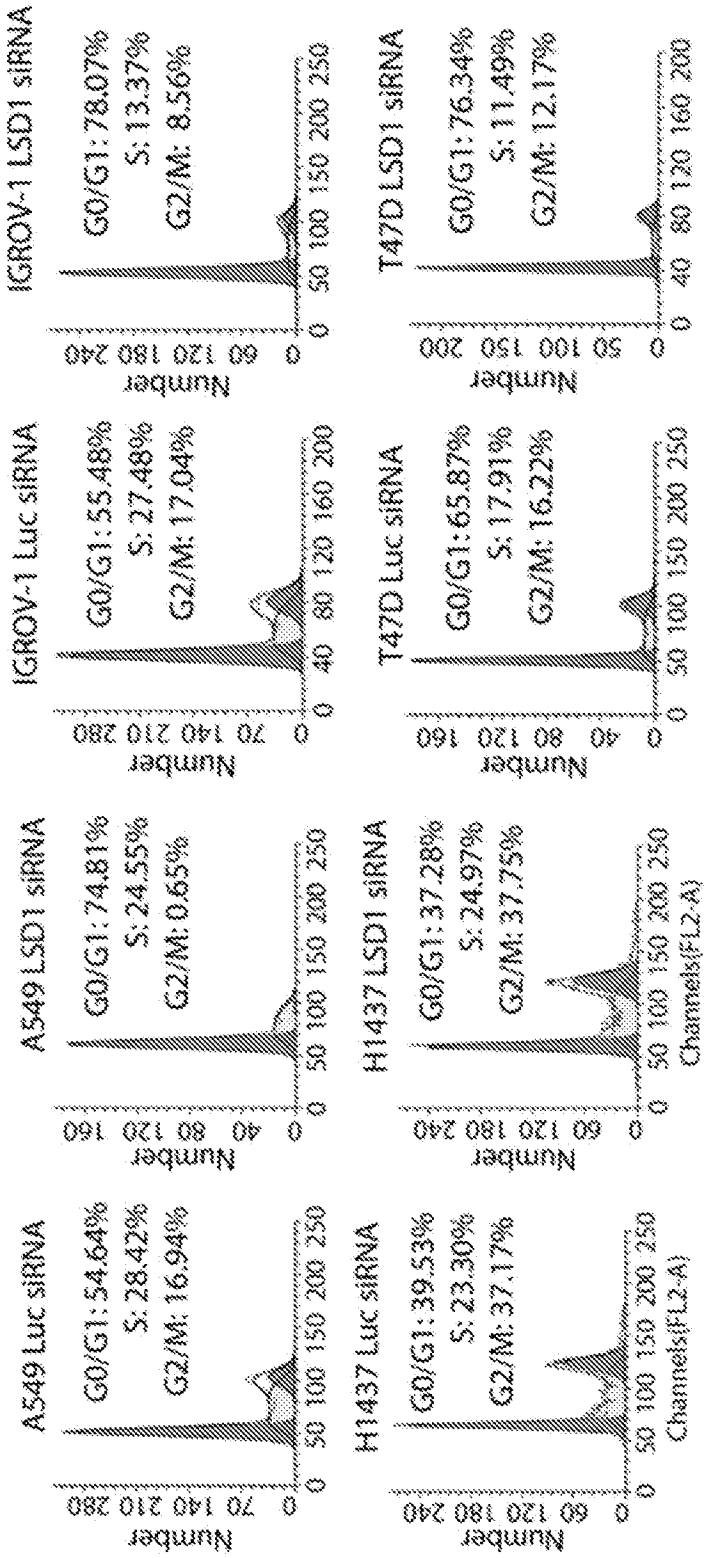

A549 Luc siRNA
G0/G1: 54.64%
S: 28.42%
G2/M: 16.94%
A549 LSD1 siRNA
G0/G1: 74.81%
S: 24.55%
G2/M: 0.65%
IGROV-1 Luc siRNA
G0/G1: 55.48%
S: 27.48%
G2/M: 17.04%
IGROV-1 LSD1 siRNA
G0/G1: 78.07%
S: 13.37%
G2/M: 8.56%
H1437 Luc siRNA
G0/G1: 39.53%
S: 23.30%
G2/M: 37.17%
H1437 LSD1 siRNA
G0/G1: 37.28%
S: 24.97%
G2/M: 37.75%
T47D Luc siRNA
G0/G1: 65.87%
S: 17.91%
G2/M: 16.22%
T47D LSD1 siRNA
G0/G1: 76.34%
S: 11.49%
G2/M: 12.17%
Number
Channels(FL2-A)

FIG. 9C

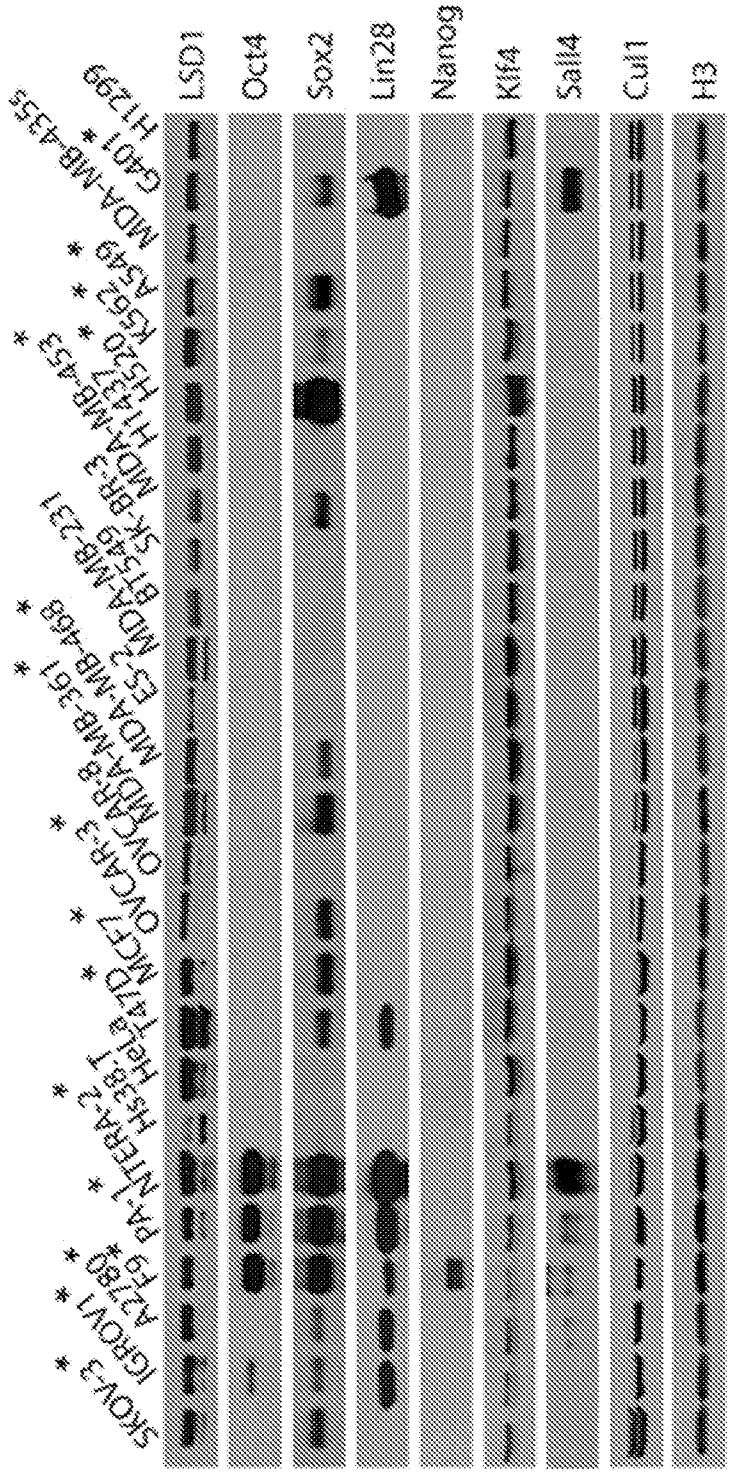

LSD1
Oct4
Sox2
Lin28
Nanog
Klf4
Sall4
Cul1
H3
SKOV-3
IGROV1
A2780
PA-1
NTERA-2
H358
HeLa
T47D
MCF7
OVCAR-3
OVCAR8
MDA-MB-361
MDA-MB-468
ES-2
MDA-MB-231
BT549
SK-BR-3
MDA-MB-453
H1437
H520
K562
A549
MDA-MB-435
G401
H1299

FIG. 10A

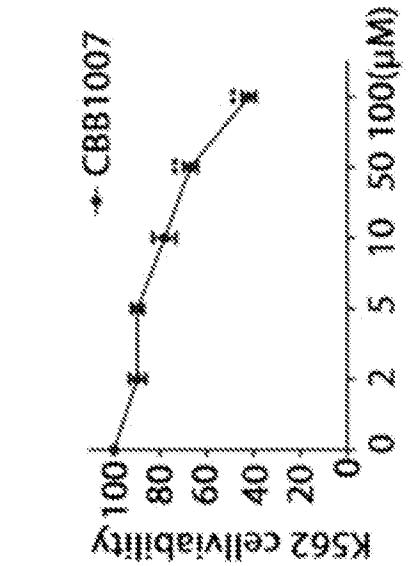


FIG. 10C

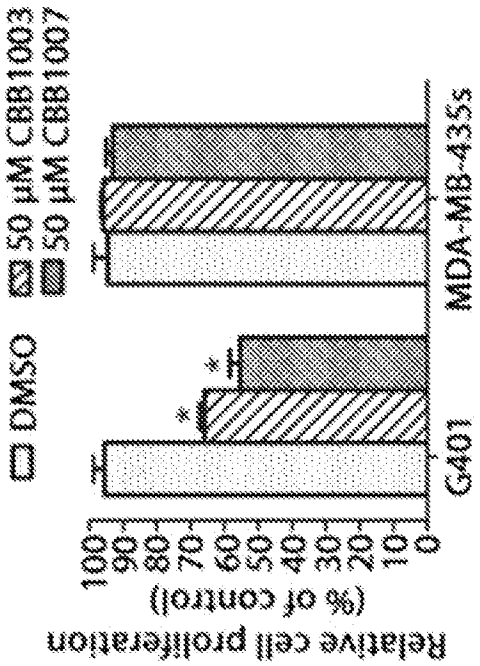


FIG. 10B

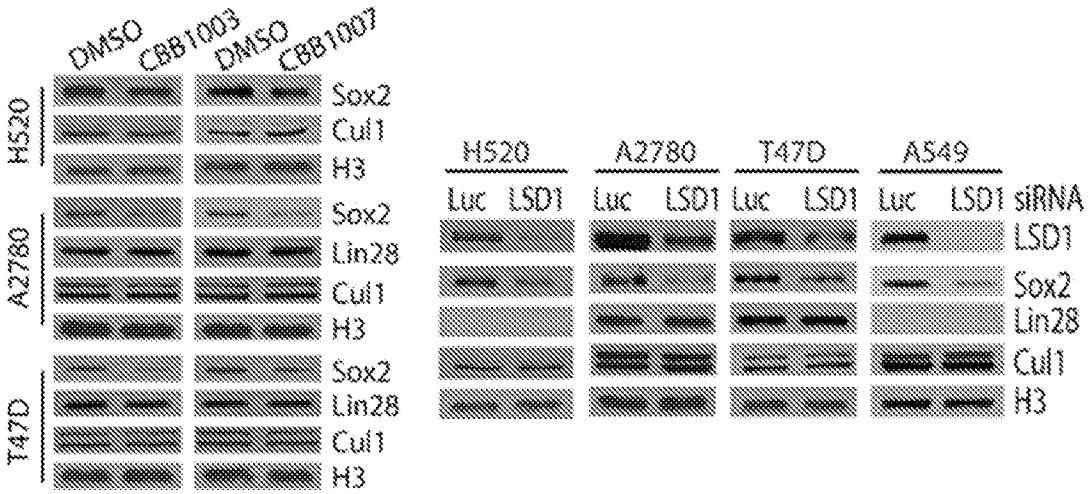


FIG. 11A

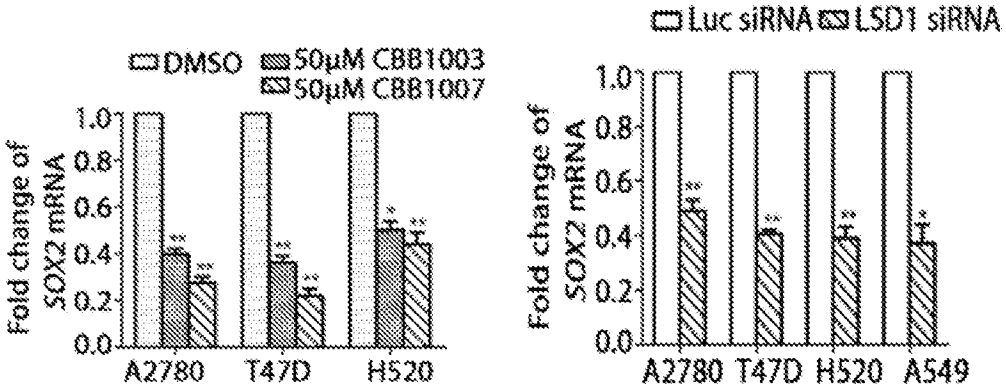


FIG. 11B

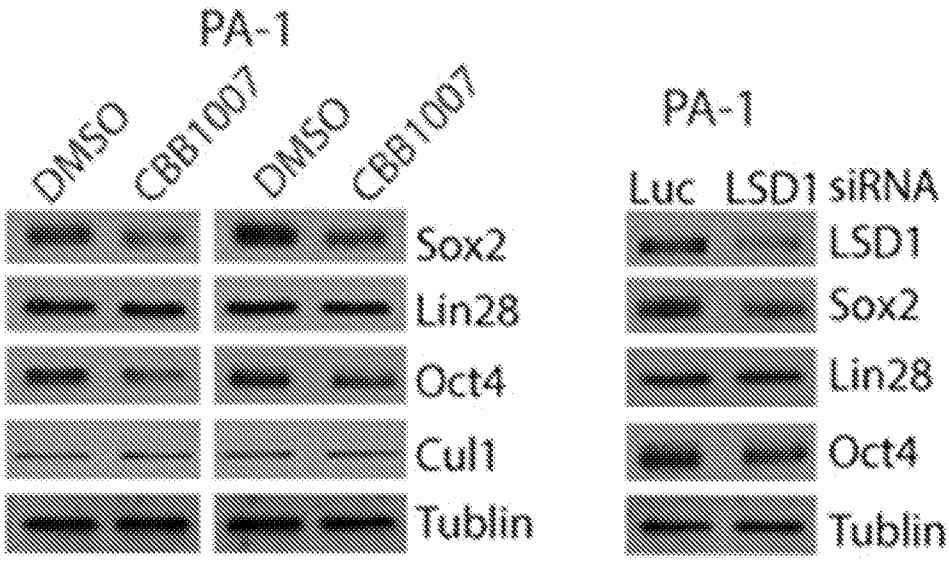

PA-1
DMSO
CBB1007
DMSO
CBB1007
Sox2
Lin28
Oct4
Cul1
Tublin
PA-1
Luc
LSD1 siRNA
LSD1
Sox2
Lin28
Oct4
Tublin

FIG. 11C

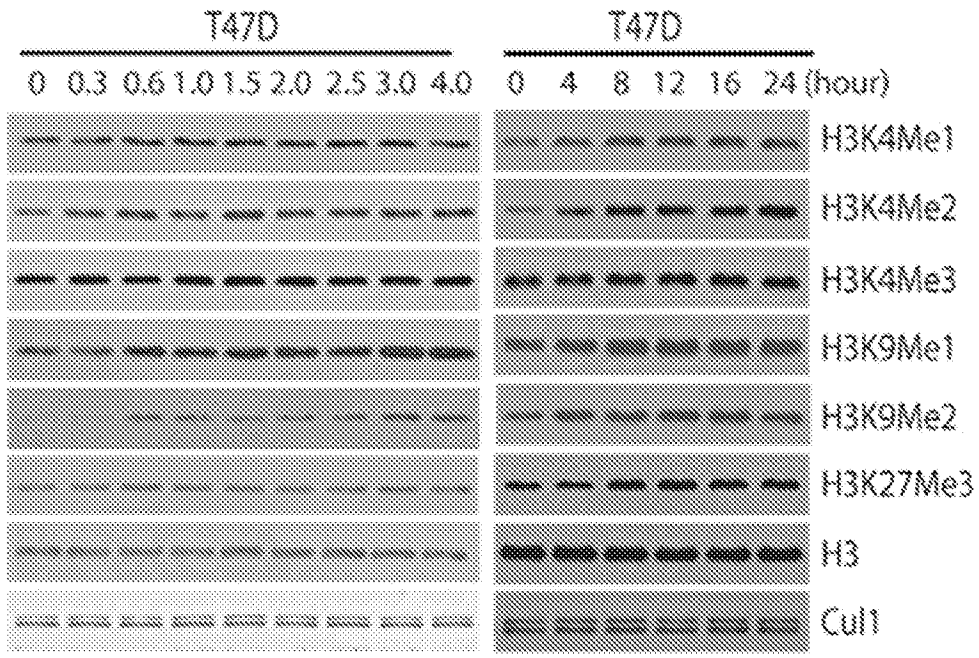


FIG. 12A

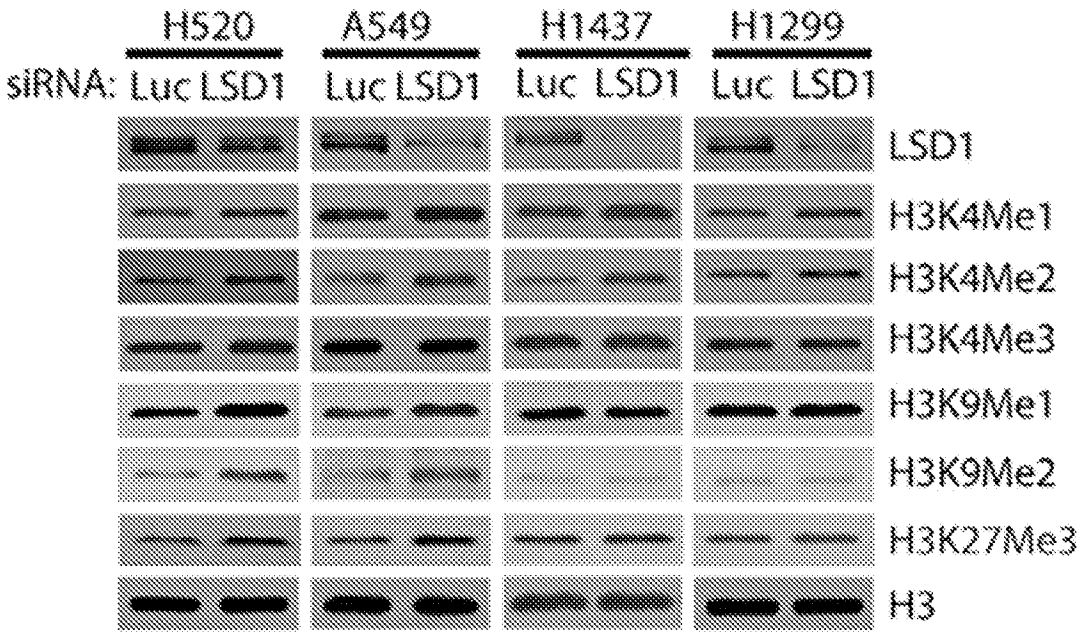


FIG. 12B

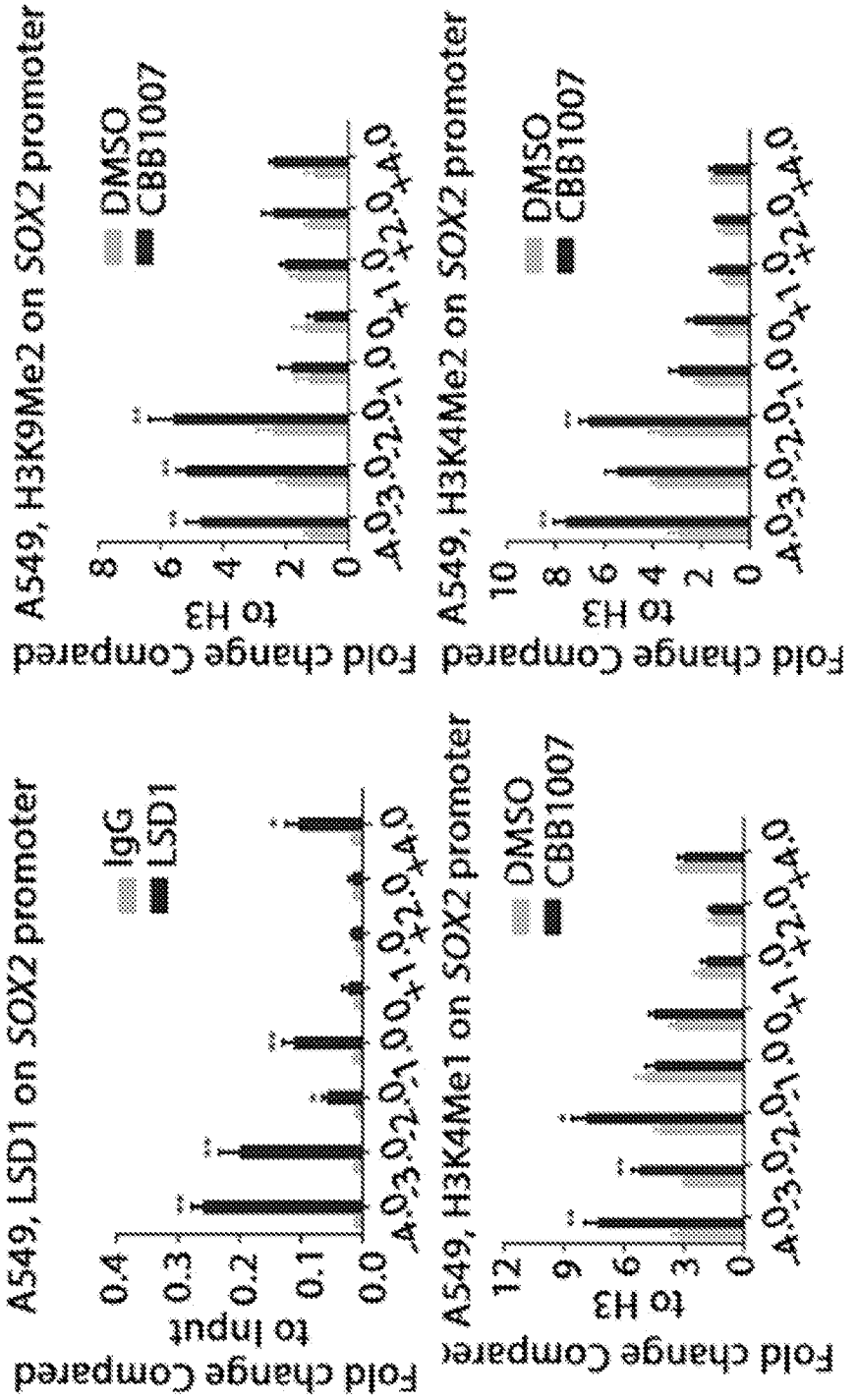

A549, LSD1 on SOX2 promoter
IgG
LSD1
Fold change Compared to Input
0.4
0.3
0.2
0.1
0.0
A549, H3K9Me2 on SOX2 promoter
DMSO
CBB1007
Fold change Compared to H3
8
6
4
2
0
A549, H3K4Me1 on SOX2 promoter
DMSO
CBB1007
Fold change Compared to H3
12
9
6
3
0
A549, H3K4Me2 on SOX2 promoter
DMSO
CBB1007
Fold change Compared to H3
10
8
6
4
2
0

FIG. 13A

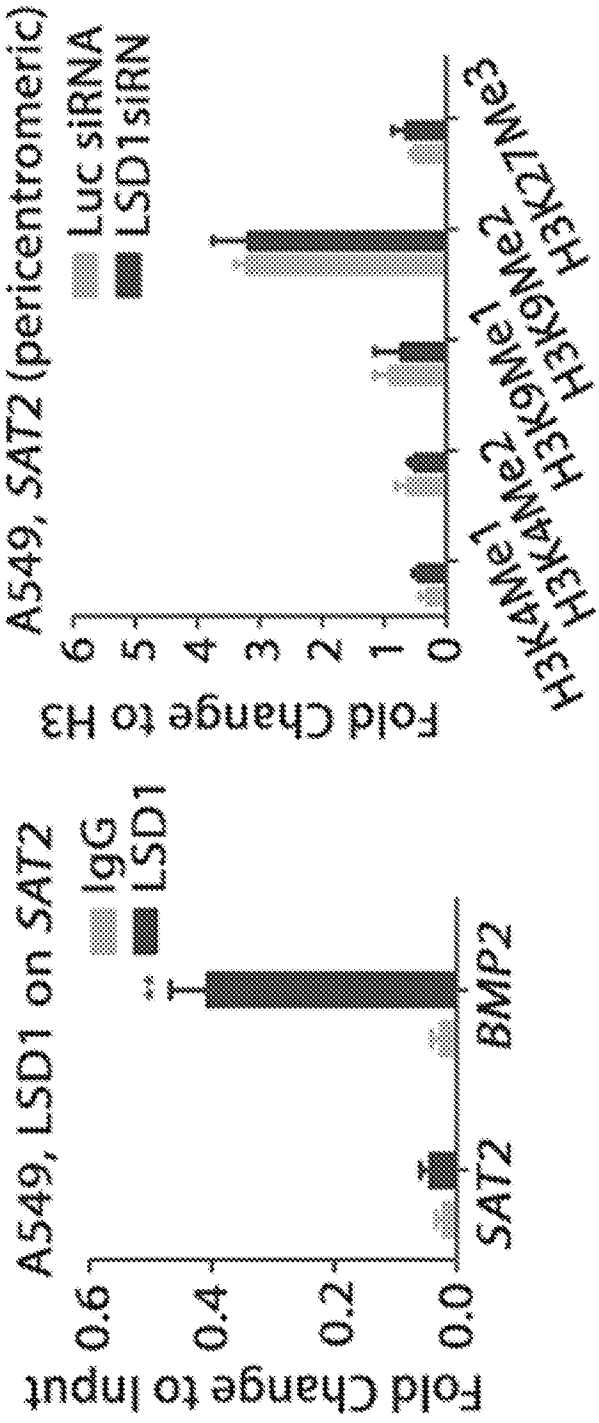

A549, SAT2 (pericentromeric)
Luc siRNA
LSD1siRN
Fold Change to H3
0
1
2
3
4
5
6
H3K4Me1
H3K4Me2
H3K9Me1
H3K9Me2
H3K27Me3
A549, LSD1 on SAT2
IgG
LSD1
**
Fold Change to Input
0.0
0.2
0.4
0.6
SAT2
BMP2

FIG. 13B

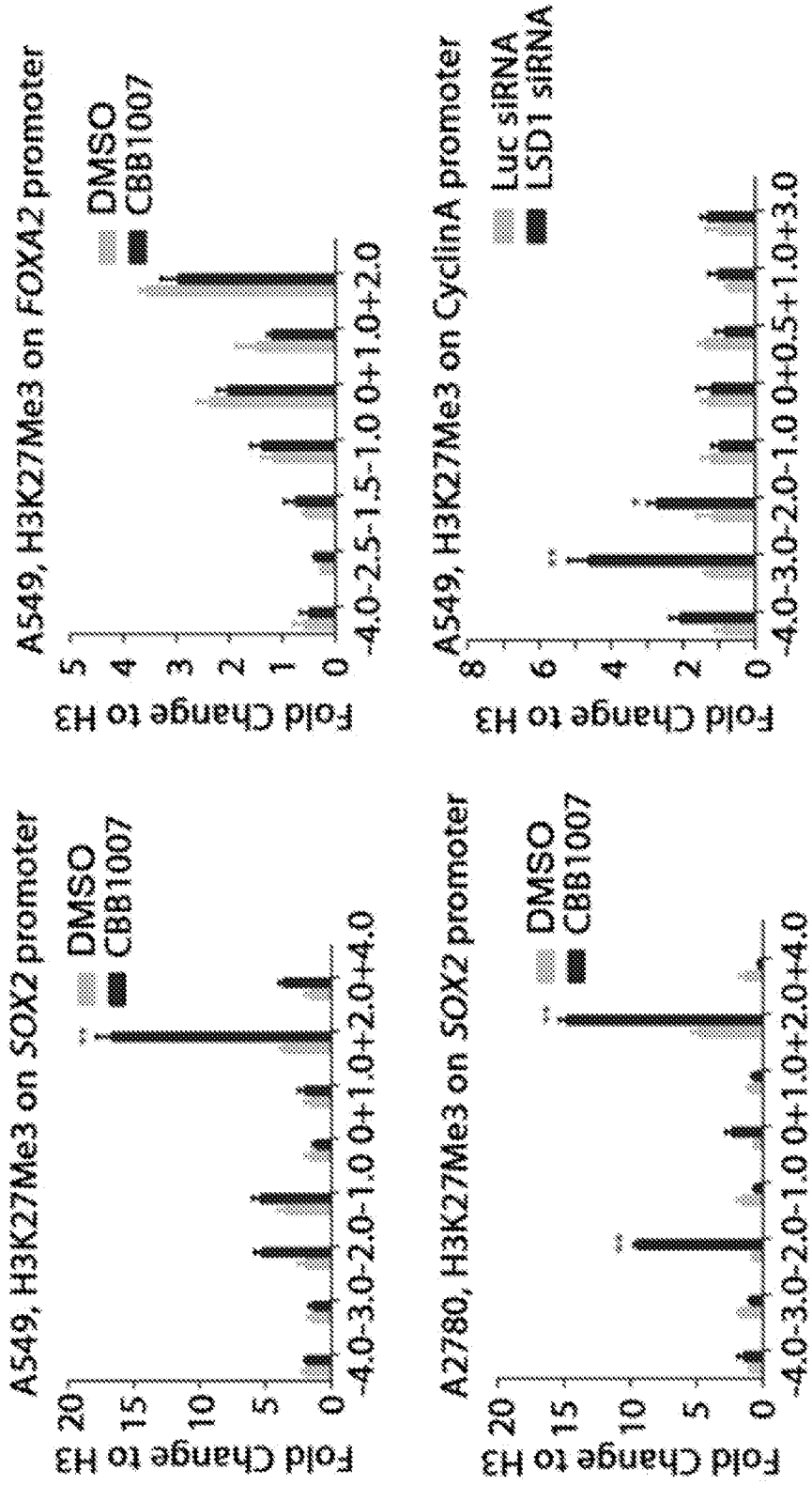

A549, H3K27Me3 on SOX2 promoter
DMSO
CBB1007
Fold Change to H3
20
15
10
5
0
-4.0 -3.0 -2.0 -1.0 0 +1.0 +2.0 +4.0
A549, H3K27Me3 on FOXA2 promoter
DMSO
CBB1007
Fold Change to H3
5
4
3
2
1
0
-4.0 -2.5 -1.5 -1.0 0 +1.0 +2.0
A2780, H3K27Me3 on SOX2 promoter
DMSO
CBB1007
Fold Change to H3
20
15
10
5
0
-4.0 -3.0 -2.0 -1.0 0 +1.0 +2.0 +4.0
A549, H3K27Me3 on CyclinA promoter
Luc siRNA
LSD1 siRNA
Fold Change to H3
8
6
4
2
0
-4.0 -3.0 -2.0 -1.0 0 +0.5 +1.0 +3.0

FIG. 13C

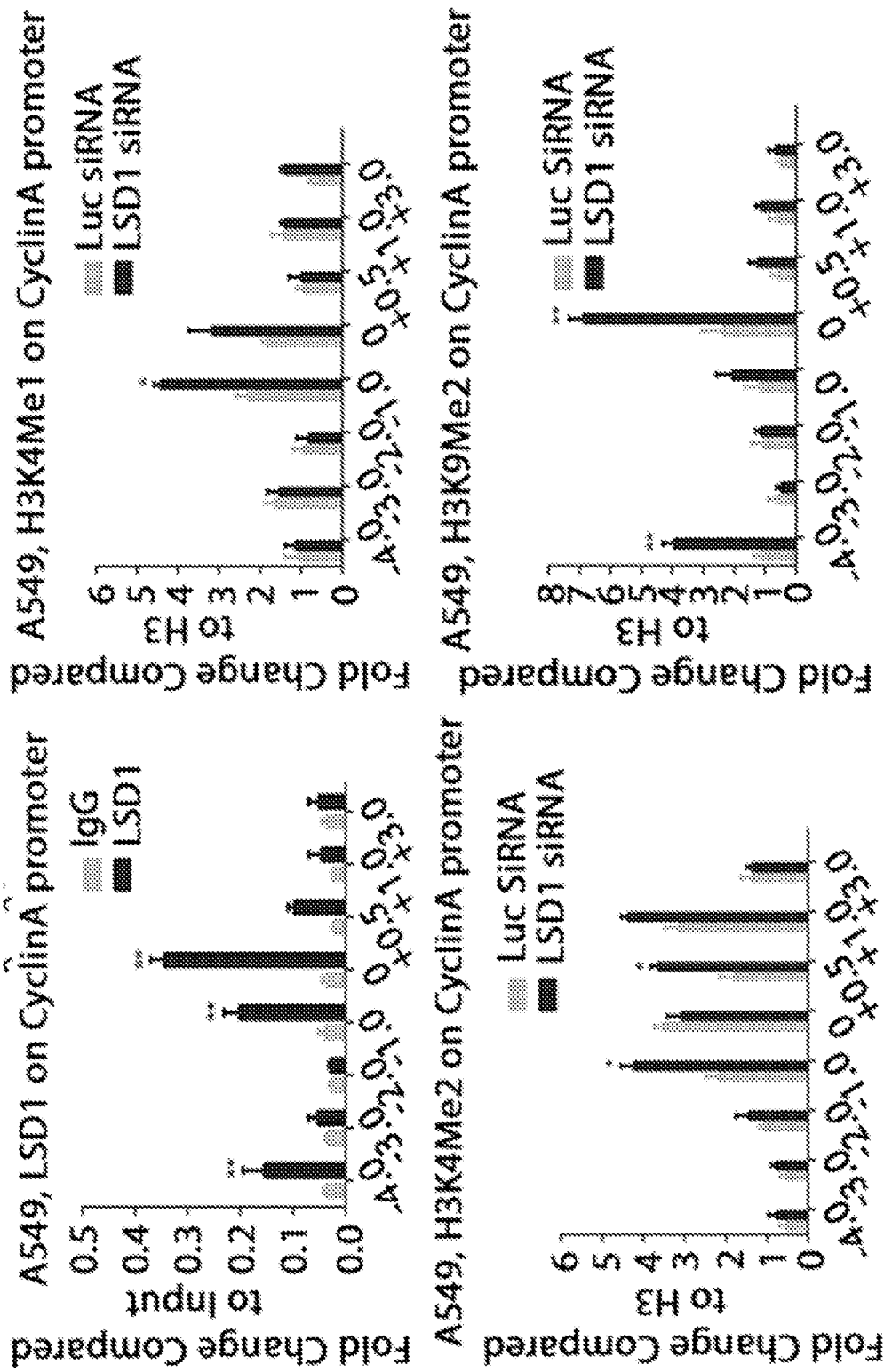

A549, LSD1 on CyclinA promoter
IgG
LSD1
Fold Change Compared to Input
A549, H3K4Me1 on CyclinA promoter
Luc siRNA
LSD1 siRNA
Fold Change Compared to H3
A549, H3K9Me2 on CyclinA promoter
Luc SiRNA
LSD1 siRNA
Fold Change Compared to H3
A549, H3K4Me2 on CyclinA promoter
Luc SiRNA
LSD1 siRNA
Fold Change Compared to H3

FIG. 14

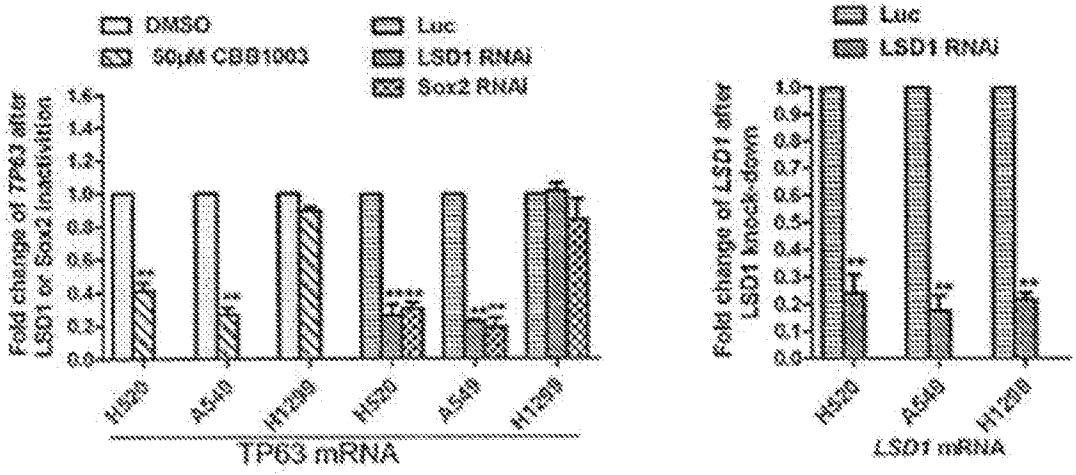


FIG. 15A

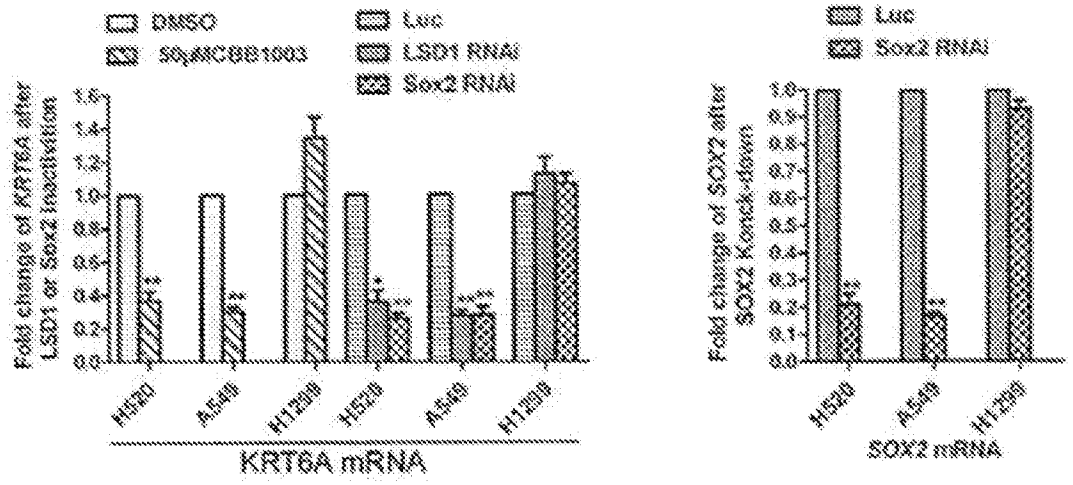


FIG. 15B

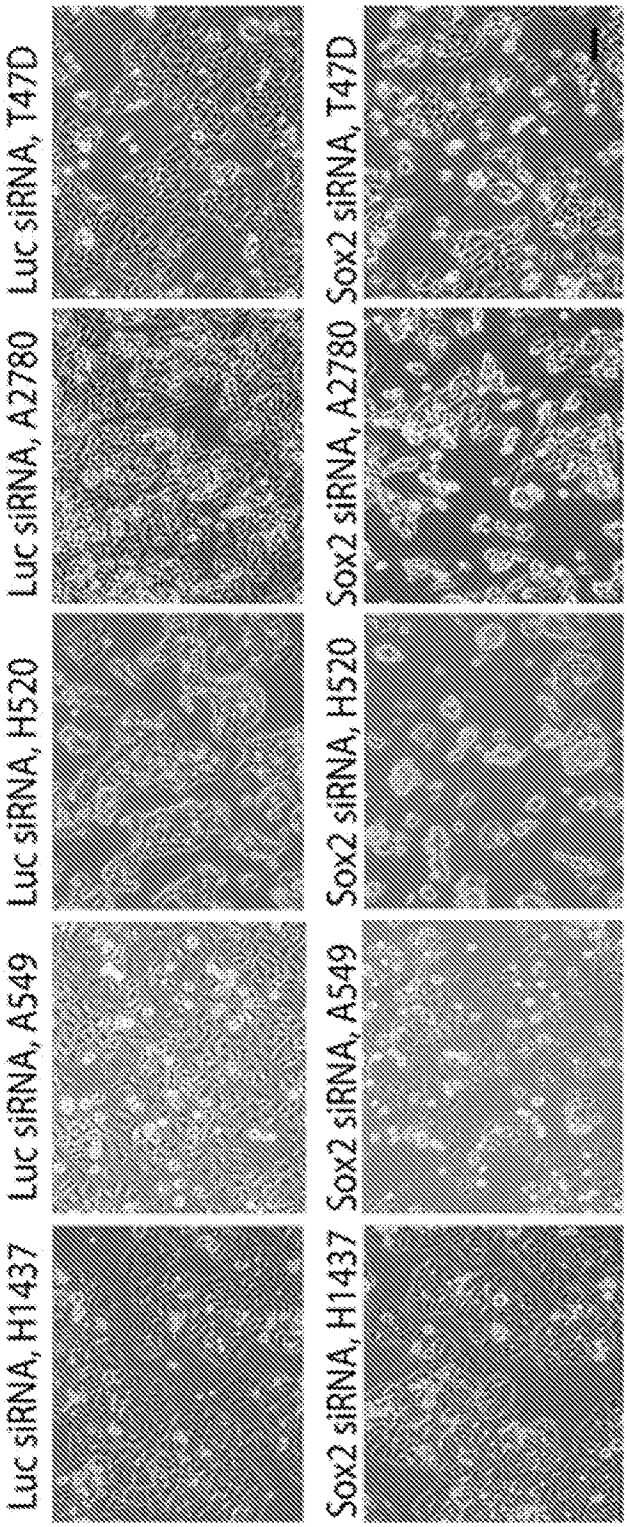

Luc siRNA, H1437
Luc siRNA, A549
Luc siRNA, H520
Luc siRNA, A2780
Luc siRNA, T47D
Sox2 siRNA, H1437
Sox2 siRNA, A549
Sox2 siRNA, H520
Sox2 siRNA, A2780
Sox2 siRNA, T47D

FIG. 16A

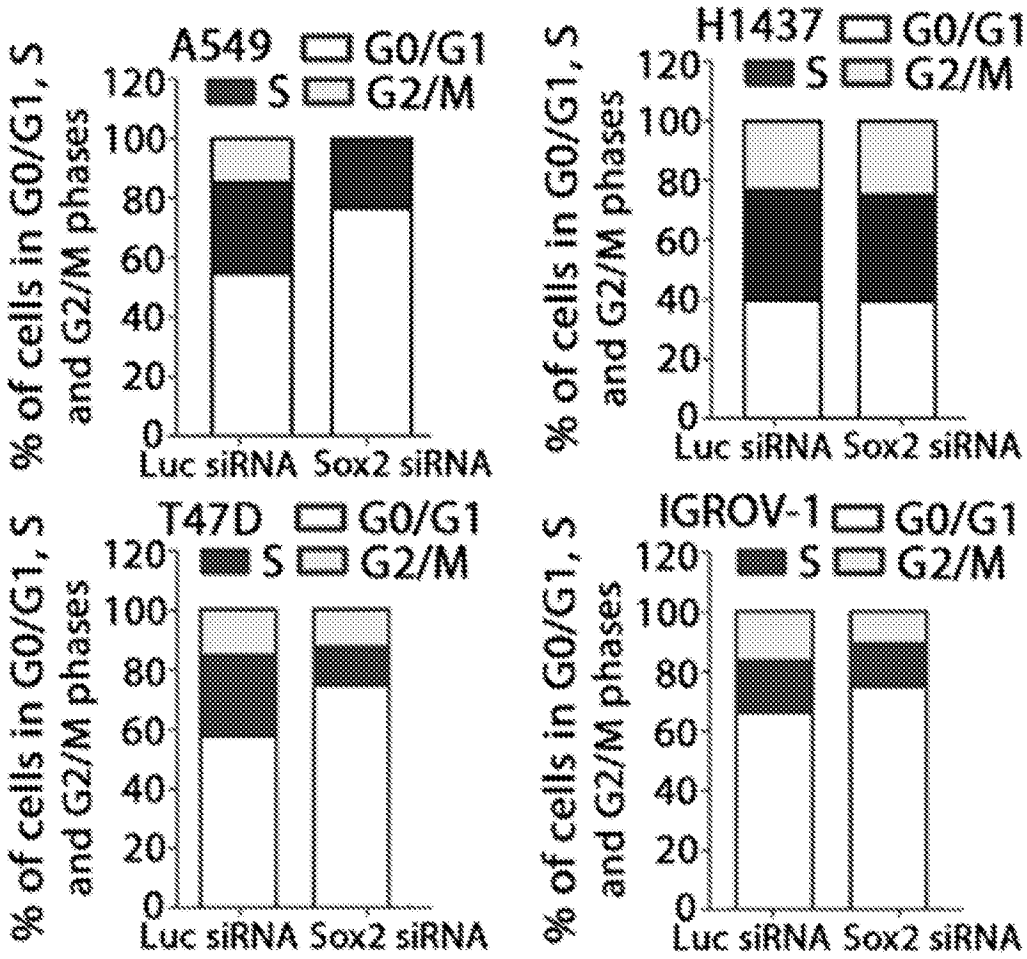

A549
H1437
T47D
IGROV-1
G0/G1
S
G2/M
% of cells in G0/G1, S and G2/M phases
0
20
40
60
80
100
120
Luc siRNA
Sox2 siRNA

FIG. 16B

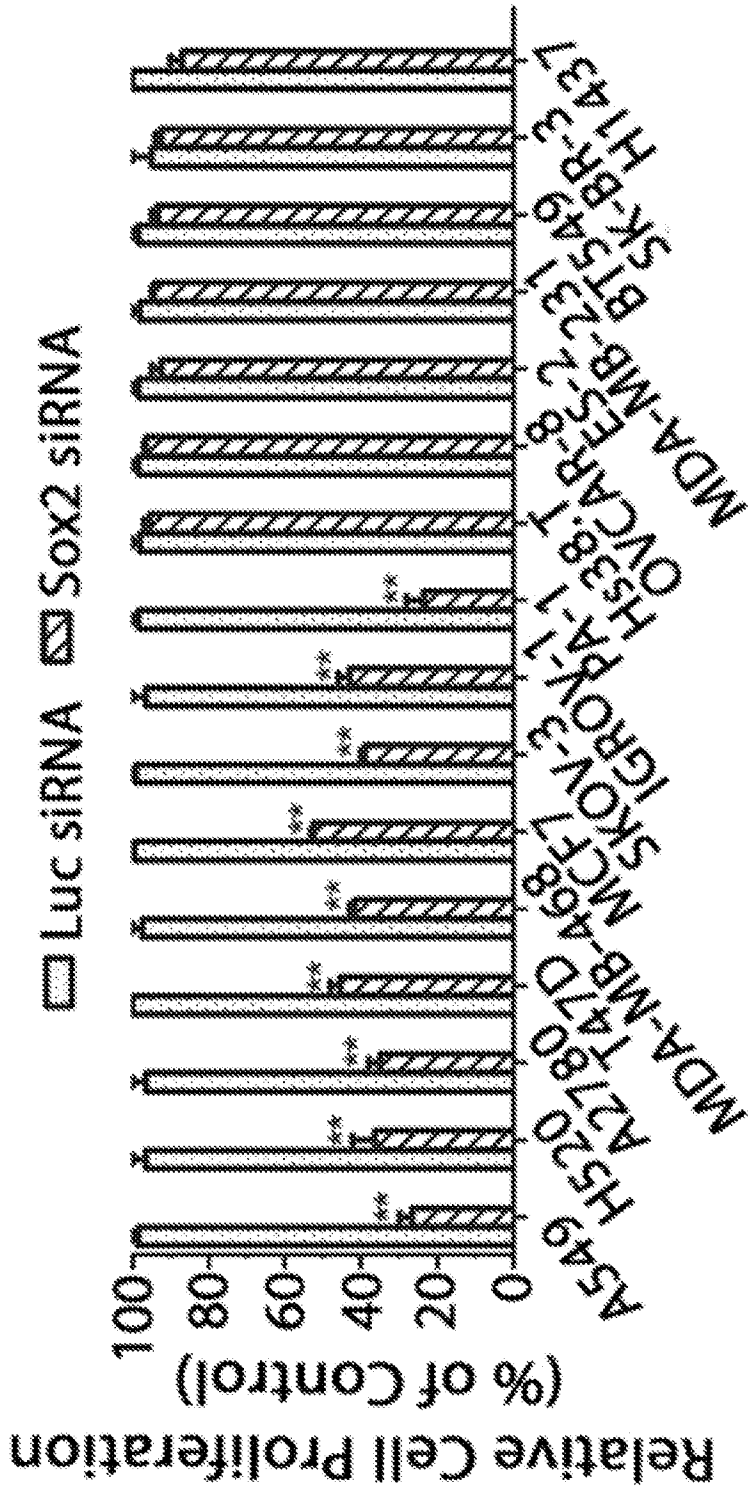

Relative Cell Proliferation
(% of Control)
100
80
60
40
20
0
Luc siRNA
Sox2 siRNA
A549
H520
A2780
T47D
MDA-MB-468
MCF7
SKOV3
IGROV1
MDA-MB-231
HS38.T
OVCAR8
ES-2
BT549
SK-BR-3
HTB37

FIG. 16C

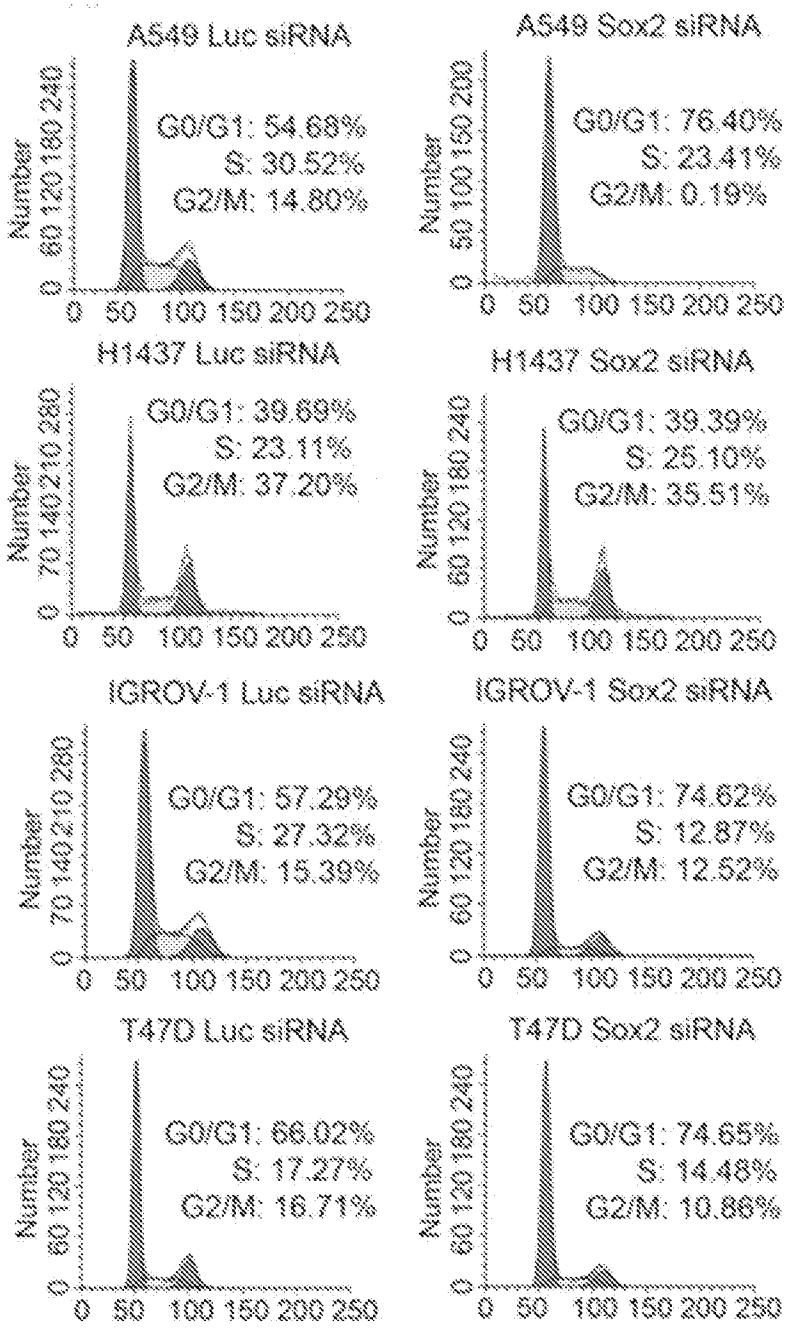

A549 Luc siRNA
G0/G1: 54.68%
S: 30.52%
G2/M: 14.80%
A549 Sox2 siRNA
G0/G1: 76.40%
S: 23.41%
G2/M: 0.19%
H1437 Luc siRNA
G0/G1: 39.69%
S: 23.11%
G2/M: 37.20%
H1437 Sox2 siRNA
G0/G1: 39.39%
S: 25.10%
G2/M: 35.51%
IGROV-1 Luc siRNA
G0/G1: 57.29%
S: 27.32%
G2/M: 15.39%
IGROV-1 Sox2 siRNA
G0/G1: 74.62%
S: 12.87%
G2/M: 12.52%
T47D Luc siRNA
G0/G1: 66.02%
S: 17.27%
G2/M: 16.71%
T47D Sox2 siRNA
G0/G1: 74.65%
S: 14.48%
G2/M: 10.86%
Number
0 50 100 150 200 250

FIG. 17A

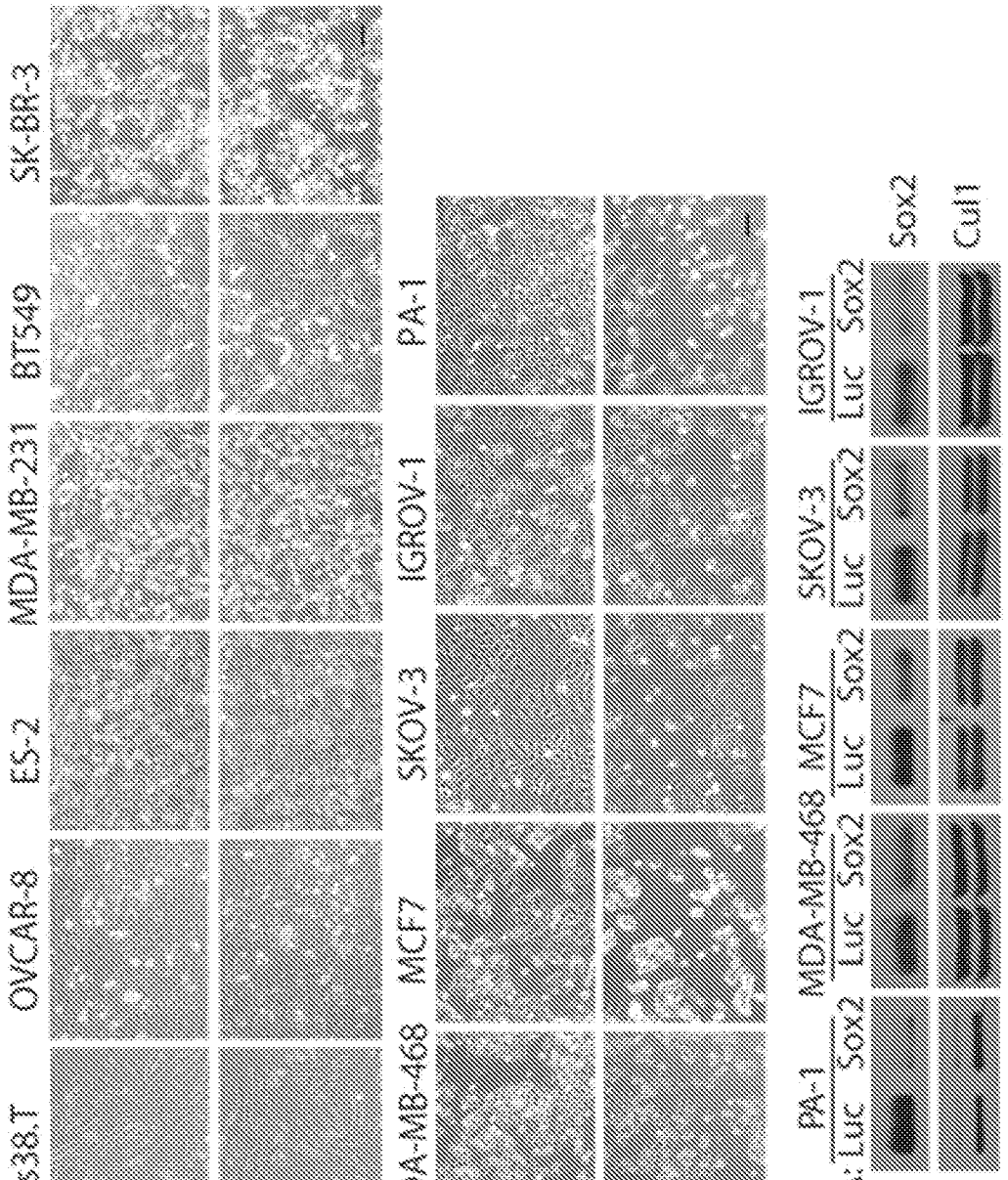

siRNA:
Hs38.T
OVCAR-8
ES-2
MDA-MB-231
BT549
SK-BR-3
Luc
Sox2
MDA-MB-468
MCF7
SKOV-3
IGROV-1
PA-1
Luc
Sox2
siRNA:
PA-1
Luc Sox2
MDA-MB-468
Luc Sox2
MCF7
Luc Sox2
SKOV-3
Luc Sox2
IGROV-1
Luc Sox2
Sox2
Cul1

FIG. 17B

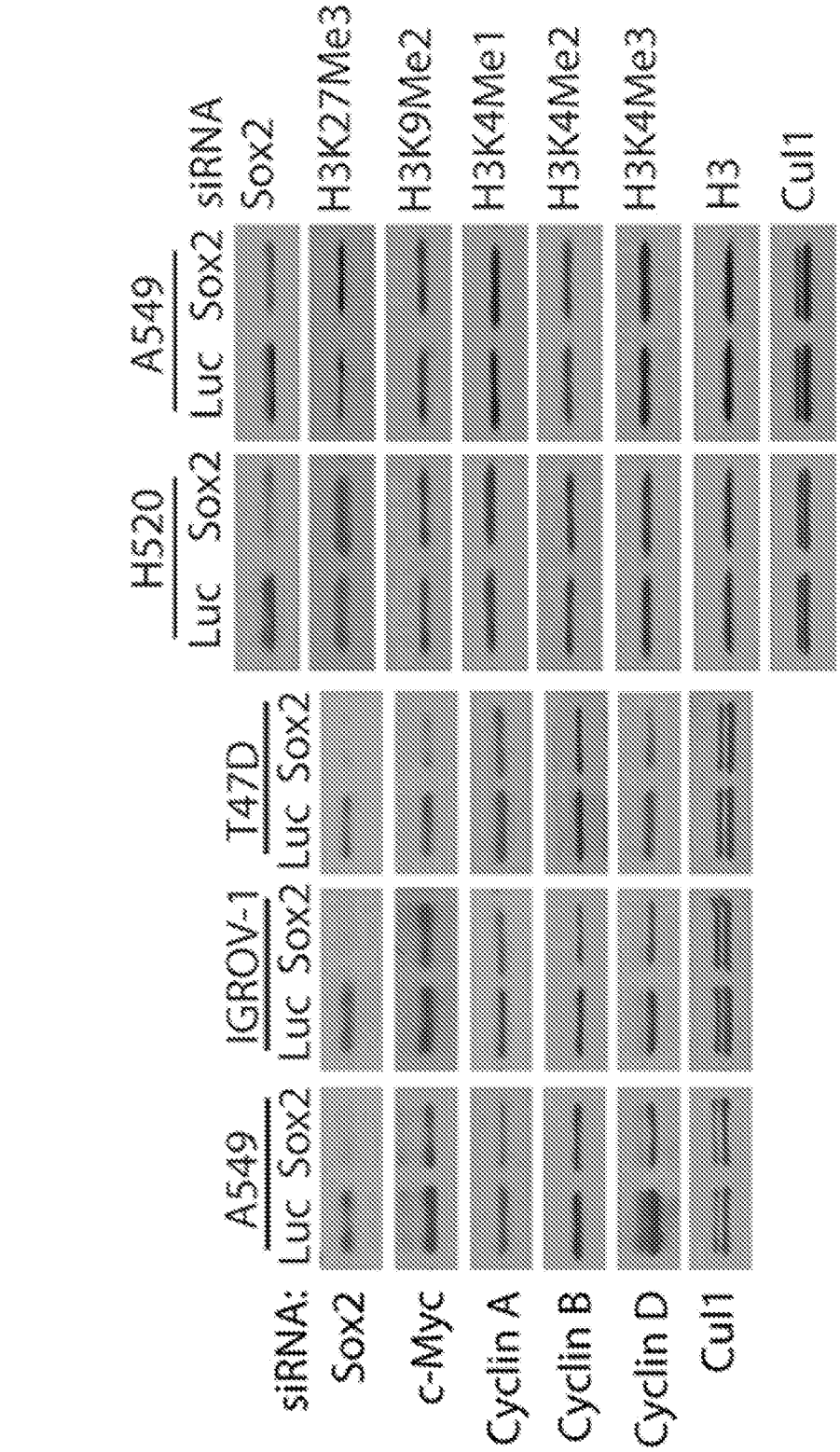

siRNA:
Sox2
c-Myc
Cyclin A
Cyclin B
Cyclin D
Cul1
A549
Luc Sox2
IGROV-1
Luc Sox2
T47D
Luc Sox2
H520
Luc Sox2
A549
Luc Sox2
siRNA
Sox2
H3K27Me3
H3K9Me2
H3K4Me1
H3K4Me2
H3K4Me3
H3
Cul1

FIG. 18A

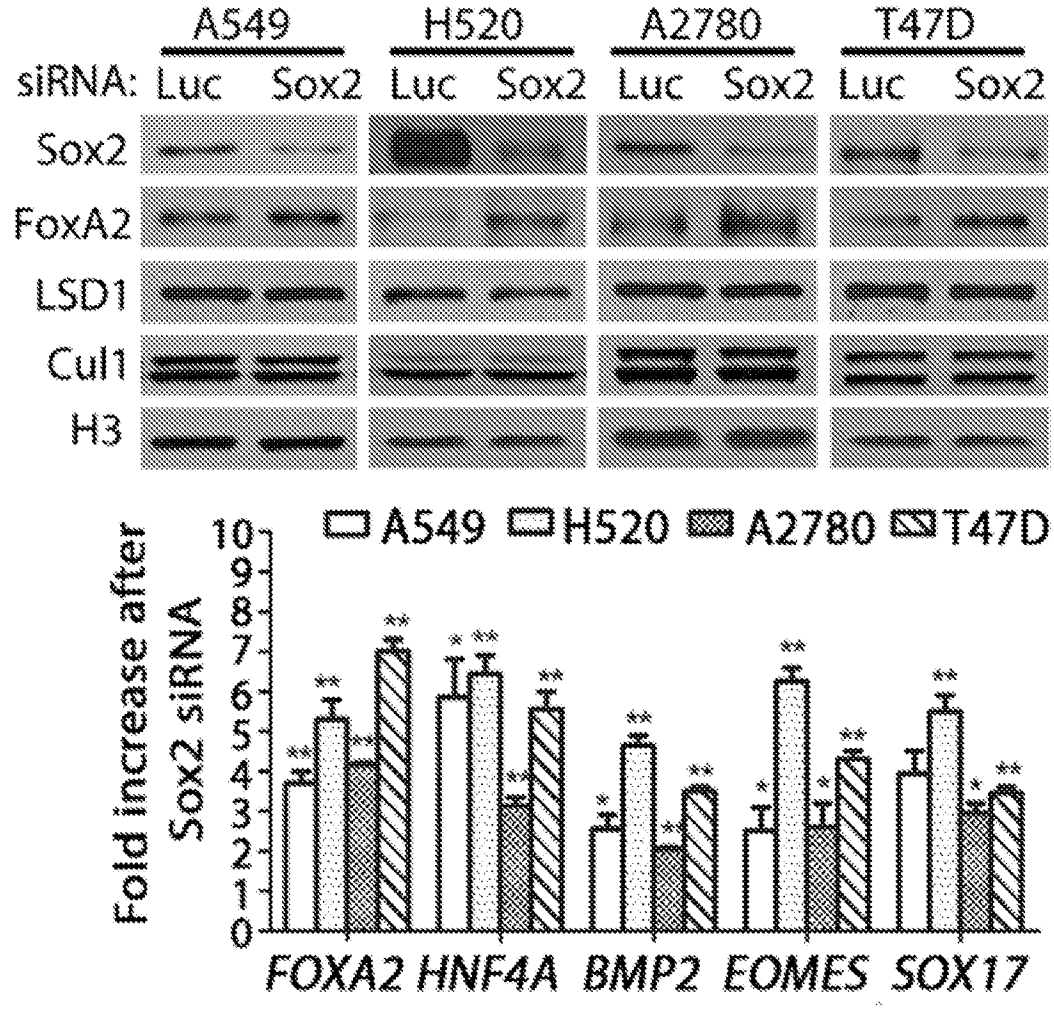

A549
H520
A2780
T47D
siRNA: Luc Sox2 Luc Sox2 Luc Sox2 Luc Sox2
Sox2
FoxA2
LSD1
Cul1
H3
A549 H520 A2780 T47D
Fold increase after Sox2 siRNA
0 1 2 3 4 5 6 7 8 9 10
FOXA2 HNF4A BMP2 EOMES SOX17

FIG. 18B

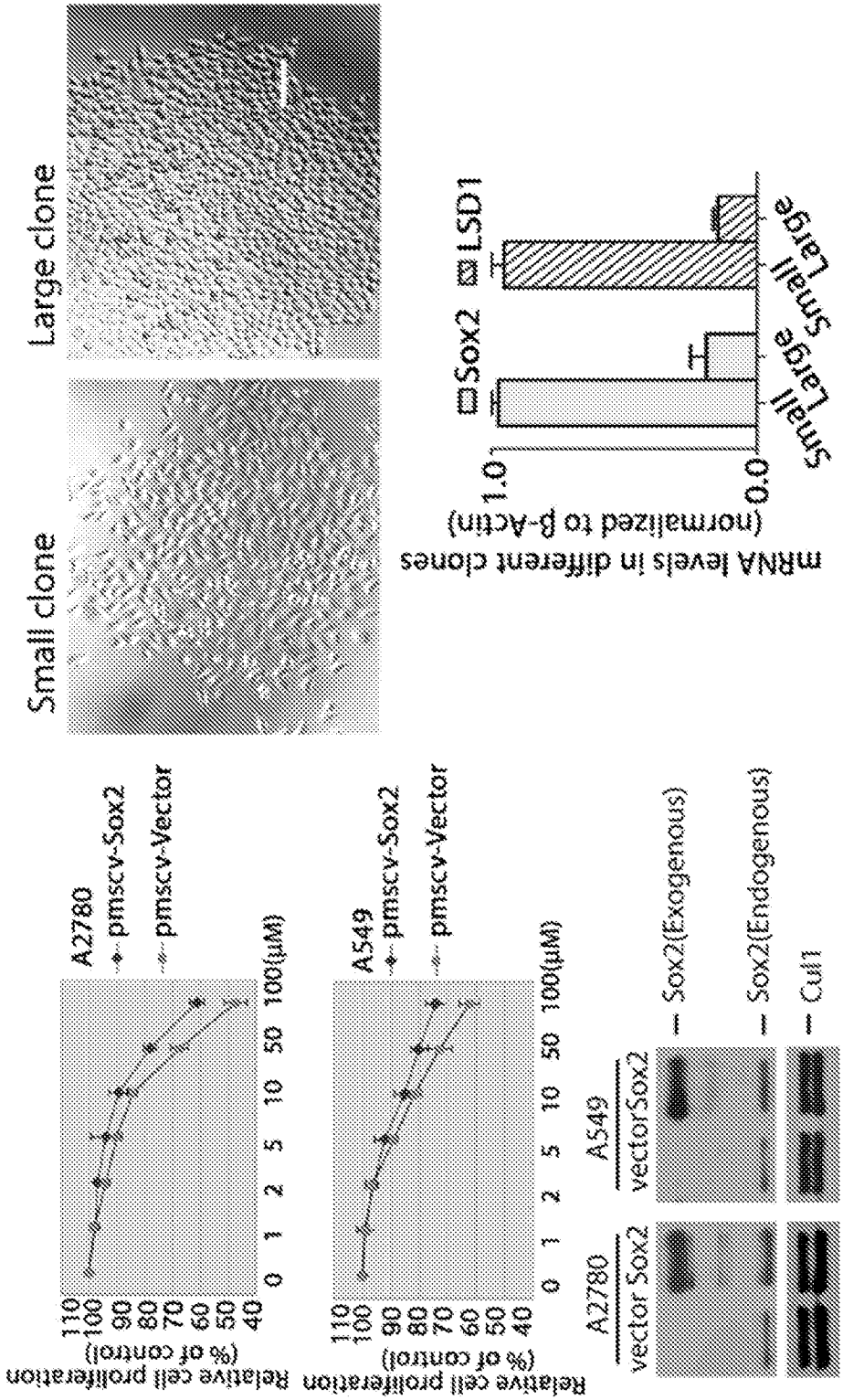


FIG. 19A

FIG. 19B

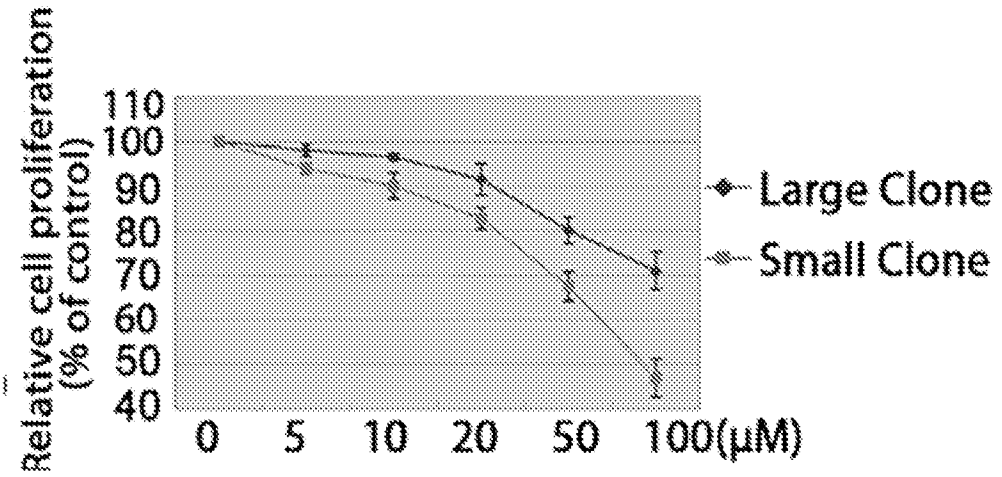


FIG. 19C

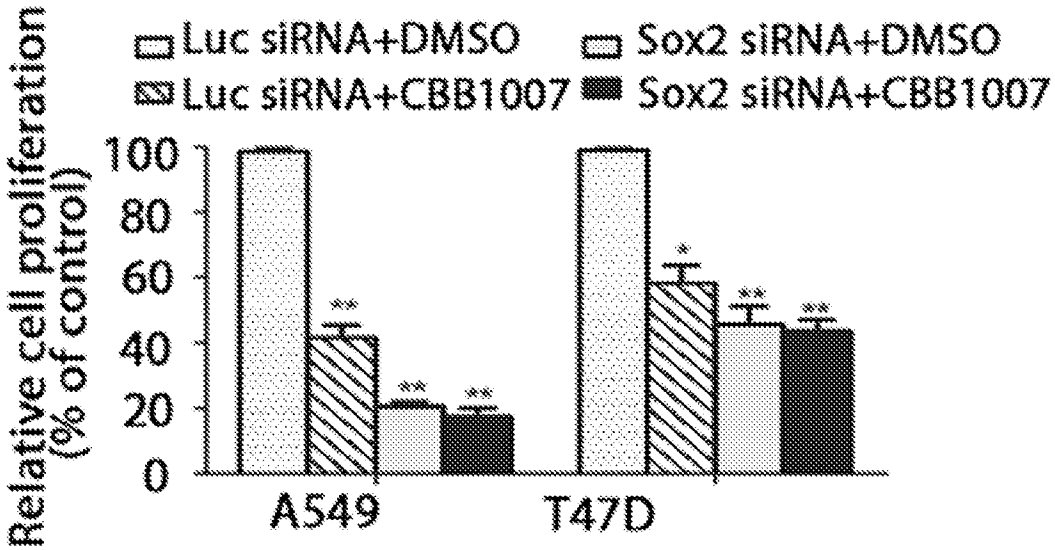


FIG. 19D

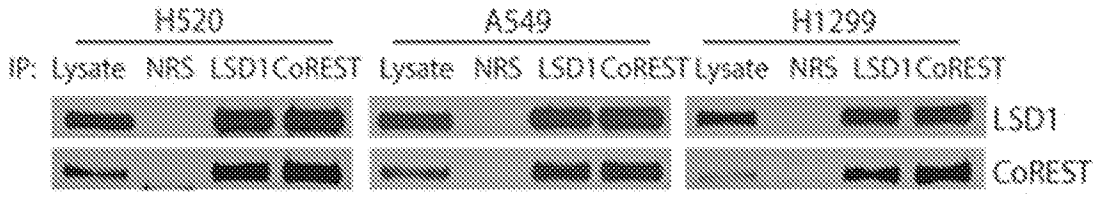


FIG. 20A

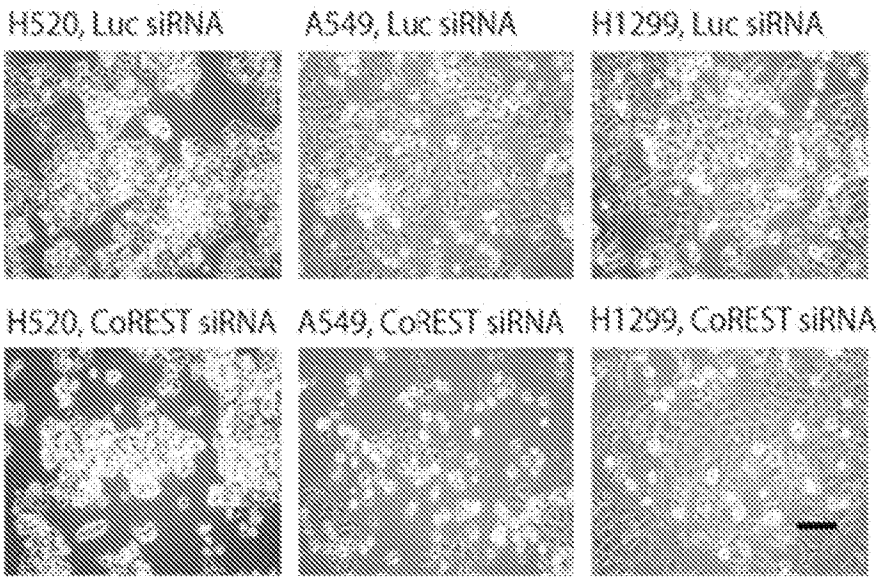


FIG. 20B

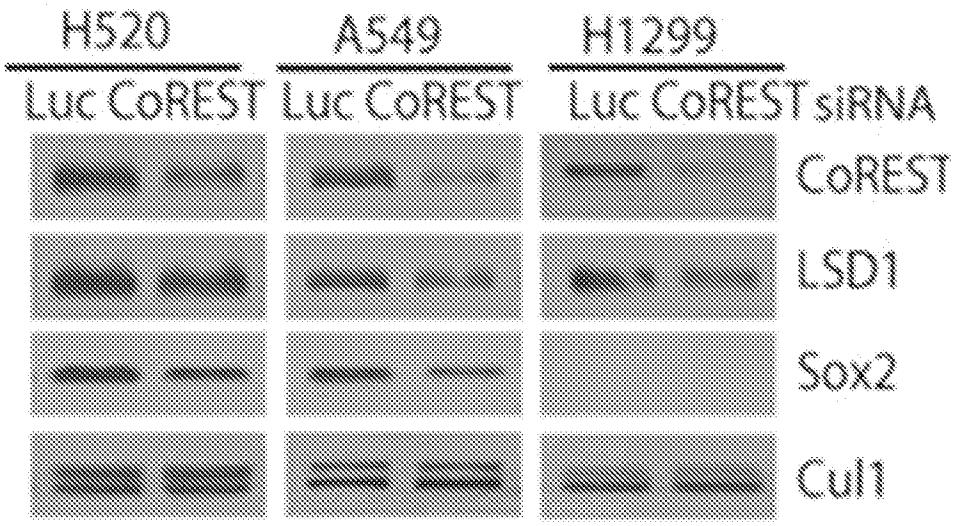


FIG. 20C

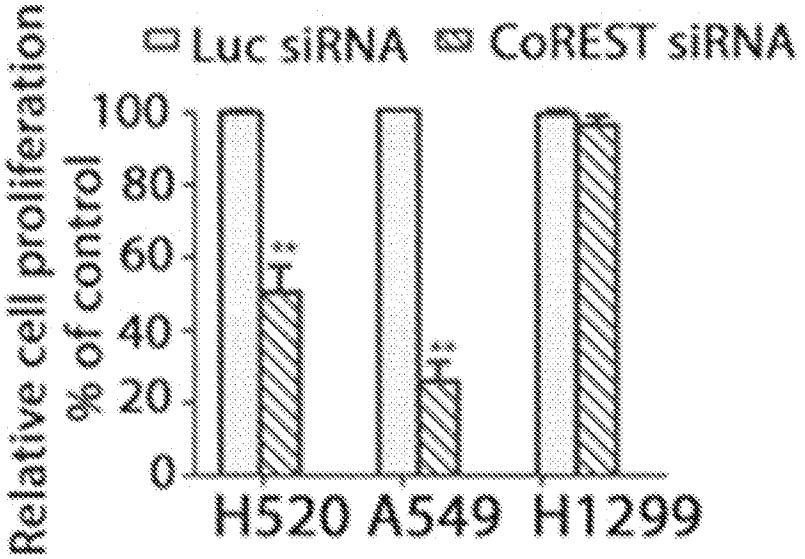


FIG. 20D

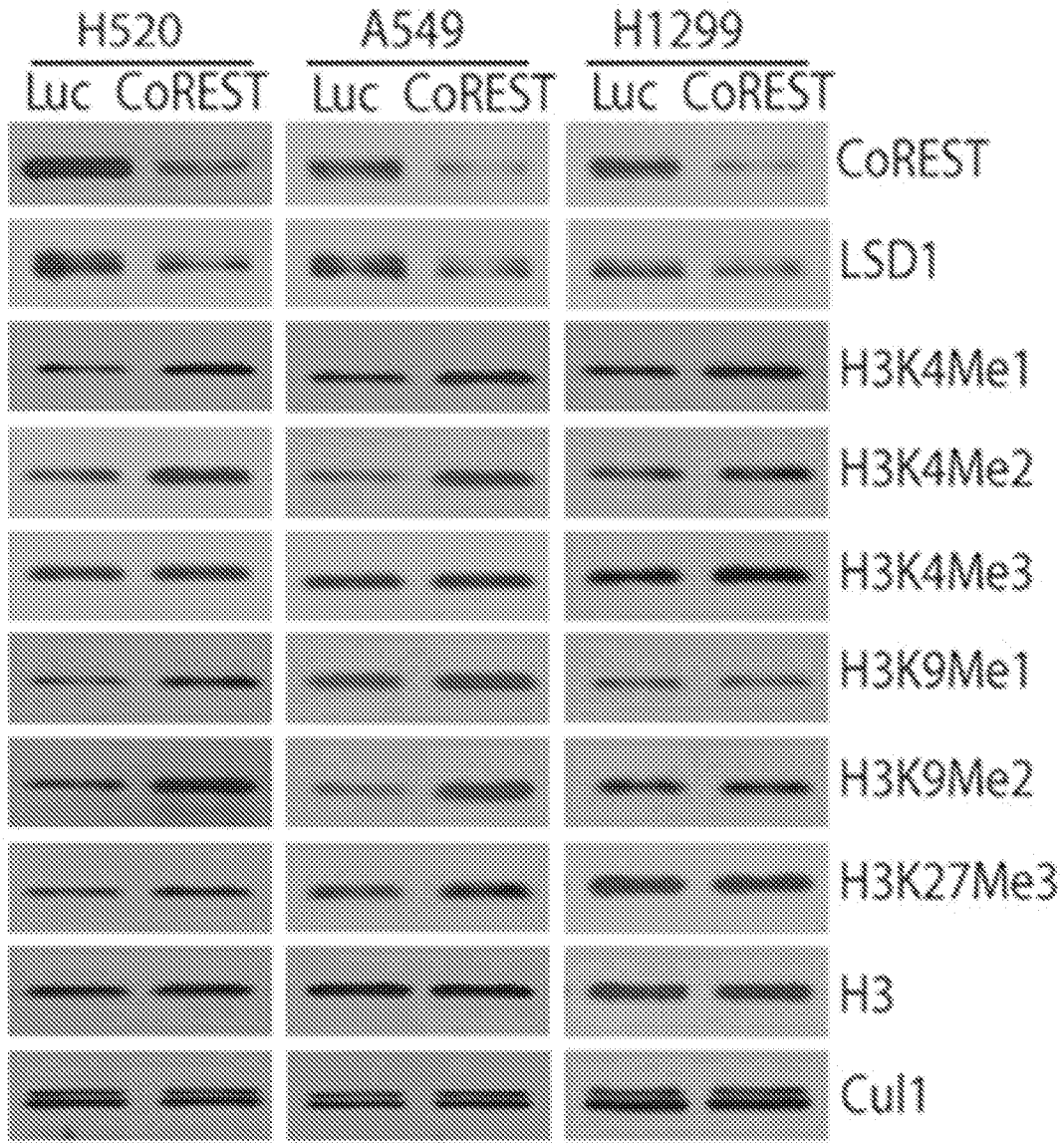

H520
Luc CoREST
A549
Luc CoREST
H1299
Luc CoREST
CoREST
LSD1
H3K4Me1
H3K4Me2
H3K4Me3
H3K9Me1
H3K9Me2
H3K27Me3
H3
Cul1

FIG. 20E

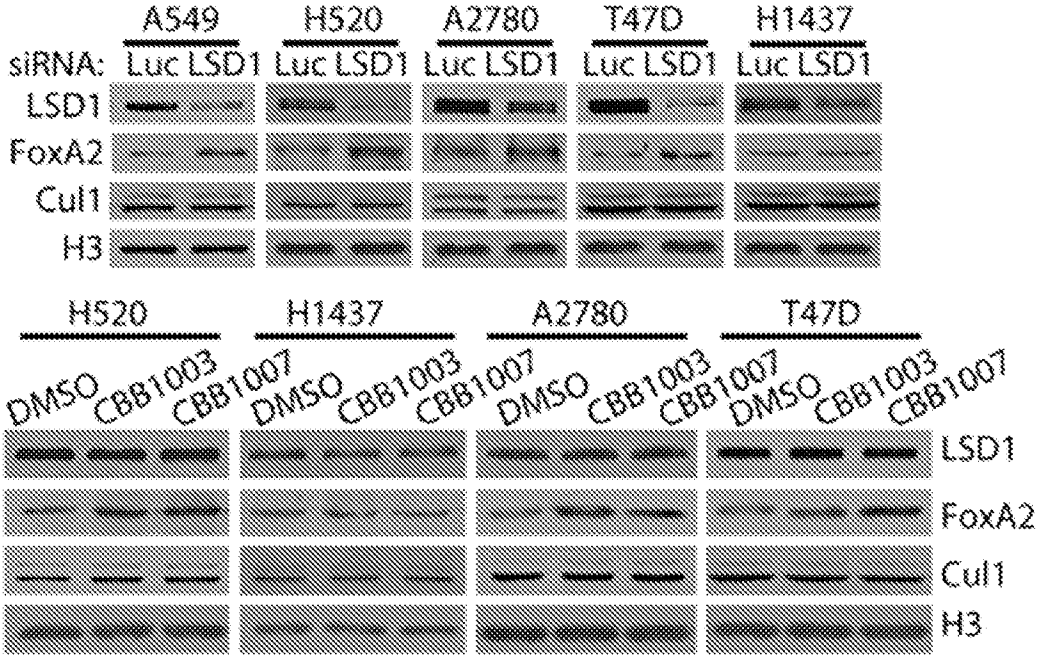


FIG. 21A

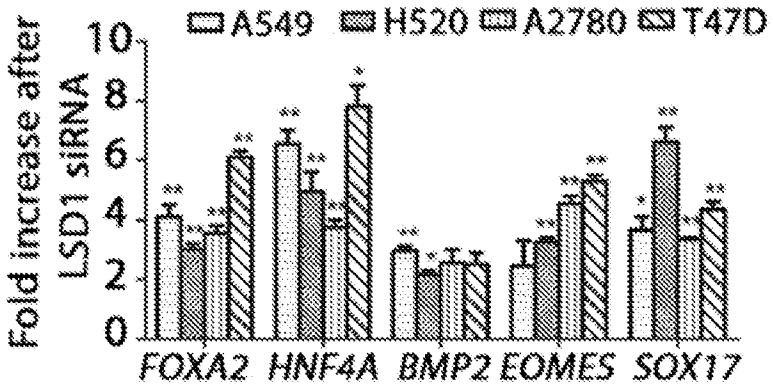


FIG. 21B

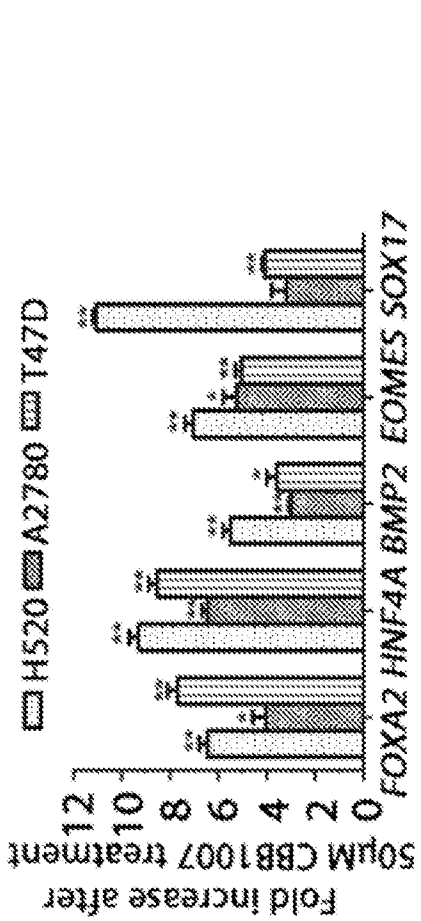


FIG. 21C

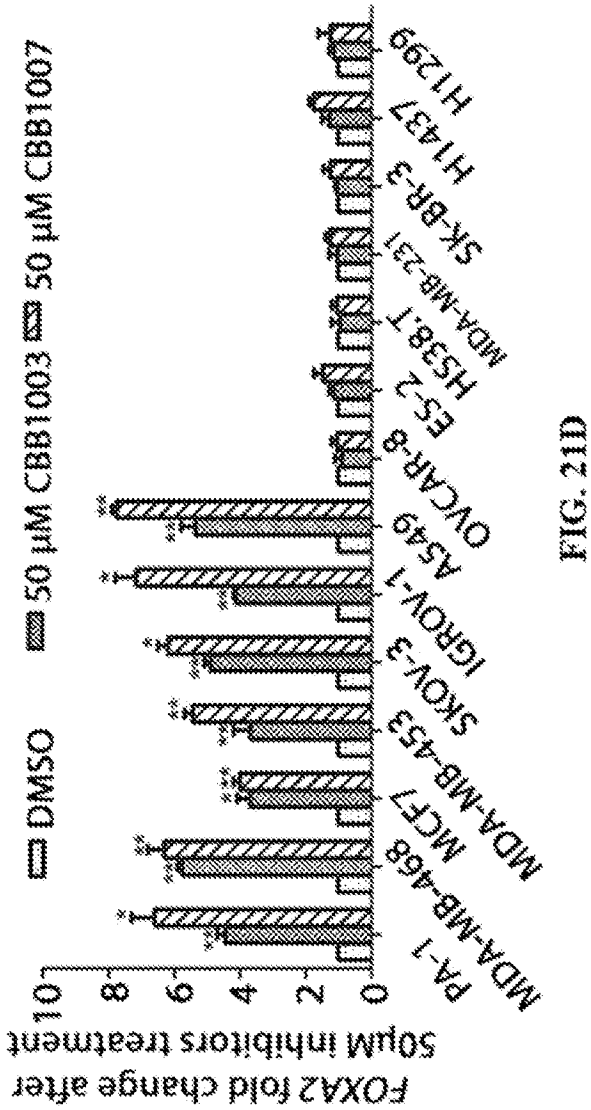


FIG. 21D

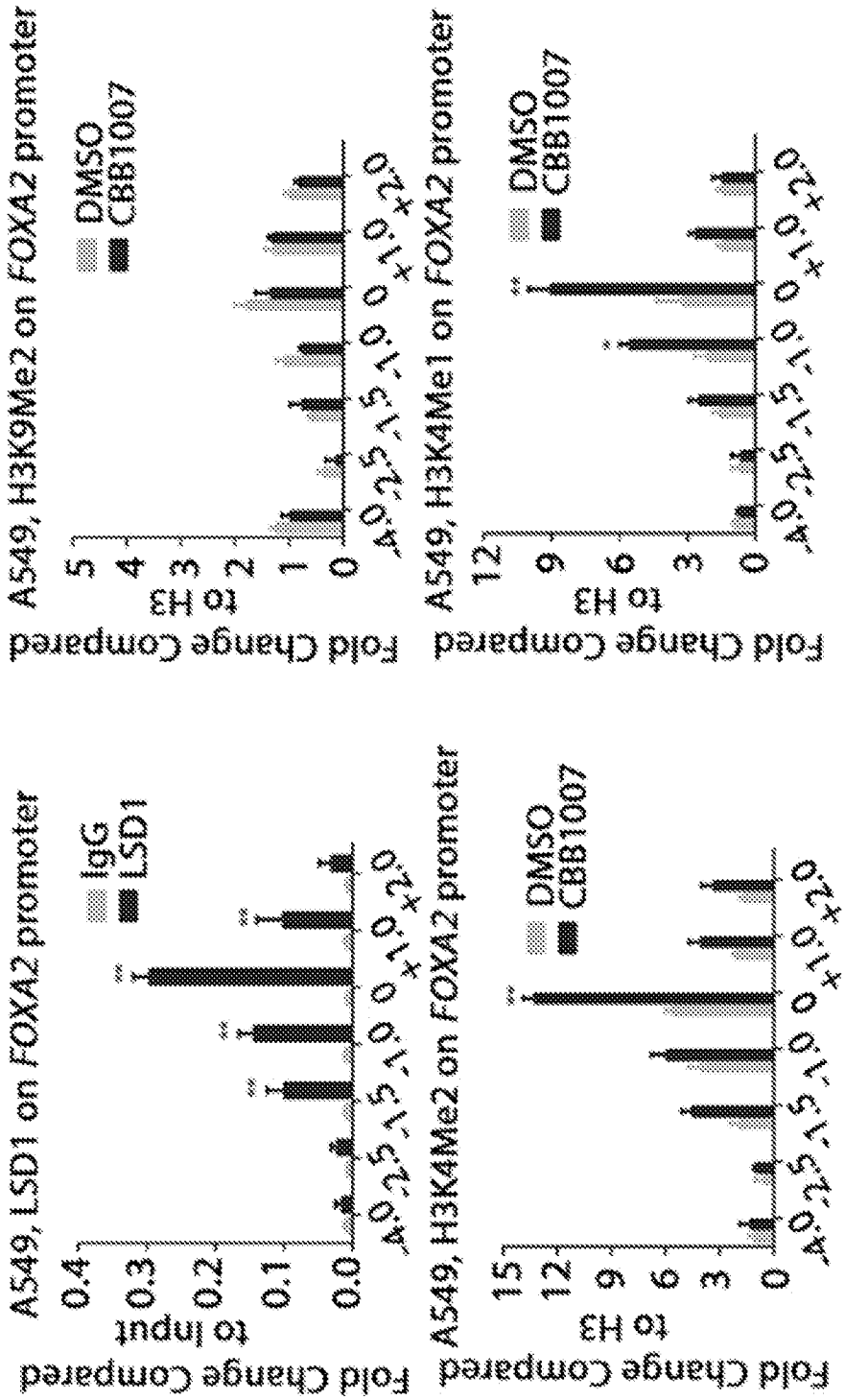

A549, LSD1 on FOXA2 promoter
IgG
LSD1
Fold Change Compared to Input
0.4
0.3
0.2
0.1
0.0
A
0
2.5
1
5
1
0
0
1
0
2.0
A549, H3K4Me2 on FOXA2 promoter
DMSO
CBB1007
Fold Change Compared to H3
15
12
9
6
3
0
A549, H3K9Me2 on FOXA2 promoter
DMSO
CBB1007
Fold Change Compared to H3
5
4
3
2
1
0
A549, H3K4Me1 on FOXA2 promoter
DMSO
CBB1007
Fold Change Compared to H3
12
9
6
3
0

FIG. 22

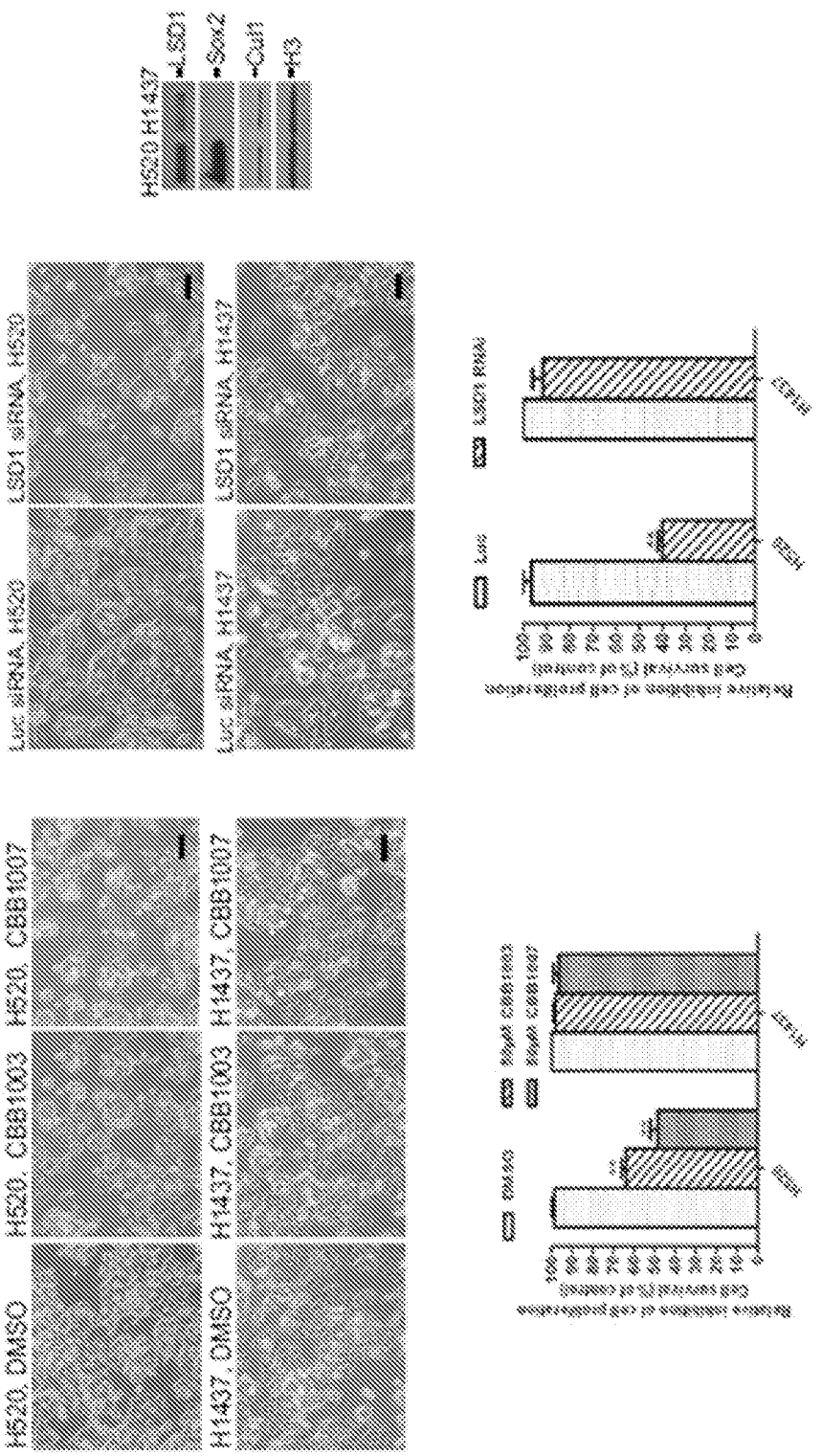


FIG. 23A

FIG. 23B

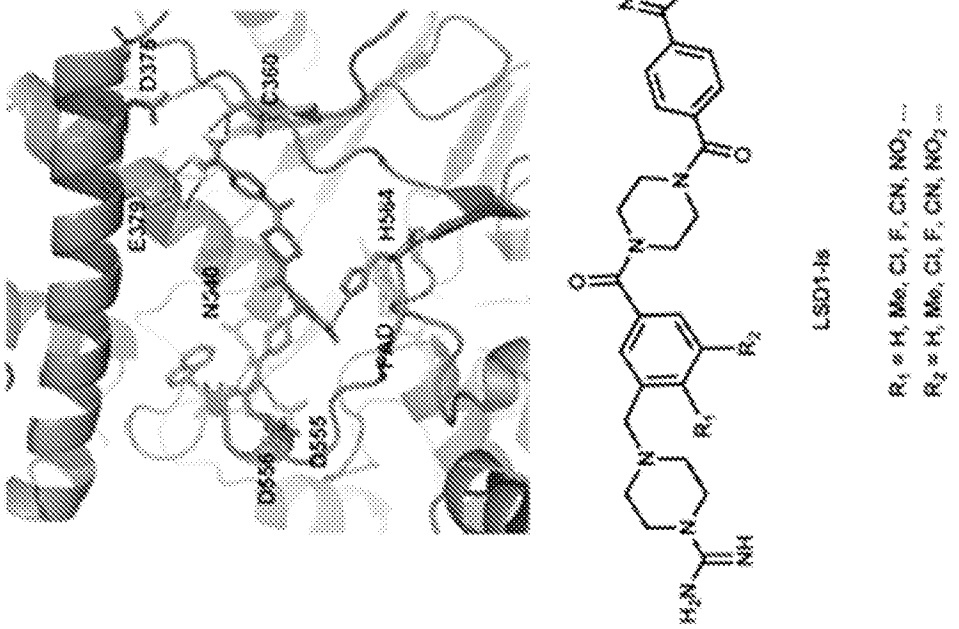


FIG. 24A

FIG. 24B

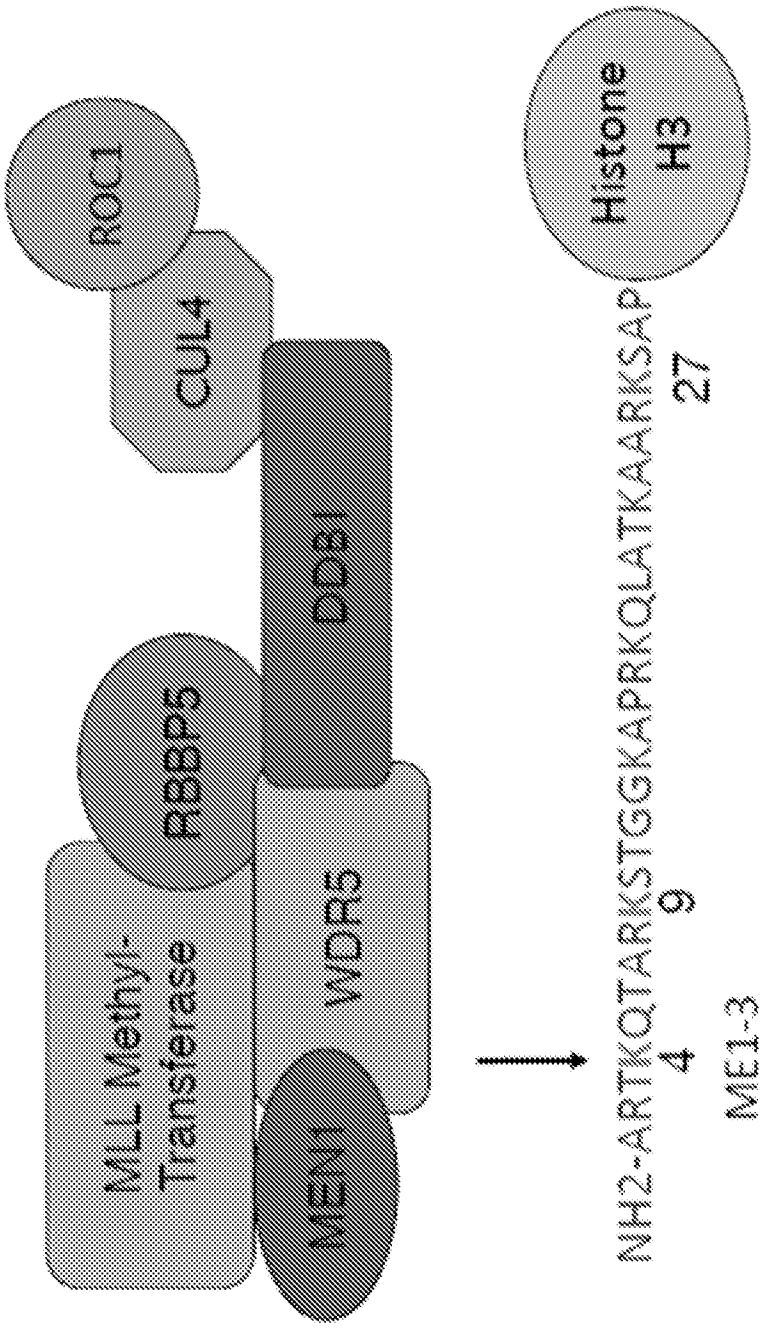
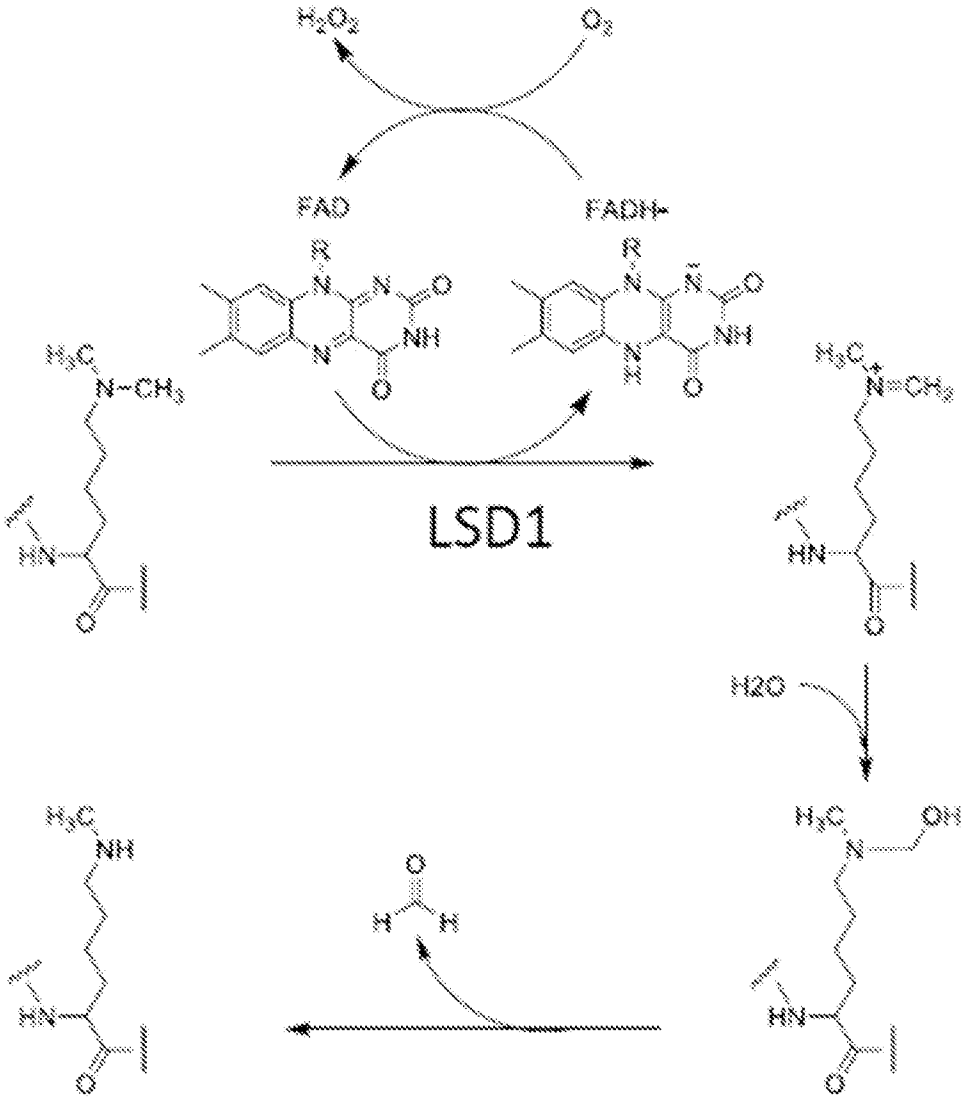

ROC1
CUL4
DDB1
RBBP5
MLL Methyl-
Transferase
WDR5
MEN1
Histone
H3
NH2-ARTKQTARKSTGGKAPRKQLATKAARKSAP
4
9
27
ME1-3
LSD1, LSD2, JARIAD1A-1D demethylases

FIG. 25



R = ribitol adenosine diphosphate

FIG. 26

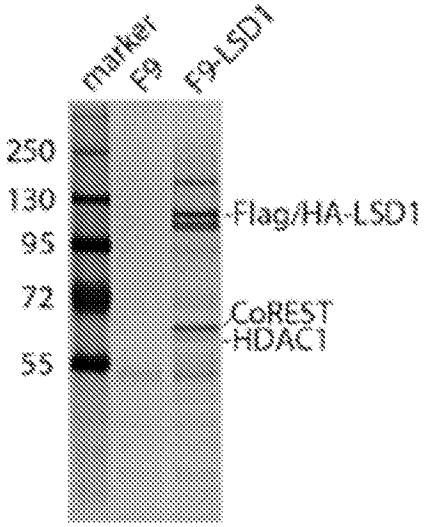


FIG. 27A

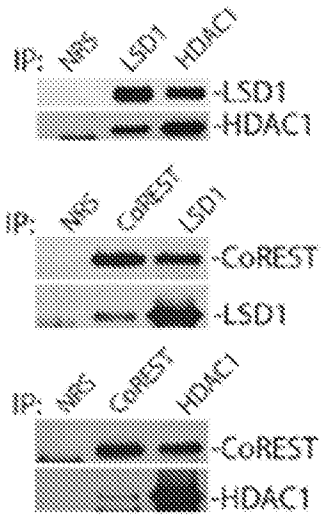


FIG. 27B

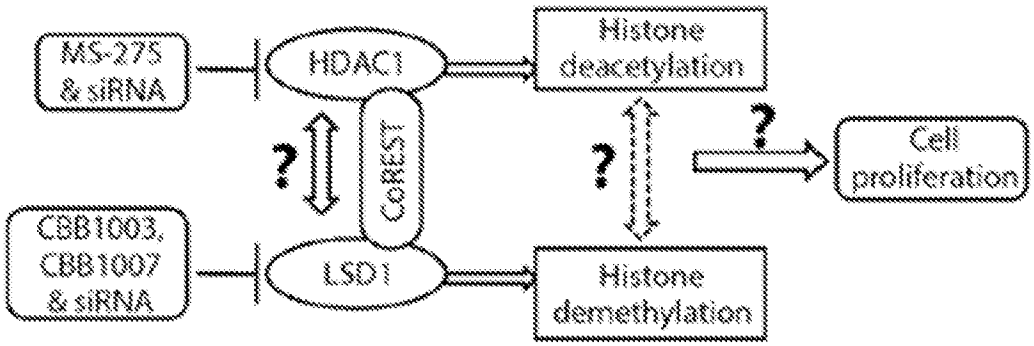


FIG. 27C

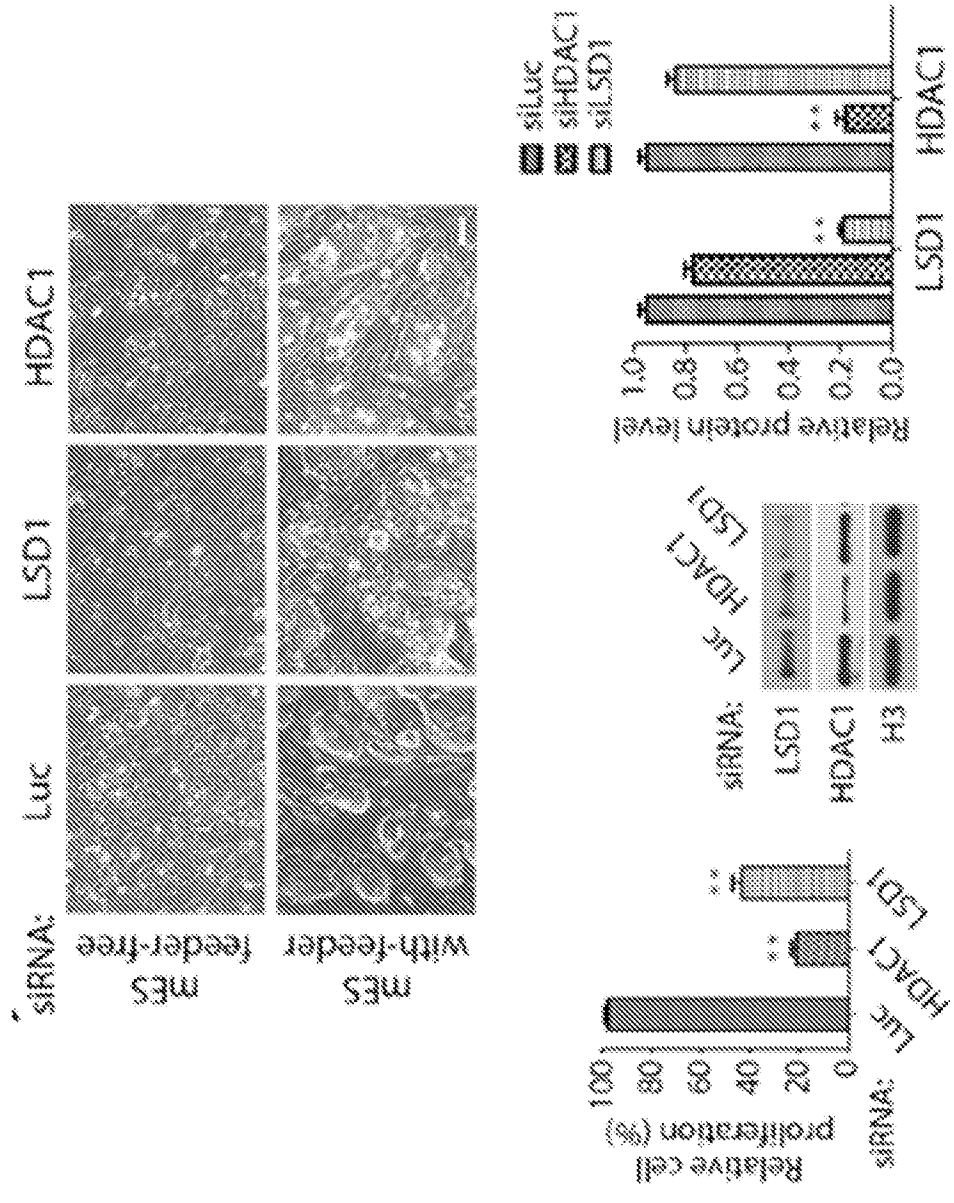

siRNA:
Luc
LSD1
HDAC1
mES
feeder-free
mES
with-feeder
siLuc
siHDAC1
siLSD1
Relative protein level
1.0
0.8
0.6
0.4
0.2
0.0
LSD1
HDAC1
siRNA:
Luc
HDAC1
LSD1
LSD1
HDAC1
H3
Relative cell proliferation (%)
100
80
60
40
20
0
siRNA:
Luc
HDAC1
LSD1

FIG. 27D

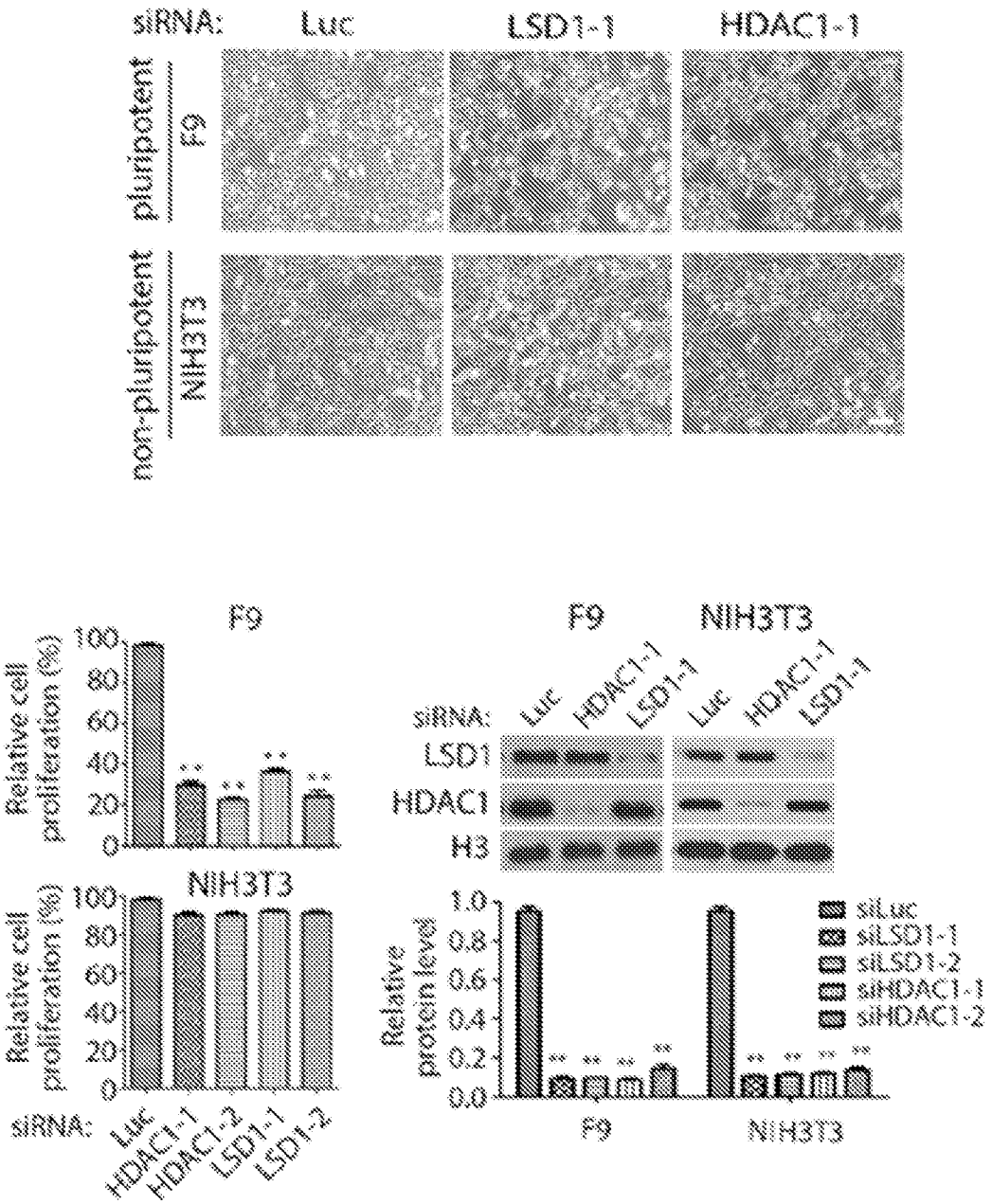

siRNA:
Luc
LSD1-1
HDAC1-1
pluripotent
F9
non-pluripotent
NIH3T3
F9
Relative cell proliferation (%)
100
80
60
40
20
0
NIH3T3
siRNA:
Luc
HDAC1-1
HDAC1-2
LSD1-1
LSD1-2
F9
NIH3T3
siRNA:
Luc
HDAC1-1
LSD1-1
LSD1
HDAC1
H3
Relative protein level
1.0
0.8
0.6
0.4
0.2
0.0
siLuc
siLSD1-1
siLSD1-2
siHDAC1-1
siHDAC1-2
F9
NIH3T3

FIG. 27E

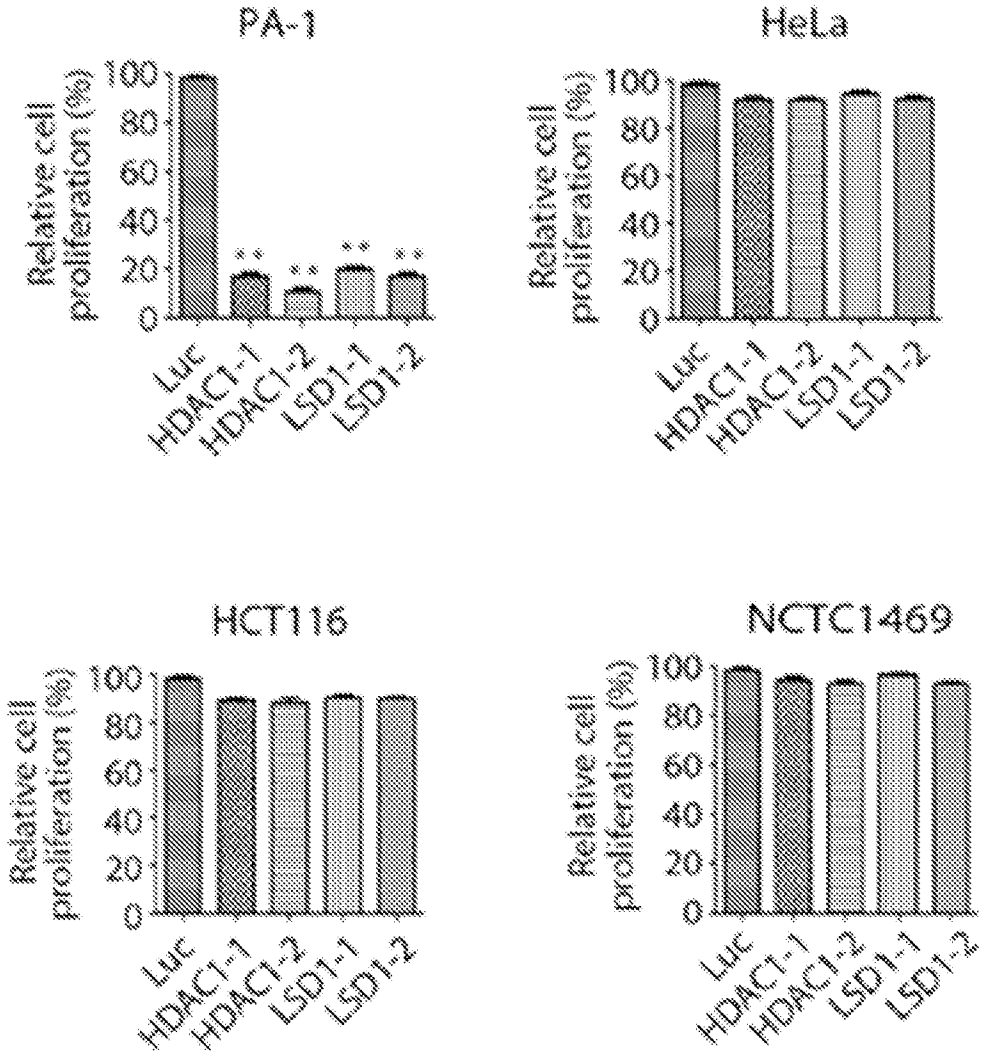

PA-1
HeLa
HCT116
NCTC1469
Relative cell proliferation (%)
100
80
60
40
20
0
Luc
HDAC1-1
HDAC1-2
LSD1-1
LSD1-2

FIG. 27F

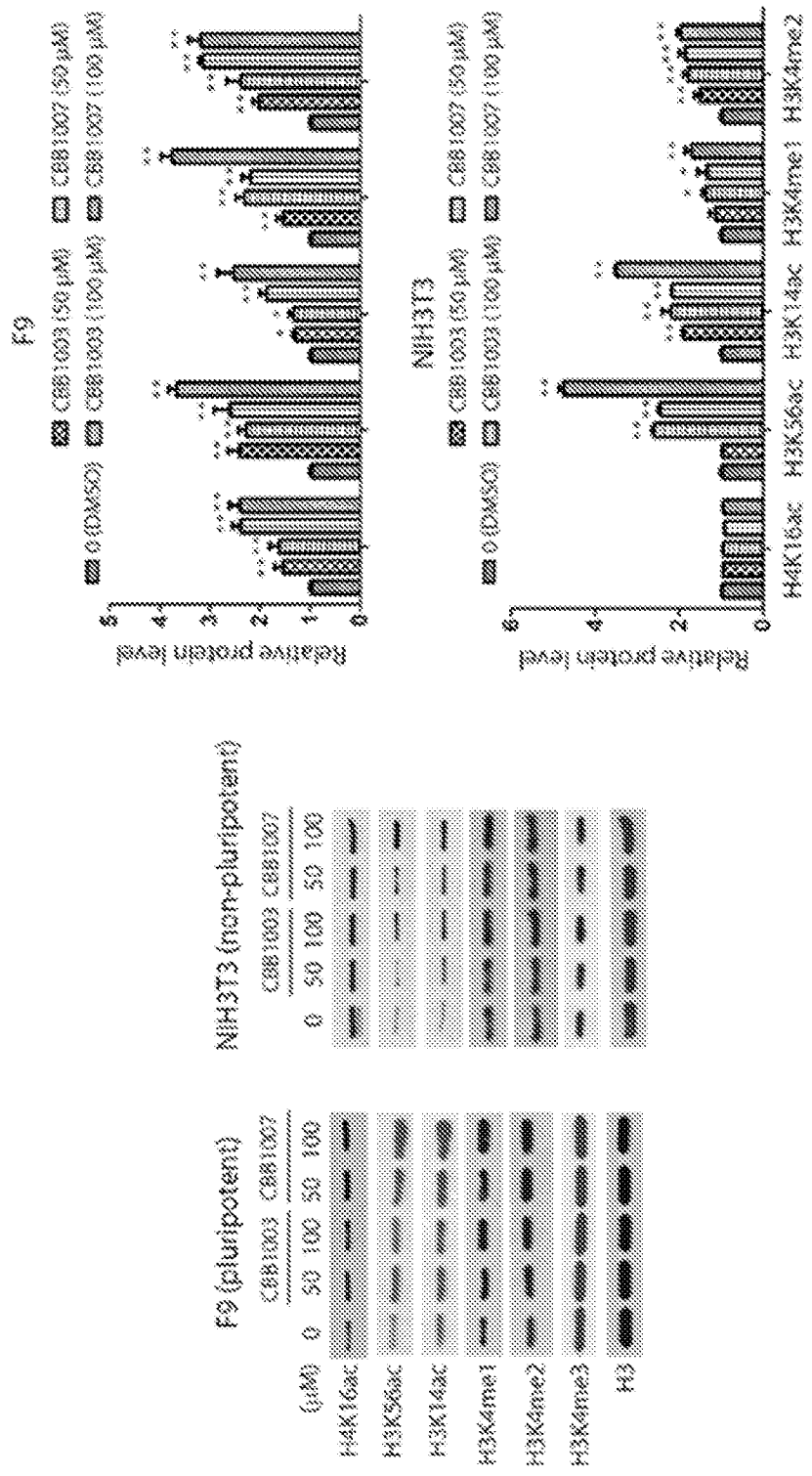

F9
0 (DMSO)
CBB1003 (50 μM)
CBB1003 (100 μM)
CBB1007 (50 μM)
CBB1007 (100 μM)
Relative protein level
NIH3T3
H4K16ac
H3K56ac
H3K14ac
H3K4me1
H3K4me2
H3K4me3
H3
F9 (pluripotent)
NIH3T3 (non-pluripotent)
(μM)
0
50
100
50
100

FIG. 28A

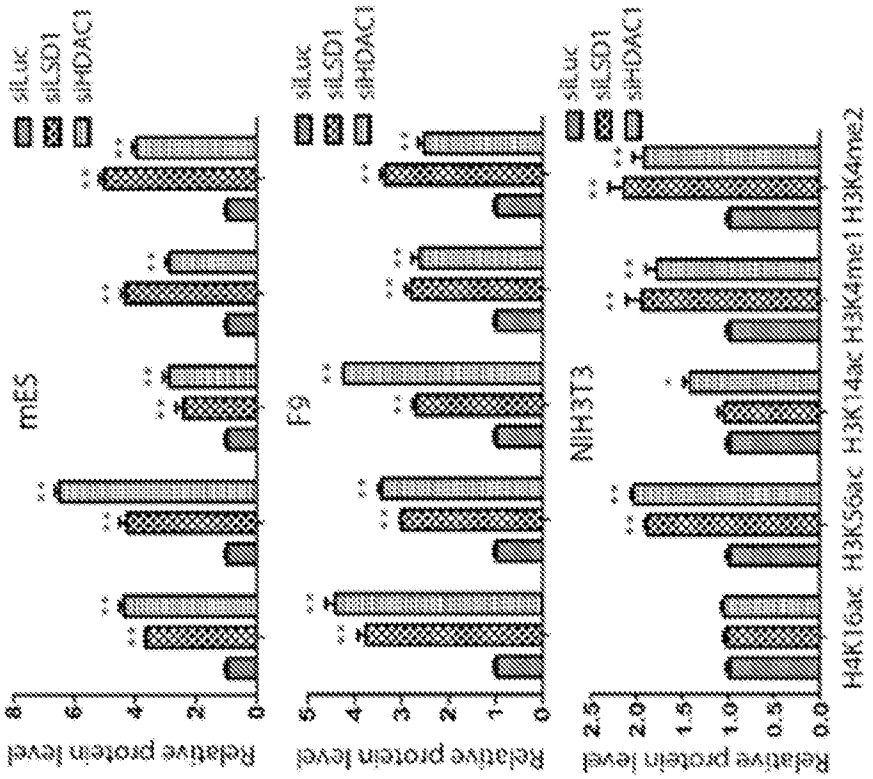

siLuc
siLSD1
siHDAC1
mES
F9
NIH3T3
Relative protein level
H4K16ac
H3K56ac
H3K14ac
H3K4me1
H3K4me2
H3K4me3
LSD1
HDAC1
H3
Luc
LSD1
HDAC1

FIG. 28B

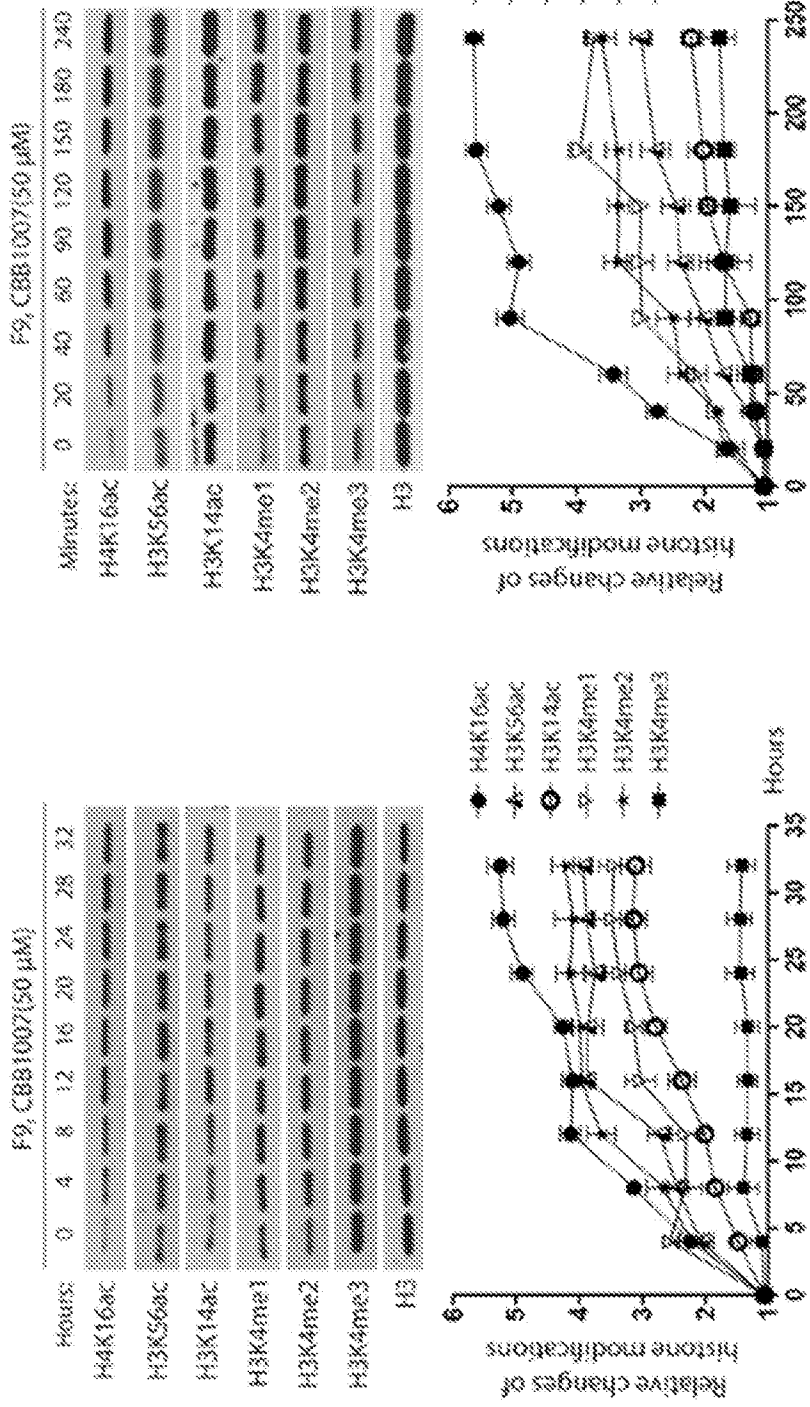


FIG. 28C

FIG. 28D

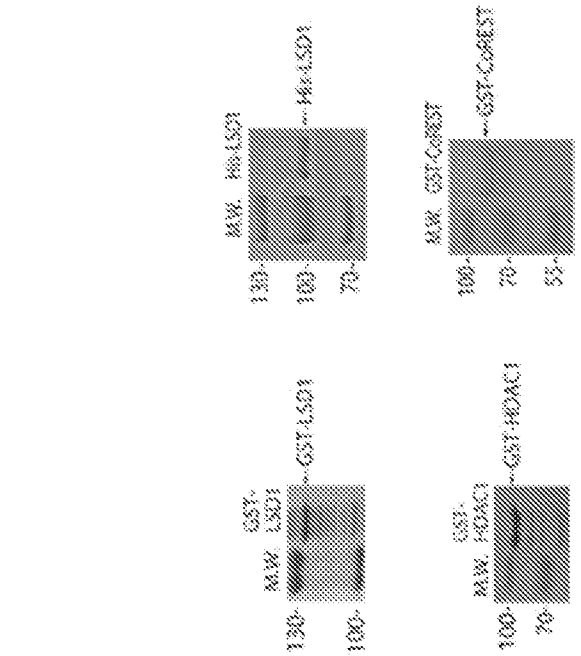


FIG. 29A

FIG. 29B

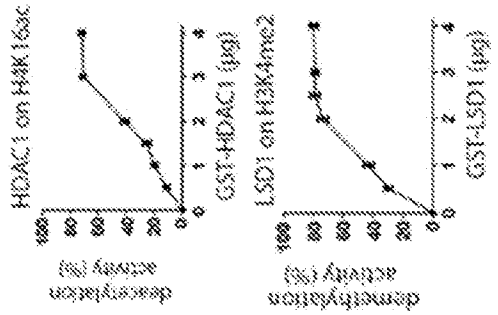


FIG. 29C

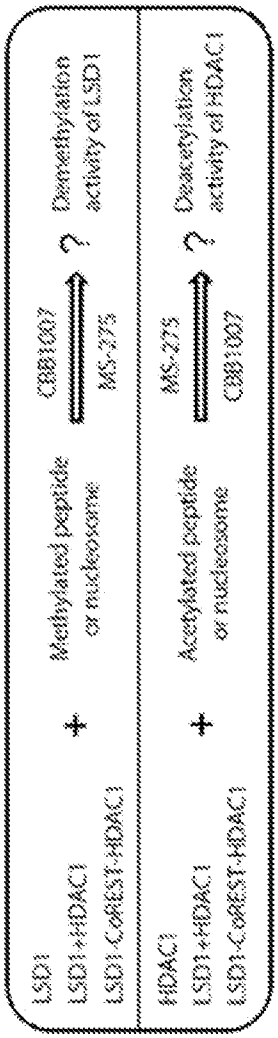


FIG. 29D

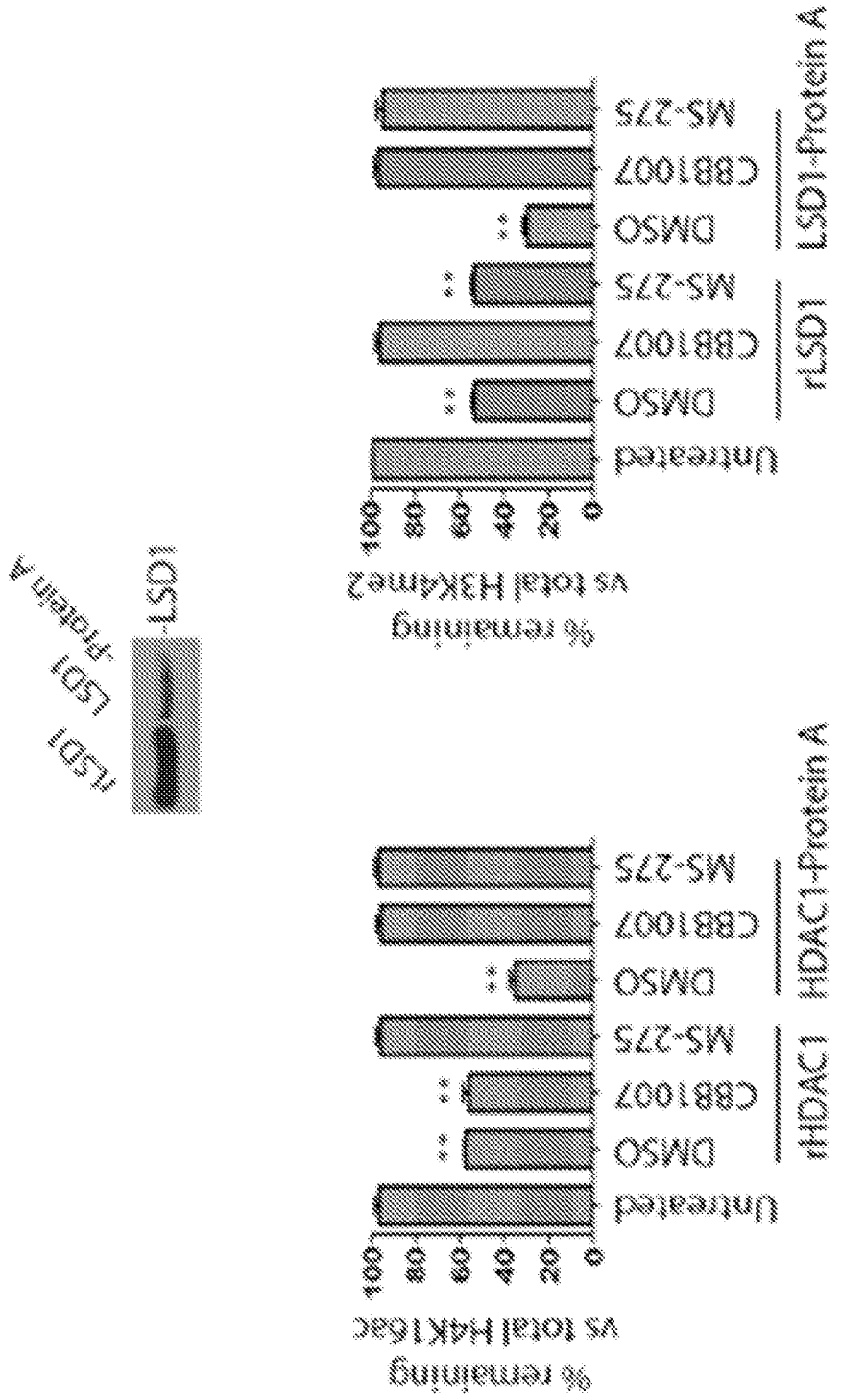

% remaining
vs total H4K16ac
100
80
60
40
20
0
Untreated
DMSO
CBB1007
MS-275
DMSO
CBB1007
MS-275
rHDAC1
rHDAC1-Protein A
% remaining
vs total H3K4me2
Untreated
DMSO
CBB1007
MS-275
DMSO
CBB1007
MS-275
rLSD1
LSD1-Protein A
rLSD1
LSD1
Protein A

FIG. 29E

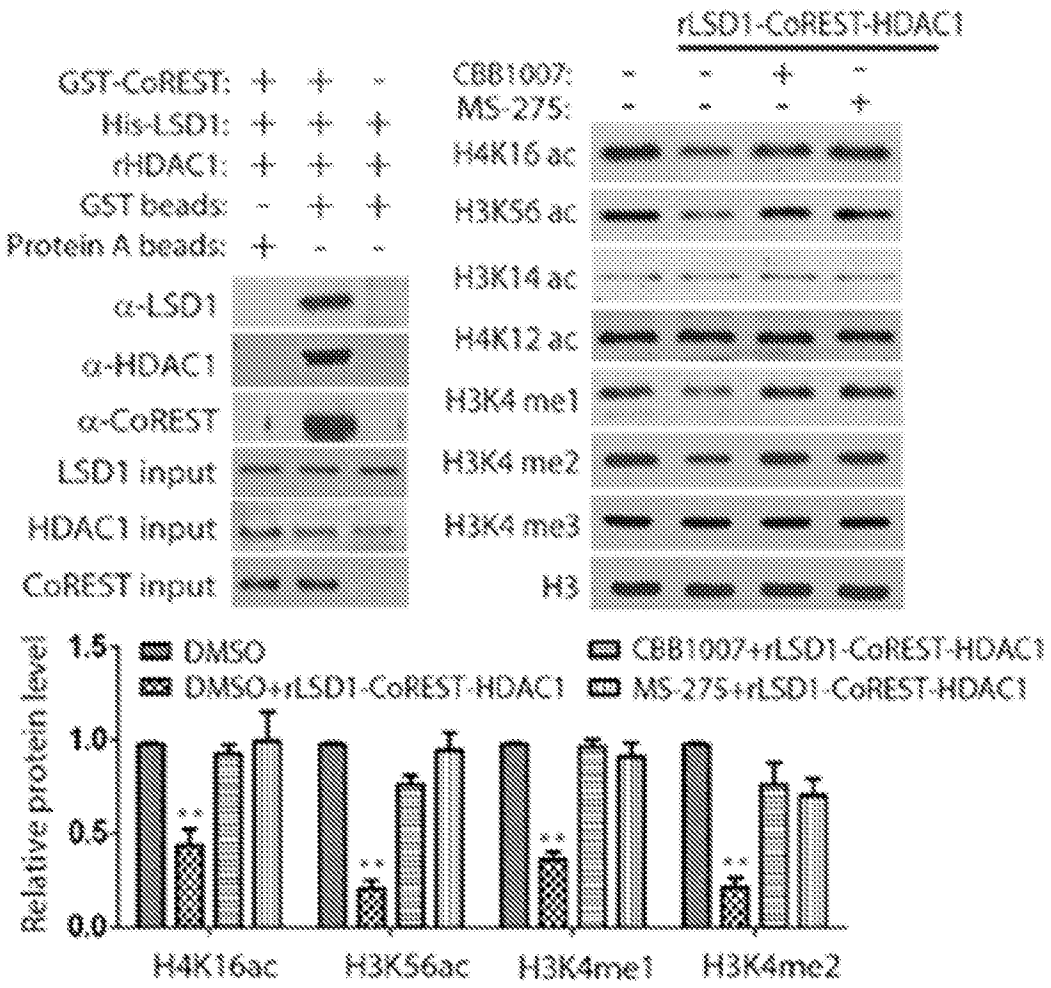

rLSD1-CoREST-HDAC1
GST-CoREST:
His-LSD1:
rHDAC1:
GST beads:
Protein A beads:
α-LSD1
α-HDAC1
α-CoREST
LSD1 input
HDAC1 input
CoREST input
CBB1007:
MS-275:
H4K16 ac
H3K56 ac
H3K14 ac
H4K12 ac
H3K4 me1
H3K4 me2
H3K4 me3
H3
DMSO
DMSO+rLSD1-CoREST-HDAC1
CBB1007+rLSD1-CoREST-HDAC1
MS-275+rLSD1-CoREST-HDAC1
Relative protein level
1.5
1.0
0.5
0.0
H4K16ac
H3K56ac
H3K4me1
H3K4me2

FIG. 29F

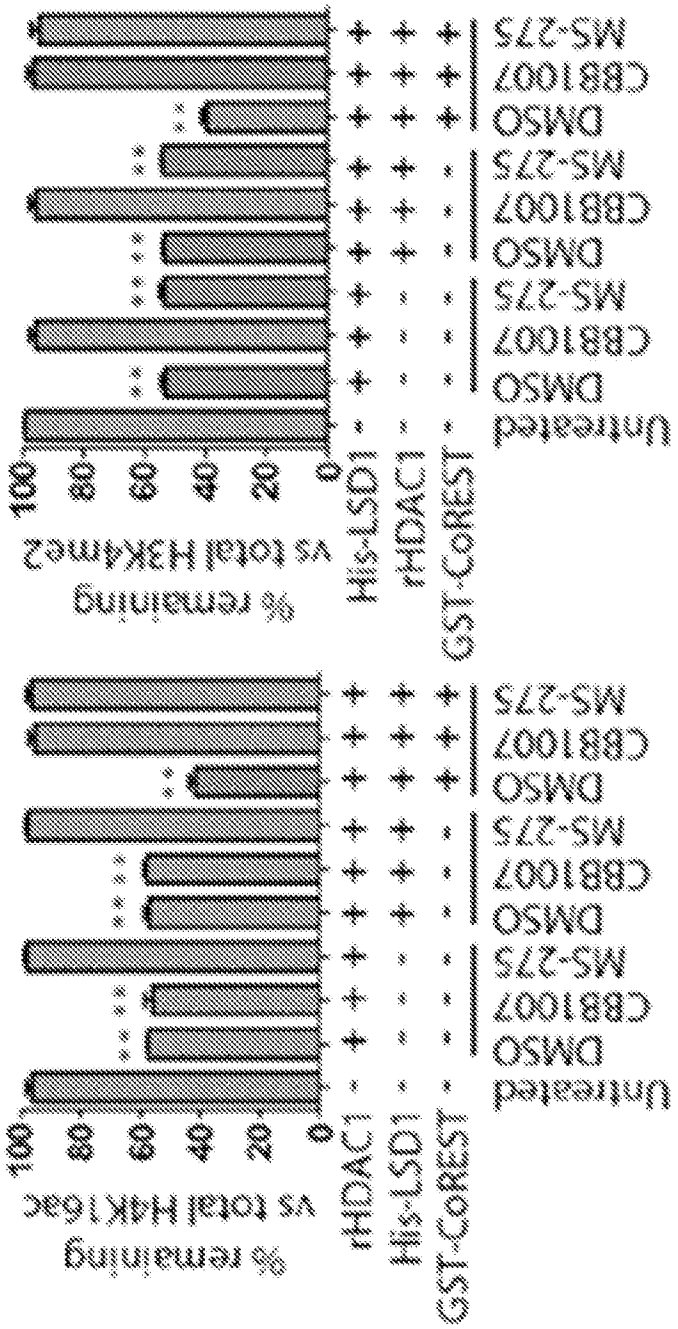

% remaining
vs total H4K16ac
100
80
60
40
20
0
rHDAC1
His-LSD1
GST-CoREST
Untreated
DMSO
CBI007
MS-275
DMSO
CBI007
MS-275
% remaining
vs total H3K4me2
100
80
60
40
20
0
His-LSD1
rHDAC1
GST-CoREST
Untreated
DMSO
CBI007
MS-275
DMSO
CBI007
MS-275

FIG. 29G

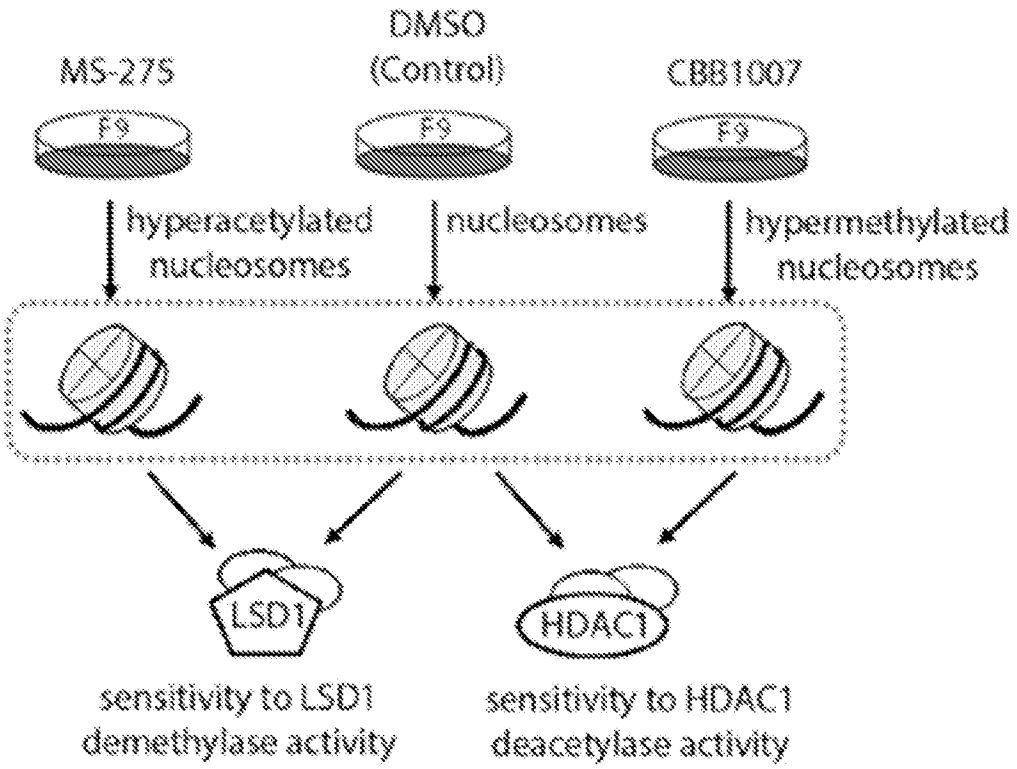

MS-275
DMSO
(Control)
CBB1007
FS
FS
FS
hyperacetylated
nucleosomes
nucleosomes
hypermethylated
nucleosomes
LSD1
HDAC1
sensitivity to LSD1
demethylase activity
sensitivity to HDAC1
deacetylase activity

FIG. 30A

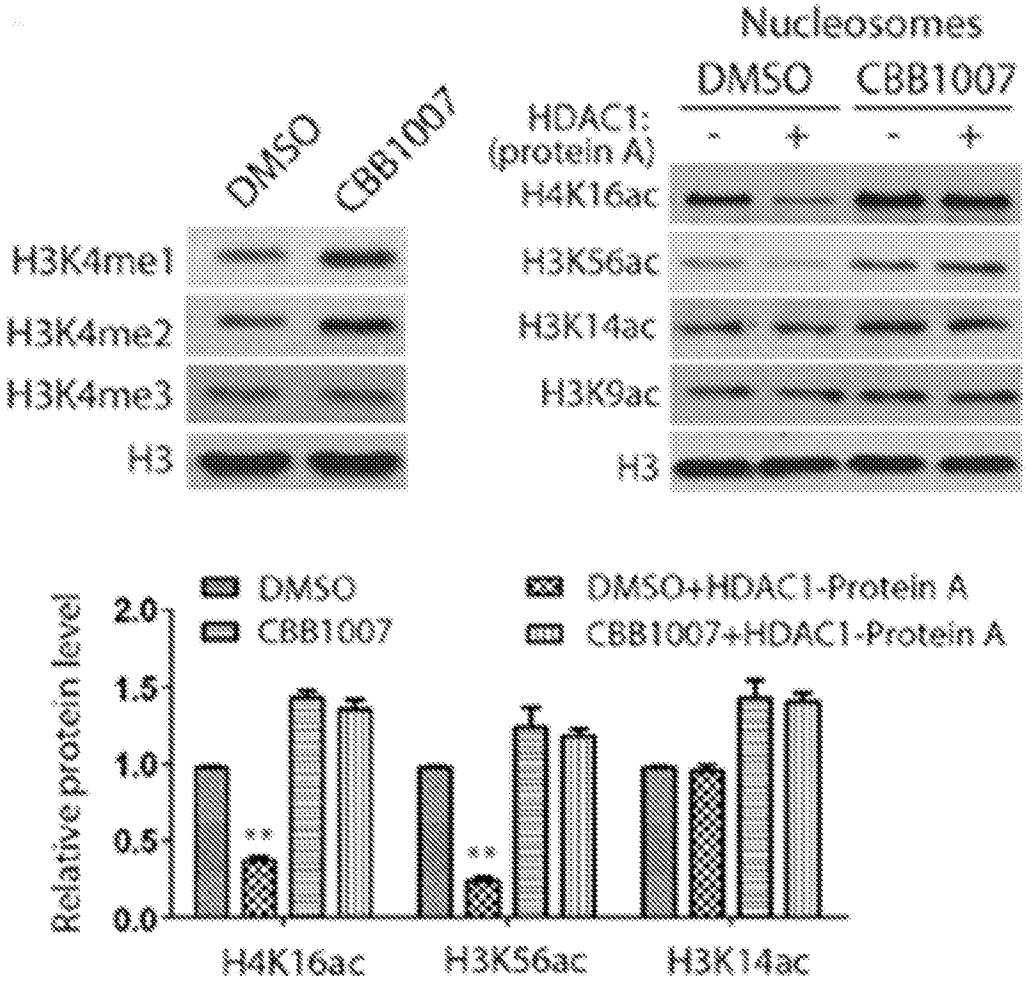

Nucleosomes
DMSO
CBB1007
HDAC1: (protein A)
- + - +
H4K16ac
H3K56ac
H3K14ac
H3K9ac
H3
H3K4me1
H3K4me2
H3K4me3
H3
DMSO
CBB1007
DMSO+HDAC1-Protein A
CBB1007+HDAC1-Protein A
Relative protein level
2.0
1.5
1.0
0.5
0.0
**
**
H4K16ac
H3K56ac
H3K14ac

FIG. 30B

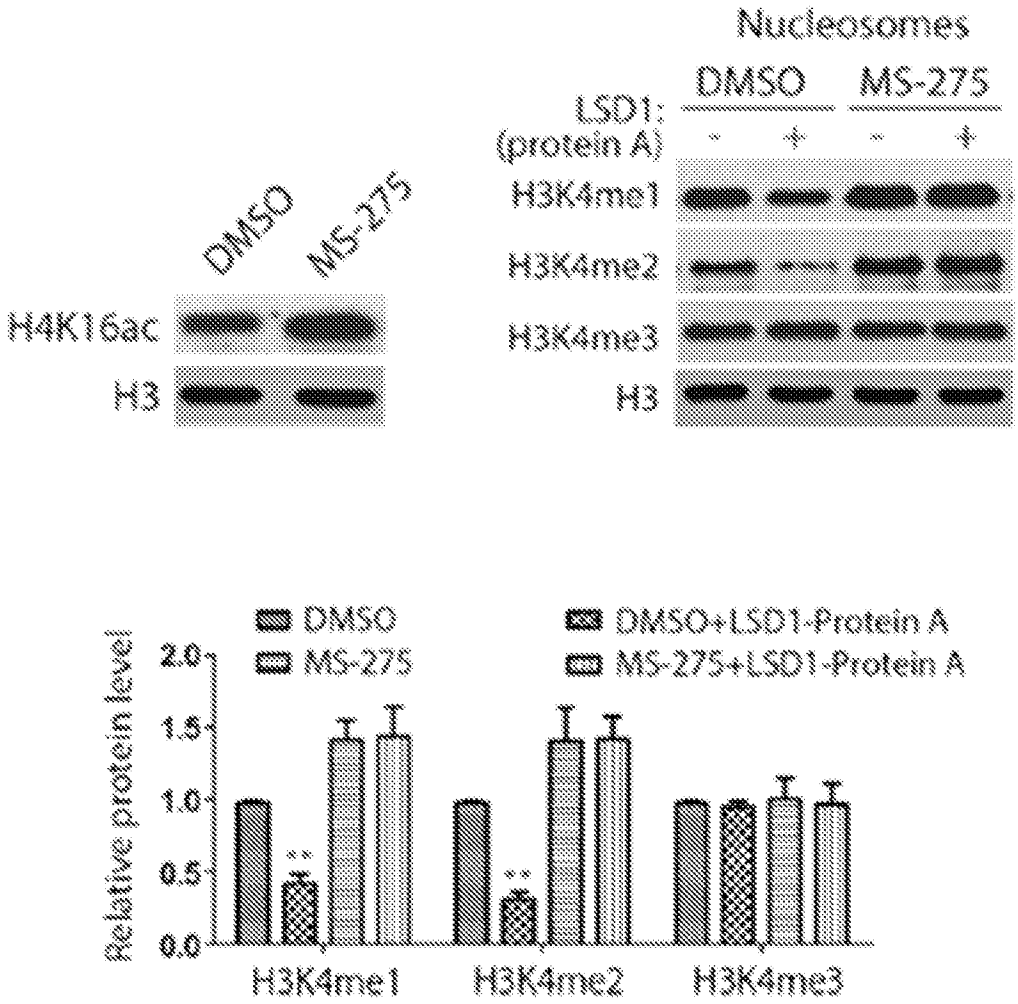

Nucleosomes
DMSO
MS-275
LSD1:
(protein A)
H3K4me1
H3K4me2
H3K4me3
H3
DMSO
MS-275
H4K16ac
H3
DMSO
MS-275
DMSO+LSD1-Protein A
MS-275+LSD1-Protein A
Relative protein level
2.0
1.5
1.0
0.5
0.0
H3K4me1
H3K4me2
H3K4me3

FIG. 30C

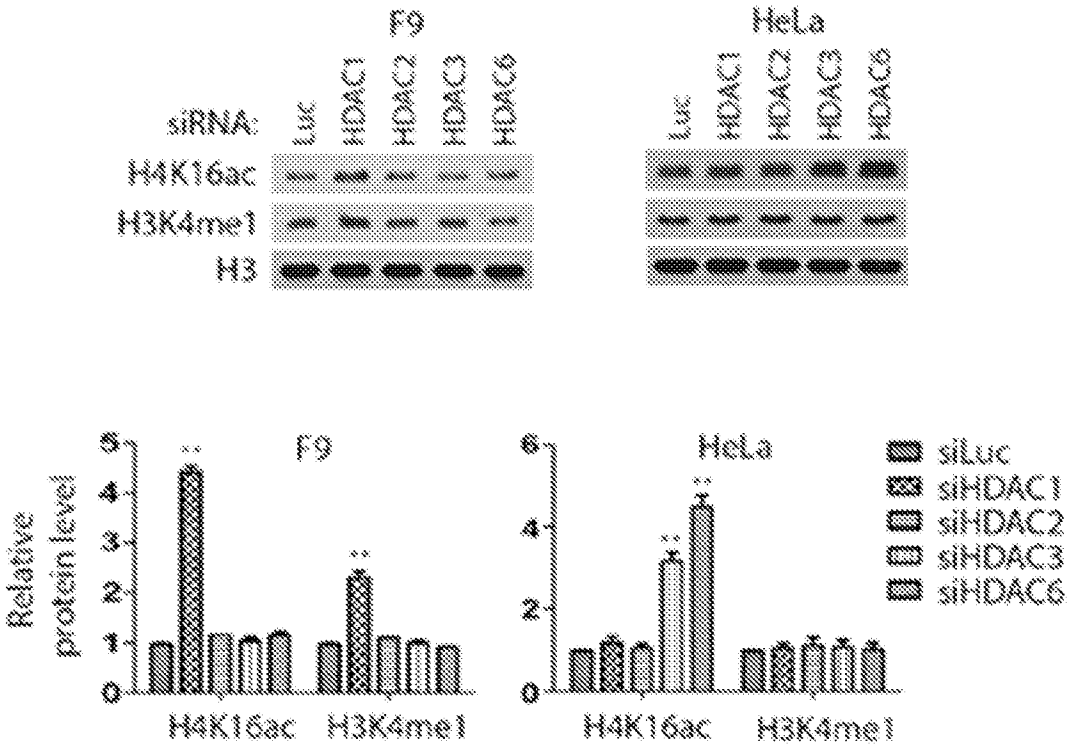

F9
HeLa
siRNA:
Luc
HDAC1
HDAC2
HDAC3
HDAC6
H4K16ac
H3K4me1
H3
Relative protein level
H4K16ac
H3K4me1
siLuc
siHDAC1
siHDAC2
siHDAC3
siHDAC6

FIG. 31A

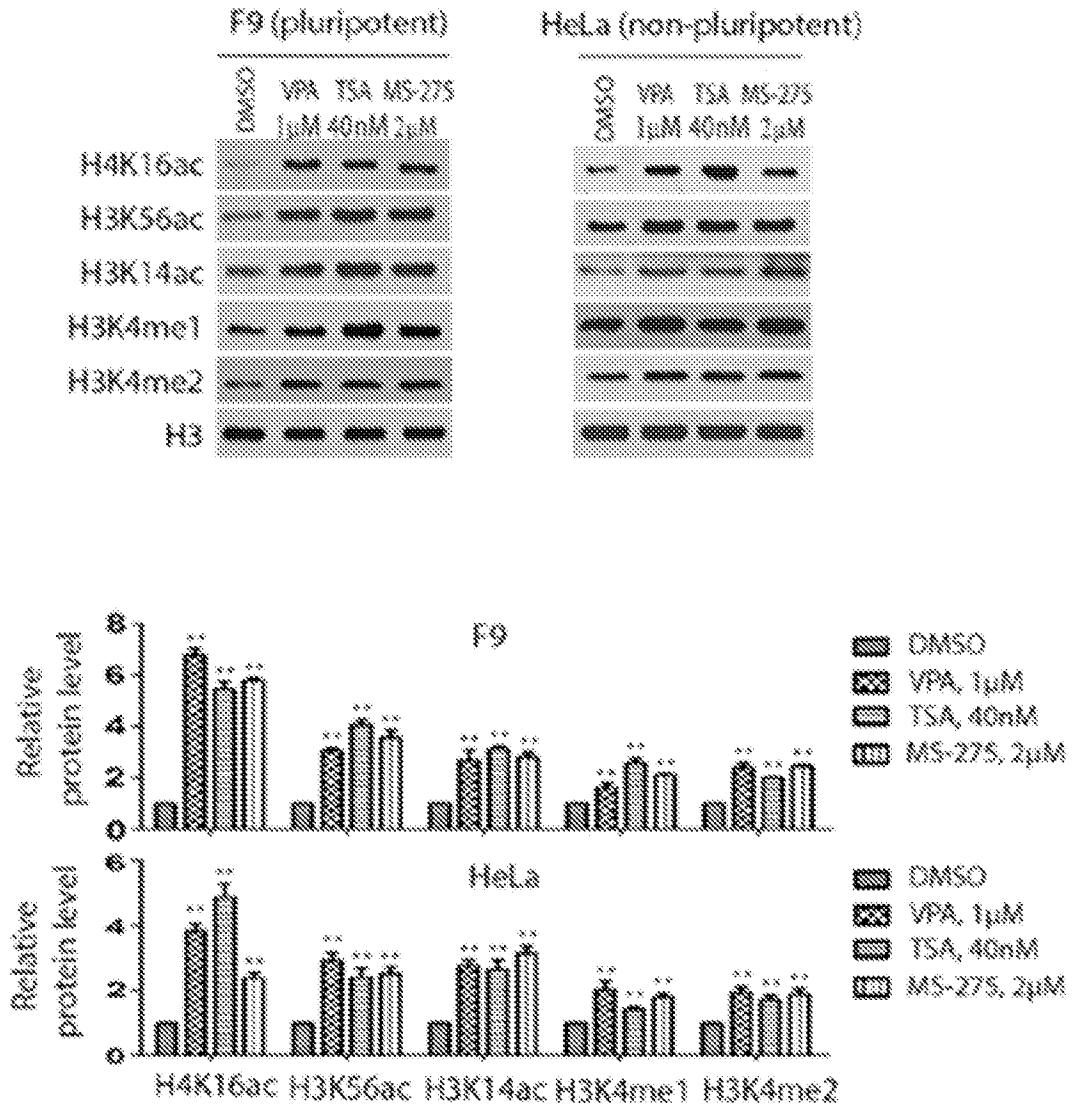

F9 (pluripotent)
HeLa (non-pluripotent)
DMSO
VPA 1μM
TSA 40nM
MS-275 2μM
H4K16ac
H3K56ac
H3K14ac
H3K4me1
H3K4me2
H3
F9
HeLa
Relative protein level
DMSO
VPA, 1μM
TSA, 40nM
MS-275, 2μM
H4K16ac
H3K56ac
H3K14ac
H3K4me1
H3K4me2

FIG. 31B

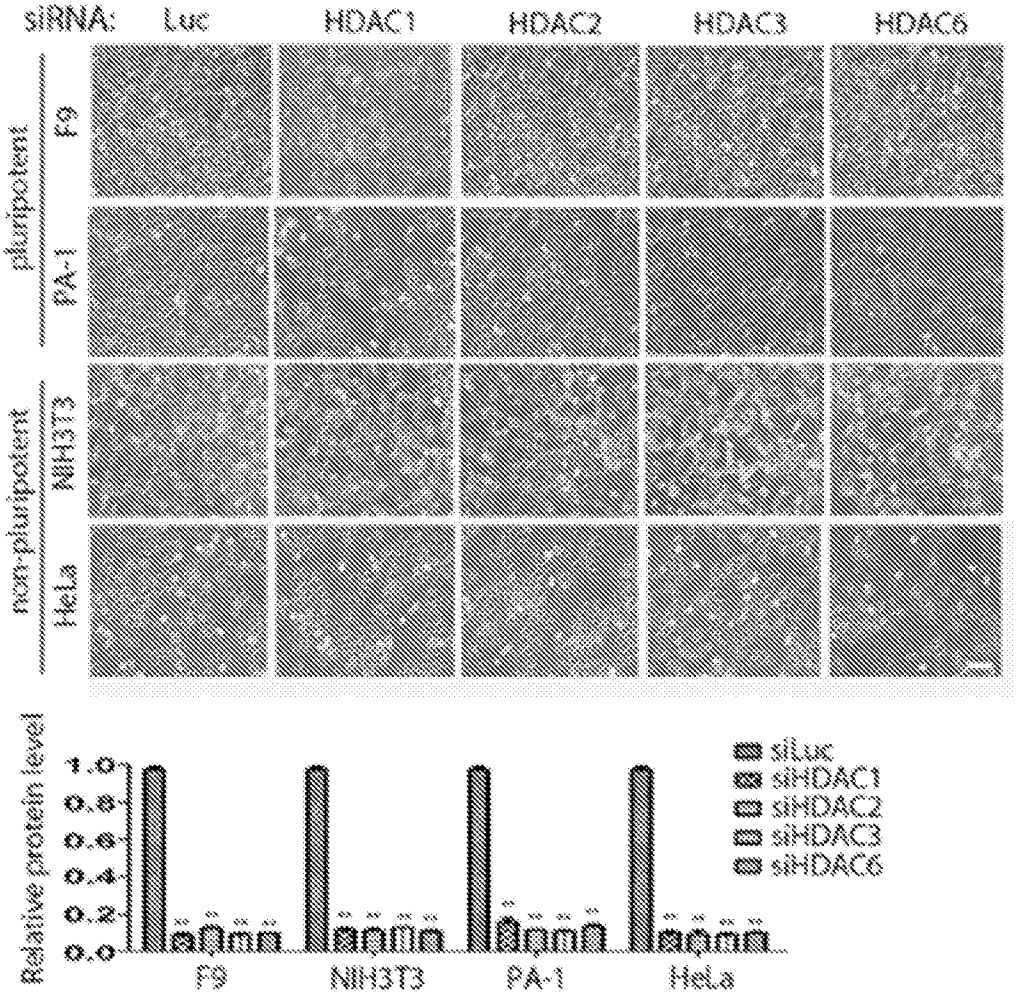

siRNA:
Luc
HDAC1
HDAC2
HDAC3
HDAC6
pluripotent
F9
PA-1
non-pluripotent
NIH3T3
HeLa
Relative protein level
1.0
0.8
0.6
0.4
0.2
0.0
siLuc
siHDAC1
siHDAC2
siHDAC3
siHDAC6
F9
NIH3T3
PA-1
HeLa

FIG. 31C

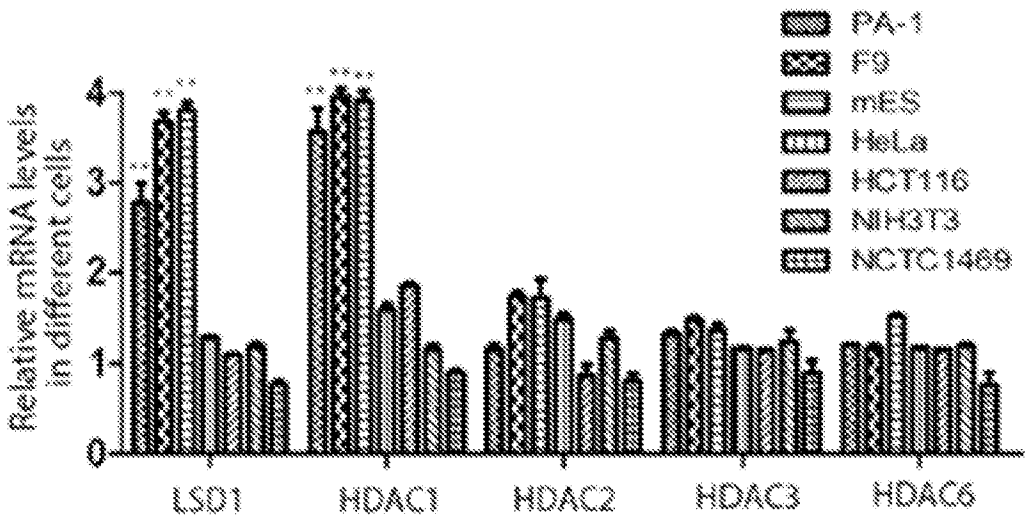


FIG. 31D

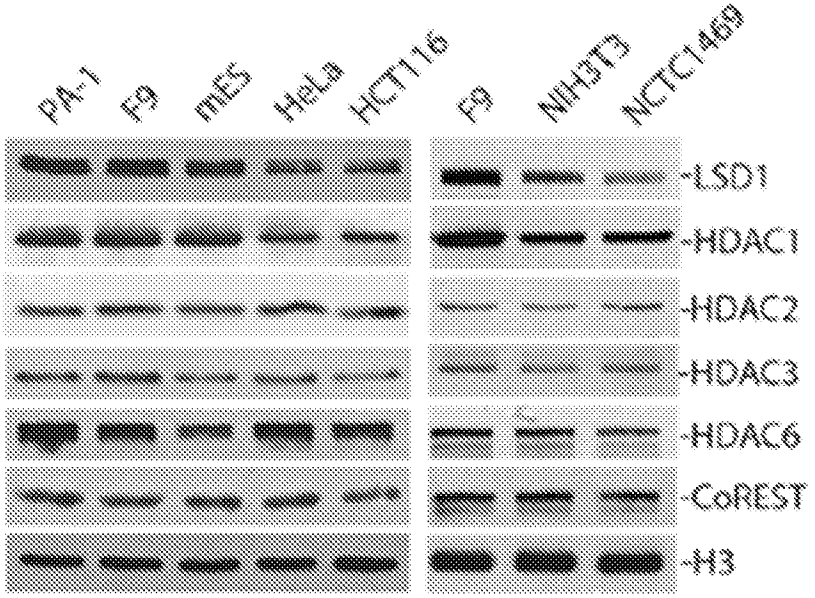


FIG. 31E

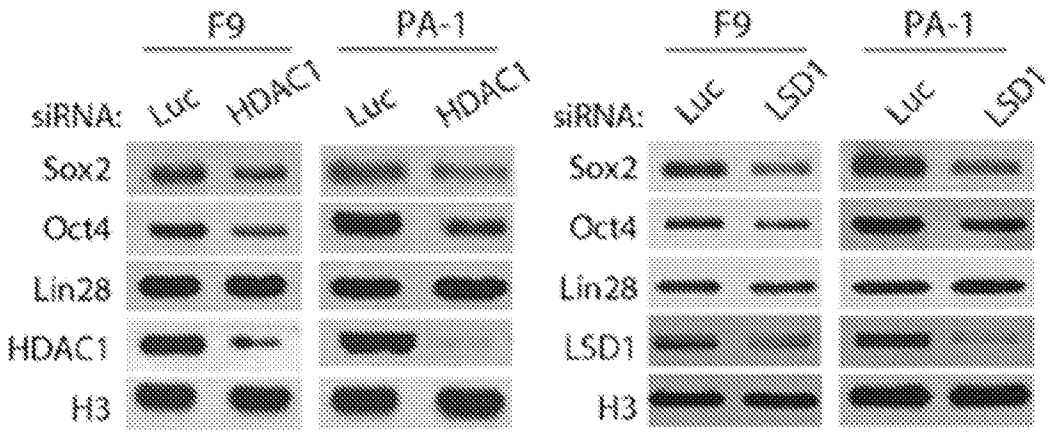


FIG. 32A

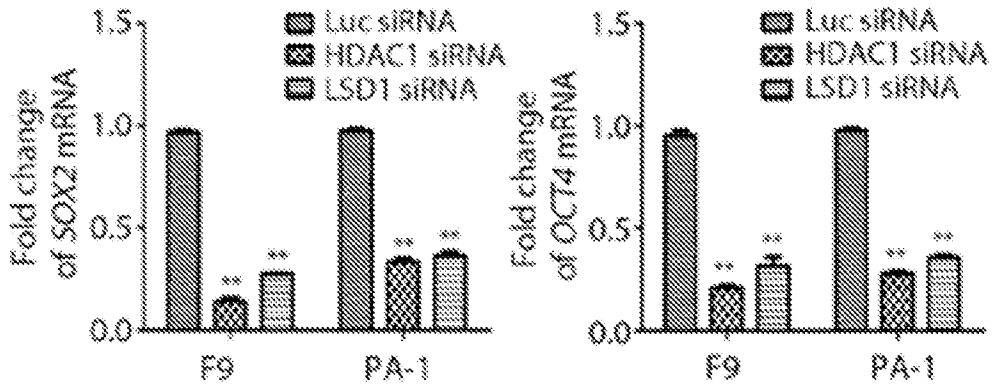


FIG. 32B

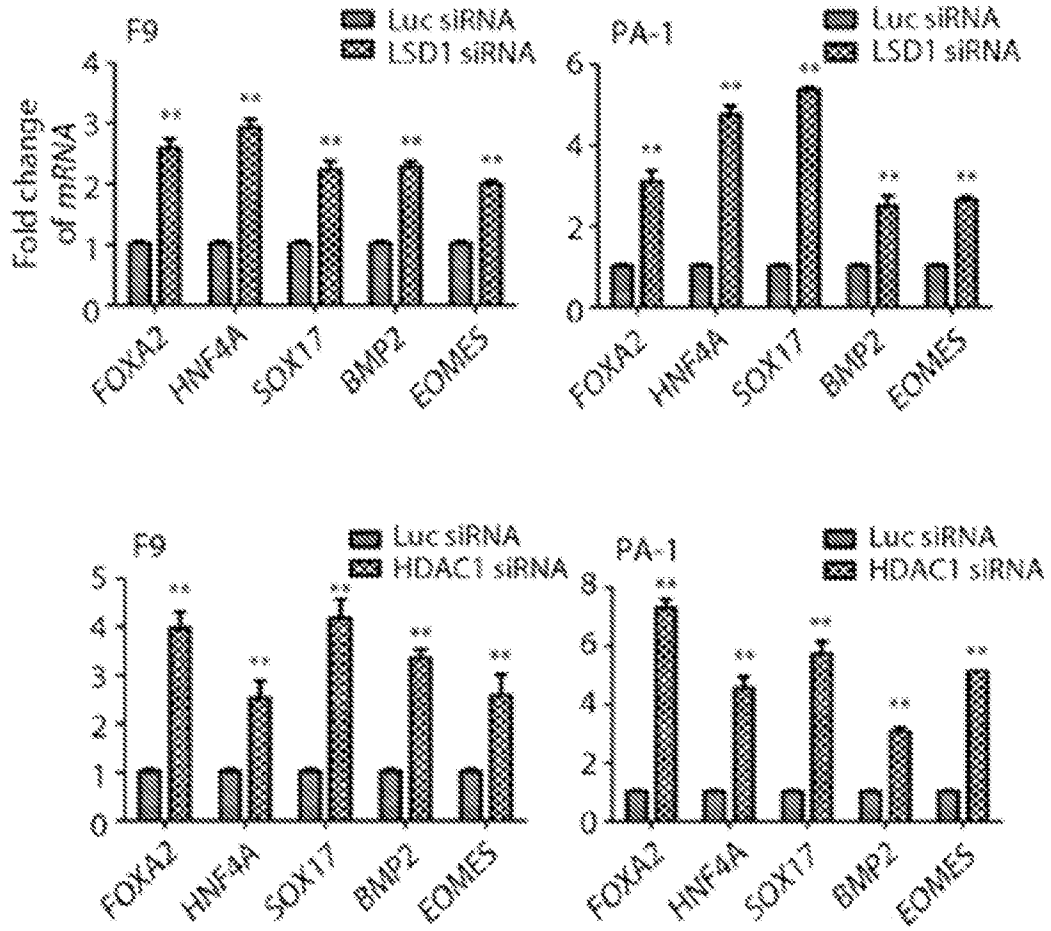

F9
Luc siRNA
LSD1 siRNA
Fold change of mRNA
FOXA2
HNF4A
SOX17
BMP2
EOMES
PA-1
Luc siRNA
LSD1 siRNA
FOXA2
HNF4A
SOX17
BMP2
EOMES
F9
Luc siRNA
HDAC1 siRNA
FOXA2
HNF4A
SOX17
BMP2
EOMES
PA-1
Luc siRNA
HDAC1 siRNA
FOXA2
HNF4A
SOX17
BMP2
EOMES

FIG. 33A

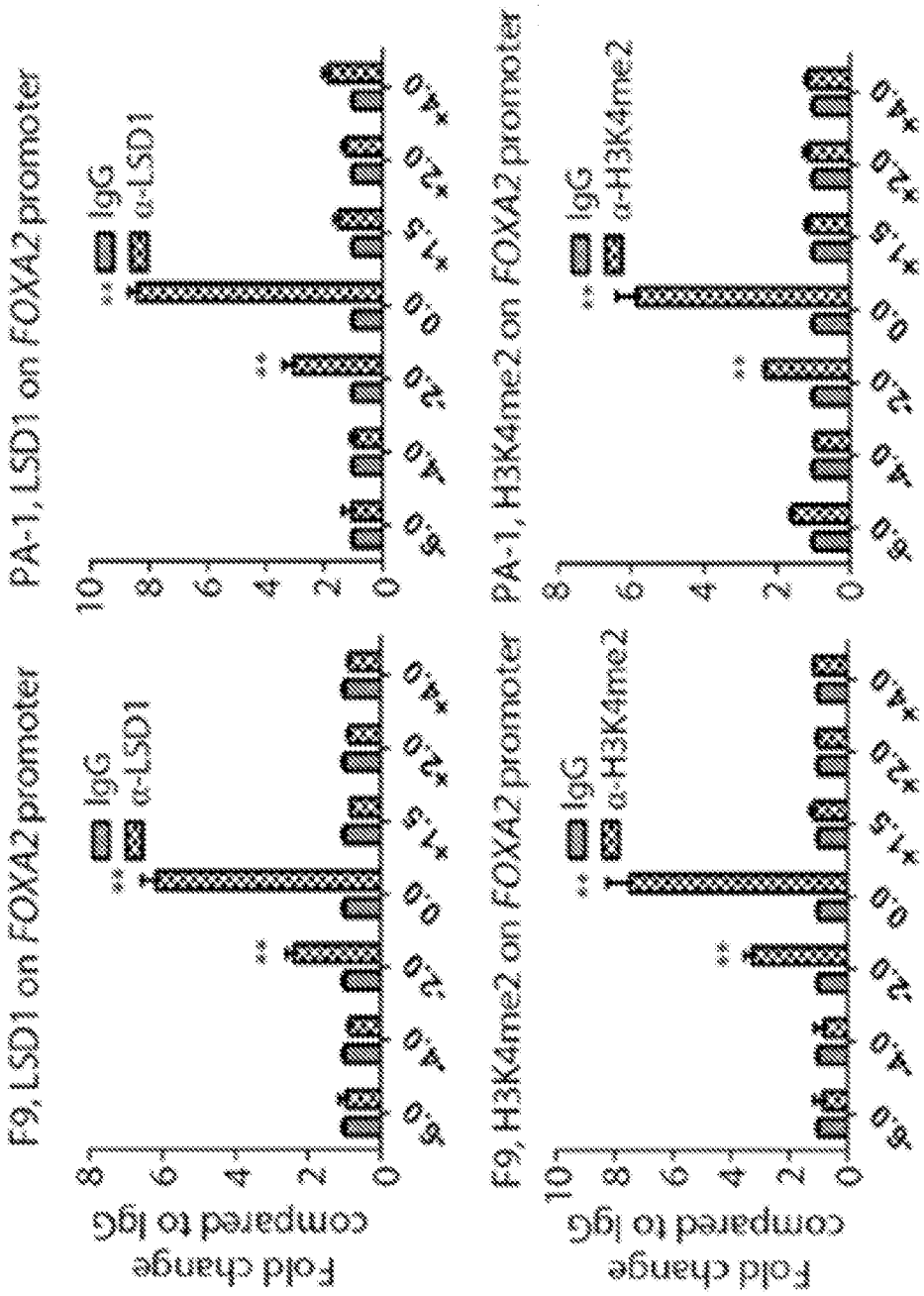

F9, LSD1 on FOXA2 promoter
PA-1, LSD1 on FOXA2 promoter
F9, H3K4me2 on FOXA2 promoter
PA-1, H3K4me2 on FOXA2 promoter
IgG
α-LSD1
α-H3K4me2
Fold change compared to IgG
0
2
4
6
8
10
**
*
-6.0
-4.0
-2.0
0.0
+1.5
+2.0
+4.0

FIG. 33B

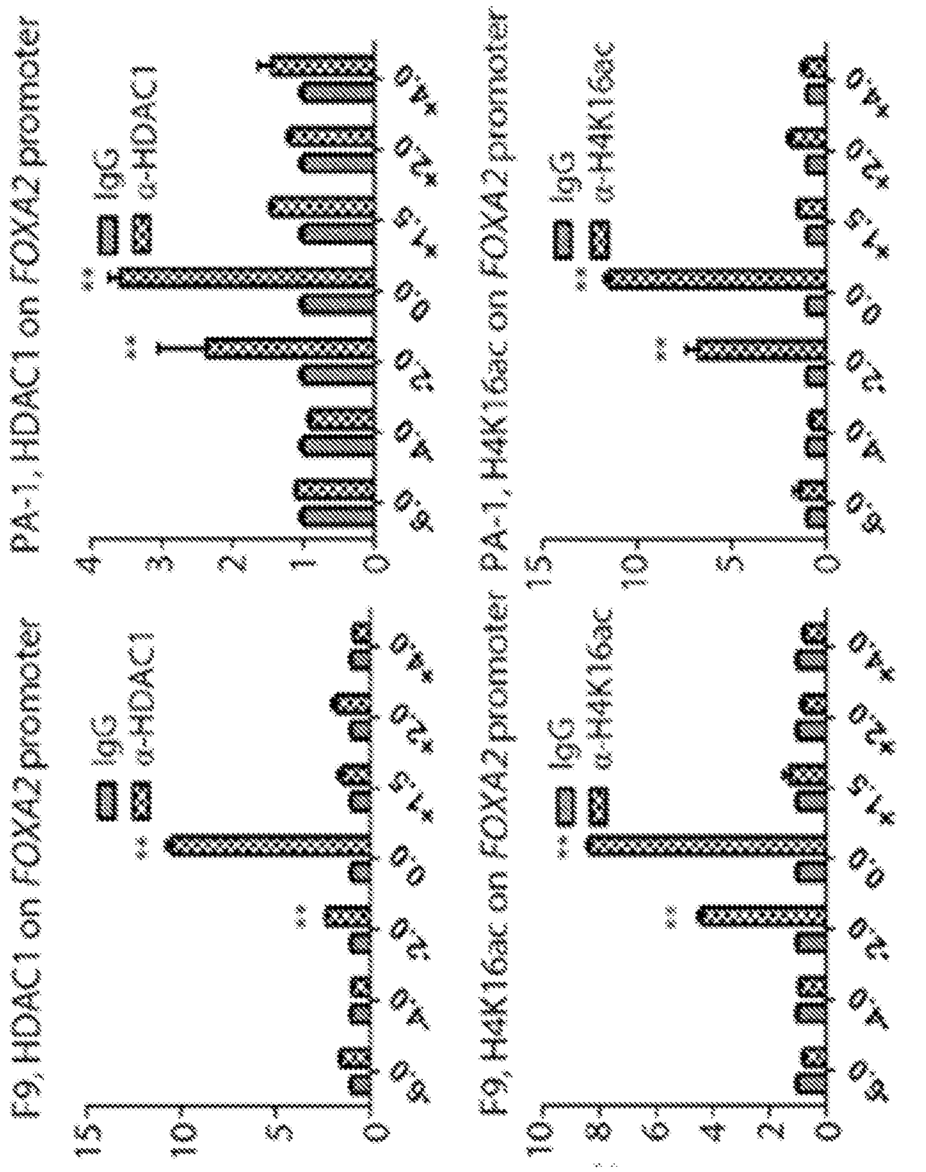

F9, HDAC1 on FOXA2 promoter
IgG
α-HDAC1
PA-1, HDAC1 on FOXA2 promoter
IgG
α-HDAC1
F9, H4K16ac on FOXA2 promoter
IgG
α-H4K16ac
PA-1, H4K16ac on FOXA2 promoter
IgG
α-H4K16ac
-6.0
-4.0
-2.0
0.0
+1.5
+2.0
+4.0

FIG. 33B (Cont.)

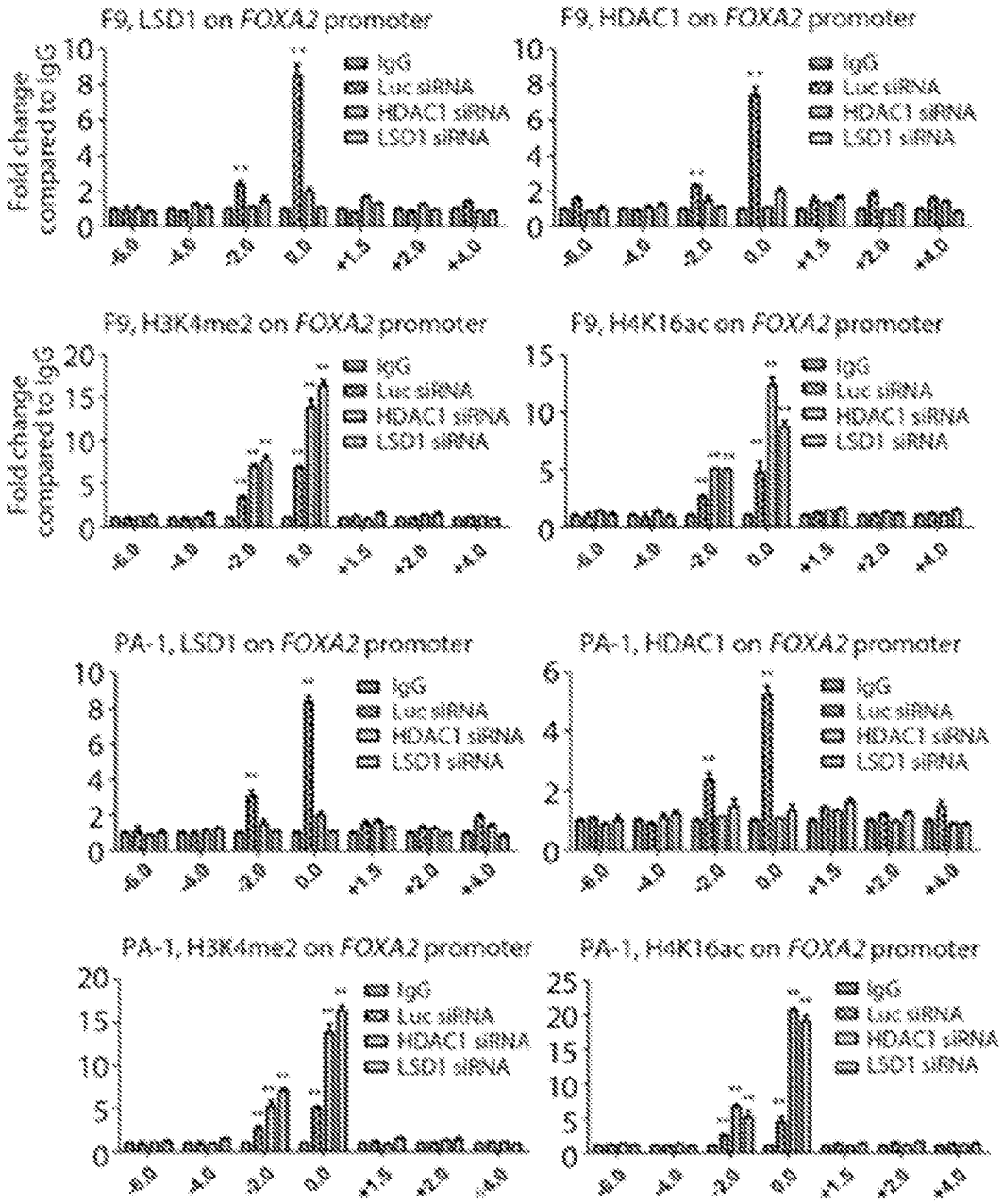

F9, LSD1 on FOXA2 promoter
F9, HDAC1 on FOXA2 promoter
F9, H3K4me2 on FOXA2 promoter
F9, H4K16ac on FOXA2 promoter
PA-1, LSD1 on FOXA2 promoter
PA-1, HDAC1 on FOXA2 promoter
PA-1, H3K4me2 on FOXA2 promoter
PA-1, H4K16ac on FOXA2 promoter
Fold change compared to IgG
IgG
Luc siRNA
HDAC1 siRNA
LSD1 siRNA

FIG. 34A

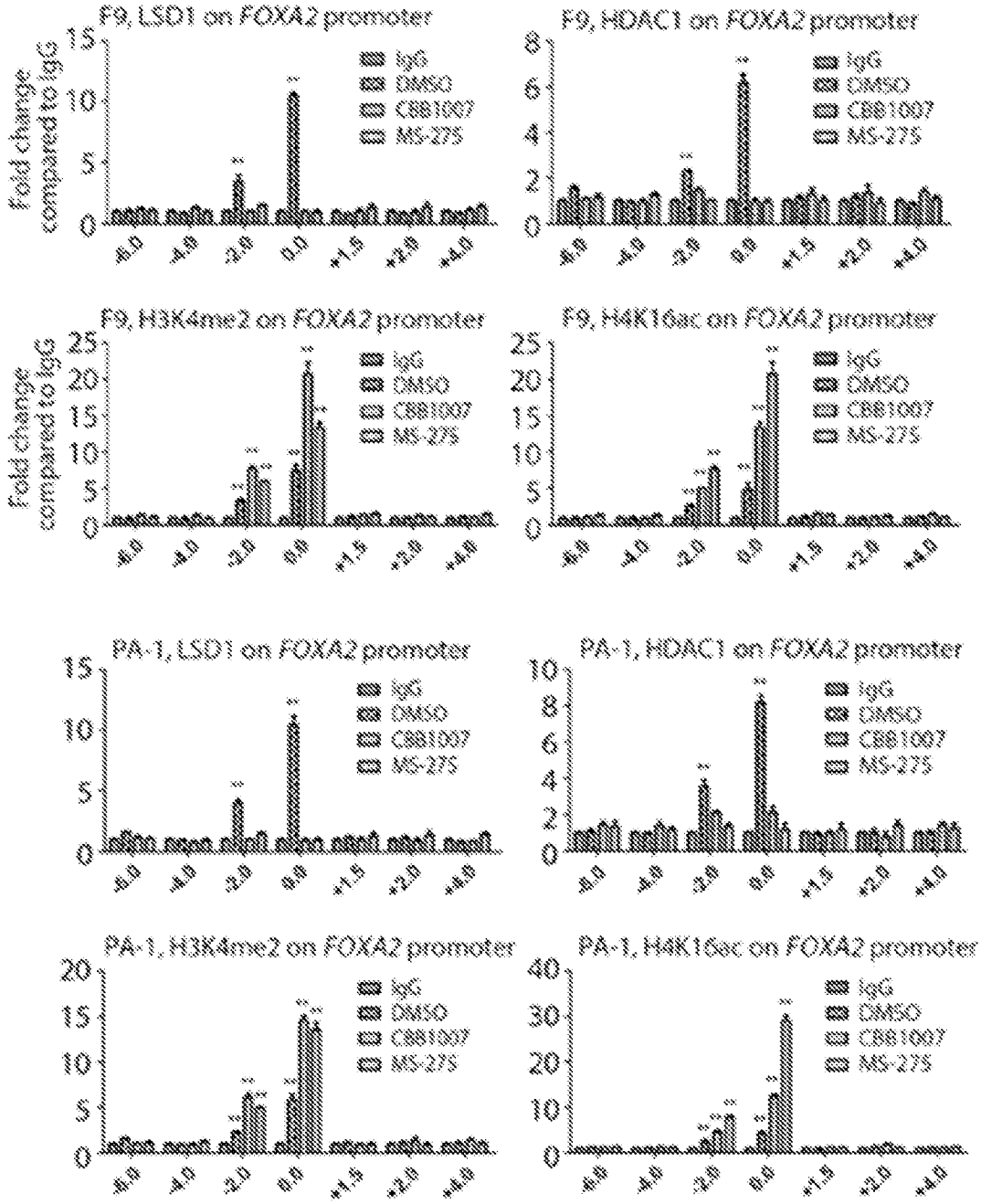

F9, LSD1 on FOXA2 promoter
F9, HDAC1 on FOXA2 promoter
F9, H3K4me2 on FOXA2 promoter
F9, H4K16ac on FOXA2 promoter
PA-1, LSD1 on FOXA2 promoter
PA-1, HDAC1 on FOXA2 promoter
PA-1, H3K4me2 on FOXA2 promoter
PA-1, H4K16ac on FOXA2 promoter
fold change compared to IgG
IgG
DMSO
CBB1007
MS-275

FIG. 34B

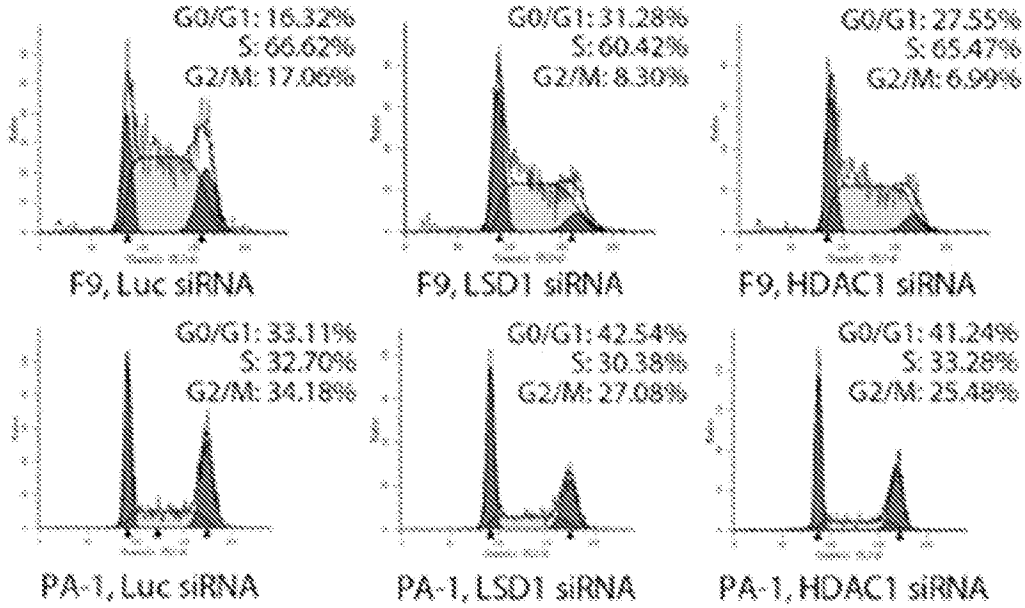


FIG. 35A

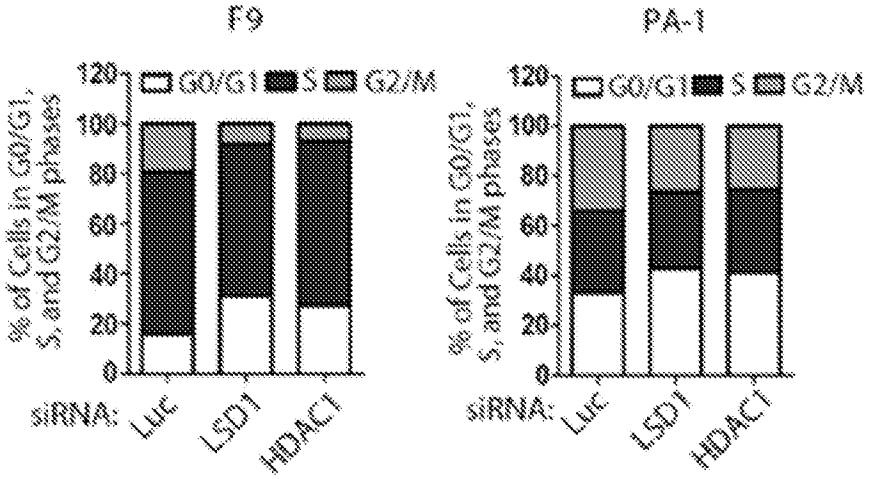


FIG. 35B

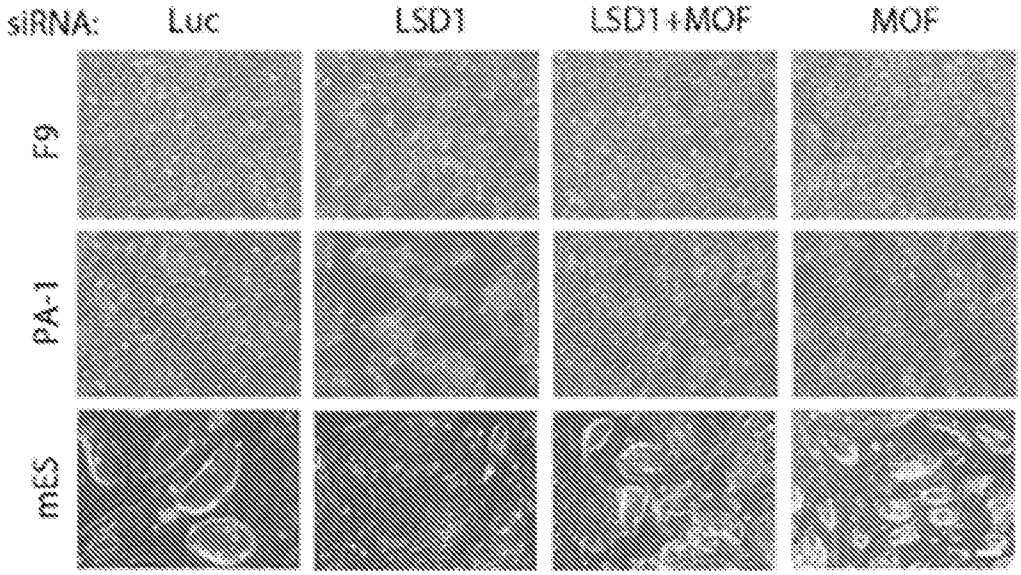


FIG. 36A

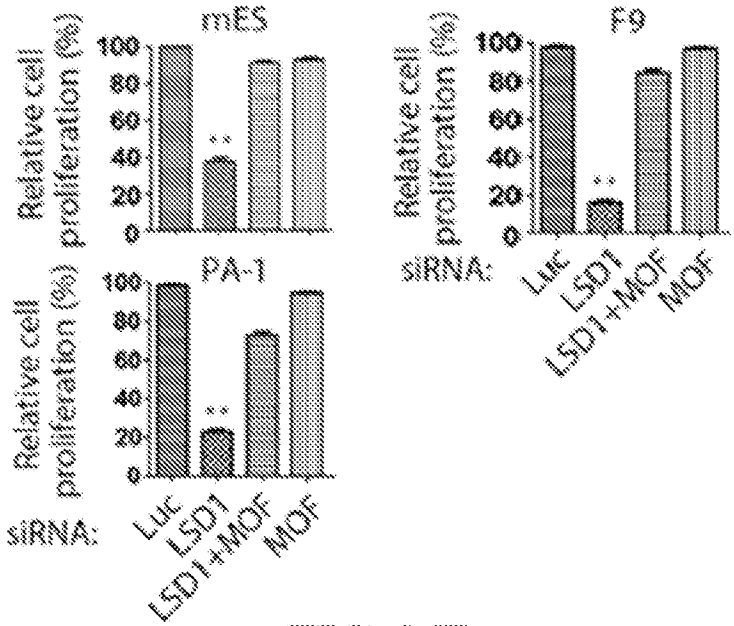


FIG. 36B

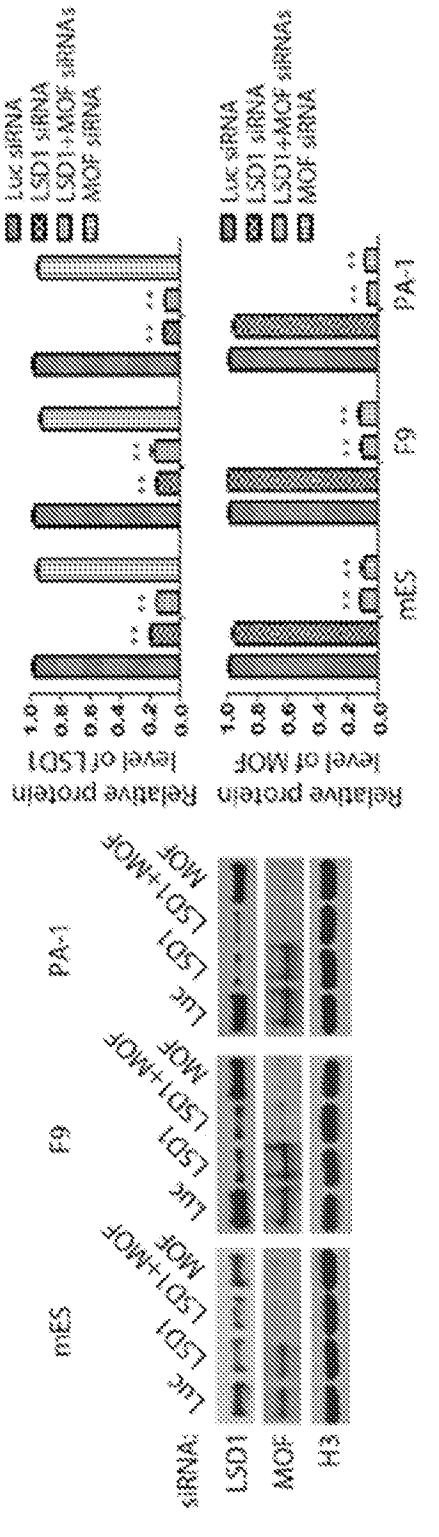


FIG. 36C

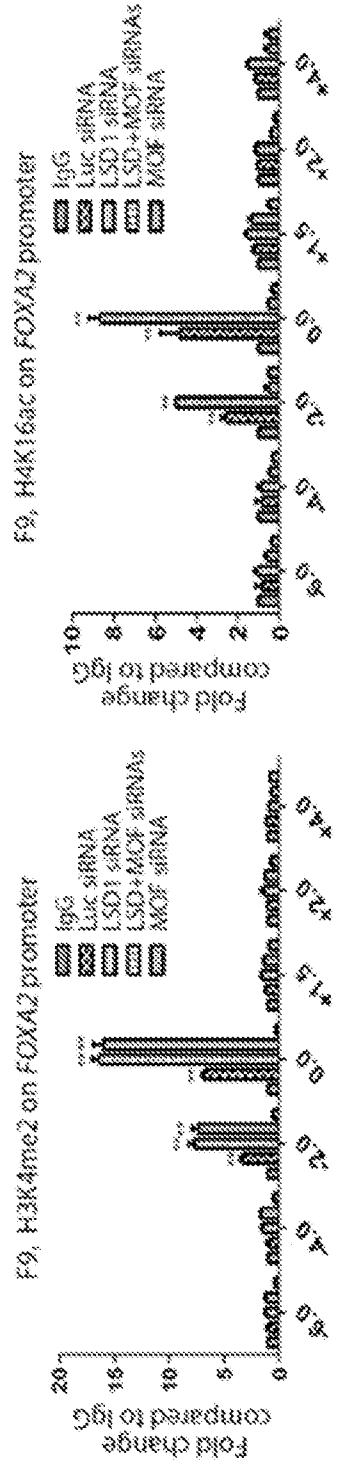


FIG. 36D

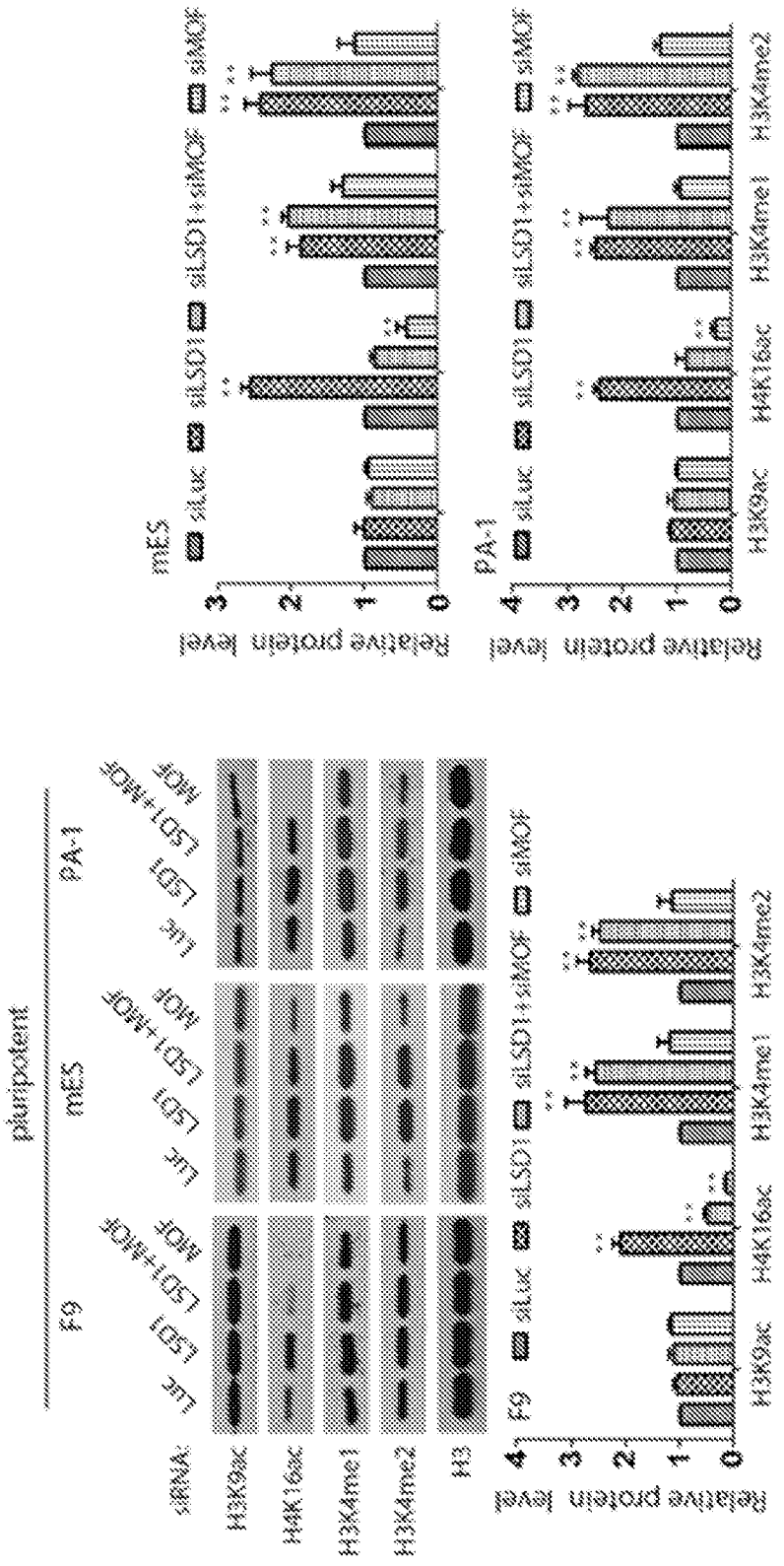

pluripotent
F9
mES
PA-1
siRNA:
luc
LSD1
LSD1+MOF
MOF
H3K9ac
H4K16ac
H3K4me1
H3K4me2
H3
Relative protein level
siLuc
siLSD1
siLSD1+siMOF
siMOF

FIG. 37A

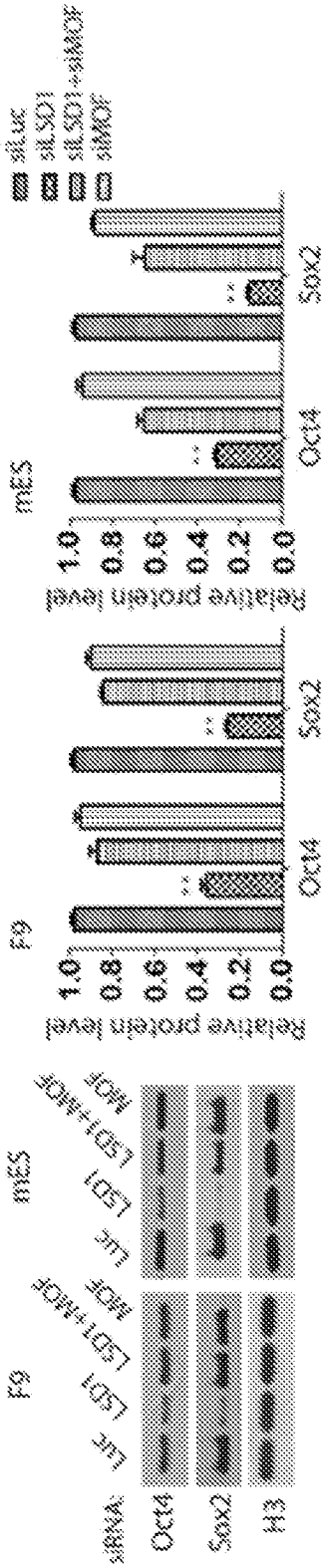


FIG. 37B

FIG. 37C

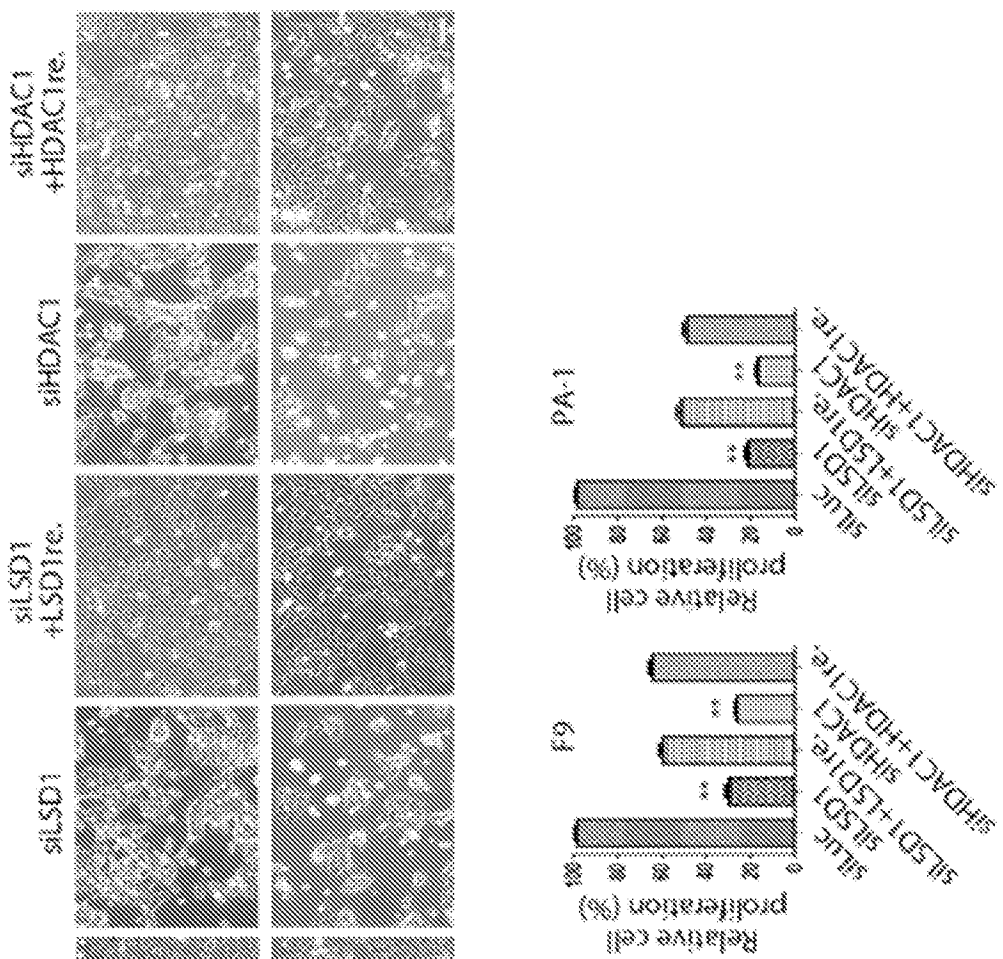

siLuc
siLSD1
siLSD1 +LSD1re.
siHDAC1
siHDAC1 +HDAC1re.
F9
PA-1
Relative cell proliferation (%)
siLuc
siLSD1
siLSD1+LSD1re.
siHDAC1
siHDAC1+HDAC1re.

FIG. 38A

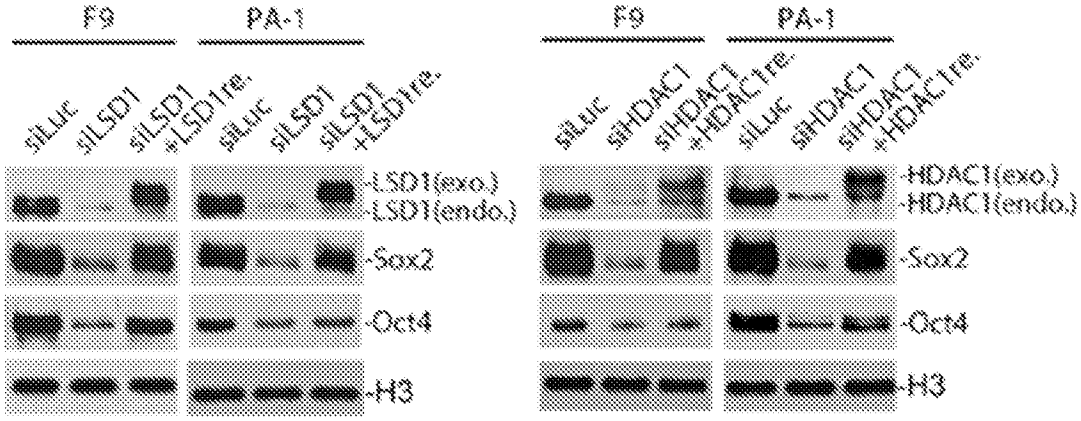


FIG. 38B

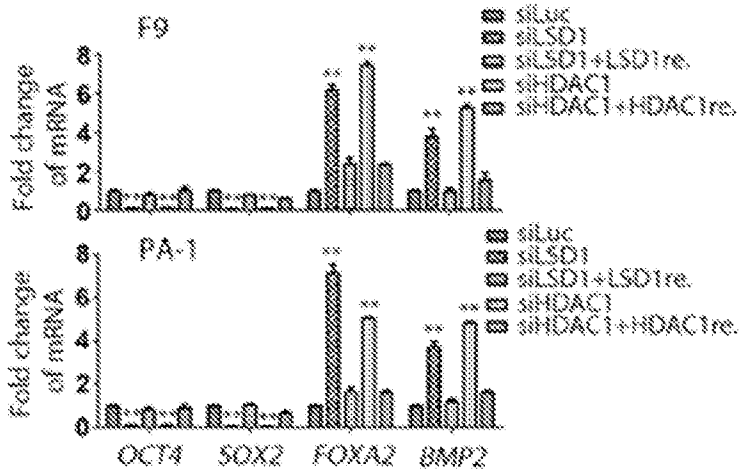


FIG. 38C

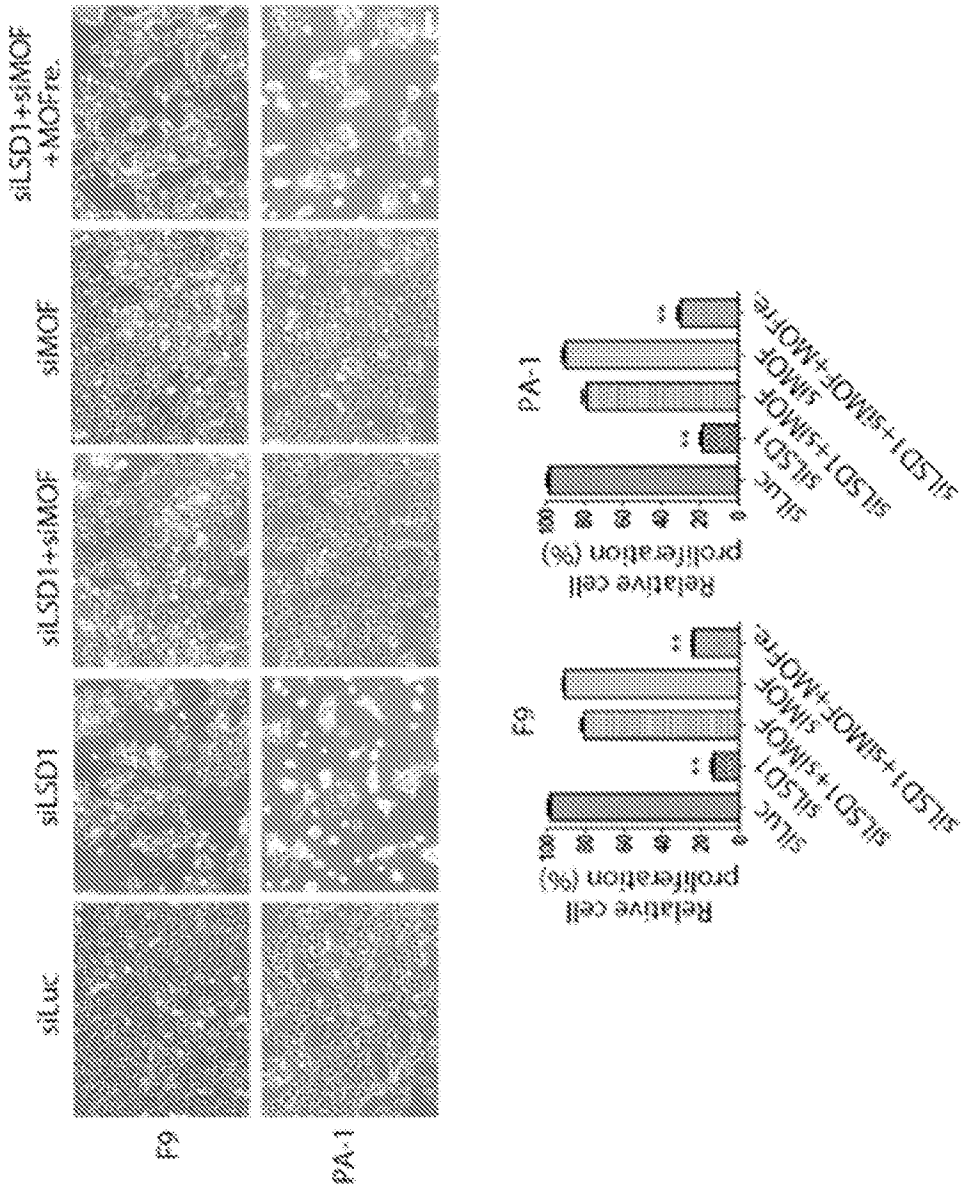

siLuc
siLSD1
siLSD1+siMOF
siMOF
siLSD1+siMOF +MOFre.
F9
PA-1
Relative cell proliferation (%)
siLuc
siLSD1
siLSD1+siMOF
siMOF
siLSD1+siMOF+MOFre.

FIG. 38D

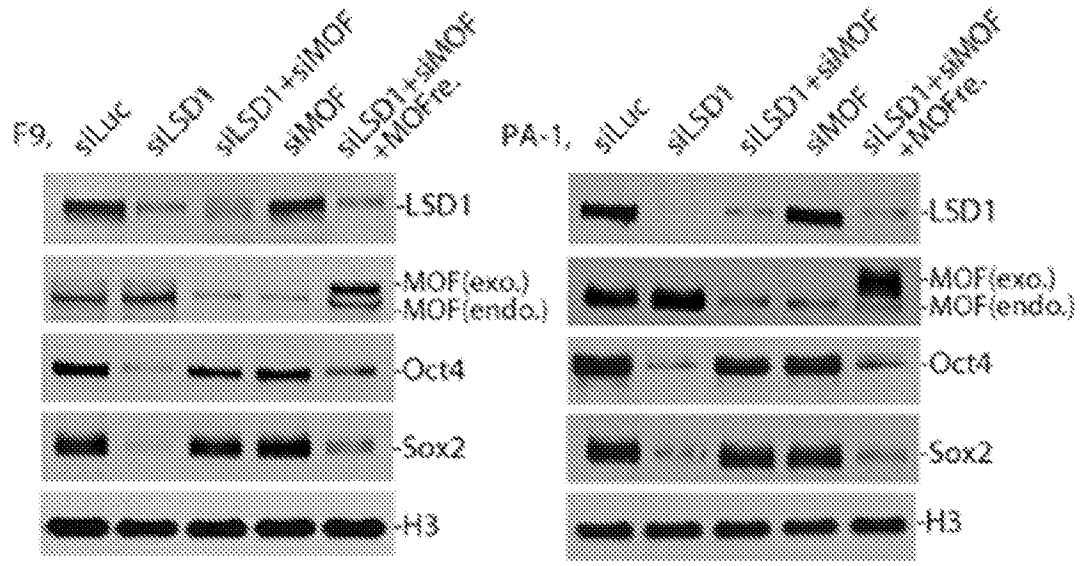


FIG. 38E

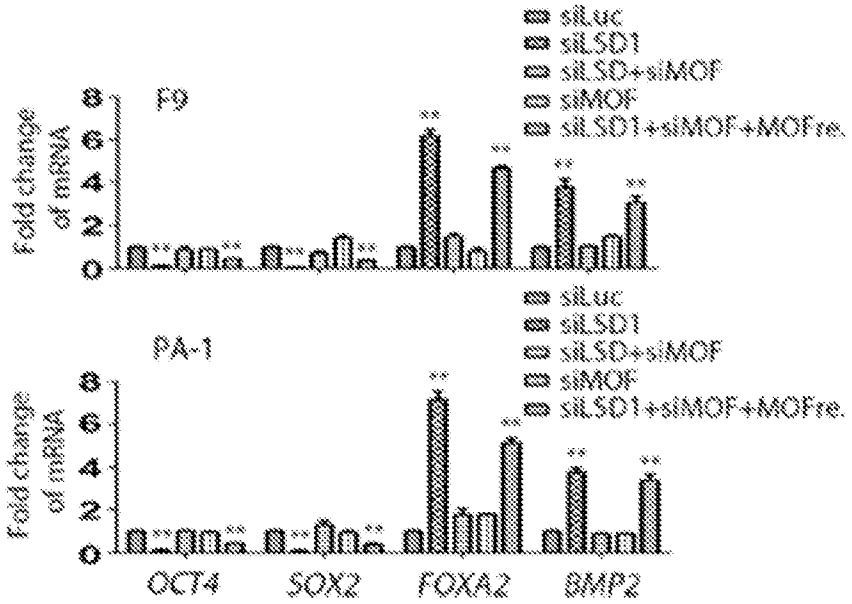


FIG. 38F

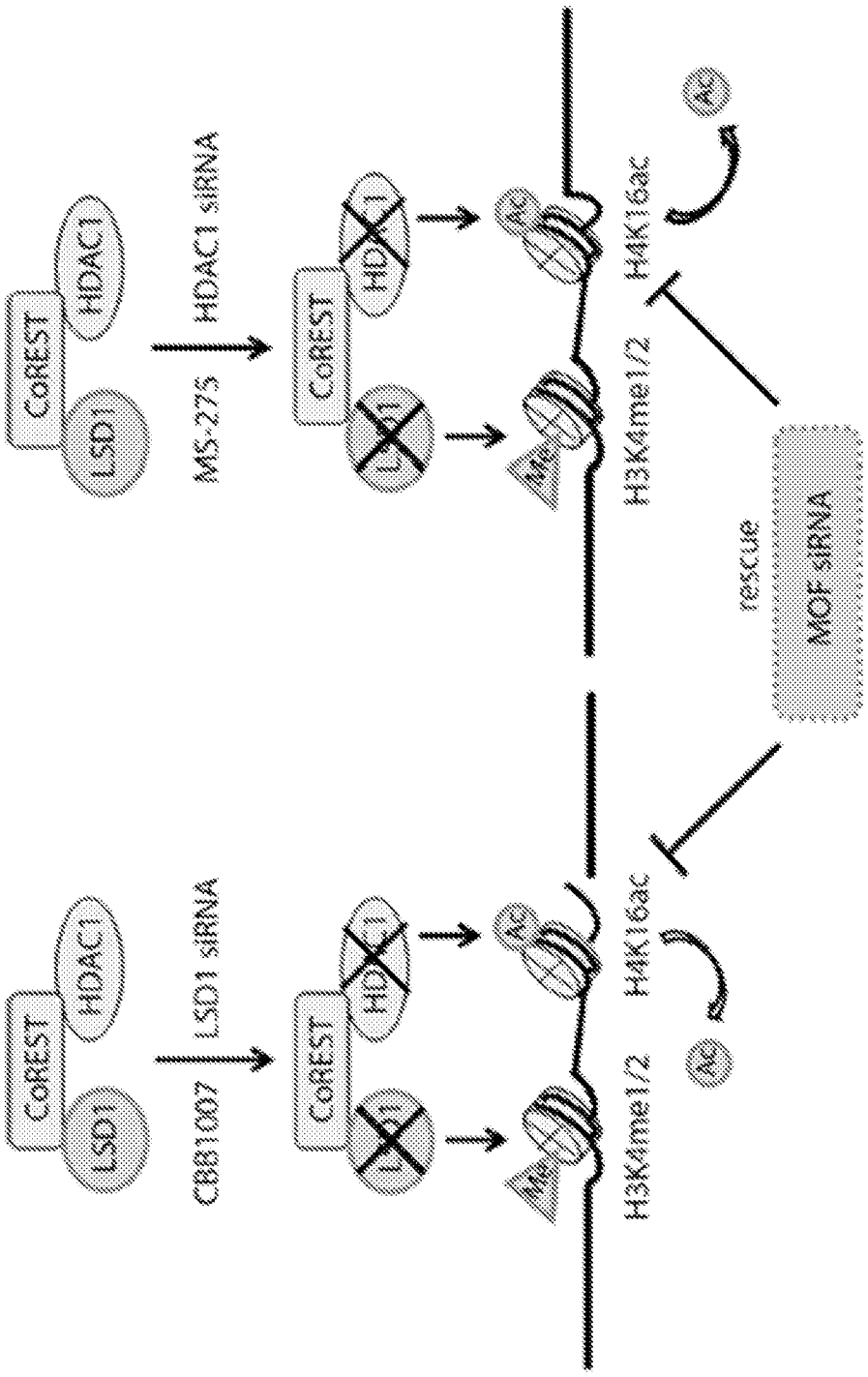

CoREST
HDAC1
LSD1
CBB1007
LSD1 siRNA
HDAC1
LSD1
Ac
H3K4me1/2
H4K16ac
MS-275
HDAC1 siRNA
rescue
MOF siRNA

FIG. 39

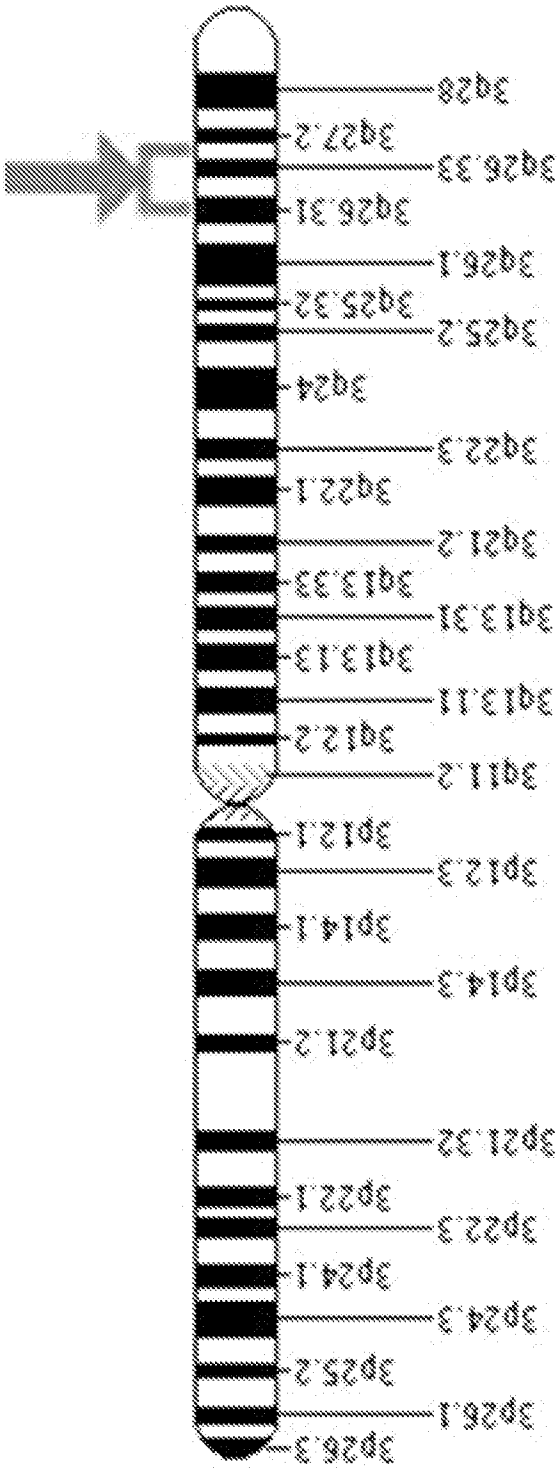

3q28
3q27.2
3q26.33
3q26.31
3q26.1
3q25.32
3q25.2
3q24
3q22.3
3q22.1
3q21.2
3q13.33
3q13.31
3q13.13
3q13.11
3q12.2
3q11.2
3p12.1
3p12.3
3p14.1
3p14.3
3p21.2
3p21.32
3p22.1
3p22.3
3p24.1
3p24.3
3p25.2
3p25.1
3p26.3

FIG. 40