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Inventor(s)	Ruppel; Sabine K. et al.

Compounds and uses thereof

Abstract

The present invention relates to methods and compositions for the treatment of BAF-related disorders such as cancers and viral infections.

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Background/Summary

BACKGROUND
(1) Disorders can be affected by the BAF complex. BRD9 is a component of the BAF complex. The present invention relates to useful compositions and methods for the treatment of BAF complex-related disorders, such as cancer and infection.
SUMMARY
(2) Bromodomain-containing protein 9 (BRD9) is a protein encoded by the BRD9 gene on chromosome 5. BRD9 is a component of the BAF (BR.sup.G1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is present in several SWI/SNF ATPase chromatin remodeling complexes and is upregulated in multiple cancer cell lines. Accordingly, agents that reduce the levels and/or activity of BRD9 may provide new methods for the treatment of disease and disorders, such as cancer and infection. The inventors have found that depleting BRD9 in cells results in the depletion of the SS18-SSX fusion protein in those cells. The SS18-SSX fusion protein has been detected in more than 95% of synovial sarcoma tumors and is often the only cytogenetic abnormality in synovial sarcoma. Additionally, evidence suggests that the BAF complex is involved in cellular antiviral activities. Thus, agents that degrade BRD9 (e.g., compounds) are useful in the treatment of disorders (e.g., cancers or infections) related to BAF, BRD9, and/or SS18-SSX.
(3) The present disclosure features compounds and methods useful for treating BAF-related disorders (e.g., cancer or infection).
(4) In an aspect, the disclosure features a compound having the structure Formula I:
(5) ##STR00001##
(6) where
(7) R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl;
(8) Z.sup.1 is CR.sup.2 or N;
(9) R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(10) X.sup.1 is N or CH, and X.sup.2 is C—R.sup.7; or X.sup.1 is C—R.sup.7, and X.sup.2 is N or CH;
(11) R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;
(12) X.sup.3 is N or CH;

(13) X.sup.4 is N or CH;
(14) G is optionally substituted C.sub.3-C.sub.10 carbocyclyl, C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl, or a pharmaceutically acceptable salt thereof.
(15) In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl.
(16) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.1 is optionally substituted C.sub.2-C.sub.6 alkenyl. In some embodiments, R.sup.1 is optionally substituted C.sub.3-C.sub.10 carbocyclyl.
(17) In some embodiments, optionally substituted C.sub.1-C.sub.6 alkyl is C.sub.1-C.sub.6 perfluoroalkyl.
(18) In some embodiments, R.sup.1 is
(19) ##STR00002##
(20) In some embodiments, R.sup.1 is
(21) ##STR00003##
(22) In some embodiments, R.sup.1 is
(23) ##STR00004##
(24) In some embodiments, R.sup.1 is H,
(25) ##STR00005##
In some embodiments, R.sup.1 is
(26) ##STR00006##
In some embodiments, R.sup.1 is H,
(27) ##STR00007##
(28) In some embodiments. R.sup.1 is H,
(29) ##STR00008##
(30) In some embodiments, R.sup.1 is H,
(31) ##STR00009##
(32) In some embodiments, R.sup.1 is H or
(33) ##STR00010##
(34) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is
(35) ##STR00011##
(36) In some embodiments, Z.sup.1 is CR.sup.2. In some embodiments, Z.sup.1 is N.
(37) In some embodiments, R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl.
(38) In some embodiments, R.sup.2 is H, halogen, or optionally substituted C.sub.1-C.sub.6 alkyl.
(39) In some embodiments, R.sup.2 is H, F, or
(40) ##STR00012##
(41) In some embodiments, R.sup.2 is H. In some embodiments, R.sup.2 is F. In some embodiments, R.sup.2 is
(42) ##STR00013##
(43) In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkoxy or optionally substituted amino. In some embodiments, R.sup.7 is optionally substituted sulfone or optionally substituted sulfonamide.

(44) In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 heteroalkyl or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(45) In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkoxy.
(46) In some embodiments, R.sup.7 is optionally substituted amino. In some embodiments, R.sup.7 is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted sulfone. In some embodiments, R.sup.7 is optionally substituted sulfonamide.
(47) In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.3 alkyl. In some embodiments, R.sup.7 is optionally substituted C.sub.1-C.sub.3 heteroalkyl.
(48) In some embodiments, R.sup.7 is
(49) ##STR00014##
(50) In some embodiments, R.sup.7 is —NR.sup.3R.sup.4 or —OR.sup.4, where R.sup.3 is H or optionally substituted C.sub.1-C.sub.6 alkyl, and R.sup.4 is optionally substituted C.sub.1-C.sub.6 alkyl.
(51) In some embodiments, R.sup.7 is —NR.sup.3R.sup.4. In some embodiments, R.sup.7 is —OR.sup.4.
(52) In some embodiments, R.sup.3 is H. In some embodiments, R.sup.3 is optionally substituted C.sub.1-C.sub.6 alkyl.
(53) In some embodiments, R.sup.3 is H and R.sup.4 is methyl. In some embodiments, R.sup.3 is methyl and R.sup.4 is methyl.
(54) In some embodiments, R.sup.7 is
(55) ##STR00015##
In some embodiments, R.sup.7 is
(56) ##STR00016##
(57) In some embodiments, R.sup.7 is optionally substituted carbocyclyl having 3 to 6 atoms or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is optionally substituted heterocyclyl having 3 to 6 atoms.
(58) In some embodiments, R.sup.7 is carbocyclyl having 3 to 6 atoms or heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7 is heterocyclyl having 3 to 6 atoms.
(59) In some embodiments, R.sup.7 is
(60) ##STR00017##
(61) In some embodiments, R.sup.7 is
(62) ##STR00018##
(63) In some embodiments, R.sup.7 is
(64) ##STR00019##
(65) In some embodiments, R.sup.7 is
(66) ##STR00020## ##STR00021##
(67) In some embodiments, R.sup.7 is
(68) ##STR00022##
In some embodiments, R.sup.7 is
(69) ##STR00023##
In some embodiments, R.sup.7 is
(70) ##STR00024##
In some embodiments, R.sup.7 is
(71) ##STR00025##
In some embodiments, R.sup.7 is

(72) ##STR00026##
(73) In some embodiments, X.sup.1 is N and X.sup.2 is C—R.sup.7. In some embodiments, X.sup.1 is CH and X.sup.2 is C—R.sup.7. In some embodiments, X.sup.1 is C—R.sup.7 and X.sup.2 is N. In some embodiments, X.sup.1 is C—R.sup.7 and X.sup.2 is CH.
(74) In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4, C—OR.sup.4,
(75) ##STR00027##
or X.sup.1 is C—NR.sup.3R.sup.4, C—OR.sup.4,
(76) ##STR00028##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4,
(77) ##STR00029##
or X.sup.1 is C—NR.sup.3R.sup.4,
(78) ##STR00030##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4 or
(79) ##STR00031##
or X.sup.1 is C—NR.sup.3R.sup.4 or
(80) ##STR00032##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4 or
(81) ##STR00033##
or X.sup.1 is C—NR.sup.3R.sup.4 or
(82) ##STR00034##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4 or
(83) ##STR00035##
or X.sup.1 is C—NR.sup.3R.sup.4 or
(84) ##STR00036##
and X.sup.2 is N or CH.
(85) In some embodiments, R.sup.7 is —NR.sup.3R.sup.4, —OR.sup.4, or optionally substituted heterocyclyl having 3 to 6 atoms.
(86) In some embodiments, X.sup.1 is N and X.sup.2 is C—NR.sup.3R.sup.4. In some embodiments, X.sup.1 is C—NR.sup.3R.sup.4 and X.sup.2 is N. In some embodiments, X.sup.1 is N and X.sup.2 is C—OR.sup.4. In some embodiments, X.sup.1 is C—OR.sup.4 and X.sup.2 is N.
(87) In some embodiments, R.sup.3 is H. In some embodiments, R.sup.3 is optionally substituted C.sub.1-C.sub.6 alkyl.
(88) In some embodiments, R.sup.3 is
(89) ##STR00037##
In some embodiments, R.sup.3 is
(90) ##STR00038##
In some embodiments, R.sup.3 is
(91) ##STR00039##
In some embodiments, R.sup.3 is methyl, ethyl,
(92) ##STR00040##
(93) In some embodiments, R.sup.4 is
(94) ##STR00041##
In some embodiments, R.sup.4 is
(95) ##STR00042##
In some embodiments, R.sup.4 is
(96) ##STR00043##
In some embodiments, R.sup.4 is methyl, ethyl,
(97) ##STR00044##

(98) In some embodiments, X.sup.3 is N. In some embodiments, X.sup.3 is CH.
(99) In some embodiments, X.sup.4 is N. In some embodiments, X.sup.4 is CH.
(100) In some embodiments, X.sup.3 is N and X.sup.4 is N.
(101) In some embodiments, X.sup.3 is N and X.sup.4 is CH.
(102) In some embodiments, X.sup.3 is CH and X.sup.4 is N.
(103) In some embodiments, X.sup.3 is CH and X.sup.4 is CH.
(104) In some embodiments, G is optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G is optionally substituted C.sub.6-C.sub.10 aryl or optionally substituted C.sub.2-C.sub.9 heteroaryl.
(105) In some embodiments, G is optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, G is optionally substituted C.sub.6-C.sub.10 aryl. In some embodiments, G is optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G is optionally substituted C.sub.2-C.sub.9 heteroaryl.
(106) In some embodiments, G is
(107) ##STR00045##
(108) where
(109) each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.8 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(110) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(111) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(112) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(113) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is,

independently, H, F, Cl,
(114) ##STR00046##
(115) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F,
(116) ##STR00047##
(117) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F, Cl,
(118) ##STR00048##
(119) In some embodiments, R.sup.G1 is H; R.sup.G2 is
(120) ##STR00049##
and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(121) ##STR00050##
R.sup.G4 is H; and R.sup.G5 is
(122) ##STR00051##
In some embodiments, R.sup.G1 is H; R.sup.G2 is
(123) ##STR00052##
R.sup.G4 is Cl or F; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(124) ##STR00053##
R.sup.G4 is H; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(125) ##STR00054##
and R.sup.G5 is H.
(126) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(127) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl.
(128) In some embodiments, G is
(129) ##STR00055##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, G is
(130) ##STR00056##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(131) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl or optionally substituted C.sub.2-C.sub.9 heteroaryl.
(132) In some embodiments, G is
(133) ##STR00057##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(134) In some embodiments, R.sup.G6 is H,
(135) ##STR00058##
(136) In some embodiments, R.sup.G6 is H or
(137) ##STR00059##
(138) In some embodiments, R.sup.G6 is H.
(139) In some embodiments, R.sup.G1 is H, F,
(140) ##STR00060##
In some embodiments, R.sup.G1 is H.
(141) In some embodiments, R.sup.G2 is H, F,

(142) ##STR00061##
In some embodiments, R.sup.G2 is H.
(143) In some embodiments, R.sup.G3 is H, F
(144) ##STR00062##
In some embodiments, R.sup.G3 is H.
(145) In some embodiments, R.sup.G4 is H, F,
(146) ##STR00063##
In some embodiments, R.sup.G4 is H.
(147) In some embodiments, R.sup.G5 is H, F,
(148) ##STR00064##
In some embodiments, R.sup.G5 is H.
(149) In some embodiments, one or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, two or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, three or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H.
(150) In some embodiments, G is
(151) ##STR00065##
(152) where
(153) each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(154) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(155) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(156) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.

(157) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, F, Cl,
(158) ##STR00066##
In some embodiments, R.sup.G8 is
(159) ##STR00067##
(160) In some embodiments, G is
(161) ##STR00068##
(162) In some embodiments, R.sup.G7 is H; R.sup.G8 is
(163) ##STR00069##
R.sup.G9 is H; and R.sup.G11 is H.
(164) In some embodiments, G is
(165) ##STR00070##
(166) where
(167) each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(168) In some embodiments, each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(169) In some embodiments, the compound of Formula I has the structure of Formula Ia:
(170) ##STR00071##
or a pharmaceutically acceptable salt thereof.
(171) In some embodiments, the compound of Formula I has the structure of Formula Ib:
(172) ##STR00072##
(173) or a pharmaceutically acceptable salt thereof.
(174) In some embodiments, the compound of Formula I has the structure of Formula Ic:
(175) ##STR00073##
or a pharmaceutically acceptable salt thereof.
(176) In some embodiments, the compound of Formula I has the structure of Formula Id:
(177) ##STR00074##
or a pharmaceutically acceptable salt thereof.
(178) In some embodiments, the compound of Formula I has the structure of Formula Ie:
(179) ##STR00075##
where each of R.sup.5 and R.sup.6 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl; or R.sup.5 and R.sup.6, together with the nitrogen to which each is attached, combine to form an optionally substituted C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

(180) In some embodiments, the compound of Formula I has the structure of Formula If:
(181) ##STR00076##
where each of R.sup.5 and R.sup.6 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl; or R.sup.5 and R.sup.6, together with the nitrogen to which each is attached, combine to form an optionally substituted C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.
(182) In some embodiments, the compound of Formula I has the structure of Formula Ig:
(183) ##STR00077##
where each of R.sup.5 and R.sup.6 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl; or R.sup.5 and R.sup.6, together with the nitrogen to which each is attached, combine to form an optionally substituted C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.
(184) In some embodiments, the compound of Formula I has the structure of Formula Ih:
(185) ##STR00078##
or a pharmaceutically acceptable salt thereof.
(186) In some embodiments, the compound of Formula I has the structure of Formula Ii:
(187) ##STR00079##
or a pharmaceutically acceptable salt thereof.
(188) In some embodiments, the compound of Formula I has the structure of Formula Ij:
(189) ##STR00080##
or a pharmaceutically acceptable salt thereof.
(190) In some embodiments, the compound of Formula I has the structure of Formula Ik:
(191) ##STR00081##
or a pharmaceutically acceptable salt thereof.
(192) In some embodiments, the compound of Formula I has the structure of Formula Im:
(193) ##STR00082##
or a pharmaceutically acceptable salt thereof.
(194) In some embodiments, the compound of Formula I has the structure of Formula In:
(195) ##STR00083##
or a pharmaceutically acceptable salt thereof.
(196) In some embodiments, the compound of Formula I has the structure of Formula Io:
(197) ##STR00084##
or a pharmaceutically acceptable salt thereof.
(198) In some embodiments, the compound of Formula I has the structure of Formula Ip:
(199) ##STR00085##
or a pharmaceutically acceptable salt thereof.
(200) In some embodiments, the compound of Formula I has the structure of Formula Iq:
(201) ##STR00086##
or a pharmaceutically acceptable salt thereof.
(202) In some embodiments, the compound of Formula I has the structure of Formula Ir:
(203) ##STR00087##
or a pharmaceutically acceptable salt thereof.
(204) In some embodiments, the compound has the structure of any one of compounds B1-B6 in Table 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds B1-B3 and B6 in Table 1, or a pharmaceutically acceptable salt thereof.
(205) In an aspect, the disclosure features a compound having the structure of any one of compounds B1-B6 in Table 1, or a pharmaceutically acceptable salt thereof.
(206) In an aspect, the disclosure features a compound having the structure of any one of compounds B1-B3 and B6 in Table 1, or a pharmaceutically acceptable salt thereof.
(207) In an aspect, the disclosure features a compound having the structure of any one of compounds B4

and B5 in Table 1, or a pharmaceutically acceptable salt thereof.
(208) TABLE-US-00001 TABLE 1 Compounds B1-B6 of the Disclosure Compound No. Structure B1  B2  B3 0  B4  B5  B6 
(209) In an aspect, the disclosure features a compound having the structure of Formula II:
A-L-B Formula II,
(210) where
(211) L is a linker;
(212) B is a degradation moiety; and
(213) A has the structure of Formula III:
(214) ##STR00094##
(215) where
(216) R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl;
(217) Z.sup.1 is CR.sup.2 or N;
(218) R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(219) X.sup.1 is N or CH, and X.sup.2 is C—R.sup.7″; or X.sup.1 is C—R.sup.7″, and X.sup.2 is N or CH;
(220) R.sup.7″ is
(221) ##STR00095##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;
(222) R.sup.7′ is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl;
(223) X.sup.3 is N or CH;
(224) X.sup.4 is N or CH;
(225) G″ is
(226) ##STR00096##
optionally substituted C.sub.3-C.sub.10 carbocyclyl, C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(227) G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene, C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; and
(228) A.sup.1 is a bond between A and the linker,
(229) where G″ is
(230) ##STR00097##
or R.sup.7″ is
(231) ##STR00098##
or a pharmaceutically acceptable salt thereof.
(232) In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl.
(233) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is optionally substituted

C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.1 is optionally substituted C.sub.2-C.sub.6 alkenyl. In some embodiments, R.sup.1 is optionally substituted C.sub.3-C.sub.10 carbocyclyl.
(234) In some embodiments, optionally substituted C.sub.1-C.sub.6 alkyl is C.sub.1-C.sub.6 perfluoroalkyl.
(235) In some embodiments, R.sup.1 is
(236) ##STR00099##
(237) In some embodiments, R.sup.1 is
(238) ##STR00100##
(239) In some embodiments, R.sup.1 is
(240) ##STR00101##
(241) In some embodiments, R.sup.1 is H,
(242) ##STR00102##
In some embodiments, R.sup.1 is
(243) ##STR00103##
In some embodiments, R.sup.1 is H,
(244) ##STR00104##
(245) In some embodiments, R.sup.1 is H,
(246) ##STR00105##
(247) In some embodiments, R.sup.1 is H,
(248) ##STR00106##
(249) In some embodiments, R.sup.1 is H or
(250) ##STR00107##
(251) In some embodiments, R.sup.1 is H. In some embodiments, R.sup.1 is
(252) ##STR00108##
(253) In some embodiments, Z.sup.1 is CR.sup.2. In some embodiments, Z.sup.1 is N.
(254) In some embodiments, R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.6-C.sub.10 aryl.
(255) In some embodiments, R.sup.2 is H, halogen, or optionally substituted C.sub.1-C.sub.6 alkyl.
(256) In some embodiments, R.sup.2 is H, F, or
(257) ##STR00109##
(258) In some embodiments, R.sup.2 is H. In some embodiments, R.sup.2 is F. In some embodiments, R.sup.2 is
(259) ##STR00110##
(260) In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 alkoxy or optionally substituted amino. In some embodiments, R.sup.7″ is optionally substituted sulfone or optionally substituted sulfonamide.
(261) In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 heteroalkyl or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 alkyl or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(262) In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.6 alkoxy. In some embodiments, R.sup.7″ is optionally substituted amino. In some embodiments, R.sup.7″ is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted sulfone. In some embodiments, R.sup.7″ is

optionally substituted sulfonamide.
(263) In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.3 alkyl. In some embodiments, R.sup.7″ is optionally substituted C.sub.1-C.sub.3 heteroalkyl.
(264) In some embodiments, R.sup.7″ is
(265) ##STR00111##
(266) In some embodiments, R.sup.7″ is —NR.sup.3R.sup.4 or —OR.sup.4, where R.sup.3 is H or optionally substituted C.sub.1-C.sub.6 alkyl, and R.sup.4 is optionally substituted C.sub.1-C.sub.6 alkyl.
(267) In some embodiments, R.sup.7″ is —NR.sup.3R.sup.4. In some embodiments, R.sup.7″ is —OR.sup.4.
(268) In some embodiments, R.sup.3 is H. In some embodiments, R.sup.3 is optionally substituted C.sub.1-C.sub.6 alkyl.
(269) In some embodiments, R.sup.3 is H and R.sup.4 is methyl. In some embodiments, R.sup.3 is methyl and R.sup.4 is methyl.
(270) In some embodiments, R.sup.7″ is
(271) ##STR00112##
In some embodiments, R.sup.7″ is
(272) ##STR00113##
(273) In some embodiments, R.sup.7″ is optionally substituted carbocyclyl having 3 to 6 atoms or optionally substituted heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is optionally substituted heterocyclyl having 3 to 6 atoms.
(274) In some embodiments, R.sup.7″ is carbocyclyl having 3 to 6 atoms or heterocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is carbocyclyl having 3 to 6 atoms. In some embodiments, R.sup.7″ is heterocyclyl having 3 to 6 atoms.
(275) In some embodiments, R.sup.7″ is
(276) ##STR00114##
(277) In some embodiments, R.sup.7″ is
(278) ##STR00115##
(279) In some embodiments, R.sup.7″ is
(280) ##STR00116##
(281) In some embodiments, R.sup.7″ is
(282) ##STR00117##
(283) In some embodiments, R.sup.7″ is
(284) ##STR00118##
In some embodiments, R.sup.7″ is
(285) ##STR00119##
In some embodiments, R.sup.7″ is
(286) ##STR00120##
In some embodiments, R.sup.7″ is
(287) ##STR00121##
In some embodiments, R.sup.7″ is
(288) ##STR00122##
(289) In some embodiments, X.sup.1 is N and X.sup.2 is C—R.sup.7″. In some embodiments, X.sup.1 is CH and X.sup.2 is C—R.sup.7″. In some embodiments, X.sup.1 is C—R.sup.7″ and X.sup.2 is N. In some embodiments, X.sup.1 is C—R.sup.7″ and X.sup.2 is CH.
(290) In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4, C—OR.sup.4,
(291) ##STR00123##
or X.sup.1 is C—NR.sup.3R.sup.4, C—OR.sup.4,
(292) ##STR00124##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4,
(293) ##STR00125##

or X.sup.1 is C—NR.sup.3R.sup.4,
(294) ##STR00126##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4 or
(295) ##STR00127##
or X.sup.1 is C—NR.sup.3R.sup.4 or
(296) ##STR00128##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4 or
(297) ##STR00129##
or X.sup.1 is C—NR.sup.3R.sup.4 or
(298) ##STR00130##
and X.sup.2 is N or CH. In some embodiments, X.sup.1 is N or CH, and X.sup.2 is C—NR.sup.3R.sup.4 or
(299) ##STR00131##
or X.sup.1 is C—NR.sup.3R.sup.4 or
(300) ##STR00132##
and X.sup.2 is N or CH.
(301) In some embodiments, R.sup.7″ is —NR.sup.3R.sup.4, —OR.sup.4, or optionally substituted heterocyclyl having 3 to 6 atoms.
(302) In some embodiments, X.sup.1 is N and X.sup.2 is C—NR.sup.3R.sup.4. In some embodiments, X.sup.1 is C—NR.sup.3R.sup.4 and X.sup.2 is N.
(303) In some embodiments, R.sup.3 is H. In some embodiments, R.sup.3 is optionally substituted C.sub.1-C.sub.6 alkyl.
(304) In some embodiments, R.sup.3 is
(305) ##STR00133##
In some embodiments, R.sup.3 is
(306) ##STR00134##
In some embodiments, R.sup.3 is
(307) ##STR00135##
In some embodiments, R.sup.3 is methyl, ethyl,
(308) ##STR00136##
(309) In some embodiments, R.sup.4 is
(310) ##STR00137##
In some embodiments, R.sup.4 is
(311) ##STR00138##
In some embodiments, R.sup.4 is
(312) ##STR00139##
In some embodiments, R.sup.4 is methyl, ethyl,
(313) ##STR00140##
(314) In some embodiments, X.sup.3 is N. In some embodiments, X.sup.3 is CH.
(315) In some embodiments, X.sup.4 is N. In some embodiments, X.sup.4 is CH.
(316) In some embodiments, X.sup.3 is N and X.sup.4 is N.
(317) In some embodiments, X.sup.3 is N and X.sup.4 is CH.
(318) In some embodiments, X.sup.3 is CH and X.sup.4 is N.
(319) In some embodiments, X.sup.3 is CH and X.sup.4 is CH.
(320) In some embodiments, G″ is
(321) ##STR00141##
(322) In some embodiments, G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene or optionally substituted C.sub.2-C.sub.9 heterocyclylene. In some embodiments, G′ is optionally substituted C.sub.6-C.sub.10 arylene or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(323) In some embodiments, G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene. In some

embodiments, G′ is optionally substituted C.sub.6-C.sub.10 arylene. In some embodiments, G′ is optionally substituted C.sub.2-C.sub.9 heterocyclylene. In some embodiments, G′ is optionally substituted C.sub.2-C.sub.9 heteroarylene.
(324) In some embodiments, G′ is
(325) ##STR00142##
(326) where
(327) each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form
(328) ##STR00143##
is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or
(329) ##STR00144##
is substituted with A.sup.1.
(330) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form
(331) ##STR00145##
is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or
(332) ##STR00146##
is substituted with A.sup.1.
(333) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form
(334) ##STR00147##
is optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or
(335) ##STR00148##
is substituted with A.sup.1.

(336) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(337) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, F, Cl,
(338) ##STR00149##
(339) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, F,
(340) ##STR00150##
(341) In some embodiments, each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, F, Cl,
(342) ##STR00151##
(343) In some embodiments, R.sup.G3′ is A.sup.1.
(344) In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(345) ##STR00152##
R.sup.G3′, is A.sup.1; R.sup.G4′, is
(346) ##STR00153##
and R.sup.G5′ is H. In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(347) ##STR00154##
R.sup.G3′ is A.sup.1; R.sup.G4′ is H; and R.sup.G5′ is
(348) ##STR00155##
In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(349) ##STR00156##
R.sup.G3′ is A.sup.1; R.sup.G4′ is Cl or F; and R.sup.G5′ is H. In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(350) ##STR00157##
R.sup.G3′ is A.sup.1; R.sup.G4′ is H; and R.sup.G5′ is H. In some embodiments, R.sup.G1′ is H; R.sup.G2′ is
(351) ##STR00158##
R.sup.G3′ is A.sup.1; R.sup.G4′ is
(352) ##STR00159##
and R.sup.G5′ is H.
(353) In some embodiments, R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form
(354) ##STR00160##
is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or
(355) ##STR00161##
is substituted with A.sup.1. In some embodiments, R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form
(356) ##STR00162##
is optionally substituted C.sub.2-C.sub.9 heteroaryl, which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or
(357) ##STR00163##
is substituted with A.sup.1.
(358) In some embodiments, G′ is
(359) ##STR00164##
where R.sup.G6′ is H, A.sup.1, or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, G′ is

(360) ##STR00165##
where R.sup.G6′ is H, A.sup.1, or optionally substituted C.sub.1-C.sub.6 alkyl.
(361) In some embodiments, R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form
(362) ##STR00166##
is optionally substituted C.sub.2-C.sub.9 heterocyclyl or optionally substituted C.sub.2-C.sub.9 heteroaryl, any of which is optionally substituted with A.sup.1, where one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or
(363) ##STR00167##
is substituted with A.sup.1.
(364) In some embodiments, G′ is
(365) ##STR00168##
where R.sup.G6′ is H, A.sup.1, or optionally substituted C.sub.1-C.sub.6 alkyl.
(366) In some embodiments, R.sup.G6′ is H, A.sup.1,
(367) ##STR00169##
(368) In some embodiments, R.sup.G6′ is H, A.sup.1, or
(369) ##STR00170##
(370) In some embodiments, R.sup.G6′ is H or A.sup.1.
(371) In some embodiments, R.sup.G6′ is H. In some embodiments, R.sup.G6′ is A.sup.1.
(372) In some embodiments, R.sup.G1′ is H, A.sup.1, F,
(373) ##STR00171##
In some embodiments, R.sup.G1′ is H.
(374) In some embodiments, R.sup.G2′ is H, A.sup.1, F,
(375) ##STR00172##
In some embodiments, R.sup.G2′ is H.
(376) In some embodiments, R.sup.G3′ is H, A.sup.1, F,
(377) ##STR00173##
In some embodiments, R.sup.G3′ is H.
(378) In some embodiments, R.sup.G4′ is H, A.sup.1, F,
(379) ##STR00174##
In some embodiments, R.sup.G4′ is H.
(380) In some embodiments, R.sup.G5′ is H, A.sup.1, F,
(381) ##STR00175##
In some embodiments, R.sup.G5′ is H.
(382) In some embodiments, one or more of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is H. In some embodiments, two or more of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is H. In some embodiments, three or more of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is H.
(383) In some embodiments, R.sup.G1′ is A.sup.1. In some embodiments, R.sup.G2′ is A.sup.1. In some embodiments, R.sup.G3′ is A.sup.1. In some embodiments, R.sup.G4′ is A.sup.1. In some embodiments, R.sup.G5′ is A.sup.1. In some embodiments,
(384) ##STR00176##
is substituted with A.sup.1.
(385) In some embodiments, G′ is
(386) ##STR00177##
(387) where
(388) each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6

heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7′ and R.sup.G8′, R.sup.G8′ and R.sup.G9′, R.sup.G9′ and R.sup.G10′, and/or R.sup.G10′ and R.sup.G11′, together with the carbon atoms to which each is attached, combine to form

(389) ##STR00178##

is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is A.sup.1; or

(390) ##STR00179##

is substituted with A.sup.1.

(391) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7′ and R.sup.G8′, R.sup.G8′ and R.sup.G9′, R.sup.G9′ and R.sup.G10′, and/or R.sup.G10′ and R.sup.G11′, together with the carbon atoms to which each is attached, combine to form

(392) ##STR00180##

is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is A.sup.1; or

(393) ##STR00181##

is substituted with A.sup.1.

(394) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G7′ and R.sup.G8′, R.sup.G8′ and R.sup.G9′, R.sup.G9′ and R.sup.G10′, and/or R.sup.G10′ and R.sup.G11′, together with the carbon atoms to which each is attached, combine to form

(395) ##STR00182##

is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is A.sup.1; or

(396) ##STR00183##

is substituted with A.sup.1.

(397) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.

(398) In some embodiments, each of R.sup.G7′, R.sup.G8′, R.sup.G9′, R.sup.G10′, and R.sup.G11′ is, independently, H, A.sup.1, F, Cl,

(399) ##STR00184##

In some embodiments, R.sup.G8′ is

(400) ##STR00185##

(401) In some embodiments, G′ is

(402) ##STR00186##
(403) In some embodiments, R.sup.G7′ is H; R.sup.G8′ is
(404) ##STR00187##
R.sup.G9′ is A.sup.1; and R.sup.G11′ is H.
(405) In some embodiments, G′ is
(406) ##STR00188##
(407) where
(408) each of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12′ and R.sup.G14′, together with the carbon atoms to which each is attached, combine to form
(409) ##STR00189##
is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is A.sup.1; or
(410) ##STR00190##
is substituted with A.sup.1.
(411) In some embodiments, each of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12′ and R.sup.G14′, together with the carbon atoms to which each is attached, combine to form
(412) ##STR00191##
is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, where one of R.sup.G12′, R.sup.G13′, and R.sup.G14′ is A.sup.1; or
(413) ##STR00192##
is substituted with A.sup.1.
(414) In some embodiments, R.sup.7″ is
(415) ##STR00193##
(416) In some embodiments, R.sup.7′ is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, R.sup.7′ is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(417) In some embodiments, R.sup.7′ is H,
(418) ##STR00194##
In some embodiments, R.sup.7′ is H or
(419) ##STR00195##
In some embodiments, R.sup.7′ is H. In some embodiments, R.sup.7′ is
(420) ##STR00196##
(421) In some embodiments, G″ is optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G″ is optionally substituted C.sub.6-

C.sub.10 aryl or optionally substituted C.sub.2-C.sub.9 heteroaryl.
(422) In some embodiments, G″ is optionally substituted C.sub.3-C.sub.10 carbocyclyl. In some embodiments, G is optionally substituted C.sub.6-C.sub.10 aryl. In some embodiments, G is optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, G″ is optionally substituted C.sub.2-C.sub.9 heteroaryl.
(423) In some embodiments, G″ is
(424) ##STR00197##
(425) where
(426) each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(427) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(428) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(429) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(430) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F, Cl,
(431) ##STR00198##
(432) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F,
(433) ##STR00199##
(434) In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is, independently, H, F, Cl,
(435) ##STR00200##

(436) In some embodiments, R.sup.G1 is H; R.sup.G2 is
(437) ##STR00201##
R.sup.G3 is
(438) ##STR00202##
R.sup.G4 is
(439) ##STR00203##
and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(440) ##STR00204##
R.sup.G3 is
(441) ##STR00205##
R.sup.G4 is H; and R.sup.G5 is
(442) ##STR00206##
In some embodiments, R.sup.G1 is H; R.sup.G2 is
(443) ##STR00207##
R.sup.G3 is
(444) ##STR00208##
R.sup.G4 is Cl or F; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2 is
(445) ##STR00209##
R.sup.G3 is
(446) ##STR00210##
R.sup.G4 is H; and R.sup.G5 is H. In some embodiments, R.sup.G1 is H; R.sup.G2
(447) ##STR00211##
is R.sup.G3 is
(448) ##STR00212##
R.sup.G4 is
(449) ##STR00213##
and R.sup.G5 is H.
(450) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(451) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl.
(452) In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, R.sup.G1 and R.sup.G2, R.sup.G2 and R.sup.G3, R.sup.G3 and R.sup.G4, and/or R.sup.G4 and R.sup.G5, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heteroaryl.
(453) In some embodiments, G″ is
(454) ##STR00214##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, G″ is
(455) ##STR00215##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(456) In some embodiments, G″ is
(457) ##STR00216##
where R.sup.G6 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(458) In some embodiments, R.sup.G6 is H,

(459) ##STR00217##
(460) In some embodiments, R.sup.G6 is H or
(461) ##STR00218##
In some embodiments, R.sup.G6 is H.
(462) In some embodiments, R.sup.G1 is H, F,
(463) ##STR00219##
In some embodiments, R.sup.G1 is H.
(464) In some embodiments, R.sup.G2 is H, F,
(465) ##STR00220##
In some embodiments, R.sup.G2 is H.
(466) In some embodiments, R.sup.G3 is H, F,
(467) ##STR00221##
In some embodiments, R.sup.G3 is H.
(468) In some embodiments, R.sup.G4 is H, F,
(469) ##STR00222##
In some embodiments, R.sup.G4 is H.
(470) In some embodiments, R.sup.G5 is H, F,
(471) ##STR00223##
In some embodiments, R.sup.G5 is H.
(472) In some embodiments, one or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, two or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, three or more of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H. In some embodiments, each of R.sup.G1, R.sup.G2, R.sup.G3, R.sup.G4, and R.sup.G5 is H.
(473) In some embodiments, G″ is
(474) ##STR00224##
(475) where
(476) each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(477) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G7 and R.sup.G8, R.sup.G8 and R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(478) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl; or R.sup.G7 and R.sup.G8, R.sup.G8 and

R.sup.G9, R.sup.G9 and R.sup.G10, and/or R.sup.G10 and R.sup.G11, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl.
(479) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, or optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl.
(480) In some embodiments, each of R.sup.G7, R.sup.G8, R.sup.G9, R.sup.G10, and R.sup.G11 is, independently, H, F, Cl,
(481) ##STR00225##
In some embodiments, R.sup.G8 is
(482) ##STR00226##
(483) In some embodiments, G″ is
(484) ##STR00227##
(485) In some embodiments, R.sup.G7 is H; R.sup.G8 is
(486) ##STR00228##
R.sup.G9 is H; and R.sup.G11 is H.
(487) In some embodiments, G″ is
(488) ##STR00229##
(489) where
(490) each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted —C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(491) In some embodiments, each of R.sup.G12, R.sup.G13, and R.sup.G14 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.G12 and R.sup.G14, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(492) In some embodiments, A has the structure of Formula IIIa:
(493) ##STR00230##
or a pharmaceutically acceptable salt thereof.
(494) In some embodiments, A has the structure of Formula IIIb:
(495) ##STR00231##
or a pharmaceutically acceptable salt thereof.
(496) In some embodiments, A has the structure of Formula IIIc:
(497) ##STR00232##
or a pharmaceutically acceptable salt thereof.
(498) In some embodiments, A has the structure of Formula IIId:
(499) ##STR00233##

or a pharmaceutically acceptable salt thereof.
(500) In some embodiments, A has the structure of Formula IIIe:
(501) ##STR00234##
or a pharmaceutically acceptable salt thereof.
(502) In some embodiments, A has the structure of Formula IIIf:
(503) ##STR00235##
or a pharmaceutically acceptable salt thereof.
(504) In some embodiments, A has the structure of Formula IIIg:
(505) ##STR00236##
or a pharmaceutically acceptable salt thereof.
(506) In some embodiments, A has the structure of Formula IIIh:
(507) ##STR00237##
or a pharmaceutically acceptable salt thereof.
(508) In some embodiments, A has the structure of Formula IIIi:
(509) ##STR00238##
or a pharmaceutically acceptable salt thereof.
(510) In some embodiments, A has the structure of Formula IIIj:
(511) ##STR00239##
or a pharmaceutically acceptable salt thereof.
(512) In some embodiments, A has the structure of Formula IIIk:
(513) ##STR00240##
or a pharmaceutically acceptable salt thereof.
(514) In some embodiments, A has the structure of Formula IIIm:
(515) ##STR00241##
or a pharmaceutically acceptable salt thereof.
(516) In some embodiments, A has the structure of Formula IIIn:
(517) ##STR00242##
or a pharmaceutically acceptable salt thereof.
(518) In some embodiments, A has the structure of Formula IIIo:
(519) ##STR00243##
or a pharmaceutically acceptable salt thereof.
(520) In some embodiments, A has the structure of Formula IIIp:
(521) ##STR00244##
or a pharmaceutically acceptable salt thereof.
(522) In some embodiments, A has the structure of Formula IIIq:
(523) ##STR00245##
or a pharmaceutically acceptable salt thereof.
(524) In some embodiments, A has the structure of Formula IIIr:
(525) ##STR00246##
or a pharmaceutically acceptable salt thereof.
(526) In some embodiments, A has the structure of Formula IIIs:
(527) ##STR00247##
or a pharmaceutically acceptable salt thereof.
(528) In some embodiments, A has the structure of Formula IIIt:
(529) ##STR00248##
or a pharmaceutically acceptable salt thereof.
(530) In some embodiments, A has the structure of Formula IIIu:
(531) ##STR00249##
or a pharmaceutically acceptable salt thereof.
(532) In some embodiments, A has the structure of Formula IIIv:
(533) ##STR00250##
or a pharmaceutically acceptable salt thereof.

(534) In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.
(535) In some embodiments, the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.
(536) In some embodiments, the degradation moiety is a ubiquitin ligase binding moiety.
(537) In some embodiments, the ubiquitin ligase binding moiety comprises Cereblon ligands, IAP (Inhibitors of Apoptosis) ligands, mouse double minute 2 homolog (MDM2), or von Hippel-Lindau (VHL) ligands, or derivatives or analogs thereof.
(538) In some embodiments, the degradation moiety includes the structure of Formula Y:
(539) ##STR00251##
(540) where
(541) A.sup.2 is a bond between the degradation moiety and the linker;
(542) v1 is 0, 1, 2, 3, 4, or 5;
(543) u1 is 1, 2, or 3;
(544) T.sup.1 is a bond or
(545) ##STR00252##
(546) T.sup.2 is
(547) ##STR00253##
(548) R.sup.5A is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;
(549) each R.sup.J1 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;
(550) J.sup.A is absent, O, optionally substituted amino, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; and
(551) J is absent, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, optionally substituted C.sub.2-C.sub.9 heterocyclylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene, or a pharmaceutically acceptable salt thereof.
(552) In some embodiments, T.sup.2 is
(553) ##STR00254##
In some embodiments, T.sup.2 is
(554) ##STR00255##
In some embodiments, T.sup.2 is
(555) ##STR00256##
In some embodiments, T.sup.2 is
(556) ##STR00257##
(557) In some embodiments, the structure of Formula Y has the structure of Formula Y1:
(558) ##STR00258##
or a pharmaceutically acceptable salt thereof.
(559) In some embodiments, T.sup.1 is a bond. In some embodiments, T.sup.1 is
(560) ##STR00259##
(561) In some embodiments, the structure of Formula Y has the structure of Formula Y2:
(562) ##STR00260##
or a pharmaceutically acceptable salt thereof.
(563) In some embodiments, the structure of Formula Y has the structure of Formula Z:
(564) ##STR00261##
or a pharmaceutically acceptable salt thereof.
(565) In some embodiments, u1 is 1. In some embodiments, u1 is 2. In some embodiments u1 is 3.
(566) In some embodiments, the structure of Formula Z has the structure of Formula AA0:
(567) ##STR00262##
or a pharmaceutically acceptable salt thereof.
(568) In some embodiments, the structure of Formula Z has the structure of Formula AB:
(569) ##STR00263##

or a pharmaceutically acceptable salt thereof.
(570) In some embodiments, the structure of Formula Z has the structure of Formula AC:
(571) ##STR00264##
or a pharmaceutically acceptable salt thereof.
(572) In some embodiments, J.sup.A is absent. In some embodiments, J.sup.A is optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, J.sup.A is optionally substituted C.sub.1-C.sub.6 heteroalkyl. In some embodiments, J.sup.A is O or optionally substituted amino.
(573) In some embodiments, J.sup.A is
(574) ##STR00265##
(575) In some embodiments, the structure of Formula AA0 has the structure of Formula AA0:
(576) ##STR00266##
or a pharmaceutically acceptable salt thereof.
(577) In some embodiments, v1 is 0, 1, 2, or 3. In some embodiments, v1 is 0. In some embodiments, v1 is 1. In some embodiments, v1 is 2. In some embodiments, v1 is 3.
(578) In some embodiments, the structure of Formula AA has the structure of Formula AA1:
(579) ##STR00267##
or a pharmaceutically acceptable salt thereof.
(580) In some embodiments, the structure of Formula AB has the structure of Formula AB1:
(581) ##STR00268##
or a pharmaceutically acceptable salt thereof.
(582) In some embodiments, the structure of Formula AC has the structure of Formula AC1:
(583) ##STR00269##
or a pharmaceutically acceptable salt thereof.
(584) In some embodiments, J is absent. In some embodiments, J is optionally substituted C.sub.3-C.sub.10 carbocyclylene or optionally substituted C.sub.6-C.sub.10 arylene. In some embodiments, J is optionally substituted C.sub.2-C.sub.9 heterocyclylene or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(585) In some embodiments, J is optionally substituted heterocyclylene. In some embodiments, J is optionally substituted C.sub.6-C.sub.10 arylene.
(586) In some embodiments, J is
(587) ##STR00270##
(588) In some embodiments, the structure of Formula AA has the structure of Formula AA2:
(589) ##STR00271##
or a pharmaceutically acceptable salt thereof.
(590) In some embodiments, the structure of Formula AA has the structure of Formula AA3:
(591) ##STR00272##
or a pharmaceutically acceptable salt thereof.
(592) In some embodiments, the structure of Formula AA has the structure of Formula AA4:
(593) ##STR00273##
or a pharmaceutically acceptable salt thereof.
(594) In some embodiments, R.sup.A5 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.A5 is optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(595) In some embodiments, R.sup.A5 is H or methyl. In some embodiments, R.sup.A5 is H. In some embodiments, R.sup.A5 is methyl. In some embodiments, R.sup.A5 is
(596) ##STR00274##
(597) In some embodiments, the structure of Formula AA has the structure of Formula A:
(598) ##STR00275##
(599) where
(600) Y1 is
(601) ##STR00276##
(602) R.sup.A5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;

(603) R.sup.A6 is H or optionally substituted C.sub.1-C.sub.6 alkyl; and R.sup.A7 is H or optionally substituted C.sub.1-C.sub.6 alkyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6 carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6 carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl;
(604) R.sup.A8 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;
(605) each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form
(606) ##STR00277##
is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or
(607) ##STR00278##
is substituted with A.sup.2, or a pharmaceutically acceptable salt thereof.
(608) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form
(609) ##STR00279##
is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or
(610) ##STR00280##
is substituted with A.sup.2, or a pharmaceutically acceptable salt thereof.
(611) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form
(612) ##STR00281##
is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or
(613) ##STR00282##
is substituted with A.sup.2.
(614) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, F,
(615) ##STR00283##
or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the carbon

atoms to which each is attached, combine to form
(616) ##STR00284##
is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or
(617) ##STR00285##
is substituted with A.sup.2.
(618) In some embodiments, R.sup.A1 is A.sup.2. In some embodiments, R.sup.A2 is A.sup.2. In some embodiments, R.sup.A3 is A.sup.2. In some embodiments, R.sup.A4 is A.sup.2. In some embodiments, R.sup.A5 is A.sup.2.
(619) In some embodiments, R.sup.A5 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(620) In some embodiments, R.sup.A5 is H or
(621) ##STR00286##
In some embodiments, R.sup.A5 is H. In some embodiments, R.sup.A5 is
(622) ##STR00287##
(623) In some embodiments, Y.sup.1 is
(624) ##STR00288##
In some embodiments, Y.sup.1 is
(625) ##STR00289##
In some embodiments, Y.sup.1 is
(626) ##STR00290##
(627) In some embodiments, each of R.sup.A6 and R.sup.A7 is, independently, H, F,
(628) ##STR00291##
or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form
(629) ##STR00292##
In some embodiments, R.sup.A6 is H and R.sup.A7 is H.
(630) In some embodiments, Y.sup.1 is
(631) ##STR00293##
In some embodiments, Y.sup.1 is
(632) ##STR00294##
In some embodiments, Y.sup.1 is
(633) ##STR00295##
(634) In some embodiments, the structure of Formula A has the structure of Formula A1:
(635) ##STR00296##
or a pharmaceutically acceptable salt thereof.
(636) In some embodiments, the structure of Formula A has the structure of Formula A2:
(637) ##STR00297##
or a pharmaceutically acceptable salt thereof.
(638) In some embodiments, the structure of Formula A has the structure of Formula A3:
(639) ##STR00298##
or a pharmaceutically acceptable salt thereof.
(640) In some embodiments, the structure of Formula A has the structure of Formula A4:
(641) ##STR00299##
or a pharmaceutically acceptable salt thereof.
(642) In some embodiments, the structure of Formula A has the structure of Formula A5:
(643) ##STR00300##
or a pharmaceutically acceptable salt thereof.
(644) In some embodiments, the structure of Formula A has the structure of Formula A6:
(645) ##STR00301##
or a pharmaceutically acceptable salt thereof.
(646) In some embodiments, the structure of Formula A has the structure of Formula A7:
(647) ##STR00302##
or a pharmaceutically acceptable salt thereof.

(648) In some embodiments, the structure of Formula A has the structure of Formula A8:
(649) ##STR00303##
or a pharmaceutically acceptable salt thereof.
(650) In some embodiments, the structure of Formula A has the structure of Formula A9:
(651) ##STR00304##
or a pharmaceutically acceptable salt thereof.
(652) In some embodiments, the structure of Formula A has the structure of Formula A10:
(653) ##STR00305##
or a pharmaceutically acceptable salt thereof.
(654) In some embodiments, wherein the structure of Formula A is
(655) ##STR00306## ##STR00307##
or derivative or analog thereof.
(656) In some embodiments, the structure of Formula A is
(657) ##STR00308##
(658) In some embodiments, the structure of Formula A is
(659) ##STR00309##
or derivative or analog thereof.
(660) In some embodiments,
(661) ##STR00310##
where R.sup.A9 is H, A.sup.2, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl.
(662) In some embodiments, the structure of Formula A is
(663) ##STR00311##
(664) In some embodiments, R.sup.A9 is H, A.sup.2, or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.A9 is H, A.sup.2, or methyl. In some embodiments, R.sup.9A is H. In some embodiments, R.sup.9A is methyl. In some embodiments, R.sup.A9 is A.sup.2.
(665) In some embodiments, the structure of Formula A is
(666) ##STR00312##
(667) In some embodiments, the structure of Formula AA has the structure of Formula B:
(668) ##STR00313##
(669) where
(670) R.sup.A5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;
(671) each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, thiol, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form
(672) ##STR00314##
is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or
(673) ##STR00315##
is substituted with A.sup.2, or a pharmaceutically acceptable salt thereof.
(674) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the

carbon atoms to which each is attached, combine to form
(675) ##STR00316##
is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or
(676) ##STR00317##
is substituted with A.sup.2.
(677) In some embodiments, each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, F,
(678) ##STR00318##
or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form
(679) ##STR00319##
is optionally substituted C.sub.2-C.sub.9 heterocyclyl, which is optionally substituted with A.sup.2, where one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or
(680) ##STR00320##
is substituted with A.sup.2.
(681) In some embodiments, R.sup.A1 is A.sup.2. In some embodiments, R.sup.A2 is A.sup.2. In some embodiments, R.sup.A3 is A.sup.2. In some embodiments, R.sup.A4 is A.sup.2. In some embodiments, R.sup.A5 is A.sup.2.
(682) In some embodiments, R.sup.A5 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(683) In some embodiments, R.sup.A5 is H or
(684) ##STR00321##
In some embodiments, R.sup.A5 is H. In some embodiments, R.sup.A5 is
(685) ##STR00322##
(686) In some embodiments, the structure of Formula B has the structure of Formula B1:
(687) ##STR00323##
or a pharmaceutically acceptable salt thereof.
(688) In some embodiments, the structure of Formula B has the structure of Formula B2:
(689) ##STR00324##
or a pharmaceutically acceptable salt thereof.
(690) In some embodiments, the structure of Formula B has the structure of Formula B3:
(691) ##STR00325##
or a pharmaceutically acceptable salt thereof.
(692) In some embodiments, the structure of Formula B has the structure of Formula B4:
(693) ##STR00326##
or a pharmaceutically acceptable salt thereof.
(694) In some embodiments, the structure of Formula B is
(695) ##STR00327##
In some embodiments, the structure of Formula B is
(696) ##STR00328##
In some embodiments, the structure of Formula B is
(697) ##STR00329##
(698) In some embodiments, the ubiquitin ligase binding moiety comprises a von Hippel-Lindau ligand.
(699) In some embodiments, the von Hippel-Lindau ligand has the structure of
(700) ##STR00330##
or derivative or analog thereof.
(701) In some embodiments, the degradation moiety includes the structure of Formula C:
(702) ##STR00331##
(703) where
(704) R.sup.B1 is H, A.sup.2, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;
(705) R.sup.B2 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-

C.sub.6 heteroalkyl;
(706) R.sup.B3 is A.sup.2, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl;
(707) R.sup.B4 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl;
(708) R.sup.B5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;
(709) v2 is 0, 1, 2, 3, or 4;
(710) each R.sup.B6 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino; and
(711) each of R.sup.B7 and R.sup.B8 is, independently, H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.6-C.sub.10 aryl,
(712) where one of R.sup.B1 and R.sup.B3 is A.sup.2, or a pharmaceutically acceptable salt thereof.
(713) In some embodiments, the structure of Formula C is
(714) ##STR00332##
or derivative or analog thereof.
(715) In some embodiments, the structure of Formula C is
(716) ##STR00333##
In some embodiments, the degrader moiety includes the structure of Formula D:
(717) ##STR00334##
(718) where
(719) A.sup.2 is a bond between B and the linker;
(720) each of R.sup.C1, R.sup.C2, and R.sup.C7 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl;
(721) R.sup.C3 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl;
(722) R.sup.C5 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl;
(723) v3 is 0, 1, 2, 3, or 4;
(724) each R.sup.C8 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;
(725) v4 is 0, 1, 2, 3, or 4; and
(726) each R.sup.C9 is, independently, halogen, optionally substituted C.sub.1-C.sub.6alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.
(727) In some embodiments, the structure of Formula D is
(728) ##STR00335##

or derivative or analog thereof.
(729) In some embodiments, the degrader moiety includes the structure of Formula E:
(730) ##STR00336##
(731) where
(732) A.sup.2 is a bond between B and the linker;
(733) each of R.sup.C10 and R.sup.C11 is, independently, H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.1-C.sub.6 alkyl C.sub.3-C.sub.10 carbocyclyl, or optionally substituted C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl;
(734) v5 is 0, 1, 2, 3, or 4;
(735) each R.sup.C12 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino;
(736) v6 is 0, 1, 2, 3, or 4; and
(737) each R.sup.21 is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxy, thiol, or optionally substituted amino, or a pharmaceutically acceptable salt thereof.
(738) In some embodiments, the structure of Formula E is
(739) ##STR00337##
or derivative or analog thereof.
(740) In some embodiments, the degradation moiety includes the structure of Formula FA:
(741) ##STR00338##
(742) where
(743) ##STR00339##
or a bicyclic moiety which is substituted with A.sup.2 and substituted with one or more groups independently selected from H, R.sup.FF1, and oxo;
(744)  custom character is a single bond or a double bond;
(745) u2 is 0, 1, 2, or 3;
(746) A.sup.2 is a bond between the degrader and the linker;
(747) Y.sup.Fa is CR.sup.FbR.sup.Fc, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2;
(748) Y.sup.Fb is NH, NR.sup.FF1, CH.sub.2, CHR.sup.FF1, C(R.sup.FF1).sub.2, O, or S;
(749) Y.sup.Fc is CR.sup.FdR.sup.Fe, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2;
(750) each of R.sup.Fb, R.sup.Fc, R.sup.Fd, and R.sup.Fe is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —NaIkyl.sub.2;
(751) or R.sup.Fb and R.sup.Fc, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;
(752) or R.sup.Fd and R.sup.Fe, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O; and
(753) or R.sup.Fd and R.sup.Fb, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;
(754) each of Y.sup.Fd and Y.sup.Ff is, independently, CH.sub.2, CHR.sup.FF2, C(R.sup.FF2).sub.2, C(O), N, NH, NR.sup.FF3, O, S, or S(O);
(755) Y.sup.Fe is a bond or a divalent moiety attached to Y.sup.Fd and Y.sup.Ff that contains 1 to 5

contiguous carbon atoms that form a 3 to 8-membered ring, wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom; wherein one of the ring atoms is substituted with A.sup.2 and the others are substituted with one or more groups independently selected from H and R.sup.FF1; and wherein the contiguous atoms of Y.sup.Fe can be attached through a single or double bond;
(756) each R.sup.FF1 is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, alkylhydroxyl, or haloalkyl;
(757) each R.sup.FF2 is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic, including alkyl), —NH(aliphatic, including alkyl), —N(aliphatic including alkyl)(aliphatic including alkyl), —NHSO.sub.2alkyl, —N(alkyl)SO.sub.2alkyl, —NHSO.sub.2aryl, —N(alkyl)SO.sub.2aryl, —NHSO.sub.2alkenyl, —N(alkyl)SO.sub.2alkenyl, —NHSO.sub.2alkynyl, —N(alkyl)SO.sub.2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and
(758) R.sup.FF3 is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl,
(759) wherein if Y.sup.Fd or Y.sup.Ff is substituted with A.sup.2, then Y.sup.Fe is a bond, or a pharmaceutically acceptable salt thereof.
(760) In some embodiments, the compound of Formula FA has the structure of Formula FA1:
(761) ##STR00340##
or a pharmaceutically acceptable salt thereof.
(762) In some embodiments, the degradation moiety includes the structure of Formula FB:
(763) ##STR00341##
(764) where
(765) ##STR00342##
or a bicyclic moiety which is substituted with A.sup.2 and substituted with one or more groups independently selected from H, R.sup.FF1, and oxo;
(766) A.sup.2 is a bond between the degrader and the linker;
(767) Y.sup.Fa is CR.sup.FbR.sup.Fc, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2;
(768) each of Y.sup.Fb and Y.sup.Fg is, independently, NH, NR.sup.FF1, CH.sub.2, CHR.sup.FF1, C(R.sup.FF1).sub.2, O, or S;
(769) Y.sup.Fc is CR.sup.FdR.sup.Fe, C═O, C═S, C═CH.sub.2, SO.sub.2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl).sub.2, P(O)alkyl, P(O)OH, P(O)NH.sub.2;
(770) each of R.sup.Fb, R.sup.Fc, R.sup.Fd, R.sup.Fe, R.sup.Ff, and R.sup.Fg is, independently, H, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclyl, hydroxyl, alkoxy, amino, —NHalkyl, or —NaIkyl.sub.2;
(771) or R.sup.Fb and R.sup.Fc, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;
(772) or R.sup.Fd and R.sup.Fe, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;
(773) or R.sup.Ff and R.sup.Fg, together with the carbon atom to which each is attached, combine to form a 3-, 4-, 5-, or 6-membered spirocarbocyclylene, or a 4-, 5-, or 6-membered spiroheterocyclylene comprising 1 or 2 heteroatoms selected from N and O;
(774) or R.sup.Fd and R.sup.Fb, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;
(775) or R.sup.Fd and R.sup.Ff, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;
(776) or R.sup.Fb and R.sup.Fg, together with the carbon atoms to which each is attached, combine to form a 1, 2, 3, or 4 carbon bridged ring;

(777) each of Y.sup.Fd and Y.sup.Ff is, independently, CH.sub.2, CHR.sup.FF2, C(R.sup.FF2).sub.2, C(O), N, NH, NR.sup.FF3, O, S, or S(O);
(778) Y.sup.Fe is a bond or a divalent moiety attached to Y.sup.Fd and Y.sup.Ff that contains 1 to 5 contiguous carbon atoms that forma 3 to 8-membered ring. wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen, or sulfur atom; wherein one of the ring atoms is substituted with A.sup.2 and the others are substituted with one or more groups independently selected from H and R.sup.FF1; and wherein the contiguous atoms of Y.sup.Fe can be attached through a single or double bond;
(779) each R.sup.FF1 is, independently, H, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclyl, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclyl, alkylamino, akylhydroxyl, or haloalkyl;
(780) each R.sup.FF2 is, independently, alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic, including alkyl), —NH(aliphatic, including alkyl), —N(aliphatic including alkyl)(aliphatic including alkyl), —NHSO.sub.2alkyl, —N(alkyl)SO.sub.2alkyl, —NHSO.sub.2aryl, —N(alkyl)SO.sub.2aryl, —NHSO.sub.2alkenyl, —N(alkyl)SO.sub.2alkenyl, —NHSO.sub.2alkynyl, —N(alkyl)SO.sub.2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, or haloalkyl; and
(781) R.sup.FF3 is alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, or —C(O)Oalkyl,
(782) wherein if Y.sup.Fd or Y.sup.Ff is substituted with A.sup.2, then Y.sup.Fe is a bond, or a pharmaceutically acceptable salt thereof.
(783) In some embodiments, the compound of Formula FB has the structure of Formula FB1:
(784) ##STR00343##
or a pharmaceutically acceptable salt thereof.
(785) In some embodiments, the degradation moiety includes the structure of Formula F1:
(786) ##STR00344##
where A.sup.2 is a bond between the degrader and the linker; and R.sup.F1 is absent or O, or a pharmaceutically acceptable salt thereof.
(787) In some embodiments, R.sup.F1 is absent. In some embodiments, R.sup.F1 is O.
(788) In some embodiments, the structure of Formula F1 is
(789) ##STR00345##
(790) In some embodiments, the degradation moiety includes the structure Formula F2:
(791) ##STR00346##
where A.sup.2 is a bond between the degrader and the linker; and Y.sup.2 is CH.sub.2 or NH, or a pharmaceutically acceptable salt thereof.
(792) In some embodiments, Y.sup.2 is NH. In some embodiments, Y.sup.2 is CH.sub.2.
(793) In some embodiments, structure of Formula F2 is
(794) ##STR00347##
(795) In some embodiments, the degradation moiety includes the structure Formula G:
(796) ##STR00348##
where A.sup.2 is a bond between the degrader and the linker; and Y.sup.3 is CH.sub.2 or NH, or a pharmaceutically acceptable salt thereof.
(797) In some embodiments, Y.sup.3 is NH. In some embodiments, Y.sup.3 is CH.sub.2.
(798) In some embodiments, structure of Formula G is
(799) ##STR00349##
(800) The degradation moiety may also include structures found in, e.g., WO2017/197036; WO2019/204354, WO2019/236483, WO2020/010177; and WO2020/010227, the structures of which are herein incorporated by reference.
(801) In some embodiments, the linker has the structure of Formula IV:
A.sup.1-(B.sup.1).sub.f—(C.sup.1).sub.g—(B.sup.2).sub.h-(D)-(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2 Formula IV
(802) where

(803) A.sup.1 is a bond between the linker and A;
(804) A.sup.2 is a bond between B and the linker;
(805) each of B.sup.1, B.sup.2, B.sup.3, and B.sup.4 is, independently, optionally substituted C.sub.1-C.sub.2 alkylene, optionally substituted C.sub.1-C.sub.3 heteroalkylene, O, S, S(O).sub.2, or NR.sup.N;
(806) each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl;
(807) each of C.sup.1 and C.sup.2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl;
(808) each of f, g, h, i, j, and k is, independently, 0 or 1; and
(809) D is optionally substituted C.sub.1-10 alkylene, optionally substituted C.sub.2-10 alkenylene, optionally substituted C.sub.2-10 alkynylene, optionally substituted C.sub.2-6 heterocyclylene, optionally substituted C.sub.6-12 arylene, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkylene, or a chemical bond linking A.sup.1-(B.sup.1).sub.f —(C.sup.1).sub.g—(B.sup.2).sub.h— to —(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2.
(810) In some embodiments, each of B.sup.1, B.sup.2, B.sup.3, and B.sup.4 is, independently, optionally substituted C.sub.1-C.sub.4 alkylene, optionally substituted C.sub.1-C.sub.4 heteroalkylene, or NR.sup.N.
(811) In some embodiments, each R.sup.N is, independently, H or optionally substituted C.sub.1-C.sub.4 alkylene.
(812) In some embodiments, each R.sup.N is, independently, H or methyl.
(813) In some embodiments, each of B.sup.1 and B.sup.4 is, independently,
(814) ##STR00350##
(815) In some embodiments, B.sup.1 is
(816) ##STR00351##
(817) In some embodiments, each of C.sup.1 and C.sup.2 is, independently,
(818) ##STR00352##
(819) In some embodiments, C.sup.1 is
(820) ##STR00353##
(821) In some embodiments, B.sup.2 is NR.sup.N. In some embodiments, B.sup.2 is optionally substituted C.sub.1-C.sub.4 alkylene.
(822) In some embodiments, f is 0. In some embodiments, f is 1. In some embodiments, g is 1. In some embodiments, h is 0. In some embodiments, h is 1. In some embodiments, i is 0. In some embodiments, j is 0. In some embodiments, k is 0.
(823) In some embodiments, the linker has the structure of
(824) ##STR00354##
(825) wherein
(826) x is 1, 2, 3, 4, 5, 6, 7, or 8;
(827) y is 1, 2, 3, or 4;
(828) R.sup.x is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl;
(829) R.sup.y is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; and
(830) W is O or NR.sup.w, wherein R.sup.w is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl.
(831) In some embodiments, the linker has the structure of
(832) ##STR00355##
(833) In some embodiments, R.sup.x is H or me optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.y is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.w is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(834) In some embodiments, R.sup.x is H or methyl. In some embodiments, R.sup.y is H or methyl. In some embodiments, R.sup.w is H or methyl.

(835) In some embodiments, the linker has the structure of
(836) ##STR00356## ##STR00357## ##STR00358##
(837) In some embodiments, the linker has the structure of
(838) ##STR00359##
(839) In some embodiments, the linker has the structure of
(840) ##STR00360##
(841) In some embodiments, the linker has the structure of Formula V:
A.sup.1-(E.sup.1)—(F.sup.1)—(C.sup.3).sub.m-(E.sup.3).sub.n-(F.sup.2).sub.o1—(F.sup.3).sub.o2-(E.sup.2).sub.p-A.sup.2, Formula V
(842) where
(843) A.sup.1 is a bond between the linker and A;
(844) A.sup.2 is a bond between B and the linker;
(845) each of m, n, o1, o2, and p is, independently, 0 or 1;
(846) each of E.sup.1 and E.sup.2 is, independently, O, S, NR.sup.N, optionally substituted C.sub.1-10 alkylene, optionally substituted C.sub.2-10 alkenylene, optionally substituted C.sub.2-10 alkynylene, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkylene;
(847) E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, O, S, or NR.sup.N;
(848) each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl;
(849) C.sup.3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and
(850) each of F.sup.1, F.sup.2, and F.sup.3 is, independently, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-10 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(851) In some embodiments, the linker has the structure of Formula Va:
A.sup.1-(E.sup.1)—(F.sup.1)—(C.sup.3).sub.m-(E.sup.2).sub.p-A.sup.2. Formula Va
(852) In some embodiments, the linker has the structure of Formula Vb:
A.sup.1-(E.sup.1)—(F.sup.1)-(E.sup.2).sub.p-A.sup.2. Formula Vb
(853) In some embodiments, the linker has the structure of Formula Vc:
A.sup.1-(E.sup.1)—(F.sup.1)-A.sup.2. Formula Vc
(854) In some embodiments, the linker has the structure of Formula Vd:
A.sup.1-(E.sup.1)—(F.sup.1)—(C.sup.3).sub.m—(F.sup.2).sub.o1-A.sup.2. Formula Vd
(855) In some embodiments, the linker has the structure of Formula Ve:
A.sup.1-(E.sup.1)—(F.sup.1)-(E.sup.3).sub.n-(F.sup.2).sub.o1-(E.sup.2).sub.p-A.sup.2. Formula Ve
(856) In some embodiments, the linker has the structure of Formula Vf:
A.sup.1-(E.sup.1)—(F.sup.1)—(C.sup.3).sub.m-(E.sup.3).sub.n-(F.sup.2).sub.o1-(E.sup.2).sub.p-A.sup.2. Formula Vf
(857) In some embodiments, the linker has the structure of Formula Vg:
A.sup.1-(E.sup.1)—(F.sup.1)-(E.sup.3).sub.n-(F.sup.2).sub.o1-A.sup.2, Formula Vg
(858) In some embodiments, each of E.sup.1 and E.sup.2 is, independently, NR.sup.N, optionally substituted C.sub.1-10 alkylene, optionally substituted C.sub.2-C.sub.10 polyethylene glycolene, or optionally substituted C.sub.1-10 heteroalkylene.
(859) In some embodiments, E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene, O, S, or NR.sup.N; In some embodiments, E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene. In some embodiments, E.sup.3 is optionally substituted C.sub.1-C.sub.3 alkylene. In some embodiments, E.sup.3 is O, S, or NR.sup.N.
(860) In some embodiments, E.sup.3 is C.sub.1-C.sub.6 alkylene. In some embodiments, E.sup.3 is C.sub.1-C.sub.3 alkylene. In some embodiments, E.sup.3 is O.
(861) In some embodiments, E.sup.3 is
(862) ##STR00361##

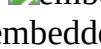
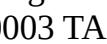
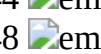
where a is 0, 1, 2, 3, 4, or 5.
(863) In some embodiments, E.sup.3 is
(864) ##STR00362##
(865) In some embodiments, each R.sup.N is, independently, H or optionally substituted C.sub.1-4 alkyl.
(866) In some embodiments, each R.sup.N is, independently, H or methyl.
(867) In some embodiments, E.sup.1 is
(868) ##STR00363##
where a is 0, 1, 2, 3, 4, or 5.
(869) In some embodiments, E.sup.1 is
(870) ##STR00364##
(871) where a is 0, 1, 2, 3, 4, or 5.
(872) In some embodiments, E.sup.1 is
(873) ##STR00365##
In some embodiments, E.sup.1 is
(874) ##STR00366##
(875) In some embodiments, E.sup.1 is
(876) ##STR00367##
(877) In some embodiments, E.sup.1 is
(878) ##STR00368## ##STR00369##
(879) where
(880) b is 0, 1, 2, 3, 4, 5, or 6;
(881) R.sup.a is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl;
(882) R.sup.b is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; and
(883) R.sup.c is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl.
(884) In some embodiments, E.sup.1 is
(885) ##STR00370## ##STR00371## ##STR00372##
(886) In some embodiments, E.sup.1 is
(887) ##STR00373##
(888) In some embodiments, E.sup.1 is
(889) ##STR00374##
(890) In some embodiments, R.sup.a is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.b is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.c is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(891) In some embodiments, R.sup.a is H or methyl. In some embodiments, R.sup.b is H or methyl. In some embodiments, R.sup.c is H or methyl.
(892) In some embodiments, b is 0, 1, 2, or 3. In some embodiments, b is 0. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3.
(893) In some embodiments, E.sup.1 is
(894) ##STR00375## ##STR00376##
(895) In some embodiments, E.sup.1 is
(896) ##STR00377##
(897) In some embodiments, E.sup.1 is
(898) ##STR00378##
(899) In some embodiments, E.sup.1 is
(900) ##STR00379##
(901) In some embodiments, E.sup.1 is
(902) ##STR00380##
(903) In some embodiments, E.sup.1 is
(904) ##STR00381##

(905) In some embodiments, E.sup.2 is O, NR.sup.w,
(906) ##STR00382##
(907) wherein
(908) c is 0, 1, 2, 3, 4, 5, 6, 7, or 8;
(909) d is 0, 1, 2, or 3;
(910) e is 0, 1, 2, 3, 4, 5, or 6;
(911) f is 0, 1, 2, 3, or 4;
(912) R.sup.d is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl;
(913) R.sup.e is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl;
(914) R.sup.f is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl;
(915) R.sup.g is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl; and
(916) W is O or NR.sup.w, wherein R.sup.w is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(917) In some embodiments, E.sup.2 is O, NR.sup.w,
(918) ##STR00383##
(919) In some embodiments, R.sup.d is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.e is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.f is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.g is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.w is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(920) In some embodiments, R.sup.d is H or methyl. In some embodiments, R.sup.e is H or methyl. In some embodiments, R.sup.f is H or methyl. In some embodiments, R.sup.g is H or methyl. In some embodiments, R.sup.w is H or methyl.
(921) In some embodiments, E.sup.2 is
(922) ##STR00384##
(923) In some embodiments, E.sup.2 is O,
(924) ##STR00385##
(925) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.3-C.sub.10 carbocyclylene.
(926) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is monocyclic. In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is polycyclic.
(927) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is bicyclic.
(928) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is bridged. In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is fused. In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is spirocyclic.
(929) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is
(930) ##STR00386##
(931) In some embodiments, F.sup.2 is
(932) ##STR00387##
(933) In some embodiments, the C.sub.3-C.sub.10 carbocyclylene is
(934) ##STR00388##
(935) In some embodiments, F.sup.1 is
(936) ##STR00389##
(937) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.2-C.sub.9 heterocyclylene.
(938) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is monocyclic. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is polycyclic.
(939) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bicyclic.
(940) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bridged. In some embodiments, the

C.sub.2-C.sub.9 heterocyclylene is fused. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is spirocyclic.
(941) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene includes a quaternary amine.
(942) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(943) ##STR00390## ##STR00391##
(944) where
(945) q1 is 0, 1, 2, 3, or 4;
(946) q2 is 0, 1, 2, 3, 4, 5, or 6;
(947) q3 is 0, 1, 2, 3, 4, 5, 6, 7, or 8;
(948) each R.sup.h is, independently, .sup.2H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4; or two R.sup.h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl; or two R.sup.h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl;
(949) R.sup.i1 is H or optionally substituted C.sub.1-C.sub.6 alkyl;
(950) R.sup.i2 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.6 carbocyclyl;
(951) R.sup.i3 is H or optionally substituted C.sub.1-C.sub.6 alkyl; and
(952) R.sup.i4 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(953) In some embodiments, each R.sup.h is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4. In some embodiments, R.sup.i1 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.i2 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.i3 is H or optionally substituted C.sub.1-C.sub.6 alkyl. In some embodiments, R.sup.i4 is H or optionally substituted C.sub.1-C.sub.6 alkyl.
(954) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(955) ##STR00392## ##STR00393##
(956) In some embodiments, each R.sup.h is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4. In some embodiments, each R.sup.h is, independently, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, or NR.sup.i3R.sup.i4.
(957) In some embodiments, each R.sup.h is, independently, .sup.2H, halogen, cyano, optionally substituted C.sub.1-C.sub.6 alkyl, OR.sup.i2, or NR.sup.i3R.sup.i4. In some embodiments, two R.sup.h groups, together with the carbon atom to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl. In some embodiments, two R.sup.h groups, together with the carbon atoms to which each is attached, combine to form optionally substituted C.sub.3-C.sub.10 carbocyclyl or optionally substituted C.sub.2-C.sub.9 heterocyclyl.
(958) In some embodiments, each R.sup.h is, independently, .sup.2H, F, methyl,
(959) ##STR00394##
(960) In some embodiments, each R.sup.h is, independently, F, methyl, or NR.sup.i3R.sup.i4.
(961) In some embodiments, q1 is 0, 1, or 2. In some embodiments, q1 is O. In some embodiments, q1 is 1. In some embodiments, q1 is 2.
(962) In some embodiments, q2 is 0, 1, or 2. In some embodiments, q2 is 0. In some embodiments, q2 is 1. In some embodiments, q2 is 2.
(963) In some embodiments, q3 is 0, 1, or 2. In some embodiments, q3 is 0. In some embodiments, q3 is 1. In some embodiments, q3 is 2.
(964) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(965) ##STR00395## ##STR00396## ##STR00397## ##STR00398##
(966) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(967) ##STR00399## ##STR00400##
(968) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(969) ##STR00401##

(970) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(971) ##STR00402##
(972) In some embodiments, F.sup.1 is
(973) ##STR00403##
(974) In some embodiments, F.sup.1 is
(975) ##STR00404##
(976) In some embodiments, F.sup.1 is
(977) ##STR00405##
(978) In some embodiments, F.sup.2 is
(979) ##STR00406##
In some embodiments, F.sup.2 is
(980) ##STR00407##
(981) In some embodiments, F.sup.3 is
(982) ##STR00408##
In some embodiments, F.sup.3 is
(983) ##STR00409##
(984) In some embodiments, R.sup.i1 is H or methyl. In some embodiments, R.sup.i2 is H or methyl. In some embodiments, R.sup.i3 is H or methyl. In some embodiments, R.sup.i4 is H or methyl.
(985) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(986) ##STR00410##
(987) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(988) ##STR00411##
(989) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(990) ##STR00412## ##STR00413##
(991) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(992) ##STR00414##
(993) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is
(994) ##STR00415##
(995) In some embodiments, F.sup.1 is
(996) ##STR00416## ##STR00417##
(997) In some embodiments, F.sup.1 is
(998) ##STR00418##
(999) In some embodiments, F.sup.1 is
(1000) ##STR00419##
(1001) In some embodiments, F.sup.2 is
(1002) ##STR00420##
(1003) In some embodiments, the C.sub.2-C.sub.9 heterocyclyl is
(1004) ##STR00421## ##STR00422## ##STR00423##
(1005) In some embodiments, the C.sub.2-C.sub.9 heterocyclyl is
(1006) ##STR00424## ##STR00425## ##STR00426##
(1007) In some embodiments, the C.sub.2-C.sub.9 heterocyclyl is
(1008) ##STR00427##
(1009) In some embodiments, the C.sub.2-C.sub.9 heterocyclyl is
(1010) ##STR00428##
(1011) In some embodiments, F.sup.1 is
(1012) ##STR00429##
(1013) In some embodiments, F.sup.1 is
(1014) ##STR00430##
(1015) In some embodiments, F.sup.1 is
(1016) ##STR00431##
(1017) In some embodiments, F.sup.1 is
(1018) ##STR00432##

(1019) In some embodiments, F.sup.1 is
(1020) ##STR00433##
(1021) In some embodiments, F.sup.2 is
(1022) ##STR00434##
(1023) In some embodiments, F.sup.2 is
(1024) ##STR00435##
(1025) In some embodiments, F.sup.2 is
(1026) ##STR00436##
(1027) In some embodiments, F.sup.2 is
(1028) ##STR00437##
(1029) In some embodiments, F.sup.3 is
(1030) ##STR00438##
(1031) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.6-C.sub.10 arylene.
(1032) In some embodiments, the C.sub.6-C.sub.10 arylene is
(1033) ##STR00439##
(1034) In some embodiments, each of F.sup.1, F.sup.2, or F.sup.3 is, independently, optionally substituted C.sub.2-C.sub.9 heteroarylene.
(1035) In some embodiments, the C.sub.2-C.sub.9 heteroarylene is
(1036) ##STR00440##
(1037) In some embodiments, F.sup.2 is
(1038) ##STR00441##
In some embodiments, F.sup.2 is
(1039) ##STR00442##
(1040) In some embodiments, C.sup.3 is
(1041) ##STR00443##
In some embodiments, C.sup.3 is
(1042) ##STR00444##
(1043) In some embodiments, m is 1. In some embodiments, p is 1.
(1044) In some embodiments, the linker has the structure of
(1045) ##STR00445## ##STR00446## ##STR00447## ##STR00448## ##STR00449## ##STR00450## ##STR00451## ##STR00452## ##STR00453##
(1046) In some embodiments, the linker has the structure of
(1047) ##STR00454## ##STR00455## ##STR00456## ##STR00457## ##STR00458## ##STR00459## ##STR00460## ##STR00461## ##STR00462## ##STR00463## ##STR00464## ##STR00465## ##STR00466## ##STR00467## ##STR00468## ##STR00469## ##STR00470##
(1048) In some embodiments, the linker has the structure of:
(1049) ##STR00471## ##STR00472## ##STR00473## ##STR00474## ##STR00475##
(1050) In some embodiments, the linker is absent.
(1051) In some embodiments, the linker is optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-10 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(1052) In some embodiments, the linker is optionally substituted C.sub.3-C.sub.10 carbocyclylene or optionally substituted C.sub.2-10 heterocyclylene. In some embodiments, the linker is optionally substituted C.sub.6-C.sub.10 arylene or optionally substituted C.sub.2-C.sub.9 heteroarylene.
(1053) In some embodiments, the linker is optionally substituted C.sub.2-10 heterocyclylene.
(1054) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is monocyclic. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is polycyclic.
(1055) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bicyclic.
(1056) In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is bridged. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is fused. In some embodiments, the C.sub.2-C.sub.9 heterocyclylene is spirocyclic.

(1057) In some embodiments, the linker has the structure of
(1058) ##STR00476##
(1059) In some embodiments, the linker has the structure of
(1060) ##STR00477##
(1061) In some embodiments, the compound has the structure of any one of compounds D1-D31 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of compounds D32-D184 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D185-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.
(1062) In some embodiments, the compound has the structure of any one of compounds D1, D7, D15-D21, D23, and D27-D30 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D32-D42, D46, D48-D63, D65-D73, D75-D83, D85-D87, D89-D93, D95-D116, D118, D120-D164, D166-D168, D170, D171, D173, D174, D176-D178, D180, D182, and D184 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D185-D190, D192-D204, D248, D254-D258, D260, D262-D269, D271-D280, D284, D286-D291, and D293-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.
(1063) In an aspect, the disclosure features compounds D1-D31 in Table 2A, or a pharmaceutically acceptable salt thereof.
(1064) In an aspect, the disclosure features compounds D32-D184 in Table 2B, or a pharmaceutically acceptable salt thereof.
(1065) In an aspect, the disclosure features compounds D185-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.
(1066) TABLE-US-00002 TABLE 2A Compounds D1-D31 of the Disclosure Com- pound No. Structure D1  D2  D3 0  D4  D5  D6  D7 D8 D9 D10 D11  D12  D13 0  D14  D15  D16  D17  D18  D19 D20 D21  D22  D23 00  D24 01  D25 02  D26 03  D27 04  D28 05  D29 06  D30 07  D31 08
(1067) TABLE-US-00003 TABLE 2B Compounds D32-D184 of the Disclosure Com- pound No. Structure D32 09  D33 0  D34  D35  D36  D37  D38 D39 D40  D41 D42 D43 0 D44 D45 D46 D47 D48 D49 D50 D51 D52 D53 0 D54 D55 D56 D57 D58 D59 D60 D61 D62 D63 0 D64 D65 D66 D67 D68 D69 D70 D71 D72 D73 0 D74 D75 D76 D77 D78 D79 D80 D81 D82 D83 0 D84 D85 D86 D87 D88 D89 D90 D91 D92 D93 0 D94 D95 D96 D97 D98 D99 D100 D101 D102 D103 0 D104 D105 D106 D107

 D108 D109 D110 D111
 D112 D113 0 D114 D115
 D116 D117 D118 D119
 D120 D121 D122 D123
00 D124 01 D125 02 D126 03
 D127 04 D128 05 D129 06 D130 07 D131 08 D132 09 D133 0
 D134 D135 D136 D137
 D138 D139 D140 D141
 D142 D143 0 D144 D145
 D146 D147 D148 D149
 D150 D151 D152 D153
0 D154 D155 D156 D157
 D158 D159 D160 D161
 D162 D163 0 D164 D165
 D166 D167 D168 D169
 D170 D171 D172 D173
0 D174 D175 D176 D177
 D178 D179 D180 D181
 D182 D183 0 D184

(1068) TABLE-US-00004 TABLE 2C Compounds D185-D316 of the Disclosure Compound No. Structure D185 D186 D187 D188
 D189 D190 D191 D192
 D193 0 D194 D195 D196
 D197 D198 D199 D200
 D201 D202 D203 0 D204
 D205 D206 D207 D208
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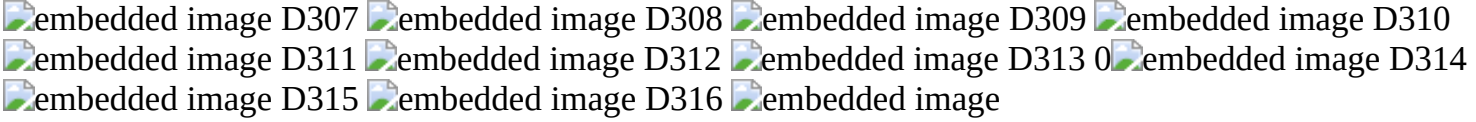
(1069) In another aspect, the disclosure features a pharmaceutical composition including any of the foregoing compounds, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable excipient.
(1070) In an aspect, the disclosure features a method of inhibiting the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.
(1071) In another aspect, the disclosure features a method of reducing the level and/or activity of BRD9 in a cell, the method involving contacting the cell with an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.
(1072) In some embodiments, the cell is a cancer cell.
(1073) In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.
(1074) In an aspect, the disclosure features a method of treating a BAF complex-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BAF complex-related disorder is cancer. In some embodiments, the BAF complex-related disorder is infection.
(1075) In another aspect, the disclosure features a method of treating an SS18-SSX fusion protein-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the SS18-SSX fusion protein-related disorder is cancer. In some embodiments, the SS18-SSX fusion protein-related disorder is infection. In some embodiments of any of the foregoing methods, the SS18-SSX fusion protein is a SS18-SSX1 fusion protein, a SS18-SSX2 fusion protein, or a SS18-SSX4 fusion protein.
(1076) In yet another aspect, the disclosure features a method of treating a BRD9-related disorder in a subject in need thereof, the method involving administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof. In some embodiments, the BRD9-related disorder is cancer. In some embodiments, the BRD9-related disorder is infection.
(1077) In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas,

gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendroglioma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia

(a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)-+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

(1078) In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

(1079) In some embodiments, the infection is viral infection (e.g., an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)); Flaviviridae family (e.g. hepatitis C virus (HCV)); Adenoviridae family (e.g. Human Adenovirus); Herpesviridae family (e.g. Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus); Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)); Parvoviridae family (e.g. Parvovirus B19); Polyomaviridae family (e.g. JC virus and BK virus); Paramyxoviridae family (e.g. Measles virus); or Togaviridae family (e.g. Rubella virus)). In some embodiments, the disorder is Coffin Siris, Neurofibromatosis (e.g., NF-1, NF-2, or Schwannomatosis), or Multiple Meningioma. In an aspect, the disclosure features a method of treating a cancer in a subject in need thereof, the method including administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions.

(1080) In some embodiments, the cancer is squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors,

meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodgkin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendroglioma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large

B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)-+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

(1081) In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, colorectal cancer, a sarcoma (e.g., a soft tissue sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma, rhabdomyosarcoma, adult fibrosarcoma, alveolar soft-part sarcoma, angiosarcoma, clear cell sarcoma, desmoplastic small round cell tumor, epithelioid sarcoma, fibromyxoid sarcoma, gastrointestinal stromal tumor, Kaposi sarcoma, liposarcoma, leiomyosarcoma, malignant mesenchymoma malignant peripheral nerve sheath tumors, myxofibrosarcoma, low-grade rhabdomyosarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is a malignant, rhabdoid tumor, a CD8+ T-cell lymphoma, endometrial carcinoma, ovarian carcinoma, bladder cancer, stomach cancer, pancreatic cancer, esophageal cancer, prostate cancer, renal cell carcinoma, melanoma, or colorectal cancer. In some embodiments, the cancer is a sarcoma (e.g., synovial sarcoma or Ewing's sarcoma), non-small cell lung cancer (e.g., squamous or adenocarcinoma), stomach cancer, or breast cancer. In some embodiments, the cancer is sarcoma (e.g., synovial sarcoma or Ewing's sarcoma). In some embodiments, the sarcoma is synovial sarcoma.

(1082) In another aspect, the disclosure features a method for treating a viral infection in a subject in need thereof. This method includes administering to the subject an effective amount of any of the foregoing compounds, or pharmaceutically acceptable salts thereof, or any of the foregoing pharmaceutical compositions. In some embodiments, the viral infection is an infection with a virus of the Retroviridae family such as the lentiviruses (e.g. Human immunodeficiency virus (HIV) and deltaretroviruses (e.g., human T cell leukemia virus I (HTLV-I), human T cell leukemia virus II (HTLV-II)); Hepadnaviridae family (e.g. hepatitis B virus (HBV)), Flaviviridae family (e.g. hepatitis C virus (HCV)), Adenoviridae family (e.g. Human Adenovirus), Herpesviridae family (e.g. Human cytomegalovirus (HCMV), Epstein-Barr virus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), human herpesvirus 6 (HHV-6), Herpesvitus K*, CMV, varicella-zoster virus), Papillomaviridae family (e.g. Human Papillomavirus (HPV, HPV E1)), Parvoviridae family (e.g. Parvovirus B19), Polyomaviridae family (e.g. JC virus and BK virus), Paramyxoviridae family (e.g. Measles virus), Togaviridae family (e.g. Rubella virus).

(1083) In another embodiment of any of the foregoing methods, the method further includes administering to the subject an additional anticancer therapy (e.g., chemotherapeutic or cytotoxic agent or radiotherapy).

(1084) In particular embodiments, the additional anticancer therapy is: a chemotherapeutic or cytotoxic agent (e.g., doxorubicin or ifosfamide), a differentiation-inducing agent (e.g., retinoic acid, vitamin D, cytokines), a hormonal agent, an immunological agent, or an anti-angiogenic agent. Chemotherapeutic and cytotoxic agents include, but are not limited to, alkylating agents, cytotoxic antibiotics, antimetabolites, vinca alkaloids, etoposides, and others (e.g., paclitaxel, taxol, docetaxel, taxotere, cis-platinum). A list of additional compounds having anticancer activity can be found in L. Brunton, B. Chabner and B. Knollman (eds). Goodman and Gilman's The Pharmacological Basis of Therapeutics,

Twelfth Edition, 2011, McGraw Hill Companies, New York, NY
(1085) In particular embodiments, the compound of the invention and the additional anticancer therapy and any of the foregoing compounds or pharmaceutical compositions are administered within 28 days of each other (e.g., within 21, 14, 10, 7, 5, 4, 3, 2, or 1 days) or within 24 hours (e.g., 12, 6, 3, 2, or 1 hours; or concomitantly) each in an amount that together are effective to treat the subject.
Chemical Terms
(1086) The terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.
(1087) For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C.sub.2 alkyl group has the formula —CH.sub.2CH.sub.3. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.
(1088) Herein a phrase of the form “optionally substituted X” (e.g., optionally substituted alkyl) is intended to be equivalent to “X, wherein X is optionally substituted” (e.g., “alkyl, wherein said alkyl is optionally substituted”). It is not intended to mean that the feature “X” (e.g., alkyl) per se is optional. As described herein, certain compounds of interest may contain one or more “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, e.g., any of the substituents or groups described herein. 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 the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. 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 embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.
(1089) The term “aliphatic,” as used herein, refers to a saturated or unsaturated, straight, branched, or cyclic hydrocarbon. “Aliphatic” is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, and thus incorporates each of these definitions. In one embodiment, “aliphatic” is used to indicate those aliphatic groups having 1-20 carbon atoms. The aliphatic chain can be, for example, mono-unsaturated, di-unsaturated, tri-unsaturated, or polyunsaturated, or alkynyl. Unsaturated aliphatic groups can be in a cis or trans configuration. In one embodiment, the aliphatic group contains from 1 to about 12 carbon atoms, more generally from 1 to about 6 carbon atoms or from 1 to about 4 carbon atoms. In one embodiment, the aliphatic group contains from 1 to about 8 carbon atoms. In certain embodiments, the aliphatic group is C.sub.1-C.sub.2, C.sub.1-C.sub.3, C.sub.1-C.sub.4, C.sub.1-C.sub.5, or C.sub.1-C.sub.6. The specified ranges as used herein indicate an aliphatic group having each member of the range described as an independent species. For example, the term C.sub.1-C.sub.6 aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term C.sub.1-C.sub.4 aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. In one embodiment, the aliphatic group is substituted with one or more functional groups that results in the formation of a stable moiety.
(1090) The term “heteroaliphatic,” as used herein, refers to an aliphatic moiety that contains at least one heteroatom in the chain, for example, an amine, carbonyl, carboxy, oxo, thio, phosphate, phosphonate,

nitrogen, phosphorus, silicon, or boron atoms in place of a carbon atom. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. “Heteroaliphatic” is intended herein to include, but is not limited to, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl moieties. In one embodiment, “heteroaliphatic” is used to indicate a heteroaliphatic group (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-20 carbon atoms. In one embodiment, the heteroaliphatic group is optionally substituted in a manner that results in the formation of a stable moiety. Nonlimiting examples of heteroaliphatic moieties are polyethylene glycol, polyalkylene glycol, amide, polyamide, polylactide, polyglycolide, thioether, ether, alkyl-heterocycle-alkyl, —O-alkyl-O-alkyl, and alkyl-O-haloalkyl.

(1091) The term “acyl,” as used herein, represents a hydrogen or an alkyl group that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

(1092) The term “alkyl,” as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 3 carbon atoms). An “alkylene” is a divalent alkyl group.

(1093) The term “alkenyl,” as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms). An “alkenylene” is a divalent alkenyl group.

(1094) The term “alkynyl,” as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6, or 2 carbon atoms). An “alkynylene” is a divalent alkynyl group.

(1095) The term “amino,” as used herein, represents —N(R.sup.N1).sub.2, wherein each R.sup.N1 is, independently, H, OH, NO.sub.2, N(R.sup.N2).sub.2, SO.sub.2OR.sup.N2, SO.sub.2R.sup.N2, SOR.sup.N2, an N-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R.sup.N1 groups can be optionally substituted; or two R.sup.N1 combine to form an alkylene or heteroalkylene, and wherein each R.sup.N2 is, independently, H, alkyl, or aryl. The amino groups of the compounds described herein can be an unsubstituted amino (i.e., —NH.sub.2) or a substituted amino (i.e., —N(R.sup.N1).sub.2).

(1096) The term “aryl,” as used herein, refers to an aromatic mono- or polycarbocyclic radical of, e.g., 6 to 12, carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

(1097) The term “arylalkyl,” as used herein, represents an alkyl group substituted with an aryl group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl, C.sub.1-C.sub.10 alkyl C.sub.6-C.sub.10 aryl, or C.sub.1-C.sub.20 alkyl C.sub.6-C.sub.10 aryl), such as, benzyl and phenethyl. In some embodiments, the alkyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

(1098) The term “azido,” as used herein, represents a —N.sub.3 group.

(1099) The term “bridged cyclyl,” as used herein, refers to a bridged polycyclic group of 5 to 20 atoms, containing from 1 to 3 bridges. Bridged cyclyl includes bridged carbocyclyl (e.g., norbornyl) and bridged heterocyclyl (e.g., 1,4-diazabicyclo[2.2.2]octane).

(1100) The term “cyano,” as used herein, represents a —CN group.

(1101) The term “carbocyclyl,” as used herein, refers to a non-aromatic C.sub.3-C.sub.12, monocyclic or polycyclic (e.g., bicyclic or tricyclic) structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups (e.g., cyclohexyl) and unsaturated carbocyclyl radicals (e.g., cyclohexenyl). Polycyclic carbocyclyl includes spirocyclic carbocyclyl, bridged carbocyclyl, and fused carbocyclyl. A “carbocyclylene” is a divalent carbocyclyl group.

(1102) The term “cycloalkyl,” as used herein, refers to a saturated, non-aromatic, monovalent mono- or

polycarbocyclic radical of 3 to 10, preferably 3 to 6 carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

(1103) The terms “halo” or “halogen,” as used herein, mean a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

(1104) The term “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an “alkoxy” which, as used herein, refers to alkyl-O— (e.g., methoxy and ethoxy), and an “alkylamino” which, as used herein, refers to —N(alkyl)R.sup.Na, where R.sup.Na is H or alkyl (e.g., methylamino). A “heteroalkylene” is a divalent heteroalkyl group.

(1105) The term “heteroalkenyl,” as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an “alkenoxy” which, as used herein, refers to alkenyl-O—. A “heteroalkenylene” is a divalent heteroalkenyl group.

(1106) The term “heteroalkynyl,” as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups. Examples of heteroalkynyl groups are an “alkynoxy” which, as used herein, refers to alkynyl-O—. A “heteroalkynylene” is a divalent heteroalkynyl group.

(1107) The term “heteroaryl,” as used herein, refers to an aromatic monocyclic or polycyclic structure of 5 to 12 atoms having at least one aromatic ring containing 1, 2, or 3 ring atoms selected from nitrogen, oxygen, and sulfur, with the remaining ring atoms being carbon. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxaxolyl, and thiazolyl. A “heteroarylene” is a divalent heteroaryl group.

(1108) The term “heteroarylalkyl,” as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C.sub.1-C.sub.6 alkyl C.sub.2-C.sub.9 heteroaryl, C.sub.1-C.sub.10 alkyl C.sub.2-C.sub.9 heteroaryl, or C.sub.1-C.sub.20 alkyl C.sub.2-C.sub.9 heteroaryl). In some embodiments, the alkyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

(1109) The term “heterocyclyl,” as used herein, refers a monocyclic or polycyclic radical (e.g., bicyclic or tricyclic) having 3 to 12 atoms having at least one non-aromatic ring containing 1, 2, 3, or 4 ring atoms selected from N, O, or S, and no aromatic ring containing any N, O, or S atoms. Polycyclic heterocyclyl includes spirocyclic heterocyclyl, bridged heterocyclyl, and fused heterocyclyl. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, and 1,3-dioxanyl. A “heterocyclylene” is a divalent heterocyclyl group.

(1110) The term “heterocyclylalkyl,” as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C.sub.1-C.sub.6 alkyl C.sub.2-C.sub.9 heterocyclyl, C.sub.1-C.sub.10 alkyl C.sub.2-C.sub.9 heterocyclyl, or C.sub.1-C.sub.20 alkyl C.sub.2-C.sub.9 heterocyclyl). In some embodiments, the alkyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

(1111) The term “hydroxyalkyl,” as used herein, represents alkyl group substituted with an —OH group.

(1112) The term “hydroxyl,” as used herein, represents an —OH group.

(1113) The term “imine,” as used herein, represents ═NR.sup.N group, where R.sup.N is, e.g., H or alkyl.

(1114) The term “N-protecting group,” as used herein, represents those groups intended to protect an

amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, “Protective Groups in Organic Synthesis,” 3rd Edition (John Wiley & Sons, New York, 1999). N-protecting groups include, but are not limited to, acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L, or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-20 dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred N-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

(1115) The term “nitro,” as used herein, represents an —NO.sub.2 group.

(1116) The term “oxo,” as used herein, represents an ═O group.

(1117) The term “thiol,” as used herein, represents an —SH group.

(1118) The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: alkyl (e.g., unsubstituted and substituted, where the substituents include any group described herein, e.g., aryl, halo, hydroxy), aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halogen (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH.sub.2 or mono- or dialkyl amino), azido, cyano, nitro, oxo, sulfonyl, or thiol. Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)).

(1119) Compounds described herein (e.g., compounds of the invention) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. “Enantiomer” means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. “Racemate” or “racemic mixture” means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of

polarized light. “Geometric isomer” means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. “R,” “S,” “S*,” “R*,” “E,” “Z,” “cis,” and “trans,” indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds described herein (e.g., the compounds of the invention) may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound, or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

(1120) Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. “Isotopes” refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

(1121) Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as .sup.2H, .sup.3H, .sup.11C, .sup.13C, .sup.14C, .sup.13N, .sup.15N, .sup.15O, .sup.17O, .sup.18O, .sup.32P, .sup.33P, .sup.35S, .sup.18F,

.sup.36Cl, .sup.123I and .sup.125I. Isotopically-labeled compounds (e.g., those labeled with .sup.3H and .sup.14C)) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., .sup.3H) and carbon-14 (i.e., .sup.14C)) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., .sup.2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by .sup.2H or .sup.3H, or one or more carbon atoms are replaced by .sup.13C- or .sup.14C-enriched carbon. Positron emitting isotopes such as .sup.15O, .sup.13N, .sup.11C, and .sup.18F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

(1122) As is known in the art, many chemical entities can adopt a variety of different solid forms such as, for example, amorphous forms or crystalline forms (e.g., polymorphs, hydrates, solvate). In some embodiments, compounds of the present invention may be utilized in any such form, including in any solid form. In some embodiments, compounds described or depicted herein may be provided or utilized in hydrate or solvate form.

(1123) Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Definitions

(1124) In this application, unless otherwise clear from context, (i) the term “a” may be understood to mean “at least one”; (ii) the term “or” may be understood to mean “and/or”; and (iii) the terms “including” and “including” may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps.

(1125) As used herein, the terms “about” and “approximately” refer to a value that is within 10% above or below the value being described. For example, the term “about 5 nM” indicates a range of from 4.5 to 5.5 nM.

(1126) As used herein, the term “administration” refers to the administration of a composition (e.g., a compound or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intratumoral, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal, and vitreal.

(1127) As used herein, the term “adult soft tissue sarcoma” refers to a sarcoma that develops in the soft tissues of the body, typically in adolescent and adult subjects (e.g., subjects who are at least 10 years old, 11 years old, 12 years old, 13 years old, 14 years old, 15 years old, 16 years old, 17 years old, 18 years old, or 19 years old). Non-limiting examples of adult soft tissue sarcoma include, but are not limited to, synovial sarcoma, fibrosarcoma, malignant fibrous histiocytoma, dermatofibrosarcoma, liposarcoma, leiomyosarcoma, hemangiosarcoma, Kaposi's sarcoma, lymphangiosarcoma, malignant peripheral nerve sheath tumor/neurofibrosarcoma, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, extraskeletal myxoid chondrosarcoma, and extraskeletal mesenchymal.

(1128) The term “antisense,” as used herein, refers to a nucleic acid comprising a polynucleotide that is sufficiently complementary to all or a portion of a gene, primary transcript, or processed mRNA, so as to interfere with expression of the endogenous gene (e.g., BRD9). “Complementary” polynucleotides are

those that are capable of base pairing according to the standard Watson-Crick complementarity rules. Specifically, purines will base pair with pyrimidines to form a combination of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. It is understood that two polynucleotides may hybridize to each other even if they are not completely complementary to each other, provided that each has at least one region that is substantially complementary to the other.

(1129) The term “antisense nucleic acid” includes single-stranded RNA as well as double-stranded DNA expression cassettes that can be transcribed to produce an antisense RNA. “Active” antisense nucleic acids are antisense RNA molecules that are capable of selectively hybridizing with a primary transcript or mRNA encoding a polypeptide having at least 80% sequence identity (e.g., 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) with the targeted polypeptide sequence (e.g., a BRD9 polypeptide sequence). The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof. In some embodiments, an antisense nucleic acid molecule is antisense to a “coding region” of the coding strand of a nucleotide sequence. The term “coding region” refers to the region of the nucleotide sequence comprising codons that are translated into amino acid residues. In some embodiments, the antisense nucleic acid molecule is antisense to a “noncoding region” of the coding strand of a nucleotide sequence. The term “noncoding region” refers to 5′ and 3′ sequences that flank the coding region that are not translated into amino acids (i.e., also referred to as 5′ and 3′ untranslated regions). The antisense nucleic acid molecule can be complementary to the entire coding region of mRNA, or can be antisense to only a portion of the coding or noncoding region of an mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides in length.

(1130) As used herein, the term “BAF complex” refers to the BR.sup.G1- or HRBM-associated factors complex in a human cell.

(1131) As used herein, the term “BAF complex-related disorder” refers to a disorder that is caused or affected by the level and/or activity of a BAF complex.

(1132) As used herein, the terms “GBAF complex” and “GBAF” refer to a SWI/SNF ATPase chromatin remodeling complex in a human cell. GBAF complex subunits may include, but are not limited to, ACTB, ACTL6A, ACTL6B, BICRA, BICRAL, BRD9, SMARCA2, SMARCA4, SMARCC1, SMARCD1, SMARCD2, SMARCD3, and SS18. The term “cancer” refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

(1133) As used herein, the term “BRD9” refers to bromodomain-containing protein 9, a component of the BAF (BR.sup.G1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is encoded by the BRD9 gene, the nucleic acid sequence of which is set forth in SEQ ID NO: 1. The term “BRD9” also refers to natural variants of the wild-type BRD9 protein, such as proteins having at least 85% identity (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) to the amino acid sequence of wild-type BRD9, which is set forth in SEQ ID NO: 2.

(1134) As used herein, the term “BRD9-related disorder” refers to a disorder that is caused or affected by the level and/or activity of BRD9. The term “cancer” refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

(1135) As used herein, a “combination therapy” or “administered in combination” means that two (or more) different agents or treatments are administered to a subject as part of a defined treatment regimen for a particular disease or condition. The treatment regimen defines the doses and periodicity of administration of each agent such that the effects of the separate agents on the subject overlap. In some embodiments, the delivery of the two or more agents is simultaneous or concurrent and the agents may be co-formulated. In some embodiments, the two or more agents are not co-formulated and are administered in a sequential manner as part of a prescribed regimen. In some embodiments, administration of two or more agents or treatments in combination is such that the reduction in a

symptom, or other parameter related to the disorder is greater than what would be observed with one agent or treatment delivered alone or in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive (e.g., synergistic). Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination may be administered by intravenous injection while a second therapeutic agent of the combination may be administered orally.

(1136) A "compound of the present invention" and similar terms as used herein, whether explicitly noted or not, refers to compounds useful for treating BAF-related disorders (e.g., cancer or infection) described herein, including, e.g., compounds of Formula I or Formula II (e.g., compounds of Table 2A, Table 2B, and Table 2C), as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof. Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, atropisomers, and tautomers) or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination. Compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C═N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms. In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton.

(1137) In certain embodiments, a tautomeric form may be a prototropic tautomer, which is an isomeric protonation states having the same empirical formula and total charge as a reference form. Examples of moieties with prototropic tautomeric forms are ketone-enol pairs, amide-imidic acid pairs, lactam-lactim pairs, amide-imidic acid pairs, enamine-imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H-isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion.

(1138) As used herein, the term "degrader" refers to a small molecule compound including a degradation moiety, wherein the compound interacts with a protein (e.g., BRD9) in a way which results in degradation of the protein, e.g., binding of the compound results in at least 5% reduction of the level of the protein, e.g., in a cell or subject.

(1139) As used herein, the term "degradation moiety" refers to a moiety whose binding results in degradation of a protein, e.g., BRD9. In one example, the moiety binds to a protease or a ubiquitin ligase that metabolizes the protein, e.g., BRD9.

(1140) By "determining the level of a protein" is meant the detection of a protein, or an mRNA encoding the protein, by methods known in the art either directly or indirectly. "Directly determining" means performing a process (e.g., performing an assay or test on a sample or "analyzing a sample" as that term is defined herein) to obtain the physical entity or value. "Indirectly determining" refers to receiving the physical entity or value from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Methods to measure protein level generally include, but are not limited to,

western blotting, immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, liquid chromatography (LC)-mass spectrometry, microcytometry, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry, as well as assays based on a property of a protein including, but not limited to, enzymatic activity or interaction with other protein partners. Methods to measure mRNA levels are known in the art.

(1141) As used herein, the terms "effective amount," "therapeutically effective amount," and "a "sufficient amount" of an agent that reduces the level and/or activity of BRD9 (e.g., in a cell or a subject) described herein refer to a quantity sufficient to, when administered to the subject, including a human, effect beneficial or desired results, including clinical results, and, as such, an "effective amount" or synonym thereto depends on the context in which it is being applied. For example, in the context of treating cancer, it is an amount of the agent that reduces the level and/or activity of BRD9 sufficient to achieve a treatment response as compared to the response obtained without administration of the agent that reduces the level and/or activity of BRD9. The amount of a given agent that reduces the level and/or activity of BRD9 described herein that will correspond to such an amount will vary depending upon various factors, such as the given agent, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject (e.g., age, sex, and/or weight) or host being treated, and the like, but can nevertheless be routinely determined by one of skill in the art. Also, as used herein, a "therapeutically effective amount" of an agent that reduces the level and/or activity of BRD9 of the present disclosure is an amount which results in a beneficial or desired result in a subject as compared to a control. As defined herein, a therapeutically effective amount of an agent that reduces the level and/or activity of BRD9 of the present disclosure may be readily determined by one of ordinary skill by routine methods known in the art. Dosage regimen may be adjusted to provide the optimum therapeutic response.

(1142) As used herein, the term "inhibitor" refers to any agent which reduces the level and/or activity of a protein (e.g., BRD9). Non-limiting examples of inhibitors include small molecule inhibitors, degraders, antibodies, enzymes, or polynucleotides (e.g., siRNA).

(1143) The term "inhibitory RNA agent" refers to an RNA, or analog thereof, having sufficient sequence complementarity to a target RNA to direct RNA interference. Examples also include a DNA that can be used to make the RNA. RNA interference (RNAi) refers to a sequence-specific or selective process by which a target molecule (e.g., a target gene, protein, or RNA) is down-regulated. Generally, an interfering RNA ("iRNA") is a double-stranded short-interfering RNA (siRNA), short hairpin RNA (shRNA), or single-stranded micro-RNA (miRNA) that results in catalytic degradation of specific mRNAs, and also can be used to lower or inhibit gene expression.

(1144) By "level" is meant a level of a protein, or mRNA encoding the protein, as compared to a reference. The reference can be any useful reference, as defined herein. By a "decreased level" or an "increased level" of a protein is meant a decrease or increase in protein level, as compared to a reference (e.g., a decrease or an increase by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more; a decrease or an increase of more than about 10%, about 15%, about 20%, about 50%, about 75%, about 100%, or about 200%, as compared to a reference; a decrease or an increase by less than about 0.01-fold, about 0.02-fold, about 0.1-fold, about 0.3-fold, about 0.5-fold, about 0.8-fold, or less; or an increase by more than about 1.2-fold, about 1.4-fold, about 1.5-fold, about 1.8-fold, about 2.0-fold, about 3.0-fold, about 3.5-fold, about 4.5-fold, about 5.0-fold, about 10-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 1000-fold, or more). A level of a protein may be expressed in mass/vol (e.g., g/dL, mg/mL, μg/mL, ng/mL) or percentage relative to total protein or mRNA in a sample.

(1145) The terms "miRNA" and "microRNA" refer to an RNA agent, preferably a single-stranded agent, of about 10-50 nucleotides in length, preferably between about 15-25 nucleotides in length, which is

capable of directing or mediating RNA interference. Naturally-occurring miRNAs are generated from stem-loop precursor RNAs (i.e., pre-miRNAs) by Dicer. The term “Dicer” as used herein, includes Dicer as well as any Dicer ortholog or homolog capable of processing dsRNA structures into siRNAs, miRNAs, siRNA-like or miRNA-like molecules. The term microRNA (“miRNA”) is used interchangeably with the term “small temporal RNA” (“stRNA”) based on the fact that naturally-occurring miRNAs have been found to be expressed in a temporal fashion (e.g., during development).

(1146) By “modulating the activity of a BAF complex,” is meant altering the level of an activity related to a BAF complex (e.g., GBAF), or a related downstream effect. The activity level of a BAF complex may be measured using any method known in the art, e.g., the methods described in Kadoch et al, Cell 153:71-85 (2013), the methods of which are herein incorporated by reference.

(1147) “Percent (%) sequence identity” with respect to a reference polynucleotide or polypeptide sequence is defined as the percentage of nucleic acids or amino acids in a candidate sequence that are identical to the nucleic acids or amino acids in the reference polynucleotide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid or amino acid sequence identity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For example, percent sequence identity values may be generated using the sequence comparison computer program BLAST. As an illustration, the percent sequence identity of a given nucleic acid or amino acid sequence, A, to, with, or against a given nucleic acid or amino acid sequence, B, (which can alternatively be phrased as a given nucleic acid or amino acid sequence, A that has a certain percent sequence identity to, with, or against a given nucleic acid or amino acid sequence, B) is calculated as follows:

100 multiplied by(the fraction X/Y)

where X is the number of nucleotides or amino acids scored as identical matches by a sequence alignment program (e.g., BLAST) in that program's alignment of A and B, and where Y is the total number of nucleic acids in B. It will be appreciated that where the length of nucleic acid or amino acid sequence A is not equal to the length of nucleic acid or amino acid sequence B, the percent sequence identity of A to B will not equal the percent sequence identity of B to A.

(1148) A “pharmaceutically acceptable excipient,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

(1149) As used herein, the term “pharmaceutically acceptable salt” means any pharmaceutically acceptable salt of the compound of any of the compounds described herein. For example, pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically

acceptable salts are described in: Berge et al., J. Pharmaceutical Sciences 66:1-19, 1977 and in Pharmaceutical Salts: Properties, Selection, and Use, (Eds. P. H. Stahl and C. G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

(1150) The compounds described herein may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds described herein, be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

(1151) The term “pharmaceutical composition,” as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

(1152) By “reducing the activity of BRD9,” is meant decreasing the level of an activity related to an BRD9, or a related downstream effect. A non-limiting example of inhibition of an activity of BRD9 is decreasing the level of a BAF complex (e.g., GBAF) in a cell. The activity level of BRD9 may be measured using any method known in the art. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 inhibitor. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 degrader.

(1153) By “reducing the level of BRD9,” is meant decreasing the level of BRD9 in a cell or subject. The level of BRD9 may be measured using any method known in the art.

(1154) By a “reference” is meant any useful reference used to compare protein or mRNA levels. The reference can be any sample, standard, standard curve, or level that is used for comparison purposes. The reference can be a normal reference sample or a reference standard or level. A “reference sample” can be, for example, a control, e.g., a predetermined negative control value such as a “normal control” or a prior sample taken from the same subject; a sample from a normal healthy subject, such as a normal cell or normal tissue; a sample (e.g., a cell or tissue) from a subject not having a disease; a sample from a subject that is diagnosed with a disease, but not yet treated with a compound described herein; a sample from a subject that has been treated by a compound described herein; or a sample of a purified protein (e.g., any described herein) at a known normal concentration. By “reference standard or level” is meant a value or number derived from a reference sample. A “normal control value” is a pre-determined value indicative of non-disease state, e.g., a value expected in a healthy control subject. Typically, a normal control value is expressed as a range (“between X and Y”), a high threshold (“no higher than X”), or a low threshold (“no lower than X”). A subject having a measured value within the normal

control value for a particular biomarker is typically referred to as “within normal limits” for that biomarker. A normal reference standard or level can be a value or number derived from a normal subject not having a disease or disorder (e.g., cancer); a subject that has been treated with a compound described herein. In preferred embodiments, the reference sample, standard, or level is matched to the sample subject sample by at least one of the following criteria: age, weight, sex, disease stage, and overall health. A standard curve of levels of a purified protein, e.g., any described herein, within the normal reference range can also be used as a reference.

(1155) The terms “short interfering RNA” and “siRNA” (also known as “small interfering RNAs”) refer to an RNA agent, preferably a double-stranded agent, of about 10-50 nucleotides in length, the strands optionally having overhanging ends comprising, for example 1, 2 or 3 overhanging nucleotides (or nucleotide analogs), which is capable of directing or mediating RNA interference. Naturally-occurring siRNAs are generated from longer dsRNA molecules (e.g., >25 nucleotides in length) by a cell's RNAi machinery (e.g., Dicer or a homolog thereof).

(1156) The term “shRNA”, as used herein, refers to an RNA agent having a stem-loop structure, comprising a first and second region of complementary sequence, the degree of complementarity and orientation of the regions being sufficient such that base pairing occurs between the regions, the first and second regions being joined by a loop region, the loop resulting from a lack of base pairing between nucleotides (or nucleotide analogs) within the loop region.

(1157) As used herein, the term “subject” refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

(1158) As used herein, the term “SS18-SSX fusion protein-related disorder” refers to a disorder that is caused or affected by the level and/or activity of SS18-SSX fusion protein.

(1159) As used herein, the terms “treat,” “treated,” or “treating” mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

(1160) As used herein, the terms “variant” and “derivative” are used interchangeably and refer to naturally-occurring, synthetic, and semi-synthetic analogues of a compound, peptide, protein, or other substance described herein. A variant or derivative of a compound, peptide, protein, or other substance described herein may retain or improve upon the biological activity of the original material.

(1161) The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) FIG. **1** is a series of graphs illustrating the effect of specific guide RNA (sgRNA) targeting of the BRD9 BAF complex subunit on synovial sarcoma cell growth. The Y-axis indicated the dropout ratio. The X-axis indicates the nucleotide position of the BRD9 gene. The grey box indicates the range of the negative control sgRNAs in the screen. The SYO1 cell line carries SS18-SSX2 fusion protein. The

breakpoint joining the N-terminal region of SS18 to the C-terminal region of SSX2 are indicated by the black lines in their respective panel. The linear protein sequence is show with BRD9 PFAM domains annotated from the PFAM database.
(2) FIG. **2** is an image illustrating dose dependent depletion of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader.
(3) FIG. **3** is an image illustrating sustained suppression of BRD9 levels in a synovial sarcoma cell line (SYO1) in the presence of a BRD9 degrader over 72 hours.
(4) FIG. **4** is an image illustrating sustained suppression of BRD9 levels in two cell lines (293T and SYO1) in the presence of a BRD9 degrader over 5 days.
(5) FIG. **5** is an image illustrating sustained suppression of BRD9 levels in synovial sarcoma cell lines (SYO1 and Yamato) in the presence of a BRD9 degrader over 7 days compared to the levels in cells treated with CRISPR reagents.
(6) FIG. **6** is an image illustrating the effect on cell growth of six cell lines (SYO1, Yamato, A549, HS-SY-II, ASKA, and 293T) in the presence of a BRD9 degrader and a BRD9 inhibitor.
(7) FIG. **7** is an image illustrating the effect on cell growth of two cell lines (SYO1 and G401) in the presence of a BRD9 degrader.
(8) FIG. **8** is an image illustrating the effect on cell growth of three synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) in the presence of a BRD9 degrader, BRD9 binder and E3 ligase binder.
(9) FIG. **9** is an image illustrating the effect on cell growth of three non-synovial sarcoma cell lines (RD, HCT116, and Calu6) in the presence of a BRD9 degrader, BRD9 binder and E3 ligase binder.
(10) FIG. **10** is a graph illustrating the percentage of SYO1 in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, or Compound 1 at 1 μM for 8 or 13 days.
(11) FIG. **11** is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μM, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.
(12) FIG. **12** is a series of contour plots illustrating the percentage of SYO1 cells in various cell cycle phases following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μM, or lenalidomide at 200 nM for 13 days. Numerical values corresponding to each contour plot are found in the table below.
(13) FIG. **13** is a series of contour plots illustrating the percentage of early- and late-apoptotic SYO1 cells following treatment with DMSO, Compound 1 at 200 nM, Compound 1 at 1 μM, or lenalidomide at 200 nM for 8 days. Numerical values corresponding to each contour plot are found in the table below.
(14) FIG. **14** is a graph illustrating the proteins present in BAF complexes including the SS18-SSX fusion protein.
DETAILED DESCRIPTION
(15) The present disclosure features compositions and methods useful for the treatment of BAF-related disorders (e.g., cancer and infection). The disclosure further features compositions and methods useful for inhibition of the level and/or activity of BRD9, e.g., for the treatment of disorders such as cancer (e.g., sarcoma) and infection (e.g., viral infection), e.g., in a subject in need thereof.
(16) Compounds
(17) Compounds described herein reduce the level of an activity related to BRD9, or a related downstream effect, or reduce the level of BRD9 in a cell or subject. Exemplary compounds described herein have the structure according to Formula I or Formula II.
(18) Formula I is:
(19) ##STR00794##
(20) where
(21) R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl;
(22) Z.sup.1 is CR.sup.2 or N;
(23) R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-

C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(24) X.sup.1 is N or CH, and X.sup.2 is C—R.sup.7; or X.sup.1 is C—R.sup.7, and X.sup.2 is N or CH;
(25) R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;
(26) X.sup.3 is N or CH;
(27) X.sup.4 is N or CH;
(28) G is optionally substituted C.sub.3-C.sub.10 carbocyclyl, C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl, or a pharmaceutically acceptable salt thereof.
(29) Formula II is:
A-L-B Formula II,
(30) where
(31) L is a linker;
(32) B is a degradation moiety; and
(33) A has the structure of Formula III:
(34) ##STR00795##
(35) where
(36) R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl;
(37) Z.sup.1 is CR.sup.2 or N;
(38) R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(39) X.sup.1 is N or CH, and X.sup.2 is C—R.sup.7″; or X.sup.1 is C—R.sup.7″, and X.sup.2 is N or CH;
(40) R.sup.7″ is
(41) ##STR00796##
optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms;
(42) R.sup.7′ is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocycylyl;
(43) X.sup.3 is N or CH;
(44) X.sup.4 is N or CH;
(45) G″ is
(46) ##STR00797##
optionally substituted C.sub.3-C.sub.10 carbocyclyl, C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
(47) G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene, C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; and
(48) A.sup.1 is a bond between A and the linker,
(49) where G″ is
(50) ##STR00798##
or a pharmaceutically acceptable salt thereof.
(51) In some embodiments, the compound has the structure of any one of compounds B1-B6 in Table 1,

or a pharmaceutically acceptable salt thereof

(52) In some embodiments, the compound has the structure of any one of compounds D1-D31 in Table 2A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D32-D184 in Table 2B, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound has the structure of any one of compounds D185-D316 in Table 2C, or a pharmaceutically acceptable salt thereof.

(53) Other embodiments, as well as exemplary methods for the synthesis of production of these compounds, are described herein.

(54) Pharmaceutical Uses

(55) The compounds described herein are useful in the methods of the invention and, while not bound by theory, are believed to exert their desirable effects through their ability to modulate the level, status, and/or activity of a BAF complex, e.g., by inhibiting the activity or level of the BRD9 protein in a cell within the BAF complex in a mammal.

(56) An aspect of the present invention relates to methods of treating disorders related to BRD9 such as cancer in a subject in need thereof. In some embodiments, the compound is administered in an amount and for a time effective to result in one of (or more, e.g., two or more, three or more, four or more of): (a) reduced tumor size, (b) reduced rate of tumor growth, (c) increased tumor cell death (d) reduced tumor progression, (e) reduced number of metastases, (f) reduced rate of metastasis, (g) decreased tumor recurrence (h) increased survival of subject, and (i) increased progression free survival of a subject.

(57) Treating cancer can result in a reduction in size or volume of a tumor. For example, after treatment, tumor size is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to its size prior to treatment. Size of a tumor may be measured by any reproducible means of measurement. For example, the size of a tumor may be measured as a diameter of the tumor.

(58) Treating cancer may further result in a decrease in number of tumors. For example, after treatment, tumor number is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to number prior to treatment. Number of tumors may be measured by any reproducible means of measurement, e.g., the number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification (e.g., 2×, 3×, 4×, 5×, 10×, or 50×).

(59) Treating cancer can result in a decrease in number of metastatic nodules in other tissues or organs distant from the primary tumor site. For example, after treatment, the number of metastatic nodules is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) relative to number prior to treatment. The number of metastatic nodules may be measured by any reproducible means of measurement. For example, the number of metastatic nodules may be measured by counting metastatic nodules visible to the naked eye or at a specified magnification (e.g., 2×, 10×, or 50×).

(60) Treating cancer can result in an increase in average survival time of a population of subjects treated according to the present invention in comparison to a population of untreated subjects. For example, the average survival time is increased by more than 30 days (more than 60 days, 90 days, or 120 days). An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating fora population the average length of survival following initiation of treatment with the compound described herein. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

(61) Treating cancer can also result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. For example, the mortality rate is decreased by more than 2% (e.g., more than 5%, 10%, or 25%). A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with a pharmaceutically acceptable salt of a compound described herein. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with a pharmaceutically acceptable salt of a compound described herein.

(62) Combination Therapies

(63) A method of the invention can be used alone or in combination with an additional therapeutic agent, e.g., other agents that treat cancer or symptoms associated therewith, or in combination with other types of therapies to treat cancer. In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65:S3-S6 (2005)). In this case, dosages of the compounds when combined should provide a therapeutic effect.

(64) In some embodiments, the second therapeutic agent is a chemotherapeutic agent (e.g., a cytotoxic agent or other chemical compound useful in the treatment of cancer). These include alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irenotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammaII and calicheamicin omegaII (see, e.g., *Agnew, Chem. Intl. Ed Engl.* 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin, including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2′,2″-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine;

arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, NJ), ABRAXANE®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, IL), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with the first therapeutic agent described herein. Suitable dosing regimens of combination chemotherapies are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18:233a (1999), and Douillard et al., *Lancet* 355(9209):1041-1047 (2000).

(65) In some embodiments, the second therapeutic agent is a therapeutic agent which is a biologic such a cytokine (e.g., interferon or an interleukin (e.g., IL-2)) used in cancer treatment. In some embodiments the biologic is an anti-angiogenic agent, such as an anti-VEGF agent, e.g., bevacizumab (AVASTIN®). In some embodiments the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response, or antagonizes an antigen important for cancer. Such agents include RITUXAN® (rituximab); ZENAPAX® (daclizumab); SIMULECT® (basiliximab); SYNAGIS® (palivizumab); REMICADE® (infliximab); HERCEPTIN® (trastuzumab); MYLOTARG® (gemtuzumab ozogamicin); CAMPATH® (alemtuzumab); ZEVALIN® (ibritumomab tiuxetan); HUMIRA® (adalimumab); XOLAIR® (omalizumab); BEXXAR® (tositumomab-I-131); RAPTIVA® (efalizumab); ERBITUX® (cetuximab); AVASTIN® (bevacizumab); TYSABRI® (natalizumab); ACTEMRA® (tocilizumab); VECTIBIX® (panitumumab); LUCENTIS® (ranibizumab); SOLIRIS® (eculizumab); CIMZIA® (certolizumab pegol); SIMPONI® (golimumab); ILARIS® (canakinumab); STELARA® (ustekinumab); ARZERRA® (ofatumumab); PROLIA® (denosumab); NUMAX® (motavizumab); ABTHRAX® (raxibacumab); BENLYSTA® (belimumab); YERVOY® (ipilimumab); ADCETRIS® (brentuximab vedotin); PERJETA® (pertuzumab); KADCYLA® (ado-trastuzumab emtansine); and GAZYVA® (obinutuzumab). Also included are antibody-drug conjugates.

(66) The second agent may be a therapeutic agent which is a non-drug treatment. For example, the second therapeutic agent is radiation therapy, cryotherapy, hyperthermia, and/or surgical excision of tumor tissue.

(67) The second agent may be a checkpoint inhibitor. In one embodiment, the inhibitor of checkpoint is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the inhibitor of checkpoint is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA4 antibody or fusion a protein such as ipilimumab/YERVOY® or tremelimumab). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1 (e.g., nivolumab/OPDIVO®; pembrolizumab/KEYTRUDA®; pidilizumab/CT-011). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PDL1 (e.g., MPDL3280A/R.sup.G7446; MEDI4736; MSB0010718C; BMS 936559). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PDL2 (e.g., a PDL2/Ig fusion protein such as AMP 224). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3 (e.g., MGA271), B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof.

(68) In some embodiments, the anti-cancer therapy is a T cell adoptive transfer (ACT) therapy. In some embodiments, the T cell is an activated T cell. The T cell may be modified to express a chimeric antigen receptor (CAR). CAR modified T (CAR-T) cells can be generated by any method known in the art. For example, the CAR-T cells can be generated by introducing a suitable expression vector encoding the CAR to a T cell. Prior to expansion and genetic modification of the T cells, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available in the art, may be used. In some embodiments, the T cell is an autologous T cell. Whether prior to or after genetic modification of the T cells to express a desirable protein (e.g., a CAR), the T cells can be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.
(69) In any of the combination embodiments described herein, the first and second therapeutic agents are administered simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to, 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to hours 16, up to 17 hours, up 18 hours, up to 19 hours up to 20 hours, up to 21 hours, up to 22 hours, up to 23 hours up to 24 hours or up to 1-7, 1-14, 1-21 or 1-30 days before or after the second therapeutic agent.
(70) Pharmaceutical Compositions
(71) The pharmaceutical compositions described herein are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration in vivo.
(72) The compounds described herein may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the methods described herein. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, intratumoral, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.
(73) A compound described herein may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound described herein may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers. A compound described herein may also be administered parenterally. Solutions of a compound described herein can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO, and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2012, 22nd ed.) and in The United States Pharmacopeia: The National Formulary (USP 41 NF36), published in 2018. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe. Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically

include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form includes an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter. A compound described herein may be administered intratumorally, for example, as an intratumoral injection. Intratumoral injection is injection directly into the tumor vasculature and is specifically contemplated for discrete, solid, accessible tumors. Local, regional, or systemic administration also may be appropriate. A compound described herein may advantageously be contacted by administering an injection or multiple injections to the tumor, spaced for example, at approximately, 1 cm intervals. In the case of surgical intervention, the present invention may be used preoperatively, such as to render an inoperable tumor subject to resection. Continuous administration also may be applied where appropriate, for example, by implanting a catheter into a tumor or into tumor vasculature.

(74) The compounds described herein may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

(75) Dosages

(76) The dosage of the compounds described herein, and/or compositions including a compound described herein, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds described herein may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds described herein are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg (e.g., 50-800 mg). In some embodiments, 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of the compound is administered.

(77) Alternatively, the dosage amount can be calculated using the body weight of the patient. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a patient may range from 0.1-100 mg/kg (e.g., 0.1-50 mg/kg (e.g., 0.25-25 mg/kg)). In exemplary, non-limiting embodiments, the dose may range from 0.5-5.0 mg/kg (e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 mg/kg) or from 5.0-20 mg/kg (e.g., 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg/kg).

(78) Kits

(79) The invention also features kits including (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, and (b) a package insert with instructions to perform any of the methods described herein. In some embodiments, the kit includes (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, (b) an additional therapeutic agent (e.g., an anti-cancer agent), and (c) a package insert with instructions to perform any of the methods described herein.

EXAMPLES

Example 1—High Density Tiling sgRNA Screen Against Human BAF Complex Subunits in Synovial

Sarcoma Cell Line SYO1

(80) The following example shows that BRD9 sgRNA inhibits cell growth in synovial sarcoma cells.

(81) Procedure: To perform high density sgRNA tiling screen, an sgRNA library against BAF complex subunits was custom synthesized at Cellecta (Mountain View, CA). Sequences of DNA encoding the BRD9-targeting sgRNAs used in this screen are listed in Table 3. Negative and positive control sgRNA were included in the library. Negative controls consisted of 200 sgRNAs that do not target human genome. The positive controls are sgRNAs targeting essential genes (CDC16, GTF2B, HSPA5, HSPA9, PAFAH1B1, PCNA, POLR2L, RPL9, and SF3A3). DNA sequences encoding all positive and negative control sgRNAs are listed in Table 4. Procedures for virus production, cell infection, and performing the sgRNA screen were previously described (Tsherniak et al, *Cell* 170:564-576 (2017); Munoz et al, *Cancer Discovery* 6:900-913 (2016)). For each sgRNA, 50 counts were added to the sequencing counts and for each time point the resulting counts were normalized to the total number of counts. The log 2 of the ratio between the counts (defined as dropout ratio) at day 24 and day 1 post-infection was calculated. For negative control sgRNAs, the 2.5 and 97.5 percentile of the log 2 dropout ratio of all non-targeting sgRNAs was calculated and considered as background (grey box in the graph). Protein domains were obtained from PFAM regions defined for the UNIPROT identifier: Q9H8M2.

(82) Results: As shown in FIG. **1**, targeted inhibition of the GBAF complex component BRD9 by sgRNA resulted in growth inhibition of the SYO1 synovial sarcoma cell line. sgRNAs against other components of the BAF complexes resulted in increased proliferation of cells, inhibition of cell growth, or had no effect on SYO1 cells. These data show that targeting various subunits of the GBAF complex represents a therapeutic strategy for the treatment of synovial sarcoma.

(83) TABLE-US-00005 TABLE 3 BRD9 sgRNA Library SEQ ID NO Nucleic Acid Sequence 203 CAAGAAGCACAAGAAGCACA 204 CTTGTGCTTCTTGCCCATGG 205 CTTCTTGTGCTTCTTGCCCA 206 ACAAGAAGCACAAGGCCGAG 207 CTCGTAGGACGAGCGCCACT 208 CGAGTGGCGCTCGTCCTACG 209 GAGTGGCGCTCGTCCTACGA 210 AGGCTTCTCCAGGGGCTTGT 211 AGATTATGCCGACAAGCCCC 212 ACCTTCAGGACTAGCTTTAG 213 AGCTTTAGAGGCTTCTCCAG 214 CTAGCTTTAGAGGCTTCTCC 215 TAGCTTTAGAGGCTTCTCCA 216 CTAAAGCTAGTCCTGAAGGT 217 GCCTCTAAAGCTAGTCCTGA 218 CTTCACTTCCTCCGACCTTC 219 AAGCTAGTCCTGAAGGTCGG 220 AGTGAAGTGACTGAACTCTC 221 GTGACTGAACTCTCAGGATC 222 ATAGTAACTGGAGTCGTGGC 223 CATCATAGTAACTGGAGTCG 224 TGACCTGTCATCATAGTAAC 225 ACTCCAGTTACTATGATGAC 226 CTTTGTGCCTCTCTCGCTCA 227 GGTCAGACCATGAGCGAGAG 228 GAAGAAGAAGAAGTCCGAGA 229 GTCCAGATGCTTCTCCTTCT 230 GTCCGAGAAGGAGAAGCATC 231 GGAGAAGCATCTGGACGATG 232 TGAGGAAAGAAGGAAGCGAA 233 ATCTGGACGATGAGGAAAGA 234 AGAAGAAGCGGAAGCGAGAG 235 GAAGAAGCGGAAGCGAGAGA 236 CCGCCCAGGAAGAGAAGAAG 237 AGAGAGGGAGCACTGTGACA 238 AGGGAGCACTGTGACACGGA 239 GAGGGAGCACTGTGACACGG 240 GCACTGTGACACGGAGGGAG 241 GAGGCTGACGACTTTGATCC 242 AGGCTGACGACTTTGATCCT 243 TCCACCTCCACCTTCTTCCC 244 CGACTTTGATCCTGGGAAGA 245 CTTTGATCCTGGGAAGAAGG 246 TGATCCTGGGAAGAAGGTGG 247 TCCTGGGAAGAAGGTGGAGG 248 CGGACTGGCCGATCTGGGGG 249 ACGCTCGGACTGGCCGATCT 250 AGGTGGAGCCGCCCCCAGAT 251 CGCTCGGACTGGCCGATCTG 252 GCTCGGACTGGCCGATCTGG 253 CACGCTCGGACTGGCCGATC 254 TGTGTCCGGCACGCTCGGAC 255 CTGGCTGTGTCCGGCACGCT 256 ATCGGCCAGTCCGAGCGTGC 257 CACCCTTGCCTGGCTGTGTC 258 CGAGCGTGCCGGACACAGCC 259 TGTTCCAGGAGTTGCTGAAT 260 CACACCTATTCAGCAACTCC 261 GCTGGCGGAGGAAGTGTTCC 262 TTTACCTCTGAAGCTGGCGG 263

CCCCGGTTTACCTCTGAAGC 264 ACTTCCTCCGCCAGCTTCAG 265
CAGGAAAAGCAAAAAATCCA 266 GCTTTCAGAAAAGATCCCCA 267
AGGAAAAGCAAAAAATCCAT 268 GGAAAAGCAAAAAATCCATG 269
GGAGCAATTGCATCCGTGAC 270 GTCACGGATGCAATTGCTCC 271
TTTATTATCATTGAATATCC 272 AATGATAATAAAACATCCCA 273
ATAAAACATCCCATGGATTT 274 TTCATGGTGCCAAAATCCAT 275
TTTCATGGTGCCAAAATCCA 276 TAATGAATACAAGTCAGTTA 277
CAAGTCAGTTACGGAATTTA 278 ATAATGCAATGACATACAAT 279
AACTTGTAGTACACGGTATC 280 CTTCGCCAACTTGTAGTACA 281
AGATACCGTGTACTACAAGT 282 GCGAAGAAGATCCTTCACGC 283
TCATCTTAAAGCCTGCGTGA 284 TTCTCAGCAGGCAGCTCTTT 285
CAATGAAGATACAGCTGTTG 286 ACTGGTACAACTTCAGGGAC 287
CTTGTACTGGTACAACTTCA 288 ACTTGTACTGGTACAACTTC 289
TTGGCAGTTTCTACTTGTAC 290 TACCTGATAACTTCTCTACT 291
AGCCGAGTAGAGAAGTTATC 292 AGCTGCATGTTTGAGCCTGA 293
GCTGCATGTTTGAGCCTGAA 294 AAGCTGCAGGCATTCCCTTC 295
GGTACTGTCCGTCAAGCTGC 296 AGGGAATGCCTGCAGCTTGA 297
CTTGACGGACAGTACCGCAG 298 CGCCAGCACGTGCTCCTCTG 299
TACCGCAGAGGAGCACGTGC 300 AGAGGAGCACGTGCTGGCGC 301
GGAGCACGTGCTGGCGCTGG 302 AGCACGCAGCTGACGAAGCT 303
GCACGCAGCTGACGAAGCTC 304 CAGCTGACGAAGCTCGGGAC 305
AAGCTCGGGACAGGATCAAC 306 CCTTGCCGCCTGGGAGGAAC 307
AGGATCAACCGGTTCCTCCC 308 ATCAACCGGTTCCTCCCAGG 309
GCACTACCTTGCCGCCTGGG 310 AGAGCACTACCTTGCCGCCT 311
CCGGTTCCTCCCAGGCGGCA 312 TCCTCTTCAGATAGCCCATC 313
ATGGGCTATCTGAAGAGGAA 314 GGGCTATCTGAAGAGGAACG 315
TGGGCTATCTGAAGAGGAAC 316 TATCTGAAGAGGAACGGGGA 317
ATCTGAAGAGGAACGGGGAC 318 TGTTGACCACGCTGTAGAGC 319
GCTCTACAGCGTGGTCAACA 320 CGGGAGCCTGCTCTACAGCG 321
CGTGGTCAACACGGCCGAGC 322 CCCACCATCAGCGTCCGGCT 323
ACGGCCGAGCCGGACGCTGA 324 GGGCACCCACCATCAGCGTC 325
GCCGAGCCGGACGCTGATGG 326 CCATGTCCGTGTTGCAGAGG 327
CCGAGCCGGACGCTGATGGT 328 CGAGCTCAAGTCCACCGGGT 329
GCGAGCTCAAGTCCACCGGG 330 AGAGCGAGCTCAAGTCCACC 331
GAGAGCGAGCTCAAGTCCAC 332 GAAGCCTGGGAGTAGCTTAC 333
CTCTCCAGTAAGCTACTCCC 334 AGCCCAGCGTGGTGAAGCCT 335
AAGCCCAGCGTGGTGAAGCC 336 ACTCCCAGGCTTCACCACGC 337
CTCCCAGGCTTCACCACGCT 338 CTCGTCTTTGAAGCCCAGCG 339
CACTGGAGAGAAAGGTGACT 340 GCACTGGAGAGAAAGGTGAC 341
AGTAGTGGCACTGGAGAGAA 342 CGAAAGCGCAGTAGTGGCAC 343
CTGCATCGAAAGCGCAGTAG 344 ATGCAGAATAATTCAGTATT 345
AGTATTTGGCGACTTGAAGT 346 CGACTTGAAGTCGGACGAGA 347
GAGCTGCTCTACTCAGCCTA 348 CACGCCTGTCTCATCTCCGT 349
TCAGCCTACGGAGATGAGAC 350 CAGGCGTGCAGTGTGCGCTG 351
CCGCGGCCCCTCTAGCCTGC 352 CATCCTTCACAAACTCCTGC 353
TAGCCTGCAGGAGTTTGTGA 354 CAGGAGTTTGTGAAGGATGC 355
AGGAGTTTGTGAAGGATGCT 356 TGGGAGCTACAGCAAGAAAG 357
GAGCTACAGCAAGAAAGTGG 358 GAAAGTGGTGGACGACCTCC 359
CGCCTGTGATCTGGTCCAGG 360 CTCCGCCTGTGATCTGGTCC 361
GACCTCCTGGACCAGATCAC 362 CTCCTGGACCAGATCACAGG 363
GCTGGAAGAGCGTCCTAGAG 364 TGCAGCCCACCTGCTTCAGC 365
GACGCTCTTCCAGCTGAAGC 366 CTCTTCCAGCTGAAGCAGGT 367

GCTCTTCCAGCTGAAGCAGG 368 CCTCCAGATGAAGCCAAGGT 369
GCTTCATCTGGAGGCTTCAT 370 GGCTTCATCTGGAGGCTTCA 371
CTTACCTTGGCTTCATCTGG 372 AAACTTACCTTGGCTTCATC 373
GAAGCCTCCAGATGAAGCCA 374 TCCTAGGGTGTCCCCAACCT 375
CCTAGGGTGTCCCCAACCTG 376 GTGTCTGTCTCCACAGGTTG 377
TGTGTCTGTCTCCACAGGTT 378 CCACAGGTTGGGGACACCCT 379
AGAGCTGCTGCTGTCTCCTA 380 CAGAGCTGCTGCTGTCTCCT 381
AGACAGCAGCAGCTCTGTTC 382 ATCCACAGAAACGTCGGGAT 383
GAGATATCCACAGAAACGTC 384 GGAGATATCCACAGAAACGT 385
GTCCTATCCCGACGTTTCTG 386 TCTCCATGCTCAGCTCTCTG 387
CTCACCCAGAGAGCTGAGCA 388 ATCTCCATGCTCAGCTCTCT 389
TATCTCCATGCTCAGCTCTC 390 ATGTCCTGTTTACACAGGGA 391
TTACACAGGGAAGGTGAAGA 392 AGTTCAAATGGCTGTCGTCA 393
TGACGACAGCCATTTGAACT 394 AAGTTCAAATGGCTGTCGTC 395
TCGTCTCATCCAAGTTCAAA 396 TGAGACGACGAAGCTCCTGC 397
GTGCTTCGTGCAGGTCCTGC 398 GCAGGACCTGCACGAAGCAC 399
GCTCCGCCTGTGCTTCGTGC 400 GGACCTGCACGAAGCACAGG 401
CACGAAGCACAGGCGGAGCG 402 AGGCGGAGCGCGGCGGCTCT 403
AGGGAGCTGAGGTTGGACGA 404 GTTGGACAGGGAGCTGAGGT 405
AGGCGTTGGACAGGGAGCTG 406 CCCTCTCGGAGGCGTTGGAC 407
CCTCTCGGAGGCGTTGGACA 408 CTGGTCCCTCTCGGAGGCGT 409
CCCTGTCCAACGCCTCCGAG 410 CCTGTCCAACGCCTCCGAGA 411
GTGGTGCTGGTCCCTCTCGG 412 CAGGTGGTGCTGGTCCCTCT 413
GCATCTCACCCAGGTGGTGC 414 CGAGAGGGACCAGCACCACC 415
GAGAGGGACCAGCACCACCT 416 GTGGGGGCATCTCACCCAGG 417
CCCCGACACTCAGGCGAGAA 418 TCCCCGACACTCAGGCGAGA 419
AGCCCTTCTCGCCTGAGTGT 420 CTGGCTGCTCCCCGACACTC 421
CCCTTCTCGCCTGAGTGTCG 422 GCCCTTCTCGCCTGAGTGTC 423
TAGGGGTCGTGGGTGACGTC 424 AAGAAACTCATAGGGGTCGT 425
GAAGAAACTCATAGGGGTCG 426 GAGACTGAAGAAACTCATAG 427
GGAGACTGAAGAAACTCATA 428 TGGAGACTGAAGAAACTCAT 429
TCTTCAGTCTCCAGAGCCTG 430 TTGGCAGAGGCCGCAGGCTC 431
TAGGTCTTGGCAGAGGCCGC 432 CTAGAGTTAGGTCTTGGCAG 433
GGTGGTCTAGAGTTAGGTCT

(84) TABLE-US-00006 TABLE 4 Control sgRNA Library SEQ ID NO. gRNA Label Gene Nucleic Acid Sequence 434 1|sg_Non_Targeting_ Non_Targeting_Human GTAGCGAACGTGTCCGGCGT Human_0001|Non_Targeting_ Human 435 1|sg_Non_Targeting_ Non_Targeting_Human GACCGGAACGATCTCGCGTA Human_0002|Non_Targeting_ Human 436 1|sg_Non_Targeting_ Non_Targeting_Human GGCAGTCGTTCGGTTGATAT Human_0003|Non_Targeting_ Human 437 1|sg_Non_Targeting_ Non_Targeting_Human GCTTGAGCACATACGCGAAT Human_0004|Non_Targeting_ Human 438 1|sg_Non_Targeting_ Non_Targeting_Human GTGGTAGAATAACGTATTAC Human_0005|Non_Targeting_ Human 439 1|sg_Non_Targeting_ Non_Targeting_Human GTCATACATGGATAAGGCTA Human_0006|Non_Targeting_ Human 440 1|sg_Non_Targeting_ Non_Targeting_Human GATACACGAAGCATCACTAG Human_0007|Non_Targeting_ Human 441 1|sg_Non_Targeting_ Non_Targeting_Human GAACGTTGGCACTACTTCAC Human_0008|Non_Targeting_ Human 442 1|sg_Non_Targeting_ Non_Targeting_Human GATCCATGTAATGCGTTCGA Human_0009|Non_Targeting_ Human 443 1|sg_Non_Targeting_ Non_Targeting_Human GTCGTGAAGTGCATTCGATC Human_0010|Non_Targeting_ Human 444 1|sg_Non_Targeting_ Non_Targeting_Human GTTCGACTCGCGTGACCGTA Human_0011|Non_Targeting_ Human 445 1|sg_Non_Targeting_ Non_Targeting_Human GAATCTACCGCAGCGGTTCG Human_0012|Non_Targeting_ Human 446 1|sg_Non_Targeting_ Non_Targeting_Human

GAAGTGACGTCGATTCGATA Human_0013|Non_Targeting_ Human 447 1|sg_Non_Targeting_ Non_Targeting_Human GCGGTGTATGACAACCGCCG Human_0014|Non_Targeting_ Human 448 1|sg_Non_Targeting_ Non_Targeting_Human GTACCGCGCCTGAAGTTCGC Human_0015|Non_Targeting_ Human 449 1|sg_Non_Targeting_ Non_Targeting_Human GCAGCTCGTGTGTCGTACTC Human_0016|Non_Targeting_ Human 450 1|sg_Non_Targeting_ Non_Targeting_Human GCGCCTTAAGAGTACTCATC Human_0017|Non_Targeting_ Human 451 1|sg_Non_Targeting_ Non_Targeting_Human GAGTGTCGTCGTTGCTCCTA Human_0018|Non_Targeting_ Human 452 1|sg_Non_Targeting_ Non_Targeting_Human GCAGCTCGACCTCAAGCCGT Human_0019|Non_Targeting_ Human 453 1|sg_Non_Targeting_ Non_Targeting_Human GTATCCTGACCTACGCGCTG Human_0020|Non_Targeting_ Human 454 1|sg_Non_Targeting_ Non_Targeting_Human GTGTATCTCAGCACGCTAAC Human_0021I|Non_Targeting_ Human 455 1|sg_Non_Targeting_ Non_Targeting_Human GTCGTCATACAACGGCAACG Human_0022|Non_Targeting_ Human 456 1|sg_Non_Targeting_ Non_Targeting_Human GTCGTGCGCTTCCGGCGGTA Human_0023-51 Non_Targeting_ Human 457 1|sg_Non_Targeting_ Non_Targeting_Human GCGGTCCTCAGTAAGCGCGT Human_0024|Non_Targeting_ Human 458 1|sg_Non_Targeting_ Non_Targeting_Human GCTCTGCTGCGGAAGGATTC Human_0025|Non_Targeting_ Human 459 1|sg_Non_Targeting_ Non_Targeting_Human GCATGGAGGAGCGTCGCAGA Human_0026|Non_Targeting_ Human 460 1|sg_Non_Targeting_ Non_Targeting_Human GTAGCGCGCGTAGGAGTGGC Human_0027|Non_Targeting_ Human 461 1|sg_Non_Targeting_ Non_Targeting_Human GATCACCTGCATTCGTACAC Human_0028|Non_Targeting_ Human 462 1|sg_Non_Targeting_ Non_Targeting_Human GCACACCTAGATATCGAATG Human_0029|Non_Targeting_ Human 463 1|sg_Non_Targeting_ Non_Targeting_Human GTTGATCAACGCGCTTCGCG Human_0030|Non_Targeting_ Human 464 1|sg_Non_Targeting_ Non_Targeting_Human GCGTCTCACTCACTCCATCG Human_0031|Non_Targeting_ Human 465 1|sg_Non_Targeting_ Non_Targeting_Human GCCGACCAACGTCAGCGGTA Human_0032|Non_Targeting_ Human 466 1|sg_Non_Targeting_ Non_Targeting_Human GGATACGGTGCGTCAATCTA Human_0033|Non_Targeting_ Human 467 1|sg_Non_Targeting_ Non_Targeting_Human GAATCCAGTGGCGGCGACAA Human_0034|Non_Targeting_ Human 468 1|sg_Non_Targeting_ Non_Targeting_Human GCACTGTCAGTGCAACGATA Human_0035|Non_Targeting_ Human 469 1|sg_Non_Targeting_ Non_Targeting_Human GCGATCCTCAAGTATGCTCA Human_0036|Non_Targeting_ Human 470 1|sg_Non_Targeting_ Non_Targeting_Human GCTAATATCGACACGGCCGC Human_0037|Non_Targeting_ Human 471 1|sg_Non_Targeting_ Non_Targeting_Human GGAGATGCATCGAAGTCGAT Human_0038|Non_Targeting_ Human 472 1|sg_Non_Targeting_ Non_Targeting_Human GGATGCACTCCATCTCGTCT Human_0039|Non_Targeting_ Human 473 1|sg_Non_Targeting_ Non_Targeting_Human GTGCCGAGTAATAACGCGAG Human_0040|Non_Targeting_ Human 474 1|sg_Non_Targeting_ Non_Targeting_Human GAGATTCCGATGTAACGTAC Human_0041|Non_Targeting_ Human 475 1|sg_Non_Targeting_ Non_Targeting_Human GTCGTCACGAGCAGGATTGC Human_0042|Non_Targeting_ Human 476 1|sg_Non_Targeting_ Non_Targeting_Human GCGTTAGTCACTTAGCTCGA Human_0043|Non_Targeting_ Human 477 1|sg_Non_Targeting_ Non_Targeting_Human GTTCACACGGTGTCGGATAG Human_0044|Non_Targeting_ Human 478 1|sg_Non_Targeting_ Non_Targeting_Human GGATAGGTGACCTTAGTACG Human_0045|Non_Targeting_ Human 479 1|sg_Non_Targeting_ Non_Targeting_Human GTATGAGTCAAGCTAATGCG Human_0046|Non_Targeting_ Human 480 1|sg_Non_Targeting_ Non_Targeting_Human GCAACTATTGGAATACGTGA Human_0047|Non_Targeting_ Human 481 1|sg_Non_Targeting_ Non_Targeting_Human GTTACCTTCGCTCGTCTATA Human_0048|Non_Targeting_ Human 482 1|sg_Non_Targeting_ Non_Targeting_Human GTACCGAGCACCACAGGCCG Human_0049|Non_Targeting_ Human 483 1|sg_Non_Targeting_ Non_Targeting_Human GTCAGCCATCGGATAGAGAT Human_0050|Non_Targeting_ Human 484 1|sg_Non_Targeting_ Non_Targeting_Human GTACGGCACTCCTAGCCGCT Human_0051|Non_Targeting_ Human 485 1|sg_Non_Targeting_ Non_Targeting_Human

GGTCCTGTCGTATGCTTGCA Human_0052|Non_Targeting_ Human 486 1|sg_Non_Targeting_ Non_Targeting_Human GCCGCAATATATGCGGTAAG Human_0053|Non_Targeting_ Human 487 1|sg_Non_Targeting_ Non_Targeting_Human GCGCACGTATAATCCTGCGT Human_0054|Non_Targeting_ Human 488 1|sg_Non_Targeting_ Non_Targeting_Human GTGCACAACACGATCCACGA Human_0055|Non_Targeting_ Human 489 1|sg_Non_Targeting_ Non_Targeting_Human GCACAATGTTGACGTAAGTG Human_0056|Non_Targeting_ Human 490 1|sg_Non_Targeting_ Non_Targeting_Human GTAAGATGCTGCTCACCGTG Human_0057|Non_Targeting_ Human 491 1|sg_Non_Targeting_ Non_Targeting_Human GTCGGTGATCCAACGTATCG Human_0058|Non_Targeting_ Human 492 1|sg_Non_Targeting_ Non_Targeting_Human GAGCTAGTAGGACGCAAGAC Human_0059|Non_Targeting_ Human 493 1|sg_Non_Targeting_ Non_Targeting_Human GTACGTGGAAGCTTGTGGCC Human_0060|Non_Targeting_ Human 494 1|sg_Non_Targeting_ Non_Targeting_Human GAGAACTGCCAGTTCTCGAT Human_0061|Non_Targeting_ Human 495 1|sg_Non_Targeting_ Non_Targeting_Human GCCATTCGGCGCGGCACTTC Human_0062|Non_Targeting_ Human 496 1|sg_Non_Targeting_ Non_Targeting_Human GCACACGACCAATCCGCTTC Human_0063|Non_Targeting_ Human 497 1|sg_Non_Targeting_ Non_Targeting_Human GAGGTGATCGATTAAGTACA Human_0064|Non_Targeting_ Human 498 1|sg_Non_Targeting_ Non_Targeting_Human GTCACTCGCAGACGCCTAAC Human_0065|Non_Targeting_ Human 499 1|sg_Non_Targeting_ Non_Targeting_Human GCGCTACGGAATCATACGTT Human_0066|Non_Targeting_ Human 500 1|sg_Non_Targeting_ Non_Targeting_Human GGTAGGACCTCACGGCGCGC Human_0067|Non_Targeting_ Human 501 1|sg_Non_Targeting_ Non_Targeting_Human GAACTGCATCTTGTTGTAGT Human_0068|Non_Targeting_ Human 502 1|sg_Non_Targeting_ Non_Targeting_Human GATCCTGATCCGGCGGCGCG Human_0069|Non_Targeting_ Human 503 1|sg_Non_Targeting_ Non_Targeting_Human GGTATGCGCGATCCTGAGTT Human_0070|Non_Targeting_ Human 504 1|sg_Non_Targeting_ Non_Targeting_Human GCGGAGCTAGAGAGCGGTCA Human_0071|Non_Targeting_ Human 505 1|sg_Non_Targeting_ Non_Targeting_Human GAATGGCAATTACGGCTGAT Human_0072|Non_Targeting_ Human 506 1|sg_Non_Targeting_ Non_Targeting_Human GTATGGTGAGTAGTCGCTTG Human_0073|Non_Targeting_ Human 507 1|sg_Non_Targeting_ Non_Targeting_Human GTGTAATTGCGTCTAGTCGG Human_0074|Non_Targeting_ Human 508 1|sg_Non_Targeting_ Non_Targeting_Human GGTCCTGGCGAGGAGCCTTG Human_0075|Non_Targeting_ Human 509 1|sg_Non_Targeting_ Non_Targeting_Human GAAGATAAGTCGCTGTCTCG Human_0076|Non_Targeting_ Human 510 1|sg_Non_Targeting_ Non_Targeting_Human GTCGGCGTTCTGTTGTGACT Human_0077|Non_Targeting_ Human 511 1|sg_Non_Targeting_ Non_Targeting_Human GAGGCAAGCCGTTAGGTGTA Human_0078|Non_Targeting_ Human 512 1|sg_Non_Targeting_ Non_Targeting_Human GCGGATCCAGATCTCATTCG Human_0079|Non_Targeting_ Human 513 1|sg_Non_Targeting_ Non_Targeting_Human GGAACATAGGAGCACGTAGT Human_0080|Non_Targeting_ Human 514 1|sg_Non_Targeting_ Non_Targeting_Human GTCATCATTATGGCGTAAGG Human_0081|Non_Targeting_ Human 515 1|sg_Non_Targeting_ Non_Targeting_Human GCGACTAGCGCCATGAGCGG Human_0082|Non_Targeting_ Human 516 1|sg_Non_Targeting_ Non_Targeting_Human GGCGAAGTTCGACATGACAC Human_0083|Non_Targeting_ Human 517 1|sg_Non_Targeting_ Non_Targeting_Human GCTGTCGTGTGGAGGCTATG Human_0084|Non_Targeting_ Human 518 1|sg_Non_Targeting_ Non_Targeting_Human GCGGAGAGCATTGACCTCAT Human_0085|Non_Targeting_ Human 519 1|sg_Non_Targeting_ Non_Targeting_Human GACTAATGGACCAAGTCAGT Human_0086|Non_Targeting_ Human 520 1|sg_Non_Targeting_ Non_Targeting_Human GCGGATTAGAGGTAATGCGG Human_0087|Non_Targeting_ Human 521 1|sg_Non_Targeting_ Non_Targeting_Human GCCGACGGCAATCAGTACGC Human_0088|Non_Targeting_ Human 522 1|sg_Non_Targeting_ Non_Targeting_Human GTAACCTCTCGAGCGATAGA Human_0089|Non_Targeting_ Human 523 1|sg_Non_Targeting_ Non_Targeting_Human GACTTGTATGTGGCTTACGG Human_0090|Non_Targeting_ Human 524 1|sg_Non_Targeting_ Non_Targeting_Human

GTCACTGTGGTCGAACATGT Human_0091|Non_Targeting_ Human 525 1|sg_Non_Targeting_ Non_Targeting_Human GTACTCCAATCCGCGATGAC Human_0092|Non_Targeting_ Human 526 1|sg_Non_Targeting_ Non_Targeting_Human GCGTTGGCACGATGTTACGG Human_0093|Non_Targeting_ Human 527 1|sg_Non_Targeting_ Non_Targeting_Human GAACCAGCCGGCTAGTATGA Human_0094|Non_Targeting_ Human 528 1|sg_Non_Targeting_ Non_Targeting_Human GTATACTAGCTAACCACACG Human_0095|Non_Targeting_ Human 529 1|sg_Non_Targeting_ Non_Targeting_Human GAATCGGAATAGTTGATTCG Human_0096|Non_Targeting_ Human 530 1|sg_Non_Targeting_ Non_Targeting_Human GAGCACTTGCATGAGGCGGT Human_0097|Non_Targeting_ Human 531 1|sg_Non_Targeting_ Non_Targeting_Human GAACGGCGATGAAGCCAGCC Human_0098|Non_Targeting_ Human 532 1|sg_Non_Targeting_ Non_Targeting_Human GCAACCGAGATGAGAGGTTC Human_0099|Non_Targeting_ Human 533 1|sg_Non_Targeting_ Non_Targeting_Human GCAAGATCAATATGCGTGAT Human_0100|Non_Targeting_ Human 534 1|sg_Non_Targeting_ Non_Targeting_Human ACGGAGGCTAAGCGTCGCAA Human_GA_0101|Non_Targeting_ Human 535 1|sg_Non_Targeting_ Non_Targeting_Human CGCTTCCGCGGCCCGTTCAA Human_GA_0102|Non_Targeting_ Human 536 1|sg_Non_Targeting_ Non_Targeting_Human ATCGTTTCCGCTTAACGGCG Human_GA_0103|Non_Targeting_ Human 537 1|sg_Non_Targeting_ Non_Targeting_Human GTAGGCGCGCCGCTCTCTAC Human_GA_0104|Non_Targeting_ Human 538 1|sg_Non_Targeting_ Non_Targeting_Human CCATATCGGGGCGAGACATG Human_GA_0105|Non_Targeting_ Human 539 1|sg_Non_Targeting_ Non_Targeting_Human TACTAACGCCGCTCCTACAG Human_GA_0106|Non_Targeting_ Human 540 1|sg_Non_Targeting_ Non_Targeting_Human TGAGGATCATGTCGAGCGCC Human_GA_0107|Non_Targeting_ Human 541 1|sg_Non_Targeting_ Non_Targeting_Human GGGCCCGCATAGGATATCGC Human_GA_0108|Non_Targeting_ Human 542 1|sg_Non_Targeting_ Non_Targeting_Human TAGACAACCGCGGAGAATGC Human_GA_0109|Non_Targeting_ Human 543 1|sg_Non_Targeting_ Non_Targeting_Human ACGGGCGGCTATCGCTGACT Human_GA_0110|Non_Targeting_ Human 544 1|sg_Non_Targeting_ Non_Targeting_Human CGCGGAAATTTTACCGACGA Human_GA_0111|Non_Targeting_ Human 545 1|sg_Non_Targeting_ Non_Targeting_Human CTTACAATCGTCGGTCCAAT Human_GA_0112|Non_Targeting_ Human 546 1|sg_Non_Targeting_ Non_Targeting_Human GCGTGCGTCCCGGGTTACCC Human_GA_0113|Non_Targeting_ Human 547 1|sg_Non_Targeting_ Non_Targeting_Human CGGAGTAACAAGCGGACGGA Human_GA_0114|Non_Targeting_ Human 548 1|sg_Non_Targeting_ Non_Targeting_Human CGAGTGTTATACGCACCGTT Human_GA_0115|Non_Targeting_ Human 549 1|sg_Non_Targeting_ Non_Targeting_Human CGACTAACCGGAAACTTTTT Human_GA_0116|Non_Targeting_ Human 550 1|sg_Non_Targeting_ Non_Targeting_Human CAACGGGTTCTCCCGGCTAC Human_GA_0117|Non_Targeting_ Human 551 1|sg_Non_Targeting_ Non_Targeting_Human CAGGAGTCGCCGATACGCGT Human_GA_0118|Non_Targeting_ Human 552 1|sg_Non_Targeting_ Non_Targeting_Human TTCACGTCGTCTCGCGACCA Human_GA_0119|Non_Targeting_ Human 553 1|sg_Non_Targeting_ Non_Targeting_Human GTGTCGGATTCCGCCGCTTA Human_GA_0120|Non_Targeting_ Human 554 1|sg_Non_Targeting_ Human_GA_0121|Non_Targeting_ Non_Targeting_Human CACGAACTCACACCGCGCGA Human 555 1|sg_Non_Targeting_ Human_GA_0122|Non_Targeting_ Non_Targeting_Human CGCTAGTACGCTCCTCTATA Human 556 1|sg_Non_Targeting_ Human_GA_0123|Non_Targetng_i Non_Targeting_Human TCGCGCTTGGGTTATACGCT Human 557 1|sg_Non_Targeting_ Human_GA_0124|Non_Targeting_ Non_Targeting_Human CTATCTCGAGTGGTAATGCG Human 558 1|sg_Non_Targeting_ Human_GA_0125|Non_Targeting_ Non_Targeting_Human AATCGACTCGAACTTCGTGT Human 559 1|sg_Non_Targeting_ Human_GA_0126|Non_Targeting_ Non_Targeting_Human CCCGATGGACTATACCGAAC Human 560 1|sg_Non_Targeting_ Human_GA_0127|Non_Targeting_ Non_Targeting_Human ACGTTCGAGTACGACCAGCT Human 561 1|sg_Non_Targeting_ Human_GA_0128|Non_Targeting_ Non_Targeting_Human CGCGACGACTCAACCTAGTC Human 562 1|sg_Non_Targeting_ Human_GA_0129|Non_Targeting_ Non_Targeting_Human GGTCACCGATCGAGAGCTAG Human 563 1|sg_Non_Targeting_

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Non_Targeting_Human CTTCGACGCCATCGTGCTCA Human_GA_0169|Non_Targeting_ Human
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Human_GA_0173|Non_Targeting_ Human 607 1|sg_Non_Targeting_ Non_Targeting_Human
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Human_GA_0176|Non_Targeting_ Human 610 1|sg_Non_Targeting_ Non_Targeting_Human
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618 1|sg_Non_Targeting_ Non_Targeting_Human TCTGGCTTGACACGACCGTT
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621 1|sg_Non_Targeting_ Non_Targeting_Human AAGGCGCGCGAATGTGGCAG
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624 1|sg_Non_Targeting_ Non_Targeting_Human TCGCAGCGGCGTGGGATCGG
Human_GA_0191|Non_Targeting_ Human 625 1|sg_Non_Targeting_ Non_Targeting_Human
ATCTGTCCTAATTCGGATCG Human_GA_0192|Non_Targeting_ Human 626 1|sg_Non_Targeting_
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627 1|sg_Non_Targeting_ Non_Targeting_Human CGAACTTAATCCCGTGGCAA
Human_GA_0194|Non_Targeting_ Human 628 1|sg_Non_Targeting_ Non_Targeting_Human
GCCGTGTTGCTGGATACGCC Human_GA_0195|Non_Targeting_ Human 629 1|sg_Non_Targeting_
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630 1|sg_Non_Targeting_ Non_Targeting_Human CCGTTGGACTATGGCGGGTC
Human_GA_0197|Non_Targeting_ Human 631 1|sg_Non_Targeting_ Non_Targeting_Human
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633 1|sg_Non_Targeting_ Non_Targeting_Human AAGAGCGAATCGATTTCGTG
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TCAACACCAGTGCCTGACGG 635 3|sg_hCDC16_CC_2|CDC16 CDC16
AAAGTAGCTTCACTCTCTCG 636 3|sg_hCDC16_CC_3|CDC16 CDC16
GAGCCAACCAATAGATGTCC 637 3|sg_hCDC16_CC_4|CDC16 CDC16
GCGCCGCCATGAACCTAGAG 638 3|sg_hGTF2B_CC_1|GTF2B GTF2B
ACAAAGGTTGGAACAGAACC 639 3|sg_hGTF2B_CC_2|GTF2B GTF2B
GGTGACCGGGTTATTGATGT 640 3|sg_hGTF2B_CC_3|GTF2B GTF2B
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ACATATAGCCCGTAAAGCTG 642 3|sg_hHSPA5_CC_1|HSPA5 HSPA5
CGTTGGCGATGATCTCCACG 643 3|sg_hHSPA5_CC_2|HSPA5 HSPA5

TGGCCTTTTCTACCTCGCGC 644 3|sg_hHSPA5_CC_3|HSPA5 HSPA5
AATGGAGATACTCATCTGGG 645 3|sg_hHSPA5_CC_4|HSPA5 HSPA5
GAAGCCCGTCCAGAAAGTGT 646 3|sg_hHSPA9_CC_1|HSPA9 HSPA9
CAATCTGAGGAACTCCACGA 647 3|sg_hHSPA9_CC_2|HSPA9 HSPA9
AGGCTGCGGCGCCCACGAGA 648 3|sg_hHSPA9_CC_3|HSPA9 HSPA9
ACTTTGACCAGGCCTTGCTA 649 3|sg_hHSPA9_CC_4|HSPA9 HSPA9
ACCTTCCATAACTGCCACGC 650 3|sg_hPAFAH1B1_CC_ PAFAH1B1
CGAGGCGTACATACCCAAGG 1|PAFAH1B1 651 3|sg_hPAFAH1B1_CC_ PAFAH1B1
ATGGTACGGCCAAATCAAGA 2|PAFAH1B1 652 3|sg_hPAFAH1B1_CC_ PAFAH1B1
TCTTGTAATCCCATACGCGT 3|PAFAH1B1 653 3|sg_hPAFAH1B1_CC_ PAFAH1B1
ATTCACAGGACACAGAGAAT 4|PAFAH1B1 654 3|sg_hPCNA_CC_1|PCNA PCNA
CCAGGGCTCCATCCTCAAGA 655 3|sg_hPCNA_CC_2|PCNA PCNA
TGAGCTGCACCAAAGAGACG 656 3|sg_hPCNA_CC_3|PCNA PCNA
ATGTCTGCAGATGTACCCCT 657 3|sg_hPCNA_CC_4|PCNA PCNA
CGAAGATAACGCGGATACCT 658 3|sg_hPOLR2L_CC_1|POLR2L POLR2L
GCTGCAGGCCGAGTACACCG 659 3|sg_hPOLR2L_CC_2|POLR2L POLR2L
ACAAGTGGGAGGCTTACCTG 660 3|sg_hPOLR2L_CC_3|POLR2L POLR2L
GCAGCGTACAGGGATGATCA 661 3|sg_hPOLR2L_CC_4|POLR2L POLR2L
GCAGTAGCGCTTCAGGCCCA 662 3|sg_hRPL9_CC_1|RPL9 RPL9
CAAATGGTGGGGTAACAGAA 663 3|sg_hRPL9_CC_2|RPL9 RPL9
GAAAGGAACTGGCTACCGTT 664 3|sg_hRPL9_CC_3|RPL9 RPL9
AGGGCTTCCGTTACAAGATG 665 3|sg_hRPL9_CC_4|RPL9 RPL9
GAACAAGCAACACCTAAAAG 666 3|sg_hSF3A3_CC_1|SF3A3 SF3A3
TGAGGAGAAGGAACGGCTCA 667 3|sg_hSF3A3_CC_2|SF3A3 SF3A3
GGAAGAATGCAGAGTATAAG 668 3|sg_hSF3A3_CC_3|SF3A3 SF3A3
GGAATTTGAGGAACTCCTGA 669 3|sg_hSF3A3_CC_4|SF3A3 SF3A3
GCTCACCGGCCATCCAGGAA 670 3|sg_hSF3B3_CC_1|SF3B3 SF3B3
ACTGGCCAGGAACGATGCGA 671 3|sg_hSF3B3_CC_2|SF3B3 SF3B3
GCAGCTCCAAGATCTTCCCA 672 3|sg_hSF3B3_CC_3|SF3B3 SF3B3
GAATGAGTACACAGAACGGA 673 3|sg_hSF3B3_CC_4|SF3B3 SF3B3
GGAGCAGGACAAGGTCGGGG

Example 2—BRD9 Degrader Depletes BRD9 Protein

(85) The following example demonstrates the depletion of the BRD9 protein in synovial sarcoma cells treated with a BRD9 degrader.

(86) Procedure: Cells were treated with DMSO or the BRD9 degrader, Compound 1 (also known as dBRD9, see Remillard et al, *Angew. Chem. Int. Ed. Engl.* 56(21):5738-5743 (2017); see structure of Compound 1 below), for indicated doses and timepoints.

(87) ##STR00799##

(88) Whole cell extracts were fractionated by SDS-PAGE and transferred to a polyvinylidene difluoride membrane using a transfer apparatus according to the manufacturer's protocols (Bio-Rad). After incubation with 5% nonfat milk in TBST (10 mM Tris, pH 8.0, 150 mM NaCl, 0.5% Tween 20) for 60 minutes, the membrane was incubated with antibodies against BRD9 (1:1,000, Bethyl laboratory A.sup.303-781A), GAPDH (1:5,000, Cell Signaling Technology), and/or MBP (1:1,000, BioRad) overnight at 4° C. Membranes were washed three times for 10 min and incubated with anti-mouse or anti-rabbit antibodies conjugated with either horseradish peroxidase (HRP, FIGS. **2-3**) or IRDye (FIG. **4**, 1:20,000, LI-COR) for at least 1 h. Blots were washed with TBST three times and developed with either the ECL system according to the manufacturer's protocols (FIGS. **2-3**) or scanned on an Odyssey CLx Imaging system (FIG. **4**).

(89) Results: Treatment of SYO1 synovial sarcoma cells with the BRD9 degrader Compound 1 results in dose dependent (FIG. **2**) and time dependent (FIG. **3**) depletion of BRD9 in the cells. Further, as shown in FIG. **4**, the depletion of BRD9 by Compound 1 is replicated in a non-synovial sarcoma cell line (293T) and may be sustained for at least 5 days.

Example 3—Inhibition of Growth of Synovial Cell Lines by BRD9 Inhibitors and BRD9 Degraders

(90) The following example demonstrates that BRD9 degraders and inhibitors selectively inhibit growth of synovial sarcoma cells.

(91) Procedures: Cells were treated with DMSO or the BRD9 degrader, Compound 1, at indicated concentrations, and proliferation was monitored from day 7 to day 14 by measuring confluency over time using an IncuCyte live cell analysis system (FIG. **5**). Growth medium and compounds were refreshed every 3-4 days.

(92) Cells were seeded into 12-well plates and treated with DMSO, 1 μM BRD9 inhibitor, Compound 2 (also known as BI-7273, see Martin et al, *J Med Chem.* 59(10):4462-4475 (2016); see structure of Compound 2 below), or 1 μM BRD9 degrader, Compound 1.

(93) ##STR00800##

(94) The number of cells was optimized for each cell line. Growth medium and compounds were refreshed every 3-5 days. SYO1, Yamato, A549, 293T and HS-SY-II cells were fixed and stained at day 11. ASKA cells were fixed and stained at day 23. Staining was done by incubation with crystal violet solution (0.5 g Crystal Violet, 27 ml 37% Formaldehyde, 100 mL 10×PBS, 10 mL Methanol, 863 dH2O to 1 L) for 30 min followed by 3× washes with water and drying the plates for at least 24 h at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system (FIG. **6**).

(95) Cells were seeded into 96-well ultra low cluster plate (Costar, #7007) in 200 μL complete media and treated at day 2 with DMSO, Staurosporin, or BRD9 degarder, Compound 1, at indicated doses (FIG. **7**). Media and compounds were changed every 5 d and cell colonies were imaged at day 14.

(96) Results: As shown in FIGS. **5**, **6**, and **7**, treatment of synovial sarcoma cell lines (SYO1, Yamato, HS-SY-II, and ASKA) with a BRD9 inhibitor, Compound 2, or a BRD9 degrader, Compound 1, results in inhibition of the growth of the cells, but does not result in inhibition of the growth of non-synovial control cancer cell lines (293T, A549, G401).

Example 4—Selective Inhibition of Growth of Synovial Cell Lines by BRD9 Degraders and BRD9 Binders

(97) The following example demonstrates that BRD9 degraders and binders selectively inhibit growth of synovial sarcoma cells.

(98) Procedure: Cells were seeded into 6-well or 12-well plates and were treated daily with a BRD9 degrader (Compound 1), a bromo-domain BRD9 binder (Compound 2), E3 ligase binder (lenalidomide), DMSO, or staurosporin (positive control for cell killing), at indicated concentrations. The number of cells was optimized for each cell line. Growth media was refreshed every 5 days. By day 14, medium was removed, cells were washed with PBS, and stained using 500 μL of 0.005% (w/v) crystal violet solution in 25% (v/v) methanol for at least 1 hour at room temperature. Subsequently plates were scanned on an Odyssey CLx Imaging system.

(99) Results: As shown in FIGS. **8** and **9**, treatment of synovial sarcoma cell lines (SYO1, HS-SY-II, and ASKA) with Compound 1 or Compound 2 resulted in inhibition of the growth of the cells, but did not result in inhibition of the growth of non-synovial control cancer cell lines (RD, HCT116, and Calu6). Overall, Compound 1 showed most significant growth inhibition in all synovial cell lines.

Example 5—Inhibition of Cell Growth in Synovial Sarcoma Cells

(100) The following example shows that BRD9 degraders inhibit cell growth and induce apoptosis in synovial sarcoma cells.

(101) Procedure: SYO1 cells were treated for 8 or 13 days with DMSO, a BRD9 degrader (Compound 1) at 200 nM or 1 μM, or an E3 ligase binder (lenalidomide) at 200 nM. Compounds were refreshed every 5 days. Cell cycle analysis was performed using the Click-iT™ Plus EdU Flow Cytometry Assay (Invitrogen). The apoptosis assay was performed using the Annexin V-FITC Apoptosis Detection Kit (Sigma A9210). Assays were performed according to the manufacturer's protocol.

(102) Results: As shown in FIGS. **10**-**13**, treatment with Compound 1 for 8 or 13 days resulted in reduced numbers of cells in the S-phase of the cell cycle as compared to DMSO and lenalidomide. Treatment with Compound 1 for 8 days also resulted in increased numbers of early- and late-apoptotic cells as compared to DMSO controls.

Example 6—Composition for SS18-SSX1-BAF

(103) The following example shows the identification of BRD9 as a component of SS18-SSX containing BAF complexes.
(104) Procedure: A stable 293T cell line expressing HA-SS18SSX1 was generated using lentiviral integration. SS18-SSX1 containing BAF complexes were subject to affinity purification and subsequent mass spectrometry analysis revealed SS18-SSX1 interacting proteins.
(105) Results: As shown in FIG. **14**, BAF complexes including the SS18-SSX fusion protein also included BRD9. More than 5 unique peptides were identified for ARID1A (95 peptides), ARID1B (77 peptides), SMARCC1 (69 peptides), SMARCD1 (41 peptides), SMARCD2 (37 peptides), DPF2 (32 peptides), SMARCD3 (26 peptides), ACTL6A (25 peptides), BRD9 (22 peptides), DPF1 Isoform 2 (18 peptides), DPF3 (13 peptides), and ACTL6B (6 peptides).
Example 7—Preparation of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-6-(methylamino)-1,2-dihydro-2,7-naphthyridin-1-one (Compound B1)
(106) ##STR00801##
(107) To a stirred mixture of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (100 mg, 0.26 mmol, 1.0 equiv) and methanamine hydrochloride (174.08 mg, 2.58 mmol, 10.0 equiv) in DMSO (3 mL) was added K.sub.2CO.sub.3 (890.82 mg, 6.45 mmol, 25.0 equiv) at room temperature. The resulting mixture was stirred for 16 hours at 130° C., and then it was allowed to cool down to room temperature. The solid was filtered off, the crude solution was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column 30*150 mm, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 40 mL/minute; Gradient: 18% B to 18% B in 2 minutes; 254/220 nm; Rt: 7.43 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-6-(methylamino)-1,2-dihydro-2,7-naphthyridin-1-one (27 mg, 26%). .sup.1H NMR (400 MHz, Methanol-d4) δ 9.08 (s, 1H), 7.40 (s, 1H), 6.74 (s, 2H), 6.44 (s, 1H), 3.88 (s, 6H), 3.69 (s, 2H), 3.58 (s, 3H), 2.88 (s, 3H), 2.33 (s, 6H). LCMS (ESI) m/z: [M+H].sup.+=383.20.
Example 8—Preparation of 6-(dimethylamino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (Compound B2)
(108) ##STR00802##
(109) To a stirred mixture of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (77.6 mg, 0.20 mmol, 1.0 equiv) and dimethylamine hydrochloride (163.14 mg, 2.0 mmol, 10.0 equiv) in DMF (6 mL) was added TEA (404.91 mg, 4.0 mmol, 20.0 equiv) at room temperature. The resulting mixture was stirred for 16 hours at 130° C. and then it was allowed to cool down to room temperature. The solid was filtered off, the filtrate was purified by Prep-HPLC with the following conditions (2#SHIMADZU (HPLC-01)): Column, X Bridge Shield RP18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.05% NH.sub.3H.sub.2O) and ACN (10% Phase B up to 70% in 8 minutes); To afford 23 mg (27%) of 6-(dimethylamino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one as a brown solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.43 (s, 1H), 6.77 (s, 2H), 6.52 (s, 1H), 3.89 (s, 6H), 3.70 (s, 2H), 3.59 (s, 3H), 3.12 (s, 6H), 2.34 (s, 6H). LCMS (ESI) m/z: [M+H].sup.+=397.40.
Example 9—Preparation of 4-[4-[(Dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-7-(methylamino)-1,2-dihydro-2,6-naphthyridin-1-one (Compound B3)
(110) ##STR00803##
(111) To a solution of 7-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,6-naphthyridin-1-one (50 mg, 0.13 mmol, 1.0 equiv) and methanamine hydrochloride (87.0 mg, 1.29 mmol, 10.0 equiv) in solvent DMSO (2 mL) was added K.sub.2CO.sub.3 (445.4 mg, 3.22 mmol, 25.0 equiv). The resulting solution was stirred at 130° C. for overnight. After cooling, the solid was filtered off, the crude solution was purified by Prep-HPLC (conditions: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% NH.sub.3H.sub.2O), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 30% B to 80% B in 8 minutes; 220 nm nm; Rt: 7.8 minutes) to afford 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-7-(methylamino)-1,2-dihydro-2,6-naphthyridin-1-one (15.5 mg, 31%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.53 (d, J=0.9 Hz, 1H), 7.24 (d, J=0.9 Hz, 1H), 7.09 (s, 1H), 6.76 (s, 2H), 3.88 (s, 6H), 3.67 (d, J=11.1

Hz, 5H), 2.97 (s, 3H), 2.31 (s, 6H). LCMS: (ES, m/z): [M+H].sup.+=383.30.
Example 10—Preparation of 6-amino-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (Compound B4) and 7-amino-4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,6-naphthyridin-1(2H)-one (Compound B5)
(112) ##STR00804## ##STR00805##
Step 1: Preparation of 4-bromo-6-chloro-N-methylpyridine-3-carboxamide (i10-2)
(113) ##STR00806##
(114) To a solution of 4-bromo-6-chloropyridine-3-carboxylic acid (2.0 g, 8.46 mmol, 1.0 equiv), methanamine hydrochloride (0.63 g, 9.30 mmol, 1.1 equiv) and DIEA (3.28 g, 25.38 mmol, 3.0 equiv) in DCM (20 mL) was added HATU (4.82 g, 12.69 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for another 1 hour. Then the reaction was washed with water (20 m×2), and the organic layer was concentrated under vacuum to give a yellow syrup. The product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=249.
Step 2: Preparation of 6-chloro-4-[(E)-2-ethoxyethenyl]-N-methylpyridine-3-carboxamide (i10-3)
(115) ##STR00807##
(116) To a solution of 4-bromo-6-chloro-N-methylpyridine-3-carboxamide (1.0 g, 4.0 mmol, 1 equiv) and 2-[(E)-2-ethoxyethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.95 g, 4.81 mmol, 1.2 equiv) in dioxane (10 mL) and H.sub.2O (2 mL) was added Cs.sub.2CO.sub.3 (3.92 g, 12.03 mmol, 3.0 equiv) and Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (0.35 g, 0.48 mmol, 0.12 equiv). The mixture was stirred for 2 hours at 90° C. under nitrogen atmosphere, and the reaction mixture was dilute with water and extracted with ethyl acetate, dried over Na.sub.2SO.sub.4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (20:1) to afford 6-chloro-4-[(E)-2-ethoxyethenyl]-N-methylpyridine-3-carboxamide (680 mg, 57%) as an off-white solid. LCMS (ESI) m/z: [M+H].sup.+=241.
Step 3: 6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i10-4)
(117) ##STR00808##
(118) Into a 20 mL pressure tube was added 6-chloro-4-[(E)-2-ethoxyethenyl]-N-methylpyridine-3-carboxamide (680 mg, 2.83 mmol, 1.0 equiv) and TFA (5 mL, 67.32 mmol, 23.83 equiv) at room temperature, the reaction was stirred over night at 80° C. The resulting mixture was concentrated under vacuum to afford 6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (580 mg, crude) as a dark yellow solid. The product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=195.
Step 4: Preparation of 4-bromo-6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i10-5)
(119) ##STR00809##
(120) To a stirred mixture of 6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (580 mg, 2.98 mmol, 1.0 equiv) in DMF (10 mL) was added NBS (583.46 mg, 3.28 mmol, 1.1 equiv), and the resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was diluted with DCM (50 mL) and washed with water (3×50 mL). The organic layer was dried over Na.sub.2SO.sub.4 and concentrated under vacuum. The crude product was purified by flash silica chromatography, eluted with 0 to 80% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford 4-bromo-6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (899 mg, 88%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=273.
Step 5: Preparation of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (i10-6)
(121) ##STR00810##
(122) To a solution of 4-bromo-6-chloro-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (843 mg, 3.08 mmol, 1.0 equiv) and [4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]boronic acid (736.88 mg, 3.08 mmol, 1.0 equiv) in dioxane (40 mL) and H.sub.2O (4 mL) was added Cs.sub.2CO.sub.3 (3.01 g, 9.25 mmol, 3.0 equiv) and Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (302.04 mg, 0.37 mmol, 0.12 equiv). After stirring for 2 hours at 90° C. under a nitrogen atmosphere, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried over Na.sub.2SO.sub.4 and then concentrated under reduced pressure. The crude product was purified by flash silica chromatography,

eluted with 0 to 80% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (670 mg, 51%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=388.

Step 6: Preparation of 6-amino-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (Compound B4)

(123) ##STR00811##

(124) To a stirred mixture of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphthyridin-1-one (232 mg, 060 mmol, 1.0 equiv) and NH.sub.4Cl (479.94 mg, 8.97 mmol, 15.0 equiv) in DMSO (10 mL) was added K.sub.2CO.sub.3 (2.07 g, 14.95 mmol, 25.0 equiv). The resulting mixture was stirred overnight at 130° C. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate, dried over Na.sub.2SO.sub.4, and then concentrated under reduced pressure. The crude product was purified by Prep-HPLC (conditions: X Select CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (hold 7% Phase B in 7 minutes); Detector, UV) to afford 3.4 mg (1.54%) of 6-amino-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-1,2-dihydro-2,7-naphth-yridin-1-one as an off-white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.44 (s, 1H), 6.84 (s, 2H), 6.54 (s, 1H), 4.34 (s, 2H), 3.97 (s, 6H), 3.59 (s, 3H), 2.85 (s, 6H). LCMS (ESI) m/z: [M+H].sup.+=369.25.

Preparation of 7-amino-4-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-2-methyl-2,6-naphthyridin-1(2H)-one (Compound B5)

(125) ##STR00812##

(126) Compound B5 was prepared in a similar manner as described above for compound B4. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.39 (s, 1H), 7.65 (d, J=2.2 Hz, 1H), 7.23 (s, 1H), 6.89 (s, 2H), 4.42 (s, 2H), 3.98 (s, 6H), 3.64 (s, 3H), 2.92 (s, 6H). LCMS (ESI) m/z: [M+H].sup.+=369.25.

Example 11—Preparation of 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]-N,N-dimethylacetamide formic acid (Compound B6 Formic Acid)

(127) ##STR00813##

(128) To a stirred mixture of [(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]acetic acid (60.0 mg, 0.141 mmol, 1.00 equiv) and dimethylamine hydrochloride (17.2 mg, 0.211 mmol, 1.50 equiv) in DMF (2.00 mL) was added DIEA (54.6 mg, 0.422 mmol, 3.00 equiv). The mixture was stirred at room temperature for 5 minutes, and then PyBOP (146.43 mg, 0.281 mmol, 2.00 equiv) was added. After stirring at room temperature for 2 hours, the reaction mixture was purified by Prep-HPLC (conditions: Sun Fire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×250 mm; mobile phase, Water (0.1% FA) and ACN (10% Phase B up to 31% in 11 minutes). This resulted in 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]-N,N-dimethyl acetamide; formic acid (10.9 mg, 17.7%) as a dark yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.51 (br s, 0.5H, FA), 8.50 (s, 1H), 7.37 (s, 1H), 7.16 (s, 1H), 6.92 (s, 2H), 4.92 (s, 2H), 4.37 (s, 2H), 3.95 (s, 6H), 3.65 (s, 3H), 3.36 (s, 6H), 3.05 (d, J=5.5 Hz, 6H). LCMS (ESI) m/z: [M+H].sup.+=454.20.

Example 12—Preparation of 1-([4-[6-(Dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide (Compound D1)

(129) ##STR00814## ##STR00815##

Step 1: Preparation of 4-[6-(Dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (i12-2)

(130) ##STR00816##

(131) To a solution of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (400.00 mg, 1.42 mmol, 1.00 eq.) in dioxane (10.00 mL) and H.sub.2O (1.00 mL) was added 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (500 mg, 1.70 mmol, 1.2 eq.), Pd(dppf)Cl.sub.2 (100.0 mg, 0.14 mmol, 0.1 eq.), and Cs.sub.2CO.sub.3 (1.39 g, 4.14 mmol, 3 eq.). The resulting solution was stirred at 90° C. for 1 hour under a nitrogen atmosphere. The crude was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-

yl]-2,6-dimethoxybenzaldehyde (416.8 mg, 119.03%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=367.4.
Step 2: Preparation of Methyl 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylate (i12-3)
(132) ##STR00817##
(133) To a solution of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (331.00 mg, 0.901 mmol, 1.00 eq.) in MeOH (10.00 mL) was added methyl azetidine-3-carboxylate hydrochloride (163.88 mg, 1.081 mmol, 1.2 eq.) and NaBH.sub.3CN (169.85 mg, 2.703 mmol, 3 eq.). The resulting solution was stirred at room temperature for 1 hour. The crude mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford methyl 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylate (279 mg, 66.38%) as a light yellow solid. LCMS (ESI) m/z: [M+H].sup.+=466.5.
Step 3: Preparation of 1-([4-[6-(Dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylic acid (i12-4)
(134) ##STR00818##
(135) To the solution of methyl 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylate (140.00 mg, 0.300 mmol, 1.00 eq.) in MeOH (3.00 mL) and H.sub.2O (3.00 mL) was added LiOH (71.87 mg, 3.001 mmol, 10.00 eq.). The resulting solution was stirred at room temperature for 3 hours. The crude mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, HCl in water, 10% to 70% gradient in 35 minutes; detector, UV 254 nm). This resulted in 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylic acid (120 mg, 88.37%) as a white solid. LCMS (ESI) m/z: [M+H]+=452.5.
Step 4: Preparation of 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide (Compound D1 Formic Acid)
(136) ##STR00819##
(137) To a solution of 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidine-3-carboxylic acid (50.00 mg, 0.110 mmol, 1.00 eq.) and 4-[(5-aminopentyl)oxy]-2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione (39.71 mg, 0.110 mmol, 1.00 eq.) in DMF (1.50 mL) was added DIEA (42.84 mg, 0.331 mmol, 3.00 eq.) and PyBOP (86.25 mg, 0.166 mmol, 1.50 eq.). The resulting solution was stirred at room temperature for 1 hour. The crude product (50 mg) was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 11% B to 27% B in 18 minutes; 254 nm; R.sub.t: 16.87 minutes) to afford 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide formate (13.5 mg) as a light yellow solid. .sup.1H NMR (300 MHz, Acetonitrile-d3) δ 9.12 (s, 1H), 8.17 (s, 0.3H, FA), 7.76 (dd, J=8.5, 7.3 Hz, 1H), 7.53-7.28 (m, 3H), 6.79 (s, 2H), 6.65 (s, 1H), 6.53 (s, 1H), 4.99 (dd, J=12.1, 5.4 Hz, 1H), 4.26 (s, 2H), 4.23-4.15 (m, 2H), 4.15-4.03 (m, 2H), 4.04-3.92 (m, 2H), 3.87 (s, 6H), 3.52 (s, 3H), 3.42 (t, J=8.1 Hz, 1H), 3.34-3.12 (m, 3H), 3.10 (s, 6H), 2.86-2.62 (m, 3H), 2.21-2.07 (m, 1H), 1.88-1.76 (m, 2H), 1.63-1.50 (m, 4H). LCMS (ESI) m/z: [M+H]+=452.45.
Example 13—Preparation of 4-(((((S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound D2)
(138) ##STR00820##
Step 1: Preparation of tert-butyl (S)-2((2,2,2-trifluoroacetamido)methyl)azetidine-1-carboxylate (i13-2)
(139) ##STR00821##
(140) To a solution of tert-butyl (2S)-2-(aminomethyl)azetidine-1-carboxylate (900.00 mg, 4.832 mmol,

1.00 equiv) and trifluoroacetic anhydride (1.522 g, 7.248 mmol, 1.5 equiv) in THF (9.00 mL) was added TEA (977.92 mg, 9.664 mmol, 2 equiv). The resulting solution was stirred at 25° C. for 12 hours. The resulting solution was diluted with of EtOAc. The resulting mixture was washed with water (3×50 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product that was applied onto a silica gel column with ethyl EA/PE (15:85) to afford tert-butyl (2S)-2-[(2,2,2-trifluoroacetamido) methyl]azetidine-1-carboxylate (1.27 g, 93.11%) as a yellow oil. LCMS (ESI) m/z: [M+H]+=283.

Step 2: Preparation of tert-butyl (S)-2-((2,2,2-trifluoro-N-methylacetamido)methyl)azetidine-1-carboxylate (i13-3)

(141) ##STR00822##

(142) To a solution of tert-butyl (2S)-2-[(2,2,2-trifluoroacetamido)methyl]azetidine-1-carboxylate (1.27 g, 4.499 mmol, 1.00 equiv) and dimethyl sulfate (681.00 mg, 5.399 mmol, 1.2 equiv) in acetone (15.00 mL) was added K.sub.2CO.sub.3 (621.83 mg, 4.499 mmol, 1 equiv). The resulting solution was stirred at 25° C. for 12 hours. The resulting mixture was filtered, and the filtrate was evaporated to dryness to afford tert-butyl (2S)-2-[(2,2,2-trifluoro-N-methylacetamido)methyl]azetidine-1-carboxylate (1.64 g, crude) as a yellow oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=297.

Step 3: Preparation of (S)—N-(azetidin-2-ylmethyl)-2,2,2-trifluoro-N-methylacetamide (i13-4)

(143) ##STR00823##

(144) A solution of tert-butyl (2S)-2-[(2,2,2-trifluoro-N-methylacetamido)methyl]azetidine-1-carboxylate (1.64 g, 5.535 mmol, 1.00 equiv) and TFA (3.50 mL, 47.121 mmol, 8.51 equiv) in DCM (16.00 mL) was stirred for 1 hour at 25° C. The mixture was concentrated to give N-[(2S)-azetidin-2-ylmethyl]-2,2,2-trifluoro-N-methylacetamide (2.08 g, crude) as a brown oil that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=197.

Step 4: Preparation of (S)—N-((1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)azetidin-2-yl)methyl)-2,2,2-trifluoro-N-methylacetamide (i13-5)

(145) ##STR00824##

(146) To a solution of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (620.00 mg, 1.688 mmol, 1.00 equiv) and N-[(2S)-azetidin-2-ylmethyl]-2,2,2-trifluoro-N-methylacetamide (496.57 mg, 2.531 mmol, 1.50 equiv) in DMF (5.00 mL, 64.609 mmol, 38.29 equiv) was added NaBH(OAc).sub.3 (715.31 mg, 3.375 mmol, 2 equiv). The resulting solution was stirred at 25° C. for 1 hour. The mixture was concentrated to give crude product that was purified by chromatography on silica gel eluted with MeOH]/DCM (4.2:95.8) to give N-[[(2S)-1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-2-yl]methyl]-2,2,2-trifluoro-N-methylacetamide (436 mg, 47.18%) as a dark yellow solid. LCMS (ESI) m/z: [M+H]+=548.

Step 5: Preparation of (S)-4-(3,5-dimethoxy-4-((2-((methylamino)methyl)azetidin-1-yl)methyl)phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1(2H)-one (6)

(147) ##STR00825##

(148) A solution of N-[[(2S)-1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-2-yl]methyl]-2,2,2-trifluoro-N-methylacetamide (400.00 mg, 0.730 mmol, 1.00 equiv) and NH.sub.3.Math.H.sub.2O (2.00 mL, 51.361 mmol, 70.31 equiv) in DMF (4.00 mL, 12.922 mmol, 196.55 equiv) was stirred at 25° C. for 12 hours. The resulting solution was concentrated to give crude product 4-(3,5-dimethoxy-4-[[(2S)-2-[(methylamino)methyl]azetidin-1-yl]methyl]phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (458 mg) as a brown solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=452.

Step 6: Preparation of 4-(S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound D2)

(149) ##STR00826##

(150) 4-(3,5-dimethoxy-4-[[(2R)-2-[(methylamino)methyl]azetidin-1-yl]methyl]phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (100.00 mg, 0.221 mmol, 1.00 equiv) and 2-(2,6-

dioxopiperidin-3-yl)-1,3-dioxoisoindole-4-carbaldehyde (63.39 mg, 0.221 mmol, 1.00 equiv) were dissolved in MeOH (2.00 mL). Then NaBH.sub.3CN (69.58 mg, 1.107 mmol, 5 equiv) was added to the mixture, and the resulting solution was stirred at 25° C. for 1 hour. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9% B to 19% B in 15 minutes; 254 nm; Rt: 17.67 minutes) to give 4-(((((S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxy benzyl)azetidin-2-yl)methyl)(methyl)amino)methyl)-2-(2,6-dioxopiperidin-3-yl)isoindoli-ne-1,3-dione (20.4 mg, 12.76%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.05 (s, 1H), 8.00-7.74 (m, 3H), 7.51 (d, J=6.9 Hz, 1H), 6.88 (d, J=5.4 Hz, 2H), 6.60 (d, J=4.5 Hz, 1H), 5.26-5.05 (m, 1H), 4.64 (dd, J=12.8, 10.2 Hz, 1H), 4.53 (dd, J=12.8, 5.7 Hz, 1H), 4.27-4.08 (m, 4H), 3.93 (d, J=10.8 Hz, 6H), 3.59 (d, J=2.1 Hz, 3H), 3.16 (s, 6H), 3.10 (s, 2H), 2.95-2.80 (m, 1H), 2.80-2.58 (m, 3H), 2.32 (dd, J=15.9, 2.4 Hz, 4H), 2.19-2.08 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=722.20.

Example 14—Preparation of 4-([[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl) azetidin-3-yl](methyl)amino]methyl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D3 Formic Acid)

(151) ##STR00827## ##STR00828##

Step 1: Preparation of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (i14-2)

(152) ##STR00829##

(153) To a solution of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (1.80 g, 6.380 mmol, 1.00 equiv) and 4-formyl-3,5-dimethoxyphenylboronic acid (1.34 g, 6.380 mmol, 1.00 equiv) in 1,4-dioxane and water was added CS.sub.2CO.sub.3 (4.16 g, 12.760 mmol, 2.00 equiv) and Pd(dppf)Cl.sub.2 (0.47 g, 0.638 mmol, 0.10 equiv). After stirring for 2 hours at 80° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (1.5 g, 57.59%) as a grey solid. LCMS (ESI) m/z: [M+H]+=368.

Step 2: Preparation of tert-butyl-N-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]-N-methylcarbamate (i14-3)

(154) ##STR00830##

(155) To a stirred mixture of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (100.00 mg, 0.272 mmol, 1.00 equiv) and tert-butyl N-(azetidin-3-yl)-N-methylcarbamate hydrochloride (90.93 mg, 0.408 mmol, 1.50 equiv) in MeOH was added NaBH.sub.3CN (34.21 mg, 0.544 mmol, 2.00 equiv) in portions. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (20:1) to afford tert-butyl-N-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]-N-methylcarbamate (103 mg, 65.46%) as an off-white solid. LCMS (ESI) m/z: [M+H].sup.+=538.

Step 3: 4-(3,5-dimethoxy-4-((3-(methylamino)azetidin-1-yl)methyl)phenyl)-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1(2H)-one (i14-44)

(156) ##STR00831##

(157) To a stirred solution of tert-butyl-N-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]-N-methylcarbamate (100.00 mg, 0.186 mmol, 1.00 equiv) in DCM (1.00 mL) was added TFA (0.20 mL, 2.693 mmol, 14.48 equiv). The resulting mixture was stirred for 2 hours at room temperature and concentrated under reduced pressure. The residue was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=438.

Step 4: Preparation of 4-([[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl) azetidin-3-yl](methyl)amino]methyl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D3 Formic Acid)

(158) ##STR00832##

(159) To a stirred mixture of 4-(3,5-dimethoxy-4-[[3-(methylamino)azetidin-1-yl]methyl]phenyl)-6-

(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (50.00 mg, 0.114 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindole-4-carbaldehyde (65.42 mg, 0.229 mmol, 2.00 equiv) in MeOH was added NaBH.sub.3CN (14.36 mg, 0.229 mmol, 2.00 equiv) in portions. The resulting mixture was stirred for 2 hours at room temperature. The mixture was purified by Prep-HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; mobile phase, Water (0.1% FA) and ACN (16% PhaseB up to 26% in 8 minutes); Detector, UV). This resulted in 4-([[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl] methyl)azetidin-3-yl] (methyl)amino]methyl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (2.8 mg, 3.17%) as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.16 (d, J=0.7 Hz, 1H), 8.56 (br s, 1H, FA), 7.90-7.79 (m, 3H), 7.43 (s, 1H), 6.85 (s, 2H), 6.47 (s, 1H), 5.14 (dd, J=12.3, 5.4 Hz, 1H), 4.37 (s, 2H), 4.06 (s, 3H), 3.98-3.85 (m, 9H), 3.59 (s, 3H), 3.55-3.45 (m 1H), 3.11 (s, 6H), 2.89-2.80 (m, 1H), 2.77-2.66 (m, 2H), 2.16 (s, 3H), 2.14-2.07 (m, 1H). LCMS (ESI) m/z: [M+H]+=708.30.

Example 15—Preparation of (2S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)methyl)-N-methylazetidine-2-carboxamide formic acid (Compound D4 Formic Acid)

(160) ##STR00833##

(161) Compound D4 was prepared in a similar manner to Example 12. (2S)-1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)methyl)-N-methylazetidine-2-carboxamide formic acid (9.1 mg, 17.56%) was obtained as a light yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.18-9.11 (m, 1H), 8.54 (s, 0.2H, FA), 7.93-7.52 (m, 2H), 7.46-7.27 (m, 2H), 6.85 (s, 2H), 6.54-6.30 (m, 1H), 5.34-4.94 (m, 4H), 4.48-4.31 (m, 2H), 4.03-3.79 (m, 8H), 3.91 (s, 3H), 3.14-2.93 (m, 9H), 2.90-2.67 (m, 4H), 2.60-2.38 (m, 1H), 2.23-2.09 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=736.45.

Example 16—Preparation of 1[[2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)phenyl] methyl]-N-(4-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]amino]butyl) azetidine-3-sulfonamide formic acid (Compound D5 Formic Acid)

(162) ##STR00834##

Step 1: Preparation of tert-butyl-N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]carbamate (i16-1)

(163) ##STR00835##

(164) Using a similar procedure as described in Example 7 and substituting with tert-butyl N-(8-aminooctyl)carbamate (945 mg, 3.867 mmol) afforded tert-butyl-N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]carbamate (140 mg, 82%) as a yellow syrup. LCMS (ESI) m/z: [M+H].sup.+=596.

Step 2: Preparation of 6-[(8-aminooctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (i16-2)

(165) ##STR00836##

(166) To a stirred mixture of tert-butyl-N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]carbamate (140 mg, 0.235 mmol, 1.00 equiv) in dichloromethane (2.0 mL) was added trifluoroacetic acid (0.50 mL, 6.732 mmol, 28.65 equiv). The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure, and the residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; mobile phase, acetonitrile in water (0.1% formic acid), 1% to 20% gradient in 20 minutes; detector, UV 254 nm) to give 6-[(8-aminooctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (100 mg, 80%) as a yellow syrup. LCMS (ESI) m/z: [M+H].sup.+=596.

Step 3: Preparation of N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide formic acid (Compound D5 Formic Acid)

(167) ##STR00837##

(168) Using a similar procedure as described in Example 11 and substituting with of 6-[(8-aminooctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-

one (50.0 mg, 0.101 mmol, 1.00 equiv) and [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (30.2 mg, 0.091 mmol, 0.90 equiv) afforded N-[8-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide formic acid (6.2 mg, 7%) as a white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.05 (d, J=0.7 Hz, 1H), 8.57 (br s, 1H, FA), 7.81 (dd, J=8.4, 7.3 Hz, 1H), 7.53 (d, J=7.3 Hz, 1H), 7.46-7.38 (m, 2H), 6.83 (s, 2H), 6.40 (s, 1H), 5.13 (dd, J=12.6, 5.5 Hz, 1H), 4.76 (s, 2H), 4.60 (s, 3H), 4.23 (s, 2H), 3.95 (s, 6H), 3.57 (s, 3H), 3.34-3.23 (m, 2H), 2.93-2.81 (m, 2H), 2.80-2.67 (m, 6H), 2.19-2.10 (m, 1H), 1.62-1.54 (m, 4H), 1.37-1.33 (m, 8H). LCMS (ESI) m/z: [M+H].sup.+=810.45.

Example 17—Preparation of 4-((5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D6 Formic Acid)

(169) ##STR00838##

Step 1: Preparation of 4-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-((5-hydroxypentyl)amino)-2-methyl-2,7-naphthyridin-1(2H)-one (i17-2)

(170) ##STR00839##

(171) Using a similar procedure as described in Example 7 and substituting with 6-chloro-4-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-2-methyl-2,7-naphthyridin-1(2H)-one (150.0 mg, 0.387 mmol, 1.00 equiv) and 5-aminopentanol (39.8 mg, 0.387 mmol, 1.00 equiv) afforded 4-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-((5-hydroxypentyl)amino)-2-methyl-2,7-naphthyridin-1(2H)-one (90 mg, 51.4%) as a brown solid. LCMS (ESI) m/z: [M+H].sup.+=455.

Step 2: Preparation of 5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl methanesulfonate (i17-3)

(172) ##STR00840##

(173) To a solution of 4-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-((5-hydroxypentyl) amino)-2-methyl-2,7-naphthyridin-1(2H)-one (90 mg, 0.198 mmol, 1.00 equiv) and triethylamine (100.2 mg, 0.990 mmol, 5.00 equiv) in dichloromethane (2.00 mL) was added methanesulfonyl chloride (45.4 mg, 0.396 mmol, 2.00 equiv) slowly at 0° C. The reaction mixture was stirred for 30 minutes at 0° C. and then warmed to room temperature slowly. The reaction was quenched with saturated sodium bicarbonate solution (50 mL) and extracted with dichloromethane (50 mL×3). The organic layers were combined and washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford 5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl methanesulfonate (80.0 mg, 68.3%) as a brown solid. LCMS (ESI) m/z: [M+H].sup.+=533.

Step 3: Preparation of 4-((5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2, 6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D6 Formic Acid)

(174) ##STR00841##

(175) To a mixture of 5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7, 8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl methanesulfonate (80.0 mg, 0.150 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione (41.2 mg, 0.150 mmol, 1.00 equiv) in DMF (2.00 mL) was added K.sub.2CO.sub.3 (41.5 mg, 0.300 mmol, 2.00 equiv). The resulting mixture was stirred for 4 hours at 60° C. The resulting mixture was filtered, and the filtrate was purified by Prep-HPLC (column: SunFire C.sub.18 OBD Prep Column, 100 Å, 5 μm, 19 mm×250 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 11% B to 26% B in 10 minutes; 254 nm; Rt: 8.78 minutes) to afford 4-((5-((5-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione; formate (15.3 mg, 11.6%) as a light yellow solid. LCMS (ESI) m/z: [M+H].sup.+=711.65. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 8.56 (br s, 0.6H, FA), 7.77 (dd, J=8.5, 7.3 Hz, 1H), 7.43 (dd, J=11.8, 7.8 Hz, 2H), 7.28 (s, 1H), 7.16 (s, 1H), 7.01 (s, 1H), 5.98 (s, 1H), 5.09 (dd, J=12.8, 5.4 Hz, 1H), 4.22 (t, J=6.2 Hz, 2H), 4.03 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 3.56 (s, 3H), 3.28 (t, J=6.6 Hz, 2H), 2.93-2.82 (m, 1H), 2.80-2.70 (m, 2H), 2.65 (s, 6H),

2.15-2.07 (m, 1H), 1.92-1.81 (m, 2H), 1.73-1.64 (m, 2H), 1.64-1.55 (m, 2H).
Example 18—Preparation of 1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide formic acid (Compound D7 Formic Acid)
(176) ##STR00842##
(177) Compound 7 was prepared in a similar manner to Example 10 and Example 12. 1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentyl)azetidine-3-carboxamide formic acid (30 mg, 30.6%) was obtained as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.7H, FA), 8.51 (d, J=0.9 Hz, 1H), 7.77 (dd, J=8.4, 7.4 Hz, 1H), 7.44 (dd, J=7.9, 2.5 Hz, 2H), 7.23 (d, J=0.9 Hz, 1H), 7.10 (s, 1H), 6.81 (s, 2H), 5.10 (dd, J=12.4, 5.5 Hz, 1H), 4.30-4.21 (m, 3H), 4.02 (d, J=8.1 Hz, 3H), 3.92 (s, 6H), 3.64 (s, 3H), 3.47 (t, J=8.2 Hz, 1H), 3.29-3.13 (m, 3H), 2.97 (s, 3H), 2.90-2.76 (m, 2H), 2.75-2.63 (m, 1H), 2.18-2.07 (m, 1H), 2.01-1.83 (m, 3H), 1.68-1.54 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=780.60.
Example 19—Preparation of N-[8-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide (Compound D8)
(178) ##STR00843##
Step 1: Preparation of tert-butyl N-[8-[(8-bromo-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (i19-2)
(179) ##STR00844##
(180) To a mixture of 4-bromo-7-chloro-2-methyl-2,6-naphthyridin-1-one (100 mg, 0.366 mmol, 1.00 equiv) and tert-butyl N-(8-aminooctyl)carbamate (268.1 mg, 1.097 mmol, 3.00 equiv) in DMSO (3.00 mL) was added K.sub.2CO.sub.3 (505.3 mg, 3.656 mmol, 10.00 equiv). The resulting solution was stirred at 130° C. for 5 hours. The resulting solution was diluted with of EtOAc (80 mL). The resulting mixture was washed with water (3×50 mL). The organic layer was concentrated under reduced pressure. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). Fractions containing the desired compound were evaporated to dryness to afford tert-butyl N-[8-[(8-bromo-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (50 mg, 28.4%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=483.
Step 2: Preparation of tert-butyl N-[8-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (i19-3)
(181) ##STR00845##
(182) To a solution of tert-butyl N-[8-[(8-bromo-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (50.0 mg, 0.104 mmol, 1.00 equiv) and 4-[(dimethylamino)methyl]-3,5-dimethoxyphenylboronic acid (37.2 mg, 0.156 mmol, 1.50 equiv) in H.sub.2O (0.50 mL) and dioxane (1.50 mL) was added Cs.sub.2CO.sub.3 (67.7 mg, 0.208 mmol, 2.00 equiv) and Pd(dppf)Cl.sub.2.Math.CH.sub.2Cl.sub.2 (7.60 mg, 0.010 mmol, 0.10 equiv). The resulting solution was stirred at 90° C. for 1 hour under N.sub.2 atmosphere. The resulting solution was diluted with of EtOAc (50 mL). The resulting mixture was washed with water (3×30 mL). The resulting mixture was concentrated under reduced pressure. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (30:70). Fractions containing the desired compound were evaporated to dryness to afford tert-butyl N-[8-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (30 mg, 48.5%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=596.
Step 3: Preparation of 7-[(8-aminooctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (i19-4)
(183) ##STR00846##
(184) To a solution of tert-butyl N-[8-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]carbamate (30 mg, 0.050 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (2.00 mL), and the resulting solution was stirred at 25° C. for 1 hour. The resulting mixture was concentrated under reduced pressure to afford 7-[(8-aminooctyl)amino]-4-[4-

[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (35 mg, crude) as a yellow liquid that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=496.
Step 4: Preparation of N-[8-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide (Compound D8)
(185) ##STR00847##
(186) To a solution of [[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetic acid (24.1 mg, 0.073 mmol, 1.20 equiv) and HATU (46.0 mg, 0.121 mmol, 2.00 equiv) in DMF (2.00 mL) were added 7-[(8-aminooctyl)amino]-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (30.0 mg, 0.061 mmol, 1.00 equiv) and DIEA (39.1 mg, 0.303 mmol, 5.00 equiv). The resulting solution was stirred at 25° C. for 2 hours. The crude product was purified by preparative HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; Rt: 7.12 minutes) to afford N-[8-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]octyl]-2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]acetamide (12 mg, 24.5%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.41 (s, 1H), 7.80 (dd, J=8.4, 7.4 Hz, 1H), 7.52 (d, J=7.3 Hz, 1H), 7.43 (d, J=9.1 Hz, 2H), 7.15 (s, 1H), 6.90 (s, 2H), 5.13 (dd, J=12.4, 5.4 Hz, 1H), 4.77 (s, 2H), 4.42 (s, 2H), 3.98 (s, 6H), 3.63 (s, 3H), 3.40-3.35 (m, 2H), 3.30-3.21 (m, 2H), 2.92 (s, 6H), 2.90-2.82 (m, 1H), 2.80-2.65 (m, 2H), 2.21-2.09 (m, 1H), 1.72-1.57 (m, 4H), 1.51-1.34 (m, 8H). LCMS (ESI) m/z: [M+H]+=810.60.
Example 20—Preparation of N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide (Compound D9)
(187) ##STR00848##
Step 1: Preparation of 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethoxy)ethoxy) propanamide (i20-2)
(188) ##STR00849##
(189) Using a similar procedure as described in Example 10, step 1 and substituting with 5-([2-[2-(3,3-dihydroxypropoxy)ethoxy]ethyl]amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (150 mg, 0.344 mmol, 1.00 equiv) and ammonium chloride (24 mg, 0.448 mmol, 1.30 equiv) afforded 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethoxy)ethoxy) propanamide (122 mg, 81.5%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=433.
Step 2: Preparation of N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide (Compound D9)
(190) ##STR00850##
(191) To a solution of 7-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,6-naphthyridin-1-one (50 mg, 0.129 mmol, 1.00 equiv) and 3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide (55.8 mg, 0.129 mmol, 1 equiv) in dioxane (4 mL) was added tris(dibenzylideneacetone)dipalladium(O) (11.8 mg, 0.013 mmol, 0.10 equiv), cesium carbonate (84.0 mg, 0.258 mmol, 2.0 equiv) and Xantphos (14.9 mg, 0.026 mmol, 0.20 equiv), and the resulting solution was stirred at 90° C. for 3 hours. The mixture filtered through a short pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×250 mm; Mobile Phase A: water (0.1% formic acid), Mobile Phase B: acetonitrile; Flow rate: 25 mL/minute; Gradient: 9 B to 22 B in 18 minutes; 254 nm) to give N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]amino]ethoxy)ethoxy]propanamide (6 mg, 5.6%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.82 (s, 1H), 8.64 (s, 1H), 7.40-7.30 (m, 2H), 6.89 (s, 2H), 6.86-6.76 (m, 2H), 4.99 (dd, J=12.4, 5.4 Hz, 1H), 4.44 (s, 2H), 4.01 (s, 6H), 3.92 (t, J=5.7 Hz, 2H), 3.82-3.72 (m, 6H), 3.64 (s, 3H), 3.39 (t, J=5.0 Hz, 2H), 2.93 (s, 6H), 2.88-2.61 (m, 5H), 2.29-2.18 (m, 1H). LCMS (ESI) m/z: [M+H]+=784.50.

Example 21—Preparation of 4-[[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D10 Formic Acid)

(192) ##STR00851##

(193) Intermediate i-21-1 was prepared in a similar manner to preparation of i19-4 in Example 19. To a stirred mixture of 6-([2-[2-(2-aminoethoxy)ethoxy]ethyl]amino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (100 mg, 0.200 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindole-1,3-dione (55.3 mg, 0.200 mmol, 1.00 equiv) in dimethylformamide (2 mL) was added diiopropylethylamine (129.3 mg, 1.001 mmol, 5.00 equiv). After stirring overnight at 90° C., the mixture was purified by Prep-HPLC (conditions: Atlantis HILIC OBD Column, 19*150 mm, 5 μm; mobile phase: A, water (0.1% formic acid) and B, acetonitrile (12% to 21% B in 9 minutes) to afford 4-[[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (4 mg, 2.5%). .sup.1H NMR (300 MHz, Methanol-d4) δ 9.03 (s, 1H), 8.57 (br s, 0.83H, formic acid), 7.51 (t, J=7.8 Hz, 1H), 7.40 (s, 1H), 7.00 (d, J=7.8 Hz, 2H), 6.83 (s, 2H), 6.50 (s, 1H), 4.96-4.90 (m, 1H), 4.32 (s, 2H), 3.96 (s, 6H), 3.71-3.63 (m, 8H), 3.56 (s, 3H), 3.53-3.48 (m, 2H), 3.42 (t, J=5.2 Hz, 2H), 2.85 (s, 6H), 2.78-2.57 (m, 3H), 2.00 (d, J=9.2 Hz, 1H). LCMS (ESI) m/z: [M+H].sup.+=756.45.

Example 22—Preparation of N-(5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)-3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propanamide formic acid (Compound D11 Formic Acid)

(194) ##STR00852##

(195) Compound D11 was prepared in a similar manner to Example 20. N-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-3-[2-(2-[[2-(2,6-dioxo piperidin-3-yl)-1,3-dioxoisoin dol-4-yl]amino]ethoxy)ethoxy]propanamide formic acid (8.1 mg, 6.62%) was obtained as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 9.10 (s, 1H), 8.57 (br s, 1H, FA), 8.45 (s, 1H), 7.64 (s, 1H), 7.34 (dd, J=8.6, 7.1 Hz, 1H), 6.90-6.75 (m, 4H), 4.86-4.82 (m, 1H), 4.61 (s, 1H), 4.33 (s, 2H), 4.02 (s, 6H), 3.94-3.84 (m, 2H), 3.77-3.71 (m, 6H), 3.65 (s, 3H), 3.36 (s, 1H), 2.85 (s, 6H), 2.75-2.66 (m, 3H), 2.63-2.54 (m, 1H), 2.47-2.31 (m, 1H), 1.84-1.73 (m, 1H). LCMS (ESI) m/z: [M+H]+=784.4.

Example 23—Preparation of 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthy ridin-3-yl)(methyl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]penty-l)acetamide formic acid (Compound D12 Formic Acid)

(196) ##STR00853##

Step 1: Preparation of tert-butyl 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetate (i22-1)

(197) ##STR00854##

(198) To a stirred solution of 4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (514 mg, 1.344 mmol, 1.00 equiv) and tert-butyl 2-bromoacetate (393.2 mg, 2.016 mmol, 1.50 equiv) in acetone was added cesium carbonate (875.8 mg, 2.688 mmol, 2.00 equiv) in portions at room temperature. The resulting mixture was stirred for 1 hour at room temperature. The resulting mixture was filtered, and the filter cake was washed with dichloromethane (3×10 mL). The filtrate was concentrated under reduced pressure. This resulted in tert-butyl 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetate (600 mg, 89.9%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=497.2

Step 2: Preparation of [(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetic acid (i22-2)

(199) ##STR00855##

(200) To a stirred solution of tert-butyl 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetate (600 mg, 1.208 mmol, 1.00 equiv) in dichloromethane was added trifluoroacetic acid (4 mL) dropwise at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC

(conditions: MeCN/water 30%) to afford [(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetic acid (450 mg, 84.6%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=441.

Step 3: Preparation of 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentyl)acetamide formic acid (Compound D12 Formic Acid)

(201) ##STR00856##

(202) Using a similar procedure as described in Example 11 and substituting with [(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]acetic acid (100 mg, 0.227 mmol, 1.00 equiv) and 4-[(5-aminopentyl)oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (122.4 mg, 0.341 mmol, 1.50 equiv) afforded 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)(methyl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentyl)acetamide formic acid (80 mg, 42.6%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (s, 1H), 8.51 (brs, 0.8H, formic acid), 7.78 (dd, J=8.6, 7.2 Hz, 1H), 7.48-7.42 (m, 2H), 7.25 (s, 1H), 7.14 (s, 1H), 6.89 (s, 2H), 5.10 (dd, J=12.4, 5.4 Hz, 1H), 4.82 (s, 2H), 4.27 (t, J=5.9 Hz, 2H), 4.08 (s, 2H), 3.94 (s, 6H), 3.66 (s, 3H), 3.40-3.36 (m, 2H), 3.28 (s, 6H), 2.98 (s, 3H), 2.90-2.67 (m, 3H), 2.19-2.08 (m, 1H), 1.97-1.86 (m, 2H), 1.74-1.61 (m, 4H). LCMS (ESI) m/z: [M+H]+=782.50.

Example 24—Preparation of N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethoxy]propanamide formic acid (Compound D13 Formic Acid)

(203) ##STR00857##

(204) Compound D13 was prepared in a similar manner to Example 20. N-(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]amino]ethoxy)ethoxy]propanamide formic acid (7 mg, 6.9%) was obtained. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.86 (d, J=0.9 Hz, 1H), 8.70 (d, J=0.9 Hz, 1H), 8.56 (brs, 0.9H, FA), 7.40 (s, 1H), 7.28 (d, J=8.4 Hz, 1H), 6.82 (s, 2H), 6.63 (d, J=2.2 Hz, 1H), 6.54 (dd, J=8.4, 2.2 Hz, 1H), 5.05-4.97 (m, 1H), 4.33 (s, 2H), 3.98 (s, 6H), 3.93 (t, J=5.6 Hz, 2H), 3.75-3.70 (m, 6H), 3.58 (s, 3H), 3.18 (t, J=5.4 Hz, 2H), 2.85 (s, 6H), 2.79-2.57 (m, 5H), 2.08-1.97 (m, 1H). LCMS (ESI) m/z: [M+H]+=784.55.

Example 25—Preparation of N-(5-(4-((dimethylamino)methyl)-3,5-dimethoxyphenyl)-7-methyl-8-oxo-7,8-dihydro-2,7-naphthyridin-3-yl)-3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)ethoxy)ethoxy)propanamide formic acid (Compound D14 Formic Acid)

(205) ##STR00858##

(206) Compound D13 was prepared in a similar manner to Example 20. N-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-3-[2-(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoin-dol-5-yl]amino]ethoxy)ethoxy]propanamide formic acid (6 mg, 6.62%) was obtained as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 9.19 (s, 1H), 8.55 (brs, 1.8H, FA), 8.51 (s, 1H), 7.65 (s, 1H), 7.33 (d, J=8.3 Hz, 1H), 6.83 (s, 2H), 6.67 (d, J=2.1 Hz, 1H), 6.56 (dd, J=8.4, 2.2 Hz, 1H), 5.05-4.98 (m, 1H), 4.36 (s, 2H), 4.00 (s, 6H), 3.87 (t, J=5.5 Hz, 2H), 3.72-3.63 (m, 6H), 3.59 (s, 3H), 3.13 (t, J=5.4 Hz, 2H), 2.90 (s, 6H), 2.83-2.60 (m, 5H), 2.11-2.00 (m, 1H). LCMS (ESI) m/z: [M+H]+=784.5.

Example 26—Preparation of 4-([5-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-5-oxopentyl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D15 Formic Acid)

(207) ##STR00859##

Step 1: Preparation of tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (i26-2)

(208) ##STR00860##

(209) To a solution of 2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]benzaldehyde (100 mg, 0.283 mmol, 1.00 equiv) and tert-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (87.1 mg, 0.340 mmol, 1.20 equiv) in MeOH (2.00 mL) was added NaBH.sub.3CN (35.6

mg, 0.566 mmol, 2.00 equiv), and the resulting solution was stirred at 25° C. for 2 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column with DCM/MeOH (20:1). This resulted in tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (110 mg, 65.5%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=594.

Step 2: Preparation of 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (i26-3)

(210) ##STR00861##

(211) To a solution of tert-butyl 9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carboxylate (100.0 mg, 0.168 mmol, 1.00 equiv) in DCM (2.00 mL) was added TFA (2.00 mL), and the resulting solution was stirred at 25° C. for 2 h. The resulting mixture was concentrated under vacuum to give 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (90 mg, crude) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H]+=494.

Step 3: Preparation of 4-([5-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-5-oxopentyl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D15 Formic Acid)

(212) ##STR00862##

(213) To a solution of 5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentanoic acid (15.2 mg, 0.041 mmol, 1.00 equiv) and HATU (30.8 mg, 0.081 mmol, 2.00 equiv), in solvent DMF (2.00 mL) was added 4-(3,5-dimethoxy-4-[1-oxa-4,9-diazaspiro[5.5]undecan-9-ylmethyl]phenyl)-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (20.0 mg, 0.041 mmol, 1.00 equiv) and DIEA (15.7 mg, 0.122 mmol, 3.00 equiv), and the resulting solution was stirred at 25° C. for 2 hours. The resulting mixture was concentrated. The crude product was purified by preparative HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; R.sub.t: 7.12 minutes) to afford 4-([5-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-5-oxopentyl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (20 mg, 52.8%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.56 (br s, 0.5H, FA), 8.51 (s, 1H), 7.83-7.74 (m, 1H), 7.50-7.42 (m, 2H), 7.24 (d, J=3.8 Hz, 1H), 7.11 (s, 1H), 6.83 (d, J=9.2 Hz, 2H), 5.12 (dd, J=12.2, 5.3 Hz, 1H), 4.33-4.22 (m, 3H), 3.93 (d, J=8.5 Hz, 7H), 3.83-3.69 (m, 3H), 3.67-3.60 (m, 5H), 3.51 (s, 2H), 3.22-3.10 (m, 2H), 2.97 (s, 3H), 2.92-2.63 (m, 5H), 2.18-1.86 (m, 8H), 1.83-1.69 (m, 2H). LCMS (ESI) m/z: [M+H]+=850.60.

Example 27—Preparation of 4-(4-(9-(2,6-dimethoxy-4-(2-methyl-7-(methylamino)-1-oxo-1,2-dihydro-2,6-naphthyridin-4-yl)benzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D16 Formic Acid)

(214) ##STR00863##

(215) Compound D16 was prepared in a similar manner to Example 26. 4-[4-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (16 mg, 20.0%) was obtained as a light brown solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.57 (brs, 0.6H, FA), 8.54 (d, J=4.5 Hz, 1H), 7.80 (t, J=7.9 Hz, 1H), 7.48 (dd, J=7.2, 5.0 Hz, 2H), 7.25 (d, J=1.0 Hz, 1H), 7.13 (d, J=4.6 Hz, 1H), 6.83 (d, J=10.9 Hz, 2H), 5.13 (dd, J=12.5, 5.5 Hz, 1H), 4.31 (t, J=5.7 Hz, 2H), 4.26-4.16 (m, 2H), 3.92 (d, J=12.1 Hz, 6H), 3.75-3.69 (m, 3H), 3.65 (s, 3H), 3.60-3.48 (m, 3H), 3.24-3.02 (m, 4H), 2.97 (s, 3H), 2.81-2.65 (m, 5H), 2.24-2.12 (m, 3H), 2.10-1.84 (m, 3H), 1.79-1.65 (m, 1H). LCMS (ESI) m/z: [M+H]+=836.45.

Example 28—Preparation of 4-(4-(4-(2,6-dimethoxy-4-(2-methyl-7-(methylamino)-1-oxo-1,2-dihydro-2,6-naphthyridin-4-yl)benzyl)piperazin-1-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D17 Formic Acid)

(216) ##STR00864##

(217) Compound D17 was prepared in a similar manner to Example 26. 4-[4-[4-([2,6-dimethoxy-4-[2-

methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (11.0 mg, 12.8%) was obtained as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.63 (s, 1H), 8.56 (brs, 0.9H, FA), 7.87-7.77 (m, 1H), 7.55 (d, J=8.5 Hz, 1H), 7.47 (d, J=7.2 Hz, 1H), 7.20 (s, 1H), 7.13 (s, 1H), 6.98 (d, J=4.8 Hz, 1H), 6.86 (s, 2H), 5.09 (dd, J=12.7, 5.4 Hz, 1H), 4.43 (d, J=12.5 Hz, 1H), 4.27 (dd, J=13.9, 7.8 Hz, 4H), 4.07 (d, J=13.6 Hz, 1H), 3.90 (s, 6H), 3.58-3.48 (m, 4H), 3.47-3.38 (m, 3H), 3.26-2.98 (m, 3H), 2.96-2.88 (m, 1H), 2.87-2.83 (m, 3H), 2.65-2.55 (m, 3H), 2.09-1.95 (m, 3H). LCMS (ESI) m/z: [M+H].sup.+=766.50.

Example 29—Preparation of 4-(4-(9-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-4-oxobutoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D18 Formic Acid)

(218) ##STR00865##

(219) Compound D18 was prepared in a similar manner to Example 26. 4-[4-[9-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-4-oxobutoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (12.7 mg) was obtained as a white solid. LCMS (ESI) m/z: [M+H]+=850.55. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.15 (s, 1H), 8.47 (brs, 1.2H, FA), 7.80 (t, J=7.9 Hz, 1H), 7.48 (d, J=9.9 Hz, 3H), 6.89 (d, J=7.2 Hz, 2H), 6.49 (d, J=3.7 Hz, 1H), 5.13 (dd, J=12.6, 5.5 Hz, 1H), 4.40 (s, 2H), 4.31 (s, 2H), 3.95 (d, J=12.5 Hz, 6H), 3.80-3.65 (m, 4H), 3.60 (d, J=3.1 Hz, 3H), 3.57-3.48 (m, 2H), 3.34 (s, 4H), 3.13 (s, 6H), 2.85-2.59 (m, 5H), 2.24-2.04 (m, 6H), 1.84-1.74 (m, 1H).

Example 30—Preparation of 5-((5-(9-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D19 Formic Acid)

(220) ##STR00866##

(221) Compound D19 was prepared in a similar manner to Example 26. 5-([5-[9-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-5-oxopentyl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (8.1 mg, 11.1%) was obtained as a white solid. LCMS (ESI) m/z: [M+H].sup.+=864.55. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.14 (d, J=1.8 Hz, 1H), 8.56 (brs, 0.5H, FA), 7.80 (t, J=9.0 Hz, 1H), 7.44 (d, J=2.6 Hz, 1H), 7.40 (dd, J=4.2, 2.2 Hz, 1H), 7.35-7.28 (m, 1H), 6.85 (d, J=6.7 Hz, 2H), 6.49 (s, 1H), 5.15-5.06 (m, 1H), 4.31-4.11 (m, 4H), 3.94 (d, J=4.9 Hz, 6H), 3.81-3.71 (m, 2H), 3.64-3.56 (m, 5H), 3.55-3.45 (m, 2H), 3.25-3.00 (m, 10H), 2.94-2.82 (m, 1H), 2.81-2.66 (m, 2H), 2.62-2.45 (m, 2H), 2.18-1.99 (m, 3H), 1.96-1.71 (m, 6H).

Example 31—Preparation of 5-(4-(2-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D20 Formic Acid)

(222) ##STR00867##

(223) To a mixture of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (30.0 mg, 0.082 mmol, 1.00 equiv) in DMF (1.00 mL) was added 2-(2,6-dioxo piperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (37.0 mg, 0.082 mmol, 1.00 equiv). The resulting mixture was stirred for 1 hour, and NaBH(OAc).sub.3 (34.6 mg, 0.163 mmol, 2.00 equiv) was added. The resulting mixture was stirred overnight at room temperature. Without any additional work-up, the mixture was purified by prep-HPLC (conditions: Phenomenex Gemini C6-Phenyl, 21.2*250 mm, 5 μm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 11% B to 17% B in 17 minutes; 254 nm; R.sub.T:14.2 minutes) to afford 5-(4-(2-(1-(4-(6-(dimethyl amino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione; formate acid (9.0 mg, 13.8%) as a yellow solid. .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.45 (brs, 0.6H, FA salt), 9.05 (s, 1H), 8.14 (s, 0.7H, FA), 7.75 (d, J=8.5 Hz, 1H), 7.61 (s, 1H), 7.46 (s, 1H), 7.34 (d, J=8.9 Hz, 1H), 6.90 (s, 2H), 6.52 (d, J=6.4 Hz, 1H), 5.09 (dd, J=12.7, 5.4 Hz, 1H), 4.21 (s, 3H), 3.91 (s, 7H), 3.50 (s, 4H), 3.47-3.37 (m, 4H), 3.20-3.05 (m, 9H), 3.04-2.86 (m, 4H), 2.74-2.54 (m, 3H), 2.09-1.98 (m, 1H), 1.97-1.75 (m, 3H), 1.70-1.48 (m, 4H). LCMS (ESI) m/z: [M+H]+=805.55.

Example 32—Preparation of 5-[4-(2-[2-[([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)(methyl)amino]ethoxy]ethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D21)

(224) ##STR00868##

Step 1: Preparation of tert-butyl N-[2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)ethyl]-N-methylcarbamate (i32-2)

(225) ##STR00869##

(226) To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (50.00 mg, 0.146 mmol, 1.00 equiv) and tert-butyl N-methyl-N-[2-(2-oxoethoxy)ethyl]carbamate (47.60 mg, 0.219 mmol, 1.50 equiv), in DMF (2.00 mL) was added NaBH.sub.3CN (18.36 mg, 0.292 mmol, 2.00 equiv), and the resulting solution was stirred at 25° C. for 3 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column with CH.sub.2Cl.sub.2/MeOH (20:1). This resulted in tert-butyl N-[2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethoxy)ethyl]-N-methylcarbamate (45 mg, 56.68%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=544.50.

Step 2: Preparation of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (i32-3)

(227) ##STR00870##

(228) A solution of tert-butyl N-[2-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]eth oxy)ethyl]-N-methylcarbamate (45.00 mg, 0.083 mmol, 1.00 equiv) in TFA (1.00 mL) and CH.sub.2Cl.sub.2 (1.00 mL) was stirred at 25° C. for 1 hour. The resulting mixture was concentrated, and the crude material was used directly without further purification. 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione was obtained as a yellow solid. LCMS (ESI) m/z: [M+H]+=444.50.

Step 3: Preparation of 5-[4-(2-[2-[([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)(methyl)amino]ethoxy]ethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D21)

(229) ##STR00871##

(230) To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(4-[2-[2-(methylamino)ethoxy]ethyl]piperazin-1-yl)isoindole-1,3-dione (50.00 mg, 0.113 mmol, 1.00 equiv) and 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (49.70 mg, 0.135 mmol, 1.20 equiv) in DMF (2.00 mL) was added NaBH.sub.3CN (14.17 mg, 0.225 mmol, 2.00 equiv), and the resulting solution was stirred at 25° C. for 3 hours. The resulting mixture was concentrated. The crude product was purified by preparative HPLC (conditions: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 20% B to 55% B in 8 minutes; 254 nm; R.sub.T: 7.12 minutes). This resulted in 5-[4-(2-[2-[([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)(methyl)amino]ethoxy]ethyl)piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindo le-1,3-dione (10 mg, 18.60%) as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 11.07 (s, 1H), 9.04 (s, 1H), 8.14 (brs, 0.2H, FA), 7.67 (d, J=8.5 Hz, 1H), 7.58 (s, 1H), 7.32 (d, J=2.3 Hz, 1H), 7.23 (dd, J=8.7, 2.3 Hz, 1H), 6.85 (s, 2H), 6.46 (s, 1H), 5.07 (dd, J=12.9, 5.4 Hz, 1H), 4.39-4.01 (m, 2H), 3.88 (s, 7H), 3.76 (s, 3H), 3.62 (t, J=5.7 Hz, 3H), 3.48 (s, 5H), 3.37-3.26 (m, 4H), 3.06 (s, 6H), 2.94-2.84 (m, 1H), 2.63-2.56 (m, 8H), 2.07-1.98 (m, 1H). LCMS (ESI) m/z: [M+H]+=795.45.

Example 33—Preparation 5-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D22 Formic Acid)

(231) ##STR00872##

(232) Compound D22 was prepared in a similar manner to Example 21. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.06 (s, 1H), 8.55 (brs, 1.7H, FA), 7.45 (d, J=8.4 Hz, 1H), 7.40 (s, 1H), 6.89 (d, J=2.2 Hz, 1H), 6.83 (s, 2H), 6.74 (dd, J=8.4, 2.2 Hz, 1H), 6.51 (d, J=0.7 Hz, 1H), 5.03 (dd, J=12.7, 5.5 Hz, 1H), 4.56 (s, 2H), 3.95 (s, 6H), 3.72-3.62 (m, 8H), 3.58-3.52 (m, 5H), 3.29 (t, J=5.3 Hz, 2H), 3.13 (s, 9H), 2.95-2.81 (m, 1H), 2.79-2.61 (m, 2H), 2.13-2.04 (m, 1H). LCMS (ESI) m/z: [M+H]+=770.45.

Example 34—Preparation 5-([5-[9-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-

naphthyridin-4-yl]phenyl]methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl]-5-oxopentyl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D23 Formic Acid)
(233) ##STR00873##
(234) Compound D22 was prepared in a similar manner to Example 26. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.58 (brs, 1.1H, formic acid), 8.51 (s, 1H), 7.80 (t, J=8.9 Hz, 1H), 7.43-7.39 (m, 1H), 7.35-7.29 (m, 1H), 7.24 (d, J=5.0 Hz, 1H), 7.10 (d, J=3.2 Hz, 1H), 6.83 (d, J=8.3 Hz, 2H), 5.10 (dt, J=11.0, 5.5 Hz, 1H), 4.22 (t, J=6.2 Hz, 3H), 4.10 (s, 1H), 3.93 (d, J=6.8 Hz, 6H), 3.81-3.75 (m, 1H), 3.75-3.70 (m, 1H), 3.65 (s, 3H), 3.63-3.49 (m, 4H), 3.22-3.03 (m, 4H), 2.97 (s, 3H), 2.90-2.71 (m, 3H), 2.52 (dt, J=30.3, 7.1 Hz, 2H), 2.18-2.08 (m, 1H), 2.07-1.97 (m, 2H), 1.96-1.69 (m, 6H). LCMS (ESI) m/z: [M+H]+=850.45.
Example 35—Preparation of 4-[[2-(2-[2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]ethoxy]ethoxy)ethyl]amino]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D24)
(235) ##STR00874##
(236) Compound D24 was prepared in a similar manner to Example 21. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.44 (d, J=0.9 Hz, 1H), 7.52-7.42 (m, 1H), 7.23 (d, J=0.9 Hz, 1H), 7.07 (s, 1H), 6.97 (dd, J=18.7, 7.8 Hz, 2H), 6.83 (s, 2H), 5.02-4.96 (m, 1H), 4.28-4.11 (m, 2H), 3.96 (s, 6H), 3.80-3.75 (m, 4H), 3.74-3.70 (m, 4H), 3.61 (s, 3H), 3.55 (t, J=5.3 Hz, 2H), 3.47 (t, J=5.1 Hz, 2H), 2.81-2.63 (m, 9H), 2.12-2.04 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=756.33.
Example 36—Preparation of 4-((5-((8-(4-((dimethylamino)methyl)-2,5-dimethoxyphenyl)-6-methyl-5-oxo-5,6-dihydro-2,6-naphthyridin-3-yl)amino)pentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (Compound D25)
(237) ##STR00875##
(238) Compound D25 was prepared in a similar manner to Example 17. .sup.1H NMR (300 MHz, Methanol-d4) δ 7.94 (s, 1H), 7.76 (dd, J=8.6, 7.2 Hz, 1H), 7.54 (s, 1H), 7.46-7.40 (m, 2H), 7.24 (s, 1H), 7.15 (s, 1H), 7.08 (s, 1H), 5.11 (d, J=10.8 Hz, 1H), 4.42 (s, 2H), 4.28 (t, J=5.8 Hz, 2H), 3.95 (s, 3H), 3.77 (s, 3H), 3.61 (s, 3H), 3.46 (t, J=6.5 Hz, 2H), 2.94 (s, 6H), 2.92-2.83 (m, 1H), 2.80-2.76 (m, 1H), 2.75-2.68 (m, 1H), 2.18-2.07 (m, 1H), 2.01-1.90 (m, 2H), 1.87-1.72 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=711.85.
Example 37—Preparation 2-[(8-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-6-methyl-5-oxo-2,6-naphthyridin-3-yl)amino]-N-(5-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-4-yl]oxy]pentyl) acetamide (Compound D26)
(239) ##STR00876##
(240) Compound D26 was prepared in a similar manner to Example 22. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.53 (br s, 1.3H, FA), 8.50 (s, 1H), 7.78 (dd, J=8.6, 7.2 Hz, 1H), 7.48-7.43 (m, 2H), 7.37 (s, 1H), 7.15 (s, 1H), 6.88 (s, 2H), 5.10 (dd, J=12.3, 5.4 Hz, 1H), 4.81 (s, 2H), 4.27 (t, J=5.9 Hz, 2H), 4.08 (s, 2H), 3.94 (s, 6H), 3.65 (s, 3H), 3.27 (s, 6H), 2.95-2.64 (m, 4H), 2.19-2.07 (m, 1H), 1.96-1.87 (m, 2H), 1.79-1.58 (m, 5H). LCMS (ESI) m/z: [M+H].sup.+=768.40.
Example 38—Preparation 4-((5-(9-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-5-oxopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione formic acid (Compound D27 Formic Acid)
(241) ##STR00877##
(242) Compound D27 was prepared in a similar manner to Example 23. .sup.1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 8.55 (brs, 1.0H, formic acid), 7.79 (t, J=7.9 Hz, 1H), 7.46 (d, J=8.4 Hz, 3H), 6.87 (d, J=7.2 Hz, 2H), 6.49 (s, 1H), 5.12 (dd, J=12.1, 5.4 Hz, 1H), 4.36-4.23 (m, 4H), 3.95 (d, J=6.4 Hz, 6H), 3.82-3.72 (m, 2H), 3.66-3.60 (m, 2H), 3.59 (s, 3H), 3.52 (s, 2H), 3.30-3.16 (m, 4H), 3.12 (s, 6H), 2.91-2.59 (m, 5H), 2.20-2.03 (m, 3H), 2.00-1.76 (m, 6H). LCMS (ESI) m/z: [M+H]+=864.40.
Example 39—Preparation of 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)azeti dine-3-sulfonamide (Compound D28)
(243) ##STR00878##
(244) A solution of N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-

yl]ethyl)azetidine-3-sulfonamide (60.00 mg, 0.119 mmol, 1.00 equiv) and 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (52.43 mg, 0.143 mmol, 1.20 equiv) in DMF (1.50 mL) was stirred for 20 minute at room temperature. Then NaBH.sub.3CN (14.95 mg, 0.238 mmol, 2.00 equiv) was added to the reaction mixture. The resulting mixture was stirred for 1 hour at room temperature. The crude product was purified by Prep-HPLC (conditions: Column, Phenomenex Gemini C6-Phenyl, 21.2*250 mm, 5 μm; mobile phase, Water (0.05% FA) and ACN (5% PhaseB up to 23% in 20 minutes); Detector, UV). This resulted in 1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-N-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl) azetidine-3-sulfonamide (13.4 mg, 13.16%) as a green solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.02 (s, 1H), 8.26 (s, 0.3H, FA), 7.66 (d, J=8.5 Hz, 1H), 7.55 (s, 1H), 7.33 (d, J=2.3 Hz, 1H), 7.23 (dd, J=8.7, 2.3 Hz, 1H), 7.07 (t, J=5.9 Hz, 1H), 6.75 (s, 2H), 6.47 (s, 1H), 5.07 (dd, J=12.9, 5.4 Hz, 1H), 4.01 (q, J=7.2 Hz, 1H), 3.81 (s, 6H), 3.62 (s, 2H), 3.49-3.45 (m, 5H), 3.44-3.39 (m, 7H), 3.06 (s, 8H), 2.94-2.82 (m, 1H), 2.59 (d, J=16.8 Hz, 3H), 2.55 (s, 2H), 2.42 (t, J=6.7 Hz, 2H), 2.07-1.97 (m, 1H). LCMS (ESI) m/z: [M+H]+=856.34.

Example 40—Preparation 4-[2-[4-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]-2-oxoethoxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D29)

(245) ##STR00879##

(246) Compound D27 was prepared in a similar manner to Example 23. .sup.1H NMR (300 MHz, Methanol-d4) δ 8.55 (d, J=0.9 Hz, 1H), 7.79 (dd, J=8.5, 7.3 Hz, 1H), 7.52 (d, J=7.2 Hz, 1H), 7.40 (d, J=8.5 Hz, 1H), 7.24 (d, J=0.9 Hz, 1H), 7.10 (s, 1H), 6.81 (s, 2H), 5.16-5.07 (m, 3H), 4.06 (s, 2H), 3.91 (s, 6H), 3.83-3.69 (m, 4H), 3.65 (s, 3H), 3.00-2.85 (m, 7H), 2.83-2.68 (m, 3H), 2.21-2.07 (m, 1H). LCMS (ESI) m/z: [M+H]+=738.45.

Example 41—Preparation of 5-(4-[2-[1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)piperidin-4-yl]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D30 Formic Acid)

(247) ##STR00880##

Step 1: Preparation of 4-bromo-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (i41-2)

(248) ##STR00881##

(249) To a stirred solution of 4-bromo-7-chloro-2-methyl-2,6-naphthyridin-1-one (200.00 mg, 0.731 mmol, 1.00 equiv) and methanamine hydrochloride (493.73 mg, 7.312 mmol, 10.00 equiv) in DMSO (15.00 mL) was added K.sub.2CO.sub.3 (2021.21 mg, 14.625 mmol, 20.00 equiv). The resulting mixture was stirred for 16 hours at 130° C. under nitrogen atmosphere. The resulting mixture was diluted with water (50 mL). The aqueous layer was extracted with EtOAc (4×15 mL). The resulting mixture was washed with brine (15 mL). The resulting mixture was concentrated under reduced pressure to afford 4-bromo-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (100 mg, 51.01%) as a yellow solid.

Step 2: Preparation of 2, 6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2, 6-naphthyridin-4-yl]benzaldehyde (i85-3)

(250) ##STR00882##

(251) To a stirred solution of 4-bromo-2-methyl-7-(methylamino)-2,6-naphthyridin-1-one (100.00 mg, 0.373 mmol, 1.00 equiv) and 4-formyl-3,5-dimethoxyphenylboronic acid (93.99 mg, 0.448 mmol, 1.20 equiv) in 1,4-dioxane/H2O (4:1) (5.00 mL) was added cesium carbonate (243.80 mg, 0.746 mmol, 2.00 equiv) and Pd(dppf)Cl.sub.2 (27.29 mg, 0.037 mmol, 0.10 equiv). The resulting mixture was stirred for 16 hours at 90° C. under nitrogen atmosphere. The resulting mixture was diluted with water (15 mL). The aqueous layer was extracted with EtOAc (3×20 mL). The organic layers were concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (40:1 to 10:1) to afford 2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]benzal dehyde (30 mg, 22.76%) as a yellow solid.

Step 3: Preparation of 5-(4-[2-[1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)piperidin-4-yl]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid (Compound D30 Formic Acid)

(252) ##STR00883##
(253) A solution of 2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]benzaldehyde (25.00 mg, 0.071 mmol, 1.00 equiv) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (32.09 mg, 0.071 mmol, 1.00 equiv) in DMF (1.00 mL) was stirred for 1 hour at 20° C. under nitrogen atmosphere. To the above mixture was added NaBH(OAc).sub.3 (29.99 mg, 0.141 mmol, 2 equiv). The resulting mixture was stirred for additional 1 hour at 20° C. The crude product was purified by Prep-HPLC (conditions: SunFire C18 OBD Prep Column, 100 Å, 5 μm, 19 mm×250 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/minute; Gradient: 9 B to 16 B in 13 minutes; 254 nm; R.sub.T: 11.47 minutes) to afford 5-(4-[2-[1-([2,6-dimethoxy-4-[2-methyl-7-(methylamino)-1-oxo-2,6-naphthyridin-4-yl]phenyl]methyl)piperidin-4-yl]ethyl]piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (11.7 mg, 20.91%) as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.54 (s, 1H), 8.15 (s, 0.9H, FA), 7.68 (d, J=8.4 Hz, 1H), 7.34 (d, J=2.4 Hz, 1H), 7.28-7.23 (m, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 6.93 (d, J=5.1 Hz, 1H), 6.78 (s, 2H), 5.07 (dd, J=12.8, 5.4 Hz, 1H), 3.85 (s, 9H), 3.53 (s, 4H), 3.44-3.42 (m, 5H), 3.12-3.08 (m, 2H), 2.91-2.87 (m, 1H), 2.85 (d, J=4.9 Hz, 3H), 2.64-2.53 (m, 3H), 2.37-2.32 (m, 3H), 2.04-1.99 (m, 1H), 1.77-1.70 (m, 2H), 1.47-1.37 (m, 3H), 1.32-1.23 (m, 3H). LCMS (ESI) m/z: [M+H]+=791.50.
Example 42—Preparation of 4-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D31)
(254) ##STR00884##
Step 1: Preparation of tert-butyl N-[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxy)ethyl]carbamate (i42-2)
(255) ##STR00885##
(256) To a stirred solution of 6-chloro-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (335.0 mg, 0.864 mmol, 1.00 equiv) and tert-butyl N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]carbamate (643.4 mg, 2.591 mmol, 3.00 equiv) in DMSO (2 mL) was added K.sub.2CO.sub.3 (238.7 mg, 1.727 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred overnight at 130 degrees C. The mixture was allowed to cool down to room temperature. The resulting mixture was filtered, and the filter cake was washed with CH.sub.2Cl.sub.2 (2×3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography (conditions: column, C18 silica gel; Mobile Phase A: Water/0.05% TFA, Mobile Phase B: ACN; Flow rate: 50 mL/min; Gradient: 0% B to 40% B in 15 min; detector, 254 nm) to afford tert-butyl N-[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxy) ethyl]carbamate (380 mg, 73.36%) as a yellow oil. LCMS (ESI) m/z: [M+H].sup.+=600.
Step 2: Preparation of tert-butyl N-[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)(methyl)amino]ethoxy]ethoxy)ethyl]carbamate (i42-3)
(257) ##STR00886##
(258) To a stirred solution/mixture of tert-butyl N-[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)amino]ethoxy]ethoxy)ethyl]carbamate (190.0 mg, 0.317 mmol, 1.00 equiv) and K.sub.2CO.sub.3 (87.6 mg, 0.634 mmol, 2 equiv) in acetone (3 mL) was added dimethyl sulfate (44.0 mg, 0.348 mmol, 1.10 equiv) at room temperature. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water at room temperature. The aqueous layer was extracted with CH.sub.2Cl.sub.2/isopropanol (3×5 mL). The combined organic layers were washed with brine (1×10 mL) and dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl N-[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)(methyl)amino]ethoxy]ethoxy)ethyl]carbamate (95.00 mg, 48.86%) as a yellow oil. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=614.
Step 3: Preparation of 3,3,3-tritfluoropropanoic acid; 6-([2-[2-(2-aminoethoxy)ethoxy]ethyl]

(methyl)amino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (i42-4)
(259) ##STR00887##
(260) To a stirred solution of tert-butyl N-[2-(2-[2-[(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl) (methyl)amino]ethoxy]ethoxy)ethyl]carbamate (75.00 mg, 0.122 mmol, 1.00 equiv) in dichloromethane (3 mL) was added TFA (1 mL) dropwise at room temperature. The resulting mixture was concentrated under vacuum to afford 3,3,3-trifluoropropanoic acid; 6-([2-[2-(2-amino ethoxy)ethoxy]ethyl] (methyl)amino)-4-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (103 mg, crude) as yellow oil. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=514.
Step 4: Preparation of 4-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (Compound D31)
(261) ##STR00888##
(262) To a stirred solution of 6-([2-[2-(2-aminoethoxy)ethoxy]ethyl](methyl)amino)-4-[4-[(dimethylamino) methyl]-3,5-dimethoxyphenyl]-2-methyl-2,7-naphthyridin-1-one (68.00 mg, 0.132 mmol, 1.00 equiv) in DMF (1 mL) was added 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindole-1,3-dione (34.6 mg, 0.125 mmol, 0.95 equiv) and DIEA (85.6 mg, 0.662 mmol, 5.00 equiv) at room temperature. The resulting mixture was stirred for overnight at 80 degrees C. The crude product was purified by Prep-HPLC (conditions: Xselect CSH F-Phenyl OBD Column 19*150 mm 5 um; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 9 B to 19 B in 12 min; 254 nm; R.sub.t:12.63 minutes) to afford 4-[10-(5-[4-[(dimethylamino)methyl]-3,5-dimethoxyphenyl]-7-methyl-8-oxo-2,7-naphthyridin-3-yl)-4,7-dioxa-1,10-diazaundecan-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (3.2 mg, 3.14%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 8.96 (s, 1H), 7.54-7.46 (m, 2H), 6.99 (dd, J=15.8, 7.7 Hz, 2H), 6.84 (s, 2H), 6.74 (s, 1H), 4.96-4.94 (m, 1H), 4.57 (s, 2H), 3.97 (s, 6H), 3.77-3.69 (m, 8H), 3.59-3.53 (m, 5H), 3.41 (t, J=5.2 Hz, 2H), 3.17-3.11 (m, 9H), 2.83-2.53 (m, 3H), 2.04-1.95 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=770.50.
Example 43—Preparation of Compounds D32-D184
(263) In analogy to the procedures described in the examples above, compounds D32-D184 were prepared using the appropriate starting materials
(264) TABLE-US-00007 Compound No. LCMS .sup.1H NMR D32 856.34 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.02 (s, 1H), 8.26 (s, 0.3H, FA), 7.66 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 7.07 (t, J = 5.9 Hz, 1H), 6.75 (s, 2H), 6.47 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.01 (q, J = 7.2 Hz, 1H), 3.81 (s, 6H), 3.62 (s, 2H), 3.49-3.45 (m, 5H), 3.44-3.39 (m, 7H), 3.06 (s, 8H), 2.94-2.82 (m, 1H), 2.59 (d, J = 16.8 Hz, 3H), 2.55 (s, 2H), 2.42 (t, J = 6.7 Hz, 2H), 2.07-1.97 (m, 1H). D33 836.6 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.03 (d, J = 1.6 Hz, 1H), 8.20 (s, 0.8H, FA), 7.82 (dd, J = 8.3, 2.3 Hz, 1H), 7.58 (s, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 6.75 (s, 2H), 6.43 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.38-4.17 (m, 3H), 3.98-3.88 (m, 1H), 3.79 (s, 6H), 3.77-3.65 (m, 6H), 3.65-3.60 (m, 3H), 3.26 (s, 2H), 3.05 (s, 6H), 2.99-2.79 (m, 4H), 2.63-2.52 (m, 4H), 2.29-2.12 (m, 1H), 2.10-1.99 (m, 1H), 1.54-1.29 (m, 2H). D34 834.37 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 7.82 (dd, J = 8.5, 7.3 Hz, 1H), 7.69 (s, 1H), 7.59-7.50 (m, 2H), 7.45 (d, J = 7.2 Hz, 1H), 6.73 (s, 2H), 6.46 (s, 1H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (t, J = 6.4 Hz, 2H), 3.80 (s, 6H), 3.48 (s, 5H), 3.07 (s, 9H), 2.94-2.81 (m, 1H), 2.62-2.54 (m, 2H), 2.04 (s, 4H), 1.91 (s, 5H), 1.82-1.72 (m, 2H), 1.53-1.39 (m, 4H). D35 847.35 1H-NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.64 (t, J = 5.8 Hz, 1H), 7.61-7.55 (m, 2H), 7.10 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.76 (s, 2H), 6.52 (t, J = 5.9 Hz, 1H), 6.47 (s, 1H), 5.05 (dd, J = 12.8, 5.4 Hz, 1H), 3.82 (s, 6H), 3.60 (s, 2H), 3.48 (s, 3H), 3.31-3.25 (m, 2H), 3.06 (s, 6H), 3.05- 3.00 (m, 2H), 2.93-2.85 (m, 1H), 2.62-2.52 (m, 4H), 2.16 (s, 3H), 2.06-1.99 (m, 1H), 1.85 (s, 6H), 1.63-1.54 (m, 2H), 1.49-1.40 (m, 2H), 1.36-1.26 (m, 2H). D36 848.4 1H-NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.66 (t, J = 5.8 Hz, 1H), 7.57 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 6.76 (s, 2H), 6.47 (s, 1H),

5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.20 (t, J = 6.3 Hz, 2H), 3.82 (s, 6H), 3.63 (s, 2H), 3.48 (s, 3H), 3.09-3.01 (m, 8H), 2.94-2.83 (m, 1H), 2.63-2.52 (m, 4H), 2.18 (s, 3H), 2.06- 1.98 (m, 1H), 1.86 (s, 6H), 1.77 (t, J = 6.9 Hz, 2H), 1.53-1.38 (m, 4H). D37 875.7 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.03 (s, 1H), 8.30 (s, 1H, FA), 7.59-7.51 (m, 2H), 7.19-7.09 (m, 2H), 7.03 (d, J = 7.0 Hz, 1H), 6.74 (s, 2H), 6.60 (t, J = 5.8 Hz, 1H), 6.46 (s, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 3.97 (t, J = 7.5 Hz, 1H), 3.80 (s, 6H), 3.63- 3.55 (m, 6H), 3.54-3.51 (m, 2H), 3.48-3.45 (m, 6H), 3.44- 3.42 (m, 5H), 3.06 (s, 8H), 2.93-2.83 (m, 1H), 2.62-2.54 (m, 2H), 2.06-1.97 (m, 1H). D38 848.35 1H-NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.03 (s, 1H), 8.17 (s, 1H, FA), 7.83 (d, J = 8.3 Hz, 1H), 7.67 (t, J = 5.8 Hz, 1H), 7.57 (s, 1H), 7.42 (d, J = 2.3 Hz, 1H), 7.34 (dd, J = 8.3, 2.3 Hz, 1H), 6.76 (s, 2H), 6.47 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.82 (s, 6H), 3.62 (s, 2H), 3.48 (s, 3H), 3.09-3.02 (m, 8H), 2.94-2.84 (m, 1H), 2.64-2.53 (m, 4H), 2.18 (s, 3H), 2.10- 2.01 (m, 1H), 1.87 (s, 6H), 1.80-1.72 (m, 2H), 1.52-1.35 (m, 4H). D39 847.4 1H-NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 9.04 (s, 1H), 8.19 (s, 1H, FA), 7.64 (t, J = 5.8 Hz, 1H), 7.56 (d, J = 9.5 Hz, 2H), 7.10 (t, J = 5.2 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.84 (dd, J = 8.5, 2.1 Hz, 1H), 6.75 (s, 2H), 6.47 (s, 1H), 5.03 (dd, J = 12.9, 5.4 Hz, 1H), 3.81 (s, 6H), 3.57 (s, 2H), 3.48 (s, 3H), 3.17-3.11 (m, 2H), 3.06 (s, 6H), 3.05-3.01 (m, 2H), 2.92-2.83 (m, 1H), 2.61-2.52 (m, 4H), 2.15 (s, 3H), 2.01-1.95 (m, 1H), 1.85 (s, 6H), 1.62-1.53 (m, 2H), 1.49- 1.40 (m, 2H), 1.39-1.30 (m, 2H). D40 834.37 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.70 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.73 (s, 2H), 6.50 (d, J = 31.5 Hz, 1H), 5.12 (dd, J = 13.1, 5.3 Hz, 1H), 4.18 (t, J = 6.5 Hz, 2H), 3.80 (s, 6H), 3.48 (s, 5H), 3.07 (s, 8H), 2.95-2.84 (m, 1H), 2.70-2.59 (m, 2H), 2.31-2.18 (m, 1H), 2.04 (s, 4H), 1.91 (s, 5H), 1.82-1.70 (m, 2H), 1.54-1.32 (m, 4H). D41 793.55 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 8.43 (s, 2H. FA). 72 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.40 (d, J = 2.2 Hz, 1H), 7.28 (dd, J = 8.6, 2.3 Hz, 1H), 7.12 (s, 1H), 7.07 (dd, J = 10.0, 1.4 Hz, 1H), 6.44 (d, J = 0.7 Hz, 1H), 5.10 (dd, J = 12.4, 5.4 Hz, 1H), 4.38 (s, 2H), 4.02 (s, 3H), 3.64-3.49 (m, 9H), 3.19-3.08 (m, 8H), 2.92-2.68 (m, 7H), 2.66-2.55 (m, 2H), 2.18-1.99 (m, 3H), 1.83-1.49 (m, 5H). D42 846.5 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.84 (d, J = 8.2 Hz, 1H), 7.59 (s, 1H), 7.35-7.26 (m, 2H), 6.80 (s, 2H), 6.47 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 5.07- 4.98 (m, 1H), 3.91 (s, 2H), 3.84 (d, J = 1.8 Hz, 6H), 3.68 (s, 2H), 3.49 (s, 4H), 3.45-3.40 (m, 3H), 3.07 (s, 7H), 2.95-2.84 (m, 1H), 2.76-2.58 (m, 5H), 2.58-2.53 (m, 3H), 2.09-1.99 (m, 1H), 1.92- 1.82 (m, 2H), 1.67-1.44 (m, 4H). D43 777.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.46-7.36 (m, 2H), 6.85 (s, 2H), 6.49 (s, 1H), 5.12 (dd, J = 12.6, 5.4 Hz, 1H), 4.23 (s, 2H), 4.13-4.05 (m, 1H), 3.96 (s, 6H), 3.92-3.88 (m, 1H), 3.87-3.80 (m, 5H), 3.79- 3.72 (m, 3H), 3.69-3.64 (m, 1H), 3.59 (s, 3H), 3.51-3.44 (m, 1H), 3.19-3.14 (m, 2H), 3.14-3.07 (m, 7H), 2.94-2.84 (m, 1H), 2.81- 2.68 (m, 2H), 2.60-2.48 (m, 1H), 2.19-2.07 (m, 2H). D44 791.4 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.14 (s, 1H, FA), 8.52 (s, 2H), 7.80 (d, J = 8.3 Hz, 1H), 7.50 (s, 1H), 7.43-7.33 (m, 2H), 6.81 (s, 2H), 6.46 (s, 1H), 5.11 (dd, J = 12.4, 5.4 Hz, 1H), 4.09 (s, 3H), 3.92 (s, 7H), 3.91-3.69 (m, 9H), 3.58 (s, 3H), 3.10 (s, 7H), 2.91-2.74 (m, 5H), 2.60-2.42 (m, 1H), 2.21-1.98 (m, 4H), 1.41-1.30 (m, 1H). D45 735.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.01 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.45-7.41 (m, 2H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 6.16-6.07 (m, 3H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.18 (t, J = 6.5 Hz, 2H), 3.71 (s, 3H), 3.44 (s, 3H), 3.30-3.24 (m, 3H), 3.07 (s, 2H), 3.03 (s, 6H), 2.95-2.84 (m, 1H), 2.67-2.57 (m, 3H), 2.09-2.01 (m, 1H), 1.82-1.71 (m, 2H), 1.61-1.49 (m, 2H), 1.48-1.40 (m, 2H), 1.47 (s, 6H). D46 816.5 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.13 (s, 1H), 8.56 (s, 1H, fa), 7.82 (d, J = 8.3 Hz, 1H), 7.31-7.23 (m, 3H), 6.19 (d, J = 4.5 Hz, 3H), 5.13 (s, 1H), 4.98-4.96 (m, 1H), 4.62 (s, 4H), 3.78 (s, 3H), 3.56 (s, 3H), 3.37 (s, 1H), 3.15-3.13 (m, 1H), 3.10 (s, 6H), 2.94- 2.83 (m, 4H), 2.80-2.67 (m, 4H), 2.64-2.56 (m, 2H), 2.18-2.10 (m, 1H), 2.08-2.03 (m, 3H), 1.98-1.85 (m, 4H), 1.83-1.67 (m, 4H), 1.57-1.44 (m, 2H). D47 735.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.01 (s, 1H), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 3.6 Hz, 2H), 6.15-6.07 (m, 3H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (t, J = 6.4 Hz, 2H), 3.71 (s, 3H), 3.44 (s, 3H), 3.32-3.22 (m, 3H), 3.09-3.05 (m, 2H), 3.03 (s, 6H), 2.93-2.83 (m, 1H), 2.68-2.55 (m, 3H), 2.07-1.98 (m, 1H), 1.77 (p, J = 6.5 Hz, 2H), 1.59-1.45 (m, 4H), 1.37 (s, 6H). D48 776.04 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.17 (s, 1H), 8.43 (s, 3H, FA), 8.37 (s, 1H), 7.75-7.66 (m, 2H), 7.50 (s, 1H), 7.41 (s, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.34 (s, 1H), 5.10 (dd, J = 12.3, 5.4 Hz, 1H), 4.50 (s, 2H), 4.01 (s, 3H), 3.71-3.52 (m, 10H), 3.19-3.09 (m, 8H), 2.96-2.82 (m, 1H),

2.79-2.71 (m, 5H), 2.61 (t, J = 7.6 Hz, 2H), 2.18-2.01 (m, 3H), 1.81-1.59 (m, 5H). D49 789.4 D50 803.5 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 8.21 (s, 2H, FA), 7.64 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 6.80-6.75 (m, 3H), 6.64 (dd, J = 8.4, 2.1 Hz, 1H), 6.47 (s, 1H), 5.05 (dd, J = 12.9, 5.3 Hz, 1H), 3.83 (d, J = 1.3 Hz, 8H), 3.74 (s, 4H), 3.59 (s, 2H), 3.49 (s, 3H), 3.17 (s, 2H), 3.08 (s, 6H), 2.93-2.84 (m, 1H), 2.66-2.53 (m, 3H), 2.48-2.42 (m, 2H), 2.29 (s, 4H), 2.05-1.96 (m, 1H), 1.79- 1.68 (m, 4H). D51 789.65 D52 777.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 8.16 (s, 1H, FA), 7.68 (d, J = 8.6 Hz, 1H), 7.59 (s, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.9 Hz, 1H), 6.77 (s, 2H), 6.49 (s, 1H), 5.07 (dd, J = 12.6, 5.3 Hz, 1H), 3.82 (s, 7H), 3.63-3.60 (m, 1H), 3.48 (s, 4H), 3.45-3.39 (m, 5H), 3.08 (s, 6H), 3.01-2.88 (m, 3H), 2.64- 2.55 (m, 5H), 2.23-2.13 (m, 2H), 2.06-1.96 (m, 1H), 1.78-1.69 (m, 2H), 1.51-1.35 (m, 2H). D53 777.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.32 (d, J = 2.3 Hz, 1H), 7.24 (dd, J = 8.7, 2.3 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.05 (d, J = 12.8 Hz, 2H), 3.81 (s, 6H), 3.56 (s, 2H), 3.48 (s, 3H), 3.28-3.20 (m, 2H), 3.07 (s, 6H), 3.01-2.83 (m, 3H), 2.64- 2.53 (m, 3H), 2.48-2.41 (m, 6H), 2.06-1.96 (m, 1H), 1.83 (d, J = 12.3 Hz, 2H), 1.51-1.36 (m, 2H). D54 846.8 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 8.19 (s, 2H, FA), 7.83 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.33-7.24 (m, 2H), 6.79 (s, 2H), 6.49 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.99 (p, J = 6.9 Hz, 1H), 3.83 (s, 6H), 3.71 (s, 2H), 3.48 (s, 3H), 3.08 (s, 6H), 3.00-2.83 (m, 3H), 2.66-2.55 (m, 2H), 2.47-2.23 (m, 8H), 2.15-2.00 (m, 3H), 1.85-1.75 (m, 2H), 1.71-1.51 (m, 7H), 1.24- 1.08 (m, 2H). D55 860.75 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.56 (s, 1H, FA), 7.82 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.25 (dd, J = 8.3, 2.3 Hz, 1H), 6.86 (s, 2H), 6.51 (s, 1H), 5.12 (dd, J = 12.6, 5.5 Hz, 1H), 5.01-4.93 (m, 1H), 4.18 (s, 2H), 3.94 (d, J = 2.2 Hz, 6H), 3.64-3.57 (m, 5H), 3.54 (s, 2H), 3.48- 3.34 (m, 4H), 3.13 (s, 6H), 2.97-2.84 (m, 3H), 2.81-2.71 (m, 2H), 2.64-2.54 (m, 2H), 2.19-2.10 (m, 1H), 2.07-2.01 (m, 2H), 2.00- 1.95 (m, 1H), 1.93-1.85 (m, 2H), 1.79-1.63 (m, 4H). D56 817.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.21 (s, 1H, FA), 7.68 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.6, 2.3 Hz, 1H), 6.76 (s, 2H), 6.48 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 3.82 (s, 6H), 3.58 (s, 3H), 3.48 (s, 3H), 3.46-3.38 (m, 5H), 3.07 (s, 6H), 2.94-2.84 (m, 1H), 2.72- 2.64 (m, 1H), 2.63-2.53 (m, 2H), 2.41-2.29 (m, 6H), 2.06-1.98 (m, 1H), 1.96-1.87 (m, 2H), 1.59-1.50 (m, 4H), 1.47 (s, 2H). D57 791.4 .sup.1H NMR (300 MHz, DMSO) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.23 (s,1H, FA), 7.68 (d, 1H), 7.58 (s, 1H), 7.33 (d, 1H), 7.25 (dd, 1H), 6.76 (s, 2H), 6.49 (s, 1H), 5.08 (dd, 1H), 3.81 (s, 6H), 3.56 (s, 2H), 3.48 (s, 3H), 3.45-3.40 (m, 4H), 3.07 (s, 6H), 2.87 (d, 3H), 2.64- 2.53 (m, 2H), 2.45 (s, 4H), 2.20-1.98 (m, 5H), 1.66 (d, 2H), 1.52- 1.45 (m, 1H), 1.21-1.99 (m, 2H). D58 749.74 D59 762.26 D60 803.3 D61 748.47 D62 776.4 D63 746.44 D64 774.16 D65 786.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.03 (s, 1H), 8.20 (s, 1H FA), 7.97-7.79 (m, 3H), 7.58 (s, 1H), 6.76 (s, 2H), 6.46 (s, 1H), 5.17 (dd, J = 12.8, 5.4 Hz, 1H), 3.81 (s, 6H), 3.63 (d, J = 15.9 Hz, 4H), 3.48 (s, 3H), 3.06 (s, 6H), 2.95-2.85 (m, 1H), 2.68 (t, J = 6.8 Hz, 2H), 2.65-2.55 (m, 2H), 2.50-2.35 (m, 6H), 2.14-1.99 (m, 1H), 1.59-1.51 (m, 6H). D66 803.45 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.92-6.83 (m, 3H), 6.48 (s, 1H), 5.08 (dd, J = 12.4, 5.4 Hz, 1H), 4.51 (s, 2H), 4.32-4.17 (m, 6H), 4.13-4.03 (m, 2H), 3.97 (s, 6H), 3.74-3.64 (m, 3H), 3.61- 3.52 (m, 5H), 3.13 (s, 6H), 2.94-2.67 (m, 3H), 2.35 (t, J = 6.9 Hz, 2H), 2.17-2.06 (m, 1H). D67 818.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.83 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.36-7.20 (m, 2H), 6.83 (s, 2H), 6.47 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.98 (p, J = 7.0 Hz, 1H), 4.03 (s, 2H), 3.89-3.76 (m, 8H), 3.53-3.36 (m, 6H), 3.08 (s, 6H), 2.96-2.83 (m, 1H), 2.80-2.70 (m, 1H), 2.64- 2.53 (m, 3H), 2.48-2.33 (m, 4H), 2.28 (s, 2H), 2.09-2.00 (m, 1H), 1.87-1.75 (m, 2H), 1.67-1.50 (m, 4H). D68 734.71 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.45 (s, 1H), 8.72 (d, J = 5.7 Hz, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.55 (d, J = 5.7 Hz, 1H), 6.84 (s, 2H), 5.14 (d, J = 13.2 Hz, 1H), 4.98 (s, 2H), 4.35 (s, 2H), 3.91-3.71 (m, 6H), 3.59 (s, 3H), 3.03-2.78 (m, 1H), 2.73 (s, 2H), 2.67-2.49 (m, 1H), 2.05 (s, 2H). D69 749.52 D70 694.5 D71 752 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.04 (s, 1H), 8.18 (s, 0H, FA)7.80 (dd, J = 8.5, 7.2 Hz, 1H), 7.58 (s, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.48-7.41 (m, 1H), 6.74 (s, 2H), 6.49 (s, 1H), 5.09 (dd, J = 12.9, 5.4 Hz, 1H), 4.28 (dd, J = 9.9, 5.2 Hz, 1H), 4.12- 4.02 (m, 1H), 3.80 (s, 6H), 3.53 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 3.03-2.76 (m, 3H), 2.64-2.54 (m, 6H), 2.40 (s, 3H), 2.08-1.98 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H). D72 772.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 9.04 (s, 1H), 7.99-7.90 (m,

3H), 7.57 (s, 1H), 6.86 (s, 2H), 6.44 (s, 1H), 5.16 (dd, J = 12.9, 5.3 Hz, 1H), 4.29 (d, J = 19.7 Hz, 6H), 3.88 (s, 6H), 3.48 (s, 6H), 3.06 (s, 6H), 2.92-2.80 (m, 1H), 2.77-2.55 (m, 3H), 2.14-2.00 (m, 1H), 1.22 (s, 6H). D73 800.5 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.03 (s, 1H), 8.22 (s, 1H, FA), 7.97-7.88 (m, 1H), 7.88-7.79 (m, 2H), 7.56 (s, 1H), 6.75 (s, 2H), 6.45 (s, 1H), 5.16 (dd, J = 12.8, 5.4 Hz, 1H), 3.80 (s, 6H), 3.69 (s, 3H), 3.48 (s, 5H), 3.14-2.96 (m, 11H), 2.93-2.87 (m, 1H), 2.69-2.67(m, 1H), 2.63-2.58 (m, 1H), 2.13-2.00 (m, 1H), 1.65 (s, 4H), 1.41 (s, 6H). D74 793.3 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.45 (s, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.92-6.83 (m, 3H), 6.48 (s, 1H), 5.08 (dd, J = 12.4, 5.4 Hz, 1H), 4.51 (s, 2H), 4.32-4.17 (m, 6H), 4.13-4.03 (m, 2H), 3.97 (s, 6H), 3.74-3.64 (m, 3H), 3.61- 3.52 (m, 5H), 3.13 (s, 6H), 2.94-2.67 (m, 3H), 2.35 (t, J = 6.9 Hz, 2H), 2.17-2.06 (m, 1H). D75 861.43 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.23 (s, 2H, TFA), 9.06 (s, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.36-7.25 (m, 2H), 6.92 (s, 2H), 6.51 (s, 1H), 5.17-4.98 (m, 2H), 4.22 (s, 2H), 3.91 (s, 6H), 3.54-3.19 (m, 9H), 3.09 (s, 8H), 2.95-2.84 (m, 2H), 2.71-2.54 (m, 3H), 2.46-2.39 (m, 1H), 2.25-2.12 (m, 1H), 2.06- 1.65 (m, 11H), 1.20 (d, J = 6.7 Hz, 3H). D76 752 .sup.1H NMR (400 MHz, DMSO-d6, D2O) δ 9.01 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 3.3 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.37 (dd, J = 8.3, 2.2 Hz, 1H), 6.83 (s, 2H), 6.47 (s, 1H), 5.08 (dd, J = 12.9, 5.5 Hz, 1H), 5.04-4.95 (m, 1H), 4.23 (s, 2H), 3.85 (s, 6H), 3.50- 3.42 (m, 4H), 3.37-3.09 (m, 5H), 3.04 (s, 8H), 2.96-2.78 (m, 5H), 2.65-2.57 (m, 1H), 2.08-1.99 (m, 1H), 1.27 (d, J = 6.0 Hz, 3H). D77 752 .sup.1H NMR (400 MHz, DMSO-d6, D2O) δ 9.00 (s, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.39 (dd, J = 8.4, 2.3 Hz, 1H), 6.82 (s, 2H), 6.48 (s, 1H), 5.06 (dd, J = 12.9, 5.5 Hz, 1H), 4.31-4.23 (m, 4H), 3.84 (s, 6H), 3.56-3.49 (m, 1H), 3.46 (s, 3H), 3.41-3.14 (m, 8H), 3.03 (s, 6H), 2.87-2.77 (m, 1H), 2.70-2.57 (m, 2H), 2.09-2.01 (m, 1H), 1.25 (d, J = 6.7 Hz, 3H) D78 766.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.59 (s, 1H), 7.51-7.37 (m, 2H), 6.77 (s, 2H), 6.49 (s, 1H), 5.13 (dd, J = 12.9, 5.3 Hz, 1H), 3.82 (s, 6H), 3.65 (s, 2H), 3.51 (s, 5H), 3.07 (s, 6H), 2.93-2.84 (m, 1H), 2.59 (d, J = 11.6 Hz, 10H), 2.06 (dd, J = 10.9, 5.3 Hz, 1H), 1.35 (s, 6H). D79 872.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.02 (s, 1H), 8.15 (s, 0H, FA)7.84 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.34-7.27 (m, 2H), 6.78 (s, 2H), 6.22 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.03 (t, J = 6.8 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.84 (d, J = 2.1 Hz, 6H), 3.76 (s, 2H), 3.49 (s, 3H), 3.44 (s, 6H), 3.07-2.97 (m, 2H), 2.94- 2.85 (m, 1H), 2.66-2.53 (m, 3H), 2.45-2.30 (m, 4H), 2.09-2.01 (m, 1H), 1.92-1.83 (m, 2H), 1.67-1.47 (m, 8H). D80 858.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.02 (s, 1H), 8.18 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.34-7.24 (m, 2H), 6.76 (s, 2H), 6.21 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.98 (p, J = 6.4 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.83 (s, 6H), 3.70 (s, 2H), 3.48 (s, 3H), 3.02-2.80 (m, 4H), 2.67-2.59 (m, 1H), 2.47- 2.39 (m, 3H), 2.37-2.22 (m, 7H), 2.14-2.01 (m, 3H), 1.87-1.75 (m, 2H), 1.71-1.48 (m, 7H), 1.22-1.03 (m, 2H). D81 766.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.65-7.56 (m, 2H), 7.52 (d, J = 7.1 Hz, 1H), 6.79 (s, 2H), 6.48 (s, 1H), 5.09 (dd, J = 12.9, 5.3 Hz, 1H), 3.83 (s, 6H), 3.73 (s, 2H), 3.48 (s, 3H), 3.43-3.35 (m, 2H), 3.07 (s, 6H), 2.95- 2.81 (m, 1H), 2.75-2.54 (m, 10H), 2.10-1.97 (m, 1H), 1.40 (s, 6H). D82 752.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.82 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.3, 2.3 Hz, 1H), 6.75 (s, 2H), 6.48 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.24 (dd, J = 10.1, 5.6 Hz, 1H), 4.04 (dd, J = 9.9, 6.1 Hz, 1H), 3.80 (s, 6H), 3.54 (s, 3H), 3.48 (s, 4H), 3.07 (s, 6H), 2.99-2.86 (m, 2H), 2.63-2.54 (m, 5H), 2.44 (s, 3H), 2.09-2.01 (m, 1H), 1.08 (d, J = 6.6 Hz, 3H). D83 752.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.32 (s, 2H, FA), 7.82 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.4, 2.3 Hz, 1H), 6.74 (s, 2H), 6.48 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.24 (dd, J = 10.0, 5.5 Hz, 1H), 4.04 (dd, J = 10.0, 6.1 Hz, 1H), 3.80 (s, 6H), 3.53 (s, 3H), 3.48 (s, 4H), 3.07 (s, 6H), 2.96-2.86 (m, 2H), 2.63-2.54 (m, 5H), 2.42 (s, 3H), 2.09-2.00 (m, 1H), 1.07 (d, J = 6.7 Hz, 3H). D84 860.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 10.72 (s, 1H, HCI), 9.01 (s, 1H), 7.86 (dd, J = 8.2, 2.4 Hz, 1H), 7.69-7.62 (m, 1H), 7.36-7.26 (m, 2H), 6.93-6.88 (m, 2H), 6.58 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 5.03 (q, J = 6.6 Hz, 1H), 4.18 (s, 2H), 3.91 (s, 6H), 3.51 (s, 3H), 3.46-3.23 (m, 8H), 3.13 (s, 7H), 3.05 (s, 2H), 2.99-2.84 (m, 3H), 2.65-2.54 (m, 4H), 2.31-2.22 (m, 1H), 2.09- 1.81 (m, 11H). D85 461.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 9.04 (s, 1H), 8.15 (s, 1H, FA), 7.69 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.35 (d, J = 2.2 Hz, 1H), 7.27 (dd, J = 8.6, 2.3 Hz, 1H), 6.78 (s, 2H), 6.49 (s, 1H), 5.71-5.60 (m, 2H), 5.27 (dd, J = 13.1, 5.4 Hz, 1H), 4.78

(p, J = 6.2 Hz, 1H), 3.83 (s, 6H), 3.66 (s, 2H), 3.48 (s, 3H), 3.43 (t, J = 5.3 Hz, 4H), 3.07 (s, 6H), 3.03-2.79 (m, 4H), 2.65-2.55 (m, 3H), 2.40-2.29 (m, 4H), 2.28- 2.04 (m, 3H), 1.66 (d, J = 12.1 Hz, 2H), 1.44-1.27 (m, 3H), 1.26- 1.15 (m, 8H). D86 651.44 D87 804.4 D88 674.62 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 9.01 (s, 1H), 8.16 (s, 2H), 7.55 (s, 1H), 6.73 (s, 2H), 6.46 (s, 1H), 3.78 (s, 6H), 3.53 (s, 2H), 3.45 (s, 3H), 3.15 (s, 2H), 3.05 (s, 6H), 2.82 (d, J = 11.4 Hz, 2H), 2.40-2.24 (m, 3H), 2.05 (t, J = 11.5 Hz, 2H), 1.80 (dd, J = 9.7, 4.5 Hz, 1H), 1.58 (d, J = 12.3 Hz, 2H), 1.32 (q, J = 7.0 Hz, 2H), 1.09 (q, J = 11.6 Hz, 2H). D89 689.53 D90 734.26 D91 720.54 D92 706.65 D93 720.4 D94 618.61 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.82 (s, 1H), 9.01 (s, 1H), 8.17 (s, 1H), 7.56 (s, 1H), 6.73 (s, 2H), 6.44 (s, 1H), 4.94 (d, J = 45.9 Hz, 1H), 3.79 (s, 6H), 3.62 (s, 2H), 3.46 (s, 3H), 3.36-3.10 (m, 3H), 3.04 (s, 6H), 2.96 (q, J = 4.9, 3.2 Hz, 2H), 2.87 (dd, J = 14.8, 7.7 Hz, 3H), 2.84-2.62 (m, 1H), 2.34-2.17 (m, 1H), 1.86-1.71 (m, 1H). D95 780.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.60-7.53 (m, 2H), 7.40 (dd, J = 8.3, 2.3 Hz, 1H), 6.74 (s, 2H), 6.48 (s, 1H), 5.13 (dd, J = 13.0, 5.4 Hz, 1H), 4.50 (s, 2H), 4.43 (q, J = 6.1 Hz, 4H), 3.79 (s, 6H), 3.55 (s, 2H), 3.47 (s, 3H), 3.07 (s, 6H), 3.04-2.81 (m, 2H), 2.65-2.54 (m, 4H), 2.49- 2.39 (m, 5H), 2.10-2.00 (m, 1H). D96 766.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.04 (s, 1H), 8.18 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.41 (dd, J = 8.2, 2.2 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 3.81 (s, 6H), 3.56 (s, 2H), 3.51- 3.45 (m, 5H), 3.06 (s, 6H), 2.94-2.84 (m, 1H), 2.59-2.53 (m, 6H), 2.49-2.43 (m, 4H), 2.08-2.01 (m, 1H), 1.35 (s, 6H). D97 831.99 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.46 (s, 1H, FA), 7.64 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 6.91 (s, 2H), 6.83 (d, J = 2.1 Hz, 1H), 6.66 (dd, J = 8.3, 2.1 Hz, 1H), 6.48 (s, 1H), 5.07 (dd, J = 12.3, 5.4 Hz, 1H), 4.45 (s, 2H), 4.06 (d, J = 9.2 Hz, 4H), 3.99 (s, 6H), 3.79 (s, 4H), 3.60 (s, 3H), 3.26-3.19 (m, 1H), 3.13 (s, 6H), 2.91-2.81 (m, 1H), 2.80-2.68 (m, 2H), 2.60 (s, 4H), 2.14-2.06 (m, 1H), 1.89 (s, 4H), 1.17 (s, 6H). D98 681.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.86-7.80 (m, 1H), 7.59 (s, 1H), 7.29-7.23 (m, 2H), 6.77 (s, 2H), 6.47 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.95 (t, J = 5.5 Hz, 1H), 3.81 (s, 6H), 3.75-3.69 (m, 4H), 3.48 (s, 3H), 3.15- 3.11 (m, 2H), 3.06 (s, 6H), 2.91-2.84 (m, 1H), 2.65-2.55 (m, 2H), 2.07-1.99 (m, 1H). D99 914.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.30 (s, 1H, FA), 7.82 (d, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.34-7.23 (m, 2H), 6.75 (s, 2H), 6.49 (s, 1H), 5.12 (dd, J = 12.8, 5.3 Hz, 1H), 5.04- 4.91 (m, 1H), 3.80 (s, 6H), 3.52-3.48 (m, 6H), 3.07 (s, 6H), 2.99- 2.67 (m, 8H), 2.44-2.40 (m, 2H), 2.08-1.94 (m, 3H), 1.89-1.75 (m, 3H), 1.64-1.45 (m, 6H), 1.35-1.12 (m, 3H). D100 780.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.85 (dd, J = 8.5, 7.3 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.48 (d, J = 7.2 Hz, 1H), 6.74 (s, 2H), 6.48 (s, 1H), 5.09 (dd, J = 12.8, 5.4 Hz, 1H), 4.55 (s, 2H), 4.43 (s, 4H), 3.79 (s, 6H), 3.55 (s, 2H), 3.47 (s, 3H), 3.06 (s, 6H), 2.92-2.81 (m, 1H), 2.63-2.54 (m, 5H), 2.48- 2.37 (m, 5H), 2.07-1.98 (m, 1H). D101 850.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.03 (s, 1H), 8.15 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.61 (s, 1H), 7.32-7.25 (m, 2H), 7.15 (d, J = 1.6 Hz, 1H), 7.11 (d, J = 1.6 Hz, 1H), 6.39 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.99 (t, J = 6.8 Hz, 1H), 3.85 (s, 3H), 3.60 (s, 2H), 3.47 (s, 3H), 3.07 (s, 6H), 2.91-2.80 (m, 3H), 2.64- 2.53 (m, 3H), 2.45-2.40 (m, 2H), 2.39-2.36 (m, 1H), 2.30-2.26 (m, 1H), 2.18-2.00 (m, 6H), 1.81 (dd, J = 12.3, 6.4 Hz, 2H), 1.68- 1.55 (m, 6H), 1.53-1.46 (m, 1H), 1.10-0.98 (m, 2H). D102 864.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.63 (s, 1H), 7.35-7.26 (m, 2H), 7.19 (d, J = 13.5 Hz, 2H), 6.40 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 5.04 (t, J = 7.3 Hz, 1H), 3.99-3.59 (m, 5H), 3.47 (s, 5H), 3.42-3.35 (m, 4H), 3.11-3.03 (m, 7H), 3.02-2.82 (m, 3H), 2.71-2.53 (m, 3H), 2.44-2.34 (m, 1H), 2.10-2.00 (m, 1H), 1.93-1.83 (m, 2H), 1.70- 1.45 (m, 8H). D103 832.6 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.09 (s, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 7.05-6.98 (m, 2H), 6.90 (s, 2H), 6.60-6.55 (m, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.95-4.89 (m, 1H), 4.54- 4.37 (m, 4H), 3.98 (s, 6H), 3.69-3.49 (m, 7H), 3.42-3.35 (m, 1H), 3.29-3.13 (m, 8H), 3.12-2.95 (m, 4H), 2.94-2.86 (m, 1H), 2.84- 2.74 (m, 1H), 2.74-2.63 (m, 1H), 2.59-2.44 (m, 2H), 2.37- 2.21 (m, 1H), 2.21-1.97 (m, 9H), 1.73-1.62 (m, 1H). D104 693.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.04 (s, 1H), 8.17 (s, 1H, FA), 7.88-7.73 (m, 3H), 7.60 (s, 1H), 6.78 (s, 2H), 6.50 (s, 1H), 5.14 (dd, J = 12.9, 5.3 Hz, 1H), 3.84 (s, 6H), 3.65 (s, 2H), 3.49 (s, 3H), 3.08 (s, 6H), 3.02 (d, J = 11.3 Hz, 2H), 2.97-2.70 (m, 3H), 2.63-2.55 (m, 1H), 2.30-2.20 (m, 2H), 2.10-2.00 (m, 1H), 1.83- 1.63 (m, 4H). D105 805.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.20 (s, 1H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.30 (d, J = 2.2 Hz,

1H), 7.22 (dd, J = 8.7, 2.3 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.07 (dd, J = 12.7, 5.4 Hz, 1H), 4.03 (d, J = 12.9 Hz, 2H), 3.80 (s, 6H), 3.54 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 3.01-2.82 (m, 4H), 2.64-2.54 (m, 2H), 2.46-2.41 (m, 3H), 2.39-2.24 (m, 6H), 2.07- 1.96 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.64-1.51 (m, 1H), 1.41- 1.30 (m, 2H), 1.24-1.08 (m, 2H). D106 791.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.97 (s, 1H), 8.16 (s, 1H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.51 (s, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.23 (dd, J = 8.7, 2.3 Hz, 1H), 7.15 (d, J = 4.9 Hz, 1H), 6.71 (s, 2H), 6.43 (s, 1H), 5.07 (dd, J = 12.7, 5.3 Hz, 1H), 4.04 (d, J = 12.7 Hz, 2H), 3.81 (s, 6H), 3.59 (s, 2H), 3.46 (s, 3H), 3.27-3.04 (m, 5H), 2.94 (t, J = 12.6 Hz, 3H), 2.80 (d, J = 4.6 Hz, 3H), 2.62- 2.55 (m, 2H), 2.46-2.34 (m, 5H), 2.05-1.96 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.65-1.51 (m, 1H), 1.44-1.32 (m, 2H), 1.25-1.11 (m, 2H). D107 832.75 .sup.1H NMR (300 MHz, MeOD) δ 9.04 (d, 1H), 7.59-7.45 (m, 2H), 7.24- 7.12 (m, 2H), 6.91 (d, 2H), 6.72-6.60 (m, 1H), 5.15 (dd, 1H), 4.85- 4.80 (m, 1H), 4.53-4.34 (m, 4H), 3.98 (d, 6H), 3.72-3.65 (m, 2H), 3.60-3.47 (m, 4H), 3.43-3.36 (m, 1H), 3.28-3.22 (m, 1H), 3.21-3.13 (m, 7H), 3.10 (d, 2H), 3.04-2.95 (m, 1H), 2.94-2.85 (m, 1H), 2.76-2.83 (m, 1H), 2.73-2.65 (m, 1H), 2.60-2.43 (m, 2H), 2.35-2.15 (m, 2H), 2.13-2.09 (m, 2H), 2.08-2.02 (m , 3H), 2.88-2.78 (m, 3H), 1.52-1.36 (m, 2H). D108 874.35 1HNMR (300 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.05 (s, 1H), 8.15 (s, 0.4H, FA), 7.83 (d, J = 8.5 Hz, 1H), 7.59 (s, 1H), 7.32-7.23 (m, 2H), 6.85 (s, 2H), 6.50 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 4.99 (t, J = 6.7 Hz, 1H), 3.96 (s, 2H), 3.87 (s, 6H), 3.49 (s, 3H), 3.27- 3.19 (m, 6H), 3.08 (s, 6H), 2.95-2.81 (m, 1H), 2.66-2.53 (m, 2H), 2.45-2.37 (m, 4H), 2.10-1.98 (m, 1H), 1.87-1.67 (m, 5H), 1.59 (d, J = 17.9 Hz, 4H), 1.49-1.32 (m, 2H), 0.88 (s, 6H). D109 764.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.05 (s, 1H), 9.00 (br s, 0.9H, TFA salt), 7.88 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 7.46 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.4, 2.3 Hz, 1H), 6.88 (s, 2H), 6.48 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.25 (s, 4H), 3.88 (s, 6H), 3.49 (s, 6H), 3.35 (d, J = 11.0 Hz, 3H), 3.08 (s, 6H), 3.06-2.81 (m, 8H), 2.68-2.53 (m, 2H), 2.10-2.00 (m, 1H), 0.76 (d, J = 5.9 Hz, 3H). D110 817.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.13 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.46 (s, 1H), 6.94-6.85 (m, 3H), 6.71 (dd, J = 8.3, 2.2 Hz, 1H), 6.52 (s, 1H), 5.08 (dd, J = 12.4, 5.5 Hz, 1H), 4.53 (s, 2H), 4.40- 4.12 (m, 4H), 3.99 (s, 6H), 3.95-3.78 (m, 5H), 3.58 (s, 3H), 3.46- 3.33 (m, 3H), 3.15 (s, 8H), 2.91-2.66 (m, 3H), 2.29-2.08 (m, 5H), 1.40 (d, J = 6.7 Hz, 3H). D111 890.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.19 (s, 1H, TFA salt), 9.05 (d, J = 1.5 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 11.1 Hz, 1H), 7.35-7.24 (m, 2H), 6.91 (d, J = 4.1 Hz, 2H), 6.51 (d, J = 12.2 Hz, 1H), 5.18-4.99 (m, 2H), 4.25 (s, 1H), 3.91 (d, J = 1.3 Hz, 6H), 3.81 (s, 1H), 3.57-3.33 (m, 9H), 3.30 (s, 3H), 3.23-3.01 (m, 8H), 2.99-2.81 (m, 2H), 2.66-2.53 (m, 2H), 2.53-2.39 (m, 2H), 2.40-2.30 (m, 1H), 2.11-2.00 (m, 1H), 1.89 (s, 2H), 1.67- 1.45 (m, 5H). D112 844.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.15 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.38-7.22 (m, 2H), 6.96 (d, J = 10.0 Hz, 2H), 6.45 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.06-4.93 (m, 1H), 3.82 (s, 3H), 3.65 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 2.95-2.81 (m, 3H), 2.82-2.72 (m, 2H), 2.70-2.53 (m, 3H), 2.49-2.38 (m, 4H), 2.38-2.13 (m, 5H), 2.11-1.98 (m, 1H), 1.84 (dd, J = 11.9, 6.4 Hz, 2H), 1.77-1.41 (m, 7H), 1.22 (t, J = 7.5 Hz, 3H), 1.18- 0.98 (m, 2H). D113 680.2 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.04 (s, 1H), 7.60 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.26 (dd, J = 8.5, 2.3 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H), 6.79 (s, 2H), 6.50 (s, 1H), 5.09 (dd, J = 13.2, 5.0 Hz, 1H), 4.41-4.14 (m, 2H), 3.84 (s, 6H), 3.67 (s, 2H), 3.48 (s, 3H), 3.19 (s, 4H), 3.08 (s, 6H), 2.91 (ddd, J = 17.9, 13.6, 5.5 Hz, 1H), 2.65 (s, 4H), 2.48-2.24 (m, 2H), 2.06-1.92 (m, 1H). D114 680.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.94 (s, 1H), 9.04 (s, 1H), 7.60 (s, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 6.79 (s, 2H), 6.50 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.40-4.10 (m, 2H), 3.84 (s, 6H), 3.65 (s, 2H), 3.48 (s, 3H), 3.33-3.20 (m, 4H), 3.08 (s, 6H), 2.96-2.83 (m, 1H), 2.59 (d, J = 14.6 Hz, 4H), 2.45- 2.25 (m, 2H), 1.95 (dd, J = 12.1, 6.5 Hz, 1H). D115 833.8 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 9.02 (s, 1H), 8.16 (s, 1H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.23 (dd, J = 8.9, 2.1 Hz, 1H), 6.74 (s, 2H), 6.40 (s, 1H), 5.06 (dd, J = 12.7, 5.3 Hz, 1H), 4.03 (d, J = 13.0 Hz, 2H), 3.80 (s, 6H), 3.57 (s, 2H), 3.55-3.44 (m, 7H), 3.03-2.71 (m, 4H), 2.64- 2.53 (m, 2H), 2.48-2.25 (m, 9H), 2.07-1.94 (m, 1H), 1.79-1.51 (m, 3H), 1.42-1.31 (m, 2H), 1.26-1.04 (m, 8H). D116 815.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.02 (s, 1H), 8.17 (s, 1H, FA), 7.64 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 6.78 (s, 3H), 6.66- 6.53 (m, 1H), 6.18 (s, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.89 (s, 2H), 3.85 (s, 6H), 3.74 (s, 4H), 3.49 (s, 3H), 3.30-3.17 (m, 4H), 2.95-2.80 (m, 1H), 2.58-2.54 (m, 2H), 2.49- 2.43 (m, 3H), 2.40-2.23 (m, 6H), 2.07-1.96 (m, 1H), 1.78- 1.70 (m, 4H). D117

688.91 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.81 (s, 1H), 9.01 (s, 1H), 8.23 (s, 2H), 7.55 (s, 1H), 6.72 (s, 2H), 6.46 (s, 1H), 3.78 (s, 6H), 3.49 (s, 2H), 3.45 (s, 3H), 3.05 (s, 6H), 2.85-2.74 (m, 2H), 2.69-2.60 (m, 1H), 2.35-2.20 (m, 3H), 1.99 (t, J = 11.3 Hz, 2H), 1.85-1.74 (m, 1H), 1.56 (d, J = 12.0 Hz, 2H), 1.40 (s, 2H), 1.15 (s, 4H), 1.04 (d, J = 11.3 Hz, 2H). D118 878.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 9.04 (s, 1H), 7.87 (d, J = 9.3 Hz, 1H), 7.61 (d, J = 4.1 Hz, 1H), 7.51 (t, J = 6.9 Hz, 1H), 6.89 (s, 2H), 6.51 (d, J = 7.4 Hz, 1H), 5.18-5.06 (m, 2H), 4.21 (s, 2H), 3.90 (d, J = 1.7 Hz, 6H), 3.50 (s, 4H), 3.41-3.29 (m, 3H), 3.32-3.18 (m, 1H), 3.09 (s, 7H), 3.00-2.79 (m, 2H), 2.78-2.53 (m, 6H), 2.10- 2.00 (m, 1H), 1.95-1.75 (m, 6H), 1.72-1.42 (m, 4H). D119 854.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.20-8.98 (m, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.78 (s, 2H), 7.50 (s, 1H), 7.31 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 8.3, 2.3 Hz, 1H), 6.37 (s, 1H), 5.12 (dd, J = 12.5, 5.4 Hz, 1H), 4.99 (t, J = 6.6 Hz, 1H), 4.75 (s, 2H), 3.88-3.75 (m, 2H), 3.68- 3.51 (m, 5H), 3.44 (t, J = 12.4 Hz, 2H), 3.15 (s, 8H), 3.11-2.92 (m, 2H), 2.91-2.83 (m, 1H), 2.81-2.67 (m, 3H), 2.61-2.53 (m, 1H), 2.40-2.25 (m, 1H), 2.15 (d, J = 14.4 Hz, 6H), 2.02 (s, 3H), 1.78 (s, 2H). D120 791.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.04 (s, 1H), 8.16 (s, 1H, FA), 7.58 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.31-7.11 (m, 2H), 6.76 (s, 2H), 6.49 (s, 1H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.41- 4.11 (m, 2H), 3.81 (s, 6H), 3.73 (d, J = 12.0 Hz, 2H), 3.57 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 2.98-2.81 (m, 1H), 2.80-2.59 (m, 3H), 2.58-2.57 (m, 1H), 2.46-2.43 (m, 3H), 2.43-2.22 (m, 7H), 2.06- 1.92 (m, 1H), 1.83-1.67 (m, 2H), 1.46-1.34 (m, 3H), 1.33- 1.17 (m, 2H). D121 791.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.04 (s, 1H), 8.14 (s, 1H, FA), 7.64-7.42 (m, 2H), 7.04 (d, J = 7.4 Hz, 2H), 6.78 (s, 2H), 6.49 (s, 1H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.42-4.14 (m, 2H), 3.88 (s, 1H), 3.82 (s, 7H), 3.65 (s, 2H), 3.48 (s, 4H), 3.07 (s, 6H), 3.00-2.69 (m, 4H), 2.69-2.54 (m, 7H), 2.48-2.24 (m, 3H), 2.04-1.88 (m, 1H), 1.74 (d, J = 11.8 Hz, 2H), 1.47 (d, J = 26.5 Hz, 3H), 1.21 (q, J = 11.7, 10.6 Hz, 2H). D122 801.5 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.11 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.37 (s, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.86 (s, 2H), 6.16 (s, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.49-4.35 (m, 4H), 4.08 (t, J = 7.4 Hz, 4H), 3.98 (s, 6H), 3.60 (d, J = 12.3 Hz, 2H), 3.41 (t, J = 4.9 Hz, 4H), 3.31-3.27 (m, 1H), 3.19 (t, J = 12.4 Hz, 2H), 2.99-2.85 (m, 1H), 2.83-2.74 (m, 5H), 2.70-2.61 (m, 1H), 2.56-2.39 (m, 3H), 2.22-2.13 (m, 3H), 1.93 (s, 2H), 1.14 (q, J = 6.8 Hz, 2H), 0.96 (dd, J = 6.3, 4.1 Hz, 2H). D123 789.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.38 (br s, 1H, TFA salt), 9.04 (s, 1H), 7.65-7.57 (m, 2H), 7.21-7.12 (m, 2H), 6.90 (s, 2H), 6.22 (s, 1H), 5.07 (dd, J = 12.9, 5.0 Hz, 1H), 4.37 (d, J = 16.9 Hz, 1H), 4.30-4.20 (m, 2H), 4.01 (q, J = 7.3 Hz, 7H), 3.93 (s, 7H), 3.66-3.56 (m, 2H), 3.26-3.04 (m, 7H), 2.95-2.85 (m, 2H), 2.80- 2.54 (m, 3H), 2.41-2.23 (m, 4H), 2.05-1.91 (m, 3H), 1.29 (t, J = 7.1 Hz, 3H). D124 819.65 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.33 (s, J = 2.3 Hz, 1H), 7.25 (d, J = 8.7, 2.3 Hz, 1H), 6.89 (s, 2H), 6.48 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.07 (d, J = 12.8 Hz, 2H), 3.88 (s, 6H), 3.62-3.26 (m, J = 7.0 Hz, 12H), 3.10 (s, 3H), 3.03-2.83 (m, 8H), 2.64-2.53 (m, 2H), 2.07-1.98 (m, 1H), 1.76 (d, J = 12.7 Hz, 2H), 1.58 (s, 3H), 1.29- 1.15 (m, 2H), 1.09 (t, J = 7.0 Hz, 3H). D125 831.25 .sup.1H NMR (400 MHz, DMSO-d6): δ 11.06 (s, 1H), 9.04 (s, 1H), 8.16 (s, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.58 (s, 1H), 6.77 (s, 3H), 6.64 (dd, J = 8, 2 Hz, 1H), 6.49 (s, 1H), 5.05 (dd, J = 13.2, 5.2 Hz, 1H), 3.81 (s, 6H), 3.74 (s, 4H), 3.64 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 2.94- 2.80 (m, 3H), 2.60-2.52 (m, 4H), 2.30-2.12 (m, 4H), 2.08 (d, J = 6.8 Hz, 2H), 2.05-1.93 (m, 1H), 1.75 (s, 3H), 1.65 (d, J = 12.8 Hz, 2H), 1.55-1.45 (m, 1H), 1.24 (s, 0.2H), 1.19-1.01 (m, 2H). D126 746.2 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.99-8.94 (m, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.59 (s, 1H), 6.88 (s, 2H), 6.87 (d, J = 2.0 Hz, 1H), 6.75-6.68 (m, 1H), 6.38 (d, J = 1.8 Hz, 1H), 5.12-5.02 (m, 1H), 4.44 (s, 2H), 4.23 (t, J = 7.6 Hz, 4H), 3.99 (s, 8H), 3.87 (s, 2H), 3.60 (s, 4H), 3.34 (s, 1H), 3.31-3.19 (m, 2H), 2.95-2.81 (m, 1H), 2.81- 2.64 (m, 2H), 2.60-2.48 (m, 2H), 2.30 (d, J = 14.4 Hz, 2H), 2.21- 2.07 (m, 3H). D127 720.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.01 (s, 1H), 8.17 (s, 1H), 7.51 (d, J = 37.4 Hz, 1H), 6.74 (s, 2H), 6.65-6.35 (m, 3H), 5.01 (dd, J = 13.3, 5.1 Hz, 1H), 4.37-3.99 (m, 2H), 3.80 (s, 5H), 3.59 (s, 3H), 3.54 (s, 2H), 3.46 (s, 2H), 3.15 (s, 1H), 3.05 (s, 5H), 2.58 (s, 1H), 2.45-2.39 (m, 5H), 2.39-2.27 (m, 1H), 1.93 (ddq, J = 10.4, 5.4, 3.2, 2.6 Hz, 1H), 1.71 (t, J = 5.4 Hz, 4H). D128 720.52 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.02 (s, 1H), 8.12 (s, 1H), 7.57 (s, 1H), 7.36 (d, J = 8.2 Hz, 1H), 6.80 (s, 2H), 6.67 (d, J = 7.5 Hz, 2H), 6.47 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.37- 4.07 (m, 2H), 3.84 (s, 7H), 3.60 (s, 4H), 3.47 (s, 3H), 3.06 (s, 6H), 2.97-2.84 (m, 1H), 2.81 (d, J = 25.0 Hz, 0H), 2.69-2.52 (m, 1H), 2.42-2.26 (m, 1H), 2.05-1.92 (m, 1H), 1.85 (s, 4H). D129 864.3 .sup.1H NMR (400 MHz,

Methanol-d4) δ 9.02 (s, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J = 6.7, 3.2 Hz, 1H), 6.91 (d, J = 4.3 Hz, 2H), 6.70 (d, J = 9.3 Hz, 1H), 5.17-5.03 (m, 2H), 4.41 (s, 2H), 3.98 (d, J = 4.1 Hz, 6H), 3.65 (d, J = 12.7 Hz, 2H), 3.60 (s, 3H), 3.54 (d, J = 15.9 Hz, 1H), 3.38 (s, 1H), 3.21 (s, 6H), 3.19-3.18 (m, 1H), 3.16- 2.95 (m, 4H), 2.92-2.82 (m, 1H), 2.82-2.65 (m, 3H), 2.58 (s, 1H), 2.27 (s, 1H), 2.22-2.07 (m, 6H), 2.07-1.93 (m, 4H), 1.66 (q, J = 12.3 Hz, 2H). D130 876.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.29 (s, 1H, TFA salt), 9.11 (s, 1H, TFA salt), 9.06 (s, 1H), 7.86 (dd, J = 8.2, 2.7 Hz, 1H), 7.63-7.55 (m, 1H), 7.37-7.24 (m, 2H), 6.96-6.87 (m, 2H), 6.56-6.46 (m, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.02 (t, J = 6.7 Hz, 1H), 4.38-4.21 (m, 2H), 3.91 (s, 6H), 3.50 (s, 3H), 3.43 (d, J = 2.2 Hz, 1H), 3.39 (s, 3H), 3.36-3.30 (m, 1H), 3.28-3.12 (m, 2H), 3.09 (s, 6H), 3.04-2.80 (m, 6H), 2.70-2.54 (m, 3H), 2.47-2.38 (m, 1H), 2.31-2.18 (m, 1H), 2.13-1.93(m, 4H), 1.94-1.69 (m, 7H). D131 775.2 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.97 (d, J = 0.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.59 (s, 1H), 7.20 (d, J = 6.5 Hz, 2H), 6.88 (s, 2H), 6.39 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.46 (d, J = 7.1 Hz, 4H), 4.23 (t, J = 7.6 Hz, 4H), 3.98 (s, 6H), 3.86-3.63 (m, 6H), 3.60 (s, 4H), 3.58-3.46 (m, 3H), 3.31-3.24 (m, 3H), 2.99-2.86 (m, 1H), 2.84-2.75 (m, 1H), 2.60-2.42 (m, 5H), 2.18 (d, J = 16.2 Hz, 3H). D132 665.55 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.97 (d, J = 0.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.59 (s, 1H), 7.20 (d, J = 6.5 Hz, 2H), 6.88 (s, 2H), 6.39 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.46 (d, J = 7.1 Hz, 4H), 4.23 (t, J = 7.6 Hz, 4H), 3.98 (s, 6H), 3.86-3.63 (m, 6H), 3.60 (s, 4H), 3.58-3.46 (m, 3H), 3.31-3.24 (m, 3H), 2.99-2.86 (m, 1H), 2.84-2.75 (m, 1H), 2.60-2.42 (m, 5H), 2.18 (d, J = 16.2 Hz, 3H). D133 693.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 2.7 Hz, 1H), 7.14 (d, J = 7.2 Hz, 2H), 6.76 (s, 2H), 6.49 (s, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 3.97 (d, J = 13.3 Hz, 1H), 3.82 (s, 6H), 3.76 (d, J = 13.1 Hz, 1H), 3.48 (s, 3H), 3.06 (s, 7H), 2.95-2.82 (m, 2H), 2.71-2.54 (m, 4H), 2.01 (d, J = 12.7 Hz, 1H), 1.85 (s, 1H), 1.72 (d, J = 11.2 Hz, 2H), 1.35 (tt, J = 33.0, 18.0 Hz, 2H). D134 831.6 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.15 (s, 0.18H, FA),7.66 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 7.27-7.20 (m, 1H), 6.79 (s, 2H), 6.50 (s, 1H), 6.06-5.96 (m, 1H), 5.23-5.13 (m, 2H), 5.07 (dd, J = 13.0, 5.4 Hz, 1H), 4.57 (d, J = 5.5 Hz, 2H), 4.05 (d, J = 12.9 Hz, 2H), 3.83 (s, 6H), 3.62 (s, 1H), 3.39 (s, 3H), 3.08 (s, 6H), 3.03-2.75 (m, 7H), 2.59 (dd, J = 12.6, 2.9 Hz, 3H), 2.56 (d, J = 2.0 Hz, 3H), 2.08-1.98 (m, 1H), 1.75 (d, J = 12.8 Hz, 2H), 1.64-1.45 (m, 3H), 1.26-1.13 (m, 2H). D135 845.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.04 (s, 1H), 8.15 (s, 0.48H, FA), 7.65 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.34-7.20 (m, 2H), 6.77 (s, 2H), 6.51 (s, 1H), 5.95-5.76 (m, 1H), 5.14-4.99 (m, 3H), 4.09-3.96 (m, 4H), 3.82 (s, 6H), 3.64 (s, 2H), 3.07 (s, 6H), 2.99-2.86 (m, 3H), 2.65-2.52 (m, 8H), 2.49-2.40 (m, 6H), 2.08- 1.94 (m, 1H), 1.74 (d, J = 12.7 Hz, 2H), 1.58 (s, 1H), 1.45-1.34 (m, 2H), 1.27-1.08 (m, 2H). D136 843.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.42 (s, 2H, TFA salt), 9.03 (s, 1H), 7.73-7.58 (m, 2H), 6.91-6.62 (m, 4H), 6.22 (d, J = 5.7 Hz, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 4.40-4.19 (m, 2H), 4.03 (t, J = 7.4 Hz, 4H), 3.91 (s, 8H), 3.84 (d, J = 5.0 Hz, 2H), 3.22 (s, 3H), 3.12-2.81 (m, 7H), 2.62 (s, 1H), 2.59-2.53 (m, 4H), 2.34 (q, J = 7.5 Hz, 2H), 2.20-2.15 (m, 3H), 2.08-1.85 (m, 6H), 1.52- 1.46(m, 2H). D137 693.1 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.01 (s, 1H), 7.88- 7.79 (m, 1H), 7.60 (s, 1H), 7.27 (d, 2H), 6.74 (s, 2H), 6.18 (s, 1H), 5.12-4.96 (m, 2H), 3.99 (t, 4H), 3.82 (s, 6H), 3.78-3.70 (m, 3H), 3.48 (s, 4H), 3.24-3.13 (m, 2H), 2.97-2.80 (m, 1H), 2.66- 2.62 (m, 1H), 2.61-2.54 (m, 1H), 2.30-2.28 (m, 2H), 2.10-1.92 (m, 1H). D138 669.15 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.04 (s, 1H), 8.16 (s, 1H, FA), 7.82 (dd, J = 7.5, 0.9 Hz, 1H), 7.59 (s, 1H), 6.76 (s, 2H), 6.46 (s, 1H), 6.38-6.30 (m, 2H), 5.29 (dd, J = 12.5, 5.2 Hz, 1H), 4.76 (t, J = 5.6 Hz, 1H), 3.81 (s, 6H), 3.76-3.63 (m, 4H), 3.48 (s, 3H), 3.10 (dd, J = 8.2, 4.8 Hz, 2H), 3.06 (s, 6H), 2.97-2.83 (m, 1H), 2.68-2.59 (m, 1H), 2.48-2.37 (m, 1H), 2.27-2.07 (m, 1H). D139 831.8 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.05 (s, 1H), 8.15 (s, 1H, FA), 7.67-7.62 (m, 2H), 7.33-7.21 (m, 3H), 6.79 (s, 2H), 6.47 (s, 1H), 6.06 (dd, J = 14.3, 6.8 Hz, 1H), 5.06 (dd, J = 12.9, 5.2 Hz, 1H), 4.03 (d, J = 12.8 Hz, 2H), 3.81 (s, 6H), 3.56 (s, 2H), 3.31 (s, 4H), 3.08 (s, 6H), 2.94-2.90 (m, 3H), 2.63-2.58 (m, 3H), 2.46- 2.37 (m, 4H), 2.02 (s, 2H), 1.82 (dd, J = 6.7, 1.7 Hz, 3H), 1.74 (d, J = 12.8 Hz, 2H), 1.58 (s, 1H), 1.38-1.36 (m, 2H), 1.17-1.17 (m, 2H). D140 848.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.03 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.40-7.23 (m, 4H), 6.34 (s, 1H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 5.04-4.94 (m, 1H), 3.65 (s, 2H), 3.47 (s, 3H), 3.06 (s, 6H), 2.89 (s, 1H) 2.86-2.76 (m, 4H), 2.63 (s, 5H), 2.13 (d, J = 11.0 Hz, 3H), 2.07 (s, 1H), 1.82 (dd, J = 11.9, 6.4 Hz, 4H), 1.68 (s, 2H), 1.63 (s, 7H), 1.24 (t, J = 7.4 Hz, 3H), 1.03 (d, J = 11.9 Hz, 2H).

D141 736.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.52 (s, 1H, TFA), 9.09 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.35 (dd, J = 8.6, 2.3 Hz, 1H), 6.90 (s, 2H), 6.67 (s, 1H), 5.10 (dd, J = 13.0, 5.3 Hz, 1H), 4.42-4.31 (m, 2H), 4.20 (d, J = 12.6 Hz, 2H), 3.92 (s, 6H), 3.70 (t, J = 4.8 Hz, 5H), 3.63-3.55 (m, 8H), 3.32 (h, J = 11.6, 10.4 Hz, 4H), 2.90 (ddd, J = 17.4, 14.0, 5.4 Hz, 1H), 2.65-2.54 (m, 2H), 2.07-2.00 (m, 1H). D142 732.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.02 (s, 1H), 8.24 (s, 1H, FA), 7.61 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.78-6.63 (m, 4H), 6.21 (s, 1H), 5.09 (dd, J = 13.2, 5.1 Hz, 1H), 4.35-4.15 (m, 2H), 4.01 (t, J = 7.3 Hz, 4H), 3.82 (s, 6H), 3.58-3.48 (m, 8H), 2.97- 2.85 (m, 1H), 2.67-2.55 (m, 2H), 2.42-2.26 (m, 7H), 1.98 (d, J = 12.6 Hz, 1H), 1.80-1.62 (m, 4H). D143 789.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.85 (br s, 2H, TFA salt), 9.05 (s, 1H), 7.59 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 3.5 Hz, 2H), 6.56-6.44 (m, 3H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.42 (d, J = 5.4 Hz, 1H), 4.37 (s, 1H), 4.35 (s, 1H), 4.29 (s, 2H), 4.25 (s, 1H), 4.05 (t, J = 8.8 Hz, 2H), 3.91 (s, 6H), 3.78 (s, 2H), 3.70 (s, 2H), 3.50 (s, 3H), 3.41 (d, J = 17.2 Hz, 4H), 3.17 (s, 1H), 3.09 (s, 6H), 3.00-2.84 (m, 3H), 2.59 (d, J = 15.0 Hz, 1H), 2.35 (dd, J = 13.0, 4.5 Hz, 1H), 2.13 (d, J = 13.8 Hz, 2H), 2.03-1.83 (m, 3H). D144 711.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.07 (s, 1H), 8.19 (s, 0.6H, FA), 7.87-7.78 (m, 1H), 7.63 (s, 1H), 6.74 (s, 2H), 6.63 (s, 1H), 6.40-6.29 (m, 2H), 5.29 (dd, J = 12.5, 5.2 Hz, 1H), 4.76 (t, J = 5.5 Hz, 1H), 3.81 (s, 6H), 3.68-3.57 (m, 8H), 3.52-3.50 (m, 7H), 3.10 (t, J = 6.4 Hz, 2H), 2.99-2.81 (m, 1H), 2.66-2.50 (m, 1H), 2.49-2.38 (m, 1H), 2.16-2.08 (m, 1H). D145 805.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.01 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 25.2 Hz, 2H), 7.25 (d, 1H), 7.20- 7.04 (m, 1H), 6.99 (s, 1H), 5.92 (s, 1H), 5.10-4.99 (m, 1H), 4.08 (d, J = 13.2 Hz, 3H), 3.79 (s, 4H), 3.69 (s, 5H), 3.46 (s, 4H), 3.13 (s, 5H), 3.01 (s, 7H), 2.96-2.79 (m, 4H), 2.74-2.55 (m, 2H), 2.06- 1.92 (m, 1H), 1.76 (d, 2H), 1.60 (s, 3H), 1.31-1.19 (m, 2H). D146 677.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.14 (s, 1H), 9.01 (s, 1H), 8.18 (s, 1H, FA), 7.90-7.82 (m, 2H), 7.81-7.74 (m, 1H), 7.62 (s, 1H), 6.75 (s, 2H), 6.19 (s, 1H), 5.15 (dd, J = 12.8, 5.4 Hz, 1H), 3.99 (t, J = 7.4 Hz, 4H), 3.83 (s, 6H), 3.79-3.60 (m, 6H), 3.48 (s, 3H), 3.26 (s, 1H), 2.98-2.80 (m, 1H), 2.66-2.52 (m, 2H), 2.33 (m, J = 7.2 Hz, 2H), 2.10-2.01 (m, 1H). D147 831.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.14 (s, 0.4H, FA), 7.47 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.20 (s, 1H), 7.02 (s, 1H), 6.74-6.65 (m, 2H), 6.05 (s, 1H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.40-4.14 (m, 4H), 4.16-4.06 (m, 2H), , 3.82 (s, 3H), 3.70-3.51 (m, 8H), 3.63 (s, 3H), 3.51-3.48 (m, 8H), 3.43-3.34 (m, 4H), 3.11-2.70 (m, 1H), 2.76-2.57 (m, 4H), , 2.41-2.27 (m, 2H),), 2.03-1.93 (m, 1H), 1.98-1.85 (m, 4H). D148 702.46 D149 702.46 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.92 (s, 1H), 8.99 (s, 1H), 8.17 (s, 1H), 7.59-7.46 (m, 1H), 7.37 (dd, J = 18.7, 7.8 Hz, 2H), 7.17- 6.87 (m, 2H), 6.67 (d, J = 8.1 Hz, 2H), 5.05 (dd, J = 13.3, 5.2 Hz, 1H), 4.39-4.05 (m, 2H), 4.07-3.89 (m, 5H), 3.82 (d, J = 7.8 Hz, 4H), 3.58 (s, 3H), 3.47 (d, J = 16.6 Hz, 5H), 2.97-2.79 (m, 1H), 2.67-2.51 (m, 2H), 2.45-2.26 (m, 9H), 2.08-1.88 (m, 2H), 1.77 (d, J = 5.4 Hz, 5H). D150 773.42 D151 845.25 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.10 (d, J = 0.7 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 4.2 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.6, 2.4 Hz, 1H), 6.87 (d, J = 1.3 Hz, 2H), 6.57 (s, 1H), 5.87-5.76 (m, 1H), 5.73-5.51 (m, 1H), 5.08 (dd, J = 12.5, 5.4 Hz, 1H), 4.75-4.69 (m, 1H), 4.57 (d, J = 6.2 Hz, 2H), 4.35 (s, 2H), 4.07 (d, J = 13.2 Hz, 2H), 3.96 (s, 6H), 3.47-3.35 (m, 4H), 3.30-3.19 (m, 3H), 3.16 (s, 6H), 3.07-2.94 (m, 4H), 2.92-2.81 (m, 1H), 2.82- 2.65 (m, 2H), 2.17-2.06 (m, 1H), 1.93-1.81 (m, 3H), 1.73 (dd, J = 6.4, 1.4 Hz, 3H), 1.71-1.60 (m, 2H), 1.44-1.31 (m, 2H). D152 789.4 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.12 (s, 1H), 7.50-7.39 (m, 2H), 6.89 (d, J = 2.7 Hz, 3H), 6.81 (dd, J = 8.2, 2.2 Hz, 1H), 6.52 (s, 1H), 5.17-5.11 (m, 1H), 4.57-4.52 (m, 2H), 4.40 (d, J = 6.5 Hz, 4H), 4.18 (s, 2H), 3.97 (s, 6H), 3.78 (s, 4H), 3.67 (s, 1H), 3.60 (s, 4H), 3.57-3.50 (m, 4H), 3.15 (s, 8H), 2.98-2.80 (m, 2H), 2.60- 2.44 (m, 1H), 2.32-2.01 (m, 5H). D153 801.6 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.02 (s, 1H), 8.22 (s, 2H, FA), 7.60 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 6.76 (s, 2H), 6.54-6.42 (m, 2H), 6.19 (s, 1H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.30 (d, J = 17.0 Hz, 1H), 4.17 (d, J = 17.0 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.83 (s, 6H), 3.78 (s, 2H), 3.62 (s, 3H), 3.59-3.52 (m, 2H), 3.48 (s, 3H), 3.13 (s, 2H), 2.91 (ddd, J = 17.8, 13.5, 5.4 Hz, 1H), 2.64-2.57 (m, 2H), 2.56-2.49 (m, 3H), 2.44 (d, J = 6.9 Hz, 2H), 2.40-2.24 (m, 5H), 2.00-1.88 (m, 1H), 1.73 (t, J = 5.4 Hz, 4H). D154 682.5 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.15 (s, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.43 (s, 1H), 6.81 (s, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.52 (s, 1H), 6.14 (s, 1H), 5.26 (d, J = 10.2 Hz, 1H), 3.92 (s, 8H), 3.59 (s, 3H), 3.42 (s, 4H), 3.12 (s, 6H), 3.0-2.80 (m, 6H), 2.70-2.52 (m, 1H), 2.40-2.20 (m, 1H). D155 791.45 .sup.1H

NMR (300 MHz, Methanol-d4) δ 9.16 (d, J = 0.7 Hz, 1H), 8.53 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.35 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.7, 2.4 Hz, 1H), 6.86 (s, 2H), 6.51 (s, 1H), 5.08 (dd, J = 12.3, 5.4 Hz, 1H), 4.21 (s, 2H), 4.06 (d, J = 13.0 Hz, 2H), 3.95 (s, 6H), 3.60 (s, 3H), 3.24-3.10 (m, 10H), 3.10-2.96 (m, 3H), 2.95- 2.77 (m, 3H), 2.76-2.62 (m, 3H), 2.36 (d, J = 6.6 Hz, 2H), 2.17- 2.06 (m, 1H), 1.98-1.86 (m, 3H), 1.39-1.22 (m, 2H). D156 859.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.28 (s, 1H), 7.85 (s, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.32 (s, 1H), 7.24 (d, J = 11.1 Hz, 2H), 6.81 (s, 2H), 5.12-5.01 (m, 1H), 4.06 (d, J = 12.9 Hz, 2H), 3.83 (s, 6H), 3.71-3.43 (m, 5H), 3.17-2.70 (m, 9H), 2.66-2.52 (m, 4H), 2.52-2.13 (m, 5H), 2.06-2.00 (m, 1H), 1.75 (d, J = 12.3 Hz, 2H), 1.59-1.53 (m, 3H), 1.24-1.14 (m, 2H). D157 682.1 .sup.1H NMR (400 MHz, DMSO) δ 11.13 (s, 1H), 9.03 (s, 1H), 7.89-7.83 (m, 1H), 7.56 (s, 1H), 7.29 (d, J = 7.5 Hz, 2H), 6.81 (s, 2H), 6.47 (s, 1H), 5.28-5.18 (m, 1H), 5.13 (dd, J = 12.9, 5.4 Hz, 1H), 4.88 (tt, J = 7.1, 7.1, 3.9, 3.9 Hz, 1H), 3.85 (s, 6H), 3.47 (s, 3H), 3.07 (s, 6H), 2.90 (ddd, J = 18.9, 13.7, 5.3 Hz, 1H), 2.69 (ddd, J = 13.4, 6.3, 3.3 Hz, 2H), 2.64-2.51 (m, 2H), 2.40 (ddd, J = 12.3, 6.7, 4.2 Hz, 2H), 2.11-2.00 (m, 1H). D158 805.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 10.20-9.86 (m, 1H), 9.30-9.10 (m, 1H), 9.02 (s, 1H), 7.84 (dd, J = 7.8, 4.2 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 6.87 (s, 2H), 6.80-6.68 (m, 1H), 6.35 (d, J = 5.7 Hz, 1H), 6.23 (d, J = 5.7 Hz, 1H), 5.27 (dd, J = 12.3, 5.1 Hz, 1H), 4.22 (d, J = 3.6 Hz, 2H), 4.10-3.96 (m, 6H), 3.90 (s, 6H), 3.65- 3.52 (m, 2H), 3.50-3.34 (m, 5H), 3.30-3.10 (m, 6H), 3.08-2.80 (m, 2H), 2.75-2.60 (m, 1H), 2.50-2.42 (m, 2H), 2.42-2.28 (m, 2H), 2.20-2.08 (m, 1H), 1.96-1.70 (m, 3H), 1.70-1.40 (m, 4H). D159 843.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.02 (s, 1H), 7.62- 7.40 (m, 2H), 7.04 (d, J = 7.9 Hz, 2H), 6.75 (s, 2H), 6.20 (s, 1H), 5.86-5.53 (m, 2H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.54 (dd, J = 34.6, 6.2 Hz, 2H), 4.38-4.14 (m, 2H), 4.01 (t, J = 7.4 Hz, 4H), 3.82 (s, 8H), 3.67 (s, 2H), 3.00-2.71 (m, 5H), 2.61 (s, 9H), 2.35 (d, J = 8.0 Hz, 3H), 1.95 (d, J = 11.4 Hz, 1H), 1.80-1.59 (m, 5H), 1.45 (s, 3H), 1.21 (d, J = 13.5 Hz, 2H). D160 772.2 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.02 (s, 1H), 8.15 (s, 1H), 7.59-7.44 (m, 2H), 6.76 (s, 2H), 6.55-6.44 (m, 2H), 6.20 (s, 1H), 5.66 (qq, J = 10.0, 5.4, 5.0 Hz, 2H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.55 (dd, J = 34.7, 6.0 Hz, 2H), 4.34-4.13 (m, 2H), 4.01 (t, J = 7.4 Hz, 4H), 3.84 (s, 6H), 3.68 (d, J = 16.8 Hz, 6H), 2.97- 2.84 (m, 1H), 2.61 (s, 5H), 2.39-2.29 (m, 3H), 1.94 (dd, J = 11.2, 5.4 Hz, 1H), 1.78 (d, J = 8.0 Hz, 5H), 1.66 (d, J = 5.6 Hz, 2H). D161 747.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.01 (s, 1H), 8.19 (s, 1H, FA salt), 7.60 (s, 1H), 7.52 (d, J = 9.1 Hz, 1H), 7.08-7.01 (m, 2H), 6.74 (s, 2H), 6.19 (s, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.33 (d, J = 16.9 Hz, 1H), 4.20 (d, J = 16.9 Hz, 1H), 4.00 (t, J = 7.4 Hz, 4H), 3.82 (s, 6H), 3.68 (s, 2H), 3.48 (s, 3H), 3.30-3.25 (m, 6H), 3.05 (t, J = 6.5 Hz, 2H), 2.97-2.80 (m, 2H), 2.63-2.54 (m, 1H), 2.44-2.26 (m, 7H), 2.00-1.92 (m, 1H). D162 679.1 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.10 (s, 1H), 8.52 (s, FA, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.47 (s, 1H), 7.25-7.16 (m, 2H), 6.83 (s, 2H), 6.19 (s, 1H), 5.16 (dd, J = 13.4, 5.2 Hz, 1H), 5.11-5.03 (m, 1H), 4.63-4.43 (m, 2H), 4.38 (d, J = 23.9 Hz, 4H), 4.08 (d, J = 7.4 Hz, 4H), 4.05 (s, 1H), 3.93 (s, 6H), 3.59 (s, 3H), 2.93 (ddd, J = 17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, J = 17.7, 4.7, 2.4 Hz, 1H), 2.60- 2.37 (m, 3H), 2.19 (dtd, J = 12.8, 5.3, 2.4 Hz, 1H), 1.49 (s, 1H). D163 639.2 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.02 (s, 1H), 7.63 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.04 (dd, J = 8.7, 2.4 Hz, 1H), 6.80 (s, 2H), 6.44 (s, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 4.68 (s, 2H), 3.88 (s, 6H), 3.46 (s, 3H), 3.13 (s, 3H), 3.05 (s, 6H), 2.95-2.82 (m, 1H), 2.63-2.56 (m, 1H), 2.55 (s, 1H), 2.06- 1.95 (m, 1H). D164 791.5 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 8.54 (s, 1H), 8.15 (s, 0.9H, FA), 7.68 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.28- 7.23 (m, 1H), 7.18 (s, 1H), 7.13 (s, 1H), 6.93 (d, J = 5.1 Hz, 1H), 6.78 (s, 2H), 5.07 (dd, J = 12.8, 5.4 Hz, 1H), 3.85 (s, 9H), 3.53 (s, 4H), 3.44-3.42 (m, 5H), 3.12-3.08 (m, 2H), 2.91-2.87 (m, 1H), 2.85 (d, J = 4.9 Hz, 3H), 2.64-2.53 (m, 3H), 2.37-2.32 (m, 3H), 2.04-1.99 (m, 1H), 1.77-1.70 (m, 2H), 1.47-1.37 (m, 3H), 1.32-1.23 (m, 3H). D165 781.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.49 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.33-7.27 (m, 2H), 7.15 (s, 1H), 6.91 (s, 2H), 5.11 (dd, J = 12.5, 5.4 Hz, 1H), 4.54 (s, 2H), 3.99 (s, 10H), 3.78 (d, J = 25.5 Hz, 3H), 3.63 (s, 3H), 3.53 (s, 8H), 2.97 (d, J = 8.7 Hz, 6H), 2.93-2.66 (m, 4H), 2.20-2.11 (m, 1H). D166 822.65 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.52 (s, 1H, FA), 8.50 (d, J = 8.1 Hz, 1H), 7.80-7.71 (m, 1H), 7.42 (dd, J = 5.6, 2.3 Hz, 1H), 7.34- 7.28 (m, 1H), 7.23 (d, J = 0.9 Hz, 1H), 7.11-7.08 (m, 1H), 6.81 (d, J = 5.0 Hz, 2H), 5.09 (dd, J = 12.7, 5.5 Hz, 1H), 4.34-4.27 (m, 2H), 4.26-3.98 (m, 4H), 3.90 (s, 6H), 3.89-3.82 (m, 5H), 3.75-3.69 (m, 1H), 3.65 (s, 6H), 2.97 (s, 3H), 2.93-2.78 (m, 2H), 2.78-2.61 (m, 4H), 2.14-2.06 (m, 1H), 2.04-1.82 (m, 2H). D167

820.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 8.51 (s, 1H), 7.82 (dd, J = 8.5, 7.2 Hz, 1H), 7.70 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 1.2 Hz, 1H), 7.17 (s, 1H), 7.11 (s, 1H), 6.93 (d, J = 5.2 Hz, 1H), 6.86-6.51 (m, 2H), 5.08 (dd, J = 12.9, 5.4 Hz, 1H), 4.21 (t, J = 6.3 Hz, 2H), 3.84 (s, 6H), 3.52 (s, 3H), 3.49 (s, 2H), 3.13-3.03 (m, 2H), 2.93-2.81 (m, 4H), 2.64-2.52 (m, 3H), 2.10-1.99 (m, 4H), 1.92 (s, 5H), 1.83-1.73 (m, 2H), 1.55-1.39 (m, 4H). D168 834.5 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.14 (s, 1H), 8.52 (s, 1H), 8.19 (s, 1H, FA), 7.81 (dd, J = 8.5, 7.2 Hz, 1H), 7.65 (t, J = 5.8 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.18 (s, 1H), 7.12 (s, 1H), 6.93 (d, J = 5.0 Hz, 1H), 6.72 (s, 2H), 5.08 (dd, J = 12.8, 5.4 Hz, 1H), 4.20 (t, J = 6.3 Hz, 2H), 3.80 (s, 6H), 3.57 (s, 2H), 3.53 (s, 3H), 3.28-3.13 (m, 2H), 3.09-3.01 (m, 2H), 2.95-2.81 (m, 4H), 2.64-2.53 (m, 2H), 2.13 (s, 3H), 2.08-1.97 (m, 1H), 1.86 (s, 6H), 1.77 (t, J = 6.7 Hz, 2H), 1.53-1.37 (m, 4H). D169 833.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.07 (s, 1H), 8.85 (s, 1H), 8.55 (s, 1H), 7.82 (t, J = 5.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 7.16-7.07 (m, 2H), 6.95 (d, J = 2.1 Hz, 1H), 6.90-6.80 (m, 3H), 5.03 (dd, J = 12.8, 5.3 Hz, 1H), 4.37 (d, J = 12.5 Hz, 1H), 4.19 (dd, J = 12.7, 7.8 Hz, 1H), 3.91 (s, 6H), 3.54 (s, 3H), 3.39-3.26 (m, 2H), 3.15 (s, 2H), 3.10-3.02 (m, 2H), 3.02-2.76 (m, 5H), 2.67 (d, J = 4.7 Hz, 3H), 2.60 (s, 1H), 2.10 (s, 6H), 2.02-1.92 (m, 1H), 1.65- 1.53 (m, 2H), 1.51-1.41 (m, 2H), 1.40-1.29 (m, 2H). D170 820.4 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.52 (d, J = 9.1 Hz, 1H), 8.07-7.67 (m, 2H), 7.43 (s, 1H), 7.36 (dd, J = 8.3, 2.2 Hz, 1H), 7.18 (d, J = 14.4 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 6.94 (s, 1H), 6.86 (d, J = 9.4 Hz, 1H), 6.70 (s, 1H), 5.12 (dd, J = 12.9, 5.4 Hz, 1H), 4.40-4.02 (m, 3H), 3.90 (d, J = 6.2 Hz, 3H), 3.79 (s, 3H), 3.53 (d, J = 3.9 Hz, 3H), 3.49 (s, 1H), 3.15-3.03 (m, 2H), 2.95-2.87 (m, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.67-2.53 (m, 4H), 2.31-2.25 (m, 2H), 2.11-2.00 (m, 3H), 1.92 (s, 3H), 1.82-1.73 (m, 2H), 1.54- 1.36 (m, 4H). D171 866.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.52 (s, 1H), 8.36 (s, 1H, FA), 7.64 (t, J = 5.8 Hz, 1H), 7.58 (dd, J = 8.6, 7.0 Hz, 1H), 7.17 (s, 1H), 7.14-7.08 (m, 2H), 7.02 (d, J = 7.1 Hz, 1H), 6.96- 6.90 (m, 1H), 6.72 (s, 2H), 6.53 (t, J = 6.0 Hz, 1H), 5.05 (dd, J = 12.9, 5.4 Hz, 1H), 3.80 (s, 6H), 3.54 (s, 2H), 3.53 (s, 3H), 3.28- 3.26 (m, 2H), 3.06-3.00 (m, 2H), 2.90-2.82 (m, 4H), 2.62-2.54 (m, 3H), 2.46 (s, 1H), 2.11 (s, 3H), 2.07-1.99 (m, 1H), 1.85 (s, 6H), 1.63-1.53 (m, 2H), 1.49-1.40 (m, 2H), 1.36-1.27 (m, 2H). D172 834.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.83 (s, 1H, TFA), 8.55 (s, 1H), 7.88-7.80 (m, 2H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 6.87 (s, 2H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.37 (d, J = 12.6 Hz, 1H), 4.24- 4.12 (m, 3H), 3.91 (s, 6H), 3.54 (s, 5H), 3.13-3.03 (m, 2H), 2.93- 2.79 (m, 4H), 2.71-2.60 (m, 4H), 2.58-2.56 (m, 1H), 2.13- 1.99 (m, 7H), 1.76 (d, J = 6.8 Hz, 2H), 1.53-1.36 (m, 4H). D173 834.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.12 (s, 1H), 8.83 (s, 1H, TFA), 8.55 (s, 1H), 7.88-7.80 (m, 2H), 7.43 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.3, 2.3 Hz, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 6.97 (s, 1H), 6.87 (s, 2H), 5.12 (dd, J = 12.9, 5.3 Hz, 1H), 4.37 (d, J = 12.6 Hz, 1H), 4.24- 4.12 (m, 3H), 3.91 (s, 6H), 3.54 (s, 5H), 3.13-3.03 (m, 2H), 2.93- 2.79 (m, 4H), 2.71-2.60 (m, 4H), 2.58-2.56 (m, 1H), 2.13- 1.99 (m, 7H), 1.76 (d, J = 6.8 Hz, 2H), 1.53-1.36 (m, 4H). D174 844.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.04 (s, 1H), 8.15 (s, 1H, FA), 7.83 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.38-7.22 (m, 2H), 6.96 (d, J = 10.0 Hz, 2H), 6.45 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.06-4.93 (m, 1H), 3.82 (s, 3H), 3.65 (s, 2H), 3.48 (s, 3H), 3.07 (s, 6H), 2.95-2.81 (m, 3H), 2.82-2.72 (m, 2H), 2.70- 2.53 (m, 3H), 2.49-2.38 (m, 4H), 2.38-2.13 (m, 5H), 2.11-1.98 (m, 1H), 1.84 (dd, J = 11.9, 6.4 Hz, 2H), 1.77-1.41 (m, 7H), 1.22 (t, J = 7.5 Hz, 3H), 1.18-0.98 (m, 2H). D175 812.2 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.28 (d, J = 1.8 Hz, 1H), 8.57 (s, 1H, FA), 7.96-7.46 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 1.9 Hz, 1H), 6.85 (d, J = 2.0 Hz, 3H), 6.81-6.73 (m, 1H), 5.12 (dd, J = 13.0, 5.3 Hz, 1H), 4.67-4.61 (m, 1H), 4.46-4.32 (m, 4H), 4.18- 4.09 (m, 2H), 3.97 (d, J = 2.0 Hz, 6H), 3.87-3.78 (m, 2H), 3.67 (d, J = 2.0 Hz, 6H), 3.43-3.39 (m, 1H), 3.12-3.04 (m, 1H), 2.99- 2.85 (m, 1H), 2.85-2.75 (m, 1H), 2.68 (d, J = 7.0 Hz, 2H), 2.57- 2.38 (m, 4H), 2.23-2.13 (m, 1H), 1.93-1.84 (m, 4H). D176 774.3 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.18 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.05 (d, J = 8.2 Hz, 2H), 6.65 (d, J = 8.9 Hz, 1H), 6.53 (s, 2H), 5.86 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.38-4.14 (m, 2H), 3.75 (s, 6H), 3.65-3.51 (m, 6H), 3.41 (s, 5H), 3.01-2.84 (m, 3H), 2.61 (s, 4H), 2.42-1.87 (m, 9H), 1.80-1.67 (m, 2H), 1.56- 1.37 (m, 2H). D177 746.2 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.02 (s, 1H), 8.26 (s, 2H, FA), 7.67-7.58 (m, 2H), 7.49 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 6.74 (s, 2H), 6.20 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 (d, J = 17.2 Hz, 1H), 4.28 (d, J = 17.3 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.82 (s, 6H), 3.64 (s, 2H),

3.49 (s, 3H), 3.35-3.34 (m, 2H), 2.97-2.92 (m, 2H), 2.90-2.86 (m, 1H), 2.82-2.73 (m, 3H), 2.66- 2.56 (m, 2H), 2.41 (d, J = 4.6 Hz, 1H), 2.37-2.30 (m, 2H), 2.03- 1.96 (m, 1H), 1.83 (t, J = 11.0 Hz, 2H), 1.78-1.71 (m, 2H), 1.70- 1.60 (m, 2H). D178 888.2 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.14 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.55-7.51 (m, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.28-7.23 (m, 1H), 6.88 (d, J = 4.7 Hz, 2H), 6.72 (s, 1H), 5.17-5.07 (m, 1H), 5.02- 4.95 (m, 1H), 4.40 (s, 2H), 3.97 (d, J = 4.4 Hz, 6H), 3.88-3.77 (m, 5H), 3.66 (d, J = 12.8 Hz, 2H), 3.61 (s, 3H), 3.58 (d, J = 4.8 Hz, 4H), 3.44-3.37 (m, 1H), 3.18 (dd, J = 13.2, 10.3 Hz, 2H), 3.13- 2.97 (m, 4H), 2.92-2.83 (m, 1H), 2.81-2.78 (m, 1H), 2.76-2.67 (m, 2H), 2.61-2.51 (m, 1H), 2.33-2.22 (m, 1H), 2.22-2.08 (m, 6H), 2.09-2.04 (m, 3H), 1.74-1.59 (m, 2H). D179 746.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.02 (s, 1H), 8.24 (s, 2H, FA), 7.62 (s, 1H), 7.58-7.48 (m, 3H), 6.74 (s, 2H), 6.20 (s, 1H), 5.11 (dd, J = 13.2, 5.0 Hz, 1H), 4.42 (d, J = 17.1 Hz, 1H), 4.28 (d, J = 17.1 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.82 (s, 6H), 3.67 (s, 2H), 3.48 (s, 3H), 3.40-3.37 (m, 2H), 3.04-2.97 (m, 2H), 2.94- 2.87 (m, 1H), 2.82-2.74 (m, 3H), 2.65-2.56 (m, 2H), 2.44-2.38 (m, 1H), 2.38-2.30 (m, 2H), 2.05-1.97 (m, 1H), 1.89-1.73 (m, 4H), 1.73- 1.60 (m, 2H). D180 780.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.04 (s, 1H), 7.85 (dd, J = 8.5, 7.3 Hz, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.48 (d, J = 7.2 Hz, 1H), 6.74 (s, 2H), 6.48 (s, 1H), 5.09 (dd, J = 12.8, 5.4 Hz, 1H), 4.55 (s, 2H), 4.43 (s, 4H), 3.79 (s, 6H), 3.55 (s, 2H), 3.47 (s, 3H), 3.06 (s, 6H), 2.92-2.81 (m, 1H), 2.63-2.54 (m, 5H), 2.48- 2.37 (m, 5H), 2.07-1.98 (m, 1H). D181 773.55 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 8.21 (s, 1H, FA), 8.07 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 2H), 6.65 (d, J = 9.0 Hz, 1H), 6.52 (s, 2H), 5.85 (d, J = 7.6 Hz, 1H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.25 (dd, J = 22.4 Hz, 2H), 3.90 (d, J = 12.2 Hz, 2H), 3.74 (s, 6H), 3.58 (d, J = 6.4 Hz, 6H), 3.55 (s, 3H), 2.95-2.85 (m, 3H), 2.82-2.66 (m, 2H), 2.61 (d, J =3.6 Hz, 1H), 2.42-2.28 (m, 1H), 2.10-2.03 (m, 4H), 1.99-1.88 (m, 1H), 1.74 (d, J = 9.0 Hz, 2H), 1.64 (d, J = 12.1 Hz, 2H), 1.31-1.10 (m, 5H), 1.05 (d, J = 9.6 Hz, 1H). D182 845.25 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.25 (br s, 1H, TFA salt), 9.14 (s, 1H), 8.11 (s, 1H), 7.64 (dd, J = 8.4, 2.3 Hz, 1H), 7.20 (d, J = 4.5 Hz, 2H), 7.06 (d, J = 2.3 Hz, 1H), 6.98 (dd, J = 8.4, 2.2 Hz, 1H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.87 (p, J = 6.7 Hz, 1H), 4.48-4.18 (m, 6H), 4.17-4.12 (m, 3H), 3.91 (s, 6H), 3.42 (s, 3H), 3.19 (s, 2H), 3.08-2.80 (m, 7H), 2.68-2.55 (m, 2H), 2.43-2.30 (m, 4H), 2.11-1.76 (m, 11H), 1.59-1.37 (m, 2H). D183 773.2 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 8.21 (s, 1H, FA), 8.07 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.49 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 6.65 (d, J = 9.0 Hz, 1H), 6.53 (s, 2H), 5.86 (d, J = 7.7 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 (d, J = 17.3 Hz, 1H), 4.28 (d, J = 17.3 Hz, 1H), 3.75 (s, 6H), 3.62-3.54 (m, 6H), 3.41 (s, 3H), 3.01-2.87 (m, 5H), 2.68- 2.56 (m, 2H), 2.44-2.24 (m, 4H), 2.15-2.00 (m, 5H), 1.80- 1.64 (m, 6H), 1.48 (q, J = 11.8 Hz, 2H). D184 776.3 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 7.57 (s, 1H), 7.41 (d, J = 8.2 Hz, 1H), 6.96-6.72 (m, 5H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.55 (s, 2H), 4.49-4.30 (m, 4H), 4.27-4.07 (m, 2H), 3.99 (d, J = 9.8 Hz, 9H), 3.78 (s, 4H), 3.64 (s, 3H), 3.59-3.48 (m, 5H), 3.27- 3.01 (m, 2H), 3.00-2.69 (m, 2H), 2.50 (dd, J = 13.1,4.8 Hz, 1H), 2.35-2.00 (m, 5H).

Example 44—Preparation of Compounds D185-D316

(265) In analogy to the procedures described in the examples above, compounds D185-D316 were prepared using the appropriate starting materials

(266) TABLE-US-00008 Compound No. LCMS .sup.1H NMR D185 829.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.02 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 6.88 (s, 2H), 6.63-6.50 (m, 2H), 6.31 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.56-4.30 (m, 6H), 4.19 (t, J = 7.5 Hz, 6H), 3.99 (s, 6H), 3.87 (s, 2H), 3.77 (s, 2H), 3.59 (s, 3H), 3.57- 3.46 (m, 3H), 3.09-2.85 (m, 3H), 2.83-2.74 (m, 1H), 2.58-2.40 (m, 3H), 2.34-2.07 (m, 5H), 1.53 (s, 6H). D186 814.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.57 (s, 1H), 8.09 (s, 1H), 7.88 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.81 (s, 2H), 6.68 (d, J = 7.9 Hz, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.36-4.14 (m, 2H), 3.81 (s, 6H), 3.67 (d, J = 15.0 Hz, 6H), 3.57 (s, 5H), 2.99 (t, J = 6.9 Hz, 2H), 2.96-2.84 (m, 1H), 2.70-2.56 (m, 2H), 2.46-2.38 (m, 2H), 2.37-2.17 (m, 5H), 2.06-1.90 (m, 1H), 1.78-1.65 (m, 4H). D187 844.40 .sup.1H NMR (400 MHz, MeOD) δ 9.11 (s, 1H), 8.49 (s, 3FA, 3H), 7.52- 7.45 (m, 2H), 7.21 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.3, 2.4 Hz, 1H), 6.87 (s, 2H), 6.21 (s, 1H), 5.17 (d, J = 5.2 Hz, 1H), 4.84-4.78 (m, 1H), 4.66-4.60 (m, 1H), 4.50-4.38 (m, 2H), 4.36-4.33(m, 2H), 4.09 (t, J = 7.4, 7.4 Hz, 4H), 3.97 (s, 6H), 3.60 (s, 3H), 3.55- 3.48 (m, 1H), 3.17-3.08 (m, 1H), 2.96-2.87 (m, 1H), 2.84-2.76 (m, 1H), 2.71-2.59 (m, 3H), 2.56-2.44 (m, 4H), 2.44-2.36 (m,

2H), 2.23-2.16 (m, 1H), 2.07-1.91 (m, 5H), 1.85-1.77 (m, 4H), 1.57-1.52 (m, 2H), 1.37-1.28 (m, 3H). D188 868.30 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.62 (s, 1H), 8.46 (s, 1H), 8.16 (s, 1H, FA), 7.91 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.21-7.16(m, 2H), 6.90 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.85-4.82 (m, 1H), 4.51-4.36 (m, 4H), 3.98 (s, 6H), 3.74 (s, 3H), 3.57 (d, J = 12.1 Hz, 2H), 3.18 (d, J = 12.3 Hz, 2H), 3.08-2.86 (m, 5H), 2.84- 2.76(m, 3H), 2.64-2.46(m, 3H), 2.20 (m, 2H), 2.12-2.06 (m, 1H), 2.1-1.98(m, 3H), 1.97-1.84 (m, 4H), 1.64 (s, 2H). D189 809.20 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.15 (d, J = 0.7 Hz, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.46 (s, 1H), 7.28 (d, J = 1.3 Hz, 1H), 7.22 (d, J = 1.3 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 6.42 (s, 1H), 5.18-5.06 (m, 1H), 4.50-4.31 (m, 2H), 3.99 (s, 1H), 3.97-3.92 (m, 4H), 3.69- 3.63 (m, 2H), 3.62-3.52 (m, 4H), 3.35 (s, 2H), 3.41-3.34 (m, 2H), 3.18-3.07 (m, 7H), 3.02-2.84 (m, 4H), 2.87-2.73 (m, 1H), 2.58- 2.39 (m, 1H), 2.24-2.09 (m, 1H), 1.93-1.83 (m, 2H), 1.81-1.70 (m, 2H), 1.69-1.63 (m, 1H), 1.55-1.36 (m, 2H), 1.36-1.23 (m, 1H). D190 861.30 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.41 (s, 1H), 7.88 (s, 1H), 7.65 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 8.3, 2.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.81 (s, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.88-4.79 (m, 1H), 4.69 (s, 1H), 4.41-4.18 (m, 2H), 3.85 (s, 6H), 3.79-3.74 (m, 2H), 3.60 (s, 3H), 3.55 (s, 2H), 3.03- 2.85 (m, 3H), 2.64-2.55 (m, 1H), 2.39 (d, J = 13.1 Hz, 9H), 2.14 (d, J = 7.0 Hz, 2H), 2.04-1.96 (m, 1H), 1.83-1.55 (m, 9H), 1.26 (s, 6H), 1.18 (s, 2H). D191 845.30 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.24-7.13 (m, 2H), 6.81 (s, 2H), 5.18 (d, J = 5.1 Hz, 1H), 4.67 (s, 2H), 4.44 (d, J = 5.3 Hz, 4H), 3.95 (s, 6H), 3.68 (s, 5H), 3.58 (s, 4H), 3.43 (s, 1H), 3.22 (m, J = 12.3 Hz, 2H), 3.10 (d, J = 6.6 Hz, 3H), 3.03 (s, 1H), 2.98-2.85 (m, 2H), 2.83 (s, 1H), 2.52 (m, J = 12.9, 4.9 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 1H), 2.10 (d, J = 14.3 Hz, 8H), 1.74 (t, J = 12.9 Hz, 2H). D192 829.40 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.05 (s, 1H), 7.52 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.91-6.86 (m, 3H), 6.83-6.77 (m, 1H), 6.27 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.56-4.31 (m, 6H), 4.26-4.11 (m, 6H), 4.00 (s, 6H), 3.82 (s, 2H), 3.72 (s, 2H), 3.63-3.46 (m, 6H), 3.11-2.75 (m, 4H), 2.58-2.43 (m, 3H), 2.36-2.07 (m, 5H), 1.53 (s, 6H). D193 786.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 9.30 (d, J = 0.7 Hz, 1H), 7.78 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.38 (s, 1H), 6.87 (d, J = 4.4 Hz, 2H), 6.70 (dd, J = 4.6, 2.3 Hz, 2H), 5.06 (dd, J = 13.3, 5.1 Hz, 1H), 4.42 (d, J = 21.9 Hz, 2H), 4.36-4.15 (m, 4H), 4.11-4.00 (m, 2H), 3.91 (s, 6H), 3.69 (d, J = 33.2 Hz, 4H), 3.57 (s, 3H), 3.38 (s, 3H), 3.25- 3.12 (m, 1H), 3.02-2.81 (m, 3H), 2.71-2.56 (m, 2H), 2.38 (dd, J = 13.3, 4.7 Hz, 1H), 2.24-2.05 (m, 3H), 1.95 (s, 3H), 1.01 (d, J = 6.4 Hz, 4H). D194 874.30 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.07 (s, 1H), 8.25 (s, 2H, FA), 7.62 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.15-7.04 (m, 2H), 6.69 (d, J = 32.4 Hz, 3H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.89- 4.78 (m, 1H), 4.45-4.19 (m, 2H), 3.80 (s, 5H), 3.69 (t, J = 4.9 Hz, 4H), 3.56 (s, 3H), 3.51 (s, 3H), 2.98-2.82 (m, 3H), 2.71-2.55 (m, 2H), 2.43-2.15 (m, 8H), 2.06 (d, J = 8.0 Hz, 6H), 1.77 (dd, J = 11.2, 6.5 Hz, 2H), 1.66-1.51 (m, 6H), 1.45 (s, 1H), 1.12-0.99 (m, 2H). D195 911.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.29 (s, 1H), 8.17 (s, FA, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.78 (s, 1H), 7.44 (s, 1H), 7.32- 7.24 (m, 2H), 6.74 (s, 2H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.02- 4.94 (m, 1H), 3.82 (s, 6H), 3.61-3.54 (m, 5H), 3.05-2.85 (m, 4H), 2.83-2.69 (m, 2H), 2.64-2.57 (m, 1H), 2.48-2.39 (m, 4H), 2.32- 2.21 (m, 1H), 2.09-2.04 (m, 3H), 1.96-1.85 (m, 1H), 1.85- 1.74 (m, 2H), 1.55-1.50 (m, 6H), 1.36-1.12 (m, 3H), 1.07-0.92 (m, 4H). D196 956.35 H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.08 (s, 1H), 8.17 (s, FA, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.32-7.24 (m, 2H), 6.73 (s, 2H), 6.65 (s, 1H), 5.12 (dd, J = 12.8, 5.4 Hz, 1H), 5.02- 4.94 (m, 1H), 3.81 (s, 6H), 3.69 (t, J = 4.7 Hz, 4H), 3.57 (s, 2H), 3.51-3.47 (m, 7H), 2.99 (s, 1H), 2.96-2.78 (m, 5H), 2.74-2.69 (m, 1H), 2.64-2.55 (m, 2H), 2.46-2.39 (m, 3H), 2.10-2.02 (m, 3H), 1.91-1.76 (m, 3H), 1.65-1.46 (m, 6H), 1.35-1.12 (m, 2H). D197 797.65 .sup.1H NMR (300 MHz, DMSO) δ 10.98 (s, 1H), 9.03 (d, J = 0.7 Hz, 1H), 8.20 (s, FA, 1H), 7.59 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.48 (d, J = 0.8 Hz, 1H), 5.10 (dd, J = 13.3, 5.0 Hz, 1H), 4.33 (d, J = 16.7 Hz, 1H), 4.19 (d, J = 16.7 Hz, 1H), 3.81 (s, 6H), 3.73 (d, J = 12.2 Hz, 3H), 3.55 (s, 3H), 3.00-2.83 (m, 2H), 2.75-2.61 (m, 3H), 2.57- 2.51 (m, 2H), 2.49-2.24 (m, 9H), 2.03-1.94 (m, 1H), 1.74 (d, J = 12.4 Hz, 2H), 1.41-1.32 (m, 3H), 1.30-1.16 (m, 2H). D198 781.55 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.25 (d, J = 0.7 Hz, 1H), 8.54 (s, 1H), 7.55 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.37-7.28 (m, 2H), 6.80 (s, 3H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.50-4.32 (m, 2H), 4.10 (s, 2H), 3.92 (s, 6H), 3.77 (d, J = 12.3 Hz, 2H), 3.64 (s, 3H), 3.01 (d, J = 23.7 Hz, 4H), 2.90 (dd, J = 13.1, 5.2 Hz, 3H), 2.85-2.75 (m, 4H), 2.72 (d, J = 9.3 Hz, 3H), 2.51 (qd, J = 13.2, 4.9 Hz, 1H), 2.24-2.13 (m, 1H), 1.88 (d, J = 12.3

Hz, 2H), 1.67-1.30 (m, 5H). D199 818.30 .sup.1H NMR (300 MHz, DMSO-d6) δ 9.17 (s, 1H), 7.71 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 1.7 Hz, 2H), 6.78 (d, J = 6.8 Hz, 1H), 6.70 (h, J = 2.3 Hz, 2H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.39-4.10 (m, 4H), 3.94 (s, 3H), 3.88 (d, J = 2.2 Hz, 6H), 3.78-3.60 (m, 4H), 3.60-3.56 (m, 3H), 3.49-3.38 (m, 4H), 3.13 (d, J = 36.5 Hz, 3H), 2.93 (dd, J = 35.7, 13.8 Hz, 4H), 2.67-2.55 (m, 1H), 2.43-2.26 (m, 1H), 2.12 (d, J = 13.1 Hz, 2H), 1.97 (d, J = 11.7 Hz, 2H), 1.86 (d, J = 13.0 Hz, 3H), 1.78-1.67 (m, 1H), 1.52 (d, J = 37.9 Hz, 4H). D200 819.40 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.06 (s, 1H), 8.16 (t, J = 1.6 Hz, 1H, FA), 7.64 (s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 6.78 (s, 2H), 6.70-6.61 (m, 2H), 6.30 (s, 1H), 5.52 (d, J = 57.4 Hz, 1H), 5.08 (dd, J = 13.3, 5.0 Hz, 1H), 4.35 (ddd, J = 21.3, 10.6, 5.8 Hz, 3H), 4.24-4.00 (m, 4H), 3.96-3.80 (m, 9H), 3.77-3.62 (m, 3H), 3.58 (s, 4H), 3.50 (s, 3H), 3.01-2.81 (m, 2H), 2.78-2.53 (m, 3H), 2.45-2.36 (m, 1H), 2.38-2.25 (m, 3H), 2.07-1.90 (m, 1H), 1.80- 1.67 (m, 4H). D201 827.00 .sup.1H NMR (400 MHz, DMSO-d6) δ 9.04-8.93 (m, 1H), 7.58 (s, 1H), 7.41 (d, 1H), 6.83 (s, 2H), 6.72 (d, J = 2.4 Hz, 2H), 6.23 (s, 1H), 5.02 (d, J = 13.1 Hz, 1H), 4.33 (t, J = 17.3 Hz, 3H), 4.19 (d, J = 16.7 Hz, 2H), 4.09 (s, 3H), 4.05-3.95 (m, 2H), 3.89-3.85 (m, 6H), 3.71 (s, 3H), 3.64 (s, 3H), 3.48 (s, 3H), 3.39 (d, J = 23.0 Hz, 4H), 3.25- 3.08 (m, 1H), 3.04-2.77 (m, 3H), 2.70-2.56 (m, 1H), 2.43-2.29 (m, 1H), 2.11 (d, J = 13.9 Hz, 2H), 2.05-1.80 (m, 3H), 0.67 (s, 4H). D202 637.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.01 (s, 1H), 7.60 (s, 1H), 7.48 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.2 Hz, 2H), 6.77 (s, 2H), 6.17 (s, 1H), 5.04 (dd, J = 13.2, 5.1 Hz, 1H), 4.58 (s, 2H), 4.31 (d, J = 16.6 Hz, 1H), 4.17 (d, J = 16.7 Hz, 1H), 4.00 (t, J = 7.4 Hz, 4H), 3.85 (s, 6H), 3.46 (s, 3H), 2.98 (s, 3H), 2.94-2.82 (m, 1H), 2.64-2.58 (m, 1H), 2.41-2.28 (m, 3H), 2.00-1.90 (m, 1H). D203 832.40 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.36 (s, 1H), 7.65 (s, 1H), 7.47- 7.39 (m, 2H), 7.37-7.27 (m, 2H), 6.78 (s, 2H), 5.14 (dd, J = 13.3, 5.2 Hz, 1H), 4.63 (s, 2H), 4.48-4.33 (m, 2H), 3.98-3.87 (m, 8H), 3.76 (d, J = 12.4 Hz, 2H), 3.71-3.64 (m, 4H), 3.62 (q, J = 7.0 Hz, 2H), 3.00-2.68 (m, 10H), 2.61-2.54 (m, 2H), 2.53-2.43 (m, 1H), 2.29 (ddd, J = 9.8, 6.1, 2.2 Hz, 1H), 2.18 (dtd, J = 12.8, 5.3, 2.4 Hz, 1H), 1.87 (d, J = 12.4 Hz, 2H), 1.61-1.50 (m, 3H), 1.47-1.33 (m, 4H), 1.18 (t, J = 7.1 Hz, 3H). D204 846.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.35 (s, 1H), 8.54 (s, 1H, Formic acid), 7.68-7.60 (m, 2H), 7.38 (d, J = 0.9 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.20 (dd, J = 8.7, 2.4 Hz, 1H), 6.76 (s, 2H), 5.06 (dd, J = 12.5, 5.5 Hz, 2H), 4.61 (s, 4H), 4.03 (d, J = 13.2 Hz, 2H), 3.89 (s, 6H), 3.71-3.64 (m, 4H), 3.60 (q, J = 7.0 Hz, 2H), 2.98 (t, J = 12.6 Hz, 3H), 2.90-2.80 (m, 3H), 2.79-2.71 (m, 2H), 2.71-2.64 (m, 2H), 2.56-2.49 (m, 2H), 2.30-2.24 (m, 1H), 2.13-2.07 (m, 1H), 1.85 (d, J = 12.9 Hz, 2H), 1.65-1.58 (m, 1H), 1.56-1.48 (m, 2H), 1.44-1.36 (m, 2H), 1.35-1.32 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H). D205 855.00 .sup.1H NMR (400 MHz, DMSO-d6) δ 9.02 (s, 1H), 7.56 (d, J = 2.5 Hz, 1H), 7.44-7.37 (m, 1H), 6.84 (s, 2H), 6.75-6.68 (m, 2H), 6.24 (d, J = 8.2 Hz, 1H), 5.05-4.96 (m, 1H), 4.37-4.16 (m, 4H), 4.07 (s, 4H), 3.87 (s, 6H), 3.67 (d, J = 28.6 Hz, 4H), 3.48 (s, 4H), 3.44 (d, 2H), 3.21-3.12 (m, 1H), 3.07-2.80 (m, 6H), 2.70-2.62 (m, 1H), 2.61-2.54 (m, 1H), 2.40-2.31 (m, 1H), 2.10 (d, J = 12.3 Hz, 3H), 2.03-1.87 (m, 5H), 1.55-1.37 (m, 2H), 0.67 (s, 4H). D206 847.60 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.45-9.14 (m, 1H, TFA), 9.07 (s, 1H), 7.65 (d, J = 2.7 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 6.90 (s, 2H), 6.80-6.63 (m, 2H), 6.34 (d, J = 6.0 Hz, 1H), 5.53 (d, J = 56.8 Hz, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.54-4.02 (m, 9H), 3.92 (s, 6H), 3.70 (d, J = 21.7 Hz, 6H), 3.52 (s, 3H), 3.31-3.13 (m, 3H), 3.09-2.83 (m, 7H), 2.22-1.68 (m, 8H), 1.62-1.38 (m, 2H). D207 843.55 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.60-9.10 (m, 2H, TFA), 9.03 (s, 1H), 7.62 (d, J = 3.8 Hz, 1H), 7.42 (d, J = 8.9, 2.9 Hz, 1H), 6.89 (s, 2H), 6.70 (dq, J = 7.0, 2.4 Hz, 2H), 6.23 (d, J = 6.0 Hz, 1H), 5.07 (dd, J = 13.3, 5.1 Hz, 1H), 4.44-4.29 (m, 3H), 4.26- 4.16 (m, 3H), 3.98-3.92 (m, 1H), 3.90 (s, 6H), 3.83-3.81 (m, 2H), 3.74 (s, 2H), 3.65 (s, 2H), 3.50 (s, 3H), 3.49-3.42 (m, 2H), 3.21 (s, 1H), 3.08-2.85 (m, 6H), 2.68-2.60 (m, 1H), 2.48-2.35 (m, 2H), 2.18-1.88 (m, 9H), 1.59-1.46 (m, 2H), 1.43 (d, J = 6.2 Hz, 3H). D208 843.80 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.22-9.12 (m, 1H, TFA salt), 9.03 (s, 1H), 7.62 (d, J = 4.1 Hz, 1H), 7.46-7.38 (m, 1H), 6.90 (s, 2H), 6.74-6.67 (m, 2H), 6.23 (d, J = 6.3 Hz, 1H), 5.07 (dd, J = 13.3, 5.2 Hz, 1H), 4.44-4.16 (m, 5H), 4.00-3.87 (m, 7H), 3.86-3.78 (m, 1H), 3.78-3.62 (m, 5H), 3.52-3.49 (m, 5H), 3.21 (s, 1H), 3.09-2.84 (m, 7H), 2.70-2.56 (m, 2H), 2.47-2.29 (m, 2H), 2.19-2.06 (m, 3H), 2.03-1.88 (m, 6H), 1.54-1.46 (m, 1H), 1.43 (d, J = 6.1 Hz, 3H). D209 873.45 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.05 (s, 1H), 7.57 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.88 (s, 3H), 6.81 (d, J = 8.1 Hz, 1H), 6.39 (d, J = 6.6 Hz, 1H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.40 (d, J = 6.0 Hz, 4H), 4.09 (d, J = 9.0 Hz, 2H), 3.98 (s, 7H), 3.95 (s, 1H), 3.83 (s, 2H), 3.75 (s, 2H), 3.65 (s, 4H), 3.60 (s, 3H), 3.40 (s, 1H),

3.30 (s, 3H), 3.23 (d, J = 12.8 Hz, 2H), 3.14 (d, J = 7.1 Hz, 4H), 2.90 (dd, J = 12.9, 4.9 Hz, 1H), 2.79 (d, J = 17.5 Hz, 1H), 2.51 (dd, J = 13.1, 4.9 Hz, 1H), 2.28 (d, J = 13.4 Hz, 2H), 2.12 (d, J = 15.8 Hz, 5H), 1.71 (t, J = 13.0 Hz, 2H), 1.56 (s, 3H). D210 845.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.32 (s, 1H), 7.58 (s, 1H), 7.38 (d, J = 8.2 Hz, 1H), 6.78 (s, 2H), 6.69 (d, J = 7.6 Hz, 2H), 6.23 (s, 1H), 5.02 (dd, J = 13.2, 5.1 Hz, 1H), 4.32 (d, J = 16.9 Hz, 1H), 4.20 (s, 1H), 4.13 (d, J = 9.2 Hz, 2H), 3.91 (d, J = 8.8 Hz, 4H), 3.85 (s, 6H), 3.82 (s, 3H), 3.56 (s, 6H), 3.47 (s, 3H), 3.17 (s, 3H), 2.84 (d, J = 13.2 Hz, 2H), 2.63 (s, 3H), 2.34 (s, 4H), 2.00 (s, 1H), 1.73 (s, 4H), 1.44 (s, 3H). D211 837.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.09 (s, 1H), 8.25 (s, 1H, FA), 7.67 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.75 (s, 2H), 6.67 (s, 2H), 6.44 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.48 (t, J = 12.3 Hz, 4H), 4.35-4.14 (m, 2H), 3.93 (d, J = 23.1 Hz, 1H), 3.83 (s, 6H), 3.69 (s, 2H), 3.57 (s, 3H), 3.51 (s, 3H), 3.46 (t, J = 7.4 Hz, 2H), 3.02 (s, 2H), 2.97-2.84 (m, 1H), 2.64-2.54 (m, 1H), 2.46- 2.33 (m, 3H), 2.28 (s, 5H), 1.98 (d, J = 12.3 Hz, 1H), 1.73 (d, J = 5.3 Hz, 4H). D212 815.40 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 10.04-9.79 (m, 2H, TFA salt), 9.03 (s, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 4.5 Hz, 2H), 6.74-6.67 (m, 2H), 6.20 (s, 1H), 5.07 (dd, J = 13.2, 5.1 Hz, 1H), 4.46-4.29 (m, 4H), 4.27-4.16 (m, 3H), 4.08- 3.99 (m, 2H), 3.97-3.90 (m, 1H), 3.90 (s, 6H), 3.86-3.77 (m, 2H), 3.73 (s, 2H), 3.68-3.63 (m, 2H), 3.50 (s, 3H), 3.46-3.43 (m, 1H), 3.39-3.32 (m, 2H), 3.23-3.14 (m, 1H), 3.03-2.84 (m, 3H), 2.68-2.55 (m, 1H), 2.46-2.30 (m, 2H), 2.12 (d, J = 13.9 Hz, 2H), 2.04-1.87 (m, 4H), 1.43 (d, J = 6.2 Hz, 3H). D213 815.40 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 10.12-9.61 (m, TFA, 2H), 9.03 (s, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.9 Hz, 1H), 6.87 (s, 2H), 6.70 (d, 2H), 6.20 (s, 1H), 5.07 (dd, J = 13.2, 5.1 Hz, 1H), 4.45-4.35 (m, 3H), 4.33-4.16 (m, 4H), 4.08-4.02 (m, 2H), 3.97- 3.93 (m, 1H), 3.90 (s, 6H), 3.83-3.81 (m, 2H), 3.74 (s, 2H), 3.65 (s, 2H), 3.50 (s, 3H), 3.47 (s, 1H), 3.41-3.34 (m, 2H), 3.19 (s, 1H), 3.05-2.95 (m, 3H), 2.64-2.57 (m, 1H), 2.48-2.37 (m, 2H), 2.19- 1.85. (m, 6H), 1.43 (d, J = 6.1 Hz, 3H). D214 845.50 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.52 (d, J = 0.8 Hz, 1H), 8.35 (s, 1H, FA), 7.73 (s, 1H), 7.63 (d, J = 0.9 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.21 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 8.2, 2.4 Hz, 1H), 6.91 (s, 2H), 5.16 (dd, J = 13.2, 5.2 Hz, 1H), 4.88-4.76 (m, 2H), 4.48-4.35 (m, 4H), 3.98 (s, 6H), 3.71 (s, 3H), 3.63-3.49 (m, 2H), 3.16- 3.12 (m, 2H), 2.90-2.74 (m, 5H), 2.70-2.60 (m, 2H), 2.60-2.44 (m, 3H), 2.29-2.11 (m, 1H), 2.11-1.92 (m, 5H), 1.91-1.80 (m, 4H), 1.71-1.45 (m, 2H), 1.39 (s, 9H). D215 861.35 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.02 (s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.25 (dd, J = 8.6, 2.2 Hz, 1H), 6.82 (s, 2H), 6.21 (s, 1H), 5.07 (dd, J = 12.9, 5.4 Hz, 1H), 4.12-3.97 (m, 6H), 3.87 (s, 6H), 3.79 (s, 2H), 3.49-3.41 (m, 10H), 3.02-2.77 (m, 4H), 3.02-2.77 (m, 5H), 2.71-2.50 (m, 3H), 2.34 (t, J = 11.3 Hz, 2H), 2.05-1.97 (m, 1H), 1.76 (d, J = 12.6 Hz, 2H), 1.62-1.57 (m, 3H), 1.26-1.16 (m, 2H). D216 816.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.31 (s, 1H), 8.17 (s, 1H, FA), 7.86 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.54 (s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 (dd, J = 8.8, 1.7 Hz, 1H), 6.80 (s, 2H), 5.08 (dd, J = 12.7, 5.4 Hz, 1H), 3.83 (s, 6H), 3.64 (s, 2H), 3.58 (s, 3H), 3.44-3.40 (m, 8H), 2.96-2.87 (m, 3H), 2.86-2.81 (m, 1H), 2.64- 2.58 (m, 1H), 2.55 (s, 1H), 2.38-2.29 (m, 2H), 2.24-2.12 (m, 2H), 2.08-1.96 (m, 1H), 1.65 (d, J = 11.9 Hz, 2H), 1.45-1.34 (m, 5H), 1.30-1.27 (m, 2H), 1.24-1.09 (m, 2H), 0.88 (q, J = 3.6 Hz, 2H). D217 667.30 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.16 (s, 1H), 7.75 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.17- 7.11 (m, 1H), 6.78 (s, 1H), 6.74 (s, 2H), 5.10 (dd, J = 13.2, 5.2 Hz, 1H), 4.34 (d, J = 16.7 Hz, 1H), 4.20 (d, J = 16.9 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 6H), 3.68-3.61 (m, 2H), 3.54 (s, 3H), 3.19-3.12 (m, 4H), 2.74 (d, J = 1.9 Hz, 1H), 2.65-2.58 (m, 5H), 2.38 (d, J = 8.0 Hz, 1H), 2.30-2.25 (m, 1H). D218 829.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.25 (br s, TFA, 1H), 9.03 (s, 1H), 7.62 (s, 1H), 7.53 (d, J = 8.3, 2.9 Hz, 1H), 6.89 (s, 2H), 6.55-6.45 (m, 2H), 6.22 (d, J = 7.8 Hz, 1H), 5.05 (dd, J = 13.3, 5.1 Hz, 1H), 4.34-4.15 (m, 4H), 4.02 (t, J = 7.4 Hz, 4H), 3.91 (s, 6H), 3.79 (d, J = 8.2 Hz, 2H), 3.72 (d, J = 6.9 Hz, 2H), 3.50 (s, 5H), 3.22 (s, 1H), 3.01-2.85 (m, 6H), 2.64-2.53 (m, 2H), 2.41- 2.33 (m, 3H), 2.14 (d, 3H) 2.03-1.87 (m, 6H), 1.56-1.42 (m, 2H). D219 731.20 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.08 (s, 1H), 9.28 (s, 1H), 8.23 (s, 1H, FA), 7.80 (s, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 6.81- 6.72 (m, 3H), 6.65 (dd, J = 8.3, 2.1 Hz, 1H), 5.06 (dd, J = 12.9, 5.4 Hz, 1H), 3.83 (s, 6H), 3.74 (s, 4H), 3.56 (d, J = 5.4 Hz, 5H), 2.95- 2.82 (m, 1H), 2.55 (s, 3H), 2.44 (s, 3H), 2.27 (tt, J = 7.8, 3.9 Hz, 1H), 2.06-1.97 (m, 1H), 1.74 (t, J = 5.4 Hz, 4H), 1.06-0.94 (m, 4H). D220 717.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.28 (s, 1H), 8.21 (s, 1H, FA), 7.80 (s, 1H), 7.53-7.42 (m, 2H), 6.75 (s, 2H), 6.54- 6.44 (m, 2H), 5.04 (dd, J = 13.2, 5.1 Hz,

1H), 4.36-4.13 (m, 2H), 3.83 (s, 6H), 3.63 (s, 4H), 3.56 (s, 5H), 2.90 (ddd, J = 17.0, 13.6, 5.4 Hz, 1H), 2.55 (s, 3H), 2.45 (s, 2H), 2.40-2.30 (m, 1H), 2.27 (td, J = 7.8, 3.9 Hz, 1H), 2.05-1.85 (m, 1H), 1.74 (t, J = 5.4 Hz, 4H), 1.06-0.94 (m, 4H). D221 819.40 .sup.1H NMR (300 MHz, MeOD) δ 8.92 (s, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.34 (s, 1H), 6.88 (d, J = 2.1 Hz, 1H), 6.79 (dd, J = 6.8, 2.1 Hz, 3H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.60-4.48 (m, 2H), 4.45-4.32 (m, 4H), 4.31-4.09 (m, 6H), 3.95 (s, 6H), 3.82-3.74 (m, 4H), 3.64- 3.46 (m, 8H), 3.27-3.03 (m, 2H), 3.00-2.73 (m, 2H), 2.61-2.35 (m, 3H), 2.30-2.04 (m, 5H). D222 845.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.53 (s, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.7, 2.4 Hz, 1H), 6.88 (s, 2H), 6.28 (s, 1H), 5.09 (dd, J = 12.5, 5.4 Hz, 1H), 4.56 (d, J = 13.5 Hz, 1H), 4.44 (d, J = 13.8 Hz, 1H), 4.16 (t, J = 7.5 Hz, 4H), 4.07 (d, J = 13.2 Hz, 2H), 3.99 (s, 6H), 3.85-3.76 (m, 1H), 3.59 (s, 3H), 3.01 (t, J = 12.3 Hz, 3H), 2.92-2.82 (m, 2H), 2.80- 2.73 (m, 2H), 2.73-2.66 (m, 2H), 2.50 (p, J = 7.5 Hz, 2H), 2.17- 2.09 (m, 1H), 1.89 (d, J = 12.9 Hz, 2H), 1.78-1.69 (m, 1H), 1.57 (d, J = 7.1 Hz, 8H), 1.45-1.27 (m, 4H), 0.91 (d, J = 7.0 Hz, 1H). D223 794.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.05 (s, 1H), 7.58 (s, 1H), 7.52 (d, J = 9.1 Hz, 1H), 7.06 (m, 2H), 6.90 (s, 2H), 6.52 (s, 1H), 5.05 (dd, J = 13.2, 5.1 Hz, 1H), 4.32 (d, J = 17.0 Hz, 2H), 4.19 (d, J = 16.8 Hz, 2H), 3.89 (s, 2H), 3.85-3.76 (m, 8H), 3.56-3.43 (m, 2H), 3.23-3.04 (m, 12H), 2.99-2.89 (m, 1H), 2.88-2.76 (m, 2H), 2.66-2.54 (m, 1H), 2.44-2.32 (m, 1H), 2.01-1.91 (m, 1H), 1.81-1.71 (m, 2H), 1.65-1.49 (m, 3H), 1.34-1.17 (m, 2H). D224 778.40 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.95 (s, 1H), 9.16 (s, 1H), 7.73 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 7.9 Hz, 2H), 6.74 (d, J = 20.0 Hz, 3H), 5.04 (dd, J = 13.3, 5.1 Hz, 1H), 4.31 (d, J = 16.8 Hz, 1H), 4.19 (d, J = 16.8 Hz, 1H), 3.93 (s, 3H), 3.85 (d, J = 12.7 Hz, 2H), 3.79 (s, 6H), 3.54 (d, J = 5.1 Hz, 5H), 2.90 (ddd, J = 17.8, 13.5, 5.5 Hz, 1H), 2.79 (t, J = 12.2 Hz, 2H), 2.69-2.55 (m, 1H), 2.47- 2.36 (m, 5H), 2.36-2.23 (m, 6H), 2.01-1.91 (m, 1H), 1.73 (d, J = 12.6 Hz, 2H), 1.50 (s, 1H), 1.43-1.30 (m, 2H), 1.23-1.12 (m, 2H). D225 778.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.16 (s, 1H), 7.73 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.4 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.74 (d, J = 20.0 Hz, 3H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.38-4.15 (m, 2H), 3.93 (s, 3H), 3.79 (s, 6H), 3.73 (d, J = 12.3 Hz, 3H), 3.57-3.52 (m, 5H), 2.97-2.84 (m, 1H), 2.75-2.64 (m, 2H), 2.64-2.55 (m, 1H), 2.48-2.38 (m, 4H), 2.38-2.20 (m, 6H), 2.03-1.94 (m, 1H), 1.74 (d, J = 12.4 Hz, 2H), 1.52-1.42 (m, 1H, 1.41-1.32 (m, 2H), 1.31-1.17 (m, 2H). D226 717.25 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.29 (s, 1H), 8.15 (s, 1H, FA), 7.81 (s, 1H), 7.44 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 6.78 (s, 2H), 6.70 (d, J = 7.9 Hz, 2H), 5.08 (dd, J = 13.3, 5.1 Hz, 1H), 4.36-4.15 (m, 2H), 3.86 (s, 6H), 3.76 (s, 2H), 3.61 (s, 4H), 3.57 (s, 4H), 2.98-2.84 (m, 1H), 2.71-2.65 (m, 2H), 2.60 (d, J = 16.6 Hz, 2H), 2.38 (dd, J = 13.3, 4.5 Hz, 1H), 2.30-2.21 (m, 1H), 1.98 (d, J = 13.1 Hz, 1H), 1.83 (s, 4H), 1.05-0.96 (m, 4H). D227 865.55 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.11 (d, J = 0.8 Hz, 1H), 8.56 (s, 0.47H, FA), 7.50-7.39 (m, 2H), 6.90-6.77 (m, 4H), 6.22 (s, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.48-4.39 (m, 2H), 4.33 (d, J = 5.4 Hz, 2H), 4.09 (t, J = 7.5 Hz, 4H), 4.03-3.99 (m, 2H), 3.97 (s, 6H), 3.73 (d, J = 7.6 Hz, 2H), 3.60 (s, 3H), 3.56-3.47 (m, 2H), 3.00- 2.91 (m, 1H), 2.90-2.82 (m, 1H), 2.81-2.74 (m, 1H), 2.74-2.63 (m, 2H), 2.60-2.40 (m, 6H), 2.39-2.31 (m, 2H), 2.22-2.12 (m, 3H), 2.03 (d, J = 14.3 Hz, 2H), 1.97-1.87 (m, 1H), 1.55-1.41 (m, 2H). D228 847.45 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.49 (s, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.24-7.13 (m, 2H), 6.90 (s, 2H), 5.15 (dd, J = 13.2, 5.2 Hz, 1H), 4.54-4.35 (m, 4H), 3.98 (s, 6H), 3.72 (s, 3H), 3.70-3.61 (m, 4H), 3.56-3.46 (m, 1H), 3.45-3.33 (m, 1H), 3.21-3.19 (m, 1H), 3.14-2.97 (m, 4H), 2.96-2.80 (m, 1H), 2.77-2.67 (m, 2H), 2.58-2.47 (m, 2H), 2.31-2.12 (m, 2H), 2.17-1.96 (m, 8H), 1.77-1.66 (m, 2H), 1.60 (s, 6H). D229 692.15 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.30 (s, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.52 (s, 1H), 7.28 (d, J = 7.9 Hz, 2H), 6.82 (s, 2H), 5.24-5.05 (m, 1H), 5.00 (s, 1H), 4.00-3.67 (m, 10H), 3.58 (s, 3H), 3.32-3.27 (m, 2H), 3.02-2.78 (m, 1H), 2.67-2.54 (m, 2H), 2.14-1.97 (m, 1H), 1.40 (s, 3H), 1.33-1.20 (m, 2H), 0.96- 0.80 (m, 2H). D230 781.25 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.26 (d, J = 0.8 Hz, 1H), 7.65 (d, J = 9.3 Hz, 1H), 7.56 (s, 1H), 7.12 (d, J = 7.3 Hz, 2H), 6.88-6.79 (m, 3H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.49-4.34 (m, 4H), 4.01 (s, 3H), 3.96 (s, 6H), 3.93 (s, 2H), 3.51-3.47 (m, 4H), 3.41-3.34 (m, 4H), 3.09 (t, J = 7.6 Hz, 2H), 2.98-2.85 (m, 3H), 2.84-2.74 (m, 1H), 2.55-2.40 (m, 1H), 2.21-2.12 (m, 1H), 1.88 (d, J = 12.8 Hz, 2H), 1.70-1.66 (m, 3H), 1.42 (q, J = 10.8 Hz, 2H). D231 781.30 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.18 (s, 1H), 7.72 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.6, 2.3 Hz, 1H), 7.19 (s, 1H), 6.84 (s, 2H), 6.78 (s, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.43-4.14 (m, 2H), 3.95 (s, 3H), 3.87 (s, 6H), 3.77 (d, J = 12.0

Hz, 2H), 3.17-3.00 (m, 8H), 2.98-2.85 (m, 2H), 2.80-2.69 (m, 2H), 2.65-2.52 (m, 3H), 2.43-2.28 (m, 2H), 1.99 (d, J = 10.8 Hz, 1H), 1.78 (d, J = 12.5 Hz, 2H), 1.61-1.45 (m, 3H), 1.35-1.27 (m, 2H). D232 865.45 .sup.1H NMR (400 MHz, DMSO-d6 with a drop of D2O) δ 8.91 (s, 1H), 7.63-7.49 (m, 2H), 6.77 (d, J = 2.2 Hz, 2H), 6.62-6.53 (m, 2H), 6.21 (d, J = 6.8 Hz, 1H), 4.92 (dd, J = 13.2, 5.2 Hz, 1H), 4.38-4.22 (m, 2H), 3.99 (t, J = 7.5 Hz, 6H), 3.86-3.75 (m, 8H), 3.53-3.36 (m, 6H), 3.20-2.74 (m, 5H), 2.87-2.70 (m, 3H), 2.71-2.57 (m, 2H), 2.34 (t, 3H), 2.24 (s, 2H), 2.01 (s, 2H), 1.91-1.70 (m, 3H), 1.43 (d, J = 12.9 Hz, 2H). D233 720.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.29 (s, 1H), 8.14 (s, 1H, FA), 7.80 (s, 1H), 7.44 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 6.75 (s, 2H), 6.69 (d, J = 8.1 Hz, 2H), 5.09 (dd, J = 13.2, 5.2 Hz, 1H), 4.41-4.06 (m, 2H), 3.84 (s, 6H), 3.59 (s, 6H), 2.95-2.84 (m, 1H), 2.64-2.61 (m, 2H), 2.42-2.34 (m, 4H), 2.05-1.92 (m, 2H), 1.76 (s, 4H), 1.01 (s, 4H). D234 710.35 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.26 (s, 1H), 7.58 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 4.7 Hz, 3H), 6.85-6.79 (m, 2H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.49-4.32 (m, 4H), 4.00 (d, J = 7.0 Hz, 9H), 3.87 (s, 2H), 3.74 (s, 2H), 3.64-3.52 (m, 2H), 3.29-3.19 (m, 2H), 3.01-2.86 (m, 1H), 2.85-2.74 (m, 1H), 2.60-2.41 (m, 1H), 2.36-2.25 (m, 2H), 2.24-2.04 (m, 3H). D235 666.30 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 8.56 (d, 1H, FA), 7.79 (d, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.54 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 6.94-6.78 (m, 3H), 5.17 (dd, J = 13.3, 5.1 Hz, 1H), 4.51 (d, J = 5.0 Hz, 2H), 4.37-4.24 (m, 2H), 4.01 (s, 3H), 3.97 (s, 6H), 3.65 (s, 3H), 3.57 (d, J = 12.0 Hz, 2H), 3.16-2.97 (m, 3H), 2.97- 2.86 (m, 1H), 2.86-2.75 (m, 1H), 2.51 (qd, J = 13.1, 4.7 Hz, 1H), 2.27-2.15 (m, 1H), 2.15-2.03 (m, 4H). D236 853.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.04 (s, 1H), 8.24 (s, 0.3H, FA), 7.60 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.78 (s, 2H), 6.72-6.64 (m, 2H), 6.49 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.31 (d, J = 16.5 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.82 (s, 6H), 3.66 (s, 2H), 3.58 (s, 4H), 3.48 (s, 3H), 3.07 (s, 6H), 2.99-2.82 (m, 3H), 2.64-2.54 (m, 2H), 2.47-2.35 (m, 4H), 2.29-2.13 (m, 4H), 2.02-1.84 (m, 3H), 1.79-1.67 (m, 4H), 1.36-1.23 (m, 1H). D237 802.30 .sup.1H NMR (300 MHz, MeOD) δ 9.41 (d, J = 0.8 Hz, 1H), 7.74 (s, 1H), 7.62-7.50 (m, 2H), 7.44-7.34 (m, 2H), 6.92 (d, J = 3.9 Hz, 2H), 5.16 (dd, J = 13.3, 5.1 Hz, 1H), 4.58-4.36 (m, 4H), 4.08-3.97 (m, 6H), 3.95-3.85 (m, 1H), 3.77-3.54 (m, 7H), 3.45-3.35 (m, 3H), 3.32-3.25 (m, 2H), 3.24-3.09 (m, 3H), 3.02-2.69 (m, 2H), 2.61- 2.40 (m, 1H), 2.24-2.17 (m, 1H), 2.12-1.89 (m, 3H), 1.85-1.79 (m, 2H), 1.71-1.58 (m, 2H), 1.47 (s, 3H), 1.38-1.26 (m, 3H), 0.98- 0.88 (m, 2H). D238 802.25 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.41 (d, J = 0.8 Hz, 1H), 7.80- 7.68 (m, 2H), 7.64-7.56 (m, 1H), 7.24-7.15 (m, 2H), 6.93 (d, J = 4.2 Hz, 2H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.55-4.36 (m, 4H), 4.30-4.02 (m, 1H), 4.00 (d, J = 4.3 Hz, 6H), 3.82 (s, 4H), 3.70- 3.64 (m, 3H), 3.47-3.35 (m, 2H), 3.30-3.20 (m, 3H), 3.18-3.07 (m, 3H), 3.02-2.78 (m, 2H), 2.57-2.39 (m, 1H), 2.27-2.11 (m, 1H), 2.10-1.90 (m, 3H), 1.82 (s, 3H), 1.68-1.52 (m, 2H), 1.48 (s, 3H), 1.38-1.25 (m, 2H), 1.00-0.90 (m, 2H). D239 657.35 .sup.1H NMR (300 MHz, Methanol-d4) δ 7.70 (s, 1H), 6.04 (d, J = 9.4 Hz, 2H), 5.76-5.64 (m, 2H), 5.31 (s, 2H), 5.25 (s, 1H), 3.75-3.57 (m, 2H), 3.25-3.19 (m, 2H), 3.15-3.05 (m, 2H), 3.00-2.89 (m, 2H), 2.89-2.75 (m, 2H), 2.50-2.34 (m, 9H), 1.45-1.20 (m, 2H), 1.08- 0.89 (m, 1H), 0.73-0.59 (m, 1H). D240 794.50 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.04 (s, 1H), 8.29 (s, 1H, FA), 7.58 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.28-7.21 (m, 1H), 7.17-7.11 (m, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.36-4.16 (m, 2H), 3.80 (s, 6H), 3.78-3.69 (m, 3H), 3.56-3.49 (m, 3H), 3.07 (s, 6H), 2.96-2.86 (m, 1H), 2.74- 2.69 (m, 1H), 2.66-2.54 (m, 3H), 2.47-2.34 (m, 5H), 2.32-2.23 (m, 3H), 2.02-1.95 (m, 1H), 1.78-1.70 (m, 2H), 1.48-1.33 (m, 3H), 1.31-1.21 (m, 2H). D241 879.50 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.10 (s, 1H), 8.15 (s, 1H, FA), 7.69 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 6.81 (s, 2H), 6.69 (d, J = 7.3 Hz, 2H), 6.48 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.49 (t, J = 12.3 Hz, 4H), 4.32 (d, J = 16.7 Hz, 1H), 4.18 (d, J = 16.6 Hz, 1H), 3.86 (s, 9H), 3.60 (s, 4H), 3.52 (s, 4H), 3.11-3.05 (m, 4H), 2.95-2.84 (m, 2H), 2.65-2.56 (m, 2H), 2.47-2.34 (m, 2H), 2.03-1.93 (m, 1H), 1.83-1.77 (m, 4H), 1.72 (d, J = 12.0 Hz, 2H), 1.48-1.20 (m, 6H). D242 657.30 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 10.29 (s, 1H, TFA), 9.17 (s, 1H), 7.77-7.66 (m, 2H), 7.24-6.99 (m, 2H), 6.80 (d, J = 30.9 Hz, 3H), 5.33-5.02 (m, 2H), 4.81-4.55 (m, 2H), 4.55-4.13 (m, 6H), 4.00-3.82 (m, 9H), 3.02-2.85 (m, 1H), 2.63 (s, 1H), 2.44- 2.31 (m, 1H), 2.08-1.93 (m, 1H). D243 897.60 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.38 (s, 1H), 8.57 (s, FA, 1H), 7.66 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 0.9 Hz, 1H), 7.23- 7.12 (m, 2H), 6.83 (s, 2H), 5.17 (dd, 1H), 4.83-4.76 (m, 1H), 4.67-4.60 (m, 1H), 4.50-4.36 (m, 2H), 4.23-4.07 (m, 2H), 3.95 (s, 6H), 3.68 (s, 3H), 3.07-2.75 (m, 7H), 2.66-2.40 (m, 6H), 2.29- 2.12 (m, 3H), 2.03-1.83 (m, 4H), 1.77-1.49 (m, 6H), 1.14- 1.03 (m, 4H).

D244 803.95 .sup.1H NMR (300 MHz, Methanol-d4) δ 8.99 (d, J = 0.7 Hz, 1H), 7.62- 7.46 (m, 4H), 6.87 (s, 2H), 6.37 (s, 1H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.57-4.39 (m, 4H), 4.21 (t, J = 7.6 Hz, 4H), 3.97 (s, 6H), 3.79 (d, J = 12.3 Hz, 2H), 3.60 (s, 3H), 3.55-3.49 (m, 4H), 3.42-3.36 (m, 4H), 3.14-3.00 (m, 4H), 2.96-2.75 (m, 1H), 2.60-2.46 (m, 3H), 2.24-2.14 (m, 1H), 2.04-1.93 (m, 2H), 1.76-1.70 (m, 3H), 1.61-1.51 (m, 2H). D245 804.10 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.10 (d, J = 0.7 Hz, 1H), 8.52 (s, 1H, FA), 7.67-7.58 (m, 1H), 7.45 (s, 1H), 7.08 (d, J = 8.2 Hz, 2H), 6.82 (s, 2H), 6.22 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.49- 4.31 (m, 2H), 4.14-4.03 (m, 6H), 4.01-3.85 (m, 8H), 3.59 (s, 3H), 3.07 (s, 4H), 2.95-2.61 (m, 9H), 2.53-2.37 (m, 3H), 2.15 (dd, J = 12.7, 4.9 Hz, 1H), 1.85 (d, J = 12.6 Hz, 2H), 1.61-1.55 (m, 3H), 1.37 (q, J = 12.5, 11.5 Hz, 2H). D246 942.50 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.20 (s, 1H), 8.55 (s, FA, 1H), 7.48 (t, J = 4.1 Hz, 2H), 7.20 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 6.87 (s, 2H), 6.64 (s, 1H), 5.16 (dd, J = 13.4, 5.1 Hz, 1H), 4.83- 4.72 (m, 1H), 4.51-4.32 (m, 4H), 3.97 (s, 6H), 3.78 (t, J = 4.9 Hz, 4H), 3.68-3.49 (m, 9H), 3.21-3.04 (m, 2H), 3.02-2.75 (m, 5H), 2.72-2.42 (m, 5H), 2.42-2.26 (m, 1H), 2.24-2.00 (m, 3H), 1.97- 1.86 (m, 2H), 1.81-1.45 (m, 6H). D247 667.35 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.39 (s, 1H), 7.72 (s, 1H), 7.63- 7.57 (m, 1H), 7.38 (d, J = 4.4 Hz, 1H), 7.32-7.19 (m, 2H), 6.89 (s, 2H), 5.17 (dd, J = 13.4, 5.2 Hz, 2H), 4.83-4.74 (m, 1H), 4.67 (d, J = 15.1 Hz, 2H), 4.51-4.30 (m, 4H), 3.98 (d, J = 16.9 Hz, 6H), 3.79- 3.54 (m, 1H), 3.01-2.77 (m, 2H), 2.60-2.45 (m, 1H), 2.25-2.13 (m, 2H), 1.11 (d, J = 8.9 Hz, 4H). D248 839.40 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.19 (d, J = 0.8 Hz, 1H), 8.54 (s, 1H, FA), 7.67-7.58 (m, 1H), 7.52 (s, 1H), 7.11-7.04 (m, 2H), 6.81 (s, 2H), 6.43 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.50-4.31 (m, 6H), 4.05 (s, 2H), 3.95 (s, 1H), 3.92 (s, 7H), 3.62 (s, 3H), 3.13- 2.99 (m, 4H), 2.95-2.73 (m, 8H), 2.68 (s, 2H), 2.56-2.37 (m, 1H), 2.25-2.08 (m, 1H), 1.85 (d, J = 12.7 Hz, 2H), 1.61-1.55 (m, 3H), 1.45-1.28 (m, 2H). D249 658.81 D250 632.41 D251 686.53 D252 686.46 D253 646.48 D254 698.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.25 (s, 1H), 8.55 (s, 1H, FA), 7.58 (s, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 7.37 (s, 1H), 6.88 (s, 2H), 6.83 (s, 1H), 5.16 (dd, J = 13.4, 5.1 Hz, 1H), 4.60 (d, J = 13.5 Hz, 1H), 4.52-4.37 (m, 3H), 4.00 (d, J = 7.0 Hz, 9H), 3.89- 3.85 (m, 2H), 3.64-3.59 (m, 2H), 3.48-3.33 (m, 2H), 2.95-2.86 (m, 1H), 2.81 (d, J = 17.2 Hz, 1H), 2.59-2.44 (m, 1H), 2.23-2.16 (m, 1H), 1.62 (d, J = 6.4 Hz, 6H). D255 708.45 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.16 (s, 1H), 8.56 (s, 1H, FA), 7.51 (d, J = 9.0 Hz, 1H), 7.44 (s, 1H), 7.35 (d, J = 7.1 Hz, 2H), 6.88 (s, 2H), 6.52 (s, 1H), 5.16 (dd, J = 13.2, 5.1 Hz, 1H), 4.64 (s, 2H), 4.52-4.35 (m, 2H), 4.25 (br s, 2H), 3.97 (s, 6H), 3.68-3.54 (m, 4H), 3.45-3.37 (m, 2H), 3.14 (s, 7H), 3.03-2.73 (m, 2H), 2.59- 2.43 (m, 1H), 2.27-2.14 (m, 1H), 1.63 (s, 6H). D256 692.20 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.09 (d, J = 3.5 Hz, 1H), 8.56 (s, 1H), 7.67-7.37 (m, 2H), 7.21 (dd, J = 8.4, 2.3 Hz, 1H), 7.11 (s, 1H), 6.85 (s, 2H), 6.18 (s, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.55-4.26 (m, 7H), 4.15-4.00 (m, 6H), 3.94 (s, 6H), 3.58 (d, J = 1.3 Hz, 3H), 2.96 (s, 3H), 2.95-2.87 (m, 1H), 2.85-2.73 (m, 1H), 2.55-2.29 (m, 3H), 2.25-2.12 (m, 1H). D257 637.15 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.14 (d, J = 0.7 Hz, 1H), 7.46- 7.36 (m, 2H), 6.94 (d, J = 2.1 Hz, 1H), 6.86 (dd, J = 8.2, 2.2 Hz, 1H), 6.73 (s, 2H), 6.52 (d, J = 0.8 Hz, 1H), 5.15 (dd, J = 13.2, 5.2 Hz, 1H), 4.55-4.33 (m, 5H), 4.14-4.00 (m, 2H), 3.80 (s, 6H), 3.58 (s, 3H), 3.12 (s, 6H), 2.98-2.86 (m, 1H), 2.85-2.76 (m, 1H), 2.57- 2.44 (m, 1H), 2.24-2.13 (m, 1H). D258 818.42 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.15 (s, 1H), 8.21 (s, 1H, FA salt), 7.72 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.5, 2.4 Hz, 1H), 7.15 (d, J = 2.3 Hz, 1H), 6.76 (s, 1H), 6.70 (s, 2H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.33-4.20 (m, 2H), 3.94 (s, 3H), 3.79 (s, 6H), 3.75 (d, J = 12.1 Hz, 3H), 3.53 (s, 4H), 2.98-2.85 (m, 1H), 2.75-2.65 (m, 2H), 2.64-2.55 (m, 1H), 2.48-2.43 (m, 3H), 2.43-2.30 (m, 8H), 2.04-1.95 (m, 1H), 1.82-1.74 (m, 6H), 1.52- 1.40 (m, 3H), 1.35-1.22 (m, 2H). D259 815.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 9.01 (s, 1H), 8.26 (s, 1H, FA), 7.58 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 6.77 (s, 2H), 6.72-6.65 (m, 2H), 6.17 (s, 1H), 5.12 (dd, J = 13.4, 5.1 Hz, 1H), 4.35-4.13 (m, 2H), 4.04-3.94 (m, 6H), 3.84 (s, 6H), 3.78-3.69 (m, 2H), 3.57 (s, 4H), 3.48 (s, 3H), 3.41-3.34 (m, 2H), 2.99 (s, 3H), 2.97-2.90 (m, 1H), 2.80-2.65 (m, 2H), 2.51-2.45 (m, 2H), 2.42-2.23 (m, 7H), 2.04- 1.94 (m, 1H), 1.76-1.69 (m, 4H). D260 695.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.26 (s, 1H), 8.56 (s, 0.49H, FA), 7.57 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 5.9 Hz, 3H), 5.16 (dd, J = 13.4, 5.2 Hz, 1H), 4.46-4.39 (m, 2H), 4.28-4.11 (m, 2H), 4.01 (s, 3H), 3.96 (s, 6H), 3.65 (s, 4H), 3.42-3.36 (m, 2H), 3.30-3.18 (m, 3H), 2.95-2.89 (m, 1H), 2.83-2.77 (m, 1H), 2.54-2.47 (m, 1H), 2.22-2.16 (m, 1H), 1.62 (s, 6H). D261 879.35 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.20 (d, J = 0.7 Hz, 1H), 7.53 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.85 (s, 3H), 6.78

(dd, J = 8.2, 2.3 Hz, 1H), 6.43 (s, 1H), 5.15 (dd, J = 13.4, 5.1 Hz, 1H), 4.53-4.28 (m, 6H), 4.26 (s, 2H), 3.96 (s, 7H), 3.67 (s, 4H), 3.62 (s, 3H), 3.43 (s, 2H), 3.16 (s, 3H), 2.95 (d, J = 12.0 Hz, 3H), 2.48 (s, 5H), 2.30 (d, J = 6.8 Hz, 2H), 2.17 (dd, J = 8.3, 3.6 Hz, 1H), 2.00 (d, J = 14.1 Hz, 2H), 1.90 (s, 5H), 1.49 (s, 2H). D262 634.30 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.02 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.36 (s, 1H), 7.34-7.25 (m, 3H), 7.21 (d, J = 2.4 Hz, 1H), 7.00-6.92 (m, 2H), 6.39 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.40-4.15 (m, 2H), 4.03-3.81 (m, 3H), 3.46 (s, 3H), 3.06 (s, 6H), 2.99-2.85 (m, 3H), 2.78 (s, 3H), 2.70-2.58 (m, 1H), 2.44-2.32 (m, 1H), 2.05-1.95 (m, 1H), 1.97-1.80 (m, 2H), 1.75 (d, J = 12.0 Hz, 2H). D263 672.35 .sup.1H NMR (400 MHz, DMSO-d6 with a drop of D2O) δ 9.28 (s, 1H), 8.22 (s, 1H, FA), 7.78 (s, 1H), 7.69-7.59 (m, 3H), 7.40 (s, 1H), 6.74 (s, 2H), 5.11 (dd, J = 13.3, 5.0 Hz, 1H), 4.51-4.32 (m, 2H), 3.83 (s, 6H), 3.63 (s, 2H), 3.56 (s, 6H), 3.20 (t, J = 6.5 Hz, 2H), 2.97- 2.85 (m, 1H), 2.64-2.57 (m, 1H), 2.46-2.37 (m, 1H), 2.28- 2.19 (m, 1H), 2.06-1.97 (m, 1H), 0.98 (t, J = 6.1 Hz, 4H). D264 730.45 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.03 (s, 1H), 8.70 (s, 1H, TFA salt), 7.59 (s, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.08 (s, 2H), 6.75-6.67 (m, 2H), 6.17 (s, 1H), 5.08 (dd, J = 13.2, 5.0 Hz, 1H), 4.34 (s, 2H), 4.31 (s, 1H), 4.20 (d, J = 16.7 Hz, 1H), 4.01 (t, J = 7.4 Hz, 4H), 3.93 (s, 3H), 3.79 (s, 2H), 3.65 (s, 2H), 3.50 (s, 3H), 3.45- 3.34 (m, 2H), 3.33-3.15 (m, 2H), 2.88-2.75 (m, 3H), 2.66-2.54 (m, 1H), 2.44-2.30 (m, 3H), 2.20-2.09 (m, 2H), 2.08-1.94 (m, 3H), 1.22 (t, J = 7.4 Hz, 3H). D265 665.30 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.04 (s, 1H), 7.57 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.36-7.29 (m, 1H), 7.20 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.55-6.49 (m, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.39-4.19 (m, 2H), 3.89-3.83 (m, 2H), 3.81 (s, 6H), 3.48 (s, 3H), 3.45-3.37 (m, 2H), 3.08 (s, 6H), 2.99-2.86 (m, 1H), 2.82-2.70 (m, 2H), 2.65-2.56 (m, 1H), 2.47-2.35 (m, 2H), 2.06- 1.96 (m, 1H), 1.61-1.53 (m, 2H). D266 707.20 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.48 (s, 1H), 8.55 (s, 1H, FA), 7.85-7.69 (m, 2H), 7.34 (d, J = 8.6 Hz, 1H), 7.08-6.93 (m, 2H), 6.86 (s, 2H), 5.24-5.06 (m, 1H), 4.82 (s, 2H), 4.63 (d, J = 8.0 Hz, 2H), 4.46-4.26 (m, 2H), 3.92-3.83 (m, 6H), 3.76-3.69 (m, 4H), 3.65 (d, J = 20.3 Hz, 3H), 3.56-3.46 (m, 2H), 3.29-3.17 (m, 2H), 2.97-2.73 (m, 2H), 2.60-2.41 (m, 1H), 2.39-2.12 (m, 3H), 2.03- 1.85 (m, 2H). D267 675.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.13 (d, J = 0.7 Hz, 1H), 8.52 (0.3H, FA), 7.77 (d, J = 1.3 Hz, 1H), 7.65 (dd, J = 7.9, 1.5 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 6.89 (s, 2H), 6.44 (s, 1H), 5.22-5.11 (m, 1H), 4.48 (d, J = 3.2 Hz, 2H), 4.22 (s, 2H), 4.16- 1.09 (m, 2H), 3.96 (s, 6H), 3.87 (s, 2H), 3.73-3.63 (ms, 1H), 3.60 (s, 3H), 3.08 (s, 6H), 3.01-2.88 (m, 1H), 2.86-2.77 (m, 1H), 2.58- 2.44 (m, 1H), 2.28-2.19 (m, 1H). D268 694.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.15 (d, J = 0.8 Hz, 1H), 8.48 (s, 0.2H, FA), 7.73 (d, J = 8.5 Hz, 1H), 7.42 (s, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.06 (dd, J = 8.5, 2.4 Hz, 1H), 6.90-6.83 (m, 2H), 6.48 (s, 1H), 5.10 (dd, J = 12.5, 5.4 Hz, 1H), 4.38-4.17 (m, 4H), 4.08- 3.77 (m, 8H), 3.67-3.54 (m, 3H), 3.22-2.96 (m, 9H), 2.95-2.67 (m, 4H), 2.16-2.07 (m, 1H). D269 700.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.01 (s, 1H), 9.28 (s, 1H), 7.80 (s, 1H), 7.71-7.53 (m, 3H), 7.42 (s, 1H), 6.78 (s, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.54-4.27 (m, 2H), 3.86 (s, 6H), 3.79-3.67 (m, 2H), 3.56 (s, 3H), 3.02-2.82 (m, 3H), 2.81-2.66 (m, 1H), 2.66- 2.53 (m, 1H), 2.47-2.16 (m, 4H), 2.08-1.83 (m, 3H), 1.80- 1.57 (m, 2H), 1.09-0.89 (m, 4H). D270 615.25 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.05 (d, J = 1.4 Hz, 2H), 7.57 (d, J = 1.4 Hz, 1H), 7.47 (d, J = 1.0 Hz, 1H), 7.41 (d, J = 0.9 Hz, 1H), 6.92 (s, 2H), 6.68 (d, J = 2.3 Hz, 1H), 5.22 (dd, J = 12.0, 5.1 Hz, 1H), 4.50 (s, 2H), 3.99 (s, 6H), 3.69-3.50 (m, 7H), 3.50-3.38 (m, 2H), 3.20 (s, 6H), 3.13-2.99 (m, 2H), 2.90-2.79 (m, 2H), 2.73- 2.55 (m, 1H), 2.42-2.29 (m, 1H). D271 672.35 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.35 (s, 1H), 8.53 (s, 1H, FA), 7.76 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 2.0 Hz, 2H), 7.60-7.53 (m, 1H), 7.33 (d, J = 0.9 Hz, 1H), 6.81 (s, 2H), 5.19-5.10 (m, 1H), 4.53- 4.38 (m, 2H), 4.20 (s, 2H), 4.10 (t, J = 8.4 Hz, 2H), 3.93 (s, 6H), 3.89-3.81 (m, 2H), 3.77-3.67 (m, 1H), 3.64 (s, 3H), 2.98-2.84 (m, 1H), 2.84-2.73 (m, 1H), 2.55-2.40 (m, 1H), 2.22-2.13 (m, 1H), 2.13-2.03 (m, 1H), (d, J = 6.5 Hz, 4H). D272 714.30 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.15 (s, 1H), 9.28 (s, 1H), 7.94-7.78 (m, 4H), 7.41 (s, 1H), 6.81 (s, 2H), 5.16 (dd, J = 12.8, 5.4 Hz, 1H), 3.87 (s, 8H), 3.57 (s, 4H), 3.02 (s, 2H), 2.96-2.78 (m, 3H), 2.67-2.55 (m, 2H), 2.21 (dd, J = 9.0, 4.1 Hz, 1H), 2.11-1.95 (m, 3H), 1.79 (s, 2H), 1.05-0.94 (m, 4H). D273 717.20 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.10 (dd, J = 9.6, 0.7 Hz, 1H), 7.93-7.80 (m, 3H), 7.49 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 7.2 Hz, 2H), 6.57 (s, 1H), 5.14 (ddd, J = 17.9, 12.7, 5.5 Hz, 1H), 4.52 (s, 1H), 4.44 (s, 1H), 4.00 (d, J = 2.0 Hz, 6H), 3.60 (d, J = 2.2 Hz, 5H), 3.51-3.40 (m, 1H), 3.31-3.18 (m, 2H), 3.16 (s, 3H), 3.07 (s, 3H), 2.93-2.63 (m, 3H), 2.37 (d, J = 13.9 Hz, 1H), 2.25-1.93 (m, 4H). D274 582.30 .sup.1H NMR (400 MHz, DMSO-d6) δ 11.01 (s, 1H), 9.05 (s,

1H), 7.68- 7.57 (m, 3H), 7.57-7.50 (m, 1H), 6.89 (s, 2H), 6.59 (s, 1H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.51 (d, J = 17.2 Hz, 1H), 4.36 (d, J = 17.2 Hz, 1H), 3.74 (s, 6H), 3.50 (s, 3H), 3.10 (s, 6H), 3.01-2.87 (m, 1H), 2.67-2.58 (m, 1H), 2.48-2.37 (m, 1H), 2.10-2.00 (m, 1H). D275 686.20 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.16 (s, 1H), 10.15 (d, 1H, TFA), 9.29 (d, J = 4.1 Hz, 1H), 7.96 (d, J = 7.3 Hz, 3H), 7.81 (s, 1H), 7.38 (d, J = 11.7 Hz, 1H), 6.88 (d, J = 3.5 Hz, 2H), 5.17 (dd, J = 12.8, 5.3 Hz, 1H), 4.48 (s, 4H), 4.22 (d, J = 41.8 Hz, 2H), 3.92 (s, 6H), 3.57 (d, J = 1.9 Hz, 3H), 2.88 (d, J = 11.7 Hz, 1H), 2.71-2.54 (m, 2H), 2.32-2.02 (m, 3H), 0.99 (d, J = 8.2 Hz, 4H). D276 711.20 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.03 (s, 1H), 7.59 (s, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.22 (dd, J = 8.5, 2.4 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.09 (dd, J = 13.3, 5.1 Hz, 1H), 4.37-4.15 (m, 2H), 3.91 (d, J = 12.1 Hz, 1H), 3.83 (s, 6H), 3.53 (d, J = 12.9 Hz, 1H), 3.15 (d, J = 10.9 Hz, 2H), 3.07 (s, 6H), 3.04-2.98 (m, 2H), 2.96-2.84 (m, 3H), 2.69-2.54 (m, 1H), 2.45- 2.30 (m, 1H), 2.04-1.92 (m, 1H), 1.22 (d, J = 6.1 Hz, 6H). D277 625.20 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.93 (s, 1H), 9.03 (s, 1H), 7.58 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.1 Hz, 2H), 6.79 (s, 2H), 6.45 (s, 1H), 5.03 (dd, J = 13.3, 5.2 Hz, 1H), 4.58 (s, 2H), 4.35- 4.15 (m, 2H), 3.85 (s, 6H), 3.46 (s, 3H), 3.06 (s, 6H), 2.98 (s, 3H), 2.92-2.80 (m, 1H), 2.66-2.55 (m, 1H), 2.41-2.32 (m, 1H), 2.02- 1.90(m, 1H). D278 756.35 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.10 (s, 1H), 7.69 (s, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.31-7.18 (m, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.75 (s, 2H), 6.49 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.49 (t, J = 12.3 Hz, 4H), 4.41-4.12 (m, 2H), 3.83 (s, 6H), 3.58 (s, 2H), 3.51 (s, 3H), 3.02 (d, J = 23.7 Hz, 5H), 2.63 (s, 3H), 2.46-2.24 (m, 1H), 2.10-1.91 (m, 1H), 1.25 (s, 6H). D279 694.40 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.99 (s, 1H), 8.13 (s, 0.2H, FA), 7.45-7.38 (m, 2H), 7.28 (dd, J = 8.6, 2.5 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 6.83 (s, 1H), 6.72 (s, 1H), 5.97 (s, 1H), 5.20-5.03 (m, 1H), 4.41-4.15 (m, 2H), 3.85 (d, J = 11.8 Hz, 2H), 3.76 (s, 3H), 3.66 (s, 3H), 3.51 (s, 1H), 3.44 (s, 3H), 3.01 (s, 6H), 5.23-4.94 (m, 1H), 2.82-2.68 (m, 5H), 2.65-2.55 (m, 1H), 2.45- 2.30 (m, 1H), 7.31-7.25 (m, 1H), 1.81 (s, 4H). D280 679.30 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.02 (s, 1H), 7.58 (s, 1H), 7.55-7.51 (m, 1H), 7.47 (s, 2H), 6.76 (s, 2H), 6.51 (s, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.39 (d, J = 17.1 Hz, 1H), 4.26 (d, J = 17.1 Hz, 1H), 3.83 (s, 6H), 3.70 (d, J = 11.9 Hz, 2H), 3.48 (s, 3H), 3.08 (s, 6H), 3.03-2.83 (m, 3H), 2.65-2.56 (m, 3H), 2.47-2.32 (m, 1H), 2.06-1.94 (m, 1H), 1.82 (s, 1H), 1.72 (d, J = 12.8 Hz, 2H), 1.54-1.47 (m, 2H). D281 695.50 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.27 (s, 1H), 7.59 (s, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 9.7 Hz, 2H), 6.89 (s, 2H), 6.83 (s, 1H), 5.17 (dd, J = 13.3, 5.2 Hz, 1H), 4.63 (d, J = 20.8 Hz, 1H), 4.57- 4.38 (m, 3H), 4.01 (d, J = 5.1 Hz, 10H), 3.96-3.85 (m, 3H), 3.65 (s, 3H), 3.60-3.44 (m, 1H), 2.99-2.87 (m, 1H), 2.86-2.75 (m, 1H), 2.59-2.45 (m, 1H), 2.25-2.13 (m, 1H), 1.74-1.51 (m, 7H). D282 628.40 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.90 (s, 1H), 9.16 (s, 1H), 8.14 (0.4 H, FA), 7.74 (s, 1H), 7.08 (t, J = 8.4 Hz, 1H), 6.79-6.72 (m, 3H), 6.56-6.49 (m, 2H), 6.46-6.40 (m, 1H), 5.18 (dd, J = 10.5, 5.2 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 6H), 3.64 (s, 2H), 3.54 (s, 3H), 3.15-3.04 (m, 4H), 2.75-2.55 (m, 6H), 2.24-2.02 (m, 2H). D283 845.3 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.04 (s, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.24-7.13 (m, 2H), 6.81 (s, 2H), 5.18 (d, J = 5.1 Hz, 1H), 4.67 (s, 2H), 4.44 (d, J = 5.3 Hz, 4H), 3.95 (s, 6H), 3.68 (s, 5H), 3.58 (s, 4H), 3.43 (s, 1H), 3.22 (m, J = 12.3 Hz, 2H), 3.10 (d, J = 6.6 Hz, 3H), 3.03 (s, 1H), 2.98-2.85 (m, 2H), 2.83 (s, 1H), 2.52 (m, J = 12.9, 4.9 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 1H), 2.10 (d, J = 14.3 Hz, 8H), 1.74 (t, J = 12.9 Hz, 2H). D284 843.4 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.22 (d, J = 9.0 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.28-7.07 (m, 3H), 6.84-6.67 (m, 3H), 6.11 (d, J = 7.6 Hz, 1H), 5.15 (dd, J = 13.2, 5.2 Hz, 1H), 4.85-4.77 (m, 1H), 4.55-4.34 (m, 4H), 3.92 (s, 6H), 3.70 (t, J = 7.3 Hz, 4H), 3.61- 3.48 (m, 5H), 3.22-3.04 (m, 2H), 2.97-2.44 (m, 11H), 2.27-1.75 (m, 12H), 1.74-1.42 (m, 2H). D285 788.6 .sup.1H NMR (400 MHz, MeOD) δ 8.85-8.50 (m, FA, 1H), 8.31 (d, J = 9.0 Hz, 1H), 7.37 (dd, J = 18.8, 8.6 Hz, 2H), 7.18 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.77 (dd, J = 8.2, 2.2 Hz, 1H), 6.75 (s, 2H), 6.32 (d, J = 7.7 Hz, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.52 (s, 2H), 4.45-4.33 (m, 2H), 4.31-4.22 (m, 2H), 4.06-3.95 (m, 2H), 3.93 (s, 6H), 3.68 (s, 4H), 3.58 (s, 3H), 3.22-3.13 (m, 1H), 2.99-2.85 (m, 1H), 2.85-2.72 (m, 3H), 2.70 (s, 6H), 2.60-2.43 (m, 5H), 2.23-2.11 (m, 1H), 1.96-1.88 (m, 4H). D286 845.4 .sup.1H NMR (300 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.35 (s, 1H), 9.14 (s, 1H), 8.11 (s, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.20-7.11 (m, 4H), 5.13-5.07 (m, 1H), 4.90-4.85 (m, 1H), 4.38 (d, J = 17.0 Hz, 1H), 4.34-4.07 (m, 7H), 3.91 (s, 6H), 3.54 (s, 3H), 3.19 (s, 2H), 2.97- 2.76 (m, 7H), 2.60 (d, J = 15.7 Hz, 2H), 2.40-2.27 (m, 5H), 2.02- 1.83 (m, 11H), 1.50 (q, J = 12.2 Hz, 2H). D287 806 .sup.1H NMR (300 MHz, DMSO-d6) δ

11.00 (s, 1H), 8.01 (dd, J = 9.5, 2.8 Hz, 1H), 7.74 (m, J = 9.1, 5.3 Hz, 1H), 7.68-7.57 (m, 2H), 7.50 (d, J = 8.3 Hz, 1H), 7.20-7.02 (m, 2H), 6.82 (s, 2H), 5.11 (m, J = 13.2, 5.1 Hz, 1H), 4.93-4.75 (m, 1H), 4.35 (m, 1H), 4.26 (m, 1H), 4.10 (m, 1H), 3.87 (s, 6H), 3.61 (s, 3H), 3.29 (s, 2H), 3.01-2.81 (m, 3H), 2.78-2.56 (m, 2H), 2.49-2.25 (m, 7H), 2.10-1.93 (m, 1H), 1.73 (m, J = 48.1 Hz, 10H), 1.43-1.22 (m, 3H). D288 666.25 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 8.56 (d, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.58 (s, 1H), 7.54 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 6.94-6.78 (m, 3H), 5.17 (dd, J = 13.3, 5.1 Hz, 1H), 4.51 (d, J = 5.0 Hz, 2H), 4.37-4.24 (m, 2H), 4.01 (s, 3H), 3.97 (s, 6H), 3.65 (s, 3H), 3.57 (d, J = 12.0 Hz, 2H), 3.16-2.97 (m, 3H), 2.97-2.86 (m, 1H), 2.86-2.75 (m, 1H), 2.51 (qd, J = 13.1, 4.7 Hz, 1H), 2.27- 2.15 (m, 1H), 2.15-2.03 (m, 4H). D289 804.45 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.17 (s, 1H), 7.73 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 5.4 Hz, 3H), 6.69 (d, J = 8.0 Hz, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.36-4.12 (m, 2H), 3.94 (s, 3H), 3.90 (s, 2H), 3.85 (s, 6H), 3.59 (s, 4H), 3.55 (s, 3H), 3.19-3.15 (m, 2H), 2.96-2.84 (m, 1H), 2.70-2.60 (m, 2H), 2.42- 2.33 (m, 2H), 2.37 (s, 4H), 2.17 (s, 2H), 1.99 (d, J = 12.8 Hz, 1H), 1.82-1.67 (m, 7H), 1.42-1.07 (m, 2H). D290 720.40 .sup.1H NMR (300 MHz, Methanol-d4) δ 9.10 (s, 1H), 8.51 (s, 0.2H, FA), 7.46 (d, J = 11.0 Hz, 2H), 7.31 (d, J = 9.3 Hz, 2H), 6.80 (s, 2H), 6.23 (s, 1H), 5.21-5.09 (m, 1H), 4.51-4.33 (m, 2H), 4.14-4.03 (m, 4H), 3.93 (s, 8H), 3.59 (s, 3H), 3.20-3.14 (m, 5H), 2.96-2.70 (m, 3H), 2.56-2.37 (m, 3H), 2.24-2.13 (m, 1H), 1.49 (s, 6H). D291 865.50 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.46 (d, J = 40.5 Hz, 1H, TFA), 9.11 (s, 1H), 7.69 (s, 1H), 7.45-7.38 (m, 1H), 6.90 (s, 2H), 6.74-6.67 (m, 2H), 6.49 (s, 1H), 5.08 (dd, J = 13.2, 5.1 Hz, 1H), 4.50 (t, J = 12.3 Hz, 4H), 4.33 (d, J = 16.6 Hz, 1H), 4.26-4.16 (m, 3H), 3.91 (s, 6H), 3.71 (dd, J = 30.9, 7.8 Hz, 4H), 3.53 (s, 3H), 3.47 (d, J = 12.9 Hz, 3H), 3.22 (s, 1H), 3.01 (s, 6H), 2.60 (d, J = 17.1 Hz, 1H), 2.39 (dd, J = 13.1, 4.5 Hz, 1H), 2.37-2.30 (m, 1H), 2.12 (d, J = 12.9 Hz, 3H), 1.97 (t, J = 16.1 Hz, 5H), 1.83 (s, 0H), 1.59-1.48 (m, 2H). D292 875.3 .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.41 (s, 1H), 8.18 (s, 2H, FA), 7.87 (s, 1H), 7.56 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 8.3, 2.4 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.77 (s, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.84 (t, J = 6.9 Hz, 1H), 4.42-4.19 (m, 2H), 3.83 (s, 7H), 3.67 (s, 2H), 3.60 (s, 3H), 3.51 (s, 3H), 3.11 (s, 3H), 2.97-2.88 (m, 3H), 2.60 (d, J = 17.2 Hz, 1H), 2.41-2.27 (m, 4H), 2.21 (d, J = 14.0 Hz, 3H), 2.10 (d, J = 7.0 Hz, 2H), 2.00 (d, J = 12.9 Hz, 1H), 1.78 (s, 2H), 1.60 (d, J = 27.7 Hz, 6H), 1.49 (s, 1H), 1.29 (s, 6H), 1.12 (t, J = 12.9 Hz, 2H). D293 681.40 .sup.1H NMR (300 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.16 (s, 1H), 7.74 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.32-7.21 (m, 1H), 7.16 (d, J = 2.3 Hz, 1H), 6.78 (s, 1H), 6.74 (s, 2H), 5.10 (dd, J = 13.2, 5.0 Hz, 1H), 4.40-4.13 (m, 2H), 4.09-3.98 (m, 1H), 3.94 (s, 3H), 3.83 (s, 6H), 3.64-3.46 (m, 5H), 3.00-2.68 (m, 4H), 2.67-2.53 (m, 3H), 2.46-2.25 (m, 2H), 2.07-1.90 (m, 1H), 1.30 (d, J = 5.0 Hz, 3H). D294 677.45 .sup.1H NMR (400 MHz, Methanol-d4) δ 8.91 (s, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.85 (dd, J = 8.3, 2.3 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.54 (s, 1H), 6.75 (s, 2H), 6.43 (s, 1H), 5.18 (dd, J = 13.3, 5.1 Hz, 1H), 4.63- 4.47 (m, 2H), 4.24 (t, J = 7.6 Hz, 4H), 3.89 (s, 6H), 3.87-3.73 (m, 3H), 3.63 (t, J = 12.1 Hz, 2H), 3.57 (s, 3H), 2.99-2.74 (m, 4H), 2.60-2.44 (m, 3H), 2.21 (ddd, J = 9.7, 5.3, 2.7 Hz, 1H), 1.86 (d, J = 13.8 Hz, 2H). D295 652.40 .sup.1H NMR (400 MHz, Methanol-d4) δ 9.23 (s, 1H), 8.09 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 8.3, 2.3 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.51 (s, 1H), 6.80 (s, 1H), 6.74 (s, 2H), 5.19 (dd, J = 13.3, 5.1 Hz, 1H), 4.67- 4.49 (m, 2H), 3.99 (s, 3H), 3.90 (s, 6H), 3.88-3.76 (m, 5H), 3.62 (s, 3H), 3.03-2.86 (m, 3H), 2.80 (ddd, J = 17.5, 4.8, 2.4 Hz, 1H), 2.53 (qd, J = 13.2, 4.7 Hz, 1H), 2.21 (ddd, J = 10.9, 5.4, 3.0 Hz, 1H), 1.95 (d, J = 13.5 Hz, 2H).

Example 45—Preparation of 4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde

(267) ##STR00889## ##STR00890##

Step 1: Preparation of 6-chloro-4-methylpyridine-3-carboxamide

(268) ##STR00891##

(269) To a stirred mixture of 6-chloro-4-methylpyridine-3-carboxylic acid (20.00 g, 116.564 mmol, 1.00 equivalent) and NH.sub.4Cl (62.35 g, 1.17 mol, 10.00 equivalent) in DCM (400 mL) was added DIEA (22.60 g, 174.846 mmol, 3.00 equivalent). After stirring for 5 min, HATU (66.48 g, 174.846 mmol, 1.50 equivalent) was added in portions. The resulting mixture was stirred for 3 hours at room temperature. The resulting mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography, eluted with PE/EtOAc from 1/1 to 3/2 to afford 6-chloro-4-methylpyridine-3-carboxamide (18.30 g, 61.3%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=171.

Step 2: Preparation of 6-chloro-N-[(1E)-(dimethylamino)methylidene]-4-methylpyridine-3-carboxamide
(270) ##STR00892##
(271) To a stirred mixture of 6-chloro-4-methylpyridine-3-carboxamide (18.30 g, 107.268 mmol, 1.00 equivalent) and in 2-methyltetrahydrofuran (100 mL) was added DMF-DMA (19.17 g, 160.903 mmol, 1.50 equivalent) at 80° C. under nitrogen atmosphere and stirred for additional 1 hour. Then the mixture was cooled and concentrated to afford 6-chloro-N-[(1E)-(dimethylamino)methylidene]-4-methylpyridine-3-carboxamide (26.3 g, 91.3%) as a yellow crude solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=226.
Step 3: Preparation of 6-chloro-2H-2,7-naphthyridin-1-one
(272) ##STR00893##
(273) To a stirred mixture of 6-chloro-N-[(1E)-(dimethylamino)methylidene]-4-methylpyridine-3-carboxamide (26.30 g) in THF (170.00 mL) was added t-BuOK (174.00 mL, 1 mol/L in THF), the resulting solution was stirred at 60° C. under nitrogen atmosphere for 30 min. Then the mixture was cooled and concentrated under reduced pressure, the crude solid was washed with saturated NaHCO.sub.3 solution (100 mL) and collected to give 6-chloro-2H-2,7-naphthyridin-1-one (14.1 g, 67.0%) as a pink solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=181.
Step 4: Preparation of 6-chloro-2-methyl-2,7-naphthyridin-1-one
(274) ##STR00894##
(275) To a stirred mixture of 6-chloro-2H-2, 7-naphthyridin-1-one (14.10 g, 78.077 mmol, 1.00 equivalent) in anhydrous THF (280.00 mL) was added NaH (9.37 g, 234.232 mmol, 3.00 equivalent, 60%) in portions at 0° C. After 10 min, to above mixture was added Mel (33.25 g, 234.232 mmol, 3.00 equivalent) at 0° C., the mixture was allowed to stir for 10 min at 0 degrees. Then the mixture was allowed to stir for 12 h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude solid was slurried with water (100 mL), and the solid was filtered and collected to give the 6-chloro-2-methyl-2,7-naphthyridin-1-one (14.6 g, 94.1%) as a yellow solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=195.
Step 5: Preparation of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one
(276) ##STR00895##
(277) To a stirred mixture of 6-chloro-2-methyl-2,7-naphthyridin-1-one (8.00 g, 41.106 mmol, 1.00 equivalent) in DMF (160.00 mL) was added NBS (8.78 g, 49.327 mmol, 1.20 equivalent), the resulting mixture was stirred for 2 h at 90° C. The reaction mixture was cooled and diluted with DCM (150 mL), and washed with water (3×100 mL), the organic layers were dried and concentrated. Then the residue was slurried with EtOAc (20 mL), the slurry was filtered, the filter cake was washed with EtOAc (20 mL) to give 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (6.32 g, 55.7%) as a white solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=273.
Step 6: Preparation of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one
(278) ##STR00896##
(279) A stirred mixture of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (6.00 g, 21.937 mmol, 1.00 equivalent), dimethylamine hydrochloride (5.37 g, 65.811 mmol, 3.00 equivalent) and K.sub.2CO.sub.3 (15.16 g, 109.685 mmol, 5.00 equivalent) in DMSO (60.00 mL) was heated at 130° C. under nitrogen atmosphere. After 3 h, the resulting mixture was cooled and diluted with water (100 mL), and then extracted with EtOAc (3×100 mL). The combined organic layers were washed with saturated NaCl solution (3×50 mL), dried over anhydrous Na.sub.2SO.sub.4, concentrated under reduced pressure to afford 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (5.91 g, 93.6%) as a yellow solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=282.
Step 7: Preparation of (4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxy benzaldehyde
(280) ##STR00897##
(281) To a stirred mixture of 4-bromo-6-(dimethylamino)-2-methyl-2,7-naphthyridin-1-one (5.70 g, 20.203 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (8.26 g, 28.284 mmol, 1.40 equivalent) in dioxane (100.00 mL) and H.sub.2O (10.00

mL) was added Pd(dppf)Cl.sub.2CH.sub.2Cl.sub.2 (1.65 g, 2.020 mmol, 0.10 equivalent) and 052003 (13.16 g, 40.405 mmol, 2.00 equivalent), then the mixture was allowed to stir for 4 h at 70° C. under nitrogen atmosphere. The resulting mixture was cooled and concentrated under reduced pressure, the residue was slurried with water (100 mL) and filtered, the filter cake was collected. And this solid was further slurried with MeOH (100 mL) and filtered, the solid was collected to afford product to afford 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (6.10 g, 77.6%) as a brown solid. LCMS (ESI) m/z: [M+H].sup.+=368.

Example 46—Preparation of 3-(6-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione formic acid; and 3-(5-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione formic acid

(282) ##STR00898## ##STR00899##

Step 1: Preparation of 5-bromo-2-(2, 6-dioxopiperidin-3-yl)isoindole-1,3-dione

(283) ##STR00900##

(284) To a stirred solution of 5-bromo-2-benzofuran-1,3-dione (10.00 g, 44.050 mmol, 1.00 equivalent), NaOAc (7.23 mg, 88.134 mmol, 2.00 equivalent) and 3-aminopiperidine-2,6-dione (11.29 g, 88.113 mmol, 2.00 equivalent) in AcOH (80.00 mL) at room temperature. The resulting mixture was stirred for 16 h at 115° C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with petroleum ether/EtOAc (10:1) to afford 5-bromo-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (13.6 g, 91.6%) as a dark brown solid. LCMS (ESI) m/z: [M+H].sup.+=337.

Step 2: Preparation of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate

(285) ##STR00901##

(286) To a stirred solution of 5-bromo-2-(2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (3.00 g, 8.899 mmol, 1.00 equivalent), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (3.30 g, 10.672 mmol, 1.20 equivalent), K.sub.3PO.sub.4 (5.67 g, 26.712 mmol, 3.00 equivalent) in dioxane (20.00 mL) and H.sub.2O (4.00 mL) was added Pd(PPh.sub.3).sub.2Cl.sub.2 (0.62 g, 0.883 mmol, 0.10 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 16 h at 80° C. under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (8/1) to afford tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.8 g, 20.5%) as a colorless oil. LCMS (ESI) m/z: [M+H].sup.+=440.

Step 3: Preparation of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperidine-1-carboxylate

(287) ##STR00902##

(288) To a stirred solution of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (0.80 g) in THF (20.00 mL) was added 10% Pd/C (500.0 mg) under nitrogen atmosphere in a 100 mL round-bottom flask. The mixture was hydrogenated at room temperature for 12 h under hydrogen atmosphere using a hydrogen balloon, filtered through a Celite pad and concentrated under reduced pressure. This resulted in tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperidine-1-carboxylate (0.73 g, crude) as a white solid that was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=442.

Step 4: Preparation of tert-butyl 4-(2-(2, 6-dioxopiperidin-3-yl)-1-hydroxy-3-oxoisoindolin-5-yl)piperidine-1-carboxylate; tert-butyl 4-(2-(2, 6-dioxopiperidin-3-yl)-3-hydroxy-1-oxoisoindolin-5-yl)piperidine-1-carboxylate

(289) ##STR00903##

(290) To a stirred solution of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperidine-1-carboxylate (0.73 g, 16.55 mmol, 1.00 equivalent) and Zn (1.08 g, 1.65 mmol, 10.00 equivalent) in AcOH (10.00 mL) at room temperature. The resulting mixture was stirred for 2 h at 60° C. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluted with PE/EtOAc (2:1) to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxoisoindolin-5-yl)piperidine-1-carboxylate; tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxoisoindolin-5-yl)piperidine-1-carboxylate (0.546 g, 74.8%, mixture of two regio-isomers) as a colorless solid. LCMS (ESI) m/z: [M+H].sup.+=444.

Step 5: Preparation of 3-(1-oxo-6-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione; 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2, 6-dione

(291) ##STR00904##

(292) To a stirred solution of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxoisoindolin-5-yl)piperidine-1-carboxylate; tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxoisoindolin-5-yl)piperidine-1-carboxylate (mixture of two regio-isomers, 573.00 mg, 1.00 equivalent) and TFA (3.00 mL) in DCM (9.00 mL) was added TES (450.7 mg, 3.876 mmol, 3.00 equivalent) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure, This was used directly without further purification, to afford 3-(1-oxo-6-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione; 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (200 mg 36.6% mixture of two regio-isomers) as an off-white oil. LCMS (ESI) m/z: [M+H].sup.+=328.

Step 6: Preparation of 3-(6-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione formic acid; and 3-(5-(1-(4-(6-(dimethylamino)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione formic acid

(293) ##STR00905##

(294) To a stirred solution of 3-[1-oxo-6-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2,6-dione (165.0 mg, 0.504 mmol, 1.00 equivalent), and 3-(1-oxo-6-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione; 3-(1-oxo-5-(piperidin-4-yl)isoindolin-2-yl)piperidine-2,6-dione (mixture of two regio-isomers, 222.2 mg, 0.605 mmol, 1.20 equivalent) in DMF (4.00 mL) was added NaBH(OAc).sub.3 (427.3 mg, 2.016 mmol, 4.00 equivalent) at room temperature. The resulting mixture was stirred for 16 h at room temperature. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, CH.sub.3CN in water (0.05% FA), 0% to 50% gradient in 30 min; detector, UV 254 nm. The crude product was purified by Prep-HPLC with the following conditions: Column, Sunfire Prep C18 OBD Column, 10 μm, 19*250 mm; mobile phase, water (0.05% FA) and CH.sub.3CN (15% to 22% CH.sub.3CN in 15 min); Detector, UV 254 nm. This resulted in 3-[6-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid (52.5 mg, 26.3%) as a white solid and 3-[5-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid (68.4 mg, 34.2%) as a yellow solid.

(295) For 3-[6-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid: .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 10.97 (s, 1H), 9.04 (s, 1H), 8.20 (s, 1H, FA), 7.58 (d, J=14.5 Hz, 2H), 7.52 (s, 2H), 6.79 (s, 2H), 6.50 (s, 1H), 5.10 (dd, J=13.4, 5.1 Hz, 1H), 4.41 (d, J=17.1 Hz, 1H), 4.28 (d, J=17.0 Hz, 1H), 3.84 (s, 6H), 3.68 (s, 2H), 3.49 (s, 3H), 3.08-3.05 (m, 8H), 2.91-2.89 (m, 1H), 2.66-2.56 (m, 2H), 2.40-2.35 (m, 1H), 2.30 (t, J=11.3 Hz, 2H), 2.03-1.95 (m, 1H), 1.88-1.57 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=679.32.

(296) For 3-[5-[1-([4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid: .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 10.98 (s, 1H), 9.05 (s, 1H), 8.15 (s, 1H, FA), 7.69 (d, J=7.8 Hz, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.40 (d, J=7.9 Hz, 1H), 6.87 (s, 2H), 6.51 (s, 1H), 5.11 (dd, J=13.3, 5.1 Hz, 1H), 4.44 (d, J=17.3 Hz, 1H), 4.31 (d, J=17.3 Hz, 1H), 4.05 (s, 2H), 3.90 (s, 6H), 3.49 (s, 3H), 3.31 (d, J=11.7 Hz, 2H), 3.09 (s, 6H), 2.99-2.71 (m, 4H), 2.65-2.56 (m, 1H), 2.47-2.33 (m, 1H), 2.04-1.96 (m, 1H), 1.92 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=679.32.

Example 47—Preparation of 3-[6-[(7-[[1-(2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]ethyl)piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-1-oxo-3H-

isoindol-2-yl]piperidine-2,6-dione bis(trifluoroacetic acid)
(297) ##STR00906## ##STR00907##
Step 1: Preparation of tert-butyl 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate
(298) ##STR00908##
(299) To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-hydroxyisoindole-1,3-dione (1.37 g, 4.996 mmol, 1.00 equivalent) and tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (1.81 g, 7.494 mmol, 1.5 equivalent) in THF (30.00 mL) was added PPh.sub.3 (1.97 g, 7.494 mmol, 1.5 equivalent). To the above mixture was added DIAD (1.52 g, 7.494 mmol, 1.5 equivalent) dropwise over 10 min at 0° C. The resulting mixture was stirred for additional 5 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, FA in water, 0% to 100% gradient in 45 min; detector, UV 254 nm. This resulted in tert-butyl 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.964 g, 79.0%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=498.
Step 2: Preparation of 5-[7-azaspiro[3.5]nonan-2-yloxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid
(300) ##STR00909##
(301) To a solution of tert-butyl 2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]-7-azaspiro[3.5]nonane-7-carboxylate (1.96 g, 3.939 mmol) in DCM (10.00 mL) was added TFA (10.00 mL). The resulting mixture was stirred for 5 h at room temperature. The reaction mixture was concentrated in vacuo to give crude 5-[7-azaspiro[3.5]nonan-2-yloxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid, which was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=398.
Step 3: Preparation of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate
(302) ##STR00910##
(303) To a solution of 5-[7-azaspiro[3.5]nonan-2-yloxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (2.65 g, 6.668 mmol, 1.00 equivalent) and tert-butyl 4-formylpiperidine-1-carboxylate (1.42 g, 6.668 mmol, 1 equivalent) in DMF (30.00 mL) was added NaBH(OAc).sub.3 (4.24 g, 20.003 mmol, 3 equivalent) at room temperature. The resulting mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of water (100 mL) at room temperature. The resulting mixture was extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine (3×150 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (3.11 g, 78.4%) as a light yellow solid; LCMS (ESI) m/z: [M+H].sup.+=595.
Step 4: Preparation of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate and tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate
(304) ##STR00911##
(305) To a solution of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (3.00 g, 5.044 mmol, 1.00 equivalent) in AcOH (60.00 mL) were added Zn (3.30 g, 50.445 mmol, 10 equivalent) at room temperature. The resulting mixture was stirred for 3 h at 60° C. The resulting mixture was filtered, and the filter cake was washed with MeCN (3×100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, FA in water, 0% to 100% gradient in 35 min; detector, UV 254 nm. This resulted in the mixture of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate and tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate

(mixture, 1.6 g, 53.2%) a light yellow solid. LCMS (ESI) m/z: [M+H].sup.+=597.
Step 5: Preparation of 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione and 3-(1-oxo-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2, 6-dione
(306) ##STR00912##
(307) To a solution of the mixture of tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate (2.40 g, 4.022 mmol, 1.00 equivalent) and tert-butyl 4-[(2-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]oxy]-7-azaspiro[3.5]nonan-7-yl)methyl]piperidine-1-carboxylate) in DCM (50.00 mL) were added TFA (5.00 mL, 67.315 mmol, 16.74 equivalent) and Et.sub.3SiH (4.68 g, 40.220 mmol, 10 equivalent) at room temperature. The resulting mixture was stirred for 12 h at room temperature. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, TFA in water, 0% to 10% gradient in 45 min; detector, UV 254 nm. This resulted in 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (600 mg, 31.0%) and 3-(1-oxo-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (1.2 g, 62.1%) as a light yellow solid. LCMS (ESI) m/z: [M+H]+=481.
Step 6: 2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]acetaldehyde
(308) ##STR00913##
(309) To a stirred mixture of 4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (150.0 mg, 0.408 mmol, 1.00 equivalent) and (methoxymethyl)triphenylphosphanium chloride (559.8 mg, 1.633 mmol, 4 equivalent) in THF (5.0 mL) was added t-BuOK (183.2 mg, 1.633 mmol, 4 equivalent). The resulting mixture was stirred for 30 min at room temperature under nitrogen atmosphere. To the above mixture was added HCl (6M, 0.5 mL, 0.30 mmol) dropwise. The resulting mixture was stirred for additional 30 min at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by reverse phase column with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 10% to 80% gradient in 15 min; detector, UV 254 nm. This resulted in 2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]acetaldehyde (160 mg, 95.1%) as a white solid. LCMS (ESI) m/z: [M+H]+=382.
Step 7: 3-[6-[(7-[[1-(2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]ethyl)piperidin-4-yl]ethyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione bis(trifluoroacetic acid)
(310) ##STR00914##
(311) To a stirred solution of 2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]acetaldehyde (150.0 mg, 0.393 mmol, 1.00 equivalent) and 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (189.0 mg, 0.393 mmol, 1 equivalent) in DMF (2.0 mL) was added NaBH(OAc).sub.3 (250.0 mg, 1.180 mmol, 3 equivalent). The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere. The crude reaction mixture was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 8 B to 25 B in 15 min; 254/220 nm; RT1: 12.28 min) to afford 3-[6-[(7-[[1-(2-[4-[6-(dimethylamino)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]ethyl)piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; bis(trifluoroacetic acid) (101.2 mg, 30.4%) as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 11.00 (s, 1H), 9.49 (d, J=109.5 Hz, 2H, TFA salt), 9.04 (s, 1H), 7.57-7.48 (m, 2H), 7.18-7.09 (m, 2H), 6.81 (d, J=2.8 Hz, 2H), 6.48 (s, 1H), 5.11 (dd, J=13.1, 5.2 Hz, 1H), 4.89 (p, J=6.8 Hz, 1H), 4.38 (d, J=17.0 Hz, 1H), 4.28-4.22 (m, 2H), 3.85 (s, 6H), 3.68 (d, J=11.3 Hz, 2H), 3.48 (s, 3H), 3.40 (d, J=11.9 Hz, 1H), 3.33-3.18 (m, 1H), 3.08 (s, 6H), 3.06-2.84 (m, 9H), 2.65-2.56 (m, 2H), 2.46-2.36 (m, 2H), 2.14-1.93 (m, 6H), 1.92-1.79 (m, 5H), 1.46 (q, J=12.2 Hz, 2H). LCMS (ESI) m/z: [M+H]+=846.25.

Example 48—Preparation 4-(6-cyclopropyl-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde

(312) ##STR00915##

Step 1: Preparation of 6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one

(313) ##STR00916##

(314) To a stirred solution of 6-chloro-2-methyl-2,7-naphthyridin-1-one (500.00 mg, 2.569 mmol, 1.00 equivalent) and cyclopropylboronic acid (441.37 mg, 5.138 mmol, 2 equivalent) in toluene (20.00 mL) and water (1.00 mL) was added tricyclohexylphosphane (144.09 mg, 0.514 mmol, 0.20 equivalent), Pd(AcO).sub.2 (57.68 mg, 0.257 mmol, 0.10 equivalent) and K.sub.3PO.sub.4 (1636.01 mg, 7.707 mmol, 3.00 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 110° C. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (50:1) to afford 6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (340 mg, 59.48%) as a brown solid. LCMS (ESI) m/z: [M+H]+=201.

Step 2: Preparation of 4-bromo-6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one

(315) ##STR00917##

(316) To a stirred solution of 6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (100.00 mg, 0.499 mmol, 1.00 equivalent) in DMF (4.00 mL) was added NBS (106.66 mg, 0.599 mmol, 1.20 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 90° C. The resulting mixture was diluted with water (12 mL), extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (2×50 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure to afford 4-bromo-6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (400 mg, 75.96%) as a brown solid. That was used directly without further purification. LCMS (ESI) m/z: [M+H]+=279.

Step 3: Preparation of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde

(317) ##STR00918##

(318) To a stirred solution of 4-bromo-6-cyclopropyl-2-methyl-2,7-naphthyridin-1-one (420.00 mg, 1.505 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (527.48 mg, 1.806 mmol, 1.2 equivalent) in dioxane (10.00 mL) and water (2.00 mL) was added Pd(dppf)Cl.sub.2 (110.09 mg, 0.150 mmol, 0.10 equivalent) and K.sub.2CO.sub.3 (415.90 mg, 3.009 mmol, 2.00 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 80° C. The mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (CH2Cl2/MeOH 50:1) to afford 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (440 mg, 72.22%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=365.

Example 49—Preparation of 5-[4-[2-(4-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperazin-1-yl)ethyl]piperidin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

(319) ##STR00919##

Step 1: Preparation of benzyl 4-(2-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)piperazine-1-carboxylate

(320) ##STR00920##

(321) To a solution of tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (4.02 g, 17.709 mmol, 1.00 equivalent) and benzyl piperazine-1-carboxylate (3.90 g, 17.727 mmol, 1.00 equivalent) in MeOH (40 mL) was added NaBH.sub.3CN (2.26 g, 35.313 mmol, 2 equivalent), the resulting solution was stirred at 25° C. for 1 hours. The resulting mixture was diluted with water (50 mL), extracted with EA (30 mL×3). The combined organic layers were dried over anhydrous Na.sub.2SO.sub.4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 45% THF in petroleum ether. Pure fractions were evaporated to dryness to afford benzyl 4-(2-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (2.76 g, 35.71%) as a colorless oil. LCMS (ESI) m/z: [M+H].sup.+=432.

Step 2: Preparation of benzyl 4-(2-(piperidin-4-yl)ethyl)piperazine-1-carboxylate

(322) ##STR00921##
(323) To a solution of benzyl 4-(2-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (2.76 g, 6.403 mmol, 1.00 equivalent) in DCM (8.00 mL) was added a solution of HCl in 1,4-dioxane (8.00 mL, 4 mol/L), the resulting mixture was stirred at 25° C. for 1 hour. The resulting mixture was filtered, the filter cake was washed with DCM (5 mL). The collected solid was dried under reduced pressure to afford 4-(2-(piperidin-4-yl)ethyl)piperazine-1-carboxylate (2.08 g, 98.11%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=331.
Step 3: Preparation of benzyl 4-(2-(1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperidin-4-yl)ethyl)piperazine-1-carboxylate
(324) ##STR00922##
(325) To a solution of 4-(2-(piperidin-4-yl)ethyl)piperazine-1-carboxylate (1.50 g, 4.532 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (1.25 g, 4.532 mmol, 1 equivalent) in DMSO (15.00 mL) was added DIEA (3.51 g, 27.192 mmol, 6 equivalent), the resulting solution was stirred at 100° C. for 2 hour. The reaction mixture was diluted with EA (500 mL).
(326) The resulting mixture was washed with water (300 mL×3) and saturated brine (300 mL×1). The organic layer was dried over Na.sub.2SO.sub.4, filtered and evaporated to afford crude product. The crude product was purified by silica gel column chromatography, elution gradient 0 to 100% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford benzyl 4-(2-(1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (1.44 g, 54.13%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=588.
Step 4: Preparation of 2-(2, 6-dioxopiperidin-3-yl)-5-(4-(2-(piperazin-1-yl)ethyl)piperidin-1-yl)isoindoline-1,3-dione
(327) ##STR00923##
(328) To a solution 4-(2-(1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperidin-4-yl)ethyl)piperazine-1-carboxylate (1.04 g, 1.772 mmol, 1.00 equivalent) in DCM (30.00 mL) was added a solution of BBr.sub.3 in DCM (20 mL, 1M), the resulting mixture was stirred at 0° C. for 1 hour. The reaction mixture was poured into ice-water (100 mL), extracted with DCM (30 mL×3), the aqueous layer was concentrated under reduced pressure. The residue was purified by flash C18-flash chromatography, elution gradient 0 to 50% MeCN in water (containing 0.1% HCl). Pure fractions were evaporated to dryness to afford 2-(2,6-dioxopiperidin-3-yl)-5-(4-(2-(piperazin-1-yl)ethyl)piperidin-1-yl)isoindoline-1,3-dione (794 mg, 98.75%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=454.
Step 5: Preparation of 5-[4-[2-(4-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperazin-1-yl)ethyl]piperidin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione
(329) ##STR00924##
(330) To a stirred mixture of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (200.00 mg, 0.549 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperazin-1-yl)ethyl]piperidin-1-yl]isoindole-1,3-dione (373.39 mg, 0.823 mmol, 1.50 equivalent) in DMF (3.00 mL) was added NaBH(OAc).sub.3 (68.98 mg, 1.098 mmol, 2.00 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 40° C. The mixture solution was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 6 B to 27 B in 16 min; 254/220 nm; RT1: 15.34 min) to afford 5-[4-[2-(4-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperazin-1-yl)ethyl]piperidin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (165 mg, 28.16%) as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 11.09 (s, 1H), 9.30 (s, 1H), 7.80 (s, 1H), 7.67 (d, J=8.5 Hz, 1H), 7.44 (s, 1H), 7.34 (s, 1H), 7.26 (d, J=8.8 Hz, 1H), 6.88 (s, 2H), 5.07 (dd, J=12.9, 5.5 Hz, 1H), 4.35 (s, 2H), 4.08 (d, J=12.7 Hz, 2H), 3.90 (s, 7H), 3.58 (s, 7H), 3.27-3.21 (m, 5H), 3.01-2.82 (m, 3H), 2.64-2.53 (m, 2H), 2.22 (t, J=6.5 Hz, 1H), 2.02 (d, J=12.0 Hz, 1H), 1.77 (d, J=12.6 Hz, 2H), 1.63 (s, 3H), 1.22 (d, J=11.6 Hz, 2H), 1.02 (d, J=8.0 Hz, 4H). LCMS (ESI) m/z: [M+H]+=802.15.
Example 50—Preparation of 3-[6-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]335zetidine-3-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione

(331) ##STR00925##
Step 1: Preparation of tert-butyl 3-[(4-methylbenzenesulfonyl)oxy]azetidine-1-carboxylate (25)
(332) ##STR00926##
(333) To a stirred solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (2.50 g, 14.433 mmol, 1.00 equivalent) and TsCl (4.13 g, 21.650 mmol, 1.50 equivalent) in DCM were added DMAP (264.49 mg, 2.165 mmol, 0.15 equivalent) and TEA (4.38 g, 43.300 mmol, 3.00 equivalent) in portions at 0° C. under air atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with Petroleum ether/EtOAc (1:1) to afford tert-butyl 3-[(4-methylbenzenesulfonyl)oxy]azetidine-1-carboxylate (4.4 g, 93.11%) as a brown oil. LCMS (ESI) m/z: [M+H].sup.+=328.
Step 2: Preparation of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy] azetidine-1-carboxylate
(334) ##STR00927##
(335) To a solution of tert-butyl 3-[(4-methylbenzenesulfonyl)oxy]azetidine-1-carboxylate (4.40 g, 13.439 mmol, 1.00 equivalent) and KI (0.22 g, 1.344 mmol, 0.10 equivalent) in DMF was added KHCO.sub.3 (4.04 g, 40.318 mmol, 3.00 equivalent) in portions at 100° C. under air atmosphere. The resulting mixture was washed with 3×150 mL of EtOAc. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 40 min; detector, UV 254 nm. This resulted in tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy]azetidine-1-carboxylate (1.73 g, 29.98%) as an off-white solid. LCMS (ESI) m/z: [M+H].sup.+=430.
Step 3: Preparation of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isoindol-5-yl]oxy]azetidine-1-carboxylate, and tert-butyl 3-[[2-(2, 6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]oxy]azetidine-1-carboxylate
(336) ##STR00928##
(337) A solution of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]oxy] azetidine-1-carboxylate (1.73 g, 4.029 mmol, 1.00 equivalent) and Zn (2.64 g, 40.286 mmol, 10.00 equivalent) in AcOH was stirred for 2 h at 60° C. under air atmosphere. The resulting mixture was washed with 3×100 mL of ethyl acetate. The resulting mixture was concentrated under reduced pressure. The crude product was used in the next step directly without further purification to afford tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isoindol-5-yl] oxy]azetidine-1-carboxylate and tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]oxy]azetidine-1-carboxylate (2.73 g, 78.53%) as an off-white solid. LCMS (ESI) m/z: [M+H].sup.+=432.
Step 4: Preparation of 3-[6-(336zetidine-3-yloxy)-1-oxo-3H-isoindol-2-yl]piperidine-2, 6-dione
(338) ##STR00929##
(339) To a solution of tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-1-hydroxy-3-oxo-1H-isoindol-5-yl]oxy]azetidine-1-carboxylate and tert-butyl 3-[[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]oxy]azetidine-1-carboxylate (2.73 g, 3.164 mmol, 1.00 equivalent) and TFA (1.50 mL, 20.195 mmol, 6.38 equivalent) in DCM was added Et.sub.3SiH (3.68 g, 31.638 mmol, 10.00 equivalent) in portions at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure. The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: Xcelect CSH F-pheny OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: can; Flow rate: 30 mL/min; Gradient: 5 B to 21 B in 10 min; 254/220 nm; RT1: 7.20/8.67 min) to afford 3-[6-(azetidin-3-yloxy)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (165 mg, 8.27%) as an off-white solid. LCMS (ESI) m/z: [M+H].sup.+=316.
Step 5: Preparation of 3-[6-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione
(340) ##STR00930##
(341) To a stirred solution of 3-[6-(azetidin-3-yloxy)-1-oxo-3H-isoindol-2-yl piperidine-2,6-dione (75.00 mg, 0.238 mmol, 1.00 equivalent) and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (86.67 mg, 0.238 mmol, 1.00 equivalent) in DMF was added

NaBH(OAc).sub.3 (100.82 mg, 0.476 mmol, 2.00 equivalent) dropwise at room temperature under air atmosphere for 2 hours. The crude product (mg) was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 15 B to 23 B in 12 min; 254/220 nm; RT1: 10.38 min) to afford 3-[6-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl] methyl]azetidin-3-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (18.9 mg, 11.69%) as an off-white solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.39 (d, J=0.8 Hz, 1H), 7.80 (d, J=4.5 Hz, 1H), 7.60 (t, J=7.2 Hz, 1H), 7.42 (d, J=5.4 Hz, 1H), 7.32-7.24 (m, 1H), 7.22 (d, J=3.2 Hz, 1H), 6.89 (s, 2H), 5.35-5.19 (m, 1H), 5.16 (dd, J=13.3, 5.2 Hz, 1H), 4.84-4.69 (m, 2H), 4.65 (s, 2H), 4.48 (d, J=10.6 Hz, 2H), 4.42 (s, 2H), 3.98 (d, J=22.6 Hz, 6H), 3.69 (s, 3H), 2.93 (ddd, J=17.6, 13.5, 5.4 Hz, 1H), 2.80 (ddd, J=17.6, 4.7, 2.4 Hz, 1H), 2.52 (qd, J=13.2, 4.7 Hz, 1H), 2.21 (dddd, J=14.5, 10.7, 6.9, 3.9 Hz, 2H), 1.23-1.12 (m, 2H), 1.09 (d, J=4.4 Hz, 2H). LCMS (ESI) m/z: [M+H].sup.+=664.

Example 51. Preparation of 5-((7-((1-(4-(6-cyclopropyl-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

(342) ##STR00931##

(343) To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]isoindole-1,3-dione (100.00 mg, 0.202 mmol, 1.00 equivalent) and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (73.68 mg, 0.202 mmol, 1 equivalent) in MeOH (3.00 mL) was added NaBH.sub.3CN (25.41 mg, 0.404 mmol, 2 equivalent). The resulting mixture was stirred at 40° C. for 4 hours. Without any additional work-up, the mixture was purified by prep-HPLC (Column: Kinetex EVO C18 Column, 21.2*150.5 μm; Mobile Phase A: Water (10 mM NH.sub.4HCO.sub.3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 25 B to 50 B in 12 min; 254/220 nm; RT1:11.92 min) to give 5-([7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (35 mg, 20.53%) as a white solid. .sup.1H NMR (300 MHz, DMSO-d.sub.6) δ 11.13 (s, 1H), 9.29 (s, 1H), 8.19 (s, 2H), 7.87-7.74 (m, 2H), 7.44 (s, 1H), 7.35-7.21 (m, 2H), 6.74 (s, 2H), 5.12 (dd, J=12.8, 5.4 Hz, 1H), 4.99 (t, J=6.9 Hz, 1H), 3.82 (s, 6H), 3.60 (s, 2H), 3.59-3.57 (m, 3H) 2.93-2.84 (m, 4H), 2.63 (s, 1H), 2.62-2.60 (s, 1H), 2.55 (s, 3H), 2.23 (d, J=6.9 Hz, 3H), 2.20-2.15 (s, 1H), 2.10 (dd, J=15.2, 4.6 Hz, 4H), 1.80 (dd, J=12.0, 6.3 Hz, 2H), 1.69-1.60 (m, 4H), 1.60-1.50 (m, 2H) 1.47 (s, 1H), 1.07 (d, J=11.5 Hz, 2H), 1.03-0.96 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=843.55.

Example 52—Preparation of 3-[6-([7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione

(344) ##STR00932##

(345) To a stirred solution of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde) and 3-(1-oxo-6-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione) in DMF (10 mL) was added NaBH(OAc).sub.3 in portions at room temperature. The resulting mixture was stirred for 12 h at room temperature. The crude product was purified by Prep-HPLC to afford 3-[6-([7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)methyl]-7-azaspiro[3.5]nonan-2-yl]oxy)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (14.6 mg, 8.0%) as an off-white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 9.40 (s, 1H), 7.76 (s, 1H), 7.51 (d, J=8.4 Hz, 1H), 7.42 (d, J=6.3 Hz, 1H), 7.25-7.14 (m, 2H), 6.89 (s, 2H), 5.16 (dd, J=13.3, 5.1 Hz, 1H), 4.92-4.83 (m, 1H), 4.58-4.35 (m, 4H), 3.99 (s, 6H), 3.69 (s, 3H), 3.67-3.44 (m, 4H), 3.28-2.63 (m, 9H), 2.61-2.46 (m, 2H), 2.36-1.86 (m, 11H), 1.68 (q, J=13.1 Hz, 2H), 1.23-1.08 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=830.01.

Example 53—Preparation of 5-[7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

(346) ##STR00933## ##STR00934##

Step 1: Preparation of tert-butyl 2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)-2,7-

diazaspiro[3.5]nonane-7-carboxylate
(347) ##STR00935##
(348) To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (5.00 g, 18.101 mmol, 1.00 equivalent) and tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (4.10 g, 0.018 mmol, 1 equivalent) in DMSO (50 mL) was added DIEA (9.36 g, 72.422 mmol, 4.00 equivalent), the resulting solution was stirred at 100° C. for 4 hours under nitrogen atmosphere. The resulting mixture was diluted with EtOAc (500 mL), the resulting mixture was washed with 3×300 mL of water and 300 mL saturated brine. The organic layer was dried over Na.sub.2SO.sub.4, filtered and evaporated to afford tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (9 g, crude) as a yellow solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=483
Step 2: Preparation of 5-[2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione
(349) ##STR00936##
(350) To a solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (9.00 g, 18.651 mmol, 1.00 equivalent) in DCM (90.00 mL) was added TFA (30.00 mL), the resulting solution was stirred at 25° C. for 1 hour. The resulting mixture were evaporated to dryness to afford 5-[2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (11.4 g, crude) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=383.
Step 3: Preparation of tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-2,7-diazaspiro[3.5] nonan-7-yl]methyl)azetidine-1-carboxylate
(351) ##STR00937##
(352) To a stirred solution of 5-[2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (3.00 g, 7.845 mmol, 1.00 equivalent) and tert-butyl 3-formylazetidine-1-carboxylate (1.45 g, 7.845 mmol, 1.00 equivalent) in DMF (30.00 mL) was added NaBH(OAc).sub.3 (3.33 g, 15.690 mmol, 2 equivalent), the resulting solution was stirred at 25° C. for 12 hours. The reaction mixture was diluted with EA (500 mL). The resulting mixture was washed with 3×300 mL of water and 300 mL saturated brine. The organic layer was dried over Na.sub.2SO.sub.4, filtered and evaporated to afford tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate (3.13 g, 72.33%) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=552
Step 4: Preparation of 5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione
(353) ##STR00938##
(354) To a stirred solution of tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate (3.13 g, 5.674 mmol, 1.00 equivalent) in DCM (30.00 mL) was added TFA (10.00 mL), the resulting solution was stirred at 25° C. for 1 hour. The resulting mixture were evaporated to dryness to afford 5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (4.1 g, crude) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=452
Step 5: Preparation of 5-[7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione
(355) ##STR00939##
(356) To a stirred solution of 5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (110.00 mg, 0.244 mmol, 1.00 equivalent) and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (88.77 mg, 0.244 mmol, 1.00 equivalent) in MeOH (2.00 mL, 24.699 mmol, 1115.22 equivalent) was added NaBH.sub.3CN (30.62 mg, 0.487 mmol, 2.00 equivalent). The resulting mixture was stirred for overnight at room temperature. The mixture solution was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 5 B to 27 B in 15 min; 254/220

nm; RT1:12.38 min) to afford 5-[7-[(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (63.9 mg, 31.71%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=800. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.39 (s, 1H), 7.79 (d, J=6.3 Hz, 1H), 7.68 (d, J=8.4, 1.2 Hz, 1H), 7.41 (d, J=2.9 Hz, 1H), 6.88 (s, 3H), 6.76-6.67 (m, 1H), 5.13-5.02 (m, 1H), 4.55 (d, 2H), 4.40 (t, J=9.3 Hz, 2H), 4.29-4.11 (m, 2H), 4.05-3.76 (m, 10H), 3.69 (s, 3H), 3.61-3.43 (m, 5H), 3.22-2.98 (m, 2H), 2.94-2.80 (m, 1H), 2.79-2.65 (m, 2H), 2.43-1.93 (m, 6H), 1.27-1.14 (m, 2H), 1.14-1.05 (m, 2H).

Example 54—Preparation of 5-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione

(357) ##STR00940## ##STR00941##

Step 1: tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazine-1-carboxylate

(358) ##STR00942##

(359) To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindole-1,3-dione (3.00 g, 10.861 mmol, 1.00 equivalent) and tert-butyl piperazine-1-carboxylate (2.02 g, 10.861 mmol, 1.00 equivalent) in NMP (30.00 mL) was added DIPEA (4.21 g, 32.574 mmol, 3.00 equivalent). The resulting mixture was stirred for 2 hours at 90° C. under nitrogen atmosphere. The resulting mixture was diluted with water (100 mL). The aqueous layer was extracted with EtOAc (3×30 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 5% to 90% gradient in 30 min; detector, UV 254 nm. This resulted in tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazine-1-carboxylate (1.6 g, 33.29%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=443.

Step 2: 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione

(360) ##STR00943##

(361) To a stirred solution of tert-butyl 4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazine-1-carboxylate (2.10 g, 4.746 mmol, 1.00 equivalent) in DCM (32.00 mL) was added TFA (8.00 mL). The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum to afford 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (2.6 g, 160%) as a yellow solid. That was used directly without further purification. LCMS (ESI) m/z: [M+H]+=343.

Step 3: tert-butyl 4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidine-1-carboxylate

(362) ##STR00944##

(363) To a stirred solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)isoindole-1,3-dione (2.00 g, 5.842 mmol, 1.00 equivalent) in DMF (25.00 mL) were added tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (1.33 g, 5.842 mmol, 1.00 equivalent) under nitrogen atmosphere. The resulting mixture was stirred for 16 hours at 15° C. under nitrogen atmosphere. To the above mixture was added NaBH(OAc).sub.3 (2.48 g, 11.684 mmol, 2.00 equivalent) at 15° C. The resulting mixture was stirred for additional 2 hours at 15° C. The resulting mixture was diluted with water (70 mL). The aqueous layer was extracted with EtOAc (4×30 mL). The organic layers were concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (50:1 to 10:1) to afford tert-butyl 4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidine-1-carboxylate (3 g, 92.75%) as a yellow oil. LCMS (ESI) m/z: [M+H]+=555.

Step 4: 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione

(364) ##STR00945##

(365) To a stirred solution tert-butyl 4-(2-[4-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperazin-1-yl]ethyl)piperidine-1-carboxylate (3.00 g, 5.418 mmol, 1.00 equivalent) in DCM (20.00 mL) was added TFA (5.00 mL) at room temperature. The resulting mixture was stirred for overnight at room temperature. The resulting mixture was concentrated under vacuum to afford 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (3.5 g, 126.33%) as a yellow oil. That was used directly without further purification. LCMS (ESI) m/z: [M+H]+=454.

Step 5: 5-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-

dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione
(366) ##STR00946##
(367) To a stirred solution of 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (150.00 mg, 0.412 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]isoindole-1,3-dione (186.69 mg, 0.412 mmol, 1.00 equivalent) in DMF (3.00 mL) was added NaBH(OAc).sub.3 (261.73 mg, 1.235 mmol, 3.00 equivalent) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for overnight at room temperature. The mixture solution was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Row rate: 25 mL/min; Gradient: 12 B to 12 B in 2 min; 254/220 nm: RT1: 11.13 min) to afford 5-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (62 mg, 18.78%) as a light yellow solid, LCMS (ESI) m/z: [M+H]+=802.30, .sup.1H NMR (400 MHz, DMSO-d6) δ 9.30 (s, 1H), 7.83 (d, J=1.7 Hz, 1H), 7.77 (dd, J=8, 4, 4.8 Hz, 1H), 7.51-7.40 (m, 2H), 7.40-7.32 (m, 1H), 6.85 (s, 2H), 5.13-5.03 (m, 1H), 4.24 (s, 4H), 3.88 (s, 6H), 3.57 (s, 5H), 3.44 (d, J=11.9 Hz, 2H), 3.20 (q, J=10.4, 9.5 Hz, 6H), 3.02 (t, J=12.2 Hz, 2H), 2.94-2.80 (m, 1H), 2.65-2.56 (m, 1H), 2.54 (d, J=4.9 Hz, 1H), 2.30-2.19 (m, 1H), 2.08-1.99 (in, 1H), 1.91-1.70 (m, 3H), 1.67-1.41 (m, 4H), 1.11-0.98 (m, 4H).
Example 55. Preparation of 3-(6-[4[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione formic acid
(368) ##STR00947##
(369) To a stirred solution of 3-(1-oxo-6-[4-[2-(piperidin-4-yl)ethyl]piperazin-1-yl]-3H-isoindol-2-yl)piperidine-2,6-dione (160.00 mg, 0.364 mmol, 1.00 equivalent) and 4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde (132.64 mg, 0.364 mmol, 1.00 equivalent) in DMF (2.00 mL) was added NaBH(AcO).sub.3 (154.29 mg, 0.728 mmol, 2.00 equivalent) and titanium isopropoxide (10.35 mg, 0.036 mmol, 0.10 equivalent). The resulting mixture was stirred for 28 h at room temperature. The mixture solution was purified by Prep-HPLC with the following conditions: Column: Xselect CSH F-Phenyl OBD column, 19*250, 5 μm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 8 B to 19 B in 10 min; 220/254 nm; RT1: 8.28 min. This resulted in 3-(6-[4-[2-(1-[[4-(6-cyclopropyl-2-methyl-1-oxo-2,7-naphthyridin-4-yl)-2,6-dimethoxyphenyl]methyl]piperidin-4-yl)ethyl]piperazin-1-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione; formic acid (16.6 mg, 5.78%) as a white solid. LCMS (ESI) m/z: [M+H]+=788. .sup.1H NMR (400 MHz, DMSO-d6) δ 10.98 (s, 1H), 9.28 (s, 1H), 8.18 (s, 4H, FA), 7.80 (s, 1H), 7.45-7.39 (m, 2H), 7.26 (dd, J=8.4, 2.4 Hz, 1H), 7.16 (d, J=2.4 Hz, 1H), 6.74 (s, 2H), 5.10 (dd, J=13.3, 5.1 Hz, 1H), 4.39-4.16 (m, 2H), 3.82 (s, 6H), 3.60 (s, 3H), 3.56 (s, 4H), 3.18 (s, 5H), 2.90 (d, J=11.6 Hz, 3H), 2.73-2.56 (m, 3H), 2.35-2.32 (m, 2H), 2.30-2.22 (m, 1H), 2.18-2.08 (m, 2H), 2.05-1.90 (m, 1H), 1.64 (d, J=12.3 Hz, 2H), 1.39 (d, J=7.7 Hz, 2H), 1.26-1.19 (m, 1H), 1.19-1.09 (m, 2H), 0.99 (dd, J=10.0, 3.7 Hz, 4H).
Example 56—Preparation of 4-(6-cyclopropyl-2-(methyl-d3)-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzaldehyde
(370) ##STR00948##
Step 1: Preparation of 6-chloro-2-(2H3)methyl-2,7-naphthyridin-1-one
(371) ##STR00949##
(372) A solution of 6-chloro-2H-2,7-naphthyridin-1-one (500.00 mg, 2.769 mmol, 1.00 equivalent) in THF (5.00 mL) was treated with NaH (132.89 mg, 5.537 mmol, 2.00 equivalent) for 5 min at 0° C. followed by the addition of CD.sub.3I (802.69 mg, 5.537 mmol, 2.00 equivalent) in portions at 0° C. After stirring at 0° C. for 1 h, the reaction mixture was poured into ice-water (50 mL), the precipitated solids were collected by filtration and washed with water (3×50 mL), then the solid was dried under vacuum to afford 6-chloro-2-(2H3)methyl-2,7-naphthyridin-1-one (500 mg, 91.37%) as a light yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=198.
Step 2: Preparation of 6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one

(373) ##STR00950##
(374) A mixture of 6-chloro-2-(2H3)methyl-2,7-naphthyridin-1-one (400.00 mg, 2.024 mmol, 1.00 equivalent), cyclopropylboronic acid (260.78 mg, 3.036 mmol, 1.50 equivalent), K.sub.3PO.sub.4 (1288.81 mg, 6.072 mmol, 3.00 equivalent), PCy.sub.3 (113.51 mg, 0.405 mmol, 0.20 equivalent) and Pd(AcO).sub.2 (45.44 mg, 0.202 mmol, 0.10 equivalent) in Toluene (20.00 mL) and H.sub.2O (1.00 mL) was stirred for 2 h at 110° C. under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (350 mg, 85.08%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=204
Step 3: Preparation of 4-bromo-6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one
(375) ##STR00951##
(376) A mixture of 6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (300.00 mg, 1.476 mmol, 1.00 equivalent) and NBS (315.23 mg, 1.771 mmol, 1.20 equivalent) in ACN (3.00 mL) was stirred for 2 h at 90° C. The resulting mixture was diluted with 1×50 mL of water. The resulting mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (3×50 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure. The resulting mixture was concentrated under reduced pressure. to afford 4-bromo-6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (350 mg, 84.04%) as a yellow solid that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=282.
Step 4: Preparation of 4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde
(377) ##STR00952##
(378) A mixture of 4-bromo-6-cyclopropyl-2-(2H3)methyl-2,7-naphthyridin-1-one (350.00 mg, 1.240 mmol, 1.00 equivalent), 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (434.86 mg, 1.489 mmol, 1.20 equivalent), Cs.sub.2CO.sub.3 (808.33 mg, 2.481 mmol, 2.00 equivalent) and Pd(dppf)Cl.sub.2 (90.76 mg, 0.124 mmol, 0.10 equivalent) in dioxane (3.00 mL) and H.sub.2O (1.00 mL) was stirred for 3 hours at 90° C. under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 4-[6-cyclopropyl-2 (2H3) methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (200 mg, 43.88%) as an orange solid. LCMS (ESI) m/z: [M+H].sup.+=368.
Example 57—Preparation of 5-(7-[[1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid
(379) ##STR00953##
(380) A mixture of 4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (120.00 mg, 0.327 mmol, 1.00 equivalent), 2-(2,6-dioxopiperidin-3-yl)-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]isoindole-1,3-dione (161.54 mg, 0.327 mmol, 1.00 equivalent) and NaBH(AcO).sub.3 (138.44 mg, 0.653 mmol, 2.00 equivalent) in DMF (3.00 mL) was stirred for 2 hours at room temperature. Without any additional work-up, the mixture was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 10 B to 18 B in 15 min; 254/220 nm; RT1:12.37; RT2: Injection Volume: mL; Number Of Runs) to afford 5-(7-[[1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (12.2 mg) as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 11.08 (s, 1H), 9.29 (s, 1H), 8.20 (s, 1H, FA), 7.78 (s, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.40 (s, 1H), 6.76 (d, J=4.0 Hz, 3H), 6.64 (dd, J=8.4, 2.1 Hz, 1H), 5.05 (dd, J=12.9, 5.4 Hz, 1H), 3.84 (s, 6H), 3.79 (s, 2H), 3.74 (s, 4H), 3.55 (s, 3H), 3.13 (s, 3H), 2.97-2.79 (m, 1H), 2.71-2.56 (m, 2H), 2.46 (d, J=7.0 Hz, 2H), 2.36-2.21 (m, 4H), 2.05-1.95 (m, 1H), 1.78-1.69 (m, 4H), 1.00 (dd, J=6.6, 4.3 Hz, 4H). LCMS (ESI) m/z: [M+H].sup.+=803.
Example 58—Preparation of 5-[(7-[[1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-

yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione
(381) ##STR00954##
(382) A mixture of 4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (60.00 mg, 0.163 mmol, 1.00 equivalent), 2-(2,6-dioxopiperidin-3-yl)-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]isoindole-1,3-dione (80.77 mg, 0.163 mmol, 1.00 equivalent) and NaBH(AcO).sub.3 (69.22 mg, 0.327 mmol, 2.00 equivalent) in DCM (2.00 mL) was stirred for 2 hours at room temperature. The crude product was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 16 B to 21 B in 13 min; 254/220 nm; RT1:10.97 min) to afford 5-[(7-[[1-([4-[6-cyclopropyl-2-(2H3)methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (11.1 mg) as a white solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 9.38 (s, 1H), 8.56 (s, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.66 (s, 1H), 7.38 (d, J=0.9 Hz, 1H), 7.31-7.20 (m, 2H), 6.86 (s, 2H), 5.13 (dd, J=12.4, 5.4 Hz, 1H), 4.32 (s, 2H), 3.97 (s, 6H), 3.50 (d, J=12.2 Hz, 2H), 3.03 (s, 2H), 2.91-2.70 (m, 3H), 2.51 (d, J=8.6 Hz, 6H), 2.33 (d, J=6.7 Hz, 2H), 2.21-2.08 (m, 2H), 2.07-1.89 (m, 5H), 1.83-1.70 (m, 4H), 1.51 (s, 2H), 1.17-1.04 (m, 4H). LCMS (ESI) m/z: [M+H]+=846.
Example 59—Preparation of 5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]ethyl]piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione formic acid
(383) ##STR00955##
Step 1: Preparation of 2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one
(384) ##STR00956##
(385) To a solution of 6-chloro-2-methyl-2,7-naphthyridin-1-one (300.0 mg, 1.541 mmol, 1.00 equivalent) and 3-bromooxetane (422.3 mg, 3.083 mmol, 2.00 equivalent) in DMF (3.00 mL) was added Zn (302.5 mg, 4.624 mmol, 3.00 equivalent) and NaI (57.8 mg, 0.385 mmol, 0.25 equivalent). The resulting mixture was stirring at 60° C. for 12 hours under a nitrogen atmosphere. The resulting mixture was concentrated. The crude mixture was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford 2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (150 mg, 45.0%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=217.
Step 2: Preparation of 4-bromo-2-methyl-6-(oxetan-3-yl)-2, 7-naphthyridin-1-one
(386) ##STR00957##
(387) To a solution of 2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (100.0 mg, 0.462 mmol, 1.00 equivalent) in DMF (3.00 mL) was added NBS (90.5 mg, 0.509 mmol, 1.10 equivalent). The resulting mixture was stirring at 25° C. for 2 hours. The resulting mixture was concentrated. The crude mixture was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford 4-bromo-2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (105 mg, 76.9%) as a white solid. LCMS (ESI) m/z: [M+H]+=295.
Step 3: Preparation of 2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde
(388) ##STR00958##
(389) To a solution of 4-bromo-2-methyl-6-(oxetan-3-yl)-2,7-naphthyridin-1-one (100.0 mg, 0.339 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (148.5 mg, 0.508 mmol, 1.50 equivalent) in dioxane (3.00 mL) and H.sub.2O (1.00 mL) were added Cs.sub.2CO.sub.3 (331.2 mg, 1.016 mmol, 3.00 equivalent) and Pd(dppf)Cl.sub.2 (24.8 mg, 0.034 mmol, 0.10 equivalent) under nitrogen atmosphere. The resulting mixture was stirring at 80 degree for 3 hours under nitrogen atmosphere. The resulting mixture was concentrated. The crude mixture was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to

afford. This resulted in (130 mg, crude) of 2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde (110 mg, 85.3%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=381.
Step 4: Preparation of 5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]ethyl]piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid
(390) ##STR00959##
(391) To a stirred mixture of 2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde (50.0 mg, 0.131 mmol, 1.00 equivalent) and 2-(2,6-dioxopiperidin-3-yl)-5-[4-[2-(piperazin-1-yl)ethyl]piperidin-1-yl]isoindole-1,3-dione (65.6 mg, 0.145 mmol, 1.10 equivalent) in DMF (2.00 mL) was added NaBH(OAc).sub.3 (55.72 mg, 0.263 mmol, 2.00 equivalent) at room temperature. The above mixture was stirred for 3 hours. Then the crude reaction mixture was directly purified by Prep-HPLC (Column: Xselect CSH F-phenyl OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 15% B to 24% B in 14 min; 254/220 nm; Rt: 12.97 min). This resulted in 5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-6-(oxetan-3-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]ethyl]piperidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione; formic acid (40 mg, 37.2%) as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 11.08 (s, 1H), 9.50 (s, 1H), 8.15 (s, 1H, FA), 7.87 (s, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.46 (s, 1H), 7.30 (d, J=2.2 Hz, 1H), 7.23 (dd, J=8.8, 2.3 Hz, 1H), 6.74 (s, 2H), 5.07 (dd, J=13.0, 5.3 Hz, 1H), 4.89 (dd, J=8.4, 5.5 Hz, 2H), 4.79 (dd, J=6.7, 5.5 Hz, 2H), 4.59-4.47 (m, 1H), 4.04 (d, J=13.0 Hz, 2H), 3.81 (s, 6H), 3.58 (d, J=8.8 Hz, 6H), 3.00-2.82 (m, 3H), 2.73-2.57 (m, 4H), 2.55-2.41 (m, 4H), 2.40-2.23 (m, 3H), 2.05-1.97 (m, 1H), 1.78-1.71 (m, 2H), 1.66-1.51 (m, 1H), 1.42-1.34 (m, 2H), 1.24-1.11 (m, 2H). LCMS (ESI) m/z: [M+H]+=818.60.
Example 60—Preparation of 3-[5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]ethyl]piperidin-1-yl)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione
(392) ##STR00960##
Step 1: Preparation of 4-methyl-6-(trifluoromethyl)pyridine-3-carbonitrile
(393) ##STR00961##
(394) To a stirred solution of 5-bromo-4-methyl-2-(trifluoromethyl)pyridine (500.00 mg, 2.083 mmol, 1.00 equivalent) and Zn(CN).sub.2 (146.79 mg, 1.250 mmol, 0.6 equivalent) in DMF (5.00 mL) was added Pd.sub.2(dba).sub.3 (38.15 mg, 0.042 mmol, 0.02 equivalent) and DPPF (46.03 mg, 0.083 mmol, 0.04 equivalent), the resulting solution was stirred at 120° C. for 3 hours. Without any additional work-up, the mixture was purified by flash C18-flash chromatography, elution gradient 0 to 80% MeCN in water (containing 0.1% NH.sub.4HCO.sub.3). Pure fractions were evaporated to dryness to afford 4-methyl-6-(trifluoromethyl)pyridine-3-carbonitrile (220 mg, 56.74%) as a yellow oil. LCMS (ESI) m/z: [M+H].sup.+=187.
Step 2: Preparation of 4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide
(395) ##STR00962##
(396) To a stirred solution of 4-methyl-6-(trifluoromethyl)pyridine-3-carbonitrile (200.00 mg, 1.074 mmol, 1.00 equivalent) and NH.sub.3.Math.H.sub.2O (1.00 mL) in EtOH (1.00 mL) was added H.sub.2O.sub.2 (0.20 mL), the resulting solution was stirred at 25° C. for 4 hours. The reaction mixture was concentrated under reduced pressure to afford 4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (372 mg, crude) as a white solid that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=205.
Step 3: Preparation of N-[(1Z)-(dimethylamino)methylidene]-4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide
(397) ##STR00963##
(398) To a stirred solution of 4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (350.00 mg, 1.714 mmol, 1.00 equivalent) and DMF-DMA (306.44 mg) in 2-methyltetrahydrofuran (5.00 mL) was stirred at 80° C. for 2 hours. Then the mixture was concentrated under reduced pressure to afford N-[(1Z)-(dimethylamino)methylidene]-4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (360 mg crude) as a yellow solid that was used in the next step directly without further purification. LCMS (ESI) m/z:

[M+H].sup.+=260.
Step 4: Preparation of 6-(trifluoromethyl)-2H-2,7-naphthyridin-1-one
(399) ##STR00964##
(400) To a stirred solution of N-[(1Z)-(dimethylamino)methylidene]-4-methyl-6-(trifluoromethyl)pyridine-3-carboxamide (350.00 mg, 1.350 mmol, 1.00 equivalent) and t-BuOK (227.25 mg, 2.025 mmol, 1.50 equivalent) in THF (4.00 mL) was stirred at 60° C. for 2 hours. The resulting mixture was cooled and concentrated under reduced pressure, the residue was washed with saturated NaHCO.sub.3 solution (100 mL). Then the solid was dried under vacuum to give 6-(trifluoromethyl)-2H-2,7-naphthyridin-1-one (295 mg, crude) as an off-white solid. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=215.
Step 5: Preparation of 2-methyl-6-(trifluoromethyl)-2, 7-naphthyridin-1-one
(401) ##STR00965##
(402) To a stirred mixture of 6-(trifluoromethyl)-2H-2,7-naphthyridin-1-one (275.00 mg, 1.284 mmol, 1.00 equivalent) in anhydrous DMF (3.00 mL) was added NaH (36.98 mg, 1.541 mmol, 1.20 equivalent, 60%) in portions at 0° C. After 10 minutes, to above mixture was added MeI (546.82 mg, 3.852 mmol, 3.00 equivalent) at 0° C. and the mixture was allowed to stir for 10 min at 0° C. Then the mixture was allowed to stir for 12 hr at room temperature under nitrogen atmosphere. The crude solid was slurried with water (100 mL), and the solid was filtered and collected to give the 2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (242 mg, 82.59%) as a yellow solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=229.
Step 6: Preparation of 4-bromo-2-methyl-6-(trifluoromethyl)-2, 7-naphthyridin-1-one
(403) ##STR00966##
(404) To a stirred mixture of 2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (220.00 mg, 0.964 mmol, 1.00 equivalent) in anhydrous DMF (5.00 mL) was added NBS (188.77 mg, 1.061 mmol, 1.10 equivalent), the mixture was stirred at 90° C. for 2 hours. Without any additional work-up, the residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 4-bromo-2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (192 mg, 64.85%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=307.
Step 7: Preparation of 2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl] benzaldehyde
(405) ##STR00967##
(406) To a solution of 4-bromo-2-methyl-6-(trifluoromethyl)-2,7-naphthyridin-1-one (142.00 mg, 0.462 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (189.13 mg, 0.647 mmol, 1.4 equivalent) in dioxane (3.00 mL) was added Pd(dppf)Cl.sub.2 (33.84 mg, 0.046 mmol, 0.10 equivalent) and Cs.sub.2CO.sub.3 (301.34 mg, 0.925 mmol, 2 equivalent), the resulting solution was stirred at 70° C. for 3 hours. Without any additional work-up, the residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]benzaldehyde (275 mg, crude) as a brown solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=393.
Step 8: Preparation of 3-[5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]phenyl]methyl)piperazin-1-yl]ethyl]piperidin-1-yl)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione
(407) ##STR00968##
(408) To a solution of 2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]benzaldehyde (78.00 mg, 0.199 mmol, 1.00 equivalent) and 3-(1-oxo-5-[4-[2-(piperazin-1-yl)ethyl]piperidin-1-yl]-3H-isoindol-2-yl)piperidine-2,6-dione (131.08 mg, 0.298 mmol, 1.50 equivalent) in DMF (2.00 mL) was added NaBH(OAc).sub.3 (84.27 mg, 0.398 mmol, 2 equivalent), the resulting solution was stirred at 25° C. for 12 hours. Without any additional work-up, the mixture was purified by prep-HPLC (Column: SunFire Prep C18 OBD Column, 19×150 mm 5 μm 10 nm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 10 B to 32 B in 10 min; 254/220 nm; RT1: 8.95 min) to afford 3-[5-(4-[2-[4-([2,6-dimethoxy-4-[2-methyl-1-oxo-6-(trifluoromethyl)-2,7-naphthyridin-4-yl]phenyl] methyl)piperazin-1-yl]ethyl]piperidin-1-yl)-1-oxo-3H-

isoindol-2-yl]piperidine-2,6-dione (25 mg, 15.41%) as a light brown solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 10.96 (s, 1H), 9.59 (s, 1H), 8.08 (s, 1H), 7.93 (s, 1H), 7.52 (d, J=8.5 Hz, 1H), 7.06 (d, J=8.2 Hz, 2H), 6.94 (d, J=18.1 Hz, 2H), 5.05 (dd, J=13.4, 5.1 Hz, 1H), 4.38-4.15 (m, 3H), 3.87 (s, 8H), 3.67 (s, 3H), 3.63 (s, 3H), 3.11-3.25 (m, 4H), 2.87 (dt, J=36.3, 12.4 Hz, 6H), 2.59 (d, J=18.0 Hz, 2H), 2.36-2.29 (m, 1H), 2.00-1.91 (m, 1H), 1.75 (d, J=12.5 Hz, 2H), 1.57 (s, 3H), 1.25 (d, J=11.0 Hz, 2H). LCMS (ESI) m/z: [M+H].sup.+=816.15.

Example 61—Preparation of 3-[5-[7-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphe nyl]methyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid

(409) ##STR00969##

Step 1: Preparation of 6-(azetidin-1-yl)-4-bromo-2-methyl-2, 7-naphthyridin-1-one

(410) ##STR00970##

(411) To a solution of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (5.00 g, 18.281 mmol, 1.00 equivalent) and azetidine hydrochloride (3.2 g, 54.843 mmol, 3 equivalent) in DMSO (50.00 mL) was added K.sub.2CO.sub.3 (12.6 g, 91.404 mmol, 5 equivalent). The resulting solution was stirred at 130° C. for 2 hours. The resulting mixture was cooled and diluted with water (100 mL), and then extracted with EtOAc (3×100 mL). The combined organic layers were washed with saturated NaCl solution (3×50 mL), dried over anhydrous Na.sub.2SO.sub.4, concentrated under reduced pressure to afford 6-(azetidin-1-yl)-4-bromo-2-methyl-2,7-naphthyridin-1-one (3.7 g, 68.8%) as a grey solid, that was used directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=294.

Step 2: Preparation of 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde

(412) ##STR00971##

(413) To a solution of 6-(azetidin-1-yl)-4-bromo-2-methyl-2,7-naphthyridin-1-one (1.42 g, 4.827 mmol, 1.00 equivalent) and 4-formyl-3,5-dimethoxyphenylboronic acid (1.52 g, 7.241 mmol, 1.5 equivalent) in dioxane (16.00 mL) and H.sub.2O (4.00 mL) were added Pd(dppf)Cl.sub.2 (353.2 mg, 0.483 mmol, 0.1 equivalent) and Cs.sub.2CO.sub.3 (3.15 g, 9.655 mmol, 2 equivalent), and the resulting solution was stirred at 70° C. for 2 hours. The resulting mixture was cooled and concentrated under reduced pressure. The residue was slurried with water (30 mL) and filtered, the filter cake was collected. And this solid was further slurried with MeOH (30 mL) and filtered. The solid was collected to afford product to afford 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (1.42 g, 77.5%) as a grey and solid. LCMS (ESI) m/z: [M+H].sup.+=380.

Example 62—Preparation of 3-[5-[7-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid

(414) ##STR00972##

Step 1: Preparation of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate

(415) ##STR00973##

(416) To a stirred solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (500.0 mg, 1.036 mmol, 1.00 equivalent) in AcOH (4.00 mL) was added Zn (677.7 mg, 10.362 mmol, 10.00 equivalent). The resulting mixture was stirred at 60° C. for 2 h. The reaction mixture was filtered, and the filtrate was evaporated to afford crude product. The crude product was purified by reverse phase column, elution gradient 0 to 30% MeCN in water (containing 0.1% formic acid). Pure fractions were evaporated to dryness to afford tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]-2,7-diaza spiro[3.5]nonane-7-carboxylate (277.3 mg, 55.2%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=485.

Step 2: Preparation of 3-(5-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione

(417) ##STR00974##

(418) To a stirred solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-hydroxy-1-oxo-3H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (250.0 mg, 0.516 mmol, 1.00 equivalent) in DCM (2.00 mL) were added TFA (0.50 mL) and Et.sub.3SiH (0.20 mL). The resulting mixture was stirred at room

temperature for 1 hour. The resulting mixture was concentrated under reduced pressure. This resulted in 3-(5-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (267.5 mg, crude) as a yellow gum. The crude product was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=369.
Step 3: Preparation of 3-[5-[7-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid
(419) ##STR00975##
(420) To a stirred solution of 3-(5-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (400.0 mg, 1.086 mmol, 1.00 equivalent) and 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (494.3 mg, 1.303 mmol, 1.20 equivalent) in DMF (3.00 mL) was added NaBH(OAc).sub.3 (920.4 mg, 4.343 mmol, 4.00 equivalent) at room temperature. The resulting mixture was stirred at room temperature for 2 hours. The crude reaction solution was directly purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 14 B to 22 B in 15 min; 254/220 nm; RT1: 11.72 min) to afford 3-[6-[7-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid (99.2 mg, 12.5%) as a white solid. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 10.94 (s, 1H), 9.02 (s, 1H), 8.15 (s, 1H, FA), 7.61 (s, 1H), 7.48 (d, J=8.2 Hz, 1H), 6.75 (s, 2H), 6.53-6.44 (m, 2H), 6.21 (s, 1H), 5.04 (dd, J=13.3, 5.2 Hz, 1H), 4.30 (d, J=17.0 Hz, 1H), 4.17 (d, J=16.9 Hz, 1H), 4.01 (t, J=7.4 Hz, 4H), 3.83 (s, 6H), 3.61 (d, J=13.2 Hz, 6H), 3.48 (s, 3H), 2.96-2.84 (m, 1H), 2.63-2.54 (m, 3H), 2.51-2.45 (m, 2H), 2.35 (q, J=6.6 Hz, 3H), 1.95 (d, J=12.9 Hz, 1H), 1.75 (s, 4H). LCMS (ESI) m/z: [M+H].sup.+=732.45.
Example 63—Preparation of 3-[5-(7-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione bis(formic acid)
(421) ##STR00976## ##STR00977##
Step 1: Preparation of methyl 5-bromo-2-(bromomethyl)benzoate
(422) ##STR00978##
(423) A solution of methyl 5-bromo-2-methylbenzoate (1.0 g, 4.365 mmol, 1.00 equivalent), BPO (223.7 mg, 0.873 mmol, 0.20 equivalent) and NBS (777.0 mg, 4.365 mmol, 1.00 equivalent) in solvent CCl.sub.4 (10.00 mL) was stirred at 80 degree for 3 hours. The resulting mixture was concentrated. The residue was applied onto a silica gel column, eluted with petroleum ether/EtOAc (20:1) to afford methyl 5-bromo-2-(bromomethyl)benzoate (1.1 g, 81.8%) as a light-yellow liquid.
Step 2: Preparation of 3-(6-bromo-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione
(424) ##STR00979##
(425) To a solution of methyl 5-bromo-2-(bromomethyl)benzoate (1.0 g, 3.247 mmol, 1.00 equivalent), 3-aminopiperidine-2,6-dione (499.26 mg, 3.896 mmol, 1.20 equivalent) in solvent DMF (10.00 mL) was added DIEA (1.26 g, 9.741 mmol, 3.00 equivalent) at room temperature, and the resulting solution was stirred at 80 degree for 12 hours. The resulting mixture was concentrated. The residue was dissolved in water (100 mL) and extracted with 30% i-PrOH/CH.sub.2Cl.sub.2 (100 mL×3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na.sub.2SO.sub.4, filtered and concentrated under reduced pressure to afford of 3-(6-bromo-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (500 mg, 47.7%) as a grey solid. LCMS (ESI) m/z: [M+H].sup.+=323.
Step 3: Preparation of 4-[6-[7-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]-4-carbamoylbutanoic acid
(426) ##STR00980##
(427) To a mixture of 3-(6-bromo-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (500.0 mg, 1.547 mmol, 1.00 equivalent), tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (350.2 mg, 1.547 mmol, 1.00 equivalent), Cs.sub.2CO.sub.3 (1.51 g, 4.642 mmol, 3.00 equivalent) and RuPhos Palladacycle Gen 3 (129.4 mg, 0.155 mmol, 0.10 equivalent) was added solvent dioxane (5.00 mL) under nitrogen atmosphere, and the resulting mixture was stirred at 100 degree for 6 hours under nitrogen atmosphere.

The resulting mixture was concentrated. The crude product was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford 4-[6-[7-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]-4-carbamoylbutanoic acid (150 mg, 19.9%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=487.
Step 4: Preparation of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate
(428) ##STR00981##
(429) To a solution of 4-[6-[7-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]-4-carbamoylbutanoic acid (200.0 mg, 0.411 mmol, 1.00 equivalent) in solvent CH.sub.3CN (5.00 mL) was added CDI (133.3 mg, 0.822 mmol, 2.00 equivalent). The resulting solution was stirred at 80 degree for 6 hours. The resulting mixture was concentrated. The crude product was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (170 mg, 88.3%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=469.
Step 5: Preparation of 3-(6-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione
(430) ##STR00982##
(431) To a solution of tert-butyl 2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonane-7-carboxylate (100.0 mg, 0.213 mmol, 1.00 equivalent) in DCM (3.00 mL) was added TFA (1.00 mL) at room temperature. The resulting mixture was stirred for 1 hour at room temperature. It was then concentrated in vacuo to give a crude product which was used directly in the next step. LCMS (ESI) m/z: [M+H].sup.+=369.
Step 6: Preparation of tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate
(432) ##STR00983##
(433) To a solution of 3-(6-[2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (100.0 mg, 0.271 mmol, 1.00 equivalent), tert-butyl 3-formylazetidine-1-carboxylate (50.3 mg, 0.271 mmol, 1.00 equivalent) in solvent DMF (3.00 mL) was added NaBH(OAc).sub.3 (172.6 mg, 0.814 mmol, 3.00 equivalent). The resulting solution was stirred at 25 degree for 3 hours. The mixture was concentrated. The crude product was purified by reverse phase column directly with the following conditions (Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 45 mL/min; Gradient: 8% B to 80% B in 20 min; 254/220 nm) to afford tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate (60 mg, 41.1%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=538.
Step 7: Preparation of 3-[6-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione
(434) ##STR00984##
(435) To a solution of tert-butyl 3-([2-[2-(2,6-dioxopiperidin-3-yl)-3-oxo-1H-isoindol-5-yl]-2,7-diazaspiro[3.5]nonan-7-yl]methyl)azetidine-1-carboxylate (100.0 mg, 0.186 mmol, 1.00 equivalent) in DCM (3.00 mL) was added TFA (1.00 mL) at room temperature. The resulting mixture was stirred for 1 hour at room temperature. It was then concentrated in vacuo to give a crude product which was used directly in the next step. LCMS (ESI) m/z: [M+H].sup.+=438.
Step 8: 3-[5-(7-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxo-3H-isoindol-2-yl]piperidine-2, 6-dione bis(formic acid)
(436) ##STR00985##
(437) To a stirred solution of 3-[5-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (35.0 mg, 0.080 mmol, 1.00 equivalent) and 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (30.4 mg, 0.080 mmol, 1.00 equivalent) in DMF (4.00 mL) was added NaBH(OAc).sub.3 (50.9 mg, 0.240 mmol, 3.00 equivalent) at room temperature. The resulting mixture was stirred for overnight at room temperature. The mixture was

filtered, and the filtrate was purified by Prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 5 B to 17 B in 12 min; 254/220 nm; RT1: 8.9-9.53 min) to afford 3-[6-(7-[[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)azetidin-3-yl]methyl]-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; bis(formic acid) (5.1 mg, 7.6%) as a light yellow solid. .sup.1H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 9.02 (s, 1H), 8.18 (s, 2H, FA), 7.61 (s, 1H), 7.38 (d, J=8.2 Hz, 1H), 6.79 (s, 2H), 6.68 (d, J=7.5 Hz, 2H), 6.18 (s, 1H), 5.08 (dd, J=13.2, 5.1 Hz, 1H), 4.31 (d, J=16.6 Hz, 1H), 4.18 (d, J=16.7 Hz, 1H), 4.11-3.97 (m, 6H), 3.86 (s, 6H), 3.82-3.69 (m, 4H), 3.58 (s, 3H), 3.49 (s, 3H), 2.96-2.85 (m, 2H), 2.78-2.71 (m, 1H), 2.64-2.60 (m, 1H), 2.59-2.55 (m, 1H), 2.43-2.26 (m, 7H), 2.06-1.95 (m, 2H), 1.78-1.67 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=800.96.

Example 64—Preparation of 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid; and 3-[6-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl] methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid

(438) ##STR00986## ##STR00987##

Step 1: Preparation of 2-(2, 6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)isoindole-1,3-dione

(439) ##STR00988##

(440) To a stirred solution of tert-butyl 4-[2-(2, 6-dioxopiperidin-3-yl)-1,3-dioxoisoindol-5-yl]piperidine-1-carboxylate (1.00 g, 2.265 mmol, 1.00 equivalent) in DCM (8 mL) was added TFA (2.00 mL) at room temperature. The resulting mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated under reduced pressure. This resulted in 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)isoindole-1,3-dione (1.23 g, crude) as a white solid that was used in the next step directly without further purification. LCMS (ESI) m/z: [M+H].sup.+=342.

Step 2: Preparation of 3-[3-hydroxy-1-oxo-5-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[1-hydroxy-3-oxo-5-(piperidin-4-yl)-1H-isoindol-2-yl]piperidine-2,6-dione

(441) ##STR00989##

(442) To a solution of 2-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)isoindole-1,3-dione (300.0 mg, 0.879 mmol, 1.00 equivalent) in AcOH (5.00 mL) was added Zn (574.9 mg, 8.788 mmol, 10 equivalent), and the resulting solution was stirred at 25° C. for 2 hours. The mixture was diluted with EtOAc (30 mL) and washed with water (30 mL×3). The organic layers were combined and dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by flash C18 chromatography (elution gradient 0 to 11% ACN in H.sub.2O) to give 3-[3-hydroxy-1-oxo-5-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[1-hydroxy-3-oxo-5-(piperidin-4-yl)-1H-isoindol-2-yl]piperidine-2,6-dione (280 mg, mixture of two regio-isomers, 92.8%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=344.

Step 3: Preparation of 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-3-hydroxy-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-hydroxy-3-oxo-1H-isoindol-2-yl]piperidine-2,6-dione

(443) ##STR00990##

(444) To a solution of 3-[3-hydroxy-1-oxo-5-(piperidin-4-yl)-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[1-hydroxy-3-oxo-5-(piperidin-4-yl)-1H-isoindol-2-yl]piperidine-2,6-dione (mixture of two regio-isomers, 260.0 mg, 0.757 mmol, 1.00 equivalent), 4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (287.3 mg, 0.757 mmol, 1 equivalent) in DMF (3 mL) was added NaBH(OAc).sub.3 (321.0 mg, 1.514 mmol, 2 equivalent), and the resulting solution was stirred at 25° C. for 4 hours. The mixture was diluted with EtOAc (20 mL) and washed with water (20 mL×3). The organic layers were combined and dried over anhydrous sodium sulfate, filtered and concentrated to give a crude product. The crude product was purified by Prep-TLC (CH.sub.2Cl.sub.2/MeOH 10:1) to give 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-3-hydroxy-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-

dimethoxyphenyl]methyl)piperidin-4-yl]-1-hydroxy-3-oxo-1H-isoindol-2-yl]piperidine-2,6-dione (208 mg, mixture of two regio-isomers, 38.9%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=707.
Step 4: Preparation of 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxy phenyl]methyl) piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid; and 3-[6-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione formic acid
(445) ##STR00991##
(446) To a solution of 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-3-hydroxy-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione and 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-hydroxy-3-oxo-1H-isoindol-2-yl]piperidine-2,6-dione (mixture of two regio-isomers, 200.0 mg, 0.141 mmol, 1.00 equivalent) in DCM (3.00 mL) was added TFA (2.00 mL, 26.926 mmol, 95.16 equivalent) and triethylsilane (1.00 mL, 6.192 mmol, 21.88 equivalent), and the resulting solution was stirred at 25° C. for 1 hour. The crude product was purified by Prep-HPLC (Column: XSelect CSH Prep C18 OBD Column, 5 μm, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 3 B to 26 B in 14 minutes; 254 nm; RT1: 13.32 min) to afford 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl) piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (39.5 mg, 39.1%) and 3-[6-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl] methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid (24.8 mg, 22.7%) both as a white solid.
(447) For 3-[5-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl) piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione: .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 10.99 (s, 1H), 9.02 (s, 1H), 8.16 (s, 1H, FA), 7.68-7.60 (m, 2H), 7.49 (s, 1H), 7.39 (dd, J=7.8, 1.4 Hz, 1H), 6.76 (s, 2H), 6.22 (s, 1H), 5.10 (dd, J=13.3, 5.1 Hz, 1H), 4.42 (d, J=17.3 Hz, 1H), 4.28 (d, J=17.3 Hz, 1H), 4.01 (t, J=7.4 Hz, 4H), 3.84 (s, 6H), 3.69 (s, 2H), 3.49 (s, 3H), 3.05 (d, J=11.2 Hz, 2H), 2.92 (ddd, J=17.3, 13.6, 5.4 Hz, 1H), 2.66-2.60 (m, 1H), 2.60-2.55 (m, 1H), 2.46-2.38 (m, 1H), 2.37-2.28 (m, 4H), 2.04-1.95 (m, 1H), 1.78-1.65 (m, 4H). LCMS (ESI) m/z: [M+H].sup.+=691.35.
(448) For 3-[6-[1-([4-[6-(azetidin-1-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione; formic acid: .sup.1H NMR (400 MHz, DMSO-d6) δ 10.99 (s, 1H), 9.02 (s, 1H), 8.18 (s, FA), 7.62 (s, 1H), 7.58-7.48 (m, 3H), 6.75 (s, 2H), 6.22 (s, 1H), 5.10 (dd, J=13.3, 5.1 Hz, 1H), 4.41 (d, J=17.1 Hz, 1H), 4.27 (d, J=17.1 Hz, 1H), 4.01 (t, J=7.4 Hz, 4H), 3.84 (s, 6H), 3.63 (s, 2H), 3.48 (s, 3H), 3.00 (d, J=11.0 Hz, 2H), 2.97-2.85 (m, 1H), 2.65-2.60 (m, 1H), 2.60-2.56 (m, 1H), 2.45-2.37 (m, 1H), 2.37-2.30 (m, 1H), 2.24 (t, J=11.3 Hz, 2H), 2.03-1.96 (m, 1H), 1.80-1.73 (m, 2H), 1.73-1.62 (m, 2H). LCMS (ESI) m/z: [M+H].sup.+=691.55.
Example 65—Preparation of 3-(5-[[1-([2,6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl]methyl)azetidin-3-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione
(449) ##STR00992##
Step 1: Preparation of 4-bromo-2-methyl-6-(morpholin-4-yl)-2,7-naphthyridin-1-one
(450) ##STR00993##
(451) To a stirred solution of 4-bromo-6-chloro-2-methyl-2,7-naphthyridin-1-one (547.00 mg, 2.000 mmol, 1.00 equivalent) and morpholine (522.71 mg, 6.000 mmol, 3.00 equivalent) in DMSO (6.00 mL) was added K.sub.2CO.sub.3 (1382.00 mg, 10.000 mmol, 5.00 equivalent). The resulting mixture was stirred for 1 h at 130° C. under nitrogen atmosphere. The reaction mixture was diluted with EA (100 mL).
(452) The resulting mixture was washed with 3×100 mL of water and 1×100 mL saturated brine. The organic layer was dried over Na.sub.2SO.sub.4, filtered and evaporated to afford crude product. The residue was purified by silica gel column chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-bromo-2-methyl-6-(morpholin-4-yl)-2,7-naphthyridin-1-one (541 mg, 83.44%) as a light yellow solid. LCMS (ESI) m/z: [M+H].sup.+=324.

Step 2: Preparation of 2, 6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2, 7-naphthyridin-4-yl]benzaldehyde

(453) ##STR00994##

(454) To a solution of 4-bromo-2-methyl-6-(morpholin-4-yl)-2,7-naphthyridin-1-one (540.00 mg, 1.666 mmol, 1.00 equivalent) and 4-formyl-3,5-dimethoxyphenylboronic acid (454.73 mg, 2.165 mmol, 1.30 equivalent), Cs.sub.2CO.sub.3 (1628.20 mg, 4.997 mmol, 3.00 equivalent) in H.sub.2O (1.00 mL) and dioxane (5.00 mL) was added Pd(dppf)Cl.sub.2 CH.sub.2Cl.sub.2 (136.03 mg, 0.167 mmol, 0.10 equivalent) under nitrogen. After stirring for 1 h at 90° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford 2,6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2,7 naphthyridin-4-yl] benzaldehyde (356 mg, 52.20%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=410.

Step 3: Preparation of 3-(5-[[1-([2, 6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2, 7-naphthyridin-4-yl]phenyl]methyl)azetidin-3-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione

(455) ##STR00995##

(456) To a stirred solution of 3-[5-(azetidin-3-yloxy)-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (100.00 mg, 0.317 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2,7-naphthyridin-4-yl]benzaldehyde (129.85 mg, 0.317 mmol, 1.00 equivalent) in DMF was added NaBH(OAc).sub.3 (134.43 mg, 0.634 mmol, 2.00 equivalent) dropwise at room temperature under air atmosphere for 2 hours. The residue was purified by reverse flash chromatography with the following conditions: column, C18 silica gel; mobile phase, MeCN in water, 0% to 100% gradient in 45 min; detector, UV 254 nm. The crude product was purified by Prep-HPLC with the following conditions (Column: Xcelect CSH F-pheny OBD Column, 19*250 mm, 5 μm; Mobile Phase A: Water (0.05% FA); Mobile Phase B: ACN; Flow rate: 30 mL/min; Gradient: 13 B to 33 B in 14 min; 254/220 nm; RT1: 12.85 min) to afford 3-(5-[[1-([2,6-dimethoxy-4-[2-methyl-6-(morpholin-4-yl)-1-oxo-2,7-naphthyridin-4-yl]phenyl]methyl)azetidin-3-yl]oxy]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (100 mg, 44.15%) as a yellow solid. .sup.1H NMR (400 MHz, Methanol-d4) δ 9.18 (s, 1H), 7.80 (t, J=6.7 Hz, 1H), 7.49 (s, 1H), 7.09 (t, J=7.3 Hz, 2H), 6.88 (s, 2H), 6.63 (d, J=4.9 Hz, 1H), 5.40-5.20 (m, 1H), 5.15 (dd, J=13.3, 5.2 Hz, 1H), 4.77 (ddd, J=24.3, 12.5, 6.8 Hz, 2H), 4.65 (d, J=22.0 Hz, 2H), 4.48 (d, J=6.3 Hz, 2H), 4.44-4.28 (m, 2H), 3.96 (d, J=23.6 Hz, 6H), 3.78 (t, J=4.8 Hz, 4H), 3.61 (s, 3H), 3.56 (d, J=4.7 Hz, 4H), 2.93 (ddd, J=18.5, 13.5, 5.3 Hz, 1H), 2.80 (ddd, J=17.5, 4.6, 2.3 Hz, 1H), 2.49 (qd, J=13.2, 4.7 Hz, 1H), 2.23-2.14 (m, 1H). LCMS (ESI) m/z: [M+H].sup.+=709.

Example 66—Preparation of 3-[5-[(7-[[1-([4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione

(457) ##STR00996##

Step 1: Preparation of ethyl 2-methyl-2-(7-methyl-8-oxo-2,7-naphthyridin-3-yl)propanoate

(458) ##STR00997##

(459) To a stirred mixture of LDA (825.63 mg, 7.707 mmol, 1.5 equivalent) in THF (20 mL) was added ethyl isobutyrate (895.28 mg, 7.707 mmol, 1.5 equivalent) dropwise at −78° C. under nitrogen atmosphere. The resulting mixture was stirred for 30 min at −78° C. under nitrogen atmosphere. To the above mixture was added 6-chloro-2-methyl-2,7-naphthyridin-1-one (1.00 g, 5.138 mmol, 1.00 equivalent) in THF (1 mL) dropwise over 2 min at −78° C. The resulting mixture was stirred for additional 2 hours at room temperature. The reaction was quenched with aqueous NH.sub.4Cl (5 mL) at 0° C. The resulting mixture was extracted with CH.sub.2Cl.sub.2 (100 mL). The combined organic layers were washed with water (100 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure. The reaction mixture was purified by reverse phase flash with the following conditions (Mobile Phase A: Water (0.3% FA); Mobile Phase B: ACN; Flow rate: 80 mL/min; Gradient: 5% B to 50% B in 30 min) to afford ethyl 2-methyl-2-(7-methyl-8-oxo-2,7-naphthyridin-3-yl)propanoate (320 mg, 11.35%) as a yellow solid. LCMS (ESI) m/z: [M+H]+=275.

Step 2: Preparation of 6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one

(460) ##STR00998##

(461) To a stirred mixture of ethyl 2-methyl-2-(7-methyl-8-oxo-2,7-naphthyridin-3-yl)propanoate (240.00 mg, 0.875 mmol, 1.00 equivalent) in EtOH (20.00 mL) was added LiBH.sub.4 (209.64 mg, 9.624 mmol, 11.00 equivalent) in portions at 0° C. under nitrogen atmosphere. The resulting mixture was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction was quenched with Water at room temperature. The resulting mixture was extracted with CH.sub.2Cl.sub.2 (20 mL). The combined organic layers were washed with water (2×20 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (20:1) to afford 6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (120 mg, 53.14%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=233.

Step 3: Preparation of 4-bromo-6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one

(462) ##STR00999##

(463) To a stirred mixture of 6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (90.00 mg, 0.387 mmol, 1.00 equivalent) in DMF (1.00 mL) was added NBS (82.75 mg, 0.465 mmol, 1.2 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at 80° C. under nitrogen atmosphere. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (17:1) to afford 4-bromo-6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (80 mg, 66.35%) as a yellow oil. LCMS (ESI) m/z: [M+H]+=311.

Step 4: Preparation of 4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde

(464) ##STR01000##

(465) To a solution of 4-bromo-6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-2,7-naphthyridin-1-one (50.00 mg, 0.161 mmol, 1.00 equivalent) and 2,6-dimethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (70.41 mg, 0.241 mmol, 1.50 equivalent) in dioxane (2.00 mL) and water (0.40 mL) were added K.sub.3PO.sub.4 (102.32 mg, 0.482 mmol, 3.00 equivalent) and Pd(PPh.sub.3).sub.2Cl.sub.2 (11.28 mg, 0.016 mmol, 0.10 equivalent). After stirring for 16 hours at 80° C. under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (17:1) to afford 4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (38 mg, 53.69%) as a yellow oil. LCMS (ESI) m/z: [M+H]+=397.

Step 5: Preparation of 3-[5-[(7-[[1-([4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]methyl]-7-azaspiro[3.5]nonan-2-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione

(466) ##STR01001##

(467) To a stirred mixture of 4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxybenzaldehyde (80.00 mg, 0.202 mmol, 1.00 equivalent) and 3-(1-oxo-5-[[7-(piperidin-4-ylmethyl)-7-azaspiro[3.5]nonan-2-yl]oxy]-3H-isoindol-2-yl)piperidine-2,6-dione (96.98 mg, 0.202 mmol, 1.00 equivalent) in DMF (1.00 mL) was added NaBH(OAc).sub.3 (85.54 mg, 0.404 mmol, 2.00 equivalent) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 hours at room temperature under nitrogen atmosphere. The crude product was purified by Prep-HPLC with the following conditions (Column: Xselect CSH F-Phenyl OBD Column 19*150 mm 5 μm; Mobile Phase A: Water (0.05% TFA); Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 12 B to 24 B in 12 min; 254/220 nm; RT1:9.07 min) to afford 3-[5-[(7-[[1-([4-[6-(1-hydroxy-2-methylpropan-2-yl)-2-methyl-1-oxo-2,7-naphthyridin-4-yl]-2,6-dimethoxyphenyl]methyl)piperidin-4-yl]methyl]-7-azaspiro[3.5] nonan-2-yl)oxy]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (73.3 mg, 41.60%) as a yellow solid. .sup.1H NMR (400 MHz, DMSO-d.sub.6) δ 9.42 (d, J=0.7 Hz, 1H), 7.89 (d, J=2.9 Hz, 1H), 7.70-7.61 (m, 2H), 7.06 (d, J=2.2 Hz, 1H), 6.98 (dd, J=8.4, 2.3 Hz, 1H), 6.91 (s, 2H), 5.05 (dd, J=13.2, 5.1 Hz, 1H), 4.87 (q, J=6.5 Hz, 1H), 4.43-4.32 (m, 2H), 4.26 (d, J=13.6 Hz, 2H), 3.91 (s, 6H), 3.55 (s, 3H), 3.45 (d, J=12.0 Hz, 2H), 3.37 (s, 4H), 3.23-3.14 (m, 1H), 3.10-2.83 (m, 6H), 2.61 (d, J=16.6 Hz, 2H), 2.45-2.33 (m, 2H), 2.08 (d, J=11.8 Hz, 1H), 1.87 (d, J=28.7 Hz, 9H), 1.55-1.41 (m, 2H), 1.27 (s, 6H). LCMS (ESI) m/z: [M+H]+=861.

Example 67—Preparation of 3-(6-[7-[(1[[2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione

(468) ##STR01002##

Step 1: Preparation of 6-methoxy-2-methyl-2,7-naphthyridin-1-one

(469) ##STR01003##

(470) A mixture of 6-chloro-2-methyl-2,7-naphthyridin-1-one (1.00 g, 5.138 mmol, 1.00 equiv) and KOH (0.43 g, 7.707 mmol, 1.50 equiv) in MeOH (10.00 mL) was stirred for 4 hours at 70° C. under nitrogen atmosphere. The resulting mixture was diluted with 100 mL of water. The resulting mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 6-methoxy-2-methyl-2,7-naphthyridin-1-one (800 mg, 81.86%) as a white solid. LCMS (ESI) m/z: [M+H]+=191.

Step 2: Preparation of 4-bromo-6-methoxy-2-methyl-2,7-naphthyridin-1-one

(471) ##STR01004##

(472) A mixture of 6-methoxy-2-methyl-2,7-naphthyridin-1-one (800.00 mg, 4.206 mmol, 1.00 equiv) and NBS (898.33 mg, 5.047 mmol, 1.20 equiv) in DMF (10.00 mL) was stirred for 2 hours at 90° C. under nitrogen atmosphere. The resulting mixture was diluted with 100 mL of water. The resulting mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 4-bromo-6-methoxy-2-methyl-2,7-naphthyridin-1-one (600 mg, 53.01%) as a white solid. LCMS (ESI) m/z: [M+H].sup.+=269.

Step 3: Preparation of tert-butyl 4-[3-(2,6-dioxopiperidin-3-yl)-2-methyl-4-oxoquinazolin-6-yl]piperazine-1-carboxylate

(473) ##STR01005##

(474) A mixture of 4-bromo-6-methoxy-2-methyl-2,7-naphthyridin-1-one (600.00 mg, 2.230 mmol, 1.00 equiv), 4-boranyl-2,6-dimethoxybenzaldehyde (396.86 mg, 2.230 mmol, 1.00 equiv), Pd(dppf)Cl.sub.2 (163.15 mg, 0.223 mmol, 0.10 equiv) and Cs.sub.2CO.sub.3 (1452.94 mg, 4.459 mmol, 2.00 equiv) in DMF (10.00 mL) was stirred for 4 hours at 70° C. under nitrogen atmosphere. The resulting mixture was diluted with 100 mL of water, the resulting mixture was extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na.sub.2SO.sub.4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH.sub.2Cl.sub.2/MeOH (10:1) to afford 2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (100 mg, 12.66%) as a yellow solid. LCMS (ESI) m/z: [M+H].sup.+=355.

Step 4: Preparation of 3-(6-[7-[(1-[[2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione

(475) ##STR01006##

(476) A mixture of 2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)benzaldehyde (80.00 mg, 0.226 mmol, 1.00 equiv), 3-[6-[7-(azetidin-3-ylmethyl)-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl]piperidine-2,6-dione (98.78 mg, 0.226 mmol, 1.00 equiv) and NaBH(AcO).sub.3 (95.69 mg, 0.452 mmol, 2.00 equiv) in DMF (2.00 mL) was stirred for 3 hours at room temperature. Without any additional work-up, the mixture was purified by Prep-HPLC with the following conditions (Column: XSelect CSH Prep C18 OBD Column 5 um, 19*150 mm; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 13 B to 20 B in 15 min; 254/220 nm; RT1:13.18-14 min) to afford 3-(6-[7-[(1[[2,6-dimethoxy-4-(6-methoxy-2-methyl-1-oxo-2,7-naphthyridin-4-yl)phenyl]methyl]azetidin-3-yl)methyl]-2,7-diazaspiro[3.5]nonan-2-yl]-1-oxo-3H-isoindol-2-yl)piperidine-2,6-dione (11.8 mg, 6.74%) as a yellow solid. .sup.1H NMR (300 MHz, Methanol-d4) δ 9.25 (s, 1H), 7.57 (s, 1H), 7.41 (d, J=8.2 Hz, 1H), 6.96-6.72 (m, 5H), 5.14 (dd, J=13.2,

5.1 Hz, 1H), 4.55 (s, 2H), 4.49-4.30 (m, 4H), 4.27-4.07 (m, 2H), 3.99 (d, J=9.8 Hz, 9H), 3.78 (s, 4H), 3.64 (s, 3H), 3.59-3.48 (m, 5H), 3.27-3.01 (m, 2H), 3.00-2.69 (m, 2H), 2.50 (dd, J=13.1, 4.8 Hz, 1H), 2.35-2.00 (m, 5H). LCMS (ESI) m/z: [M+H].sup.+=776.

Example 68—BRD9 Bromodomain TR-FRET Competition Binding Assay

(477) This example demonstrates the ability of the compounds of the disclosure to biochemically inhibit BRD9 bromodomain in a competition binding assay.

(478) Procedure: His-Flag-BRD9 (P133-K239; Swiss Prot Q9H8M2; SEQ ID NO:1 mgsshhhhhhenlyfq/gdykddddkgslevlfqg/PAENESTPIQQLLEHFLRQLQRKDPHGFFAFPVTDAIAPGYSMII KHPMDFGTMKDKIVANEYKSVTEFKADFKLMCDNAMTYNRPDTVYYKLAKKILHAGFKMMSK) was cloned, expressed, purified, and then treated with TEV protease. Cleaved His tag was removed by purification. The binding of a biotinylated small molecule ligand of BRD9 was assessed via the LANCE® TR-FRET platform (PerkinElmer), and the compounds were assayed for inhibitory activity against this interaction.

(479) Results: A mixture of biotinylated-ligand and SureLight™ Allophycocyanin-Streptavidin (APC-SA, PerkinElmer AD0201) in 50 mM HEPES (pH 7.4), 50 mM NaCl, 1 mM TCEP (pH 7), 0.01% (v/v) Tween-20, 0.01% (w/v) bovine serum albumin was added to a white 384-well PerkinElmer Proxiplate Plus plate. DMSO or 3-fold serially diluted compounds were then added to the Proxiplate followed by addition of Flag-BRD9. After a 10-minute incubation at room temperature, Eu-W1024 anti-FLAG (PerkinElmer, AD0273) was added. The final reaction mixture that contained 3.75 nM biotinylated ligand, 3 nM Flag-BRD9, 7.5 nM SureLight™ Allophycocyanin-Streptavidin, and 0.2 nM Eu-W1024 anti-FLAG was incubated at room temperature for 90 minutes.

(480) The plates were then read on a PerkinElmer Envision plate reader to determine the ratio of emission at 665 nm over 615 nm. Data was normalized to a DMSO control (100%) and a no protein control (0%) and then fit to a four parameter, non-linear curve fit to calculate an IC.sub.50 (μM) as shown in Table 5. As shown by the results in Table 5, a number of compounds of the present disclosure exhibit an IC.sub.50 value of <1 μM for BRD9 binding, indicating their affinity for targeting BRD9.

(481) TABLE-US-00009 TABLE 5 Bromodomain TR-FRET Binding Bromodomain Compound No. TR-FRET BRD9 IC.sub.50 (nM) B1 ++++ B2 ++++ B3 +++ B4 +++ B5 +++ B6 +++ D1 ++++ D2 ++++ D3 ++++ D4 ++++ D5 +++ D6 +++ D7 ++++ D8 +++ D9 ++ D10 +++ D11 +++ D12 ++++ D13 ++ D14 +++ D15 ++++ D16 ++++ D17 +++ D18 ++++ D19 ++++ D20 ++++ D21 ++++ D22 +++ D23 ++++ D24 +++ D25 + D26 +++ D27 ++++ D28 ++++ D29 ++++ D30 ++++ D31 +++ “+” indicates inhibitory effect of ≥ 1000 nM; “++” indicates inhibitory effect of ≥ 100 nM; “+++” indicates inhibitory effect of ≥ 10 nM; “++++” indicates inhibitory effect of < 10 nM; “NT” indicates not tested

Example 69—SYO1 BRD9 NanoLuc Degradation Assay

(482) This example demonstrates the ability of the compounds of the disclosure to degrade a Nanoluciferase-BRD9 fusion protein in a cell-based degradation assay.

(483) Procedure: A stable SYO-1 cell line expressing 3×FLAG-NLuc-BRD9 was generated. On day 0 cells were seeded in 30 μL media into each well of 384-well cell culture plates. The seeding density was 8000 cells/well. On day 1, cells were treated with 30 nL DMSO or 30 nL of 3-fold serially DMSO-diluted compounds (10 points in duplicates with 1 μM as final top dose). Subsequently plates were incubated for 6 hours in a standard tissue culture incubator and equilibrated at room temperature for 15 minutes. Nanoluciferase activity was measured by adding 15 μL of freshly prepared Nano-Glo Luciferase Assay Reagent (Promega N1130), shaking the plates for 10 minutes and reading the bioluminescence using an EnVision reader.

(484) Results: The Inhibition % was calculated using the following formula: % Inhibition=100×(Lum.sub.HC−Lum.sub.sample)/(Lum.sub.HC−Lum.sub.LC). DMSO treated cells are employed as High Control (HC) and 1 μM of a known BRD9 degrader standard treated cells are employed as Low Control (LC). The data was fit to a four parameter, non-linear curve fit to calculate IC.sub.50 (μM) values as shown in Table 6A, Table 6B, and Table 6C. As shown by the results in Table 6A, Table 6B, and Table 6C, a number of compounds of the present disclosure exhibit an IC.sub.50 value of <1 μM for the degradation of BRD9, indicating their use as compounds for reducing the levels and/or activity of BRD9 and their potential for treating BRD9-related disorders.

(485) TABLE-US-00010 TABLE 6A SYO1 BRD9-NanoLuc Degradation SYO1 BRD9-NanoLuc Compound No. degradation IC.sub.50 (nM) D1 ++++ D2 ++ D3 +++ D4 ++ D5 ++ D6 +++ D7 ++++ D8 +++ D9 + D10 +++ D11 ++ D12 +++ D13 + D14 ++ D15 ++++ D16 ++++ D17 ++++ D18 ++++ D19 ++++ D20 ++++ D21 ++++ D22 ++ D23 ++++ D24 +++ D25 ++ D26 +++ D27 ++++ D28 ++++ D29 ++++ D30 ++++ D31 ++ "+" indicates inhibitory effect of ≥ 1000 nM; "++" indicates inhibitory effect of ≥ 100 nM; "+++" indicates inhibitory effect of ≥ 10 nM; "++++" indicates inhibitory effect of < 10 nM; "NT" indicates not tested

(486) TABLE-US-00011 TABLE 6B SYO1 BRD9-NanoLuc Degradation SYO1 BRD9-NanoLuc Compound No. degradation IC.sub.50 (nM) D32 ++++ D33 ++++ D34 ++++ D35 ++++ D36 ++++ D37 ++++ D38 ++++ D39 ++++ D40 ++++ D41 ++++ D42 ++++ D43 + D44 +++ D45 ++ D46 ++++ D47 +++ D48 ++++ D49 ++++ D50 ++++ D51 ++++ D52 ++++ D53 ++++ D54 ++++ D55 ++++ D56 ++++ D57 ++++ D58 ++++ D59 ++++ D60 ++++ D61 ++++ D62 ++++ D63 ++++ D64 ++ D65 ++++ D66 ++++ D67 ++++ D68 ++++ D69 ++++ D70 ++++ D71 ++++ D72 ++++ D73 ++++ D74 +++ D75 ++++ D76 ++++ D77 ++++ D78 ++++ D79 ++++ D80 ++++ D81 ++++ D82 ++++ D83 ++++ D84 +++ D85 ++++ D86 ++++ D87 ++++ D88 +++ D89 ++++ D90 ++++ D91 ++++ D92 ++++ D93 ++++ D94 +++ D95 ++++ D96 ++++ D97 ++++ D98 ++++ D99 ++++ D100 ++++ D101 ++++ D102 ++++ D103 ++++ D104 ++++ D105 ++++ D106 ++++ D107 ++++ D108 ++++ D109 ++++ D110 ++++ D111 ++++ D112 ++++ D113 ++++ D114 ++++ D115 ++++ D116 ++++ D117 +++ D118 ++++ D119 +++ D120 ++++ D121 ++++ D122 ++++ D123 ++++ D124 ++++ D125 ++++ D126 ++++ D127 ++++ D128 ++++ D129 ++++ D130 ++++ D131 ++++ D132 ++++ D133 ++++ D134 ++++ D135 ++++ D136 ++++ D137 ++++ D138 ++++ D139 ++++ D140 ++++ D141 ++++ D142 ++++ D143 ++++ D144 ++++ D145 ++++ D146 ++++ D147 ++++ D148 ++++ D149 ++++ D150 ++++ D151 ++++ D152 ++++ D153 ++++ D154 ++++ D155 ++++ D156 ++++ D157 ++++ D158 ++++ D159 ++++ D160 ++++ D161 ++++ D162 ++++ D163 ++++ D164 ++++ D165 +++ D166 ++++ D167 ++++ D168 ++++ D169 +++ D170 ++++ D171 ++++ D172 +++ D173 ++++ D174 ++++ D175 + D176 ++++ D177 ++++ D178 ++++ D179 + D180 ++++ D181 + D182 ++++ D183 + D184 ++++ "+" indicates inhibitory effect of ≥ 1000 nM; "++" indicates inhibitory effect of ≥ 100 nM; "+++" indicates inhibitory effect of ≥ 10 nM; "++++" indicates inhibitory effect of < 10 nM; "NT" indicates not tested

(487) TABLE-US-00012 TABLE 6C SYO1 BRD9-NanoLuc Degradation SYO1 BRD9-NanoLuc Compound No. degradation IC.sub.50 (nM) D185 ++++ D186 ++++ D187 ++++ D188 ++++ D189 ++++ D190 ++++ D191 ++ D192 ++++ D193 ++++ D194 ++++ D195 ++++ D196 ++++ D197 ++++ D198 ++++ D199 ++++ D200 ++++ D201 ++++ D202 ++++ D203 ++++ D204 ++++ D205 +++ D206 ++++ D207 ++++ D208 ++++ D209 ++++ D210 ++++ D211 ++++ D212 ++++ D213 ++++ D214 ++++ D215 ++++ D216 ++++ D217 ++++ D218 ++++ D219 ++++ D220 ++++ D221 ++++ D222 ++++ D223 ++++ D224 ++++ D225 ++++ D226 ++++ D227 ++++ D228 ++++ D229 ++++ D230 ++++ D231 ++++ D232 ++++ D233 ++++ D234 ++++ D235 ++++ D236 ++++ D237 ++++ D238 ++++ D239 ++++ D240 ++++ D241 ++++ D242 ++++ D243 ++++ D244 ++++ D245 ++++ D246 ++++ D247 ++++ D248 ++++ D249 ++ D250 ++ D251 + D252 +++ D253 + D254 ++++ D255 ++++ D256 ++++ D257 ++++ D258 ++++ D259 + D260 ++++ D261 + D262 ++++ D263 ++++ D264 ++++ D265 ++++ D266 ++ D267 ++++ D268 ++++ D269 ++++ D270 +++ D271 ++++ D272 ++++ D273 ++++ D274 ++++ D275 ++++ D276 ++++ D277 ++++ D278 ++++ D279 ++++ D280 ++++ D281 ++++ D282 +++ D283 ++ D284 ++++ D285 + D286 ++++ D287 ++++ D288 ++++ D289 ++++ D290 ++++ D291 ++++ D292 +++ D293 ++++ D294 ++++ D295 ++++ D296 ++++ D297 ++++ D298 ++++ D299 ++++ D300 ++++ D301 ++++ D302 ++++ D303 ++++ D304 ++++ D305 ++++ D306 ++++ D307 ++++ D308 ++++ D309 ++++ D310 ++++ D311 ++++ D312 ++++ D313 ++++ D314 ++++ D315 ++++ D316 ++++ "+" indicates inhibitory effect of ≥ 1000 nM; "++" indicates inhibitory effect of ≥ 100 nM; "+++" indicates inhibitory effect of ≥ 10 nM; "++++" indicates inhibitory effect of < 10 nM; "NT" indicates not tested

Other Embodiments

(488) All publications, patents, and patent applications mentioned in this specification are incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.
(489) While the invention has been described in connection with specific embodiments thereof, it will be understood that invention is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.
(490) Other embodiments are in the claims.

Claims

1. A compound having the structure of Formula II:
A-L-B Formula II, wherein L is a linker having the structure of Formula IV
A.sup.1-(B.sup.1).sub.f—(C.sup.1).sub.g—(B.sup.2).sub.h-(D)-(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2 Formula IV wherein A.sup.1 is a bond between the linker and A; A.sup.2 is a bond between B and the linker; each of B.sup.1, B.sup.2, B.sup.3, and B.sup.4 is, independently, optionally substituted C.sub.1-C.sub.2 alkyl, optionally substituted C.sub.1-C.sub.3 heteroalkyl, O, S, S(O).sub.2, or NR.sup.N; each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl; each of C.sup.1 and C.sup.2 is, independently, carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; each of f, g, h, i, j, and k is, independently, 0 or 1; and D is optionally substituted C.sub.1-10 alkyl, optionally substituted C.sub.2-10 alkenyl, optionally substituted C.sub.2-10 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkyl, or a chemical bond linking A.sup.1-(B.sup.1).sub.f—(C.sup.1).sub.g—(B.sup.2).sub.h-to —(B.sup.3).sub.i—(C.sup.2).sub.j—(B.sup.4).sub.k-A.sup.2; B is a degradation moiety having the structure of Formula A ##STR01007## wherein in Y.sup.1 is ##STR01008## R.sup.A5 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; R.sup.A6 is H or optionally substituted C.sub.1-C.sub.6 alkyl; and R.sup.A7 is H or optionally substituted C.sub.1-C.sub.6 alkyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6 carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl; or R.sup.A6 and R.sup.A7, together with the carbon atom to which each is bound, combine to form optionally substituted C.sub.3-C.sub.6 carbocyclyl or optionally substituted C.sub.2-C.sub.5 heterocyclyl; R.sup.A8 is H, optionally substituted C.sub.1-C.sub.6 alkyl, or optionally substituted C.sub.1-C.sub.6 heteroalkyl; each of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is, independently, H, A.sup.2, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted-O—C.sub.3-C.sub.6 carbocyclyl, hydroxyl, mercapto, or optionally substituted amino; or R.sup.A1 and R.sup.A2, R.sup.A2 and R.sup.A3, and/or R.sup.A3 and R.sup.A4, together with the carbon atoms to which each is attached, combine to form ##STR01009## is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.2, wherein one of R.sup.A1, R.sup.A2, R.sup.A3, and R.sup.A4 is A.sup.2, or ##STR01010## is substituted with A.sup.2; and A has the structure of Formula III: ##STR01011## wherein R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; Z.sup.1 is CR.sup.2 or N; R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-

C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl; X.sup.1 is N or CH, and X.sup.2 is C—R.sup.7″; or X.sup.1 is C—R.sup.7″, and X.sup.2 is N or CH; R.sup.7″ is ##STR01012## optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms; R.sup.7′ is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocycylyl; X.sup.3 is N or CH; X.sup.4 is N or CH; G″ is ##STR01013## optionally substituted C.sub.3-C.sub.10 carbocyclyl, C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl; G′ is optionally substituted C.sub.3-C.sub.10 carbocyclylene, C.sub.2-C.sub.9 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene; and A.sup.1 is a bond between A and the linker, where G″ is ##STR01014## or R.sup.7″ is ##STR01015## or a pharmaceutically acceptable salt thereof, wherein optionally substituted moieties when substituted comprise a substituent selected from alkyl, aryl, carbocyclyl, halogen, hydroxyl, heteroalkyl, heteroaryl, heterocyclyl, amino, azido, cyano, nitro, oxo, sulfonyl, or thiol.

2. The compound of claim 1, wherein R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl.

3. The compound of claim 2, wherein R.sup.1 is optionally substituted C.sub.1-C.sub.6 alkyl.

4. The compound of claim 1, wherein R.sup.1 is ##STR01016##

5. The compound of claim 1, wherein Z.sup.1 is CR.sup.2.

6. The compound of claim 1, wherein R.sup.2 is H, F, or ##STR01017##

7. The compound of claim 1, wherein X.sup.1 is N and X.sup.2 is C—R.sup.7″.

8. The compound of claim 1, wherein R.sup.7″ is optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms.

9. The compound of claim 8, wherein R.sup.7″ is optionally substituted heterocyclyl having 3 to 6 atoms.

10. The compound of claim 9, wherein R.sup.7″ is ##STR01018##

11. The compound of claim 9, wherein R.sup.7″ is ##STR01019##

12. The compound of claim 1, wherein G″ is ##STR01020##

13. The compound of claim 1, wherein G′ is ##STR01021## wherein each of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is, independently, H, A.sup.1, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted —O—C.sub.3-C.sub.6 carbocyclyl, optionally substituted-C.sub.1-C.sub.3 alkyl-C.sub.3-C.sub.6 carbocyclyl, optionally substituted-C.sub.1-C.sub.3 alkyl-C.sub.2-C.sub.5 heterocyclyl, hydroxyl, mercapto, or optionally substituted amino; or R.sup.G1′ and R.sup.G2′, R.sup.G2′ and R.sup.G3′, R.sup.G3′ and R.sup.G4′, and/or R.sup.G4′ and R.sup.G5′, together with the carbon atoms to which each is attached, combine to form ##STR01022## and ##STR01023## is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or optionally substituted C.sub.2-C.sub.9 heterocyclyl, any of which is optionally substituted with A.sup.1, wherein one of R.sup.G1′, R.sup.G2′, R.sup.G3′, R.sup.G4′, and R.sup.G5′ is A.sup.1, or ##STR01024## is substituted with A.sup.1.

14. The compound of claim 13, wherein R.sup.G1′ is H; R.sup.G2′ is ##STR01025## R.sup.G3′ is A.sup.1; R.sup.G4′ is ##STR01026## and R.sup.G5′ is H.

15. The compound of claim 1, wherein Y.sup.1 is ##STR01027##

16. The compound of claim 1, wherein Y.sup.1 is ##STR01028##

17. The compound of claim 1, wherein the structure of Formula A has the structure of Formula A.sup.9: ##STR01029## or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1, wherein the structure of Formula A has the structure of Formula A.sup.10:

##STR01030## or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein the structure of Formula A is ##STR01031##

20. The compound of claim 1, wherein the compound has the structure; TABLE-US-00013 Com- pound No. Structure D2  D3  D4  D5  D6  D8  D9  D10  D11  D12  D13  D14 D17 D21 D22 D23  D24  D25  D26  D29  D31  D45  D47  D59  D61  D62  D63  D70  D71  D74  D76  D77  D78  D81  D82  D83  D86  D88  D90  D91  D92 D93 D94 D96 D98 D104 D113 D114 D117 D132 D133 D137 D138 D141 D144 D146 D150 D154 D158 D163 D164 D166 D229 D235 D239 D242 D247 D254 D255 D256 D257 D260 D262 D265 D268 D270 D274 D276 D277 D278 D279 D280 D281 D288 D290 D293 D294 D295 D296 D297 D300 D312 D313 D314 or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

22. A method of treating synovial sarcoma in a subject in need thereof, the method including administering to the subject an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.