International Patent Classification:
C07D 401/14 (2006.01)  C07D 401/06 (2006.01)
C07D 405/14 (2006.01)  A61K 31/4725 (2006.01)
C07D 413/14 (2006.01)  A61P 35/00 (2006.01)

International Filing Date:
9 June 2015 (09.06.2015)


Inventors: KUMPF, Robert Arnold; 3280 Avenida Anacapa, Carlsbad, California 92009 (US). KUNG, Pei-Pei; 5504 Shannon Ridge Lane, San Diego, California 92130 (US). SUTTON, Scott Channing; 11660 Weatherwood Place, San Diego, California 92131 (US). WYTHES, Martin James; 756 North Granados Avenue, Solana Beach, California 92075 (US).

Agent: PUGMIRE, Matthew J.; Pfizer Worldwide Research & Development, 10555 Science Center Drive, CB-10, San Diego, California 92121 (US).


Declarations under Rule 4.17:
— as to the identity of the inventor (Rule 4.1.7(i))
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.1.7(ii))
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.1.7(iii))

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

Title: ARYL FUSED LACTAMS AS EZH2 MODULATORS

Abstract: This invention relates to compounds of Formula (I) in which R₁, R₂, R₃, R₄, X and Z are as defined herein, and the pharmaceutically acceptable salts thereof, to pharmaceutical compositions comprising such compounds and salts, and to methods of using such compounds, salts and compositions for the treatment of abnormal cell growth, including cancer.
ARYL FUSED LACTAMS AS EZH2 MODULATORS

Cross-Reference to Related Applications

This application claims the benefit of priority to U.S. Provisional Application No. 62/013,400, filed on June 17, 2014, which is incorporated by reference herein in its entirety.

Field of the Invention

The present invention relates to compounds of Formula I, and their pharmaceutically acceptable salts, to pharmaceutical compositions comprising such compounds and salts, and to the uses thereof. The compounds, salts and compositions of the present invention are useful for treating or ameliorating abnormal cell proliferative disorders, such as cancer.

Background

Epigenetic alterations play an important role in the regulation of cellular processes, including cell proliferation, cell differentiation and cell survival. The epigenetic silencing of tumor suppressor genes and activation of oncogenes may occur through alteration of CpG island methylation patterns, histone modification, and dysregulation of DNA binding protein. Polycomb genes are a set of epigenetic effectors. EZH2 (enhancer of zeste homolog 2) is the catalytic component of the Polycomb Repressor Complex 2 (PRC2), a conserved multi-subunit complex that represses gene transcription by methylating lysine 27 on Histone H3 (H3K27). EZH2 plans a key role in regulating gene expression patterns that regulate cell fate decisions, such as differentiation and self-renewal. EZH2 is overexpressed in certain cancer cells, where it has been linked to cell proliferation, cell invasion, chemoresistance and metastasis.

Recurring somatic mutations in EZH2 have been identified in diffuse large B-cell lymphoma (DLBCL) and follicular lymphomas (FL). Mutations altering EZH2 tyrosine 641 (e.g., Y641C, Y641F, Y641N, Y641S, and Y641H) were reportedly observed in up to 22% of germinal center B-cell DLBCL and 7% of FL. Morin et al. Nat. Genetics 2010 Feb; 42(2): 181-185. Mutations of alanine 677 (A677) and alanine 687 (A687) have also been reported. McCabe et al., Proc. Natl. Acad. Sci. USA 2012, 109:2989-2994; Majer et al. FEBS Letters 2012, 586:3448-3451. EZH2 activating mutations have been suggested to alter substrate specificity resulting in elevated levels of trimethylated H3K27 (H3K27me3).

Accordingly, compounds that inhibit the activity of wild type and/or mutant forms of EZH2 are of interest for the treatment of cancer.

**Summary**

The present invention provides, in part, novel compounds and pharmaceutically acceptable salts that can modulate the activity of EZH2, thereby effecting biological functions, including but not limited to inhibiting cell proliferation and cell invasiveness, inhibiting metastasis, inducing apoptosis or inhibiting angiogenesis. Also provided are pharmaceutical compositions and medicaments, comprising the compounds or salts of the invention, alone or in combination with other therapeutic agents or palliative agents.

The present invention also provides, in part, methods for preparing the novel compounds, salts and compositions thereof, and methods of using the foregoing.

In one aspect, the invention provides a compound of formula (I):

![Chemical structure](image)

or a pharmaceutically acceptable salt thereof,
wherein:

R is C1 or Br;

R² is selected from the group consisting of H, C₁-C₆ alkoxy, -OR⁵, -NR⁶R⁷, 3-12
membered heterocyclyl and 5-12 membered heteroaryl, where said C₁-C₆ alkoxy is
optionally substituted by one or more R⁴, and said 3-12 membered heterocyclyl or 5-12
membered heteroaryl is optionally substituted by one or more R⁷;

R³ is H or CH₃;

R⁴ is H, Cl, Br, F or CH₃;

R⁵ is C₃-C₈ cycloalkyi, 3-12 membered heterocyclyl or 5-12 membered
heteroaryl, where each said C₃-C₈ cycloalkyi, 3-12 membered heterocyclyl or 5-12
membered heteroaryl is optionally substituted by one or more R⁸;

R⁶ is H, C₁-C₆ alkyl or C₇-C₁₂ arylalkyl;

R⁷ is H, C₁-C₆ alkyl, C₇-C₁₂ arylalkyl or C(O)R⁸;

R⁸ is C₁-C₆ alkyl or NR⁹R¹⁰;

R⁹ and R¹⁰ are independently H or CH₃;

each R⁴ is independently OH, F, CN or C₄ alkoxy;

each R⁷ is independently OH, F, C₁-C₄ alkyl, C₁-C₄ fluoroalkyl, C₁-C₄ alkoxy, C₁-
C₄ fluoroalkoxy, C₁-C₄ hydroxyalkyl, C₁-C₄ aminoalkyl, C(O)R¹¹, SO₂R¹¹, SO₂NR¹²R¹³ or
3-12 membered heterocyclyl, where said 3-12 membered heterocyclyl is optionally
substituted by one or more R¹²;

each R¹¹ is independently C₁-C₆ alkyl, C₃-C₈ cycloalkyi or 3-12 membered
heterocyclyl, where said C₁-C₆ alkyl is optionally substituted by one or more R⁵, and
said C₃-C₈ cycloalkyi or 3-12 membered heterocyclyl is optionally substituted by one or
more R¹²;

each R⁵ is independently OH, F, CN or C₁-C₄ alkoxy;

each R¹² is independently OH, C₁-C₄ alkyl, C₁-C₄ fluoroalkyl, C₁-C₄ hydroxyalkyl
or C₁-C₄ aminoalkyl;

each R¹³ is independently H or C₁-C₆ alkyl; and

X and Z are independently C₄ alkoxy, C₄ fluoroalkyl, C₄ alkoxy or C₄
flouroalkoxy.
In another aspect, the invention provides a compound selected from the group consisting of:

(3R)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-([3R]-tetrahydrofuran-3-yloxy)-3,4-dihydroisoquinolin-1 (2H)-one;

(3S)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-([3R]-tetrahydrofuran-3-yloxy)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-7-(3,6-dihydro-2H-pyran-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

7-tert-butoxy-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-((1-[(2R)-2-hydroxypropanoylpiperidin-4-yl]oxy)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-((1-[(2S)-2-hydroxypropanoylpiperidin-4-yl]oxy)-3,4-dihydroisoquinolin-1 (2H)-one;

7-(benzylamino)-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(methylamino)-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[1,4-dimethyl-1H-1,2,3-triazol-5-yl]-3,4-dihydroisoquinolin-1(2H)-one;
5,8-dichloro-2-[(4-chloro-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one;
8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3R)-1-[(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]oxy]-3,4-dihydroisoquinolin-1(2H)-one;
1-{5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-1,3-dimethylurea;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one;
(±)-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[[1-[(2-hydroxybutanoyl)piperidin-4-yl]oxy]-3,4-dihydroisoquinolin-1(2H)-one;
3,6-anhydro-1,4-dideoxy-5-0-(5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-2-C-methyl-L-arabino-hexitol;
1,4-anhydro-3,6-dideoxy-2-0-(5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-5-C-methyl-L-arabino-hexitol;
7-amino-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-{[1-[(2R)-2-hydroxybutanoyl]piperidin-4-yl]oxy}-3,4-dihydroisoquinolin-1(2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-{{1-[(1-hydroxycyclobutyl)carbonyl]piperidin-4-yl}oxy}-3,4-dihydroisoquinolin-1(2H)-one;
8-chloro-7-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one;
5,8-dichloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one;
7-[3-(aminomethyl)-5-methyl-1,2-oxazol-4-yl]-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one; and
5,8-dichloro-7-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one;
or a pharmaceutically acceptable salt thereof.

In a further aspect, the invention provides a compound selected from the group consisting of Compounds 33 to 44 according to Table 2, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a pharmaceutical composition comprising a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition comprises two or more pharmaceutically acceptable carriers and/or excipients.

The invention also provides therapeutic methods and uses comprising administering a compound of the invention, or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method for the treatment of abnormal cell growth in a subject comprising administering to the subject a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a subject comprising administering to the subject an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with an amount of an anti-tumor agent, which amounts are together effective in treating said abnormal cell growth. In some embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, antimetabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

In frequent embodiments of the methods provided herein, the abnormal cell growth is cancer. In some embodiments, the methods provided result in one or more of the following effects: (1) inhibiting cancer cell proliferation; (2) inhibiting cancer cell invasiveness; (3) inducing apoptosis of cancer cells; (4) inhibiting cancer cell metastasis; or (5) inhibiting angiogenesis.
In another aspect, the invention provides a method for the treatment of a disorder mediated by EZH2 in a subject comprising administering to the subject a compound of the invention, or a pharmaceutically acceptable salt thereof, in an amount that is effective for treating said disorder. The compounds and salts of the present invention inhibit wild-type and certain mutant forms of human histone methyltransferase EZH2.

In another aspect, the invention provides a compound of one of the formulae described herein, or pharmaceutically acceptable salt thereof, for use in the treatment of abnormal cell growth in a subject.

In a further aspect, the invention provides the use of a compound of one of the formulae described herein, or pharmaceutically acceptable salt thereof, for the treatment of abnormal cell growth in a subject.

In yet another aspect, the invention provides the use of a compound of one of the formulae described herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of abnormal cell growth.

In frequent embodiments, the abnormal cell growth is cancer and the subject is a human.

In some embodiments, the methods described herein further comprise administering to the subject an amount of an anti-cancer therapeutic agent or a palliative agent, which amounts are together effective in treating said abnormal cell growth. In some such embodiments, one or more anti-cancer therapeutic agent are selected from anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents, which amounts are together effective in treating said abnormal cell growth.

In other embodiments, the uses described herein comprise the use of a compound of one of the formulae described herein or pharmaceutically acceptable salt thereof, in combination with one or more substances selected from anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents.

In some embodiments, the medicaments described herein are adapted for use in combination with one or more substances selected from anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents.

Each of the embodiments of the compounds of the present invention described below can be combined with one or more other embodiments of the compounds of the present invention described herein not inconsistent with the embodiment(s) with which it
is combined. In addition, each of the embodiments below describing the invention envisions within its scope the pharmaceutically acceptable salts of the compounds of the invention. Accordingly, the phrase "or a pharmaceutically acceptable salt thereof" is implicit in the description of all compounds described herein.

5

**Detailed Description**

The present invention may be understood more readily by reference to the following detailed description of the preferred embodiments of the invention and the Examples included herein. It is to be understood that the terminology used herein is for the purpose of describing specific embodiments only and is not intended to be limiting. It is further to be understood that unless specifically defined herein, the terminology used herein is to be given its traditional meaning as known in the relevant art.

As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" substituent includes one or more substituents.

"Alkyl" refers to a saturated, monovalent aliphatic hydrocarbon radical including straight chain and branched chain groups having the specified number of carbon atoms. Alkyl substituents typically contain 1 to 20 carbon atoms ("C1-C20 alkyl"), preferably 1 to 12 carbon atoms ("C1-C12 alkyl"), more preferably 1 to 8 carbon atoms ("C1-C8 alkyl"), or 1 to 6 carbon atoms ("C1-C6 alkyl"), or 1 to 4 carbon atoms ("C1-C4 alkyl"). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl and the like. Alkyl groups may be substituted or unsubstituted. In particular, unless otherwise specified, alkyl groups may be substituted by one or more halo groups, up to the total number of hydrogen atoms present on the alkyl moiety. Thus, C1-C4 alkyl includes halogenated alkyl groups, and in particular fluorinated alkyl groups, having 1 to 4 carbon atoms, e.g., trifluoromethyl or difluoroethyl (i.e., CF3 and -CH2CHF2).

Alkyl groups described herein as optionally substituted by may be substituted by one or more substituent groups, which are selected independently unless otherwise indicated. The total number of substituent groups may equal the total number of hydrogen atoms on the alkyl moiety, to the extent such substitution makes chemical sense. Optionally substituted alkyl groups typically contain from 1 to 6 optional
substituents, sometimes 1 to 5 optional substituents, preferably from 1 to 4 optional substituents, or more preferably from 1 to 3 optional substituents.

Optional substituent groups suitable for alkyl include, but are not limited to C₃-C₈ cycloalkyl, 3-12 membered heterocyclyl, C₆-C₁₂ aryl and 5-12 membered heteroaryl, halo, =O (oxo), =S (thiono), =N-CN, =N-OR, =NR, =C(O)R, =CO₂R, -C(O)NR'R', =SO₂R, =SO₂NR'R', =NO₂, =NR'R, =NR'C(O)R', -NR'C(O)NR'R', =NR'C(O)OR', =NR'SO₂R, =NR'SO₂NR'R', =OR, =OC(O)R' and -OC(O)NR'R', where each R' is independently H, C₁-C₈ alkyl, C₁-C₈ acyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, 3-12 membered heterocyclyl, C₆-C₁₂ aryl, or C₅-C₁₂ heteroaryl; and wherein each said C₃-C₈ cycloalkyl, 3-12 membered heterocyclyl, C₆-C₁₂ aryl and C₅-C₁₂ heteroaryl is optionally substituted as further defined herein.

Typical substituent groups on alkyl include halo, -OH, CrC₄ alkoxy, -O-C₆-C₁₂ aryl, =CN, =O, =COOR, =OC(O)R, =C(O)NR'R', =NR'C(O)R', -NR'C(O)OR', -NR'SO₂R, -NR'SO₂NR'R', -OR, =OC(O)R' and -OC(O)NR'R', where each R' is independently H or C₁-C₄ alkyl, or R' and R'' may be taken together with the N atom to which they are attached to form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; wherein each R' is independently H, C₁-C₈ alkyl, C₁-C₈ acyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, 3-12 membered heterocyclyl, C₆-C₁₂ aryl, or C₅-C₁₂ heteroaryl; and wherein each said C₃-C₈ cycloalkyl, 3-12 membered heterocyclyl, C₆-C₁₂ aryl and C₅-C₁₂ heteroaryl is optionally substituted as further defined herein.

- 9 -
In some embodiments, alkyl is optionally substituted by one or more substituents, and preferably by 1 to 3 substituents, which are independently selected from the group consisting of halo, -OH, C₁-C₄ alkoxy, -O-C₆-H₂ ary1, -CN, =O, -COOR, -OC(O)R, -C(O)NRₓRᵧ, -NRₓC(O)Rᵧ, -NRₓRᵧ, C₃-C₈ cycloalkyl, C₆-H₂ ary1, 5-12 membered heteroaryl and 3-12 membered heterocyclyl; where each Rₓ and Rᵧ is independently H or CrC₄ alkyl, or Rₓ and Rᵧ may be taken together with the N to which they are attached form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; and each said C₃-C₈ cycloalkyl, C₆-H₂ ary1, 5-12 membered heteroaryl and 3-12 membered heterocyclyl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, -OH, =O, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₆ haloalkyl, d-C₆ hydroxyalkyl, d-C₄ alkoxy-C₁-C₆ alkyl, -CN, -NH₂, -NH(C₁-C₄ alkyl) and -N(C₁-C₄ alkyl)₂.

In other embodiments, alkyl is optionally substituted by one or more substituent, and preferably by 1 to 3 substituents, independently selected from the group consisting of halo, -OH, C₁-C₄ alkoxy, -CN, -NRₓRᵧ, C₃-C₈ cycloalkyl, 3-12 membered heterocyclyl, C₆-H₂ ary1 and 5-12 membered heteroaryl; where each Rₓ and Rᵧ is independently H or CrC₄ alkyl, or Rₓ and Rᵧ may be taken together with the N to which they are attached form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; and where each said cycloalkyl, heterocyclyl, ary1 or heteroaryl is optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, -OH, =O, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₄ alkoxy-d-C₆ alkyl, -CN, -NH₂, -NH(d-C₄ alkyl) and -N(d-C₄ alkyl)₂.

In some instances, substituted alkyl groups may be specifically named with reference to the substituent group. For example, "haloalkyl" refers to an alkyl group having the specified number of carbon atoms that is substituted by one or more halo substituents, and typically contain 1-6 carbon atoms and 1, 2 or 3 halo atoms (i.e., "d-C₆ haloalkyl") or sometimes 1-4 carbon atoms and 1, 2 or 3 halo atoms (i.e., "C₁-C₄ haloalkyl"). Thus, a C₁-C₄ haloalkyl group includes trifluoromethyl (-CF₃) and difluoromethyl (-CF₂H). More specifically, fluorinated alkyl groups may be specifically referred to as fluoroalkyl groups, e.g., d-C₆ or CrC₄ fluoroalkyl groups.
Similarly, "hydroxyalkyl" refers to an alkyl group having the specified number of carbon atoms that is substituted by one or more hydroxy substituents, and typically contain 1-6 carbon atoms and 1, 2 or 3 hydroxy (i.e., "C1-C6 hydroxyalkyl"). Thus, C1-C6 hydroxyalkyl includes hydroxymethyl (-CH₂OH) and 2-hydroxyethyl (-CH₂CH₂OH).

"Alkoxyalkyl" refers to an alkyl group having the specified number of carbon atoms that is substituted by one or more alkoxy substituents. Alkoxyalkyl groups typically contain 1-6 carbon atoms in the alkyl portion and are substituted by 1, 2 or 3 C1-C₄ alkoxy substituents. Such groups are sometimes described herein as C1-C₄ alkoxy-CrC₆ alkyl.

"Aminoalkyl" refers to alkyl group having the specified number of carbon atoms that is substituted by one or more substituted or unsubstituted amino groups, as such groups are further defined herein. Aminoalkyl groups typically contain 1-6 carbon atoms in the alkyl portion and are substituted by 1, 2 or 3 amino substituents. Thus, a C1-C6 aminoalkyl group includes, for example, aminomethyl (-CH₂NH₂), N,N-dimethylamino-ethyl (-CH₂CH₂N(CH₃)₂), 3-(/V-cyclopropylamino)propyl (-CH₂CH₂CH₂NH-Pr) and /V-pyrrolidinylethyl (-CH₂CH₂N-pyrrolidinyl).

"Alkenyl" refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. Typically, alkenyl groups have 2 to 20 carbon atoms ("C₂-C₂₀ alkenyl"), preferably 2 to 12 carbon atoms ("C₂-C₈ alkenyl"), more preferably 2 to 8 carbon atoms ("C₂-C₈ alkenyl"), or 2 to 6 carbon atoms ("C₂-C₆ alkenyl"), or 2 to 4 carbon atoms ("C₂-C₄ alkenyl"). Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like. Alkenyl groups may be unsubstituted or substituted by the same groups that are described herein as suitable for alkyl.

"Alkynyl" refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. Alkynyl groups have 2 to 20 carbon atoms ("C₂-C₂₀ alkynyl"), preferably 2 to 12 carbon atoms ("C₂-C₈ alkynyl"), more preferably 2 to 8 carbon atoms ("C₂-C₈ alkynyl"), or 2 to 6 carbon atoms ("C₂-C₆ alkynyl"), or 2 to 4 carbon atoms ("C₂-C₄ alkynyl"). Representative examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2-, or 3-butylnyl, and the like. Alkynyl groups may be unsubstituted or substituted by the same groups that are described herein as suitable for alkyl.
"Alkylene" as used herein refers to a divalent hydrocarbyl group having the specified number of carbon atoms which can link two other groups together. Sometimes it refers to a group -(CH₂)ₙ- where n is 1-8, and preferably n is 1-4. Where specified, an alkylene can also be substituted by other groups and may include one or more degrees of unsaturation (i.e., an alkenylene or alkynylene moiety) or rings. The open valences of an alkylene need not be at opposite ends of the chain. Thus branched alkylene groups such as -CH(Me) - and -C(Me)₂ - are also included within the scope of the term 'alkylenes', as are cyclic groups such as cyclopropan-1₁-diyI and unsaturated groups such as ethylene (-CH=CH-) or propylene (-CH₂-CH=CH₂). Where an alkylene group is described as optionally substituted, the substituents include those typically present on alkyl groups as described herein.

"Heteroalkylene" refers to an alkylene group as described above, wherein one or more non-contiguous carbon atoms of the alkylene chain are replaced by -N(R)-, -O- or -S(0)q-, where R is H or CrC₄ alkyl and q is 0-2. For example, the group -0-(CH₂)₁,₄- is a 'C₂-C₅'-heteroalkylene group, where one of the carbon atoms of the corresponding alkylene is replaced by 0.

"Alkoxy" refers to a monovalent -O-alkyl group, wherein the alkyl portion has the specified number of carbon atoms. Alkoxy groups typically contain 1 to 8 carbon atoms ("C₁-C₄ alkoxy"), or 1 to 6 carbon atoms ("C₁-C₆ alkoxy"), or 1 to 4 carbon atoms ("C₁-C₄ alkoxy"). For example, C₁-C₄ alkoxy includes -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -OC(CH₃)₃, and the like. Such groups may also be referred to herein as methoxy, ethoxy, isopropoxy, fe/f-butyloxy, etc. Alkoxy groups may be unsubstituted or substituted on the alkyl portion by the same groups that are described herein as suitable for alkyl. In particular, alkoxy groups may be substituted by one or more halo groups, up to the total number of hydrogen atoms present on the alkyl portion. Thus, C₁-C₄ alkoxy includes halogenated alkoxy groups, e.g., trifluoromethoxy and 2,2-difluoroethoxy (i.e., -OCF₃ and -OCH₂CHF₂). In some instances, such groups may be referred to as "haloalkoxy" (or, where fluorinated, more specifically as "fluoroalkoxy") groups having the specified number of carbon atoms and substituted by one or more halo substituents, and typically contain 1-6 carbon atoms and 1, 2 or 3 halo atoms (i.e., "C₁-C₆ haloalkoxy") or sometimes 1-4 carbon atoms and 1, 2 or 3 halo atoms (i.e., "C₁-C₄ haloalkoxy"). Thus, a C₁-C₄ haloalkoxy group includes trifluoromethoxy (-OCF₃)
and difluoromethoxy (-OCF₂H). More specifically, fluorinated alkyl groups may be specifically referred to as fluoroalkoxy groups, e.g., C₁-C₆ or C₁-C₄ fluoroalkoxy groups.

Similarly, "thioalkoxy" refers to a monovalent -S-alkyl group, wherein the alkyl portion has the specified number of carbon atoms, and may be optionally substituted on the alkyl portion by the same groups that are described herein as suitable for alkyl. For example, a C₁-C₄ thioalkoxy includes -SCH₃ and -SCH₂CH₃.

"Cycloalkyi" refers to a non-aromatic, saturated or partially unsaturated carbocyclic ring system containing the specified number of carbon atoms, which may be a monocyclic, bridged or fused bicyclic or polycyclic ring system that is connected to the base molecule through a carbon atom of the cycloalkyi ring. Typically, the cycloalkyi groups of the invention contain 3 to 12 carbon atoms ("C₃-C₁₂ cycloalkyi"), preferably 3 to 8 carbon atoms ("C₃-C₈ cycloalkyi"). Representative examples include, e.g., cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptatriene, adamantane, and the like. Cycloalkyi groups may be unsubstituted or substituted by the same groups that are described herein as suitable for alkyl.

Illustrative examples of cycloalkyi rings include, but are not limited to, the following:

"Cycloalkylalkyl" may be used to describe a cycloalkyi ring, typically a C₃-C₈ cycloalkyi, which is connected to the base molecule through an alkylene linker, typically a C₁-C₄ alkylene. Cycloalkylalkyl groups are described by the total number of carbon atoms in the carbocyclic ring and linker, and typically contain from 4-12 carbon atoms ("C₄-C₁₂ cycloalkylalkyl"). Thus a cyclopropylmethyl group is a C₄-cycloalkylalkyl group and a cyclohexylethyl is a C₆-cycloalkylalkyl. Cycloalkylalkyl groups may be unsubstituted or substituted on the cycloalkyi and/or alkylene portions by the same groups that are described herein as suitable for alkyl groups.

The terms "heterocycli", "heterocyclic" or "heteroalicyclic" may be used interchangeably herein to refer to a non-aromatic, saturated or partially unsaturated ring
system containing the specified number of ring atoms, including at least one heteroatom selected from N, 0 and S as a ring member, wherein the heterocyclic ring is connected to the base molecule via a ring atom, which may be C or N. Heterocyclic rings may be fused to one or more other heterocyclic or carbocyclic rings, which fused rings may be saturated, partially unsaturated or aromatic. Preferably, heterocyclic rings contain 1 to 4 heteroatoms selected from N, 0, and S as ring members, and more preferably 1 to 2 ring heteroatoms, provided that such heterocyclic rings do not contain two contiguous oxygen atoms. Heterocyclyl groups may be unsubstituted or substituted by the same groups that are described herein as suitable for alkyl, aryl or heteroaryl. In addition, ring N atoms may be optionally substituted by groups suitable for an amine, e.g., alkyl, acyl, carbamoyl, sulfonyl substituents, etc., and ring S atoms may be optionally substituted by one or two oxo groups (i.e., S(0)_q, where q is 0, 1 or 2). Preferred heterocycles include 3-12 membered heterocyclyl groups in accordance with the definition herein.

Illustrative examples of partially unsaturated heterocyclic groups include, but are not limited to:

\[
\begin{align*}
3,4\text{-dihydro-2H-pyran} & \quad (3,4\text{-dihydro-2H-pyranyl}) \\
5,6\text{-dihydro-2H-pyran} & \quad (5,6\text{-dihydro-2H-pyranyl}) \\
2\text{H-pyran} & \quad (2\text{H-pyranyl}) \\
1,2,3,4\text{-tetrahydropyridine} & \quad (1,2,3,4\text{-tetrahydropyridinyl}) \\
1,2,5,6\text{-tetrahydropyridine} & \quad (1,2,5,6\text{-tetrahydropyridinyl})
\end{align*}
\]

Illustrative examples of bridged and fused heterocyclic groups include, but are not limited to:

\[
\begin{align*}
\text{2-oxa-5-azabicyclo-[2.2.1]heptane} \\
\text{3-oxa-8-azabicyclo-[3.2.1]octane} \\
\text{3-azabicyclo-[3.1.0]hexane} \\
\text{2-azabicyclo-[3.1.0]hexane}
\end{align*}
\]
Illustrative examples of saturated heterocyclic groups include, but are not limited to:

- Oxirane (oxiranyl)
- Thiarane (thiaranyl)
- Aziridine (aziridinyl)
- Oxetane (oxetanyl)
- Thiatane (thiatanyl)
- Azetidine (azetidinyl)
- Tetrahydrofuran (tetrahydrofuranyl)

- Tetrahydrothiophene (tetrahydrothiophenyl)
- Pyrrolidine (pyrrolidinyl)
- Tetrahydropyran (tetrahydropyranly)
- Tetrahydrothiopyran (tetrahydrothiopyranly)

- Piperidine (piperidinyl)
- 1,4-Dioxane (1,4-dioxanyl)
- 1,4-Oxathiane (1,4-oxathianyl)
- Morpholine (morpholinyl)
- 1,4-Dithiane (1,4-dithianyl)

- Piperazine (piperazinyl)
- 1,4-Azathiane (1,4-azathianyl)
- Oxepane (oxepanyl)
- Thiepane (thiepanyl)
- Azepepane (azepanyl)

- 1,4-Dioxepane (1,4-dioxepanyl)
- 1,4-Oxathiepane (1,4-oxathiepanyl)
- 1,4-Oxaazepane (1,4-oxaazepanyl)
- 1,4-Dithiepane (1,4-dithiepanyl)

- 1,4-Thieazepane (1,4-thieazepanyl)
- 1,4-Diazepane (1,4-diazepanyl)

In frequent embodiments, heterocyclic groups contain 3-12 ring members, including both carbon and non-carbon heteroatoms, and preferably 4-6 ring members. In certain preferred embodiments, substituent groups comprising 3-12 membered...
heterocycles are selected from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl rings, each of which may be optionally substituted per the particular substituent group, to the extent such substitution makes chemical sense.

It is understood that no more than two N, 0 or S atoms are ordinarily connected sequentially, except where an oxo group is attached to N or S to form a nitro or sulfonyl group, or in the case of certain heteroaromatic rings, such as triazine, triazole, tetrazole, oxadiazole, thiadiazole, and the like.

The term "heterocyclylalkyl" may be used to describe a heterocyclic group of the specified size that is connected to the base molecule through an alkylene linker of the specified length. Typically, such groups contain an optionally substituted 3-12 membered heterocycle attached to the base molecule through a C1-C4 alkylene linker. Where so indicated, such groups may be optionally substituted on the alkylene portion by the same groups that are described herein as suitable for alkyl groups and on the heterocyclic portion by groups described as suitable for heterocyclic rings.

"Aryl" or "aromatic" refer to an optionally substituted monocyclic or fused bicyclic or polycyclic ring system having the well-known characteristics of aromaticity, wherein at least one ring contains a completely conjugated pi-electron system. Typically, aryl groups contain 6 to 20 carbon atoms ("C6-C20 aryl") as ring members, preferably 6 to 14 carbon atoms ("C6-C14 aryl") or more preferably, 6 to 12 carbon atoms ("C6-C12 aryl"). Fused aryl groups may include an aryl ring (e.g., a phenyl ring) fused to another aryl ring, or fused to a saturated or partially unsaturated carbocyclic or heterocyclic ring. The point of attachment to the base molecule on such fused aryl ring systems may be a C atom the aromatic portion or a C or N atom of the non-aromatic portion of the ring system. Examples, without limitation, of aryl groups include phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and tetrahydronaphthyl. The aryl group may be unsubstituted or substituted as further described herein.

Similarly, "heteroaryl" or "heteroaromatic" refer to monocyclic or fused bicyclic or polycyclic ring systems having the well-known characteristics of aromaticity that contain the specified number of ring atoms and include at least one heteroatom selected from N, O and S as a ring member in an aromatic ring. The inclusion of a heteroatom permits aromaticity in 5-membered rings as well as 6-membered rings. Typically, heteroaryl groups contain 5 to 20 ring atoms ("5-20 membered heteroaryl"), preferably 5 to 14 ring atoms ("5-14 membered heteroaryl"), and more preferably 5 to 12 ring atoms.
("5-12 membered heteroaryl"). Heteroaryl rings are attached to the base molecule via a ring atom of the heteroaromatic ring, such that aromaticity is maintained. Thus, 6-membered heteroaryl rings may be attached to the base molecule via a ring C atom, while 5-membered heteroaryl rings may be attached to the base molecule via a ring C or N atom. Examples of unsubstituted heteroaryl groups often include, but are not limited to, pyrrole, furan, thiophene, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, oxadiazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, benzofuran, benzothiophene, indole, benzimidazole, indazole, quinoline, isoquinoline, purine, triazine, naphthyridine and carbazole. In frequent preferred embodiments, 5- or 6-membered heteroaryl groups are selected from the group consisting of pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, pyridinyl and pyrimidinyl, pyrazinyl or pyridazinyl rings.

The heteroaryl group may be unsubstituted or substituted as further described herein.

Aryl, heteroaryl and heterocyclyl moieties described herein as optionally substituted by may be substituted by one or more substituent groups, which are selected independently unless otherwise indicated. The total number of substituent groups may equal the total number of hydrogen atoms on the aryl, heteroaryl or heterocyclyl moiety, to the extent such substitution makes chemical sense and aromaticity is maintained in the case of aryl and heteroaryl rings. Optionally substituted aryl, heteroaryl or heterocyclyl groups typically contain from 1 to 5 optional substituents, sometimes 1 to 4 optional substituents, preferably 1 to 3 optional substituents, or more preferably from 1-2 optional substituents.

Optional substituent groups suitable for aryl, heteroaryl and heterocyclyl rings include, but are not limited to: CrC₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₈ cycloalkyl, 3-12 membered heterocyclyl, c₆-C₁₂ aryl and 5-12 membered heteroaryl; and halo, =0, -CN, -C(O)Rₓ, -CO₂Rₓ, -C(O)NRₓRᵧ, -SRₓ, -SORₓ, -SO₂Rₓ, -SO₂NRₓRᵧ, -NO₂, -NRₓRᵧ, -NRₓC(O)Rᵧ, -NRₓC(O)NRₓRᵧ, -NRₓC(O)ORₓ, -NRₓSO₂Rᵧ, -NRₓSO₂NRₓRᵧ, -ORₓ, -OC(O)Rₓ and -OC(O)NRₓRᵧ; where each Rₓ and Rᵧ is independently H, Ci-C₈ alkyl, Ci-C₈ acyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, c₆-C₈ cycloalkyl, 3-12 membered heterocyclyl, c₆-C₁₂ aryl, or 5-12 membered heteroaryl, or Rₓ and Rᵧ may be taken together with the N atom to which they are attached to form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl, each optionally containing 1, 2 or 3 additional heteroatoms selected from O, N and S; each Rₓ and Rᵧ is optionally
substituted with 1 to 3 substituents independently selected from the group consisting of halo, \(-O, =S, =N-CN, =N-OR\) \text{ or } \text{ any combination thereof}, \(-\text{C}(0)\text{R}^x, -\text{C}(0)\text{NR}^y, -\text{SR}, -\text{SOR}, -\text{S}0_2\text{R}^x, -\text{SO}_2\text{NR}^y, -\text{NO}_2\), \(-\text{NR}^x\text{C}(0)\text{R}^y, -\text{NR}^x\text{C}(0)\text{NR}^y, -\text{NR}^x\text{S0}_2\text{R}^y, -\text{NR}^x\text{SO}_2\text{NR}^y\), wherein each \(\text{R}^x\) is independently \(H, \text{Cl}\)-\(\text{C}_8\) alkyl, \(\text{Cl}\)-\(\text{C}_8\) acyl, \(\text{C}_2\)-\(\text{C}_8\) alkenyl, \(\text{C}_2\)-\(\text{C}_8\) alkynyl, \(3\)-\(12\) membered heterocyclyl, \(\text{C}_6\)-\(\text{C}_2\) aryl, or \(5\)-\(12\) membered heteroaryl; and each said \(\text{Cl}\)-\(\text{C}_8\) alkyl, \(\text{C}_2\)-\(\text{C}_8\) alkenyl, \(\text{C}_2\)-\(\text{C}_8\) alkynyl, \(\text{C}_3\)-\(\text{C}_8\) cycloalkyl, \(3\)-\(12\) membered heterocyclyl, \(\text{C}_6\)-\(\text{C}_2\) aryl, \(5\)-\(12\) membered heteroaryl, and \(5\)-\(12\) membered heteroaryl is optionally substituted as further defined herein.

In typical embodiments, optional substitution on aryl, heteroaryl and heterocyclyl rings includes one or more substituents, and preferably 1 to 3 substituents, independently selected from the group consisting of halo, \(\text{CrC}_8\) alkyl, \(-\text{OH}, \text{Cl}\)-\(\text{C}_8\) alkoxy, \(-\text{CN}, =O, =\text{C}(\text{O})\text{R}^x, =\text{COOR}^x, =\text{OC}(\text{O})\text{R}^x, =\text{C}(\text{O})\text{NR}^y\text{R}^y, =\text{SR}^x, =\text{SOR}^x, =\text{SO}_2\text{R}^x, =\text{SO}_2\text{NR}^y\text{R}^y, =\text{NO}_2, =\text{NR}^x\text{R}^y, =\text{NR}^x\text{C}(\text{O})\text{R}^y, =\text{NR}^x\text{C}(\text{O})\text{NR}^y\text{R}^y, =\text{NR}^x\text{C}(\text{O})\text{OR}^y, =\text{NR}^x\text{SO}_2\text{R}^y, =\text{NR}^x\text{SO}_2\text{NR}^y\text{R}^y, =\text{OC}(\text{O})\text{R}^x, =\text{OC}(\text{O})\text{NR}^x\text{R}^y, =\text{C}_3\)-\(\text{C}_8\) cycloalkyl, \(3\)-\(12\) membered heterocyclyl, \(\text{C}_6\)-\(\text{C}_2\) aryl, \(5\)-\(12\) membered heteroaryl, \(-\text{OC}\)-\(\text{C}_3\)-\(\text{C}_8\) cycloalkyl), \(-\text{O}(3\)-\(12\) membered heterocyclyl), \(-\text{O}(\text{C}_6\)-\(\text{C}_2\) aryl) and \(-\text{O}(5\)-\(12\) membered heteroaryl); where each \(\text{R}^x\) and \(\text{R}^y\) is independently \(H\) or \(\text{Cl}\)-\(\text{C}_4\) alkyl, or \(\text{R}^x\) and \(\text{R}^y\) may be taken together with the \(N\) to which they are attached form a \(3\)-\(12\) membered heterocyclyl or \(5\)-\(12\) membered heteroaryl ring, each optionally containing 1, 2 or 3 additional heteroatoms selected from \(O, N\) and \(S\); and wherein each said \(\text{CrC}_8\) alkyl, \(\text{Cl}\)-\(\text{C}_8\) alkoxy, \(\text{C}_3\)-\(\text{C}_8\) cycloalkyl, \(3\)-\(12\) membered heterocyclyl, \(\text{C}_6\)-\(\text{C}_2\) aryl, \(5\)-\(12\) membered heteroaryl, \(-\text{O}(\text{C}_3\)-\(\text{C}_8\) cycloalkyl), \(-\text{O}(3\)-\(12\) membered heterocyclyl), \(-\text{O}(\text{C}_6\)-\(\text{C}_12\) aryl) and \(-\text{O}(5\)-\(12\) membered heteroaryl) that is described as an optional substituent or is part of \(\text{R}^y\) or \(\text{R}^y\) is optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, \(-\text{OH}, =\text{O}, \text{Cl}\)-\(\text{C}_4\) alkoxy, \(\text{Cl}\)-\(\text{C}_6\) haloalkyl, \(\text{CrC}_6\) hydroxyalkyl, \(\text{CrC}_4\) alkoxy \(-\text{Cl}\)-\(\text{C}_6\) alkoxy, \(-\text{CN}, =\text{NH}_2\), \(-\text{NH}(\text{Cl}\)-\(\text{C}_4\) alkoxy), \(-\text{N}(\text{Cl}\)-\(\text{C}_4\) alkoxy) and \(\text{N}\)-pyrrolidinyl.

Illustrative examples of monocyclic heteroaryl groups include, but are not limited to:
Illustrative examples of fused ring heteroaryl groups include, but are not limited to:

- Benzofuran (benzofuranyl)
- Benzothiophene (benzothiophenyl)
- Indole (indolyl)
- Benzimidazole (benzimidazolyl)
- Indazole (indazolyl)
- Benzotriazole (benzotriazolyl)
- Pyrrolo[2,3-b]pyridine (pyrrolo[2,3-b]pyridinyl)
- Pyrrolo[2,3-c]pyridine (pyrrolo[2,3-c]pyridinyl)
- Pyrrolo[3,2-c]pyridine (pyrrolo[3,2-c]pyridinyl)
- Pyrrolo[3,2-b]pyridine (pyrrolo[3,2-b]pyridinyl)
- Pyrazolo[4,3-c]pyridine (pyrazolo[4,3-c]pyridinyl)
- Pyrazolo[4,3-b]pyridine (pyrazolo[4,3-b]pyridinyl)
- Pyrazolo[1,5-a]pyridine (pyrazolo[1,5-a]pyridinyl)
- Pyrazolo[1,2-b]pyridazine (pyrazolo[1,2-b]pyridazinyl)
- Pyrazolo[1,2-c]pyrimidine (pyrazolo[1,2-c]pyrimidinyl)
- Pyrazolo[4,3-d]pyridine (pyrazolo[4,3-d]pyridinyl)
- Pyrazolo[4,3-c]pyridine (pyrazolo[4,3-c]pyridinyl)
- Pyrazolo[3,4-c]pyridine (pyrazolo[3,4-c]pyridinyl)
- Pyrazolo[3,4-b]pyridine (pyrazolo[3,4-b]pyridinyl)
- Pyrazolo[1,5-a]pyridine (pyrazolo[1,5-a]pyridinyl)
- Pyrazolo[1,2-b]pyridazine (pyrazolo[1,2-b]pyridazinyl)
- Pyrazolo[1,2-c]pyrimidine (pyrazolo[1,2-c]pyrimidinyl)
- Pyrazolo[4,3-d]pyridine (pyrazolo[4,3-d]pyridinyl)
- Pyrazolo[4,3-c]pyridine (pyrazolo[4,3-c]pyridinyl)
- Pyrazolo[3,4-c]pyridine (pyrazolo[3,4-c]pyridinyl)
- Pyrazolo[3,4-b]pyridine (pyrazolo[3,4-b]pyridinyl)
- Pyrazolo[1,5-a]pyridine (pyrazolo[1,5-a]pyridinyl)
- Pyrazolo[1,2-b]pyridazine (pyrazolo[1,2-b]pyridazinyl)
- Pyrazolo[1,2-c]pyrimidine (pyrazolo[1,2-c]pyrimidinyl)
An "arylalkyl" group refers to an aryl group as described herein which is linked to the base molecule through an alkylene or similar linker. Arylalkyl groups are described by the total number of carbon atoms in the ring and linker. Thus a benzyl group is a C\textsubscript{7-5} arylalkyl group and a phenylethyl is a C\textsubscript{8}-arylalkyl. Typically, arylalkyl groups contain 7-16 carbon atoms ("C\textsubscript{7-C16} arylalkyl"), wherein the aryl portion contains 6-12 carbon atoms and the alkylene portion contains 1-4 carbon atoms. Such groups may also be represented as -C\textsubscript{1-4}alkylene-C\textsubscript{6-C12} aryl.

"Heteroarylalkyl" refers to a heteroaryl group as described above that is attached to the base molecule through an alkylene linker, and differs from "arylalkyl" in that at
least one ring atom of the aromatic moiety is a heteroatom selected from N, O and S. Heteroarylalkyl groups are sometimes described herein according to the total number of non-hydrogen atoms (i.e., C, N, S and 0 atoms) in the ring and linker combined, excluding substituent groups. Thus, for example, pyridinylmethyl may be referred to as a "C₇"-heteroarylalkyl. Typically, unsubstituted heteroarylalkyl groups contain 6-20 non-hydrogen atoms (including C, N, S and 0 atoms), wherein the heteroaryl portion typically contains 5-12 atoms and the alkylene portion typically contains 1-4 carbon atoms. Such groups may also be represented as -CrC₄ alkylene-5-12 membered heteroaryl.

Similarly, "arylalkoxy" and "heteroarylalkoxy" refer to aryl and heteroaryl groups, attached to the base molecule through a heteroalkylene linker (i.e., -O-alkylene-), wherein the groups are described according to the total number of non-hydrogen atoms (i.e., C, N, S and 0 atoms) in the ring and linker combined. Thus, -0-CH₂-phenyl and -0-CH₂-pyridinyl groups would be referred to as C₈-arylalkoxy and C₈-heteroarylalkoxy groups, respectively.

Where an arylalkyl, arylalkoxy, heteroarylalkyl or heteroarylalkoxy group is described as optionally substituted, the substituents may be on either the divalent linker portion or on the aryl or heteroaryl portion of the group. The substituents optionally present on the alkylene or heteroalkylene portion are the same as those described above for alkyl or alkoxy groups generally, while the substituents optionally present on the aryl or heteroaryl portion are the same as those described above for aryl or heteroaryl groups generally.

"Hydroxy" refers to an -OH group.

"Acyloxy" refers to a monovalent group -OC(O)alkyl, wherein the alkyl portion has the specified number of carbon atoms (typically C₁-C₈, preferably C₁-C₆ or C₁-C₄) and may be optionally substituted by groups suitable for alkyl. Thus, C₁-C₄ acyloxy includes an -OC(O)C₁-C₄ alkyl substituent, e.g., -OC(O)CH₃.

"Acylamino" refers to a monovalent group, -NHC(O)alkyl or -NRC(O)alkyl, wherein the alkyl portion has the specified number of carbon atoms (typically C₁-C₈, preferably C₁-C₆ or C₁-C₄) and may be optionally substituted by groups suitable for alkyl. Thus, C₁-C₄ acylamino includes an -NHC(O)C₁-C₄ alkyl substituent, e.g., -NHC(O)CH₃.
"Aryloxy" or "heteroaryloxy" refer to optionally substituted \(-O-\)aryl or \(-O-\)heteroaryl, in each case where aryl and heteroaryl are as further defined herein.

"Arylamino" or "heteroarylamino" refer to optionally substituted \(-NH-\)aryl, \(-NR-\)aryl, \(-NH\) -heteroaryl or \(-NR\)-heteroaryl, in each case where aryl and heteroaryl are as further defined herein and \(R\) represents a substituent suitable for an amine, e.g., an alkyi, acyl, carbamoyl or sulfonyl group, or the like.

"Cyano" refers to a \(-\text{C}≡\text{N}\) group.

"Unsubstituted amino" refers to a group \(-\text{NH}_2\). Where the amino is described as substituted or optionally substituted, the term includes groups of the form \(-\text{NR}^x\text{R}^y\), where each or \(\text{R}^x\) and \(\text{R}^y\) is independently \(\text{H}\), alkyi, alkenyl, alkynyl, cycloalkyl, heterocyclyl, acyl, thioacetyl, aryl, heteroaryl, cycloalkylalkyl, arylalkyl or heteroarylalkyl, in each case having the specified number of atoms and optionally substituted as described herein. For example, "alkylamino" refers to a group \(-\text{NR}^x\text{R}^y\), wherein one of \(\text{R}^x\) and \(\text{R}^y\) is an alkyi moiety and the other is \(\text{H}\), and "dialkylamino" refers to \(-\text{NR}^x\text{R}^y\) wherein both of \(\text{R}^x\) and \(\text{R}^y\) are alkyi moieties, where the alkyi moieties having the specified number of carbon atoms (e.g., \(-\text{NH} -\text{C}i -\text{C}_4\) alkyi or \(-\text{N}(\text{C}i -\text{C}_4\) alkyl)_2). Typically, alkyi substituents on amines contain 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, or more preferably 1 to 4 carbon atoms. The term also includes forms wherein \(\text{R}^x\) and \(\text{R}^y\) are taken together with the \(\text{N}\) atom to which they are attached to form a 3-12 membered heterocyclyl or 5-12 membered heteroaryl ring, each of which may itself be optionally substituted as described herein for heterocyclyl or heteroaryl rings, and which may contain 1 to 3 additional heteroatoms selected from \(\text{N}, 0\) and \(\text{S}\) as ring members, provided that such rings do not contain two contiguous oxygen atoms.

"Halogen" or "halo" refers to fluoro, chloro, bromo and iodo (\(\text{F}, \text{Cl}, \text{Br}, \text{I}\)). Preferably, halo refers to fluoro or chloro (\(\text{F}\) or \(\text{Cl}\)).

"Heteroform" is sometimes used herein to refer to a derivative of a group such as, e.g., an alkyi, aryl, or acyl, wherein at least one carbon atom of the designated carbocyclic group has been replaced by a heteroatom selected from \(\text{N}, 0\) and \(\text{S}\). Thus the heteroforms of alkyi, alkenyl, alkynyl, acyl, aryl, and arylalkyl are heteroalkyl, heteroalkenyl, heteroalkynyl, heteroacyl, heteroaryl, and heteroarylalkyl, respectively. It
is understood that no more than two N, O or S atoms are ordinarily connected sequentially, except where an oxo group is attached to N or S to form a nitro or sulfanyl group.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and the description includes instances where the event or circumstance occurs and instances in which it does not.

The terms "optionally substituted" and "substituted or unsubstituted" may be used interchangeably to indicate that the particular group being described may have no non-hydrogen substituents (i.e., unsubstituted), or the group may have one or more non-hydrogen substituents (i.e., substituted). If not otherwise specified, the total number of substituents that may be present is equal to the number of H atoms present on the unsubstituted form of the group being described, to the extent that such substitution makes chemical sense. Where an optional substituent is attached via a double bond, such as an oxo (=O) substituent, the group occupies two available valences, so the total number of other substituents that may be included is reduced by two. In the case where optional substituents are selected independently from a list of alternatives, the selected groups may be the same or different.

In one aspect, the invention provides a compound of formula (I):

\[
\begin{align*}
Z & \quad HN-\quad \text{X} \\
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4
\end{align*}
\]

(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R\(^1\) is Cl or Br;

R\(^2\) is selected from the group consisting of H, CI-C\(_6\) alkoxy, -OR\(^5\), -NR\(^6\)R\(^7\), 3-12 membered heterocyclyl and 5-12 membered heteroaryl, where said CI-C\(_6\) alkoxy is optionally substituted by one or more R\(^A\), and said 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more R\(^B\);

R\(^3\) is H or CH\(_3\);

R\(^4\) is H, Cl, Br, F or CH\(_3\);
$R^5$ is C$_3$-C$_8$ cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl, where each said C$_3$-C$_8$ cycloalkyl, 3-12 membered heterocyclyl or 5-12 membered heteroaryl is optionally substituted by one or more $R^B$;

$R^6$ is H, C$_1$-C$_6$ alkyl or C$_7$-C$_{12}$ arylalkyl;

5

$R^7$ is H, C$_1$-C$_6$ alkyl, C$_7$-C$_{12}$ arylalkyl or C(0)R$^6$;

$R^8$ is C$_1$-C$_6$ alkyl or NR$^9$R$^{10}$;

$R^9$ and $R^{10}$ are independently H or CH$_3$;

10 each $R^A$ is independently OH, F, CN or CrC$_4$ alkoxy;

each $R^B$ is independently OH, F, C$_i$-C$_4$ alkyl, C$_i$-C$_4$ fluoroalkyl, C$_i$-C$_4$ alkoxy, C$_1$-C$_4$ fluoroalkoxy, C$_1$-C$_4$ hydroxyalkyl, C$_1$-C$_4$ aminoalkyl, C(0)R$^{11}$, SO$_2$R$^{11}$, SO$_2$NR$^{12}$R$^{13}$ or 3-12 membered heterocyclyl, where said 3-12 membered heterocyclyl is optionally substituted by one or more $R^D$;

15 each $R^{11}$ is independently C$_1$-C$_6$ alkyl, C$_3$-C$_8$ cycloalkyl or 3-12 membered heterocyclyl, where said C$_1$-C$_6$ alkyl is optionally substituted by one or more $R^C$, and said C$_3$-C$_8$ cycloalkyl or 3-12 membered heterocyclyl is optionally substituted by one or more $R^D$;

each $R^C$ is independently OH, F, CN or C$_i$-C$_4$ alkoxy;

each $R^D$ is independently OH, C$_1$-C$_4$ alkyl, C$_1$-C$_4$ fluoroalkyl, C$_1$-C$_4$ hydroxyalkyl or C$_i$-C$_4$ aminoalkyl;

10 each $R^{12}$ and $R^{13}$ is independently H or CrC$_4$ alkyl; and

20 X and Z are independently CrC$_4$ alkyl, CrC$_4$ fluoroalkyl, CrC$_4$ alkoxy or CrC$_4$ fluoroalkoxy.

In compounds of Formula (I), $R^1$ is Cl or Br. In some such embodiments, $R^1$ is Cl or Br. In other such embodiments, $R^1$ is Cl.

25 In compounds of Formula (I), $R^4$ is H, Cl, Br, F or CH$_3$. In certain embodiments, $R^4$ is Cl or Br. In some such embodiments, $R^4$ is Cl. In other such embodiments, $R^4$ is Cl. In further embodiments, $R^4$ is H. In other embodiments, $R^4$ is CH$_3$. In additional embodiments, $R^4$ is F.

In compounds of Formula (I), $R^3$ is H or CH$_3$. In some such embodiments, $R^3$ is CH$_3$. In other such embodiments, $R^3$ is H.
In compounds of Formula (I), X and Z are independently Ci-C\(_4\) alkyl, Ci-C\(_4\) fluoroalkyl, Ci-C\(_4\) alkoxy or Ci-C\(_4\) fluoroalkoxy. In some embodiments, Z is Ci-C\(_4\) alkyl, for example CH\(_3\) or C\(_2\)H\(_5\) (i.e., methyl or ethyl). In some embodiments, X is Ci-C\(_4\) alkyl, Ci-C\(_4\) fluoroalkyl, Ci-C\(_4\) alkoxy. In specific embodiments, X is CH\(_3\), OCH\(_3\) or OCHF\(_2\) (i.e., methyl, methoxy or difluoromethoxy). In further embodiments, X is CH\(_3\), OCH\(_3\) or OCHF\(_2\); and Z is CH\(_3\).

In some embodiments of Formula (I), R\(^2\) is Ci-C\(_6\) alkyl optionally substituted by one or more R\(^A\), where each R\(^A\) is independently OH, F, CN or CrC\(_4\) alkoxy.

In other embodiments of Formula (I), R\(^2\) is -OR\(^5\), where R\(^5\) is C\(_3\)-C\(_8\) cycloalkyl, 3-12 membered heterocydyl or 5-12 membered heteroaryl, each optionally substituted by one or more R\(^B\).

In some embodiments, R\(^5\) is C\(_3\)-C\(_8\) cycloalkyl optionally substituted by one or more R\(^B\). In specific embodiments, R\(^5\) is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each optionally substituted one or more by R\(^B\).

In other embodiments, R\(^5\) is 3-12 membered heterocydyl optionally substituted by one or more R\(^B\). In specific embodiments, said 3-12 membered heterocydyl is selected from the group consisting of tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, pyrrolidinyl, piperidinyl and morpholinyl, each optionally substituted by one or more R\(^B\).

In still other such embodiments, R\(^5\) is 5-12 membered heteroaryl, where each said 5-12 membered heteroaryl is optionally substituted one or more by R\(^B\). In some such embodiments, R\(^5\) is a 5- or 6-membered heteroaryl. In specific embodiments, said 5- or 6-membered heteroaryl is selected from the group consisting of pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, and triazolyl groups, each optionally substituted by one or more R\(^B\).

In other embodiments of Formula (I), R\(^2\) is -NR\(^6\)R\(^7\), where R\(^6\) is H, Ci-C\(_6\) alkyl or C\(_7\)-C\(_12\) arylalkyl, and R\(^7\) is H, Ci-C\(_6\) alkyl, C\(_7\)-C\(_12\) arylalkyl or C(O)R\(^8\). In some embodiments when R\(^7\) is C(O)R\(^8\), R\(^8\) is C\(_1\)-C\(_6\) alkyl such that R\(^7\) comprises a carboxamide moiety. In other embodiments when R\(^7\) is C(O)R\(^8\), R\(^8\) is NR\(^9\)R\(^{10}\) and R\(^9\) and R\(^{10}\) are independently H or CH\(_3\), such that R\(^7\) comprises a urea moiety.

In yet other embodiments of Formula (I), R\(^2\) is 3-12 membered heterocydyl optionally substituted by one or more R\(^B\). In specific embodiments, said 3-12 membered heterocydyl is selected from the group consisting of tetrahydrofuranyl,
tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, pyrrolidinyl, piperidinyl and morpholinyl, each optionally substituted by one or more R^B.

In further embodiments of Formula (I), R^2 is 5-12 membered heteroaryl optionally substituted by one or more R^B. In some such embodiments, R^5 is a 5- or 6-membered heteroaryl. In specific embodiments, said 5- or 6-membered heteroaryl is selected from the group consisting of pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, and triazolyl groups, each optionally substituted by one or more R^B.

In each of the foregoing embodiments wherein a group is optionally substituted by one or more R^B, each R^B is independently OH, F, Ci-C_4 alkyl, Ci-C_4 fluoroalkyl, C_1-C_4 alkoxy, C_1-C_4 fluoroalkoxy, Ci-C_4 hydroxyalkyl, C_1-C_4 aminoalkyl, C(O)R^i, SO_2R^i, SO_2NR_1R_2R^3 or 3-12 membered heterocyclyl, where said 3-12 membered heterocyclyl is optionally substituted by one or more R^D.

When R^B is C(O)R^i or SO_2R^i, each R^i is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 3-12 membered heterocyclyl, where said C_1-C_6 alkyl is optionally substituted by one or more R^E, and said C_3-C_8 cycloalkyl or 3-12 membered heterocyclyl is optionally substituted by one or more R^D.

In such embodiments, each R^E is independently OH, F, CN or Ci-C_4 alkoxy, and each R^D is independently OH, Ci-C_4 alkyl, Ci-C_4 fluoroalkyl, Ci-C_4 hydroxyalkyl or CrC_4 aminoalkyl. When R^B is SO_2NR_1R_2R^3, each R^12 and R^13 is independently H or Ci-C_6 alkyl.

In another aspect, the invention provides a compound selected from the group consisting of:

(3R)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-[(3R)-tetrahydropyran-3-yloxy]-3,4-dihydroisoquinolin-1 (2H)-one;

(3S)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-[(3R)-tetrahydropyran-3-yloxy]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-7-(3,6-dihydro-2H-pyran-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1-[(2R)-2-hydroxypropanoyl]piperidin-4-yl]oxy)-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(1-{1-(2S)-2-hydroxypropanoyl}piperidin-4-yl)oxy]-3,4-dihydroisoquinolin-1 (2H)-one;
7-tert-butoxy-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-{[1-(2,3,4-tetrahydroisoquinolin-7-yl)]-L-threo-pentitol; 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[5-(hydroxymethyl)-3-methyl-2-oxazol-4-yl]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3-methyl-1,2-oxazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;
7-(benzylamino)-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3-methyl-1,2-oxazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4-chloro-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1 (2H)-one;
8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3R)-1-{[(2R)-2-hydroxy-2-methylpropanoyl]pyrrolidin-3-yl}oxy]-3,4-dihydroisoquinolin-1 (2H)-one;
1-{5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-oxy-1,2,3,4-tetrahydroisoquinolin-7-yl]-1,3-dimethylurea;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3S)-1-{[(2R)-2-hydroxy-2-methylpropanoyl]pyrrolidin-3-yl}oxy]-3,4-dihydroisoquinolin-1 (2H)-one;
3,6-anhydro-1,4-dideoxy-5-0-{5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-2-C-methyl-L-arabino-hexitol;

1,4-anhydro-3,6-dideoxy-2-0-{5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-5-C-methyl-L-arabino-hexitol;

7-amino-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methoxy]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-({1-[(2R)-2-hydroxybutanoyl]piperidin-4-yl}oxy)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-({1-[(1-hydroxycyclobutyl)carbonyl]piperidin-4-yl}oxy)-3,4-dihydroisoquinolin-1 (2H)-one;

8-chloro-7-[(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

7-[3-(aminomethyl)-5-methyl-1,2-oxazol-4-yl]-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one; and

5,8-dichloro-7-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

or a pharmaceutically acceptable salt thereof.

In a further aspect, the invention provides a compound selected from the group consisting of Compounds 33 to 44 according to Table 2, or a pharmaceutically acceptable salt thereof.

In certain preferred embodiments, the compounds of Formula (I) have two, three, four, or more than four of the following preferred features, to the extent they are not inconstant with each other:

1) \( R^1 \) is Cl;

2) \( R^4 \) is Cl or Br;
R₄ is CI; or
R₄ is H;
3) R₃ is H;
4) Z is CH₃ or C₂H₅;
5) X is CH₃, OCH₃ or OCHF₂;
6) R² is Cl-C₆ alkoxy optionally substituted by one or more R⁸;
R² is -OR⁵ and R⁵ is C₃-C₆ cycloalkyl optionally substituted by one or more R⁸;
R² is -OR⁵ and R⁵ is 3-12 membered heterocyclyl optionally substituted by
one or more R⁸;
R² is -OR⁵ and R⁵ is 5-12 membered heteroaryl optionally substituted by one
or more R⁸;
R² is -NR⁶R⁷;
R² is 3-12 membered heterocyclyl optionally substituted by one or more R⁸;
or
R² is 5-12 membered heteroaryl optionally substituted by one or more R⁸.

A "pharmaceutical composition" refers to a mixture of one or more of the
compounds described herein, or a pharmaceutically acceptable salt, solvate, hydrate or
prodrug thereof as an active ingredient, and at least one pharmaceutically acceptable
carrier or excipient. The purpose of a pharmaceutical composition is to facilitate
administration of a compound to a subject.

In another aspect the invention provides a pharmaceutical composition
comprising a compound of one of the formulae described herein, or a pharmaceutically
acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. In
some embodiments, the pharmaceutical composition comprises two or more
pharmaceutically acceptable carriers and/or excipients.

In some embodiments, the pharmaceutical composition further comprises at
least one additional an anti-cancer therapeutic agent or a palliative agent. In some
such embodiments, the at least one additional medicinal or pharmaceutical agent is an
anti-cancer agent as described below. In some such embodiments, the combination
provides an additive, greater than additive, or synergistic anti-cancer effect. In some
such embodiments, the one or more anti-cancer therapeutic agent is selected from the
group consisting of anti-tumor agents, anti-angiogenesis agents, signal transduction inhibitors and antiproliferative agents.

In one aspect, the invention provides a method for the treatment of abnormal cell growth in a subject comprising administering to the subject a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a subject comprising administering to the subject an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with an amount of an anti-tumor agent, which amounts are together effective in treating said abnormal cell growth. In some embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

In frequent embodiments of the methods provided herein, the abnormal cell growth is cancer. In some embodiments, the methods provided result in one or more of the following effects: (1) inhibiting cancer cell proliferation; (2) inhibiting cancer cell invasiveness; (3) inducing apoptosis of cancer cells; (4) inhibiting cancer cell metastasis; or (5) inhibiting angiogenesis.

In another aspect, the invention provides a method for the treatment of a disorder mediated by EZH2 in a subject comprising administering to the subject a compound of the invention, or a pharmaceutically acceptable salt thereof, in an amount that is effective for treating said disorder.

In preferred embodiments of the methods provided herein, the subject is a mammal, in particular a human.

Unless indicated otherwise, all references herein to the inventive compounds include references to salts, solvates, hydrates and complexes thereof, and to solvates, hydrates and complexes of salts thereof, including polymorphs, stereoisomers, and isotopically labeled versions thereof.

Compounds of the invention may exist in the form of pharmaceutically acceptable salts such as, e.g., acid addition salts and base addition salts of the compounds of one of the formulae provided herein. As used herein, the term "pharmaceutically acceptable salt" refers to those salts which retain the biological
effectiveness and properties of the parent compound. The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the formulae disclosed herein.

For example, the compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention can be prepared by treating the base compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Examples of salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, carbonate, chloride, caproate, caprylate, clavulanate, citrate, decanoate, dihydrochloride, dihydrogenphosphate, edetate, edislyate, estolate, esylate,
ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexyresorcinate, hydrabamine, hydrobromide, hydrochloride, γ-hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, maleate, maleate, malonate, mandelate, mesylate, metaphosphate, methane-sulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phenylacetates, phenylbutyrate, phenylpropionate, phthalate, phosphatidiphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

The compounds of the invention that include a basic moiety, such as an amino group, may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

Those compounds of the invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds herein. These salts may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. These salts can also be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide
together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of the compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to, those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds of the invention are known to one of skill in the art.

Salts of the present invention can be prepared according to methods known to those of skill in the art. A pharmaceutically acceptable salt of the inventive compounds can be readily prepared by mixing together solutions of the compound and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

It will be understood by those of skill in the art that the compounds of the invention in free base form having a basic functionality may be converted to the acid addition salts by treating with a stoichiometric excess of the appropriate acid. The acid addition salts of the compounds of the invention may be reconverted to the corresponding free base by treating with a stoichiometric excess of a suitable base, such as potassium carbonate or sodium hydroxide, typically in the presence of aqueous solvent, and at a temperature of between about 0° C. and 100° C. The free base form may be isolated by conventional means, such as extraction with an organic solvent. In addition, acid addition salts of the compounds of the invention may be interchanged by

- 34 -
taking advantage of differential solubilities of the salts, volatilities or acidities of the acids, or by treating with the appropriately loaded ion exchange resin. For example, the interchange may be affected by the reaction of a salt of the compounds of the invention with a slight stoichiometric excess of an acid of a lower pK than the acid component of the starting salt. This conversion is typically carried out at a temperature between about 0°C and the boiling point of the solvent being used as the medium for the procedure. Similar exchanges are possible with base addition salts, typically via the intermediacy of the free base form.

The compounds of the invention may exist in both unsolvated and solvated forms. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when the solvent is water. Pharmaceutically acceptable solvates in accordance with the invention include hydrates and solvates wherein the solvent of crystallization may be isotopically substituted, e.g. D$_2$O, D$_6$-acetone, D$_6$-DMSO.

Also included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975), the disclosure of which is incorporated herein by reference in its entirety.

The invention also relates to prodrugs of the compounds of the formulae provided herein. Thus, certain derivatives of compounds of the invention which may have little or no pharmacological activity themselves can, when administered to a patient, be converted into the inventive compounds, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS
Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association), the disclosures of which are incorporated herein by reference in their entirety.

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the inventive compounds with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985), the disclosure of which is incorporated herein by reference in its entirety.

Some non-limiting examples of prodrugs in accordance with the invention include:

(i) where the compound contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (CrC 2)alkyl;

(ii) where the compound contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (Cr-C6)alkanoyloxymethyl; and

(iii) where the compound contains a primary or secondary amino functionality (-NH 2 or -NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with a suitably metabolically labile group, such as an amide, carbamate, urea, phosphonate, sulfonate, etc..

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Finally, certain inventive compounds may themselves act as prodrugs of other of the inventive compounds.

Also included within the scope of the invention are metabolites of compounds of the formulae described herein, i.e., compounds formed in vivo upon administration of the drug.

The compounds of the formulae provided herein may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the invention may be depicted herein using a solid line (-----), a solid wedge (—————), or a dotted wedge (··········). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g. specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to
asymmetric carbon atoms is meant to indicate that only the stereoisomer shown is meant to be included. It is possible that compounds of the invention may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it is intended that the compounds of the invention can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of the invention and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

Compounds of the invention that have chiral centers may exist as stereoisomers, such as racemates, enantiomers, or diastereomers.

Stereoisomers of the compounds of the formulae herein can include cis and trans isomers, optical isomers such as (R) and (S) enantiomers, diastereomers, geometric isomers, rotational isomers, atropisomers, conformational isomers, and tautomers of the compounds of the invention, including compounds exhibiting more than one type of isomerism; and mixtures thereof (such as racemates and diastereomeric pairs). Also included are acid addition or base addition salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-arginine.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

The compounds of the invention may exhibit the phenomena of tautomerism and structural isomerism. For example, the compounds may exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of compounds of the invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of the formulae provided.
In addition, some of the compounds of the invention may form atropisomers (e.g., substituted biaryls). Atropisomers are conformational stereoisomers which occur when rotation about a single bond in the molecule is prevented, or greatly slowed, as a result of steric interactions with other parts of the molecule and the substituents at both ends of the single bond are unsymmetrical. The interconversion of atropisomers is slow enough to allow separation and isolation under predetermined conditions. The energy barrier to thermal racemization may be determined by the steric hindrance to free rotation of one or more bonds forming a chiral axis.

Where a compound of the invention contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to one skilled in the art.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art; see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994), the disclosure of which is incorporated herein by reference in its entirety.
"Enantiomerically pure" as used herein, describes a compound that is present as a single enantiomer and which is described in terms of enantiomeric excess (e.e.). Preferably, wherein the compound is present as an enantiomer, the enantiomer is present at an enantiomeric excess of greater than or equal to about 80%, more preferably, at an enantiomeric excess of greater than or equal to about 90%, more preferably still, at an enantiomeric excess of greater than or equal to about 95%, more preferably still, at an enantiomeric excess of greater than or equal to about 98%, most preferably, at an enantiomeric excess of greater than or equal to about 99%. Similarly, "diastereomERICALLY pure" as used herein, describes a compound that is present as a diastereomer and which is described in terms of diastereomeric excess (d.e.). Preferably, wherein the compound is present as a diastereomer, the diastereomer is present at an diastereomeric excess of greater than or equal to about 80%, more preferably, at an diastereomeric excess of greater than or equal to about 90%, more preferably still, at an diastereomeric excess of greater than or equal to about 95%, more preferably still, at an diastereomeric excess of greater than or equal to about 98%, most preferably, at an diastereomeric excess of greater than or equal to about 99%.

The present invention also includes isotopically-labeled compounds, which are identical to those recited in one of the formulae provided, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

Examples of isotopes that may be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to, $^2$H, $^3$H, $^{13}$C, $^{14}$C, $^{15}$N, $^{16}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, and $^{36}$Cl. Certain isotopically-labeled compounds of the invention, for example those into which radioactive isotopes such as $^3$H and $^{14}$C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., $^3$H, and carbon-14, i.e., $^{14}$C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., $^2$H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased
in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labeled compounds of the invention may generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products, or mixtures thereof. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

**Therapeutic Methods and Uses**

The invention further provides therapeutic methods and uses comprising administering the compounds of the invention, or pharmaceutically acceptable salts thereof, alone or in combination with other therapeutic agents or palliative agents.

In one aspect, the invention provides a method for the treatment of abnormal cell growth in a subject comprising administering to the subject a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a subject comprising administering to the subject an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with an amount of an anti-tumor agent, which amounts are together effective in treating said abnormal cell growth. In some such embodiments, the anti-tumor agent is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

Compounds of the invention include compounds of any of the formulae described herein, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of abnormal cell growth in a subject comprising administering to the subject an amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, that is effective in treating abnormal cell growth.
In still another aspect, the invention provides a method of inhibiting cancer cell proliferation in a subject, comprising administering to the subject a compound of the invention, or pharmaceutically acceptable salt thereof, in an amount effective to inhibit cell proliferation.

In another aspect, the invention provides a method of inhibiting cancer cell invasiveness in a subject, comprising administering to the subject a compound of the invention, or pharmaceutically acceptable salt thereof, in an amount effective to inhibit cell invasiveness.

In another aspect, the invention provides a method of inducing apoptosis in cancer cells in a subject, comprising administering to the subject a compound of the invention, or pharmaceutically acceptable salt thereof, in an amount effective to induce apoptosis.

In a further aspect, the invention provides a method of inducing apoptosis in a subject, comprising administering to the subject a therapeutically effective amount of a compound of one of the formulae described herein, or pharmaceutically acceptable salt thereof.

In frequent embodiments of the methods provided herein, the abnormal cell growth is cancer, wherein said cancer is selected from the group consisting of basal cell cancer, medulloblastoma cancer, liver cancer, rhabdomyosarcoma, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.

In some embodiments, the compounds of the invention are selective for the mutant form of the EZH2, such that trimethylation of H3K27, which is associated with
certain cancers, is inhibited. The methods and uses provided herein can be used
to treat cancers including follicular lymphoma and diffuse large B-cell lymphoma (DLBCL).

The compounds of the invention are useful for the treatment of cancers,
including, e.g., tumors such as brain, breast, cervical, colorectal, endometrial,
esophageal, gastric/stomach, head and neck, hepatocellular, laryngeal, lung, oral,
ovidian, prostate, testicular and thyroid carcinomas and sarcomas.

The term "therapeutically effective amount" as used herein refers to that amount
of a compound being administered which will relieve to some extent one or more of the
symptoms of the disorder being treated. In reference to the treatment of cancer, a
therapeutically effective amount refers to that amount which has the effect of (1)
reducing the size of the tumor, (2) inhibiting (that is, slowing to some extent, preferably
stopping) tumor metastasis, (3) inhibiting to some extent (that is, slowing to some
extent, preferably stopping) tumor growth or tumor invasiveness, and/or (4) relieving to
some extent (or, preferably, eliminating) one or more signs or symptoms associated
with the cancer.

As used herein, "subject" refers to a human or animal subject. In certain
preferred embodiments, the subject is a human.

The term "treating", as used herein, unless otherwise indicated, means
reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition
to which such term applies, or one or more symptoms of such disorder or condition.
The term "treatment", as used herein, unless otherwise indicated, refers to the act of
treating as "treating" is defined immediately above. The term "treating" also includes
adjuvant and neo-adjuvant treatment of a subject.

The terms "abnormal cell growth" and "hyperproliferative disorder" are used
interchangeably in this application.

"Abnormal cell growth", as used herein, unless otherwise indicated, refers to cell
growth that is independent of normal regulatory mechanisms (e.g., loss of contact
inhibition). Abnormal cell growth may be benign (not cancerous), or malignant
(cancerous). This includes the abnormal growth of: (1) tumor cells (tumors) that show
increased expression of EZH2; (2) benign and malignant cells of other proliferative
diseases in which EZH2 is over-expressed; (3) tumors that proliferate by aberrant EZH2
activation; and (4) benign and malignant cells of other proliferative diseases in which
aberrant EZH2 activation occurs.
As used herein "cancer" refers to any malignant and/or invasive growth or tumor caused by abnormal cell growth. As used herein "cancer" refers to solid tumors named for the type of cells that form them, cancer of blood, bone marrow, or the lymphatic system. Examples of solid tumors include but not limited to sarcomas and carcinomas. Examples of cancers of the blood include but not limited to leukemias, lymphomas and myeloma. The term "cancer" includes but is not limited to a primary cancer that originates at a specific site in the body, a metastatic cancer that has spread from the place in which it started to other parts of the body, a recurrence from the original primary cancer after remission, and a second primary cancer that is a new primary cancer in a person with a history of previous cancer of different type from latter one. The compounds of the invention inhibit EZH2, and thus are all adapted to therapeutic use as antiproliferative agents (e.g., cancer) or antitumor agent (e.g., effect against solid tumors) in mammals, particularly in humans. In particular, the compounds of the invention are useful in the prevention and treatment of a variety of human hyperproliferative disorders including both malignant and benign abnormal cell growth.

The compounds, compositions and methods provided herein are useful for the treatment of cancers including but not limited to cancers of the:

- circulatory system, for example, heart (sarcoma [angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma], myxoma, rhabdomyoma, fibroma, lipoma and teratoma), mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue;
- respiratory tract, for example, nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung such as small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;
- gastrointestinal system, for example, esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), gastric, pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi’s sarcoma, leiomyoma, hemangioma, lipoma,
neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

genitourinary tract, for example, kidney (adenocarcinoma, Wilm’s tumor [nephroblastoma], lymphoma, leukemia), bladder and/or urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (semiroma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

liver, for example, hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioendothelioma, pancreatic endocrine tumors (such as pheochromocytoma, insulinoma, vasoactive intestinal peptide tumor, islet cell tumor and glucagonoma);

bone, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing’s sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor of bone (chondroma, osteochondromyxofibroma, osteoid osteoma and giant cell tumors);

nervous system, for example, neoplasms of the central nervous system (CNS), primary CNS lymphoma, skull cancer (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain cancer (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma);

reproductive system, for example, gynecological, uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma) and other sites associated with female genital organs; placenta, penis, prostate, testis, and other sites associated with male genital organs;
hematologic system, for example, blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; oral cavity, for example, lip, tongue, gum, floor of mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx; skin, for example, malignant melanoma, cutaneous melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids; adrenal glands: neuroblastoma; and other tissues including connective and soft tissue, retroperitoneum and peritoneum, eye, intraocular melanoma, and adnexa, breast, head or/and neck, anal region, thyroid, parathyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

More specifically, examples of "cancer" when used herein in connection with the present invention include cancer selected from lung cancer (NSCLC and SCLC), cancer of the head or neck, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, breast cancer, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, non-Hodgkin's lymphoma, spinal axis tumors, or a combination of one or more of the foregoing cancers.

Still more specifically, examples of "cancer" when used herein in connection with the present invention include cancer selected from lung cancer (NSCLC and SCLC), breast cancer, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, or a combination of one or more of the foregoing cancers.

In one embodiment of the present invention the non-cancerous conditions include such hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) and benign hyperplasia of the prostate (e.g., BPH).
In another aspect, the invention provides a method for inhibiting cell proliferation, comprising contacting cells with a compound of the invention or a pharmaceutically acceptable salt thereof in an amount effective to inhibit proliferation of the cells.

In another aspect, the invention provides methods for inducing cell apoptosis, comprising contacting cells with a compound described herein in an amount effective to induce apoptosis of the cells.

"Contacting" refers to bringing a compound or pharmaceutically acceptable salt of the invention and a cell expressing EZH2 together in such a manner that the compound can affect the activity of EZH2, either directly or indirectly. Contacting can be accomplished in vitro (i.e., in an artificial environment such as, e.g., without limitation, in a test tube or culture medium) or in vivo (i.e., within a living organism such as, without limitation, a mouse, rat or rabbit.)

In some embodiments, the cells are in a cell line, such as a cancer cell line. In other embodiments, the cells are in a tissue or tumor, and the tissue or tumor may be in a subject, including a human.

**Dosage Forms and Regimens**

Administration of the compounds of the invention may be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

Dosage regimens may be adjusted to provide the optimum desired response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the chemotherapeutic agent and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations
inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

Thus, the skilled artisan would appreciate, based upon the disclosure provided herein, that the dose and dosing regimen is adjusted in accordance with methods well-known in the therapeutic arts. That is, the maximum tolerable dose can be readily established, and the effective amount providing a detectable therapeutic benefit to a patient may also be determined, as can the temporal requirements for administering each agent to provide a detectable therapeutic benefit to the patient. Accordingly, while certain dose and administration regimens are exemplified herein, these examples in no way limit the dose and administration regimen that may be provided to a patient in practicing the present invention.

It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated, and may include single or multiple doses. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. For example, doses may be adjusted based on pharmacokinetic or pharmacodynamic parameters, which may include clinical effects such as toxic effects and/or laboratory values. Thus, the present invention encompasses intra-patient dose-escalation as determined by the skilled artisan. Determining appropriate dosages and regimens for administration of the chemotherapeutic agent are well-known in the relevant art and would be understood to be encompassed by the skilled artisan once provided the teachings disclosed herein.

The amount of the compound of the invention administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to about 7 g/day, preferably about 0.1 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that
such larger doses are first divided into several small doses for administration throughout the day.

Formulations and Routes of Administration

As used herein, a "pharmaceutically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

The pharmaceutical acceptable carrier may comprise any conventional pharmaceutical carrier or excipient. The choice of carrier and/or excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents (such as hydrates and solvates). The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Non-limiting examples of materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.
Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms may be suitably buffered, if desired.

The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages.

Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation can be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995), the disclosure of which is incorporated herein by reference in its entirety.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be used as fillers in soft or hard capsules and typically include a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11(6), 981-986 by Liang and Chen (2001), the disclosure of which is incorporated herein by reference in its entirety.

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium...
carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are typically in amounts of from 0.2 wt% to 5 wt% of the tablet, and glidants typically from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally are present in amounts from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other conventional ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80 wt% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may include one or more layers and may be coated or uncoated; or encapsulated.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles can be found in Verma et al, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298. The disclosures of these references are incorporated herein by reference in their entireties.

Parenteral Administration

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous.

Suitable devices for parenteral administration include needle (including micro needle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active
compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated; see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and micro needle or needle-free (e.g. Powderject™, Bioject™, etc.) injection. The disclosures of these references are incorporated herein by reference in their entireties.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may include a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 microns).
This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µL to 100µL. A typical formulation includes a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing a desired mount of the compound of the invention. The overall daily dose may be administered in a single dose or, more usually, as divided doses throughout the day.

Compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.
Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

Other Technologies

Compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in PCT Publication Nos. WO 91/11172, WO 94/02518 and WO 98/55148, the disclosures of which are incorporated herein by reference in their entireties.
Dosage

The amount of the active compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is typically in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 0.01 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.07 to about 7000 mg/day, preferably about 0.7 to about 2500 mg/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be used without causing any harmful side effect, with such larger doses typically divided into several smaller doses for administration throughout the day.

Kit-of-Parts

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention includes two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically includes directions for administration and may be provided with a memory aid.

Combination Therapy

As used herein, the term "combination therapy" refers to the administration of a compound of the invention together with an at least one additional pharmaceutical or medicinal agent (e.g., an anti-cancer agent), either sequentially or simultaneously.

As noted above, the compounds of the invention may be used in combination with one or more additional anti-cancer agents which are described below. When a
combination therapy is used, the one or more additional anti-cancer agents may be administered sequentially or simultaneously with the compound of the invention. In one embodiment, the additional anti-cancer agent is administered to a mammal (e.g., a human) prior to administration of the compound of the invention. In another embodiment, the additional anti-cancer agent is administered to the mammal after administration of the compound of the invention. In another embodiment, the additional anti-cancer agent is administered to the mammal (e.g., a human) simultaneously with the administration of the compound of the invention.

The invention also relates to a pharmaceutical composition for the treatment of abnormal cell growth in a mammal, including a human, which comprises an amount of a compound of the invention, as defined above (including hydrates, solvates and polymorphs of said compound or pharmaceutically acceptable salts thereof), in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of anti-angiogenesis agents and signal transduction inhibitors and a pharmaceutically acceptable carrier, wherein the amounts of the active agent and the combination anti-cancer agents when taken as a whole is therapeutically effective for treating said abnormal cell growth.

In one embodiment of the present invention the anti-cancer agent used in conjunction with a compound of the invention and pharmaceutical compositions described herein is an anti-angiogenesis agent (e.g., an agent that stops tumors from developing new blood vessels). Examples of anti-angiogenesis agents include for example VEGF inhibitors, VEGFR inhibitors, TIE-2 inhibitors, PDGFR inhibitors, angiopoietin inhibitors, PKOβ inhibitors, COX-2 (cyclooxygenase II) inhibitors, integrins (alpha-v/beta-3), MMP-2 (matrix-metalloprotiensase 2) inhibitors, and MMP-9 (matrix-metalloprotiensinase 9) inhibitors.

Preferred anti-angiogenesis agents include sunitinit (Sutent™), bevacizumab (Avastin™), axitinib (AG 13736), SU 14813 (Pfizer), and AG 13958 (Pfizer).

Additional anti-angiogenesis agents include vatalanib (CGP 79787), Sorafenib (Nexavar™), pegaptanib octasodium (Macugen™), vandetanib (Zactima™), PF-0337210 (Pfizer), SU 14843 (Pfizer), AZD 2171 (AstraZeneca), ranibizumab (Lucentis™), Neovastat™ (AE 941), tetrathiomolybdata (Coplexa™), AMG 706 (Amgen), VEGF Trap (AVE 0005), CEP 7055 (Sanofi-Aventis), XL 880 (Exelixis), telatinib (BAY 57-9352), and CP-868,596 (Pfizer).
Other anti-angiogenesis agents include enzastaurin (LY 317615), midostaurin (CGP 41251), perifosine (KRX 0401), teprenone (Selbex™) and UCN 01 (Kyowa Hakko).

Other examples of anti-angiogenesis agents which can be used in conjunction with a compound of the invention and pharmaceutical compositions described herein include celecoxib (Celebrex™), parecoxib (Dynastat™), deracoxib (SC 59046), lumaracoxib (Preige™), valdecoxib (Bextra™), rofecoxib (Vioxx™), iguratimod (Careram™), IP 751 (Invedus), SC-58125 (Pharmacia) and etoricoxib (Arcoxia™).

Other anti-angiogenesis agents include exisulind (Aptosyn™), salsalate (Amigesic™), diflunisal (Dolobid™), ibuprofen (Motrin™), ketoprofen (Orudis™), nabumetone (Relafen™), piroxicam (Feldene™), naproxen (Aleve™, Naprosyn™), diclofenac (Voltaren™), indomethacin (Indocin™), sulindac (Clinoril™), tolmelan (Tolectin™), etodolac (Lodine™), ketorolac (Toradol™), and oxaprozin (Daypro™).

Other anti-angiogenesis agents include ABT 510 (Abbott), apratastat (TMI 005), AZD 8955 (AstraZeneca), incyclinide (Metastat™), and PCK 3145 (Procyon).

Other anti-angiogenesis agents include acitretin (Neotigason™), plitidepsin (aplidine™), cilenstide (EMD 121974), combretastatin A4 (CA4P), fenretinide (4 HPR), halofuginone (Tempostatin™), Panzem™ (2-methoxyestradiol), PF-03446962 (Pfizer), rebimastat (BMS 275291), catumaxomab (Removab™), lenalidomide (Revlimid™), squalamine (EVIZON™), thalidomide (Thalomid™), Ukrain™ (NSC 631570), Vitaxin™ (MEDI 522), and zoledronic acid (Zometa™).

In another embodiment the anti-cancer agent is a so-called signal transduction inhibitor (e.g., inhibiting the means by which regulatory molecules that govern the fundamental processes of cell growth, differentiation, and survival communicated within the cell). Signal transduction inhibitors include small molecules, antibodies, and antisense molecules. Signal transduction inhibitors include for example kinase inhibitors (e.g., tyrosine kinase inhibitors or serine/threonine kinase inhibitors) and cell cycle inhibitors. More specifically signal transduction inhibitors include, for example, farnesyl protein transferase inhibitors, EGF inhibitor, ErbB-1 (EGFR), ErbB-2, pan erb, IGF1 R inhibitors, MEK, c-Kit inhibitors, FLT-3 inhibitors, K-Ras inhibitors, PI3 kinase inhibitors, JAK inhibitors, STAT inhibitors, Raf kinase inhibitors, Akt inhibitors, mTOR inhibitor, P70S6 kinase inhibitors, inhibitors of the WNT pathway and so-called multi-targeted kinase inhibitors.
Preferred signal transduction inhibitors include gefitinib (Iressa™), cetuximab (Erbitux™), erlotinib (Tarceva™), trastuzumab (Herceptin™), sunitinib (Sutent™), imatinib (Gleevec™), and PD325901 (Pfizer).

Additional examples of signal transduction inhibitors which may be used in conjunction with a compound of the invention and pharmaceutical compositions described herein include BMS 214662 (Bristol-Myers Squibb), lonafarnib (Sarasar™), pelitrexol (AG 2037), matuzumab (EMD 7200), nimotuzumab (TheraCIM h-R3™), panitumumab (Vectibix™), Vandetanib (Zactima™), pazopanib (SB 786034), ALT 110 (Alteris Therapeutics), BIBW 2992 (Boehringer Ingelheim), and Cervene™ (TP 38).

Other examples of signal transduction inhibitors which may be used in conjunction with a compound of the invention and pharmaceutical compositions described herein include PF-2341066 (Pfizer), PF-299804 (Pfizer), canertinib (CI 1033), pertuzumab (Omnitarg™), Lapatinib (Tycerb™), pelitinib (EKB 569), miltefosine (Miltefosin™), BMS 599626 (Bristol-Myers Squibb), Lapuleucel-T (Neuvengen™), NeuVax™ (E75 cancer vaccine), Osidem™ (IDM 1), mubritinib (TAK-165), CP-724,714 (Pfizer), panitumumab (Vectibix™), lapatinib (Tycerb™), PF-299804 (Pfizer), pelitinib (EKB 569), and pertuzumab (Omnitarg™).

Other examples of signal transduction inhibitors which may be used in conjunction with a compound of the invention and pharmaceutical compositions described herein include ARRY 142886 (Array Biopharm), everolimus (Certican™), zotarolimus (Endeavor™), temsirolimus (Torisel™), AP 23573 (ARIAD), and VX 680 (Vertex).

Additionally, other signal transduction inhibitors include XL 647 (Exelixis), sorafenib (Nexavar™), LE-AON (Georgetown University), and GI-4000 (GlobalImmune).

Other signal transduction inhibitors include ABT 751 (Abbott), alvocidib (flavopiridol), BMS 387032 (Bristol Myers), EM 1421 (Erimos), indisulam (E 7070), seliciclib (CYC 200), BIO 112 (One Bio), BMS 387032 (Bristol-Myers Squibb), PD 0332991 (Pfizer), and AG 024322 (Pfizer).

This invention contemplates the use of compounds of the invention together with classical antineoplastic agents. Classical antineoplastic agents include but are not limited to hormonal modulators such as hormonal, anti-hormonal, androgen agonist, androgen antagonist and anti-estrogen therapeutic agents, histone deacetylase (HDAC) inhibitors, gene silencing agents or gene activating agents, ribonucleases, proteosomics, Topoisomerase I inhibitors, Camptothecin derivatives, Topoisomerase II inhibitors, alkylating agents, antimetabolites, poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor, microtubulin inhibitors, antibiotics, plant derived spindle inhibitors, platinum-
coordinated compounds, gene therapeutic agents, antisense oligonucleotides, vascular targeting agents (VTAs), and statins

Examples of classical antineoplastic agents used in combination therapy with a compound of the invention, optionally with one or more other agents include, but are not limited to, glucocorticoids, such as dexamethasone, prednisone, prednisolone, methylprednisolone, hydrocortisone, and progestins such as medroxyprogesterone, megestrol acetate (Megace), mifepristone (RU-486), Selective Estrogen Receptor Modulators (SERMs; such as tamoxifen, raloxifene, lasofoxifene, afimoxifene, arzoxifene, bazedoxifene, fispemifene, ormeloxifene, ospemifene, tesselifene, toremifene, trilostane and CHF 4227 (Cheisi)), Selective Estrogen-Receptor Downregulators (SERD’s; such as fulvestrant), exemestane (Aromasin), anastrozole (Arimidex), atamestane, fadrozole, letrozole (Femara), gonadotropin-releasing hormone (GnRH; also commonly referred to as luteinizing hormone-releasing hormone [LHRH]) agonists such as buserelin (Suprefact), goserelin (Zoladex), leuprorelin (Lupron), and triptorelin (Trelstar), abarelix (Plenaxis), bicalutamide (Casodex), cyproterone, flutamide (Eulexin), megestrol, nilutamide (Nilandron), and osaterone, dutasteride, epristeride, finasteride, Serenoa repens, PHL 00801, abarelix, goserelin, leuprorelin, triptorelin, bicalutamide, tamoxifen, exemestane, anastrozole, fadrozole, formestane, letrozole, and combinations thereof.

Other examples of classical antineoplastic agents used in combination with compounds of the invention include but are not limited to suberolanilide hydroxamic acid (SAHA, Merck Inc./Aton Pharmaceuticals), depsipeptide (FR901228 or FK228), G2M-777, MS-275, pivaloyloxymethyl butyrate and PXD-101; Onconase (ranpirnase), PS-341 (MLN-341), Velcade (bortezomib), 9-aminocamptothecin, belotecan, BN-80915 (Roche), camptothecin, diflomotecan, edotecarin, exatecan (Daiichi), gimatecan, 10-hydroxycamptothecin, irinotecan HCl (Camptosar), lurtotecan, Orathecin (rubitecan, Supergen), SN-38, topotecan, camptothecin, 10-hydroxycamptothecin, 9-aminocamptothecin, irinotecan, SN-38, edotecarin, topotecan, aclacurubicin, adriamycin, amonafide, amrubucin, annamycin, daunorubicin, doxorubicin, elsamitricin, eprubicin, etoposide, idarubicin, galarubicin, hydroxycarbamide, nemorubicin, novantrone (mitoxantrone), pirarubicin, pixantrone, procarbazine, rebeccamycin, sobuzoxane, tafloposide, valrubicin, Zinecard (dexrazoxane), nitrogen mustard N-oxide, cyclophosphamide, AMD-473, altretamine, AP-5280, apaziquone,
brostallicin, bendamustine, busulfan, carboquone, carbustine, chlorambucil, dacarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-21 70, lomustine, mafosfamide, mechlorethamine, melphalan, mitobronitol, mitolactol, mitomycin C, mitoxatrone, nimustine, ranimustine, temozolomide, thiopeta, and platinum-coordinated alkylating compounds such as cisplatin, ParaPlatin (carboplatin), eptaplatin, lobaplatin, nedaplatin, Eloxatin (oxaliplatin, Sanofi), streptozocin, satrplatin, and combinations thereof.

The invention also contemplates the use of the compounds of the invention together with dihydrofolate reductase inhibitors (such as methotrexate and NeuTrexin (trimetresate glucuronate)), purine antagonists (such as 6-mercaptopurine riboside, mercaptopurine, 6-thioguanine, cladribine, clofarabine (Clolar), fludarabine, nelarabine, and raltitrexed), pyrimidine antagonists (such as 6-mercaptopurine riboside, mercaptopurine, 6-thioguanine, cladribine, clofarabine (Clolar), fludarabine, Nelarabine, and raltitrexed), pyrimidine antagonists (such as 5-fluorouracil (5-FU), Alimta (premetrexed disodium, LY231514, MTA), capecitabine (Xeloda™), cytosine arabinoside, Gemzar™ (gemcitabine, Eli Lilly), Tegafur (UFT Orzel or Uforal and including TS-1 combination of tegafur, gimestat and otostat), doxifluoridine, carbomorph, cytarabine (including ocfosfate, phosphate stearate, sustained release and liposomal forms), enocitabine, 5-azacitidine (Vidaza), decitabine, and ethynylcytidine) and other antimetabolites such as efirontinilne, hydroxyurea, leucovorin, nolatrexed (Thymitaq), triapine, trimetrexate, N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid, AG-014699 (Pfizer Inc.), ABT-472 (Abbott Laboratories), INO-1001 (Inotek Pharmaceuticals), KU-0687 (KuDOS Pharmaceuticals) and GPI 18180 (Guilford Pharm Inc) and combinations thereof.

Other examples of classical antineoplastic cytotoxic agents used in combination therapy with a compound of the invention, optionally with one or more other agents include, but are not limited to, Abraxane (Abraxis Bioscience, Inc.), Batabulin (Amgen), EPO 906 (Novartis), Vinflunine (Bristol-Myers Squibb Company), actinomycin D, bleomycin, mitomycin C, neocarzinostatin (Zinostatin), vinblastine, vincristine, vindesine, vinorelbine (Navelbine), docetaxel (Taxotere), Ortaxaxel, paclitaxel (including Taxoprexin a DHA/paclitaxel conjugate), cisplatin, carboplatin, Nedaplatin, oxaliplatin (Eloxatin), Satraplatin, Camptosar, capecitabine (Xeloda), oxaliplatin (Eloxatin), Taxotere altretinoin, Canfosfamide (Telcyta™), DMXAA (Antisoma), ibandronic acid, L-asparaginase, pegaspargase (Oncaspar™), Efaproxiral (Efaproxyn™ - radiation therapy)), bexarotene (Targretin™), Tesmilifene (DPPE - enhances efficacy of
cytotoxics), Theratope™ (Biomira), Tretinoin (Vesanoid™), tirapazamine (Trizaone™), motexafin gadolinium (Xcytrin™) Cotara™ (mAb), and NBI-3001 (Protox Therapeutics), polyglutamate-paclitaxel (Xyotax™) and combinations thereof.

Further examples of classical antineoplastic agents used in combination therapy with a compound of the invention, optionally with one or more other agents include, but are not limited to, as Advexin (ING 201), TNFerade (GeneVec, a compound which express TNFalpha in response to radiotherapy), RB94 (Baylor College of Medicine), Genasense (Oblimersen, Genta), Combretastatin A4P (CA4P), Oxi-4503, AVE-8062, ZD-6126, TZT-1027, Atorvastatin (Lipitor, Pfizer Inc.), Provastatin (Pravachol, Bristol-Myers Squibb), Lovastatin (Mevacor, Merck Inc.), Simvastatin (Zocor, Merck Inc.), Fluvastatin (Lescol, Novartis), Cerivastatin (Baycol, Bayer), Rosuvastatin (Crestor, AstraZeneca), Lovostatin, Niacin (Advico, Kos Pharmaceuticals), Caduet, Lipitor, torcetrapib, and combinations thereof.

Another embodiment of the present invention of particular interest relates to a method for the treatment of breast cancer in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of trastuzumab, tamoxifen, docetaxel, paclitaxel, capecitabine, gemcitabine, vinorelbine, exemestane, letrozole and anastrozole.

In one embodiment the invention provides a method of treating colorectal cancer in a mammal, such as a human, in need of such treatment, by administering an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents. Examples of particular anti-cancer agents include those typically used in adjuvant chemotherapy, such as FOLFOX, a combination of 5-fluorouracil (5-FU) or capecitabine (Xeloda), leucovorin and oxaliplatin (Eloxatin). Further examples of particular anti-cancer agents include those typically used in chemotherapy for metastatic disease, such as FOLFOX or FOLFOX in combination with bevacizumab (Avastin); and FOLFIRI, a combination of 5-FU or capecitabine, leucovorin and irinotecan (Camptosar). Further examples include 17-DMAG, ABX-EFR, AMG-706, AMT-2003, ANX-510 (CoFactor), aplidine (plitidepsin, Aplidin), Aroplatin, axitinib (AG-13736), AZD-0530, AZD-2171, bacillus Calmette-Guerin (BCG), bevacizumab (Avastin), BIO-117, BIO-145, BMS-184476, BMS-275183, BMS-528664, bortezomib (Velcade), C-1311 (Symadex), cantuzumab mertansine, capecitabine
(Xeloda), cetuximab (Erbitux), clofarabine (Clofarex), CMD-1 93, combretastatin, Cotara, CT-2106, CV-247, decitabine (Dacogen), E-7070, E-7820, edotecarin, EMD-273066, enzastaurin (LY-317615)epothilone B (EPO-906), erlotinib (Tarceva), flavopyridol, GCAN-101, gefitinib (Iresssa), huA33, huC242-DM4, imatinib (Gleevec), indisulam, ING-1, irinotecan (CPT-11, Camptosar) ISIS 2503, ixabepilone, lapatinib (Tykerb), mapatumumab (HGS-ETR1), MBT-0206, MEDI-522 (Abregrin), Mitomycin, MK-0457 (VX-680), MLN-8054, NB-1011, NGR-TNF, NV-1020, oblimersen (Genasense, G3139), OncoVex, ONYX 015 (CI-1042), oxaliplatin (Eloxatin), panitumumab (ABX-EGF, Vectibix), pemetrexed (Alimta), PD-325901, PF-0337210, PF-2341066, RAD-001 (Everolimus), RAV-12, Resveratrol, Rexin-G, S-1 (TS-1), seliciclib, SN-38 liposome, Sodium stibogluconate (SSG), sorafenib (Nexavar), SU-14813, sunitinib (Sutent), temsirolimus (CCI 779), tetrathiomolybdate, thalomid, TLK-286 (Telcyta), topotecan (Hycamint), trabectedin (Yondelis), vatalanib (PTK-787), vorinostat (SAHA, Zolinza), WX-UK1, and ZYC300, wherein the amounts of the active agent together with the amounts of the combination anticancer agents are effective in treating colorectal cancer.

Another embodiment of the present invention of particular interest relates to a method for the treatment of renal cell carcinoma in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of axitinib (AG 13736), capecitabine (Xeloda), interferon alpha, interleukin-2, bevacizumab (Avastin), gemcitabine (Gemzar), thalidomide, cetuximab (Erbitux), vatalanib (PTK-787), sunitinib (Sutent™), AG-13736, SU-1 1248, Tarceva, Iressa, Lapatinib and Gleevec, wherein the amounts of the active agent together with the amounts of the combination anticancer agents is effective in treating renal cell carcinoma.

Another embodiment of the present invention of particular interest relates to a method for the treatment of melanoma in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of interferon alpha, interleukin-2, temozolomide (Temodar), docetaxel (Taxotere), paclitaxel, Dacarbazine (DTIC), carmustine (also known as BCNU), Cisplatin, vinblastine, tamoxifen, PD-325,901, axitinib (AG 13736),
bevacizumab (Avastin), thalidomide, sorafenib, vatalanib (PTK-787), sunitinib (Sutent™), CpG-7909, AG-13736, Iressa, Lapatinib and Gleevec, wherein the amounts of the active agent together with the amounts of the combination anticancer agents is effective in treating melanoma.

Another embodiment of the present invention of particular interest relates to a method for the treatment of lung cancer in a human in need of such treatment, comprising administering to said human an amount of a compound of the invention, in combination with one or more (preferably one to three) anti-cancer agents selected from the group consisting of capecitabine (Xeloda), axitinib (AG 13736), bevacizumab (Avastin), gemcitabine (Gemzar), docetaxel (Taxotere), paclitaxel, premetrexed disodium (Alimta), Tarceva, Iressa, Vinorelbine, Irinotecan, Etoposide, Vinblastine, sunitinib (Sutent™), and Paraplatin (carboplatin), wherein the amounts of the active agent together with the amounts of the combination anticancer agents is effective in treating lung cancer.

**Synthetic Methods**

Compounds of the invention are prepared according to the exemplary procedures provided herein and modifications thereof known to those of skill in the art. In addition, synthetic routes for the formation of various compounds useful as starting materials for the preparation of the compounds claimed herein are described in International Application No. PCT/IB2013/060682, the content of which is incorporated by reference herein in its entirety.

These and other methods are exemplified in the preparation of the examples provided herein. It will be understood by those of skill in the art that the selection of starting materials and the particular order of the steps, including, e.g., formation of the lactam ring, installation or manipulation of various substituent groups on the fused lactam or its precursors, and installation of the pyridinone moiety, can be varied by selection of a suitable synthetic strategy.

Synthetic examples are provided throughout the Examples and in Table 1 below. Table 2 includes additional compounds envisaged within the scope of the invention. The compounds of Table 2 can be prepared according to the methods described herein or by modifications of those methods. EZH2 IC₅₀ values (µΜ) for WT EZH2 and Mutant Y641 N EZH2 are provided in Table 3 for exemplary compounds of the invention.
The following abbreviations are used throughout the Examples: "Ac" means acetyl, "AcO" or "OAc" means acetoxy, "Ac₂O" means acetic anhydride, "ACN" or "MeCN" means acetonitrile, "AlBN" means azobisisobutyronitrile, "BOC", "Boc" or "boc" means N-tert-butoxycarbonyl, "Bn" means benzyl, "BPO" means dibenzoyl peroxide, "Bu" means butyl, "iBu" means isobutyl, "sBu" means sec-butyl, "tBu" means tert-butyl, "BuOK" or "KOtBu" means potassium tert-butoxide, "CDI" means carbonyldiimidazole, "DCM" (CH₂Cl₂) means methylene chloride, "DEAD" means diethyl azodicarboxylate, "DIAD" means diisopropyl azodicarboxylate, "DIPEA" or "DIEA" means diisopropyl ethyl amine, "DBU" means 1,8-diazabicyclo[5.4.0]undec-7-ene, "DIBAL-H" means diisobutylaluminum hydride, "DMA" means N,N-dimethylacetamide, "DMAP" means 4-dimethylaminopyridine, "DME" means dimethoxyethane, "DMF" means N,N-dimethyl formamide, "DMS" means dimethylsulfide, "DMSO" means dimethylsulfoxide, "dppf" means (diphenylphosphino)ferrocene, "DPPP" means 1,3-bis(diphenylphosphino)propane, "Et" means ethyl, "EtOAc" means ethyl acetate, "EtOH" means ethanol, "HATU" means 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, "HOAc" or "AcOH" means acetic acid, "i-Pr" or ""Pr" means isopropyl, "IPA" means isopropyl alcohol, "KHMDS" means potassium hexamethyldisilazide (potassium bis(trimethylsilyl)amide), "LiHMDS" means lithium hexamethyldisilazide (lithium bis(trimethylsilyl)amide), "mCPBA" means metachloroperoxy-benzoic acid, "Me" means methyl, "MeOH" means methanol, "Ms" means methanesulfonate (commonly called 'mesylate'), "MTBE" means methyl t-butyl ether, "NBS" means N-bromosuccinimide, "NCS" means N-chlorosuccinimide, "NIS" means N-iodosuccinimide, "NMM" means N-methylmorpholine, "NMP" means 1-methyl 2-pyrrolidinone, "Ph" means phenyl, "RuPhos" means 2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl, "Selectfluor" means Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoro-borate), "TEA" means triethyl amine, "TFA" means trifluoroacetic acid, "Tf" means trifluoromethanesulfonate (commonly called 'triflate'), "THF" means tetrahydrofuran, "TMS" means trimethylsilyl, "TMSA" means trimethylsilylazide, "TsCl" means toluenesulfonyl chloride (commonly called 'tosylate'), "SFC" means supercritical fluid chromatography, "TLC" means thin layer chromatography, "RF" means retention fraction, "~" means approximately, "rt" means room temperature, "h" means hours, "min" means minutes, "eq." means equivalents.
Preparation of Synthetic Intermediates

**Compound A**: 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine

![Chemical Structure Diagram]

To a solution of 2-hydroxy-4,6-dimethylpyridine-3-carbonitrile (85.0 g, 0.574 mol) and benzyl chloride (87.0 g, 0.688 mol) in toluene (800 mL) was added Ag$_2$O (146 g, 0.631 mol). The reaction mixture was stirred at 110 °C overnight. The reaction mixture was filtered through CELITE® and the solids were washed with dichloromethane. The filtrate was concentrated under vacuum and purified by column chromatography (petroleum ether/ethyl acetate) to give 2-(benzyloxy)-4,6-dimethylpyridine-3-carbonitrile (A1, 89 g, 65%) as a white solid.

44.5 g x 2 batches: To a stirred solution of 2-(benzyloxy)-4,6-dimethylpyridine-3-carbonitrile (A1, 44.5 g, 187 mmol) in dichloromethane (500 mL) was added dropwise DIBAL-H (224 mL, 224 mmol, 1M in toluene) at 0 ~ 5 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 3 hours. The mixture was quenched with 1N HCl (200 mL) and was stirred vigorously for 30 minutes. The reaction mixture was neutralized with 4N NaOH (20 mL) and the biphasic mixture was filtered and washed with dichloromethane (500 mL). The aqueous layer was extracted with dichloromethane (200 mL), the combined organic layers were dried over sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/EtOAc) to give 2-(benzyloxy)-4,6-dimethylpyridine-3-carbaldehyde (A2, 70 g, 78%) as a yellow solid.

35 g x 2 batches: To a 0 °C solution of 2-(benzyloxy)-4,6-dimethylpyridine-3-carbaldehyde (A2, 35.0 g, 145 mmol) in methanol (1000 mL) was added sodium borohydride (6.60 g, 174 mmol) in portions. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under vacuum and the residue was diluted with NaHCO$_3$ (sat., aq.). After the bubbling had stopped, the
aqueous solution was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were dried over sodium sulfate, concentrated under vacuum, and purified by column chromatography (petroleum ether/ethyl acetate) to give [2-(benzyloxy)-4,6-dimethylpyridin-3-yl]methanol \((\text{A3, 43 g, 61\%})\) as a colorless oil.

2.1.5 g x 2 batches: To a solution of [2-(benzyloxy)-4,6-dimethylpyridin-3-yl]methanol \((\text{A3, 21.5 g, 88.5 mmol})\) in anhydrous dichloromethane (400 mL) was added thionyl chloride (16.0 g, 133 mmol) at -40 °C under \(\text{N}_2\). The mixture was stirred at -40 °C for 30 minutes. The reaction mixture was poured into ice-water (300 mL) and adjusted to pH 7~8 with \(\text{NaHCO}_3\) (solid). The mixture was separated and the aqueous layer was extracted with dichloromethane (300 mL). The combined organic layers were washed with brine (300 mL), dried over sodium sulfate, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 100:1) to give 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine \((\text{Cpd A, 27.5 g, 60\%})\) as a white solid. \(^1\text{H NMR}\) (400 MHz, chloroform-d) \(\delta \) 7.51 - 7.49 (d, 2H), 7.41 - 7.37 (t, 2H), 7.34 - 7.30 (t, 1H), 6.62 (s, 1H), 5.45 (s, 2H), 4.73 (s, 2H), 2.42 (s, 3H), 2.37 (s, 3H). MS: 261.9 [M+H]^+.

Compound B: 2-(benzyloxy)-3-(chloromethyl)-4-ethyl-6-methylpyridine

A solution of 2-cyano-acetamide (841 mg, 10.0 mmol) and potassium tert-butoxide (1.18 g, 10.5 mmol) in dimethylsulfoxide (20 mL) was stirred at 23 °C for 30 minutes. The mixture was cooled to 0 °C, pent-3-yn-2-one (1.1 mL, 10 mmol) was added, and the reaction mixture was stirred for 2 hours. The reaction mixture was quenched with saturated ammonium chloride (3 mL) then diluted with water (10 mL) causing a solid to precipitate out. The suspension was filtered and the solids dried
under vacuum to give 4-ethyl-2-hydroxy-6-methylnicotinonitrile (B1, 1.2 g, 71%) as a white solid.

A mixture of 4-ethyl-2-hydroxy-6-methylnicotinonitrile (B1, 1.1 g, 6.8 mmol), (chloromethyl)benzene (1.1 mL, 9.4 mmol) and silver(I) oxide (1.8 g, 7.7 mmol) in anhydrous toluene (22.7 mL) was heated at 110 °C for 17 hours. The reaction mixture was cooled to 23 °C then filtered through CELITE®. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography (heptane/EtOAc) to give 2-(benzyloxy)-4-ethyl-6-methylnicotinonitrile (B2, 1.42 g, 83%) as a colorless oil.

To a -5 °C solution of 2-(benzyloxy)-4-ethyl-6-methylnicotinonitrile (B2, 0.687 g, 2.72 mmol) in dichloromethane (9 mL) was added 1M diisobutylaluminum hydride in dichloromethane (3 mL, 3 mmol). After 3 hours the reaction mixture was quenched with 1M aqueous hydrochloric acid (3 mL) then stirred for 15 minutes. A 2M aqueous solution of Rochelle's salt (3 mL) was added then the resulting mixture was filtered through CELITE®. The filtrate was concentrated under vacuum and the residue was extracted with ethyl acetate (40 mL), washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography (heptane/EtOAc) to give 2-(benzyloxy)-4-ethyl-6-methylnicotinaldehyde (B3, 323 mg, 46%) as a colorless oil.

Sodium borohydride (54 mg, 1.41 mmol) was added to a 0 °C solution of 2-(benzyloxy)-4-ethyl-6-methylnicotinaldehyde (B3, 323 mg, 1.28 mmol) in methanol (4.27 mL). After stirring for 1 hour, the reaction mixture was concentrated under vacuum and the residue partitioned between ethyl acetate (20 mL) and water (10 mL). The organic layer was washed with brine (5 mL), dried over sodium sulfate, filtered, concentrated under vacuum, and purified by column chromatography (heptane/EtOAc) to give (2-(benzyloxy)-4-ethyl-6-methylpyridin-3-yl)methanol (B4, 280 mg, 85%) as a colorless oil.

To a 0 °C solution of N-chlorosuccinimide (81.5 mg, 0.598 mmol) in dichloromethane (2.47 mL) was added dimethylsulfide (48 µL, 0.653 mmol). The reaction mixture was then cooled to -20 °C and a solution of (2-(benzyloxy)-4-ethyl-6-methylpyridin-3-yl)methanol (B4, 140 mg, 0.554 mmol) in dichloromethane (1 mL) was added drop wise. After 2 hours the reaction mixture was poured into brine (5 mL) and extracted with dichloromethane (10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by column chromatography.
chromatography (heptane/EtOAc) to give 2-(benzyloxy)-3-(chloromethyl)-4-ethyl-6-methylpyridine (Cpd B, 35 mg, 23%) as a colorless oil. \(^1\)H NMR (chloroform-d) \(\delta\) 7.52 (d, \(J=7.3\) Hz, 2H), 7.29-7.44 (m, 3H), 6.65 (s, 1H), 5.46 (s, 2H), 4.74 (s, 2H), 2.72 (q, \(J=7.6\) Hz, 2H), 2.44 (s, 3H), 1.28 (t, \(J=7.6\) Hz, 3H).

5

**Compound C:** 2-(benzyloxy)-3-(chloromethyl)-4-(difluoromethoxy)-6-methylpyridine

To a cooled (-10 °C) suspension of sodium hydride (60 wt% dispersion in mineral oil, 59.9 g, 1500 mmol) in dry tetrahydrofuran (1200 mL) was added solution of malononitrile (100 g, 1190 mmol) in dry tetrahydrofuran (30 mL) dropwise, slowly enough to maintain the internal temperature below 5 °C. After the addition was complete, the mixture was stirred at 0 °C for 1.5 hours, then diketene (80.1 g, 1190 mmol) was added dropwise, slowly enough to maintain the internal temperature below 0 °C. The mixture was stirred at -10 °C for 1.5 hours, then neutralized with 4N aq. HCl, and concentrated to remove volatiles. The remaining suspension in 4N aq. HCl (2000 mL) was stirred at reflux for 5 hours, then stirred at room temperature overnight. The resulting white precipitate was collected by suction filtration. The filter cake was washed sequentially with water (500 mL), ethanol (500 mL) and MTBE (300 mL). The solid was dried to obtain 4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (C1, 108 g,
60.3%) as a yellow powder. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 12.40 (br. s., 1H), 11.72 (br. s., 1H), 5.82 (s, 1H), 2.17 (s, 2.17 H).

A suspension of 4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (C1, 91 g, 610 mmol), phosphorus oxychloride (195 g, 1270 mmol) and phosphorus pentachloride (265 g, 1270 mmol) in chloroform (1200 mL) was heated at reflux for 5 hours, resulting in a red homogeneous mixture. The mixture was poured into water (2000 mL) carefully with stirring, then neutralized by ammonium hydroxide (28% aqueous). The resulting solid precipitate was filtered off, washed sequential with dichloromethane (400 mL) and ethanol (500 mL), and dried to give 4-chloro-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (C2, 78 g, 76%) as a yellow solid. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 12.43 (br. s., 1H), 6.53 (s, 1H), 2.28 (s, 3H).

A suspension of 4-chloro-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (C2, 90 g, 530 mmol), silver(I) oxide (136 g, 587 mmol) and benzyl chloride (81.1 g, 641 mmol) in anhydrous toluene (1500 mL) was heated at reflux for 12 hours. The mixture was filtered through a CELITE® pad and the filter cake washed with dichloromethane (500 mL). The filtrate was concentrated to give a residue (~100 g), which was purified by column chromatography (silica gel, petroleum ether/EtOAc= 50:1-30:1) affording 2-(benzyloxy)-4-chloro-6-methylnicotinonitrile (C3, 70 g, 51%) as a light yellow solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49-7.47 (m, 2H), 7.40-7.33 (m, 3H), 6.91 (s, 1H), 5.05 (s, 2H), 2.50 (s, 3H).

To a stirred solution of 2-(benzyloxy)-4-chloro-6-methylnicotinonitrile (C3, 70 g, 270.58 mmol) in N,N-dimethylformamide (300 mL) was added cesium acetate (156.0 g, 812 mmol) at room temperature. The resulting mixture was stirred at 80°C for 40 hours. The mixture was diluted with ethyl acetate (500 mL) and washed with brine (3 x 400 mL). The organic phase was dried over sodium sulfate, filtered, and concentrated to give a residue (~50 g), which was purified by column chromatography (silica gel, petroleum ether/EtOAc= 10:1-3:1) to give 2-(benzyloxy)-4-hydroxy-6-methylnicotinonitrile (C4, 31 g, 48%) as a light yellow solid. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 12.28 (br. s., 1H), 7.51-6.98 (m, 5H), 6.50 (s, 1H), 5.41 (s, 2H), 2.34 (s, 3H). MS 226.8 [M+Na]$.^+$

To a suspension of 2-(benzyloxy)-4-hydroxy-6-methylnicotinonitrile (C4, 20.0 g, 83 mmol) and sodium chlorodifluoroacetate (25.4 g, 166 mmol) in N,N-dimethylformamide (200 mL) was added potassium carbonate (34.5 g, 250 mmol) at
room temperature. The resulting mixture was heated to 100 °C for 10 minutes. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with sat. aq. NH4Cl (3 x 400 mL), and brine (3 x 400 mL). The aqueous layer was back-extracted with ethyl acetate (400 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a residue (18 g), which was purified by column chromatography (silica gel, petroleum ether/EtOAc = 50:1 ~20:1 ) to give 2-(benzyloxy)-4-(difluoromethoxy)-6-methyl nicotinonitrile (C5, 16.3 g, 67%) as a light yellow solid. 1H NMR (400 MHz, CDCl3) δ 7.49-7.46 (m, 2H), 7.40-7.33 (m, 3H), 6.69 (t, J=71 Hz, 1H), 6.67 (s, 1H), 5.51 (s, 2H), 2.52 (s, 3H).

To a solution of 2-(benzyloxy)-4-(difluoromethoxy)-6-methyl nicotinonitrile (C5, 11 g, 38 mmol) in dry dichloromethane (250 mL) under nitrogen was added diisobutylaluminium hydride (1.0 M in toluene, 72 mL, 72 mmol) dropwise at 0 °C. After the addition was complete, the mixture was stirred at room temperature for 2.5 hours. The mixture was acidified to pH ~ 5 with 1M aq. HCl. After stirring at room temperature for 2 hours, the mixture was neutralized with 4.0 M aq. NaOH. The mixture was filtered off through a CELITE® pad and the filter cake was washed with dichloromethane (300 mL). The filtrate was extracted with dichloromethane (2 x 500 mL). The combined organic layers were washed with brine (800 mL), dried over sodium sulfate, and concentrated to give a residue (13.4 g), which was purified by column chromatography (silica gel, petroleum ether/EtOAc = 30:1 -6:1 ) to give 2-(benzyloxy)-4-(difluoromethoxy)-6-methyl nicotinaldehyde (C6, 6 g, 50%) as a light yellow solid. 1H NMR (400 MHz, CDCl3) δ 10.40 (s, 1H), 7.49-7.48 (m, 2H), 7.40-7.31 (m, 3H), 6.68 (t, J=72 Hz, 1H), 6.62 (s, 1H), 5.53 (s, 2H), 2.50 (s, 3H).

To a solution of 2-(benzyloxy)-4-(difluoromethoxy)-6-methyl nicotinaldehyde (C6, 12 g, 41 mmol) in methanol (120 mL) was added sodium borohydride (1.86 g, 49.16 mmol) portion-wise at 0 °C. After the addition was complete, the mixture was stirred at room temperature for 2 hours. The reaction was quenched with sat. aq. NH4Cl (50 mL), then diluted with ethyl acetate (500 mL) and water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (300 mL), dried over sodium sulfate and concentrated to give a residue (~13.1 g), which was purified by column chromatography (silica gel, petroleum ether/EtOAc =6:1 ) to give 2-(benzyloxy)-4-(difluoromethoxy)-6-methylpyridin-3-yl)methanol (C7, 11.7 g, 97%) as a
white solid. $^1$H NMR (400 MHz, CDCI3) δ 7.52-7.46 (m, 2H), 7.44-7.33 (m, 3H), 6.60 (t, J=73 Hz, 1H), 6.55 (s, 1H), 5.46 (s, 2H), 2.46 (s, 3H).

To a solution of (2-(benzyloxy)-4-(difluoromethoxy)-6-methylpyridin-3-yl)methanol (C7, 7.6 g, 26 mmol) in anhydrous dichloromethane (120 ml) was added thionyl chloride (3.67 g, 30.9 mmol) dropwise at -20 °C. The mixture was stirred at -20 °C for 1 hour, then poured into water (50 ml), and neutralized with saturated aq. NaHC03. The aqueous phase was extracted with dichloromethane (2 x 90 ml). The combined organic phases were dried over sodium sulfate, filtered and concentrated to give a residue (~6.1 g), which was purified by silica gel chromatography (petroleum ether/EtOAc=6:1) to give the title compound, 2-(benzyloxy)-3-(chloromethyl)-4-(difluoromethoxy)-6-methylpyridine (Cpd C, 5.7 g, 71%) as a white solid. $^1$H NMR (400 MHz, CDCI3) δ 7.50 (d, J = 7.2, 2H), 7.41 -7.33 (m, 3H), 6.64 (t, J=73 Hz, 1H), 6.56 (s, 1H), 5.48 (s, 2H), 4.69 (s, 2H), 2.47 (s, 3H). MS: 314 [M+H]+.

**Compound D**: 2-(benzyloxy)-4-chloro-3-(chloromethyl)-6-methylpyridine

A solution of 2-(benzyloxy)-4-chloro-6-methylnicotinonitrile (C3, 5 g, 19.33 mmol) in dry dichloromethane (100 ml) was treated with diisobutylaluminum hydride (1.0M in toluene, 40 ml, 40 mmol) dropwise at 0 °C. The mixture was stirred for an additional 2 hours at 25 °C, then acidified to pH ~ 5 with 1M HCl. After stirring for 2 hours, the mixture was neutralized with 4M aq. NaOH. The resulting solids were removed by filtration through a CELITE® pad. The filter cake was washed with dichloromethane (300 ml). The filtrate was extracted with dichloromethane (2 x 100 ml), and the combined organic layers were washed with brine (100 ml), dried over sodium sulfate, and concentrated. The crude product was purified by column chromatography (silica gel, petroleum ether: EtOAc = 200:1) to give 2-(benzyloxy)-4-chloro-6-methylnicotinaldehyde (D1, 2.7 g, 53.4%) as a light yellow solid. $^1$H NMR (400 MHz, CDCI3) δ 10.47 (s, 1H), 7.50-7.48 (m, 2H), 7.41 -7.32 (m, 3H), 6.87 (s, 1H), 5.53 (s, 2H), 2.49 (s, 3H).
Sodium borohydride (468 mg, 2.25 mmol) was added to a cooled (0 °C) solution of 2-(benzyloxy)-4-chloro-6-methylnicotinaldehyde (D1, 2.7 g, 10.32 mmol) in methanol (50 mL), and the mixture stirred at room temperature for 2 hours. The reaction was quenched with sat. aq. ammonium chloride (10 mL), then partitioned between ethyl acetate (100 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether: EtOAc = 70:1) to give (2-(benzyloxy)-4-chloro-6-methylpyridin-3-yl)methanol (D2, 2.3 g, 84.5%) as colorless oil. \(^1\)H NMR (400 MHz, CDCl3) δ 7.40-7.38 (m, 2H), 7.35-7.28 (m, 3H), 6.75 (s, 1H), 5.39 (s, 2H), 4.76 (s, 2H), 2.37 (s, 3H).

Thionyl chloride (1.0 mL, 13.8 mmol) was added dropwise to a solution of (2-(benzyloxy)-4-chloro-6-methylpyridin-3-yl)methanol (D2, 2.0 g, 7.58 mmol) in dry dichloromethane (50 mL) at -30 °C. Stirring was continued at -30 °C for 3 hours, then the mixture was quenched with ice water (50 mL) and neutralized with NaHCO3. The mixture was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (petroleum ether) to give 2-(benzyloxy)-4-chloro-3-(chloromethyl)-6-methylpyridine (Cpd D, 1 g, 46.7%) as a white solid. \(^1\)H NMR (400 MHz, CDCl3) δ 7.50-7.48 (m, 2H), 7.41-7.31 (m, 3H), 6.83 (s, 1H), 5.46 (s, 2H), 4.77 (s, 2H), 2.43 (s, 3H). MS: 282 [M+H]^+.

**Compound E:** 2-(benzyloxy)-3-(chloromethyl)-4-methoxy-6-methylpyridine

Iodomethane (10.6 g, 74.9 mmol) was added dropwise to a cooled (0 °C) solution of 2-(benzyloxy)-4-hydroxy-6-methylnicotinonitrile (C4, 9 g, 30 mmol) and...
cesium carbonate (24.4 g, 74.9 mmol) in dry N,N-dimethylformamide (120 mL). After stirring at room temperature for 30 minutes, the mixture was filtered, and the filter cake was washed with ethyl acetate (100 mL). The filtrate was diluted with water (120 mL) and then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over sodium sulfate and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc=10/1 ~3/1 , Rf -0.6) to give 2-(benzyloxy)-4-methoxy-6-methyl nicotinonitrile (E1, 7 g, 94%) as a yellow solid. $^1$H NMR (400 MHz, CDCl3) δ 7.50-7.48 (m, 2H), 7.39-7.31 (m, 3H), 6.41 (s, 1H), 5.49 (s, 2H), 3.95 (s, 3H), 2.48 (s, 3H).

Diisobutylaluminum hydride (1.0M in toluene, 56.5 mL, 56.5 mmol) was added dropwise to a cooled (0 °C) solution of 2-(benzyloxy)-4-methoxy-6-methyl nicotinonitrile (E1, 7.18 g, 28.24 mmol). After addition, the mixture was stirred at room temperature for 3 hours, then quenched by adding 1M HCl at 0 °C until pH~5. The resulting mixture was stirred at room temperature for 2 hours., then basified by adding 1M NaOH at 0 °C until pH~8. The mixture was diluted with dichloromethane (200 mL) and filtered through a CELITE® pad. The filter cake was washed with dichloromethane (2 x 150 mL). The combined filtrate was extracted with dichloromethane (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over sodium sulfate, concentrated, and purified by column chromatography (silica gel, petroleum ether/EtOAc= 20:1 -2:1 ) to give 2-(benzyloxy)-4-methoxy-6-methyl nicotinaldehyde (E2, 4 g, 55%), as a light yellow solid. $^1$H NMR (400 MHz, CDCl3) δ 10.44 (s, 1H), 7.50-7.48 (m, 2H), 7.39-7.31 (m, 3H), 6.44 (s, 1H), 5.51 (s, 2H), 3.94 (s, 3H), 2.45 (s, 3H).

Sodium borohydride (529 mg, 14.0 mmol) was added to a cooled (0 °C) solution of 2-(benzyloxy)-4-methoxy-6-methyl nicotinaldehyde (E2, 3 g, 11.66 mmol) in methanol (60 mL), and the resulting mixture stirred at room temperature for 1 hour. The mixture was quenched at 0 °C with sat. aq. ammonium chloride (20 mL), diluted with water (40 mL), and extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc=3/1 , Rf ~0.55 in petroleum ether/EtOAc=1/1 ) to give 2-(benzyloxy)-4-methoxy-6-methylpyridin-3-yl)methanol (E3, 2.35 g, 77.7%) as an off-white solid. $^1$H NMR (400 MHz, CDCl3) δ 7.47-7.45 (m, 2H), 7.39-7.30 (m, 3H), 6.41 (s, 1H), 5.43 (s, 2H), 4.73 (d, J=6.4 Hz, 2H), 3.86 (s, 3H), 2.44 (s, 3H), 2.33 (t, J=6.4 Hz, 1H).

- 73 -
Thionyl chloride (551 mg, 4.63 mmol) was added dropwise to a solution of (2-(benzyloxy)-4-methoxy-6-methylpyridin-3-yl)methanol (E3, 1 g, 3.857 mmol) in dry dichloromethane (30 mL) at -20 °C. The resulting mixture was stirred at -20 °C for 2 hours, then basified by adding triethylamine until pH~8. The mixture was diluted with water (100 mL) and extracted with dichloromethane (3 x 60 mL). The combined organic layers were washed sequentially with water (50 mL), sat. NaHCO3 (2 x 50 mL) and brine (2 x 50 mL), dried over sodium sulfate and concentrated to give ~1.2 g of crude product. This residue was poured into petroleum ether (80 mL) and stirred at room temperature for 30 minutes. The solids were collected by filtration and the filtrate reserved. The solids from the filter cake were suspended in petroleum ether (80 mL) and stirred at room temperature for 30 minutes. The mixture was filtered, and the filtrate was collected. The combined filtrates were concentrated to give 2-(benzyloxy)-3-(chloromethyl)-4-methoxy-6-methylpyridine (Cpd E, 750 mg, 70%) as an off-white solid.

1H NMR (400 MHz, CDCl3) δ 7.51-7.49 (m, 2H), 7.40-7.31 (m, 3H), 6.39 (s, 1H), 5.46 (s, 2H), 4.72 (s, 2H), 3.90 (s, 3H), 2.44 (s, 3H). MS: 242 [M-35].

**Compound F**: 7-bromo-5,8-dichloro-3,4-dihydroisoquinolin-1-(2H)-one.

A mixture of 3-chloro-2-methylbenzoic acid (100 g, 0.58 mol), N-chlorosuccinimide (90 g, 0.67 mol) and palladium (II) acetate (14.7 g, 65.7 mmol) in N,N-dimethylformamide (1 L) was stirred at 110 °C under a nitrogen atmosphere overnight. After cooling to room temperature, cesium carbonate (378 g, 1.16 mol) and iodoethane (317 g, 2.03 mol) were added and stirring continued at room temperature for 1.5 hours. The reaction mixture was poured into a mixture of water (1 L) and methyl
fe/f-butyl ether (800 ml). Solids were removed by filtration, and the filtrate layers separated. The aqueous layer was extracted with more methyl fe/f-butyl ether (600 ml). The combined organic extracts were washed with saturated aqueous sodium chloride solution (1.2 L), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography (eluting with 50:1 petroleum ether/ethyl acetate), affording ethyl 3,6-dichloro-2-methylbenzoate (F2, 110 g, ~ 80% pure, 80% yield) as a yellow oil.

A solution of ethyl 3,6-dichloro-2-methylbenzoate (F2, 120 g, 0.52 mol) and N-bromosuccinimide (147 g, 0.82 mol) in chloroform (1 L) was treated with azobisisobutyronitrile (25.3 g, 0.15 mol) and the mixture refluxed overnight. After cooling to room temperature, the mixture was diluted with dichloromethane (800 ml) and washed with water (1.2 L). The aqueous layer was extracted with dichloromethane (800 ml). The combined organic extracts were washed with saturated aqueous sodium chloride solution (1.5 L), dried over sodium sulfate, and concentrated in vacuo to give ethyl 2-(bromomethyl)-3,6-dichlorobenzoate (F3, 160 g, 100% yield) which was used without further purification.

A solution of sodium cyanide (75.12 g, 1.53 mol) in water (300 ml) was added dropwise to a solution of ethyl 2-(bromomethyl)-3,6-dichlorobenzoate (F3, 320 g, 1.03 mol) in dimethylsulfoxide (2.4 L) at room temperature. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was poured into a mixture of water (4 L) and methyl fe/f-butyl ether (2 L), and the layers separated. The organic layer was washed with water (2L) and with saturated aqueous sodium chloride solution (2 L), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography (eluting with 30:1 petroleum ether/ethyl acetate), affording ethyl 3,6-dichloro-2-(cyanomethyl)benzoate (F4, 150 g, ~75% pure, 47% yield) as a yellow oil.

Cobalt (II) chloride hexahydrate (166 g, 0.70 mol) was added to a room temperature solution of ethyl 3,6-dichloro-2-(cyanomethyl)benzoate (F4, 90 g, 0.35 mol) in ethanol (1.5 L), and the resulting mixture cooled to 0 °C. Sodium borohydride (66.3 g, 1.74 mol) was added in portions. The mixture was stirred at room temperature for 1 hour, and then refluxed overnight. The resulting suspension was filtered and the filtrate concentrated in vacuo. The solids in the filter cake were stirred in ethyl acetate (600 ml), and then filtered again. This procedure was repeated a second time. The
combined filtrates were added to the original filtrate residue, and this organic solution
washed with water (800 mL) and saturated aqueous sodium chloride solution (800 mL),
dried over sodium sulfate, and concentrated in vacuo to give 5,8-dichloro-3,4-
dihydroisoquinolin-1 (2/-)-one (F5, 29.3 g, 39% yield) as an off-white solid.

To a solution of 5,8-dichloro-3,4-dihydroisoquinolin-1 (2/-)-one (F5, 40 g, 0.186
mol) in concentrated sulfuric acid (200 mL) at 60°C was added N-bromosuccinimide
(49.7 g, 0.279 mol) in portions. Stirring was continued at 60 °C for 2 hours, then more
N-bromosuccinimide (5 g, 28 mmol) was added. After stirring at 60 °C for 1 hour more,
the mixture was poured onto ice water (500 mL), then extracted with dichloromethane
(3 x 500 mL). The combined organic extracts were washed with saturated aqueous
sodium chloride solution (800 mL), dried over sodium sulfate, and concentrated in
vacuo. The residue was stirred in ethyl acetate (40 mL) and petroleum ether (20 mL),
and the resulting solids collected by filtration and dried under vacuum to give 7-bromo-
5,8-dichloro-3,4-dihydroisoquinolin-1 (2/-)-one (Cpd F, 41 g, 75% yield) as an off-white
solid. 1H NMR (400 MHz, DMSO-d6) δ 8.36 (br. s., 1H), 8.11 (s, 1H), 3.31 (dt, J=3.97,
6.08 Hz, 2H), 2.92 (t, J=6.30 Hz, 2H).

**Compound G**: 7-bromo-8-chloro-3,4-dihydroisoquinolin-1 (2H)-one.

A solution of 7-amino-3,4-dihydroisoquinolin-1 (2H)-one (1.01 g, 6.23 mmol) and
N-chlorosuccinimide (832 mg, 6.23 mmol) in N,N-dimethylformamide (10 mL) was and
heated to 55 °C for 5 hours. The mixture was poured into water and extracted with ethyl
acetate (3 x). The combined ethyl acetate layers were concentrated, and residual N,N-
dimethylformamide was removed on high vacuum overnight. The resulting dark oil was
purified on silica gel (Biotage SNAP, 50g, gradient of 50-100% ethyl acetate in
heptanes) to give 7-amino-8-chloro-3,4-dihydroisoquinolin-1 (2H)-one (G1, 0.539g, 44%)
as a white solid. 1H NMR (400 MHz, DMSO-d6) δ 7.87 (br. s., 1H), 6.96 (d, J=8.1 9 Hz,
1H), 6.87 (d, J=8.1 9 Hz, 1H), 5.32 (s, 2H), 3.20 (dt, J=3.79, 6.1 7 Hz, 2H), 2.69 (t,
J=6.24 Hz, 2H); MS 197 [M+H]+.
A suspension of copper(I) bromide (1.04 g, 7.28 mmol) in acetonitrile (20 mL) was stirred at 60 °C for 10 minutes. Isomyl nitrite (0.348 mL, 2.91 mmol) was added, followed by 7-amino-8-chloro-3,4-dihydroisoquinolin-1 (2H)-one (G1, 0.477 g, 2.43 mmol) in one portion. The reaction mixture was stirred at 60 °C for 1 hour. After cooling to room temperature, sat. aq. NH₄Cl and EtOAc were added to the solution, and the biphasic mixture stirred vigorously for 20 minutes. The layers were separated, the organic layer concentrated, and the residue was purified on silica gel (Biotage SNAP, 10g, HP-Sil, gradient of 40-100% ethyl acetate in heptane) to give 7-bromo-8-chloro-3,4-dihydroisoquinolin-1 (2H)-one (Cpd G, 0.287 g, 45%) as a yellow solid. ¹H NMR (400 MHz, chloroform-d) δ 7.70 (d, J=8.07 Hz, 1H), 7.03 (d, J=8.07 Hz, 1H), 6.14 (br. s., 1H), 3.43-3.57 (m, 2H), 2.95 (t, J=6.36 Hz, 2H); MS 260, 262 [M+H]+.

**Compound H**: 5,8-dichloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one

Oxalyl chloride (34 mL, 0.395 mol) was added to a solution of 3-methoxy-2-nitrobenzoic acid (60 g, 0.305 mol) in dry dichloromethane (600 mL), followed by N,N-dimethylformamide (0.6 mL, 7.8 mmol), which initiates mild gas evolution. The mixture was stirred at room temperature for two hours, then concentrated under vacuum to remove volatiles. The crude acid chloride was dissolved in dry dichloromethane (150 mL) then added dropwise to a cooled (5 °C) solution of aminoacetaldehyde.
diethylacetal (48 mL, 0.33 mol) and triethylamine (52 mL, 0.374 mol) in dry dichloromethane (250 mL). The mixture was stirred at room temperature for two hours, then washed with saturated aqueous sodium bicarbonate (2 x 100 mL) and brine (100 mL). The organics were dried over sodium sulfate and concentrated to give N-(2,2-diethoxyethyl)-3-methoxy-2-nitrobenzamide (H1, 92 g, 97% yield) as a yellow solid. MS: 335 [M+1].

A mixture of /V-(2,2-diethoxyethyl)-3-methoxy-2-nitrobenzamide (H1, 92 g, 0.295 mol) in concentrated sulfuric acid (1 L) was stirred at 70 °C for three hours. After cooling to room temperature, the mixture was slowly poured into ice water (3 L), causing a solid precipitate to form. The precipitate was collected by filtration. The filter cake was washed with water (1 L) and dried to yield 7-methoxy-8-nitroisoquinolin-1 (2/-)-one (H2, 60 g, 92% yield) as a brown solid. 1H NMR (400 MHz, DMSO-d6) δ 7.92-7.89 (d, J = 9.2 Hz, 1H), 7.81-7.79 (d, J = 9.2 Hz, 1H), 7.1 8-7.15 (t, J = 6.6 Hz, 1H), 6.66-6.64 (d, J = 7.2 Hz, 1H), 3.95 (s, 3H).

A suspension of 7-methoxy-8-nitroisoquinolin-1 (2/-)-one (H2, 30 g, 0.136 mol) and 10% palladium on carbon (15 g, 0.014 mol) in ethanol (1 L) was stirred at 40 °C under hydrogen (20 psi) for 72 hours. The mixture was filtered through celite, the flask and filter pad washed with ethanol (1 L), and the combined filtrates concentrated under vacuum to give 8-amino-7-methoxy-3,4-dihydroisoquinolin-1 (2/-)-one (H3, 24 g, 92% yield) as a brown oil. MS: 193 [M+1].

N-chlorosuccinimide (20 g, 0.147 mol) was added to a solution of 8-amino-7-methoxy-3,4-dihydroisoquinolin-1 (2/-)-one (H3, 24 g, 0.125 mol) in N,N-dimethylformamide (250 mL) and stirred at room temperature overnight. The solution was partitioned between water (100 mL) and ethyl acetate (5 x 100 mL). The combined organic extracts were washed with brine (5 x 100 mL), dried over sodium sulfate, and concentrated to dryness. The residue was triturated with acetonitrile (200 mL), and the solids collected by filtration. After drying, 8-amino-5-chloro-7-methoxy-3,4-dihydroisoquinolin-1 (2/-)-one (H4, 12.5 g, 44% yield) was obtained as a blue solid. 1H NMR (400 MHz, DMSO-d6): δ 7.84 (s, 1H), 6.93 (s, 1H), 3.80 (s, 3H), 3.29-3.25 (m, 2H), 2.81 -2.78 (t, J= 6.6 Hz, 2H).

Isopentyl nitrite (20 mL, 0.149 mol) was added dropwise to a heated (55 °C) suspension of copper (II) chloride (40 g, 0.298 mol) and lithium chloride (38 g, 0.905 mol) in acetonitrile (500 mL). The mixture was stirred at that temperature for 5 minutes,
then 8-amino-5-chloro-7-methoxy-3,4-dihydroisoquinolin-1 (2/-/-)-one (H4, 20 g, 0.089 mol) was added in portions. After the addition was complete, stirring was continued at 55 °C for 45 minutes. The reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (300 mL), and extracted with ethyl acetate (4 x 200 mL). The combined organic layers were washed with aqueous ammonium chloride (200 mL) and brine (100 mL), dried over sodium sulfate, and concentrated under vacuum to give crude 5,8-dichloro-7-methoxy-3,4-dihydroisoquinolin-1 (2/-/-)-one (H5, 20 g, 90% purity, 92% yield) as a brown solid. MS: 245 [M+1].

Di-fe/f-butyl dicarbonate (76 g, 0.352 mol) was added in portions to a cooled (0 °C) solution of crude 5,8-dichloro-7-methoxy-3,4-dihydroisoquinolin-1 (2/-/-)-one (H5, 20 g, 0.082 mol) and 4-dimethylaminopyridine (30 g, 0.246 mol) in N,N-dimethylformamide (200 mL). After the addition was complete, the solution was stirred at room temperature overnight, and then partitioned between water (200 mL) and ethyl acetate (5 x 200 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (eluting with petroleum ether/ethyl acetate 100:1 to 10:1) to give fe/f-butyl 5,8-dichloro-7-methoxy-1-oxo-3,4-dihydroisoquinoline-2(1/-/-)-carboxylate (H6, 11 g, 39% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-d6): δ 7.50 (s, 1H), 4.00 (s, 3H), 3.86-3.83 (t, J = 6.8 Hz, 2H), 2.99-2.96 (t, J = 5.8 Hz, 2H), 1.54 (s, 9H).

Boron tribromide (10 mL) was added to a cooled (0 °C) solution of fe/f-butyl 5,8-dichloro-7-methoxy-1-oxo-3,4-dihydroisoquinoline-2(1/-/-)-carboxylate (H6, 14.5 g, 45.4 mmol) in dry dichloromethane (100 mL). The mixture was stirred at room temperature overnight, then water (10 mL) was added, causing a precipitate to form. The precipitate was collected by filtration, washed with water (500 mL), and dried to give 5,8-dichloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2/-/-)-one (Cpd H, 9.2 g, 95% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-d6): δ 10.58 (s, 1H), 8.17 (s, 1H), 7.13 (s, 1H), 3.25-3.23 (m, 2H), 2.83-2.80 (t, J=6.2 Hz, 2H). MS: 232 [M+1].
**Compound I**: 8-chloro-7-hydroxy-3,4-dihydroisoquinolin-1(2H)-one.

Oxalyl chloride (5.0 mL, 58 mmol) was added to a suspension of 2-chloro-3-methoxybenzoic acid (10.00 g, 53.59 mmol) in dichloromethane (100 mL), followed by slow, dropwise addition of catalytic N,N-dimethylformamide (0.25 mL, 3.2 mmol), which initiates mild gas evolution. Stirred at room temperature 50 minutes, by which time the solution had become clear and gas evolution has stopped. The solution was evaporated to dryness, the residue dissolve again in dichloromethane (20 mL), and evaporated to dryness again (2 cycles). The light orange solid residue was dissolved in dichloromethane (60 mL) and used as described below.

In a separate flask, aminoacetaldehyde diethyl acetal (8.5 mL, 58 mmol) was dissolved in dichloromethane (40 mL), triethylamine (9.5 mL, 68 mmol) was added, and the solution cooled to 0 °C. The acid chloride solution prepared above was added via dropping addition funnel over 25 minutes, then the cooling bath removed and the mixture stirred at room temperature for 45 minutes. The reaction solution was diluted with ethyl acetate (250 mL) and washed with sat. aq. NaHCO3 (50 mL) + deionized water (50 mL). The organic layer was washed again with sat. aq. NaHCO3 (100 mL), then the combined aqueous washes were back-extracted with ethyl acetate (150 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to give crude 2-chloro-N-(2,2-diethoxyethyl)-3-methoxybenzamide (11, 16.17 g, 100%) as a light orange solid. $^1$H NMR (400 MHz, DMSO-d6) δ 8.46 (t, J=5.87 Hz, 1H), 7.34 (t, J=7.58 Hz, 1H), 7.18 (dd, J=1.28, 8.38 Hz, 1H), 6.92 (dd, J=1.34, 7.58 Hz, 1H), 4.61 (t, J=5.56 Hz, 1H), 3.87 (s, 3H), 3.64 (qd, J=7.02, 9.51 Hz, 2H), 3.50 (qd, J=7.02, 9.51 Hz, 2H), 3.28 (t, J=5.81 Hz, 2H), 1.13 (t, J=7.03 Hz, 6H).
A solution of 2-chloro-N-(2,2-diethoxyethyl)-3-methoxybenzamide (11, 16.17 g, 53.59 mmol) in cone. sulfuric acid (180 mL) was heated in a 60 °C oil bath for 80 minutes. After cooling to room temperature, the reaction mixture was poured into crushed ice (~800 cc), stirred until all the ice had melted, and the resulting precipitate was collected by suction filtration. The filter cake was washed with water (3 x 50 mL) and dried in a 50 °C vacuum oven overnight, affording 8-chloro-7-methoxyisoquinolin-1(2H)-one (12, 10.31 g, 92%) as an off-white solid. 1H NMR (400 MHz, DMSO-d6) δ 11.08 (br. s., 1H), 7.61 (d, J=8.93 Hz, 1H), 7.57 (d, J=8.80 Hz, 1H), 7.02 (dd, J=5.99, 6.72 Hz, 1H), 6.47 (d, J=6.97 Hz, 1H), 3.92 (s, 3H).

A suspension of 8-chloro-7-methoxyisoquinolin-1 (2H)-one (12, 10.31 g, 49.18 mmol) and 10% palladium on carbon catalyst (2.76 g, 2.6 mmol Pd) in ethanol (250 mL) was stirred under a hydrogen balloon while heated in a 60 °C oil bath for 3.5 hours. Another portion of 10% palladium on carbon catalyst (1.65 g, 4.1 mmol total Pd) was then added and stirring resumed under a fresh hydrogen balloon at 60 °C for 19 hours more (22.5 hours total). The reaction mixture was filtered through CELITE® to remove the catalyst, and the filter cake rinsed several times with methanol. The filtrates and rinses were concentrated to give crude 7-methoxy-3,4-dihydroisoquinolin-1 (2H)-one, (13, 12.81 g, 100%) as a yellow oil which crystallizes on standing. 1H NMR (400 MHz, DMSO-d6) δ 7.94 (br. s., 1H), 7.35 (d, J=2.81 Hz, 1H), 7.22 (d, J=8.31 Hz, 1H), 7.04 (dd, J=2.87, 8.25 Hz, 1H), 3.77 (s, 3H), 3.33 (dt, J=2.45, 6.60 Hz, 2H), 2.81 (t, J=6.54 Hz, 2H).

The crude 7-methoxy-3,4-dihydroisoquinolin-1 (2H)-one, (13, 12.81 g, 49.18 mmol) was dissolved in cone. sulfuric acid (100 mL) and cooled in an ice/water bath to 5 °C internal. Added solid N-chlorosuccinimide (6.96 g, 52.1 mmol) in small portions. Stirred in the cooling bath for 15 minutes, then removed the cooling bath and continued stirring for 1.5 hours. The reaction mixture was poured onto crushed ice (~600 cc), causing a gummy precipitate to form. The flask was cooled in an ice bath, and solid sodium hydroxide was added to bring the pH of the solution to ~8. The solution was extracted with ethyl acetate (500 mL, then 2 x 200 mL), then the combined organic extracts dried over magnesium sulfate, filtered, and concentrated. Ethyl acetate (100 mL) was added to the gummy residue, and the mixture sonicated until a fine white precipitate was obtained. The precipitate was collected by suction filtration, and the filtrate concentrated to ~20 mL, allowing a second crop of precipitate to be collected.
The combined precipitate crops were dried in a 50°C vacuum oven, affording 8-chloro-7-methoxy-3,4-dihydroisoquinolin-1 (2H)-one (I4, 7.36 g, 66%). $^1$H NMR (400 MHz, DMSO-d6) δ 8.06 (br. s., 1H), 7.25 (d, J=8.56 Hz, 1H), 7.23 (d, J=8.44 Hz, 1H), 3.84 (s, 3H), 3.24 (dt, J=3.79, 6.24 Hz, 2H), 2.80 (t, J=6.24 Hz, 2H).

Boron tribromide (7.10 ml, 73.7 mmol) was added to a cooled (0°C) solution of 8-chloro-7-methoxy-3,4-dihydroisoquinolin-1 (2H)-one (I4, 7.82 g, 36.9 mmol) in dichloromethane (185 ml). After stirring at 0°C for 30 minutes, the mixture was warmed to room temperature and stirred for an additional 1.5 hours. The mixture was cooled again in an ice/water bath to 5°C internal. Deionized water (75 ml) was added dropwise over 20 minutes (causing the internal temperature to rise to 30°C), and after stirring in the cooling bath for an additional 10 minutes, the resulting precipitate was collected by suction filtration. The precipitate was dried overnight, but the mass was still much higher than expected. The solids were stirred in deionized water (250 ml) at room temperature for 2 hours, then collected by suction filtration. The filter cake was rinsed with deionized water (4 x 50 ml), air-dried until free-flowing, and then dried in a 50°C vacuum oven overnight. After drying, 8-chloro-7-hydroxy-3,4-dihydroisoquinolin-1(2H)-one (Cpd J, 6.52 g, 89%) was obtained as a white solid. $^1$H NMR (400 MHz, DMSO-d6) δ 9.97 (s, 1H), 7.95 (br. s., 1H), 7.07 (d, J=8.19 Hz, 1H), 7.02 (d, J=8.19 Hz, 1H), 3.23 (dt, J=3.79, 6.24 Hz, 2H), 2.75 (t, J=6.24 Hz, 2H). MS: 198 [M+H]+.

**Compound J**: (+)-8-chloro-7-hydroxy-3-methyl-3,4-dihydroisoquinolin-1 (2H)-one
Oxalyl chloride (14.65 g, 115.5 mmol) was added to a cooled (0 °C) solution of 3-methoxy-2-nitrobenzoic acid (17.5 g, 88.8 mmol) and N,N-dimethylformamide (0.5 mL) in dry dichloromethane (250 mL). After stirring at room temperature for 2 hours, the mixture was concentrated in vacuo to give crude 3-methoxy-2-nitrobenzoyl chloride as a white solid.

A solution of the crude 3-methoxy-2-nitrobenzoyl chloride in dichloromethane (50 mL) was added to a cooled (0 °C) solution of 1,1-dimethoxypropan-2-amine (11.55 g, 97.68 mmol) and triethylamine (10.76 g, 106.56 mmol) in dry dichloromethane (300 mL). The mixture was washed sequentially with sat. aq. NaHC03 (2 x 100 mL), 0.1 N HCl (2 x 50 mL), and brine (100 mL), dried over Na2SO4, and concentrated in vacuum to give N-(1,1-dimethoxypropan-2-yl)-3-methoxy-2-nitrobenzamide (J1, 25 g, 94%) as a white solid. 1H NMR (400 MHz, CDCl3) δ 7.47 (t, J=8.0 Hz, 1H), 7.16-7.13 (m, 2H), 6.12 (d, J=8.0 Hz, 1H), 4.32-4.25 (m, 2H), 3.92 (s, 3H), 3.47 (s, 3H), 3.46 (s, 3H), 1.20 (d, J=6.8 Hz, 3H).

A solution of N-(1,1-dimethoxypropan-2-yl)-3-methoxy-2-nitrobenzamide (J1, 15 g, 50.1 mmol) in cone. sulfuric acid (200 mL) was heated in a 60 °C oil bath for 4 hours. After cooling to room temperature, the mixture was slowly poured into ice-water (600 mL). The resulting precipitate was collected by filtration. The wet filter cake was washed with sat. aq. NaHC03 (100 mL) and ethyl acetate (45 mL) and then dried via infrared baking to give 7-methoxy-3-methyl-8-nitroisoquinolin-1 (2H)-one (J2, 4 g, 33.5%) as a brown solid. 1H NMR (400 MHz, DMSO-d6) δ 7.76 (d, J= 8.8 Hz, 1H), 7.71 (d, J= 8.8 Hz, 1H), 6.43 (s, 1H), 3.91 (s, 3H), 2.19 (s, 3H).

A mixture of 7-methoxy-3-methyl-8-nitroisoquinolin-1 (2H)-one (J2, 4 g, 17 mmol) and 10% Pd/C (2 g) in ethanol (200 mL) was hydrogenated under 30 Psi H2 at 40 °C for 72 hours, then under 45 Psi H2 at 40 °C for another 72 hours. The mixture was filtered through a CELITE® pad, and the filter cake washed with a mixture of dichloromethane and methanol (4:1 4 x 50 mL). The combined filtrates were concentrated under vacuum to give (±)-8-amino-7-methoxy-3-methyl-3,4-dihydroisoquinolin-1 (2H)-one (J3, 3 g, 85.7%) as a tan solid. MS: 206.8 [M+H]+.

Isoamyl nitrite (1.91 g, 16.3 mmol) was added to a heated (55 °C) mixture of lithium chloride (4.32 g, 101.9 mmol) and copper(II) chloride (4.65 g, 34.6 mmol) in acetonitrile (60 mL). The mixture was stirred at 55 °C for 5 minutes, then (±)-8-amino-7-methoxy-3-methyl-3,4-dihydroisoquinolin-1 (2H)-one (J3, 2.10 g, 10.2 mmol) was added.
and, the resulting mixture stirred at this temperature for 1 hour. The reaction mixture was quenched with sat. aq. NH4Cl (50 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate, concentrated, and purified via column chromatography (silica gel, Petroleum ether/EtOAc from 10:1 to 1:1) to give (±)-8-chloro-7-methoxy-3-methyl-3,4-dihydroisoquinolin-1 (2H)-one (J4, 1.1 g, 47.9%) as a yellow solid. \(^1\)H NMR (400 MHz, CDCl3) \(\delta 7.08 \ (d, J=8.4 \ Hz, 1H), \ 7.00 \ (d, J=8.4 \ Hz, 1H), \ 5.93 \ (br. s., 1H), \ 3.92 \ (s, 3H), \ 3.74 \ (m, 1H), \ 2.87-2.74 \ (m, 2H), \ 1.31 \ (d, J=6.0 \ Hz, 3H)\).

Boron tribromide (6.59 g, 26.3 mmol) was added dropwise to a cooled (0 °C) solution of (±)-8-chloro-7-methoxy-3-methyl-3,4-dihydroisoquinolin-1 (2H)-one (J4, 1.1 g, 4.4 mmol) in dry dichloromethane (40 mL). The resulting solution was stirred at room temperature overnight. The reaction mixture was cooled (0 °C) and quenched with water (10 mL). The resulting mixture was then extracted with ethyl acetate (6 x 50 mL). The combined organic layers were washed with sat. aq. NaHCO3 (50 mL) and brine (2 x 50 mL), dried over sodium sulfate and concentrated in vacuo to give (±)-8-chloro-7-hydroxy-3-methyl-3,4-dihydroisoquinolin-1 (2H)-one (Cpd J, 850 mg, 92%) as a yellow solid. \(^1\)H NMR (400 MHz, CDCl3) \(\delta 7.12 \ (d, J=8.4 \ Hz, 1H), \ 7.04 \ (d, J=8.0 \ Hz, 1H), \ 6.09 \ (s, 1H), \ 5.94 \ (br. s., 1H), \ 3.79-3.74 \ (m, 1H), \ 2.84 \ (dd, J=3.6, 14.8 \ Hz, 1H), \ 2.74 \ (dd, J=1.0, 15.4 \ Hz, 1H), \ 1.31 \ (d, J=6.4 \ Hz, 3H)\).

**Compound K**: fe/f-butyl 4-((5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)piperidine-1-carboxylate.

\[
\begin{array}{c}
\text{O}\text{Ms}
\end{array} + 
\begin{array}{c}
\begin{array}{c}
\text{HO}
\end{array}
\end{array} \xrightarrow{\text{Cs}_2\text{CO}_3} \text{DMF}
\begin{array}{c}
\begin{array}{c}
\text{O}
\end{array}
\end{array} \xrightarrow{\text{Cs}_2\text{CO}_3} \text{DMF}
\begin{array}{c}
\text{N}
\end{array} \xrightarrow{\text{Cs}_2\text{CO}_3} \text{DMF}
\begin{array}{c}
\text{Cl}
\end{array} \xrightarrow{\text{Cs}_2\text{CO}_3} \text{DMF}
\begin{array}{c}
\text{K}
\end{array}
\end{array}
\]

A mixture of 5,8-dichloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one (Cpd H, 300 mg, 1.29 mmol), ier-f-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (CAS# 141699-59-4, 397 mg, 1.42 mmol), cesium carbonate (843 mg, 2.59 mmol), and anhydrous N,N-dimethylformamide (10 mL) was stirred at 100 °C for 3 hours. After cooling room temperature, the reaction mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic phase was separated, washed with water
and brine (2 x 1000 ml), dried over sodium sulfate, concentrated to dryness, and purified by silica gel column chromatography with a gradient elution of 20→100% EtOAc/heptane to afford fe/f-butyl 4-(5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)piperidine-1-carboxylate (Cpd K, 301 mg, 56%) as a solid. $^1$H NMR (400 MHz, CHLOROFORM-d) $\delta$ 7.11 (s, 1H), 6.07 (br. s., 1H), 4.53 (m, 1H), 3.61-3.72 (m, 2H), 3.41-3.52 (m, 4H), 3.03 (t, $J$=6.36 Hz, 2H), 1.79-1.96 (m, 4H), 1.48 (s, 9H). MS: 359, [M-tBu]$^+$.  

**Compound L**: 2-{[2-(benzyloxy)-4,6-dimethylpyridin-3-yl1methyl)-7-bromo-5,8-dichloro-3,4-dihydroisoquinolin-1 (2/-)-one.  

![Chemical Structure]

Potassium fe/f-butoxide solution in tetrahydrofuran (1.0 M, 190 mL, 0.19 mol) was added dropwise to a cooled (0 °C) solution of 7-bromo-5,8-dichloro-3,4-dihydroisoquinolin-1 (2/-)-one (Cpd F, 47 g, 0.16 mol) in anhydrous N,N-dimethylformamide (500 mL) under a nitrogen atmosphere. Stirring was continued at 0 °C for 5 minutes, then 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine (Cpd A, 40.2 g, 0.15 mol) was added in one portion. After stirring for 10 minutes at 0 °C, the mixture was treated with concentrated acetic acid (2 mL) and poured into methyl fe/f-butyl ether (600 mL). The organic solution was washed with water (800 mL) and saturated aqueous sodium chloride solution (800 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography (eluting with 30:1 to 20:1 petroleum ether/ethanol acetate), affording 2-{[2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-bromo-5,8-dichloro-3,4-dihydroisoquinolin-1 (2H)-one (Cpd L, 50 g, 64% yield) as an off-white solid. $^1$H NMR (400 MHz, DMSO-d6) $\delta$ 8.08 (s, 1H), 7.45-7.43 (m, 2H), 7.32-7.29 (m, 3H), 6.76 (s, 1H), 5.38 (s, 2H), 4.71 (s, 2H), 3.24 (t, $J$ = 6 Hz, 2H), 2.72 (t, $J$ = 6 Hz, 2H), 2.36 (s, 3H), 2.31 (s, 3H). MS: 521 [M+H]$^+$.  

- 85 -
**Compound M**: 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-bromo-8-chloro-3,4-dihydro-isoquinolin-1 (2H)-one.

Potassium t-BuOK solution in tetrahydrofuran (1.0 M, 1.3 mL, 1.3 mmol) was added to a cooled (0 °C) solution of 7-bromo-8-chloro-3,4-dihydroisoquinolin-1(2H)-one (Cpd G, 0.287 g, 1.10 mmol) in DMF (10 mL). After 5 minutes, 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine (Cpd A, 0.311 g, 1.19 mmol) was added in one portion. The mixture was stirred for 30 minutes, then quenched with acetic acid (3 drops), diluted with MTBE, and washed with water (2x). The organic layer was concentrated, and the resulting oil purified on silica gel (Biotage SNAP, 10 g, gradient of 0-25% ethyl acetate in heptane) to 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-bromo-8-chloro-3,4-dihydroisoquinolin-1 (2H)-one (Cpd M, 0.387 g, 72%) as a clear gum. ¹H NMR (400 MHz, chloroform-d) δ 7.61 (d, J=8.07 Hz, 1H), 7.42-7.47 (m, 2H), 7.28-7.38 (m, 3H), 6.89 (d, J=8.07 Hz, 1H), 6.63 (s, 1H), 5.43 (s, 2H), 4.90 (s, 2H), 3.22-3.29 (m, 2H), 2.60-2.66 (m, 2H), 2.42 (s, 3H), 2.34 (s, 3H); MS 485, 487 [M+H]⁺.

**Compound N**: 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one.
A mixture of 5,8-dichloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one (Cpd H, 1 g, 4.309 mmol) and diethylcarbamoyl chloride (643 mg, 4.74 mmol) in pyridine (15 mL) was stirred at 100 °C for 18 hours. The reaction mixture was cooled to room temperature, poured into water (50 mL), acidified to pH ~3 with 3M HCl, and extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over sodium sulfate, and concentrated under vacuum to give 5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (N1, 1.42 g, ~81% purity, 80.5% yield) as an off-white solid, which was used for the next step without further purification. MS: 353 [M+Na]+.

Sodium hydride (60 wt% dispersion in mineral oil, 279 mg, 6.99 mmol) was added to a cooled (0 °C) solution of 5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (N1, 1.43 g, ~81% pure, 3.49 mmol) in dry N,N-dimethylformamide (30 mL). The mixture was stirred at room temperature for 30 minutes, then cooled again to 0 °C and a solution of 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine (Cpd A, 1.01 g, 3.84 mmol) in N,N-dimethylformamide (5 mL) was added dropwise. The cooling bath was removed and the mixture stirred at room temperature for 1 hour. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over sodium sulfate, concentrated, and purified by column chromatography (silica gel, Petroleum ether/EtOAc from 20: 1 to 4:1) to give 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (N2, 1.85 g, 95.2%) as yellow gum. $^1$H NMR (400 MHz, chloroform-d) δ 7.46-7.44 (m, 2H), 7.37-7.30 (m, 4H), 6.62 (s, 1H), 5.43 (s, 2H), 4.87 (s, 2H), 3.49 (q, J=6.8 Hz, 2H), 3.38 (q, J=6.8 Hz, 2H), 3.26 (t, J=6.0 Hz, 2H), 2.75 (t, J=6.0 Hz, 2H), 2.42 (s, 3H), 2.31 (s, 3H), 1.30 (t, J=6.8 Hz, 3H), 1.21 (t, J=7.2 Hz, 3H).

A mixture of 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (N2, 1.85 g, 3.324 mmol) and sodium hydroxide (1.33 g, 33.2 mmol) in ethanol (40 mL) was refluxed for 16 hours. The reaction mixture was concentrated in vacuo and the residue diluted with water (50 mL). The mixture was acidified with 3N HCl to pH ~ 5 and then extracted with ethyl acetate (6 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over sodium sulfate and concentrated in vacuo to give a residue, which was washed with ethyl acetate (10 mL) to give 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-}
yl)methyl)-5,8-dichloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one (Cpd N, 1.4 g, 92.1 %) as an off-white solid. \(^1\)H NMR (400 MHz, DMSO-D6) \(\delta\) 7.45 (d, \(J=6.8\) Hz, 2H), 7.35-7.32 (m, 3H), 6.89 (s, 1H), 6.75 (s, 1H), 5.77 (s, 1H), 5.38 (s, 2H), 4.70 (s, 2H), 3.17 - 3.14 (m, 2H), 2.58-2.55 (m, 2H), 2.35 (s, 3H), 2.29 (m, 3H). MS: 457 [M+H]^+.

**Compound O**: 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-8-chloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one.

A mixture of 8-chloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2/-/)-one (Cpd I, 5.6 g, 28 mmol), and diethylcarbamoyl chloride (4.3 g, 31 mmol) in pyridine (100 mL) was stirred at 100 °C for 5 hours. Water (300 mL) was added and the mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with 1 N HCl (2 x 300 mL) and brine (300 mL), dried over sodium sulfate, concentrated under vacuum, and purified by column chromatography (EtOAc) to give 8-chloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (O1, 7.6 g, 90%) as brown oil.

A solution of 8-chloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (O1, 8.0 g, 27 mmol) in dry N,N-dimethylformamide (40 mL) was added dropwise to a cooled (0 °C) suspension of sodium hydride (60 wt% in mineral oil, 2.2 g, 54 mmol) in dry N,N-dimethylformamide (20 mL). The mixture was stirred at 0 °C for 15 minutes, then 2-(Benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine (Cpd A, 8.5 g, 32.4 mmol) was added. Stirring was continued at room temperature overnight. Water (200 mL) was carefully added dropwise to the reaction mixture, which was then extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with brine (4 x 200 mL), dried...
over sodium sulfate, concentrated, and purified by column chromatography (petroleum ether/EtOAc, 3:1) to give 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-8-chloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (O2, 14 g, 99%) as yellow oil.

A mixture of 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-8-chloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl diethylcarbamate (O2, 14.0 g, 26.8 mmol) and sodium hydroxide (10.7 g, 268 mmol) in ethanol (200 mL) was refluxed overnight. The reaction mixture was concentrated under vacuum, the residue dissolved in water (200 mL), and the solution acidified to pH 3 with 1 N HCl and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over sodium sulfate, and to the residue was added ethyl acetate (20 mL) and petroleum ether (100 mL). The resulting suspension was filtered and the solids were dried under vacuum to give 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-8-chloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one (Cpd O, 9.8 g, 87%) as an off-white solid. ^1H NMR (400 MHz, DMSO-d6) δ 10.01 (s, 1H), 7.45 (d, J=6.85 Hz, 2H), 7.25-7.37 (m, 3H), 6.94-7.04 (m, 2H), 6.75 (s, 1H), 5.38 (s, 2H), 4.71 (s, 2H), 3.16 (t, J=6.24 Hz, 2H), 2.60 (t, J=6.11 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H).

Examples

General Methods and Representative Examples

Method A

Example 1: 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one
A solution of 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-bromo-5,8-dichloro-3,4-dihydroisoquinolin-1 (2H)-one (Cpd L, 500 mg, 0.961 mmol), 1-Boc-3,5-dimethylpyrazole-4-boronic acid pinacol ester (460 mg, 1.43 mmol), tripotassium phosphate (408 mg, 1.92 mmol), palladium(II) acetate (32.4 mg, 0.144 mmol), and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-phos, 118 mg, 0.288 mmol) in toluene (15 mL) and water (1.5 mL) was degassed with nitrogen and stirred at 120 °C overnight. After cooling to room temperature, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, concentrated, and purified by silica gel chromatography (petroleum ether/EtOAc =3/1 , Rf~0.3) to give fe/f-butyl 4-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3,5-dimethyl-1-H-pyrazole-1-carboxylate (1a, 290 mg, 47.5%) as a yellow gum. MS: 635 [M+H]+.

A solution of fe/f-butyl 4-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3,5-dimethyl-1-H-pyrazole-1-carboxylate (1a, 300 mg, 0.472 mmol) and trifluoroacetic acid (8 mL) in dichloromethane (8 mL) was stirred at room temperature overnight. The mixture was concentrated in vacuo and the residue was basified with sat. aq. NaHCO3 (15 mL). The mixture was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, concentrated, and purified by silica gel chromatography (DCM/MeOH =10/1 , Rf -0.5) to give 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-1 H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one (Example 1, 134.9 mg, 64.2%) as a yellow solid. 1H NMR (400 MHz, CDCl3) δ 7.30 (s, 1H), 5.96 (s, 1H), 4.81 (s, 2H), 3.73 (t, J= 6 Hz, 2H), 3.00 (t, J= 6.4 Hz, 2H), 2.39 (s, 3H), 2.31 (s, 3H), 2.16 (s, 6H). MS: 445 [M+H]+.
Method B

**Example 2**: 5,8-dichloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl1-3,4-dihydroisoquinolin-1(2H)-one

A solution of methyl 5-bromo-2-methyl-3-nitrobenzoate (29.0 g, 106 mmol) and N,N-dimethylformamide dimethyl acetal (42.0 mL, 317 mmol) in N,N-dimethylformamide (200 mL) was stirred at 110 °C overnight. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate (300 mL) and water (300 mL). The organic phase was separated, washed with water (2 x 300 mL) and brine (1 x 300 mL), concentrated to dryness in the presence of silica gel, and purified by silica gel chromatography (eluting with a gradient of 0-80% ethyl acetate in heptane) to give 7-bromo-5-nitro-1H-isochromen-1-one (2a, 9.62 g, 32%) as a solid. $^1$H NMR (400 MHz, CHLOROFORM-d) δ 8.76 (d, J=1.47 Hz, 1H), 8.60 (d, J=2.20 Hz, 1H), 7.46 (d, J=6.1 Hz, 1H), 7.34 (d, J=6.11 Hz, 1H). MS: 269 [M+H]$^+$.
A sealed tube containing 7-bromo-5-nitro-1H-isochromen-1-one (2a, 9.20 g, 34.1 mmol) and 7 N ammonia solution in methanol (100 mL) was stirred at 60 °C overnight. After chilling in an ice bath, the resulting precipitate was collected by filtration, washed with cold methanol, and air-dried to give 7-bromo-5-nitroisoquinolin-1(2H)-one (2b, 7.6 g, 83%). as a yellow solid. $^1$H NMR (400 MHz, DMSO-d6) δ 11.82 (br. s., 1H), 8.56 - 8.64 (m, 2H), 7.48 (d, J=7.58 Hz, 1H), 6.89 (d, J=7.58 Hz, 1H). MS: 267/269 [M-1].

A mixture of 7-bromo-5-nitroisoquinolin-1(2/-/-)-one (2b, 4.00 g, 14.9 mmol), 1,4-dimethyl-1H-2,3-triazole (2.17 g, 22.3 mmol), palladium acetate (334 mg, 1.49 mmol), CataCXiumA (butyl di-1-adamantylphosphine) (1.10 g, 2.97 mmol), and potassium acetate (7.30 g, 74.3 mmol) in 2-methyl-2-butanol (100 mL) was degassed with nitrogen, and heated at 120 °C in a sealed tube overnight. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate (300 mL) and water (300 mL). The organic phase was separated, washed with brine (300 mL), dried over sodium sulfate, concentrated to dryness, and purified by silica gel chromatography (eluting with a gradient of 0%-10% methanol in ethyl acetate), affording 7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-5-nitroisoquinolin-1(2H)-one (2c, 2.55 g, 60%) as a solid. $^1$H NMR (400 MHz, DMSO-d6) δ 11.95 (br. s., 1H), 8.57 (s, 2H), 7.55 (d, J=5.38 Hz, 1H), 6.98 (d, J=7.34 Hz, 1H), 4.00 (s, 3H), 2.29 (s, 3H). MS: 284 [M-1].

A sealed tube containing a solution of 7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-5-nitroisoquinolin-1(2/-/-)-one (2c, 1.0 g, 3.5 mmol) and Raney Nickel (6 g) in 2-propanol (60 mL) was heated at 110-120 °C for three days. Sixteen 1 g batches (16 g 2c total) were prepared by this method, and then combined for purification. The combined solutions were cooled to room temperature and filtered. The filtrate was concentrated under vacuum to ~30 mL, causing a precipitate to form. The precipitate was collected by filtration to give 5-amino-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one (2d, 4.0 g, 26%) as a white solid. The Raney nickel-containing first filter cake was dissolved in methanol/dichloromethane (1:1, 4 x 400 mL), stirred for 30 minutes, filtered, and the filtrate concentrated under vacuum to give a second batch of 5-amino-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one (2d, 8.0 g, 54%) as a grey solid.

N-iodosuccinimide (5.27 g, 23.43 mmol) was added in portions to a solution of 5-amino-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one (2d, 5.5 g, 21.3 mmol) in glacial acetic acid (400 mL) and the resulting mixture stirred at room
temperature for three days. A second portion of N-iodosuccinimide (2.6 g, 12.7 mmol) was then added and stirring continued at room temperature overnight. The mixture was concentrated under vacuum to remove acetic acid. The residue was dissolved in methanol (200 mL), concentrated to dryness, and purified by silica gel chromatography (eluting with 1:1 to 1:2 petroleum ether/ethyl acetate and then with 100:1 to 50:1 dichloromethane/methanol), to give 5-amino-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-6-iodo-3,4-dihydroisoquinolin-1 (2/-)-one (2e, 5.0 g, 60%) as a yellow solid.

Two batches of 5-amino-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-6-iodo-3,4-dihydroisoquinolin-1 (2/-)-one (2e, 2.5 g/6.5 mmol each batch, 5.0 g/13 mmol total) in glacial acetic acid (100 mL each batch) were treated with sulfuryl chloride (1 g, 75 mmol each batch), added dropwise at 20-25 °C. The mixtures were stirred for 2 hours, then combined and concentrated under vacuum to remove volatiles. The residue was purified by silica gel chromatography (10:1 dichloromethane/methanol) to give 5-amino-8-chloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-6-iodo-3,4-dihydroisoquinolin-1 (2/-)-one (2f, 5.5 g, 90% purity, 90% yield) as a yellow solid.

Two batches were prepared by the following method: a mixture of 5-amino-8-chloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-6-iodo-3,4-dihydroisoquinolin-1 (2/-)-one (2f, 2.9 g, 6.9 mmol each batch) and palladium on carbon (2.9 g) in glacial acetic acid (29 mL) and methanol (290 mL) was stirred under a hydrogen balloon at room temperature overnight. The combined reaction mixtures were filtered through celite, and the filter pad washed with methanol (300 mL). The filtrate was concentrated and the residue purified by silica gel chromatography (eluting with 10:1 dichloromethane/methanol) affording 5-amino-8-chloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1 (2/-)-one (2g, 3.6 g, 65% combined yield) as yellow solid.

\[^{1}H\text{ NMR}\ (400 \text{ MHz, DMSO-d6})\ \delta\ 8.12\ (s, 1H), 6.82\ (s, 1H), 3.75\ (s, 3H), 3.29-3.28\ (m, 2H), 2.70-2.67\ (m, 2H), 2.07\ (s, 3H). MS: 292\ [M+H]^+.

A mixture of copper(II) chloride (3.15 g, 23.4 mmol) and lithium chloride (3.05 g, 72.0 mmol) in acetonitrile (68.0 mL) was stirred in an oil bath (60 °C) for 5 minutes. Isopropyl nitrite (1.29 g, 11.0 mmol) was added dropwise via syringe. After the addition, the mixture was stirred at 55 °C for 2 minutes, then 5-amino-8-chloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1 (2/-)-one (2g, 2.0 g, 6.86 mmol) was added in small portions. The resulting mixture was stirred at 55 °C for 45 minutes. The reaction was quenched with sat. aq. NH₄Cl (68 mL), stirred at room temperature for 20 minutes,
then extracted with ethyl acetate (2 x 60 mL). The combined organic layers were washed with brine (150 mL), dried over sodium sulfate, concentrated and purified by column chromatography on silica gel (petroleum ether/EtOAc = 1:1 ~ 1:3, Rf ~ 0.5 in EtOAc) to give 5,8-dichloro-7-(1,4-dimethyl-1 H-1,2,3-triazol-5-yl)-3,4-dihydropyridin-1(2H)-one (2h, 1.0 g, 46.9%) as a brown solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.40 (s, 1H), 6.32 (br. s., 1H), 3.87 (s, 3H), 3.61 - 3.57 (m, 2H), 3.21 - 3.16 (m, 2H), 2.23 (s, 3H). MS: 462 [M+H]^+.

Potassium tert-butoxide (1.0 M solution in THF, (0.432 mL, 0.432 mmol) was added dropwise to a cooled (0 °C) solution of 5,8-dichloro-7-(1,4-dimethyl-1 H-1,2,3-triazol-5-yl)-3,4-dihydropyridin-1(2H)-one (2h, 119 mg, 0.382 mmol) in dry N,N-dimethylformamide (8 mL). The resulting mixture was stirred at 0 °C for 5 minutes, then 2-(benzyloxy)-3-(chloromethyl)-4-methoxy-6-methylpyridine (Cpd E, 100 mg, 0.360 mmol) was added in one-portion. After stirring at 0 °C for 10 minutes, the mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over sodium sulfate, concentrated, and purified by column chromatography (silica gel, petroleum ether/EtOAc=1/1 , Rf -0.4) to give 2-[(2-(benzyloxy)-4-methoxy-6-methylpyridin-3-yl)methyl]-5,8-dichloro-7-(1,4-dimethyl-1 H-1,2,3-triazol-5-yl)-3,4-dihydropyridin-1(2H)-one (2i, 170 mg, 85.5%) as a yellow gum. MS: 552 [M+H]^+.

A solution of 2-[(2-(benzyloxy)-4-methoxy-6-methylpyridin-3-yl)methyl]-5,8-dichloro-7-(1,4-dimethyl-1 H-1,2,3-triazol-5-yl)-3,4-dihydropyridin-1 (2H)-one (2i, 170 mg, 0.308 mmol) and trifluoroacetic acid (8 mL) in dichloromethane (8 mL) was stirred at room temperature for 12 hours. The mixture was concentrated and the residue basified to pH~8 with sat. aq. NaHC03. The resulting mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, concentrated, and purified by prep.TLC (EtOAc/MeOH=1/0, Rf -0.5) to give 5,8-dichloro-7-(1,4-dimethyl-1 H-1,2,3-triazol-5-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydropyridin-1(2H)-one (Example 2, 56.5 mg, 39.7%) as a white solid. ^1H NMR (400 MHz, CDC13) δ 12.64 (br. s., 1H), 7.30 (s, 1H), 5.94 (s, 1H), 4.84 (d, J=1 3.6 Hz, 1H), 4.74 (d, J=1 3.6 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.60-3.59 (m, 2H), 3.06-3.02 (m, 2H), 2.37 (s, 3H), 2.22 (s, 3H). MS: 462 [M+H]^+.
Method C

Example 3: 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(methylamino)-3,4-dihydroisoquinolin-1 (2H)-one.

\[
\begin{align*}
\text{Cpd L} & \quad \text{Pd}_2(\text{dba})_3 \quad \text{Xantphos} \\
\text{H}_2\text{NOCOR} & \quad \text{dioxane} \\
\text{CH}_3\text{I} & \quad \text{DMF}
\end{align*}
\]

Example 3

A solution of 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-bromo-5,8-dichloro-3,4-dihydroisoquinolin-1 (2H)-one (Cpd L, 864.6 mg, 1.662 mmol), fe/f-butyl carbamate (1.20 g, 10.2 mmol), Xantphos (500.0 mg, 0.864 mmol), tris(dibenzylideneacetone)dipalladium (226.6 mg, 0.247 mmol), and cesium carbonate (1.48 g, 4.54 mmol) in 1,4-dioxane (11.0 mL) in a sealed vial was heated to 110 °C for 60 minutes in a microwave reactor. After cooling to room temperature, the mixture was filtered to remove a green precipitate. The reaction flask and filter cake were rinsed with deionized water (2 x 20 mL) and ethyl acetate (2 x 20 mL). The biphasic filtrate was transferred to a separatory funnel, shaken, and the layers separated. The organic layer was dried over magnesium sulfate, filtered, concentrated onto silica, and purified on a 40 g silica column, eluting with 0-30% ethyl acetate in heptane, affording fe/f-butyl (2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)carbamate (3a, 376 mg, 41%) as an off-white foam. $^1$H NMR (400 MHz, DMSO-d6) δ 8.73 (s, 1H), 7.82 (s, 1H), 7.40-7.47 (m, 2H), 7.24-7.35 (m, 3H), 6.74 (s, 1H), 5.37 (s, 2H), 4.70 (s, 2H), 3.22 (t, J=6.17 Hz, 2H), 2.71 (t, J=6.1 Hz, 2H), 2.35 (s, 3H), 2.29 (s, 3H), 1.47 (s, 9H). MS: 556 [M+H]+.

Iodomethane (0.11 mL, 1.8 mmol) was added to a solution of fe/f-butyl (2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)carbamate (3a, 376 mg, 41%) as an off-white foam.
tetrahydroisoquinolin-7-yl)carbamate (3a, 372 mg, 0.668 mmol) and cesium carbonate (699 mg, 2.1 mmol) in N,N-dimethylformamide (6.0 ml). After stirring at room temperature for 1 hour, water (10 ml) was added and the solution extracted with ethyl acetate (2 x 20 ml). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to a yellow gum. Methanol (5 ml) was added to the gum, and the resulting suspension sonicated until a fine dispersion was obtained. The precipitate was collected by suction filtration. The filtrate was concentrated to dryness, suspended in methanol, and a second crop of precipitate obtained in the same manner. The combined precipitate crops were air-dried to give fe/f-butyl (2-((2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)(methyl)carbamate (3b, 294 mg, 77%) as a white solid. ¹H NMR (400 MHz, DMSO-d6) δ 7.72 (s, 1H), 7.43 (d, J=7.34 Hz, 2H), 7.23-7.34 (m, 3H), 6.75 (s, 1H), 5.38 (s, 2H), 4.71 (s, 2H), 3.24 (t, J=6.11 Hz, 2H), [3.07 (br. s., 1H), 3.03 (s, 2H), N-CH₃ rotamers], 2.70-2.80 (m, 2H), 2.35 (s, 3H), 2.30 (s, 3H), [1.46 (br. s., 3H), 1.28 (s, 6H), N-Boc rotamers]. MS: 570 [M+H]^+.

A suspension of fe/f-butyl (2-((2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1,2,3,4-tetrahydroisoquinolin-7-yl)(methyl)carbamate (3b, 289.0 mg, 0.507 mmol) in acetonitrile (5.0 ml) was treated with 4.0 M HCl/dioxane solution (0.90 ml, 3.6 mmol), and stirred at room temperature for 1 hour. Concentrated under vacuum, and dried the residue under high vacuum overnight to give crude product as 249.0 mg yellow foam. Acetonitrile (7 ml) was added, and the suspension sonicated until a precipitate formed. The precipitate was collected by suction filtration. The filtrate was concentrated to dryness, the residue treated with acetonitrile (3 ml), sonicated, and a second crop of precipitate collected in the same way. The combined precipitate crops were air-dried to give 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(methylamino)-3,4-dihydroisoquinolin-1 (2H)-one monohydrochloride (Example 3, 176 mg, 83%) as a light yellow solid. ¹H NMR (400 MHz, DMSO-d6) δ 11.54 (br. s., 1H), 6.76 (s, 1H), 6.76 (s, 1H), 5.88 (s, 1H), 5.49-6.24 (m, 2H), 4.56 (s, 2H), 3.37 (t, J=6.11 Hz, 2H), 2.76 (s, 3H), 2.70-2.75 (m, 2H), 2.14 (s, 3H), 2.12 (s, 3H). MS: 380 [M+H]^+. 
Method D

**Example 4**: 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-4H-1,2,4-tiazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one.

![Chemical Structure](image)

A suspension of 1,5-bicycle (4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5,8-dichloro-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)carbamate (3a, 1.58 g, 2.84 mmol) in acetonitrile (28 mL) was treated with 4.0 M HCl/dioxane solution (5.0 ml, 20 mmol) at room temperature for 1 hour. The resulting precipitate was collected by suction filtration, then it was dissolved in sat. aq. NaHCO3 (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to a yellow gum/foam. Acetonitrile (10 mL) was added and the suspension sonicated until a fine suspension was obtained. The solids were collected by suction filtration and air-dried to give 7-amino-2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-3,4-dihydroisoquinolin-1 (2H)-one (4a, 591.2 mg, 46%) as a white solid. ¹H NMR (400 MHz, DMSO-d6) δ 7.44 (d, J=6.60 Hz, 2H), 7.24-7.37 (m, 3H), 6.99 (s, 1H), 6.74 (s, 1H), 5.65 (s, 2H), 5.37 (s, 2H), 4.69 (s, 2H), 3.16 (t, J=6.1 Hz, 2H), 2.57 (t, J=6.1 1 Hz, 2H), 2.34 (s, 3H), 2.28 (s, 3H). MS: 456 [M+H]^+.

A solution of 7-amino-2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-3,4-dihydroisoquinolin-1 (2H)-one (4a, 184 mg, 0.404 mmol) and p-toluene sulfinic acid monohydrate (9.9 mg, 0.052 mmol) in neat 2,5-dimethyl-1,3,4-oxadiazole (614.6 mg, ~ 0.5 mL, 6.26 mmol) was stirred at 120 °C for 4 days. After cooling to room temperature, the entire reaction mixture was applied to silica gel and purified by column chromatography (eluting with 0-20%[EtOH+5%NH4OH] in ethyl acetate), to give 5,8-
dichloro-2-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-3,4-dihydroisoquinolin-1-(2H)-one (Example 4, 37 mg, 19%) as a light orange solid. $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.54 (br. s., 1H), 8.02 (s, 1H), 5.89 (s, 1H), 4.56 (s, 2H), 3.57 (t, $J=6.1$ Hz, 2H), 3.01 (t, $J=6.1$ Hz, 2H), 2.20 (s, 3H), 2.13 (s, 3H), 2.09 (s, 6H). MS: 446 [M+H]$.^+$.

Method E

**Example 5**: (5£)-1,4-anhydro-3,6-dideoxy-2-O-[5,8-dichloro-2-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-L-threo-hexitol.

To an ice-chilled mixture of (2R)-oxiran-2-ylmethanol (2.00 g, 27.0 mmol) and imidazole (3.68 g, 54.0 mmol) in anhydrous dichloromethane (60 mL) was added tert-
butyl(chloro)diphenylsilane (8.40 mL, 32.4 mmol) dropwise, causing the formation of a white precipitate. The mixture was stirred at 0 °C for 15 minutes, then the cooling bath removed and stirring continued at room temperature for one hour. Aqueous ammonium chloride solution (2M, 100 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (100 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (eluting with a gradient of 0-30% ethyl acetate in heptane), affording fe/f-butyl[(2S)-oxiran-2-ylmethoxy]diphenylsilane (5a, 8.40 g, 99% yield) as an oil. 1H NMR (400 MHz, CDCl3) δ 7.65 - 7.76 (m, 4H), 7.36 - 7.49 (m, 6H), 3.88 (dd, J=1.86, 3.30 Hz, 1H), 3.74 (dd, J=1.80, 4.71 Hz, 1H), 3.10 - 3.20 (m, 1H), 2.76 (dd, J=5.14, 4.16 Hz, 1H), 2.63 (dd, J=5.14, 2.69 Hz, 1H), 1.09 (s, 9H). MS: 330 [M+H]+.

Copper (I) cyanide (3.60 g, 40.2 mmol) was placed in a three-necked flask under nitrogen and dried by gentle heating with a heat gun under vacuum. It was then allowed to cool to room temperature under nitrogen. This process was repeated three times, and then anhydrous tetrahydrofuran (80 mL) was added. The resulting mixture was cooled to -78 °C, and then vinyl magnesium bromide (1 M solution in tetrahydrofuran, 88.5 mL, 88.5 mmol) was added dropwise while maintaining the internal temperature below -68 °C. The heterogeneous mixture was warmed to -20 °C and stirred at this temperature for 30 minutes. After cooling the solution back to -78 °C, fe/f-butyl[(2S)-oxiran-2-ylmethoxy]diphenylsilane (5a, 8.38 g, 26.8 mmol) was added dropwise. The mixture was stirred, and allowed to gradually warm to room temperature, overnight. The reaction mixture was quenched with 100 mL ammonium hydroxide/ammonium chloride (1/10 2M NH₄Cl), and extracted with ethyl acetate (200mL). The organic layer was washed with brine (200 mL), dried over sodium sulfate, concentrated to dryness, and purified by silica gel chromatography (eluting with a gradient of 0-20% ethyl acetate in heptane), to give (2S)-1-[(ferf-butyl(diphenyl)silyl]oxy)pent-4-en-2-ol (5b, 5.68 g, 62% yield) as a clear oil. 1H NMR (400 MHz, CDCl3) δ 7.65 - 7.71 (m, 4H), 7.36 - 7.49 (m, 6H), 5.75 - 5.87 (m, 1H), 5.03 - 5.14 (m, 2H), 3.76 - 3.85 (m, 1H), 3.66 - 3.72 (m, 1H), 3.54 - 3.61 (m, 1H), 2.45 (d, J=4.03 Hz, 1H), 2.23 - 2.30 (m, 2H), 1.09 (s, 9H). MS: 358 [M+18].

A solution of (2S)-1-[(fe/f-butyl(diphenyl)silyl]oxy)pent-4-en-2-ol (5b, 5.60 g, 16.4 mmol) in anhydrous tetrahydrofuran (30 mL) was cooled to 0 °C and treated with tetrabutylammonium fluoride solution (1 M in tetrahydrofuran, 18.3 mL, 18.3 mmol). The
mixture was stirred and allowed to warm to room temperature over one hour, then
concentrated and purified by silica gel chromatography (eluting with a gradient of 0-
100% ethyl acetate in heptane), affording (2S)-pent-4-ene-1,2-diol (5c, 1.25 g, 73%
yield) as an oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.83 (ddt, $J=17.16$, 10.10, 7.15, 7.15 Hz, 
1H), 5.08 - 5.21 (m, 2H), 3.73 - 3.83 (m, 1H), 3.67 (d, $J=11.13$ Hz, 1H), 3.48 (dd, 
$J=1$ 0.94, 7.40 Hz, 1H), 2.51 (br. s., 1H), 2.42 (br. s., 1H), 2.17 - 2.32 (m, 2H).

A mixture of (2S)-pent-4-ene-1,2-diol (5c, 1.20 g, 11.7 mmol) and sodium
bicarbonate (2.96 g, 35.2 mmol) in anhydrous acetonitrile (40 mL) was stirred for ten
minutes at room temperature, then cooled to 0 °C in an ice bath. Iodine (8.95 g, 35.2 
mmol) was added, and stirring continued for two hours, as the mixture was allowed to
warm to room temperature. The solution was diluted with diethyl ether (100 mL),
 washed with 1M aqueous sodium thiosulfate (100 mL) and brine (100 mL), dried over
sodium sulfate, concentrated, and purified by silica gel chromatography (eluting with a
gradient of 0-100% ethyl acetate in heptane), affording a mixture of (3S,5S)-5-
(iodomethyl)tetrahydrofuran-3-ol and (3S,5R)-5-(iodomethyl)tetrahydrofuran-3-ol (5d,
2.19 g, 82% yield).

The mixture of (3S,5S)-5-(iodomethyl)tetrahydrofuran-3-ol and (3S,5R)-5-
(iodomethyl)tetrahydrofuran-3-ol (5d, 2.16 g, 9.47 mmol) was dissolved in anhydrous
dimethylsulfoxide (40 mL). Potassium 4-nitrobenzoate (2.98 g, 14.2 mmol) and 18-
crown-6 (3.76 g, 14.2 mmol) were added and the mixture stirred at 90 °C overnight.
After cooling to room temperature, the reaction mixture was partitioned between ethyl
acetate (100 mL) and water (100 mL). The organic phase was washed with water (100 
Ml) and brine (100 mL), dried over sodium sulfate, concentrated to dryness, and
purified by silica gel chromatography (eluting with a gradient of 0-100% ethyl acetate in
heptane), to give the product as a mixture of diastereomers: ((2S,4S)-4-
hydroxytetrahydrofuran-2-yl)methyl 4-nitrobenzoate and ((2R,4S)-4-
hydroxytetrahydrofuran-2-yl)methyl 4-nitrobenzoate (5e, 1.13 g, 45% yield) as a solid.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 - 8.33 (m, 4H), 4.46 - 4.64 (m, 3H), 4.36 (dd, 
$J=1$ 1.68, 6.66 Hz, 1H), 4.05 (dd, $J=9.90$, 4.03 Hz, 0.76Hz), 3.93 - 3.99 (m, 0.24H), 3.80 -
3.88 (m, 1H), 2.34 - 2.45 (m, 0.25H), 2.08 - 2.17 (m, 0.77H), 1.81 - 1.96 (m, 1H), 1.57
(br. s., 1H).

The mixture of ((2S,4S)-4-hydroxytetrahydrofuran-2-yl)methyl 4-nitrobenzoate
and ((2R,4S)-4-hydroxytetrahydrofuran-2-yl)methyl 4-nitrobenzoate (5e, 700 mg, 2.62
was combined with triethylamine (1.10 mL, 7.89 mmol) in anhydrous dichloromethane (12 mL). Methanesulfonyl chloride (400 µL, 5.17 mmol) was added, causing a slight exotherm. After stirring at room temperature for three hours, the reaction mixture was partitioned between water (50 mL) and dichloromethane (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, concentrated, and purified by silica gel chromatography (eluting with a gradient of 20-100% ethyl acetate in heptane). The less polar peak was the desired single diastereomer, ((2R,4S)-4-((methylsulfonyl)oxy)tetrahydrofuran-2-yl)methyl 4-nitrobenzoate (5f, 672 mg, 74% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.26 - 8.33 (m, 2H), 8.17 - 8.25 (m, 2H), 5.34 - 5.43 (m, 1H), 4.50 - 4.60 (m, 2H), 4.34 - 4.43 (m, 1H), 4.13 - 4.20 (m, 1H), 4.05 - 4.12 (m, 1H), 3.07 (s, 3H), 2.47 (dd, \(J=14.24, 5.81\) Hz, 1H), 2.00 - 2.13 (m, 1H).

A solution of ((2R,4S)-4-((methylsulfonyl)oxy)tetrahydrofuran-2-yl)methyl 4-nitrobenzoate (5f, 300 mg, 0.869 mmol), 5,8-dichloro-7-hydroxy-3,4-dihydroisoquinolin-1(2/-)-one (Cpd H, 222 mg, 0.956 mmol), and cesium carbonate (566 mg, 1.74 mmol) in N,N-dimethylformamide (8 mL) was heated to 100 °C for three hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50mL), washed with water (2 x 50mL) and brine (50mL), dried over sodium sulfate, concentrated to dryness, and purified by silica gel chromatography (eluting with a gradient of 0-100% ethyl acetate in heptane) to give 2,5-anhydro-3-deoxy-4-O-(5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-1 -O-(4-nitrobenzoyl)-L-/?reo-pentitol (5g, 128 mg, 31% yield) as a solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.18 - 8.33 (m, 4H), 7.03 (s, 1H), 6.09 (br. s., 1H), 4.99 (td, \(J=4.28, 1.96\) Hz, 1H), 4.56 - 4.62 (m, 2H), 4.42 - 4.52 (m, 1H), 4.27 (d, \(J=1.64\) Hz, 1H), 4.02 (dd, \(J=1.05, 4.34\) Hz, 1H), 3.48 (td, \(J=6.36, 3.91\) Hz, 2H), 2.99 - 3.09 (m, 2H), 2.56 (ddd, \(J=14.24, 8.19, 6.42\) Hz, 1H), 2.18 (dd, \(J=14.12, 5.07\) Hz, 1H).

MS: 481 [M+H]^+.

Potassium tert-butoxide solution in tetrahydrofuran (1.0 M, 645 µL, 0.645 mmol) was added dropwise to a cooled (0 °C) solution of 2,5-anhydro-3-deoxy-4-O-(5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-1 -O-(4-nitrobenzoyl)-L-/?reo-pentitol (5g, 120 mg, 0.249 mmol) in anhydrous N,N-dimethylformamide (4 mL). After stirring for 30 minutes, a solution of 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine (Cpd A, 71 mg, 0.273 mmol) in anhydrous N,N-dimethylformamide (1 mL) was added and stirring continued at 0 °C for 30 more minutes. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (2 x 50 mL) and brine (50 mL), dried over
sodium sulfate, concentrated to dryness, and purified by silica gel chromatography (eluting with a gradient of 0-100% ethyl acetate in heptane), affording 1,4-anhydro-2-O- (2-[(2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl]-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-deoxy-L-/?reo-pentitol (5h, 36 mg, 26% yield) as a solid.

1H NMR (400 MHz, CDCl₃) δ 7.45 (d, J=7.21 Hz, 2H), 7.29 - 7.40 (m, 3H), 6.94 (s, 1H), 6.62 (s, 1H), 5.43 (s, 2H), 4.92 (br. s., 1H), 4.87 (s, 2H), 4.15 - 4.26 (m, 2H), 3.91 (dd, J=1.03, 3.91 Hz, 1H), 3.75 - 3.84 (m, 1H), 3.66 - 3.75 (m, 1H), 3.25 (t, J=6.05 Hz, 2H), 2.69 (t, J=6.05 Hz, 2H), 2.42 (s, 3H), 2.34 - 2.40 (m, 1H, 2.32 (s, 3H), 2.03 - 2.16 (m, 2H). MS: 557 [M+H]+.

To a solution of 1,4-anhydro-2-O- (2-[(2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl]-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-deoxy-L-/?reo-pentitol (5h, 233 mg, 0.418 mmol) in chloroform (10 mL) was added Dess-Martin periodinane (266 mg, 0.627 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 16 hours. The mixture was diluted with dichloromethane (10 mL), washed sequentially with sat. aq. NaHCO₃ (3 x 10 mL) and saturated aq. NaCl (10 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by prep. TLC (petroleum ether/EtOAc = 1:1) to give 2,5-anhydro-4-O- (2-[(2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl]-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-deoxy-L-ffreo-pentose (5i, 110 mg, 47%) as a yellow solid.

Methylmagnesium bromide (3.0 M in diethyl ether, 0.036 mL, 0.13 mmol) was added to a cooled (0 °C) solution of 2,5-anhydro-4-O- (2-[(2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl]-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3-deoxy-L-ffreo-pentose (5i, 60 mg, 0.11 mmol) in dry tetrahydrofuran (10 mL). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with sat. aq. NH₄Cl (3 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with saturated aq. NaCl (5 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by prep. TLC (petroleum ether/EtOAc=1:1, Rf~0.35) to give (5ζ)-1,4-anhydro-2-O- (2-[(2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl]-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3,6-dideoxy-L-/?reo-hexitol (5j, 29 mg, 47%) as a white solid.

Trifluoroacetic acid (5 mL) was added to a cooled (0 °C) solution of (5ζ)-1,4-anhydro-2-O- (2-[(2-(benzylxy)-4,6-dimethylpyridin-3-yl)methyl]-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-3,6-dideoxy-L-/?reo-hexitol (5j, 40 mg, 0.07 mmol) in
dichloromethane (5 mL). The ice bath was removed and the stirring continued at 25 °C for 6 hours. The mixture was concentrated and the residue dissolved in dichloromethane (20 mL) and sat. aq. NaHCO₃ (10 mL). The mixture was stirred at room temperature for 15 minutes, the layers separated, and the aqueous layer extracted with dichloromethane (2 x 5 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by prep. TLC (DCM/MeOH=1 0:1 , Rf~0.55) to give (5ξ)-1,4-anhydro-3,6-dideoxy-2-0-{5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-L-arabino-hexitol (Example 5, 9.6 mg, 28%) as a white solid. Based on the analysis of the ¹H NMR (specifically the CH₃ and H at the secondary alcohol), the isolated material was prepared as a single enantiomer with unknown absolute configuration at the secondary alcohol. ¹H NMR (400 MHz, Methanol-d₄) δ D7.25 (s, 1H), 6.11 (s, 1H), 5.08-5.06 (m, 1H), 4.74 (s, 2H), 4.1-3.92 (m, 1H), 3.91-3.89 (m, 1H), 3.84-3.82 (m, 1H), 3.77-3.75 (m, 1H), 3.48 (t, J=6 Hz, 2H), 2.91 (t, J=6.2 Hz, 2H), 2.44-2.42 (m, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 2.14-2.13 (m, 1H), 1.19 (d, J=6.4 Hz, 3H). MS 481 [M+H]⁺.

Method F

Example 6: 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methylH-7-(((2R)-2-hydroxybutanoyl)piperidin-4-yl)oxy)-3,4-dihydroisoquinolin-1 (2H)-one.
Potassium fe/f-butoxide (1.0 M solution in THF, 0.80 mL, 0.80 mmol) was added to an icebath-cooled solution of fe/f-buty 4-((5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)piperidine-1 -carboxylate (Cpd K, 294 mg, 0.708 mmol) in anhydrous N,N-dimethylformamide (6 mL). After stirring the mixture for 30 minutes, a solution of 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine (Cpd A, 210 mg, 0.779 mmol) in anhydrous N,N-dimethylformamide (4 mL) was added in one portion. The resulting mixture was stirred at 0 °C for 30 minutes, then partitioned between ethyl acetate (100 mL) and water (100 mL). The organic phase was separated, washed sequentially with water (2 x 100 mL) and brine (1 x 100 mL), dried over sodium sulfate, and concentrated to afford fe/f-buty 4-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)piperidine-1 -carboxylate (6a, 450 mg, 99%) as a foam-like solid. 1H NMR (400 MHz, CHLOROFORM-d) δ 7.42-7.48 (m, 2H), 7.29-7.39 (m, 3H), 7.03 (s, 1H), 6.63 (s, 1H), 5.43 (s, 2H), 4.88 (s, 2H), 4.49 (t, J=6.28 Hz, 1H), 3.62 - 3.71 (m, 2H), 3.40 - 3.49 (m, 2H), 3.26 (t, J=6.24 Hz, 2H), 2.69 (t, J=6.24 Hz, 2H), 2.42 (s, 3H), 2.33 (s, 3H), 1.78 - 1.94 (m, 4H), 1.48 (s, 9H). MS: 640 [M+H]+.

A solution of fe/f-buty 4-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-5,8-dichloro-1 -oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)piperidine-1 -carboxylate (6a, 530 mg, 0.827 mmol) and trifluoroacetic acid (15 mL) in dichloromethane (15 mL) was stirred at room temperature for 16 hours. The reaction mixture was concentrated and the residue treated saturated aqueous sodium bicarbonate until solution pH ~9. The mixture was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried over sodium sulfate, concentrated, and purified by silica gel chromatography (DCM/MeOH 10:1) to give 5,8-dichloro-2-((4,6-dimethyl-2 -oxo-1,2-dihydropyridin-3-yl)methyl)-7-(piperidin-4-yloxy)-3,4-dihydroisoquinolin-1 (2H)-one (6b, 150 mg, 40%) as off-white solid. The combined aqueous layers from the extraction were lyophilized and the residue was purified in the same manner to afford a second batch of 5,8-dichloro-2-((4,6-dimethyl-2 -oxo-1,2-dihydropyridin-3-yl)methyl)-7-(piperidin-4-yloxy)-3,4-dihydroisoquinolin-1 (2H)-one (6b, 200 mg, 54%) as an off-white solid. MS: 450 [M+H]+.

To a cooled (0 °C) mixture of 5,8-dichloro-2-((4,6-dimethyl-2 -oxo-1,2-dihydropyridin-3-yl)methyl)-7-(piperidin-4-yloxy)-3,4-dihydroisoquinolin-1 (2H)-one (6c, 80 mg, 0.18 mmol), (R)-2-hydroxybutanoic acid (22.2 mg, 0.213 mmol) and
diisopropylethyl amine (45.9 mg, 0.355 mmol) in N,N-dimethylformamide (10 mL) was added HATU (74.3 mg, 0.195 mmol), and the mixture stirred at room temperature for 3 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over sodium sulfate, concentrated, and purified by prep. HPLC (Column: Phenomenex Gemini c18 250’21.2mm*10um Mobile phase: from 27% MeCN in water (0.225% FA) to 47% MeCN in water (0.225% FA) Wavelength: 220 nm Workup: lyophilization) to give 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydro-3-yl)methyl]-7-([1-[(2R)-2-hydroxybutanoyl]piperidin-4-yl]oxy)-3,4-dihydroisoquinolin-1 (2H)-one. (Example 6, 32 mg, 34%) as a white solid. 

\[ \text{Example 6} \]

Method G

Example 7: 2-[(4,6-dimethyl-2-oxo-1,2-dihydro-3-yl)methyl]-7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile

\[ \text{H3} \quad \overset{\text{f-BuONO}}{\text{CuCN}} \quad \{	ext{DMSO} \} \quad \overset{\text{TFA}}{\text{CH}_2\text{Cl}_2} \quad \text{7a} \quad \text{7b} \]

7e/f-butyl nitrite (5.68 g, 16.5 mmol) was added to a solution of copper(I) cyanide (1.4 g, 15.04 mmol) in dimethylsulfoxide (30 mL) at 60 °C. To this was added dropwise a solution of 8-amino-7-methoxy-3,4-dihydroisoquinolin-1 (2H)-one (H3, 2.89 g, 15.04 mmol) in dimethylsulfoxide (20 mL). The mixture was stirred at 60 °C for 30 minutes, cooled to 45 °C, and aq. HCl (4M, 30 mL) was added dropwise. The solution was stirred at 45 °C for 5 minutes and then cooled to room temperature. The mixture was diluted...
with water (50 mL) and filtered. The filtrate was extracted with dichloromethane (4 x 40 mL). The combined organic layers were washed sequentially with water (3 x 30 mL) and brine (40 mL), dried over sodium sulfate, filtered, and purified by silica gel chromatography (EtOAc/MeOH=20:1) to give crude 7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile (7a, 390 mg, ~70% purity) as a yellow solid, which was used on next step without further purification.

Potassium fe/f-butoxide (1.0 M solution in THF, 1.96 mL, 1.96 mmol) was added to a cooled (0 °C) solution of crude 7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile (7a, 330 mg, ~ 1.63 mmol) in anhydrous N,N-dimethylformamide (20 mL). After stirring for 5 minutes at 0 °C, a solution of 2-(benzyloxy)-3-(chloromethyl)-4,6-dimethylpyridine (Cpd A, 403 mg, 1.54 mmol) in dry N,N-dimethylformamide (2 mL) was added dropwise and stirring continued for 10 minutes more. The mixture was quenched with concentrated acetic acid (0.5 mL) and partitioned between water (20 mL) and MTBE (3 x 30 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over sodium sulfate, concentrated, and purified by silica gel chromatography (petroleum ether/EtOAc=1:1, Rf1: ~ 0.3, Rf2: ~ 0.7) to give 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile (7b, 230 mg, 33.0%) as a yellow solid. MS: 428 [M+H]^+.

Trifluoroacetic acid (3.5 mL) was added to a cooled (0 °C) solution of 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile (7b, 270 mg, 0.632 mmol) in dichloromethane (10 mL). The cooling bath was removed and the mixture stirred at room temperature overnight. LCMS showed the reaction was incomplete, so more trifluoroacetic acid (5 mL) was added and the mixture stirred at 40 °C for 8 hours. After cooling to room temperature, sat. aq. NaHC03 (40 mL) was added to bring the solution pH to ~8. The mixture was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, concentrated, and purified by silica gel chromatography (DCM/MeOH 10:1) to give 2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile (Example 7, 44.7 mg, 21%) as a light yellow solid. 1H NMR (400 MHz, DMSO-d6) δ 11.59 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.37 (s, J = 8.4 Hz, 1H), 5.90 (s, 1H), 4.58 (s, 2H), 3.92 (s, 3H), 3.45 (t, J = 6.6 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.17 (s, 3H), 2.13 (s, 3H). MS: 360 [M+Na]^+. 

- 106 -
Method H

Example 8: 7-tert-butoxy-8-chloro-2-[4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl]methyl-3,4-dihydroisoquinolin-1 (2H)-one

\[
\begin{align*}
\text{Cpd O} & \quad \text{to} \quad \text{toluene} \\
\text{8a} & \quad \text{Pd/C, H}_2 \quad \text{EtOAc}
\end{align*}
\]

A solution of 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-8-chloro-7-hydroxy-3,4-dihydroisoquinolin-1 (2H)-one (Cpd O, 200 mg, 0.47 mmol) in toluene (10 mL) and the mixture heated to reflux overnight. After cooling to room temperature, the mixture was concentrated under vacuum and the residue partitioned between ethyl acetate (100 mL) and sat. aq. NaHCO\textsubscript{3} (50 mL). The organic layer was washed with brine (30 mL), dried over sodium sulfate, concentrated, and purified by silica gel chromatography (petroleum ether/EtOAc 1:1), affording 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-(tert-butoxy)-8-chloro-3,4-dihydroisoquinolin-1 (2H)-one (8a, 120 mg, 53%) as a yellow oil. MS: 479 [M+H]⁺.

\[\text{H NMR (400 MHz, CDCl}_3) \delta 1.43 (s, 1 H), 7.72 (d, J = 8 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), \]

A solution of 2-((2-(benzyloxy)-4,6-dimethylpyridin-3-yl)methyl)-7-(tert-butoxy)-8-chloro-3,4-dihydroisoquinolin-1 (2H)-one (8a, 120 mg, 0.25 mmol) in methanol (10 mL) was treated with 10% palladium on carbon catalyst (wet, 15 mg) and stirred under hydrogen (15 psi) at room temperature for 5 hours. The mixture was filtered and concentrated to give 7-tert-butoxy-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one (Example 8, 63.2 mg, 65%) as a grey solid. 

\[\text{H NMR (400 MHz, CDCl}_3) \delta 11.43 (s, 1 H), 7.72 (d, J = 8 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), \]
5.93 (s, 1H), 4.79 (s, 2H), 3.61 (t, J = 8Hz, 2H), 2.79 (t, J = 8Hz, 2H), 2.36 (s, 3H), 2.27 (s, 3H), 1.42 (s, 9H). MS: 389 [M+H]^+.

Additional compounds of the invention were prepared by modifications of the methods exemplified herein. Selected compounds prepared and their corresponding characterization data are presented in Table 1 below. Additional compounds envisaged within the scope of the invention are shown in Table 2. The compounds in Table 2 can be prepared by modifications of the methods provided herein.

Table 1

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure / IUPAC name</th>
<th>Method</th>
<th>LCMs (M+H)</th>
<th>^1H NMR (ppm)</th>
<th>Stereochem. Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /> 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>447</td>
<td>1H NMR (400 MHz, CDCl3) δ 7.30 (s, 1H), 5.96 (s, 1H), 4.81 (s, 2H), 3.73 (t, J = 6 Hz, 2H), 3.00 (t, J = 6.4 Hz, 2H), 2.39 (s, 3H), 2.31 (s, 3H), 2.16 (s, 6H).</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /> 5,8-dichloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>B</td>
<td>462</td>
<td>1H NMR (400 MHz, CDCl3) δ ppm 12.64 (br. s., 1H), 7.30 (s, 1H), 5.94 (s, 1H), 4.86-4.83 (m, 1H), 4.76, 4.72 (m, 1H), 3.89-3.85 (m, 6H), 3.60-3.59 (m, 2H), 3.06-3.02 (m, 2H), 2.37 (s, 3H), 2.22 (s, 3H).</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>3</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(methylamino)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C</td>
<td>380</td>
<td>1H NMR (400 MHz, DMSO-d6) $\delta$ 11.54 (br. s., 1H), 6.76 (s, 1H), 5.88 (s, 1H), 5.49- 6.24 (m, 2H), 4.56 (s, 2H), 3.37 (t; J=6.11 Hz, 2H), 2.76 (s, 3H), 2.70-2.75 (m, 2H), 2.14 (s, 3H), 2.12 (s, 3H) [1.0 HCl salt]</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>D</td>
<td>446</td>
<td>1H NMR (400 MHz, DMSO-d6) $\delta$ 11.54 (br. s., 1H), 8.02 (s, 1H), 5.89 (s, 1H), 4.56 (s, 2H), 3.57 (t; J=6.11 Hz, 2H), 3.01 (t; J=6.11 Hz, 2H), 2.20 (s, 3H), 2.13 (s, 3H), 2.09 (s, 6H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1" alt="Structure" /> (5c)-1,4-anhydro-3,6-dideoxy-2-O-[(5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-L-threo-hexitol</td>
<td>E</td>
<td>481</td>
<td>1H NMR (400 MHz, Methanol-d4) δ 7.25 (s, 1H), 6.11 (s, 1H), 5.08-5.06 (m, 1H), 4.74 (s, 2H), 4.1-3.92 (m, 1H), 3.91-3.89 (m, 1H), 3.84-3.82 (m, 1H), 3.77-3.75 (m, 1H), 3.48 (t, J=6 Hz, 2H), 2.91 (t, J=6.2 Hz, 2H), 2.44-2.42 (m, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 2.14-2.13 (m, 1H), 1.19 (d, J=6.4 Hz, 3H)</td>
<td>Single enantiomer, THF centers known to be 3R,5R, unknown stereochemistry at alcohol.</td>
</tr>
<tr>
<td>6</td>
<td><img src="image2" alt="Structure" /> 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(1-[(2R)-2-hydroxybutanoyl]piperidin-4-yl]oxy)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>F</td>
<td>536</td>
<td>1H NMR (400 MHz, DMSO-d6) δ 11.57 (s, 1H), 7.54 (s, 1H), 5.88 (s, 1H), 4.81 (s, 1H), 4.55 (s, 2H), 4.24-4.21 (m, 1H), 3.72-3.66 (m, 2H), 3.41-3.36 (m, 5H), 2.81 (t, J=6 Hz, 2H), 2.15 (s, 3H), 2.11 (s, 3H), 1.64-1.63 (m, 2H), 1.62-1.59 (m, 3H), 1.46-1.43 (m, 1H), 0.87 (t, J= 7.4 Hz, 3H)</td>
<td>Single enantiomer from chiral reagents</td>
</tr>
<tr>
<td>No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>7</td>
<td><img src="image1" alt="Structure Image" /> 2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-8-carbonitrile</td>
<td>G</td>
<td>[M+Na] 360</td>
<td>1H NMR (400 MHz, DMSO-d6) δ 11.59 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.37 (s, J = 8.4 Hz, 1H), 5.90 (s, 1H), 4.58 (s, 2H), 3.92 (s, 3H), 3.45 (t, J = 6.6 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.17 (s, 3H), 2.13 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td><img src="image2" alt="Structure Image" /> 7-tert-butoxy-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>H</td>
<td>[M+Na] 411</td>
<td>1H NMR (400 MHz, CDCl3) δ 11.43 (s, 1H), 7.72 (d, J = 8Hz, 1H), 6.94 (d, J = 8Hz, 1H), 5.93 (s, 1H), 4.79 (s, 2H), 3.61 (t, J = 8Hz, 2H), 2.79 (t, J = 8Hz, 2H), 2.36 (s, 3H), 2.27 (s, 3H), 1.42 (s, 9H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------</td>
<td>--------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>9</td>
<td>3(\infty)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-[(3R)-tetrahydrofuran-3-yloxy]-3,4-dihydroisoquinolin-1(2H)-one Isomer A</td>
<td>E</td>
<td>417</td>
<td>1H NMR (400 MHz, Methanol-d4) 6 7.19-7.13 (m, 2H), 6.13 (s, 1H), 5.10-5.09 (m, 1H), 4.96-4.93 (d, J=14.0 Hz, 1H), 4.66-4.63 (d, J=14.0 Hz, 1H), 4.03-3.93 (m, 5H), 3.33-3.13 (m, 1H), 2.63-2.59 (m, 1H), 2.31-2.19 (m, 8H), 3.10 (s, 1H), 1.01-0.99 (d, J=6.8 Hz, 3H)</td>
<td>Single enantiomer. THF ether is [R] form chiral reagent. Lactam methyl unknown. Peak 1: 100% Purity. Column: Chiralcel OD-H 150×4.6mm I.D., 5μm Retention Time: 7.263 min, Mobile phase: Ethanol (0.05% DEA) in CO2 from 5% to 40% Flow rate: 2.35mL/min Column: AS-H 250×4.6mm I.D., 5μm Retention Time: 5.061 min, Mobile phase: 15% methanol in CO2 Flow rate: 2.35mL/min</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>-------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>10</td>
<td><img src="image1" alt="Structure 10" /> (3E)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-[{(3R)-tetrahydrofuran-3-yloxy}-3,4-dihydroisoquinolin-1(2H)-one Isomer B</td>
<td>E</td>
<td>417</td>
<td>1H NMR (400 MHz, Methanol-d4) δ 7.19-7.13 (m, 2H), 6.13 (s, 1H), 5.10-5.09 (m, 1H), 4.96-4.93 (d, J=14.0 Hz, 1H), 4.66-4.63 (d, J=14.0 Hz, 1H), 4.04-3.92 (m, 5H), 3.33-3.13 (m, 1H), 2.63-2.59 (m, 1H), 2.31-2.19 (m, 8H), 3.10 (s, 1H), 1.01-0.99 (d, J=6.4 Hz, 3H)</td>
<td>Single enantiomer. THF ether is [R] form chiral reagent. Lactam methyl unknown. Peak 2: 97.616% Purity Column: Chiralcel OD-H 150×4.6mm I.D., 5um, Retention Time: 8.223 min, Mobile phase: Ethanol (0.05% DEA) in CO2 from 5% to 40% Flow rate: 2.35mL/min Column: AS-H 250×4.6mm I.D., 5um, Retention Time: 5.343 min, Mobile phase: 15% methanol in CO2 Flow rate: 2.35mL/min</td>
</tr>
<tr>
<td>11</td>
<td><img src="image2" alt="Structure 11" /> 5,8-dichloro-7-(3,6-dihydro-2H-pyran-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>433</td>
<td>1H NMR (400 MHz, DMSO-d6) δ 7.44 (s, 1 H) 5.89 (s, 1 H) 5.75 (br. s., 1 H) 4.57 (s, 2 H) 4.18 (br. s., 2 H) 3.80 (t, J=4.77 Hz, 3 H) 2.87 (t, J=5.50 Hz, 2 H) 2.32 (br. s., 2 H) 2.15 (s, 3 H) 2.12 (s, 3 H) [2H obscured by H2O peak at 3.4 ppm]</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- 113 -
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure / IUPAC name</th>
<th>Method</th>
<th>LCMs (M+H)</th>
<th>$^1$H NMR (ppm)</th>
<th>Stereochem. Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-{(2R)-2-hydroxypropanoyl}piperidin-4-yl}oxy}-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>F</td>
<td>536</td>
<td>1H NMR (400 MHz, solvent?) δ 11.32 (br. s., 1H), 7.05 (s, 1H), 5.98 (s, 1H), 4.89 (s, 2H), 4.81-4.65 (m, 1H), 4.51-4.47 (m, 1H), 4.01-3.91 (m, 2H), 3.69-3.62 (m, 3H), 3.46-3.43 (m, 1H), 2.88 (t, J = 6.4 Hz, 2H), 2.73 (q, J = 7.6 Hz, 2H), 2.63 (s, 1H), 2.30 (s, 3H), 1.93-1.91 (m, 4H), 1.35 (d, J = 6.4 Hz, 3H), 1.14 (t, J = 7.4 Hz, 3H)</td>
<td>Single enantiomer from chiral reagents</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>--------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>13</td>
<td>5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(1-[(2S)-2-hydroxypropanoyl]piperidin-4-yl]oxy)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>F</td>
<td>536</td>
<td>1H NMR (400 MHz, CDCl3) δ 11.49 (br. s., 1H), 7.01 (s, 1H), 5.98 (s, 1H), 4.81 (s, 2H), 4.63 (s, 1H), 4.51-4.47 (m, 1H), 4.05-3.90 (m, 2H), 3.69-3.68 (m, 1H), 3.63-3.61 (m, 2H), 3.46-3.43 (m, 1H), 2.88 (t, J=6.2 Hz, 2H), 2.73 (q, J=8.0 Hz, 2H), 2.63 (s, 1H), 2.30 (s, 3H), 1.94-1.92 (m, 4H), 1.36 (d, J=6.8 Hz, 3H), 1.14 (t, J=7.6 Hz, 3H).</td>
<td>Single enantiomer from chiral reagents</td>
</tr>
<tr>
<td>14</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[5-(hydroxymethyl)-3-methyl-1,2-oxazol-4-yl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>[M+Na]$^+$ 484</td>
<td>1H NMR (400 MHz, CDCl3) δ 11.51 (br. s., 1H), 7.36 (s, 1H), 5.96 (s, 1H), 4.81-4.73 (m, 2H), 4.70-4.66 &amp; 4.58-4.55 (m, 2H), 3.74 (t, J= 6.0 Hz, 2H), 3.01 (t, J= 6.2 Hz, 2H), 2.38 (s, 3H), 2.30 (s, 3H), 2.19 (s, 3H).</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>--------</td>
<td>------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>15</td>
<td>1,4-anhydro-3-deoxy-2-O-{5,8-dichloro-2-{[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-L-threo-pentitol</td>
<td>E</td>
<td>481</td>
<td>1H NMR (400 MHz, DMSO-d6) (\delta) 11.6 (s, 1H), 7.38 (s, 1H), 5.95 (s, 1H), 5.14-5.13 (m, 1H), 4.74 (t, J=6 Hz, 1H), 4.61 (s, 2H), 3.96-3.93 (m, 2H), 3.85-3.81 (m, 1H), 3.49-3.39 (m, 5H), 2.84-2.8 (m, 2H), 2.43-2.36 (m, 1H), 2.14 (s, 3H), 1.77 (dd, J=14 Hz, 5.6 Hz, 1H), 1.01 (t, J=7.4 Hz, 3H)</td>
<td>Single isomer from chiral reagents</td>
</tr>
<tr>
<td>16</td>
<td>5,8-dichloro-2-{[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-{3-(hydroxymethyl)-5-methyl-1,2-oxazol-4-yl}-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>462</td>
<td>1H NMR (400 MHz, DMSO-d6) (\delta) 11.60 (s, 1H), 7.67 (s, 1H), 5.90 (s, 1H), 5.27 (t, J= 5.6 Hz, 1H), 4.60 (s, 2H), 4.42-4.50 (m, 1H), 4.25-4.35 (m, 1H), 3.50 (t, J= 6.0 Hz, 2H), 2.94 (t, J= 6.4 Hz, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>--------</td>
<td>-------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>17</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3-methyl-1,2-oxazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>432</td>
<td>1H NMR (400 MHz, CDC13) δ &lt;br&gt; 12.21 (s, 1H), 8.38 (s, 1H), 7.34 (s, 1H), 5.96 (s, 1H), 4.78 (s, 2H), 3.72 (t, J = 6.4 Hz, 2H), 3.00 (t, J = 6.0 Hz, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>18</td>
<td>7-(benzylamino)-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C</td>
<td>456</td>
<td>1H NMR (400 MHz, DMSO-d6) δ &lt;br&gt; 11.52 (br. s., 1H), 7.32 (d, J=4.40 Hz, 4H), 7.22 (qd, J=4.21, 8.53 Hz, 1H), 6.66 (s, 1H), 6.54 (s, J=6.17 Hz, 1H), 5.87 (s, 1H), 4.56 (s, 2H), 4.44 (d, J=6.11 Hz, 2H), 3.35 (t, J=6.05 Hz, 2H), 2.68 (t, J=5.93 Hz, 2H), 2.14 (s, 3H), 2.12 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------</td>
<td>--------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>19</td>
<td>5,8-dichloro-2-[(4- (difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>B</td>
<td>498</td>
<td>1H NMR (400 MHz, Methanol-d4) $\delta$ 7.67 (s, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.24 (s, 1H), 4.75 (s, 2H), 3.88 (s, 3H), 3.62 (t, J = 6.4 Hz, 2H), 3.14 (t, J = 6.4 Hz, 2H), 2.34 (s, 3H), 2.19 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>20</td>
<td>5,8-dichloro-2-[(4-chloro-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>B</td>
<td>468</td>
<td>1H NMR (400 MHz, Methanol-d4) $\delta$ 7.68 (s, 1H), 6.34 (s, 1H), 4.86 (s, 2H), 3.88 (s, 3H), 3.59 (t, J = 6.4 Hz, 2H), 3.14 (t, J = 6.4 Hz, 2H), 2.30 (s, 3H), 2.20 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>21</td>
<td>8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3R)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]oxy]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>F</td>
<td>488</td>
<td>1H NMR (400 MHz, DMSO-d6) $\delta$  7.28 (d, J=8.31 Hz, 1 H) 7.14 - 7.22 (m, 1 H) 6.26 (s, 1 H) 5.87 (s, 1 H) 4.98 - 5.13 (m, 1 H) 4.56 (s, 2 H) 4.05 - 4.13 (m, 1 H) 3.78 - 3.87 (m, 1 H) 3.52 (d, J=11.98 Hz, 2 H) 2.75 (t, J=5.87 Hz, 2 H) 2.14 (s, 3 H) 2.12 (s, 3 H) 1.98 - 2.05 (m, 1 H) 1.97 - 1.97 (m, 1 H) 1.64 (s, 2 H) 1.17 - 1.34 (m, 7 H)</td>
<td>Single enantiomer [R] from chiral starting materials</td>
</tr>
<tr>
<td>22</td>
<td>1-(5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-1,3-dimethylurea</td>
<td>C</td>
<td>437</td>
<td>1H NMR (400 MHz, DMSO-d6) $\delta$  11.54 (br. s., 1H), 7.63 (br. s., 1H), 5.93 (br. s., 1H), 5.88 (br. s., 1H), 4.56 (br. s., 2H), 3.48 (br. s., 2H), 3.01 (br. s., 3H), 2.90 (br. s., 2H), 2.17 (br. s., 3H) 2.12 (br. s., 3H) $[3H$ obscured by DMSO signal at 2.50 ppm]</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>23</td>
<td>(±)-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[[1-(2-hydroxybutanoyl)piperidin-4-yl]oxy]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>F</td>
<td>536</td>
<td>1H NMR (400 MHz, DMSO-d6) δ 11.57 (s, 1H), 7.54 (s, 1H), 5.88 (s, 1H), 4.81 (s, 1H), 4.55 (s, 2H), 4.24-4.21 (m, 1H), 3.72-3.66 (m, 5H), 2.81 (t, J= 6Hz, 2H), 2.15 (s, 3H), 2.12 (s, 3H), 1.89-1.85 (m, 3H), 1.62-1.58 (m, 3H), 1.46-1.44 (m, 1H), 0.99-0.97 (m, 1H), 0.87 (t, J= 7.4 Hz, 3H)</td>
<td>racemic mixture</td>
</tr>
<tr>
<td>24</td>
<td>3,6-anhydro-1,4-dideoxy-5-O- {5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-2-C-methyl-L-arabino-hexitol</td>
<td>E</td>
<td>495</td>
<td>1H NMR (400 MHz, CDCl3) δ 10.68 (br. s., 1H), 6.94 (s, 1H), 5.92 (s, 1H), 4.90-4.88 (m, 1H), 4.77 (s, 2H), 4.23-4.21 (m, 1H), 3.83-3.80 (m, 2H), 3.64-3.59 (m, 2H), 2.89-4.87 (m, 2H), 2.33 (s, 3H), 2.26-2.16 (m, 5H), 1.30 (s, 3H), 1.16 (s, 3H)</td>
<td>Single enantiomer from chiral reagents</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>-----------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>25</td>
<td>1,4-anhydro-3,6-dideoxy-2-O-{5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-5-C-methyl-L-arabino-hexitol</td>
<td>E</td>
<td>495</td>
<td>1H NMR (400 MHz, CDCl3) δ 11.89 (br. s., 1H), 6.97 (s, 1H), 5.94 (s, 1H), 4.95-4.93 (m, 1H), 4.78 (s, 2H), 4.18-4.17 (m, 1H), 4.07-4.05 (m, 2H), 3.63-3.61 (m, 2H), 2.89-4.86 (m, 2H), 2.35 (s, 3H), 2.28 (s, 3H), 2.13-2.10 (m, 2H), 1.92 (br. s., 1H), 1.31 (s, 3H), 1.14 (s, 3H)</td>
<td>Single enantiomer from chiral reagents</td>
</tr>
<tr>
<td>26</td>
<td>7-amino-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydropyridin-1(2H)-one</td>
<td>C</td>
<td>366</td>
<td>$^1$H NMR (400 MHz, DMSO-d6) δ 11.52 (br. s., 1H), 6.99 (s, 1H), 5.87 (s, 1H), 5.63 (s, 2H), 4.55 (s, 2H), 3.36 (t, J=6.17 Hz, 2H), 2.70 (t, J=6.17 Hz, 2H), 2.14 (s, 3H), 2.12 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------</td>
<td>--------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>27</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>G</td>
<td>351</td>
<td>1H NMR (400 MHz, DMSO-d6) δ 11.56 (br. s., 1H), 7.56 (d, J=8.56 Hz, 1H), 7.42 (d, J=8.56 Hz, 1H), 5.89 (s, 1H), 4.56 (s, 2H), 3.45 (t, J=6.17 Hz, 2H), 2.90 (t, J=6.17 Hz, 2H), 2.16 (s, 3H), 2.12 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>28</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[[1-hydroxycyclobutyl]carbonyl]piperidin-4-yl]oxy]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>F</td>
<td>548</td>
<td>1H NMR (DMSO-d6) δ 11.56 (s, 1H), 7.53 (s, 1H), 5.93 (s, 1H), 5.88 (s, 1H), 4.79 (s, 1H), 4.55 (s, 2H), 3.72-3.68 (m, 2H), 3.40-3.43 (m, 6H), 2.80 (t, J= 6 Hz, 2H), 2.15 (s, 3H), 2.12 (s, 3H), 2.03-1.99 (m, 2H), 1.88-1.87 (m, 2H), 1.73-1.64 (m, 3H), 1.44-142 (m, 1H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>$^1$H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>29</td>
<td>8-chloro-7-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>412</td>
<td>1H NMR (700 MHz, DMSO-d6) δ 7.37 (d, J=7.52 Hz, 1H), 7.30 (d, J=7.52 Hz, 1H), 5.94 (s, 1H), 4.56 (s, 2H), 3.42 (t, J=6.15 Hz, 2H), 2.85 (t, J=6.15 Hz, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>30</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>459</td>
<td>1H NMR (400 MHz, DMSO-d6) d 12.35 (br. s., 1H), 7.46 (s, 1H), 6.05 (s, 1H), 4.60 (s, 2H), 3.52 (t, J=6.11 Hz, 2H), 3.44 (s, 3H), 2.92 (t, J=6.11 Hz, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 2.04 (br. s., 3H), 1.97 (br. s., 3H)</td>
<td>N/A</td>
</tr>
<tr>
<td>31</td>
<td>7-[3-(aminomethyl)-5-methyl-1,2-oxazol-4-yl]-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>461</td>
<td>1H NMR (400 MHz, CDCl3) δ 10.46 (br. s., 2H), 7.34 (s, 1H), 5.93 (s, 1H), 5.35 (br. s., 1H), 4.76 (s, 2H), 3.81-3.72 (m, 4H), 3.05-3.29 (m, 2H), 2.38 (s, 3H), 2.78 (d, J = 7.6 Hz, 6H)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure / IUPAC name</td>
<td>Method</td>
<td>LCMs (M+H)</td>
<td>^1H NMR (ppm)</td>
<td>Stereochem. Note</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>--------</td>
<td>------------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>32</td>
<td><img src="image" alt="Structure" /> 5,8-dichloro-7-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>A</td>
<td>462</td>
<td>1H NMR (400 MHz, CDCl3) δ 12.29 (br. s., 1H), 7.28 (s, 2H), 5.95 (s, 1H), 4.80 (s, 2H), 3.89 (s, 3H), 3.57 (t, J= 6.8 Hz, 2H), 3.01 (t, J= 6.4 Hz, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 2.17 (s, 3H) 22/21</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Cpd No.</th>
<th>Structure / IUPAC NAME</th>
<th>Mol_Formula</th>
<th>MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td><img src="image" alt="Structure" /> 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[3-(2-hydroxyethyl)-5-methyl-1,2-oxazol-4-yl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C23H23Cl2N3O4</td>
<td>476.352</td>
</tr>
<tr>
<td>34</td>
<td><img src="image" alt="Structure" /> 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[5-(1-hydroxyethyl)-3-methyl-1,2-oxazol-4-yl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C23H23Cl2N3O4</td>
<td>476.352</td>
</tr>
<tr>
<td>Cpd No.</td>
<td>Structure / IUPAC NAME</td>
<td>Mol_Formula</td>
<td>MW</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>----------</td>
</tr>
<tr>
<td>35</td>
<td><img src="image" alt="Structure" /> 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3-(1-hydroxyethyl)-5-methyl-1,2-oxazol-4-yl)]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C23H23Cl2N3O4</td>
<td>476.352</td>
</tr>
<tr>
<td>36</td>
<td><img src="image" alt="Structure" /> 5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3-(1-hydroxyethyl)-5-methyl-1,2-oxazol-4-yl)]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C23H23Cl2N3O4</td>
<td>476.352</td>
</tr>
<tr>
<td>37</td>
<td><img src="image" alt="Structure" /> 5-bromo-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3-(5-hydroxymethyl)-3-methyl-1,2-oxazol-4-yl)]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C22H21BrCIN3O4</td>
<td>506.777</td>
</tr>
<tr>
<td>38</td>
<td><img src="image" alt="Structure" /> 5-bromo-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(3-(5-hydroxymethyl)-5-methyl-1,2-oxazol-4-yl)]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C22H21BrCIN3O4</td>
<td>506.777</td>
</tr>
<tr>
<td>Cpd No.</td>
<td>Structure / IUPAC NAME</td>
<td>Mol_Formula</td>
<td>MW</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>39</td>
<td>5,8-dichloro-7-[3-(1-hydroxyethyl)-5-methyl-1,2-oxazol-4-yl]-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C23H23Cl2N3O5</td>
<td>492.352</td>
</tr>
<tr>
<td>40</td>
<td>5,8-dichloro-7-[3-(1-hydroxyethyl)-5-methyl-1,2-oxazol-4-yl]-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C23H23Cl2N3O5</td>
<td>492.352</td>
</tr>
<tr>
<td>41</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[3-(hydroxymethyl)-5-(trifluoromethyl)-1,2-oxazol-4-yl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C22H18Cl2F3N3O4</td>
<td>516.297</td>
</tr>
<tr>
<td>42</td>
<td>5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[5-(hydroxymethyl)-3-(trifluoromethyl)-1,2-oxazol-4-yl]-3,4-dihydroisoquinolin-1(2H)-one</td>
<td>C22H18Cl2F3N3O4</td>
<td>516.297</td>
</tr>
</tbody>
</table>
Biological Assays and Data

Purification of WT and mutant EZH2 Y641 N

WT and mutant EZH2 were purified using the same procedure. The genes for EZH2, EED, SUZ12, and RBBP4 proteins were cloned into pBacPAK9 vectors (Clontech). RBBP4 was FLAG tagged on the N-terminal end. The baculovirus expressions of these proteins were used to co-infect SF9 insect cells. Insect cell pellets were lysed in a buffer containing 25mM Tris pH8.0, 300mM NaCl, 0.5mM TCEP, complete EDTA-free protease inhibitor (Roche), 0.1% NP-40. The supernatant from the lysate was incubated with FLAG® M2 antibody resin (Sigma). The resin was washed on the chromatography column and eluted with 0.2 mg/ml FLAG peptide. The elute was incubated with omnicleave nucleases (Epicentre Technologies) at 4°C overnight, then concentrated and loaded onto a Superdex 200 (GE Healthcare) column. The Superdex 200 column was eluted with 25mM Tris pH8.0, 150mM NaCl, 0.5mM TCEP. Fractions containing the PRC2 complex were pooled.

Nucleosome Assay Protocol: (The same protocol was used for the WT and mutant EZH2 Y6412N assays)

A. Compound preparation

1. Prepare 10 mM stock solutions in 100% DMSO from solid material
2. Serial dilute 10 mM compound stocks either 2 or 3-fold in 100% DMSO to generate compounds for 11 point dose response

B. Reagent preparation

1. Prepare 1x assay buffer containing 100 mM Tris pH 8.5, 4 mM DTT and 0.01% Tween-20

2. Dilute purified HeLa oligonucleosomes and recombinant histone H1 (New England Biolabs) in assay buffer to 1.67x.

3. Dilute PRC2 4 protein complex (EZH2, EED, SUZ12, RbAp48) to 3.5x in assay buffer

4. Prepare 10x ³H SAM solution in assay buffer using 0.94 µCi/µl of radioactive SAM (Perkin Elmer) and sufficient non-labeled SAM (Sigma) for 1.5 µM final concentration.

5. Dilute TCA to 20% in DI water

C. Enzyme reaction

1. Final reaction conditions are PRC2 4-protein complex at 4 nM when using WT EZH2 or 6 nM when using Y641N mutant EZH2, 1.5 µM SAM, 25 µg/mL oligonucleosomes, 50 nM rH1 in a 50 µl reaction volume.

2. Add 1 µl of diluted compound to the assay plate (96-well V-bottom polypropylene plates) or 1 µl of DMSO for control wells.

3. Add 30 µl of nucleosomes to the assay plate

4. Add 14 µl of either WT or Y641N mutant PRC2 4 protein complex to the assay plate

5. Add 5 µl of ³H SAM to start the reaction.

6. Stop the reaction after 60 minutes with the addition of 100 µl of 20% TCA

7. Transfer 150 µl of quenched reaction into a prepared filterplate (Millipore #MSIPN4B10)

8. Apply vacuum to the filterplate to filter the reaction mix through the membrane.

9. Wash the filterplate with 5x200 µl of PBS, blot dry and dry in an oven for 30 minutes

10. Add 50 µl of microscint-20 scintillation fluid (Perkin Elmer) to each well, wait 30 minutes and count on a liquid scintillation counter.
11. Some compounds were tested under high SAM conditions. In this case, the assay is as described above except that the reaction contains 15 uM SAM. SAM is added to the assay as a 3.3x stock with a total of 14.5 uCi/well.

D. Data analysis

1. IC₅₀ values were determined by fitting the data to a 4-parameter IC₅₀ equation using proprietary curve fitting software.

2. For compounds tested under high SAM conditions, Kᵦ values were obtained by fitting the dose response curve to a model for competitive inhibition using proprietary curve fitting software.

Preparation of HeLa oligonucleosomes:

Reagents
- Cell Pellet: 15L HeLa S3 (Accelgen) + 6L HeLa S3 (in house)
- Mnase (Worthington Biochemicals)

Equipment
- SW-28 Rotor
- Dounce Homogenizer/ B Pestle

Buffers
- Lysis: 20 mM Hepes pH 7.5, 0.25M Sucrose, 3 mM MgCl₂, 0.5% Nonidet P-40, 0.5 mM TCEP, 1 Roche Protease Tablet
- B: 20 mM Hepes pH7.5, 3 mM MgCl₂, 0.5mM EDTA, 0.5 mM TCEP, 1 Roche Protease Tablet
- MSB: 20 mM Hepes pH7.5, 0.4 M NaCl, 1mM EDTA, 5% v/v Glycerol, 0.5 mM TCEP, 0.2mM PMSF
- LSB: 20 mM Hepes pH7.5, 0.1M NaCl, 1mM EDTA, 0.5mM TCEP, 0.2 mM PMSF
- NG: 20 mM Hepes pH7.5, 1 mM EDTA, 0.4m NaCl, 0.2 mM PMSF, 0.5 mM TCEP
- Storage: 20 mM Hepes pH7.5, 1mM EDTA, 10% Glycerol, 0.2 mM PMSF, 0.5 mM TCEP

Protocol

A. Nuclei
1. Resuspend ~10L pellet in 2x40 mL lysis using dounce homogenizer
2. Spin 3000xg 15’
3. Repeat 2 more times
4. Resuspend pellet in 2x40 mL B
5. Spin 3000xg 15’

B. Nuclei Resuspension
1. Resuspend pellet in 2x40 mL MSB. Spin 5000xg 20’
2. Resuspend pellet in 2x1 5 mL HSB
3. Pool and Homogenize 40 Strokes to shear DNA
4. Pellet 10000xg 20’
5. Dialyze O/N 4°C in LSB except for Batch A which was Dialyzed LSB at 50nM NaCl for 3hr

C. Mnase Digestion
Test Mnase digestion (200ul)
1. Warm to 37°C for 5’
2. Add CaCl$_2$ to 3mM and add 10U of Mnase
3. 37°C 30’ taking 25µL sample every 5’
4. Process reaction with 1 µL 0.5M EDTA, 40 µL H$_2$O, 15 µL 10% SDS, 10 µL 5M NaCl, and 100 µL phenol-chloroform vortexing after each addition
5. Spin 5’ 13k
6. Run 5 µL of Aqueous phase on 1% agarose gel
7. Take time that yields ~2kb fragments
8. Selected 15’ for A & B and 20’ for C & D for scale up

Added NaCl to 0.6M

D. Sucrose Gradient 1
1. Poured 6x 34 mL gradient from 5 to 35% sucrose in NG using AKTA purifier in 38.5 mL pollyallomer tubes
2. Lead ~4.0mL on top of MN1 digest
3. Spin 26k 16hr 4°C
4. Take 2 mL fractions from top
5. Run on Page Gel
6. Dialyze Fractions 7-14 O/N 4°C in 4L LSB except Batch D which had 2x 2hr
7. Repeat 3X
E. Final

1. Pool all and concentrate in Amicon (somewhat cloudy)
2. Added 10% Glycerol
3. Spun 5K 15’
4. 1.8 mg/mL at 80 mL for 144mg Total

**Biological Activity**

Biological activity of selected examples in the EZH2 nucleosome assay are provided in Table 3. Data are presented as WT and Mutant Y641 N EZH2 IC$_{50}$ value ($\mu$M) or $K_{\text{app}}$ ($\mu$M) as indicated.

### Table 3.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>WT EZH2 Nucleosome assay IC$_{50}$ ($\mu$M)</th>
<th>WT EZH2 Nucleosome assay (10X SAM) $K_i$ ($\mu$M)</th>
<th>EZH2 Mutant Y641N Nucleosome assay IC$_{50}$ ($\mu$M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.070</td>
<td></td>
<td>0.532</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.001</td>
<td>0.010</td>
</tr>
<tr>
<td>3</td>
<td>0.134</td>
<td></td>
<td>0.770</td>
</tr>
<tr>
<td>4</td>
<td>0.149</td>
<td></td>
<td>2.100</td>
</tr>
<tr>
<td>5</td>
<td>0.074</td>
<td></td>
<td>0.275</td>
</tr>
<tr>
<td>6</td>
<td>0.006</td>
<td></td>
<td>0.021</td>
</tr>
<tr>
<td>7</td>
<td>168.736</td>
<td></td>
<td>200.000</td>
</tr>
<tr>
<td>8</td>
<td>0.501</td>
<td></td>
<td>3.592</td>
</tr>
<tr>
<td>9</td>
<td>73.234</td>
<td></td>
<td>200.000</td>
</tr>
<tr>
<td>10</td>
<td>0.030</td>
<td></td>
<td>0.297</td>
</tr>
<tr>
<td>11</td>
<td>0.033</td>
<td></td>
<td>0.288</td>
</tr>
<tr>
<td>12</td>
<td>0.005</td>
<td></td>
<td>0.027</td>
</tr>
<tr>
<td>13</td>
<td>0.011</td>
<td></td>
<td>0.054</td>
</tr>
<tr>
<td>14</td>
<td>0.005</td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>15</td>
<td>0.006</td>
<td></td>
<td>0.051</td>
</tr>
<tr>
<td>16</td>
<td>0.005</td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>17</td>
<td>0.008</td>
<td></td>
<td>0.020</td>
</tr>
<tr>
<td>18</td>
<td>0.101</td>
<td></td>
<td>1.186</td>
</tr>
<tr>
<td>19</td>
<td>0.009</td>
<td></td>
<td>0.036</td>
</tr>
<tr>
<td>20</td>
<td>0.015</td>
<td></td>
<td>0.122</td>
</tr>
<tr>
<td>21</td>
<td>0.123</td>
<td></td>
<td>0.779</td>
</tr>
<tr>
<td>22</td>
<td>0.035</td>
<td></td>
<td>0.245</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>WT EZH2 Nucleosome assay IC₅₀ (µM)</td>
<td>WT EZH2 Nucleosome assay (10X SAM) Ki (µM)</td>
<td>EZH2 Mutant Y641N Nucleosome assay IC₅₀ (µM)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>23</td>
<td>0.009</td>
<td></td>
<td>0.047</td>
</tr>
<tr>
<td>24</td>
<td>0.027</td>
<td></td>
<td>0.291</td>
</tr>
<tr>
<td>25</td>
<td>0.028</td>
<td></td>
<td>0.244</td>
</tr>
<tr>
<td>26</td>
<td>1.824</td>
<td>1.820</td>
<td>11.627</td>
</tr>
<tr>
<td>27</td>
<td>0.007</td>
<td>1.820</td>
<td>15.673</td>
</tr>
<tr>
<td>28</td>
<td>0.007</td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>29</td>
<td>0.002</td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>30</td>
<td>2.001</td>
<td></td>
<td>4.861</td>
</tr>
<tr>
<td>31</td>
<td>0.006</td>
<td></td>
<td>0.045</td>
</tr>
<tr>
<td>32</td>
<td>0.000</td>
<td></td>
<td>0.002</td>
</tr>
</tbody>
</table>

All publications and patent applications cited in the specification are herein incorporated by reference in their entirety. Although the foregoing invention has been described in some detail by way of illustration and example, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.
We Claim:

1. A compound selected from the group consisting of:

(3R)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-
[(3R)-tetrahydrofuran-3-yloxy]-3,4-dihydroisoquinolin-1 (2H)-one;

(3S)-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3-methyl-7-
[(3R)-tetrahydrofuran-3-yloxy]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-7-(3,6-dihydro-2H-pyran-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-({1-
[(2R)-2-hydroxypropanoyl]piperidin-4-yl}oxy)-3,4-dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-({1-
[(2S)-2-hydroxypropanoyl]piperidin-4-yl}oxy)-3,4-dihydroisoquinolin-1 (2H)-one;

7-tert-butoxy-8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-
dihydroisoquinolin-1 (2H)-one;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-([5-
(hydroxymethyl)-3-methyl-1,2-oxazol-4-yl]-3,4-dihydroisoquinolin-1 (2H)-one;

1,4-anhydro-3-deoxy-2-0-{5,8-dichloro-2-[(4-ethyl-6-methyl-2-oxo-1,2-
dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-L-threo-pentitol;

2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-methoxy-1-oxo-1,2,3,4-
tetrahydroisoquinoline-8-carbonitrile;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(5-
(hydroxymethyl)-5-methyl-1,2-oxazol-4-yl]-3,4-dihydroisoquinolin-1 (2H)-one;

(5ξ)-1,4-anhydrO-3,6-dideoxy-2-0-{5,8-dichlo rO-2-[(4,6-dimethyl-2-oxo-1,2-
dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-L-threo-hexitol;

5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3-methyl-
1,2-oxazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;

7-(benzylamino)-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-
yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(methylamino)-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4-(difluoromethoxy)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,4-dimethyl-1H-2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4-chloro-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-3,4-dihydroisoquinolin-1 (2H)-one;
8-chloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[[3(3R)-1-(2-hydroxy-2-methylpropanoyl)pyrrolidin-3-yl]oxy]-3,4-dihydroisoquinolin-1 (2H)-one;
1-(5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-1,3-dimethylurea;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;
(±)-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(1R)-1-(2-hydroxybutanoyl)piperidin-4-yl]oxy]-3,4-dihydroisoquinolin-1 (2H)-one;
3,6-anhydro-1,4-dideoxy-5-O-[5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-2-C-methyl-L-arabino-hexitol;
1,4-anhydro-3,6-dideoxy-2-O-[5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-5-C-methyl-L-arabino-hexitol;
7-amino-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(1R)-1-(2-hydroxybutanoyl)piperidin-4-yl]oxy]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-[(1R)-1-hydroxycyclobutyl]carbonyl)piperidin-4-yl]oxy]-3,4-dihydroisoquinolin-1 (2H)-one;
8-chloro-7-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-7-(3,5-trimethyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-1 (2H)-one;
5,8-dichloro-7-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one; 7-[3-(aminomethyl)-5-methyl-1,2-oxazol-4-yl]-5,8-dichloro-2-[(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one; and 5,8-dichloro-7-(3,5-dimethyl-1,2-oxazol-4-yl)-2-[(4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl]-3,4-dihydroisoquinolin-1(2H)-one; or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

3. A method for the treatment of abnormal cell growth in a subject, comprising administering to the subject a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

4. The method of claim 3, wherein the abnormal cell growth is cancer.

5. The method of claim 3 or 4, wherein the subject is a human.

6. A compound of claim 1, or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of abnormal cell growth in a subject.

7. The compound of claim 6, wherein the abnormal cell growth is cancer.

8. The compound of claim 6 or 7, wherein the subject is a human.


- 135 -
### INTERNATIONAL SEARCH REPORT

**International application No:** PCT/IB2015/054353

**A. CLASSIFICATION OF SUBJECT MATTER**

<table>
<thead>
<tr>
<th>INV.</th>
<th>C07D401/14</th>
<th>C07D4G5/14</th>
<th>C07D413/14</th>
<th>C07D401/Q6</th>
<th>A61K31/4725</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**B. FIELDS SEARCHED**

**Minimum documentation searched (classification system followed by classification symbols)**

C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 2013/049770 A2 (GLAXOSMITHKLINE LLC [US]; CRESBY CARETHA L [US]; GANJI G0PINATH [US]); 4 Apr 2013 page 2, line 19</td>
<td>1-9</td>
</tr>
</tbody>
</table>

*Further documents are listed in the continuation of Box C.*  

**See patent family annex.**

**Special categories of cited documents:**

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

**Document other than international publication published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention**

**Document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone**

**Document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art**

**Document of the same patent family**

**Date of the actual completion of the international search:** 30 July 2G15  
**Date of mailing of the international search report:** 07/08/2015

**Name and mailing address of the ISA/European Patent Office, P.O. Box 5818 Patentlaan 2 NL-2280 HV Rijswijk  
Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016**

Authorized officer:  
Beligny, Samuel
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 2014049488 Al</td>
<td>03-04-2014</td>
<td>CA 2884848 Al</td>
<td>03-04-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2900653 Al</td>
<td>05-08-20 15</td>
</tr>
<tr>
<td>WO 2014049488 Al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO 2013049770 A2</td>
<td>04-04-2013</td>
<td>AU 2012315566 Al</td>
<td>17-04-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2850570 Al</td>
<td>04-04-20 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 103987842 A</td>
<td>13-08-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2014534178 A</td>
<td>12-12-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20140082742 A</td>
<td>02-07-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014378470 Al</td>
<td>25-12-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2013049770 A2</td>
<td>04-04-20 13</td>
</tr>
<tr>
<td>WO 2014097041 Al</td>
<td>26-06-2014</td>
<td>AU 2013365908 Al</td>
<td>11-06-20 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2893339 Al</td>
<td>26-06-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 201446753 A</td>
<td>16-12-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2014179667 Al</td>
<td>26-06-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2015175572 Al</td>
<td>25-06-20 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UY 35225 A</td>
<td>31-07-20 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2014097041 Al</td>
<td>26-06-20 14</td>
</tr>
</tbody>
</table>