DOCUMENT MADE AVAILABLE UNDER THE PATENT COOPERATION TREATY (PCT)

International application number: PCT/US2015/051055
International filing date: 18 September 2015 (18.09.2015)
Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 62/150,812
Filing date: 21 April 2015 (21.04.2015)

Date of receipt at the International Bureau: 11 October 2015 (11.10.2015)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a),(b) or (b-bis)
October 10, 2015

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FILING DATE.

APPLICATION NUMBER: 62/150,812
FILING DATE: April 21, 2015
RELATED PCT APPLICATION NUMBER: PCT/US15/51055

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APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS
CONVENTION, IS US62/150,812

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Fig. 1 Potency of IDH1 inhibitors in IDH1-R132H Enzymatic Assay

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>IC50 [μM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>0.033</td>
</tr>
<tr>
<td>I-5</td>
<td>0.742</td>
</tr>
<tr>
<td>I-20</td>
<td>0.02</td>
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PYRIDIN-2(1H)-ONE QUINOLINONE DERIVATIVES AS MUTANT-ISOCITRATE DEHYDROGENASE INHIBITORS

Field of Invention

[0001] The present invention is directed to inhibitors of mutant isocitrate dehydrogenase (mt-IDH) proteins with neomorphic activity useful in the treatment of diseases or disorders associated with such mutant IDH proteins including cell-proliferation disorders and cancers. Specifically, the invention is concerned with compounds and compositions inhibiting mt-IDH, methods of treating diseases or disorders associated with mt-IDH, and methods of synthesis of these compounds.

Background of the Invention

[0002] Isocitrate dehydrogenases (IDHs) are enzymes that participate in the citric acid cycle (cellular metabolism). They catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (i.e., α-ketoglutarate, α-KG). There are three isoforms within the IDH family. IDH-1, expressed in the cytoplasm and peroxisome, IDH-2, localized in the mitochondria, both utilize NADP+ as the cofactor and exist as homodimers. IDH-3 is localized in mitochondrial matrix and utilizes NAD+ as a cofactor and exists as tetramer. Mutations in IDH-1 (cytosolic) and IDH-2 (mitochondrial) have been identified in various diseases or disorders including glioma, glioblastoma multiforme, paraganglioma, supratentorial primordial neuroectodermal tumors, acute myeloid leukemia (AML), prostate cancer, thyroid cancer, colon cancer, chondrosarcoma, cholangiocarcinoma, peripheral T-cell lymphoma, and melanoma (L. Deng et al., Trends Mol. Med., 2010, 16, 387; T. Shibata et al., Am. J. Pathol., 2011, 178(3), 1395; Gaal et al., J. Clin. Endocrinol. Metab. 2010; Hayden et al., Cell Cycle, 2009; Balss et al., Acta Neuropathol., 2008). The mutations have been found at or near key residues in the active site: G97D, R100, R132, H133Q, and A134D for IDH1, and R140 and R172 for IDH2. (See L. Deng et al., Nature, 2009, 462, 739; L. Sellner et al., Eur. J. Haematol., 2011, 85, 457).

[0003] Mutant forms of IDH-1 and IDH-2 have been shown to lose wild type activity, and instead exhibit a neomorphic activity (also known as a gain of function activity), of reducing alpha-ketoglutarate to 2-hydroxyglutarate (2-HG). (See P.S. Ward et al., Cancer Cell, 2010, 17, 225; Zhao et. al., Science 324, 261(2009); Dang et.al Nature 462, 739 (2009)). In general,
production of 2-HG is enantiospecific, resulting in generation of the D-enantiomer (also known as the R enantiomer or R-2-HG). Normal cells have low basal levels of 2-HG, whereas cells harboring mutations in IDH1 or IDH2 show significantly elevated levels of 2-HG. High levels of 2-HG have also been detected in tumors harboring the mutations. For example, high levels of 2-HG have been detected in the plasma of patients with mutant IDH containing AML. (See S. Gross et al., J. Exp. Med., 2010, 207(2), 339). High levels of 2-HG have been shown to block α-KG dependent DNA and histone demethylases, and ultimately to result in improper dedifferentiation of hematopoietic progenitor cells in AML patients (Wang et al., Science 340, 622 (2013); Losman et al., Science 339, 1621 (2013)).

Furthermore, patients with OIlier Disease and Maffucci Syndrome (two rare disorders that predispose to cartilaginous tumors) have been shown to be somatically mosaic for IDH1 and 2 mutations and exhibit high levels of D-2-HG. (See Amary et al., Nature Genetics, 2011 and Pansuriya et al., Nature Genetics, 2011).

The inhibition of mt-IDHs and their neomorphic activity with small molecule inhibitors therefore has the potential to be a treatment for cancers and other disorders of cellular proliferation.

**Summary of the Invention**

A first aspect of the invention relates to compounds of Formula I:

![Chemical Structure](image)

(I)

and pharmaceutical salts, enantiomers, hydrates, solvates, prodrugs, isomers, and tautomers thereof,

wherein:
each \( W_1 \) and \( W_2 \) is independently CH, CF or N;

\( W_3 \) is independently CR\(_2\) or N;

\( U \) is N or CR\(_6\);

\( A \) is selected from the group consisting of H, D, halogen, CN, -CHO, -COOH, -COOR, -C(O)NH\(_2\), -C(O)NHR, R'S(O)\(_2\), -O(CH\(_2\)_nC(O)R', and R'S(O)-, heteroaryl, and-SOMe,

\[
\begin{align*}
\begin{array}{c}
\text{Y}
\end{array}
\end{align*}
\]

wherein X and Y are independently in each occurrence C, N, NR', S, and O, provided that the ring containing X and Y cannot have more than 4 N or NH atoms or more than one S or O atoms, and wherein the S and O are not contiguous;

\( R \) and \( R' \) at each occurrence are independently selected from the group consisting of H, OH, CN, -CH\(_2\)CN, halogen, -NR\(_2\)R\(_8\), CHCF\(_2\), CF\(_3\), C\(_1\)-C\(_6\) alkyl, R\(_2\)S(O)\(_2\), C\(_1\)-C\(_6\) alkoxy, C\(_2\)-C\(_6\) alkenyl, C\(_2\)-C\(_6\) alkynyl, C\(_3\)-C\(_8\) cycloalkyl, C\(_3\)-C\(_8\) cycloalkylalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl, wherein each \( R \) is optionally substituted with one or more substituents selected from the group consisting of OH, halogen, C\(_1\)-C\(_6\) alkoxy, NH\(_2\), R\(_7\)S(O)\(_2\)+, CN, C\(_3\)-C\(_8\) cycloalkyl, 3- to 8-membered heterocyclyl, aryl, heteroaryl, and R\(_7\)S(O)-;

\( R_1 \) is independently H, OH, CN, halogen, CHCF\(_2\), CF\(_3\), C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) alkoxy, C\(_2\)-C\(_6\) alkenyl, C\(_2\)-C\(_6\) alkynyl, C\(_3\)-C\(_8\) cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl, wherein each C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_6\) alkenyl, C\(_2\)-C\(_6\) alkynyl, C\(_3\)-C\(_8\) cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl is optionally substituted one or more times with substituents selected from the group consisting of halogen, OH, NH\(_2\), CN, C\(_1\)-C\(_6\) alkyl, and C\(_1\)-C\(_6\) alkoxy;

each \( R_2 \) is independently H, OH, CN, halogen, CF\(_3\), CHF\(_2\), benzyl, C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) alkoxy, NH\(_2\), -O(CH\(_2\)_nR', -O(CH\(_2\)_nC(O)NHR', -O(CH\(_2\)_nC(O)R', NHR\(_7\), -N(R\(_7\))(R\(_8\)), NHC(O)R\(_7\), NHS(O)R\(_7\), NHS(O)R\(_2\)R\(_7\), NHC(O)OR\(_7\), NHC(O)NHR\(_7\), -S(O)\(_2\)NHR\(_7\), NHC(O)N(R\(_3\))R\(_7\), OCH\(_2\)R\(_7\), CHRR' or OCHR'R\(_7\), wherein C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) alkoxy is optionally substituted with one or more substituents selected from the group consisting of C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) alkoxy, C\(_2\)-C\(_6\) alkenyl, C\(_2\)-C\(_6\) alkynyl, C\(_3\)-C\(_8\) cycloalkyl, C\(_3\)-C\(_8\) cycloalkyl substituted
with one or more halogen, 3- to 8-membered heterocyclyl, aryl, -heteroaryl-C(O)NH₂, and heteroaryl;

or R₁ and R₂ can combine to form a C₄-C₆ cycloalkyl or a 3- to 8-membered heterocyclyl containing at least one atom selected from the group consisting of N, O, and S;

R₁ is H, D, C₁-C₆ alkyl, or -OH;

R₄ and R₅ are independently H, D, halogen, CH₃OH, C₁-C₅ alkyl, or C₁-C₅ alkyl substituted with halogen, or R₄ and R₅ when combined can form a C₃-C₅ cycloalkyl or C₃-C₅ heterocyclyl;

each R₆ is H, halogen, C₁-C₆ alkyl, C₁-C₆ alkyl substituted with halogen, C₁-C₆ alkoxy, C₁-C₆ alkoxy substituted with one or more halogen, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl;

R₇ and R₈ are independently H, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl; or when combined R₇ and R₈ can form a 3- to 8-membered heterocyclyl or heteroaryl ring;

R₉ is independently H, D, CD₃, CF₃, C₁-C₅ alkyl, C₂-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₈ cycloalkyl, wherein the alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with amino, OH, halo, or alkoxy;

n is 0, 1, or 2; and

r is 0, 1, or 2;

with the proviso that when A is H, then R₁ is not C₁-C₆ alkyl or C₁-C₆ alkoxy and R₁ and R₂ cannot combine to form a 3- to 8-membered heterocyclyl.

[0007] Another aspect of the invention relates to a method of treating a disease or disorder associated with mutant isocitrate dehydrogenase. The method involves administering to a patient in need of a treatment for diseases or disorders associated with mutant isocitrate dehydrogenase an effective amount of a compound of Formula I.

[0008] Another aspect of the invention is directed to a method inhibiting mutant isocitrate dehydrogenase. The method involves administering to a patient in need thereof an effective amount of the compound of Formula I.
Another aspect of the invention relates to method of reducing alpha-ketoglutarate. The method comprises administering to a patient in need thereof an effective amount of the compound of Formula I.

Another aspect of the invention is directed to pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may further include an excipient, diluent, or surfactant.

The present invention further provides methods of treating cell proliferative diseases and cancers including, without limitation, glioma, glioblastoma multiforme, paraganglioma, supratentorial primordial neuroectodermal tumors, acute myeloid leukemia (AML), prostate cancer, thyroid cancer, colon cancer, chondrosarcoma, cholangiocarcinoma, peripheral T-cell lymphoma, melanoma, intrahepatic cholangiocarcinoma (IHCC), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), and other solid tumors.

The present invention also provides potent mt-IDH inhibitors with excellent drug-like properties to cancers and other cell proliferative disorders. The inhibitors of the present invention may target mutated IDH1 or IDH2.

The present invention further provides development of potent, orally active, and selective IDH inhibitors as therapeutic agents for various diseases or disorders including cancers. The invention also provides treatment for solid and hematologic cancers for which there are no currently targeted therapies available for patients suffering from these conditions or disorders.

**Brief Description of the Drawings of the Invention**

Figure 1 illustrates a graph showing the potency of IDH1 inhibitors in IDH1-R132H Enzymatic Assay using compounds I-1, I-5, and I-20.

**Detailed Description of the Invention**

IDH1 or IDH2 mutations are a genetically validated target in many solid and hematologic cancers, but there are currently no targeted therapies available for patients in need of treatment for specific conditions associated with mt-IDH activity. Non-mutant IDH (e.g., wild-type) catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate thereby reducing NAD⁺ (NADP⁺) to NADH (NADPH) (WO 2013/102431 to Cianchetta et al., hereby
incorporated by reference in its entirety). Mutations of IDH present in certain cancer cells result in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α-ketoglutarate R(−)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH. The production of 2HG contributes to the formation and progression of cancer (Dang, L et al., Nature, 2009, 462:739-44, hereby incorporated by reference in its entirety). The present invention provides inhibitors of mt-IDH, and prophylactic measures to reduce the formation and progression of 2HG in cells.

[0016] In a first aspect of the invention, are described the compounds of Formula I:

\[
\begin{align*}
&\text{R}_1 - \text{W}_2 - \text{W}_1 - \text{N} - \text{R}_3 \\
&\text{R}_2 - \text{W}_3 - \text{N} - \text{R}_3 \\
&\text{R}_4 - \text{W}_4 - \text{N} - \text{R}_3 \\
&\text{U} - \text{N} - \text{R}_6 \\
&\text{A} - \text{N} - \text{R}_9 \\
&\text{R}_5
\end{align*}
\]

(I)

and pharmaceutically acceptable salts, enantiomers, hydrates, solvates, prodrugs, isomers, and tautomers thereof, where A, U, W, R, and R₉ are as described above.

[0017] The details of the invention are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definitions

[0018] The articles "a" and "an" are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0019] The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.
The term “optionally substituted” is understood to mean that a given chemical moiety (e.g. an alkyl group) can (but is not required to) be bonded other substituents (e.g. heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (i.e. a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus the term “optionally substituted” means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further functional groups. Suitable substituents used in the optional substitution of the described groups include, without limitation, halogen, oxo, CN, -COOH, -CH₂CN, -O-C₁-C₆alkyl, C₁-C₆alkyl, -OC₁-C₆alkenyl, -OC₁-C₆alkynyl, -C₁-C₆alkenyl, -C₁-C₆alkynyl, -OH, -OP(O)(OH)₂, -OC(O)C₁-C₆alkyl, -C(O)C₁-C₆alkyl, -OC(O)OC₁-C₆alkyl, NH₂, NH(C₁-C₆alkyl), N(C₁-C₆alkyl), -NHC(O)C₁-C₆alkyl, -C(O)NHC₁-C₆alkyl, -S(O)₂-C₁-C₆alkyl, -S(O)NHC₁-C₆alkyl, and S(O)N(C₁-C₆alkyl)₂.

Unless otherwise specifically defined, the term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl). The aryl group may be optionally substituted by one or more substituents, e.g., 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, -H, -halogen, -O-C₁-C₆alkyl, C₁-C₆alkyl, -OC₁-C₆alkenyl, -OC₁-C₆alkynyl, -C₁-C₆alkenyl, -C₁-C₆alkynyl, -OH, -OP(O)(OH)₂, -OC(O)C₁-C₆alkyl, -C(O)C₁-C₆alkyl, -OC(O)OC₁-C₆alkyl, NH₂, NH(C₁-C₆alkyl), N(C₁-C₆alkyl)₂, -S(O)₂-C₁-C₆alkyl, -S(O)NHC₁-C₆alkyl, and S(O)N(C₁-C₆alkyl)₂. The substituents can themselves be optionally substituted. Furthermore when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these aryl groups include indanyl, indenyl, tetrahydronapthalenyl, and tetrahydrobenzoannulenyl.

Unless otherwise specifically defined, "heteroaryl" means a monovalent monocyclic aromatic radical of 5 to 10 ring atoms or a polycyclic aromatic radical, containing one or more ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. Heteroaryl as herein defined also means a bicyclic heteroaromatic group wherein the heteroatom
is selected from N, O, or S. The aromatic radical is optionally substituted independently with
one or more substituents described herein. Examples include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyrimidinyl, imidazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyryl, thiazolyl, and derivatives thereof. Furthermore when containing two
fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring
fused with a fully saturated ring. Exemplary ring systems of these heteroaryl groups include
indolyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl,
tetrahydroquinolinyl, dihydrobenzothiazine, and dihydrobenzoxanyl.

[0023] Halogen or “halo” refers to fluorine, chlorine, bromine and iodine.

[0024] Alkyl refers to a straight or branched chain saturated hydrocarbon containing 1-
12 carbon atoms. Examples of a C₁-C₆ alkyl group include, but are not limited to, methyl, ethyl,
propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, and
isohexyl.

[0025] “Alkoxy” refers to a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal “O” in the chain. Examples of alkoxy
groups include without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy
groups.

[0026] “Alkenyl” refers to a straight or branched chain unsaturated hydrocarbon
containing 2-12 carbon atoms. The “alkenyl” group contains at least one double bond in the
chain. Examples of alkenyl groups include ethenyl, propenyl, n-buteny, iso-buteny, pentenyl,
or hexenyl.

[0027] “Alkynyl” refers to a straight or branched chain unsaturated hydrocarbon
containing 2-12 carbon atoms. The “alkynyl” group contains at least one double bond in the
chain. Examples of alkenyl groups include ethynyl, propargyl, n-butynyl, iso-butynyl, pentynyl,
or hexynyl.

[0028] “Cycloalkyl” means monocyclic saturated carbon rings containing 3-18 carbon
atoms. Examples of cycloalkyl groups include, without limitations, cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, norboranyl, norborenyl,
bicyclo[2.2.2]octanyl, or bicyclo[2.2.2]octenyl.
"Cycloalkylalkyl" means monocyclic saturated carbon rings containing 3-18 carbon atoms further substituted with C_1-C_6 alkyl groups. In general cycloalkylalkyl groups herein described display the following Formula \[ \text{where } m \text{ is an integer from 1 to 6 and } n \text{ is an integer from 1 to 16.} \]

"Heterocyclyl" or "heterocycloalkyl" monocyclic rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized \( \pi \) electrons (aromaticity) shared among the ring carbon or heteroatoms; heterocyclyl rings include, but are not limited to, oxetanyl, azetadiny1, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl.

The term "solvate" refers to a complex of variable stoichiometry formed by a solute and solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, MeOH, EtOH, and AcOH. Solvates wherein water is the solvent molecule are typically referred to as hydrates. Hydrates include compositions containing stoichiometric amounts of water, as well as compositions containing variable amounts of water.

The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers). With regard to stereoisomers, the compounds of Formula (1) may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers.

The disclosure also includes pharmaceutical compositions comprising an effective amount of a disclosed compound and a pharmaceutically acceptable carrier. Representative "pharmaceutically acceptable salts" include, e.g., water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate,
calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulinate, dihydrochloride, edetate, edisylate, estolate, esylate, fluorate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, olate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, cibonate), pantothenate, phosphate/diphosphate, picroate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triiodide, and valerate salts.

[0034] A "patient" or "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

[0035] An "effective amount" when used in connection with a compound is an amount effective for treating or preventing a disease in a subject as described herein.

[0036] The term "carrier", as used in this disclosure, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.

[0037] The term "treating" with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

[0038] The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0039] The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the
compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

[0040] The term "prodrug," as used in this disclosure, means a compound which is convertible in vivo by metabolic means (e.g., by hydrolysis) to a disclosed compound.

[0041] In one embodiment of the invention, A is CN. In this embodiment, R₉ may further be H, C1-C6 alkyl or C₅-C₆ cycloalkyl. In another embodiment, R₉ may also be methyl or Ethyl.

[0042] In another embodiment of the compounds of Formula I, U is N. In this embodiment, A may further be CN.

[0043] In other embodiments of the invention, are describe the compounds of Formula I where A is H or F.

[0044] In other embodiments of the invention, are describe the compounds of Formula I where A is

[0045] Another embodiment of the invention pertains to compounds of Formula I where R₄ and R₅ are H.

[0046] In another embodiment of the invention, R₃ is methyl or ethyl.

[0047] In another embodiment of the compounds of Formula I, R₄ is H and R₅ is methyl.

[0048] In yet another embodiment of the invention, R₄ is H and R₅ is (S)-methyl.

[0049] In another embodiment, R₄ and R₅ are halogen.

[0050] In another embodiment of the compounds of Formula I, R₄ is F and R₅ is methyl.

[0051] In another embodiment, R₄ and R₅ can combine to form a C₃-C₅ cycloalkyl.

[0052] In one embodiment of the compounds of Formula I, W₁, W₂, and W₃ are all CH.

[0053] In one embodiment of the compounds of Formula I, W₁, W₂, or W₃ are CF.
In one embodiment, $W_1$ or $W_2$ is CH or N.

In one embodiment, $W_3$ is CR$_2$.

In another embodiment of the invention, $R_1$ can be halogen. In another embodiment, $R_1$ is chloro.

In one embodiment of the invention $R_2$ can be H, halogen, or C$_1$-C$_6$ alkoxy. In another embodiment, $R_2$ can also be C$_1$-C$_6$ alkoxy substituted with heteroaryl or 3- to 8-membered heterocyclyl.

In another embodiment, illustrative compounds of Formula I are:

5-[[6-chloro-2-oxo-1,2-dihydroquinolin-3-yl]methyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

6-chloro-3-[[1-ethyl-2-oxo-1,2-dihydropyridin-3-yl]amino]methyl]-1,2-dihydroquinolin-2-one;

6-chloro-3-[[1-methyl-2-oxo-1,2-dihydropyridin-3-yl]amino]methyl]-1,2-dihydroquinolin-2-one;

5-[[6-chloro-2-oxo-1,2-dihydroquinolin-3-yl]methyl]amino]-6-oxo-1,6-dihydropyridine-2-carbonitrile;

6-chloro-3-[[1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl]amino]methyl]-1,2-dihydroquinolin-2-one;

6-chloro-3-[[1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl]amino]methyl]-1,2-dihydroquinolin-2-one;

3-[[6-bromo-2-oxo-1,2-dihydropyridin-3-yl]amino]methyl]-6-chloro-1,2-dihydroquinolin-2-one;

6-chloro-3-[[2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl]amino]methyl]-1,2-dihydroquinolin-2-one;

6-chloro-3-[[1-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl]amino]methyl]-1,2-dihydroquinolin-2-one;

methyl 5-[[6-chloro-2-oxo-1,2-dihydroquinolin-3-yl]methyl]amino]-6-oxo-1,6-dihydropyridine-3-carboxylate;

6-chloro-7-methoxy-3-[[1-methyl-2-oxo-1,2-dihydropyridin-3-yl]amino]methyl]-1,2-dihydroquinolin-2-one;
6-chloro-3-{{(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino}methyl}-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one;  
5-{{(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyrazine-2-carbonitrile;  
5-{{(1R)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1R)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1R)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;  
5-{{(1S)-1-[6-chloro-2-oxo-7-{(1R)-1-(pyridin-2-yl)ethoxy}-1,2-dihydroquinolin-3-yl]ethyl}amino}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl\}ethy]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1-6-chloro-7-[3,3-difluorocyclobutyl]methoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-2-oxo-7-\{propan-2-yl\}oxy\}-1,2-dihydroquinolin-3-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1R)-1-\{7-chloro-3-oxo-3,4-dihydroquinoxalin-2-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile; and
5-\{[(1S)-1-\{7-chloro-3-oxo-3,4-dihydroquinoxalin-2-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile.

[0059] In another embodiment, illustrative compounds of Formula I include:

5-\{[(1S)-1-\{6-chloro-2-oxo-1,2-dihydro(4a,5,6,7,8,8a\textsuperscript{13}C\textsubscript{6})quinolin-3-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)(2,2,2\textsuperscript{3}H\textsubscript{3})ethylamino\}-1-(\textsuperscript{3}H\textsubscript{3})methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-2-oxo-1,2-dihydroquinolin-3-yl\}ethylamino\}-6-oxo-1-(trifluoromethyl)-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-7-(2-hydroxypropan-2-yl)-2-oxo-1,2-dihydroquinolin-3-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-2-oxo-1,2-dihydroquinolin-3-yl\}ethylamino\}-1-(\textsuperscript{3}H\textsubscript{3})methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-2-oxo-1,2-dihydroquinolin-3-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-\{6-chloro-7-cyclopropyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl\}ethylamino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-[(1S)-1-(6-chloro-7-methyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[6-chloro-2-oxo-1,2-dihydro(8-^2H)quinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[6-chloro-2-oxo-1,2-dihydro(5,7,8-^3H_3)quinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[6-chloro-7-((2-hydroxy-2-methylpropyl)amino)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[7-(azetidin-1-yl)-6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[7-(azetidin-1-yl)-6-chloro-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[6-chloro-7-(3,3-difluorooazetidin-1-yl)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

6-chloro-3-[(1S)-1-[[1-methyl-2-oxo-6-(1H-1,2,3,4-tetrazol-1-yl)-1,2-dihydropyridin-3-yl]amino]ethyl]-1,2-dihydroquinolin-2-one; and

5-[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide.

[0060] In one embodiment, the compounds of the invention have the Formula Ia:

![Formula Ia](image)

[0061] In another embodiment, the compounds of the invention have he Formula Ia-1:
In another embodiment, the compounds of the invention have the Formula Ia-2:

\[
\text{(Ia-2).}
\]

In another embodiment, the compounds of the invention have the Formula Ib:

\[
\text{(Ib).}
\]

In another embodiment, the compounds of the invention have the Formula Ib-1:

\[
\text{(Ib-1).}
\]

In another embodiment of the invention, the compounds of Formula I are enantiomers. In some embodiments the compounds are (S)-enantiomer. In other embodiments the compounds may also be (R)-enantiomer. In yet other embodiments, the compounds of Formula I may be (+) or (-) enantiomers.

In another embodiment of the invention, the compounds of Formula I contain isotopes of atoms forming the structure of Formula I. Isotopes herein means, each of two or more forms of the same element (e.g., H and D; \(^{12}\)C and \(^{13}\)C) that contain equal numbers of protons but different numbers of neutrons in their nuclei, and hence differ in relative atomic mass.
It should be understood that all isomeric forms are included within the present invention, including mixtures thereof. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis or trans configuration. All tautomeric forms are also intended to be included.

Methods of Using the Disclosed Compounds

Another aspect of the invention relates to a method of treating a disease or disorder associated with mutant isocitrate dehydrogenase. The method involves administering to a patient in need of a treatment for diseases or disorders associated with mutant isocitrate dehydrogenase an effective amount of the compositions and compounds of Formula I.

Another aspect of the invention is directed to a method inhibiting mutant isocitrate dehydrogenase. The method involves administering to a patient in need thereof an effective amount of the compositions or compounds of Formula I.

Examples of a mutant IDH protein having a neomorphic activity are mutant IDH1 and mutant IDH2. A neomorphic activity associated with mutant IDH1 and mutant IDH2 is the ability to produce 2-hydroxyglutarate (2-HG neomorphic activity), specifically R-2-HG (R-2-HG neomorphic activity). Mutations in IDH 1 associated with 2-HG neomorphic activity, specifically R-2-HG neomorphic activity, include mutations at residues 97, 100, and 132, e.g. G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. Mutations in IDH2 associated with 2-HG neocactivity, specifically R-2-HG neomorphic activity, include mutations at residues 140 and 172, e.g. R140Q, R140G, R172K, R172M, R172S, R172G, and R172W.

Another aspect of the invention relates to method of reducing alphaketoglutarate. The method comprises administering to a patient in need thereof an effective amount of the compositions or compounds of Formula I.

One therapeutic use of the compounds or compositions of the present invention which inhibit mt-IDH is to provide treatment to patients or subjects suffering from cell proliferative diseases and cancers including, without limitation, glioma, glioblastoma multiforme, paraganglioma, supratentorial primordial neuroectodermal tumors, acute myeloid leukemia (AML), prostate cancer, thyroid cancer, colon cancer, chondrosarcoma, cholangiocarcinoma, peripheral T-cell lymphoma, melanoma, intrahepatic cholangiocarcinoma
(IHCC), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), and other solid tumors. Targeted treatments for these cancers and cell proliferative diseases are not currently available to patients suffering from these conditions. Therefore, there is a need for new therapeutic agents selective to these conditions.

[0073] The disclosed compounds of the invention can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects.

[0074] Administration of the disclosed compounds can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

[0075] Depending on the intended mode of administration, the disclosed compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, and all using forms well known to those skilled in the pharmaceutical arts.

[0076] Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a Compound of the Invention and a pharmaceutically acceptable carrier, such as a) a diluent, e.g., purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil, or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA, or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, e.g., starches, agar, methyl cellulose,
bentonite, xanthan gum, algiic acid or its sodium salt, or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcitol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

[0077] Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, the disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the disclosed compounds.

[0078] The disclosed compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

[0079] The disclosed compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, containing cholesterol, stearylamine or phosphatidylcholines. In some embodiments, a film of lipid components is hydrated with an aqueous solution of drug to a form lipid layer encapsulating the drug, as described in U.S. Pat. No. 5,262,564.

[0080] Disclosed compounds can also be delivered by the use of monoclonal antibodies as individual carriers to which the disclosed compounds are coupled. The disclosed compounds can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the Disclosed compounds can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyranos, polycyanoacrylates and cross-linked or amphipathic block copolymers of
hydrogels. In one embodiment, disclosed compounds are not covalently bound to a polymer, e.g., a polycarboxylic acid polymer, or a polycrylate.

[0081] Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

[0082] Another aspect of the invention is directed to pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

[0083] Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of the disclosed compound by weight or volume.

[0084] The dosage regimen utilizing the disclosed compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular disclosed compound employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[0085] Effective dosage amounts of the disclosed compounds, when used for the indicated effects, range from about 0.5 mg to about 5000 mg of the disclosed compound as needed to treat the condition. Compositions for in vivo or in vitro use can contain about 0.5, 5, 20, 50, 75, 100, 150, 250, 500, 750, 1000, 1250, 2500, 3500, or 5000 mg of the disclosed compound, or, in a range of from one amount to another amount in the list of doses. In one embodiment, the compositions are in the form of a tablet that can be scored.

**Method of Synthesizing the Compounds**

[0086] The compounds of the present invention may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.
The compounds of Formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula (I).

Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula (I). Accordingly, the present invention includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

**Preparation of compounds**

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Compounds of the present invention Formula (I) can be synthesized by following the steps outlined in Schemes 1-2, which comprise different sequences of
assembling intermediates II, III, IV, and V. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

**Scheme 1**

![Scheme 1 Diagram](image)

**Scheme 2**

![Scheme 2 Diagram](image)

wherein A, U, W₁, W₂, W₃, R₁-R₉ are defined in Formula (I).

[0091] The general ways of preparing target molecules of Formula I by using intermediates II, III, IV, and V are outlined in Scheme 1 and 2. Displacement of aryl halides (III) with intermediates amine (II) under standard nucleophilic substitution conditions using base such as N,N-diisopropylethylamine, and/or potassium carbonate, cesium carbonate in solvent DMSO or DMF gives the compounds of Formula I. Reductive amination of aldehyde (IV) with amine (V) is performed under standard procedure (AcOH and NaBH(OAc)₃) to prepare the compound of Formula I (where R₄=R₅=H). A mixture of enantiomers, diastereomers, cis/trans isomers resulted from the process can be separated into their single components by chiral salt technique, chromatography using normal phase, reverse phase or chiral column, depending on the nature of the separation.
[0092] It should be understood that in the description and formulae shown above, the various groups A, U, W₁, W₂, W₃, R₁-R₉, and R₉ and other variables are as defined above, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds of schemes 1 and 2 are mere representative with elected radicals to illustrate the general synthetic methodology of the compound of Formula I as defined herein.

Examples

[0093] The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.


Analytical Methods, Materials, and Instrumentation

[0095] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker or Varian spectrometers at 300 MHz. Spectra are given in ppm (δ) and coupling constants, J, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Mass spectra were collected using a Waters ZQ Single Quad Mass Spectrometer (ion trap electrospray ionization (ESI)). High performance liquid chromatograph (HPLC) analyses were obtained using a XBridge Phenyl or C18 column (5 μm, 50x4.6 mm, 150x4.6 mm or 250x4.6 mm) with UV detection (Waters 996 PDA) at 254 nm or 223 nm using a standard solvent gradient program (Method 1-4).

LCMS Method 1 (ESI, 4 min method):

Instruments:

HPLC: Waters HT2790 Alliance MS: Waters ZQ Single Quad Mass Spectrometer
UV: Waters 996 PDA

**Conditions:**

- **Mobile phase A**: 95% water/5% methanol with 0.1% Formic Acid
- **Mobile phase B (B)**: 95% methanol/5% water with 0.1% Formic Acid
- **Column**: XBridge Phenyl or C18, 5 μm 4.6 x 50 mm
- **Column temperature**: Ambient
- **LC gradient**: Linear 5-95% B in 2.5 min, hold 95% B to 3.5 min
- **LC Flow rate**: 3 mL/min
- **UV wavelength**: 220 nm and 254 nm
- **Ionization Mode**: Electrospray Ionization; positive/negative

**LCMS method 2 (ESI, 10 min method):**

**Instruments:**

- **HPLC**: Waters HT2790 Alliance
- **MS**: Waters ZQ Single Quad Mass Spectrometer
- **UV**: Waters 996 PDA

**Conditions:**

- **Mobile phase A (A)**: 95% water/5% methanol with 0.1% Formic Acid
- **Mobile phase B (B)**: 95% methanol/5% water with 0.1% Formic Acid
- **Column**: XBridge C18, 5 μm 4.6 x 150 mm
- **Column temperature**: Ambient
- **LC gradient**: Linear 5-95% B in 5.5 min, hold 95% B to 7.5 min
- **LC Flow rate**: 1.2 mL/min
- **UV wavelength**: 220 nm and 254 nm
- **Ionization Mode**: Electrospray Ionization; positive/negative

**LCMS method 3: (APCI, 20 min)**

**Instruments and conditions:**

HPLC-Agilent 1100 series.
Column: Agela Technologies Durashell C18, 3 μm, 4.6 x 50 mm.
Mobile Phase A: ACN + 0.1 % TFA.
Mobile Phase B: Water + 0.1 % TFA.

Gradient: 

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Flow Rate: 1 mL/min.
Column Temperature: Ambient.
Detector: 254 nm.

**LCMS Method 4 (ESI, 2.5 min method):**

**Instruments and conditions:**

HPLC: Waters Acquity Binary Solvent
Manager  
MS: Waters ZQ Mass Detector
UV: Waters Acquity PDA

Mobile phase A (A)  
95% water/5% acetonitrile with 0.1% formic acid in 10 mM ammonium formate

Mobile phase B (B)  
95% acetonitrile/5% water with 0.09% formic acid

Column  
Waters Acquity UPLC BEH C18, 1.7 μm, 2.1 x 50 mm

Column temperature  
35 °C

LC gradient  
5-100% B in 2.0 min, hold 100% B to 2.2 min

LC Flow rate  
0.6 mL/min

UV wavelength  
220 nm and 254 nm

Ionization Mode  
Electrospray Ionization; positive/negative

**Abbreviations used in the following examples and elsewhere herein are:**

Ac₂O  
acetic anhydride
ACN    Acetonitrile
BOP    ammonium 4-(3-(pyridin-3-ylmethyl)ureido)benzenesulfinate
CDCl₃  deuterated chloroform
Cs₂CO₃ cesium carbonate CuSO₄ copper sulfate
δ      chemical shift
DCM    dichloromethane or methylene chloride
DCE    1,2-dichloroethane
DEAD   diethyl azodicarboxylate
DIAD   diisopropyl azodicarboxylate
DIEA   N,N-diisopropylethylamine
DMA    N,N-dimethylacetamide
DME    dimethoxyethane
DMF    N,N-dimethylformamide
DMP    Dess-Martin Periodinane
DMSO   dimethylsulfoxide
DMSO-d₆ deuterated dimethylsulfoxide
dppf   1,1'-Bis(diphenylphosphino)ferrocene
EDCI   N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EDTA   ethylenediaminetetraacetic acid
ee     enantiomeric excess
EtOAc  ethyl acetate
EtOH   ethanol
¹H NMR proton nuclear magnetic resonance
HOAc   acetic acid
HATU   2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate
HCl    hydrochloric acid
HOBT   1H-benzo[d][1,2,3]triazol-1-ol hydrate
HPLC   high pressure liquid chromatography
Hz     hertz
IPA    isopropyl alcohol
Example 1 -- Intermediate II-1:(S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride
**Step 1:** (R,E)-N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide.

![Moleculer structure](image)

To a mixture of 2,6-dichloroquinoine-3-carbaldehyde (15.0 g, 66.37 mmol) and (R)-2-methylpropane-2-sulfinamide (8.85 g, 73.14 mmol) in 1,2-dichloroethane (150 mL) was added CuSO₄ (16.0 g, 100.25 mmol). The resulting mixture was heated to 55 °C and stirred at 55 °C overnight. After TLC and MS showed complete disappearance of starting materials, the mixture was cooled to room temperature and filtered through a pad of Celite®. The pad of celite was then rinsed with CH₂Cl₂. The filtrate was evaporated to dryness *in vacuo* and purified by SiO₂ column chromatography (0 to 25% hexanes/EtOAc) to afford the title compound, (R,E)-N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide, as a yellow solid (17.7 g, 81% yield).

**Step 2:** (R)-N-((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide.

![Moleculer structure](image)

To a solution of (R,E)-N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (8.85 g, 26.88 mmol) in anhydrous CH₂Cl₂ (200 mL) at -60 °C was added dropwise MeMgBr (3M solution in diethyl ether, 13.5 mL, 40.54 mmol). The resulting reaction mixture was stirred at about -60 to -50 °C for 3 hours and then stirred at -20 °C overnight under an atmosphere of N₂. After TLC and MS showed complete disappearance of starting materials, saturated NH₄Cl (163 mL) was added at -20 °C and the resulting mixture was stirred for 10 minutes. The aqueous phase was extracted with CH₂Cl₂ (100 mL x 3), dried over anhydrous Na₂SO₄, filtered, and evaporated. The residue was purified by column chromatography on an ISCO® chromatography system (SiO₂: Gold column; gradient; hexanes to 100% EtOAc) to provide the title compound, (R)-N-((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide, as a yellow solid (5.8 g, 63% yield).

**Step 3:** (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-1).
A mixture of (R)-N-((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (6.6 g, 19.13 mmol) in 1,4-dioxane (41 mL) and 1N HCl (41 mL) was heated at reflux overnight. The solvents were evaporated in vacuo and the resulting residue was dissolved in hot water and lyophilized. The crude product was triturated with diethyl ether to afford the title compound II-1 as a yellow solid (9.0 g, ee: 98.4%). $^1$H NMR (300 MHz, DMSO-d$_6$): δ ppm 12.4 (br s, 1 H), 8.32 (br s, 2 H), 8.07 (s, 1 H), 7.85 (d, J = 2.2 Hz, 1 H), 7.63 (dd, J$_1$ = 8.8 Hz, J$_2$ = 2.5 Hz, 1 H), 7.40 (d, J = 8.8 Hz, 1 H), 4.40-4.45 (m, 1 H), 1.53(d, J = 8.5 Hz, 3 H). LCMS (Method 3): Rt 3.42 min, m/z 223.1 [M+H]$^+$.

Example 2-- Intermediate II-2:(R)-3-(1-aminomethyl)-6-chloroquinolin-2(1H)-one hydrochloride.

![Chemical structure of II-2](image)

**Step 1: (R)-N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide.**

To a mixture of 2,6-dichloroquinoline-3-carbaldehyde (500 mg, 2.21 mmol) and (R)-2-methylpropane-2-sulfinamide (295 g, 2.43 mmol) in 1,2-dichloroethane (15 mL) was added CuSO$_4$ (530 mg, 3.31 mmol). The resulting mixture was heated to 55 °C and stirred at 55 °C for 18 hours. Once TLC and MS showed complete disappearance of starting materials, the reaction mixture was cooled to room temperature and filtered through a pad of Celite®. The pad of celite was then rinsed with CH$_2$Cl$_2$. The filtrate was evaporated to dryness in vacuo and purified by column chromatography on an ISCO® chromatography system (SiO$_2$; hexanes to 60%...
EtOAc/hexanes) to afford the title compound, \((R)-N\-\((2,6\-dichloroquinolin-3\-yl)\)methylene\)-2-methylpropane-2-sulfinamide, as a yellow solid (510 mg, 70% yield).

**Step-2**: \((R)-N\-\((R)-1\-\(2,6\-dichloroquinolin-3\-yl\)ethyl\)\)-2-methylpropane-2-sulfinamide.

To a solution of \((R)-N\-\((2,6\-dichloroquinolin-3\-yl)\)methylene\)-2-methylpropane-2-sulfinamide (505 mg, 1.534 mmol) in anhydrous THF (8 mL) at 0 °C was added dropwise MeMgBr (3M solution in diethyl ether, 0.56 mL, 1.687 mmol). The mixture was stirred at 0 °C for 3 hours under an atmosphere of N₂. After TLC and MS showed complete disappearance of starting materials, saturated NH₄Cl (5mL) was added at 0 °C and the resulting mixture was stirred for 10 minutes. The aqueous phase was extracted with EtOAc (10 mL x 3), dried over anhydrous Na₂SO₄, filtered, and evaporated. The residue was purified by column chromatography on an ISCO® chromatography system (SiO₂; hexanes to 80% EtOAc/hexanes) to afford the title compound as the \(R,R\) isomer as a pale yellow solid (200 mg, 38%) and the \(R,S\) isomer as a pale yellow solid (93 mg, 18% yield).

**Step-3**: \((R)-3\-(1\-aminoethyl\)-6\-chloroquinolin-2(1\-H\)-one hydrochloride (II-2).

![Chemical Structure](image)

**[0101]** A mixture of \((R)-N\-\((R)-1\-\(2,6\-dichloroquinolin-3\-yl\)ethyl\)\)-2-methylpropane-2-sulfinamide (190 mg, 0.55 mmol) in 1,4-dioxane (2 mL) and 1N HCl (1.1 mL, 1.1 mmol) was heated to 150 °C for 30 minutes in a microwave reactor. The solvents were evaporated and the residue was dissolved in hot water and lyophilized to afford the title compound II-2 as a yellow solid (148 mg, quantitative yield). ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.35 (br s, 1 H), 8.28 (br s, 2 H), 8.05 (s, 1 H), 7.86 (d, \(J = 2.2\) Hz, 1 H), 7.63 (dd, \(J₁ = 8.8\) Hz, \(J₂ = 2.5\) Hz, 1 H), 7.40 (d, \(J = 8.8\) Hz, 1 H), 4.40-4.45 (m, 1 H), 1.53 (d, \(J = 8.5\) Hz, 3 H). LCMS (Method 3): Rt 3.40 min, m/z 223.1 [M+H]⁺.

Example 3 -- An alternative approach to Intermediate II-1
**Step-1: 3-acetyl-6-chloroquinolin-2(1H)-one.**

[0102] A mixture of 2-amino-5-chlorobenzaldehyde (0.5 g, 3.21 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.594 g, 4.18 mmol) in xylene (10 mL) under an atmosphere of nitrogen was heated to reflux for 3 hours and then cooled to room temperature. The reaction mixture was filtered and washed with xylene twice to afford the title compound, 3-acetyl-6-chloroquinolin-2(1H)-one (330 mg, 46.3%). $^1$H NMR (300 MHz, DMSO-$d_6$): δ ppm 12.22 (br, 1 H), 8.41 (s, 2 H), 8.00 (s, 1 H), 7.63 (d, $J = 8.8$ Hz, 1 H), 7.32 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.5$ Hz, 1 H), 2.58 (s, 3 H). LCMS (Method 1): m/z 222.94 [M+H]$^+$. 

**Step-2: ((S)-N-((S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide.**

[0103] A mixture of tetraethoxytitanium (144 mg, 0.632 mmol), (S)-2-methylpropane-2-sulfinamide (38.3 mg, 0.316 mmol), and 3-acetyl-6-chloroquinolin-2(1H)-one (70 mg, 0.316 mmol) in THF (20 mL) was heated to 80 °C overnight and then cooled to room temperature. To this mixture was added NaBH$_4$ (59.7 mg, 1.579 mmol) at -50 °C. The mixture was then slowly warmed up to room temperature overnight. MeOH (2 mL) was added to quench excess NaBH$_4$ and was followed by the addition of water. The resulting mixture was filtered to remove solids and the aqueous phase was extracted with EtOAc twice, dried over Na$_2$SO$_4$ and concentrated.
The residue was purified on a Biotage® chromatography system using a 25 g SiO₂ column with gradient elution (20% to 100% EtOAc/Hexanes, then 0-5% MeOH/DCM) to afford (S)-N-((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (39 mg, 38% yield). ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.05 (br, 1 H), 7.95 (s, 1 H), 7.84 (s, 1 H), 7.38 (d, J = 8.8 Hz, 1 H), 5.76 (d, J = 8.06 Hz, 1 H), 5.37 (m, 1 H), 4.55 (m, 1 H), 1.44 (d, J = 6.82 Hz, 3 H), 1.18 (s, 9 H). LCMS (Method 1): Rt 2.22 min; m/z 327.96 [M+H]⁺.

Step-3: (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-1).

[0104] To a solution of ((S)-N-((S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (150 mg, 0.459 mmol) in MeOH (5 mL) was added HCl (2 mL, 8.0 mmol, 4M in 1,4-dioxane). The mixture was stirred at room temperature overnight. To this mixture was added 6 mL of ethyl ether and the resulting precipitate was collected by filtration, washed with ethyl ether (2 x), and then dried to afford (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (50 mg, 42% yield). ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.4 (br s, 1 H), 8.32 (br s, 2 H), 8.07 (s, 1 H), 7.85 (d, J = 2.2 Hz, 1 H), 7.63 (dd, J₁ = 8.8 Hz, J₂ = 2.5 Hz, 1 H), 7.40 (d, J = 8.8 Hz, 1 H), 4.40-4.45 (m, 1 H), 1.53 (d, J = 8.5 Hz, 3 H). LCMS (Method 1): Rt 1.22 min, m/z 223.1 [M+H]⁺. The enantiomer purity (ee %) of II-1 (>98%) was determined by chiral HPLC analysis.

Example 4 – Alternate approach (R)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-2).
**Step-1:** ((R)-N-((R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide

![Chemical Structure](image)

[0105] A mixture of tetraethoxytitanium (412 mg, 1.805 mmol) (R)-2-methylpropane-2-sulfinamide (131 mg, 1.083 mmol) and 3-acetyl-6-chloroquinolin-2(1H)-one (160 mg, 0.722 mmol) in THF (20 mL) was heated to 80 °C overnight, then cooled to room temperature. To this mixture was added NaBH₄ (137 mg, 3.61 mmol) -50 °C. The mixture was then slowly warmed up to room temperature overnight. MeOH (2 mL) was added to quench excess NaBH₄ and was followed by the addition of water. The resulting mixture was filtered to remove solids and the aqueous phase was extracted with EtOAc twice, dried over Na₂SO₄ and concentrated. The residue was purified on a Biotage® chromatography system using a 25 g SiO₂ column with gradient elution (20 to 100% EtOAc/Hexanes, then 0-5% MeOH/DCM) to afford ((R)-N-((R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide (157 mg, 66% yield). ¹H NMR (300 MHz, CDCl₃): δ ppm 11.31 (br, 1 H), 7.35 (s, 1 H), 7.07-7.22 (m, 2 H), 5.86 (d, J = 9.3 Hz, 1 H), 5.37 (m, 1 H), 4.55 (m, 1 H), 1.56 (d, J = 6.94 Hz, 3 H), 1.32 (s, 9H). LCMS (Method 1): Rt 2.20 min, m/z 327.96 [M+H]⁺.

**Step-2:** (R)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-2).

![Chemical Structure](image)

[0106] To a solution of (R)-N-((R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (150 mg, 0.459 mmol) in MeOH (5 mL) was added HCl (2 mL, 8.00 mmol, 4M in 1,4-dioxane). The mixture was added 6 mL of ethyl ether and the resulting precipitate was collected by filtration, washed with ethyl ether (2 x), and then dried to afford (R)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (80 mg, 67% yield). ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.32 (br s, 1 H), 8.34 (br, 2 H), 8.06 (s, 1 H), 7.81 (s, 1 H), 7.58 (d, J = 8.82 Hz, 1 H), 7.31 (d, J = 8.83 Hz, 1 H), 4.40-4.45 (m, 1 H), 1.53 (d, J = 6.81 Hz, 3 H). LCMS (Method 1): Rt 1.20 min, m/z
223.1 [M+H]+. The enantiomer purity (ee %) of II-2 (>98%) was determined by chiral HPLC analysis.

**Example 5 -- Intermediate II-3: (S)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one.**

**Step-1: N-(4-chloro-3-fluorophenyl)acetamide.**

To a solution of 4-chloro-3-fluoroaniline (10.00 g, 68.7 mmol) and DIEA (13.2 mL, 76 mmol) in EtOAc (200 mL) was added Ac₂O (7.1 mL, 75 mmol) dropwise. The solution was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, the solution was washed with water (2 x 100 mL) and brine (100 mL), dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide the product as a white solid. LCMS and ¹H NMR are consistent with N-(4-chloro-3-fluorophenyl)acetamide (12.39 g, 66.0 mmol, 96 % yield) ¹H NMR (300 MHz, DMSO-d₆): δ ppm 10.26 (s, 1 H), 7.77 (dd, J = 12.17, 2.20 Hz, 1 H), 7.49 (dd, J = 8.60, 8.60 Hz, 1 H), 7.30 (dd, J = 8.79, 2.35 Hz, 1 H), 2.06 (s, 3 H). LCMS (Method 1): m/z 188 [M+H]+.

**Step-2: 2,6-dichloro-7-fluoroquinoline-3-carbaldehyde.**

A tube was capped with a septum and placed under an atmosphere of nitrogen. DMF (9.5 mL, 123 mmol) was added by syringe and then cooled on an ice bath. POCl₃ (37 mL, 397
mmol) was added dropwise by syringe (over 25 minutes). The red solution was allowed to warm to room temperature (over 20 minutes), then the septum was removed and the mixture was treated with N-(4-chloro-3-fluorophenyl)acetamide (7.00 g, 37.3 mmol). The tube was then sealed and the solution was stirred at 80 °C overnight. The solution was pipetted onto ice, resulting in formation of a yellow precipitate. The precipitate was collected on a Buchner funnel and washed with water (500 mL), during which most of the precipitate dissolved. The filter cake was dried to provide 427.6 mg of the title compound as a pale yellow solid. LCMS and \textsuperscript{1}H NMR are consistent with impure 2,6-dichloro-7-fluoroquinoline-3-carbaldehyde (427.6 mg, 1.752 mmol, 4.70% yield). The material was used as is. \textsuperscript{1}H NMR (300 MHz, DMSO-\textit{d}_6): \delta ppm 10.36 (s, 1 H), 8.99 (s, 1 H), 8.67 (d, \textit{J} = 8.21 Hz, 1 H), 8.13 (d, \textit{J} = 10.26 Hz, 1 H), 5.76 (s, 1 H). LCMS (Method 1): \textit{m/z} 244 [M+H]+.

**Step-3: N-((2,6-dichloro-7-fluoroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide.**

![Chemical Structure](image)

[0109] A mixture of 2,6-dichloro-7-fluoroquinoline-3-carbaldehyde (424.4 mg, 1.739 mmol) and 2-methylpropane-2-sulfinamide (253.8 mg, 2.094 mmol) was placed under an atmosphere of nitrogen. THF (4 mL) and titanium (IV) isopropoxide (Ti(O\textit{Pr})\textsubscript{4}) (1.00 mL, 3.41 mmol) were then added by syringe and the resulting suspension was stirred at room temperature for 48 hours. Once LCMS indicated the reaction had gone cleanly to completion. The reaction was quenched by dropwise addition of aqueous saturated NH\textsubscript{4}Cl (2 mL). The mixture was triturated with EtOAc (100 mL), and the solid was collected on a Buchner funnel, and was washed with EtOAc (50 mL). The filtrate was washed with brine (50 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, and evaporated under reduced pressure to provide 574.3 mg of the title compound as a yellow solid. LCMS and \textsuperscript{1}H NMR are consistent with (\textit{E})-N-((2,6-dichloro-7-fluoroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (574.3 mg, 1.654 mmol, 95% yield). \textsuperscript{1}H NMR (300 MHz, DMSO-\textit{d}_6): \delta ppm 9.13 (s, 1 H), 8.87 (s, 1 H), 8.67 (d, \textit{J} = 8.21 Hz, 1 H), 8.11 (d, \textit{J} = 10.26 Hz, 1 H), 1.25 (s, 9 H). LCMS (Method 1): \textit{m/z} 347 [M+H]+.

**Step-4: N-(1-(2,6-dichloro-7-fluoroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide.**
[0110] *N*-(2,6-dichloro-7-fluoroquinolin-3-yl)methylene)-2-methylpropane-2-sulfamid (573.6 mg, 1.652 mmol) was placed in a 100 mL round-bottom flask under an atmosphere of nitrogen. DCM (14 mL) was added and the resulting suspension was cooled in a dry ice/chloroform bath (to approx. -60 °C). Methyl magnesium bromide (MeMgBr) (3 M in ethyl ether, 0.83 mL, 2.490 mmol) was then added dropwise. The reaction was stirred at -60 °C for several hours, then at -20 °C overnight. The mixture was placed in an ice bath and treated dropwise with water (7 mL). The mixture was diluted with water (150 mL) and extracted with EtOAc (3 x 50 mL). Silica gel was added to the combined extracts and the sample was evaporated under reduced pressure. The sample was purified by column chromatography on a Biotage® MPLC chromatography system (eluted with 0 to 100% EtOAc in hexanes and with isocratic elution when peaks eluted) to provide 226.3 mg of the title compound as a yellowish solid. LCMS and \(^{1}H\) NMR are consistent with *N*-(1-(2,6-dichloro-7-fluoroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfamid (226.3 mg, 0.623 mmol, 25.02% yield). \(^{1}H\) NMR indicates a single diastereomer. \(^{1}H\) NMR (300 MHz, DMSO-*d_6*): \(\delta\) ppm 8.52 (s, 1 H), 8.47 (\(d, J = 7.92\) Hz, 1 H), 8.01 (\(d, J = 10.26\) Hz, 1 H), 5.66 (\(d, J = 6.16\) Hz, 1 H), 4.83 (q, \(J = 6.60\) Hz, 1 H), 1.60 (\(d, J = 6.74\) Hz, 3 H), 1.13 (s, 9 H). LCMS (Method 1): \(m/z\) 363 [M+H]^+.  

**Step-5: 3-(1-amoethy)-6-chloro-7-fluoroquinolin-2(1H)-one hydrochloride (II-3).**

[0111] A sample of *N*-(1-(2,6-dichloro-7-fluoroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfamid (226.3 mg, 0.623 mmol) was mixed with 1,4-dioxane (3.5 mL) and 3.6% HCl (aqueous, 3.5 mL) and stirred at 95 °C overnight; the material quickly went into solution upon heating. Once LCMS showed the reaction had gone to completion, the solution was evaporated under reduced pressure. The residue was dissolved in MeOH (~10 mL), treated with heptane (~15 mL), and evaporated again under reduced pressure. The resulting residue was then triturated with Et₂O, collected on a Hirsch funnel, and washed with Et₂O (20 mL) to provide
179.8 mg of the title compound as a yellow solid. LCMS and $^1$H NMR are consistent with 3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one hydrochloride (179.8 mg, 0.649 mmol, 104% yield). $^1$H NMR (300 MHz, Methanol-$d_4$): δ ppm 8.02 (s, 1 H), 7.92 ($d, J = 7.62$ Hz, 1 H), 7.23 ($d, J = 9.97$ Hz, 1 H), 4.53 ($q, J = 6.84$ Hz, 1 H), 1.68 ($d, J = 6.74$ Hz, 3 H). LCMS (Method 1): $m/z$ 241 [M+H]$^+$. 

**Example 6 -- Intermediate II-4: (S)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one (II-4)**

![Chemical reaction diagram]

**Step-1:** 2-Amino-5-chloro-4-fluorobenzoic acid

[0112] 2-Amino-4-fluorobenzoic acid (50 g, 322.6 mmol) was dissolved in 700 mL of DMF and N-chlorosuccinimide (41 g, 305.5 mmol) was added portion wise. The reaction mixture was heated at 50 °C for 5 h. The mixture was cooled to room temperature, poured on to ice cold water to get the solid. The solid was filtered and dissolovled in EtOAc, then sat. NaCl (300 mL) was added. The aqueous layer was extracted with EtOAc (3 x 200 mL). The combined
organic phase was dried (Na₂SO₄) and evaporated to a brown solid (42 g, 69%) as desired product 2-amino-5-chloro-4-fluorobenzoic acid.

**Step-2: (2-Amino-5-chloro-4-fluorophenyl)methanol**

![Structure of (2-Amino-5-chloro-4-fluorophenyl)methanol](image)

[0113] 2-Amino-5-chloro-4-fluorobenzoic acid (42 g, 221 mmol) was dissolved in 100 mL of THF and BH₃·THF (712 mL of 1 M solution in THF, 712 mmol) was added dropwise over the period of 1 h at room temperature. The reaction mixture was heated at 50 °C overnight (18 h). The mixture was cooled to room temperature, poured onto ice cold water, and sat. NaCl solution was added. The aqueous was extracted with EtOAc (3 x 200 mL). The combined organic phase was dried (Na₂SO₄), evaporated and purified by flash chromatography using 0-100% hexanes/ethyl acetate as eluent to afford the desired product as a brown solid (17 g, 45%).

**Step-3: 2-Amino-5-chloro-4-fluorobenzaldehyde**

![Structure of 2-Amino-5-chloro-4-fluorobenzaldehyde](image)

[0114] To a solution of (2-amino-5-chloro-4-fluorophenyl)methanol (22 g, 125.7 mmol) in 1000 mL of chloroform was added MnO₂ (109 g, 1250 mmol) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was filtered, washed with EtOAc and evaporated. The resulting crude product was passed through a pad of silica gel eluting with 0 to 20% hexanes/EtOAc to give the pure product as a brown solid (19 g, 87%).

**Step-4: 3-acetyl-6-chloro-7-fluoroquinolin-2(1H)-one**

![Structure of 3-acetyl-6-chloro-7-fluoroquinolin-2(1H)-one](image)

[0115] A mixture of 2-Amino-5-chloro-4-fluorobenzaldehyde (14 g, 173.6 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (16 mL, 121 mmol) in m-xylene (500 mL) was refluxed for 1.5 h. The reaction mixture was cooled to room temperature and filtered. The collected solid was washed with m-xylene and dried to yield the desired product (9.6 g, 50%) as off-white solid.
Step-5: (S)-N-((S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide.

[0116] To a mixture of 3-acetyl-6-chloro-7-fluoroquinolin-2(1H)-one (6.4 g, 26.7 mmol) and (S)-2-methylpropane-2-sulfinamide (4.85 g, 40.06 mmol) in THF (450 mL) was added Ti(OEt)$_4$ (14 mL, 66.7 mmol). The resultant mixture was stirred at 80 °C overnight. Upon the completion of the reaction, the reaction mixture was cooled to -60 °C and NaBH$_4$ (5.1 g, 134 mmol) was added portion wise and then allowed to warm to room temperature overnight. The excess NaBH$_4$ was quenched with MeOH (20 mL), then with water (20 mL) and EtOAc (300 mL). The solution was filtered through a pad of celite. The filtrate was taken into a separatory funnel and the organic layer was separated, dried (Na$_2$SO$_4$), concentrated and purified by flash chromatography (SiO$_2$: hexanes/PrOH 0 to 20%) to give the title compound (4.5 g, 49%) as a yellow solid.

Step-6: (S)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one. HCl, (II-4)

[0117] To a mixture of (S)-N-((S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide (3.5 g, 10.1 mmol) in MeOH (80 mL) was added 3N methanolic HCl (80 mL, 121 mmol). The resultant mixture was stirred at room temperature overnight. To this mixture was added diethyl ether (60 mL) and the resulting solid was filtered and dried to give the desired product II-4 (2.1 g, 75%) as a yellow solid. $^1$H NMR (300 MHz, DMSO-d$_6$): δ 12.40 (br s, 1H), 8.24 (br s, 2H), 8.07- 8.05(m, 2H), 7.32 (d, $J$ = 10.4 Hz, 1H), 4.5-4.15 (m, 1H), 1.53 (d, $J$ = 6.8 Hz, 3H). LCMS (method LCMS3, APCLI): Rt 3.47 min, m/z 241.1 [M+H$^+$].

Example 7 -- Intermediate II-5: (R)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one
**Step 1: 6-chloro-7-fluoro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde**

[0118] 2,6-dichloro-7-fluoroquinoline-3-carbaldehyde (2.56 g, 10.49 mmol) was heated at reflux in concentrated HCl (12M, 100 mL) overnight, during which the material did not appear to go into solution. The mixture was allowed to cool, then was poured into water (750 mL). The slurry was filtered on a Buchner funnel, washed with water (750 mL), and dried to provide impure 6-chloro-7-fluoro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (2.1991 g, 9.75 mmol, 93% yield) as a reddish brown solid. The material was suitable for use as is. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ ppm 12.41 (s, 1 H), 10.20 (s, 1 H), 8.49 (s, 1 H), 8.28 (d, $J=7.92$ Hz, 1 H), 7.25 (d, $J=10.26$ Hz, 1 H). LCMS: m/z +226 [M+H]$^+$. 

**Step 2: (R,E)-N-((6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide**

[0119] A mixture of 6-chloro-7-fluoro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (2.20 g, 9.75 mmol) and (R)-2-methylpropane-2-sulfinamide (1.42 g, 11.72 mmol) was placed in a 50 mL round bottom flask under an atmosphere of nitrogen. THF (20 mL) and titanium (IV) isopropoxide (Ti(O’Pr)$_4$) (5.8 mL, 19.79 mmol) were added by syringe and the resulting suspension was stirred at room temperature for one day, during which the mixture turned dark.
The reaction mixture was quenched by dropwise addition of saturated aqueous NH₄Cl, resulting in precipitation. The mixture was triturated with EtOAc (400 mL) and filtered on a Buchner funnel. The filter cake was then sonicated in 300 mL EtOAc for 15 minutes. The mixture was filtered on a Buchner funnel, and the filtrates from the two filtrations were combined. The combined filtrate solution was washed with brine (200 mL), dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide (R,E)-N-((6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (3.22 g, 9.79 mmol, 100% yield) as an orange solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.40 (br s, 1 H), 8.75 (br s, 1 H), 8.65 (s, 1 H), 8.27 (d, J = 8.21 Hz, 1 H), 7.25 (d, J = 10.26 Hz, 1 H), 1.20 (s, 9 H). LCMS: m/z 329 [M+H]⁺.

**Step-3:** (R)-N-((R)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide.

![Chemical Structure](image)

[0120] (R,E)-N-((6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (3.22 g, 9.79 mmol) was placed in a 500 mL round-bottom flask under an atmosphere of nitrogen. DCM (100 mL) was added and the resulting suspension was cooled on a dry ice/chloroform bath (to approximately -60 °C). Methyl magnesium bromide (MeMgBr) (3M in ether, 10 mL, 30.0 mmol) was added dropwise. The reaction mixture was stirred at -60 °C for several hours, and then allowed to warm to room temperature overnight, resulting in a red solution. The solution was then cooled on an ice bath, treated dropwise with water (40 mL) and concentrated under reduced pressure. The resulting slurry was diluted with water (300 mL) and washed with EtOAc. The resulting emulsion was allowed to separate overnight. The layers were separated, and silica gel was added to the organic layer. Most of the solvent was evaporated under reduced pressure. MeOH and heptane were added and the mixture was evaporated under reduced pressure to dryness. The material was purified by column chromatography on a Biotage® MPLC chromatography system (using 50 g silica gel column; eluted with 0 to 50% EtOAc in hexanes, with isocratic elution when peaks eluted) to provide (R)-N-((R)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-
sulfinamide (774.3 mg, 2.245 mmol, 23% yield) as a greenish solid. $^1$H NMR shows a single
diastereomer. $^1$H NMR (300 MHz, DMSO-$d_6$): δ ppm 12.03 (s, 1 H), 7.98 (d, $J = 7.92$ Hz, 1 H),
7.89 (s, 1 H), 7.22 (d, $J = 10.26$ Hz, 1 H), 5.67 (d, $J = 7.92$ Hz, 1 H), 4.41 - 4.55 (m, 1 H), 1.37
(d, $J = 6.74$ Hz, 3 H), 1.12 (s, 9 H). LCMS: m/z $+345$ [M+H]$^+$. 

Step 4: (R)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one hydrochloride (II-5).

![Chemical Structure](image)

[0121] A solution of (R)-N-[(R)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]-2-methylpropane-2-sulfinamide (773 mg, 2.242 mmol) in MeOH (20 mL) was cooled on an ice bath and treated dropwise with 4M HCl in dioxane (12 mL), during which the material went into solution. The reaction was stirred 25 minutes, during which time precipitate formed. The solvents were evaporated under reduced pressure at room temperature. The residue was triturated with ethyl ether (50 mL), then the solid was collected on a Hirsch funnel and washed with more ethyl ether (50 mL) to provide (R)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one hydrochloride (613.5 mg, 2.214 mmol, 99% yield) as a yellow solid. $^1$H NMR (300 MHz, Methanol-$d_4$): δ ppm 7.99 (s, 1 H), 7.90 (d, $J = 7.62$ Hz, 1 H), 7.22 (d, $J = 9.67$ Hz, 1 H), 4.51 (q, $J = 6.64$ Hz, 1 H), 1.66 (d, $J = 7.04$ Hz, 3 H). LCMS: m/z $+241$ [M+H]$^+$. 

Example 8 -- Intermediate II-6: 3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one.

![Chemical Reaction Diagram](image)

Step 1: 2,6-dichloro-7-methoxyquinoline-3-carbaldehyde.
A tube was capped with a septum and placed under an atmosphere of nitrogen. DMF (6.4 mL, 83 mmol) was added by syringe and then cooled on an ice bath. POCl₃ (25 mL, 268 mmol) was added dropwise by syringe (over 20 minutes). The red solution was allowed to warm to room temperature (over 20 minutes), then the septum was removed, and the mixture was treated with N-(4-chloro-3-methoxyphenyl)acetamide (5 g, 25.05 mmol). The tube was sealed and the solution was stirred at 80 °C overnight. The solution was then pipetted onto ice, resulting in formation of a yellow precipitate. The precipitate was collected on a Buchner funnel, washed with water (1200 mL), and dried to provide 5.06 g of the title compound as a pale yellow solid. LCMS and ¹H NMR are consistent with 2,6-dichloro-7-methoxyquinoline-3-carbaldehyde (5.06 g, 19.76 mmol, 79% yield). ¹H NMR (300 MHz, DMSO-ｄ₆): δ ppm 10.33 (s, 1 H), 8.87 (s, 1 H), 8.47 (s, 1 H), 7.64 (s, 1 H), 4.08 (s, 3 H). LCMS (Method 1): m/z 256 [M+H]+.

**Step-2: 6-chloro-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde.**

2,6-Dichloro-7-methoxyquinoline-3-carbaldehyde (5.06 g, 19.76 mmol) was heated at reflux in concentrated HCl (12M, 185 mL) overnight. The material went into solution during heating and then a solid precipitated during the course of the reaction. The mixture was allowed to cool and then was poured into water (1500 mL) resulting in further precipitation. The slurry was filtered on a Buchner funnel, washed with water (1500 mL), and dried to provide 4.04 g of the title compound as a yellowish-brown solid. LCMS and ¹H NMR are consistent with 6-chloro-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (4.04 g, 17.00 mmol, 86% yield). ¹H NMR (300 MHz, DMSO-ｄ₆): δ ppm 12.22 (s, 1 H), 10.16 - 10.18 (m, 1 H), 8.43 (s, 1 H), 8.08 (s, 1 H), 6.95 (s, 1 H), 3.94 (s, 3 H). LCMS (Method 1): m/z 238 [M+H]+.
Step-3: \(N\)-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide.

[0124] A mixture of 6-chloro-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (2.00 g, 8.42 mmol) and 2-methylpropane-2-sulfinamide (1.22 g, 10.07 mmol) was placed under an atmosphere of nitrogen. THF (20 mL) and titanium (IV) isopropoxide (Ti(O\(^\text{OPr})_4\)) (5.0 mL, 17.06 mmol) were added by syringe and the resulting suspension was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, the reaction was quenched by dropwise addition of aqueous saturated NH\(_4\)Cl (10 mL). The mixture was triturated with EtOAc (450 mL), then filtered through Celite\(^\circledR\) 545, and the Celite\(^\circledR\) was washed further with EtOAc (200 mL). The filter cake was then sonicated in EtOAc (450 mL) for 15 minutes, then filtered on a Buchner funnel. The two filtrates were combined, washed with brine (200 mL), dried (Na\(_2\)SO\(_4\)), filtered, and evaporated under reduced pressure to provide 1.01 g of the title compound as a yellow solid. LCMS and \(^1\)H NMR are consistent with \((E)-N\)-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (1.01 g, 2.96 mmol, 35.2% yield). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)); \(\delta\) ppm 12.21 (s, 1 H), 8.74 (s, 1 H), 8.59 (s, 1 H), 8.08 (s, 1 H), 6.97 (s, 1 H), 3.94 (s, 3 H), 1.19 (s, 9 H). LCMS (Method 1): \(m/z\) 341 [M+H]\(^+\).

Step-4: \(N\)-(1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide.

[0125] \(N\)-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (265 mg, 0.778 mmol) was placed in a 50 mL round-bottom flask under an atmosphere of nitrogen. DCM (7 mL) was added, and the suspension was cooled on a dry ice/chloroform bath (to approx. -60 °C). Methylmagnesium bromide (MeMgBr) (3M in
ether, 0.80 mL, 2.40 mmol) was added dropwise. The reaction mixture was stirred at -60 °C for several hours, then allowed to warm to room temperature overnight, resulting in an orange solution. Once LCMS indicated the reaction had gone to completion, the suspension was cooled on an ice bath and treated dropwise with water (3 mL). The resulting mixture was diluted with water (75 mL) and extracted with EtOAc (75 mL + 20 mL). Silica gel was added and the EtOAc was evaporated under reduced pressure to provide a wet globular mass. Heptane and MeOH were added and the mixture was evaporated under reduced pressure to provide a powder. The material was purified by column chromatography on a Biotage® MPLC chromatography system (eluted with 0 to 4.2% MeOH in DCM, with isocratic elution when peaks eluted). The product fractions provided 152.7 mg of the title compound as a blue-green brittle foam. LCMS and 1H NMR are consistent with N-(1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfamidem (152.7 mg, 0.428 mmol, 55% yield). LCMS (Method 1): m/z 357 [M+H]⁺.

Step 5: 3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride (II-6).

[0126] A solution of N-(1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfamidem (149.6 mg, 0.419 mmol) in MeOH (3.8 mL) was cooled on an ice bath and treated dropwise with 4M HCl in 1,4-dioxane (2.2 mL). The reaction was stirred for 25 minutes, during which time a small amount of precipitate formed. The solvents were evaporated under reduced pressure at room temperature. The residue was triturated with 10 mL of ethyl ether, then collected on a Hirsch funnel, and washed with more ethyl ether to provide 115.6 mg of the title compound as a pale green solid. LCMS and 1H NMR are consistent with 3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride (115.6 mg, 0.400 mmol, 95% yield). 1H NMR (300 MHz, Methanol-d₄): δ ppm 7.95 (s, 1 H), 7.77 (s, 1 H), 6.97 (s, 1 H), 4.51 (q, J = 6.84 Hz, 1 H), 3.98 (s, 3 H), 1.68 (d, J = 7.04 Hz, 3 H). LCMS (Method 1): m/z 253 [M+H]⁺.

Example 9 -- Intermediate II-7: (S)-3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one.

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Step-1: N-(4-chloro-3-methoxyphenyl)acetamide

[0127] To a solution of 4-chloro-3-methoxyaniline (50 g, 317 mmol) and DIPEA (110 mL, 635 mmol) in CH₂Cl₂ (700 mL) was added acetic anhydride (36 mL, 381 mmol) dropwise at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction then was quenched with water (250 mL) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (100 mL x 3). The combined organic layers were dried (Na₂SO₄), concentrated and purified by flash chromatography with CH₂Cl₂/MeOH to give N-(4-chloro-3-methoxy phenyl)acetamide (71 g, quantitative yield) as a white solid.

Step-2: 2,6-Dichloro-7-methoxyquinoline-3-carbaldehyde

[0128] To POC₁₃ (450 g, 274 mL, 2.95 mol) in a 2 L flask was added anhydrous DMF (83.5 g, 89 mL, 14 mol) drop wise. The reaction mixture was warmed up to room temperature and stirred for 20 min. After that N-(4-chloro-3-methoxyphenyl)acetamide (65 g, 327 mmol) was added portion wise at room temperature and the mixture was heated to 90 °C overnight. The
reaction mixture was then cooled to room temperature and carefully quenched into aqueous NaHCO₃ solution. The precipitation obtained was filtered, washed with water (100 mL x 3) and then dried in vacuum oven to give 60 g of title compound (73%).

**Step-3: 6-Chloro-2,7-dimethoxyquinoline-3-carbaldehyde**

![Chemical structure](image)

[0129] To 2,6-dichloro-7-methoxyquinoline-3-carbaldehyde (40 g, 157 mmol) in MeOH (1 L) and THF (200 mL) was added NaOMe (16.9 g, 314 mmol) portion wise at room temperature. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction was quenched by addition of aqueous NH₄Cl solution (200 mL). The mixture was extracted with EtOAc (200 mL x 3). The combined organic layers were dried (Na₂SO₄), concentrated and purified by flash chromatography with hexanes/ EtOAc (3:1) to give the desired product (37.89 g, 96%) as a yellow solid.

**Step-4: 1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethanol**

![Chemical structure](image)

[0130] To a solution of 6-chloro-2,7-dimethoxyquinoline-3-carbaldehyde (36.74 g, 151 mmol) in THF (1 L) at -78 °C was added a solution of MeMgCl in THF (3 M, 75.5 mL, 226 mmol) drop wise. The reaction was stirred at room temperature for 3 h and then quenched with aqueous NH₄Cl solution (250 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL X 3). The combined organic layers were dried (Na₂SO₄), concentrated, and purified by silica gel chromatography with hexanes/ EtOAc (3:1) to afford the title compound (38.06 g, 91%).

**Step-5: 1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethanone**

![Chemical structure](image)
To 1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethanol (36.74 g, 137.6 mmol) in CH₂Cl₂ (1 L) at 0 °C was added DMP (70.0 g, 165.1 mmol) portion wise. The reaction was stirred at room temperature for 2 h, and then was quenched with an aqueous solution of NaHCO₃ and Na₂S₂O₅. After stirring for 15 min, both layers became clear. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (100 mL X 2). The combined organic layers were dried (Na₂SO₄), concentrated and purified by silica gel chromatography with hexanes/ EtOAc (4:1) to afford the title compound (30.02 g, 80%) as a white solid.

**Step 6:** (R,E)-N-(1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide

To 1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethanone (30.07 g, 113.5 mmol) in THF/toluene (100 mL/1 L) at room temperature was added (R)-2-methylpropane-2-sulfinamide (27.5 g, 227 mmol, ) and Ti(OiPr)₄ (97 mL, 340.5 mmol,). The reaction was refluxed with a Dean-Stark apparatus. After the reaction was refluxed for 4 h and 300 mL of solvent was removed, the reaction was cooled to room temperature. The solvent was removed under vacuum, and 200 mL of EtOAc was added to the residue, followed by 100 mL of saturated aqueous NaHCO₃ solution. After stirring for 10 min, the reaction mixture was passed through a pad of celite. The filtrate was extracted with EtOAc (200 mL x 2), dried (Na₂SO₄), concentrated and purified by silica gel chromatography with hexanes/ EtOAc (1:1) to give the title compound (34.28 g, 82%).

**Step 7:** (R)-N-((S)-1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide
To (R,E)-N-(1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethylidene)-2-methylpropane-2-sulfonamide (34.28 g, 93.15 mmol) in THF (600 mL) at -78 °C, was added 1 M L-selectride (121 mL, 121 mmol) in THF drop wise. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with aqueous saturated NH₄Cl (300 mL) solution and then extracted with EtOAc (200 mL X 2). The combined organic layers were dried (Na₂SO₄), concentrated and purified by silica gel chromatography with hexanes/ EtOAc (1:1) to afford the title compound (29.27 g, 85%).

**Step-8:** (S)-3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride salt (II-7).

![Chemical Structure](image)

To (R)-N-((S)-1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (30.35 g, 82 mmol) in dioxane (250 mL) was added 2 N HCl (250 mL) at rt. The reaction mixture was refluxed for 3 h, cooled to room temperature and the solvent was removed under vacuum. The crude residue obtained was dried under vacuum to give a crude product, which was further purified by trituration (CH₂Cl₂/MeOH/hexane) to obtain pure title compound II-7 (17.65 g, 75%) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ 12.18 (s, 1H), 8.24 (br, s, 3H), 7.99 (s, 1H), 7.86 (s, 1H), 7.02 (s, 1H), 4.41 (m, 1H), 3.91 (s, 3H), 1.52 (d, J = 6.87 Hz, 3H). LCMS (Method 3): Rt 3.48 min, m/z 253.1 [M+H]⁺.

**Example 10 -- Intermediate II-8:** (R)-3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one

![Chemical Structure](image)

The title compound II-8 was prepared in the same procedure described for II-7, except using (S)-2-methylpropane-2-sulfonamide in Step-6 (Scheme-3). ¹H NMR (300 MHz, Methanol-d₄): δ ppm 7.92 (s, 1H), 7.75 (s, 1H), 6.95 (s, 1H), 4.48 (q, J = 6.84 Hz, 1H), 3.96 (s, 3H), 1.65 (d, J = 6.74 Hz, 3H). LCMS: m/z 253 [M+H]⁺.
Example 11 -- Intermediate II-9: 3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one.

\[ \text{Step-1: 4-chloro-3-(pyridin-2-ylmethoxy)aniline.} \]

[0136] A solution of 5-amino-2-chlorophenol (2.00 g, 13.93 mmol pyridin-2-ylmethanol (1.4 mL, 14.51 mmol), and triphenylphosphine (4.30 g, 16.39 mmol) in THF (250 mL) was placed under an atmosphere of nitrogen and treated with DEAD (2.6 mL, 16.42 mmol) The solution was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, the solution was treated with silica gel and evaporated under reduced pressure. The material was purified by column chromatography on a Biotage® MPLC chromatography system (using a 340 g silica gel column, eluted with 0 to 100% EtOAc in hexanes, then 2.3% MeOH in EtOAc) to provide the title compound as a light brown solid. LCMS and \(^1\)H NMR are consistent with 4-chloro-3-(pyridin-2-ylmethoxy)aniline (2.29 g, 9.76 mmol, 70.0% yield) with residual
triphenylphosphine oxide. The crude was used in the next step without further purification. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) ppm 8.55 - 8.62 (m, 1 H), 7.86 (ddd, \(J = 7.77, 7.77, 1.76\) Hz, 1 H), 7.52 (d, \(J = 7.92\) Hz, 1 H), 7.35 (dd, \(J = 6.89, 5.42\) Hz, 1 H), 7.02 (d, \(J = 8.50\) Hz, 1 H), 6.37 (d, \(J = 2.35\) Hz, 1 H), 6.15 (dd, \(J = 8.50, 2.35\) Hz, 1 H), 5.28 (s, 2 H), 5.14 (s, 2 H). LCMS (Method 1, ESI): \(m/z\) 235 [M+H]+.

Step-2: \(N\)-(4-chloro-3-(pyridin-2-ylmethoxy)phenyl)acetamide.

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{O} & \quad \text{N} \\
\text{H} & \quad \text{N}
\end{align*}
\]

0137 A solution of 4-chloro-3-(pyridin-2-ylmethoxy)aniline (5.22 g, 22.24 mmol) and DIEA (4.30 mL, 24.62 mmol) in EtOAc (125 mL) was treated with \(\text{Ac}_2\text{O}\) (2.30 mL, 24.38 mmol). The solution was stirred at room temperature overnight, after which a thick white precipitate formed. EtOAc (300 mL) was added and the mixture was shaken until most of the precipitate dissolved. The organic layer was then washed with water and brine (125 mL each), dried (\(\text{Na}_2\text{SO}_4\)) and filtered. Silica gel was added, and the mixture was evaporated under reduced pressure. The residue was purified by column chromatography on a Biotage® MPLC chromatography system (using a100 g silica gel column, eluted with 0 to 5% MeOH in DCM) to provide 3.23 g of the title compound as a white solid. LCMS and \(^1\)H NMR are consistent with \(N\)-(4-chloro-3-(pyridin-2-ylmethoxy)phenyl)acetamide (3.23 g, 11.67 mmol, 52.5% yield) \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) ppm 10.06 (s, 1 H), 8.56 - 8.62 (m, 1 H), 7.87 (ddd, \(J = 7.80, 7.80, 1.80\) Hz, 1 H), 7.53 (d, \(J = 7.62\) Hz, 1 H), 7.49 (d, \(J = 2.05\) Hz, 1 H), 7.33 - 7.40 (m, 2 H), 7.22 (dd, \(J = 8.65, 2.20\) Hz, 1 H), 5.21 (s, 2 H), 2.02 (s, 3 H). LCMS (Method 1): \(m/z\) 277 [M+H]+.

Step-3: 2,6-dichloro-7-(pyridin-2-ylmethoxy)quinoline-3-carbaldehyde.

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{O} & \quad \text{N} \\
\text{Cl} & \quad \text{H}
\end{align*}
\]
A tube was capped with a septum and placed under an atmosphere of nitrogen. DMF (2.9 mL, 37.5 mmol) was added by syringe and then cooled on an ice bath. POCl₃ (11.4 mL, 122 mmol) was added dropwise by syringe (over 20 minutes). The solution was allowed to warm to room temperature (over 15 minutes) and the septum was removed. The mixture was treated with N-(4-chloro-3-(pyridin-2-ylmethoxy)phenyl)acetamide (3.16 g, 11.42 mmol). The tube was again sealed and the solution was stirred at 80 °C overnight. The solution was then pipetted onto ice, resulting in the formation of a yellow precipitate. The precipitate was collected on a Buchner funnel, washed with water (500 mL), and dried to provide 2.88 g of the title compound as a pale yellow solid. LCMS and ¹H NMR are consistent with 2,6-dichloro-7-(pyridin-2-ylmethoxy)quinoline-3-carbaldehyde (2.88 g, 8.64 mmol, 76% yield). ¹H NMR (300 MHz, DMSO-d₆): δ ppm 10.34 (s, 1 H), 8.89 (s, 1 H), 8.66 (br d, J = 4.10 Hz, 1 H), 8.52 (s, 1 H), 7.92 - 8.01 (m, 1 H), 7.75 (s, 1 H), 7.69 (br d, J = 7.62 Hz, 1 H), 7.41 - 7.50 (m, 1 H), 5.55 (s, 2 H). LCMS (Method 1): m/z 333 [M+H]⁺.

**Step-4: 6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinoline-3-carbaldehyde IV-3**

A solution of 2,6-dichloro-7-(pyridin-2-ylmethoxy)quinoline-3-carbaldehyde (2.88 g, 8.64 mmol) in concentrated HCl (81 mL) was stirred at reflux (bath temperature 100 °C) for one day, during which time the solution turned orange. The solution was diluted with water (900 mL), resulting in the formation of a yellow precipitate. The precipitate was collected on a Buchner funnel, washed with water (750 mL), and dried under vacuum at 60 °C to provide 2.27 g of the title compound as a yellow solid. LCMS and ¹H NMR are consistent with 6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinoline-3-carbaldehyde IV-3 (2.27 g, 7.21 mmol, 83% yield). ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.20 (s, 1 H), 10.16 - 10.19 (m, 1 H), 8.60 - 8.64 (m, 1 H), 8.44 (s, 1 H), 8.14 (s, 1 H), 7.90 (ddd, J = 7.60, 7.60, 1.80 Hz, 1 H), 7.57 (d, J = 7.62 Hz, 1 H), 7.36-7.43 (m, 1 H), 7.05 (s, 1 H), 5.37 (s, 2 H). LCMS (Method 1): m/z 315 [M+H]⁺.
Step-5: (E)-N-((6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide.

[0140] A mixture of 6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinoline-3-carbaldehyde (2.27 g, 7.21 mmol) and 2-methylpropane-2-sulfinamide (1.05 g, 8.66 mmol) was placed in a 25 mL round bottom flask under an atmosphere of nitrogen. THF (9 mL) and titanium (IV) isopropoxide (Ti(OiPr)₄) (4.3 mL, 14.68 mmol) were added by syringe and the suspension was stirred at room temperature for one day. Once LCMS indicated the reaction had gone to completion, the material was triturated with EtOAc (400 mL), then filtered through Celite® 545, and the filter cake was washed with EtOAc (100 mL). The filter cake was sonicated in EtOAc (400 mL) for fifteen minutes and then filtered on a Buchner funnel. The two filtrates were combined and washed with brine (250 mL). The aqueous layer was back-extracted with EtOAc (200 mL + 100 mL). The three combined organic layers were dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide 1.44 g of the title compound as a yellow solid. LCMS and ¹H NMR are consistent with (E)-N-((6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (1.44 g, 3.45 mmol, 47.8% yield). ¹H NMR (300 MHz, DMSO-δ₆): δ ppm 12.20 (s, 1 H), 8.74 (s, 1 H), 8.62 (d, J = 4.10 Hz, 1 H), 8.60 (s, 1 H), 8.13 (s, 1 H), 7.90 (ddd, J = 7.80, 7.80, 1.80 Hz, 1 H), 7.58 (d, J = 7.92 Hz, 1 H), 7.40 (dd, J = 7.18, 4.54 Hz, 1 H), 7.06 (s, 1 H), 5.36 (s, 2 H), 1.19 (s, 9 H). LCMS (Method 1): m/z 418 [M+H]⁺.

Step-6: N-(1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide.
(E)-N-(((6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)methylene)-2-methyl propane-2-sulfamamide (1.44 g, 3.45 mmol) was placed in a 250 mL round-bottom flask under an atmosphere of nitrogen. DCM (27 mL) was added and the suspension was cooled on a dry ice/chloroform bath (to approx. -60 °C). Methylmagnesium bromide (MeMgBr) (3M in ether, 3.50 mL, 10.50 mmol) was added dropwise. The cold bath was allowed to warm to room temperature overnight resulting in an orange suspension. Once LCMS indicated the reaction had gone to completion, the suspension was cooled on an ice bath and treated dropwise with water (10 mL) resulting in emulsification. The emulsion was diluted with EtOAc (400 mL) and washed with water (400 mL). Silica gel was added to the organic layer and the solvent was evaporated under reduced pressure. The material was purified by column chromatography on a Biotage® MPLC chromatography system (eluted with 0 to 6% MeOH in DCM with isocratic elution when peaks eluted) to provide 1.17 g of the title compound as a yellow brittle foam. LCMS and \textsuperscript{1}H NMR are consistent with N-((6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfamamide (1.17 g, 2.70 mmol, 78% yield). NMR indicated a mixture of diastereomers. LCMS (Method 1): m/z 434 [M+H]+.

**Step 7:** 3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one hydrochloride (II-9).

![Chemical structure of 3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one hydrochloride](attachment:image)

A solution of N-((6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfamamide (167.3 mg, 0.386 mmol) in MeOH (3.5 mL) was cooled on an ice bath and treated dropwise with 4M HCl in 1,4-dioxane (2 mL). The reaction was stirred for 20 minutes and within five minutes a precipitate began to form. The solvents were evaporated under reduced pressure at room temperature. The residue was triturated with 10 mL of ethyl ether, collected on a Hirsch funnel and washed with more ethyl ether to provide 145.8 mg of the title compound as a pale yellow solid. LCMS and \textsuperscript{1}H NMR are consistent with 3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one hydrochloride (145.8 mg, 0.398 mmol, 103% yield). \textsuperscript{1}H NMR (300 MHz, Methanol-\textit{d}_{4}): δ ppm 8.91-8.95 (\textit{m}, 1 H),
8.68 (\textit{dd}, J = 7.90, 7.90, 1.50 Hz, 1 H), 8.29 (\textit{d}, J = 7.62 Hz, 1 H), 8.04-8.11 (\textit{m}, 1 H), 8.00 (s, 1 H), 7.90 (s, 1 H), 7.17 (s, 1 H), 5.66 (s, 2 H), 4.53 (q, J = 6.84 Hz, 1 H), 1.69 (d, J = 6.74 Hz, 3 H). LCMS (Method 1): \textit{m/z} 352 [M+Na\textsuperscript{+}].

**Example 12 -- Intermediate II-10: (S)-3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy) quinolin-2(1\textit{H})-one.**

**Step 1:** 1-(2,6-Dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethanone.

[0143] To a solution of 2,6-dichloro-7-(pyridin-2-ylmethoxy)quinoline-3-carbaldehyde (1.0 g, 3.0 mmol) (prepared in the same procedure described for step 1-3 shown in Scheme-4) in CH\textsubscript{2}Cl\textsubscript{2} (40 mL) was added dropwise methyl magnesium bromide (MeMgBr) (3 M solution in diethyl ether, 1.5 mL, 4.50 mmol) at 0 °C. The resulting mixture was then stirred at ambient temperature for 1.5 hours. Upon completion of reaction, the mixture was slowly quenched with water (3 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (50 mL). The organic layer was separated and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The solvents were evaporated to dryness. The resulting residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (25 mL) and treated with Dess-Martin Periodinolate (2.54 g, 6.00 mmol). The
mixture was stirred at ambient temperature overnight. The mixture was then quenched with an aqueous co-solution of 20% NaHCO₃ and 20% Na₂S₂O₃ (10 mL) and stirred for 5 minutes at room temperature. The solution was extracted with CH₂Cl₂ (40 mL), dried over anhydrous Na₂SO₄, filtered and evaporated. The resulting residue was purified by column chromatography on an ISCO® chromatography system (SiO₂ column: eluted with CH₂Cl₂ /MeOH 0 to 10%) to afford the title compound (800 mg, 79%).

**Step-2:** **(R,E)-N-(1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide.**

![Chemical Structure](image)

[0144] To a mixture of 1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethanone (2.18 g, 6.56 mmol) and (R)-2-methylpropane-2-sulfinamid (1.19 g, 9.84 mmol) in THF:Toluene (40 mL:180 mL), was added titanium (IV) isopropoxide (Ti(O'Pr)₄) (3.96 mL, 13.30 mmol). The resulting mixture was refluxed with a Dean-Stark apparatus for 7 hours. The mixture was then cooled to room temperature, quenched with water, and diluted with EtOAc (300 mL). The organic layer was washed with water (100 mL), dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on an ISCO® chromatography system (SiO₂ column: eluted with Hex/EtOAc 0 to 100%) to afford the title compound as yellow solid (1.4 g, 50% yield). The starting material ketone was also recovered (250 mg, 11% yield).

**Step-3:** **(R)-N-((S)-1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide.**

![Chemical Structure](image)

[0145] To a solution of (R,E)-N-(1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethylidene)-2-methyl propane-2-sulfinamid (900 mg, 1.99 mmol) in THF (25 mL) at 0 to 50 °C was added L-selectride (1M in THF, 1.98 mL, 2.59 mmol) dropwise. The resulting
mixture was stirred at -40 to -50°C for 2 hours. Upon completion of reaction, the mixture was quenched with ice at -50°C, extracted with EtOAc (100 mL), dried, and evaporated. The resulting residue was purified by column chromatography on an ISCO® chromatography system (SiO2 column: Hex/EtOAc 0 to 100%) followed by trituration with hexanes-methylene chloride to afford the title compound (266 mg, 30% yield).

Step-4: (S)-3-(1-Aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one TFA salt (II-10).

[0146] To a mixture of (R)-N-((S)-1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (1.1 g, 2.43 mmol) in 1,4-dioxane (6.6 mL), was added aqueous 1N HCl (6.6 mL) at room temperature. The resulting mixture was heated to 120°C overnight. After TLC and MS showed completion of reaction, the solvents were removed on a rotary evaporator and lyophilized to provide yellow solid. The crude solid was purified by reverse phase chromatography on an ISCO® chromatography system (C18 column: eluted with H2O/MeCN/0.1% CF3CO2H 0 to 100%) and the fractions were monitored by LCMS. The pure fractions were combined and lyophilized to afford the title compound II-10 (920 mg, 86% yield) as the TFA salt. 1H NMR (300 MHz, DMSO-d6): δ 12.17 (br s, 1 H), 8.62 (d, J = 4.95 Hz, 1 H), 8.09 (br s, 2 H), 7.96-7.85 (m, 3 H), 7.59 (d, J = 7.9 Hz, 1 H), 7.42-7.37 (m, 1 H), 7.08 (d, J = 2.5 Hz, 1 H), 5.33 (s, 2 H), 4.39-4.38 (m, 1 H), 1.51 (d, J = 6.8 Hz, 3 H). LCMS (method 3): Rt 3.3 min, m/z 329.1 [M+H]+.

Example 13 -- Intermediate II-11: (S)-3-(1-aminoethyl)-6-chloro-1,8-naphthyridin-2(1H)-one.
**Step-1:** 3-acetyl-6-chloro-1,8-naphthyridin-2(1H)-one.

A mixture of 2-amino-5-chloronicotinaldehyde (1 g, 6.39 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.362 g, 9.58 mmol) in xylenes (10 mL) was heated to reflux for 3 hours, then cooled to room temperature, filtered, and washed with xylenes twice to afford 914 mg of 3-acetyl-6-chloro-1,8-naphthyridin-2(1H)-one (64.3% yield). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 12.68 (br, 1 H), 8.63 (s, 1 H), 8.49 (s, 1 H), 8.39 (s, 1 H), 2.48 (s, 3 H). LCMS (Method 1): Rt 1.60 min, m/z 223.03[M+H]\(^+\).

**Step-2:** (S)-N-((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide.

A mixture of tetraethoxytitanium (512 mg, 2.25 mmol), (\(R\))-2-methylpropane-2-sulfinamide (163 mg, 1.35 mmol) and 3-acetyl-6-chloro-1,8-naphthyridin-2(1H)-one (200 mg, 0.898 mmol) in THF (15 mL) was heated to 80 °C overnight, then cooled to room temperature. To this mixture was added NaBH\(_4\) (170 mg, 4.49 mmol) and the mixture was slowly warmed up to room temperature overnight. MeOH was then added to quench any excess NaBH\(_4\), followed by the addition of water. The mixture was filtered to remove solids, then extracted with EtOAc twice, dried over Na\(_2\)SO\(_4\), and concentrated. The residue was purified on a Biotage\(^\circledR\) chromatography system using a 25 g SiO\(_2\) column eluted on a gradient (first 20% to 100%
EtOAc /Hexanes, then 0-5% MeOH/DCM) to afford (S)-N-((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (123 mg, 42% yield). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 8.40 (s, 1 H), 7.74 (s, 1 H), 7.75 (s, 1 H), 7.24 (s, 1 H), 5.24 ($d, J = 9.45$ Hz, 1 H), 4.42 ($m$, 3 H), 1.54 ($d, J = 6.93$ Hz, 3 H), 1.20 (s, 9H). LCMS (Method 1): Rt 2.07 min, m/z 328.98 [M+H]$^+$. 

**Step-3:** (S)-3-(1-aminooethyl)-6-chloro-1,8-naphthyridin-2(1H)-one (II-11).

[0149] To a solution of (S)-N-((S)-1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (123 mg, 0.375 mmol) in MeOH (5 mL) was added HCl (2 mL, 8.00 mmol, 4M in 1,4-dioxane). The mixture was then stirred at room temperature overnight. To this mixture was added 6 mL of ethyl ether and the resulting precipitate was filtered, washed with ethyl ether (2 x), dried and concentrated to afford (S)-3-(1-aminooethyl)-6-chloro-1,8-naphthyridin-2(1H)-one, HCl (96 mg, 98% yield). $^1$H NMR (300 MHz, DMSO-$d_6$): δ 12.75 ($br s$, 1 H), 8.60-8.35 (s, 1 H), 8.26 ($br s$, 1 H) 8.07 (s, 1 H), 4.40-4.50 ($m$, 1 H), 1.51 ($d$, $J = 6.78$ Hz, 3 H). LCMS (Method 1): Rt 0.87 min, m/z 224.99 [M+H]$^+$. 

**Example 14 -- Intermediate II-12:** (R)-3-(1-aminooethyl)-6-chloroquinoxalin-2(1H)-one
Step 1: Ethyl 3-((4-chloro-2-nitrophenyl)amino)-3-oxopropionate.

To a solution of 4-chloro-2-nitroaniline (42.3 g, 245 mmol) in CH₂Cl₂ (1 L) was added ethyl 3-chloro-3-oxopropanoate (48 g, 319 mmol) dropwise and the reaction mixture was stirred at room temperature overnight. The solvent was removed under vacuum and the resulting residue was dissolved in a minimum amount of MTBE (200 mL) and hexanes (800 mL) which was slowly added. Any product that precipitated out from solution was filtered and the filtrate was concentrated and purified by column chromatography ISCO® chromatography system with hexanes/ethyl acetate gradient elution to afford additional desired product. The title compound was obtained in 98% yield (69.85 g).
**Step 2:** 7-Chloro-2-(ethoxycarbonyl)-3-oxo-3,4-dihydroquinoxaline 1-oxide (A) and 7-Chloro-2-(methoxycarbonyl)-3-oxo-3,4-dihydroquinoxaline 1-oxide (B).

![Structural formulas of A and B](image)

[0151] To a solution of ethyl 3-((4-chloro-2-nitrophenyl)amino)-3-oxopropanoate (68 g, 238 mmol) and methyl benzoate (150 mL) in anhydrous DMF (500 mL) at 0 °C was added dropwise KO'Bu (1M solution in THF, 500 mL, 500 mmol). The reaction mixture was stirred at 0 °C for 4 hours and then quenched with saturated NH₄Cl aqueous solution. The mixture was extracted with CH₂Cl₂ (300 mL x 3). The combined organic layers were dried (Na₂SO₄), concentrated, and purified by SiO₂ flash chromatography and eluted with CH₂Cl₂/MeOH to afford a mixture of A/B (42.54 g, 67% yield, A/B ratio 1:2) as a solid. This was used in the next step without further purification.

**Step 3:** Ethyl 7-chloro-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (D) and methyl 7-chloro-3-oxo-3,4-dihydroquinoxaline-2-carboxylate (C).

![Structural formulas of C and D](image)

[0152] To a mixture of compounds A and B (42.54 g, 159 mmol) in DMF (200 mL) was added PBr₃ (85.9 g, 318 mmol) dropwise at room temperature. The reaction mixture was stirred at room temperature for 3 hours and was then quenched with ice water and extracted with CH₂Cl₂ (200 mL x 3). The combined organic layers were dried (Na₂SO₄), concentrated, and purified by flash chromatography using CH₂Cl₂/MeOH (9:1) as eluent to afford C/D (36.6 g, 91% yield) as a solid. This was used in the next step without further purification.

**Step 4:** Ethyl 3,7-dichloroquinoxaline-2-carboxylate (E) and methyl 3,7-dichloroquinoxaline-2-carboxylate (F).
[0153] To a mixture of compounds C/D (36.6 g, 145 mmol) in a 1 L flask was added POCl₃ (150 mL) in one portion and the resulting mixture was refluxed for 3 hours. The mixture was then cooled to room temperature and carefully quenched with aqueous NaHCO₃ solution. The mixture was extracted with CH₂Cl₂ (200 mL x 3). The combined organic layer was dried (Na₂SO₄), concentrated, and purified by SiO₂ flash chromatography using hexane/ethyl acetate (9:1) as eluent to afford E/F (23.7 g, 61% yield) as a solid. This mixture was used in the next step without further purification.

**Step-5: Methyl 7-chloro-3-methoxyquinoxaline-2-carboxylate.**
To methyl 7-chloro-3-methoxyquinoxaline-2-carboxylate (5.3 g, 20 mmol) in CH₂Cl₂ (250 mL) was added diisobutylaluminum hydride (1 M, 30 mL) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 3 hours and was then quenched with MeOH (at -78 °C, 20 mL). After stirring for 0.5 hours, the mixture was warmed to room temperature and potassium sodium L-tartrate aqueous solution (100 mL) was added. The organic layer was then separated, and the aqueous layer was extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were dried (Na₂SO₄), concentrated, and purified by SiO₂ flash chromatography using hexanes/ethyl acetate (1:1) as eluent to afford G (1.02 g, 23 % yield) and H (2.24 g, 50% yield). The structure of H was assigned based on MS and ¹H NMR.

**Step-7:** (R,E)-N-((7-chloro-3-methoxyquinoxalin-2-yl)methylene)-2-methylpropane-2-sulfonamide.

![Chemical structure of (R,E)-N-((7-chloro-3-methoxyquinoxalin-2-yl)methylene)-2-methylpropane-2-sulfonamide](image)

To compound H (2.24 g, 5.1 mmol) in DCE (300 mL) at room temperature was added (R)-2-methylpropane-2-sulfonamide (2.44 g, 20.1 mmol) and CuSO₄ (4.85 g, 30.3 mmol). The reaction was heated to 60 °C and stirred for 4 hours. The reaction mixture was then cooled to room temperature and quenched with 50 mL of saturated aqueous NaHCO₃ solution. After stirring for 10 minutes, the reaction mixture was filtered through a pad of Celite®. The filtrate was extracted with CH₂Cl₂ (50 mL x 3), dried (Na₂SO₄), concentrated, and purified by column chromatography on an ISCO® chromatography system using hexanes/ethyl acetate as eluent to afford the title compound (2.21 g, 67% yield).

**Step-8:** (R)-N-((R)-1-(7-chloro-3-methoxyquinoxalin-2-yl)ethyl)-2-methylpropane-2-sulfonamide.

![Chemical structure of (R)-N-((R)-1-(7-chloro-3-methoxyquinoxalin-2-yl)ethyl)-2-methylpropane-2-sulfonamide](image)

To (R,E)-N-((7-chloro-3-methoxyquinoxalin-2-yl)methylene)-2-methylpropane-2-sulfonamide (2.21 g, 6.8 mmol) in CH₂Cl₂ (150 mL) was added methyl magnesium chloride (MeMgCl) (3M in THF, 3.4 mL) dropwise at -78 °C. The resulting mixture was stirred at -78 °C...
for 2 hours and was then quenched with aqueous NH₄Cl solution (20 mL). After stirring for 10 minutes, the organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (25 mL x 3). The combined organic layers were dried (Na₂SO₄), concentrated, and purified by column chromatography on an ISCO® chromatography system using hexanes/ethyl acetate as eluent to afford the title compound (1.18 g, 51% yield).

_Step-9:_ (R)-3-(1-aminoethyl)-6-chloroquinoxalin-2(1H)-one (II-12).

![Chemical Structure](image)

[0158] To the compound (R)-N-(1-(7-chloro-3-methoxyquinoxalin-2-yl)ethyl)-2-methylpropane-2-sulfonamide (1.29 g, 3.46 mmol) in CH₃CN (100 mL) was added iodotrimethylsilane (3.46 g, 17.3 mmol) dropwise at 0 °C. The mixture was then refluxed for 2 hours, cooled to room temperature, and quenched with MeOH (10 mL). The solvent was removed under vacuum, and the residue was purified by reverse C-18 chromatography on an ISCO® chromatography system using water (0.1% TFA)/CH₃CN (0.1% TFA) as eluent to afford the compound II-12 (1.22 g, 95% yield) as a TFA salt.

**Example 15 -- Intermediate II-13: (S)-3-(1-aminoethyl)-6-chloroquinoxalin-2(1H)-one**

![Chemical Reaction](image)

_Step-1:_ (S,E)-N-(7-chloro-3-methoxyquinoxalin-2-yl)methylene)-2-methylpropane-2-sulfonamide.
To compound H (2.31 g, 5.2 mmol) in DCE (300 mL) at room temperature was added (S)-2-methylpropane-2-sulfinamide (2.52 g, 20.8 mmol) and CuSO₄ (5.0 g, 31.2 mmol). The resulting reaction mixture was heated to 60 °C and stirred for 4 hours. The reaction mixture was then cooled to room temperature and quenched with 50 mL of saturated aqueous NaHCO₃ solution. After stirring for 10 minutes, the mixture was filtered through a pad of Celite®. The filtrate was extracted with CH₂Cl₂ (50 mL x 3), dried (Na₂SO₄), concentrated, and purified by column chromatography on an ISCO® chromatography system using hexanes/ethyl acetate as eluent to afford the title compound (2.62 g, 78% yield).

**Step-2:** (S)-N-((S)-1-(7-chloro-3-methoxyquinoxalin-2-yl)ethyl)-2-methylpropane-2-sulfinamide.

To compound (S,E)-N-((7-chloro-3-methoxyquinoxalin-2-yl)methylene)-2-methylpropane-2-sulfinamide (2.62 g, 8.0 mmol) in CH₂Cl₂ (150 mL) was added methyl magnesium chloride (MeMgCl) (3M in THF, 4.0 mL) dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 2 hours and was then quenched with aqueous NH₄Cl solution (20 mL). After stirring for 10 minutes, the organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (25 mL x 3). The combined organic layers were dried (Na₂SO₄), concentrated, and purified by column chromatography on an ISCO® chromatography system using hexanes/ethyl acetate as eluent to afford the title compound (1.69 g, 62%).

**Step-14:** (S)-3-(1-aminoethyl)-6-chloroquinoxalin-2(1H)-one (II-13).

To the compound (S)-N-((S)-1-(7-chloro-3-methoxyquinoxalin-2-yl)ethyl)-2-methylpropane-2-sulfinamide (350 mg, 1.03 mmol) in CH₃CN (40 mL) was added
iodotrimethylsilane (1.03 g, 5.15 mmol) dropwise at 0 °C. The mixture was then refluxed for 2 hours. After it was cooled to room temperature, the reaction was quenched with MeOH (2 mL). The solvent was removed under vacuum, and the residue was purified by reverse C-18 chromatography on an ISCO® chromatography system using water (0.1% TFA)/CH₃CN (0.1% TFA) as eluent to afford the title compound (267 mg, 79% yield) as a TFA salt.

Example 16 -- Intermediate II-14: (3-((S)-1-aminoethyl)-6-chloro-7-((R)-1-(pyridin-2-yl)ethoxy)quinolin-2(1H)-one

Step-1: tert-butyl (3-((tert-butyldimethylsilyl)oxy)-4-chlorophenyl)carbamate.

A solution of 5-amino-2-chlorophenol (10.00 g, 69.7 mmol) in THF (350 mL) was treated with di-tert-butyl dicarbonate (20 mL, 86 mmol) and stirred at reflux overnight. The solvent was evaporated under reduced pressure to provide a brown oil. The oil was then
dissolved in EtOAc (300 mL), washed with water, saturated aqueous NaHCO₃, and brine (300 mL each), dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide 21.01 g of impure tert-butyl (4-chloro-3-hydroxyphenyl)carbamate as a brown oil (LCMS: m/z 244 [M+H]⁺). This material was dissolved in DMF (130 mL) and cooled on an ice bath. Imidazole (11.74 g, 172 mmol) was then added slowly (over ~10 minutes). A solution of TBDMS-Cl (14.98 g, 99 mmol) in DMF (45 mL) was added (over ~2 minutes). The ice bath was removed and the solution was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, the solution was diluted with EtOAc (1L) and washed with water (2 x 600 mL), half-saturated aqueous NaHCO₃ (600 mL), half-saturated aqueous NH₄Cl (600 mL), saturated NaHCO₃ (600 mL), and brine (600 mL). The organic layer was dried (MgSO₄), filtered, and evaporated under reduced pressure to provide 28.00 g of a brown solid. The sample was dissolved in EtOAc, silica gel (33 g) was added, and the solvent was evaporated under reduced pressure. The material was divided into two batches, each of which was purified by column chromatography on a Biotage® MPLC chromatography system using a 330 g silica gel column eluted with 0 to 5% EtOAc in hexanes and with isocratic elution at 4.5% or 5% EtOAc when the product eluted. The product fractions were collected and provided 21.76 g of tert-butyl (3-((tert-butyldimethylsilyloxy)-4-chlorophenyl)carbamate (21.76 g, 60.8 mmol, 88% yield) as a peach-colored solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 9.43 (s, 1 H), 7.23-7.28 (m, 1 H), 7.22 (d, J = 2.35 Hz, 1 H), 7.09-7.16 (m, 1 H), 1.46 (s, 9 H), 0.99 (s, 9 H), 0.21 (s, 6 H). LCMS (Method 1): m/z 358 [M+H]⁺.

**Step-2: tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate (J).**

![Chemical structure of tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate (J).]

[0163] An oven-dried 3-necked 500 mL round bottom flask was charged with tert-butyl (3-((tert-butyldimethylsilyloxy)-4-chlorophenyl)carbamate (10 g, 27.9 mmol). An oven-dried addition funnel was attached, and the system was flushed with nitrogen. Ethyl ether (113 mL) was added by syringe. The resulting yellow solution was cooled on an acetonitrile/dry ice bath (to approximately -40 °C). t-BuLi (1.7 M in pentane, 40 mL, 68.0 mmol) was then added to the
addition funnel by cannula. The t-BuLi solution was added dropwise to the ether solution (over ~10 minutes), during which time the ether solution gradually became cloudy with a precipitate. The mixture was stirred at about -40 °C for 2.5 hours, then DMF (11 mL) was added dropwise by syringe (over ~10 minutes), during which time the solids went back into solution. The acetonitrile / dry ice bath was replaced with an ice bath, and the yellow solution was stirred at 0 °C for 1.75 hours. The reaction was then quenched by dropwise addition of water (25 mL), resulting in formation of an orange precipitate. The ice bath was removed and the sample was diluted with water (125 mL), resulting in dissolution of the precipitate. The mixture was shaken, and the layers were separated. The aqueous layer was acidified to pH ~4-5 with AcOH. The resulting precipitate was extracted with EtOAc (200 mL), washed with water (2 x 100 mL), dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate as a yellow solid (4.79 g, 17.63 mmol, 63% yield). ¹H NMR (300 MHz, DMSO-d₆): δ ppm 11.72 (s, 1 H), 10.50 (s, 1 H), 9.68 (br s, 1 H), 7.99 (s, 1 H), 7.88 - 7.91 (m, 1 H), 1.48 (s, 9 H). LCMS (Method 1): m/z 216 (M-56, loss of t-Bu).

Step-3: (R)-tert-butyl (4-chloro-2-formyl-5-(1-(pyridin-2-yl)ethoxy)phenyl)carbamate.

![Chemical Structure](image)

A mixture of (S)-1-(pyridin-2-yl)ethanol (454.3 mg, 3.69 mmol), tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate (1 g, 3.68 mmol) and triphenylphosphine (1.158 g, 4.42 mmol) was placed in a 100 mL round bottom flask under an atmosphere of nitrogen. THF (40 mL) was added by syringe. The resulting yellow solution was cooled on an ice bath and then DIAD (0.86 mL, 4.42 mmol) was added dropwise. The ice bath was removed and the solution was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, silica gel was added and the solvent was evaporated under reduced pressure. The sample was purified by column chromatography on a Biotage® MPLC chromatography system (using a 50 g silica gel column eluted with 0 to 13% EtOAc in hexanes) to provide 473.7 mg of a white solid. LCMS and NMR are consistent with (R)-tert-butyl (4-chloro-2-formyl-5-(1-(pyridin-2-yl)ethoxy)phenyl)carbamate contaminated with phenolic starting material (~5:1
product to starting material by NMR. The material was used for next step without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$): δ ppm 10.42 (s, 1 H), 9.73 (s, 1 H), 8.54-8.60 (m, 1 H), 7.98 (s, 1 H), 7.92 (s, 1 H), 7.82 (ddd, $J = 7.80, 7.80, 1.80$ Hz, 1 H), 7.44 (br d, $J = 7.90$ Hz, 1 H), 7.30-7.36 (m, 1 H), 5.64 (q, $J = 6.35$ Hz, 1 H), 1.67 (d, $J = 6.45$ Hz, 3 H), 1.46 (s, 9 H). LCMS (Method 1): $m/z$ 377 [M+H]$^+$. 

**Step-4:** (S)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate (K).

[0165] A suspension of (S)-3-aminobutanoic acid (6.25 g, 60.6 mmol) in EtOH (27.5 mL) was cooled on an ice bath. Thionyl chloride (7.5 mL, 103 mmol) was then added dropwise over 40 minutes, during which time the amino acid went into solution. The ice bath was allowed to melt, and the solution was stirred at room temperature overnight. The mixture was evaporated under reduced pressure, and the residue was mixed with more EtOH (60 mL) and again evaporated under reduced pressure to provide an oil. The oil was dissolved in DCM (55 mL) and cooled on an ice bath. TEA (25 mL, 179 mmol) was added dropwise over 15 minutes with stirring, resulting in a milky mixture. Di-tert-butyl dicarbonate (17 mL, 73.2 mmol) was then added. The ice bath was allowed to melt, and the mixture was stirred at room temperature for five days. The resulting mixture was filtered through Celite® 545 on a Buchner funnel, and the filter cake was washed with DCM (50 mL). The filtrate was washed with saturated aqueous citric acid (20 mL) and water (2 x 100 mL), dried (MgSO$_4$), filtered, and evaporated under reduced pressure to provide the title compound as a clear oil. $^1$H NMR is consistent with (S)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate (13.47 g, 58.2 mmol, 96% yield). $^1$H NMR (300 MHz, CDCl$_3$): δ ppm 4.95 (br s, 1 H), 4.15 (q, $J = 7.13$, 2 H), 3.98-4.10 (m, 1 H), 2.40-2.57 (m, 2 H), 1.44 (s, 9 H), 1.27 (t, $J = 7.18$, 3 H), 1.22 (d, $J = 6.74$, Hz, 3 H).

**Step-5 & 6:** 3-((S)-1-aminoethyl)-6-chloro-7-((R)-1-(pyridin-2-yl)ethoxy)quinolin-2(1H)-one hydrochloride (II-14).
An oven-dried 25 mL round bottom flask and stir bar were placed under an atmosphere of nitrogen. THF (2.25 mL) and diisopropylamine (0.27 mL, 1.894 mmol) were then added by syringe. The solution was cooled using a dry ice/acetone bath (-78 °C) and n-BuLi (1.6 M in hexane, 1.15 mL, 1.84 mmol) was added dropwise over 5 minutes. After stirring for 10 minutes, a solution of (S)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate K (115.3 mg, 0.499 mmol) in THF (0.5 mL) was added dropwise (over 5 minutes). The solution was stirred for 75 minutes at -78 °C and then a solution of (R)-tert-butyl (4-chloro-2-formyl-5-(1-(pyridin-2-yl)ethoxy)phenyl)carbamate (188.7 mg, 0.501 mmol) in THF (1.0 mL) was added dropwise by syringe. The reaction solution became yellow when the aldehyde was added. The reaction was stirred at -78 °C for 13 minutes and then quenched by the addition of saturated aqueous NH₄Cl solution (2.5 mL). The mixture was partitioned between EtOAc and water (10 mL each). The organic layer was dried (MgSO₄), filtered, and evaporated under reduced pressure to provide an impure mixture of isomers of (3S)-ethyl 3-((tert-butoxycarbonyl)amino)-2-((2-((tert-butoxycarbonyl)amino)-5-chloro-4-((R)-1-(pyridin-2-yl)ethoxy)phenyl)(hydroxy)methyl)butanoate as a yellow oil (344.8 mg; LCMS: m/z 608 [M+H]+). The crude material (334 mg) was dissolved in 1,4-dioxane (5 mL), treated with 12 M aqueous HCl (0.125 mL), and stirred at 110 °C for 90 minutes, during which time a red material precipitated. The mixture was allowed to cool and the supernatant was decanted and discarded. Heptane (~4 mL) was added to the red precipitate remaining in the round bottom and then evaporated under reduced pressure to provide 161.8 mg of a red solid. The material was triturated with ¹PrOH (5 mL) and the resulting precipitate was collected on a Hirsch funnel and washed with ¹PrOH (1 mL) and ethyl ether (~20 mL) to provide 3-((S)-1-aminoethyl)-6-chloro-7-((R)-1-(pyridin-2-yl)ethoxy)quinolin-2(1H)-one hydrochloride (104.2 mg, 0.274 mmol, 55% yield) as a red solid, impure but suitable for use as it is. ¹H NMR (300 MHz, Methanol-d₄): δ ppm 8.81-8.87 (m, 1 H), 8.55-8.64 (m, 1 H), 8.18 (d, J = 7.92 Hz, 1 H), 7.96-8.04 (m, 1 H), 7.95 (s, 1 H), 7.85 (s, 1 H), 6.99 (s, 1 H), 5.98 (q, J = 6.84 Hz, 1 H), 4.48 (q, J = 6.84 Hz, 1 H), 1.86 (d, J = 6.45 Hz, 3 H), 1.64 (d, J = 6.74 Hz, 3 H). LCMS (Method 1): m/z 344 [M+H]+. 
Example 17 -- Intermediate II-15: (S)-3-(1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy) quinolin-2(1H)-one

Step 1: tert-butyl (4-chloro-5-(cyclopropylmethoxy)-2-formylphenyl)carbamate.

[0167] A mixture of cyclopropylmethanol (0.145 mL, 1.838 mmol), tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate J (499.4 mg, 1.838 mmol) and triphenylphosphine (579.4 mg, 2.209 mmol) was placed in a 100 mL round bottom flask under an atmosphere of nitrogen and THF (20 mL) was then added by syringe. The resulting orange solution was cooled on an ice bath and DIAD (0.43 mL, 2.184 mmol) was added dropwise. The ice bath was removed and the solution was stirred at room temperature for 48 hours. Once LCMS indicated the reaction had gone to completion, silica gel was added and the solvent was evaporated under reduced pressure. The sample was purified by column chromatography on a Biotage® MPLC chromatography system using a 25 g silica gel column eluted with 0 to 3% EtOAc in hexanes to provide tert-butyl (4-chloro-5-(cyclopropylmethoxy)-2-formylphenyl)carbamate (410.6 mg, 1.260 mmol, 68.6% yield) as a yellowish solid. 1H NMR (300 MHz, DMSO-d6): δ ppm 10.57 (s, 1 H), 9.75 (s, 1 H), 7.95-8.00 (m, 2 H), 4.02 (d, J = 7.04 Hz, 2 H), 1.49 (s, 9 H), 1.23-1.31 (m, 1 H), 0.57-0.66 (m, 2 H), 0.38-0.46 (m, 2 H). LCMS (Method 1): m/z 270 (loss of t-Bu).

Step 2 & 3: (S)-3-(1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy)quinolin-2(1H)-one hydrochloride (II-15).
An oven-dried 25 mL round bottom flask and stir bar were placed under an atmosphere of nitrogen and THF (5.6 mL) and diisopropylamine (0.53 mL, 3.72 mmol) were added by syringe. The solution was cooled on a dry ice/acetone bath (to -78 °C) and n-BuLi (1.6 M in hexane, 2.35 mL, 3.76 mmol) was added dropwise over a 5 minute period. After stirring for 15 minutes, a solution of (S)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate K (286 mg, 1.238 mmol) in THF (1.25 mL) was added dropwise (over 5 minutes). The solution was stirred for 80 minutes at -78 °C and a solution of tert-butyl (4-chloro-5-(cyclopropylmethoxy)-2-formylphenyl)carbamate (403.2 mg, 1.238 mmol) in THF (2.5 mL) was added dropwise by syringe. The reaction solution became yellow when the aldehyde was added. The reaction was stirred at -78 °C for 12 minutes and then quenched by addition of saturated aqueous NH₄Cl solution (6 mL). The mixture was partitioned between EtOAc and water (25 mL each) and the organic layer was dried (MgSO₄), filtered, and evaporated under reduced pressure to provide 724.5 g of a yellowish oil. The material was dissolved in 1,4-dioxane (12.5 mL), treated with 12M HCl (aqueous; 0.32 mL), and stirred at 110 °C for 70 minutes during which time the solution became thick with a pink precipitate. The sample was allowed to cool and the solvent was evaporated under reduced pressure to provide 1.13 g of a fibrous red solid. The material was triturated with i-PrOH (15 mL) and the resulting precipitate was collected on a Buchner funnel and washed with i-PrOH (20 mL) and ethyl ether (~60 mL) to provide (S)-3-(1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy)quinolin-2(1H)-one hydrochloride (146.1 mg, 0.444 mmol, 36 % yield) as a papery white solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.13 (br s, 1 H), 8.21 (br s, 3 H), 7.98 (s, 1 H), 7.86 (s, 1 H), 6.98 (s, 1 H), 4.32-4.46 (m, 1 H), 3.96 (d, J = 6.40 Hz, 2 H), 1.51 (d, J = 6.70 Hz, 3 H), 1.21-1.35 (m, 1 H), 0.55-0.68 (m, 2 H), 0.35-0.46 (m, 2 H). LCMS (Method 1): m/z 293 [M+H]⁺.

Example 18 -- Intermediate II-16: 3-(1-Aminoethyl)-6-chloro-7-((3,3-difluorocyclobutyl)methoxy)quinolin-2(1H)-one
Step 1: \(N-(4\text{-Chloro-3-((3,3\text{-difluorocyclobutyl)}methoxy)phenyl)acetamide.}\)

[0169] A solution of 5-amino-2-chlorophenol (3 g, 20.90 mmol) (3,3-difluorocyclobutyl)methanol (2.66 g, 21.78 mmol) in THF (375 mL) was placed under an atmosphere of nitrogen and treated with DEAD (3.90 mL, 24.63 mmol). The solution was stirred at room temperature for 48 hours. Once LCMS indicated adequate progression of the reaction, the silica gel was added to the solution and evaporated under reduced pressure. The material was purified by column chromatography on a Biotage® MPLC chromatography system (using a 340 g silica gel column eluted with 0 to 100% EtOAc in hexanes with isocratic elution when peaks eluted) to provide 3.89 g of the title compound as a brown liquid. LCMS was consistent with impure 4-chloro-3-((3,3-difluorocyclobutyl)methoxy)aniline (m/z 248 [M+H]⁺).

The sample was dissolved in EtOAc (80 mL) and treated with DIEA (3.00 mL, 17.18 mmol) and Ac₂O (1.60 mL, 16.96 mmol). The solution was stirred at room temperature overnight. The solution was then washed with water and brine (50 mL each), dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on a Biotage® MPLC chromatography system (using a 50 g silica gel column, eluted with 0 to 50% EtOAc in hexanes with isocratic elution when peaks eluted) to provide 3.16 g of the title compound as a light brown oil, which slowly crystallized on standing. LCMS and \(^1\)H NMR are
consistent with N-(4-chloro-3-((3,3-difluorocyclobutyl)methoxy)phenyl)acetamide (3.16 g, 10.91 mmol, 52% yield) In the NMR one proton is obscured by the solvent signal. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) ppm 11.91 (s, 1 H), 8.54-8.67 (m, 1 H), 7.80-7.95 (m, 2 H), 7.68 (s, 1 H), 7.56 (d, \(J = 7.30\) Hz, 1 H), 7.34-7.44 (m, 1 H), 7.29 (d, \(J = 9.10\) Hz, 1 H), 7.13-7.22 (m, 1 H), 7.03 (s, 1 H), 6.31 (br s, 1 H), 6.22 (d, \(J = 7.90\) Hz, 1 H), 5.30 (s, 2 H), 4.10-4.26 (m, 2 H), 3.78 (s, 3 H). LCMS (Method 1): \(m/z\) 290 [M+H]\(^+\).

**Step-2:** \(2,6\)-**Dichloro-7-((3,3-difluorocyclobutyl)methoxy)quinoline-3-carbaldehyde.  

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A tube was capped with a septum and placed under an atmosphere of nitrogen. DMF (2.15 mL, 27.8 mmol) was then added by syringe and the resulting reaction mixture was cooled on an ice bath. POCl\(_3\) (8.40 mL, 90 mmol) was added dropwise by syringe (10 minutes) during which time a white material precipitated. The solution was then allowed to warm to room temperature over 10 minutes and the mixture was treated with \(N\)-(4-chloro-3-((3,3-difluorocyclobutyl)methoxy)phenyl)acetamide (2.44 g, 8.42 mmol). The mixture was stirred at 80 °C for two days. The resulting thick red solution was pipetted onto ice, resulting in a yellow precipitate. The precipitate was collected on a Buchner funnel, washed with water (~500 mL), and dried to provide 2.38 g of the title compound as a pale yellow solid. LCMS and \(^1\)H NMR are consistent with 2,6-dichloro-7-((3,3-difluorocyclobutyl)methoxy)quinoline-3-carbaldehyde (2.38 g, 6.88 mmol, 82% yield). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) ppm 10.31-10.36 (m, 1 H), 8.88 (s, 1 H), 8.48 (s, 1 H), 7.65 (s, 1 H), 4.37 (d, \(J = 4.69\) Hz, 2 H), 2.53-2.84 (m, 5 H). LCMS (Method 1): \(m/z\) 346 [M+H]\(^+\).

**Step-3:** \(6\)-**Chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinoline-3-carbaldehyde.  

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A solution of 2,6-dichloro-7-((3,3-difluorocyclobutyl)methoxy)quinoline-3-carbaldehyde (2.66 g, 7.68 mmol) in concentrated HCl (75 mL) was stirred at 100 °C for one day during which time a red crust formed on the surface of the flask. The mixture was diluted with water (800 mL), resulting in formation of a red precipitate. The mixture was allowed to stand at room temperature for 4 days. The precipitate was then collected on a Buchner funnel, washed with water (1 L), and dried under vacuum at 50 °C to provide 2.16 g of the title compound as a red solid. LCMS and $^1$H NMR are consistent with 6-chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (2.16 g, 6.59 mmol, 86% yield). $^1$H NMR (300 MHz, DMSO- $d_6$): $\delta$ ppm 12.21 (s, 1 H), 10.16-10.18 (m, 1 H), 8.43 (s, 1 H), 8.09 (s, 1 H), 6.94 (s, 1 H), 4.20 (d, $J = 4.10$ Hz, 2 H), 2.54-2.80 (m, 5 H). LCMS (Method 1): $m/z$ +328 [M+H]$^+$.

**Step-4:** (E)-N-((6-Chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide.

A mixture of 6-chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (499.6 mg, 1.525 mmol) and 2-methylpropane-2-sulfinamide (222.1 mg, 1.832 mmol) was placed in a 25 mL round bottom flask under an atmosphere of nitrogen. THF (3.0 mL) and titanium (IV) isopropoxide (Ti(O$'$/Pr)$_4$) (0.90 mL, 3.07 mmol) were added by syringe, and the suspension was stirred at room temperature overnight. Once LCMS indicated near completion of reaction, the reaction was quenched by dropwise addition of saturated aqueous NH$_4$Cl solution (2 mL). The material was then triturated with EtOAc (100 mL) and the resulting precipitate was filtered through Celite®. The filter cake was washed with EtOAc (50 mL), sonicated in EtOAc for 15 minutes and filtered using a Buchner funnel. The filtrates were combined and washed with brine (100 mL), dried (Na$_2$SO$_4$), filtered, and evaporated under reduced pressure to provide 413 mg of the title compound as a yellow solid. LCMS and $^1$H NMR are consistent with (E)-N-((6-chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (413 mg, 0.958
mmol, 62.9% yield). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) ppm 12.21 (s, 1 H), 8.74 (s, 1 H), 8.59 (s, 1 H), 8.09 (s, 1 H), 6.95 (s, 1 H), 4.19 (\(d, J = 4.40\) Hz, 2 H), 2.55-2.79 (m, 5 H), 1.19 (s, 9 H).

LCMS (Method 1): \(m/z\) 431 [M+H]\(^+\).

Step-5: \(N\)-(1-(6-Chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide.

\[\text{[0173]}\] \((E)-N\-((6-Chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl) methylene)-2-methylpropane-2-sulfonamide (411.3 mg, 0.955 mmol) was placed in a 100 mL round-bottom flask under an atmosphere of nitrogen. DCM (7.6 mL) was added, and the suspension was cooled on a dry ice/chloroform bath (to approx. -60 °C). Methylmagnesium bromide (MeMgBr, 3M in ether) (0.95 mL, 2.85 mmol) was added dropwise. The cold bath was then allowed to warm to room temperature overnight, resulting in an orange solution. Once LCMS indicated reaction completion, the solution was cooled on an ice bath and treated dropwise with water (5 mL), resulting in precipitation. The mixture was diluted with EtOAc (100 mL) and washed with water (100 mL). Silica gel was added to the organic layer and the solvent was evaporated under reduced pressure. The material was purified by column chromatography on a Biotage\(^\circledR\) MPLC chromatography system (eluted with 0 to 5% MeOH in DCM with isocratic elution at 3.2% MeOH) to provide 345.5 mg of the title compound as a brown brittle foam. LCMS and \(^1\)H NMR are consistent with \(N\)-(1-(6-chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (345.5 mg, 0.773 mmol, 81% yield). NMR shows a \(~1:1\) mixture of diastereomers. LCMS (Method 1): \(m/z\) 447 [M+H]\(^+\).

Step-6: 3-(1-Aminoethyl)-6-chloro-7-((3,3-difluorocyclobutyl)methoxy)quinolin-2(1H)-one hydrochloride (II-16).
A solution of N-(1-(6-chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (342.7 mg, 0.767 mmol) in MeOH (7.0 mL) was cooled on an ice bath and treated dropwise with 4M HCl in 1,4-dioxane (4 mL). The solution was then stirred for 25 minutes. The solvents were evaporated under reduced pressure at room temperature. The residue was triturated with 20 mL ethyl ether and the resulting precipitate was collected on a Hirsch funnel and washed with more ethyl ether to provide 271.4 mg of a pink solid. LCMS and $^1$H NMR are consistent with 3-(1-aminoethyl)-6-chloro-7-((3,3-difluorocyclobutyl)methoxy)quinolin-2(1H)-one hydrochloride (271.4 mg, 0.716 mmol, 93% yield). $^1$H NMR (300 MHz, Methanol-$d_4$): $\delta$ ppm 7.95 (s, 1 H), 7.79 (s, 1 H), 6.96 (s, 1 H), 4.48-4.55 (m, 1 H), 4.20 ($d, J = 4.10$ Hz, 2 H), 2.56 - 2.79 (m, 5 H), 1.68 ($d, J = 7.04$ Hz, 3 H). LCMS (Method 1): $m/z$ 343 [M+H]$^+$. 

Example 19 -- Intermediate II-17: (S)-3-(1-Aminoethyl)-6-chloro-8-fluoroquinolin-2(1H)-one

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Step 1: tert-Butyl (4-chloro-2-fluorophenyl)carbamate.
A solution of 4-chloro-2-fluoroaniline (2 g, 13.74 mmol) and di-tert-butyl dicarbonate (6.4 mL, 27.6 mmol) in 1,4-dioxane (50 mL) was stirred at reflux for 2 days. The solvent was then evaporated. The resulting oil was diluted with MeOH, water, and aqueous ammonium hydroxide solution (10 mL each) and vigorously stirred for 45 minutes. The organic lower layer was separated. The organic material was diluted with EtOAc (50 mL), and washed with water (50 mL), 3.6% aqueous HCl solution (2 x 50 mL), saturated aqueous NaHCO₃ solution (50 mL), and then again with water (2 x 50 mL). The organic layer was dried (MgSO₄), filtered, and evaporated under reduced pressure to provide tert-butyl (4-chloro-2-fluorophenyl)carbamate (3.0011 g, 12.22 mmol, 89% yield) as a reddish liquid that solidified on standing. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 9.12 (s, 1 H), 7.63 (t, J = 8.65 Hz, 1 H), 7.42 (dd, J = 10.85, 2.35 Hz, 1 H), 7.18-7.24 (m, 1 H), 1.45 (s, 9 H). LCMS (Method 1): m/z 246 [M+H]⁺.

Step-2: tert-Butyl (4-chloro-2-fluoro-6-formylphenyl)carbamate.

An oven-dried 3-necked 500 mL round bottom flask was fitted with an oven-dried addition funnel and placed under an atmosphere of nitrogen. tert-Butyl (4-chloro-2-fluorophenyl)carbamate (5.44 g, 22.14 mmol) and ethyl ether (91 mL) were added by syringe. The clear solution was cooled on an acetonitrile/dry ice bath (to approximately -40 °C). tert-Butyllithium (1.7M in pentane, 33 mL, 22.14 mmol) was added to the addition funnel by cannula. The t-BuLi solution was added dropwise to the ether solution (over ~10 minutes), during which time the ether solution began to turn orange. The solution was stirred at about -40 °C for 2 hours, during which time it progressively became more orange. DMF (8.7 mL, 112 mmol) was added dropwise (over ~10 minutes), resulting in precipitation of a yellow solid. The MeCN/dry ice bath was replaced with an ice bath and the mixture was stirred for an additional 2 hours. The reaction was then quenched by dropwise addition of water (20 mL), resulting in a brown mixture and the ice bath was removed. The mixture was diluted with EtOAc (100 mL), washed with water (2 x 100 mL), dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide 5.45 g of an oily black solid. The material was triturated with hexanes (50 mL), collected on a Buchner funnel and washed with more hexanes to provide 2.73 g tert-butyl
(4-chloro-2-fluoro-6-formylphenyl)carbamate as a yellow powder. The filtrate was evaporated under reduced pressure, the residue was triturated in hexanes (~15 mL), and the resulting yellow solid was collected on a Hirsch funnel to provide a second crop of the title compound (0.66 g). A total of 3.39 g (12.4 mmol, 56% yield) of tert-butyl (4-chloro-2-fluoro-6-formylphenyl)carbamate was recovered. $^1$H NMR (300 MHz, DMSO-d$_6$): δ ppm 9.93 (d, $J = 0.88$ Hz, 1 H), 9.47 (s, 1 H), 7.81-7.90 (m, 1 H), 7.55-7.61 (m, 1 H), 1.44 (s, 9 H). LCMS (Method 1): m/z 296 [M+Na].

Steps 3 & 4: (S)-3-(1-Aminoethyl)-6-chloro-8-fluoroquinolin-2(1H)-one hydrochloride (II-17).

An oven-dried 200 mL round bottom flask and stir bar were placed under an atmosphere of nitrogen. THF (17 mL) and diisopropylamine (1.59 mL, 11.16 mmol) were added by syringe. The resulting solution was cooled on a dry ice/acetone bath (to approximately -78 °C) and then n-butyllithium (1.6M in hexane, 7.1 mL, 11.36 mmol) was added dropwise over a 5 minute period. After stirring for 15 minutes, a solution of (S)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate K (860.7 mg, 3.72 mmol) in THF (3.75 mL) was added dropwise over 5 minutes. The solution was stirred for 80 minutes at -78 °C, and a solution of tert-butyl (4-chloro-2-fluoro-6-formylphenyl)carbamate (1016.4 mg, 3.71 mmol) in THF (7.5 mL) was then added dropwise by syringe. The reaction was stirred at -78 °C for another 22 minutes and then quenched by addition of saturated aqueous NH$_4$Cl solution (17 mL). The mixture was partitioned between EtOAc and water (100 mL each). The organic layer was dried (MgSO$_4$), filtered, and evaporated under reduced pressure to provide 1.88 g of the title compound as an orange gum. The material was dissolved in 1,4-dioxane (38 mL), treated with 12M aqueous HCl (0.96 mL), and stirred at 110 °C for 50 minutes. The sample was then allowed to cool. The solvent was evaporated under reduced pressure to provide 1.24 g of a red solid. The material was triturated in IPA (25 mL), collected on a Hirsch funnel and washed sequentially with IPA (5 mL) and ethyl ether (~20 mL) to provide (S)-3-(1-aminoethyl)-6-chloro-8-fluoroquinolin-2(1H)-one hydrochloride (370.4 mg, 1.337 mmol, 36% yield) as a red
solid. $^1$H NMR (300 MHz, DMSO-$d_6$): δ ppm 12.41 (s, 1 H), 8.33 (br s, 3 H), 8.10 (s, 1 H), 7.67-7.76 (m, 2 H), 4.38-4.53 (m, 1 H), 1.52 ($d, J = 7.04$ Hz, 3 H). LCMS (Method 1): m/z 241 [M+H]$^+$. 

Example 20 -- Intermediate II-18: (S)-3-(1-aminoethyl)-6-chloro-7-isoproxyquinolin-2(1H)-one

![Chemical Reaction Diagram]

**Step-1: 4-Chloro-3-isoproxyaniline**

[0178] A mixture of 5-amino-2-chlorophenol (20 g, 139 mmol) and 2-bromopropane (26 mL, 278 mmol) and K$_2$CO$_3$ (38.4 g, 278 mmol) in CH$_3$CN (300 mL) was refluxed for 24 h. The reaction mixture was cooled to room temperature, filtered and the solid was washed with ethyl acetate (150 mL). The filtrate was concentrated and the residue was purified by ISCO (SiO$_2$: Hex/EtOAc 0 to 40%) to give the title compound, 4-Chloro-3-isoproxyaniline (22.6 g, 87%).

**Step 2: N-(4-Chloro-3-isoproxyphenyl)acetamide**
To a mixture of 4-chloro-3-isopropoxyaniline (22.5 g, 121 mmol) in CH₂Cl₂ (200 mL) was added DIPEA (42 mL, 242 mmol) followed by acetic anhydride (17 mL, 181 mmol). The resultant mixture was stirred at room temperature for 3 h. Upon the completion of the reaction, water (100 mL) was added and stirred for 10 minutes. The organic layer was separated, washed with 1N HCl (aq, 200 mL), brine (150 mL) and dried over anhydrous Na₂SO₄. The solution was filtered and concentrated. The crude residue was recrystallized from CH₂Cl₂/hexanes to give desired compound N-(4-Chloro-3-isopropoxyphenyl)acetamide (19.6 g, 71%).

Step-3: 2,6-Dichloro-7-isopropoxyquinoline-3-carbaldehyde

DMF (15 mL, 193.6 mmol) was added to a 350 mL seal tube and cooled to 0 °C. To this solution was added phosphorous oxychloride (60.1 mL, 645.6 mmol) dropwise during 40-50 min. The resultant mixture was brought to room temperature followed by addition of N-(4-chloro-3-isopropoxyphenyl)acetamide (14.7 g, 64.5 mmol) in portions and heated at 80 °C overnight. The mixture was cooled to room temperature and carefully poured onto crushed ice. The yellow precipitate was filtered, washed with water and dried over P₂O₅ overnight to afford 2,6-Dichloro-7-isopropoxyquinoline-3-carbaldehyde as yellow solid (17.5 g, 95%).

Step-4: 6-Chloro-7-isopropoxy-2-methoxyquinoline-3-carbaldehyde

To 2,6-dichloro-7-isopropoxyquinoline-3-carbaldehyde (5.8 g, 20.4 mmol) in a co-solvent of MeOH:THF (1:1, 100 mL) was added NaOMe (2.2 g, 40.8 mmol) portion wise at rt. The reaction mixture was refluxed for 3 h. After cooling to rt, the reaction was quenched with aqueous NH₄Cl solution (20 mL). The mixture was extracted with EtOAc (25 mL x 3). The combined organic layer was dried (Na₂SO₄), concentrated and purified by flash chromatography with Hexane/EA (3:1) to give 6-Chloro-7-isopropoxy-2-methoxyquinoline-3-carbaldehyde (5.07 g, 89%) as a yellow solid.
Step 5: 1-(6-Chloro-7-isoproxy-2-methoxyquinolin-3-yl)ethanol

[0182] To 6-chloro-7-isoproxy-2-methoxyquinoline-3-carbaldehyde (5.07 g, 18.17 mmol) in THF (100 mL) at -78 °C was added a solution of MeMgCl in THF( 3 M, 9.1 mL, 27.2 mmol) drop wise. The reaction was stirred at room temperature (rt) for 3 h and then quenched with aqueous NH₄Cl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (25 mL X 3). The combined organic layers were dried (Na₂SO₄), concentrated, and purified by silica gel chromatography with hexane/EA (3:1) to give compound 1-(6-Chloro-7-isoproxy-2-methoxyquinolin-3-yl)ethanol (4.06 g, 76%).

Step 6: 1-(6-Chloro-7-isoproxy-2-methoxyquinolin-3-yl)ethanone

[0183] To 1-(6-chloro-7-isoproxy-2-methoxyquinolin-3-yl)ethanol (4.06 g, 13.8 mmol) in CH₂Cl₂ (50 mL) at rt was added DMP (7.0 g, 16.5 mmol) portion wise. The reaction was stirred at rt for 2 h, and then was quenched with an aqueous solution of NaHCO₃ and Na₂S₂O₃. After stirring for 15 min, both layers became clear. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (30 mL X 2). The combined organic layers were dried (Na₂SO₄), concentrated and purified by silica gel chromatography with hexane/EA (4:1) to give 1-(6-Chloro-7-isoproxy-2-methoxyquinolin-3-yl)ethanone (3.67 g, 72%) as a white solid.

Step 7: \((R,E)-N-(1-(6-chloro-7-isoproxy-2-methoxyquinolin-3-yl)ethylidene)-2-methyl propane-2-sulfinamide

[0184] To 1-(6-chloro-7-isoproxy-2-methoxyquinolin-3-yl)ethanone (3.67 g, 12.5 mmol) in THF/toluene (20 mL : 400 mL) at rt was added \((R)-2\)-methylpropane-2-sulfinamide (3.03 g,
25 mmol, and Ti(O’Pr)$_4$ (11 mL, 37.5 mmol). The reaction was refluxed with a Dean-Stark apparatus. After the reaction was refluxed for 4 h and 150 mL of solvent was removed, the reaction was cooled to rt. The solvent was removed under vacuum, and 50 mL of EtOAc was added to the residue, followed by addition of 20 mL of saturated aqueous NaHCO$_3$ solution. After stirring for 10 min, the solid was removed through a pad of celite. The filtrate was extracted with EtOAc (200 mL X 2), dried (Na$_2$SO$_4$), concentrated and purified by silica gel chromatography with hexane/EA (1:1) to give the title compound (4.32 g, 87%).

Step-8: (R)-N-((S)-1-(6-chloro-7-isopropoxy-2-methoxyquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide

![Chemical Structure](image)

To (R,E)-N-(1-(6-chloro-7-isopropoxy-2-methoxyquinolin-3-yl)ethylidene)-2-methylpropane-2-sulfonamide (4.32 g, 10.9 mmol) in THF (100 mL) at -78 °C, was added 1 M L-selectride (14.2 mL, 14.2 mmol) in THF dropwise. The reaction mixture was warmed to rt and stirred for 3 h. The reaction was quenched with aqueous saturated NH$_4$Cl (30 mL) solution and then extracted with EtOAc (20 mL X 3). The combined organic layers were dried (Na$_2$SO$_4$), concentrated and purified by silica gel chromatography with hexane/EA (1:1) to give the desired compound (3.58 g, 82%).

Step-9: (S)-3-(1-aminoethyl)-6-chloro-7-isopropoxyquinolin-2(1H)-one hydrochloride salt (II-18).

![Chemical Structure](image)

To (R)-N-((S)-1-(6-chloro-7-isopropoxy-2-methoxyquinolin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (3.58 g, 8.99 mmol) in dioxane (50 mL) was added 2 N HCl (50 mL) at rt. The reaction was refluxed for 3 h. The solvent was removed under vacuum and the residue was dried under vacuum to afford crude II-18, which was further purified by trituration (CH$_2$Cl$_2$/MeOH/hexane) to give pure compound II-18 (2.44 g, 86%) as a white solid. $^1$H NMR
(300 MHz, DMSO-d6): δ 12.10 (s, 1H), 8.29 (br, s, 3H), 7.98 (s, 1H), 7.83 (s, 1H), 7.08 (s, 1H), 4.66 (m, 1H), 4.38 (m, 1H), 3.91 (s, 3H), 1.52 (d, J = 6.87 Hz, 3H), 1.37 (d, J = 6.03 Hz, 6H).

LCMS (Method 3, APCI): RT = 8.06 min, m/z = 281.1 [M+H]+.

Example 21 -- Intermediate III-1: 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile

Step 1: 2-cyano-5-fluoropyridine 1-oxide.

[0187] A solution of 5-fluoropicolinonitrile (7.27 g, 59.5 mmol) in CHCl₃ (60 mL) was added dropwise by addition funnel to a solution of m-CPBA (<77%, 22.00 g, 98 mmol) in CHCl₃ 160 mL). The solution was stirred at reflux 4 days, at which time LCMS showed ~85% conversion. The sample was allowed to cool, then sodium sulfite (12.4 g, 98 mmol) was added and the sample was stirred at room temperature three hours, during which time the solution became thick with a white precipitate. The sample was diluted with DCM (300 mL) and filtered on a Buchner funnel, and the filter cake was washed with DCM (~400 mL). A white material precipitated in the filtrate. The filtrate mixture was washed with saturated aqueous NaHCO₃ (400 mL), during which the solids went into solution. The organic layer was washed with water (300 mL), then dried (MgSO₄) and filtered. Silica gel was added and the mixture was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (340 g silica gel column) with 0 to 100% EtOAc in hexanes, with isocratic elution when peaks came off to provide 2-cyano-5-fluoropyridine 1-oxide (4.28 g, 31.0 mmol, 52 % yield) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 8.85 - 8.93 (m, 1 H), 8.23 (dd, J=9.09, 6.74 Hz, 1 H), 7.53 - 7.64 (m, 1 H). LCMS (Method 1): Rt 0.57 min., m/z 138.9 [M+H]+.
Step 2: 6-cyano-3-fluoropyridin-2-yl acetate

![Chemical Structure]

[0188] A solution of 2-cyano-5-fluoropyridine 1-oxide (4.28 g, 31.0 mmol) in acetic anhydride (40 ml, 424 mmol) was heated at reflux (150 °C bath) three days, during which the clear solution turned dark. The sample was concentrated under reduced pressure. The residue was dissolved in MeOH (30 mL) and stirred 1 hour. Silica gel was added and the solvent was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (100 g silica gel column) with 0 to 23% EtOAc in hexanes to provide 6-cyano-3-fluoropyridin-2-yl acetate (3.32 g, 18.43 mmol, 60 % yield) as a clear liquid that solidified on cooling. ¹H NMR (300 MHz, CHLOROFORM-d): δ ppm 7.65 - 7.75 (m, 2 H), 2.42 (s, 3 H). LCMS (Method 1): Rt 1.54 min., m/z 138.8 (loss of acetate).

Step 3: 5-fluoro-6-oxo-1,6-dihydropyridine-2-carbonitrile.

![Chemical Structure]

[0189] A solution of 6-cyano-3-fluoropyridin-2-yl acetate (3.32 g, 18.43 mmol) in MeOH (40 ml) was treated with potassium carbonate (5.10 g, 36.9 mmol) and stirred at room temperature four hours. LCMS at 2 hours showed the reaction had gone to completion. The solvent was evaporated under reduced pressure. The residue was dissolved in water (100 mL) and acidified to pH ≤1 with 1M HCl. The solution was extracted with EtOAc (3x100 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and evaporated under reduced pressure to provide 5-fluoro-6-oxo-1,6-dihydropyridine-2-carbonitrile (2.34 g, 16.94 mmol, 92 % yield) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.92 (br s, 1 H), 7.73 (br s, 1 H), 7.43 (br s, 1 H). LCMS (Method 1): Rt 0.70 min., m/z 138.9 [M+H]+.
Step 4: 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (III-1)

[0190] A mixture of 5-fluoro-6-oxo-1,6-dihydropyridine-2-carbonitrile (2.31 g, 16.73 mmol) and potassium carbonate (4.86 g, 35.2 mmol) in a 200 mL round bottom flask was treated with DMF (46 ml) and stirred 15 minutes. MeI (1.2 ml, 19.19 mmol) was added and the mixture was stirred at room temperature 45 minutes. The solvent was evaporated under reduced pressure. The residue was mixed with water (150 mL) and extracted with DCM (2x150 mL). The combined organic extracts were dried (MgSO₄), filtered, treated with silica gel, and evaporated under reduced pressure, then evaporated further at 60 °C under high vacuum. The material was chromatographed by Biotage MPLC with 0 to 35% EtOAc in hexanes, with isocratic elution at 16% EtOAc and 35% EtOAc while peaks came off. The peak that came off with 16% EtOAc was O-methylated material and was discarded. The peak that came off with 35% EtOAc provided the title compound III-1 (1.70 g, 11.17 mmol, 67 % yield) as a solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 7.53 (dd, J=9.38, 7.62 Hz, 1 H), 7.18 (dd, J=7.77, 4.84 Hz, 1 H), 3.60 (s, 3 H). LCMS (Method 1): Rt 0.94 min., m/z 152.9 [M+H]⁺.

Example 22 -- Intermediate V-2: 5-amino-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile

Step-1: N-(6-Cyanopyridin-3-yl)-2,2,2-trifluoroacetamide.

[0191] A solution of 5-aminopicolinonitrile (5.50 g, 46 mmol, 1 eq.) in 300 mL DCM was cooled to 0°C, and then treated with TEA (20 mL, 144 mmol, 3.1 eq.) followed by dropwise addition of trifluoroacetic anhydride (20 mL, 144 mmol, 3.1 eq.). After stirring overnight at
room temperature, the reaction mixture was poured onto ice, and extracted with DCM. Purification by passing over a silica gel plug (hexane/EtOAc, 75/25) provided N-(6-Cyanopyridin-3-yl)-2,2,2-trifluoroacetamide (7.24 g, 73%) as a white solid. TLC: Hexane/EtOAc, 8/2.

**Step-2: N-(6-cyanopyridin-3-yl)-2,2,2-trifluoroacetamide-N-oxide.**

[0192] A solution of N-(6-Cyanopyridin-3-yl)-2,2,2-trifluoroacetamide (7.24 g, 33.7 mmol, 1 eq.) in 270 mL CHCl₃ was cooled in an ice bath, then treated dropwise with a solution of mCPBA (7.68 g, 39 mmol, 1.15 eq.) in 65 mL CHCl₃. The reaction mixture was refluxed for 24 hours and then poured into H₂O. After stirring with 10% aqueous NaHSO₄ and NaHCO₃, the solid was collected and rinsed with H₂O, then CHCl₃. This provided 1.86 g (24%) of the title compound as a white solid. Unreacted N-(6-Cyanopyridin-3-yl)-2,2,2-trifluoroacetamide (4.70 g, 65%) was recovered by extraction of the filtrate, and purification by chromatography on silica gel (hexane/EtOAc, 75/25).

**Step-3: 5-Amino-6-oxo-1,6-dihydropyridine-2-carbonitrile.**

[0193] A suspension of N-(6-cyanopyridin-3-yl)-2,2,2-trifluoroacetamide-N-oxide (0.81 g, 3.5 mmol, 1 eq.) in 10.5 mL THF was treated with TEA (0.75 mL, 5.3 mmol, 1.5 eq.) followed by dropwise addition of trifluoroacetic anhydride (1.74 mL, 12.5 mmol, 3.5 eq.). After stirring overnight at room temperature, ice chips and 12 mL 10% NaOH were added. After stirring at room temperature for 1 hour, the reaction mixture was acidified to pH ~ 4 with HOAc and the precipitated solid was collected, providing 0.31 g 5-Amino-6-oxo-1,6-dihydropyridine-2-carbonitrile (64%) as a beige solid. TLC: DCM/MeOH, 97/3.

**Step-4: 5-Amino-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (V-2).**

[0194] A solution of 5-Amino-6-oxo-1,6-dihydropyridine-2-carbonitrile (500mg, 3.7 mmol, 1 eq.) in 18 mL DMF was treated with anhydrous K₂CO₃ (1.0 g, 7.26 mmol, 2 eq.) and CH₃I (0.175 mL, 4.0 mmol, 1.1 eq) and stirred at room temperature for 1.5 h. To the reaction mixture water was added followed by extraction with EtOAc (2x), the extracts were dried (Na₂SO₄) and evaporated to provide a tan solid. Analysis of the crude product by NMR indicated a ~ 8/2 ratio of desired product vs the O-methylated isomer. Trituration of the solid with Et₂O provided 160
mg of the desired product (29%). Purification of the Et<sub>2</sub>O washes by C18 ISCO preparative chromatography provided an additional 82 mg of the title compound V-1 as the TFA salt (15%).

TLC: Hexane/EtOAc, 1/1. <sup>1</sup>H-NMR (300 MHz, d<sub>6</sub>DMSC) δ: 6.94 (d, <i>J</i> = 7.68), 6.42 (broad s, 2H), 6.33 (d, <i>J</i> = 7.68), 3.55 (s, 3H). LC/MS (Methods 3): Rt 3.0 min., m/z 150 [M+H]<sup>+</sup>.

**Table 1:** The Intermediates listed in Table 1 were either prepared using the methods described above or obtained from commercial sources.

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Note: All amines are hydrochloride salts, except that II-5a is TFA salt

**Example 23** – 5-(((6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-1)

![Chemical structures](image)

[0195] To a 100 mL round bottle flask was added 6-chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde IV-1 (69.6 mg, 0.335 mmol), 5-amino-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile V-2 (50 mg, 0.335 mmol) and acetic acid (0.096 ml, 1.676 mmol) in DCM (10 ml). Finally sodium triacetoxyborohydride (107 mg, 0.503 mmol) was charged and stir vigorously at room temperature under N₂ flow overnight. The reaction mixture was diluted with EtOAc (60 mL), then washed with saturated NaHCO₃, water (x2) and brine. The organic extract was dried over Na₂SO₄, filtered and concentrated to yield a crude, which was purified by reverse phase preparative HPLC on Gilson to yield a mixture of product and unknown by-product (~32 mg, 28% yield, 81% HPLC purity). The mixture was subjected 2nd HPLC purification to afford a pure desired product (4 mg, 3.5% yield). ¹H NMR (300 MHz, CDCl₃) δ ppm 7.97 (s, 1 H), 7.56
(br s, 1 H), 7.45 (br d, J=11.43 Hz, 2 H), 7.36 (br d, J=8.79 Hz, 1 H), 7.12 - 7.20 (m, 1 H), 6.66 - 6.78 (m, 1 H), 6.00 (br d, J=7.92 Hz, 1 H), 3.68 (s, 2 H), 3.31 (br s, 3 H). LCMS (Method 1): Rt 2.37 min, m/z 340.97 [M+H]^+

**Example 24 – 6-chloro-3-((1-ethyl-2-oxo-1,2-dihydropyridin-3-ylamino)methyl)quinolin-2(1H)-one (I-2)**

\[
\text{EtI} \quad \text{K}_2\text{CO}_3 \quad \text{DMF, 60°}
\]

\[
\text{SnCl}_2\cdot 2\text{H}_2\text{O} \quad \text{EtOAc, 80°}
\]

\[
\text{STAB, HOAc, MeOH, toluene, DCM}
\]

**Step 1: 1-ethyl-3-nitropyridin-2(1H)-one.**

[0196] A mixture of 3-nitropyridin-2(1H)-one (1.00 g, 7.14 mmol) and K₂CO₃ (3.00 g, 21.71 mmol) in DMF (30 mL) was treated with ethyl iodide (0.60 mL, 7.42 mmol) and stirred at 50 °C overnight. LCMS indicated a 4:1 mixture of product and starting material. More ethyl iodide (0.25 mL) was added and the reaction was stirred at 60 °C five hours. The yellow mixture was diluted with water (100 mL) and extracted with EtOAc (3x100 mL). The combined organic extracts were dried (MgSO₄), filtered, and evaporated under reduced pressure to provide 1.08 g yellow solid. The material was dissolved in a few mL DCM and chromatographed by Biotage MPLC (25 g silica gel column, 0 to 10% MeOH in DCM, with isocratic elution at 3% MeOH) to provide 1-ethyl-3-nitropyridin-2(1H)-one (898.9 mg, 5.35 mmol, 74.9 % yield) as a yellow solid.

\[^1\text{H}\text{ NMR (300 MHz, DMSO-\text{d}_6):} \delta \text{ ppm 8.38 (dd, } J=7.92, 2.05 \text{ Hz, 1 H), 8.24 (dd, } J=6.60, 2.20\]
Hz, 1 H), 6.44 (dd, J=7.62, 6.45 Hz, 1 H), 4.05 (q, J=7.04 Hz, 2 H), 1.26 (t, J=7.18 Hz, 3 H).
LCMS (Method 1): Rt 0.96 min., m/z 169.0 [M+H]+.

**Step 2: 3-amino-1-ethylpyridin-2(1H)-one**

A solution of 1-ethyl-3-nitropyridin-2(1H)-one (891.2 mg, 5.30 mmol) and tin (II) chloride dihydrate (5.03 g, 22.29 mmol) in EtOAc (30 ml) in a 200 mL round bottom flask was stirred at 80 °C two hours; LCMS at 1.5 hours showed the reaction had gone cleanly to completion. The solution was allowed to cool and was diluted with EtOAc (50 mL), then NaHCO3 (8 g) was added in small portions and the mixture was stirred 20 minutes, by which time little effervescence had occurred and the mixture was still strongly acidic (pH ~1). Water (50 mL) was added in portions with thorough stirring, first magnetically and then by hand as a precipitate formed, resulting in a dark blue mixture of pH ~8. The mixture was filtered on a Buchner funnel and the filter cake was washed with several portions of EtOAc (~100 mL total). The filtrate layers were separated. The aqueous phase was extracted with EtOAc (3x50 mL), and all the organics were combined and dried (Na2SO4), filtered, and evaporated under reduced pressure. The resulting bluish solid (0.64 g) was dissolved in a few mL DCM and chromatographed by Biotage MPLC (25 g silica gel snap column, 0 to 9% MeOH in DCM, with isocratic elution at 3.8% MeOH). The blue solid thus obtained was dissolved in DCM, treated with silica gel, and evaporated under reduced pressure. The material was rechromatographed by Biotage MPLC (25 g silica gel column, 0 to 100% EtOAc in hexanes, with isocratic elution at 67% EtOAc) to provide 3-amino-1-ethylpyridin-2(1H)-one (517.7 mg, 3.75 mmol, 70.7 % yield) as a slightly blue solid. 1H NMR (300 MHz, DMSO-d6): δ ppm 6.88 (dd, J=6.89, 1.91 Hz, 1 H), 6.41 (dd, J=7.04, 1.76 Hz, 1 H), 6.03 (dd, J=6.90, 6.90 Hz, 1 H), 5.06 (s, 2 H), 3.89 (q, J=7.13 Hz, 2 H), 1.19 (t, J=7.18 Hz, 3 H). LCMS (Method 1): Rt 0.76 min., m/z 139.0 [M+H]+.
Step 3: 6-chloro-3-((1-ethyl-2-oxo-1,2-dihydropyridin-3-ylamino)methyl)quinolin-2(1H)-one (I-2).

![Chemical Structure](image)

[0198] A suspension of 6-chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (100.1 mg, 0.482 mmol) and 3-amino-1-ethylpyridin-2(1H)-one (67.1 mg, 0.486 mmol) in MeOH (1.5 mL) and toluene (1.5 mL) was treated with AcOH (27.6 µL) and shaken at 50 °C for 5.5 hours, during which the blue color of the pyridinone starting material was discharged. The solvents were evaporated under reduced pressure. The red residue was treated with successively with two aliquots of toluene (3 mL each) and evaporated under reduced pressure. The residue was suspended in DCM (3 mL) and treated with AcOH (135.4 µL) and sodium triacetoxyborohydride (164.3 mg, 0.775 mmol), then placed under nitrogen and stirred at room temperature overnight; within a few minutes the material went into solution, and within an hour a material precipitated out. The sample was diluted with DCM/MeOH/EtOAc, treated with silica gel, and evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (0 to 100% EtOAc in hexanes) to provide the title compound (I-2) (25.7 mg, 0.078 mmol, 16.16 % yield, HPLC purity 100% at 220 nm) as a greenish solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.02 (s, 1 H), 7.79 (d, J=2.05 Hz, 1 H), 7.65 (s, 1 H), 7.49 (dd, J=8.65, 2.20 Hz, 1 H), 7.30 (d, J=8.79 Hz, 1 H), 6.90 (dd, J=4.30, 4.30 Hz, 1 H), 5.95 - 6.11 (m, 3 H), 4.16 (d, J=5.90 Hz, 2 H), 3.93 (q, J=6.84 Hz, 2 H), 1.22 (t, J=7.04 Hz, 3 H). LCMS (Method 4): Rt 1.15 min., m/z 330.0 [M+H]⁺.

Table 2: The compounds listed in Table 2 were prepared using methods similar to those described for the preparation of 1-1 & 1-2.
Table 3. LCMS signal and NMR chemical shifts of each compound listed in Table 2.

<table>
<thead>
<tr>
<th>Cmpd no</th>
<th>LCMS</th>
<th>1H NMR (300 MHz) δ ppm</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-1</td>
<td>m/z: 340.93 (M+H)+</td>
<td>1H NMR (300 MHz, CHLOROFORM-d) δ ppm 7.97 (s, 1 H), 7.56 (br s, 1 H), 7.45 (br d, J=11.43 Hz, 2 H), 7.36 (br d, J=8.79 Hz, 1 H), 7.12 - 7.20 (m, 1 H), 6.66 - 6.78 (m, 1 H), 6.00 (br d, J=7.92 Hz, 1 H), 3.68 (s, 2 H), 3.31 (br s, 3 H).</td>
<td>5-(((6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-2</td>
<td>m/z: 329.99 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.02 (s, 1 H), 7.79 (d, J=2.05 Hz, 1 H), 7.65 (s, 1 H), 7.49 (dd, J=8.65, 2.20 Hz, 1 H), 7.30 (d, J=8.79 Hz, 1 H), 6.90 (dd, J=4.30, 4.30 Hz, 1 H), 5.95 - 6.11 (m, 3 H), 4.16 (d, J=5.90 Hz, 2 H), 3.93 (q, J=6.84 Hz, 2 H), 1.22 (t, J=7.04 Hz, 3 H).</td>
<td>6-chloro-3-(((1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)amino)methyl)-1,2-dihydroquinolin-2-one</td>
</tr>
<tr>
<td>I-3</td>
<td>m/z: 315.98 (M+H)+</td>
<td>1H NMR (300 MHz, CHLOROFORM-d) δ ppm 11.42 (br s, 1 H), 7.58 (s, 1 H), 7.41 (d, J=2.05 Hz, 1 H), 7.31 - 7.38 (m, 1 H), 7.21 - 7.27 (m, 1 H), 6.62 (d, J=6.45 Hz, 1 H), 6.13 (br s, 1 H), 5.95 - 6.04 (m, 1 H), 4.34 (s, 2 H), 3.55 (s, 4 H).</td>
<td>6-chloro-3-(((1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino)methyl)-1,2-dihydroquinolin-2-one</td>
</tr>
<tr>
<td>I-4</td>
<td>m/z: 327.04 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.01(br, 1H), 7.74(s, 1H), 7.55(s, 1H), 7.45(dd, J1=2.35Hz, J2=8.8Hz, 1H), 7.27(d, J=8.79Hz, 1H), 6.60-6.80(m, 2H), 6.00(d, J=7.62Hz, 1H), 4.17(d, J=6.16Hz, 2H)</td>
<td>5-(((6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-5</td>
<td>m/z: 342.01 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.00 (s, 1 H), 7.77 (d, J=2.35 Hz, 1 H), 7.62 (s, 1 H), 7.48 (dd, J=8.79, 2.35 Hz, 1 H), 7.30 (d, J=8.79 Hz, 1 H), 5.98 - 6.04 (m, 1 H), 5.88 - 5.95 (m, 1 H), 5.78 (t, J=6.30 Hz, 1 H), 4.14 (d, J=6.20 Hz, 2 H), 3.47 (s, 3 H), 2.22 (s, 3 H).</td>
<td>6-chloro-3-(((1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino)methyl)-1,2-dihydroquinolin-2-one</td>
</tr>
<tr>
<td>I-6</td>
<td>m/z: 329.99 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.00(br, 1H), 7.76(d, J=2.32Hz, 1H), 7.59(s, 1H), 7.45(dd, J1=2.40Hz, J2=8.78Hz, 1H), 7.27(d, J=8.72Hz, 1H), 6.42(br, 1H), 6.18(br, 1H), 5.89(br, 1H), 5.82 (d, J=8.98Hz, 1H), 4.13(d,J=5.38Hz, 2H)</td>
<td>6-chloro-3-(((1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)amino)methyl)-1,2-dihydroquinolin-2-one</td>
</tr>
<tr>
<td>I-7</td>
<td>m/z: 379.86 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.00(br, 1H), 7.76(d, J=2.32Hz, 1H), 7.59(s, 1H), 7.45(dd, J1=2.40Hz, J2=8.78Hz, 1H), 7.27(d, J=8.72Hz, 1H), 6.42(br, 1H), 6.18(br, 1H), 5.89(br, 1H), 5.82 (d, J=8.98Hz, 1H), 4.13(d,J=5.38Hz, 2H)</td>
<td>3-(((6-bromo-2-oxo-1,2-dihydropyridin-3-yl)amino)methyl)-6-chloro-1,2-dihydroquinolin-2-one</td>
</tr>
<tr>
<td>I-8</td>
<td>m/z: 369.90 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.00(br, 1H), 7.76(d, J=2.32Hz, 1H), 7.59(s, 1H), 7.45(dd, J1=2.40Hz, J2=8.78Hz, 1H), 7.27(d, J=8.72Hz, 1H), 6.42(br, 1H), 6.18(br, 1H), 5.89(br, 1H), 5.82 (d, J=8.98Hz, 1H), 4.13(d,J=5.38Hz, 2H)</td>
<td>6-chloro-3-(((1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)amino)methyl)-1,2-dihydroquinolin-2-one</td>
</tr>
<tr>
<td>Cmpd no</td>
<td>LCMS</td>
<td>1H NMR (300 MHz) δ ppm</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>I-9</td>
<td>m/z: 383.93 (M+H)+&lt;br&gt;Rt (min): 1.43</td>
<td>6-chloro-3-([(1-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-y]amino)methyl]-1,2-dihydroquinolin-2-one</td>
<td></td>
</tr>
<tr>
<td>I-10</td>
<td>m/z: 359.99 (M+H)+&lt;br&gt;Rt (min): 1.01</td>
<td>methyl 5-([(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)-6-oxo-1,6-dihydropyridine-3-carboxylate</td>
<td></td>
</tr>
<tr>
<td>I-11</td>
<td>m/z: 346.04 (M+H)+&lt;br&gt;Rt (min): 1.05</td>
<td>6-chloro-7-methoxy-3-[[1-methyl-2-oxo-1,2-dihydropyridin-3-yl]amino[methyl]-1,2-dihydroquinolin-2-one</td>
<td></td>
</tr>
<tr>
<td>I-12</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm</td>
<td>6-chloro-3-[[1-methyl-2-oxo-1,2-dihydropyridin-3-yl]amino[methyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one</td>
<td></td>
</tr>
</tbody>
</table>

LCMS data are determined by *Method 4*.

**Example 25** — *(S)-5-([(1-(6-chloro-2-oxo-1,2-dihydropyridin-3-yl)ethyl]amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-13)*

![Chemical structure](attachment:chemical_structure.png)

[0199] A mixture of 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile **III-1** (1.23 g, 8.09 mmol), *(S)-3-[(1-aminoethyl)-6-chlorquinolin-2(1H)-one hydrochloride **II-1** (1.91 g, 7.37 mmol) and *N*,*N*-diisopropylethylamine (3.8 mL, 21.8 mmol) in anhydrous dimethyl sulfoxide (57 mL) under N₂ was heated to 110 °C and stirred for 6 hours. After cooling to room temperature, the mixture was partitioned between EtOAc/H₂O (750 mL/750 mL). The organic layer was separated, dried (Na₂SO₄) and concentrated in vacuum. The residue was purified on ISCO twice (40 g silica gel column, EtOAc/hexanes 0~100%; 80 g silica gel column, MeOH/dichloromethane 0~5%). The colorless fractions were combined and dichloromethane was removed under reduced pressure on rotavap until a lot of white solid precipitated out. The white solid was collected by filtration and washed with cold MeOH. It was then mixed with
MeCN/H₂O (10 mL/25 mL) and lyophilized to afford the title compound I-13 as a white solid (790 mg), m.p. 262-264 °C. ¹H NMR (300 MHz, DMSO-d₆) δ: 12.07 (s, 1H), 7.75 (s, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.51 (dd, J = 8.6, 2.3 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 7.7 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.68 (m, 1H), 3.58 (s, 3H), 1.50 (d, J = 6.6 Hz, 3H). LCMS (Method 3): 100% pure @ 254 nm, Rt 10.78 min, m/z 355, 357 [M+H]+.

The filtrate and the colored fractions (TLC pure) from the second ISCO were combined and treated with activated charcoal and filtered (until the filtrate is colorless). The filtrate was then concentrated under reduced pressure on rotavap to remove dichloromethane until a lot of white solid precipitated out. The white solid was collected by filtration and washed with cold MeOH. It was then mixed with MeCN/H₂O (10 mL/25 mL) and lyophilized to afford the title compound I-13 as a white solid (970 mg), m.p. 262-264 °C. ¹H NMR (300 MHz, DMSO-d₆) δ: 12.06 (s, 1H), 7.75 (s, 1H), 7.73 (d, J = 2.5 Hz, 1H), 7.51 (dd, J = 8.6, 2.3 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 4.68 (m, 1H), 3.58 (s, 3H), 1.50 (d, J = 6.9 Hz, 3H). LCMS (Method 3): 100% pure @ 254 nm, m/z 355, 357 [M+H]+.

The total yield for combined two batches is 67%.

**Example 26 -- (S)-5-(((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-14)**

![Diagram](image)

[0200] A mixture of DIEA (0.165 ml, 0.943 mmol), (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one II-I (70 mg, 0.314 mmol), and 5-fluoro-6-oxo-1,6-dihydropyridine-2-carbonitrile (52.1 mg, 0.377 mmol) in DMSO (1 ml) was heated to 110 °C for 2 hrs. The reaction mixture was cooled to room temperature, then was treated with EtOAc, washed with water twice, dried and concentrated. The biotage purification with 0 to 10 % MeOH/DCM on a 10 g column afforded (S)-5-(((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-6-oxo-1,6-dihydropyridine-2-carbonitrile (12.1 mg, 11.3%). ¹H NMR (300 MHz, DMSO-d₆) δ ppm 12.03 (s, 1 H),
7.72 (s, 2 H), 7.47 (m, 1 H), 7.28 (m, 1 H), 6.84 (m, 1 H), 6.68 (m, 1 H), 5.93 (m, 1 H), 4.66 (m, 1 H), 1.45 (d, J=6.74 Hz, 3 H). LCMS (Method 3): Rt 2.35 min, m/z 361.05 [M+Na]⁺.

Example 27 -- (S)-5-((1-(6-Chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-16)

[0201] A mixture of (S)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one hydrochloride II-4 (1.00 g, 3.61 mmol), 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-1 (604 mg, 3.97 mmol), N,N-diisopropylethylamine (1.9 mL, 10.8 mmol) in DMSO (15 mL) was heated at 110 °C in a seal tube for 16 h. MS and TLC showed complete conversion. The reaction mixture was poured into water (300 mL) with vigorous stirring. The solid was filtered and washed with water, and then dissolved in EtOAc and dried over sodium sulfate. After filtration, the solution was concentrated with silica gel and purified by flash column chromatography (SiO₂: dichloromethane/EtOAc 0 to 50%) to afford the target compound I-16 as a pale yellow solid (1.20 g, 89%). 1H NMR (300 MHz, DMSO-d₆) δ 12.12 (s, 1 H), 7.95 (d, J = 7.9 Hz, 1 H), 7.74 (s, 1 H), 7.21 (d, J = 10.4 Hz, 1 H), 6.94 (d, J = 7.9 Hz, 1 H), 6.92 (d, J = 7.4 Hz, 1 H), 5.94 (d, J = 8.2 Hz, 1 H), 4.69-4.62 (m, 1 H), 3.58 (s, 3 H), 1.49 (d, J = 6.6 Hz, 3 H); LCMS (Method 3): Rt 5.00 min, m/z = 373.1, 375.1 [M + H]⁺.

Example 28 -- (S)-5-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyrazine-2-carbonitrile (I-17)
Step 1: 6-bromo-3-chloro-1-methylpyrazin-2(1H)-one.

[0202] A mixture of 6-bromo-3-chloropyrazin-2(1H)-one (2 g, 9.55 mmol) and potassium carbonate (2.77 g, 20.04 mmol) in a 200 mL round bottom flask was treated with DMF (25 ml) and stirred 15 minutes. Mel (0.69 ml, 11.04 mmol) was added and the mixture was stirred at room temperature for 45 minutes. The solvent was evaporated under reduced pressure. The residue was mixed with water (75 mL) and extracted with DCM (2x75 mL). The combined organic extracts were dried (MgSO₄), filtered, treated with silica gel, and evaporated under reduced pressure, then evaporated further at 60 °C under high vacuum. The material was chromatographed by Biotage MPLC (silica gel, 0 to 35% EtOAc in hexanes), with isocratic elution at 16% EtOAc and 30% EtOAc while peaks of the desired mass came off. The peak that came off with 30% EtOAc provided 6-bromo-3-chloro-1-methylpyrazin-2(1H)-one (1.30 g, 5.82 mmol, 61 % yield) as a white solid. 

\[ \text{H NMR (300 MHz, DMSO-}d_6) : \delta \text{ ppm 7.50 (s, 1 H), 3.63 (s, 3 H)} \]

LCMS (Method 1): Rt 1.44 min, m/z 222.9, 224.9 [M+H]^+.

Step 2: (S)-3-(1-((5-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)ethyl)-6-chloroquinolin-2(1H)-one
[0203] A mixture of (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride II-1 (200 mg, 0.772 mmol) and 6-bromo-3-chloro-1-methylpyrazin-2(1H)-one (189.2 mg, 0.847 mmol) in DMSO (5 ml) was treated with DIEA (400 μL, 2.290 mmol) and stirred at 110 °C five hours. The sample was mixed with water (75 mL) and extracted with DCM (2×50 mL). The combined organic layers were dried (Na₂SO₄) and filtered, silica gel was added, and the solvent was evaporated under reduced pressure. The sample was chromatographed by Biotage MPLC (25 g silica gel column, 0 to 100% EtOAc in hexanes, with isocratic elution when peaks came off) to provide (S)-3-(1-((5-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)ethyl)-6-chloro quinolin-2(1H)-one (32.9 mg, 0.080 mmol, 10 % yield) as an orange solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 11.99 (s, 1 H), 7.70 - 7.75 (m, 2 H), 7.56 (d, J=7.92 Hz, 1 H), 7.46 - 7.52 (m, 1 H), 7.30 (d, J=8.79 Hz, 1 H), 6.88 - 6.96 (m, 1 H), 5.02 - 5.17 (m, 1 H), 3.50 - 3.60 (m, 3 H), 1.44 (d, J=6.74 Hz, 3 H). LCMS (Method 1): Rt 2.55 min., m/z 410.8 [M+H].

Step 3: (S)-5-((1-(6-chloro-2-oxo-1,2-dihydropyrazin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyrazine-2-carbonitrile (I-17).

[0204] A mixture of (S)-3-(1-((5-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)ethyl)-6-chloroquinolin-2(1H)-one (31.0 mg, 0.076 mmol), Pd₂(dba)₃ (7.4 mg, 8.08 μmol), 1,1'-bis(diphenylphosphino)ferrocene (8.7 mg, 0.016 mmol), and dicyanozinc (18.1 mg, 0.154 mmol) was placed under nitrogen in a 2-dram vial. DMF (1.4 ml) was added by syringe. The atmosphere was evacuated and replaced with nitrogen three times. The mixture was stirred at room temperature overnight. LCMS indicated the reaction had gone cleanly to completion. The solvent was evaporated under reduced pressure. The residue was partitioned between water (15 mL) and DCM (2×15 mL). The combined organic extracts were dried (Na₂SO₄) and filtered, silica gel was added, and the solvent was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (0 to 65% EtOAc in hexanes, with isocratic elution when peaks came off) to provide the title compound I-17 (20.1 mg, 0.055 mmol, 72.0 % yield, HPLC purity 96.5% at 220 nm) as an orange solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 12.03 (s, 1 H), 8.59 (d, J=8.50 Hz, 1 H), 7.77 (s, 1 H), 7.72 (d, J=2.35 Hz, 1 H), 7.47 - 7.55 (m, 2 H), 7.31
(d, J=8.79 Hz, 1 H), 5.18 - 5.31 (m, 1 H), 3.48 (s, 3 H), 1.48 (d, J=6.74 Hz, 3 H). LCMS (Method 4): Rt 1.25 min., m/z 356.1 [M+H]^+.

**Example 29 -- (S)-5-((1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-20)**

![Chemical structure of II-7 and III-1 reacting with DIPEA to form I-20](image)

[0205] A mixture of 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-I (58 mg, 0.38 mmol), (S)-3-(1-aminomethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride II-7 (100 mg, 0.35 mmol) and N,N-diisopropylethylamine (180 μL, 1.04 mmol) in n-BuOH (3 mL) was heated to 110°C in a sealed tube under N2 and stirred overnight. The mixture was then concentrated under reduced pressure and the residue was purified on ISCO (20 g silica gel column, EtOAc/hexanes 0–100%). The off-white solid obtained was triturated with EtOAc/hexanes, filtered, dissolved in hot MeCN/H2O (10 mL/10 mL) and then lyophilized to afford the title compound I-20 as a white solid (78 mg, 58%). ^1H NMR (300 MHz, DMSO-d6): δ: 11.90 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.95 (s, 1H), 6.90 (d, J = 7.9 Hz, 1H), 5.95 (d, J = 7.9 Hz, 1H), 4.65 (m, 1H), 3.88 (s, 3H), 3.58 (s, 3H), 1.48 (d, J = 6.9 Hz, 3H). LCMS (Method 3): Rt 4.98 min, m/z 385 [M+H]^+.

**Example 30 -- 5-((S)-1-(6-chloro-2-oxo-7-((R)-1-(pyridin-2-yl)ethoxy)-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-26)**

![Chemical structure of II-14 and III-1 reacting with DIEA to form I-26](image)
[0206] A mixture of 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-1 (35.2 mg, 0.231 mmol) and 3-((S)-1-aminoethyl)-6-chloro-7-((R)-1-(pyridin-2-yl)ethoxy)quinolin-2(1H)-one hydrochloride II-14 (80 mg, 0.210 mmol) II-8 was treated with DMSO (1.5 ml) and DIEA (111 μL, 0.636 mmol). The solution was stirred at 110 °C for five hours. The sample was mixed with water (20 mL) and extracted with DCM (2x15 mL). The extracts were washed with water (2x20 mL), dried (Na₂SO₄) and filtered, silica gel was added, and the solvent was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (10 g silica gel column) with 0 to 3.4% MeOH in hexanes. The material thus obtained was dissolved in MeCN (2 mL), treated with water (1 mL), frozen on a dry ice/acetone bath, and lyophilized to provide the title compound (I-26) (32.7 mg, 0.069 mmol, 33% yield, HPLC purity 100% at 220 nm) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 11.75 (s, 1 H), 8.55 - 8.62 (m, 1 H), 7.80 (dd, J=7.50, 7.50 Hz, 1 H), 7.74 (s, 1 H), 7.64 (s, 1 H), 7.39 (d, J=7.62 Hz, 1 H), 7.32 (dd, J=7.48, 4.84 Hz, 1 H), 6.96 (d, J=7.62 Hz, 1 H), 6.82 - 6.89 (m, 2 H), 5.93 (d, J=7.92 Hz, 1 H), 5.50 (q, J=6.16 Hz, 1 H), 4.61 (s, 1 H), 3.57 (s, 3 H), 1.66 (d, J=6.16 Hz, 3 H), 1.44 (d, J=6.74 Hz, 3 H). LCMS (Method 1): Rt 2.61 min., m/z 475.9 [M+H]⁺.

Example 31 -- (S)-5-((1-(6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-27)

[0207] A solution of 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-1 (18.3 mg, 0.120 mmol) and (S)-3-((1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy)quinolin-2(1H)-one hydrochloride II-15 (35 mg, 0.106 mmol) was treated with DMSO (0.8 ml) and DIEA (57 μL, 0.326 mmol). The solution was stirred at 110 °C for 3.5 hours. The sample was mixed with water (20 mL) and extracted with DCM (2x10 mL). The combined extracts were washed with water (2x20 mL), dried (Na₂SO₄) and filtered, silica gel was added, and the solvent was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (10 g silica gel column) with 0 to 70% EtOAc in hexanes. The material thus obtained was dissolved in
MeCN (0.8 mL), treated with water (0.4 mL), frozen on a dry ice/acetone bath, and lyophilized to provide the title compound (I-27) (23.9 mg, 0.056 mmol, 52.9 % yield, HPLC purity > 99% at 220 nm) as a white solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 11.83 (s, 1 H), 7.73 (s, 1 H), 7.67 (s, 1 H), 6.97 (d, J=7.92 Hz, 1 H), 6.92 (s, 1 H), 6.89 (d, J=7.92 Hz, 1 H), 5.95 (d, J=7.92 Hz, 1 H), 4.61 - 4.70 (m, 1 H), 3.92 (d, J=6.74 Hz, 2 H), 3.58 (s, 3 H), 1.48 (d, J=6.74 Hz, 3 H), 1.21 - 1.33 (m, 1 H), 0.56 - 0.65 (m, 2 H), 0.34 - 0.44 (m, 2 H). LCMS (Method 1): Rt 2.61 min., m/z 424.9 [M+H]⁺.

Example 32 -- 5-((1-(6-chloro-7-((3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-28)

[0208] A mixture of 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-1 (26.7 mg, 0.176 mmol) and 3-(1-aminoethyl)-6-chloro-7-((3,3-difluorocyclobutyl)methoxy)quinolin-2(1H)-one hydrochloride II-16 (59.7 mg, 0.157 mmol) was treated with DMSO (1 ml) and DIEA (84 µL, 0.481 mmol). The solution was stirred at 110 °C eight hours. LCMS indicated the reaction had gone to completion. The sample was mixed with water (15 mL) and extracted with DCM (3×10 mL). The extracts were dried (Na₂SO₄), filtered, treated with silica gel, and evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (10 g silica gel column, 0 to 75% in EtOAc in hexanes) to provide the title compound Compd 28 (40.5 mg, 0.085 mmol, 54.2 % yield, HPLC purity 100% at 220 nm) as an off-white solid. ¹H NMR (300 MHz, DMSO-d₆): δ ppm 11.90 (s, 1 H), 7.76 (s, 1 H), 7.68 (s, 1 H), 6.97 (d, J=7.62 Hz, 1 H), 6.94 (s, 1 H), 6.91 (d, J=7.62 Hz, 1 H), 5.95 (d, J=7.62 Hz, 1 H), 4.65 (quin, J=6.82 Hz, 1 H), 4.12 (d, J=4.10 Hz, 2 H), 3.58 (s, 3 H), 2.52 - 2.80 (m, 5 H), 1.48 (d, J=6.74 Hz, 3 H). LCMS (Method 4): Rt 1.51 min., m/z 475.1 [M+H]⁺.

Example 33 -- (S)-5-((1-(6-chloro-7-isoproxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-29)
[0209] A mixture of (S)-3-(1-aminoethyl)-6-chloro-7-isopropoxyquinolin-2(1H)-one hydrochloride II-18 (128 mg, 0.4 mmol, 1 eq.), 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (67 mg, 0.44 mmol, 1.1 eq.) and DIPEA (148 mg, 1.2 mmol, 3 eq.) in 4 mL DMSO was heated at 130-135 °C for 80 minutes. The reaction mixture was then poured into water and the resulting solid collected and rinsed with water. Chromatography on 3.5 g silica gel using a DCM to DCM/EtOH (98/2) gradient followed by trituration with H2O/MeOH afforded I-29 (93 mg, 56%) as an off-white solid. 1H NMR(300 MHz, DMSO-d6) δ: 11.80 (broad s, 0.7H), 7.72 (s, 1H), 7.66 (s, 1H), 6.98 (s, 1H), 6.96 (s, 1H), 6.89 (d, J = 7.41, 1H), 5.93 (d, J = 7.68, 1H), 4.62 (m, 2H), 3.57 (s, 3H), 1.47 (d, J = 7.41, 3H), 1.33 (d, J = 6.03, 6H). LC/MS (Method 3), Rt 5.5 min, m/z 413 [M+H]^+.

Example 34 – (S)-5-((1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-30)

[0210] A solution of (S)-3-(1-aminoethyl)-6-chloro-8-fluorquinolin-2(1H)-one hydrochloride II-17 (91.7 mg, 0.331 mmol) and 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-1 (56.8 mg, 0.373 mmol) in DMSO (2.0 ml) was treated with DIEA (172 µl, 0.985 mmol) and stirred at 110 °C for four hours. The sample was added to water (30 mL), and the resulting precipitate was extracted with DCM (2x20 mL) and EtOAc (10 mL). The combined organic extracts were dried (Na2SO4), filtered, treated with silica gel, and evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (10 g silica gel column) with 0 to 45% EtOAc in hexanes, with isocratic elution when peaks came off. Product fractions were combined, washed with water (2x30 mL), and evaporated under reduced pressure.
The residue was dissolved in MeCN (4 mL) and water (2 mL), frozen (dry ice & acetone bath), and lyophilized to provide the title compound I-30 (62.0 mg, 0.166 mmol, 50.3 % yield, HPLC purity 100% at 220 nm) as a grayish-yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$): δ ppm 12.15 (s, 1 H), 7.77 (s, 1 H), 7.56 - 7.65 (m, 2 H), 6.97 (d, $J$=7.92 Hz, 1 H), 6.93 (d, $J$=7.62 Hz, 1 H), 5.94 (d, $J$=7.92 Hz, 1 H), 4.61 - 4.75 (m, 1 H), 3.58 (s, 3 H), 1.50 (d, $J$=6.74 Hz, 3 H). LCMS (Method 1): Rt 2.39 min., m/z 373.0 [M+H]$^+$. 

Example 35 -- (S)-5-((1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-31)

![Chemical structure of II-11, III-1, and I-31](image)

[0211] The mixture of (S)-3-(1-aminoethyl)-6-chloro-1,8-naphthyridin-2(1H)-one II-11 (100 mg, 0.447 mmol), 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-1 (82 mg, 0.537 mmol) and DIEA (0.234 ml, 1.341 mmol) in DMSO (1 ml) was heated to 110°C for two hours. LC-MS showed the formation of the product. The reaction mixture was then cooled to room temperature, follow by addition of water and filtration. The biotage purifciation of the crude with 0-10% MeOH/DCM on a 25g column afforded (S)-5-((1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile I-31 (53.8mg, 33.8%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ ppm 12.52 (s, 1 H), 8.49 (d, $J$=2.64 Hz, 1 H), 8.24 (d, $J$=2.64 Hz, 1 H), 7.72 (s, 1 H), 6.71 - 7.07 (m, 2 H), 5.91 (d, $J$=8.21 Hz, 1 H), 4.52 - 4.85 (m, 1 H), 3.46 - 3.74 (s, 3 H), 1.48 (d, $J$=6.74 Hz, 3 H). LCMS (Method 1): Rt 2.22 min, m/z 356.01 [M+H]$^+$. 

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Example 36 -- (S)-5-((1-(7-chloro-3-o xo-3,4-dihydroquinoxalin-2-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile (I-33)

![Chemical structure diagram]

[0212] To compound II-13 (59 mg, 0.175 mmol) in DMSO (5 mL) in a sealed tube was added 5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile III-1 (35 mg, 0.23 mmol) and DIEA (0.5 mL). The reaction mixture was heated up to 110 °C and stirred for 3 h. The reaction mixture was then cooled to rt, diluted with water (30 mL) and extracted with EtOAc (50 mL X 4). The combined organic layers were dried (Na2SO4), concentrated and purified by reverse C-18 ISCO with water (0.1% TFA) to CH3CN (0.1% TFA) to give the title compound (I-33) (22 mg, 34%) as a white solid. 1H NMR (300 MHz, DMSO-d6): δ 12.71 (s, 1H), 7.82 (d, J = 6.57 Hz, 1H), 7.90 (s, 1H), 7.81 (s, 1 H), 7.59 (d, J = 2.19 Hz, 1H), 7.59 (dd, J = 9.06 Hz, 2.19 Hz, 1H), 7.32 (d, J = 8.79 Hz,1H), 7.05 (d, J = 7.71 Hz, 1H), 6.93 (d, J = 7.98 Hz, 1H), 6.31 (d, J = 7.98 Hz, 1H), 5.00 (m, 1H), 3.59 (s, 3H), 1.49 (d, J = 6.60 Hz, 3H). LCMS (Method 3): Rf 5.30 min, m/z 357.1 [M+H]+.

Table 4: The compounds listed in Table 4 were prepared using methods similar to those described for the preparation of I-13 to I-33.
Table 5. LCMS signal and NMR chemical shifts of each compound listed in Table 4.

<table>
<thead>
<tr>
<th>Cmpd no</th>
<th>LCMS</th>
<th>1H NMR (300 MHz) δ ppm</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-13</td>
<td>m/z: 355.02 (M+H)+&lt;br&gt;Rt (min): 1.22</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm&lt;br&gt;12.07 (s, 1 H), 7.71 - 7.76 (m, 2 H), 7.51 (dd, J=8.79, 2.35 Hz, 1 H), 7.31 (d, J=8.79 Hz, 1 H), 6.97 (d, J=7.92 Hz, 1 H), 6.93 (d, J=7.92 Hz, 1 H), 4.62 - 4.75 (m, 1 H), 3.58 (s, 3 H), 1.50 (d, J=6.74 Hz, 3 H).</td>
<td>5-[[1(S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-14</td>
<td>m/z: 341.19 (M+H)+&lt;br&gt;Rt (min): 1.06</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm&lt;br&gt;12.03 (s, 1 H), 7.72 (s, 2 H), 7.47 (m, 1 H), 7.28(m, 1H), 6.84 (m, 1 H), 6.68(m, 1H), 5.93(m, 1H), 4.66(m, 1H), 1.45(d, J=6.74Hz, 3H)</td>
<td>5-[[1(S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-15</td>
<td>m/z: 355.17 (M+H)+&lt;br&gt;Rt (min): 1.22</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm&lt;br&gt;12.07 (s, 1 H), 7.75 (s, 1 H), 7.74 (d, J=2.35 Hz, 1 H), 7.51 (dd, J=8.79, 2.35 Hz, 1 H), 7.31 (d, J=8.79 Hz, 1 H), 6.97 (d, J=7.92 Hz, 1 H), 6.93 (d, J=7.92 Hz, 1 H), 4.68 (quin, J=6.89 Hz, 1 H), 3.58 (s, 3 H), 1.50 (d, J=6.74 Hz, 3 H).</td>
<td>5-[[1(R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-16</td>
<td>m/z: 373.09 (M+H)+&lt;br&gt;Rt (min): 1.35</td>
<td></td>
<td>5-[[1(S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<td>LCMS</td>
<td>1H NMR (300 MHz) δ ppm</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
<td>------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>I-17</td>
<td>m/z: 356.07 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.03 (s, 1H), 8.59 (d, J=8.50 Hz, 1H), 7.77 (s, 1H), 7.72 (d, J=2.35 Hz, 1H), 7.47 - 7.55 (m, 2H), 7.31 (d, J=8.79 Hz, 1H), 5.18 - 5.31 (m, 1H), 3.48 (s, 3H), 1.48 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyrazine-2-carbonitrile</td>
</tr>
<tr>
<td>I-18</td>
<td>m/z: 373.09 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.12 (s, 1H), 7.95 (d, J=7.92 Hz, 1H), 7.74 (s, 1H), 7.21 (d, J=10.26 Hz, 1H), 6.97 (d, J=7.62 Hz, 1H), 6.91 (d, J=7.62 Hz, 1H), 5.93 (d, J=7.92 Hz, 1H), 4.65 (quin, J=6.90 Hz, 1H), 3.58 (s, 3H), 1.49 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1R)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-19</td>
<td>m/z: 373.04 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.12 (s, 1H), 7.95 (d, J=7.92 Hz, 1H), 7.74 (s, 1H), 7.21 (d, J=10.26 Hz, 1H), 6.97 (d, J=7.62 Hz, 1H), 6.91 (d, J=7.62 Hz, 1H), 5.93 (d, J=7.92 Hz, 1H), 4.65 (quin, J=6.90 Hz, 1H), 3.58 (s, 3H), 1.49 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-20</td>
<td>m/z: 385.12 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.92 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 6.97 (d, J=7.92 Hz, 1H), 6.95 (s, 1H), 6.90 (d, J=7.62 Hz, 1H), 5.95 (d, J=7.92 Hz, 1H), 4.65 (quin, J=7.04 Hz, 1H), 3.88 (s, 3H), 3.57 (s, 3H), 1.48 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1R)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-21</td>
<td>m/z: 385.14 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.92 (s, 1H), 7.74 (s, 1H), 7.68 (s, 1H), 6.97 (d, J=7.92 Hz, 1H), 6.95 (s, 1H), 6.90 (d, J=7.62 Hz, 1H), 5.95 (d, J=7.92 Hz, 1H), 4.65 (quin, J=7.04 Hz, 1H), 3.88 (s, 3H), 3.57 (s, 3H), 1.48 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-22</td>
<td>m/z: 385.06 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.89 (s, 1H), 8.61 (d, J=4.69 Hz, 1H), 7.88 (td, J=7.70, 1.91 Hz, 1H), 7.79 (s, 1H), 7.68 (s, 1H), 7.54 (d, J=7.92 Hz, 1H), 7.36 (dd, J=7.33, 4.98 Hz, 1H), 7.03 (s, 1H), 6.96 (d, J=7.62 Hz, 1H), 6.90 (d, J=7.62 Hz, 1H), 5.94 (d, J=7.92 Hz, 1H), 5.30 (s, 2H), 4.57 - 4.72 (m, 1H), 3.56 (s, 3H), 1.48 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<tr>
<td>I-23</td>
<td>m/z: 462.20 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.89 (s, 1H), 8.61 (d, J=4.69 Hz, 1H), 7.88 (td, J=7.70, 1.91 Hz, 1H), 7.79 (s, 1H), 7.68 (s, 1H), 7.54 (d, J=7.92 Hz, 1H), 7.36 (dd, J=7.33, 4.98 Hz, 1H), 7.03 (s, 1H), 6.96 (d, J=7.62 Hz, 1H), 6.90 (d, J=7.62 Hz, 1H), 5.94 (d, J=7.92 Hz, 1H), 5.30 (s, 2H), 4.57 - 4.72 (m, 1H), 3.56 (s, 3H), 1.48 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1R)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<td>I-24</td>
<td>m/z: 462.17 (M+H)+</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.88 (s, 1H), 8.61 (d, J=4.40 Hz, 1H), 7.88 (td, J=7.70, 1.91 Hz, 1H), 7.79 (s, 1H), 7.68 (s, 1H), 7.54 (d, J=7.92 Hz, 1H), 7.36 (dd, J=7.33, 4.98 Hz, 1H), 7.03 (s, 1H), 6.96 (d, J=7.62 Hz, 1H), 6.90 (d, J=7.62 Hz, 1H), 5.94 (d, J=7.92 Hz, 1H), 5.30 (s, 2H), 4.57 - 4.72 (m, 1H), 3.56 (s, 3H), 1.48 (d, J=6.74 Hz, 3H).</td>
<td>5-[(1R)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<td>Compd no</td>
<td>LCMS</td>
<td>1H NMR (300 MHz) δ ppm</td>
<td>Chemical Name</td>
</tr>
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<td>I-25</td>
<td>m/z: 462.08 (M+H)+ Rt (min): 1.2925</td>
<td>7.83 - 7.93 (m, 1 H), 7.79 (s, 1 H), 7.68 (s, 1 H), 7.54 (d, J=7.62 Hz, 1 H), 7.33 - 7.43 (m, 1 H), 7.03 (s, 1 H), 6.96 (d, J=7.92 Hz, 1 H), 6.90 (br d, J=7.33 Hz, 1 H), 5.94 (d, J=7.92 Hz, 1 H), 5.30 (s, 2 H), 4.57 - 4.71 (m, 1 H), 3.58 (s, 3 H), 1.48 (d, J=6.74 Hz, 3 H).</td>
<td>dihydroquinolin-3-y[ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<tr>
<td>I-26</td>
<td>m/z: 476.24 (M+H)+ Rt (min): 1.4</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.89 (s, 1 H), 8.58 - 8.63 (m, 1 H), 7.88 (ddd, J=7.58, 7.67, 1.76 Hz, 1 H), 7.79 (s, 1 H), 7.68 (s, 1 H), 7.54 (d, J=7.92 Hz, 1 H), 7.38 (dd, J=6.89, 5.42 Hz, 1 H), 7.03 (s, 1 H), 6.97 (d, J=7.92 Hz, 1 H), 6.90 (d, J=7.62 Hz, 1 H), 6.94 (d, J=7.92 Hz, 1 H), 5.30 (s, 2 H), 4.56 - 4.71 (m, 1 H), 3.58 (s, 3 H).</td>
<td>5-[[1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)]-1,2-dihydroquinolin-3-y[ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-27</td>
<td>m/z: 425.55 (M+H)+ Rt (min): 1.48</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.83 (s, 1 H), 7.73 (s, 1 H), 7.67 (s, 1 H), 6.97 (d, J=7.92 Hz, 1 H), 6.92 (s, 1 H), 6.89 (d, J=7.92 Hz, 1 H), 5.95 (d, J=7.92 Hz, 1 H), 4.61 - 4.70 (m, 1 H), 3.58 (s, 3 H), 1.48 (d, J=6.74 Hz, 3 H), 0.34 - 0.44 (m, 2 H).</td>
<td>5-[[[1S]-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-y[ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<td>I-28</td>
<td>m/z: 475.05 (M+H)+ Rt (min): 1.51</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 11.90 (s, 1 H), 7.76 (s, 1 H), 7.68 (s, 1 H), 6.97 (d, J=7.62 Hz, 1 H), 6.94 (s, 1 H), 6.91 (d, J=7.62 Hz, 1 H), 5.95 (d, J=7.62 Hz, 1 H), 4.65 (quin, J=6.82 Hz, 1 H), 4.12 (d, J=4.10 Hz, 2 H), 3.58 (s, 3 H), 2.52 - 2.80 (m, 5 H), 1.48 (d, J=6.74 Hz, 3 H).</td>
<td>5-[[[1-[6-chloro-7-[(3,3-difluorocyclobutyl)methoxy]-2-oxo-1,2-dihydroquinolin-3-y[ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
<tr>
<td>I-29</td>
<td>m/z: 373.22 (M+H)+ Rt (min): 1.27</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.15 (s, 1 H), 7.77 (s, 1 H), 7.56 - 7.65 (m, 2 H), 6.97 (d, J=7.92 Hz, 1 H), 6.93 (d, J=7.62 Hz, 1 H), 5.94 (d, J=7.92 Hz, 1 H), 4.61 - 4.75 (m, 1 H), 3.58 (s, 3 H), 1.50 (d, J=6.63 Hz, 3 H).</td>
<td>5-[[[1S]-1-[6-chloro-2-oxo-7-(propan-2-yl oxy)-1,2-dihydroquinolin-3-y[ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<tr>
<td>I-30</td>
<td>m/z: 372.04 (M+H)+ Rt (min): 1.27</td>
<td>1H NMR (300 MHz, DMSO-d6): δ ppm 12.15 (s, 1 H), 7.77 (s, 1 H), 7.65 - 7.63 (m, 3 H), 6.97 (d, J=7.92 Hz, 1 H), 6.94 (d, J=7.62 Hz, 1 H), 4.56 (d, J=4.70 Hz, 2 H), 3.56 (s, 3 H), 1.50 (d, J=6.63 Hz, 3 H).</td>
<td>5-[[[1S]-1-[6-chloro-2-oxo-7-(propan-2-yl oxy)-1,2-dihydroquinolin-3-y[ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<tr>
<td>Compd no</td>
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<td>1H NMR (300 MHz) δ ppm</td>
<td>Chemical Name</td>
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<tr>
<td>I-31</td>
<td>m/z: 356.20 (M+H)^+</td>
<td>J=6.74 Hz, 3 H</td>
<td>5-([(1S)-1-(6-chloro-2-oxo-1,2-dihyadro-1,8-naphthyridin-3-yl)ethyl]amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<tr>
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<td>Rt (min): 1.09</td>
<td>1H NMR (300 MHz, DMSO-d6) δ ppm</td>
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<td>12.52 (s, 1 H), 8.49 (d, J=2.64 Hz, 1 H), 8.24 (d, J=2.64 Hz, 1 H), 7.72 (s, 1 H), 6.71 - 7.07 (m, 2 H), 5.91 (d, J=8.21 Hz, 1 H), 4.52 - 4.85 (m, 1 H), 3.46 - 3.74 (s, 3 H), 1.48 (d, J=6.74 Hz, 3 H).</td>
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<td>I-32</td>
<td>m/z: 356.15 (M+H)^+</td>
<td>1H NMR (300 MHz, DMSO-d6) δ ppm</td>
<td>5-([(1R)-1-(7-chloro-3-oxo-3,4-dihydroquinoxalin-2-yl)ethyl]amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
</tr>
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<td>Rt (min): 1.28</td>
<td>1H NMR (300 MHz, DMSO-d6) δ ppm</td>
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<tr>
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<td>12.71 (s, 1H), 7.82 (d, J = 6.57 Hz, 1H), 7.90 (s, 1H), 7.81 (s, 1H), 7.59 (d, J = 2.19 Hz, 1H), 7.59 (dd, J = 9.06 Hz, 2.19 Hz, 1H), 7.32 (d, J = 8.79 Hz,1H), 7.05 (d, J = 7.71 Hz, 1H), 6.93 (d, J = 7.98 Hz, 1H), 6.31 (d, J = 7.98 Hz, 1H), 5.00 (m, 1H), 3.59 (s, 3H), 1.49 (d, J = 6.60 Hz, 3H).</td>
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<tr>
<td>I-33</td>
<td>m/z: 356.20 (M+H)^+</td>
<td>1H NMR (300 MHz, DMSO-d6) δ ppm</td>
<td>5-([(1S)-1-(7-chloro-3-oxo-3,4-dihydroquinoxalin-2-yl)ethyl]amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile</td>
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<tr>
<td></td>
<td>Rt (min): 1.28</td>
<td>1H NMR (300 MHz, DMSO-d6) δ ppm</td>
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<tr>
<td></td>
<td>12.71 (s, 1H), 7.82 (d, J = 6.57 Hz, 1H), 7.90 (s, 1H), 7.81 (s, 1H), 7.59 (d, J = 2.19 Hz, 1H), 7.59 (dd, J = 9.06 Hz, 2.19 Hz, 1H), 7.32 (d, J = 8.79 Hz,1H), 7.05 (d, J = 7.71 Hz, 1H), 6.93 (d, J = 7.98 Hz, 1H), 6.31 (d, J = 7.98 Hz, 1H), 5.00 (m, 1H), 3.59 (s, 3H), 1.49 (d, J = 6.60 Hz, 3H).</td>
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LCMS data are determined by Method 4.

**Example 37 -- IDH1-R132H and IDH1-R132C Enzymatic Assay**

[0213] Assays were performed in a 384-well black plate. An aliquot of 250 nL of compound was incubated with 10 μL of 30 nM IDH1-R132H or 10 nM IDH1-R132C recombinant protein in assay buffer (50 mM Tris pH = 7.5, 150 mM NaCl, 5 mM MgCl₂, 0.1% (w/v) Bovine Serum Albumin, and 0.01% Triton X-100) in each well at 25 °C for 15 minutes. After the plate was centrifuged briefly, an aliquot of 10 μL of 2 mM α-ketoglutarate and 20 μM NADPH solution prepared in assay buffer was then added to each well and the reaction was maintained at 25 °C for 45 minutes. An aliquot of 10 μL of diaphorase solution (0.15U/mL diaphorase and 30 μM Resazurin in assay buffer) was added to each well. The plate was maintained at 25 °C for 15 minutes and then read on a plate reader with excitation and emission wavelengths at 535 nm and 590 nm, respectively. The IC₅₀ of a given compound was calculated by fitting the dose response curve of inhibition of NADPH consumption at a given concentration with the four parameter logistic equation.
Example 38 -- Cellular 2-HG assay using HCT116 mutant IDH1 cells

HCT116 isogenic IDH1-R132H and IDH1-R132C mutant cells were cultured in growth media (McCoy’s 5A, 10% fetal bovine serum, 1X antibiotic-antimycotic solution and 0.3 mg/mL G418) in 5% CO₂ in an incubator at 37 °C. To prepare the assay, cells were trypsinized and resuspended in assay media (McCoy’s 5A with no L-glutamine, 10% fetal bovine serum, 1X antibiotic-antimycotic solution and 0.3 mg/mL G418). An aliquot of 10,000 cells/100 µL was transferred to each well of a clear 96-well tissue culture plate. The cells were incubated in 5% CO₂ at 37 °C in an incubator overnight to allow for proper cell attachment. An aliquot of 50 µL of compound containing assay media were then added to each well and the assay plate was kept in 5% CO₂ at 37 °C in an incubator for 24 hours. The media was then removed from each well and 150 µL of a methanol/water mixture (80/20 v/v) was added to each well. The plates were kept at -80 °C freezer overnight to allow for complete cell lysis. An aliquot of 125 µL of extracted supernatant was analyzed by RapidFire high-throughout-mass spectrometry (Agilent) to determine the cellular 2-HG level. The IC₅₀ of a given compound was calculated by fitting the dose response curve of cellular 2-HG inhibition at a given concentration with the four parameter logistic equation.

Table 6 below provides activity of each compound according to the legend that “++++” indicates an inhibition at a concentration < 0.01 µM; “+++” indicates inhibition at a concentration between 0.01 µM and 0.1 µM of the disclosed compound; “++” indicates inhibition at a concentration from 0.1 µM to 1 µM of the disclosed compound; and “+” indicates inhibition at a concentration > 1 µM for Enzyme IDH1 R132H, HCT116 IDH1 R132H, and HCT116 IDH1 R132C.

For Enzyme IDH1 R132C, “++++” indicates an inhibition at a concentration < 0.1 µM; “+++” indicates inhibition at a concentration between 0.1 µM and 1 µM of the disclosed compound; “++” indicates inhibition at a concentration from 1 µM to 10 µM of the disclosed compound; and “+” indicates inhibition at a concentration > 10 µM.
Table 6 Results of the illustrative compounds of Formula 1 in IDH1-R132H, IDH1-R132C, IDH1-MS-HTC116-R132H, and IDH1-MS-HTC116-R132C assays.

<table>
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<tr>
<th>Cmpd no</th>
<th>Enzyme IDH1 R132H Range</th>
<th>Enzyme IDH1 R132C Range</th>
<th>HCT116 IDH1 R132H Range</th>
<th>HCT116 IDH1 R132C Range</th>
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**Equivalents**

[0217] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.
CLAIMS:

1. A compound of Formula I:

   ![Chemical Structure](image)

   or pharmaceutical salt, enantiomer, hydrate, solvate, prodrug, isomer, or tautomer thereof,

   wherein:

   each $W_1$ and $W_2$ is independently CH, CF or N;

   $W_3$ is independently, CR$_2$ or N;

   U is N or CR$_6$;

   A is selected from the group consisting of H, D, halogen, CN, -CHO, -COOH, -COOR, -C(O)NH$_2$, -C(O)NHR, R'S(O)$_2$, -O(CH$_2$)$_n$C(O)R', and R'S(O)-, heteroaryl, and-SOMe,

   $\text{SO}_2$Me, $\text{N} \equiv \text{N}$, $\text{N} \equiv \text{N}$ and $\text{Y}$;

   wherein X and Y are independently in each occurrence C, N, NR', S, and O, provided that the ring containing X and Y cannot have more than 4 N or NH atoms or more than one S or O atoms, and wherein the S and O are not contiguous;

   R and R' at each occurrence are independently selected from the group consisting of H, OH, CN, -CH$_2$CN, halogen, -NR$_2$R$_8$, CHCF$_2$, CF$_3$, C$_1$-C$_6$ alkyl, R$_7$S(O)$_2$, C$_1$-C$_6$ alkoxy, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, C$_3$-C$_8$ cycloalkyl, C$_3$-C$_8$ cycloalkylalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl, wherein each R is optionally substituted with one or more substituents selected from the group consisting of OH, halogen, C$_1$-C$_6$ alkoxy, NH$_2$, R$_7$S(O)$_2$, CN, C$_3$-C$_8$ cycloalkyl, 3- to 8-membered heterocyclyl, aryl, heteroaryl, and R$_7$S(O)-;
R₁ is independently H, OH, CN, halogen, CHCF₂, CF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkenyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl, wherein each C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl is optionally substituted one or more times with substituents selected from the group consisting of halogen, OH, NH₂, CN, C₁₋₆ alkyl, and C₁₋₆ alkoxy;

each R₂ is independently H, OH, CN, halogen, CF₃, CHF₂, benzyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, NH₂, -O(CH₂)bR’, -O(CH₂)bC(O)NHR’, -O(CH₂)bC(O)R’, NHR₇, -N(R₇)(R₈), NHC(O)R₇, NHC(O)OR₇, NH(O)R₇, NHC(O)OR₇, NHC(O)NHR₇, -S(O)₂NHR₇, NHC(O)N(R₃)R₇, OCH₂R₇, CHRR’ or OCHR’R₇, wherein C₁₋₆ alkyl, C₁₋₆ alkoxy is optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkyl substituted with one or more halogen, 3- to 8-membered heterocyclyl, aryl, -heteroaryl-C(O)NH₂, and heteroaryl;

or R₁ and R₂ can combine to form a C₄₋₆ cycloalkyl or a 3- to 8- membered heterocyclyl containing at least one atom selected from the group consisting of N, O, and S;

R₁ is H, C₁₋₆ alkyl, or -OH;

R₄ and R₅ are independently H, halogen, CH₂OH, C₁₋₃ alkyl, or C₁₋₃ alkyl substituted with halogen, or R₄ and R₅ when combined can form a C₃₋₅ cycloalkyl or C₃₋₅ heterocyclyl;

each R₆ is H, halogen, C₁₋₆ alkyl, C₁₋₆ alkyl substituted with halogen, C₁₋₆ alkoxy, C₁₋₆ alkoxy substituted with one or more halogen, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl;

R₇ and R₈ are independently H, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl; or when combined R₇ and R₈ can form a 3- to 8-membered heterocyclyl or heteroaryl ring;

R₉ is independently H, D, CD₃, CF₃, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, C₃₋₈ cycloalkyl, wherein the alkyl, alkenyl, alkynyl, and cycloalkyl is optionally substituted with amino, OH, halo, or alkoxy;

n is 0, 1, or 2; and

r is 0, 1, or 2;
with the proviso that when A is H, then R₁ is not C₁-C₆ alkyl or C₁-C₆ alkoxy and R₁ and R₂ cannot combine to form a 3- to 8-membered heterocyclyl.

2. The compound of claim 1, wherein A is CN.
3. The compound of claim 2, wherein U is N.
4. The compound of claim 1, wherein A is CN and R₆ is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl.
5. The compound of claim 4, wherein R₆ is methyl.
6. The compound of claim 1, wherein A is H or F.
7. The compound of claim 1, wherein R₃ is methyl or ethyl.
8. The compound of claim 1, wherein R₄ and R₅ are H.
9. The compound of claim 1, wherein R₄ is H and R₅ is methyl.
10. The compound of claim 1, wherein R₄ is H and R₅ is (S)-methyl.
11. The compound of claim 1, wherein R₄ and R₅ are halogen.
12. The compound of claim 1, wherein R₄ is F and R₅ is methyl.
13. The compound of claim 1, wherein R₄ and R₅ can combine to form a C₃-C₅ cycloalkyl.
14. The compound of claim 1, wherein W₁, W₂, and W₃ are CH₃ or CF₃.
15. The compound of claim 1, wherein W₁ or W₃ is N.
16. The compound of claim 1, wherein R₁ is halogen.
17. The compound of claim 16, wherein R₁ is chloro.
18. The compound of claim 1, wherein R₂ is H, halogen, or C₁-C₆ alkoxy.
19. The compound of claim 1, wherein R₂ is C₁-C₆ alkoxy substituted with heteroaryl or 3- to 8-membered heterocyclyl.
20. The compound of claim 1 selected from the group consisting of:

5-\{[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

6-chloro-3-\{[(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)amino]methyl\}-1,2-dihydroquinolin-2-one;

6-chloro-3-\{[(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino]methyl\}-1,2-dihydroquinolin-2-one;

5-\{[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino\}-6-oxo-1,6-dihydropyridine-2-carbonitrile;
6-chloro-3-\{[(1-cyclopropyl-2-oxo-1,2-dihydropyridin-3-yl)amino]methyl\}-1,2-dihydroquinolin-2-one;

6-chloro-3-\{[(1,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)amino]methyl\}-1,2-dihydroquinolin-2-one;

3-\{[(6-bromo-2-oxo-1,2-dihydropyridin-3-yl)amino]methyl\}-6-chloro-1,2-dihydroquinolin-2-one;

6-chloro-3-\{[(2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl)amino]methyl\}-1,2-dihydroquinolin-2-one;

6-chloro-3-\{[(1-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridin-3-yl)amino]methyl\}-1,2-dihydroquinolin-2-one;

methyl 5-\{[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino\}-6-oxo-1,6-dihydropyridine-3-carboxylate;

6-chloro-7-methoxy-3-\{[(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino]methyl\}-1,2-dihydroquinolin-2-one;

6-chloro-3-\{[(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino]methyl\}-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one;

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyrazine-2-carbonitrile;
5-\{[(1R)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1R)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1R)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1R)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1R)-1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-(3,3-difluorocyclobutyl)methoxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-(propan-2-yloxy)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1R)-1-(7-chloro-3-oxo-3,4-dihydroquinoxalin-2-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile; and

5-\{[(1S)-1-(7-chloro-3-oxo-3,4-dihydroquinoxalin-2-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile.

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

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydro(4a,5,6,7,8,8a-^{13}C_6)quinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)(2,2,2-^{3}H_3)ethyl]amino\}-1-(^{3}H_3)methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-6-oxo-1-(trifluoromethyl)-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-(2-hydroxypropan-2-yl)-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino\}-1-(^{3}H_3)methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)(2,2,2-^{3}H_3)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-7-methyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-\{[(1S)-1-(6-chloro-2-oxo-1,2-dihydro(8-^{7}H)quinolin-3-yl)ethyl]amino\}-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;
5-[(1S)-1-[6-chloro-2-oxo-1,2-dihydro(5,7,8-3H₃)quinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[6-chloro-7-{([2-hydroxy-2-methylpropyl]amino)-2-oxo-1,2-dihydroquinolin-3-yl}ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[7-(azetidin-1-yl)-6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[7-(azetidin-1-yl)-6-chloro-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

5-[(1S)-1-[6-chloro-7-(3,3-difluoroazetidin-1-yl)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile;

6-chloro-3-[(1S)-1-[1-methyl-2-oxo-6-(1H-1,2,3,4-tetrazol-1-yl)-1,2-dihydropyridin-3-yl]amino]ethyl]-1,2-dihydroquinolin-2-one; and

5-[(1S)-1-[6-chloro-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino]-1-methyl-6-oxo-1,6-dihydropyridine-2-carboxamide.

22. The compound of claim 1 having the Formula Ia:

![Formula Ia](attachment:image.png)

23. The compound of claim 22 having the Formula Ia-1:

![Formula Ia-1](attachment:image.png)

24. The compound of claim 22 having the Formula Ia-2:
25. The compound of claim 1 having the Formula Ib:

26. The compound of claim 25 having the Formula Ib-1:

27. A pharmaceutical composition comprising the compound according to claim 1 and pharmaceutically acceptable carrier.

28. A method of treating a disease or disorder associated with mutant isocitrate dehydrogenase comprising administering to a patient in need thereof a compound of claim 1.

29. The method of claim 28, wherein the disease is glioma, glioblastoma multiforme (GBM), acute myeloid leukemia (AML), chondrosarcoma, intrahepatic cholangiocarcinoma (IHCC), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD) or a solid tumor.

30. The method of claim 28, wherein administering is performed orally, parentally, subcutaneously, by injection, or by infusion.

31. A method of inhibiting mutant isocitrate dehydrogenase comprising administering to a patient in need thereof a compound of claim 1.

32. A method of reducing alpha-ketoglutarate comprising administering to a patient in need thereof a compound of claim 1.

33. A compound of any one of claims 1-26 for use in the manufacture of a medicament for treating a disease mediated by mutant isocitrate dehydrogenase.
34. Use of a compound of any one of claims 1-26 for treating a disease mediated by mutant isocitrate dehydrogenase.
ABSTRACT

The invention relates to inhibitors of mutant isocitrate dehydrogenase (mut-IDH) proteins with neomorphic activity useful in the treatment of cell-proliferation disorders and cancers, having the Formula:

where A, U, W₁, W₂, W₃, R₁-R₆, and R₉ are described herein.
**Provisional Application for Patent Cover Sheet**

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

### Inventor(s)

<table>
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All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the Add button.

**Title of Invention**
PYRIDIN-2(1H)-ONE QUINOLINONE DERIVATIVES AS MUTANT-ISOCITRATE DEHYDROGENASE INHIBITORS

**Attorney Docket Number (if applicable)**
FOTH-004/04US 314575-2041

**Correspondence Address**
Direct all correspondence to (select one):

- The address corresponding to Customer Number
- Firm or Individual Name

Customer Number
58249

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- No.
- Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:
- Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:
Entity Status
Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29

- Applicant asserts small entity status under 37 CFR 1.27
- Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- No

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Signature
Please see 37 CFR 1.4(d) for the form of the signature.

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<td>/J. Dean Farmer/</td>
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<td>57917</td>
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First Name | Last Name | Farmer
---|---|---
J. Dean | | Farmer

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.
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The information provided by you in this form will be subject to the following routine uses:

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6. A record from this system of records may be disclosed, as a routine use, to an other federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency’s responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.
## Application Data Sheet 37 CFR 1.76

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## Secrecy Order 37 CFR 5.2

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## Inventor Information:

### Inventor 1

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**Residence Information (Select One):**
- ☐ US Residency
- ☐ Non US Residency
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**Mailing Address of Inventor:**

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- ☐ US Residency
- ☐ Non US Residency
- ☐ Active US Military Service

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**Residence Information (Select One):**
- ☐ US Residency
- ☐ Non US Residency
- ☐ Active US Military Service

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**Mailing Address of Inventor:**

**Address 1**

248 Webb Circle

**Address 2**

**City**

Monroe

**State/Province**

CT

**Postal Code**

06468

**Country**

US

**Inventor 4**

**Prefix**

Gary

**Given Name**

Gustafson

**Legal Name**

**Middle Name**

**Family Name**

**Suffix**


**Residence Information (Select One)**

- US Residency
- Non US Residency
- Active US Military Service

**City**

Ridgefield

**State/Province**

CT

**Country of Residence**

US

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**Mailing Address of Inventor:**

**Address 1**

33 Ridgecrest Drive

**Address 2**

**City**

Ridgefield

**State/Province**

CT

**Postal Code**

06877

**Country**

US

**Inventor 5**

**Prefix**

Zhonguo

**Given Name**

Wang

**Legal Name**

**Middle Name**

**Family Name**

**Suffix**


**Residence Information (Select One)**

- US Residency
- Non US Residency
- Active US Military Service

**City**

Lexington

**State/Province**

MA

**Country of Residence**

US

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**Mailing Address of Inventor:**

**Address 1**

19 Earl Street

**Address 2**

**City**

Lexington

**State/Province**

MA

**Postal Code**

02421

**Country**

US

**Inventor 6**

**Prefix**

R. Bruce

**Given Name**

Diebold

**Legal Name**

**Middle Name**

**Family Name**

**Suffix**


**Residence Information (Select One)**

- US Residency
- Non US Residency
- Active US Military Service

**City**

Waltham

**State/Province**

MA

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**Mailing Address of Inventor:**

| Address 1 | 121 Sciarappa St.#3 |
| City | Cambridge |
| State/Province | MA |
| Postal Code | 02141 |
| Country | US |

**Legal Name**

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**Residence Information (Select One)**

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- [ ] Non US Residency
- [ ] Active US Military Service

| City | Newton |
| State/Province | MA |
| Country of Residence | US |

**Mailing Address of Inventor:**

| Address 1 | 40 Broadlawn Drive |
| City | Newton |
| State/Province | MA |
| Postal Code | 02467 |
| Country | US |

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.

**Correspondence Information:**

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

- [ ] An Address is being provided for the correspondence Information of this application.

**Customer Number**

| 58249 |

**Email Address**

| zpatdocdocketing@cooley.com |

**Application Information:**

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**Suggested Figure for Publication (if any)**
**Application Data Sheet 37 CFR 1.76**

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</table>

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., “Domestic Benefit/National Stage Information” and “Foreign Priority Information”).

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

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**Publication Information:**

- Request Early Publication (Fee required at time of Request 37 CFR 1.219)
- Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

**Representative Information:**

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).

Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:  
- [ ] Customer Number  
- [ ] US Patent Practitioner  
- [ ] Limited Recognition (37 CFR 11.9)

Customer Number: 58249

**Domestic Benefit/National Stage Information:**

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the application number blank.

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Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.

**Foreign Priority Information:**
Application Data Sheet 37 CFR 1.76

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This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX), the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Additional Foreign Priority Data may be generated within this form by selecting the Add button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☑ Authorization to Permit Access to the Instant Application by the Participating Offices
Application Data Sheet 37 CFR 1.76

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If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application, and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an assignee or person who otherwise shows sufficient proprietary interest on which the inventor is obligated to assign, then the joint inventor or inventors who are also the applicant should be identified in this section.

- Assignee
- Legal Representative under 35 U.S.C. 117
- Joint Inventor

(☐) Person to whom the inventor is obligated to assign.
(☐) Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name: Forma Therapeutics, Inc.

Mailing Address Information:

| Address 1 | 500 Arsenal Street, Suite 100 |
| Address 2 | City | Watertown | State/Province | MA |
| Country | US | Postal Code | 02472 |
| Phone Number | Fax Number | |

EFS Web 2.2.10
Application Data Sheet 37 CFR 1.76

Title of Invention: PYRIDIN-2(1H)-ONE QUINOLINONE DERIVATIVES AS MUTANT-ISOCITRATE DEHYDROGENASE INHIBITORS

Attorney Docket Number: FOTH-004/04US 314575-2041
Application Number:

Email Address

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Assignee Information" section will appear on the patent application publication as an assignant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here.

Prefix
Given Name
Middle Name
Family Name
Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1
Address 2
City
State/Province
Country
Postal Code
Phone Number
Fax Number
Email Address

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Add

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature: J. DEAN FARMER/  Date (YYYY-MM-DD)  2015-04-21
First Name: J. DEAN  Last Name: FARMER  Registration Number: 57917

Additional Signature may be generated within this form by selecting the Add button.

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This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.
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<td>Kenneth W. Bair</td>
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<td>Customer Number:</td>
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<td><strong>Filer:</strong></td>
<td>J. Dean Farmer/Donna Doyle</td>
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<td>J. Dean Farmer</td>
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<td>FOTH-004/04US 314575-2041</td>
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:
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| 2               |                                                   | 2FOTH-004-04US SPEC.pdf   | 1404888                         | yes             | 125             |

**Multipart Description/PDF files in .zip description**

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### Information:

| 3               | Provisional Cover Sheet (SB16)                    | FOTH-004-04US ProvisionalCover.pdf | 1477762 | no | 4 |

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### Information:

| 4               | Application Data Sheet                            | FOTH-004-04US ADS.pdf            | 1290116  | no | 10 |

### Warnings:

### Information:

| 5               | Fee Worksheet (SB06)                              | fee-info.pdf                   | 30294    | no | 2 |

### Warnings:

### Information:

**Total Files Size (in bytes)**: 5225759
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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
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Application Number: 62150812  Document Date: 04/21/2015

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• Drawing

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Form Revision Date: August 26, 2013