INDAZOLE AND BENZOISOXAZOLE DHYDROOROTATE DEHYDROGENASE INHIBITORS

Abstract: Disclosed are compounds, compositions and methods for treating diseases, disorders, or medical conditions that are affected by the modulation of DHODH. Such compounds are represented by Formula (I) as follows, wherein R¹, R², R³ and R⁵ are defined herein.
INDAZOLE AND BENZOISOXAZOLE DIHYDROOROTATE DEHYDROGENASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is entitled to priority pursuant to 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 63/031,815, filed on May 29, 2020, the disclosure of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds that are dihydroorotate dehydrogenase (DHODH) inhibitors. These compounds may be useful for the treatment of a disease, disorder, or medical condition where there is an advantage in inhibiting DHODH. The invention also relates to pharmaceutical compositions comprising one or more of such compounds, to processes to prepare such compounds and compositions, and to the use of such compounds or pharmaceutical compositions for the method of treatment of cancer, and autoimmune and inflammatory diseases, syndromes, and disorders.

BACKGROUND OF THE INVENTION

Acute myelogenous leukemia (AML) is a clonal disease of the blood and bone marrow resulting from mutations that occur in normal hematopoietic stem cells. AML is a heterogenous disease in that it presents with a range of cytogenetic, morphological and immunophenotypic features, and is characterized by an accumulation of clonal, abnormal myeloid progenitor cells, known as myeloblasts. These cells demonstrate disruption of normal myeloid differentiation and excessive proliferation, resulting in the decreased formation of hematopoietic cells. Disease remission can be achieved with standard induction chemotherapy, but refractory and relapsed disease remains a challenge due to persistence of leukemic stem cells. Therefore, AML represents an unmet medical need with >20,000 new cases per year in the US with 5-year overall survival below 30% (Stein ET al., Health Qual Life Outcomes 16: 193, 2018).
Differentiation therapy is considered an attractive approach to AML treatment based on the knowledge that differentiation and loss of stem cell self-renewal are coupled in normal cells. Treatment of acute promyelocytic leukemia, which represents 10-15% of all AML, with all-trans retinoic acid is the paradigm for differentiation therapy. Retinoic acid targets the promyelocytic leukemia protein (PML)-retinoic acid receptor-α (RAR-α) fusion protein encoded by a t(15,17) chromosomal translocation. Targeting PML-RAR specifically lifts the transcriptionally mediated differentiation block induced by the fusion protein and early clinical trials with single agent ATRA demonstrated complete hematologic remission in all treated patients (McCulloch D et al. Onco Targets Ther 2017; 10: 1585–1601; Nowak D et al. Blood 113: 3655, 2009).

Although differentiation therapy is successful, it is only applicable to a small population of AML patients. Research efforts have aimed at identifying additional differentiation inducing agents, but with limited success. Recently dihydroorotate dehydrogenase (DHODH) emerged as a potentially more broadly applicable differentiation target in a phenotypic screen aimed at identifying small molecules that overcome blockade of the maturation of primary murine bone marrow cells expressing the homeobox protein HoxA9. This protein is a key transcription factor involved in balancing stem cell maintenance/differentiation and is normally expressed in hematopoietic progenitor cells and downregulated upon induction of differentiation and has been found to be widely overexpressed in AML (Sykes et al., Cell 167: 171, 2016).

DHODH is a flavin mononucleotide (FMN) flavoprotein located in the inner mitochondrial membrane that catalyzes the oxidation of dihydroorotate to orotate, the fourth step in the de novo pyrimidine biosynthesis pathway. Inhibition of DHODH leads to decreased pyrimidine synthesis important precursors for nucleotide synthesis, but also glycoprotein and phospholipid biosynthesis (Reis RAG et al., Archives Biochem Biophysics 632: 175, 2017; Vyas VK et al., Mini Rev Med Chem 11: 1039, 2011). DHODH is a validated target for the treatment of autoimmune diseases with the FDA approved small molecule DHODH inhibitors leflunomide and teriflunomide for rheumatoid arthritis and multiple sclerosis, respectively (Lolli ML et al., Recent patents on Anti-Cancer Drug Discovery 13: 86, 2018).
Since the first observation by Sykes et al. demonstrating that DHODH inhibition drives AML differentiation in vitro, as evidenced by upregulation of the differentiation markers CD11b and CD14, and results in dose dependent anti-leukemic effects, decreased leukemic stem cells and prolonged survival in vivo, additional evidence emerged demonstrating that small molecule DHODH inhibitors mediate antiproliferative activity against AML cells with concomitant cell cycle arrest, upregulation of CD11b and CD14, and induction of apoptosis (Wu D et al., Haematologica 103: 1472, 2018; Sainas S et al., J Med Chem 61: 6034, 2018; Cao L et al., Mol Cancer Ther, October 23rd Epub ahead of print). Moreover, preclinical solid tumor in vitro and in vivo models demonstrated effectiveness of DHODH inhibition and DHODH was identified as a synthetic lethality in PTEN and KRAS mutant solid tumors (Pharmacology and Therapeutics, Epub October 19th, 2018; Mathur D et al., Cancer Discovery 7: 1, 2017; Cell Chemical Biology 25: 1, 2018).

Thus, there remains a need for DHODH inhibitors that provide a therapeutic benefit to patients suffering from cancer and/or inflammatory and immunological diseases.

SUMMARY OF THE INVENTION

Embodiments of the invention relate to compounds of Formula I,

![Formula I](image)

wherein

![Images of substituent options](image)

\[ R^1 \text{ is } R^b, \quad R^a \text{ is } -C_{(1-4)}\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C_{(1-4)}\text{alkyl is optionally substituted with up to three fluorine atoms; } \]

\[ R^b \text{ is } -\text{CH}_2\text{OH, } -C_{(1-2)}\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C_{(1-2)}\text{alkyl is optionally substituted with up to three fluorine atoms; } \]
$R^e$ is -C(1-2)alkyl, or -CH$_2$OCH$_3$; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;

$R^d$ is -C(CH$_3$)$_2$OH, -C(CF$_3$)$_2$OH, -CH$_2$OH, or -CH(CH$_3$)OH;

$R^2$ is -CH(CH$_3$)$_2$,

wherein $R^e$ is -H, -CH$_3$, or -CH(CH$_3$)$_2$;

$R^3$ is -O-R$^4$, or -NH-R$^4$

wherein $R^4$ is -CH(CH$_2$OCH$_3$)$_2$,

$R^f$ is -H, -Cl, -F, -CN, -OCH$_3$, -OCHF$_2$, -OCH$_2$F, -OCH$_3$, -NO$_2$, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;

$R^g$ is -H, -Cl, -F, -CN, -OCH$_3$, -OCHF$_2$, -OCH$_2$F, -OCH$_3$, -NO$_2$, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;

$R^h$ is -H, -Cl, -F, -CN, -OCH$_3$, -OCHF$_2$, -OCH$_2$F, -OCH$_3$, -NO$_2$, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;

$R^i$ is selected from the group consisting of: -H, -CH$_3$, and -C(2-3)alkyl; wherein said -CH$_3$ is optionally substituted with a member selected from the group consisting of: -OCH$_3$, -SCH$_3$, and -OCF$_3$; and wherein said -CH$_3$ is optionally substituted with up to three fluorine atoms; and wherein said -C(2-3)alkyl is optionally substituted with a member selected from the group consisting of: -OH, -OCH$_3$, -SCH$_3$, and -OCF$_3$; and wherein said -C(1-3)alkyl is optionally substituted with up to six fluorine atoms;

$R^5$ is -H, -C(1-3)alkyl, -F, or -Cl;

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention relate to compounds, pharmaceutical compositions containing them, methods of making and purifying them, methods of using them as inhibitors of DHODH enzymatic activity and methods for using them in the treatment of a subject suffering from or diagnosed with a disease, disorder, or medical condition such as autoimmune or inflammatory disorders, or diseases such as cancer.

Embodiments of this invention include a compound of Formula I

![Chemical Structure](image)

wherein

\[
\begin{align*}
R^1 & \text{ is } R^0, \\
R^a & \text{ is } -C_{(1-4)}\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C_{(1-4)}\text{alkyl is optionally substituted with up to three fluorine atoms;}
R^b & \text{ is } -\text{CH}_2\text{OH, } -C_{(1-2)}\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C_{(1-2)}\text{alkyl is optionally substituted with up to three fluorine atoms;}
R^c & \text{ is } -C_{(1-2)}\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C_{(1-2)}\text{alkyl is optionally substituted with up to three fluorine atoms;}
R^d & \text{ is } -C(\text{CH}_3)_2\text{OH, } -C(\text{CF}_3)_2\text{OH, } -\text{CH}_2\text{OH, or } -\text{CH}(\text{CH}_3)\text{OH;}
R^2 & \text{ is } -\text{CH}(\text{CH}_3)_2, \\
Q & \text{ is } O, \text{ or } N-R^e
\end{align*}
\]

wherein \(R^e\) is \(-\text{H}, -\text{CH}_3, \text{ or } -\text{CH}(\text{CH}_3)\);
\(R^3\) is \(-\text{O}-R^4, \text{ or } -\text{NH}-R^4\)
wherein $R^4$ is $-CH(CH_2OCH_3)_2$, $R^5$ is $-H$, $-Cl$, $-F$, $-CN$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-NO_2$, or $-C_{(1-2)}$alkyl; wherein said $C_{(1-2)}$alkyl is optionally substituted with up to three fluorine atoms;

$R^6$ is $-H$, $-Cl$, $-F$, $-CN$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-NO_2$, or $-C_{(1-2)}$alkyl; wherein said $C_{(1-2)}$alkyl is optionally substituted with up to three fluorine atoms;

$R^7$ is $-H$, $-Cl$, $-F$, $-CN$, $-OCH_3$, $-OCHF_2$, $-OCH_2F$, $-NO_2$, or $-C_{(1-2)}$alkyl; wherein said $C_{(1-2)}$alkyl is optionally substituted with up to three fluorine atoms;

$R^8$ is selected from the group consisting of: $-H$, $-CH_3$, and $-C_{(2-5)}$alkyl; wherein said $-CH_3$ is optionally substituted with a member selected from the group consisting of: $-OCH_3$, $-\text{SCH}_3$, and $-\text{OCF}_3$; and wherein said $-CH_3$ is optionally substituted with up to three fluorine atoms; and wherein said $-C_{(2-5)}$alkyl is optionally substituted with a member selected from the group consisting of: $-\text{OH}$, $-\text{OCH}_3$, $-\text{SCH}_3$, and $-\text{OCF}_3$; and wherein said $-C_{(1-5)}$alkyl is optionally substituted with up to six fluorine atoms;

$R^9$ is $-H$, $-C_{(1-5)}$alkyl, $-F$, or $-Cl$;

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or $N$-oxide thereof.

In another embodiment of the invention:

$R^1$ is $R^b$, $R^c$, $R^d$; wherein

$R^2$ is $-C_{(1-4)}$alkyl, or $-CH_2OCH_3$; wherein said $-C_{(1-4)}$alkyl is optionally substituted with up to three fluorine atoms;
R^b is -CH₂OH, -C_{1-2}alkyl, or -CH₂OCH₃; wherein said -C_{1-2}alkyl is optionally substituted with up to three fluorine atoms;
R^c is -C_{1-2}alkyl, or -CH₂OCH₃; wherein said -C_{1-2}alkyl is optionally substituted with up to three fluorine atoms;
R^d is -C(CH₃)₂OH, -C(CF₃)₂OH, -CH₂OH, or -CH(CH₃)OH;
R^2 is \begin{align*}
\text{CF}_3 & \quad \text{or} \\
\text{CF}_3 & \quad \text{or} \\
\text{CF}_3 & \quad \text{or} \\
\end{align*}
Q is O, or N-R^c
wherein R^c is -H, -CH₃, or -CH(CH₃);
R^3 is -O-R^t, or -NH-R^t
wherein R^t is -CH(CH₂OCH₃)₂,
R^f is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₃, -NO₂, or -C_{1-2}alkyl; wherein said -C_{1-2}alkyl is optionally substituted with up to three fluorine atoms;
R^g is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₃, -NO₂, or -C_{1-2}alkyl; wherein said -C_{1-2}alkyl is optionally substituted with up to three fluorine atoms;
R^h is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₃, -NO₂, or -C_{1-2}alkyl; wherein said -C_{1-2}alkyl is optionally substituted with up to three fluorine atoms;
R^5 is -H, -C_{1-3}alkyl, -F, or -Cl;
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

In another embodiment of the invention:

wherein
R\(^a\) is -C\(_{1-4}\)alkyl, or -CH\(_2\)OCH\(_3\); wherein said -C\(_{1-4}\)alkyl is optionally substituted with up to three fluorine atoms;

R\(^b\) is -CH\(_2\)OH, -C\(_{1-2}\)alkyl, or -CH\(_2\)OCH\(_3\); wherein said -C\(_{1-2}\)alkyl is optionally substituted with up to three fluorine atoms;

R\(^c\) is -C\(_{1-2}\)alkyl, or -CH\(_2\)OCH\(_3\); wherein said -C\(_{1-2}\)alkyl is optionally substituted with up to three fluorine atoms;

R\(^d\) is -C(CH\(_3\))\(_2\)OH, -C(CH\(_3\))\(_2\)O, -CH\(_2\)OH, or -CH(CH\(_3\))OH;

\[ R^2 \text{ is } \bigg\{ \begin{array}{l} \bigg\langle \begin{array}{c} \text{O} \text{ or } \text{N-R}^c \bigg\rangle \end{array} \end{array} \bigg\} \]

Q is O, or N-R\(^c\)

5 wherein R\(^e\) is -H, -CH\(_3\), -CH(CH\(_3\))\(_3\);

R\(^3\) is -O-R\(^4\), or -NH-R\(^4\)

\[ \bigg\langle \begin{array}{l} \text{R}^f \text{ is } \bigg\langle \begin{array}{c} \text{R}^g \text{ or } \text{R}^h \bigg\rangle \end{array} \end{array} \bigg\} \]

wherein R\(^3\) is -CH(CH\(_2\)OCH\(_3\))\(_2\),

R\(^f\) is -H, -Cl, -F, -CN, -OCH\(_3\), -OCHF\(_2\), -OCH\(_2\)F, -NO\(_2\), or -C\(_{1-2}\)alkyl; wherein said -C\(_{1-2}\)alkyl is optionally substituted with up to three fluorine atoms;

R\(^g\) is -H, -Cl, -F, -CN, -OCH\(_3\), -OCHF\(_2\), -OCH\(_2\)F, -NO\(_2\), or -C\(_{1-2}\)alkyl; wherein said -C\(_{1-2}\)alkyl is optionally substituted with up to three fluorine atoms;

R\(^h\) is -H, -Cl, -F, -CN, -OCH\(_3\), -OCHF\(_2\), -OCH\(_2\)F, -NO\(_2\), or -C\(_{1-2}\)alkyl; wherein said -C\(_{1-2}\)alkyl is optionally substituted with up to three fluorine atoms;

R\(^5\) is -H, -C\(_{1-3}\)alkyl, -F, or -Cl;

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

In another embodiment of the invention:

\[ \bigg\langle \begin{array}{l} \text{R}^1 \text{ is } \bigg\langle \begin{array}{c} \text{R}^b \text{ or } \text{R}^c \bigg\rangle \end{array} \end{array} \bigg\} \]

R\(^1\) is -R\(^b\), or -R\(^c\)
wherein

R\(^a\) is -C\(_\{1-4\}\)alkyl; wherein said -C\(_{\{1-4\}}\)alkyl is optionally substituted with up to three fluorine atoms;

R\(^b\) is -CH\(_2\)OH, -CH\(_3\), -CF\(_3\), -CHF\(_2\), or -CH\(_2\)F;

R\(^c\) is -CH\(_3\), -CF\(_3\), -CHF\(_2\), or -CH\(_2\)F;

R\(^d\) is -C(CH\(_3\))\(_2\)OH, -C(CF\(_3\))\(_2\)OH, or -CH(CH\(_3\))OH;

\[ \text{R}^2 \text{ is } \begin{array}{c} \text{CF}_3 \\
\text{O} \\
\text{CF}_3 \\
\end{array} \text{, or } \begin{array}{c} \text{CF}_3 \\
\text{O} \\
\text{CF}_3 \\
\end{array} \]

Q is O, or N-R\(^e\)

wherein R\(^e\) is -H, -CH\(_3\), or -CH(CH\(_3\))\(_2\);

R\(^3\) is -O-R\(^4\), or -NH-R\(^4\)

\[ \begin{array}{c} \text{R}^f \text{ is } \begin{array}{c} \text{R}^g \\
\text{R}^h \end{array} \\
\text{R}^i \\
\end{array} \text{, or } \begin{array}{c} \text{R}^f \text{ is } \begin{array}{c} \text{R}^g \\
\text{R}^h \end{array} \\
\text{R}^i \end{array} \] where R\(^f\) is -CH(CH\(_3\))OCH\(_3\), R\(^g\) is -CH\(_3\), -CF\(_3\), -CHF\(_2\), -OCH\(_3\), or -NO\(_2\);

R\(^h\) is -H, -Cl, -F, -CN, -CH\(_3\), -CHF\(_2\), -OCH\(_3\), or -NO\(_2\);

R\(^i\) is -H, -Cl, -F, -CN, -CH\(_3\), -CHF\(_2\), -OCH\(_3\), or -NO\(_2\);

R\(^5\) is -H, -CH\(_3\), -F, or -Cl;

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

In another embodiment of the invention:

\[ \begin{array}{c} \text{R}^a \text{ is } \begin{array}{c} \text{R}^b \\
\text{R}^c \\
\end{array} \\
\text{R}^d \\
\text{R}^e \end{array} \text{, or } \begin{array}{c} \text{R}^a \text{ is } \begin{array}{c} \text{R}^b \\
\text{R}^c \\
\end{array} \\
\text{R}^d \\
\text{R}^e \end{array} \] where R\(^a\) is -CH\(_2\)CH\(_3\);

R\(^b\) is -CH\(_2\)OH;

R\(^c\) is -CH\(_3\);
R^d is -C(CH_3)_2OH;

R^2 is \( \frac{1}{3} O\) CF_3, \( \frac{1}{3} O\) CF_3, or \( \frac{1}{3} O\) CF_3;

Q is O, or N-R^6

wherein R^6 is -H, -CH_3, or -CH(CH_3)_2

R^3 is -OCH(CH_2OCH_2)_2,

R^5 is -H, or -F, or -Cl;

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

In another embodiment of the invention:

R^1 is R^0, or R^d

wherein

R^a is -CH_2CH_2;
R^b is -CH_2OH;
R^c is -CH_3;
R^d is -C(CH_3)_2OH;
R² is \( \frac{\text{CF}_3}{\text{O}} \), \( \frac{\text{CF}_3}{\text{O}} \), or \( \frac{\text{CF}_3}{\text{O}} \);

Q is O, or N-R⁶

wherein R⁶ is -H, or -CH₃;

R³ is -OCH(CH₂OCH₃)₂,

\[ \text{N} \]
\[ \frac{\text{Cl}}{\text{NH}}, \frac{\text{F}}{\text{NH}}, \frac{\text{F}}{\text{NH}}, \frac{\text{F}}{\text{NH}}, \frac{\text{Cl}}{\text{NH}} \]

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

Another embodiment of the invention is a compound selected from the group consisting of:
and
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in art. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

The singular forms "a", "an" and "the" encompass plural references unless the context clearly indicates otherwise.

Unless qualified specifically in particular instances of use, the term “alkyl” refers to a straight- or branched-chain alkyl group having from 1 to 8 carbon atoms in the chain. Examples of alkyl groups include methyl (Me), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, iso hexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

The term C\(_{(n-m)}\) alkyl refers to an aliphatic chain, whether straight or branched, with a total number N of carbon members in the chain that satisfies \( n \leq N \leq m \), with \( m > n \). For example and without limitation, the term “C\(_{1-6}\)alkyl” refers to straight- or branched-chain alkyl group having from 1 to 6 carbon atoms in the chain. “C\(_{1-4}\)alkyl” refers to straight- or branched-chain alkyl group having from 1 to 4 carbon atoms in the chain.

With reference to substituents, the term “independently” refers to the situation where when more than one substituent is possible, the substituents may be the same or different from each other.
The term “substituted” means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system.

The term “variable point of attachment” means that a group is allowed to be attached at more than one alternative position in a structure. The attachment will always replace a hydrogen atom on one of the ring atoms. In other words, all permutations of bonding are represented by the single diagram, as shown in the illustrations below.

![Diagram](image)

Those skilled in the art will recognize that that if more than one such substituent is present for a given ring, the bonding of each substituent is independent of all of the others. The groups listed or illustrated above are not exhaustive.

As used herein, the term "or" means "and/or" unless stated otherwise.
As used herein, the terms "including", "containing" and “comprising” are used in their open, non-limiting sense.
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.
As used herein, the term “treat”, “treating”, or “treatment” of any disease, condition, syndrome or disorder refers, in one embodiment, to ameliorating the disease, condition, syndrome or disorder (i.e. slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment, “treat”, “treating”, or “treatment” refers to alleviating or ameliorating at least one physiological or biochemical parameter associated with or causative of the disease, condition, syndrome or disorder, including those which may not be discernible by the patient. In a further embodiment, “treat”, “treating”, or “treatment” refers to modulating the disease, condition, syndrome or disorder either physically (e.g. stabilization of a discernible symptom), physiologically, (e.g. stabilization of a physical parameter), or both. In yet another embodiment, “treat”, “treating”, or “treatment” refers to preventing or delaying the onset or development or progression of the disease, condition, syndrome or disorder.

The terms “subject” and “patient” are used interchangeably herein and may refer to an animal, preferably a mammal, most preferably a human.

As used herein, the terms active compound, pharmaceutical agent and active ingredient are used interchangeably to refer to a pharmaceutically active compound. Other ingredients in a drug composition, such as carriers, diluents or excipients, may be substantially or completely pharmaceutically inert. A pharmaceutical composition (also referred to herein as a composition or formulation) may comprise the active ingredient in combination with one or more carriers and/or one or more excipients and/or one or more diluents.

The term “therapeutically effective amount” (used interchangeably herein with “effective amount”) refers to an amount (e.g., of an active compound or pharmaceutical agent, such as a compound of the present invention), which elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, including reduction or inhibition of an enzyme or a protein activity, or ameliorating symptoms, alleviating conditions, slowing or delaying disease progression, or preventing a disease. Stated another way, the term therapeutically effective amount may refer to an amount that, when administered to a particular subject, achieves a therapeutic effect by inhibiting, alleviating or curing a disease, condition, syndrome or disorder in the subject or by prophylactically inhibiting, preventing or delaying the onset of a disease, condition, syndrome or disorder, or
symptom(s) thereof. A therapeutically effective amount may be an amount which relieves
to some extent one or more symptoms of a disease, condition, syndrome or disorder in a
subject; and/or returns to normal either partially or completely one or more physiological
or biochemical parameters associated with or causative of the disease, condition, syndrome
or disorder; and/or reduces the likelihood of the onset of the disease, condition, syndrome
or disorder, or symptom(s) thereof.
"Pharmaceutically acceptable" means that, which is useful in preparing a pharmaceutical
composition that is generally safe, non-toxic and neither biologically nor otherwise
undesirable and includes that which is acceptable for veterinary as well as human
pharmaceutical use.
A "pharmaceutically acceptable salt" is intended to mean a salt of an acid or base of a
compound represented by Formula (I) (as well as compounds of Formula (II) and others
described herein) that is non-toxic, biologically tolerable, or otherwise biologically suitable
for administration to the subject. See, generally, S.M. Berge, et al., "Pharmaceutical
Preferred pharmaceutically acceptable salts are those that are pharmacologically effective
and suitable for contact with the tissues of patients without undue toxicity, irritation, or
allergic response.
Non-limiting examples of pharmaceutically acceptable salts include sulfates, pyrosulfates,
bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates,
dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides,
acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates,
heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates,
maleates, butyene-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates,
methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates,
sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbuty rates, citrates,
lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates,
naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.
A compound of Formula (I) may possess a sufficiently acidic group, a sufficiently basic group, or both types of functional groups, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

Compounds of Formula (I) may contain at least one nitrogen of basic character, so desired pharmaceutically acceptable salts may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tarteric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, any compatible mixture of acids such as those given as examples herein, and any other acid and mixture thereof that are regarded as equivalents.

Compounds of Formula (I) may contain a carboxylic acid moiety, a desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide, alkaline earth metal hydroxide, any compatible mixture of bases such as those given as examples herein, and any other base and mixture thereof that are regarded as equivalents or acceptable substitutes in light of the ordinary level of skill in this technology. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, carbonates, bicarbonates, primary, secondary, and tertiary amines, and cyclic amines, such as benzylamines, pyrrolidines, piperidine, morpholine, piperazine, N-methyl-glucamine and tromethamine and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.
Each compound used herein may be discussed interchangeably with respect to its chemical formula, chemical name, abbreviation, etc. Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of such formula. The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Thus, any formula given herein is intended to represent a racemate, one or more of its enantiomeric forms, one or more of its diastereomeric forms, and mixtures thereof. Additionally, any formula given herein is intended to refer also to any one of hydrates, solvates, polymorphs and of such compounds, and mixtures thereof, even if such forms are not listed explicitly.

The term “R” at a stereocenter designates that the stereocenter is purely of the R-configuration as defined in the art; likewise, the term “S” means that the stereocenter is purely of the S-configuration. As used herein, the term “RS” refers to a stereocenter that exists as a mixture of the R- and S-configurations.

Compounds containing one stereocenter drawn without a stereo bond designation are a mixture of 2 enantiomers. Compounds containing 2 stereocenters both drawn without stereo bond designations are a mixture of 4 diastereomers. Compounds with 2 stereocenters both labeled “RS” and drawn with stereo bond designations are a 2-component mixture with relative stereochemistry as drawn. Unlabeled stereocenters drawn without stereo bond designations are a mixture of the R- and S-configurations. For unlabeled stereocenters drawn with stereo bond designations, the absolute stereochemistry is as depicted.

Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.
Reference to a compound herein stands for a reference to any one of: (a) the recited form of such compound, and (b) any of the forms of such compound in the medium in which the compound is being considered when named. For example, reference herein to a compound such as R-COOH, encompasses reference to any one of, for example, R-COOH(s), R-COOH(sol), and R-COO-(sol). In this example, R-COOH(s) refers to the solid compound, as it could be for example in a tablet or some other solid pharmaceutical composition or preparation; R-COOH(sol) refers to the undissociated form of the compound in a solvent; and R-COO-(sol) refers to the dissociated form of the compound in a solvent, such as the dissociated form of the compound in an aqueous environment, whether such dissociated form derives from R-COOH, from a salt thereof, or from any other entity that yields R-COO- upon dissociation in the medium being considered. In another example, an expression such as “exposing an entity to compound of formula R-COOH” refers to the exposure of such entity to the form, or forms, of the compound R-COOH that exists, or exist, in the medium in which such exposure takes place. In still another example, an expression such as “reacting an entity with a compound of formula R-COOH” refers to the reacting of (a) such entity in the chemically relevant form, or forms, of such entity that exists, or exist, in the medium in which such reacting takes place, with (b) the chemically relevant form, or forms, of the compound R-COOH that exists, or exist, in the medium in which such reacting takes place. In this regard, if such entity is for example in an aqueous environment, it is understood that the compound R-COOH is in such same medium, and therefore the entity is being exposed to species such as R-COOH(aq) and/or R-COO-(aq), where the subscript “(aq)” stands for “aqueous” according to its conventional meaning in chemistry and biochemistry. A carboxylic acid functional group has been chosen in these nomenclature examples; this choice is not intended, however, as a limitation but it is merely an illustration. It is understood that analogous examples can be provided in terms of other functional groups, including but not limited to hydroxyl, basic nitrogen members, such as those in amines, and any other group that interacts or transforms according to known manners in the medium that contains the compound. Such interactions and transformations include, but are not limited to, dissociation, association, tautomerism, solvolysis, including hydrolysis, solvation, including hydration, protonation, and deprotonation. No further examples in this regard are provided herein because these
interactions and transformations in a given medium are known by any one of ordinary skill in the art.

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number in an enriched form. Examples of isotopes that can be incorporated into compounds of the invention in a form that exceeds natural abundances include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as $^2$H (or chemical symbol D), $^3$H (or chemical symbol T), $^{11}$C, $^{13}$C, $^{14}$C, $^{15}$N, $^{18}$O, $^{17}$O, $^{31}$P, $^{32}$P, $^{35}$S, $^{18}$F, $^{36}$Cl, and $^{125}$I, respectively. Such isotopically labelled compounds are useful in metabolic studies (preferably with $^{14}$C), reaction kinetic studies (with, for example $^2$H or $^3$H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an $^{18}$F or $^{11}$C labeled compound may be particularly preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$H, or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased \textit{in vivo} half-life or reduced dosage requirements. Isotopically labeled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

When the same plurality of substituents is assigned to various groups, the specific individual substituent assignment to each of such groups is meant to be independently made with respect to the specific individual substituent assignments to the remaining groups. By way of illustration, but not as a limitation, if each of groups Q and R can be H or F, the choice of H or F for Q is made independently of the choice of H or F for R, so the choice of assignment for Q does not determine or condition the choice of assignment for R, or vice-versa, unless it is expressly indicated otherwise. Illustrative claim recitation in this regard would read as “each of Q and R is independently H or F”, or “each of Q and R is independently selected from the group consisting of H and F”.

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In another example, a zwitterionic compound would be encompassed herein by referring to a compound that is known to form a zwitterion, even if it is not explicitly named in its zwitterionic form. Terms such as zwitterion, zwitterions, and their synonyms zwitterionic compound(s) are standard IUPAC-endorsed names that are well known and part of standard sets of defined scientific names. In this regard, the name zwitterion is assigned the name identification CHEBI:27369 by the Chemical Entities of Biological Interest (ChEBI) dictionary of molecular entities. As generally well known, a zwitterion or zwitterionic compound is a neutral compound that has formal unit charges of opposite sign. Sometimes these compounds are referred to by the term “inner salts”. Other sources refer to these compounds as “dipolar ions”, although the latter term is regarded by still other sources as a misnomer. As a specific example, aminoethanoic acid (the amino acid glycine) has the formula $\text{H}_2\text{NCH}_2\text{COOH}$, and it exists in some media (in this case in neutral media) in the form of the zwitterion $^{+}\text{H}_2\text{NCH}_2\text{COO}^-$. Zwitterions, zwitterionic compounds, inner salts and dipolar ions in the known and well-established meanings of these terms are within the scope of this invention, as would in any case be so appreciated by those of ordinary skill in the art. Because there is no need to name each and every embodiment that would be recognized by those of ordinary skill in the art, no structures of the zwitterionic compounds that are associated with the compounds of this invention are given explicitly herein. They are, however, part of the embodiments of this invention. No further examples in this regard are provided herein because the interactions and transformations in a given medium that lead to the various forms of a given compound are known by any one of ordinary skill in the art.

When referring to any formula given herein, the selection of a particular moiety from a list of possible species for a specified variable is not intended to define the same choice of the species for the variable appearing elsewhere. In other words, where a variable appears more than once, the choice of the species from a specified list is independent of the choice of the species for the same variable elsewhere in the formula, unless stated otherwise.
By way of a first example on substituent terminology, if substituent $S^1_{\text{example}}$ is one of $S_1$ and $S_2$, and substituent $S^2_{\text{example}}$ is one of $S_3$ and $S_4$, then these assignments refer to embodiments of this invention given according to the choices $S^1_{\text{example}}$ is $S_1$ and $S^2_{\text{example}}$ is $S_3$; $S^1_{\text{example}}$ is $S_1$ and $S^2_{\text{example}}$ is $S_4$; $S^1_{\text{example}}$ is $S_2$ and $S^2_{\text{example}}$ is $S_3$; $S^1_{\text{example}}$ is $S_2$ and $S^2_{\text{example}}$ is $S_4$; and equivalents of each one of such choices. The shorter terminology “$S^1_{\text{example}}$ is one of $S_1$ and $S_2$, and $S^2_{\text{example}}$ is one of $S_3$ and $S_4$” is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing first example on substituent terminology, which is stated in generic terms, is meant to illustrate the various substituent assignments described herein.

Furthermore, when more than one assignment is given for any member or substituent, embodiments of this invention comprise the various groupings that can be made from the listed assignments, taken independently, and equivalents thereof. By way of a second example on substituent terminology, if it is herein described that substituent $S_{\text{example}}$ is one of $S_1$, $S_2$, and $S_3$, this listing refers to embodiments of this invention for which $S_{\text{example}}$ is $S_1$; $S_{\text{example}}$ is $S_2$; $S_{\text{example}}$ is $S_3$; $S_{\text{example}}$ is one of $S_1$ and $S_2$; $S_{\text{example}}$ is one of $S_1$ and $S_3$; $S_{\text{example}}$ is one of $S_2$ and $S_3$; $S_{\text{example}}$ is one of $S_1$, $S_2$ and $S_3$; and $S_{\text{example}}$ is any equivalent of each one of these choices. The shorter terminology “$S_{\text{example}}$ is one of $S_1$, $S_2$, and $S_3$” is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing second example on substituent terminology, which is stated in generic terms, is meant to illustrate the various substituent assignments described herein.

Disclosed herein are embodiments including a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition comprising inhibiting or altering dihydroorotate oxygenase enzyme activity in the subject by administering to the subject an effective amount of at least one compound according to any of the embodiments described herein, such as compounds of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
Disclosed herein are embodiments including a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition comprising inhibiting or altering dihydroorotate oxygenase enzyme activity in the subject by administering to the subject an effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof, wherein the disorder, disease or medical condition is selected from the group consisting of: inflammatory disorders and autoimmune disorders.

Disclosed herein are embodiments including a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition comprising inhibiting or altering dihydroorotate oxygenase enzyme activity in the subject by administering to the subject an effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof, wherein the disorder, disease or medical condition is cancer.

Disclosed herein are embodiments including a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition comprising inhibiting or altering dihydroorotate oxygenase enzyme activity in the subject by administering to the subject an effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof, wherein the disorder, disease or medical condition is selected from the group consisting of: lymphomas, leukemias, carcinomas, and sarcomas.

Disclosed herein are embodiments including a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition comprising inhibiting or altering dihydroorotate oxygenase enzyme activity in the subject by administering to the subject an effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof, wherein the disorder, disease or medical condition is selected from the group consisting of: acute lymphoblastic leukemia, acute myeloid leukemia, (acute) T-cell leukemia, acute lymphoblastic leukemia, acute lymphocytic leukemia, acute monocytic leukemia, acute
promyelocytic leukemia, biphenotypic B myelomonocytic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, large granular lymphocytic leukemia, plasma cell leukemia, and also myelodysplastic syndrome, which can develop into an acute myeloid leukemia.

5 Disclosed herein are embodiments including a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition comprising inhibiting or altering dihydroorotate oxygenase enzyme activity in the subject by administering to the subject an effective amount of at least one compound of Formula I, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof, wherein the disorder, disease or medical condition is acute myeloid leukemia.

Also within the scope of the invention are enantiomers and diastereomers of the compounds of Formula (I). Also within the scope of the invention are the pharmaceutically acceptable salts, N-oxides or solvates of the compounds of Formula (I). Also within the scope of the invention are the pharmaceutically acceptable prodrugs of compounds of Formula (I), and pharmaceutically active metabolites of the compounds of Formula (I). Also within the scope of the invention are isotopic variations of compounds of Formula (I), such as, e.g., deuterated compounds of Formula (I). Also within the scope of the invention are the pharmaceutically acceptable salts, N-oxides or solvates of the isotopic variations of the compounds of Formula (I). Also within the scope of the invention are the pharmaceutically acceptable prodrugs of the isotopic variations of the compounds of Formula (I), and pharmaceutically active metabolites of the isotopic variations of the compounds of Formula (I).

25 Even though the compounds of embodiments of the present invention (including their pharmaceutically acceptable salts and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient and/or a pharmaceutically acceptable diluent selected with regard to the intended route of administration and standard pharmaceutical or veterinary practice.
Thus, particular embodiments of the present invention are directed to pharmaceutical and veterinary compositions comprising compounds of Formula (I) and at least one pharmaceutically acceptable carrier, pharmaceutically acceptable excipient, and/or pharmaceutically acceptable diluent. By way of example, in the pharmaceutical compositions of embodiments of the present invention, the compounds of Formula (I) may be admixed with any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilizing agent(s), and combinations thereof.

An embodiment of the invention relates to a pharmaceutical composition comprising an effective amount of at least one compound selected from compounds of Formula (I), and pharmaceutically acceptable salts, isotopes, N-oxides, solvates, and stereoisomers thereof, in accordance with any embodiment described herein; and at least one pharmaceutically acceptable excipient.

Another embodiment of the invention is a pharmaceutical composition comprising an effective amount of at least one compound selected from compounds of Formula (I).

An additional embodiment of the invention is a pharmaceutical composition comprising an effective amount of a compound of Formula I (e.g., a compound selected from Examples 1-21), or a pharmaceutically acceptable salt, isotope, N-oxide, solvate, or stereoisomer of the compound of Formula I, a pharmaceutically acceptable prodrug of the compound of Formula I, or a pharmaceutically active metabolite of the compound of Formula I, and at least one pharmaceutically acceptable excipient.

Solid oral dosage forms such as, tablets or capsules, containing one or more compounds of the present invention may be administered in at least one dosage form at a time, as appropriate. It is also possible to administer the compounds in sustained release formulations.

Additional oral forms in which the present inventive compounds may be administered include elixirs, solutions, syrups, and suspensions; each optionally containing flavoring agents and coloring agents.

Alternatively, one or more compounds of Formula I can be administered by inhalation (intratracheal or intranasal) or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting
powder. For example, they can be incorporated into a cream comprising, consisting of, and/or consisting essentially of an aqueous emulsion of polyethylene glycols or liquid paraffin. They can also be incorporated, at a concentration of between about 1% and about 10% by weight of the cream, into an ointment comprising, consisting of, and/or consisting essentially of a wax or soft paraffin base together with any stabilizers and preservatives as may be required. An alternative means of administration includes transdermal administration by using a skin or transdermal patch.

The pharmaceutical compositions of the present invention (as well as the compounds of the present invention alone) can also be injected parenterally, for example, intracavernosally, intravenously, intramuscularly, subcutaneously, intradermally, or intrathecally. In this case, the compositions will also include at least one of a suitable carrier, a suitable excipient, and a suitable diluent.

For parenteral administration, the pharmaceutical compositions of the present invention are best used in the form of a sterile aqueous solution that may contain other substances, for example, enough salts and monosaccharides to make the solution isotonic with blood.

For buccal or sublingual administration, the pharmaceutical compositions of the present invention may be administered in the form of tablets or lozenges, which can be formulated in a conventional manner.

By way of further example, pharmaceutical compositions containing at least one of the compounds of Formula 1 as the active ingredient can be prepared by mixing the compound(s) with a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, and/or a pharmaceutically acceptable excipient according to conventional pharmaceutical compounding techniques. The carrier, excipient, and diluent may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral, etc.). Thus, for liquid oral preparations such as, suspensions, syrups, elixirs and solutions, suitable carriers, excipients and diluents include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations such as, powders, capsules, and tablets, suitable carriers, excipients and diluents include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations also may be optionally coated.
with substances such as, sugars, or be enterically coated so as to modulate the major site of absorption and disintegration. For parenteral administration, the carrier, excipient and diluent will usually include sterile water, and other ingredients may be added to increase solubility and preservation of the composition. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives such as, solubilizers and preservatives.

According to particular embodiments, a therapeutically effective amount of a compound of Formula I or a pharmaceutical composition thereof may comprise a dose range from about 0.1 mg to about 3000 mg, or any particular amount or range therein, in particular from about 1 mg to about 1000 mg, or any particular amount or range therein, of active ingredient in a regimen of about 1 to about (4x) per day for an average (70 kg) human; although, it is apparent to one skilled in the art that the therapeutically effective amount for a compound of Formula I will vary as will the diseases, syndromes, conditions, and disorders being treated.

An embodiment of the present invention is directed to a pharmaceutical composition for oral administration, comprising a compound of Formula I in an amount of from about 1 mg to about 500 mg.

Advantageously, a compound of Formula I may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three and (4x) daily.

Optimal dosages of a compound of Formula I to be administered may be readily determined and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease, syndrome, condition or disorder. In addition, factors associated with the particular subject being treated, including subject gender, age, weight, diet and time of administration, will result in the need to adjust the dose to achieve an appropriate therapeutic level and desired therapeutic effect. The above dosages are thus exemplary of the average case. There can be, of course, individual instances wherein higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of Formula I may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever use of a compound of Formula I is administered.
to a subject in need thereof.

According to particular embodiments, one or more compounds of Formula I are useful in methods for treating, ameliorating and / or preventing a disease, a syndrome, a condition or a disorder that is affected by the inhibition of DHODH enzymatic activity.

An additional embodiment of the invention relates to the use of compounds of Formula I, e.g., by inhibiting dihydroorotate oxygenase enzyme activity, in treating disorders like inflammatory disorders, autoimmune disorders, or cancer.

In a further aspect the present invention provides a method for inhibiting or altering Dihydroorotate Dehydrogenase (DHODH) enzymatic activity, the method comprising contacting DHODH with any compound of Formula I, aspect or embodiment disclosed herein, thereby inhibiting or otherwise altering DHODH enzymatic activity.

An additional embodiment of the present invention provides methods for treating diseases, disorders, or medical conditions mediated or otherwise affected by dihydroorotate dehydrogenase (DHODH) enzyme activity comprising administering a compound of Formula I to a subject in need thereof.

As used herein, the term "DHODH inhibitor" may refer to an agent that inhibits or reduces DHODH activity.

In one embodiment, the term “therapeutically effective amount” (or “effective amount”) refers to the amount of a compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent, and/ or ameliorate a condition, or a disorder or a disease (i) mediated by DHODH enzymatic activity; or (ii) associated with DHODH enzymatic activity; or (iii) characterized by activity (normal or abnormal) of DHODH enzyme; or (2) reduce or inhibit the activity of DHODH enzyme; or (3) reduce or inhibit the expression of DHODH, or (4) modify the protein levels of DHODH. Without being bound by a particular theory, DHODH inhibitors are believed to act by inhibiting nucleic acid synthesis, cell cycle arrest or altering post-translational glycosylation of proteins involved in regulating myeloid differentiation within progenitor tumor cells.
An additional embodiment of the invention is a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated or otherwise affected by DHODH enzymatic activity, comprising administering to a subject in need of such treatment an effective amount of at least one compound selected from: compounds of Formula I, enantiomers and diastereomers of the compounds of Formula I, isotopic variations of the compounds of Formula I, and pharmaceutically acceptable salts of all of the foregoing. Stated another way, according to an embodiment, a method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition, such as cancer, comprises administering to the subject an effective amount of at least one compound selected from: compounds of Formula I, and pharmaceutically acceptable salts of all the foregoing (e.g., by inhibiting or otherwise altering dihydroorotate oxygenase enzyme activity in the subject).

In another embodiment, inhibitors of DHODH of the present invention may be used for the treatment of immunological diseases including, but not limited to, autoimmune and inflammatory disorders, e.g. arthritis, inflammatory bowel disease, gastritis, ankylosing spondylitis, ulcerative colitis, pancreatitis, Crohn’s disease, celiac disease, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, gout, organ or transplant rejection, chronic allograft rejection, acute or chronic graft-versus-host disease, dermatitis including atopic, dermatomyositis, psoriasis, Behcet’s diseases, uveitis, myasthenia gravis, Grave’s disease, Hashimoto thyroiditis, Sjogren’s syndrome, blistering disorders, antibody-mediated vasculitis syndromes, immune-complex vasculitides, allergic disorders, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, pulmonary diseases including edema, embolism, fibrosis, sarcoidosis, hypertension and emphysema, silicosis, respiratory failure, acute respiratory distress syndrome, BENTA disease, berylliosis, and polymyositis.

As used herein, unless otherwise noted, the term “affect” or “affected” (when referring to a disease, disorder, or medical condition that is affected by the inhibition or alteration of DHODH enzymatic activity) includes a reduction in the frequency and/or severity of one or more symptoms or manifestations of said disease, syndrome, condition or disorder; and/or includes the prevention of the development of one or more symptoms or manifestations of said disease, syndrome, condition or disorder or the development of the disease.
condition, syndrome or disorder.

An additional embodiment of the invention provides a method of treatment of cancer comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, isotope, N-oxide, solvate, or stereoisomer thereof.

According to an embodiment, the cancer is selected from but not limited to, lymphomas, leukemias, carcinomas, and sarcomas.

An additional embodiment of the invention provides the use of a compound of Formula I, or a pharmaceutically acceptable salt, isotope, N-oxide, solvate, or stereoisomer thereof, for the treatment of one or more cancer types.

According to particular embodiments, the uses and methods of treatment described herein are directed to the treatment of cancer, wherein the cancer is selected from but not limited to:

leukemias including but not limited to acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), (acute) T-cell leukemia, acute monocyctic leukemia, acute promyelocytic leukemia (APL), biphenotypic B myelomonocytic leukemia, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), large granular lymphocytic leukemia, plasma cell leukemia, and also myelodysplastic syndrome (MDS), which can develop into an acute myeloid leukemia,

lymphomas including but not limited to AIDS-related lymphoma, Hodgkin lymphoma, non-Hodgkin's lymphoma (NHL), T-non-Hodgkin lymphoma (T-NHL), subtypes of NHL such as Diffuse Large Cell Lymphoma (DLBCL), activated B-cell DLBCL, germinal center B-cell DLBCL, double-hit lymphoma and double-expressor lymphoma; anaplastic large cell lymphoma, marginal B cell lymphoma and primary mediastinal B-cell lymphoma, immunoblastic large cell lymphoma, Burkitt lymphoma, follicular lymphoma, hairy cell leukemia, Hodgkin's disease, mantle cell lymphoma (MCL), lymphoplasmatic lymphoma, precursor B -lymphoblastic lymphoma, lymphoma of the central nervous system, small lymphocytic lymphoma (SLL) and chronic lymphocytic leukemia (CLL); T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma,
subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma sarcomas including but not limited to sarcoma of the soft tissue, gliosarcoma, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma; and other cancers, such as solid tumors, including but not limited to breast cancer, colorectal carcinoma, gastric cancer, gliosarcoma, head & neck cancer, hepatocellular carcinoma, lung cancer, multiple myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma and sarcoma.

In an embodiment, cancers that may benefit from a treatment with inhibitors of DHODH of the present invention include, but are not limited to, lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin’s lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), marginal zone lymphoma, T-cell lymphoma, Hodgkin’s lymphoma, Burkitt’s lymphoma, multiple myeloma, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head & neck cancer, testicular cancer, Ewing’s sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor).

In another embodiment of the present invention, the compounds of the present invention may be employed in combination with one or more other medicinal agents, more particularly with one or more anti-cancer agents, e.g. chemotherapeutic, anti-proliferative or immunomodulating agents, or with adjuvants in cancer therapy, e.g. immunosuppressive or anti-inflammatory agents. Additional non-limiting examples of anti-cancer agents that may be administered in combination with a compound of the present invention include biologic compounds, such as monoclonal antibodies (e.g., that mediate effector function upon binding to cancer cell-associated antigens, or block interaction of a receptor expressed on cancer cells with a soluble or cell bound ligand), bispecific antibodies that
mediate immune cell redirection, etc. According to an embodiment, a method of treating cancer comprises administering an effective amount of a compound of the present invention (e.g., selected from the compounds described in Examples 1-21, pharmaceutically acceptable salts, isotopes, N-oxides, solvates, and stereoisomers thereof) and an effective amount of one or more additional anti-cancer agents, wherein the method comprises administering the compound of the present invention and the additional anti-cancer agent(s) either simultaneously (e.g., as part of the same pharmaceutical composition) or sequentially. According to an embodiment, a pharmaceutical composition comprises an effective amount of a compound of the present invention (e.g., selected from the compounds described in Examples 1-21, pharmaceutically acceptable salts, isotopes, N-oxides, solvates, and stereoisomers thereof), an effective amount of one or more additional anti-cancer agents, and optionally one or more excipients.

An additional embodiment of the invention provides the use of a compound of Formula I, or pharmaceutically acceptable salts, isotopes, N-oxides, solvates, or stereoisomers thereof, as part of chemotherapeutic regimens for the treatment of cancers, lymphomas and leukemias alone or in combination with classic antitumoral compounds well known by the one skilled in the art.

GENERAL SYNTHETIC METHODS

Exemplary compounds useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula I. Reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Reactions may be heated employing conventional heating or microwave heating.
Reactions may also be conducted in sealed pressure vessels above the normal reflux temperature of the solvent.

**ABBREVIATIONS**

Abbreviations used in the instant specification, particularly the schemes and examples, are as follows:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>acac</td>
<td>acetyl acetonate</td>
</tr>
<tr>
<td>ACN or MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′-bis(diphenylphosphino)-1,1′-binaphthalene</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>potassium tert-butoxide</td>
</tr>
<tr>
<td>calc.</td>
<td>calculated</td>
</tr>
<tr>
<td>CPhos</td>
<td>(2-dicyclohexylphosphino-2′,6′-bis(N,N-dimethylamino)biphenyl)</td>
</tr>
<tr>
<td>DAST</td>
<td>diethylamino sulfur trifluoride</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DIEA, DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dpdpf</td>
<td>1,1′-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>EDCI</td>
<td>N-ethyl-N′-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethyl alcohol</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>h or hr(s)</td>
<td>hour or hours</td>
</tr>
<tr>
<td>HATU</td>
<td>N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-(b)]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide</td>
</tr>
</tbody>
</table>
HPLC  high performance liquid chromatography
Me  methyl
MeOH  methanol
MHz  megahertz
5 min  minute or minutes
MS  mass spectrometry
NMR  nuclear magnetic resonance
OAc  acetate
Ph  phenyl
10 PyBrop  bromotripyrrolidinophosphonium
hexafluorophosphate
RP  reverse-phase
rt or RT  room temperature
TEA  triethylamine
15 TFAA  trifluoroacetic anhydride
TFA  trifluoroacetic acid
THF  tetrahydrofuran
Xantphos  (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)
XPhos Pd G3  (2-Dicyclohexylphosphino-2′,4′,6′-triisopropyl-
20 1,1′-biphenyl)[2-(2′-amino-1,1′-
biphenyl)]palladium(II) methanesulfonate

GENERAL SCHEMES

The following schemes and examples are for illustrative purposes only and are in no way meant to be a limitation of the invention.

Exemplary compounds useful in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples to follow.
According to SCHEME 1, commercially available aldehyde of Formula (II) where R^5 is F is treated with a suitable hydroxylamine source such as hydroxylamine-o-sulfonic acid, hydroxylamine HCl salt, and the like; in a solvent such as water, and the like; at temperatures ranging from 80 °C to about 120 °C, for example at about 105 °C, to provide an oxime of Formula (III).

A compound of Formula (III) is reacted with an acylating agent such as trifluoroacetic anhydride (TFAA), and the like; in a suitable solvent such as DCM, THF, ether and the like; at temperatures ranging from 0 °C to about 30 °C; in a suitable base such as TEA, DIPEA, and the like; to afford a nitrile of Formula (IV).

A compound of Formula (IV) is reacted with a commercially available hydrazine source such as compounds of Formula (V) NH_2NHR^e, such as hydrazine, methyl hydrazine, and the like; in a suitable solvent such as isopropanol, n-butanol, and the like; at temperatures ranging from 80 °C to about 120 °C; to afford amine indazole compound
of Formula (VI).

A compound of Formula (VI) is reacted with a commercially available or synthetically accessible alcohol of Formula R²H (VII), in the presence of a suitable base such as NaH, and the like; in an aprotic solvent such as DMF, and the like; at temperatures ranging from 0 °C to 100 °C, preferably 30 °C; to provide a compound of Formula (VIII).

A compound of Formula (VIII) is reacted with an commercially available compound of Formula R⁴I (IX) under Buchwald-Hartwig amination conditions, in the presence of a suitable catalyst such as Pd(Ph₃P)₄, Pd₂(dba)₃, PdCl₂(Ph₃P)₂, and the like; with a suitable base such a K₃PO₄, Cs₂CO₃, t-BuOK and the like; with a suitable ligand such as Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), CPhos (2-dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)triphenyl), BINAP and the like; in a suitable solvent such as dioxane, DMF, DMSO, and the like; at temperatures ranging from 60 °C to about 120 °C; to provide a compound of Formula compound (XI).

Alternatively, a compound of Formula (VIII) is reacted with an commercially available compound of Formula R⁴B(OH)₂ (X) under Chan-Lam coupling conditions, in the presence of a suitable catalyst such as CuO, CuSO₄, Cu(OAc)₂ and the like; in a suitable solvent such as MeOH, EtOH, and the like; under air or oxygen; at temperatures ranging from 25 °C to about 80 °C; to provide a compound of Formula compound (XI).

A compound of Formula compound (XI) is reacted with a compound of Formula (XII) prepared by the procedure described in PCT Int. Appl. WO 2018077923 A1 under Ullman N-arylation conditions, with a suitable catalyst such as Cul, Cu(acac)₂, CuO, and the like; a suitable base such a K₃PO₄, Cs₂CO₃, t-BuOK and the like; with or without a suitable ligand such as picolinic acid, trans-N,N-dimethylcyclohexane-1,2-diamine, dimethylglycine and the like; in a suitable solvent such as dioxane, DMF, DMSO, and the like; at temperatures ranging from 80 °C to about 120 °C; to provide a compound of Formula (Ia).
According to SCHEME 2, commercially available tert-butyl 4-bromo-2,6-difluorobenzoate is reacted with a commercially available or synthetically accessible alcohol of Formula R²H (VII), in the presence of a suitable base such as NaH, and the like; in an aprotic solvent such as DMF, and the like; at temperatures ranging from 0 °C to 100 °C, preferably 30 °C; to provide a compound of Formula (XIII).

A compound of Formula (XIII) is de-protected under an acidic solvent such as TFA, HCl in dioxane, and the like; at temperatures ranging from 25 °C to about 80 °C; to provide a compound of Formula (XIV).

A compound of Formula (XIV) was coupled with a commercially available hydrazine source of Formula NH₂NR² (XV) with a suitable coupling agent such as HATU, PyBrop, EDCI, and the like; in a suitable base such a TEA, DIPEA and the like; in a suitable solvent such as dioxane, DMF, DCM, and the like; at temperatures ranging from
0 °C to about 50 °C; to provide a compound of Formula (XVI).

A compound of Formula (XVI) is de-protected under an acidic solvent such as TFA, HCl in dioxane, and the like; at temperatures ranging from 25 °C to about 80 °C; to provide a compound of Formula (XVII).

A compound of Formula (XVII) is treated with a suitable base such a NaH, t-BuOK and the like; in a suitable solvent such as dioxane, DMF, THF, and the like; at temperatures ranging from 25 °C to about 80 °C; to provide a compound of Formula (XVIII).

A compound of Formula compound (XVIII) is reacted with a compound of Formula (XII) prepared by the procedure described in PCT Int. Appl. WO 2018077923 A1 under Ullman N-arylation conditions; with a suitable catalyst such as Cul, Cu(acac)₂, CuO, and the like; a suitable base such a K₃PO₄, Cs₂CO₃, t-BuOK and the like; with or without a suitable ligand such as picolinic acid, trans-N,N-dimethylcyclohexane-1,2-diamine, dimethylglycine and the like; in a suitable solvent such as dioxane, DMF, DMSO, and the like; at temperatures ranging from 80 °C to about 120 °C; to provide a compound of Formula (XIX).

A compound of Formula (XIX) is coupled with a commercially available compound of Formula R¹X (where X is F or Cl or Br) (XX) with a suitable base such a K₂CO₃, Cs₂CO₃ and the like; in a suitable solvent such as dioxane, DMF, DMSO, and the like; at temperatures ranging from 25 °C to about 100 °C; to provide a compound of Formula (Ib).
According to SCHEME 3, commercially available 4-bromo-2,6-difluorobenzonitrile is reacted with a commercially available or synthetically accessible alcohol of Formula $R^2H$ (VII), in the presence of a suitable base such as NaH, and the like; in an aprotic solvent such as DMF, and the like; at temperatures ranging from 0 °C to 100 °C, preferably 30 °C; to provide a compound of Formula (XI).

A compound of Formula (XI) is reacted with a commercially available compound propan-2-one oxime, in the presence of a suitable base such as t-BuOK, NaH, and the like; in an aprotic solvent such as THF, DMF, and the like; at temperatures ranging from 25 °C to 100 °C, preferably 60 °C; to provide a compound of Formula (XII).

A compound of Formula (XII) is de-protected followed by cyclization in the presence of a suitable acid such as HCl, TFA, and the like; in a suitable solvent such as THF, MeOH and the like; at temperatures ranging from 25 °C to 80 °C, preferably 60 °C; to provide a compound of Formula (XXIII).

A compound of Formula (XXIII) is reacted with an commercially available compound of Formula $R^4I$ (IX) under Buchwald-Hartwig amination conditions, in the presence of a suitable catalyst such as Pd(Ph$_3$P)$_4$, Pd$_2$(dba)$_3$, PdCl$_2$(Ph$_3$P)$_2$, and the like; with a suitable base such as K$_3$PO$_4$, Cs$_2$CO$_3$, t-BuOK and the like; with a suitable ligand such as Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), Cphos (2-
dicyclohexylphosphino-2',6'-bis(N,N-dimethylamino)biphenyl), BINAP and the like; in a suitable solvent such as dioxane, DMF, DMSO, and the like; at temperatures ranging from 60 °C to about 120 °C; to provide a compound of Formula compound (XXIV).

Alternatively, a compound of Formula (XXIII) is reacted with an commercially available compound of Formula R^4B(OH)₂ (X) under Chan-Lam coupling conditions, in the presence of a suitable catalyst such as CuO, CuSO₄, Cu(Oac)₂ and the like; in a suitable solvent such as MeOH, EtOH, and the like; under air or oxygen; at temperatures ranging from 25 °C to about 80 °C; to provide a compound of Formula (XXIV).

A compound of Formula (XXIV) is reacted with a compound of Formula (XII) prepared by the procedure described in PCT Int. Appl. WO 2018077923 A1 20180503 under Ullman N-arylation conditions; with a suitable catalyst such as CuI, Cu(acac)₂, CuO, and the like; a suitable base such a K₂PO₄, Cs₂CO₃, t-BuOK and the like; with or without a suitable ligand such as picolinic acid, trans- N,N-dimethylcyclohexane-1,2-diamine, dimethylglycine and the like; in a suitable solvent such as dioxane, DMF, DMSO, and the like; at temperatures ranging from 80 °C to about 120 °C; to provide a compound of Formula (Ic).

According to SCHEME 4, a compound of Formula (XI), is reacted with boron source such as bis(pinacolato)diborane, and the like; with a suitable catalyst such as Pd₂(dba)₃, Pd(Oac)₂, and the like; a suitable base such a NaOAc, Na₂CO₃ and the like; in a suitable solvent such as THF, dioxane, DMF and the like; at temperatures ranging from 80 °C to about 120 °C; to provide a compound of Formula (XXIV).

A compound of Formula (XXIV) is coupled with a compound of Formula (XXV)
under Suzuki coupling conditions; with a catalyst such as Pd(Ph₃P)₄, PdCl₂(Ph₃P)₂, Pd G₃, and the like; with a ligand such as dppf, Xphos, and the like; with an inorganic base such as KOAc, Na₂CO₃, and the like; in an organic solvent such as dioxane, water and the like; at temperatures ranging from 80 °C to about 120 °C; to afford a compound of Formula (Id).

Deprotection of protecting group is achieved according to procedures known to one skilled in the art and employing established methodologies, such as those described in T. W. Greene and P. G. M. Wuts, “Protective Groups in Organic Synthesis,” 3 ed., John Wiley & Sons, 1999. For example, when protecting group is benzyl, deprotection is achieved employing Pd/C; under an H₂; in a suitable solvent such as EtOH, MeOH, ethyl acetate, or a mixture thereof, preferably EtOH; with or without the presence HCl, preferably 0.75 equivalent for 4 to 72 hours, to provide a compound of Formula (I). Additionally, when protecting group is benzyl, deprotection can be employed using trifluoroacetic acid as solvent. Alternatively, it is deprotected employing conditions known to one skilled in the art, preferably with BCl₃ in a suitable solvent such as DCM, THF, and the like; at a temperature ranging from -78 °C to 0 °C to afford a compound of Formula (I).

EXAMPLES

In obtaining the compounds described in the examples below and the corresponding analytical data, the following experimental and analytical protocols were followed unless otherwise indicated.

Unless otherwise stated, reaction mixtures were magnetically stirred at room temperature (rt) under a nitrogen atmosphere. Where solutions were “dried,” they were generally dried over a drying agent such as Na₂SO₄ or MgSO₄. Where mixtures, solutions, and extracts were “concentrated”, they were typically concentrated on a rotary evaporator under reduced pressure.

Normal-phase silica gel chromatography (FCC) was performed on silica gel (SiO₃) using prepacked cartridges.

Preparative reverse-phase high performance liquid chromatography (RP HPLC) was performed on either:
METHOD A. A Gilson GX-281 semi-prep-HPLC with Phenomenex Synergi C18 (10µm, 150 x 25mm), or Boston Green ODS C18 (5µm, 150 x 30mm), and mobile phase of 5-99% I in water (with 0.225% FA) over 10 min and then hold at 100% I for 2 min, at a flow rate of 25 mL/min.

or

METHOD B. A Gilson GX-281 semi-prep-HPLC with Phenomenex Synergi C18 (10µm, 150 x 25mm), or Boston Green ODS C18 (5µm, 150 x 30mm), and mobile phase of 5-99% I in water (0.1% TFA) over 10 min and then hold at 100% I for 2 min, at a flow rate of 25 mL/min.

or

METHOD C. A Gilson GX-281 semi-prep-HPLC with Phenomenex Synergi C18 (10µm, 150 x 25mm), or Boston Green ODS C18 (5µm, 150 x 30mm), and mobile phase of 5-99% I in water (0.05% HCl) over 10 min and then hold at 100% I for 2 min, at a flow rate of 25 mL/min.

or

METHOD D. a Gilson GX-281 semi-prep-HPLC with Phenomenex Gemini C18 (10µm, 150 x 25mm), AD (10µm, 250mm x 30mm), or Waters Xbridge C18 column (5µm, 150 x 30mm), mobile phase of 0-99% I in water (with 0.05% ammonia hydroxide v/v) over 10 min and then hold at 100% I for 2 min, at a flow rate of 25 mL/min.

or

METHOD E. a Gilson GX-281 semi-prep-HPLC with Phenomenex Gemini C18 (10µm, 150 x 25mm), or Waters Xbridge C18 column (5µm, 150 x 30mm), mobile phase of 5-99% I in water (10mM NH₄HCO₃) over 10 min and then hold at 100% I for 2 min, at a flow rate of 25 mL/min.

Preparative supercritical fluid high performance liquid chromatography (SFC) was performed either on a Thar 80 Prep-SFC system, or Waters 80Q Prep-SFC system from Waters. The ABPR was set to 100bar to keep the CO2 in SF conditions, and the flow rate may verify according to the compound characteristics, with a flow rate ranging from 50g/min to 70g/min. The column temperature was ambient temperature.
Mass spectra (MS) were obtained on a SHIMADZU LCMS-2020 MSD or Agilent 1200xG6110A MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass.

Nuclear magnetic resonance (NMR) spectra were obtained on Bruker model AVIII 400 spectrometers. Definitions for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. It will be understood that for compounds comprising an exchangeable proton, said proton may or may not be visible on an NMR spectrum depending on the choice of solvent used for running the NMR spectrum and the concentration of the compound in the solution.

Chemical names were generated using ChemDraw Ultra 17.1 (CambridgeSoft Corp., Cambridge, MA) or OEMetaChem V1.4.0.4 (Open Eye).

Compounds designated as R or S are enantiopure compounds where the absolute configuration was determined. Compounds designated as RS are racemic compounds.

**Intermediate 1: 6-Bromo-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine**

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

**Step A: 4-Bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzonitrile**

1,1,1-Trifluoropropan-2-ol (1.15 g, 12.6 mmol) was treated with NaH portion wise (60%, 506 mg, 12.7 mmol) at room temperature in THF (17 mL) for 5 min. 4-Bromo-2,6-difluorobenzonitrile (2.3 g, 10.55 mmol) in THF (5 mL) was dropwise added into the reaction at 0 °C over 5 min. The reaction was warmed to room temperature and stirred for 1 hour. It was then heated at 70 °C for another 4 hours. The reaction was cooled and the solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and concentrated to give the crude product, which was purified by silica gel column on an Isco system using 20-60% ethyl acetate/heptanes to give the title
compound as a white solid. MS (ESI): mass calcd. For C_{10}H_{16}BrF_{4}NO, 312.06; m/z found, 313.1 [M+H]^+

Step B: 6-Bromo-1-methyl-4-(((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine

4-Bromo-2-fluoro-6-(((1,1,1-trifluoropropan-2-yl)oxy)benzonitrile (1.4 g, 4.49 mmol) and hydrazine (0.22 mL, 4.94 mmol) in EtOH (10 mL) were heated to 70 °C for 3 hours. The reaction was cooled and the solvent was removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine and concentrated to give the crude product, which was purified by silica gel on an Isco system using 20-100% ethyl acetate in heptanes to give the title compound as a white solid. MS (ESI): mass calcd. For C_{11}H_{11}BrF_{3}N_{3}O, 338.13; m/z found, 339.1 [M+H]^+. ^1H NMR (400 MHz, CDCl₃) δ 7.35 (s, 1H), 6.68 (s, 1H), 4.95 (m, J = 3.9 Hz, 1H), 3.80 (s, 3H), 1.78 (d, J = 8.4 Hz, 3H).

Intermediate 2: 6-Bromo-1-(4-methoxybenzyl)-4-(((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine

Step A: 6-Bromo-4-(((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine

To a solution of 4-bromo-2-fluoro-6-(((1,1,1-trifluoropropan-2-yl)oxy)benzonitrile (Intermediate 1, Step A, 202.6 mg, 0.649 mmol) in n-butanol (5 mL) was added hydrazine hydrate (195 mg, 3.895 mmol). The resulting mixture was stirred at 115 °C overnight. The reaction was cooled and the solvent was removed under vacuum. The residue was washed with ether and the solid was collected through filtration to give the title compound as a white solid. MS (ESI): mass calcd. For C_{10}H_{16}BrF_{3}N_{3}O, 322.99; m/z found, 323.4 [M+H]^+.
Step B: 6-Bromo-1-(4-methoxybenzyl)-4-((1,1,1-trifluoropropan-2-y1)oxy)-1H-indazol-3-amine.
To a solution of 6-bromo-4-((1,1,1-trifluoropropan-2-y1)oxy)-1H-indazol-3-amine (2.1 g, 6.48 mmol) in DMSO (20 mL) was added 1-(chloromethyl)-4-methoxybenzene (1.22 g, 7.80 mmol) and KOH (0.73 g, 13.0 mmol). The reaction was stirred at room temperature for 4 hours. The reaction was quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (0-20% ethyl acetate/petroleum ether) to afford the 6-bromo-1-(4-methoxybenzyl)-4-((1,1,1-trifluoropropan-2-y1)oxy)-1H-indazol-3-amine as a grey solid. MS (ESI): mass calcd. For C_{18}H_{17}BrF_{5}N_{3}O_{2}, 443.05; m/z found, 444.1 [M+H]^+.

Intermediate 3: 6-Bromo-1-isopropyl-4-((1,1,1-trifluoropropan-2-y1)oxy)-1H-indazol-3-amine.

4-Bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-y1)oxy)benzonitrile (Intermediate 1, Step A, 1.0 g, 3.21 mmol) and iso-propylhydrazine (0.18 mL, 3.85 mmol) in EtOH (5 mL) were heated to 70 °C for 3 hours. The reaction was cooled and the solvent was removed under vacuum. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine and concentrated to give the crude product, which was purified by silica gel on an Isco system using 20-100% ethyl acetate in heptanes to give the title compound as a white solid. MS (ESI): mass calcd. For C_{15}H_{15}BrF_{5}N_{3}O, 366.18; m/z found, 365.1, 367.1 [M+H]^+.

Intermediate 4: 6-Bromo-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-y1)oxy)-1H-indazol-3-amine.
Step A: 4-Bromo-2,3,6-trifluorobenzonitrile and 4-bromo-2,3,6-trifluorobenzaldehyde oxime.

A suspension of 4-bromo-2,3,6-trifluorobenzaldehyde (1.55 g, 6.49 mmol) and hydroxylamine-\(\text{o}\)-sulfonylic acid (0.830 g, 7.34 mmol) in water (17 mL) was placed in a 50 mL flask fitted with a condenser. After the mixture was heated at 105 °C for 3 hours, some clear crystalline material accumulated on the wall of condenser. This material was collected and dried to give 4-bromo-2,3,6-trifluorobenzonitrile. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39 – 7.29 (m, 1H).

The mixture in the reaction flask was extracted with EtOAc. The extracts were dried over Na\(_2\)SO\(_4\), filtered, and concentrated to give 4-bromo-2,3,6-trifluorobenzaldehyde oxime as a brown solid. MS (ESI): mass calc. For C\(_\text{r}\)H\(_\text{r}\)BrF\(_\text{r}\)NO, 252.94/254.94; m/z found, 253.9/255.9 [M+H]\(^+\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.57 (br s, 1H), 8.33 – 8.17 (m, 1H), 7.39 – 7.12 (m, 1H).

Step B: 4-Bromo-2,3,6-trifluorobenzonitrile

To a solution of 4-bromo-2,3,6-trifluorobenzaldehyde oxime (2.43 g, 9.57 mmol) and Et\(_3\)N (3.3 mL, 23.8 mmol) in THF (22 mL) at 4 °C was added trifluoroacetic anhydride (1.6 mL, 11.4 mmol) slowly. The mixture was stirred at 4 °C to RT for 24 h and concentrated. The residue was partitioned between DCM and water. The organic layer was dried over Na\(_2\)SO\(_4\), filtered, concentrated, and purified by flash column chromatography (0-20% EtOAc in DCM) to give the title compound as a solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41 – 7.28 (m, 1H).

Step C: 6-Bromo-4,7-difluoro-1-methyl-1H-indazol-3-amine

A mixture of 4-bromo-2,3,6-trifluorobenzonitrile (2.28 g, 9.66 mmol) and methylhydrazine (0.500 g, 10.9 mmol) in \(n\)-butanol (50 mL) was heated at 70 °C for 0.5 h and then 120 °C.
for 3 h. After cooling to room temperature, the precipitated solid was filtered, washed with water and dried to give the title compound as a pinkish solid. MS (ESI): mass calcd. For CsHsBrF2N3, 260.97/262.97; m/z found, 262.0/264.0 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 6.70 (dd, J = 3.9, 8.8 Hz, 1H), 4.24 (br s, 2H), 3.97 (s, 3H).

Step D: 6-Bromo-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine

To a solution of 6-bromo-4,7-difluoro-1-methyl-1H-indazol-3-amine (1.39 g, 5.30 mmol) and 1,1,1-trifluoro-2-propanol (0.666 g, 5.84 mmol) in DMF (70 mL) at 4 °C was added 60% NaH in mineral oil (0.487 g, 12.2 mmol). The mixture was stirred at 4 °C to room temperature for 6 h, and more 60% NaH in mineral oil (0.300 g, 7.50 mmol) was added. After stirring at room temperature for 15 h, a few drops of water were added, and the mixture was concentrated. The residue was partitioned between DCM and water. The organic layer was dried over Na2SO4, filtered, concentrated and purified by flash column chromatography (10-35% EtOAc in heptane) to give the title compound as a brown solid. 1H NMR (400 MHz, CDCl3) δ 6.33 (d, J = 3.4 Hz, 1H), 4.85 – 4.67 (m, 1H), 4.37 (br s, 2H), 3.93 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H).

Intermediate 5: (S)-2-(3-Amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

Step A: (S)-6-Bromo-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine
To a solution of 6-bromo-4,7-difluoro-1-methyl-1H-indazol-3-amine (Intermediate 4, Step C, 6.96 g, 26.6 mmol) and (S)-1,1,1-trifluoro-2-propanol (3.33 g, 29.2 mmol) in DMF (185 mL) at 4 °C was added 60% NaH in mineral oil (2.65 g, 66.3 mmol). The cooling bath was removed, and the mixture was stirred at RT for 19 h. A few drops of water were added, and the mixture was concentrated. The residue was partitioned between DCM and water. The organic layer was dried over Na₂SO₄, filtered, concentrated and purified by flash column chromatography (10-35% EtOAc in heptane) to give the title compound as an off-white solid. MS (ESI): mass calcd. For C₁₁H₁₀BrF₃N₅O, 354.99/356.99; m/z found, 356.0/358.0 [M+H]^+.

Step B: (S)-2-(3-Amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-((benzyl oxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one

A reaction flask containing (S)-6-bromo-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (3.47 g, 9.74 mmol), 5-((benzyl oxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (2.95 g, 12.7 mmol), KI (323 mg, 1.95 mmol), potassium phosphate tribasic (3.10 g, 14.6 mmol) and dioxane (100 ml) was purged with argon for ~10 min. Copper (I) iodide (557 mg, 2.92 mmol) was added in a separate vial followed by ~1.5 ml of dioxane and trans-N,N'-dimethylcyclohexane-1,2-diamine (277 mg, 1.95 mmol). The dark grey mixture was purged with argon while stirring and then added to the above reaction flask. After purging with argon for ~10 min, the reaction flask was heated at 110 °C for 5 h. More copper (I) iodide (371 mg, 1.95 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (277 mg, 0.195 mmol) were added. After purging with argon for ~5 min, the mixture was heated at 110 °C for 12 h and filtered. The filtrate was concentrated and purified by flash column chromatography (15-70% EtOAc in heptane) to give the title compound as a clear oil. MS (ESI): mass calcd. For C₂₃H₂₅FaN₆O₃, 508.18; m/z found, 509.1 [M+H]^+. ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.29 (m, 5H), 6.37 (d, J = 3.9 Hz, 1H), 4.88 – 4.75 (m, 1H), 4.62 (s, 2H), 4.52 (s, 2H), 4.37 (s, 2H), 3.97 (s, 3H), 3.86 (q, J = 7.3 Hz, 2H), 1.63 – 1.54 (m, 3H), 1.37 (t, J = 7.3 Hz, 3H).

Step C: (S)-2-(3-Amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxy methyl)-2,4-dihydro-3H-1,2,4-triazol-3-one
A mixture of (S)-2-(3-amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-((benzoyl(methyl))-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (2.26 g, 4.44 mmol), 10% Pd/C (312 mg, 0.290 mmol), a solution of 4M HCl in dioxane (1.2 mL, 4.8 mmol), EtOH (24 mL) and THF (8 mL) was shaken under 40 – 17 psi H₂ for 17 h. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was partitioned between EtOAc and NaHCO₃ aqueous solution. The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound as a foam. MS (ESI): mass calc'd. For C₁₆H₁₈F₄N₆O₅, 418.14; m/z found, 419.1 [M+H]⁺.

¹H NMR (400 MHz, CDCl₃) δ 6.36 (d, J = 3.9 Hz, 1H), 4.86 – 4.75 (m, 1H), 4.67 (d, J = 5.9 Hz, 2H), 4.39 (s, 2H), 3.97 (s, 3H), 3.91 (q, J = 7.0 Hz, 2H), 2.34 (br s, 1H), 1.58 (d, J = 6.4 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H).

**Intermediate 6**: (S)-6-bromo-4-((1,1,1-trifluoropropan-2-yl)oxy)benzo[d]isoxazol-3-amine

**Step A**: (S)-4-bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzonitrile

(S)-1,1,1-Trifluoropropan-2-ol (1.0 g, 11 mmol) was treated with NaH portion wise (60%, 440 mg, 11 mmol) at room temperature in THF (10 mL) for 5 min. 4-Bromo-2,6-difluorobenzonitrile (2.0 g, 9.2 mmol) in THF (4 mL) was dropwise added into the reaction at 0 °C over 5 min. The reaction was warmed to room temperature and stirred for 1 hour. It was then heated at 70 °C for another 4 hours. The reaction was cooled and the solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and concentrated to give the crude product, which was purified by silica gel column on an Isco system using 20-60% ethyl acetate/heptanes to give the title compound as a white solid. MS (ESI): mass calc'd. For C₁₀H₅BrF₄NO, 312.06; m/z found, 313.1 [M+H]⁺.

**Step B**: (S)-4-bromo-2-((propan-2-ylideneamino)oxy)-6-((1,1,1-trifluoropropan-2-yl)oxy)benzonitrile
Propan-2-one oxime (97 mg, 1.39 mmol) in DMF (5 mL) was treated with t-BuOK (150 mg, 1.34 mmol) at 60 °C for 2 hours. The solution was cooled to room temperature and treated with (S)-4-bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzonitrile (380 mg, 1.22 mmol) for another 2 hours at room temperature. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed by brine, dried and concentrated to give the crude product, which was then purified by silica gel on an Isco system using 10-40% ethyl acetate in heptanes to give the title compound as a colorless oil. MS (ESI): mass calcd. For C_{13}H_{12}BrF_{3}N_{2}O_{2}, 365.15; m/z found, 366.0 [M+H]^+.

Step C: (S)-6-bromo-4-(((1,1,1-trifluoropropan-2-yl)oxy)benzo[d]isoxazol-3-amine

(S)-4-bromo-2-(((propan-2-ylideneamino)oxy)-6-((1,1,1-trifluoropropan-2-yl)oxy)benzonitrile (300 mg, 0.82 mmol) in mixed solvent of 1N HCl (5 mL) and EtOH (5 mL) were heated to reflux for 3 hours. The reaction was cooled and quenched with 1N NaOH until pH = 7. The solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and concentrated to give the crude product, which was purified by silica gel column on an Isco system using 10-70% ethyl acetate/heptanes to give the title compound as a white solid. MS (ESI): mass calcd. For C_{10}H_{8}BrF_{3}N_{2}O_{2}, 325.09; m/z found, 326.0 [M+H]^+. H NMR (400 MHz, CDCl_{3}) δ 7.28 (s, 1H), 7.10 (s, 1H), 4.86 (m, 1H), 1.45 (t, J = 7.0 Hz, 3H).

Intermediate 7: 6-Bromo-1-methyl-4-(((1,1,1-trifluoropropan-2-yl)oxy)-1,2-dihydro-3H-indazol-3-one.

Step A: tert-Butyl 4-bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzoate

1,1,1-Trifluoropropan-2-ol (1.34 mL, 14.7 mmol) was treated with NaH portion wise (60%, 540 mg, 13.5 mmol) at room temperature in DMF (10 mL) for 5 min. 4-tert-Butyl 4-bromo-2,6-difluorobenzoate (3.6 g, 12.3 mmol) in DMF (5 mL) was dropwise added into the reaction at 0 °C over 5 min. The reaction was warmed to room temperature and stirred
for 2 hours. The reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and concentrated to give the crude product, which was purified by silica gel column on an Isco system using 20-60% ethyl acetate/heptanes to give the title compound as a white solid. MS (ESI): mass calcd. For C_{14}H_{18}BrF_{4}O, 387.17; m/z found, 329.1, 331.1 [M-t-Bu]^+.

**Step B:** 4-Bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzoic acid
tert-Butyl 4-bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzoate (2.0 g, 5.06 mmol) in mixed solvent of DCM (6 mL) and TFA (2 mL) was stirred at room temperature overnight. The solvent was removed and the residue was obtained without further purification. MS (ESI): mass calcd. For C_{10}H_{15}BrF_{4}O_{3}, 331.06; m/z found, 331.1 [M+H]^+.

**Step C:** tert-Butyl 2-(4-bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzoyl)-1-methylhydrazine-1-carboxylate
4-Bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzoic acid (900 mg, 2.72 mmol), tert-butyl 1-methylhydrazine-1-carboxylate (397 mg, 2.72 mmol), HATU (1.03 g, 2.72 mmol) and DIPEA (0.56 mL, 3.62 mmol) in DMF (5 mL) were stirred at room temperature overnight. The solution was partitioned between DCM and water. The organic layer was washed with brine, dried and concentrated to give the crude product, which was then purified by silica gel on an Isco system suing 20 to 60% ethyl acetate in heptanes to give the title compound as an off white solid. MS (ESI): mass calcd. For C_{16}H_{19}BrF_{4}N_{2}O_{4}, 459.24; m/z found, 479.0, 481.0 [M+Na]^+.

**Step D:** 4-Bromo-2-fluoro-N'-methyl-6-((1,1,1-trifluoropropan-2-yl)oxy)benzohydrazide
tert-Butyl 2-(4-bromo-2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzoyl)-1-methylhydrazine-1-carboxylate (400 mg, 0.87 mmol) in mixed solvent of DCM (4 mL) and TFA (1 mL) was stirred at room temperature overnight. The solvent was removed and the residue was dried without further purification. MS (ESI): mass calcd. For C_{11}H_{13}BrF_{4}N_{2}O_{2}, 359.12; m/z found, 359.0, 361.0 [M+H]^+.

**Step E:** 6-Bromo-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1,2-dihydro-3H-indazol-3-one.
4-Bromo-2-fluoro-N'-methyl-6-((1,1,1-trifluoropropan-2-yl)oxy)benzohydrazide (300 mg, 0.80 mmol) and K₂CO₃ (230 mg, 1.67 mmol) in DMF (3 mL) were heated to 120 °C for 2 hours. The solution was cooled and then partitioned between ethyl acetate and water. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated, which was then purified by flash silica gel using 10-60% ethyl acetate in heptanes to give the title compound as an off-white solid. MS (ESI): mass calcd. For C₁₁H₁₀BrF₃N₂O₂, 339.11; m/z found, 338.0, 340.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.11 (s, 1H), 6.62 (s, 1H), 4.95 (m, J = 7.0 Hz, 1H), 3.75 (s, 3H), 1.82 (d, J = 8.5 Hz, 3H).

Intermediate 8: 2-(4-Bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol

\[ \begin{array}{c}
\text{Br} \\
\text{N} \quad \text{N} \\
\text{HOH}
\end{array} \]

To a solution of methyl 4-bromo-1-methyl-1H-imidazole-2-carboxylate (CAS 864076-05-1, 1.18 g, 5.39 mmol) in THF (30 mL) at -78 °C was dropwise added methylmagnesium bromide (3 M, 5.39 mL, 16.2 mmol). The reaction was slowly warmed to room temperature and stirred overnight. It was then quenched with water. The solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and concentrated to give the crude product, which was then purified by silica gel column on a CombiFlash system using 20–100% ethyl acetate in heptanes to give the title compound as a white solid. MS (ESI): mass calcd. For C₁₁H₁₁BrN₂O, 219.08; m/z found, 220.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ = 6.78 (s, 1H), 3.82 (s, 3H), 1.66 (s, 6H).

Example 1: 2-(3-((2-Chloro-6-fluorophenyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.
Step A: 6-Bromo-N-(2-chloro-6-fluorophenyl)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine

A mixture of 6-Bromo-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (200 mg, 0.59 mmol), (2-chloro-6-fluorophenyl)boronic acid (257 mg, 1.47 mmol), Cu(OAc)$_2$ (11 mg, 0.059 mmol), and pyridine (1 drop) in MeOH (5 mL) was opened to air and stirred at room temperature overnight. The solution partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated and purified by a CombiFlash system using 20~100% ethyl acetate in heptanes to give the title compound as a white solid. MS (ESI): mass calcd. For C$_{17}$H$_{15}$BrClF$_4$N$_5$O, 466.66; m/z found, 465.0, 467.1 [M+H]$^+$.

Step B: 5-((Benzylxylo)methyl)-2-(3-((2-chloro-6-fluorophenyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one

A reaction flask containing 6-bromo-N-(2-chloro-6-fluorophenyl)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (100 mg, 0.214 mmol), 5-((benzylxylo)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (60 mg, 0.26 mmol), KI (7 mg, 0.043 mmol), potassium phosphate tribasic (82 mg, 0.39 mmol) and dioxane (5 ml) was purged with argon for ~10 min. Copper (I) iodide (9 mg, 0.043 mmol) was added in a separate vial followed by ~1 ml of dioxane and trans-$N,N'$-dimethylcyclohexane-1,2-diamine (0.06 mL, 0.043 mmol). The dark grey mixture was purged with argon while stirring and then added to the above reaction flask. After purging with argon for ~10 min, the reaction flask was heated at 110 °C for 5 h. The reaction was cooled and filtered through a pad of Celite. The filtrate was concentrated and purified by flash column
chromatography (15-70% EtOAc in heptanes) to give the title compound as a clear oil.

MS (ESI): mass calcd. for C_{29}H_{27}ClF_4N_6O_3, 619.02; m/z found, 620.1 [M+H]^+.

**Step C:** 2-(3-((2-Chloro-6-fluorophenyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.

5-((Benzzyloxy)methyl)-2-(3-((2-chloro-6-fluorophenyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (65 mg, 0.11 mmol) in TFA (2 mL) was heated to reflux for 3 hours in a sealed tube. The solvent was removed under vacuum and the residue was purified by prep-HPLC using 20-80% ACN/water 0.1% TFA to give the title compound as a white solid after lyophilizing.

MS (ESI): mass calcd. for C_{29}H_{27}ClF_4N_6O_3, 528.89; m/z found, 529.0 [M+H]^+. ^1H NMR (400 MHz, CDCl_3) δ 7.52 (s, 1H), 7.30 (m, 2H), 7.05 (m, J = 5.9 Hz, 2H), 6.72 (br, s, 1H), 5.03 (m, 1H), 4.68 (s, 2H), 3.91 (m, J = 6.5 Hz, 2H), 3.80 (s, 3H), 1.65 (d, J = 7.5 Hz, 3H), 1.48 (t, J = 8.5 Hz, 3H).

**Example 2:** 2-(3-((2-Chloro-6-fluorophenyl)(methyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.

**Step A:** 5-((Benzzyloxy)methyl)-2-(3-((2-chloro-6-fluorophenyl)(methyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one
5-((Benzyloxy)methyl)-2-(3-((2-chloro-6-fluorophenyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 1, Step B, 30 mg, 0.049 mmol) in DMF (2 mL) at 0 °C was treated with NaH (60%, 4 mg, 0.097 mmol) for 10 min and then MeI (0.005 mL, 0.073 mmol) was added and the reaction was warmed to room temperature slowly. The solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried and concentrated to give the crude product, which was purified by silica gel on an Isco system using 10-60% ethyl acetate in heptanes to give the title compound as a colorless oil. MS (ESI): mass calcd. for C_{30}H_{29}ClF_{4}N_{6}O_{3}, 633.05; m/z found, 634.0 [M+H]^+

Step B: 2-(3-((2-Chloro-6-fluorophenyl)(methyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.

The title compound was prepared in a manner analogous to Example 1, Step C using TFA deprotection as a white solid. MS (ESI): mass calcd. for C_{32}H_{27}F_4N_6O_4, 553.21; m/z found, 554.3 [M+H]^+.

^1H NMR (400 MHz, CDCl_3) δ 7.55 (m, J = 4.5 Hz, 1H), 7.28 (m, 2H), 7.11 (m, 1H), 7.02 (m, J = 3.9 Hz, 1H), 4.88 (m, 1H), 4.62 (s, 2H), 3.92 (m, J = 6.0 Hz, 2H), 3.83 (s, 3H), 3.45 (s, 3H), 1.68 (d, J = 7.5 Hz, 3H), 1.48 (t, J = 7.5 Hz, 3H).

Example 3: (S)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one and (R)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one
Step A: (+)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

The title compound was prepared as a white solid in a manner analogous to Example 1, Steps A, B and C using 6-bromo-1-(4-methoxybenzyl)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (Intermediate 2) as starting material. MS (ESI): mass calcd. for C_{24}H_{25}ClF_{4}N_{6}O_{5}, 514.87; m/z found, 515.1 [M+H]^+.

\[ ^1H \text{NMR (400 MHz, CDC13)} \delta 10.5 \text{ (br, s, 1H), } 7.55 \text{ (m, } J = 3.5 \text{ Hz, 1H), } 7.20 \text{ (m, 2H), } 7.12 \text{ (m, 2H), } 5.02 \text{ (m, 1H), } 4.71 \text{ (s, 2H), } 3.80 \text{ (m, } J = 5.5 \text{ Hz, 2H), } 1.65 \text{ (d, } J = 6.5 \text{ Hz, 3H), } 1.45 \text{ (t, } J = 6.5 \text{ Hz, 3H).} \]

Step B: (S)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one and (R)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

The racemic mixture was separated by Prep-Chiral-HPLC separation. The collected fractions were combined and concentrated under vacuum. This resulted in fraction 1: (S)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one as a grey solid and fraction 2: (R)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one as a grey solid.

(S)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one: MS (ESI): mass calcd. for C_{24}H_{25}ClF_{4}N_{6}O_{5}, 514.87; m/z found, 515.1 [M+H]^+.

(R)-2-(3-((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one: MS (ESI): mass calcd. for C_{24}H_{25}ClF_{4}N_{6}O_{5}, 514.87; m/z found, 515.1 [M+H]^+.

Example 4: 2-(3-((2-Chloro-6-fluorophenyl)amino)-1-isopropyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.
The title compound was prepared as a white solid in a manner analogous to Example 1, Steps A, B and C using 6-bromo-1-isopropyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (Intermediate 3) as starting material. MS (ESI): mass calcd. for C_{24}H_{25}ClF_{4}N_{6}O_{3}, 556.95; m/z found, 557.1 [M+H]^+. ^1H NMR (400 MHz, CDCl₃) δ 7.75 (m, J = 3.5 Hz, 1H), 7.25 (m, 2H), 7.10 (m, 2H), 5.05 (m, 1H), 4.82 (m, 1H), 4.65 (s, 2H), 3.82 (m, J = 6.5 Hz, 2H), 1.68 (d, J = 7.5 Hz, 3H), 1.48 (t, J = 7.5 Hz, 3H), 1.39 (d, J = 9.5 H, 6H).

Example 5: 2-(3-((2-Chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

Step A: 6-Bromo-N-(2-chloro-6-fluorophenyl)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine
A reaction mixture of 6-bromo-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (Intermediate 4, 103 mg, 0.290 mmol), 1-chloro-3-fluoro-2-iodobenzene (111 mg, 0.430 mmol), Pd(dba)$_2$ (27 mg, 0.029 mmol), (9,9-dimethyl-9H-xanthen-4,5-diyl)bis[diphenylphosphine] (Xantphos, 25 mg, 0.043 mmol), Cs$_2$CO$_3$ (151 mg, 0.460 mmol), and dioxane (2 mL) was purged with argon for ~ 5 min, and then heated at 110 °C for 17.5 h. The mixture was filtered through Celite, and the filtrate was concentrated and purified by flash column chromatography (0-30% EtOAc in heptane) to give the title compound as a clear solid. MS (ESI): mass calcd. for $\text{C}_{17}\text{H}_{12}\text{BrClF}_{5}\text{N}_{3}\text{O}$, 482.98/484.98; m/z found, 483.9/485.9 [M+H]$^+$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.24 (d, $J = 6.8$ Hz, 1H), 7.15 - 6.98 (m, 2H), 6.52 (s, 1H), 6.42 (d, $J = 3.9$ Hz, 1H), 4.87 - 4.76 (m, 1H), 3.97 (s, 3H), 1.62 (d, $J = 6.4$ Hz, 3H).

**Step B:** 5-((Benzzyloxy)methyl)-2-(3-((2-chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.

A reaction tube containing 6-bromo-N-(2-chloro-6-fluorophenyl)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (119 mg, 0.250 mmol), 5-((benzzyloxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (70 mg, 0.30 mmol), KI (9.0 mg, 0.054 mmol), copper (I) iodide (10 mg, 0.053 mmol), potassium phosphate tribasic (80 mg, 0.38 mmol), trans-N,N'-dimethylcyclohexane-1,2-diamine (8.0 mg, 0.056 mmol) and dioxane (2.5 mL) was purged with argon for ~ 5 min, and then heated at 105 °C for 14.5 h. More copper (I) iodide (20 mg, 0.11 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (16 mg, 0.11 mmol) were added. After purging with argon for ~ 5 min, the mixture was heated at 110 °C for 17.5 h and filtered through Celite. The filtrate was concentrated and purified by flash column chromatography (30-70% EtOAc in heptane) to give the title compound as a white foam. MS (ESI): mass calcd. for $\text{C}_{29}\text{H}_{26}\text{ClF}_{5}\text{N}_{3}\text{O}_3$, 636.17; m/z found, 637.0 [M+H]$^+$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.46 - 7.32 (m, 5H), 7.27 - 7.20 (m, 1H), 7.15 - 6.97 (m, 2H), 6.56 (s, 1H), 6.45 (d, $J = 3.9$ Hz, 1H), 4.94 - 4.80 (m, 1H), 4.63 (s, 2H), 4.53 (s, 2H), 4.01 (s, 3H), 3.87 (q, $J = 7.2$ Hz, 2H), 1.61 (d, $J = 6.9$ Hz, 3H), 1.38 (t, $J = 7.1$ Hz, 3H).
Step C: 2-(3-((2-Chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

A solution of 5-((benzyl oxy)methyl)-2-(3-((2-chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (69 mg, 0.11 mmol) in TFA (1.5 mL) was heated at 70 °C for 10 h and concentrated. To the residue 2 mL of toluene was added and the mixture was concentrated in vacuo. The residue was dissolved in THF (1 mL) and treated with 2N K₂CO₃ (0.2 mL) for 1 h to hydrolyze the by-product, 1-(3-((2-chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl 2,2,2-trifluoroacetate. After concentration, the residue was partitioned between DCM and water. The organic layer was dried over Na₂SO₄, filtered, concentrated, and purified by flash column chromatography (30-70% EtOAc in heptane) to give the title compound as a solid. MS (ESI): mass calcd. for C₂₂H₂₀ClF₅N₅O₃, 546.12; m/z found, 547.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, J = 7.3 Hz, 1H), 7.15 - 6.99 (m, 2H), 6.56 (s, 1H), 6.45 (d, J = 3.9 Hz, 1H), 4.95 - 4.80 (m, 1H), 4.66 (s, 2H), 4.00 (s, 3H), 3.90 (q, J = 7.3 Hz, 2H), 2.42 (br s, 1H), 1.61 (d, J = 6.4 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H).

Example 6: 4-Ethyl-2-(7-fluoro-1-methyl-3-(o-toly lamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one and 4-Ethyl-2-(7-fluoro-1-methyl-3-(phenylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.
Step A: 2-(3-Amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-((benzzyloxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one.

A reaction tube containing 6-bromo-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (Intermediate 4, 100 mg, 0.280 mmol), 5-((benzzyloxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (82 mg, 0.35 mmol), KI (10 mg, 0.060 mmol), copper (I) iodide (11 mg, 0.058 mmol), potassium phosphate tribasic (108 mg, 0.510 mmol), trans-N,N’-dimethylcyclohexane-1,2-diamine (8.0 mg, 0.056 mmol) and dioxane (3 ml) was purged with argon for ~ 5 min, and then heated at 105 °C for 16 h. More copper (I) iodide (11 mg, 0.058 mmol) and trans-N,N’-dimethylcyclohexane-1,2-diamine (8.0 mg, 0.056 mmol) were added. After purging with argon for ~ 5 min, the mixture was heated at 110 °C for 17.5 h and filtered through Celite. The filtrate was concentrated and purified by flash column chromatography (30-70% EtOAc in heptane) to give the title compound as a white solid. MS (ESI): mass calcd. for C_{23}H_{24}F_{3}N_{6}O_{3}, 508.18; m/z found, 509.1 [M+H]^+.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 - 7.29 (m, 5H), 6.36 (d, $J = 3.9$ Hz, 1H), 4.87 - 4.75 (m, 1H), 4.62 (s, 2H), 4.52 (s, 2H), 4.37 (s, 2H), 3.97 (s, 3H), 3.86 (q, $J = 7.0$ Hz, 2H), 1.64 - 1.56 (m, 3H), 1.37 (t, $J = 7.3$ Hz, 3H).

Step B: 5-((Benzzyloxy)methyl)-4-ethyl-2-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

A reaction mixture of 2-(3-amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-((benzzyloxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (71 mg, 0.14 mmol), 2-iodotoluene (46 mg, 0.21 mmol), Pd$_2$(dba)$_3$ (13 mg, 0.014 mmol), (9,9-
dimethyl-9H-xanthene-4,5-diylbis[diphenylphosphine] (Xantphos, 13 mg, 0.022 mmol), Cs$_2$CO$_3$ (73 mg, 0.22 mmol), and dioxane (2 mL) was purged with argon for ~ 5 min, and then heated at 105 °C for 14.5 h. The mixture was filtered through Celite, and the filtrate was concentrated and purified by flash column chromatography (30-70 EtOAc in heptane) to give the title compound as a yellow oil. MS (ESI): mass calcd. for C$_{30}$H$_{30}$F$_4$N$_6$O$_3$, 598.23; m/z found, 599.1 [M+H]$^+$. 

Step C: 4-Ethyl-2-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one and 4-ethyl-2-(7-fluoro-1-methyl-3-(phenylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

A solution of 5-((benzyl oxy)methyl)-4-ethyl-2-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one (65 mg, 0.11 mmol) in TFA (1.5 mL) was heated at 70 °C for 16 h and concentrated. To the residue 2 mL of toluene was added and the mixture was concentrated in vacuo. The residue was dissolved in THF (1 mL) and treated with 2N K$_2$CO$_3$ (0.2 mL) for 1 h to hydrolyze the by-product. (4-ethyl-1-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl 2,2,2-trifluoroacetate. After concentration, the residue was partitioned between DCM and water. The organic layer was dried over Na$_2$SO$_4$, filtered, concentrated, and purified by RF-HPLC (Gemini C18 110A, 5 µM 100x30 mm, 20-100% CH$_3$CN in water with 10 mM NH$_4$OH, 45 mL/min) to give major product 4-ethyl-2-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one as a white solid. MS (ESI): mass calcd. for C$_{23}$H$_{22}$F$_4$N$_6$O$_3$, 508.18; m/z found, 509.1 [M+H]$^+$. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.41 (d, J = 7.8 Hz, 1H), 7.35 - 7.26 (m, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.10 (s, 1H), 6.89 (t, J = 7.1 Hz, 1H), 6.44 (d, J = 3.9 Hz, 1H), 4.98 - 4.86 (m, 1H), 4.68 (d, J = 6.4 Hz, 2H), 4.10 (s, 3H), 3.92 (q, J = 7.0 Hz, 2H), 2.34 (s, 3H), 2.24 - 2.08 (m, 1H), 1.71 - 1.61 (m, 3H), 1.43 (t, J = 7.1 Hz, 3H). 4-Ethyl-2-(7-fluoro-1-methyl-3-(phenylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one was isolated as a side product. MS (ESI): mass calcd. for C$_{22}$H$_{22}$F$_4$N$_6$O$_3$, 508.18; m/z found, 509.1 [M+H]$^+$. 

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494.17; m/z found, 495.1 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 7.57 (d, J = 8.3 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.22 (s, 1H), 6.95 (t, J = 7.1 Hz, 1H), 6.42 (d, J = 3.9 Hz, 1H), 4.96 – 4.80 (m, 1H), 4.66 (d, J = 5.9 Hz, 2H), 4.09 (s, 3H), 3.91 (q, J = 7.0 Hz, 2H), 2.45 - 2.29 (m, 1H), 1.64 (d, J = 6.4 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H).

Example 7: (S)-4-Ethyl-2-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

A reaction mixture of (S)-2-(3-amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (Intermediate 5, 35 mg, 0.084 mmol), 2-iodotoluene (27 mg, 0.13 mmol), Pd2(dba)3 (8 mg, 0.0087 mmol), (9,9-dimethyl-9H-xanthen-4,5-diyi)bis[diphenylphosphine] (Xantphos, 8 mg, 0.014 mmol), Cs2CO3 (44 mg, 0.14 mmol), and dioxane (1 mL) was purged with argon for ~ 5 min, and then heated at 105 °C for 12 h. The mixture was filtered through a syringe filter, and the filtrate was concentrated and purified by RF-HPLC (Gemini C18 110A, 5 µM 100x30 mm, 10-100% CH3CN in water with 10 mM NH4OH, 45 mL/min) to give the title compound as a solid. MS (ESI): mass calcd. for C23H24F4N6O3, 508.18; m/z found, 509.3 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 8.40 (d, J = 7.8 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.10 (s, 1H), 6.89 (t, J = 7.6 Hz, 1H), 6.44 (d, J = 3.9 Hz, 1H), 5.00 - 4.85 (m, 1H), 4.70 - 4.59 (m, 2H), 4.09 (s, 3H), 3.90 (q, J = 7.5 Hz, 2H), 2.55 – 2.44 (m, 1H), 2.33 (s, 3H), 1.71 - 1.57 (m, 3H), 1.41 (t, J = 7.3 Hz, 3H).
Example 8: (S)-2-(3-(((2-Chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

The title compound was prepared in a manner analogous to Example 7 using 1-chloro-3-fluoro-2-iodobenzene instead of 2-iodotoluene. MS (ESI): mass calcd. for C_{22}H_{20}ClF_{3}N_{5}O_{3}, 546.12; m/z found, 547.2 [M+H]^+. ^1H NMR (400 MHz, CDCl_3) δ 7.28 - 7.19 (m, 1H), 7.15 - 6.99 (m, 2H), 6.56 (s, 1H), 6.45 (d, J = 3.9 Hz, 1H), 4.93 – 4.81 (m, 1H), 4.66 (s, 2H), 4.00 (s, 3H), 3.91 (q, J = 7.2 Hz, 2H), 2.57 - 2.40 (m, 1H), 1.60 (d, J = 6.4 Hz, 3H), 1.42 (t, J = 7.3 Hz, 3H).

Example 9: (S)-2-(3-(((2-(Difluoromethyl)phenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.
The title compound was prepared in a manner analogous to Example 7 using 1-(difluoromethyl)-2-iodobenzene instead of 2-iodotoluene. MS (ESI): mass calcd. for C_{23}H_{22}F_{6}N_{6}O_{3}, 544.17; m/z found, 545.3 [M+H]^+. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 8.52 (d, J = 8.3 Hz, 1H), 7.71 (br s, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.38 (d, J = 7.3 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.73 (t, J = 54.0 Hz, 1H), 6.49 (d, J = 3.9 Hz, 1H), 4.99 – 4.87 (m, 1H), 4.67 (d, J = 3.9 Hz, 2H), 4.10 (s, 3H), 3.91 (q, J = 7.2 Hz, 2H), 2.41 – 2.26 (m, 1H), 1.63 (d, J = 6.8 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H).

Example 10: (S)-2-((2-Chloro-4,6-difluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

The title compound was prepared in a manner analogous to Example 7 using 6-chloro-2,4-difluoroiodobenzene instead of 2-iodotoluene. MS (ESI): mass calcd. for C_{22}H_{19}ClF_{6}N_{6}O_{3}, 564.11; m/z found, 565.2 [M+H]^+. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.09 - 6.98 (m, 1H), 6.90 (ddd, J = 2.9, 8.6, 10.0 Hz, 1H), 6.45 (d, J = 3.9 Hz, 1H), 6.37 (s, 1H), 4.94 - 4.80 (m, 1H), 4.65 (s, 2H), 3.98 (s, 3H), 3.91 (q, J = 7.0 Hz, 2H), 2.96 - 2.83 (m, 1H), 1.61 (d, J = 6.8 Hz, 3H), 1.42 (t, J = 7.1 Hz, 3H).
Example 11: (S)-2-(3-((2-Chloro-4-methylpyridin-3-yl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
& \quad \text{N} \\
\text{F}_3\text{C} & \quad \text{O} \\
& \quad \text{N} \\
\text{Cl} & \quad \text{CN}
\end{align*}
\]

The title compound was prepared in a manner analogous to Example 7 using 2-chloro-3-iodo-4-methylpyridine instead of 2-iiodotoluene. MS (ESI): mass calcd. for C\textsubscript{22}H\textsubscript{22}ClF\textsubscript{4}N\textsubscript{7}O\textsubscript{3}, 543.14; m/z found, 544.2 [M+H]\textsuperscript{+}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textdelta 8.09 (d, J = 4.9 Hz, 1H), 7.16 (d, J = 4.9 Hz, 1H), 6.67 (s, 1H), 6.46 (d, J = 3.9 Hz, 1H), 4.96 - 4.83 (m, 1H), 4.68 (d, J = 6.4 Hz, 2H), 3.96 (s, 3H), 3.92 (q, J = 7.0 Hz, 2H), 2.43 - 2.36 (m, 1H), 2.39 (s, 3H), 1.64 (d, J = 6.7 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H).

Example 12: (S)-4-((6-(4-Ethyl-3-(hydroxymethyl)-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-yl)amino)-3-methylbenzonitrile.

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
& \quad \text{N} \\
\text{F}_3\text{C} & \quad \text{O} \\
& \quad \text{N} \\
\text{CN}
\end{align*}
\]
The title compound was prepared in a manner analogous to Example 7 using 4-iodo-3-methylbenzonitrile instead of 2-iodotoluene. MS (ESI): mass calcd. for C$_{24}$H$_{23}$F$_4$N$_5$O$_3$, 533.18; m/z found, 534.3 [M+H]$^+$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.51 (d, $J$ = 8.8 Hz, 1H), 7.54 (dd, $J$ = 2.0, 8.8 Hz, 1H), 7.42 (s, 1H), 7.38 - 7.27 (m, 1H), 6.49 (d, $J$ = 3.9 Hz, 1H), 4.99 - 4.86 (m, 1H), 4.69 (d, $J$ = 3.4 Hz, 2H), 4.12 (s, 3H), 3.92 (q, $J$ = 7.3 Hz, 2H), 2.40 - 2.31 (m, 1H), 2.31 (s, 3H), 1.64 (d, $J$ = 6.4 Hz, 3H), 1.43 (t, $J$ = 7.1 Hz, 3H).

Example 13: (S)-4-Ethyl-2-(7-fluoro-3-((4-fluoro-2-methylphenyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

The title compound was prepared in a manner analogous to Example 7 using 5-fluoro-2-iodotoluene instead of 2-iodotoluene. MS (ESI): mass calcd. for C$_{25}$H$_{25}$F$_5$N$_6$O$_3$, 526.18; m/z found, 527.3 [M+H]$^+$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.32 (dd, $J$ = 5.4, 9.3 Hz, 1H), 7.00 - 6.81 (m, 3H), 6.44 (d, $J$ = 3.9 Hz, 1H), 4.98 - 4.85 (m, 1H), 4.67 (d, $J$ = 5.9 Hz, 2H), 4.07 (s, 3H), 3.91 (q, $J$ = 7.2 Hz, 2H), 2.31 (s, 3H), 2.22 (t, $J$ = 6.4 Hz, 1H), 1.63 (d, $J$ = 6.4 Hz, 3H), 1.42 (t, $J$ = 7.1 Hz, 3H).
Example 14: (S)-4-Ethyl-2-(7-fluoro-3-((2-methoxy-4,6-dimethylpyridin-3-yl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

The title compound was prepared in a manner analogous to Example 7 using 3-iodo-2-methoxyl-4,6-dimethylpyridine instead of 2-iodotoluene. MS (ESI): mass calcd. for C_{24}H_{27}F_{4}N_{7}O_{4}, 553.21; m/z found, 554.3 [M+H]^+ . \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 6.66 (s, 1H), 6.51 (s, 1H), 6.41 (d, J = 3.9 Hz, 1H), 4.92 - 4.80 (m, 1H), 4.70 - 4.55 (m, 2H), 3.98 - 3.70 (m, 8H), 2.40 (s, 3H), 2.30 (s, 3H), 1.75 – 1.52 (m, 1H), 1.63 (d, J = 6.8 Hz, 3H), 1.42 (dt, J = 1.7, 7.2 Hz, 3H).

Example 15: (S)-2-(3-((2,4-Dimethylpyridin-3-yl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one
The title compound was prepared in a manner analogous to Example 7 using 3-bromo-2,4-dimethylpyridine instead of 2-iodotoluene and in the presence of KI (1.6 eq). MS (ESI): mass calcd. for C_{25}H_{25}F_{4}N_{3}O_{3}, 523.20; m/z found, 524.3 [M+H]^+. 1H NMR (400 MHz, CDCl₃) δ 8.29 - 8.14 (m, 1H), 7.09 (d, J = 4.9 Hz, 1H), 6.43 (d, J = 3.9 Hz, 1H), 6.18 (s, 1H), 4.97 - 4.81 (m, 1H), 4.66 (s, 2H), 4.01 - 3.83 (m, 5H), 2.54 (s, 3H), 2.33 (s, 3H), 1.63 (d, J = 6.4 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H).

Example 16: (S)-2-(4-((2-Chloro-4-methylpyridin-3-yl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-1-methyl-1H-imidazol-2-yl)propan-2-ol.

Step A: (S)-7-Fluoro-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine.

A mixture of (S)-6-bromo-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (Intermediate 5, Step A, 606 mg, 1.70 mmol), bis(pinacolato)diboron (610 mg, 2.40 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (95 mg, 0.12 mmol), and KOAc (300 mg, 3.06 mmol) in 1,4-dioxane (20 mL) was purged with argon for ~12 min, and then heated at 100 °C for 16 h. After cooling to room temperature, the mixture was filtered, and the filtrate was concentrated and purified by flash column chromatography (20-70% EtOAc in heptane) to give the title compound as a brown oil. MS (ESI): mass calcd. for C_{17}H_{22}BF_{4}N_{3}O_{3}, 403.17; m/z found, 404.1 [M+H]^+. 1H NMR (400 MHz, CDCl₃) δ 6.43 (d,
\( J = 2.4 \text{ Hz, 1H}, 4.96 - 4.85 \text{ (m, 1H), 4.39 (s, 2H), 3.97 (s, 3H), 1.59 (d, } J = 6.4 \text{ Hz, 3H), 1.39 (s, 12H).} \)

**Step B: (S)-2-(4-(3-amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-1-methyl-1H-imidazol-2-yl)propan-2-ol.**

A reaction mixture of (S)-7-fluoro-1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-amine (170 mg, 0.420 mmol), 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 8, 150 mg, 0.680 mmol), XphosPdG3 (36 mg, 0.043 mmol), Cs2CO3 (280 mg, 0.860 mmol) in dioxane (4 mL) and water (1 mL) was purged with argon for ~ 6 min, and then heated at 100 °C for 9 h. The mixture was filtered through a syringe filter, and the filtrate was concentrated. To the residue was added water and DCM. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na2SO4, filtered, concentrated, and purified by flash column chromatography (30-70% EtOAc in heptane) to give the title compound as a white solid. MS (ESI): mass calcd. for C_{18}H_{23}F_{4}N_{5}O_{2}, 415.16; m/z found, 416.3 [M+H]^+.

\(^1\text{H NMR (400 MHz, CDCl}_3\) \( \delta 7.31 \text{ (d, } J = 4.0 \text{ Hz, 1H), 7.05 (d, } J = 3.9 \text{ Hz, 1H), 5.05 - 4.89 \text{ (m, 1H), 4.34 (s, 2H), 3.96 (s, 3H), 3.87 (s, 3H), 3.38 (s, 1H), 1.72 (s, 3H), 1.71 (s, 3H), 1.61 (d, } J = 6.4 \text{ Hz, 3H).} \)

**Step C: (S)-2-(4-(3-Chloro-4-methylpyridin-3-yl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-1-methyl-1H-imidazol-2-yl)propan-2-ol.**

The title compound was prepared in a manner analogous to Example 7 using (S)-2-(4-(3-amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-1-methyl-1H-imidazol-2-yl)propan-2-ol and 2-chloro-3-iodo-4-methylpyridine instead of (S)-2-(3-amino-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one and 2-iodotoluene. MS (ESI): mass calcd. for C_{24}H_{22}ClF_{4}N_{6}O_{2}, 540.17; m/z found, 541.0 [M+H]^+.

\(^1\text{H NMR (400 MHz, CDCl}_3\) \( \delta 8.08 \text{ (d, } J = 4.9 \text{ Hz, 1H), 7.36 (d, } J = 3.9 \text{ Hz, 1H), 7.17 (d, } J = 3.9 \text{ Hz, 1H), 7.15 (d, } J = 4.9 \text{ Hz, 1H), 6.72 (s, 1H), 5.16 - 5.02 \text{ (m, 1H), 3.96 (d, } J = 1.0 \text{ Hz, 3H), 3.89 (s, 3H), 2.41 (s, 3H), 1.74 (s, 6H), 1.66 (d, } J = 6.4 \text{ Hz, 3H).} \)
Example 17: (S)-2-(3-((2-Chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)benzo[d]isoxazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

The title compound was prepared a white solid in a manner analogous to Example 5, Step A, B and C using (S)-6-bromo-4-((1,1,1-trifluoropropan-2-yl)oxy)benzo[d]isoxazol-3-amine (Intermediate 6) as start material. MS (ESI): mass calcd. for C_{21}H_{18}ClF_{4}N_{5}O_{4}, 515.85; m/z found, 516.0 [M+H]^+. ^1H NMR (400 MHz, CDCl₃) δ 7.72 (m, 1H), 7.25 (m, 2H), 7.11 (2H), 6.68 (s, 1H), 5.01 (m, J = 3.9 Hz, 1H), 4.62 (s, 2H), 3.91 (q, J = 6.5 Hz, 2H), 1.68 (d, J = 6.4 Hz, 3H), 1.39 (t, J = 7.3 Hz, 3H).

Example 18: 2-(3-((2-Chloro-6-fluoro-4-nitrophenoxo)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.
Step A: 6-Bromo-3-(2-chloro-6-fluoro-4-nitrophenoxy)-1-methyl-4-((1,1,1-
trifluoropropan-2-yl)oxy)-1H-indazole

6-Bromo-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1,2-dihydro-3H-indazol-3-one
(Intermediate 7, 500 mg, 1.47 mmol), Cs₂CO₃ (480 mg, 1.47 mmol) and 1-chloro-2,3-
difluoro-5-nitrobenzene (285 mg, 1.47 mmol) in DMF (10 mL) were stirred at room
temperature for 2 hours. The reaction solution was partitioned between ethyl acetate and
water. The organic layer was washed by brine, dried and concentrated to give the crude
product, which was then purified by flash column chromatography (30-70% EtOAc in
heptanes) to give the title compound as a white solid. MS (ESI): mass calcld. for
C₁₈H₁₂F₄N₄O₂, 512.64; m/z found, 513.0 [M+H]⁺.

Step B: 5-((Benzzyloxy)methyl)-2-(3-(2-chloro-6-fluoro-4-nitrophenoxy)-1-methyl-4-
(1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-
one

A reaction flask containing 6-bromo-3-(2-chloro-6-fluoro-4-nitrophenoxy)-1-methyl-4-
((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazole (137 mg, 0.27 mmol), 5-
((benzzyloxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (125 mg, 0.53 mmol), KI
(9 mg, 0.053 mmol), potassium phosphate tribasic (113 mg, 0.53 mmol) and dioxane (5
mL) was purged with argon for ~10 min. Copper (I) iodide (10 mg, 0.053 mmol) was
added in a separate vial followed by ~1 ml of dioxane and trans-N,N-
dimethylcyclohexane-1,2-diamine (0.008 mL, 0.053 mmol). The dark grey mixture was
purged with argon while stirring and then added to the above reaction flask. After purging
with argon for ~10 min, the reaction flask was heated at 110 °C for 5 h. The reaction was
cooled and filtered through a pad of Celite. The filtrate was concentrated and purified by
flash column chromatography (15-70% EtOAc in heptanes) to give the title compound as a
clear oil. MS (ESI): mass calcld. for C₂₉H₂₅ClF₁N₅O₆, 665.00; m/z found, 666.0 [M+H]⁺.

Step C: 2-(3-(2-Chloro-6-fluoro-4-nitrophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-
2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one
5-((Benzzyloxy)methyl)-2-(3-(2-chloro-6-fluoro-4-nitrophenoxy)-1-methyl-4-((1,1,1-
trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (10
mg, 0.015 mmol) in TFA (0.5 mL) was heated to reflux in a sealed tube for 4 hours. The solvent was removed under vacuum and the residue was purified by prep-HPLC using 20-80% ACN in water 0.1% TFA to give the title compound as a white solid after lyophilizing. MS (ESI): mass calcd. for C_{22}H_{19}ClF_{4}N_{6}O_{6}, 574.88; m/z found, 575.0

\[ [M+H]^+ \]  

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.21 (s, 1H), 8.05 (s, 1H), 7.62 (m, 1H), 7.36 (m, 1H), 4.95 (m, $J = 4.1$ Hz, 1H), 4.72 (s, 2H), 3.92 (q, $J = 6.5$ Hz, 2H), 3.80 (s, 3H), 1.56 (d, $J = 7.4$ Hz, 3H), 1.39 (t, $J = 7.5$ Hz, 3H).

Example 19: 2-((3-(2-chloro-6-fluorophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yloxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

Step A: 2-((4-Amino-2-chloro-6-fluorophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yloxy)-1H-indazol-6-yl)-5-((benzyloxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one

5-((Benzyloxy)methyl)-2-((3-(2-chloro-6-fluoro-4-nitrophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yloxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (Example 18, Step B, 100 mg, 0.15 mmol) and tin chloride (86 mg, 0.45 mmol) in EtOH (5 mL) were stirred at room temperature for 2 hours and then heated at 60 °C for another 1 hour. The reaction was cooled and quenched by saturated sodium bicarbonate and filtered. The filtrate was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated to give the crude product, which was then purified by silica
gel flash system using 10-70% ethyl acetate in heptanes to give the title compound as a yellow solid. MS (ESI): mass calcd. for C_{29}H_{27}ClF_{4}N_{5}O_{4}, 635.02; m/z found, 636.0 [M+H]^+.

**Step B:** 5-((Benzyloxy)methyl)-2-(3-(2-chloro-6-fluorophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one

Sodium nitrite (38 mg, 0.55 mmol) in water (10 mL) was slowly added into a solution of 2-(3-(4-amino-2-chloro-6-fluorophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-((benzyloxy)methyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (100 mg, 0.16 mmol) in ethanol (24 mL) and sulfuric acid (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. Then zinc (102 mg, 1.58 mmol) was added, into the reaction and it was stirred for another 1 hour at 0 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extract was washed with water, dried over anhydrous Na₂SO₄ and concentrated to give the crude product, which was then purified by silica gel chromatography on an Isco system using 20-70% ethyl acetate in heptanes to give the title compound as a white solid. MS (ESI): mass calcd. for C_{29}H_{26}ClF_{4}N_{5}O_{4}, 620.00; m/z found, 621.0 [M+H]^+.

**Step C:** 2-(3-(2-Chloro-6-fluorophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

5-((Benzyloxy)methyl)-2-(3-(2-chloro-6-fluorophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one (38 mg, 0.081 mmol) in TFA (1 mL) was heated to reflux in a sealed tube for 6 hours. The solvent was removed under vacuum and the residue was purified by prep-HPLC using 20-80% ACN in water 0.1% TFA to give the title compound as a white solid after lyophilizing. MS (ESI): mass calcd. for C_{23}H_{20}ClF_{4}N_{5}O_{4}, 529.88; m/z found, 530.0 [M+H]^+. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.30 (s, 1H), 7.25 (m, 2H), 7.11 (m, 1H), 4.95 (m, J = 4.1 Hz, 1H), 4.72 (s, 2H), 3.92 (q, J = 6.5 Hz, 2H), 3.80 (s, 3H), 1.56 (d, J = 7.4 Hz, 3H), 1.39 (t, J = 7.5 Hz, 3H).
Example 20: 2-(3-((3-(Difluoromethyl)pyridin-2-yl)oxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

![Chemical Structure](image)

Step A: 2-((6-3-((Benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-yl)oxy)nicotinaldehyde

The title compound was prepared as a white solid in a manner analogous to Example 18, Step A and B by reacting 6-bromo-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1,2-dihydro-3H-indazol-3-one (Intermediate 7) with 2-chloronicotinaldehyde followed by Ullman coupling. MS (ESI): mass calcd. for C_{29}H_{27}F_{3}N_{6}O_{5}, 596.57; m/z found, 597.0 [M+H]^+.

Step B: 5-((Benzyloxy)methyl)-2-(3-((3-(difluoromethyl)pyridin-2-yl)oxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one

2-((6-3-((Benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-yl)oxy)nicotinaldehyde (60 mg, 0.10 mmol) in DCM (2 mL) was treated with DAST (81 mg, 0.50 mmol) at -78 °C for 1 hour. The reaction was warmed to room temperature and the solution was partitioned between DCM and water. The organic layer was washed by brine, dried and concentrated to give the crude product, which was then purified by flash silica gel on an Isco system using 10-
60% ethyl acetate in heptanes to give the title compound as a white solid. MS (ESI): mass calcld. for C_{29}H_{27}F_{5}N_{6}O_{4}, 618.57; m/z found, 619.0 [M+H]^+.

Step C: 2-(3-((3-(Difluoromethyl)pyridin-2-y1)oxy)-1-methyl-4-((1,1,1-trifluoropropan-2-y1)oxy)-1H-indazol-6-y1)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one

The title compound was prepared in a manner analogous to Example 18, Step C through TFA de-protection as a white solid. MS (ESI): mass calcld. for C_{22}H_{21}F_{5}N_{6}O_{4}, 528.44; m/z found, 529.0 [M+H]^+. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (m, 1H), 8.08 (m, 1H), 7.69 (s, 1H), 7.28 (m, 1H), 7.15 (m, 1H), 6.98 (m, 1H), 4.82 (m, J = 4.5 Hz, 1H), 4.70 (s, 2H), 4.08 (q, J = 5.5 Hz, 2H), 3.88 (s, 3H), 1.46 (d, J = 5.4 Hz, 3H), 1.21 (t, J = 6.5 Hz, 3H).

Example 21: 2-(3-((1,3-dimethoxypropan-2-y1)oxy)-1-methyl-4-((1,1,1-trifluoropropan-2-y1)oxy)-1H-indazol-6-y1)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one.

The title compound was prepared as a white solid in a manner analogous to Example 18, Step A, B and C by reacting 6-bromo-1-methyl-4-((1,1,1-trifluoropropan-2-y1)oxy)-1,2-dihydro-3H-indazol-3-one (Intermediate 7) with 2-bromo-1,3-dimethoxypropane followed by Ullman coupling and TFA de-protection. MS (ESI): mass calcld. for C_{31}H_{38}F_{5}N_{6}O_{6}, 503.48; m/z found, 504.0 [M+H]^+. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 1H), 7.23 (s, 1H), 5.15 (m, 1H), 5.01 (m, J = 3.9 Hz, 1H), 4.52 (s, 2H), 3.92 (s, 6H), 3.85 (d, J = 6.5 Hz, 4H), 3.75 (s, 3H), 3.66 (m, 2H), 1.65 (d, J = 7.4 Hz, 3H), 1.42 (t, J = 7.0 Hz, 3H).
BIOLOGICAL ASSAYS

Biological Data

DHODH inhibitory activities of the compounds of Examples 1-21 were assessed using the following assays. The half maximal inhibitory concentration values (IC50) are summarized in Table 1.

*In vitro* Assay: DHODH enzymatic assay

To detect DHODH enzyme activities, dichloroindophenol (DCIP) is added as the final electron acceptor in the assay. DCIP can accept electrons from the reduced coenzyme Q generated in the assay, or from dihydroorotate (DHO) via FMN by binding presumably to the ubiquinone pocket. DCIP solutions are blue, with an intense absorbance around 600 nm, but becomes colorless upon reduction (*J. Biol. Chem.* (1986) 261, 11386). The assay buffer contained 50 mM HEPES, pH 7.5, 150 mM NaCl, 0.5 mM EDTA, and 0.1% Triton X-100 in MilliQ water. Substrate consisting of 20 mM DHO, 5mM CoQ6, and 1mM DCIP in assay buffer, initiates the reaction. The assay is run in end-point mode by quenching the reaction with the potent DHODH inhibitor brequinar. Absorbance measurements were obtained using the BMG Phera Star plate-reading spectrophotometer. Purified human DHODH was purchased from Proteros (cat. No. PR-0044). Chemicals were purchased from Sigma-Aldrich, Teknova, and Avanti Polar Lipids. Liquid handling was performed using Labcyte Echo and Formulatrix Tempest.

*In vitro* Assay: MOLM-13 Cellular Assay

MOLM-13 cells were obtained from DSMZ and were maintained in RPMI 1640 + Glutamax + 25mM HEPES (Invitrogen, catalog number 72400) supplemented with 10% heat inactivated fetal bovine serum (FBS; Invitrogen, catalog number 16140). The day prior to assay set-up, cells were pelleted, resuspended in fresh media, counted, and cells were plated at 0.4 x 10⁶ cell/mL in a T150 flask. On the day of the assay, cells were pelleted, resuspend in fresh media, counted and seeded at 5,000 cells/well in white opaque 96-well tissue culture treated microplates (Perkin Elmer, catalog number 6005680). Cells were exposed to different concentrations of test compounds at 37 °C, 5% CO₂ for 72 hours immediately after seeding. Cell viability was acquired on a Perkin Elmer Envision 2104
multilabel reader using the CellTiter-Glo assay (Promega) according to the manufacturer’s instructions.

<table>
<thead>
<tr>
<th>Example #</th>
<th>Compound Name</th>
<th>MOLM-13 IC$_{50}$ (nM)</th>
<th>hDHODH IC$_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-(3-(((2-Chloro-6-fluorophenyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
<td>3</td>
<td>8</td>
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<tr>
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<td>2-(3-(((2-Chloro-6-fluorophenyl)(methyl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>388</td>
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<td>(S)-2-(3-(((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>(R)-2-(3-(((2-chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>2-(3-(((2-Chloro-6-fluorophenyl)amino)-1-isopropyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-4-ethyl-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>2-(3-(((2-Chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
<td>1.2</td>
<td>3</td>
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<td>MOLM-13 IC₅₀ (nM)</td>
<td>hDHODH IC₅₀ (nM)</td>
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<td>4-Ethyl-2-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-Indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>4-Ethyl-2-(7-fluoro-1-methyl-3-(phenylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-Indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>(S)-4-Ethyl-2-(7-fluoro-1-methyl-3-(o-tolylamino)-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-Indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>(S)-2-(3-((2-Chloro-6-fluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-Indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>2</td>
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<td>(S)-2-(3-((2-(Difluoromethyl)phenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-Indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>(S)-2-(3-((2-Chloro-4,6-difluorophenyl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-Indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>15</td>
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<td>(S)-2-(3-((2-Chloro-4-methylpyridin-3-yl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-Indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
<td>5.7</td>
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<td>hDHODH IC$_{50}$ (nM)</td>
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<td>(S)-4-((6-(4-Ethyl-3-(hydroxymethyl)-5-oxo-4,5-dihydro-1H,1,2,4-triazol-1-yl)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-3-yl)amino)-3-methylbenzonitrile</td>
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<td>(S)-4-Ethyl-2-(7-fluoro-3-((2-methoxy-4,6-dimethylpyridin-3-yl)amino)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>(S)-2-((3-(2,4-Dimethylpyridin-3-yl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
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<td>(S)-2-((4-((3-((2-Chloro-4-methylpyridin-3-yl)amino)-7-fluoro-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-1-methyl-1H-imidazol-2-yl)propan-2-ol)</td>
<td>0.1</td>
<td>1</td>
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<td>(S)-2-((3-((2-Chloro-6-fluorophenyl)amino)-4-((1,1,1-trifluoropropan-2-yl)oxy)benzod[1][9]azol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
<td>0.7</td>
<td>2</td>
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<td>18</td>
<td>2-(3-((2-Chloro-6-fluoro-4-nitrophenoxoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-(hydroxymethyl)benzod[1][9]azol-6-yl)-1-methyl-1H-imidazol-2-yl)propan-2-ol</td>
<td>&gt;100</td>
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<td>Example #</td>
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<td>MOLM-13 IC₅₀ (nM)</td>
<td>hDHODH IC₅₀ (nM)</td>
</tr>
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<tr>
<td>19</td>
<td>ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>2-(3-(2-chloro-6-fluorophenoxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>21</td>
<td>2-(3-((1,3-dimethoxypropan-2-yl)oxy)-1-methyl-4-((1,1,1-trifluoropropan-2-yl)oxy)-1H-indazol-6-yl)-4-ethyl-5-(hydroxymethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one</td>
<td>nt</td>
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NT means not tested.
We claim:

1. A compound of Formula I

wherein

\[ R^1 = \text{alkyl}, \text{CH}_2\text{OH}, \text{CH}_2\text{OCH}_3, \text{or } -\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3 \]

wherein

\[ R^2 = \text{alkyl}, \text{CH}_2\text{OH}, \text{CH}_2\text{OCH}_3, \text{or } -\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3 \]

wherein

\[ R^3 = \text{alkyl}, \text{CH}_2\text{OH}, \text{CH}_2\text{OCH}_3, \text{or } -\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3 \]

wherein

\[ R^4 = \text{alkyl}, \text{CH}_2\text{OH}, \text{CH}_2\text{OCH}_3, \text{or } -\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3 \]
R^f is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₅, -NO₂, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;
R^g is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₅, -NO₂, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;
R^h is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₅, -NO₂, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;
R^i is selected from the group consisting of: -H, -CH₃, and -C(2-3)alkyl; wherein said -CH₃ is optionally substituted with a member selected from the group consisting of: -OCH₃, -SCH₃, and -OCF₃; and wherein said -CH₃ is optionally substituted with up to three fluorine atoms; and wherein said -C(2-3)alkyl is optionally substituted with a member selected from the group consisting of: -OH, -OCH₃, -SCH₃, and -OCF₃; and wherein said -C(1-3)alkyl is optionally substituted with up to six fluorine atoms;
R^j is -H, -C(1-3)alkyl, -F, or -Cl;
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

2. The compound of claim 1

![Chemical structure diagram]

wherein R^k is -CH(CH₃OCH₃)₂,
R^f is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₅, -NO₂, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;
R^g is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₅, -NO₂, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;
R^h is -H, -Cl, -F, -CN, -OCH₃, -OCHF₂, -OCH₅, -NO₂, or -C(1-2)alkyl; wherein said -C(1-2)alkyl is optionally substituted with up to three fluorine atoms;
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
3. The compound of claim 1 wherein

\[
\begin{align*}
R^1 & \text{ is } \begin{array}{c} R^b \text{, or } R^d \\
\end{array} \\
\text{wherein } \quad R^a & \text{ is } -C(1-4)\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C(1-4)\text{alkyl is optionally substituted with up to three fluorine atoms;} \\
R^b & \text{ is } -\text{CH}_2\text{OH, } -C(1-2)\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C(1-2)\text{alkyl is optionally substituted with up to three fluorine atoms;} \\
R^c & \text{ is } -C(1-2)\text{alkyl, or } -\text{CH}_2\text{OCH}_3; \text{ wherein said } -C(1-2)\text{alkyl is optionally substituted with up to three fluorine atoms;} \\
R^d & \text{ is } -\text{C}(\text{CH}_3)\text{OH, } -\text{C}(\text{CF}_3)\text{OH, } -\text{CH}_2\text{OH, or } -\text{CH}(\text{CH}_3)\text{OH; } \\
R^2 & \text{ is } -\text{CH}(\text{CH}_3)\text{, or } -\text{CF}_3; \\
Q & \text{ is } O, \text{ or } N-R^e \\
\text{wherein } R^e & \text{ is } -H, -\text{CH}_3, \text{ or } -\text{CH}(\text{CH}_3); \\
R^3 & \text{ is } -O-R^4, \text{ or } -\text{NH-R}^4 \\
\text{wherein } R^4 & \text{ is } -\text{CH}(\text{CH}_3\text{OCH}_3)_2, \\
R^f & \text{ is } -H, -\text{Cl}, -\text{F}, -\text{CN}, -\text{OCH}_3, -\text{OCHF}_2, -\text{OCH}_2, -\text{NO}_2, \text{ or } -\text{C}(1-2)\text{alkyl; wherein said } -\text{C}(1-2)\text{alkyl is optionally substituted with up to three fluorine atoms;} \\
R^6 & \text{ is } -H, -\text{Cl}, -\text{F}, -\text{CN}, -\text{OCH}_3, -\text{OCHF}_2, -\text{OCH}_2, -\text{NO}_2, \text{ or } -\text{C}(1-2)\text{alkyl; wherein said } -\text{C}(1-2)\text{alkyl is optionally substituted with up to three fluorine atoms;} \\
R^h & \text{ is } -H, -\text{Cl}, -\text{F}, -\text{CN}, -\text{OCH}_3, -\text{OCHF}_2, -\text{OCH}_2, -\text{NO}_2, \text{ or } -\text{C}(1-2)\text{alkyl; wherein said } -\text{C}(1-2)\text{alkyl is optionally substituted with up to three fluorine atoms;} \\
R^5 & \text{ is } -H, -\text{C}(1-3)\text{alkyl, } -\text{F}, \text{ or } -\text{Cl;} \\
\text{or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or } N\text{-oxide thereof.}
\end{align*}
\]
4. The compound of claim 3, wherein

\[
\begin{align*}
R^a & \text{ is } -C(1-4) \text{alkyl; wherein said } -C(1-4) \text{alkyl is optionally substituted with up to three fluorine atoms;} \\
R^b & \text{ is } -\text{CH}_2\text{OH}, -\text{CH}_3, -\text{CF}_3, -\text{CHF}_2, \text{ or } -\text{CH}_2\text{F;} \\
R^c & \text{ is } -\text{CH}_3, -\text{CF}_3, -\text{CHF}_2, \text{ or } -\text{CH}_2\text{F;} \\
R^d & \text{ is } -\text{C(CH}_3)_2\text{OH}, -\text{C(CF}_3)_2\text{OH}, \text{ or } -\text{CH(CH}_3)\text{OH;} \\
R^3 & \text{ is } -\text{O-R}^4, \text{ or } -\text{NH-R}^4
\end{align*}
\]

wherein \( R^3 \) is \(-\text{CH(CH}_2\text{OCH}_3)_2, \)
\( R^f \) is \(-\text{H}, -\text{Cl}, -\text{F}, -\text{CN}, -\text{CH}_3, -\text{CHF}_2, -\text{OCH}_3, \text{ or } -\text{NO}_2; \)
\( R^g \) is \(-\text{H}, -\text{Cl}, -\text{F}, -\text{CN}, -\text{CH}_3, -\text{CHF}_2, -\text{OCH}_3, \text{ or } -\text{NO}_2; \)
\( R^h \) is \(-\text{H}, -\text{Cl}, -\text{F}, -\text{CN}, -\text{CH}_3, -\text{CHF}_2, -\text{OCH}_3, \text{ or } -\text{NO}_2; \)
\( R^5 \) is \(-\text{H}, -\text{CH}_3, -\text{F}, \text{ or } -\text{Cl}; \)
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

5. The compound of claim 4, wherein

\[
\begin{align*}
R^1 & \text{ is } R^b, \text{ or } R^d
\end{align*}
\]

wherein
\( R^a \) is \(-\text{CH}_2\text{CH}_3; \)
\( R^b \) is \(-\text{CH}_2\text{OH}; \)
\( R^c \) is -CH₃;
\( R^d \) is -C(CH₃)₂OH;

\( R^3 \) is -OCH(CH₂OCH₃)₂,

\( R^5 \) is -H, or -F;

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

6. The compound of claim 5, wherein
\( Q \) is O, or N-\( R^c \)
wherein \( R^c \) is -H, or -CH₃;

or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

7. A compound selected from the group consisting of:
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
8. A method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition comprising inhibiting or altering dihydroorotate oxygenase enzyme activity in the subject by administering to the subject an effective amount of at least one compound according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

9. The method according to claim 8, wherein the disorder, disease or medical condition is selected from the group consisting of: inflammatory disorders and autoimmune disorders.

10. The method according to claim 8, wherein the disorder, disease or medical condition is cancer.

11. The method according to claim 8, wherein the disorder, disease or medical condition is selected from the group consisting of: lymphomas, leukemias, carcinomas, and sarcomas.

12. The method according to claim 8, wherein the disorder, disease or medical condition is selected from the group consisting of: acute lymphoblastic leukemia, acute myeloid leukemia, (acute) T-cell leukemia, acute lymphoblastic leukemia, acute lymphocytic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, bisphenotypic B myelomonocytic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloid leukemia, chronic myelomonocytic leukemia, large granular lymphocytic leukemia, plasma cell leukemia, and also myelodysplastic syndrome, which can develop into an acute myeloid leukemia.

13. The method according to claim 8, wherein the disorder, disease or medical condition is acute myeloid leukemia.

14. A pharmaceutical composition comprising: (A) a compound according to any of claims 1-7, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof; and (B) at least one pharmaceutically acceptable excipient.
INTERNATIONAL SEARCH REPORT

PCT/IB2021/054636

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04 C07D403/14 C07D413/04 A61K31/4196 A61K31/423
ADD. A61K31/4439 A61P29/00 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

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"Z" document member of the same patent family

Date of the actual completion of the international search: 20 July 2021

Date of mailing of the international search report: 02/08/2021

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-3040, Fax: (+31-70) 340-3016

Authorized officer: Moriggi, J
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