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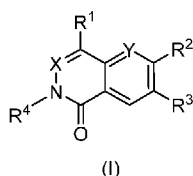
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(57) Abstract: Disclosed are compounds, compositions and methods for treating diseases, disorders, or medical conditions that are affected by the modulation of DHODH. Such compounds are represented by Formula (I) as follows, wherein R¹, R², R³, R⁴, X, and Y are defined herein.



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
5 Patent Application No. 63/085,313, filed on September 30, 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
10 (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,
15 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
20 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
25 represents an unmet medical need with >20,000 new cases per year in the US with 5-year overall
survival below 30% (Stein ET 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
30 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

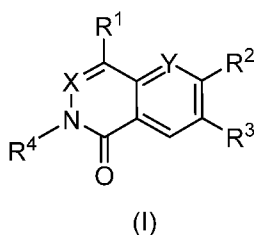
a synthetic lethality in PTEN and KRAS mutant solid tumors (Pharmacology and Therapeutics, Epub October 19th, 2018; Mathur D et al., Cancer Discovery 7: 1, 2017; Cell Chemical Biology 25: 1, 2018).

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 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 compounds of Formula (I),



wherein

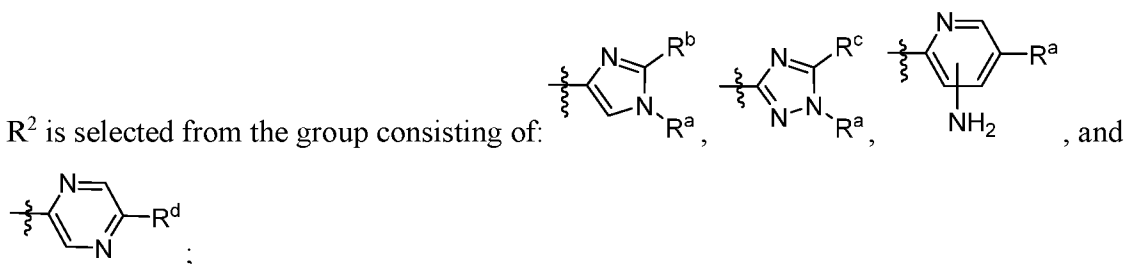
X is CH or N;

Y is CH or N;

wherein when X is N then Y is CH;

R¹ is C₁₋₆alkyl or C₁₋₆haloalkyl;

R² is selected from the group consisting of:



wherein

R^a is C₁₋₆alkyl;

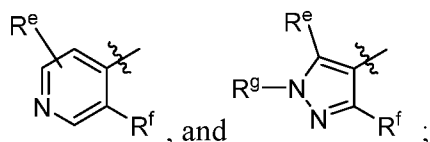
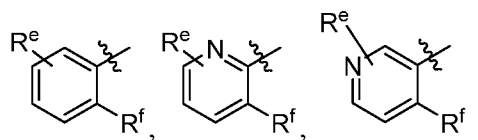
R^b is C₁₋₆alkyl substituted with one OH member;

R^c is C_{1-6} alkyl substituted with one OH member; or $C(=O)CH_3$;

R^d is C_{3-6} cycloalkyl;

R^3 is H or halo; and

R^4 is selected from the group consisting of:



wherein

R^e is selected from the group consisting of: H; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with one member selected from the group consisting of: OH, OCH_3 , and OCF_3 ;

C_{1-6} haloalkyl; C_{1-6} haloalkyl substituted with one member selected from the group consisting of: OH, and OCH_3 ; and OC_{1-6} alkyl;

R^f is selected from the group consisting of: H; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with one member selected from the group consisting of: OH, OCH_3 , and OCF_3 ;

C_{1-6} haloalkyl; C_{1-6} haloalkyl substituted with one member selected from the group consisting of: OH, and OCH_3 ; and OC_{1-6} alkyl; and

R^g is H or C_{1-6} alkyl;

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

The present invention further provides methods for treating or ameliorating a disease, syndrome, condition, or disorder in a subject, including a mammal and/or human in which the disease, syndrome, condition, or disorder is affected by the inhibition of DHODH enzymatic activity, including but not limited to, cancer and/or inflammatory or immunological diseases, using a compound of Formula (I) or a pharmaceutically acceptable salt, isotope, N-oxide, solvate, or stereoisomer thereof.

Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

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.

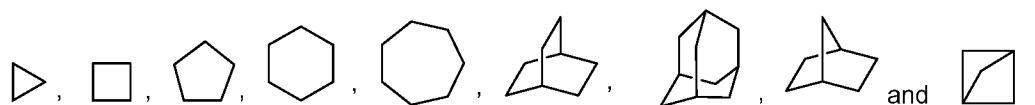
The singular forms "a", "an" and "the" encompass plural references unless the context clearly indicates otherwise.

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.

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, isohexyl, 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. "C₁₋₆alkyl" refers to straight- or branched-chain alkyl group having from 1 to 6 carbon atoms in the chain. "C₁₋₄alkyl" refers to straight- or branched-chain alkyl group having from 1 to 4 carbon atoms in the chain.

The term "cycloalkyl" refers to a saturated or partially saturated, monocyclic, fused polycyclic, or spiro polycyclic carbocycle having from 3 to 12 ring atoms per carbocycle. "C₃₋₆cycloalkyl" refers to a carbocycle having from 3 to 6 ring atoms per carbocycle. Illustrative examples of cycloalkyl groups include the following entities, in the form of properly bonded moieties:



The term "halogen" or "halo" represents chlorine, fluorine, bromine, or iodine.

The term "haloalkyl" refers to a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms in the chain optionally substituting hydrogens with halogens. The term "C₁₋₆

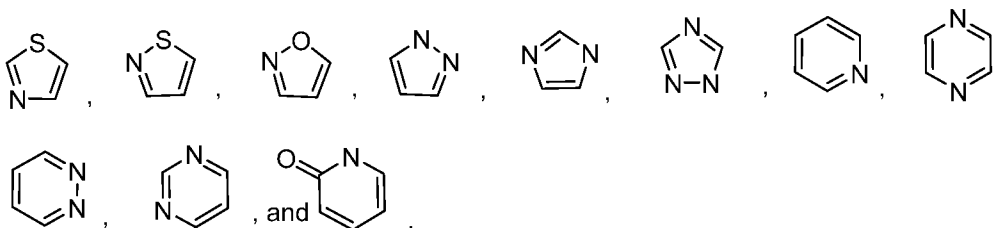
haloalkyl” as used here refers to a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms in the chain, optionally substituting hydrogens with halogens. The term “C₁₋₄ haloalkyl” as used here refers to a straight- or branched-chain alkyl group having from 1 to 4 carbon atoms in the chain, optionally substituting hydrogens with halogens. Examples of “haloalkyl” groups include trifluoromethyl (CF₃), difluoromethyl (CF₂H), monofluoromethyl (CH₂F), pentafluoroethyl (CF₂CF₃), tetrafluoroethyl (CHFCH₂CF₃), monofluoroethyl (CH₂CH₂F), trifluoroethyl (CH₂CF₃), tetrafluorotrifluoromethylethyl (CF(CF₃)₂), 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 “aryl” refers to a monocyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) having 6 atoms per ring. (Carbon atoms in the aryl groups are sp² hybridized.)

The term “phenyl” represents the following moiety:



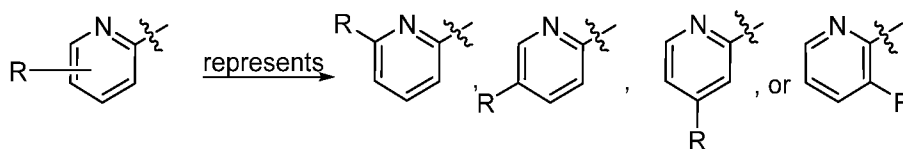
The term “heteroaryl” refers to a monocyclic or fused bicyclic heterocycle (ring structure having ring atoms selected from carbon atoms and up to four heteroatoms selected from nitrogen, oxygen, and sulfur) having from 3 to 9 ring atoms per heterocycle. Illustrative examples of heteroaryl groups include the following entities, in the form of properly bonded moieties:



Those skilled in the art will recognize that the species of cycloalkyl, heteroaryl and aryl groups listed or illustrated above are not exhaustive, and that additional species within the scope of these defined terms may also be selected.

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.



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 (IA), (IB), and (IC)) that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, *et al.*, “Pharmaceutical Salts”, J. Pharm. Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002. 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, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, 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 α -hydroxy acid, such as mandelic acid, citric acid, or tartaric 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 ^2H (or chemical symbol D), ^3H (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 ^2H or ^3H), 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., ^2H , or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *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.

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 $m > n$.

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”.

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

5 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,
10 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 $^+\text{H}_3\text{NCH}_2\text{COO}^-$.

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
15 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
20 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
25 the same variable elsewhere in the formula, unless stated otherwise.

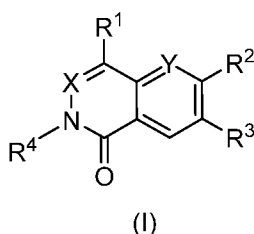
By way of a first example on substituent terminology, if substituent $\text{S}^1_{\text{example}}$ is one of S_1 and S_2 , and substituent $\text{S}^2_{\text{example}}$ is one of S_3 and S_4 , then these assignments refer to embodiments of this invention given according to the choices $\text{S}^1_{\text{example}}$ is S_1 and $\text{S}^2_{\text{example}}$ is S_3 ; $\text{S}^1_{\text{example}}$ is S_1 and $\text{S}^2_{\text{example}}$ is S_4 ; $\text{S}^1_{\text{example}}$ is S_2 and $\text{S}^2_{\text{example}}$ is S_3 ; $\text{S}^1_{\text{example}}$ is S_2 and $\text{S}^2_{\text{example}}$ is S_4 ; and equivalents of
30 each one of such choices. The shorter terminology “ $\text{S}^1_{\text{example}}$ is one of S_1 and S_2 , and $\text{S}^2_{\text{example}}$ 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_{example} is one of S_1 , S_2 , and S_3 , this listing refers to embodiments of this invention for which S_{example} is S_1 ; S_{example} is S_2 ; S_{example} is S_3 ; S_{example} is one of S_1 and S_2 ; S_{example} is one of S_1 and S_3 ; S_{example} is one of S_2 and S_3 ; S_{example} is one of S_1 , S_2 and S_3 ; and S_{example} is any equivalent of each one of these choices. The shorter terminology " S_{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.

The nomenclature " C_i-C_j " with $j > i$, when applied herein to a class of substituents, is meant to refer to embodiments of this invention for which each and every one of the number of carbon members, from i to j including i and j , is independently realized. By way of example, the term C_1-C_3 refers independently to embodiments that have one carbon member (C_1), embodiments that have two carbon members (C_2), and embodiments that have three carbon members (C_3).

Embodiments of this invention include compounds of Formula (I),



wherein

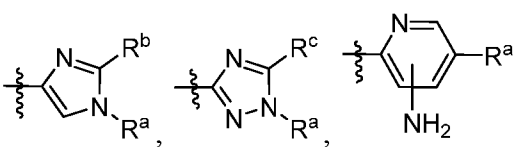
X is CH or N;

Y is CH or N;

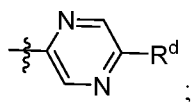
wherein when X is N then Y is CH;

R^1 is C_{1-6} alkyl or C_{1-6} haloalkyl;

R^2 is selected from the group consisting of:



, and



wherein

R^a is C_{1-6} alkyl;

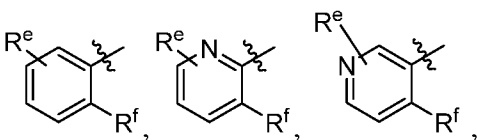
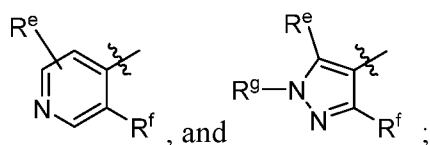
5 R^b is C_{1-6} alkyl substituted with one OH member;

R^c is C_{1-6} alkyl substituted with one OH member; or $C(=O)CH_3$;

R^d is C_{3-6} cycloalkyl;

R^3 is H or halo; and

R^4 is selected from the group consisting of:

wherein

R^e is selected from the group consisting of: H; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with one member selected from the group consisting of: OH, OCH_3 , and OCF_3 ;

15 C_{1-6} haloalkyl; C_{1-6} haloalkyl substituted with one member selected from the group consisting of: OH, and OCH_3 ; and OC_{1-6} alkyl;

R^f is selected from the group consisting of: H; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with one member selected from the group consisting of: OH, OCH_3 , and OCF_3 ;

C_{1-6} haloalkyl; C_{1-6} haloalkyl substituted with one member selected from the group consisting of: OH, and OCH_3 ; and OC_{1-6} alkyl; and

20 R^g is H or C_{1-6} alkyl;

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

An additional embodiment of the invention is a compound of Formula (I) wherein X is CH and Y is CH.

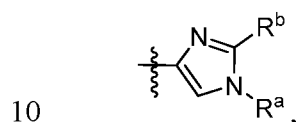
An additional embodiment of the invention is a compound of Formula (I) wherein X is CH and Y is N.

An additional embodiment of the invention is a compound of Formula (I) wherein X is N and Y is CH.

5 An additional embodiment of the invention is a compound of Formula (I) wherein R¹ is C₁₋₄alkyl.

An additional embodiment of the invention is a compound of Formula (I) wherein R¹ is CH(CH₃)₂.

An additional embodiment of the invention is a compound of Formula (I) wherein R² is

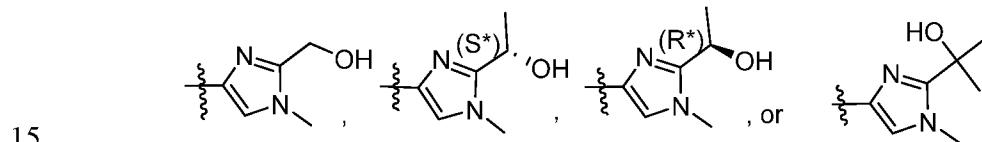


wherein

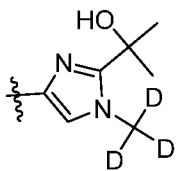
R^a is CH₃; and

R^b is CH₂OH, CH(OH)CH₃, or C(OH)(CH₃)₂.

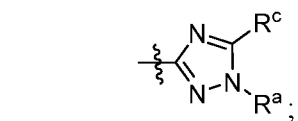
An additional embodiment of the invention is a compound of Formula (I) wherein R² is



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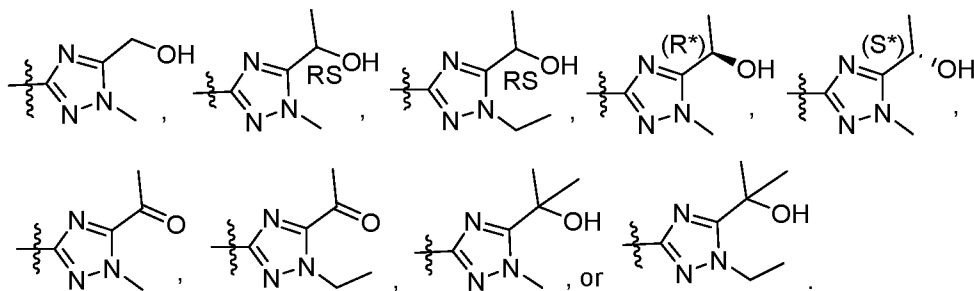


wherein

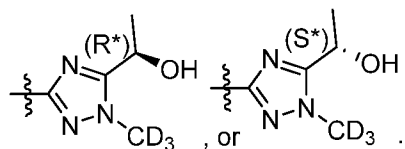
R^a is CH₃, or CH₂CH₃; and

R^c is CH₂OH, C(=O)CH₃, CH(OH)CH₃, or C(OH)(CH₃)₂.

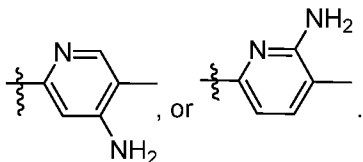
An additional embodiment of the invention is a compound of Formula (I) wherein R² is



An additional embodiment of the invention is a compound of Formula (I) wherein R^2 is

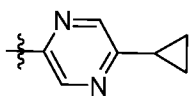


An additional embodiment of the invention is a compound of Formula (I) wherein R^2 is



5

An additional embodiment of the invention is a compound of Formula (I) wherein R^2 is

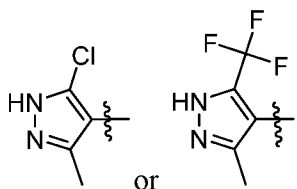


An additional embodiment of the invention is a compound of Formula (I) wherein R^3 is

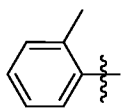
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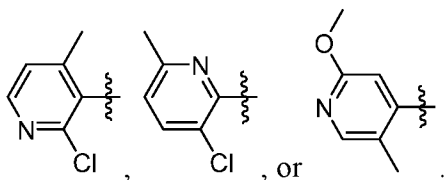
An additional embodiment of the invention is a compound of Formula (I) wherein R^4 is



An additional embodiment of the invention is a compound of Formula (I) wherein R^4 is



An additional embodiment of the invention is a compound of Formula (I) wherein R⁴ is



An additional embodiment of the current invention is a compound selected from the compounds shown below in Table 1, and pharmaceutically acceptable salts, isotopes, N-oxides, solvates, and stereoisomers thereof:

Table 1

Example #	Compound Name
1	6-(5-Cyclopropylpyrazin-2-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
2	6-(6-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
3	6-(4-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
4	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
5	Racemic 7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
6	6-(5-Acetyl-1-methyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
7	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
8	7-Fluoro-6-(2-(hydroxymethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
9	7-Fluoro-6-(5-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
10	(S*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;

Example #	Compound Name
11	(R*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
12	(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
13	(S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
14	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)phthalazin-1(2H)-one;
15	(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)phthalazin-1(2H)-one;
16	2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
17	2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
18	2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
19	2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
20	6-(1-Ethyl-5-(2-hydroxypropan-2-yl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
21	(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
22	(S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
23	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-(methyl-d3)-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
24	6-(5-Acetyl-1-ethyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;

Example #	Compound Name
25	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;
26	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;
27	2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
28	6-(1-Ethyl-5-(1-hydroxyethyl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;
29	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)phthalazin-1(2H)-one;
30	2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
31	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one;
32	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one; and
33	3-Fluoro-2-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-8-isopropyl-6-(<i>o</i> -tolyl)-1,6-naphthyridin-5(6H)-one.

A further embodiment of the current invention is a compound selected from the group consisting of:

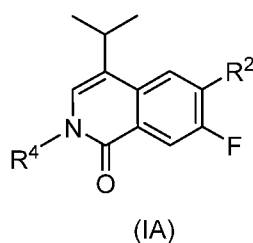
- 5 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one;
- 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;

2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one; and

2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;

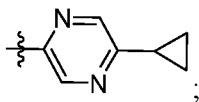
and, optionally, one or more of pharmaceutically acceptable salts, isotopes, N-oxides, solvates, and stereoisomers thereof:

An additional embodiment of the invention is a compound of Formula (I) having the Formula (IA):



wherein

R^2 is selected from the group consisting of:



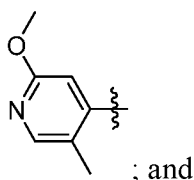
wherein

R^a is C_{1-4} alkyl;

R^b is C_{1-4} alkyl substituted with one OH member;

R^c is C_{1-4} alkyl substituted with one OH member; or $C(=O)CH_3$;

R^4 is selected from the group consisting of:

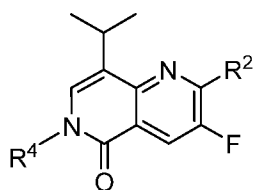


R^e is Cl or CF_3 ;

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

An additional embodiment of the invention is a compound of Formula (I) having the Formula

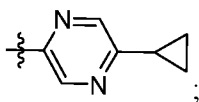
(IB):



(IB)

wherein

R^2 is selected from the group consisting of:



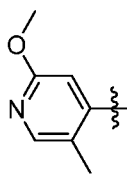
wherein

R^a is C_{1-4} alkyl;

R^b is C_{1-4} alkyl substituted with one OH member;

R^c is C_{1-4} alkyl substituted with one OH member; or $C(=O)CH_3$;

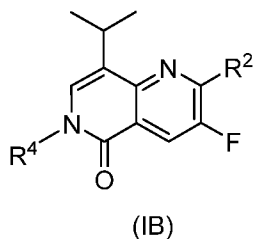
R^4 is selected from the group consisting of:



R^e is Cl or CF_3 ;

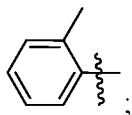
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

An additional embodiment of the invention is a compound of Formula (I) having the Formula (IB):



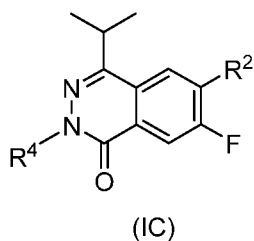
wherein

5 R^2 is R^a is C₁₋₄alkyl, R^b is C₁₋₄alkyl substituted with one OH member, and R^4 is



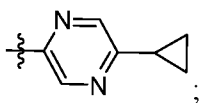
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

10 An additional embodiment of the invention is a compound of Formula (I) having the Formula (IC):



wherein

R^2 is selected from the group consisting of: , , , and



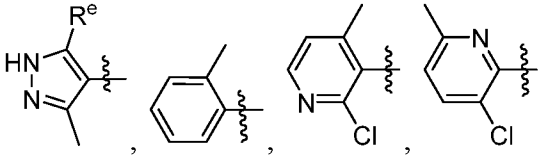
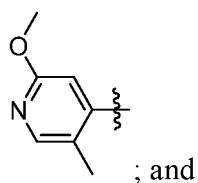
15 wherein

R^a is C₁₋₄alkyl;

R^b is C₁₋₄alkyl substituted with one OH member;

R^c is C_{1-4} alkyl substituted with one OH member; or $C(=O)CH_3$;

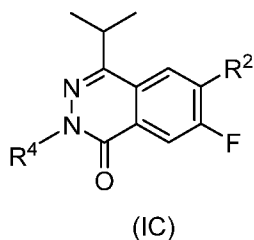
R^4 is selected from the group consisting of:

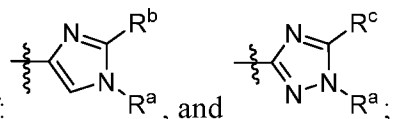
R^e is Cl or CF_3 ;

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

An additional embodiment of the invention is a compound of Formula (I) having the Formula (IC):



10 wherein R^2 is selected from the group consisting of:



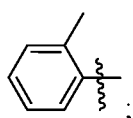
wherein

R^a is C_{1-4} alkyl;

R^b is C_{1-4} alkyl substituted with one OH member;

R^c is C_{1-4} alkyl substituted with one OH member; and

15 R^4 is



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

Also within the scope of the invention are enantiomers and diastereomers of the compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC)). Also within

the scope of the invention are the pharmaceutically acceptable salts, N-oxides or solvates of the compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC)). Also within the scope of the invention are the pharmaceutically acceptable prodrugs of compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC)), and pharmaceutically active metabolites of the compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC)).

Also within the scope of the invention are isotopic variations of compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC)), 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) (as well as compounds of Formula (IA), (IB), and (IC)). Also within the scope of the invention are the pharmaceutically acceptable prodrugs of the isotopic variations of the compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC)), and pharmaceutically active metabolites of the isotopic variations of the compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC)).

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.

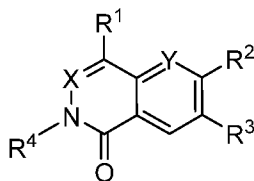
Thus, particular embodiments of the present invention are directed to pharmaceutical and veterinary compositions comprising compounds of Formula (I) and at least one pharmaceutically acceptable carrier, pharmaceutically acceptable excipient, and/or pharmaceutically acceptable diluent. By way of example, 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.

An additional embodiment of the invention is a pharmaceutical composition comprising:

(A) an effective amount of at least one compound selected from compounds of Formula (I)



(I)

wherein

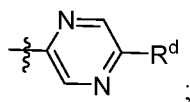
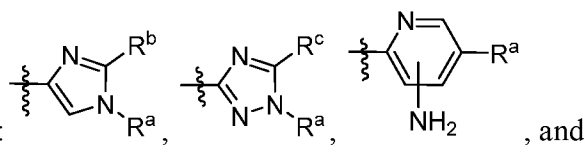
X is CH or N;

Y is CH or N;

wherein when X is N then Y is CH;

R¹ is C₁₋₆alkyl or C₁₋₆haloalkyl;

R² is selected from the group consisting of:



wherein

R^a is C₁₋₆alkyl;

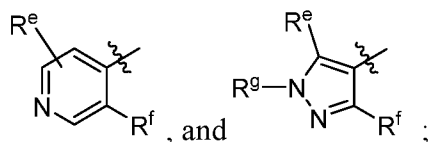
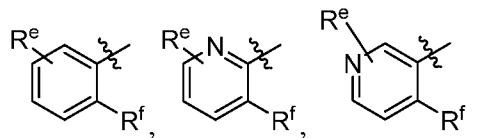
R^b is C₁₋₆alkyl substituted with one OH member;

R^c is C₁₋₆alkyl substituted with one OH member; or C(=O)CH₃;

R^d is C₃₋₆cycloalkyl;

R³ is H or halo;

R⁴ is selected from the group consisting of:



wherein

R^e is selected from the group consisting of: H; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with one member selected from the group consisting of: OH, OCH₃, and OCF₃;

C₁₋₆haloalkyl; C₁₋₆haloalkyl substituted with one member selected from the group consisting of: OH, and OCH₃; and OC₁₋₆alkyl;

R^f is selected from the group consisting of: H; halo; C₁₋₆alkyl; C₁₋₆alkyl substituted with one member selected from the group consisting of: OH, OCH₃, and OCF₃;

C₁₋₆haloalkyl; C₁₋₆haloalkyl substituted with one member selected from the group consisting of: OH, and OCH₃; and OC₁₋₆alkyl; and

R^g is H or C₁₋₆alkyl;

or pharmaceutically acceptable salts, isotopes, N-oxides, solvates, or stereoisomers thereof; and (B) at least one pharmaceutically acceptable excipient.

An additional embodiment of the invention is a pharmaceutical composition comprising an effective amount of a compound shown in Table 1 (*e.g.*, a compound selected from Examples 1-33), or a pharmaceutically acceptable salt, isotope, N-oxide, solvate, or stereoisomer of the compound of Table 1, a pharmaceutically acceptable prodrug of the compound of Table 1, or a pharmaceutically active metabolite of the compound of Table 1; 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 (I) 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;

or pharmaceutically acceptable salts, isotopes, N-oxides, solvates, or stereoisomers thereof.

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.

5 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.

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

15 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.

20 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) (as well as compounds of Formula (IA), (IB), and (IC), such as a compound of Table 1), enantiomers and diastereomers of the compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC) such as a compound of Table 1), isotopic variations of the compounds of Formula (I) (as well as compounds of Formula (IA), (IB), and (IC), such as a compound of Table 1), 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) (as well as compounds of Formula (IA), (IB), and (IC), such as a compound of Table 1), and pharmaceutically acceptable salts of all the foregoing (e.g., by inhibiting or otherwise altering dihydroorotate oxygenase enzyme activity in the subject).

5 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
10 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,
15 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
20 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.

25 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,
30 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:

5 leukemias including but not limited to acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), (acute) T-cell leukemia, acute monocytic leukemia, acute promyelocytic leukemia (APL), bisphenotypic B myelomonocytic leukemia, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), large granular lymphocytic leukemia, plasma cell leukemia, and also myelodysplastic
10 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
15 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
20 (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
25 sarcomas including but not limited to sarcoma of the soft tissue, gliosarcoma, osteosarcoma, malignant fibrous histiocyoma, lymphosarcoma, and rhabdomyosarcoma;

and

other cancers, such as solid tumors, including but not limited to breast cancer, colorectal
30 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 compounds of Formula (I), such as a compound shown in Table 1, 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 compounds of Formula (I), such as a compound shown in Table 1, 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 used in the instant specification, particularly the schemes and examples, are as follows in Table 2:

Table 2.

Abbreviation	Name
Å	angstrom
ACN or MeCN	acetonitrile
AcOH	glacial acetic acid

Abbreviation	Name
AcOK	Potassium acetate
AlMe ₃	Trimethylaluminium
Ar	Argon
aq.	aqueous
BCl ₃	Boron trichloride
Bn or Bzl	benzyl
Boc	tert-butyloxycarbonyl
Catacxium A Pd G2	Chloro[(di(1-adamantyl)- <i>N</i> -butylphosphine)-2-(2-aminobiphenyl)]palladium(II)
Celite®	diatomaceous earth
CO ₂	Carbon dioxide
(COCl) ₂	Oxalyl chloride
Cs ₂ CO ₃	Cesium carbonate
DCE	dichloroethane
DCM	dichloromethane
DIBALH or DIBAL-H	Diisobutylaluminium hydride
DIPEA or DIEA	diisopropyl-ethyl amine
DEA	Diethanolamine
DMA	dimethylaniline
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
Dppf or DPPF	1,1'-Bis(diphenylphosphino)ferrocene
ES-API	electrospray-atmospheric pressure ionization
ESI	electrospray ionization
EtOAc or EA	ethyl acetate
EtOH	ethanol
h or hr(s)	hour or hours

Abbreviation	Name
H ₂	Hydrogen gas
HCl	Hydrogen chloride
HPLC	high performance liquid chromatography
isovaleraldehyde	3-methylbutanal
KI	Potassium iodide
K ₂ CO ₃	Potassium carbonate
LCMS or LC/MS	Liquid chromatography–mass spectrometry
MeOH	methanol
MeONa	Sodium methoxide
MeMgBr	methylmagnesium bromide
MgSO ₄	Magnesium sulfate
MHz	megahertz
min	minute or minutes
MS	mass spectrometry
NaBH ₄	Sodium borohydride
NaOH	Sodium hydroxide
NaHCO ₃	Sodium bicarbonate
Na ₂ CO ₃	Sodium carbonate
Na ₂ SO ₄	Sodium sulfate
N ₂	Nitrogen gas
NBS	N-Bromosuccinimide
NH ₂ NH ₂ .H ₂ O	Hydrazine monohydrate
NIS	N-iodosuccinimide
NH ₄ Cl	Ammonium chloride
NH ₄ HCO ₃	Ammonium bicarbonate
NH ₃ .H ₂ O or NH ₄ OH	Ammonium hydroxide
NMR	nuclear magnetic resonance

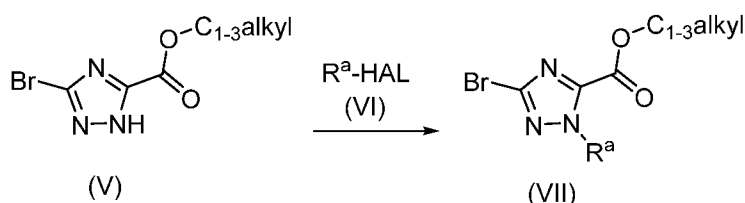
Abbreviation	Name
$[\text{Pd}(\text{allyl})\text{Cl}]_2$	Allylchloropalladium dimer or Bis(allyl)dichlorodipalladium or Bis(allyl)dichloropalladium or Bis(allylchloropalladium) or Diallyldichlorodipalladium
$\text{PdCl}_2(\text{PPh}_3)_2$ or $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	bis(triphenylphosphine)palladium(II) dichloride
Pd-118	Dichloro [1,1'-bis(di-tertbutylphosphino)ferrocene] palladium(II)
PPh_3	triphenylphosphine
ppm	parts per million
$\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ or $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
Pd/C	Palladium on carbon
PG	Protecting group
RP	reverse-phase
rt or RT	room temperature
R_t	retention time
Sec	second or seconds
SFC	supercritical fluid chromatography
SiO_2	silica gel
O_2	Oxygen gas
TES	triethylsilane
TEA or Et_3N	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TF_2NPh	N-phenylbis(trifluoromethanesulfonimide)
triflate	trifluoromethanesulfonyl
Tf_2O	Triflic anhydride or Trifluoromethanesulfonic anhydride

PREPARATIVE EXAMPLES

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.

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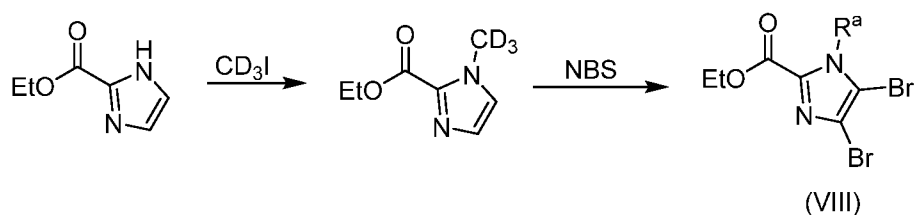
SCHEME 1



According to SCHEME 1, a compound of formula (VII), R^a is C_{1-6} alkyl or CD_3 , is prepared from a commercially available or synthetically accessible compound of formula (V), by employing an alkyl halide of formula (VI), where HAL is I, and R^a is C_{1-6} alkyl or CD_3 , and the like; a base, such as Cs_2CO_3 , K_2CO_3 , and the like; in a suitable solvent such as DMF, acetone, DMSO, and the like; at ambient temperature.

10

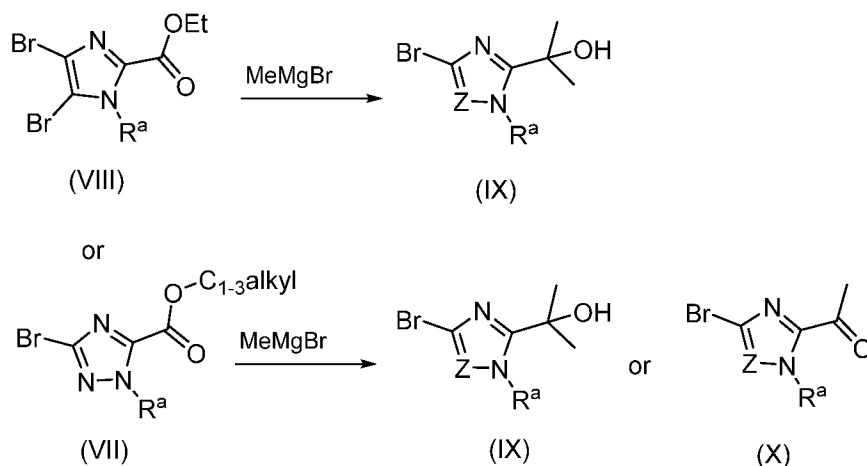
SCHEME 2



According to Scheme 2, commercially available or synthetically accessible ethyl 1H-imidazole-2-carboxylate is alkylated employing a base such as Cs_2CO_3 , K_2CO_3 , and the like; an alkylating agent such as, CD_3I , and the like; in a suitable solvent such as DMF, acetone, DMSO and the like; to provide ethyl 1-(methyl- d_3)-1H-imidazole-2-carboxylate. Ethyl 1-(methyl- d_3)-1H-imidazole-2-carboxylate is brominated employing bromination conditions known to one skilled in the art, for example, using a suitable brominating agent such as NBS, and the like; in a suitable solvent such as DMF, to afford a compound of formula (VIII), where R^a is CD_3 .

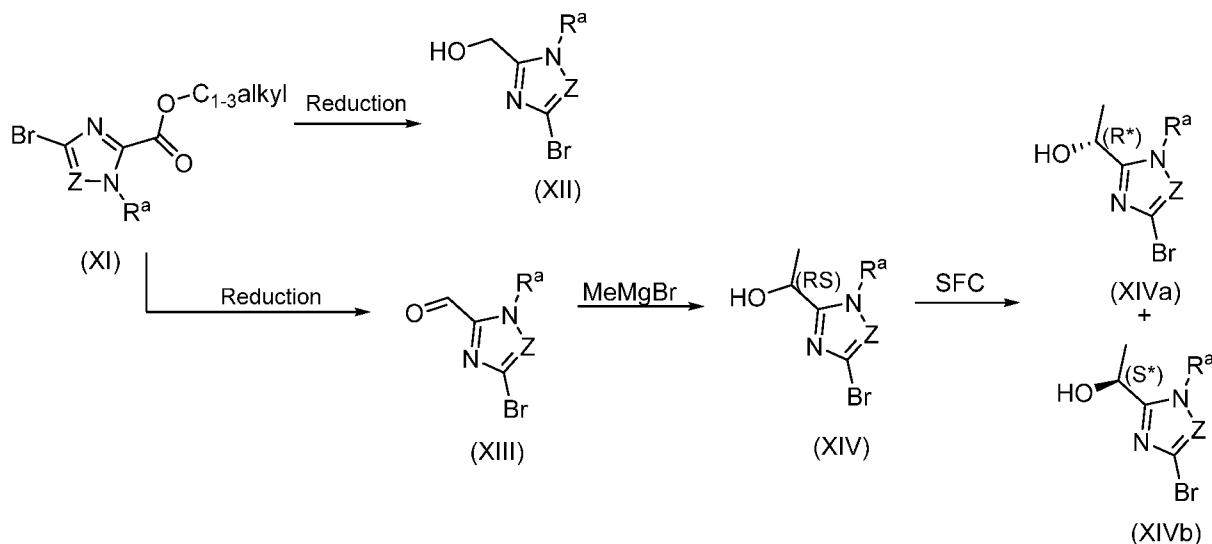
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SCHEME 3



According to SCHEME 3, a commercially available or synthetically accessible ester of formula (VIII), where R^a is $\text{C}_{1-6}\text{alkyl}$ or CD_3 , is reacted with a Grignard reagent, such as MeMgBr, in a suitable solvent such as THF, ether, 1,4-dioxane and the like; at low temperatures, preferably 0°C ; to provide a compound of formula (IX), where R^a is $\text{C}_{1-6}\text{alkyl}$ or CD_3 ; and Z is CH. In a similar fashion, a compound of formula (VII), where R^a is $\text{C}_{1-6}\text{alkyl}$ or CD_3 ; is reacted with a Grignard reagent such as MeMgBr, to provide a compound of formula (IX), where Z is N. It is noted that under certain controlled conditions, when Z is N, only a single addition occurs to provide a compound of formula (X), where R^a is $\text{C}_{1-6}\text{alkyl}$.

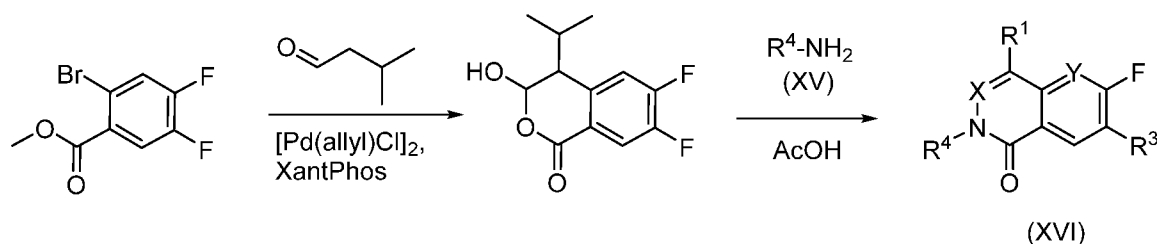
SCHEME 4



According to SCHEME 4, a commercially available or synthetically accessible ester compound of formula (XI) where R^a is $\text{C}_{1-6}\text{alkyl}$, and Z is CH or N, is reduced employing conditions known to one skilled in the art. For example, treatment of a compound of formula

(XI) where R^a is C_{1-6} alkyl, and Z is CH or N; with a suitable reducing agent such as $NaBH_4$, and the like; an additive such as $CaCl_2$, and the like; in a suitable solvent such as EtOH, MeOH, and the like; at ambient temperatures provides a compound of formula (XII). A commercially available or synthetically accessible ester compound of formula (XI) where R^a is C_{1-6} alkyl or CD_3 , and Z is CH or N, is reduced to the aldehyde compound of formula (XIII) employing conditions known to one skilled in the art. For example, a compound of formula (XI) where R^a is C_{1-6} alkyl or CD_3 , and Z is CH or N is reacted with a reducing agent such as DIBALH; in a suitable solvent, such as DCM, DCE, and the like; at low temperatures such as $-78\text{ }^\circ\text{C}$ to rt; to provide a compound of formula (XIII). A compound of formula (XIII) is reacted with Grignard reagent, such as $MeMgBr$, employing conditions previously described to provide a compound of formula (XIV) as a racemic mixture of compounds. The racemic mixture of compounds is separated by SFC to provide the secondary alcohols of formulas (XIVa) and (XIVb) in enantiopure form.

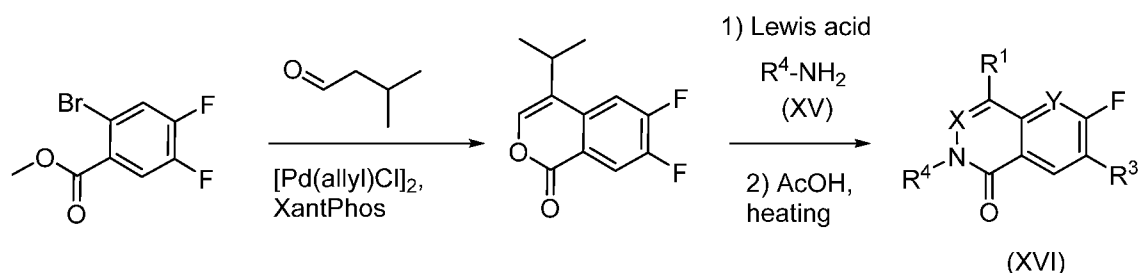
SCHEME 5



According to SCHEME 5, methyl 2-bromo-4,5-difluorobenzoate is reacted with 3-methylbutanal; employing a palladium catalyst such as allylpalladium(II) chloride dimer, and the like; a ligand such as XantPhos, and the like; a suitable base such as Cs_2CO_3 , and the like; in the presence of a water scavenger such as molecular sieves (4A); in a suitable solvent such as 1,4-dioxane; to provide 6,7-difluoro-3-hydroxy-4-isopropylisochroman-1-one. A compound of formula (XV), where R^4 is as described in claim 1; is reacted with trimethyl aluminum; in a suitable solvent such as dichloromethane, dichloroethane, toluene, or a mixture thereof; the resulting solution is combined with 6,7-difluoro-3-hydroxy-4-isopropylisochroman-1-one, followed by subsequent treatment with acetic acid under heating temperature of $80-100\text{ }^\circ\text{C}$ for a period of time ranging from 5 to 24 hours; to provide a compound of formula (XVI); where X and Y are CH, R^1 is isopropyl, and R^3 is F. In certain cases, a compound of formula (XV), such as *o*-toluidine and the like; is directly condensed with 6,7-difluoro-3-hydroxy-4-

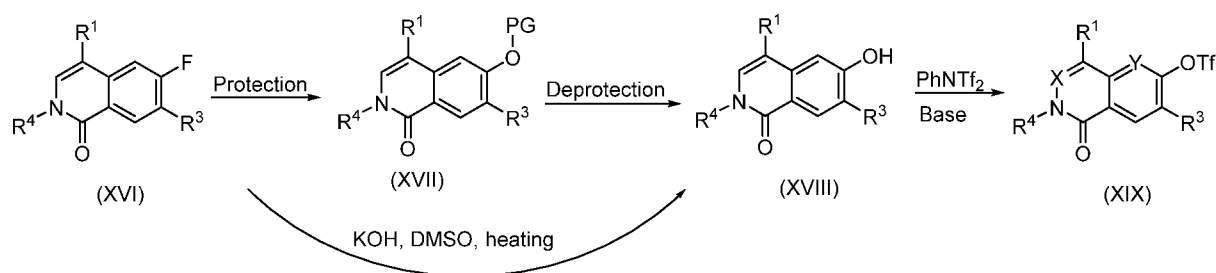
isopropylisochroman-1-one in acetic acid under heating temperature of 80-100 °C for a period of time ranging from 10 to 24 hours; to provide a compound of formula (XVI), where X and Y are CH.

SCHEME 6



According to SCHEME 2, the reaction of methyl 2-bromo-4,5-difluorobenzoate with 3-methylbutanal employing a palladium catalyst such as allylpalladium(II) chloride dimer, and the like; a ligand such as XantPhos, and the like; a suitable base such as Cs₂CO₃, and the like; in the presence of water scavenger such as molecular sieve (4A); in a suitable solvent such as 1,4-dioxane thereof; to provide 6,7-difluoro-4-isopropyl-1H-isochromen-1-one. A compound of formula (XV), where R⁴ is as defined in claim 1; is reacted with a Lewis acid such as AlMe₃, AlCl₃, or the like; in a suitable solvent such as dichloromethane, dichloroethane, toluene, or a mixture thereof; the resulting solution is combined with 6,7-difluoro-3-hydroxy-4-isopropylisochroman-1-one, followed by subsequent treatment with acetic acid under heating temperature of 80-100 °C for a period of time ranging from 5 to 24 hours; to provide a compound of formula (XVI); where X and Y are CH, R¹ is isopropyl and R³ is F.

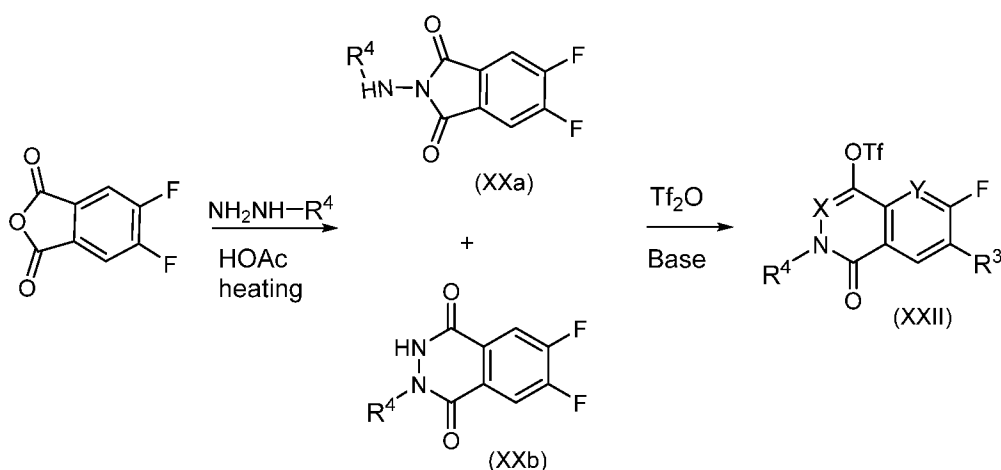
SCHEME 7



According to SCHEME 7, a compound of formula (XVI) is reacted with benzyl alcohol employing a suitable base such as NaH, and the like; in a suitable solvent such as THF; to provide a compound of formula (XVII); where 6-fluoro group is selectively displaced by a benzyloxy group. The removal of benzyl group in a compound of formula (XVII) is achieved by

employing BCl_3 , at a temperature ranging from $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, in a suitable solvent such as in DCM, DCE, and the like; to afford a compound of formula (XVIII). Alternatively, the treatment of a compound of formula (XVI) with KOH or NaOH in a suitable solvent such as DMSO under a heating temperature between $80\text{--}100\text{ }^\circ\text{C}$; to provide a compound of formula (XVIII) in one step directly. Finally a compound of formula (XVIII) is reacted with a triflating agent such as N-phenylbis(trifluoromethanesulfonimide) (TF_2NPh), a base such as TEA, DIEA, and the like, in a suitable solvent such as DCM, and the like; under room temperature; to provide a triflate compound of formula (XIX), where X is CH, Y is CH, R^3 is F, and R^4 are defined as previously described. The other triflating agents such as trifluoromethanesulfonic anhydride (Tf_2O), a base such as triethylamine (TEA), pyridine, and the like; may also be used.

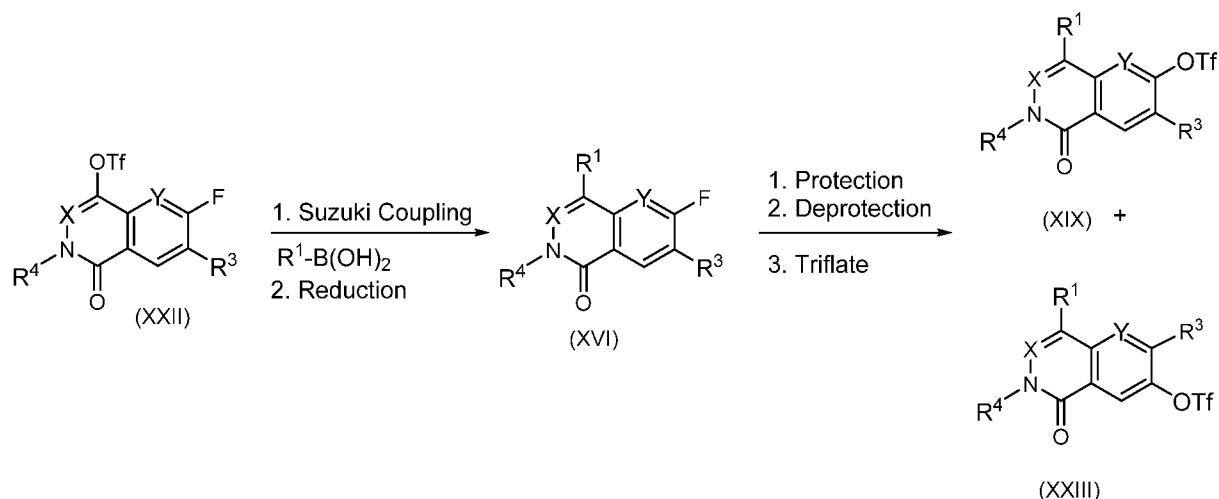
SCHEME 8



According to SCHEME 8, commercially available or synthetically accessible 4,5-difluorophthalic anhydride is reacted with a hydrazine compound of formula $\text{R}^4\text{-NHNH}_2$, where R^4 is as defined in claim 1; in acetic acid; at a temperature of $100\text{ }^\circ\text{C}$ - $125\text{ }^\circ\text{C}$; for a period of 24 h to 48 h; to afford the mixture of a compound of formula (XXa) and a compound of formula (XXb). The mixture can be separated by chromatography, trituration, or precipitation to afford a compound of formula (XXb). The conversion of a compound of formula (XXb), either in high purity or as a crude mixture with a compound of formula (XXa), with a sulfonate-based leaving group such as trifluoromethanesulfonyl (triflate), is achieved by reaction with a triflating agent such as trifluoromethanesulfonic anhydride (Tf_2O), a base such as triethylamine (TEA), pyridine, and the like; in a suitable solvent such as DCM and the like; to provide a compound of formula (XXII), where X is N and Y is CH. Milder triflating agents such as N-

phenylbis(trifluoromethanesulfonimide) (TF₂NPh), a base such as TEA, DIEA, and the like, in a suitable solvent such as DCM, and the like; may be used.

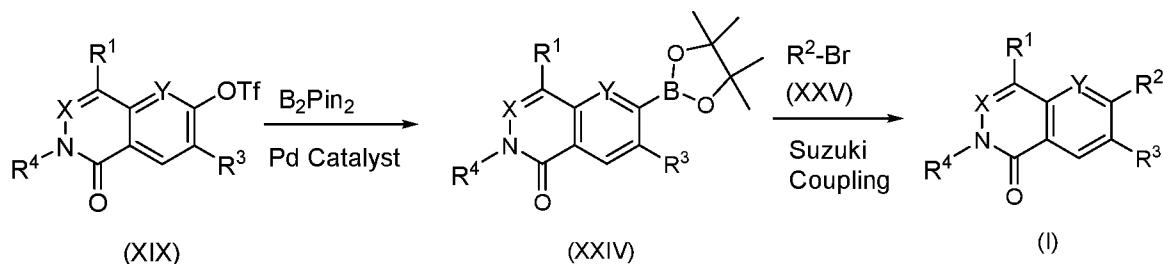
SCHEME 9



According to SCHEME 9, a compound of formula R¹-B(OH)₂ is reacted under Suzuki coupling conditions previously described, with a compound of formula (XXII), to provide a compound of formula (XVI), where R¹ and R⁴ are as defined in claim 1. For example, a compound of formula (XXII), where X is N and Y is CH, and R³ is F, is reacted with a commercially available or synthetically accessible boronic acid (or boronic ester) such as R¹-B(OH)₂, where R¹ is C₂₋₆alkenyl or C₂₋₆haloalkenyl; a palladium catalyst such as bis(triphenylphosphine)palladium(II) dichloride, and the like; a suitable base such as a potassium phosphate, Cs₂CO₃, and the like; in a suitable solvent such as dioxane, water, ethanol, or a mixture thereof. Subsequent reduction of the C₂₋₆alkenyl or C₂₋₆haloalkenyl under hydrogenation conditions using catalyst such as Pd/C or the like; in a suitable solvent such as EtOAc or the like; under an atmosphere of hydrogen (15-40 psi) for a period of 4-24 h; provides a compound of formula (XVI), where R¹ is C₂₋₆alkyl or C₂₋₆haloalkyl.

A compound of formula (XVI) is reacted with benzyl alcohol employing conditions previously described to provide a mixture of two compounds which is carried on without separation. Deprotection and triflation of the mixture of compounds is achieved employing conditions previously described to afford the triflate compounds of formula (XIX) and formula (XXIII), where X is N, Y is CH, R³ is F, and R¹ and R⁴ are as described in claim 1. A compound of formula (XIX) is obtained in high purity by preparative HPLC or SFC separation.

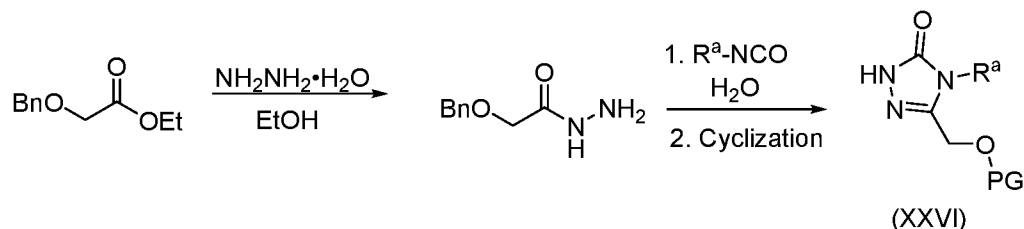
SCHEME 10



According to SCHEME 10, a compound of formula (XIX) is borylated employing methods known to those skilled in the art. For example, a compound of formula (XIX), where X is CH or N, Y is CH, R³ is H or F, R¹ is C₁₋₆alkyl or C₁₋₆haloalkyl, and R⁴ is as defined as in claim 1; is reacted with transition metal catalyst, such as bis(triphenylphosphine)palladium(II) dichloride, 1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl₂), and the like; in a suitable solvent such as dimethylsulfoxide (DMSO), 1,4-dioxane, and the like; a base such as KOAc, and the like; a borylation reagent such as 4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (bis(pinacolato)diboron), and the like; employing microwave irradiation or conventional heating; at temperatures ranging from of 90 to 130 °C; to provide a compound of formula (XXIV).

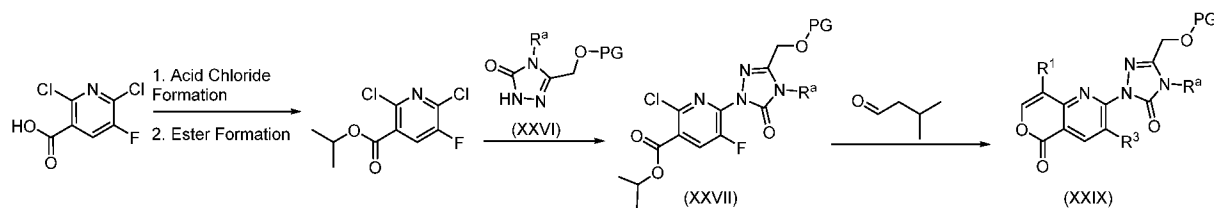
A commercially available or synthetically accessible compound of formula (XXV), (which includes compounds of formulas (IX), (X), (XII), (XIV), (XIVa), and (XIVb)); is reacted under Suzuki coupling conditions as previously described, with a compound of formula (XXIV), provides a compound of Formula (I). For example, a compound of formula (XXIV), is reacted with a commercially available or synthetically accessible heteroaryl bromide of formula (XXV), where R² is optionally substituted imidazolyl, pyrazinyl, pyridinyl, or triazolyl as defined in claim 1; a palladium catalyst such as bis(triphenylphosphine)palladium(II) dichloride, 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride, XPhos Pd G3, Pd-118, and the like; a suitable base such as Cs₂CO₃, Na₂CO₃, and the like; in a suitable solvent such as 1,4-dioxane, water, ethanol, or a mixture thereof; employing microwave irradiation or conventional heating; at temperatures ranging from 80 to 100 °C; to provide a compound of Formula compound (I).

SCHEME 11



According to SCHEME 11, a 1,2,4-triazol-5(4H)-one compound of formula (XXVI), where PG is Bn, is prepared from ethyl 2-(benzyloxy)acetate in three steps. In a first step 2-(benzyloxy)acetohydrazide is prepared by the reaction of ethyl 2-(benzyloxy)acetate with hydrazine hydrate, in a suitable solvent such as EtOH, and the like; at temperatures ranging from 70 to 85 °C. Reaction of the hydrazide with an isocyanate of formula R^a-NCO, where R^a is C₁₋₆₆alkyl, in a suitable solvent such as water, and the like; provides the corresponding semicarbazide. Subsequent cyclization of the semicarbazide with a suitable base such as NaOH, in a suitable solvent such as water, provides a compound of formula (XXVI), where PG is Bn.

SCHEME 12

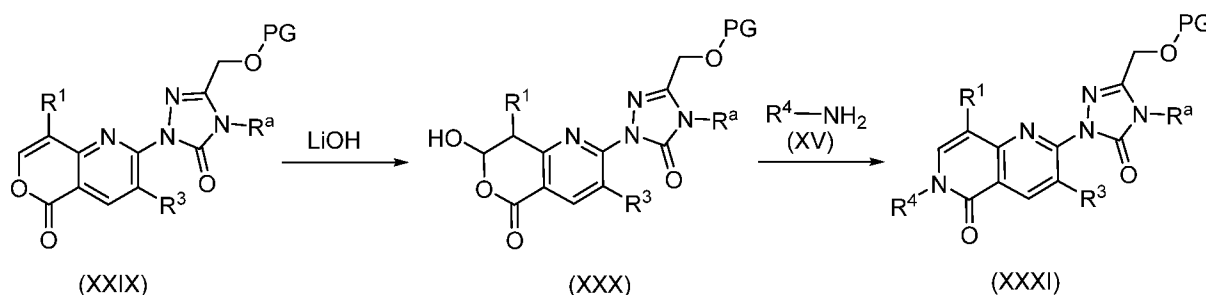


According to SCHEME 12, isopropyl 2,6-dichloro-5-fluoronicotinate is prepared in two steps from 2,6-dichloro-5-fluoronicotinic acid. In a first step, 2,6-dichloro-5-fluoronicotinic acid is reacted with (COCl)₂, a catalytic amount of DMF, in a suitable solvent such as THF, and the like, at temperatures ranging from 0 °C to 25 °C, for a period of 1 h, to provide 2,6-dichloro-5-fluoronicotinoyl chloride. Subsequent reaction of 2,6-dichloro-5-fluoronicotinoyl chloride with propan-2-ol, a suitable base such as pyridine, in a suitable solvent such as THF, provides isopropyl 2,6-dichloro-5-fluoronicotinate. Isopropyl 2,6-dichloro-5-fluoronicotinate is reacted with a commercially available or synthetically accessible nucleophilic compound of formula (XXVI), where PG is benzyl, and R^a is C₁₋₆₆alkyl; in the presence of a base such as K₂CO₃, Cs₂CO₃, NaHCO₃, triethylamine, and the like; in a suitable solvent such as dimethylsulfoxide (DMSO), DMF, THF, ACN, and the like; to afford a compound of formula (XXVII). A compound of formula (XXVII) is reacted with 3-methylbutanal; a palladium catalyst such as allylpalladium(II) chloride dimer, and the like; a ligand such as 1,1'-

bis(diphenylphosphino)ferrocene (dppf), and the like; a suitable base such as, Cs_2CO_3 , and the like; in the presence of a water scavenger such as molecular sieves (4A); in a suitable solvent such as 1,4-dioxane; to provide a compound of formula compound (XXIX), where R^1 is isopropyl, R^3 is F, PG is benzyl, and R^a is C_{1-6} alkyl.

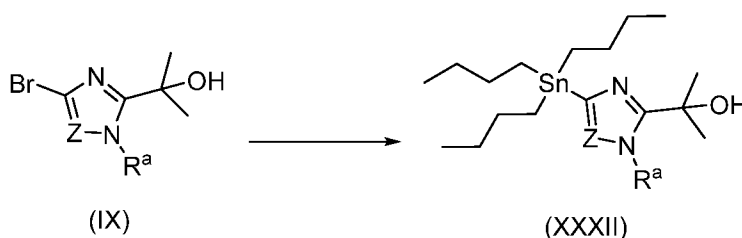
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SCHEME 13



10 According to SCHEME 13, a compound of formula (XXX) is prepared by hydration of a compound of formula (XXIX) using a base, such as LiOH, and the like; in a suitable solvent mixture, such as EtOH and water. Treatment of a compound of formula (XXX) with a commercially available or synthetically accessible amine compound of formula (XV) and acetic acid (AcOH); at elevated temperatures, preferably 85 °C; to provide a compound of formula (XXXI) where R^1 is isopropyl, R^3 is F, PG is benzyl, R^a is C_{1-6} alkyl, and R^4 is as defined in claim 1.

SCHEME 14

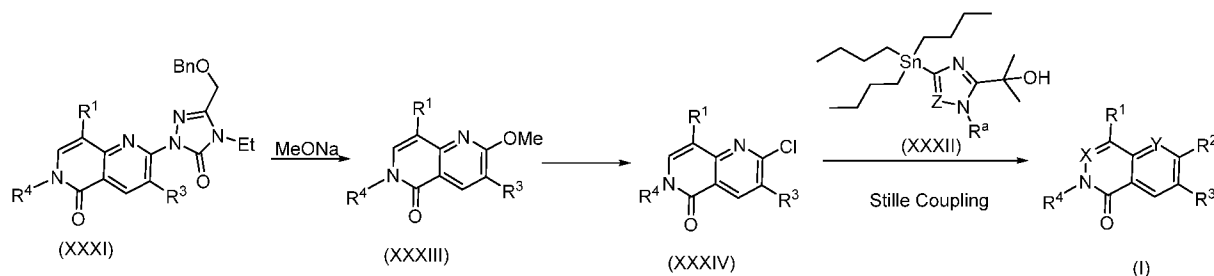


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According to SCHEME 14, a compound of formula (IX), where Z is CH, and R^a is C_{1-6} alkyl, is reacted with a source of Bu_3Sn radical such as hexa-*n*-butylditin; a palladium catalyst such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, and the like; in a suitable solvent such as toluene; at a temperature of about 100 °C; for a period of 12-18 h; to provide a compound of formula (XXXI), where Z is CH, and R^a is C_{1-6} alkyl.

20

SCHEME 15



According to SCHEME 15, a compound of formula (XXXI) is reacted with an alkoxide reagent, preferably MeONa; in a suitable polar solvent such as DMF, DMSO, and the like; to afford a compound of formula (XXXIII). Further reaction of a compound of formula (XXXIII) with a chlorinating reagent such as POCl₃, and the like; in a suitable polar solvent such as DMF, and the like; at elevated temperatures of about 100 °C; affords a compound of formula (XXXIV). A compound of formula (XXXIV), undergoes a Stille cross coupling reaction, with an alkyl stannane of formula (XXXII), employing conditions known to one skilled in the art, to provide a compound of Formula (I). For example, a compound of formula (XXXIV) is reacted with a commercially available or synthetically accessible organostannane compound of formula (XXXII), where Z is CH and R^a is C₁₋₆alkyl, using a palladium catalyst such as Pd(PPh₃)₃Cl₂, Pd(dppf)Cl₂, and the like; in a suitable solvent such as 1,4-dioxane, toluene, and the like; at refluxing temperatures for a period of 2.5 h; to provide a compound of Formula (I), where X is CH, Y is N, R¹, R², R³, R⁴ are defined as described in Claim 1.

Compounds of Formula (I) may be converted to their corresponding salts using methods known to one of ordinary skill in the art. For example, an amine of Formula (I) is treated with trifluoroacetic acid, HCl, or citric acid in a solvent such as Et₂O, CH₂Cl₂, THF, MeOH, chloroform, or isopropanol to provide the corresponding salt form. Alternately, trifluoroacetic acid or formic acid salts are obtained as a result of reverse phase HPLC purification conditions. Crystalline forms of pharmaceutically acceptable salts of compounds of Formula (I) may be obtained in crystalline form by recrystallization from polar solvents (including mixtures of polar solvents and aqueous mixtures of polar solvents) or from non-polar solvents (including mixtures of non-polar solvents).

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they

may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

Compounds prepared according to the schemes described above may be obtained as single forms, such as single enantiomers, by form-specific synthesis, or by resolution. Compounds prepared according to the schemes above may alternately be obtained as mixtures of various forms, such as racemic (1:1) or non-racemic (not 1:1) mixtures. Where racemic and non-racemic mixtures of enantiomers are obtained, single enantiomers may be isolated using conventional separation methods known to one of ordinary skill in the art, such as chiral chromatography, recrystallization, diastereomeric salt formation, derivatization into diastereomeric adducts, biotransformation, or enzymatic transformation. Where regioisomeric or diastereomeric mixtures are obtained, as applicable, single isomers may be separated using conventional methods such as chromatography or crystallization.

The following specific examples are provided to further illustrate the invention and various preferred embodiments.

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 (SiO₂) 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% ACN in water (with 0.225%FA) over 10 min and then hold at 100% ACN 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(10 μ m, 150 x 25mm), or Boston Green ODS C18(5 μ m, 150 x 30mm), and mobile phase of 5-99% ACN in water(0.1%TFA) over 10 min and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min.

5 or

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

10 or

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

15 or

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

20 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 vary according to the compound characteristics, with a flow rate ranging from 50g/min to 70g/min. The column temperature was ambient temperature

25 Mass spectra (MS) were obtained on a SHIMADZU LCMS-2020 MSD or Agilent 1200\G6110A MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass.

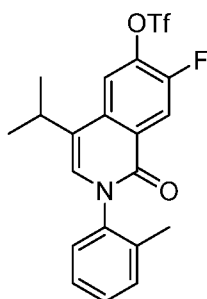
30 Nuclear magnetic resonance (NMR) spectra were obtained on Bruker model AVIII 400 spectrometers. Definitions for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dt = doublet of triplets, spt = septet, quin = quintet, 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 12.0, ChemDraw Ultra 14.0 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 10.01 (Advanced Chemistry).

Compounds designated as R* or S* are enantiopure compounds where the absolute configuration was not determined.

Intermediate 1: 7-Fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate.



Step A. 6,7-Difluoro-3-hydroxy-4-isopropylisochroman-1-one. To a mixture of methyl 2-bromo-4,5-difluorobenzoate (2 g, 8.0 mmol), Xantphos (476 mg, 0.8 mmol), [Pd(allyl)Cl]₂ (73 mg, 0.2 mmol), Cs₂CO₃ (5.2 g, 16 mmol) in 1,4-dioxane (30 mL) was added isovaleraldehyde (1.4 g, 16 mmol) slowly by syringe. The reaction mixture was degassed with nitrogen for 2 min and then heated at 85 °C for 14 h. The mixture was cooled to room temperature, filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The combined filtrate was concentrated. The residue was purified by column chromatography (SiO₂, gradient elution: 30-60% ethyl acetate in heptane) to give the title compound as a light yellow amorphous solid (560 mg, 29% yield). LCMS (ES-API): mass calcd. for C₁₂H₁₂F₂O₃, 242.1; m/z found, 243.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, *J* = 8.07, 10.03 Hz, 1H), 7.08 (dd, *J* = 7.09, 10.03 Hz, 1H), 5.94 (s, 1H), 5.26 (br s, 1H), 2.78 (br d, *J* = 6.85 Hz, 1H), 1.90 (br d, *J* = 9.78 Hz, 1H), 1.06 (d, *J* = 6.85 Hz, 3H), 0.91 (d, *J* = 6.85 Hz, 3H) ppm.

Step B. 6,7-Difluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one. To a stirred solution of *o*-toluidine (0.91 mL, 8.6 mmol) in DCM (10 mL) was added a toluene solution (2 M) of AlMe₃ (3.2 mL, 6.4 mmol) under nitrogen. The mixture was stirred at rt for 0.5 h, then a DCM solution

(10 mL) of 6,7-difluoro-3-hydroxy-4-isopropylisochroman-1-one (520 mg, 2.2 mmol) was added. The mixture was stirred at room temperature for 16 h. Aqueous HCl (1N, 1 mL) was added, and the mixture was stirred for 2 min, then poured into water (20 mL), and extracted with DCM (40 mL) and ethyl acetate (40 mL). The combined organic extract was washed with brine (20 mL), dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, 10-30% EtOAc in heptane) to give the title compound as a yellow oil (790 mg, 70% yield). LCMS (ES-API): mass calcd. for C₁₉H₁₇F₂NO, 313.1; m/z found, 314.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.31 (dd, *J* = 8.31, 10.76 Hz, 1H), 7.53 (dd, *J* = 7.09, 11.98 Hz, 1H), 7.30-7.40 (m, 3H), 7.25 (d, *J* = 7.34 Hz, 1H), 6.85 (s, 1H), 2.93-3.27 (m, 1H), 2.15 (s, 3H), 1.30 (dd, *J* = 1.96, 6.85 Hz, 6H) ppm.

Step C. 6-(Benzyloxy)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one. To a solution of benzyl alcohol (2.1 g, 19 mmol) in anhydrous THF (40 mL) was slowly added NaH (60%, 0.96 g, 24 mmol). The mixture was heated at 80 °C for 0.5 h, and then cooled to -10 °C. 6,7-difluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one (2.5 g, 7.98 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was poured into aqueous saturated NH₄Cl solution and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, 10-30% EtOAc in heptane) to give the title compound as a colorless amorphous solid (3.1 g, 96% yield). LCMS (ES-API): mass calcd. for C₂₆H₂₄FNO₂, 401.2; m/z found, 402.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 11.74 Hz, 1H), 7.17-7.56 (m, 10H), 6.78 (s, 1H), 5.32 (s, 2H), 3.10 (td, *J* = 6.79, 13.33 Hz, 1H), 2.14 (s, 3H), 1.22 (dd, *J* = 1.22, 6.60 Hz, 6H) ppm.

Step D. 7-Fluoro-6-hydroxy-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one. To a solution of 6-(benzyloxy)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one (3.1 g, 7.7 mmol) in DCM (30 mL) at -78 °C under nitrogen was added a DCM solution (1 M) of BCl₃ (23 mL, 23 mmol). The reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with MeOH (5 mL) at -78 °C. Then aqueous saturated NaHCO₃ solution was added, and the mixture was extracted with DCM and ethyl acetate. The combined organic extract was dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, 50-100% EtOAc in heptane) to give the title compound as a white solid (2.3 g, 96% yield). LCMS (ES-API): mass calcd. for C₁₉H₁₈FNO₂, 311.1; m/z found, 312.0 [M+H]⁺. ¹H NMR (400 MHz,

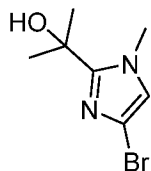
CDCl₃) δ 8.22 (d, J = 10.76 Hz, 1H), 7.29-7.41 (m, 3H), 7.21-7.26 (m, 2H), 6.79 (s, 1H), 6.04 (br s, 1H), 3.01-3.32 (m, 1H), 2.15 (s, 3H), 1.29 (dd, J = 1.96, 6.85 Hz, 6H) ppm.

Step E. 7-Fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl

trifluoromethanesulfonate. To a solution of 7-fluoro-6-hydroxy-4-isopropyl-2-(*o*-

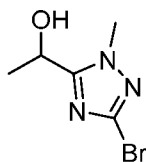
5 tolyl)isoquinolin-1(2H)-one (2.3 g, 7.4 mmol), DMAP (0.45 g, 3.7 mmol) and TEA (5.1 mL, 37 mmol) in DCM (50 mL) was added PhNTf₂ (7.9 g, 22 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was partitioned between water and DCM. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over MgSO₄, filtered, and concentrated. The residue was purified by
10 flash column chromatography (SiO₂, 0-50% ethyl acetate in heptane) to give the title compound as a white solid. (3.1 g, 95% yield). LCMS (ES-API): mass calcd. for C₂₀H₁₇F₄NO₄S, 443.1; m/z found, 444.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, J = 10.27 Hz, 1H), 7.73 (d, J = 6.36 Hz, 1H), 7.30-7.41 (m, 2H), 7.13-7.27 (m, 2H), 6.91 (s, 1H), 3.19 (td, J = 6.79, 13.33 Hz, 1H), 2.15 (s, 3H), 1.32 (dd, J = 2.20, 6.60 Hz, 6H) ppm.

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



To a solution of methyl 4-bromo-1-methyl-1*H*-imidazole-2-carboxylate (2 g, 9.1 mmol) in THF (40 mL) at 0 °C was added an ether solution (3 M) of MeMgBr (15 mL, 46 mmol) dropwise. The
20 resulting reaction mixture was stirred at 0 °C for 2 h. The mixture was slowly poured into sat. aq. NH₄Cl (30 mL) and extracted with DCM (30 mL $\times$ 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, gradient elution: 0 – 60% ethyl acetate in petroleum ether) to give the title compound as a white solid (1.72 g, 86% yield). MS (ESI): mass calcd. for C₇H₁₁BrN₂O, 218.0; m/z found, 219.1
25 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 6.76 (s, 1H), 3.81 (s, 3H), 2.37 (s, 1H), 1.65 (s, 6H) ppm.

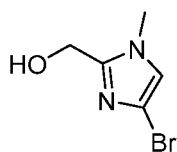
Intermediate 3: Racemic 1-(3-bromo-1-methyl-1*H*-1,2,4-triazol-5-yl)ethan-1-ol.



Step A. 3-Bromo-1-methyl-1H-1,2,4-triazole-5-carbaldehyde. To a mixture of methyl 3-bromo-1-methyl-1H-1,2,4-triazole-5-carboxylate (10.5 g, 47.7 mmol) in DCM (160 mL) under an atmosphere of nitrogen at -70 °C was added a toluene solution (1 M) of DIBAL-H (95.3 mL, 95.3 mmol) dropwise. The reaction mixture was stirred at -70 °C for 1 h. The reaction mixture was quenched by sat. aq. Rochelle salt (100 mL). The mixture was stirred at room temperature for 1 h, and then extracted with DCM (100 mL × 8). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, gradient elution: 0-20% ethyl acetate in petroleum ether) to give the title compound as a colorless oil (7 g, 77% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.92 - 9.86 (m, 1H), 4.22 - 4.16 (m, 3H) ppm.

Step B. Racemic 1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethanol. To a solution of 3-bromo-1-methyl-1H-1,2,4-triazole-5-carbaldehyde (7 g, 37 mmol) in THF (160 mL) at 0 °C was added an ether solution (3 M) of MeMgBr (37 mL, 111 mmol) dropwise. Then the resulting mixture was stirred at room temperature for 1 h. The mixture was slowly poured into sat. aq. NH₄Cl (100 mL) and extracted with DCM (100 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, gradient elution: 0-60% ethyl acetate in petroleum ether) to give the title compound as a colorless oil (6.9 g, 86% yield). MS (ESI): mass calcd. for C₅H₈BrN₃O, 205.0; m/z found, 206.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 5.01 (br t, *J* = 6.5 Hz, 1H), 3.93 (s, 3H), 2.55 (br d, *J* = 7.3 Hz, 1H), 1.65 (d, *J* = 6.5 Hz, 3H) ppm.

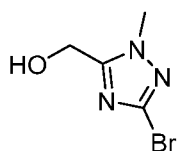
Intermediate 4: (4-Bromo-1-methyl-1H-imidazol-2-yl)methanol.



To a stirred solution of methyl 4-bromo-1-methyl-1H-imidazole-2-carboxylate (1.0 g, 4.56 mmol) in EtOH (20 mL) was added NaBH₄ (207 mg, 5.5 mmol) and CaCl₂ (304 mg, 2.7 mmol) under nitrogen. Then the mixture was stirred at room temperature overnight. The solvent was

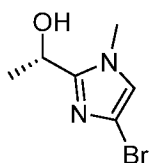
evaporated under reduced pressure. The residue was dissolved in sat. aq. NH_4Cl (30 mL) and the mixture was extracted with ethyl acetate (50 mL $\times$ 3). The organic layers were separated, combined, washed with brine (60 mL), dried over Na_2SO_4 , filtered, and concentrated to give the title compound as a white solid (800 mg, 88% yield). MS (ESI): mass calcd. for $\text{C}_5\text{H}_7\text{BrN}_2\text{O}$, 190.0; m/z found, 191.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.22 (s, 1H), 5.36 (t, J = 5.8 Hz, 1H), 4.41 (d, J = 5.8 Hz, 2H), 3.62 (s, 3H) ppm.

Intermediate 5: (3-Bromo-1-methyl-1H-1,2,4-triazol-5-yl)methanol.



To a mixture of methyl 3-bromo-1-methyl-1H-1,2,4-triazole-5-carboxylate (250 mg, 1.1 mmol) in EtOH (15 mL) at 0 °C was added NaBH_4 (52 mg, 1.3 mmol) and CaCl_2 (76 mg, 0.68 mmol) under nitrogen. The reaction mixture was warmed to room temperature and stirred at room temperature for 12 h. The mixture was concentrated. The residue was diluted with water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the title compound as a colorless oil (155 mg, 69% yield). MS (ESI): m/z 192.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 4.76 (d, J = 6.6 Hz, 2 H), 3.93 (s, 3 H), 3.56 (t, J = 6.0 Hz, 1 H) ppm.

Intermediate 6: (S*)-1-(4-Bromo-1-methyl-1H-imidazol-2-yl)ethan-1-ol.



Step A. 4-Bromo-1-methyl-1H-imidazole-2-carbaldehyde. To a mixture of methyl 4-bromo-1-methyl-1H-imidazole-2-carboxylate (18 g, 82 mmol) in DCM (250 mL) under an atmosphere of nitrogen at -78 °C was added a toluene solution (1 M) of DIBAL-H (150 mL, 150 mmol) dropwise. The reaction mixture was stirred at -78 °C for 2 h. The reaction was quenched by sat. aq. Rochelle salt (100 mL). The mixture was stirred at room temperature for 1 h, and then extracted with DCM (100 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (SiO_2 , gradient

elution: 0-50% ethyl acetate in petroleum ether) to give the title compound as a white powder (13.0 g, 84% yield). MS (ESI): mass calcd. for $C_5H_5BrN_2O$, 188.0; m/z found, 188.8 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.10 (s, 1H), 4.02 (s, 3H) ppm.

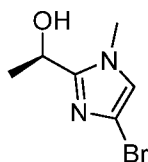
Step B. Racemic 1-(4-Bromo-1-methyl-1H-imidazol-2-yl)ethanol. To a solution of 4-bromo-1-

methyl-1H-imidazole-2-carbaldehyde (13.0 g, 68.8 mmol) in THF (200 mL) at 0 °C was added an ether solution (3 M) of MeMgBr (60.8 mL, 183 mmol) dropwise. Then the resulting mixture was stirred at room temperature for 1 h. The mixture was slowly poured into sat. aq. NH_4Cl (150 mL) and extracted with DCM (150 mL $\times$ 6). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (SiO_2 , gradient elution: 0-100% ethyl acetate in petroleum ether) to give the title compound as a light-yellow powder (12.8 g, 98% yield). MS (ESI): mass calcd. for $C_6H_9BrN_2O$, 204.0; m/z found, 207.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 4.88 (q, $J = 6.8$ Hz, 1H), 3.70 (s, 4H), 1.58 (d, $J = 6.8$ Hz, 3H) ppm.

Step C. (S*)-1-(4-Bromo-1-methyl-1H-imidazol-2-yl)ethanol. Racemic 1-(4-bromo-1-methyl-

1H-imidazol-2-yl)ethanol (8 g, 39.0 mmol) was separated by chiral SFC (Stationary phase: DAICEL CHIRALPAK AD-H, 5 μm , 250mm $\times$ 30mm); Mobile phase: Supercritical CO_2 (A) - EtOH (0.1% $NH_3 \cdot H_2O$) (B), gradient elution: 15% B in A at 60 mL/min) to give the title compound as a white powder (3.4 g, 42% yield). SFC: 99.7% ee [retention time 2.512 min; SFC analytical method: AD-3_EtOH (DEA)_5_40_2]. MS (ESI): mass calcd. for $C_6H_9BrN_2O$, 204.0; m/z found, 207.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (s, 1H), 4.89 (q, $J = 6.6$ Hz, 1H), 3.70 (s, 3H), 3.10 (br s, 1H), 1.61 (d, $J = 6.5$ Hz, 3H) ppm.

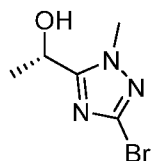
Intermediate 7: (R*)-1-(4-Bromo-1-methyl-1H-imidazol-2-yl)ethan-1-ol.



In the separation of racemic 1-(4-bromo-1-methyl-1H-imidazol-2-yl)ethanol (8 g, 39.0 mmol) by chiral SFC (Stationary phase: DAICEL CHIRALPAK AD-H, 5 μm , 250mm $\times$ 30mm); Mobile phase: Supercritical CO_2 (A) - EtOH (0.1% $NH_3 \cdot H_2O$) (B), gradient elution: 15% B in A at 60 mL/min), the title compound was obtained as the second product: a white powder (2.0 g, 25% yield). SFC: 99.6% ee [retention time 2.72 min; SFC analytical method: AD-3_EtOH

(DEA)_5_40_2]. MS (ESI): mass calcd. for $C_6H_9BrN_2O$, 204.0; m/z found, 205.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 1H), 4.89 (q, J = 6.6 Hz, 1H), 3.70 (s, 3H), 3.36 (br s, 1H), 1.60 (d, J = 6.7 Hz, 3H) ppm.

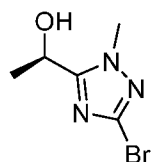
5 Intermediate 8: (S*)-1-(3-Bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-ol.



The racemic 1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethanol (Intermediate 3, 6.9 g, 34 mmol) was separated by chiral SFC (Stationary phase: DAICEL CHIRALPAK IC, 10 μ m 250 mm $\times$ 50 mm); Mobile phase: Supercritical CO_2 (A) - EtOH (0.1% $NH_3 \cdot H_2O$) (B), gradient elution: 30% B in A at 200 mL/min) to give the title compound as a white solid (1.6 g, 25% yield) SFC: 99.8% ee [retention time 2.226 min; SFC analytical method: IC-3_EtOH(DEA)_5_40_2,5ML_7MIN]. MS (ESI): mass calcd. for $C_5H_8BrN_3O$, 205.0; m/z found, 206.0 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 5.01 (t, J = 6.8 Hz, 1H), 3.93 (s, 3H), 2.82 (d, J = 7.3 Hz, 1H), 1.64 (d, J = 6.5 Hz, 3H) ppm.

15

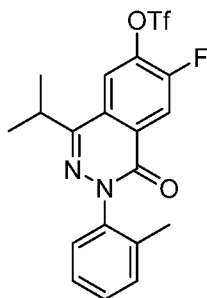
Intermediate 9: (R*)-1-(3-Bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-ol.



In the separation of racemic 1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethanol (Intermediate 3, 6.9 g, 33.5 mmol) by chiral SFC (Stationary phase: DAICEL CHIRALPAK IC, 10 μ m 250 mm $\times$ 50 mm); Mobile phase: Supercritical CO_2 (A) - EtOH (0.1% $NH_3 \cdot H_2O$) (B), gradient elution: 30% B in A at 200 mL/min), the title compound was obtained as the second product: a white solid (2.9 g, 44% yield). SFC: 95.3% ee [retention time 2.673 min; SFC analytical method: IC-3_EtOH(DEA)_5_40_2,5ML_7MIN]. MS (ESI): mass calcd. for $C_5H_8BrN_3O$, 205.0; m/z found, 206.0 $[M+H]^+$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 5.01 (t, J = 6.9 Hz, 1H), 3.93 (s, 3H), 2.67 (d, J = 7.3 Hz, 1H), 1.64 (d, J = 6.8 Hz, 3H) ppm.

25

Intermediate 10: 7-Fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydrophthalazin-6-yl trifluoromethanesulfonate.



Step A: 5,6-Difluoro-2-(*o*-tolylamino)isoindoline-1,3-dione and 6,7-Difluoro-2-(*o*-tolyl)-2,3-

5 dihydrophthalazine-1,4-dione. A mixture of 4,5-difluorophthalic anhydride (4.4 g, 24 mmol) and *o*-tolylhydrazine hydrochloride (5.7 g, 36 mmol) in AcOH (50 mL) was heated at 120 °C for 24 h then allowed to cool to room temperature. The precipitated solid was filtered, and the filtrate was concentrated. The residue was partitioned between ethyl acetate and saturated NaHCO₃ aqueous solution. The organic layer was separated, and the aqueous layer was extracted with

10 DCM. The combined organic extract was dried over MgSO₄ and concentrated to give a crude mixture of 6,7-difluoro-2-(*o*-tolyl)-2,3-dihydrophthalazine-1,4-dione and 5,6-difluoro-2-(*o*-tolylamino)isoindoline-1,3-dione as a yellow gum (~2:1 ratio, 5.7 g, 83% yield). A small amount of the mixture (100 mg) was purified by column chromatography (30-100% EtOAc in heptane) to give two pure products.

15 6,7-Difluoro-2-(*o*-tolyl)-2,3-dihydrophthalazine-1,4-dione: an off white solid (60 mg). LCMS (ES-API): mass calcd. for C₁₅H₁₀F₂N₂O₂, 288.07; *m/z* found, 289.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.23 (dd, *J* = 7.8, 9.3 Hz, 1H), 7.90 - 7.68 (m, 1H), 7.47 - 7.28 (m, 4H), 2.22 (s, 3H) ppm;

5,6-Difluoro-2-(*o*-tolylamino)isoindoline-1,3-dione: a yellow solid (30 mg). LCMS (ES-API):

20 mass calcd. for C₁₅H₁₀F₂N₂O₂, 288.07; *m/z* found, 289.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (t, *J* = 7.1 Hz, 2H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.06 (s, 1H), 2.39 (s, 3H) ppm

Step B: 6,7-Difluoro-4-oxo-3-(*o*-tolyl)-3,4-dihydrophthalazin-1-yl trifluoromethanesulfonate. To

a mixture of 6,7-difluoro-2-(*o*-tolyl)-2,3-dihydrophthalazine-1,4-dione and 5,6-difluoro-2-(*o*-tolylamino)isoindoline-1,3-dione (ratio ~2:1, 5.6 g, 19 mmol) in DCM (50 mL) at 0 °C was

25 added a DCM solution (1 M) of Tf₂O (25.7 mL, 25.7 mmol) followed by Et₃N (7.1 mL, 51

mmol). The reaction mixture was stirred at room temperature for 17 h. The mixture was partitioned between DCM and water. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic extract was washed with water, dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash column chromatography (10-30% EtOAc in heptane) to give the title compound as a yellow solid (3.2 g, 40% yield). LCMS (ES-API): mass calcd. for $\text{C}_{16}\text{H}_9\text{F}_5\text{N}_2\text{O}_4\text{S}$, 420.02; m/z found, 421.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.32 (dd, $J = 7.6, 9.5$ Hz, 1H), 7.70 (dd, $J = 7.1, 9.0$ Hz, 1H), 7.46 - 7.28 (m, 4H), 2.20 (s, 3H) ppm.

Step C: 6,7-Difluoro-4-(prop-1-en-2-yl)-2-(*o*-tolyl)phthalazin-1(2H)-one. A reaction mixture of 6,7-difluoro-4-oxo-3-(*o*-tolyl)-3,4-dihydrophthalazin-1-yl trifluoromethanesulfonate (3.1 g, 7.4 mmol), isopropenylboronic acid pinacol ester (2.5 g, 14.8 mmol), bis(triphenylphosphine)palladium(II) dichloride (518 mg, 0.74 mmol), and Cs_2CO_3 (7.2 g, 22 mmol) in 1,4-dioxane (55 mL) was heated at 85 °C under nitrogen for 3.5 h. The mixture was cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The filtrate was combined and concentrated. The residue was purified by flash column chromatography (0-30% EtOAc in heptane) to give the title compound as an off-white solid (2.03 g, 88% yield). LCMS (ES-API): mass calcd. for $\text{C}_{18}\text{H}_{14}\text{F}_2\text{N}_2\text{O}$, 312.11; m/z found, 313.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.32 (dd, $J = 7.8, 9.8$ Hz, 1H), 7.79 (dd, $J = 7.3, 10.3$ Hz, 1H), 7.39 - 7.27 (m, 4H), 5.64 - 5.54 (m, 1H), 5.31 (s, 1H), 2.22 - 2.15 (m, 6H) ppm.

Step D: 6,7-Difluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one. A mixture of 6,7-difluoro-4-(prop-1-en-2-yl)-2-(*o*-tolyl)phthalazin-1(2H)-one (2.0 g, 6.5 mmol) and Pd/C (10%, 1.8 g, 1.7 mmol) in EtOAc (40 mL) was vigorously shaken under an atmosphere of hydrogen (20 psi) in a Parr shaker for 16 h. The mixture was filtered through a short pad of Celite. The filtrate was concentrated to give the title compound as a white solid (1.8 g, 88% yield). LCMS (ES-API): mass calcd. for $\text{C}_{18}\text{H}_{16}\text{F}_2\text{N}_2\text{O}$, 314.12; m/z found, 315.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.32 (dd, $J = 7.8, 9.8$ Hz, 1H), 7.68 (dd, $J = 7.3, 10.8$ Hz, 1H), 7.39 - 7.27 (m, 4H), 3.46 - 3.32 (m, 1H), 2.17 (s, 3H), 1.35 (d, $J = 6.4$ Hz, 6H) ppm.

Step E: 6-(Benzyloxy)-7-fluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one and 7-(Benzyloxy)-6-fluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one. To a solution of benzyl alcohol (1.2 g, 11 mmol) in anhydrous THF (40 mL) was slowly added NaH (60% dispersion in mineral oil, 0.91 g,

23 mmol). The mixture was heated at 80 °C for 0.5 h, and then cooled to -40 °C, followed by the addition of 6,7-difluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one (1.8 g, 5.7 mmol) under nitrogen. The reaction mixture was slowly warmed to room temperature and stirred overnight. The mixture was poured into aqueous saturated NH₄Cl solution and extracted with ethyl acetate.

5 The organic layer was separated, washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, 10-30% EtOAc in heptane) to give a mixture of 6-(benzyloxy)-7-fluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one and 7-(benzyloxy)-6-fluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one in a ratio of ~2:1, as a white foam (2.0 g, 85% yield). LCMS (ES-API): mass calcd. for C₂₅H₂₃FN₂O₂, 402.2; m/z
10 found, 403.2 [M+H]⁺.

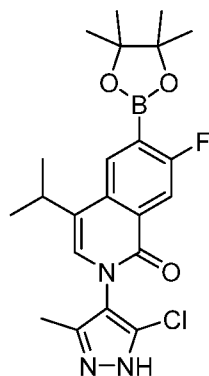
Step F. 7-Fluoro-6-hydroxy-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one and 6-Fluoro-7-hydroxy-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one. To a mixture of 6-(benzyloxy)-7-fluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one and 7-(benzyloxy)-6-fluoro-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one (ratio ~2:1, 1.95 g, 4.8 mmol) in DCM (50 mL) at -78 °C under
15 nitrogen was added a DCM solution (1 M) of BCl₃ (9.7 mL, 9.7 mmol). The reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with MeOH (5 mL) at -78 °C. Then aqueous saturated NaHCO₃ solution was added, and the mixture was extracted with DCM and ethyl acetate. The combined organic extract was dried over MgSO₄, filtered, and concentrated to give a crude mixture of 7-fluoro-6-hydroxy-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one and 6-
20 fluoro-7-hydroxy-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one in a ratio ~2:1, as a white foam (1.0 g, 99% yield). LCMS (ES-API): mass calcd. for C₁₈H₁₇FN₂O₂, 312.1; m/z found, 313.0 [M+H]⁺.

Step G. 7-Fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate and 7-fluoro-1-isopropyl-4-oxo-3-(*o*-tolyl)-3,4-dihydrophthalazin-6-yl trifluoromethanesulfonate. To a mixture of 7-fluoro-6-hydroxy-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one and 6-fluoro-7-hydroxy-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one (ratio ~2:1, 1.05 g, 3.2 mmol), DMAP (0.13 g, 1.1 mmol) and TEA (1.5 mL, 11 mmol) in DCM (50 mL) was added PhNTf₂ (2.3 g, 6.4 mmol). The reaction mixture was stirred at room
25 temperature for 16 h. The mixture was partitioned between water and DCM. The organic layer
30 was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extract was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash

column chromatography (SiO₂, 0-50% ethyl acetate in heptane) to give the mixture of 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate and 7-fluoro-1-isopropyl-4-oxo-3-(*o*-tolyl)-3,4-dihydrophthalazin-6-yl trifluoromethanesulfonate as a colorless oil (ratio ~2:1, 1.35 g, 95% yield).

- 5 The mixture (320 mg) was further separated by SFC [OJ-H (2 x 25 cm); 25% ethanol/CO₂, 100 bar; 70 mL/min, 220 nm] to give 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 10) as the major product: a white foam (152 mg, 48% yield). LCMS (ES-API): mass calcd. for C₁₉H₁₆F₄N₂O₄S, 444.1; m/z found, 445.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.40 (d, *J* = 9.29 Hz, 1H), 7.89 (d, *J* = 6.85 Hz, 1H),
 10 7.29-7.41 (m, 4H), 3.35-3.49 (m, 1H), 2.18 (s, 3H), 1.37 (d, *J* = 6.36 Hz, 6H) ppm.
 7-Fluoro-1-isopropyl-4-oxo-3-(*o*-tolyl)-3,4-dihydrophthalazin-6-yl trifluoromethanesulfonate was obtained as a minor product: a white foam (65 mg, 20% yield). LCMS (ES-API): mass calcd. for C₁₉H₁₆F₄N₂O₄S, 444.1; m/z found, 445.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, *J* = 7.34 Hz, 1H), 7.76 (d, *J* = 9.78 Hz, 1H), 7.30-7.41 (m, 4H), 3.34-3.47 (m, 1H), 2.19 (s, 3H), 1.36 (d, *J* = 6.85 Hz, 6H) ppm.
 15

Intermediate 11: 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one.



- 20 Step A. 6,7-Difluoro-4-isopropyl-1H-isochromen-1-one. To a mixture of methyl 2-bromo-4,5-difluorobenzoate (3.0 g, 12 mmol), Pd(allyl)Cl₂ (87 mg, 2.4 mmol), Xantphos (550 mg, 956 mmol), Cs₂CO₃ (7.8 g, 24 mmol) and 4Å molecular sieve (6 g) in anhydrous 1,4-dioxane (30 mL) was added isovaleraldehyde (5.2 g, 59.8 mmol) under nitrogen. The reaction mixture was heated and stirred at 95 °C for 24 h. The mixture was cooled to room temperature and filtered
 25 through a pad of Celite. The pad was washed with 1,4-dioxane (150 mL). The filtrate was

combined and the pH was adjusted to 7~8 by using AcOH. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 - 3% ethyl acetate in petroleum ether) to give the title compound as an off-white solid (1.8 g, 67% yield). MS (ESI): mass calcd. for C₁₂H₁₀F₂O₂, 224.1; m/z found, 225.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (dd, *J* = 8.1, 10.0 Hz, 1H), 7.39 (dd, *J* = 7.2, 11.2 Hz, 1H), 7.14 (s, 1H), 3.00 (spt, *J* = 6.8 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (376MHz, CDCl₃) δ -125.31 (br d, *J* = 24.3 Hz, 1F), -134.62 - -134.94 (m, 1F) ppm.

Step B. 6,7-Difluoro-3-hydroxy-4-isopropylisochroman-1-one. To a suspension of 6,7-difluoro-4-isopropyl-1H-isochromen-1-one (1.8 g, 8.0 mmol) in EtOH (18 mL) and H₂O (1.8 mL) was added an aqueous solution (1.8 mL) of LiOH.H₂O (337 mg, 8.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 1 h. The mixture was neutralized to pH 7-8 by using aq. HCl solution (6 M, 1.3 mL). The mixture was concentrated to a small volume (3.6 mL), and then water (5.4 mL) was added. The mixture was stirred at room temperature for 0.5 h and extracted with ethyl acetate (20 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give the title compound as a light yellow solid (1.8 g, 88% yield). MS (ESI): mass calcd. for C₁₂H₁₂F₂O₃, 242.1; m/z found, 243.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (dd, *J* = 7.9, 9.9 Hz, 1H), 7.08 (dd, *J* = 7.3, 10.0 Hz, 1H), 5.94 (s, 1H), 4.86 (br s, 1H), 2.78 (d, *J* = 7.3 Hz, 1H), 1.92 (qd, *J* = 6.9, 13.7 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -127.69 - -127.99 (m, 1F), -137.40 - -137.74 (m, 1F) ppm.

Step C. 2-(3-Chloro-5-methyl-1H-pyrazol-4-yl)-6,7-difluoro-4-isopropylisoquinolin-1(2H)-one.

A mixture of 6,7-difluoro-3-hydroxy-4-isopropylisochroman-1-one (3.2 g, 12.3 mmol) and 3-chloro-5-methyl-1H-pyrazol-4-amine (1.8 g, 13.5 mmol) in AcOH (35 mL) was heated with stirring at 80 °C for overnight. The mixture was cooled to room temperature and concentrated to a small volume (~8 mL). The resulting mixture was triturated with the addition of water (20 mL). The cloudy mixture was filtered, and the precipitate was collected, dried *in vacuo* to give the title compound as a light red solid (4.0 g, 93% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.17 (br s, 1H), 8.18 (dd, *J* = 8.5, 10.8 Hz, 1H), 7.95 (dd, *J* = 7.5, 12.3 Hz, 1H), 7.07 (s, 1H), 3.24 (td, *J* = 6.8, 13.6 Hz, 1H), 2.12 (s, 3H), 1.23 (br d, *J* = 5.0 Hz, 6H) ppm.

Step D. 6-(Benzyloxy)-2-(3-chloro-5-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropylisoquinolin-1(2H)-one. To a solution of benzyl alcohol (8.0 g, 74 mmol) in THF (10 mL) was added NaH

(60% dispersion in mineral oil, 1.6 g, 67 mmol) carefully. The mixture was stirred at 80 °C for 20 min, then cooled to 0 °C. Then a THF solution (15 mL) of 2-(3-chloro-5-methyl-1H-pyrazol-4-yl)-6,7-difluoro-4-isopropylisoquinolin-1(2H)-one (2.5 g, 7.1 mmol) was added. The reaction mixture was stirred at 0 °C for 0.5 h, and then warmed to room temperature and stirred for 5 h.

- 5 The reaction was quenched by the addition of sat. aq. NH₄Cl (30 mL). The mixture was extracted with ethyl acetate (50 mL×2). The combined organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was triturated with petroleum ether/ethyl acetate (5/1, 15 mL). The precipitate was collected and dried *in vacuo* to give the title compound as a white solid (2.2 g, 69% yield). MS (ESI): mass calcd. for C₂₃H₂₁ClFN₃O₂, 425.9; m/z found, 426.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.14 (s, 1H), 7.95 (d, *J* = 11.7 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.48 - 7.29 (m, 4H), 6.96 (s, 1H), 5.45 (s, 2H), 3.25 (td, *J* = 6.7, 13.5 Hz, 1H), 2.10 (s, 3H), 1.17 (br t, *J* = 7.4 Hz, 6H) ppm.

- Step E. 2-(3-Chloro-5-methyl-1H-pyrazol-4-yl)-7-fluoro-6-hydroxy-4-isopropylisoquinolin-1(2H)-one. BCl₃ (1 M in toluene, 26 mL, 26 mmol) was added to a flask charged with 6-(benzyloxy)-2-(3-chloro-5-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropylisoquinolin-1(2H)-one (2.2 g, 5.1 mmol) under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with MeOH (20 mL), followed by addition of water (20 mL). The pH of the mixture was adjusted to 6-7 by using aqueous NaHCO₃ solution. The mixture was then extracted with ethyl acetate (50 mL × 2). The combined organic extract was dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was triturated with petroleum ether/ethyl acetate (10:1, 15 mL). The precipitate was collected by filtration and dried *in vacuo* to give the crude title compound as a light red powder (2.1 g, 100% yield). MS (ESI): mass calcd. for C₁₆H₁₅ClFN₃O₂, 335.1; m/z found, 336.1 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ 13.78 - 12.68 (m, 1H), 11.09 (br s, 1H), 7.90 (d, *J* = 11.7 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 3.14 - 2.97 (m, 1H), 2.11 (s, 3H), 1.33 - 1.17 (m, 6H) ppm.

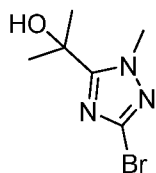
- Step F. 2-(3-Chloro-5-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate. To a solution of 2-(3-chloro-5-methyl-1H-pyrazol-4-yl)-7-fluoro-6-hydroxy-4-isopropylisoquinolin-1(2H)-one (2.1 g, 6.3 mmol) in DCM (25 mL) was added PhNTf₂ (2.2 g, 6.3 mmol), DMAP (0.38 g, 3.1 mmol) and TEA (1.3 g, 12.5 mmol) respectively. The reaction mixture was stirred at room temperature for 2 h. Water (30 mL) was added, and the resulting mixture was extracted with DCM (30 mL × 2). The combined

organic extract was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0-50% ethyl acetate in petroleum ether) to give the title compound as a light yellow solid (1.7 g, 70 % yield for two steps). MS (ESI): mass calcd. for C₁₇H₁₄ClFN₃O₄S, 467.8; m/z found, 468.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.21 (s, 1H), 8.31 (d, *J* = 10.5 Hz, 1H), 8.26 (d, *J* = 7.0 Hz, 1H), 7.15 (s, 1H), 3.30 - 3.24 (m, 1H), 2.14 (s, 3H), 1.24 (br s, 6H) ppm.

Step G. 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one.

To a solution of 2-(3-chloro-5-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (1.1 g, 2.3 mmol) in anhydrous 1,4-dioxane (20 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.2 g, 4.5 mmol), Pd(dppf)Cl₂ (370 mg, 0.45 mmol) and AcOK (553 mg, 5.6 mmol) respectively. The reaction mixture was stirred under nitrogen and heated at 90 °C overnight. The mixture was cooled to room temperature and directly purified by flash column chromatography (SiO₂, gradient elution: 0- 33% ethyl acetate in petroleum ether) to give the title compound as a brown solid (670 mg, 60% yield). MS (ESI): mass calcd. for C₂₂H₂₆BClFN₃O₃, 445.2; m/z found, 446.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.94 (br s, 1H), 8.19 (d, *J* = 5.2 Hz, 1H), 8.15 (d, *J* = 9.5 Hz, 1H), 6.79 (s, 1H), 3.40 (td, *J* = 6.8, 13.6 Hz, 1H), 2.21 (s, 3H), 1.42 (s, 12H), 1.34 (br d, *J* = 6.6 Hz, 6H) ppm.

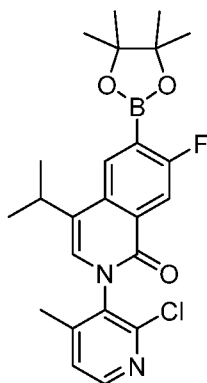
Intermediate 12: 2-(3-Bromo-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol.



To a solution of 3-bromo-1-methyl-1H-1,2,4-triazole-5-carboxylate (8.0 g, 35 mmol) in THF (160 mL) at 0 °C was added an ether solution (3 M) of MeMgBr (78 mL, 233 mmol) dropwise. The resulting reaction mixture was stirred at 0 °C for 4 h. The mixture was slowly poured into sat. aq. NH₄Cl (200 mL) and extracted with DCM (200 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, gradient elution: 0 – 50% ethyl acetate in petroleum ether) to give the title compound as a white solid (4.7 g, 59% yield). MS (ESI): mass calcd. for C₆H₁₀BrN₃O,

219.0; m/z found, 220.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3H), 2.25 (s, 1H), 1.69 (s, 6H) ppm.

Intermediate 13: 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one.



Step A. 2-(2-Chloro-4-methylpyridin-3-yl)-6,7-difluoro-4-isopropylisoquinolin-1(2H)-one. To a solution of 2-chloro-4-methylpyridin-3-amine (3.8 g, 27 mmol) in DCM (20 mL) at 0 °C was added a toluene solution (2 M) of $AlMe_3$ (16 mL, 32 mmol) under nitrogen. The mixture was stirred for 0.5 h, and then a DCM solution (20 mL) of 6,7-difluoro-4-isopropyl-1H-isochromen-1-one (prepared in Intermediate 11, Step A, 3.0 g, 13.4 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with aq. HCl (1 M, 10 mL). The mixture was stirred at room temperature for 2 min, and then poured into water (10 mL), and extracted with DCM (20 mL $\times$ 3). The combined organic extract was washed with brine (20 mL $\times$ 2), dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was dissolved in AcOH (75 mL) and the reaction mixture was stirred at 85 °C for overnight. The mixture was cooled to room temperature, poured into water (10 mL), and then extracted with DCM (20 mL $\times$ 3). The combined organic extract was washed with brine (15 mL $\times$ 3), dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2 , gradient elution: 0 – 29% ethyl acetate in petroleum ether) to give the title compound as a yellow solid (4.0 g, 83% yield). MS (ESI): mass calcd. for $C_{18}H_{15}ClF_2N_2O$, 348.0; m/z found, 349.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 4.9 Hz, 1H), 8.30 (dd, J = 8.3, 10.5 Hz, 1H), 7.56 (dd, J = 7.3, 11.7 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H), 6.69 (s, 1H), 3.18 (td, J = 6.8, 13.6 Hz, 1H), 2.23 (s, 3H), 1.32 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -128.18 - -128.54 (m, 1F), -136.50 (br d, J = 24.3 Hz, 1F) ppm.

Step B. 6-(Benzyloxy)-2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropylisoquinolin-

1(2H)-one. To a solution of benzyl alcohol (13 g, 118 mmol) in THF (45 mL) was added NaH (60% dispersion in mineral oil, 4.2 g, 106 mmol) carefully. The mixture was stirred at 80 °C for 20 min, then cooled to 0 °C. Then a THF solution (45 mL) of 2-(2-chloro-4-methylpyridin-3-yl)-6,7- difluoro-4-isopropylisoquinolin-1(2H)-one (4.0 g, 11.5 mmol) was added. The reaction mixture was stirred at 0 °C for 0.5 h, and then warmed to room temperature and stirred for 1 h. The reaction was quenched by the addition of sat. aq. NH₄Cl (10 mL). The mixture was poured into water (10 mL), and then extracted with ethyl acetate (20 mL×3). The combined organic extract was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 50% ethyl acetate in petroleum ether) to the title compound as a yellow oil (5.7 g, 91% yield). MS (ESI): mass calcd. for C₂₅H₂₂ClFN₂O₂, 436.1; m/z found, 437.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.35 (d, *J* = 4.9 Hz, 1H), 8.19 (d, *J* = 11.4 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.39 - 7.31 (m, 1H), 7.26 (br s, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 6.62 (s, 1H), 5.34 (s, 2H), 3.12 (td, *J* = 6.7, 13.5 Hz, 1H), 2.22 (s, 3H), 1.27 - 1.22 (m, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -132.86 (s, 1F) ppm.

Step C. 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-hydroxy-4-isopropylisoquinolin-1(2H)-one.

To a solution of 6-(benzyloxy)-2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropylisoquinolin-1(2H)-one (5.7 g, 13.1 mmol,) in DCM (80 mL) at -78 °C was added a toluene solution (1 M) of BCl₃ (83 mL, 83 mmol) under nitrogen. The reaction mixture was stirred at -78 °C for 1 h. The reaction was quenched with MeOH (30 mL), followed by addition of sat. aq. NaHCO₃ (40 mL). The mixture was then extracted with DCM (40 mL × 3). The combined organic extract was dried over Na₂SO₄, filtered and evaporated under reduced pressure to give the crude title compound as a yellow oil (5.2 g, 100% yield). MS (ESI): mass calcd. for C₁₈H₁₆ClFN₂O₂, 346.0; m/z found, 347.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.36 (d, *J* = 5.0 Hz, 1H), 8.22 (d, *J* = 11.0 Hz, 1H), 7.41 - 7.35 (m, 2H), 6.63 (s, 1H), 6.16 (s, 1H), 3.25 - 3.13 (m, 1H), 2.24 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -139.11 (s, 1F) ppm.

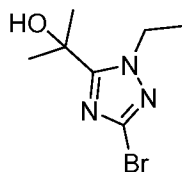
Step D. 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate.

To a solution of 2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-6-hydroxy-4-isopropylisoquinolin-1(2H)-one (5.2 g, 15 mmol) in DCM (50 mL) was added PhNTf₂ (16 g, 45 mmol), DMAP (0.91 g, 7.4 mmol) and TEA (7.6 g, 75 mmol) respectively. The

reaction mixture was stirred at room temperature overnight. Water (30 mL) was added, and the resulting mixture was extracted with ethyl acetate (30 mL $\times$ 2). The combined organic extract was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0-38% ethyl acetate in petroleum ether) to give the title compound as an off white solid (4.6 g, 81% yield over two steps). MS (ESI): mass calcd. for C₁₉H₁₅ClF₄N₂O₄S, 478.0; m/z found, 479.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.40 (d, *J* = 2.0 Hz, 1H), 8.38 (d, *J* = 3.0 Hz, 1H), 7.76 (d, *J* = 6.7 Hz, 1H), 7.30 (s, 1H), 6.74 (s, 1H), 3.21 (td, *J* = 6.8, 13.6 Hz, 1H), 2.24 (s, 3H), 1.34 (t, *J* = 6.9 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -72.87 (s, 1F), -72.89 (s, 1F), -75.36 (s, 1F), -126.12 - -130.39 (m, 1F) ppm.

Step E. 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one. To a solution of 2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-1-oxo-1,2-dihydro isoquinolin-6-yl trifluoromethanesulfonate (3.3 g, 6.7 mmol) in anhydrous 1,4-dioxane (40 mL) was added 4,4,4',4',5,5,5',5'- octamethyl- 2,2'-bi(1,3,2-dioxaborolane) (2.6 g, 10.1 mmol), Pd(dppf)Cl₂ (493 mg, 0.67 mmol) and AcOK (2.0 g, 20.2 mmol) respectively. The reaction mixture was stirred under nitrogen and heated at 80 °C for overnight. The mixture was cooled to room temperature and directly purified by flash column chromatography (SiO₂, gradient elution: 0- 50% ethyl acetate in petroleum ether) to give the title compound as a light yellow gum (1785 mg, 57% yield). MS (ESI): mass calcd. for C₂₄H₂₇BClF₄N₂O₃, 456.1; m/z found, 457.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 5.0 Hz, 1H), 8.21 (d, *J* = 5.2 Hz, 1H), 8.13 (d, *J* = 9.4 Hz, 1H), 7.29 (s, 1H), 6.62 (s, 1H), 3.46 - 3.32 (m, 1H), 2.23 (s, 3H), 1.42 (s, 12H), 1.34 (t, *J* = 7.0 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -104.07 (s, 1F) ppm.

Intermediate 14: 2-(3-Bromo-1-ethyl-1H-1,2,4-triazol-5-yl)propan-2-ol.

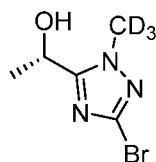


Step A. Ethyl 3-bromo-1-ethyl-1H-1,2,4-triazole-5-carboxylate. To a solution of ethyl 3-bromo-1H-1,2,4-triazole-5-carboxylate (0.98 g, 4.5 mmol) and Cs₂CO₃ (5.8 g, 18 mmol) in anhydrous DMF (20 mL) was added iodoethane dropwise (2.1 g, 13 mmol) at room temperature. Then the

resulting reaction mixture was stirred at room temperature for 12 h. The mixture was poured into water (50 mL), extracted with DCM (30 mL $\times$ 2). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, gradient elution: 0-50% ethyl acetate in heptane) to give the title compound as a white solid (0.98 g, 88% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.65 (q, J = 7.17 Hz, 2H), 4.45-4.52 (m, 2H), 1.48-1.55 (m, 3H), 1.41-1.47 (m, 3H) ppm.

Step B. 2-(3-Bromo-1-ethyl-1H-1,2,4-triazol-5-yl)propan-2-ol. To a solution of ethyl 3-bromo-1-ethyl-1H-1,2,4-triazole-5-carboxylate (0.98 g, 3.9 mmol) in THF (30 mL) at -78 °C was added an ether solution (3 M) of MeMgBr (5.3 mL, 16 mmol) dropwise. The resulting reaction mixture was stirred at room temperature overnight. The mixture was slowly poured into sat. aq. NH₄Cl (30 mL) and extracted with DCM (30 mL) and ethyl acetate (30 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, 20-100% ethyl acetate in heptane) to give the title compound as a white solid (0.68 g, 73% yield). LCMS (ES-API): mass calcd. for C₇H₁₂BrN₃O, 233.0; m/z found, 233.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 4.44 (q, J = 7.17 Hz, 2H), 2.71 (s, 1H), 1.69 (s, 6H), 1.48 (t, J = 7.09 Hz, 3H) ppm.

Intermediate 15: (S*)-1-(3-Bromo-1-(methyl-*d*₃)-1H-1,2,4-triazol-5-yl)ethan-1-ol.



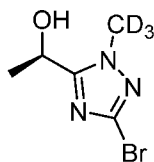
Step A: Methyl 3-bromo-1-(methyl-*d*₃)-1H-1,2,4-triazole-5-carboxylate. To a mixture of methyl 3-bromo-1H-1,2,4-triazole-5-carboxylate (5 g, 24 mmol) and K₂CO₃ (6.7 g, 48.5 mmol) in acetone (90 mL) at room temperature was added CD₃I (5.3 g, 36 mmol) dropwise. The resulting reaction mixture was stirred at room temperature for 2 h. The mixture was poured into H₂O (100 mL) and extracted with DCM (100 mL $\times$ 2). The combined organic extract was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 20% ethyl acetate in petroleum ether) to give the title compound as a white solid (2.0 g, 36% yield). MS (ESI): mass calcd. for C₅H₃D₃BrN₃O₂, 222.0; m/z found, 222.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 4.01 (s, 3H) ppm.

Step B. 3-Bromo-1-(methyl-*d*₃)-1H-1,2,4-triazole-5-carbaldehyde. To a mixture of methyl 3-bromo-1-(methyl-*d*₃)-1H-1,2,4-triazole-5-carboxylate (14 g, 62 mmol) in DCM (200 mL) under atmosphere of nitrogen at -70 °C was added a toluene solution (1 M) of DIBAL-H (123 mL, 123 mmol) dropwise. The reaction mixture was stirred at -70 °C for 1 h. The reaction mixture was quenched by the addition of sat. aq. Rochelle salt (100 mL). The mixture was stirred for another 1 h and then extracted with DCM (100 mL × 8). The combined organic extract was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 20% ethyl acetate in petroleum ether) to give the title compound as a white solid (7.8 g, 66% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.92 (s, 1H) ppm.

Step C. Racemic 1-(3-Bromo-1-(methyl-*d*₃)-1H-1,2,4-triazol-5-yl)ethan-1-ol. To a solution of 3-bromo-1-(methyl-*d*₃)-1H-1,2,4-triazole-5-carbaldehyde (7.8 g, 40 mmol) in THF (180 mL) at 0 °C was added an ether solution (3 M) of MeMgBr (41 mL, 124 mmol) dropwise. The resulting reaction mixture was stirred at room temperature for 2 h. The mixture was slowly poured into sat. aq. NH₄Cl (100 mL) and then extracted with DCM (100 mL × 5). The combined organic extract was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 40% ethyl acetate in petroleum ether) to give the title compound as a light-yellow oil (6.7 g, 76% yield). MS (ESI): mass calcd. for C₅H₅BrD₃N₃O, 208.0; m/z found, 209.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 5.01 (q, *J* = 6.5 Hz, 1H), 2.73 - 2.35 (m, 1H), 1.65 (d, *J* = 6.5 Hz, 3H) ppm.

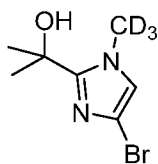
Step D. (S*)-1-(3-Bromo-1-(methyl-*d*₃)-1H-1,2,4-triazol-5-yl)ethan-1-ol. Racemic 1-(3-bromo-1-(methyl-*d*₃)-1H-1,2,4-triazol-5-yl)ethan-1-ol (6.7 g, 31 mmol) was separated by chiral SFC [Stationary phase: DAICEL CHIRALPAK IC, 10 μm 250 mm × 50 mm; Mobile phase: Supercritical CO₂ (A) - EtOH (0.1% NH₃.H₂O) (B), gradient elution: 30% B in A at 200 mL/min] to give the title compound as a white solid (2.2 g, 33% yield). SFC: 99.1% ee [retention time 2.233 min; SFC analytical method: IC-3_EtOH (DEA)_5_40_2,5ML_7MIN]. MS (ESI): mass calcd. for C₅H₅BrD₃N₃O, 208.0; m/z found, 208.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 5.01 (t, *J* = 6.8 Hz, 1H), 2.66 (d, *J* = 7.3 Hz, 1H), 1.64 (d, *J* = 6.7 Hz, 3H) ppm.

Intermediate 16: (R*)-1-(3-Bromo-1-(methyl-*d*₃)-1H-1,2,4-triazol-5-yl)ethan-1-ol.



In the separation of racemic 1-(3-bromo-1-(methyl- d_3)-1H-1,2,4-triazol-5-yl)ethan-1-ol (6.7 g, 31 mmol) by chiral SFC [Stationary phase: DAICEL CHIRALPAK IC, 10 μ m 250 mm $\times$ 50 mm; Mobile phase: Supercritical CO₂ (A) - EtOH (0.1% NH₃.H₂O) (B), gradient elution: 30% B in A at 200 mL/min], the title compound was obtained as the second product: a white solid (2.6 g, 38% yield). SFC: 100% ee [retention time 2.698 min; SFC analytical method: IC-3_EtOH (DEA)_5_40_2,5ML_7MIN]. MS (ESI): mass calcd. for C₅H₅BrD₃N₃O, 208.0; m/z found, 208.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 5.01 (quin, J = 6.8 Hz, 1H), 2.62 (d, J = 7.3 Hz, 1H), 1.65 (d, J = 6.8 Hz, 3H) ppm.

Intermediate 17: 2-(4-Bromo-1-(methyl- d_3)-1H-imidazol-2-yl)propan-2-ol.



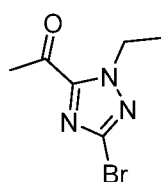
Step A. Ethyl 1-(methyl- d_3)-1H-imidazole-2-carboxylate. To a solution of ethyl 1H-imidazole-2-carboxylate (48 g, 343 mmol) and K₂CO₃ (95 g, 685 mmol) in acetone (500 mL) was added iodomethane- d_3 (50 g, 343 mmol). Then the reaction mixture was stirred at 60 °C overnight. The mixture was cooled to room temperature and filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 30% MeOH in DCM) to give the title compound as a yellow oil (40 g, 74% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.08 (s, 1H), 6.96 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H) ppm.

Step B. Ethyl 4,5-dibromo-1-(methyl- d_3)-1H-imidazole-2-carboxylate. To a solution of ethyl 1-(methyl- d_3)-1H-imidazole-2-carboxylate (39 g, 250 mmol) in anhydrous DMF (230 mL) at 0° C was added NBS (224 g, 1.3 mol). The mixture was stirred at 33° C overnight. The mixture was diluted with sat. aq. Na₂SO₃ solution (300 mL) and then extracted with DCM (300 mL $\times$ 3). The organic layer was separated, dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 100% ethyl acetate in

petroleum ether) to give the title compound as a yellow solid (63 g, 66% yield). MS (ESI): mass calcd. for $C_7H_5Br_2D_3N_2O_2$, 312.9; m/z found, 313.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (q, $J = 7.0$ Hz, 2H), 1.43 (t, $J = 7.2$ Hz, 3H) ppm.

Step C. 2-(4-Bromo-1-(methyl- d_3)-1H-imidazol-2-yl)propan-2-ol. To the solution of ethyl 4,5-dibromo-1-(methyl- d_3)-1H-imidazole-2-carboxylate (9 g, 24 mmol) in THF (70 mL) at 0 °C was slowly added an ether solution (3 M) of MeMgBr (60 mL, 180 mmol) under nitrogen. The reaction mixture was stirred at 0 °C for 1 h. Sat. aq. NH_4Cl (20 mL) was added dropwise to quench the reaction. The resulting mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (200 mL $\times$ 3). The combined organic extract was dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 100% ethyl acetate in petroleum ether) to give the title compound as an off-white solid (3 g, 57% yield). MS (ESI): mass calcd. for $C_7H_8BrD_3N_2O$, 221.0; m/z found, 221.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 2.27 (s, 1H), 1.59 (s, 6H) ppm.

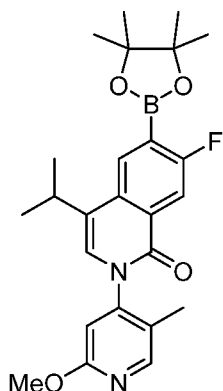
Intermediate 18: 1-(3-Bromo-1-ethyl-1H-1,2,4-triazol-5-yl)ethan-1-one.



Step A. Methyl 3-bromo-1-ethyl-1H-1,2,4-triazole-5-carboxylate. To a solution of methyl 3-bromo-1H-1,2,4-triazole-5-carboxylate (3 g, 14.5 mmol) and Cs_2CO_3 (19 g, 58 mmol) in anhydrous DMF (50 mL) was added dropwise of iodoethane (6.8 g, 44 mmol) at room temperature. Then the resulting reaction mixture was stirred at room temperature for 24 h. The mixture was poured into water (150 mL), extracted with DCM (150 mL) and ethyl acetate (150 mL). The combined organic extract was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, 0-60% ethyl acetate in heptane) to give the title compound as a white solid (1.2 g, 35% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (q, $J = 7.34$ Hz, 2H), 4.01 (s, 3H), 1.51 (t, $J = 7.34$ Hz, 3H) ppm. Ethyl 3-bromo-1-ethyl-1H-1,2,4-triazole-5-carboxylate was also obtained as the second product: a white solid (0.9 g, 25% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 4.64 (q, $J = 7.17$ Hz, 2H), 4.47 (q, $J = 7.17$ Hz, 2H), 1.51 (t, $J = 7.34$ Hz, 3H), 1.45 (t, $J = 7.09$ Hz, 3H) ppm.

Step B. 1-(3-Bromo-1-ethyl-1H-1,2,4-triazol-5-yl)ethan-1-one. To a solution of methyl 3-bromo-1-ethyl-1H-1,2,4-triazole-5-carboxylate (1.2 g, 5.1 mmol) in THF (30 mL) at -78 °C was added an ether solution (3 M) of MeMgBr (4.3 mL, 12.8 mmol) dropwise. The resulting reaction mixture was gradually warmed to room temperature and stirred overnight. The mixture was slowly poured into sat. aq. NH₄Cl (30 mL) and extracted with DCM (30 mL) and ethyl acetate (30 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, 20-100% ethyl acetate in heptane) to give the title compound as a white solid (0.68 g, 61% yield). LCMS (ES-API): mass calcd. for C₆H₈BrN₃O, 217.0; m/z found, 218.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 4.59 (q, *J* = 7.17 Hz, 2H), 2.70 (s, 3H), 1.46 (t, *J* = 7.09 Hz, 3H) ppm.

Intermediate 19: 7-Fluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one.



Step A. 6,7-Difluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one. To a solution of 2-methoxy-5-methylpyridin-4-amine (2.3 g, 17 mmol) in DCE (10 mL) at 0 °C was added a toluene solution (2 M) of AlMe₃ (12.7 mL, 25.4 mmol) under nitrogen. The mixture was stirred for 0.5 h, and then a DCE solution (10 mL) of 6,7-difluoro-4-isopropyl-1H-isochromen-1-one (prepared in Intermediate 11, Step A, 1.9 g, 8.5 mmol) was added dropwise. The reaction mixture was stirred at 90 °C for overnight. The reaction was quenched with aq. HCl (1 M, 17 mL). The mixture was stirred at room temperature for 10 min, and then poured into water (100 mL), and extracted with ethyl acetate (100 mL × 2). The combined organic extract was washed with brine (20 mL × 2), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was dissolved in AcOH (10 mL) and the reaction mixture was stirred at 90 °C overnight. The mixture was cooled to room temperature and poured into water (100 mL). The pH of the mixture

was adjusted to 7-8 by using aq. Na_2CO_3 solution and then the mixture was extracted with ethyl acetate ($100\text{ mL} \times 2$). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by flash column chromatography (SiO_2 , gradient elution: 0 – 25% ethyl acetate in petroleum ether) to give the title compound as a brown solid (4.0 g, 83% yield). MS (ESI): mass calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_2$, 344.1; m/z found, 345.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (dd, $J = 8.4, 10.7$ Hz, 1H), 8.17 (s, 1H), 7.54 (dd, $J = 7.3, 11.8$ Hz, 1H), 6.77 (s, 1H), 6.69 (s, 1H), 3.98 (s, 3H), 3.29 - 3.06 (m, 1H), 2.07 (s, 3H), 1.31 (d, $J = 6.8$ Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -128.68 (1F), -136.53 (1F) ppm.

Step B. 7-Fluoro-6-hydroxy-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one. To a stirred solution of 6,7-difluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one (1.4 g, 4.1 mmol) in DMSO (15 mL) was added an aqueous solution (10 M) of KOH (4.1 mL, 41 mmol) at the room temperature. The reaction mixture was stirred at 90 °C overnight. The reaction was cooled to room temperature, adjusted to pH 4 by using aq. HCl solution (1 M, 45 mL), and then extracted with ethyl acetate ($100\text{ mL} \times 2$). The combined organic extract was washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the title compound as a crude brown solid (1.3 g, 100% yield). MS (ESI): mass calcd. for $\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_3$, 342.1; m/z found, 343.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 11.0$ Hz, 1H), 8.15 (s, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 6.72 (s, 1H), 6.70 (s, 1H), 3.96 (s, 3H), 3.16 (spt, $J = 6.8$ Hz, 1H), 2.08 (s, 3H), 1.30 - 1.27 (m, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -138.44 (1F) ppm.

Step C. 7-Fluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate. To a solution of 7-fluoro-6-hydroxy-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl) isoquinolin-1(2H)-one (1.3 g, 3.8 mmol) in DCM (20 mL) was added PhNTf_2 (2.8 g, 7.5 mmol), DMAP (250 mg, 1.9 mmol) and TEA (823 mg, 7.5 mmol) respectively. The reaction mixture was stirred at room temperature overnight. Water (50 mL) was added, and the resulting mixture was extracted with DCM ($80\text{ mL} \times 2$). The combined organic extract was dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 , gradient elution: 0-20% ethyl acetate in petroleum ether) to give the title compound as an off white solid (1.6 g, 85% yield over two steps). MS (ESI): mass calcd. for $\text{C}_{20}\text{H}_{18}\text{F}_4\text{N}_2\text{O}_5\text{S}$, 474.1; m/z found, 475.0

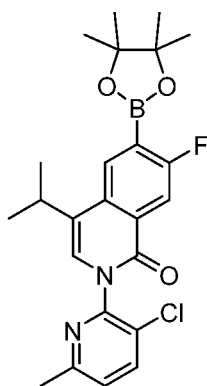
[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.38 (d, *J* = 10.0 Hz, 1H), 8.18 (s, 1H), 7.73 (d, *J* = 6.8 Hz, 1H), 6.83 (s, 1H), 6.68 (s, 1H), 3.98 (s, 3H), 3.37 - 3.09 (m, 1H), 2.08 (s, 3H), 1.32 (dd, *J* = 1.3, 6.7 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -72.88 (3F), -127.95 (1F) ppm.

Step D. 7-Fluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)isoquinolin-1(2H)-one. To a solution of 7-fluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (1.64 g, 3.64 mmol) in anhydrous 1,4-dioxane (20 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.8 g, 6.9 mmol), Pd(dppf)Cl₂ (565 mg, 0.69 mmol) and AcOK (848 mg, 8.6 mmol) respectively. The reaction mixture was stirred under nitrogen and heated at 90 °C

overnight. The mixture was cooled to room temperature and directly purified by flash column chromatography (SiO₂, gradient elution: 0- 25% ethyl acetate in petroleum ether) to give the title compound as a light-yellow gum (1.2 g, 75% yield). MS (ESI): mass calcd. for C₂₅H₃₀BFN₂O₄, 452.2; *m/z* found, 453.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, *J* = 5.1 Hz, 1H), 8.16 (s, 1H), 8.12 (d, *J* = 9.5 Hz, 1H), 6.71 (s, 2H), 3.97 (s, 3H), 3.47 - 3.34 (m, 1H), 2.06 (s, 3H), 1.31 (br d, *J* = 6.8 Hz, 6H), 1.24 (s, 12H); ¹⁹F NMR (376 MHz, CDCl₃) δ -101.45 - -110.48 (1F) ppm.

Intermediate 20: 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one.



Step A. 2-(3-Chloro-6-methylpyridin-2-yl)-6,7-difluoro-4-isopropylisoquinolin-1(2H)-one. To a solution of 3-chloro-6-methylpyridin-2-amine (318 mg, 2.2 mmol) in DCE (5 mL) at 0 °C was added a toluene solution (2 M) of AlMe₃ (1.6 mL, 3.2 mmol) under nitrogen. The mixture was stirred for 0.5 h, and then a DCE solution (5 mL) of 6,7-difluoro-4-isopropyl-1H-isochromen-1-one (prepared in Intermediate 11, Step A, 0.5 g, 2.2 mmol) was added dropwise. The reaction

mixture was stirred at 90 °C overnight. The reaction was quenched with aq. HCl (1 M, 0.6 mL). The mixture was stirred at room temperature for 10 min, and then poured into water (10 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic extract was washed with brine (20 mL × 2), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was dissolved in AcOH (8 mL) and the reaction mixture was stirred at 85 °C overnight. The mixture was cooled to room temperature and poured into water (10 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic extract was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0 – 20% ethyl acetate in petroleum ether) to give the title compound as a yellow oil (608 mg, 78% yield). MS (ESI): mass calcd. for C₁₈H₁₅ClF₂N₂O, 348.0; m/z found, 349.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.31 (dd, *J* = 8.4, 10.7 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 7.3, 11.8 Hz, 1H), 7.38 - 7.28 (m, 1H), 6.93 (s, 1H), 3.21 - 3.12 (m, 1H), 2.61 (s, 3H), 1.33 (dd, *J* = 2.6, 6.9 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -127.32 - -130.48 (1F), -136.11 - -138.57 (1F) ppm.

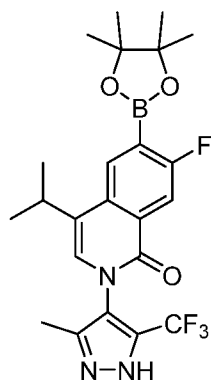
Step B. 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-hydroxy-4-isopropylisoquinolin-1(2H)-one. To a stirred solution of 2-(3-chloro-6-methylpyridin-2-yl)-6,7-difluoro-4-isopropylisoquinolin-1(2H)-one (608 mg, 1.7 mmol) in DMSO (10 mL) was added an aqueous solution (10 M) of KOH (1.7 ml, 17 mmol) at the room temperature. The reaction mixture was stirred at 85 °C overnight. The reaction was cooled to room temperature, adjusted to pH 3-4 by using aq. HCl solution (1 M, 5 mL), and then extracted with ethyl acetate (20 mL × 2). The combined organic extract was washed with brine, dried over Na₂SO₄, filtered and concentrated to give the title compound as a yellow oil (574 mg, 100% yield). MS (ESI): mass calcd. for C₁₈H₁₆ClFN₂O₂, 346.0; m/z found, 347.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J* = 11.1 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.28 (s, 1H), 7.27 - 7.26 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 6.82 (s, 1H), 3.21 - 3.08 (m, 1H), 2.63 (s, 3H), 1.34 - 1.28 (m, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -132.10 - -142.77 (1F) ppm.

Step C. 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-4-isopropyl-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate. To a solution of 2-(3-chloro-6-methylpyridin-2-yl)-7-fluoro-6-hydroxy-4-isopropylisoquinolin-1(2H)-one (574 mg, 1.65 mmol) in DCM (20 mL) was added PhNTf₂ (1.8 g, 5.0 mmol), DMAP (100 mg, 0.82 mmol) and TEA (1.2 mL, 8.3 mmol) respectively. The reaction mixture was stirred at room temperature overnight. Water (10 mL) was

added, and the resulting mixture was extracted with DCM (20 mL $\times$ 2). The combined organic extract was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0-22% ethyl acetate in petroleum ether) to give the title compound as an off white solid (455 mg, 48% yield over for two steps). MS (ESI): mass calcd. for C₁₉H₁₅ClF₄N₂O₄S, 478.0; m/z found, 479.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 10.0 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.29 (s, 1H), 6.99 (s, 1H), 3.25 - 3.09 (m, 1H), 2.61 (s, 3H), 1.35 (dd, *J* = 2.5, 6.8 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -72.92 (1F), -75.30 (1F), -128.46 (1F) ppm.

Step D. 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one. To a solution of 2-(3-chloro-6-methylpyridin-2-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (455 mg, 0.83 mmol) in anhydrous 1,4-dioxane (10 mL) was added 4,4,4',4',5,5,5',5'- octamethyl- 2,2'-bi(1,3,2-dioxaborolane) (318 mg, 1.25 mmol), Pd(dppf)Cl₂ (102 mg, 0.13 mmol) and AcOK (245 mg, 2.5 mmol) respectively. The reaction mixture was stirred under nitrogen and heated at 80 °C overnight. The mixture was cooled to room temperature and directly purified by flash column chromatography (SiO₂, gradient elution: 0- 25% ethyl acetate in petroleum ether) to give the title compound as a light brown gum (368 mg, 81% yield). MS (ESI): mass calcd. for C₂₄H₂₇BClFN₂O₃, 456.1; m/z found, 457.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, *J* = 5.2 Hz, 1H), 8.13 (d, *J* = 9.7 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.25 (s, 1H), 6.90 - 6.83 (m, 1H), 3.80 (s, 1H), 2.61 (s, 3H), 1.41 (s, 12H), 1.36 - 1.33 (m, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -104.64 ppm.

Intermediate 21: 7-Fluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one.



Step A. 6,7-Difluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one. A mixture of 6,7-difluoro-3-hydroxy-4-isopropylisochroman-1-one (3.0 g, 12.4

mmol) and 5-methyl-3-(trifluoromethyl)-1H-pyrazol-4-amine (2.3 g, 13.6 mmol) in AcOH (30 mL) was stirred at 90 °C overnight. The mixture was concentrated to about 8 mL. The remaining mixture was triturated with H₂O (20 mL). The suspension was filtered and the filter cake was collected, dried under vacuum to give the title compound (4.2 g, 89% yield) as yellow solid. MS (ESI): mass calcd. for C₁₇H₁₄F₅N₃O, 371.1; m/z found, 372.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.48 (br s, 1H), 8.32 (dd, *J* = 8.3, 10.5 Hz, 1H), 7.56 (dd, *J* = 7.3, 11.5 Hz, 1H), 6.85 (s, 1H), 3.16 (spt, *J* = 6.9 Hz, 1H), 2.13 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -61.96 (3F), -128.04 (1F), -132.59 - -139.27 (1F) ppm.

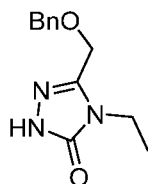
Step B. 7-Fluoro-6-hydroxy-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one. KOH (10 M in H₂O, 11.3 mL, 113 mmol) was added to a stirred solution of 6,7-difluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one (4.2 g, 11.3 mmol) in DMSO (30 mL) at the room temperature, and the mixture was stirred at 90 °C for 2 hours. To the mixture was added HCl solution (1 M, 130 mL) to adjust the pH to around 4. The mixture was extracted with ethyl acetate (70 mL × 4). The combined organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude was triturate with petroleum ether (50 mL). The solid layer was separated and dried under vacuum to give the title compound (4.3 g, crude) as brown solid. MS (ESI): mass calcd. for C₁₇H₁₅F₄N₃O₂, 369.1; m/z found, 370.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.73 (s, 1H), 11.07 (s, 1H), 7.90 (d, *J* = 11.6 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 6.94 (s, 1H), 3.17 - 3.01 (m, 1H), 2.12 (s, 3H), 1.22 (dd, *J* = 1.5, 6.8 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -60.62 (3F), -134.99 (1F) ppm.

Step C. 7-Fluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate. A mixture of 7-fluoro-6-hydroxy-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one (4.3 g, 11.6 mmol), PhNTf₂ (5.4 g, 15.1 mmol), DMAP (711 mg, 5.8 mmol) and TEA (2.4 g, 23.3 mmol) in DCM (40 mL) was stirred at r.t. for 2 hours. To the mixture was added H₂O (50 mL) and extracted with DCM (60 mL × 2). The combined organic layer was dried over Na₂SO₄, filtered and evaporated under vacuum. The crude was purified by column chromatography (SiO₂, gradient elution: 0 – 40% ethyl acetate in petroleum ether) to give the title compound (5.6 g,

71% yield over two steps) as light yellow solid. MS (ESI): mass calcd. for $C_{18}H_{14}F_7N_3O_4S$, 501.1; m/z found, 502.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 11.53 (br s, 1H), 8.40 (d, $J = 9.8$ Hz, 1H), 7.75 (d, $J = 6.8$ Hz, 1H), 6.90 (s, 1H), 3.30 - 3.10 (m, 1H), 2.16 (s, 3H), 1.33 (d, $J = 6.8$ Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.90 (3F), -72.87 (3F), -127.69 (1F) ppm.

- 5 Step D. 7-Fluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one. To a solution of 7-fluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-1-oxo-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (5.5 g, 11 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (5.6 g, 22 mmol), $Pd(dppf)Cl_2$ (1.6 g, 2.2 mmol) and AcOK (2.7 g, 27 mmol) in 10 1,4-dioxane (60 mL) was stirred at 90 °C under N_2 overnight. The mixture was cooled to room temperature and purified by column chromatography (SiO_2 , gradient elution: 0 – 50% ethyl acetate in petroleum ether) to give the title compound (4.6 g, 87% yield) as a red sticky solid. MS (ESI): mass calcd. for $C_{23}H_{26}BF_4N_3O_3$, 479.2; m/z found, 480.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, $J = 5.3$ Hz, 1H), 8.14 (d, $J = 9.5$ Hz, 1H), 6.78 (s, 1H), 3.39 (td, $J = 6.7$, 15 13.5 Hz, 1H), 2.17 (s, 3H), 1.42 (s, 12H), 1.32 (d, $J = 6.8$ Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.95 (3F), -103.95 (1F) ppm.

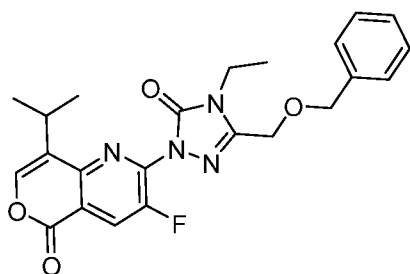
Intermediate 22: 3-((Benzyloxy)methyl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one



- 20 Step A. 2-(Benzyloxy)acetohydrazide. To a solution of ethyl 2-(benzyloxy)acetate (55 g, 283.17 mmol) in EtOH (500 mL) was added $NH_2NH_2 \cdot H_2O$ (28.3 g, 566 mmol, 27.5 mL). The reaction mixture was heated at 78 °C for 6 h. The reaction mixture was concentrated under reduced pressure to afford the title product (52 g, crude) as a colorless oil, which was used directly in the next step without further purification.
- 25 Step B. 3-((Benzyloxy)methyl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one. To a solution of 2-(benzyloxy)acetohydrazide (52 g, 288 mmol) in H_2O (500 mL) was added dropwise isocyanatoethane (25.1 g, 346 mmol, 27.9 mL) at 0 °C. After the addition was complete, the mixture was stirred at 25 °C for 12 hr. To the mixture was added H_2O (20 mL), and an aqueous

solution (120 mL) of NaOH (57.7 g, 1.44 mol). The mixture was stirred at 95 °C for 12 hr. The reaction mixture was cooled to rt, then quenched with HCl (12 M) at 0 °C and adjusted to “pH” 6. The solid was filtered and dried under reduced pressure to afford the title compound as a white solid (61 g, 91% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.23 - 9.09 (m, 1H), 7.41 - 7.31 (m, 5H), 4.58 - 4.53 (m, 2H), 4.45 - 4.42 (m, 2H), 3.82 - 3.75 (m, 2H), 1.33 - 1.29 (m, 3H) ppm.

Intermediate 23: 2-(3-((Benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-3-fluoro-8-isopropyl-5H-pyrano[4,3-*b*]pyridin-5-one.



Step A. 2,6-Dichloro-5-fluoronicotinoyl chloride. To a solution of 2,6-dichloro-5-fluoronicotinic acid (20 g, 95 mmol) in THF (200 mL) was added (COCl)₂ (12.7 g, 10.0 mmol) and DMF (69.6 mg, 0.952 mmol) at 0 °C dropwise. The mixture was stirred at 0 °C for 30 min, then warmed to 25 °C, and stirred for 1 h. The reaction mixture was concentrated under reduced pressure to afford desired product (21.7 g, crude) as a colorless oil, which was used without further purification.

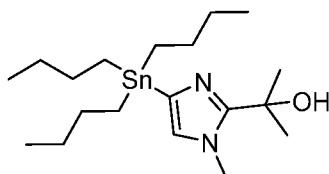
Step B. Isopropyl 2,6-dichloro-5-fluoronicotinate. To a mixture of propan-2-ol (8.56 g, 142 mmol, 10.9 mL) and pyridine (9.02 g, 114 mmol) in THF (200 mL) was added a solution of 2,6-dichloro-5-fluoronicotinoyl chloride (21.7 g, 96.0 mmol) in THF (50 mL) at 0 °C. The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (300 mL). The aqueous phase was extracted with ethyl acetate (300 mL). The combined organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 10:1) to afford the title compound (21 g, 87% yield). MS (ESI): mass calcd. for C₉H₈Cl₂FNO₂, 250.1; m/z found, 252.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.97 - 7.95 (d, *J* = 7.2 Hz, 1H), 5.32 - 5.25 (m, 1H), 1.58 - 1.39 (m, 6H) ppm.

Step C. Isopropyl 6-(3-((benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-

chloro-5-fluoronicotinate. To a mixture of isopropyl 2,6-dichloro-5-fluoronicotinate (4 g, 15.87 mmol) in DMSO (40 mL) was added 3-((benzyloxy)methyl)-4-ethyl-1H-1,2,4-triazol-5(4H)-one (Intermediate 22, 3.89 g, 16.66 mmol) and K₂CO₃ (3.29 g, 23.80 mmol). The mixture was stirred at 80 °C for 3 hr. The mixture was diluted with H₂O (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/0 to 1:1) to afford the title compound (5.7 g, 80% yield). MS (ESI): mass calcd. for C₂₁H₂₂ClFN₄O₄, 448.1; m/z found, 449.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 8.8 Hz, 1H), 7.43 - 7.31 (m, 5H), 5.30 (td, *J* = 6.3, 12.5 Hz, 1H), 4.61 (s, 2H), 4.54 (s, 2H), 3.85 (q, *J* = 7.2 Hz, 2H), 1.41 (d, *J* = 6.2 Hz, 6H), 1.37 - 1.31 (m, 3H) ppm.

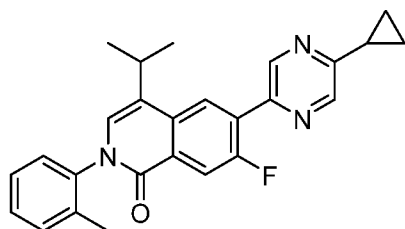
Step D. 2-(3-((Benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-3-fluoro-8-isopropyl-5H-pyrano[4,3-b]pyridin-5-one. To a flask charged with isopropyl 6-(3-((benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-2-chloro-5-fluoronicotinate (1 g, 2.23 mmol), DPPF (61.7 mg, 111.30 μmol), [Pd(allyl)Cl]₂ (16.3 mg, 44.56 μmol), Cs₂CO₃ (1.45 g, 4.46 mmol) and 4Å MS (1 g) in glovebox was added a solution of 3-methylbutanal (1.19 mL, 11.14 mmol) in dioxane (15 mL) slowly by syringe. The reaction mixture was heated to 100 °C for 16 h. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (SiO₂, gradient elution: 10 – 25% ethyl acetate in petroleum ether) to give the title compound as light yellow solid (370 mg, 37.6% yield). MS (ESI): mass calcd. for C₂₃H₂₃FN₄O₄, 438.2; m/z found, 439.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 9.2 Hz, 1H), 7.43 - 7.34 (m, 5H), 7.31 (s, 1H), 4.63 (s, 2H), 4.55 (s, 2H), 3.88 (q, *J* = 7.2 Hz, 2H), 3.44 (td, *J* = 7.0, 13.8 Hz, 1H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.32 (d, *J* = 6.9 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -122.48 (s, 1F) ppm.

Intermediate 24: 2-(1-Methyl-4-(tributylstannyl)-1H-imidazol-2-yl)propan-2-ol.



To a solution of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2, 120 mg, 548 μ mol) and hexa-n-butylditin (635 mg, 1.1 mmol) in toluene (1.5 mL) was added Pd(PPh₃)₂Cl₂ (39 mg, 54 μ mol) under N₂. The mixture was stirred at 100 °C overnight. The mixture was filtered. The filter cake was washed by sat. aq. KF solution (1 mL). The filtrate was concentrated to give the title compound (1.5 g, crude) as yellow oil and used in the next step directly. MS (ESI): mass calcd. for C₁₉H₃₈N₂OSn, 430.2; m/z found, 431.2 [M+H]⁺.

Example 1: 6-(5-Cyclopropylpyrazin-2-yl)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



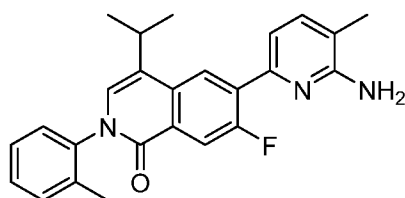
Step A. 7-Fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(*o*-tolyl)isoquinolin-1(2H)-one. To a solution of 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1, 154 mg, 0.17 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (88 mg, 0.35 mmol), and AcOK (42.5 mg, 0.43 mmol) in 1,4-dioxane (4 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (29 mg, 0.035 mmol). The reaction mixture was sealed under nitrogen and heated under microwave irradiation at 120 °C for 2 h. The mixture was cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The combined filtrate was concentrated to give the crude title compound as a brown solid (57 mg, 79% yield), which was used directly to the next step without further purification.

Step B. 6-(5-Cyclopropylpyrazin-2-yl)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.

To a mixture of crude 7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(*o*-tolyl)isoquinolin-1(2H)-one (57 mg, 0.14 mmol), 2-bromo-5-cyclopropyl-pyrazine (54 mg, 0.27 mmol) and Cs₂CO₃ (132 mg, 0.41 mmol) in 1,4-dioxane/H₂O (v/v, 2/1, 6 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (5.5 mg, 0.007 mmol). The reaction mixture was sealed in a tube under nitrogen and heated under microwave irradiation at 80 °C for 1 h. The mixture cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl

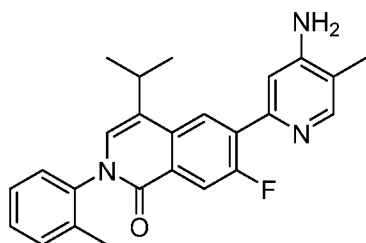
acetate. The combined filtrate was concentrated. The residue was purified by flash column chromatography (SiO₂, 30-50% ethyl acetate in heptane). The product (36 mg) was further purified by preparative reversed phase HPLC (Stationary phase: C18 30 x 100 mm*5 um Gemini; Mobile phase: water (0.05% NH₃H₂O) (A) - MeCN (B), gradient elution: 10- 90% B in A over 9 min, flow rate: 60 mL/min) to give the title compound as a white powder (25 mg, 45% yield). LCMS (ES-API): mass calcd. for C₂₆H₂₄FN₃O, 413.2; m/z found, 414.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.01 (br s, 1H), 8.65 (s, 1H), 8.44 (br d, *J* = 6.85 Hz, 1H), 8.30 (br d, *J* = 11.74 Hz, 1H), 7.26-7.44 (m, 4H), 6.84 (s, 1H), 6.76-6.94 (m, 1H), 3.42 (td, *J* = 6.48, 13.45 Hz, 1H), 2.18 (s, 3H), 2.11-2.18 (m, 1H), 1.33 (br d, *J* = 6.36 Hz, 6H), 1.05-1.24 (m, 4H) ppm.

Example 2: 6-(6-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 1, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using 6-bromo-3-methylpyridin-2-amine instead of 2-bromo-5-cyclopropylpyrazine in Step B. LCMS (ES-API): mass calcd. for C₂₅H₂₄FN₃O, 401.2; m/z found, 402.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.36 (br d, *J* = 6.85 Hz, 1H), 8.24 (br d, *J* = 11.74 Hz, 1H), 7.32-7.47 (m, 4H), 7.22-7.31 (m, 2H), 6.80 (s, 1H), 4.57 (br s, 2H), 3.14-3.56 (m, 1H), 2.22 (s, 3H), 2.16 (s, 3H), 1.32 (br d, *J* = 5.38 Hz, 6H) ppm.

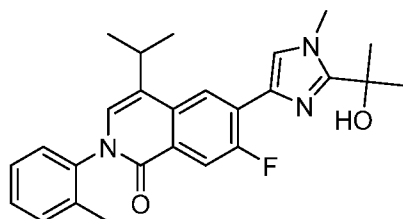
Example 3: 6-(4-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 1, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using 2-bromo-5-methylpyridin-4-amine instead of 2-bromo-5-cyclopropylpyrazine in Step B. LCMS (ES-API): mass calcd. for C₂₅H₂₄FN₃O, 401.2; m/z found, 402.1

5 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (d, *J* = 7.34 Hz, 1H), 8.30 (s, 1H), 8.25 (d, *J* = 11.74 Hz, 1H), 7.31-7.44 (m, 3H), 7.29 (br d, *J* = 6.36 Hz, 1H), 7.16 (d, *J* = 1.47 Hz, 1H), 6.81 (s, 1H), 4.23 (br s, 2H), 3.29-3.65 (m, 1H), 2.20 (s, 3H), 2.17 (s, 3H), 1.31 (dd, *J* = 2.93, 6.85 Hz, 6H) ppm.

10 Example 4: 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



Step A: 7-Fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(*o*-tolyl)isoquinolin-1(2H)-one. To a solution of 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-

15 dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1, 1 g, 2.3 mmol), 4,4,4',4',5,5,5',5'- octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.2 g, 4.5 mmol), and AcOK (552 mg, 5.6 mmol) in 1,4-dioxane (25 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (382 mg, 0.45 mmol). The reaction mixture was sealed under nitrogen and heated under microwave irradiation at 130 °C for 2.5 h. The mixture was cooled to room temperature and filtered through a short pad of silica gel.

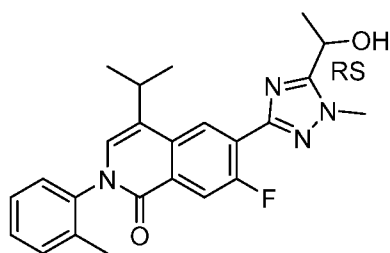
20 The silica gel was washed with ethyl acetate. The combined filtrate was concentrated to give the crude title compound as a brown solid (948 mg, 100% yield), which was used directly to the next step without further purification.

Step B: 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one. To a mixture of crude 7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-

25 1,3,2-dioxaborolan-2-yl)-2-(*o*-tolyl)isoquinolin-1(2H)-one (948 mg, 2.3 mmol), 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2, 986 mg, 4.5 mmol) and Cs₂CO₃ (2.2 g, 6.8 mmol) in 1,4-dioxane/H₂O (v/v, 5/1, 30 mL) was added XPhos Pd G3 (190 mg, 0.23 mmol). The reaction mixture was sealed in a tube under nitrogen and heated under microwave irradiation

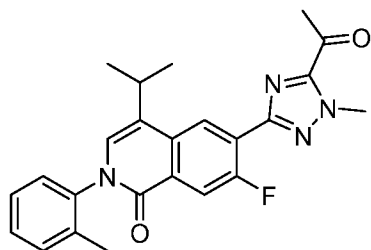
at 82 °C for 1 h. The mixture cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed with ethyl acetate. The combined filtrate was concentrated. The residue was purified by flash column chromatography (SiO₂, 30-50% ethyl acetate in heptane). The product (500 mg) was further purified by preparative reversed phase HPLC (Stationary phase: C18 30 x 100 mm*5 um Gemini; Mobile phase: water (0.03% NH₃H₂O) (A) - MeCN (B), gradient elution: 10- 90% B in A over 9 min, flow rate: 60 mL/min) to give the title compound as a white powder (420 mg, 43% yield). LCMS (ES-API): mass calcd. for C₂₆H₂₈FN₃O₂, 433.2; m/z found, 434.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.48-8.60 (m, 1H), 8.18 (d, *J* = 12.23 Hz, 1H), 7.47 (d, *J* = 3.91 Hz, 1H), 7.27-7.41 (m, 4H), 6.79 (s, 1H), 3.89 (s, 3H), 3.38-3.51 (m, 1H), 3.36 (s, 1H), 2.17 (s, 3H), 1.75 (s, 6H), 1.33 (dd, *J* = 2.93, 6.85 Hz, 6H) ppm.

Example 5: Racemic 7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



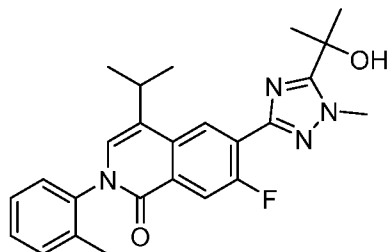
The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using racemic 1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-ol (Intermediate 3) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₄H₂₅FN₄O₂, 420.2; m/z found, 421.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.47 (d, *J* = 6.85 Hz, 1H), 8.27 (d, *J* = 11.25 Hz, 1H), 7.31-7.41 (m, 3H), 7.26-7.30 (m, 1H), 6.82 (s, 1H), 5.14 (t, *J* = 6.60 Hz, 1H), 4.04 (s, 3H), 3.41 (td, *J* = 6.66, 13.57 Hz, 1H), 3.12-3.30 (m, 1H), 2.18 (s, 3H), 1.70 (d, *J* = 6.85 Hz, 3H), 1.33 (dd, *J* = 2.45, 6.85 Hz, 6H) ppm.

Example 6: 6-(5-Acetyl-1-methyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using 1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-one instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₄H₂₃FN₄O₂, 418.2; m/z found, 419.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, *J* = 6.85 Hz, 1H), 8.32 (d, *J* = 11.25 Hz, 1H), 7.32-7.41 (m, 3H), 7.27-7.30 (m, 1H), 6.81 (s, 1H), 4.32 (s, 3H), 3.42 (td, *J* = 6.66, 13.57 Hz, 1H), 2.84 (s, 3H), 2.18 (s, 3H), 1.35 (dd, *J* = 2.45, 6.85 Hz, 6H) ppm.

Example 7: 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.

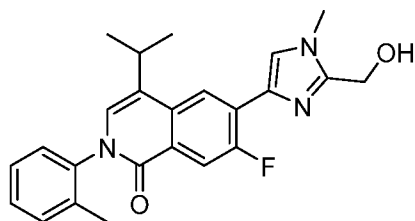


To a solution of 6-(5-acetyl-1-methyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one (135 mg, 0.32 mmol) in THF (20 mL) at -78 °C was added an ether solution (3 M) of MeMgBr (0.32 mL, 0.97 mmol) dropwise. The resulting reaction mixture was stirred at 0 °C for 2 h. The mixture was slowly poured into sat. aq. NH₄Cl (30 mL) and extracted with DCM (30 mL) and ethyl acetate (30 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (SiO₂, 30-70% ethyl acetate in heptane) to give a crude product, which was further purified by preparative reversed phase HPLC (Stationary phase: C18 30 x 100 mm*5 um Gemini; Mobile phase: water (0.27% NH₃H₂O) (A) - MeCN (B), gradient elution: 10- 90% B in A over 9 min, flow rate: 60 mL/min) to give the title compound as a white powder (71 mg, 51% yield). LCMS

(ES-API): mass calcd. for $C_{25}H_{27}FN_4O_2$, 434.2; m/z found, 435.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (br d, $J = 6.36$ Hz, 1H), 8.19-8.34 (m, 1H), 7.37 (br s, 4H), 6.81 (s, 1H), 4.18 (s, 3H), 3.30-3.54 (m, 1H), 2.49 (s, 1H), 2.17 (s, 3H), 1.79 (s, 6H), 1.33 (br d, $J = 5.38$ Hz, 6H) ppm.

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Example 8: 7-Fluoro-6-(2-(hydroxymethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one.

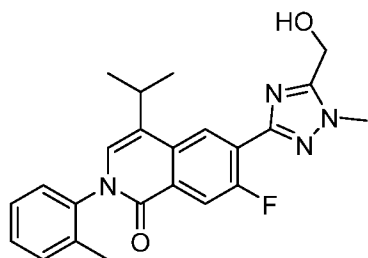


The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(o-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using (4-bromo-1-methyl-1H-imidazol-2-yl)methanol (Intermediate 4) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B.

LCMS (ES-API): mass calcd. for $C_{24}H_{24}FN_3O_2$, 405.2; m/z found, 406.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (br d, $J = 7.34$ Hz, 1H), 8.20 (br d, $J = 11.74$ Hz, 1H), 7.50 (br d, $J = 3.91$ Hz, 1H), 7.26-7.44 (m, 4H), 6.80 (s, 1H), 4.79 (s, 2H), 3.90 (br d, $J = 3.42$ Hz, 1H), 3.74 (s, 3H), 3.49 (td, $J = 6.48, 13.45$ Hz, 1H), 2.18 (s, 3H), 1.34 (br dd, $J = 3.18, 6.60$ Hz, 6H) ppm.

15

Example 9: 7-Fluoro-6-(5-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one.



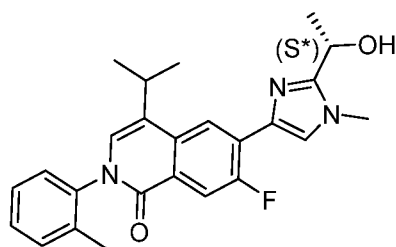
20

The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(o-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using (3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)methanol (Intermediate 5)

instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B.

LCMS (ES-API): mass calcd. for $C_{23}H_{23}FN_4O_2$, 406.2; m/z found, 407.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, $J = 6.85$ Hz, 1H), 8.29 (d, $J = 11.25$ Hz, 1H), 7.28-7.40 (m, 4H), 6.83 (s, 1H), 4.90 (d, $J = 5.87$ Hz, 2H), 4.04 (s, 3H), 3.36-3.49 (m, 1H), 3.23 (br t, $J = 6.11$ Hz, 1H), 2.18 (s, 3H), 1.33 (dd, $J = 2.93, 6.85$ Hz, 6H) ppm.

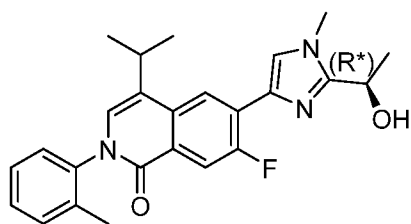
Example 10: (S*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(o-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using (S*)-1-(4-bromo-1-methyl-1H-imidazol-2-yl)ethan-1-ol (Intermediate 6) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B.

LCMS (ES-API): mass calcd. for $C_{25}H_{26}FN_3O_2$, 419.2; m/z found, 420.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (br d, $J = 5.87$ Hz, 1H), 8.10-8.27 (m, 1H), 7.29-7.53 (m, 5H), 6.80 (br s, 1H), 5.03 (br d, $J = 5.38$ Hz, 1H), 3.73 (br s, 3H), 3.42-3.57 (m, 1H), 3.18-3.38 (m, 1H), 2.18 (br s, 3H), 1.68 (br d, $J = 5.87$, 3H), 1.17-1.34 (m, 6H) ppm.

Example 11: (R*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one.

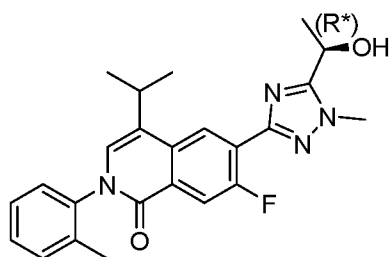


The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(o-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using (R*)-1-(4-bromo-1-methyl-1H-imidazol-2-yl)ethan-1-ol (Intermediate

7) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B.

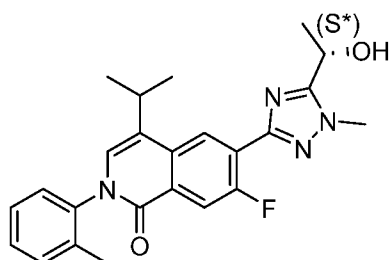
LCMS (ES-API): mass calcd. for $C_{25}H_{26}FN_3O_2$, 419.2; m/z found, 420.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, $J = 6.85$ Hz, 1H), 8.19 (d, $J = 12.23$ Hz, 1H), 7.48 (d, $J = 4.40$ Hz, 1H), 7.28-7.41 (m, 4H), 6.80 (s, 1H), 5.03 (br d, $J = 6.36$ Hz, 1H), 3.74 (s, 3H), 3.36-3.57 (m, 1H), 3.12 (br s, 1H), 2.18 (s, 3H), 1.69 (d, $J = 6.36$ Hz, 3H), 1.16-1.37 (m, 6H) ppm.

Example 12: (R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using (R*)-1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-ol (Intermediate 9) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for $C_{24}H_{25}FN_4O_2$, 420.2; m/z found, 421.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, $J = 6.85$ Hz, 1H), 8.22-8.38 (m, 1H), 7.27-7.46 (m, 4H), 6.82 (s, 1H), 5.16 (quin, $J = 6.60$ Hz, 1H), 4.06 (s, 3H), 3.42 (td, $J = 6.85, 13.69$ Hz, 1H), 2.64 (d, $J = 6.85$ Hz, 1H), 2.18 (s, 3H), 1.73 (d, $J = 6.85$ Hz, 3H), 1.33 (dd, $J = 2.45, 6.85$ Hz, 6H) ppm.

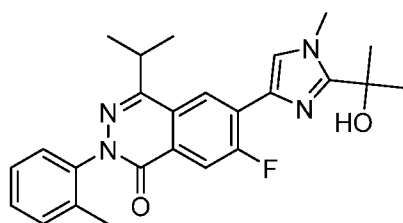
Example 13: (S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate

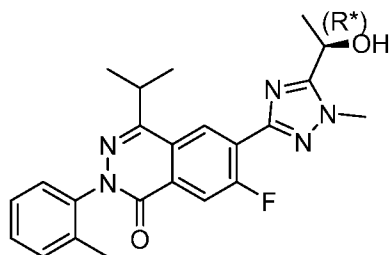
(Intermediate 1) and using (S*)-1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-ol (Intermediate 8) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₄H₂₅FN₄O₂, 420.2; m/z found, 421.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.48 (d, *J* = 6.85 Hz, 1H), 8.29 (d, *J* = 11.25 Hz, 1H), 7.27-7.46 (m, 4H), 6.82 (s, 1H), 5.16 (quin, *J* = 6.85 Hz, 1H), 4.06 (s, 3H), 3.42 (td, *J* = 6.85, 13.69 Hz, 1H), 2.56 (dd, *J* = 1.47, 6.85 Hz, 1H), 2.18 (s, 3H), 1.73 (d, *J* = 6.85 Hz, 3H), 1.33 (dd, *J* = 2.45, 6.85 Hz, 6H) ppm.

Example 14: 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one.



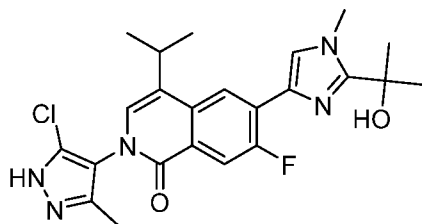
The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydrophthalazin-6-yl trifluoromethanesulfonate (Intermediate 10) instead of 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) in Step A and using 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₅H₂₇FN₄O₂, 434.2; m/z found, 435.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.70 (d, *J* = 6.85 Hz, 1H), 8.16 (d, *J* = 11.25 Hz, 1H), 7.49 (d, *J* = 4.40 Hz, 1H), 7.29-7.42 (m, 4H), 3.91 (s, 3H), 3.66 (td, *J* = 6.85, 13.69 Hz, 1H), 3.19 (s, 1H), 2.19 (s, 3H), 1.75 (s, 6H), 1.38 (d, *J* = 6.85 Hz, 6H) ppm.

Example 15: (R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)phthalazin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydrophthalazin-6-yl trifluoromethanesulfonate (Intermediate 10) instead of 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) in Step A and using (R*)-1-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)ethan-1-ol (Intermediate 9) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₃H₂₄FN₅O₂, 421.2; m/z found, 422.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.65 (d, *J* = 6.36 Hz, 1H), 8.27 (d, *J* = 10.76 Hz, 1H), 7.36 (s, 4H), 5.16 (quin, *J* = 6.60 Hz, 1H), 4.07 (s, 3H), 3.64 (td, *J* = 6.79, 13.33 Hz, 1H), 2.65 (d, *J* = 6.85 Hz, 1H), 2.20 (s, 3H), 1.73 (d, *J* = 6.36 Hz, 3H), 1.38 (d, *J* = 6.85 Hz, 6H) ppm.

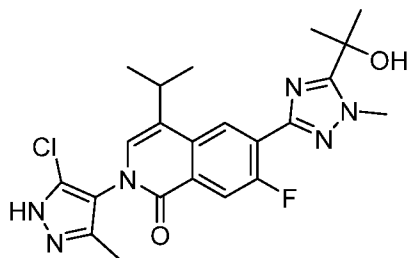
Example 16: 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one.



To a mixture of 2-(5-chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 11, 100 mg, 0.22 mmol) in 1,4-dioxane/H₂O (v/v, 5/1, 3 mL) was added 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2, 54 mg, 0.22 mmol), K₂CO₃ (93 mg, 0.67 mmol) and XPhos Pd G3 (19 mg, 0.022 mmol) under nitrogen respectively. The reaction mixture was stirred under nitrogen at 60 °C for 12 h. The mixture was diluted with water (2 mL) and then extracted with DCM (2 mL × 2). The combined organic extract was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, gradient elution: 0- 40% ethyl acetate in petroleum ether) to give the title compound as a white solid (34 mg, 27% yield). The product was further purified by preparative reversed phase HPLC (Stationary phase: Boston Prime C18, 5μm, 150 × 30 mm ; Mobile phase: water (0.05% NH₃H₂O + 10 mM NH₄HCO₃) (A) - MeCN (B), gradient elution: 30 - 60% B in A over 7 min, flow rate: 35 mL/min) to give the title compound as a white solid (25 mg, 24% yield). MS (ESI): mass calcd. for C₂₃H₂₅ClFN₅O₂, 457.2; m/z found, 458.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.95 (br

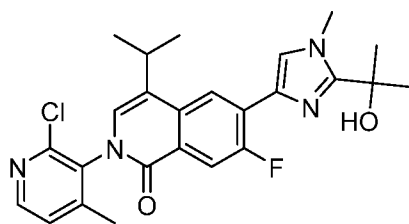
s, 1H), 8.57 (br d, $J = 7.0$ Hz, 1H), 8.18 (d, $J = 11.8$ Hz, 1H), 7.48 (d, $J = 4.0$ Hz, 1H), 6.79 (s, 1H), 3.90 (s, 3H), 3.55 - 3.25 (m, 2H), 2.22 (s, 3H), 1.76 (s, 6H), 1.36 (br d, $J = 4.0$ Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -115.47 (s, 1F) ppm.

5 Example 17: 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 16, using 2-(5-chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 11) and using 2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol (Intermediate 12) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for $\text{C}_{22}\text{H}_{24}\text{ClFN}_6\text{O}_2$, 458.9; m/z found, 459.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 11.15 (br s, 1H), 8.49 (d, $J = 6.8$ Hz, 1H), 8.28 (d, $J = 11.2$ Hz, 1H), 6.82 (s, 1H), 4.19 (s, 3H), 3.41 (spt, $J = 6.7$ Hz, 1H), 2.71 (br s, 1H), 2.23 (s, 3H), 1.80 (s, 6H), 1.36 (br d, $J = 5.5$ Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -113.58 (s, 1F) ppm.

Example 18: 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one.

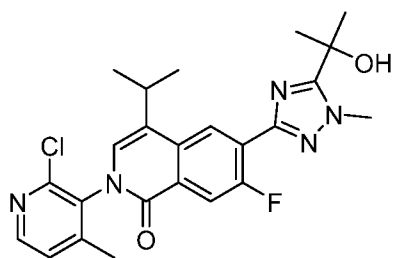


20 To a solution of 2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 13, 160 mg, 0.35 mmol) in dioxane/ H_2O (v/v, 4/1, 11 mL) was added 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2, 77 mg, 0.35 mmol), K_2CO_3 (121 mg, 0.88 mmol), and Pd-118 (23 mg, 0.035 mmol) respectively. The reaction mixture was stirred and heated under nitrogen at 80 °C for 2 h.

The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (SiO₂, eluent: 0 – 60% ethyl acetate in petroleum ether) to give the crude product as a light-yellow oil. The product was further purified by

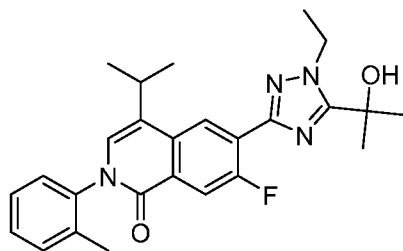
preparative reversed phase HPLC [Stationary phase: Phenomenex Gemini-NX 150*30mm*5um; Mobile phase: water (0.05% NH₃ H₂O) (A) - MeCN (B), gradient elution: 40- 70% B in A over 7 min, flow rate: 35mL/min] to give the pure title compound as a white powder (13 mg, 8% yield). MS (ESI): mass calcd. for C₂₅H₂₆ClFN₄O₂, 468.1; m/z found, 469.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.59 (d, *J* = 6.9 Hz, 1H), 8.36 (d, *J* = 5.0 Hz, 1H), 8.18 (d, *J* = 11.9 Hz, 1H), 7.49 (d, *J* = 4.3 Hz, 1H), 7.29 (s, 1H), 6.63 (s, 1H), 3.90 (s, 3H), 3.46 (td, *J* = 6.7, 13.5 Hz, 1H), 3.32 (s, 1H), 2.25 (s, 3H), 1.76 (s, 6H), 1.36 (t, *J* = 6.7 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -115.35 (s, 1F) ppm.

Example 19: 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 18, using 2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 13) and using 2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol (Intermediate 12) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for C₂₄H₂₅ClFN₅O₂, 469.1; m/z found, 470.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (d, *J* = 6.7 Hz, 1H), 8.37 (d, *J* = 5.0 Hz, 1H), 8.27 (d, *J* = 11.1 Hz, 1H), 7.29 (d, *J* = 5.0 Hz, 1H), 6.65 (s, 1H), 4.20 (s, 3H), 3.47 - 3.36 (m, 1H), 2.55 (s, 1H), 2.25 (s, 3H), 1.80 (s, 6H), 1.36 (t, *J* = 7.0 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -113.33 (s, 1F) ppm.

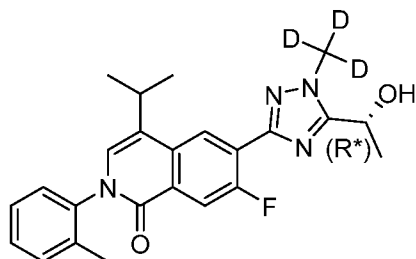
Example 20: 6-(1-Ethyl-5-(2-hydroxypropan-2-yl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-

(*o*-tolyl)isoquinolin-1(2H)-one.

The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate

(Intermediate 1) and using 2-(3-bromo-1-ethyl-1H-1,2,4-triazol-5-yl)propan-2-ol (Intermediate 14) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B.

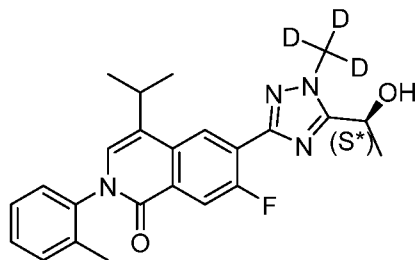
LCMS (ES-API): mass calcd. for $C_{26}H_{29}FN_4O_2$, 448.2; m/z found, 449.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, $J = 6.85$ Hz, 1H), 8.23-8.30 (m, 1H), 7.28-7.42 (m, 4H), 6.82 (s, 1H), 4.55 (q, $J = 7.34$ Hz, 2H), 3.34-3.46 (m, 1H), 2.58 (s, 1H), 2.18 (s, 3H), 1.79 (s, 6H), 1.52-1.63 (m, 3H), 1.33 (dd, $J = 1.96, 6.85$ Hz, 6H) ppm.

Example 21: (*R*^{*})-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-*d*₃)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.

The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using (*R*^{*})-1-(3-bromo-1-(methyl-*d*₃)-1H-1,2,4-triazol-5-yl)ethan-1-ol (Intermediate 16) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for $C_{24}H_{22}D_3FN_4O_2$, 423.2; m/z found, 424.2

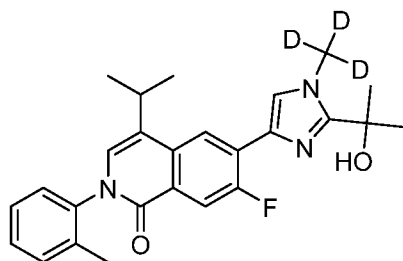
$[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (br d, $J = 6.85$ Hz, 1H), 8.29 (br d, $J = 11.25$ Hz, 1H), 7.27-7.48 (m, 4H), 6.82 (s, 1H), 5.10-5.24 (m, 1H), 3.33-3.49 (m, 1H), 2.58 (br d, $J = 6.36$ Hz, 1H), 2.18 (s, 3H), 1.73 (br d, $J = 6.85$ Hz, 3H), 1.33 (br d, $J = 6.36$ Hz, 6H) ppm.

Example 22: (S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d₃)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



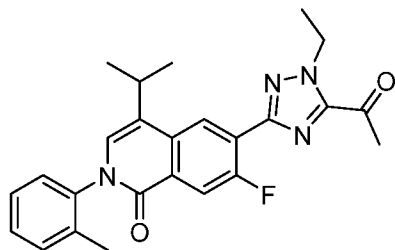
The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using (S*)-1-(3-bromo-1-(methyl-d₃)-1H-1,2,4-triazol-5-yl)ethan-1-ol (Intermediate 15) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₄H₂₂D₃FN₄O₂, 423.2; m/z found, 424.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.48 (d, *J* = 6.36 Hz, 1H), 8.29 (d, *J* = 11.25 Hz, 1H), 7.27-7.47 (m, 4H), 6.82 (s, 1H), 5.16 (quin, *J* = 6.73 Hz, 1H), 3.42 (td, *J* = 6.66, 13.57 Hz, 1H), 2.56-2.61 (m, 1H), 2.18 (s, 3H), 1.73 (d, *J* = 6.85 Hz, 3H), 1.33 (dd, *J* = 2.45, 6.85 Hz, 6H) ppm.

Example 23: 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-(methyl-d₃)-1H-imidazol-4-yl)-4-isopropyl-2-(*o*-tolyl)isoquinolin-1(2H)-one.



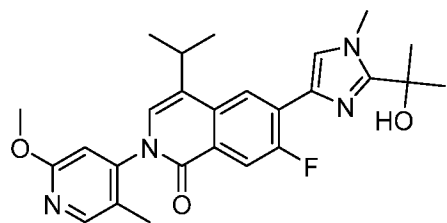
The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using 2-(4-bromo-1-(methyl-d₃)-1H-imidazol-2-yl)propan-2-ol (Intermediate 17) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₆H₂₅D₃FN₃O₂, 436.2; m/z found, 424.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, *J* = 6.85 Hz, 1H), 8.07-8.28 (m, 1H), 7.47 (d, *J* = 4.40 Hz, 1H), 7.27-7.41 (m, 4H), 6.79 (s, 1H), 3.27-3.50 (m, 2H), 2.17 (s, 3H), 1.74 (s, 6H), 1.33 (dd, *J* = 2.93, 6.85 Hz, 6H) ppm.

Example 24: 6-(5-Acetyl-1-ethyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one.



- 5 The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(o-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) and using 1-(3-bromo-1-ethyl-1H-1,2,4-triazol-5-yl)ethan-1-one (Intermediate 18) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for $C_{25}H_{25}FN_4O_2$, 432.2; m/z found, 433.2 $[M+H]^+$. ^1H NMR (400
- 10 MHz, $CDCl_3$) δ 8.51 (d, $J = 6.36$ Hz, 1H), 8.32 (d, $J = 11.25$ Hz, 1H), 7.27-7.43 (m, 4H), 6.84 (s, 1H), 4.73 (q, $J = 7.34$ Hz, 2H), 3.36-3.48 (m, 1H), 2.84 (s, 3H), 2.18 (s, 3H), 1.55 (t, $J = 7.09$ Hz, 3H), 1.35 (dd, $J = 1.96, 6.85$ Hz, 6H) ppm.

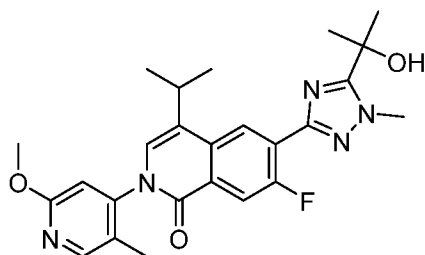
Example 25: 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one.



- The title compound was prepared in a manner analogous to Example 18, using 7-fluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 19) instead of 2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 13) and using 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for $C_{26}H_{29}FN_4O_3$, 464.2; m/z found, 465.1 $[M+H]^+$. ^1H NMR (400
- 20 MHz, $CDCl_3$) δ 8.56 (d, $J = 7.0$ Hz, 1H), 8.22 - 8.10 (m, 2H), 7.48 (d, $J = 4.2$ Hz, 1H), 6.72 (d, J

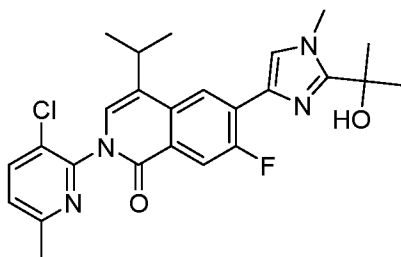
= 5.6 Hz, 2H), 3.97 (s, 3H), 3.90 (s, 3H), 3.44 (td, $J = 6.8, 13.6$ Hz, 1H), 3.36 (br s, 1H), 2.09 (s, 3H), 1.75 (s, 6H), 1.34 (br d, $J = 6.4$ Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -115.32 ppm.

Example 26: 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 18, using 7-fluoro-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 19) instead of 2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 13) and using 2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol (Intermediate 12) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for $\text{C}_{25}\text{H}_{28}\text{FN}_5\text{O}_3$, 465.2; m/z found, 466.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, $J = 6.5$ Hz, 1H), 8.26 (d, $J = 11.3$ Hz, 1H), 8.17 (s, 1H), 6.74 (s, 1H), 6.72 (s, 1H), 4.19 (s, 3H), 3.98 (s, 3H), 3.41 (td, $J = 6.8, 13.6$ Hz, 1H), 2.57 (s, 1H), 2.09 (s, 3H), 1.79 (s, 6H), 1.34 (br d, $J = 6.5$ Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -113.41 ppm.

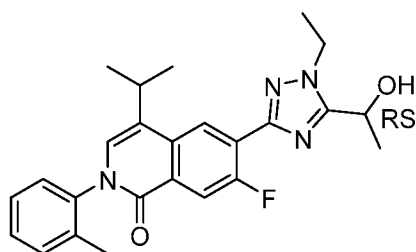
Example 27: 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 18, using 2-(3-chloro-6-methylpyridin-2-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 20) instead of 2-(2-chloro-4-methylpyridin-3-yl)-7-

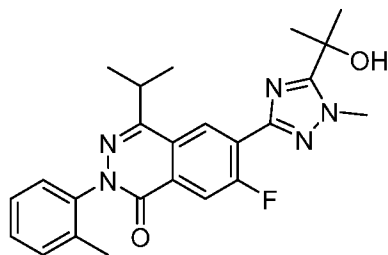
fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 13) and using 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for $C_{25}H_{26}ClFN_4O_2$, 468.2; m/z found, 469.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, $J = 7.0$ Hz, 1H), 8.18 (d, $J = 11.8$ Hz, 1H), 7.81 (d, $J = 8.2$ Hz, 1H), 7.47 (d, $J = 4.3$ Hz, 1H), 7.25 (s, 1H), 6.87 (s, 1H), 3.90 (s, 3H), 3.49 - 3.40 (m, 1H), 3.33 (s, 1H), 2.62 (s, 3H), 1.75 (s, 6H), 1.37 (t, $J = 6.4$ Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.79 (1F) ppm.

Example 28: 6-(1-Ethyl-5-(1-hydroxyethyl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one.

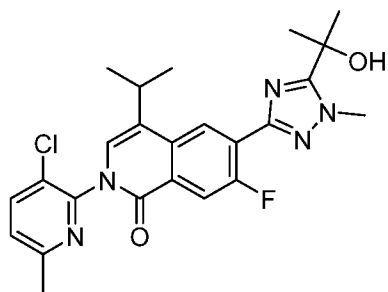


To a solution of 6-(5-acetyl-1-ethyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one (200 mg, 0.46 mmol) in methanol (10 mL) at 0 °C was added $NaBH_4$ (35 mg, 0.93 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. The mixture was slowly poured into sat. aq. NH_4Cl (30 mL) and extracted with DCM (30 mL) and ethyl acetate (30 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (SiO_2 , 30-70% ethyl acetate in heptane) to give a crude product, which was further purified by preparative reversed phase HPLC (Stationary phase: C18 30 x 100 mm*5 μm Gemini; Mobile phase: water (0.27% NH_3 H_2O) (A) - MeCN (B), gradient elution: 10- 90% B in A over 9 min, flow rate: 60 mL/min) to give the title compound as a white powder (130 mg, 65% yield). LCMS (ES-API): mass calcd. for $C_{25}H_{27}FN_4O_2$, 434.2; m/z found, 435.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (br d, $J = 5.87$ Hz, 1H), 8.29 (br d, $J = 11.25$ Hz, 1H), 7.37 (br s, 4H), 6.82 (s, 1H), 5.09-5.18 (m, 1H), 4.33-4.42 (m, 2H), 3.37-3.49 (m, 1H), 2.67 (br d, $J = 6.85$ Hz, 1H), 2.18 (s, 3H), 1.73 (br d, $J = 6.36$ Hz, 3H), 1.55-1.59 (m, 3H), 1.33 (br d, $J = 4.89$ Hz, 6H) ppm.

Example 29: 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-

2-(*o*-tolyl)phthalazin-1(2H)-one.

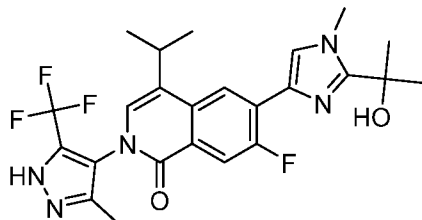
The title compound was prepared in a manner analogous to Example 4, Steps A-B, using 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydrophthalazin-6-yl trifluoromethanesulfonate (Intermediate 10) instead of 7-fluoro-4-isopropyl-1-oxo-2-(*o*-tolyl)-1,2-dihydroisoquinolin-6-yl trifluoromethanesulfonate (Intermediate 1) in Step A and using 2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol (Intermediate 12) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2) in Step B. LCMS (ES-API): mass calcd. for C₂₄H₂₆FN₅O₂, 435.2; m/z found, 436.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.63 (br d, *J* = 6.36 Hz, 1H), 8.26 (br d, *J* = 10.27 Hz, 1H), 7.35 (br s, 4H), 4.19 (s, 3H), 3.63 (td, *J* = 6.60, 13.21 Hz, 1H), 2.50 (s, 1H), 2.19 (s, 3H), 1.79 (s, 6H), 1.38 (br d, *J* = 6.36 Hz, 6H) ppm.

Example 30: 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one.

The title compound was prepared in a manner analogous to Example 18, using 2-(3-chloro-6-methylpyridin-2-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 20) instead of 2-(2-chloro-4-methylpyridin-3-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 13) and using 2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol (Intermediate 12) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for C₂₄H₂₅ClFN₅O₂, 469.1; m/z found, 470.1 [M+H]⁺. ¹H NMR (400

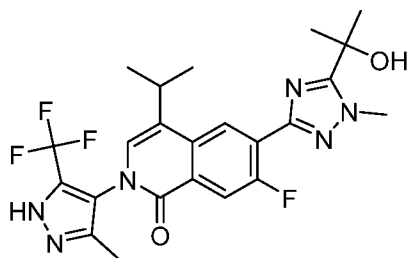
MHz, CDCl₃) δ 8.46 (d, J = 6.7 Hz, 1H), 8.28 (d, J = 11.1 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.28 (br s, 1H), 6.90 (s, 1H), 4.19 (s, 3H), 3.41 (quin, J = 6.7 Hz, 1H), 2.62 (s, 3H), 2.46 (s, 1H), 1.80 (s, 6H), 1.37 (dd, J = 4.8, 6.7 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -114.00 (1F) ppm.

5 Example 31: 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 16, using 7-fluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 21) instead of 2-(5-chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 11) and using 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for C₂₄H₂₅F₄N₅O₂, 491.5; m/z found, 492.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.51 (br s, 1H), 8.58 (d, J = 7.0 Hz, 1H), 8.18 (d, J = 12.0 Hz, 1H), 7.49 (d, J = 4.3 Hz, 1H), 6.79 (s, 1H), 3.91 (s, 3H), 3.43 (td, J = 6.8, 13.6 Hz, 1H), 3.35 (s, 1H), 2.14 (s, 3H), 1.76 (s, 6H), 1.34 (d, J = 6.8 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -61.94 (3F), -115.31 (1F) ppm.

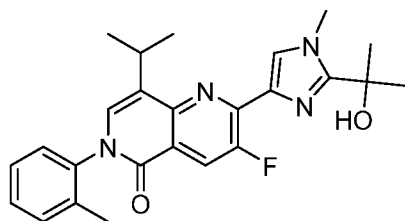
20 Example 32: 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one.



The title compound was prepared in a manner analogous to Example 16, using 7-fluoro-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 21) instead of 2-(5-chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-4-isopropyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (Intermediate 11) and using 2-(3-bromo-1-methyl-1H-1,2,4-triazol-5-yl)propan-2-ol (Intermediate 12) instead of 2-(4-bromo-1-methyl-1H-imidazol-2-yl)propan-2-ol (Intermediate 2). MS (ESI): mass calcd. for C₂₃H₂₄F₄N₆O₂, 492.2; m/z found, 493.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.71 (br s, 1H), 8.51 (d, *J* = 6.7 Hz, 1H), 8.28 (d, *J* = 11.2 Hz, 1H), 6.82 (s, 1H), 4.20 (s, 3H), 3.41 (td, *J* = 6.8, 13.5 Hz, 1H), 2.61 (s, 1H), 2.15 (s, 3H), 1.80 (s, 6H), 1.34 (d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -61.90 (3F), -113.35 (1F) ppm.

10 Example 33: 3-Fluoro-2-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-8-isopropyl-6-(*o*-tolyl)-1,6-naphthyridin-5(6H)-one.



Step A. 2-(3-((Benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-3-fluoro-7-hydroxy-8-isopropyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridin-5-one. To a suspension of 2-(3-

15 ((benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-3-fluoro-8-isopropyl-5H-pyrano[4,3-*b*]pyridin-5-one (Intermediate 23, 600 mg, 1.4 mmol) in EtOH (6 mL) and H₂O (0.6 mL) was added dropwise of a solution of LiOH·H₂O (57 mg, 1.4 mmol) in H₂O (0.6 mL). The mixture was stirred at room temperature for 1 hour. 1 M HCl solution was added dropwise into the mixture to adjust pH to around 5. The mixture was concentrated to 8 mL and water (20 mL)

20 was added. The mixture was extracted with ethyl acetate (20 mL × 2). The combined organic layers were dried, filtered and concentrated under vacuum to give the title compound (700 mg, crude) as yellow solid. MS (ESI): mass calcd. for C₂₃H₂₅FN₄O₅, 456.2; m/z found, 479.1 [M+H]⁺.

Step B. 2-(3-((Benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-3-fluoro-8-isopropyl-6-(*o*-tolyl)-1,6-naphthyridin-5(6H)-one. A mixture of 2-(3-((benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-3-fluoro-7-hydroxy-8-isopropyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridin-5-one (700 mg, crude) and *o*-toluidine (181 mg, 1.7 mmol) in AcOH (8 mL) was stirred at 90 °C for 2 hours. The mixture was added H₂O (10 mL) and extracted with

ethyl acetate (20 mL × 2). The combined organic layers were added sat. aq. NaHCO₃ solution to adjust pH to around 8. The organic layer was dried by Na₂SO₄, filtered and concentrated in vacuo to give the crude. The crude was purified by column chromatography (SiO₂, gradient elution: 0 – 30% ethyl acetate in petroleum ether) to give the title compound (600 mg, 70% yield) as light yellow solid. MS (ESI): mass calcd. for C₃₀H₃₀FN₅O₃, 527.2; m/z found, 528.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.56 (d, *J* = 9.5 Hz, 1H), 7.47 - 7.32 (m, 8H), 7.29 (s, 1H), 7.04 (s, 1H), 4.64 (s, 2H), 4.57 (s, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 3.77 - 3.59 (m, 1H), 2.17 (s, 3H), 1.40 (t, *J* = 7.3 Hz, 3H), 1.32 (dd, *J* = 1.9, 6.9 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -125.69 (1F) ppm.

Step C. 3-Fluoro-8-isopropyl-2-methoxy-6-(*o*-tolyl)-1,6-naphthyridin-5(6H)-one. A mixture of 2-(3-((benzyloxy)methyl)-4-ethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)-3-fluoro-8-isopropyl-6-(*o*-tolyl)-1,6-naphthyridin-5(6H)-one (580 mg, 1.1 mmol) and CH₃ONa (58 mg, 1.1 mmol) was added DMF at 0 °C. The solution was stirred at 0 °C for 1 hour. Then the mixture was added CH₃ONa (29 mg) at 0 °C. The mixture was stirred at 0 °C for another 2 hours. The mixture was quenched by sat. aq. NH₄Cl solution (40 mL). Then the mixture was extracted with ethyl acetate (30 mL × 3). The combined organic phase was dried by Na₂SO₄, filtered and concentrated under vacuum. The crude was purified by column chromatography (SiO₂, gradient elution: 0 – 16% ethyl acetate in petroleum ether) to give the title compound (310 mg, 89% yield, 100% purity) as white solid. MS (ESI): mass calcd. for C₁₉H₁₉FN₂O₂, 326.1; m/z found, 326.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 10.0 Hz, 1H), 7.40 - 7.32 (m, 4H), 6.99 (s, 1H), 4.19 (s, 3H), 3.65 - 3.46 (m, 1H), 2.16 (s, 3H), 1.32 (dd, *J* = 2.0, 6.8 Hz, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -139.49 (1F) ppm.

Step D. 2-Chloro-3-fluoro-8-isopropyl-6-(*o*-tolyl)-1,6-naphthyridin-5(6H)-one. A mixture of 3-fluoro-8-isopropyl-2-methoxy-6-(*o*-tolyl)-1,6-naphthyridin-5(6H)-one (300 mg, 920 μmol) in DMF (1.5 mL) was added POCl₃ (2.6 g, 16.6 mmol) at room temperature. The mixture was stirred at 100 °C overnight. The mixture was added ethyl acetate (10 mL). Then the mixture was added to ice-water (15 mL) slowly and added sat. aq. NaHCO₃ (50 mL) to adjust pH to around 7. The mixture was extracted with ethyl acetate (30 mL × 2). The combined organic phase was dried by Na₂SO₄, filtered and concentrated under vacuum to give the title compound. (320 mg, crude) as brown sticky. MS (ESI): mass calcd. for C₁₈H₁₆ClFN₂O, 330.1; m/z found, 331.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 7.8 Hz, 1H), 7.45 - 7.32 (m, 3H), 7.25 (d, *J*

= 7.5 Hz, 1H), 7.04 (s, 1H), 3.73 - 3.56 (m, 1H), 2.16 (s, 3H), 1.30 (dd, $J = 2.3, 7.0$ Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -120.01 (1F) ppm.

Step E. 3-Fluoro-2-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-8-isopropyl-6-(o-tolyl)-1,6-naphthyridin-5(6H)-one. To a solution of 2-chloro-3-fluoro-8-isopropyl-6-(o-tolyl)-

1,6-naphthyridin-5(6H)-one (100 mg, crude), 2-(1-methyl-4-(tributylstannyl)-1H-imidazol-2-yl)propan-2-ol (Intermediate 24, 1.5 g, crude) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (21 mg, 30 μmol) in dioxane (2 mL) was stirred at 100 °C for 2.5 hours under N_2 . To the mixture was added sat. aq. KF solution (10 mL) and stirred for 2 minutes. The mixture was extracted with ethyl acetate (10 mL $\times$ 2). The combined organic layer was concentrated in vacuo. The crude product was purified by

preparative reversed phase HPLC (Stationary phase: Phenomenex Gemini-NX C18, 3 μm , 75 $\times$ 30 mm; Mobile phase: water (0.05% $\text{NH}_3\text{H}_2\text{O}$ + 10 mM NH_4HCO_3) (A) - MeCN (B), gradient elution: 40 - 70% B in A over 6 min, flow rate: 25 mL/min) to give the title compound (15 mg, 11% yield) as light yellow powder. MS (ESI): mass calcd. For $\text{C}_{25}\text{H}_{27}\text{FN}_4\text{O}_2$, 434.2; m/z found, 435.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.37 (d, $J = 11.2$ Hz, 1H), 7.71 (d, $J = 2.9$ Hz, 1H), 7.48 - 7.31 (m, 3H), 7.31 - 7.28 (m, 1H), 6.98 (s, 1H), 3.96 (s, 3H), 3.85 (td, $J = 6.9, 13.7$ Hz, 1H), 3.07 (br s, 1H), 2.17 (s, 3H), 1.78 (s, 6H), 1.34 (d, $J = 6.8$ Hz, 6H); ^{19}F NMR (376 MHz, CDCl_3) δ -123.63 (1F) ppm.

Biological Data

DHODH inhibitory activities of the compounds of Examples 1-33 were assessed using the following assays. The half maximal inhibitory concentration values (IC_{50}) are summarized in Table 3.

Biological Assays

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 (human acute myeloid leukemia 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 0.4×10^6 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.

NT means not tested.

Table 3.

Example #	Compound Name	MOLM-13 IC ₅₀ (nM)	hDHODH IC ₅₀ (nM)
1	6-(5-Cyclopropylpyrazin-2-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	1.4	2.6
2	6-(6-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.02	0.18
3	6-(4-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	1.6	3.6
4	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.08	0.38

Example #	Compound Name	MOLM-13 IC ₅₀ (nM)	hDHODH IC ₅₀ (nM)
5	Racemic 7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.36	1.1
6	6-(5-Acetyl-1-methyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.48	1.7
7	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.08	0.57
8	7-Fluoro-6-(2-(hydroxymethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.37	1.2
9	7-Fluoro-6-(5-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	1.2	2.6
10	(S*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.13	0.73
11	(R*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.1	0.51
12	(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.34	1.6
13	(S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.11	0.48
14	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)phthalazin-1(2H)-one;	0.09	0.45

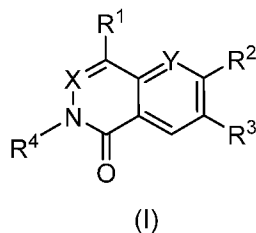
Example #	Compound Name	MOLM-13 IC ₅₀ (nM)	hDHODH IC ₅₀ (nM)
15	(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)phthalazin-1(2H)-one;	1.2	2.6
16	2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;	0.28	0.51
17	2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;	0.40	0.71
18	2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;	0.40	2.0
19	2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;	0.70	2.5
20	6-(1-Ethyl-5-(2-hydroxypropan-2-yl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	4.3	26.5
21	(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.33	2.0
22	(S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.17	1.1
23	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-(methyl-d3)-1H-imidazol-4-yl)-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	0.04	0.54
24	6-(5-Acetyl-1-ethyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	2.9	6.2

Example #	Compound Name	MOLM-13 IC ₅₀ (nM)	hDHODH IC ₅₀ (nM)
25	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;	0.27	1.2
26	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;	0.50	1.2
27	2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;	0.38	1.4
28	6-(1-Ethyl-5-(1-hydroxyethyl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(<i>o</i> -tolyl)isoquinolin-1(2H)-one;	3.2	18.6
29	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(<i>o</i> -tolyl)phthalazin-1(2H)-one;	0.12	0.64
30	2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;	0.61	NT
31	7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one;	0.22	NT
32	7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one; and	0.40	NT
33	3-Fluoro-2-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-8-isopropyl-6-(<i>o</i> -tolyl)-1,6-naphthyridin-5(6H)-one.	5.20	NT

CLAIMS

What is claimed is:

1. A compound having the structure of Formula (I):



wherein

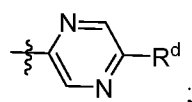
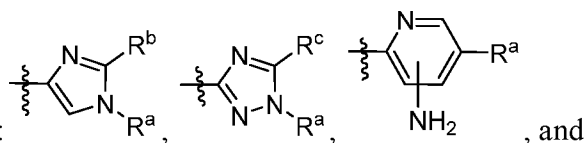
X is CH or N;

Y is CH or N;

wherein when X is N then Y is CH;

R¹ is C₁₋₆alkyl or C₁₋₆haloalkyl;

R² is selected from the group consisting of:



wherein

R^a is C₁₋₆alkyl;

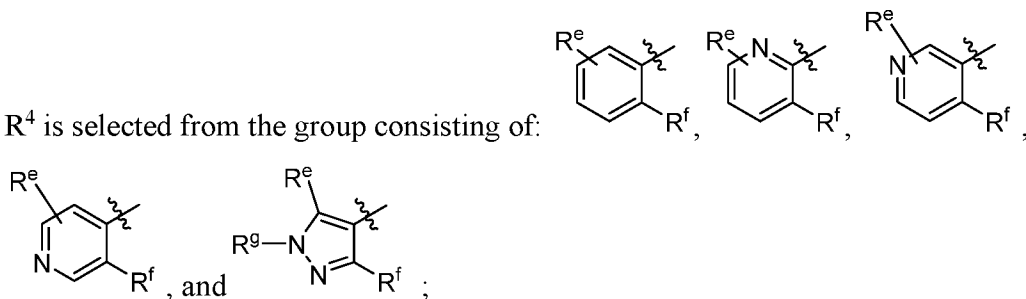
R^b is C₁₋₆alkyl substituted with one OH member;

R^c is C₁₋₆alkyl substituted with one OH member; or C(=O)CH₃;

R^d is C₃₋₆cycloalkyl;

R³ is H or halo;

R⁴ is selected from the group consisting of:



wherein

R^e is selected from the group consisting of: H; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with one member selected from the group consisting of: OH, OCH_3 , and OCF_3 ;

C_{1-6} haloalkyl; C_{1-6} haloalkyl substituted with one member selected from the group consisting of: OH, and OCH_3 ; and OC_{1-6} alkyl;

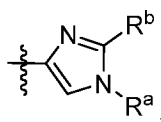
R^f is selected from the group consisting of: H; halo; C_{1-6} alkyl; C_{1-6} alkyl substituted with one member selected from the group consisting of: OH, OCH_3 , and OCF_3 ;

C_{1-6} haloalkyl; C_{1-6} haloalkyl substituted with one member selected from the group consisting of: OH, and OCH_3 ; and OC_{1-6} alkyl; and

R^g is H or C_{1-6} alkyl;

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

2. The compound according to claim 1, wherein X is CH and Y is CH; or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
3. The compound according to claim 1, wherein X is CH and Y is N; or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
4. The compound according to claim 1, wherein X is N and Y is CH; or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
5. The compound according to any of claims 1-4, wherein R^1 is C_{1-4} alkyl; or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
6. The compound according to any of claims 1-4, wherein R^1 is $CH(CH_3)_2$; or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.



7. The compound according to any of claims 1-6, wherein R^2 is

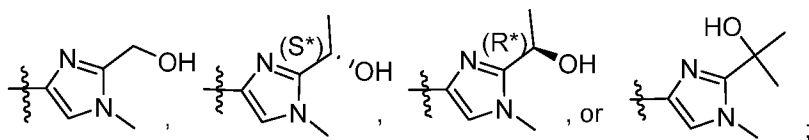
wherein

R^a is CH_3 ; and

R^b is CH_2OH , $CH(OH)CH_3$, or $C(OH)(CH_3)_2$;

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

8. The compound according to any of claims 1-6, wherein R^2 is



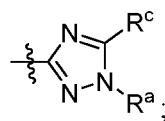
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

9. The compound according to any of claims 1-6, wherein R^2 is wherein

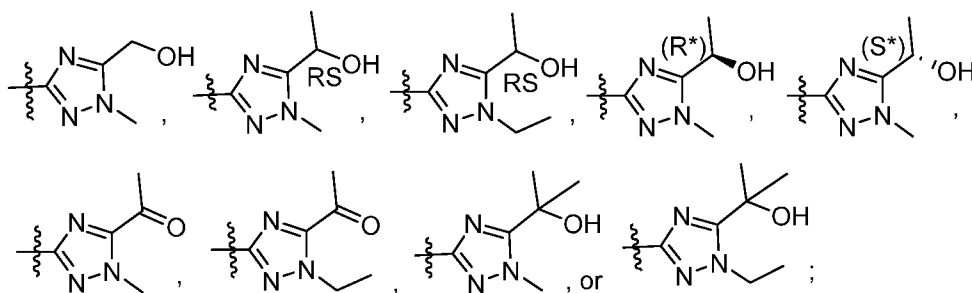
R^a is CH_3 or CH_2CH_3 ; and

R^c is CH_2OH , $C(=O)CH_3$, $CH(OH)CH_3$, or $C(OH)(CH_3)_2$;

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



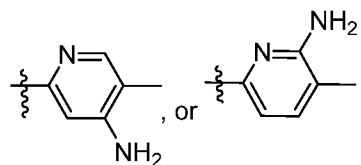
10. The compound according to any of claims 1-6, wherein R^2 is



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

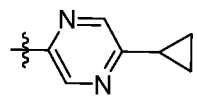
11. The compound according to any of claims 1-6, wherein R^2 is

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

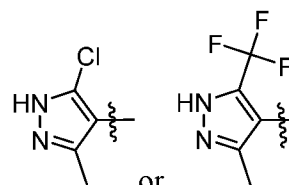


12. The compound according to any of claims 1-6, wherein R^2 is

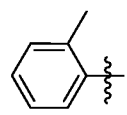
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.



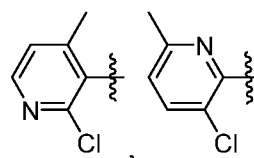
13. The compound according to any of claims 1-12, wherein R^3 is F.



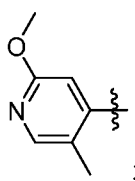
14. The compound according to any of claims 1-13, wherein R^4 is
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.



15. The compound according to any of claims 1-13, wherein R^4 is
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

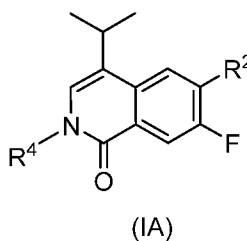


16. The compound according to any of claims 1-13, wherein R^4 is

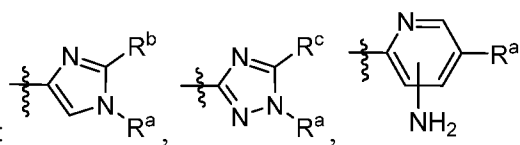


or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

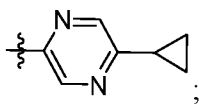
17. The compound according to claim 1, having the structure of Formula (IA):



wherein



R^2 is selected from the group consisting of: , and



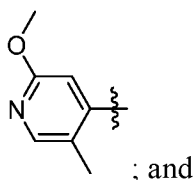
wherein

R^a is C_{1-4} alkyl;

R^b is C_{1-4} alkyl substituted with one OH member;

R^c is C_{1-4} alkyl substituted with one OH member; or $C(=O)CH_3$;

R^4 is selected from the group consisting of:

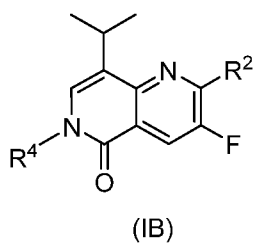


; and

R^e is Cl or CF_3 ;

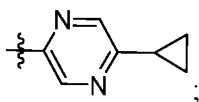
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

18. The compound according to claim 1, having the structure of Formula (IB):



wherein

R^2 is selected from the group consisting of:



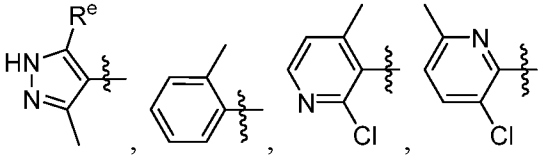
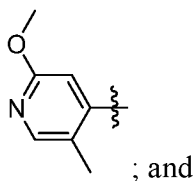
wherein

R^a is C_{1-4} alkyl;

R^b is C_{1-4} alkyl substituted with one OH member;

R^c is C_{1-4} alkyl substituted with one OH member; or $C(=O)CH_3$;

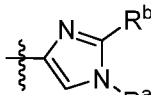
R^4 is selected from the group consisting of:

R^e is Cl or CF_3 ;

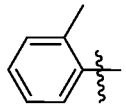
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

19. The compound according to claim 18, wherein R^2 is

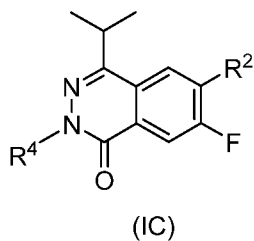


R^a is C_{1-4} alkyl, R^b is

C_{1-4} alkyl substituted with one OH member, and R^4 is

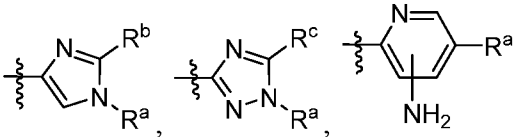
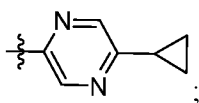


20. The compound according to claim 1, having the structure of Formula (IC):



wherein

R^2 is selected from the group consisting of:

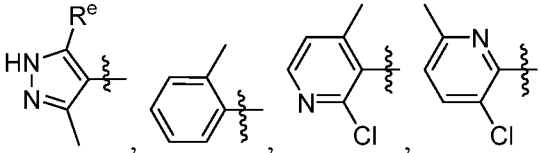
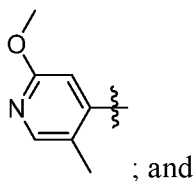
wherein

R^a is C_{1-4} alkyl;

R^b is C_{1-4} alkyl substituted with one OH member;

R^c is C₁₋₄alkyl substituted with one OH member; or C(=O)CH₃;

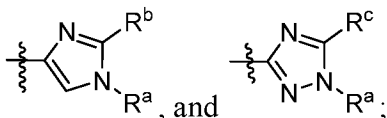
R⁴ is selected from the group consisting of:

R^e is Cl or CF₃;

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

21. The compound according to claim 20, wherein R² is selected from the group consisting of:

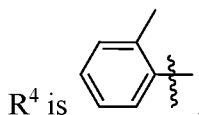


wherein

R^a is C₁₋₄alkyl;

R^b is C₁₋₄alkyl substituted with one OH member;

R^c is C₁₋₄alkyl substituted with one OH member; and



22. A compound selected from the group consisting of:

6-(5-Cyclopropylpyrazin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

6-(6-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

6-(4-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

Racemic 7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

6-(5-Acetyl-1-methyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(2-(hydroxymethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(5-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(S*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(R*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;

(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;

2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;

2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;

2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;

2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;

6-(1-Ethyl-5-(2-hydroxypropan-2-yl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-

tolyl)isoquinolin-1(2H)-one;
 (S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-
 tolyl)isoquinolin-1(2H)-one;
 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-(methyl-d3)-1H-imidazol-4-yl)-4-isopropyl-2-(o-
 tolyl)isoquinolin-1(2H)-one;
 6-(5-Acetyl-1-ethyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-
 one;
 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(2-
 methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;
 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(2-
 methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;
 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-
 imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
 6-(1-Ethyl-5-(1-hydroxyethyl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-
 tolyl)isoquinolin-1(2H)-one;
 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-
 tolyl)phthalazin-1(2H)-one;
 2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-
 1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(3-methyl-
 5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one;
 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(3-
 methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one; and
 3-Fluoro-2-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-8-isopropyl-6-(o-tolyl)-
 1,6-naphthyridin-5(6H)-one;
 or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide
 thereof.

23. A compound selected from the group consisting of:

7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-
 tolyl)isoquinolin-1(2H)-one;

- 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
- 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one; and
- 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
- or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
24. A pharmaceutical composition comprising: (A) a compound according to any of claims 1-23, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof; and (B) at least one pharmaceutically acceptable excipient.
25. A pharmaceutical composition comprising an effective amount of:
- 6-(5-Cyclopropylpyrazin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 6-(6-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 6-(4-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- Racemic 7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 6-(5-Acetyl-1-methyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(2-(hydroxymethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(5-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- (S*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-

tolyl)isoquinolin-1(2H)-one;

(R*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;

(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;

2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;

2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;

2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;

2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;

6-(1-Ethyl-5-(2-hydroxypropan-2-yl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

(S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-(methyl-d3)-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

6-(5-Acetyl-1-ethyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;

7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;
2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
6-(1-Ethyl-5-(1-hydroxyethyl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;
2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one;
7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one;
3-Fluoro-2-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-8-isopropyl-6-(o-tolyl)-1,6-naphthyridin-5(6H)-one;
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof; and at least one pharmaceutically acceptable excipient.

26. 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 1-23, or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.
27. The method according to claim 26, wherein the disorder, disease or medical condition is selected from the group consisting of: inflammatory disorders and autoimmune disorders.
28. The method according to claim 26, wherein the disorder, disease or medical condition is cancer.

29. The method according to claim 26, wherein the disorder, disease or medical condition is selected from the group consisting of: lymphomas, leukemias, carcinomas, and sarcomas.
30. The method according to claim 26, 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.
31. The method according to claim 26, wherein the disorder, disease or medical condition is acute myeloid leukemia.
32. The method according to any of claims 26-31, wherein the at least one compound is:
- 6-(5-Cyclopropylpyrazin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 6-(6-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 6-(4-Amino-5-methylpyridin-2-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- Racemic 7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 6-(5-Acetyl-1-methyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(2-(hydroxymethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(5-(hydroxymethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;

- (S*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- (R*)-7-Fluoro-6-(2-(1-hydroxyethyl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- (R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- (S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;
- (R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;
- 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
- 2-(5-Chloro-3-methyl-1H-pyrazol-4-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
- 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
- 2-(2-Chloro-4-methylpyridin-3-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
- 6-(1-Ethyl-5-(2-hydroxypropan-2-yl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- (R*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- (S*)-7-Fluoro-6-(5-(1-hydroxyethyl)-1-(methyl-d3)-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-(methyl-d3)-1H-imidazol-4-yl)-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 6-(5-Acetyl-1-ethyl-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
- 7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(2-

methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;
7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(2-methoxy-5-methylpyridin-4-yl)isoquinolin-1(2H)-one;
2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropylisoquinolin-1(2H)-one;
6-(1-Ethyl-5-(1-hydroxyethyl)-1H-1,2,4-triazol-3-yl)-7-fluoro-4-isopropyl-2-(o-tolyl)isoquinolin-1(2H)-one;
7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(o-tolyl)phthalazin-1(2H)-one;
2-(3-Chloro-6-methylpyridin-2-yl)-7-fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropylisoquinolin-1(2H)-one;
7-Fluoro-6-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one;
7-Fluoro-6-(5-(2-hydroxypropan-2-yl)-1-methyl-1H-1,2,4-triazol-3-yl)-4-isopropyl-2-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)isoquinolin-1(2H)-one;
3-Fluoro-2-(2-(2-hydroxypropan-2-yl)-1-methyl-1H-imidazol-4-yl)-8-isopropyl-6-(o-tolyl)-1,6-naphthyridin-5(6H)-one;
or a pharmaceutically acceptable salt, solvate, stereoisomer, isotopic variant, or N-oxide thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/058904

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/04 C07D401/14 C07D403/04 C07D471/04 A61P35/02
A61K31/4725 A61K31/502

ADD.

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

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2020/161663 A1 (JANSSEN BIOTECH INC [US]) 13 August 2020 (2020-08-13) examples: 10, 13, 36-37, 43-44, 66-67, 70-72, 74-75; claims; table 3 -----	1-32
Y	JP 2007 015952 A (SHIONOGI & CO) 25 January 2007 (2007-01-25) paragraph [0120]; claims; compounds 4,5 -----	1-32
X,P	WO 2020/212897 A1 (JANSSEN BIOTECH INC [US]) 22 October 2020 (2020-10-22) claims; examples -----	1-32



Further documents are listed in the continuation of Box C.



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"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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