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(71) Applicant(s)  
**Hutchison MediPharma Limited**

(72) Inventor(s)  
**SU, Wei-Guo;DAI, Guangxiu;XIAO, Kun**

(74) Agent / Attorney  
**MINTER ELLISON, Level 40 1 Farrer Place, Sydney, NSW, 2000, AU**

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(71) Applicant: HUTCHISON MEDIPHARMA LIMITED

[CN/CN]; Building 4, 720 Cailun Road, Pilot Free Trade Zone, Shanghai 201203 (CN).

(72) Inventors: SU, Wei-Guo; Building 4, 720 Cailun Road,

Pilot Free Trade Zone, Shanghai 201203 (CN). DAI, Guangxiu; Building 4, 720 Cailun Road, Pilot Free Trade Zone, Shanghai 201203 (CN). XIAO, Kun; Building 4, 720 Cailun Road, Pilot Free Trade Zone, Shanghai 201203 (CN).

(74) Agent: ZHONGZI LAW OFFICE; 7F, New Era Building,

26 Pinganli Xidajie, Xicheng District, Beijing 100034 (CN).

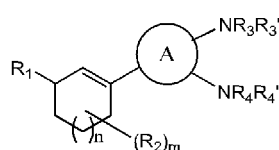
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(54) Title: CYCLOOLEFIN SUBSTITUTED HETEROAROMATIC COMPOUNDS AND THEIR USE



(I)

(57) Abstract: Compounds of formula (I) or a pharmaceutically acceptable salt thereof, and/or solvates, racemic mixtures, enantiomers, diastereomers, and tautomers thereof, wherein A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3</sub>', R<sub>4</sub>, R<sub>4</sub>', R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, m, and n are as defined in the detailed description. (I)



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## Cycloolefin substituted heteroaromatic compounds and their use

### Field of the Invention

- 5 The present invention relates to cycloolefin substituted heteroaromatic compounds and their use in the treatment of diseases induced by IDH mutations.

### Background of the Invention

10 The survival way of tumor cells is different from that of normal cells, so does the energy intake and utilization. The common metabolic pathway in aerobic organisms is tricarboxylic acid cycle, in which isocitrate dehydrogenase (IDH) catalyzing the conversion of isocitrate to  $\alpha$ -ketoglutaric acid ( $\alpha$ -KG) is a rate-limiting step. The known IDH family comprises three isozymes, IDH1, IDH2 and IDH3, which are located in different organelles and perform the same biological functions, i.e., catalyzing the formation of  $\alpha$ -KG. Recent studies have shown that heterozygous  
15 IDH1/2 mutations were present in a certain proportion of a variety of tumors, such as glioma (60-80%), chondrosarcoma (55%), acute myeloid leukemia (15-25 %), etc. The mutant IDH1 or IDH2 loses the capability of catalyzing the conversion of isocitrate to  $\alpha$ -KG, whereas has the ability of catalyzing the reaction of  $\alpha$ -KG to  $\alpha$ -hydroxyglutaric acid (2-HG). As the structure of 2-HG is similar to the structure of  $\alpha$ -KG, 2-HG can competitively inhibit the activity of many  
20  $\alpha$ -KG dependent enzymes (for example: histone demethylase and methylcytosine hydroxylase of the TET family, and the like) when it accumulates to a certain extent, and thus effects the demethylation of histones and DNA, interferes with normal cell differentiation, and results in the proliferation of immature cells.

Agios Pharmaceuticals published its research results in Science magazine in 2013: the mutant  
25 IDH1 enzyme inhibitor AGI-5198 (Science, 2013, 340, 626-630) and the mutant IDH2 enzyme inhibitor AGI-6780 (Science, 2013, 340, 622-626) developed by the company can effectively inhibit the generation of 2HG mediated by mutant IDH1/IDH2 in cells and can induce differentiation of abnormally proliferating cancer cells. Both the treatment of glioma cells harboring mutant IDH1 gene with AGI-5198 and the treatment of leukemia cells carrying mutant  
30 IDH2 gene with AG-6780 lead to increase of the expression of mature markers in cells.

The Phase I clinical trial of AG-120, a mutant IDH1 inhibitor developed by Agios Pharmaceuticals, showed that in patients with acute myeloid leukemia (AML) or



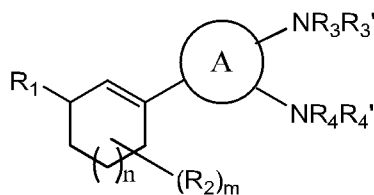
myelodysplastic syndrome (MDS) having IDH1 mutations, it can be observed that 98% of the patients have decreased levels of  $\alpha$ -hydroxyglutaric acid (2HG).

Acute myeloid leukemia (AML) is one of the most difficult diseases to be controlled in common hematological malignancies. Its recurrence rate is high. The development of new drug for the disease is slow resulting in the lack of effective drug therapy. Some studies have shown that about 15% of the patients with acute myeloid leukemia have IDH2 gene mutations. Enasidenib (former name AG-221), a mutant IDH2 inhibitor, developed by Agios Pharmaceuticals and Celgene, showed a significant effect on relapsed and refractory acute myelogenous leukemias with IDH2 gene mutations in clinical trial.

New IDH mutant inhibitors are needed to be developed to meet the need for treatment of patients with hematological tumors, especially acute myeloid leukemia, gliomas and other IDH mutation associated tumors. The present invention addresses these needs.

### Summary of the Invention

The present invention provides a compound of formula (I):



(I)

and/or a pharmaceutically acceptable salt thereof, and/or solvates, racemic mixtures, enantiomers, diastereomers, and tautomers thereof, wherein A, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3</sub>' , R<sub>4</sub>, R<sub>4</sub>' , R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, m, and n are as defined in the detailed description of the invention.

Also provided is a pharmaceutical composition, comprising at least one compound of formula (I) (e.g., any of the compounds described herein) and/or a pharmaceutically acceptable salt thereof, and optionally comprising at least one pharmaceutically acceptable excipient (e.g., a pharmaceutically acceptable carrier).

Also provided is a method of treating a disease induced by IDH mutation, comprising administering to the subject in need thereof an effective amount of at least one compound of formula (I) (e.g., any of the compounds described herein) and/or at least one pharmaceutically acceptable salt thereof.

Also provided is a use of at least one compound of formula (I) (e.g., any of the compounds described herein) and/or at least one pharmaceutically acceptable salt thereof for treating a disease induced by IDH mutation.

5 Also provided is a use of at least one compound of formula (I) (e.g., any of the compounds described herein) and/or at least one pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease induced by IDH mutation.

### **Brief Description of the Drawings**

Figure 1 shows the general synthetic route I for preparation of the compounds described herein.

10 Figure 2 shows the general synthetic route II for preparation of the compounds described herein.

Figure 3 shows the general synthetic route III for preparation of the compounds described herein.

Figure 4 shows the general synthetic route IV for preparation of the compounds described herein.

Figure 5 shows the general synthetic route V for preparation of the compounds described herein.

Figure 6 shows the general synthetic route VI for preparation of the compounds described herein.

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### **Detailed Description of the Invention**

#### **Definitions**

As used in the present application, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

20 A dash (“-”) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -OR<sub>4</sub> is attached through the oxygen. However, when the point of attachment of a group is apparent to those skilled in the art, e.g., a halo substituent, the “-” sign may be omitted.

25 Unless clearly indicated otherwise, use of the terms “a”, “an” and the like refer to one or more.

The term “alkyl” as used herein refers to a straight or branched saturated hydrocarbon radical containing 1-18 carbon atoms, preferably 1-10 carbon atoms, more preferably 1-6 carbon atoms, and even more preferably 1-4 carbon atoms. For example, “C<sub>1-6</sub> alkyl” refers to an alkyl containing 1-6 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl

("Me"), ethyl ("Et"), n-propyl ("n-Pr"), i-propyl ("i-Pr"), n-butyl ("n-Bu"), i-butyl ("i-Bu"), s-butyl ("s-Bu") and t-butyl ("t-Bu").

The term "alkenyl" as used herein refers to a straight or branched hydrocarbon radical containing one or more, for example 1, 2, or 3 carbon-carbon double bonds (C=C) and 2-10 carbon atoms, preferably 2-6 carbon atoms, more preferably 2-4 carbon atoms. For example, "C<sub>2-6</sub> alkenyl" refers to an alkenyl containing 2-6 carbon atoms. Examples of alkenyl groups include, but are not limited to, vinyl, 2-propenyl, and 2-butenyl. The point of attachment for the alkenyl can be on or not on the double bonds.

The term "alkynyl" as used herein refers to a straight or branched hydrocarbon radical containing one or more, for example 1, 2, or 3, carbon-carbon triple bonds (C≡C) and 2-10 carbon atoms, preferably 2-6 carbon atoms, more preferably 2-4 carbon atoms. For example, "C<sub>2-6</sub> alkynyl" refers to an alkynyl containing 2-6 carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl, 2-propynyl, and 2-butyryl. The point of attachment for the alkynyl can be on or not on the triple bonds.

The term "halogen" or "halo" as used herein means fluoro, chloro, bromo, and iodo, preferably fluoro, chloro and bromo, more preferably fluoro and chloro.

The term "haloalkyl" as used herein refers to an alkyl radical, as defined herein, in which one or more, for example 1, 2, 3, 4, or 5, hydrogen atoms are replaced with halogen atom, and when more than one hydrogen atoms are replaced with halogen atoms, the halogen atoms may be the same or different from each other. In certain an embodiment, the term "haloalkyl" as used herein refers to an alkyl radical, as defined herein, in which two or more, such as 2, 3, 4, or 5 hydrogen atoms are replaced with halogen atoms, wherein the halogen atoms are identical to each other. In another embodiment, the term "haloalkyl" as used herein refers to an alkyl radical, as defined herein, in which two or more hydrogen atoms, such as 2, 3, 4, or 5 hydrogen atoms are replaced with halogen atoms, wherein the halogen atoms are different from each other. Examples of haloalkyl groups include, but are not limited to, -CF<sub>3</sub>, -CHF<sub>2</sub>, -CH<sub>2</sub>CF<sub>3</sub>, and the like.

The term "alkoxy" as used herein refers to the group -O-alkyl, wherein the alkyl is as defined above. Examples of alkoxy groups include, but are not limited to, C<sub>1-6</sub> alkoxy, such as methoxy, ethoxy, n-propyloxy, i-propyloxy, n-butyloxy, i-butyloxy, t-butyloxy, pentyloxy, and hexyloxy, including their isomers.

The term "cycloalkyl" as used herein refers to saturated or partially unsaturated cyclic hydrocarbon radical having 3 to 12 ring carbon atoms, such as 3 to 8 ring carbon atoms, 5-7 ring carbon atoms, 4-7 ring carbon atoms or 3 to 6 ring carbon atoms, which may have one or more

rings, such as 1, 2, or 3 rings, preferably 1 or 2 rings. For example, "C<sub>3-12</sub> cycloalkyl" refers to a cycloalkyl containing 3-12 carbon atoms in the ring. "Cycloalkyl" also includes a fused or bridged ring, or a spirocyclic ring. The rings of the cycle group may be saturated or has one or more, for example, one or two double bonds (i.e. partially unsaturated), but not fully conjugated, and not an aryl as defined herein. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[4.1.0]heptyl, bicyclo[3.1.1]heptyl, spiro[3.3]heptyl, spiro[2.2]pentyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and bicyclo[3.1.1]hepta-2-ene.

The term "heterocycle", "heterocyclyl" or "heterocyclic" as used herein refers to monocyclic, bicyclic or tricyclic saturated or partially unsaturated cyclic radicals having 3-12 ring atoms, such as 3-8 ring atoms, 5-7 ring atoms, 4-7 ring atoms or 3-6 ring atoms, and containing one or more, for example 1, 2 or 3, preferably 1 or 2 heteroatoms independently chosen from N, O and S in the rings, with the remaining ring atoms being carbon. The heterocycle group also includes those wherein the N or S heteroatom are optionally oxidized to various oxidation states. The point of attachment of heterocyclyl can be on the N heteroatom or carbon. For example, "3-8 membered heterocyclyl" refers to a heterocyclyl containing 3-8 ring atoms and containing at least one heteroatom independently chosen from N, O and S.

The heterocycle group also includes a fused or bridged ring, or a spirocyclic ring, wherein, at least one ring contains at least one heteroatom chosen from O, S, and N and none of the other rings is aryl or heteroaryl as defined herein. The rings of the heterocycle group may be saturated or has one or more, for example, one or two double bonds (i.e. partially unsaturated), but not fully conjugated, and not a heteroaryl as defined herein. Examples of heterocyclyl groups include, but are not limited to, oxetanyl, azetidiny, pyrrolidinyl, tetrahydrofuryl, dioxolaneyl, morpholinyl, thiomorpholinyl, piperidyl, piperazinyl, pyrazolidinyl, and oxaspiro[3.3]heptanyl.

The term "aryl" as used herein refers to carbocyclic hydrocarbon radical of 6 to 14 carbon atoms consisting of one ring or more fused rings, wherein at least one ring is an aromatic ring. Examples of aryl groups include, but are not limited to, phenyl, naphthalenyl, 1,2,3,4-tetrahydronaphthalenyl, indenyl, indanyl, azulenyl, preferably phenyl and naphthalenyl.

The term "heteroaryl" as used herein refers to:

- monocyclic aromatic hydrocarbon radical having 5, 6 or 7 ring atoms, preferably having 6 ring atoms, and containing one or more, for example 1, 2 or 3, preferably 1 or 2 heteroatoms

independently chosen from N, O, and S (preferably N) in the ring, with the remaining ring atoms being carbon; and

- bicyclic aromatic hydrocarbon radical having 8-12 ring atoms, preferably having 9 or 10 ring atoms, and containing one or more, for example, 1, 2, 3 or 4, preferably 2, 3 or 4 heteroatoms independently chosen from N, O, and S (preferably N) in the rings, with the remaining ring atoms being carbon, wherein at least one of the rings is aromatic. For example, the bicyclic heteroaryl includes a 5- to 6-membered heterocyclic aromatic ring fused to a 5- to 6-membered cycloalkyl ring.

When the total number of S and O atoms in the heteroaryl group exceeds 1, said S and O heteroatoms are not adjacent to one another.

The heteroaryl group also includes those wherein the N heteroatom occurs as N-oxide, such as pyridyl N-oxides.

Examples of the heteroaryl group include, but are not limited to, pyridyl, pyridyl N-oxide, pyrazinyl, pyrimidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, triazolyl, thienyl, furyl, pyranyl, pyrrolyl, pyridazinyl, benzodioxolyl, benzooxazolyl, benzoisoxazolyl, benzothienyl, benzothiazolyl, benzoisothiazolyl, imidazopyridyl (such as imidazo[1,2-a]pyridyl), pyrrolopyridyl, pyrrolopyrimidinyl, pyrazolopyridinyl (such as pyrazolo[1,5-a]pyridyl), pyrazolopyrimidinyl, triazolopyridinyl (such as [1,2,4]triazolo[1,5-a]pyridyl), tetrazolopyridinyl, tetrahydropyrazolopyridyl (such as 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridyl), benzofuryl, benzoimidazolyl, indolyl, indazolyl, purinyl, quinolinyl, and isoquinolinyl.

“Hydroxyl” as used herein refers to the –OH radical.

“Mercapto” as used herein refers to the –SH radical.

“Oxo” as used herein refers to the =O radical.

When a structure herein contains an asterisk “\*”, it means that the chiral center of the compound marked by “\*” is in either R-configuration or S-configuration, and the content of the compound with single configuration marked by “\*” is at least 90% (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 100%, or any value between those enumerated values). The configuration of the compounds can be determined using a variety of analytical techniques, for example single crystal X-ray crystallography and/or optical polarimetry according to routine protocols by those of ordinary skill in the art.

When a structure herein contains “(RS)”, it means that the chiral center of the compound marked by “(RS)” contains both R-configuration and S-configuration.

The term “optional” or “optionally” as used herein means that the subsequently described event or circumstance may or may not occur, and the description includes instances wherein the event or circumstance occur and instances in which it does not occur. For example, “optionally substituted alkyl” encompasses both “unsubstituted alkyl” and “substituted alkyl” as defined herein. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, chemically incorrect, synthetically non-feasible and/or inherently unstable.

The term “substituted” or “substituted with.....”, as used herein, means that one or more hydrogens on the designated atom or group are replaced with one or more selections from the indicated group of substituents, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo (i.e., =O), then 2 hydrogens on a single atom are replaced by the oxo. Combinations of substituents and/or variables are permissible only if such combinations result in a chemically correct and stable compound. A chemically correct and stable compound is meant to imply a compound that is sufficiently robust to survive sufficient isolation from a reaction mixture to be able to identify the chemical structure of the compound, and also sufficiently robust to allow subsequent formulation as an agent having at least one practical utility.

Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion.

The term “substituted with one or more substituents” as used herein means that one or more hydrogens on the designated atom or group are independently replaced with one or more selections from the indicated group of substituents. In some embodiments, “substituted with one or more substituents” means that the designated atom or group is substituted with 1, 2, 3, or 4 substituents independently chosen from the indicated group of substituents.

It will be appreciated by the person of ordinary skill in the art (“POSITA”) that some of the compounds of formula (I) may contain one or more chiral centers and therefore exist in two or more stereoisomeric forms. The racemates of these isomers, the individual isomers and mixtures enriched in one enantiomer, as well as diastereomers when there are two chiral centers, and mixtures partially enriched with specific diastereomers are within the scope of the present

invention. It will be further appreciated by the POSITA that the present invention includes all the individual stereoisomers (e.g. enantiomers), racemic mixtures or partially resolved mixtures of the compounds of formula (I) and, where appropriate, the individual tautomeric forms thereof.

In other words, in some embodiments, the present invention provides compounds of various stereoisomeric purities, i.e., diastereomeric or enantiomeric purity expressed as various "ee" or "de" Values. In some embodiments, the compound of formula (I) (e.g., as described herein) has an enantiomeric purity of at least 60% ee (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% ee, or any value between those enumerated values). In some embodiments, the compound of formula (I) (e.g., as described herein) has an enantiomeric purity of greater than 99.9% ee, extending up to 100% ee. In some embodiments, the compound of formula (I) (e.g., as described herein) has a diastereomeric purity of at least 60% de (e.g., 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% de, or any value between those enumerated values). In some embodiments, the compound of formula (I) (e.g., as described herein) has a diastereomeric purity of greater than 99.9% de.

The term "enantiomeric excess" or "ee" designates how much of one enantiomer is present compared to the other. For a mixture of R and S enantiomers, the percent enantiomeric excess is defined as  $|R - S| * 100$ , where R and S are the respective mole or weight fractions of enantiomers in a mixture such that  $R + S = 1$ . With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as  $([a]_{obs}/[a]_{max}) * 100$ , where  $[a]_{obs}$  is the optical rotation of the mixture of enantiomers and  $[a]_{max}$  is the optical rotation of the pure enantiomer.

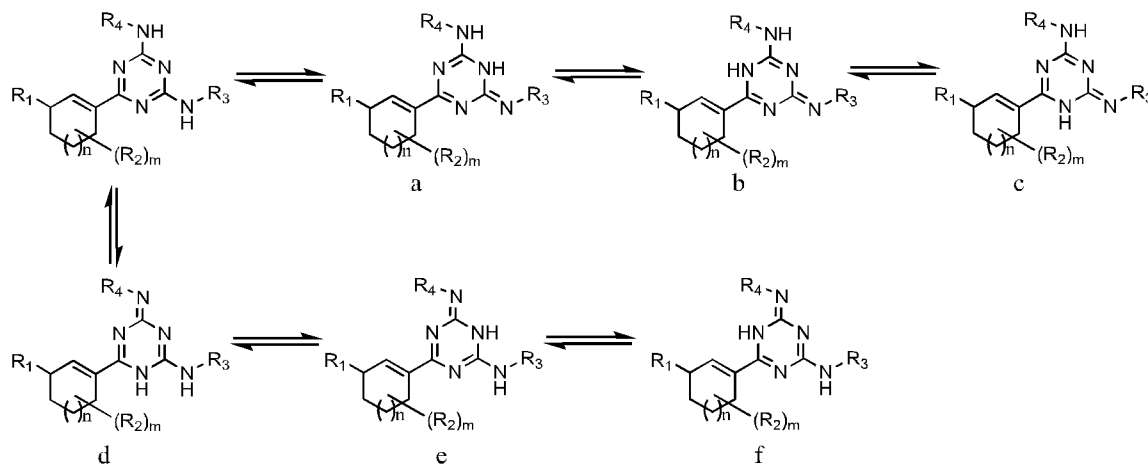
The term "diastereomeric excess" or "de" designates how much of one diastereomer is present compared to the other and is defined by analogy to enantiomeric excess. Thus, for a mixture of diastereomers, D1 and D2, the percent diastereomeric excess is defined as  $|D1 - D2| * 100$ , where D1 and D2 are the respective mole or weight fractions of diastereomers in a mixture such that  $D1 + D2 = 1$ .

The determination of diastereomeric and/or enantiomeric excess can be accomplished using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography and/or optical polarimetry according to routine protocols familiar to those skilled in the art.

The racemates can be used as such or can be resolved into their individual isomers. The resolution can afford stereochemically pure compounds or mixtures enriched in one or more isomers. Methods for separation of isomers are well known (cf. Allinger N. L. and Eliel E. L. in

"Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) and include physical methods such as chromatography using a chiral adsorbent. Individual isomers can be prepared in chiral form from chiral precursors. Alternatively, individual isomers can be separated chemically from a mixture by forming diastereomeric salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alpha-bromocamphoric acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, fractionally crystallizing the salts, and then freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; i.e., in a form having an optical purity of, for example, at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 99.5% by weight of the desired stereoisomer. Alternatively, the racemates can be covalently linked to a chiral compound (auxiliary) to produce diastereomers which can be separated by chromatography or by fractional crystallization after which time the chiral auxiliary is chemically removed to afford the pure enantiomers, as is known to the POSITA.

The term "tautomer" as used herein refers to constitutional isomers of compounds generated by rapid movement of an atom in two positions in a molecule. Tautomers readily interconvert into each other, e.g., enol form and ketone form are typical tautomers. For example, some compounds disclosed herein can exist in the forms of a, b, c, d, e, f, etc., as shown in the figure below, i.e., compounds in the forms of a, b, c, d, e, f are possible the tautomers of the compound of Formula (I). The single tautomer and the mixture of these tautomers in any ratio are all included in the compounds described herein.



A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid or base of a compound of Formula (I) that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. For examples, 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.



In addition, if a compound described herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be produced by dissolving the free base in a suitable solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. The POSITA will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable acid addition salts.

The term “solvates” means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the solid state, thus forming a solvate. If the solvent is water, the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substances in which the water retains its molecular state as H<sub>2</sub>O, such combination being able to form one or more hydrates, for example, hemihydrates, monohydrate, and dihydrate, as well as variable hydrates.

As used herein, the terms “group”, “radical” and “moiety” are synonymous and are intended to indicate functional groups or fragments of molecules attachable to other fragments of molecules.

The term “active ingredient” is used to indicate a chemical substance which has biological activity. In some embodiments, an “active ingredient” is a chemical substance having pharmaceutical utility. In the United States, practical pharmaceutical activity can be established by appropriate pre-clinical assays, whether in vitro or in vivo. Pharmaceutical activity sufficient to be accepted by a regulatory agency, such as FDA in the U.S., is a higher standard than the pre-clinical assay. Such a higher standard of pharmaceutical activity, the success of which cannot generally be reasonably expected from the pre-clinical results, can be established by appropriate and successful randomized, double blind, controlled clinical trials in humans.

The terms “treating”, “treat,” or “treatment” of a disease or disorder, in the context of achieving therapeutic benefit, refer to administering one or more pharmaceutical substances, especially a compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein to a subject that has the disease or disorder, or has a symptom of a disease or disorder, or has a predisposition toward a disease or disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease or disorder, the symptoms of the disease or disorder, or the predisposition toward the disease or disorder. In some embodiments, the disease or disorder is cancer.

The terms “treating”, “contacting” and “reacting,” in the context of a chemical reaction, mean adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately lead to the formation of the indicated and/or the desired product.

The term “effective amount” as used herein refers to an amount or dose of an IDH mutation inhibiting agent sufficient to generally bring about a therapeutic benefit in patients in need of treatment for a disease or disorder induced by IDH mutation. Effective amounts or doses of the active ingredient of the present disclosure may be ascertained by methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease or disorder, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the attending physician. In the United States, the determination of effective doses is generally difficult to predict from preclinical trials. In fact, the dose is completely unpredictable and the dose will develop a new unpredictable dosing regimen after initial use in a randomized, double-blind, controlled clinical trials.

An exemplary dose is in the range of from about 0.0001 to about 200 mg of active agent per kg of subject's body weight per day, such as from about 0.001 to 100 mg/kg/day, or about 0.01 to 35 mg/kg/day, or about 0.1 to 10 mg/kg daily in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 5 g/day. Once improvement of the patient's disease or disorder has occurred, the dose may be adjusted for maintenance treatment. For example, the dosage or the frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

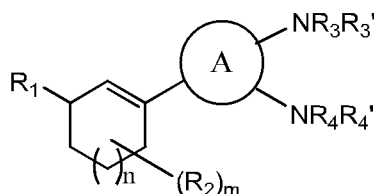
The term “subject” as used herein means mammals and non-mammals. Mammals means any member of the mammalia class including, but not limited to, humans; non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but

are not limited to, birds, and the like. The term “subject” does not denote a particular age or sex. In some embodiments, the subject is a human.

In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 20%.

- 5 Technical and scientific terms used herein and not specifically defined have the meaning commonly understood by the POSITA to which the present disclosure pertains.

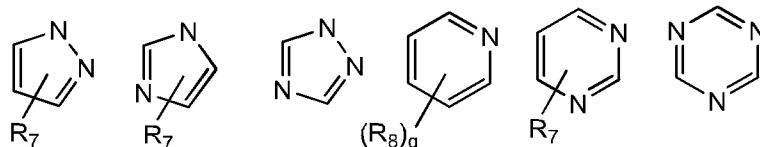
Provided is a compound of formula (I):



10

(I)

and/or a pharmaceutically acceptable salt thereof, and/or solvates, racemic mixtures, enantiomers, diastereomers, and tautomers thereof, wherein



A is chosen from , wherein, R<sub>7</sub> is chosen from H, halo, -CN, -OH, or -NH<sub>2</sub>; R<sub>8</sub> is chosen from halo, -CN, -OH, or -NH<sub>2</sub>; q is 1 or 2;

15

R<sub>1</sub> is chosen from H, -OH, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1-4</sub> alkyl), -N(C<sub>1-4</sub> alkyl)<sub>2</sub>, oxo, or C<sub>3-8</sub> cycloalkyl;

20

each of R<sub>2</sub> is independently chosen from H, deuterium, halo, -OH, -NH<sub>2</sub>, -CN, -SH, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-8</sub> cycloalkyl, oxo, -OR<sub>5</sub>, -OCOR<sub>5</sub>, -NHR<sub>5</sub>, -N(R<sub>5</sub>)(C<sub>1-4</sub> alkyl), -COR<sub>5</sub>, -NHCOR<sub>5</sub>, or 3-8 membered heterocyclyl; in which each of said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-8</sub> cycloalkyl or 3-8 membered heterocyclyl is optionally substituted with one or more groups chosen from deuterium, halo, -CN, -OH, -SH, -NH<sub>2</sub>, -NH(C<sub>1-4</sub> alkyl), -N(C<sub>1-4</sub> alkyl)<sub>2</sub>, or C<sub>1-6</sub> alkoxy; or two R<sub>2</sub>, which attach to the same carbon atom, together with the carbon atom they are attached to form a 3-5 membered cycloalkyl which is optionally substituted with one or more halo or deuterium;

25

R<sub>3</sub>, R<sub>3</sub>', R<sub>4</sub> and R<sub>4</sub>' are independently chosen from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl, phenyl, 5-12 membered heteroaryl, -C(O)R<sub>5</sub>, -OR<sub>5</sub>, or

-NHR<sub>5</sub>, in which each of said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl, phenyl, or 5-12 membered heteroaryl is optionally substituted with one or more R<sub>6</sub>; wherein R<sub>3</sub>, R<sub>3</sub>', R<sub>4</sub> and R<sub>4</sub>' are not H simultaneously; provided that when one of R<sub>3</sub> and R<sub>4</sub> is optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl, the other one is -OR<sub>5</sub> or -NHR<sub>5</sub>;

or R<sub>3</sub> and R<sub>3</sub>' are independently chosen from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl, phenyl, 5-12 membered heteroaryl, -C(O)R<sub>5</sub>, -OR<sub>5</sub>, or -NHR<sub>5</sub>, in which each of said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl, phenyl, or 5-12 membered heteroaryl is optionally substituted with one or more R<sub>6</sub>; R<sub>4</sub> and R<sub>4</sub>' together with the N atom they are attached to form a 3-8 membered heterocyclic ring optionally substituted by one or more R<sub>6</sub>;

R<sub>5</sub> is chosen from C<sub>1-6</sub> alkyl or C<sub>3-8</sub> cycloalkyl, each of which is optionally substituted with one or more groups independently chosen from halo, -CN, -OH, -SH, -NH<sub>2</sub>, or C<sub>1-6</sub> alkoxy;

each of R<sub>6</sub> is independently chosen from deuterium, halo, -CN, -OH, -SH, -NH<sub>2</sub>, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>3-8</sub> cycloalkyl, 3-8 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl, in which each of said C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, 3-8 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one or more groups independently chosen from halo, -CN, -OH, -SH, -NH<sub>2</sub>, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkynyl, or C<sub>1-6</sub> alkyl;

m is 0, 1, 2, 3, 4, 5, or 6;

n is 0, 1, or 2.

In some embodiments of the compound of formula (I), R<sub>1</sub> is chosen from H, -OH or halo.

In some embodiments of the compound of formula (I), R<sub>1</sub> is chosen from -OH or halo.

In some embodiments of the compound of formula (I), R<sub>1</sub> is -OH.

In some embodiments of the compound of formula (I), R<sub>1</sub> is halo chosen from F, Cl, or Br. In some  
25 embodiments of the compound of formula (I), R<sub>1</sub> is F.

In some embodiments of the compound of formula (I), the two R<sub>2</sub>, which attach to the same carbon atom, together with the carbon atom they are attached to form a 3-5 membered cycloalkyl optionally substituted by one or more F.

In some embodiments of the compound of formula (I), the two R<sub>2</sub>, which attach to the same carbon  
30 atom, together with the carbon atom they are attached to form a cyclopropyl.

In some embodiments of the compound of formula (I), each of R<sub>2</sub> is independently chosen from H, deuterium, halo, -OH, -NH<sub>2</sub>, -CN, -SH, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-8</sub> cycloalkyl, oxo, -OR<sub>5</sub>, -OCOR<sub>5</sub>, -NHR<sub>5</sub>, -N(R<sub>5</sub>)(C<sub>1-4</sub> alkyl), -NHCOR<sub>5</sub>, or 3-8 membered heterocyclyl.

- 5 In some embodiments of the compound of formula (I), each of R<sub>2</sub> is independently chosen from H, deuterium, halo, -OH, -NH<sub>2</sub>, -CN, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, oxo, -OR<sub>5</sub>, -NHR<sub>5</sub>, or -N(R<sub>5</sub>)(C<sub>1-4</sub> alkyl).

In some embodiments of the compound of formula (I), each of R<sub>2</sub> is independently chosen from H, deuterium, halo, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl.

- 10 In some embodiments of the compound of formula (I), each of R<sub>2</sub> is independently chosen from halo, such as F, Cl, or Br.

In some embodiments of the compound of formula (I), R<sub>2</sub> is F.

In some embodiments of the compound of formula (I), m is 0, 1, 2, 3, or 4.

In some embodiments of the compound of formula (I), m is 0, 1, or 2.

- 15 In some embodiments of the compound of formula (I), m is 1. In some embodiments of the compound of formula (I), m is 2. In some embodiments of the compound of formula (I), m is 3. In some embodiments of the compound of formula (I), m is 4.

- In some embodiments of the compound of formula (I), R<sub>3</sub> and R<sub>4</sub> are independently chosen from C<sub>1-6</sub> alkyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl, phenyl, 5-12 membered heteroaryl, 20 -C(O)R<sub>5</sub>, -OR<sub>5</sub>, or -NHR<sub>5</sub>, in which each of said C<sub>1-6</sub> alkyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl, phenyl, or 5-12 membered heteroaryl is optionally substituted with one or more R<sub>6</sub>; R<sub>3</sub>' and R<sub>4</sub>' are independently chosen from H or C<sub>1-6</sub> alkyl.

In some embodiments of the compound of formula (I), R<sub>3</sub>' and R<sub>4</sub>' are both H.

- 25 In some embodiments of the compound of formula (I), R<sub>3</sub> and R<sub>4</sub> are independently chosen from C<sub>1-6</sub> alkyl, C<sub>3-12</sub> cycloalkyl, or 3-12 membered heterocyclyl, each of which is optionally substituted with one or more R<sub>6</sub>; R<sub>3</sub>' and R<sub>4</sub>' are both H.

In some embodiments of the compound of formula (I), R<sub>3</sub> and R<sub>4</sub> are independently chosen from C<sub>1-6</sub> alkyl substituted with one or more halo, 5-12 membered heteroaryl substituted with C<sub>1-6</sub> haloalkyl, or -OR<sub>5</sub>; R<sub>3</sub>' and R<sub>4</sub>' are both H.

- 30 In some embodiments of the compound of formula (I), R<sub>3</sub> and R<sub>4</sub> are independently chosen from C<sub>1-6</sub> alkyl optionally substituted with one or more halo; R<sub>3</sub>' and R<sub>4</sub>' are both H.

In some embodiments of the compound of formula (I),  $R_3$  is 5-12 membered heteroaryl substituted with  $C_{1-6}$  haloalkyl,  $R_4$  is  $C_{1-6}$  alkoxy;  $R_3'$  and  $R_4'$  are both H.

In some embodiments of the compound of formula (I),  $R_3$  is 5-7 membered heteroaryl substituted with  $CF_3$ ,  $R_4$  is  $C_{1-6}$  alkoxy;  $R_3'$  and  $R_4'$  are both H.

In some embodiments of the compound of formula (I),  $R_3$  is chosen from H,  $C_{1-6}$  alkyl optionally substituted by  $C_{1-6}$  haloalkyl, or 5-12 membered heteroaryl optionally substituted by  $C_{1-6}$  haloalkyl;  $R_3'$  is H;  $R_4$  and  $R_4'$  together with the N atom they are attached to form a 3-8 membered heterocyclic ring optionally substituted by one or more groups chosen from halo, -OH, or  $C_{1-6}$  haloalkyl.

In some embodiments of the compound of formula (I),  $R_5$  is  $C_{1-6}$  alkyl or  $C_{3-8}$  cycloalkyl.

In some embodiments of the compound of formula (I),  $R_5$  is  $C_{1-6}$  alkyl optionally substituted with one or more halo.

In some embodiments of the compound of formula (I), each of  $R_6$  is independently chosen from deuterium, halo, -CN, -OH, -NH<sub>2</sub>,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{3-8}$  cycloalkyl, 3-8 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl, in which each of said  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl,  $C_{3-8}$  cycloalkyl, 3-8 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl is optionally substituted with one or more halo.

In some embodiments of the compound of formula (I), each of  $R_6$  is independently chosen from deuterium, halo, -OH,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl,  $C_{3-8}$  cycloalkyl, 3-8 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl.

In some embodiments of the compound of formula (I), each of  $R_6$  is independently chosen from deuterium, halo, -CN, -OH, -NH<sub>2</sub>,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl, or  $C_{3-8}$  cycloalkyl.

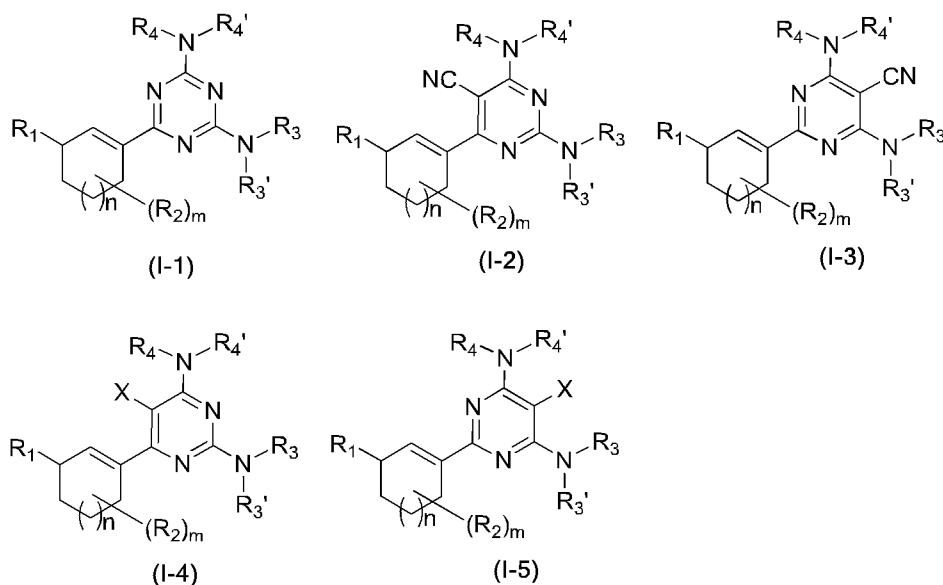
In some embodiments of the compound of formula (I), each of  $R_6$  is independently chosen from deuterium, halo, or  $C_{1-6}$  haloalkyl.

In some embodiments of the compound of formula (I), n is 1.

25 In some embodiments of the compound of formula (I),  $R_7$  and  $R_8$  are independently chosen from halo or -CN.

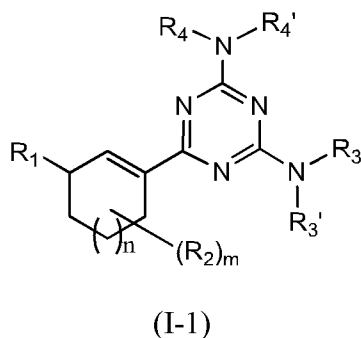
In some embodiments of the compound of formula (I),  $R_7$  and  $R_8$  are independently chosen from F or -CN.

In some embodiments of the compound of formula (I), the compound of formula (I) is chosen from

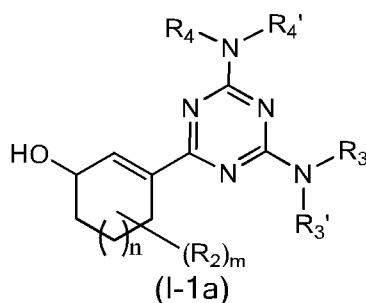


wherein X is halo;  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I).

In some embodiments of the compound of formula (I), formula (I) is formula (I-1), wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I),

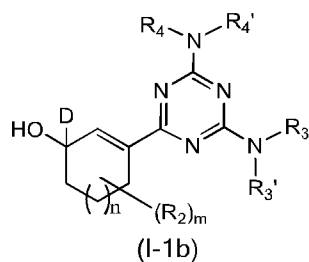


In some embodiments of the compound of formula (I), formula (I) is formula (I-1a), wherein  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I),

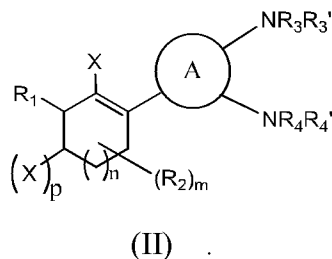


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In some embodiments of the compound of formula (I), formula (I) is formula (I-1b), wherein  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I),



In some embodiments of the compound of formula (I), formula (I) is formula (II), wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $n$  and  $A$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2,



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In some embodiments of the compound of formula (II),  $X$  is F.

In some embodiments of the compound of formula (II),  $R_1$  is F.

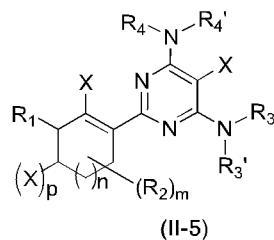
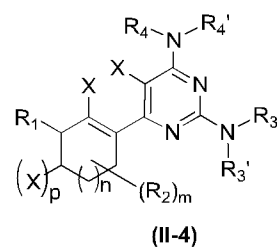
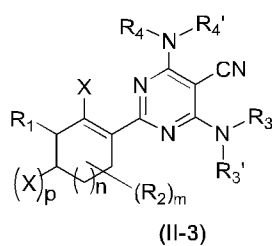
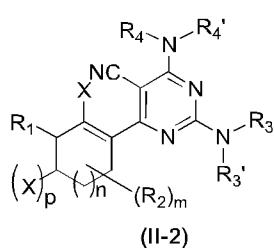
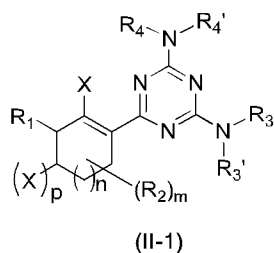
In some embodiments of the compound of formula (II),  $R_1$  is -OH.

10 In some embodiments of the compound of formula (II),  $p$  is 0.

In some embodiments of the compound of formula (II),  $p$  is 1.

In some embodiments of the compound of formula (II),  $p$  is 2.

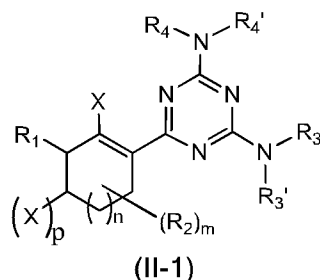
In some embodiments of the compound of formula (I), formula (II) is chosen from



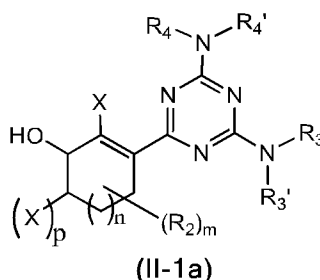
15 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2.



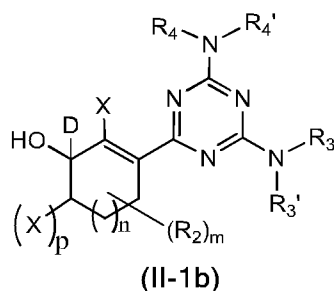
In some embodiments of the compound of formula (I), formula (II) is formula (II-1), wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2,



5 In some embodiments of the compound of formula (I), formula (II) is formula (II-1a), wherein  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2,



10 In some embodiments of the compound of formula (I), formula (II) is formula (II-1b), wherein  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2,



In some embodiments of the compound of formula (II-1) - formula (II-5),  $X$  is F.

In some embodiments of the compound of formula (II-1) - formula (II-5),  $R_1$  is F.

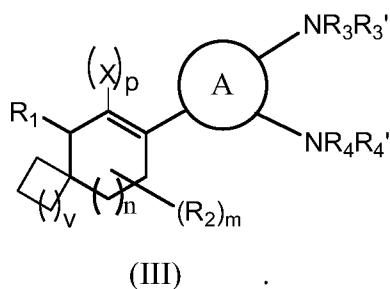
15 In some embodiments of the compound of formula (II-1) - formula (II-5),  $R_1$  is -OH.

In some embodiments of the compound of formula (II-1) - formula (II-5),  $p$  is 0.

In some embodiments of the compound of formula (II-1) - formula (II-5),  $p$  is 1.

In some embodiments of the compound of formula (II-1) - formula (II-5),  $p$  is 2.

In some embodiments of the compound of formula (I), formula (I) is formula (III), wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $n$  and  $A$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2;  $v$  is 0, 1, or 2,



In some embodiments of the compound of formula (III),  $X$  is F.

In some embodiments of the compound of formula (III),  $R_1$  is F.

In some embodiments of the compound of formula (III),  $R_1$  is -OH.

In some embodiments of the compound of formula (III),  $p$  is 0.

In some embodiments of the compound of formula (III),  $p$  is 1.

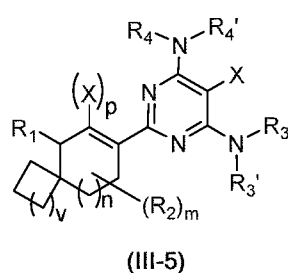
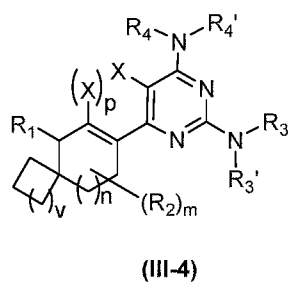
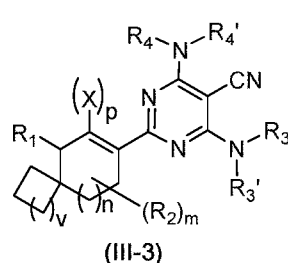
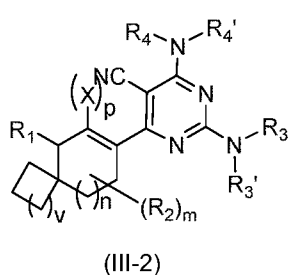
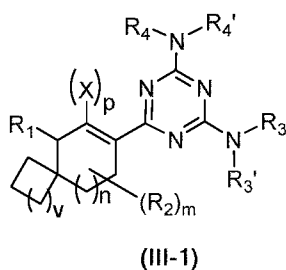
In some embodiments of the compound of formula (III),  $p$  is 2.

In some embodiments of the compound of formula (III),  $v$  is 0.

In some embodiments of the compound of formula (III),  $v$  is 1.

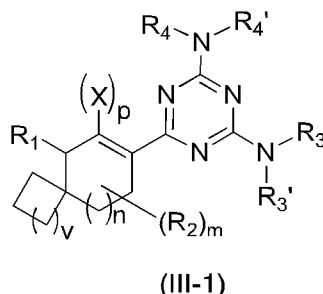
In some embodiments of the compound of formula (III),  $v$  is 2.

In some embodiments of the compound of formula (I), formula (III) is chosen from



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2;  $v$  is 0, 1, or 2.

In some embodiments of the compound of formula (I), formula (III) is formula (III-1), wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $m$  and  $n$  are as defined in the compound of formula (I);  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2;  $v$  is 0, 1, or 2,



- 5 In some embodiments of the compound of formula (III-1) - formula (III-5),  $X$  is F.
- In some embodiments of the compound of formula (III-1) - formula (III-5),  $R_1$  is F.
- In some embodiments of the compound of formula (III-1) - formula (III-5),  $R_1$  is -OH.
- In some embodiments of the compound of formula (III-1) - formula (III-5),  $p$  is 0.
- In some embodiments of the compound of formula (III-1) - formula (III-5),  $p$  is 1.
- 10 In some embodiments of the compound of formula (III-1) - formula (III-5),  $p$  is 2.
- In some embodiments of the compound of formula (III-1) - formula (III-5),  $v$  is 0.
- In some embodiments of the compound of formula (III-1) - formula (III-5),  $v$  is 1.
- In some embodiments of the compound of formula (III-1) - formula (III-5),  $v$  is 2.
- Also provided is a compound chosen from Compounds 1-87, 89-184, 186-301, as numbered in
- 15 the experimental section, and/or a pharmaceutically acceptable salt thereof.
- In another aspect, provided is a pharmaceutical composition, comprising a compound of formula (I) (e.g., any of the compounds described herein) and/or a pharmaceutically acceptable salt thereof, and optionally comprising at least one pharmaceutically acceptable excipient (e.g., a pharmaceutically acceptable carrier).
- 20 In another aspect, provided is a method of treating a disease induced by IDH mutation in a subject, comprising administering to the subject in need thereof an amount of a compound of formula (I) (e.g., any of the compounds described herein) and/or a pharmaceutically acceptable salt thereof effective to inhibit the increase of  $\alpha$ -hydroxyglutaric acid (2HG) induced by IDH mutation in said subject.
- 25 In another aspect, provided is a method of treating a disease induced by IDH mutation in a subject, comprising administering to the subject in need thereof an amount of a pharmaceutical

composition comprising a compound of formula (I) (e.g., any of the compounds described herein) and/or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient (e.g., a pharmaceutically acceptable carrier) effective to inhibit the increase of  $\alpha$ -hydroxyglutaric acid (2HG) induced by IDH mutation in said subject.

- 5 In another aspect, provided is a use of a compound of formula (I) (e.g., any of the compounds described herein) and/or a pharmaceutically acceptable salt thereof described herein for treating a disease induced by IDH mutation by inhibiting the increase of  $\alpha$ -hydroxyglutaric acid (2HG) induced by IDH mutation in a subject.

10 In another aspect, provided is a use of a compound of formula (I) (e.g., any of the compounds described herein) and/or a pharmaceutically acceptable salt thereof described herein in the manufacture of a medicament for treating a disease induced by IDH mutation.

In some embodiments, the IDH mutation is IDH1 gene mutation.

In some embodiments, the IDH mutation is IDH2 gene mutation.

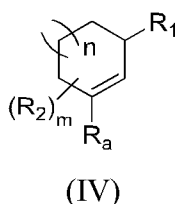
In some embodiments, the IDH mutation is IDH1-R132H or IDH2-R140Q gene mutation.

- 15 In some embodiments, the disease induced by IDH mutation is cancer.

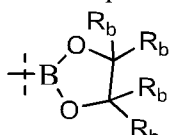
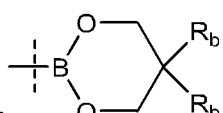
In some embodiments, the cancer is chosen from solid cancer, neurogliocytoma, or hematological malignant tumor, such as leukemia, lymphoma, or myeloma.

20 In some embodiments, the cancer is chosen from acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), glioblastoma (GBM), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), cholangiocarcinoma, such as intrahepatic cholangiocarcinoma (IHCC), chondrosarcoma, giant cell tumor, intestinal cancer, melanoma, lung cancer, or non-Hodgkin's lymphoma (NHL).

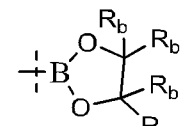
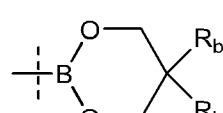
25 In another aspect, provided is a compound of formula (IV) and/or a salt thereof, and/or racemic mixtures or enantiomers thereof, which can be used in the manufacture of compounds of formula (I) (e.g., any of the compounds described herein),



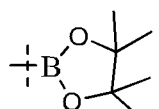
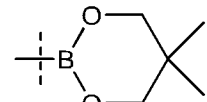
wherein,  $R_1$ ,  $R_2$ ,  $m$  and  $n$  are as defined in the compound of formula (I);  $R_a$  is chosen from halo,

$-\text{OS(O)}_2\text{CF}_3$ ,  $-\text{B(OH)}_2$ ,  $-\text{B(OC}_{1-6}\text{ alkyl)}_2$ , , or ;  $R_b$  is H or  $\text{C}_{1-6}$  alkyl.

In some embodiments of the compound of formula (IV),  $R_a$  is chosen from  $-\text{B(OH)}_2$ ,  $-\text{B(OC}_{1-6}$

5  $\text{alkyl)}_2$ , , or ;  $R_b$  is H or  $\text{C}_{1-6}$  alkyl.

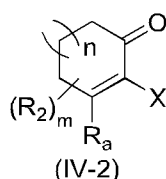
In some embodiments of the compound of formula (IV),  $R_a$  is chosen from  $-\text{B(OH)}_2$ ,  $-\text{B(OCH}_3)_2$ ,

$-\text{B[OCH(CH}_3)_2]_2$ , , or .

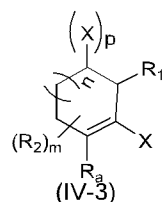
In some embodiments of the compound of formula (IV), formula (IV) is formula (IV-1), wherein  $m$  is 0, 1, or 2;



In some embodiments of the compound of formula (IV), formula (IV) is formula (IV-2), wherein  $X$  is halo;  $m$  is 0, 1, or 2;



15 In some embodiments of the compound of formula (IV), formula (IV) is formula (IV-3), wherein  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2;



In some embodiments of the compound of formula (IV),  $R_1$  is  $-\text{OH}$  or oxo.

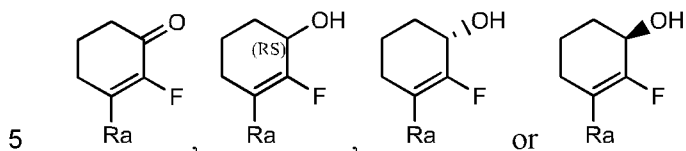
In some embodiments of the compound of formula (IV),  $X$  is F.

In some embodiments of the compound of formula (IV),  $p$  is 0.

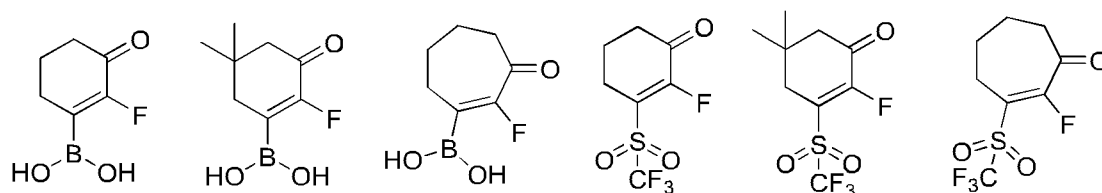
In some embodiments of the compound of formula (IV), p is 1.

In some embodiments of the compound of formula (IV), p is 2.

In some embodiments of the compound of formula (IV), the compound of formula (IV) is chosen from



In some embodiments of the compound of formula (IV), the compound of formula (IV) is chosen from



## 10 General Synthetic Methods for Disclosed Embodiments

The compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein can be synthesized from commercially available starting material by methods well known in the art, taken together with the disclosure in this patent application. The drawings 1-6 illustrate general methods for preparation of the compounds described herein.

15 As shown in Figure 1, substitution reaction of 2,4,6-trichloro-1,3,5-triazine with an amine substituted with  $R_3$  and  $R_3'$  provides compound of formula 1-1. Substitution reaction of the compound of formula 1-1 with an amine substituted with  $R_4$  and  $R_4'$  provides compound of formula 1-2. Suzuki coupling reaction of compound of formula 1-2 with an intermediate represented by formula (IV) under the catalysis of a suitable palladium reagent gives a  
 20 compound of formula (I-1) as described herein, wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ , Ra, m, and n are as defined herein. The Pd-catalyzed C-C coupling reaction can be carried out under suitable conditions, and the solvent used can be selected from polar solvents such as 1,4-dioxane, DMF, THF, a mixture of 1,4-dioxane and water and the like, the base used can be selected from  $\text{Cs}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$  and the like, and the catalyst used can be selected from  
 25  $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ ,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Pd}(\text{OAc})_2$  and the like.

As shown in Scheme 2, Suzuki coupling reaction of compound of formula 1-1 with an intermediate represented by formula (IV) under the catalysis of a suitable palladium reagent

affords compound of formula 2-1. Substitution reaction of compound of formula 2-1 with an amine substituted with  $R_4$  and  $R_4'$  gives a compound of formula (I-1) as described herein, wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_3'$ ,  $R_4$ ,  $R_4'$ ,  $R_a$ ,  $m$ , and  $n$  are as defined herein.

As shown in Scheme 3, Suzuki coupling reaction of compound of formula 1-2 with an intermediate represented by formula (IV-1) under the catalysis of a suitable palladium reagent provides compound of formula 3-1. The Pd-catalyzed C-C coupling reaction can be carried out under suitable conditions, and the solvent used can be selected from polar solvents such as 1,4-dioxane, DMF, THF, a mixture of 1,4-dioxane and water and the like, the base used can be selected from  $Cs_2CO_3$ ,  $Na_2CO_3$ ,  $K_3PO_4$  and the like, and the catalyst used can be selected from  $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ ,  $Pd(PPh_3)_4$ ,  $Pd(OAc)_2$  and the like. Reduction of compound of formula 3-1 provides compound of formula (I-1a) as described herein.

As shown in Scheme 4, Suzuki coupling reaction of compound of formula 1-1 with an intermediate represented by formula (IV-1) under the catalysis of a suitable palladium reagent affords compound of formula 4-1. Reduction of Compound of formula 4-1 provides compound of formula 4-2. Substitution reaction of compound of formula 4-2 with an amine substituted with  $R_4$  and  $R_4'$  gives a compound of formula (I-1a) as described herein.

As shown in Scheme 5, Suzuki coupling reaction of compound of formula 1-2 with an intermediate represented by formula (IV-2) under the catalysis of a suitable palladium reagent provides compound of formula 5-1. Halogenation of compound of formula 5-1 using a halogenating reagent such as NFSI and the like, in presence of a base such as LiHMDS, KHMDS, LDA and the like, and in suitable polar solvents such as THF, DCM and the like, results in compound of formula 5-2. Reduction of compound of formula 5-2 provides compound of formula (II-1a) as described herein.

As shown in Scheme 6, compound of formula 3-1 reacts with a deuterating reagent such as  $NaBD_4$ , deuterated borane and the like gives a compound of formula (I-1b) as described herein.

The substituents of the compounds thus obtained can be further modified to provide other desired compounds. Synthetic chemistry transformations are described, for example, in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

Before use, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein can be purified by column chromatography, high performance liquid chromatography, crystallization or other suitable methods.

## 5 **Pharmaceutical Compositions and Practical Utility**

The compound of formula (I) (e.g., any of those described herein) and/or a pharmaceutically acceptable salt thereof described herein is used, alone or in combination with one or more additional active ingredients, to formulate pharmaceutical compositions. A pharmaceutical composition comprises: (a) an effective amount of a compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein; and (b) a pharmaceutically acceptable excipient (e.g., a pharmaceutically acceptable carrier).

A pharmaceutically acceptable carrier refers to a carrier that is compatible with active ingredients of the composition (and in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which form specific, more soluble complexes with the the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10. Suitable pharmaceutically acceptable carriers are disclosed in Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in the art.

A pharmaceutical composition comprising a compound of formula (I) (e.g., any of those described herein) and/or a pharmaceutically acceptable salt thereof described herein can be administered in various known manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

A pharmaceutical composition described herein can be prepared in the form of tablet, capsule, sachet, dragee, powder, granule, lozenge, powder for reconstitution, liquid preparation, or suppository. In some embodiments, a pharmaceutical composition comprising a compound of formula (I) and/or a pharmaceutically acceptable salt thereof is formulated for intravenous infusion, topical administration, or oral administration.



An oral composition can be any orally acceptable dosage form including, but not limited to, tablets, capsules, emulsions, and aqueous suspensions, dispersions and solutions. Commonly used carriers for tablets include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added to tablets. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof can be present in an amount of 1, 5, 10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a tablet. In some embodiments, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof can be present in an amount of 1, 5, 10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a capsule.

A sterile injectable composition (e.g., aqueous or oleaginous suspension) can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable Intermediate can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the pharmaceutically acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or di-glycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the Intermediate of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents.

An inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

A topical composition can be formulated in form of oil, cream, lotion, ointment, and the like. Suitable carriers for the composition include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohols (greater than C12). In some embodiments, the pharmaceutically acceptable carrier is one in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants

may also be included as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers may be employed in those topical formulations. Examples of such enhancers can be found in U.S. Patents 3,989,816 and 4,444,762.

5 Creams may be formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of an oil, such as almond oil, is admixed. An example of such a cream is one which includes, by weight, about 40 parts water, about 20 parts beeswax, about 40 parts mineral oil and about 1 part almond oil. Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil, such as almond oil, with warm soft paraffin and allowing the mixture to cool. An example of such an ointment is one  
10 which includes about 30% by weight almond oil and about 70% by weight white soft paraffin.

Suitable in vitro assays can be used to evaluate the practical utility of the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein, in inhibiting the IDH mutation. The compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein can further be examined for additional practical utility in treating cancer by in vivo assays. For example, the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein can be administered to an animal (e.g., a mouse model) having cancer and its therapeutic effects can be accessed. If the pre-clinical results are successful, the dosage range and administration route for animals, such as humans, can be projected.  
15

The compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein can be shown to have sufficient pre-clinical practical utility to merit clinical trials hoped to demonstrate a beneficial therapeutic or prophylactic effect, for example, in subjects with cancer.  
20

As used herein, the term "cancer" refers to a cellular disorder characterized by uncontrolled or disregulated cell proliferation, decreased cellular differentiation, inappropriate ability to invade surrounding tissue, and/or ability to establish new growth at ectopic sites. The term "cancer" includes, but is not limited to, solid tumors and hematologic malignancies. The term "cancer" encompasses diseases of skin, tissues, organs, bone, cartilage, blood, and vessels. The term "cancer" further encompasses primary and metastatic cancers.  
25

Non-limiting examples of solid tumors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical  
30

cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; skin cancer, including e.g., malignant melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; soft tissue sarcoma; and thyroid carcinoma.

Non-limiting examples of hematologic malignancies include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's lymphoma; non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma; T-cell lymphoma; multiple myeloma (MM); Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes.

In some embodiment, exemplary hematologic malignancies include leukemia, such as acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML); multiple myeloma (MM); and lymphoma, such as Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, B-cell lymphoma, T-cell lymphoma, and diffuse large B-cell lymphoma (DLBCL).

The compound of formula (I) and/or a pharmaceutically acceptable salt described herein can be used to achieve a beneficial therapeutic or prophylactic effect, for example, in subjects with cancer.

In addition, the compound of formula (I) (e.g., any of those described herein) and/or a pharmaceutically acceptable salt thereof described herein may be used in combination with additional active ingredients in the treatment of cancer. The additional active ingredients may be coadministered separately with the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein or included with such an ingredient in a pharmaceutical composition according to the disclosure, such as a fixed-dose combination drug product. In an exemplary embodiment, additional active ingredients are those that are known or discovered to be effective in the treatment of diseases induced by IDH mutation, such as another mutant IDH inhibitor or a compound active against another target associated with the particular disease. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein), decrease one or more side effects, or

decrease the required dose of the compound of formula (I) and/or a pharmaceutically acceptable salt thereof described herein.

In some embodiments, the compound of formula (I) (e.g., any of those described herein) and/or a pharmaceutically acceptable salt thereof described herein is administered in conjunction with an anti-neoplastic agent. As used herein, the term "anti-neoplastic agent" refers to any agent that is administered to a subject with cancer for purposes of treating the cancer. Nonlimiting examples anti-neoplastic agents include: radiotherapy; immunotherapy; DNA damaging chemotherapeutic agents; and chemotherapeutic agents that disrupt cell replication.

Non-limiting examples of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, mitoxantrone, idarubicin, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitabine, gemcitabine, fludarabine, cytarabine, azacitidine(VIDAZA®); mercaptopurine, thioguanine, pentostatin, and hydroxyurea).

Chemotherapeutic agents that disrupt cell replication include: paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); proteasome inhibitors (e.g., bortezomib); NF-kappa B inhibitors, including inhibitors of I kappa B kinase; antibodies which bind to proteins overexpressed in cancers and thereby downregulate cell replication (e.g., trastuzumab, rituximab, cetuximab, and bevacizumab); and other inhibitors of proteins or enzymes known to be upregulated, over-expressed or activated in cancers, the inhibition of which downregulates cell replication.

## EXAMPLES

The examples below are intended to be exemplary and should not be considered to be limiting in any way. Efforts have been made to ensure accuracy with respect to numbers used (for example, amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric. All MS data was determined by agilent 6120 or agilent 1100. All NMR data were generated using a Varian 400-MR machine. All reagents, except

intermediates, used in this invention are commercially available. All compound names except the reagents were generated by Chemdraw 12.0.

If there is any atom with empty valence(s) in any one of the structures disclosed herein, the empty balance(s) is(are) the hydrogen atom(s) which is(are) omitted for convenience purpose.

In the present application, in the case of inconsistency of the structure and name of a compound, when the two of which are both given for the compound, it is subject to the structure of the compound, unless the context shows that the structure of the compound is incorrect and the name is correct.

In the following examples, the abbreviations below are used:

AcOK	potassium acetate
BAST	bis(2-methoxyethyl)aminosulfur trifluoride
BINAP	(±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
t-BuONa	sodium tert-butoxide
(n-Bu <sub>3</sub> Sn) <sub>2</sub>	1,1,1,2,2,2-hexabutyl-distannane
(S)-CBS	(S)-3,3-diphenyl-1-methylpyrrolidino[1,2-c]-1,3,2-oxazaborole
CD <sub>3</sub> OD	methanol-d <sub>4</sub>
DAST	diethylaminosulphur trifluoride
DCM	dichloromethane
DIEA	N,N-diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO-d <sub>6</sub>	dimethyl sulfoxide-d <sub>6</sub>
EA/ EtOAc	ethyl acetate
Et <sub>3</sub> N	triethylamine
EtOH	ethanol
Et <sub>2</sub> Zn	diethyl zinc
g	gram
HC(OMe) <sub>3</sub>	trimethyl orthoformate
L	litre
LiHMDS	lithium bis(trimethylsilyl)amide
M	mol/L
MeOH	methanol
MeCN	acetonitrile
mg	milligram
mL	milliliter

mmol	millimole
Mol	mole
NaBH(OAc) <sub>3</sub>	sodium triacetoxyborohydride
NaOMe	sodium methoxide
NaOEt	sodium ethoxide
NCS	N- chlorosuccinimide
NFSI	N- fluorobenzenesulfonimide
PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	bis(triphenylphosphine)palladium(II) dichloride
Pd <sub>2</sub> (dba) <sub>3</sub>	tris(dibenzylideneacetone)dipalladium(0)
Pd(dppf)Cl <sub>2</sub>	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Pd(dppf)Cl <sub>2</sub> ·CH <sub>2</sub> Cl <sub>2</sub>	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex
Pd(PPh <sub>3</sub> ) <sub>4</sub>	tetrakis(triphenylphosphine)palladium(0)
PE	petroleum ether
Selectfluor®	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate),
TBAF	tetrabutylammonium fluoride
TBSOTf	tert-butyltrimethylsilyltrifluoromethanesulfonate
TFA	trifluoroacetic acid
Tf <sub>2</sub> O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TsOH·H <sub>2</sub> O	4-methylbenzenesulfonic acid monohydrate

### Example 1

#### Preparation of intermediates

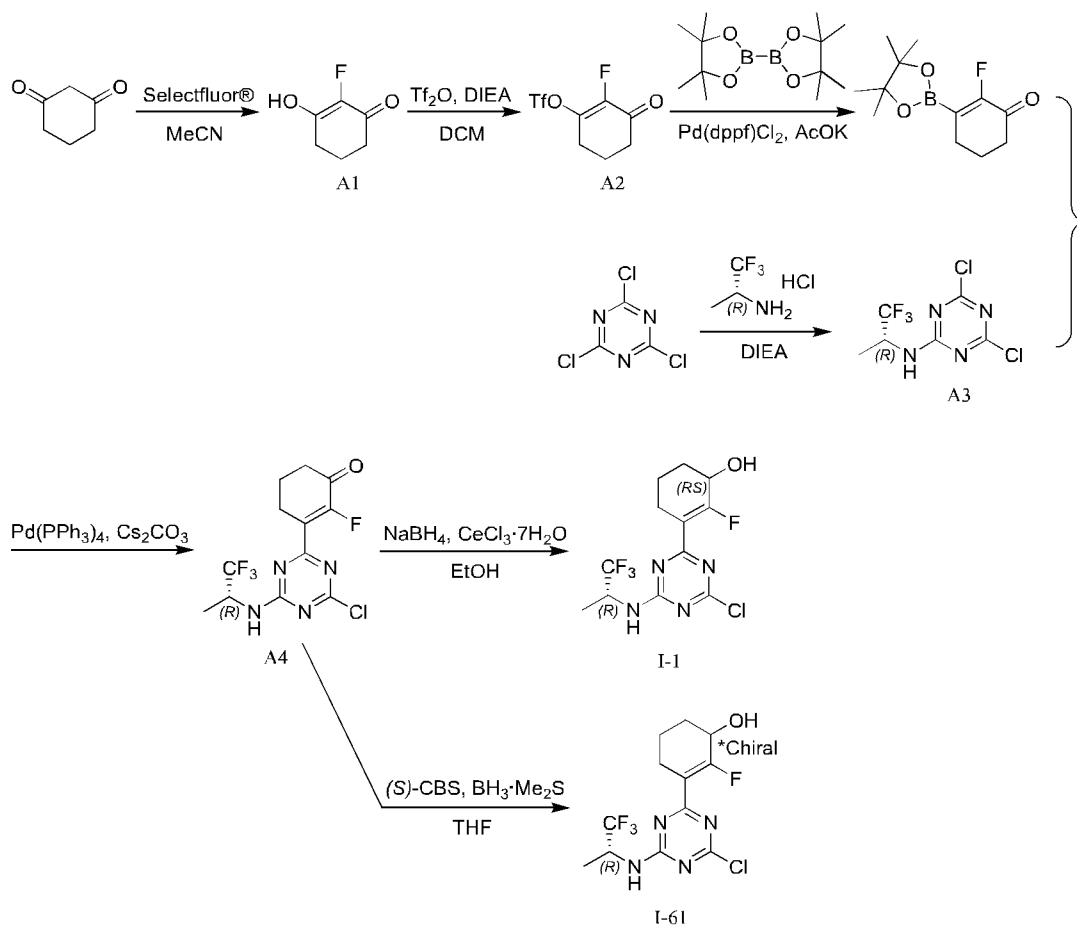
##### Intermediate I-1

3-(4-Chloro-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-ol and

5

##### Intermediate I-61

(\*)3-(4-Chloro-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-ol



### (A) 2-Fluoro-3-hydroxycyclohex-2-en-1-one (A1)

A mixture of cyclohexane-1,3-dione (30 g, 268 mmol) and Selectfluor® (94.8 g, 268 mmol) in MeCN (1.2 L) was stirred at 70 °C for 96 hours under nitrogen atmosphere. Then, the mixture was concentrated in vacuo. The residue was dissolved in DCM (1.2 L) and filtered. The filtrate was concentrated in vacuo and purified by flash column chromatography (eluting with gradient PE/EA= 100:0-0:100) to give compound A1 as white solid (7.7 g, yield: 22%). MS (m/z): 131.1 [M+H]<sup>+</sup>

### (B) 2-Fluoro-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (A2)

Under nitrogen atmosphere, compound A1 (208 mg, 1.6 mmol) was dissolved in DCM and cooled to 0°C. Then, DIEA (415 mg, 3.2 mmol) and Tf<sub>2</sub>O (540 mg, 1.92 mmol) were added at 0°C and the mixture was stirred for 2 hours at 0°C under nitrogen atmosphere. After the reaction was completed, it was quenched by the addition of water and extracted with DCM. The organic layer was collected, condensed and purified by flash column chromatography (eluting with PE/EA) to give compound A2 as yellow oil (220 mg, yield: 52.5%). MS (m/z): 263.0 [M+H]<sup>+</sup>

### (C) (R)-4,6-dichloro-N-(1,1,1-trifluoropropan-2-yl)-1,3,5-triazin-2-amine (A3)

A solution of 2,4,6-trichloro-1,3,5-triazine (9.1 g, 49.3 mmol) in dry THF was cooled to 0 °C and (R)-1,1,1-trifluoropropan-2-amine hydrochloride (7.37 g, 49.3 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. After reaction was completed, the mixture was adjusted to pH = 7 by the addition of saturated NaHCO<sub>3</sub> aqueous solution and extracted with EtOAc. The organic layer was collected, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give compound A3 as colorless oil (7.8 g, yield: 60.6%). MS (m/z): 260.9[M+H]<sup>+</sup>

**(D) (R)-3-(4-chloro-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-one (A4)**

Under nitrogen atmosphere, a mixture of compound A2 (4.0 g, 15.3 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (4.3 g, 16.8 mmol), AcOK (3.8 g, 38.3 mmol), Pd(dppf)Cl<sub>2</sub> (0.63 g, 0.77 mmol) in 1,4-dioxane (40 mL) was stirred at reflux for 2 hours. Then, the reaction mixture was cooled to room temperature, then was added compound A3 (4.0 g, 15.3 mmol), Cs<sub>2</sub>CO<sub>3</sub> (14.4 g, 38.3 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.89 g, 0.77 mmol) and water (8 mL) in sequence. The reaction was stirred at 80 °C for another 2 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give compound A4 as white solid (0.8 g, yield: 15.4%). MS (m/z): 339.0[M+H]<sup>+</sup>

**(E) 3-(4-Chloro-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-ol (I-1)**

To a flask were added compound A4 (1150 mg, 3.41 mmol), CeCl<sub>3</sub>·7H<sub>2</sub>O (1269 mg, 3.41 mmol) and EtOH (20 mL). The mixture was cooled to 0 °C, NaBH<sub>4</sub> (130 mg, 3.41 mmol) was added and the mixture was stirred at 0 °C for 2 hours. After the reaction was completed, the mixture was quenched by the addition of saturated NH<sub>4</sub>Cl aqueous solution (10 mL) and water (50 mL) and extracted with EtOAc. The organic layer was collected, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give I-1 as white solid (800 mg, yield: 68.9%). MS (m/z): 341.2 [M+H]<sup>+</sup>

**(F) (\*3-(4-Chloro-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-ol (I-61)**

Under nitrogen atmosphere, to dry THF (5 mL) was added 1 mol/L (S)-CBS/THF solution (2.4 mL, 2.4 mmol) under ice bath cooling °C, then 2 mol/L BH<sub>3</sub>·Me<sub>2</sub>S/THF solution (2.4 mL, 4.8 mmol) was added in one-portion. After stirred for 2 minutes, to the above solution was added compound A4 (800 mg, 2.4 mmol) in THF (3 mL) dropwise. After stirring under ice bath



cooling<sup>o</sup>C for 1 hour, to the reaction mixture was added MeOH (0.5 mL), EtOAc (10 mL) and water (20 mL). The organic layer was collected. The aqueous phase was extracted with EtOAc (10 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered. The filtrate was condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give Intermediate I-61 as white solid (360 mg). MS (m/z): 341.2 [M+H]<sup>+</sup>

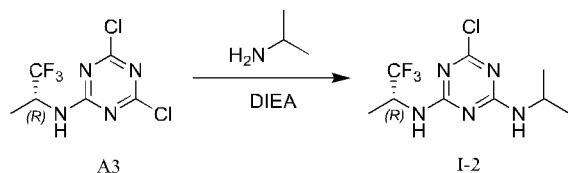
The compounds in the below table were prepared according to the procedure of Intermediate I-1 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by the POSITA:

Intermediate	Structure	MS (M+H) <sup>+</sup>	Intermediate	Structure	MS (M+H) <sup>+</sup>
I-22		314.0	I-25		323.0
I-23		279.1	I-80		285.0
I-24		265.1			

10

### Intermediate I-2

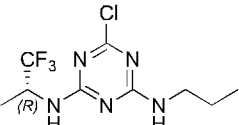
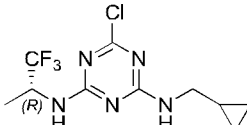
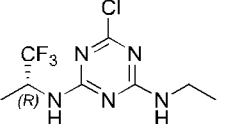
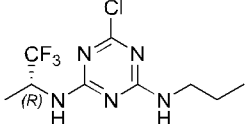
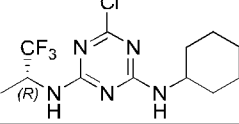
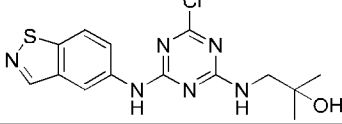
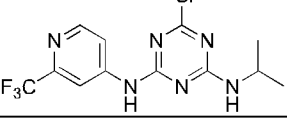
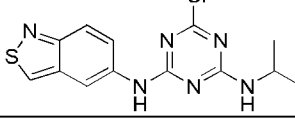
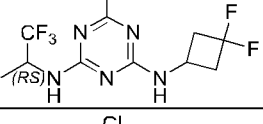
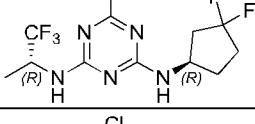
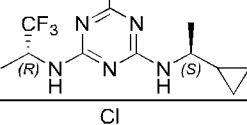
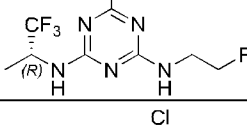
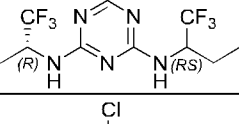
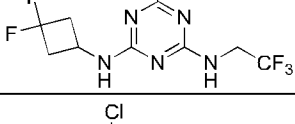
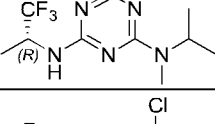
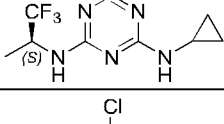
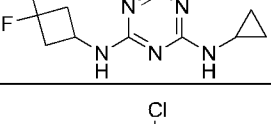
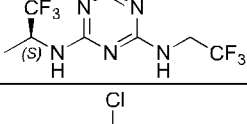
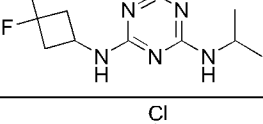
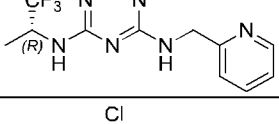
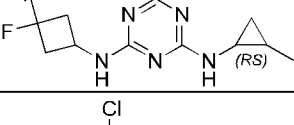
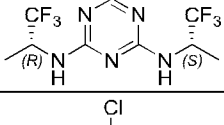
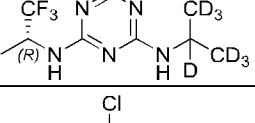
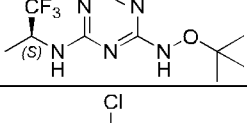
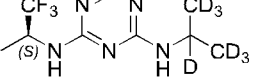
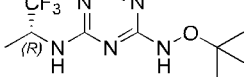
#### (R)-6-Chloro-N<sup>2</sup>-isopropyl-N<sup>4</sup>-(1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine



To a sealed tube was added compound A3 (3.5 g, 13.4 mmol), propan-2-amine (872 mg, 14.7 mmol), DIEA (3.5 g, 26.8 mmol) and THF (20 mL) in sequence, and the mixture was stirred at 50<sup>o</sup>C overnight. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to give Intermediate I-2 as white solid (3.8 g, yield: 100%). MS (m/z): 284.0 [M+H]<sup>+</sup>

The compounds in the below table were prepared according to the procedure of Intermediate I-2 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

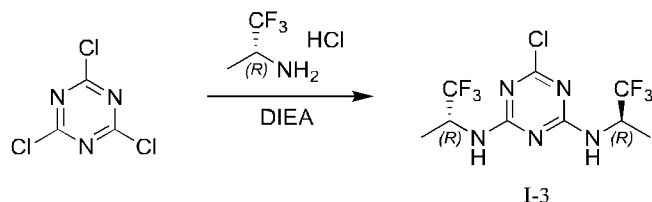
Inter- mediate	Structure	MS (M+H) <sup>+</sup>	Inter- mediate	Structure	MS (M+H) <sup>+</sup>
I-7		314.0	I-50		318.0
I-8		312.0	I-51		321.0
I-9		332.0	I-54		332.0
I-11		346.0	I-55		362.1
I-12		310.0	I-71		284.0
I-13		298.1	I-72		320.4
I-14		346.0	I-73		308.1
I-15		296.0	I-74		296.1
I-16		282.0	I-75		350.9
I-17		300.0	I-76		323.9

I-18		284.0	I-77		296.0
I-19		270.0	I-78		284.0
I-20		324.1	I-79		351.0
I-21		333.0	I-81		321.0
I-30		332.0	I-82		346.0
I-31		310.0	I-83		288.0
I-33		352.2	I-84		318.0
I-35		298.1	I-85		282.2
I-36		276.0	I-86		324.0
I-37		278.0	I-87		333.0
I-38		290.0	I-89		338.0
I-39		291.1	I-90		314.1
I-40		291.1	I-91		314.1

I-42		285.1	I-101		318.0
I-49		318.0	I-102		318.1

### Intermediate I-3

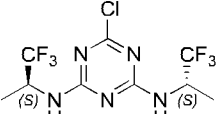
#### 6-Chloro-N<sup>2</sup>,N<sup>4</sup>-bis((R)-1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine



- 5 At 0°C, to a flask were added 1,4-dioxane (50 mL), 2,4,6-trichloro-1,3,5-triazine (1.84 g, 10 mmol), (R)-1,1,1-trifluoropropan-2-amine hydrochloride (2.99 g, 20 mmol) and DIEA (5.17 g, 40 mmol). The reaction was heated to 60 °C and stirred for 4 hours. After the reaction was completed, the mixture was condensed and purified by flash column chromatography (eluting with gradient water/MeOH = 100:0:0:100) to give Intermediate I-3 as yellow solid (2.50 g, yield: 10 74%). MS (m/z): 338.0 [M+H]<sup>+</sup>

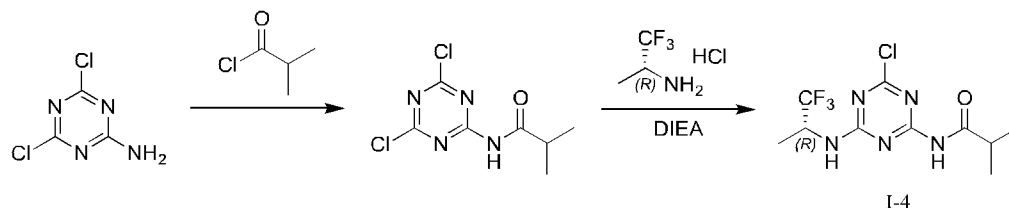
The compounds in the below table were prepared according to the procedure of Intermediate I-3 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Inter- mediate	Structure	MS (M+H) <sup>+</sup>	Inter- mediate	Structure	MS (M+H) <sup>+</sup>
I-6		254.1	I-34		230.1
I-10		326.0	I-106		446.0

I-32		338.0					
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### Intermediate I-4

#### (R)-N-(4-Chloro-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)isobutyramide

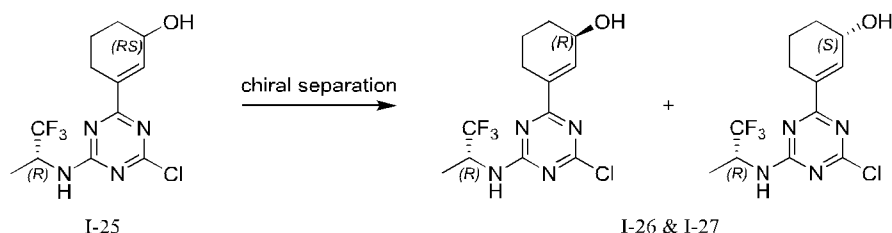


- 5 A mixture of 4,6-dichloro-1,3,5-triazin-2-amine (1 g, 6.06 mmol) in isobutyryl chloride (5 mL) was stirred at 100 °C for 2 hours. After the reaction was completed, the mixture was cooled to room temperature and concentrated to dryness in vacuo to afford N-(4,6-dichloro-1,3,5-triazin-2-yl)isobutyramide as yellow solid. Then, to 1,4-dioxane (10 mL) was added N-(4,6-dichloro-1,3,5-triazin-2-yl)isobutyramide obtained above,
- 10 (R)-1,1,1-trifluoropropan-2-amine hydrochloride (900 mg, 6.06 mmol) and DIEA (2.34 g, 18.18 mmol). The mixture was heated to reflux and stirred for 2 hours. After the reaction was completed, the mixture was quenched by the addition of water, extracted with EtOAc (20 mL). The organic layer was collected, concentrated under reduced pressure and purified by flash column chromatography (eluting with PE/EA) to give Intermediate I-4 (80 mg). MS (m/z): 312.1
- 15  $[M+H]^+$

### Intermediates I-26 and I-27

#### 3-(4-Chloro-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol optically pure diastereoisomers

20



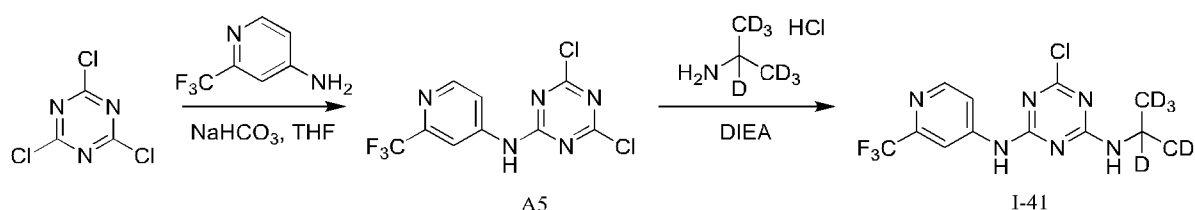
Intermediates I-26 and I-27 were obtained by resolution of Intermediate I-25 using chiral HPLC (chiral HMPL conditions: column: AS-H; mobile phase: n-heptane/isopropanol = 80:20; flow

rate: 0.5 mL/min; detection wavelength: UV 254 nm). The isomer obtained from the first eluent (RT = 1.703 min) was named as I-26, de% = 100%, MS (m/z): 400.1 [M+H]<sup>+</sup>. The isomer obtained from the second eluent (RT = 2.067 min) was named as I-27, de% = 99.4%, MS (m/z): 400.1 [M+H]<sup>+</sup>.

5

### Intermediate I-41

#### 6-Chloro-N<sup>2</sup>-(propan-2-yl-d<sub>7</sub>)-N<sup>4</sup>-(2-(trifluoromethyl)pyridin-4-yl)-1,3,5-triazine-2,4-diamine



10

#### (A) 4,6-Dichloro-N-(2-(trifluoromethyl)pyridin-4-yl)-1,3,5-triazin-2-amine (A5)

To a solution of 2,4,6-trichloro-1,3,5-triazine (1.84 g, 10 mmol) and 2-(trifluoromethyl)pyridin-4-amine (1.62 g, 10 mmol) in dry THF (20 mL) was added NaHCO<sub>3</sub> (1.68 g, 20 mmol) at 0 °C. The mixture was stirred at room temperature for 16 hours. After reaction was completed, the mixture was filtered. The filtrate was condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give compound A5 as white solid (2.68 g, yield: 86%). MS (m/z): 309.9 [M+H]<sup>+</sup>

15

#### (B) 6-Chloro-N<sup>2</sup>-(propan-2-yl-d<sub>7</sub>)-N<sup>4</sup>-(2-(trifluoromethyl)pyridin-4-yl)-1,3,5-triazine-2,4-diamine

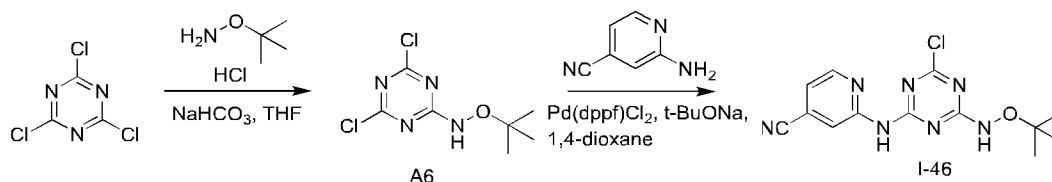
To a sealed tube were added compound A5 (465 mg, 1.5 mmol), propan-d<sub>7</sub>-2-amine hydrochloride (154 mg, 1.5 mmol), DIEA (388 mg, 3.0 mmol) and 1,4-dioxane (20 mL) in sequence. The mixture was heated to 60 °C and stirred for 5 hours. After reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give Intermediate I-41 as white solid (485 mg, yield: 95%). MS (m/z): 340.0 [M+H]<sup>+</sup>

25

The compounds in the below table were prepared according to the procedure of Intermediate I-41 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Inter- mediate	Structure	MS (M+H) <sup>+</sup>	Inter- mediate	Structure	MS (M+H) <sup>+</sup>
I-43		268.0	I-94		361.1
I-44		308.0	I-96		329.0
I-45		304.0	I-97		349.1
I-53		334.0	I-98		381.1
I-59		329.0	I-99		385.0
I-63		363.0	I-100		366.9
I-66		363.0	I-101		318.0
I-68		364.0	I-103		428.9
I-92		321.1	I-104		416.9
I-93		335.1	I-105		362.1

**Intermediate I-46****2-((4-(Tert-butoxyamino)-6-chloro-1,3,5-triazin-2-yl)amino)isonicotinonitrile**



**(A) O-(Tert-butyl)-N-(4,6-dichloro-1,3,5-triazin-2-yl)hydroxylamine (A6)**

To a solution of 2,4,6-trichloro-1,3,5-triazine (0.92 g, 5 mmol) and O-(tert-butyl)hydroxylamine hydrochloride (0.63 g, 5 mmol) in dry THF (50 mL) was added NaHCO<sub>3</sub> (1.26 g, 15 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 hours. After the reaction was completed, the mixture was filtered. The filtrate was condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give compound A6 as colorless oil (0.83 g, yield: 80%). MS (m/z): 237.0 [M+H]<sup>+</sup>

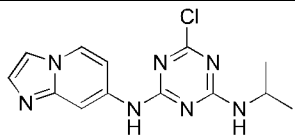
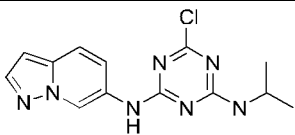
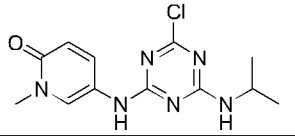
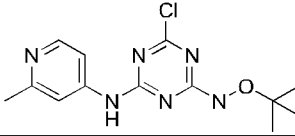
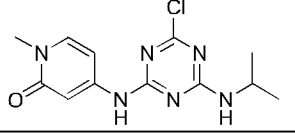
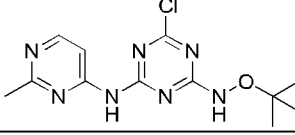
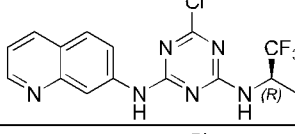
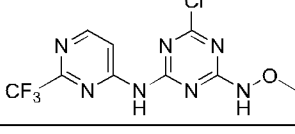
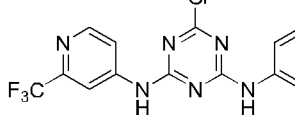
**(B) 2-((4-(Tert-butoxyamino)-6-chloro-1,3,5-triazin-2-yl)amino)isonicotinonitrile**

To a sealed tube were sequentially added compound A6 (0.83 g, 4.0 mmol), 2-aminoisonicotinonitrile (0.48 g, 4.0 mmol), Pd(dppf)Cl<sub>2</sub> (0.15 g, 0.2 mmol), t-BuONa (0.77 g, 8.0 mmol) and 1,4-dioxane (10 mL). The mixture was heated to 90°C and stirred for 3 hours. After reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give Intermediate I-46 as yellow solid (109 mg, yield: 8%). MS (m/z): 320.0 [M+H]<sup>+</sup>

The compounds in the below table were prepared according to the procedure of Intermediate I-46 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

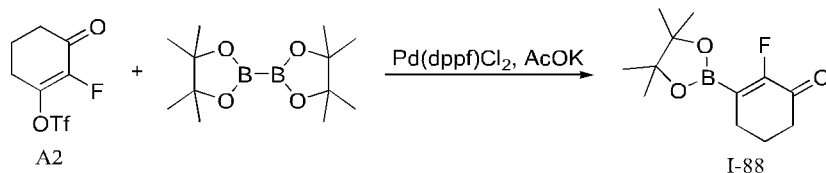
Inter-mediate	Structure	MS (M+H) <sup>+</sup>	Inter-mediate	Structure	MS (M+H) <sup>+</sup>
I-47		329.0	I-65		313.0
I-48		315.0	I-67		283.0
I-52		305.0	I-69		304.0
I-56		358.0	I-70		308.0



I-57		304.1	I-5		304.0
I-58		295.0	I-28		309.0
I-60		295.1	I-29		310.0
I-62		369.0	I-95		363.9
I-64		385.0			

### Intermediate I-88

#### 2-Fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-one



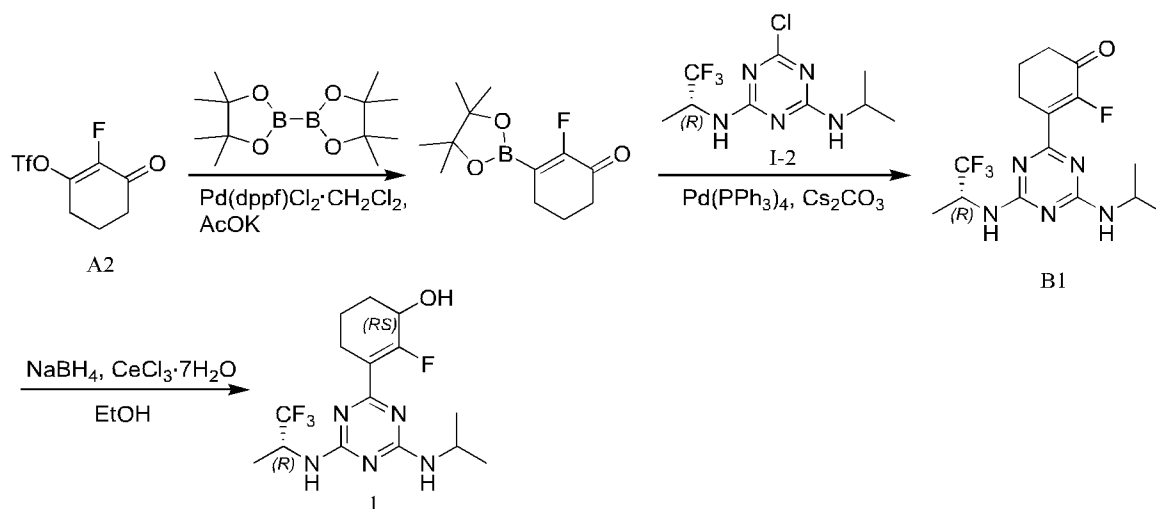
- 5 Under nitrogen atmosphere, to a flask were added compound A2 (80 g, 305 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (80 g, 315 mmol), AcOK (74.8 g, 763 mmol), Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (12.4 g, 15.3 mmol) and 1,4-dioxane (1.4 L) in sequence. The mixture was stirred at 90 °C for 4 hours, then cooled to room temperature, and filtered. The filtrate was condensed and purified by flash column chromatography (eluting with PE/EA = 4/1)
- 10 to give Intermediate I-88 as yellow solid (76 g, yield 100%). MS (m/z): 159.0 [M+H]<sup>+</sup>
- <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 2.47- 2.36 (m, 4H), 1.91-1.82 (m, 2H), 1.22 (s, 12H).

### Example 2

#### Synthesis of Compounds 1-87, 89-184, 186-301

#### 15 Compound 1

#### 2-Fluoro-3-(4-(isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol



**(A) (R)-2-fluoro-3-(4-(isopropylamino)-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one (B1)**

Under nitrogen atmosphere, to a flask were added compound A2 (220 mg, 0.84 mmol),  
 5 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (234 mg, 0.92 mmol), AcOK (206 mg, 2.10 mmol), Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (32 mg, 0.04 mmol) and 1,4-dioxane (20 mL) in sequence and stirred at reflux for 16 hours. Then, the mixture was cooled to room temperature, and was added Intermediate I-2 (238 mg, 0.84 mmol), Cs<sub>2</sub>CO<sub>3</sub> (682 mg, 2.1 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (46.2 mg, 0.04 mmol) and water (4 mL) in sequence, and stirred at 80°C for 2 hours. After the reaction was  
 10 completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give compound B1 as white solid (160 mg, yield: 52.8%). MS (m/z): 362.1 [M+H]<sup>+</sup>

**(B) 2-Fluoro-3-(4-(isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol**

15 To a flask were added compound B1 (80 mg, 0.22 mmol), CeCl<sub>3</sub>·7H<sub>2</sub>O (107 mg, 0.29 mmol) and EtOH (5 mL). The mixture was cooled to 0 °C. Then, NaBH<sub>4</sub> (11 mg, 0.29 mmol) was added and the mixture was stirred at 0 °C for 2 hours. After the reaction was completed, the mixture was quenched by the addition of saturated NH<sub>4</sub>Cl aqueous solution (2 mL) and water (20 mL), and extracted with EtOAc. The organic layer was collected, condensed and purified by flash column  
 20 chromatography (eluting with gradient PE/EA = 100:0-0:100) to give Compound 1 as a white solid (61 mg, yield: 76.3%). MS (m/z): 364.1 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 4.99-4.87 (m, 1H), 4.33-4.23 (m, 1H), 4.19-4.07 (m, 1H), 2.61-2.47 (m, 1H), 2.40-2.24 (m, 1H), 1.89-1.73 (m, 3H), 1.70-1.61 (m, 1H), 1.38-1.31 (m, 3H), 1.22-1.16 (m, 6H).

The compounds in the below table were prepared according to the procedure of Compound 1 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter- mediate
2		418.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.88 (m, 2H), 4.36-4.24 (m, 1H), 2.66-2.50 (m, 1H), 2.41-2.31 (m, 1H), 1.97-1.60 (m, 4H), 1.38-1.30 (m, 6H).	I-3
3		392.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.06-4.90 (m, 1H), 4.61-4.46 (m, 1H), 4.37-4.21 (m, 1H), 4.04-3.87 (m, 2H), 3.85-3.76 (m, 1H), 3.73-3.60 (m, 1H), 2.66-2.49 (m, 1H), 2.44-2.14 (m, 2H), 2.01-1.60 (m, 5H), 1.45-1.30 (m, 3H).	I-8
4		412.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.87 (m, 1H), 4.37-4.15 (m, 2H), 3.05-2.84 (m, 2H), 2.77-2.49 (m, 3H), 2.42-2.24 (m, 1H), 1.96-1.56 (m, 4H), 1.44-1.31 (m, 3H).	I-30
5		406.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.37-4.22 (m, 3H), 3.02-2.86 (m, 4H), 2.73-2.50 (m, 5H), 2.41-2.25 (m, 1H), 1.91-1.72 (m, 3H), 1.72-1.62 (m, 1H).	I-10
6		426.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.90 (m, 1H), 4.51-4.41 (m, 1H), 4.34-4.25 (m, 1H), 2.62-2.47 (m, 2H), 2.38-2.17 (m, 3H), 2.14-1.96 (m, 2H), 1.90-1.75 (m, 4H), 1.70-1.61 (m, 1H), 1.40-1.31 (m, 3H).	I-11
7		376.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.89 (m, 1H), 4.33-4.24 (m, 1H), 4.19-4.06 (m, 1H), 2.63-2.47 (m, 1H), 2.40-2.25 (m, 1H), 1.92-1.60 (m, 4H), 1.40-1.30 (m, 3H), 1.23-1.15 (m, 6H).	I-15
8		390.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.99-4.87 (m, 1H), 4.36-4.22 (m, 1H), 3.60-3.40 (m, 1H), 2.66-2.47 (m, 1H), 2.40-2.26 (m, 1H), 1.91-1.62 (m, 4H), 1.37-1.31 (m, 3H), 1.27-1.21 (m, 3H), 1.01-0.85 (m, 1H), 0.55-0.15 (m, 4H).	I-31

9		392.3	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 4.99-4.88 (m, 1H), 4.42-4.34 (m, 1H), 4.18-4.07 (m, 1H), 2.40-2.17 (m, 2H), 1.91-1.80 (m, 1H), 1.62-1.53 (m, 1H), 1.38-1.31 (m, 3H), 1.22-1.15 (m, 6H), 1.06 (s, 3H), 1.00 (s, 3H).	I-2
10		390.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.89 (m, 1H), 4.37-4.16 (m, 2H), 2.64-2.47 (m, 1H), 2.40-2.24 (m, 1H), 2.04-1.44 (m, 12H), 1.39-1.31 (m, 3H).	I-12
11		418.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.04-4.90 (m, 2H), 4.35-4.24 (m, 1H), 2.66-2.52 (m, 1H), 2.43-2.27 (m, 1H), 1.95-1.60 (m, 4H), 1.43-1.31 (m, 6H).	I-3
12		378.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.89 (m, 1H), 4.35-4.23 (m, 1H), 3.26-3.05 (m, 2H), 2.66-2.48 (m, 1H), 2.42-2.25 (m, 1H), 1.97-1.59 (m, 5H), 1.41- 1.30 (m, 3H), 0.96-0.88 (m, 6H).	I-13
13		426.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.89 (m, 1H), 4.35-4.23 (m, 1H), 3.63-3.40 (m, 2H), 2.65-2.51 (m, 3H), 2.47-2.21 (m, 4H), 1.89-1.61 (m, 4H), 1.39-1.31 (m, 3H).	I-14
14		418.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.90 (m, 2H), 4.36-4.23 (m, 1H), 2.67-2.49 (m, 1H), 2.42-2.26 (m, 1H), 1.94-1.61 (m, 4H), 1.40-1.31 (m, 6H).	I-32
15		432.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.04-4.93 (m, 1H), 4.82-4.70 (m, 1H), 4.34-4.23 (m, 1H), 2.65-2.51 (m, 1H), 2.43-2.28 (m, 1H), 1.91-1.74 (m, 4H), 1.71-1.61 (br, 2H), 1.40-1.31 (m, 3H), 1.04-0.93 (m, 3H).	I-33
16		380.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.12-4.92 (m, 1H), 4.80-4.53 (m, 1H), 4.37-4.26 (m, 1H), 2.87-2.77 (m, 1H), 2.68-2.51 (m, 1H), 2.46-2.27 (m, 1H), 1.97- 1.60 (m, 4H), 1.43-1.31 (m, 3H), 1.2-1.06 (m, 1H), 1.02-0.87 (m, 1H).	I-1
17		380.4	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.92 (m, 1H), 4.22-4.07 (m, 2H), 2.50-2.27 (m, 2H), 1.95-1.81 (m, 3H), 1.76-1.66 (m, 1H), 1.41-1.32 (m, 3H), 1.23-1.18 (m, 6H).	I-2

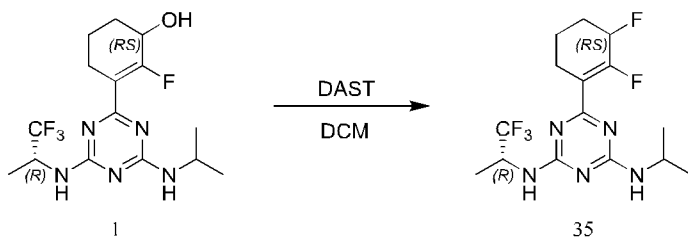
18		419.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.02-4.87 (m, 2H), 2.68-2.51 (m, 1H), 2.44-2.28 (m, 1H), 1.92-1.63 (m, 4H), 1.42-1.30 (m, 6H).	I-3
19		407.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.38-4.15 (m, 2H), 3.05-2.85 (m, 4H), 2.72-2.48 (m, 5H), 2.40-2.26 (m, 1H), 1.90-1.61 (m, 4H).	I-10
20		420.2	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.52-4.38 (m, 1H), 4.33-4.17 (m, 2H), 2.99-2.84 (m, 4H), 2.71-2.48 (m, 5H), 2.37-2.23 (m, 1H), 2.01-1.82 (m, 3H), 1.74-1.60 (m, 3H).	I-10
21		432.3	$^1\text{H NMR}$ (400MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.02-4.89 (m, 2H), 4.53-4.41 (m, 1H), 2.77-2.62 (m, 1H), 2.40-2.27 (m, 1H), 2.02-1.83 (m, 3H), 1.74-1.61 (m, 3H), 1.39-1.32 (m, 6H).	I-3
22		421.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.36-4.16 (m, 2H), 3.00-2.84 (m, 4H), 2.73-2.50 (m, 5H), 2.39-2.21 (m, 1H), 2.01-1.82 (m, 3H), 1.75-1.59 (m, 3H).	I-10
23		365.2	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.99-4.86 (m, 1H), 4.20-4.07 (m, 1H), 2.61-2.47 (m, 1H), 2.37-2.25 (m, 1H), 1.88-1.62 (m, 4H), 1.37-1.29 (m, 3H), 1.20-1.17 (m, 6H).	I-2
24		427.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.99-4.86 (m, 1H), 4.34-4.15 (m, 1H), 2.97-2.83 (m, 2H), 2.73-2.51 (m, 3H), 2.37-2.25 (m, 1H), 2.01-1.82 (m, 3H), 1.72-1.60 (m, 3H), 1.39-1.13 (m, 3H).	I-9
25		310.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.36-4.24 (m, 1H), 4.24-4.00 (m, 2H), 2.62-2.43 (m, 1H), 2.39-2.22 (m, 1H), 1.91-1.82 (m, 2H), 1.82-1.72 (m, 1H), 1.70-1.60 (m, 1H), 1.19 (s, 12H).	I-34
26		378.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.19-4.88 (m, 2H), 4.38-4.22 (m, 1H), 2.96 (s, 3H), 2.68-2.49 (m, 1H), 2.43-2.28 (m, 1H), 1.91-1.83 (m, 2H), 1.83-1.70 (m, 1H), 1.70-1.59 (m, 1H), 1.35 (d, $J = 5.3$ Hz, 3H), 1.16 (d, $J = 6.5$ Hz, 6H).	I-35

27		356.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.42-4.13 (m, 2H), 3.02-2.86 (m, 2H), 2.83-2.46 (m, 4H), 2.44-2.21 (m, 1H), 1.92-1.83 (m, 2H), 1.83-1.60 (m, 2H), 0.82-0.67 (m, 2H), 0.60-0.45 (m, 2H).	I-36
28		358.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.36-4.20 (m, 2H), 4.20-4.04 (m, 1H), 3.01-2.84 (m, 2H), 2.71-2.45 (m, 3H), 2.40-2.23 (m, 1H), 1.90-1.83 (m, 2H), 1.83-1.60 (m, 2H), 1.20 (s, 6H).	I-37
29		372.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.98-4.88 (m, 1H), 2.65-2.43 (m, 1H), 2.41-2.23 (m, 1H), 1.92-1.70 (m, 3H), 1.70-1.59 (m, 1H), 1.37-1.29 (m, 3H).	I-39
30		372.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.97-4.89 (m, 1H), 2.70-2.42 (m, 1H), 2.41-2.21 (m, 1H), 1.90-1.72 (m, 3H), 1.69-1.59 (m, 1H), 1.37-1.29 (m, 3H).	I-40
31		412.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.02-4.89 (m, 1H), 4.38-4.14 (m, 2H), 3.03-2.86 (m, 2H), 2.80-2.49 (m, 3H), 2.44-2.26 (m, 1H), 1.95-1.59 (m, 4H), 1.41-1.31 (m, 3H).	I-9
32		412.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.03-4.90 (m, 1H), 4.38-4.16 (m, 2H), 3.02-2.86 (m, 2H), 2.82-2.50 (m, 3H), 2.43-2.25 (m, 1H), 1.94-1.60 (m, 4H), 1.42-1.32 (m, 3H).	I-54
33		364.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.02-4.90 (m, 1H), 4.38-4.22 (m, 1H), 4.18-4.04 (m, 1H), 2.66-2.49 (m, 1H), 2.39-2.20 (m, 1H), 2.03-1.58 (m, 4H), 1.42-1.29 (m, 3H), 1.23-1.10 (m, 6H).	I-71
34		431.0	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.93-8.75 (m, 2H), 7.98-7.93 (m, 1H), 7.83-8.77 (m, 1H), 4.37-4.29 (m, 1H), 2.72-2.60 (m, 1H), 2.47-2.35 (m, 341H), 1.92-1.85 (m, 2H), 1.84-1.75 (m, 1H), 1.73-1.65 (m, 1H), 1.32 (s, 9H).	I-75
200		384.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 9.55 (s, 1H), 7.91-7.78 (m, 1H), 7.64-7.48 (m, 1H), 7.33-7.13 (m, 1H), 6.62-6.47 (m, 1H), 4.41-4.14 (m, 2H), 2.72-2.32 (m, 2H), 1.91-1.63 (m, 4H), 1.29-1.20 (m, 6H).	I-5

205		390.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.59-8.34 (m, 2H), 4.39-4.28 (m, 1H), 2.74-2.61 (m, 1H), 2.55 (s, 3H), 2.51-2.37 (m, 1H), 1.98-1.66 (m, 4H), 1.31 (s, 9H).	I-29
219		444.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.05-4.86 (m, 2H), 3.49-3.39 (m, 1H), 2.73-2.58 (m, 1H), 2.53-2.38 (m, 1H), 2.22-2.09 (m, 1H), 1.39-1.32 (m, 6H), 1.03-0.94 (m, 1H), 0.78-0.68 (m, 1H), 0.51-0.40 (m, 3H).	I-3
229		401.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 9.34-9.19 (m, 1H), 8.60-8.36 (m, 1H), 7.73-7.54 (m, 2H), 4.39-4.30 (m, 1H), 4.26-4.15 (m, 1H), 2.72-2.56 (m, 1H), 2.48-2.33 (m, 1H), 1.93-1.63 (m, 4H), 1.29-1.21 (m, 6H).	I-81

### Compound 35

#### 6-(2,3-Difluorocyclohex-1-en-1-yl)-N<sup>2</sup>-isopropyl-N<sup>4</sup>-((R)-1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine



At 0 °C, Compound 1 (20 mg, 0.06 mmol) was dissolved in DCM (3 mL), and DAST (17 mg, 0.12 mmol) was added. The mixture was stirred at 0 °C for 2.5 hours. After the reaction was completed, the mixture was quenched by the addition of saturated NH<sub>4</sub>Cl aqueous solution (5 mL) and water (5 mL), and extracted with EtOAc. The organic layer was collected, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give the title compound as a white solid (14 mg, yield: 70%). MS (m/z): 366.2 [M+H]<sup>+</sup>

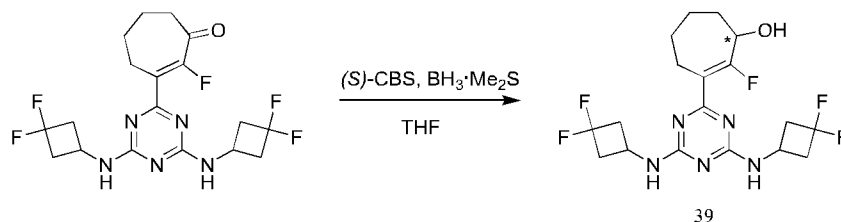
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 5.15-4.86 (m, 2H), 4.21-4.08 (m, 1H), 2.70-2.51 (m, 1H), 2.42-2.26 (m, 1H), 2.20-2.08 (m, 1H), 1.92-1.67 (m, 3H), 1.37-1.31 (m, 3H), 1.21-1.16 (m, 6H).

15 The compounds in the below table were prepared according to the procedure of Compound 35 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
36		348.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.16-6.94 (m, 1H), 5.25-5.06 (m, 1H), 5.05-4.89 (m, 1H), 4.27-4.06 (m, 1H), 2.63-2.26 (m, 2H), 1.95-1.63 (m, 4H), 1.39-1.30 (d, J = 5.2 Hz, 3H), 1.24-1.16 (m, 6H).	Comp. 124
37		348.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.26-7.00 (m, 1H), 5.08-4.85 (m, 2H), 4.26-4.07 (m, 1H), 2.87-2.70 (m, 1H), 2.68-2.53 (m, 1H), 2.44-2.26 (m, 2H), 1.95-1.80 (m, 2H), 1.36-1.30 (m, 3H), 1.20-1.16 (m, 6H).	Comp. 144
38		348.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.13-6.85 (m, 1H), 5.03-4.85 (m, 2H), 4.24-4.07 (m, 1H), 2.63-2.35 (m, 4H), 2.01-1.82 (m, 2H), 1.36-1.31 (m, 3H), 1.20-1.16 (m, 6H).	Com. 145

### Compound 39

#### (\*)-3-(4,6-Bis((3,3-difluorocyclobutyl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohept-2-en-1-ol



- 5 Under nitrogen atmosphere, 1 mol/L (S)-CBS/THF solution (1.4 mL, 1.4 mmol) was added to dry THF (5 mL) under ice bath cooling °C, then to the solution was added 2 mol/L BH<sub>3</sub>·Me<sub>2</sub>S/THF solution (1.4 mL, 2.8 mmol) in one-portion. After stirred for 2 minutes, 3-(4,6-bis((3,3-difluorocyclobutyl)amino)-1,3,5-triazin-2-yl)-2-fluoro cyclohept-2-en-1-one (prepared according to the procedure of Compound 1 using Intermediate I-10, 600 mg, 1.4 mmol)
- 10 in THF (3 mL) was added dropwise and the mixture was stirred in ice-bath for 1 hour. Then, MeOH (0.5 mL), EtOAc (10 mL) and water (20 mL) were added to the reaction mixture. The organic layer was collected. The aqueous was extracted with EtOAc (10 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give the title compound
- 15 as white solid (60 mg, yield: 10%). MS (m/z): 420.1 [M+H]<sup>+</sup>



$^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  4.52-4.38 (m, 1H), 4.33-4.17 (m, 2H), 2.99-2.84 (m, 4H), 2.71-2.48 (m, 5H), 2.37-2.23 (m, 1H), 2.01-1.82 (m, 3H), 1.74-1.60 (m, 3H).

5 The compounds in the below table were prepared according to the procedure of Compound 39 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	$^1\text{H}$ NMR	Inter-mediate
40		426.1	$^1\text{H}$ NMR (400MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.98-4.87 (m, 1H), 4.51-4.41 (m, 1H), 4.31-4.16 (m, 1H), 2.97-2.84 (m, 2H), 2.73-2.49 (m, 3H), 2.37-2.23 (m, 1H), 2.00-1.81 (m, 3H), 1.72-1.58 (m, 3H), 1.39-1.30 (m, 3H).	I-9
41		400.1	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.00-4.89 (m, 1H), 4.69-4.44 (m, 5H), 4.34-4.22 (m, 1H), 2.65- 2.50 (m, 1H), 2.40-2.25 (m, 1H), 1.89-1.57 (m, 4H), 1.38-1.29 (m, 3H).	I-72
42		388.2	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.00-4.89 (m, 1H), 4.33-4.21 (m, 1H), 3.13-2.99 (m, 1H), 2.62- 2.47 (m, 1H), 2.37-2.18 (m, 1H), 1.87-1.61 (m, 4H), 1.37-1.30 (m, 3H), 1.25-1.19 (m, 1H), 1.00- 0.71 (m, 5H).	I-73
43		376.1	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.51-4.18 (m, 5H), 3.01-2.82 (m, 2H), 2.71-2.45 (m, 3H), 2.38- 2.20 (m, 1H), 1.87-1.59 (m, 4H), 1.27-1.19 (m, 3H).	I-74
44		438.1	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.47-8.11 (m, 2H), 7.66 (s, 1H), 7.49-7.37 (m, 1H), 7.18-7.05 (m, 1H), 5.08-4.94 (m, 1H), 4.40- 4.27 (m, 1H), 2.75-2.61 (m, 1H), 2.51-2.37 (m, 1H), 1.92-1.66 (m, 4H), 1.43-1.37 (m, 3H).	I-56
45		384.1	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.37-8.29 (br, 1H), 8.29-8.16 (m, 1H), 7.65 (s, 1H), 7.47-7.38 (m, 1H), 7.15-6.99 (m, 1H), 4.37-4.18 (m, 2H), 2.74-2.56 (m, 1H), 2.51-2.34 (m, 1H), 1.90- 1.64 (m, 4H), 1.29-1.22 (m, 6H).	I-57

46		375.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.63-8.10 (m, 1H), 7.69-7.53 (m, 1H), 6.52 (d, J = 9.6 Hz, 1H), 4.36-4.24 (m, 1H), 4.22-4.04 (m, 1H), 3.57 (s, 3H), 2.68-2.50 (m, 1H), 2.43-2.28 (m, 1H), 1.89-1.61 (m, 4H), 1.23-1.16 (m, 6H).	I-58
47		409.2	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 8.48-8.19 (m, 1H), 8.14-8.04 (m, 1H), 7.65-7.46 (m, 1H), 4.38-4.26 (m, 1H), 2.73-2.58 (m, 1H), 2.49-2.34 (m, 1H), 1.91-1.64 (m, 4H), 1.32 (s, 9H).	I-59
48		375.2	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 7.50-7.42 (m, 1H), 7.26-7.20 (m, 1H), 6.81-6.68 (m, 1H), 4.36-4.13 (m, 2H), 3.48 (s, 3H), 2.74-2.55 (m, 1H), 2.46-2.32 (m, 1H), 1.89-1.62 (m, 4H), 1.27-1.17 (m, 6H).	I-60
49		356.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.39-4.18 (m, 2H), 2.99-2.86 (m, 2H), 2.80-2.46 (m, 4H), 2.39-2.23 (m, 1H), 1.89-1.82 (m, 2H), 1.81-1.62 (m, 2H), 0.79-0.67 (m, 2H), 0.55-0.48 (m, 2H).	I-36
50		370.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.45-4.14 (m, 2H), 3.05-2.82 (m, 2H), 2.79-2.23 (m, 5H), 1.91-1.61 (m, 4H), 1.18-0.45 (m, 6H).	I-38
51		358.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.35-4.20 (m, 2H), 4.20-4.06 (m, 1H), 2.98-2.86 (m, 2H), 2.70-2.45 (m, 3H), 2.38-2.23 (m, 1H), 1.89-1.82 (m, 2H), 1.81-1.60 (m, 2H), 1.19 (s, 6H).	I-37
52		371.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.99-4.87 (m, 1H), 4.33-4.23 (m, 1H), 2.64-2.45 (m, 1H), 2.40-2.21 (m, 1H), 1.89-1.71 (m, 3H), 1.70-1.58 (m, 1H), 1.36-1.30 (m, 3H).	I-39
53		371.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.98-4.88 (m, 1H), 4.35-4.19 (m, 1H), 2.63-2.44 (m, 1H), 2.44-2.21 (m, 1H), 1.93-1.70 (m, 3H), 1.70-1.53 (m, 1H), 1.39- 1.29 (m, 3H).	I-40
54		420.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.60-8.22 (m, 2H), 8.09-7.74 (m, 1H), 4.38-4.27 (m, 1H), 2.75- 2.58 (m, 1H), 2.48-2.33 (m, 1H), 1.91-1.75 (m, 3H), 1.73-1.64 (m, 1H).	I-41

55		365.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.36-4.15 (m, 2H), 3.02-2.81 (m, 2H), 2.73-2.41 (m, 3H), 2.40- 2.19 (m, 1H), 1.89-1.71 (m, 3H), 1.70-1.59 (m, 1H).	I-42
56		360.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.32-4.19 (m, 2H), 4.19-4.04 (m, 1H), 2.98-2.83 (m, 2H), 2.72- 2.43 (m, 3H), 2.39-2.21 (m, 1H), 1.80-1.70 (m, 1H), 1.68-1.58 (m, 1H), 1.25-1.11 (br, 6H).	I-37
57		348.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.16-7.44 (m, 2H), 4.38-4.24 (m, 1H), 4.24-4.10 (m, 1H), 3.84 (s, 3H), 2.69-2.49 (m, 1H), 2.47- 2.27 (m, 1H), 1.91-1.74 (m, 3H), 1.72-1.61 (m, 1H), 1.29-1.18 (m, 6H).	I-43
58		388.0	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.61-8.24 (m, 2H), 8.04-7.81 (m, 1H), 4.39-4.27 (m, 1H), 2.75- 2.58 (m, 1H), 2.51-2.31 (m, 1H), 1.92-1.75 (m, 3H), 1.73-1.64 (m, 1H).	I-44
59		348.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.39-8.25 (m, 2H), 7.86-7.79 (m, 1H), 7.13-7.02 (m, 1H), 6.42- 6.36 (m, 1H), 4.37-4.28 (m, 1H), 4.26-4.15 (m, 1H), 2.72-2.55 (m, 1H), 2.47-2.34 (m, 1H), 1.91- 1.85 (m, 2H), 1.85-1.74 (m, 1H), 1.73-1.64 (m, 1H), 1.28-1.21 (m, 6H).	I-45
60		400.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 9.07-8.95 (m, 1H), 8.49-8.43 (m, 1H), 7.68-7.57 (m, 2H), 7.57- 7.52 (m, 1H), 7.30-7.25 (m, 1H), 4.39-4.28 (m, 1H), 2.75-2.59 (m, 1H), 2.48-2.35 (m, 1H), 1.92- 1.84 (m, 2H), 1.84-1.76 (m, 1H), 1.74-1.65 (m, 1H), 1.33 (s, 9H).	I-46
61		409.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.91-8.64 (m, 1H), 8.27-8.16 (m, 1H), 7.11-6.99 (m, 1H), 4.38-4.28 (m, 1H), 2.74-2.56 (m, 1H), 2.48-2.33 (m, 1H), 1.92- 1.84 (m, 2H), 1.84-1.76 (m, 1H), 1.73-1.64 (m, 1H), 1.33 (s, 9H).	I-47
62		395.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.75-8.53 (m, 1H), 8.25-8.15 (m, 1H), 7.83-7.73 (m, 2H), 7.66-7.59 (m, 1H), 7.45-7.36 (m, 1H), 4.39-4.28 (m, 1H), 4.26- 4.15 (m, 1H), 2.73-2.56 (m, 1H), 2.48-2.33 (m, 1H), 1.92-1.85 (m, 2H), 1.85-1.75 (m, 1H), 1.72- 1.63 (m, 1H), 1.27-1.20 (m, 6H).	I-48

63		398.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.18-8.11 (m, 1H), 8.09-8.01 (m, 1H), 7.52-7.46 (m, 1H), 7.46- 7.32 (m, 1H), 4.35-4.26 (m, 1H), 4.22-4.16 (m, 1H), 4.15 (s, 3H), 2.70-2.29 (m, 2H), 1.90-1.84 (m, 2H), 1.84-1.74 (m, 1H), 1.71- 1.63 (m, 1H), 1.25-1.18 (m, 6H).	I-49
64		398.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.25-8.10 (m, 1H), 7.94-7.86 (m, 1H), 7.66-7.39 (m, 2H), 4.35- 4.25 (br, 1H), 4.23-4.11 (m, 1H), 4.02 (s, 3H), 2.70-2.51 (m, 1H), 2.45-4.28 (m, 1H), 1.91- 1.83 (m, 2H), 1.83-1.74 (m, 1H), 1.71-1.62 (m, 1H), 1.26-1.17 (m, 6H).	I-50
65		401.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.89-8.84 (m, 1H), 8.83-8.66 (m, 1H), 7.98-7.91 (m, 1H), 7.82- 7.70 (m, 1H), 4.36-4.28 (m, 1H), 4.25-4.18 (m, 1H), 2.71-2.56 (m, 1H), 2.47-2.34 (m, 1H), 1.91- 1.85 m, 2H), 1.85-1.77 (m, 1H), 1.72-1.64 (m, 1H), 1.28-1.22 (m, 6H).	I-51
66		385.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD/ CDCl <sub>3</sub> = 2/1): δ 8.63-8.54 (m, 1H), 7.62-7.57 (m, 2H), 7.13- 7.04 (m, 1H), 4.38-4.12 (m, 2H), 2.70-2.32 (m, 2H), 1.91-1.84 (m, 2H), 1.84-1.74 (m, 1H), 1.73- 1.63 (m, 1H), 1.25-1.20 (m, 6H).	I-52
67		414.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.38-8.22 (m, 2H), 7.89-7.76 (m, 1H), 7.12-7.01 (m, 1H), 6.45- 6.34 (m, 1H), 4.38-4.27 (m, 1H), 3.51-3.42 (m, 2H), 2.70-2.56 (m, 1H), 2.46-2.34 (m, 1H), 1.91- 1.84 (m, 2H), 1.83-1.74 (m, 1H), 1.72-1.64 (m, 1H), 1.26-1.18 (m, 6H).	I-53
68		449.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.86-7.07 (m, 6H), 5.19-4.97 (m, 1H), 4.41-4.27 (m, 1H), 2.78- 2.60 (m, 1H), 2.53-2.37 (m, 1H), 1.94-1.78 (m, 3H), 1.76-1.65 (m, 1H), 1.45-1.36 (m, 3H).	I-62
69		418.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.87 (m, 2H), 4.36-4.22 (m, 1H), 2.65-2.51 (m, 1H), 2.43- 2.29 (m, 1H), 1.89-1.60 (m, 4H), 1.38-1.29 (m, 6H).	I-32
70		443.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.64-7.73 (m, 3H), 4.43-4.27 (m, 1H), 3.53-3.43 (m, 2H), 2.79- 2.61 (m, 1H), 2.52-2.36 (m, 1H), 1.92-1.67 (m, 4H), 1.24-1.16 (m, 6H).	I-66

71		443.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.55-8.36 (m, 2H), 8.01-7.90 (m, 1H), 4.41-4.30 (m, 1H), 2.77- 2.62 (m, 1H), 2.52-2.32 (m, 1H), 1.96-1.64 (m, 4H), 1.31 (s, 9H).	I-63
72		465.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.58-7.52 (m, 5H), 7.14-6.94 (m, 2H), 4.42-4.27 (m, 1H), 2.80- 2.65 (m, 1H), 2.56-2.37 (m, 1H), 1.94-1.66 (m, 4H).	I-64
73		393.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.09-7.85 (m, 2H), 7.51-7.39 (m, 1H), 4.41- 4.26 (m, 1H), 2.74- 2.57 (m, 1H), 2.49-2.32 (m, 1H), 1.96-1.64 (m, 4H), 1.32-1.29 (m, 9H).	I-65
74		363.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.02-7.88 (m, 1H), 7.85-7.72 (m, 1H), 7.52-7.39 (m, 1H), 4.39- 4.29 (m, 1H), 4.26-4.12 (m, 1H), 2.76-2.56 (m, 1H), 2.49-2.32 (m, 1H), 1.99-1.61 (m, 4H), 1.28- 1.20 (m, 6H).	I-67
75		444.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 9.18-8.77 (m, 2H), 4.45-4.24 (m, 1H), 2.81-2.64 (m, 1H), 2.53- 2.34 (m, 1H), 2.00-1.66 (m, 4H), 1.37-1.26 (m, 9H).	I-68
76		384.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 9.63-9.01 (m, 1H), 7.74 (s, 1H), 7.54-7.48 (m, 1H), 7.47-7.40 (m, 1H), 7.38-7.22 (m, 1H), 4.39- 4.29 (m, 1H), 4.25-4.12 (m, 1H), 2.73-2.55 (m, 1H), 2.50-2.31 (m, 1H), 1.96-1.63 (m, 4H), 1.29- 1.18 (m, 6H).	I-69
77		388.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 6.59-6.32 (m, 1H), 4.36-4.27 (m, 1H), 4.23-4.10 (m, 1H), 4.03-3.90 (m, 2H), 2.82-2.72 (m, 2H), 2.65-2.51 (m, 1H), 2.46- 2.29 (m, 1H), 2.09-1.97 (m, 2H), 1.90-1.63 (m, 6H), 1.25-1.16 (m, 6H).	I-70
78		378.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.04-4.89 (m, 1H), 4.34-4.24 (m, 1H), 3.25-3.07 (m, 2H), 2.65-2.48 (m, 1H), 2.40-2.20 (m, 1H), 1.96-1.59 (m, 5H), 1.38- 1.30 (m, 3H), 0.95-0.87 (m, 6H).	I-13
79		404.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.90 (m, 1H), 4.35-4.26 (m, 1H), 4.21-4.00 (m, 2H), 2.65- 2.49 (m, 1H), 2.43-2.24 (m, 1H), 1.93-1.59 (m, 4H), 1.42-1.30 (m, 3H).	I-76

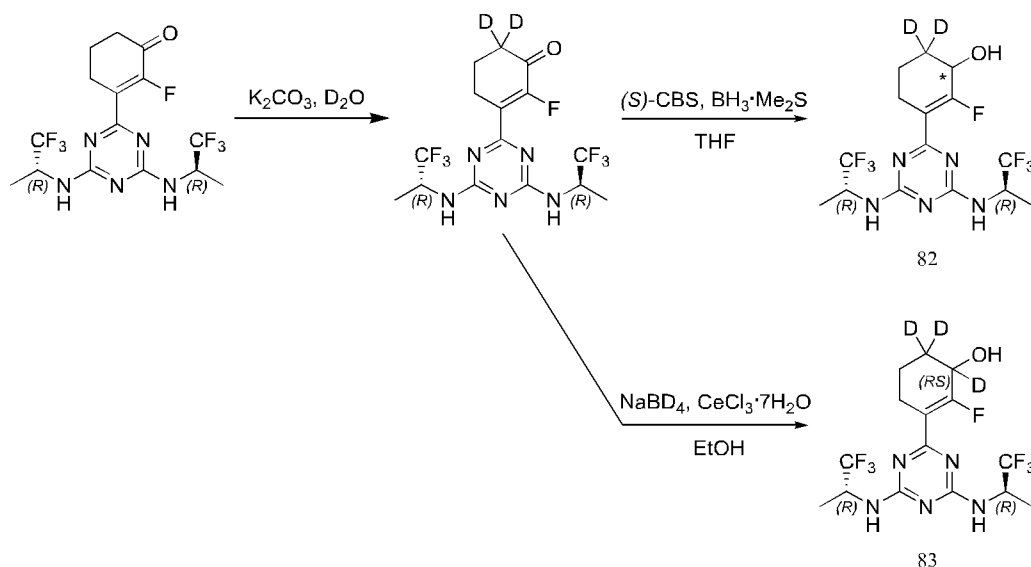
80		376.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.50-4.87 (m, 1H), 4.34-4.23 (m, 1H), 3.26-3.14 (m, 2H), 2.62- 2.47 (m, 1H), 2.39-2.22 (m, 1H), 1.89-1.82 (m, 2H), 1.82-1.73 (m, 1H), 1.71-1.63 (br, 1H), 1.37- 1.31 (m, 3H), 1.14-0.99 (m, 1H), 0.51-0.42 (m, 2H), 0.26-0.19 (m, 2H).	I-77
81		364.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.01-4.87 (m, 1H), 4.34-4.22 (m, 1H), 3.37-3.30 (m, 1H), 3.28- 3.23 (m, 1H), 2.62-2.48 (m, 1H), 2.38-2.22 (m, 1H), 1.88-1.82 (m, 2H), 1.82-1.72 (m, 1H), 1.69- 1.62 (m, 1H), 1.62-1.53 (m, 2H), 1.37-1.30 (m, 3H), 0.96-0.89 (m, 3H).	I-78
199		431.0	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ) : $\delta$ 8.91-8.85 (m, 1H), 8.80-8.66 (m, 1H), 7.99-7.91 (m, 1H), 7.82-7.72 (m, 1H), 4.38-4.28 (m, 1H), 3.53-3.40 (m, 2H), 2.72- 2.58 (m, 1H), 2.48-4.34 (m, 1H), 1.93-1.85 (m, 2H), 1.84-1.76 (m, 1H), 1.73-1.65 (m, 1H), 1.25- 1.19 (m, 6H).	I-79
204		389.1	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 8.30-8.09 (m, 1H), 7.93 -7.58 (m, 2H), 4.40-4.28 (m, 1H), 2.75-2.60 (m, 1H), 2.52-2.36 (m, 4H), 1.95-1.65 (m, 4H), 1.32 (s, 9H).	I-28
224		362.0	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.12-4.89 (m, 1H), 4.36-4.21 (m, 1H), 2.81-2.66 (m, 1H), 2.65- 2.46 (m, 1H), 2.41-2.21 (m, 1H), 1.90-1.82 (m, 2H), 1.82-1.72 (m, 1H), 1.70-1.59 (m, 1H), 1.39- 1.29 (m, 3H), 0.77-0.68 (m, 2H), 0.55-0.47 (m, 2H).	I-16
240		368.0	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.98-4.90 (m, 1H), 4.60-4.52 (m, 1H), 4.49-4.40 (m, 1H), 4.35- 4.20 (m, 1H), 3.74-3.54 (m, 2H), 2.68-2.45 (m, 1H), 2.43-2.22 (m, 1H), 1.91-1.81 (m, 2H), 1.81- 1.72 (m, 1H), 1.70-1.60 (m, 1H), 1.34 (s, 3H).	I-83
241		398.0	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.35-4.17 (m, 2H), 4.16-4.04 (m, 2H), 3.00-2.84 (m, 2H), 2.71-2.48 (m, 3H), 2.42-2.26 (m, 1H), 1.91-1.82 (m, 2H), 1.82- 1.73 (m, 1H), 1.70-1.60 (m, 1H).	I-84

## Compounds 82 and 83

(\*)-3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-6,6-D<sub>2</sub>-1-ol and

3-(4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1,6,6-D<sub>3</sub>-1-ol

5



(A) 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-one-6,6-D<sub>2</sub>

To a solution of 3-(4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-one (prepared according to the procedure of Compound 1 using Intermediate I-3, 114 mg, 0.27 mmol) in 1,4-dioxane (6 mL) was added D<sub>2</sub>O (2 mL) and K<sub>2</sub>CO<sub>3</sub> (75 mg, 0.54 mmol). The mixture was stirred at 80 °C for 4.5 hours. Then, the solvent was removed in vacuo and the residue was purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to afford the title compound as yellow oil (64 mg, yield: 56%).  
MS (m/z): 418.0 [M+H]<sup>+</sup>

(B) (\*)-3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-6,6-D<sub>2</sub>-1-ol

Compound 82 was prepared according to the procedure of Compound 39. MS (m/z): 420.1 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 5.00-4.87 (m, 2H), 4.32-4.23 (m, 1H), 2.63-2.53 (m, 1H), 2.37-2.26 (m, 1H), 1.81-1.69 (m, 1H), 1.67-1.60 (m, 1H), 1.37-1.31 (m, 6H).

(C) 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1,6,6-D<sub>3</sub>-1-ol

Compound 83 was prepared according to the procedure of Compound 1 step (B), using NaBD<sub>4</sub>.  
MS (m/z): 421.1 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 5.00-4.87 (m, 2H), 2.63-2.53 (m, 1H), 2.37-2.26 (m, 1H), 1.81-1.69 (m, 1H), 1.67-1.60 (m, 1H), 1.37-1.31 (m, 6H).

5

The compounds in the below table were prepared according to the procedure of Compound 82 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
84		414.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.98-4.89 (m, 1H), 4.35-4.13 (m, 2H), 3.02-2.81 (m, 2H), 2.75-2.46 (m, 3H), 2.44-2.24 (m, 1H), 1.82-1.71 (m, 1H), 1.69-1.58 (m, 1H), 1.38-1.28 (m, 3H).	I-54
85		408.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.36-4.14 (m, 3H), 2.98-2.85 (m, 4H), 2.67-2.46 (m, 5H), 2.39-2.22 (m, 1H), 1.82-1.71 (m, 1H), 1.68-1.57 (m, 1H).	I-10
86		422.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.60-8.23 (m, 2H), 8.10-7.75 (m, 1H), 4.36-4.28 (m, 1H), 2.72-2.56 (m, 1H), 2.48-2.33 (m, 1H), 1.83-1.73 (m, 1H), 1.71-1.63 (m, 1H).	I-41
87		420.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.88 (m, 2H), 4.34-4.24 (m, 1H), 2.60-2.48 (m, 1H), 2.42-2.30 (m, 1H), 1.88-1.72 (m, 1H), 1.70-1.58 (m, 1H), 1.36-1.31 (m, 6H).	I-32
89		445.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.54-8.35 (m, 2H), 8.03-7.83 (m, 1H), 4.40-4.24 (m, 1H), 2.74-2.60 (m, 1H), 2.48-2.32 (m, 1H), 1.85-1.74 (m, 1H), 1.71-1.60 (m, 1H), 1.31 (s, 9H).	I-63

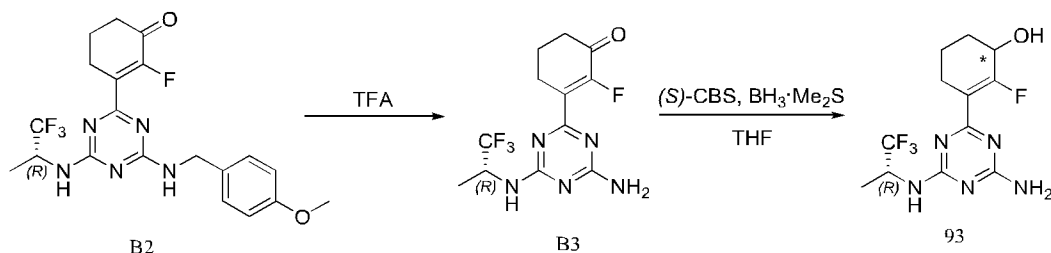


The compounds in the below table were prepared according to the procedure of Compound 83 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
90		415.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.98-4.89 (m, 1H), 4.35-4.13 (m, 1H), 3.02-2.81 (m, 2H), 2.75-2.46 (m, 3H), 2.44-2.24 (m, 1H), 1.82-1.71 (m, 1H), 1.69-1.58 (m, 1H), 1.38-1.28 (m, 3H).	I-54
91		409.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.36-4.14 (m, 2H), 2.98-2.85 (m, 4H), 2.67-2.46 (m, 5H), 2.39-2.22 (m, 1H), 1.82-1.71 (m, 1H), 1.68-1.57 (m, 1H).	I-10
92		361.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.34-4.18 (m, 1H), 4.18-4.00 (m, 1H), 3.01-2.81 (m, 2H), 2.72-2.41 (m, 3H), 2.41-2.18 (m, 1H), 1.80-1.70 (m, 1H), 1.69-1.58 (m, 1H), 1.25-1.11 (br, 6H).	I-37

## 5 Compound 93

**(\*)3-(4-Amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluoro-cyclohex-2-en-1-ol**



**(A) (R)-2-fluoro-3-(4-((4-methoxybenzyl)amino)-6-((1,1,1-trifluoro-2-propyl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one (B2)**

The title Compound B2 was prepared according to the procedure of Compound 1, using Intermediate I-55. MS (m/z): 440.1 [M+H]<sup>+</sup>

**(B) (R)-3-(4-amino-6-((1,1,1-trifluoro-2-propyl)amino)-1,3,5-triazin-2-yl)-2-fluoro-cyclohex-2-en-1-one (B3)**

A solution of Compound B2 (1.1 g, 2.5 mmol) in TFA (10 mL) was stirred at reflux for 4 hours. The solvent was removed. The residue was washed with saturated NaHCO<sub>3</sub> aqueous solution and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give Compound B3 as pale yellow solid. MS (m/z): 320.0[M+H]<sup>+</sup>

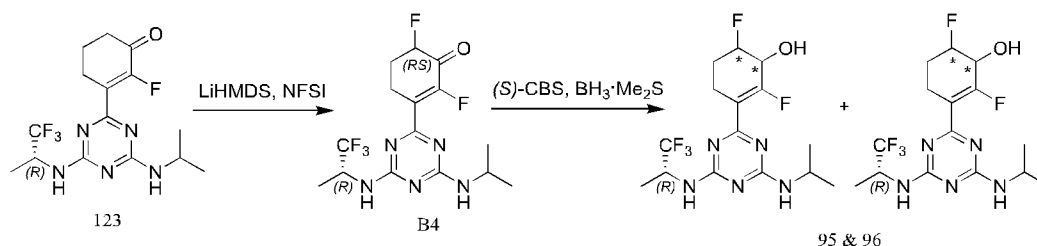
5 **(C) (\*)-3-(4-Amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-ol**

Compound 93 was prepared according to the procedure of Compound 39. MS (m/z): 322.0 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 5.01-4.89 (m, 1H), 4.38-4.19 (m, 1H), 2.62-2.47 (m, 1H),  
10 2.38-2.24 (m, 1H), 1.89-1.61 (m, 4H), 1.36-1.29 (m, 3H).

**Compounds 95 and 96**

**2,6-Difluoro-3-(4-(isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol, optically pure diastereoisomers**



15

**(A) 2,6-difluoro-3-(4-(isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one (B4)**

Under nitrogen atmosphere, to 1 mol/L of LiHMDS/THF solution (14.85 mL, 14.85 mmol) was added dripwise a solution of Compound 123 (1.2 g, 3.30 mmol) in THF (20 mL) at -78 °C. The mixture was stirred at 0 °C for 2 hours. A solution of NFSI (3.12 g, 9.90 mmol) in THF added drop-wise slowly, then the mixture was warmed to room temperature and stirred for 3 hours. After the reaction was completed, the mixture was quenched by the addition of saturated NH<sub>4</sub>Cl aqueous solution (30 mL). The organic layer was collected and the aqueous was extracted with EtOAc. The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was condensed in vacuo and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give Compound B4 as white solid (190 mg, yield: 15.2%). MS (m/z): 380.2 [M+H]<sup>+</sup>

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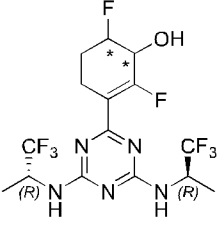
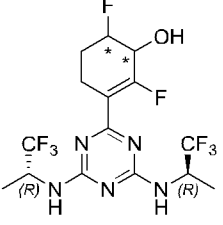
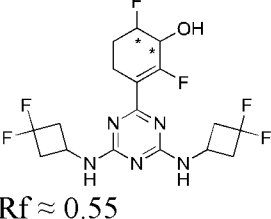
**(B) 2,6-Difluoro-3-(4-(isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol**

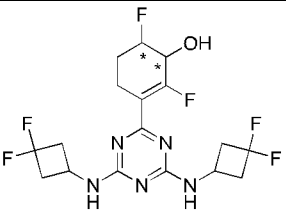
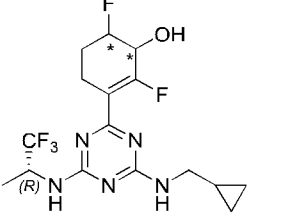
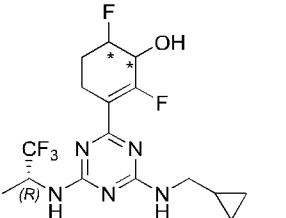
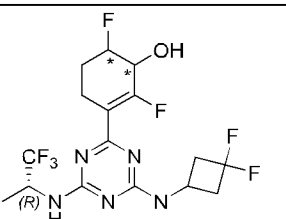
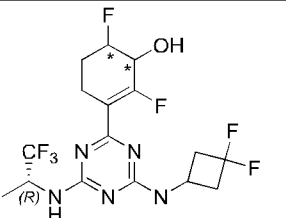
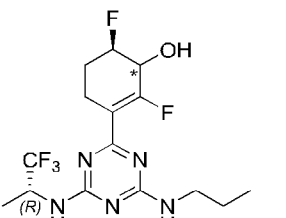
Compounds 95 and 96 were prepared according to the procedure of Compound 39, and purified by preparative TLC (eluting with PE/EA = 2/1).

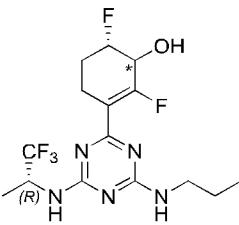
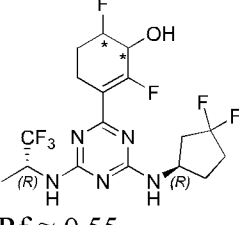
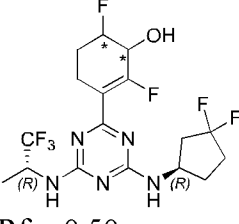
- 5 **Compound 95**,  $R_f \approx 0.55$ , MS (m/z): 382.1  $[M+H]^+$ ;  $^1H$  NMR (400MHz,  $CD_3OD$ ):  $\delta$  4.97-4.90 (m, 1H), 4.72-4.55 (m, 1H), 4.38-4.03 (m, 2H), 2.63-2.46 (m, 2H), 2.06-1.90 (m, 2H), 1.38-1.31 (m, 3H), 1.23-1.13 (s, 6H).

- Compound 96**,  $R_f \approx 0.50$ , MS (m/z): 382.2  $[M+H]^+$ ;  $^1H$  NMR (400MHz,  $CD_3OD$ ):  $\delta$  4.97-4.90 (m, 1H), 4.71-4.55 (m, 1H), 4.51-4.40 (m, 1H), 4.20-4.05 (m, 1H), 2.76-2.58 (m, 1H), 2.48-2.31 (m, 1H), 2.15-2.01 (m, 1H), 1.98-1.81 (m, 1H), 1.40-1.30 (m, 3H), 1.22-1.12 (m, 6H).
- 10

The compounds in the below table were prepared according to the procedure of Compounds 95 and 96 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
97	 <p><math>R_f \approx 0.55</math></p>	436.2	$^1H$ NMR (400 MHz, $CD_3OD$ ): $\delta$ 4.98-4.88 (m, 2H), 4.82-4.63 (m, 1H), 4.35-4.18 (m, 1H), 2.64-2.49 (m, 2H), 2.06-1.90 (m, 2H), 1.37-1.31 (m, 6H).	I-3
98	 <p><math>R_f \approx 0.50</math></p>	436.1	$^1H$ NMR (400MHz, $CD_3OD$ ): $\delta$ 5.03-4.89 (m, 2H), 4.80-4.65 (m, 1H), 4.55-4.38 (m, 1H), 2.80-2.62 (m, 1H), 2.52-2.34 (m, 1H), 2.17-2.02 (m, 1H), 1.98-1.84 (m, 1H), 1.40-1.29 (m, 6H).	I-3
201	 <p><math>R_f \approx 0.55</math></p>	424.2	$^1H$ NMR (400 MHz, $CD_3OD$ ): $\delta$ 4.79-4.64 (m, 1H), 4.37-4.15 (m, 3H), 2.99-2.83 (m, 4H), 2.70-2.47 (m, 6H), 2.06-1.88 (m, 2H).	I-10

202	 <p>Rf ≈ 0.50</p>	424.2	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 4.81-4.64 (m, 1H), 4.52-4.38 (m, 1H), 4.34-4.17 (m, 2H), 2.99-2.83 (m, 4H), 2.70-2.32 (m, 6H), 2.13-2.01 (m, 1H), 1.96-1.81 (m, 1H).	I-10
225	 <p>Rf ≈ 0.55</p>	394.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.90 (m, 1H), 4.79-4.62 (m, 1H), 4.35-4.19 (m, 1H), 3.27-3.11 (m, 2H), 2.65-2.43 (m, 2H), 2.07-1.87 (m, 2H), 1.40-1.29 (m, 3H), 1.13-1.00 (m, 1H), 0.55-0.40 (m, 2H), 0.31-0.15 (m, 2H).	I-77
226	 <p>Rf ≈ 0.50</p>	394.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.89 (m, 1H), 4.80-4.64 (m, 1H), 4.51-4.37 (m, 1H), 3.27-3.09 (m, 2H), 2.78-2.57 (m, 1H), 2.52-2.30 (m, 1H), 2.15-2.01 (m, 1H), 1.97-1.80 (m, 1H), 1.40-1.27 (m, 3H), 1.13-0.98 (m, 1H), 0.55-0.40 (m, 2H), 0.30-0.14 (m, 2H).	I-77
227	 <p>Rf ≈ 0.55</p>	430.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.90 (m, 1H), 4.80 -4.63 (m, 1H), 4.35-4.11 (m, 2H), 3.01-2.86 (m, 2H), 2.55 (s, 4H), 2.09-1.92 (m, 2H), 1.42-1.31 (m, 3H).	I-9
228	 <p>Rf ≈ 0.50</p>	430.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.05-4.88 (m, 1H), 4.82 - 4.64 (m, 1H), 4.54-4.40 (m, 1H), 4.36-4.17 (m, 1H), 3.00-2.84 (m, 2H), 2.77-2.34 (m, 4H), 2.16-2.02 (m, 1H), 1.96-1.83 (m, 1H), 1.41-1.30 (m, 3H).	I-9
230& 231		382.1	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ): δ 7.89-7.69 (m, 1H), 7.54-7.36 (m, 1H), 5.82-5.56 (m, 1H), 4.93-4.59 (m, 2H), 4.39-4.28 (m, 1H), 3.22-3.10 (m, 2H), 2.56-2.39 (m, 1H), 2.38-2.20 (m, 1H), 1.98-1.88 (m, 1H), 1.86-1.73 (m, 1H), 1.50-1.41 (m, 2H), 1.29-1.23 (m, 3H), 0.86-0.79 (m, 3H).	I-18

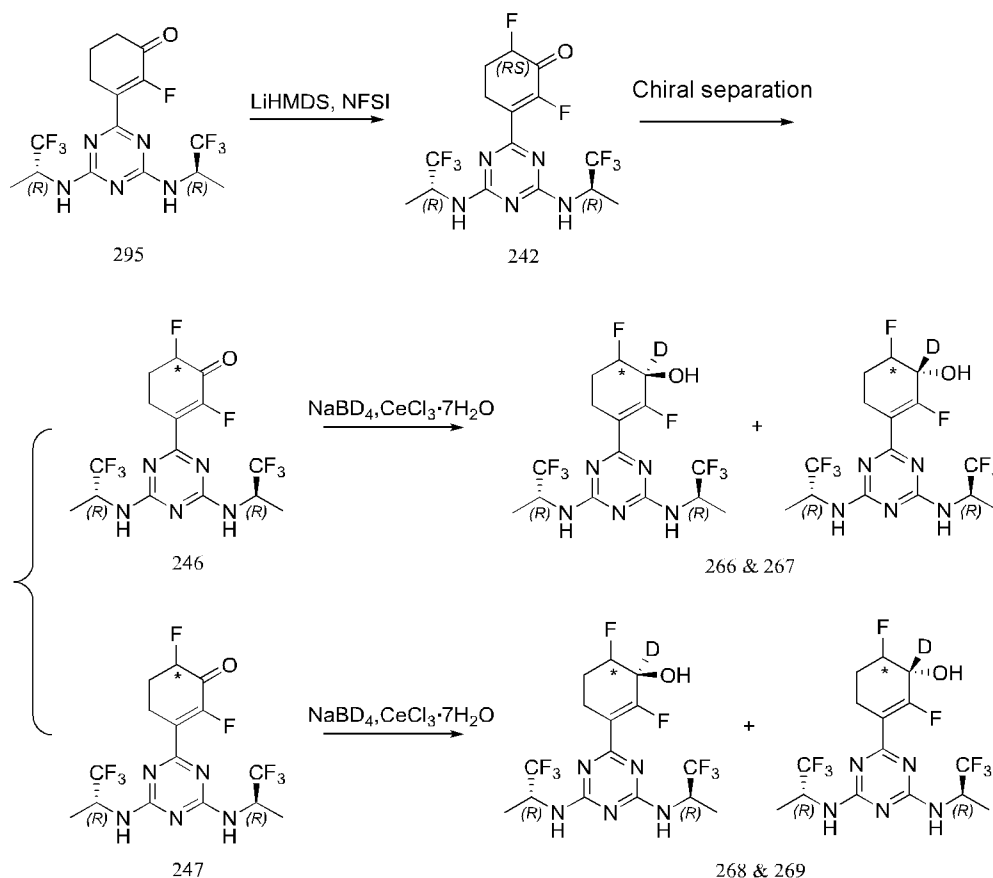
		382.0	$^1\text{H NMR}$ (400 MHz, $\text{DMSO-d}_6$ ): $\delta$ 7.92-7.69 (m, 1H), 7.60-7.34 (m, 1H), 6.11-5.82 (m, 1H), 4.96-4.59 (m, 2H), 4.24-4.08 (m, 1H), 3.22-3.09 (m, 2H), 2.45-2.29 (m, 2H), 1.97-1.89 (m, 2H), 1.52-1.40 (m, 2H), 1.29-1.22 (m, 3H), 0.86-0.78 (m, 3H).	I-18
232	 $R_f \approx 0.55$	444.2	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.00-4.89 (m, 1H), 4.81-4.63 (m, 1H), 4.52-4.37 (m, 1H), 4.36-4.19 (m, 1H), 2.65-2.46 (m, 3H), 2.28-2.14 (m, 2H), 2.13-1.91 (m, 4H), 1.85-1.70 (m, 1H), 1.39-1.29 (m, 3H).	I-82
233	 $R_f \approx 0.50$	444.2	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.01-4.89 (m, 1H), 4.80-4.62 (m, 1H), 4.57-4.29 (m, 2H), 2.74-2.34 (m, 3H), 2.29-1.71 (m, 7H), 1.41-1.27 (m, 3H).	I-82

Note: Compounds 230 and 231 were obtained via flash column chromatography (eluting with gradient  $\text{H}_2\text{O}/\text{MeOH} = 100:0-0:100$ ). The compound obtained from the first elution was named as Compound 230 and the compound obtained from the second elution was named as Compound 231.

5

### Compounds 242, 266-269

**3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6-difluorocyclohex-2-en-1-D-1-ol, optically pure diastereoisomers**



**(A) 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6-difluorocyclohex-2-en-1-one**

Compound 242 was prepared according to the procedure of Step A of Compounds 95 and 96, using Compound 295 and corresponding reagents. MS (m/z): 434.0 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 5.31-5.06 (m, 1H), 5.03-4.90 (m, 2H), 3.09-3.00 (br, 1H), 2.90-2.74 (m, 1H), 2.57-2.42 (m, 1H), 2.31-2.12 (m, 1H), 1.39-1.31 (m, 6H).

**(B) 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6-difluorocyclohex-2-en-1-one, optically pure diastereoisomers**

Compound 242 was separated by chiral HPLC to give a pair of optically pure diastereoisomers, Compounds 246 and 247 (Chiral HPLC conditions: Column: AD-H (0.46 cm I.D. × 15 cm L); mobile phase: n-heptane/isopropanol = 80/20; flow rate: 0.5 mL/min; detection wavelength: UV 254 nm). The first elution (Compound 246: RT = 2.025 min, de% = 100%, MS (m/z): 434.0 [M+H]<sup>+</sup>). The second elution (Compound 247: RT = 2.083 min, de% = 100%, MS (m/z): 434.0 [M+H]<sup>+</sup>).

**(C) 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6-difluorocyclohex-2-en-1-D-1-ol, optically pure diastereoisomers**

Compounds 266 and 267 were prepared according to the procedure of Compound 1, using Compound 246 and NaBD<sub>4</sub>, purified by flash column chromatography (eluting with PE/EA).

**Compound 266:** R<sub>f</sub> ≈ 0.55, MS (m/z): 437.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.93-4.80 (m, 2H), 4.71-4.55 (m, 1H), 2.54-2.40 (m, 2H), 1.97-1.83 (m, 2H), 1.30-1.22 (m, 6H).

- 5 **Compound 267:** R<sub>f</sub> ≈ 0.50, MS (m/z): 437.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.95-4.79 (m, 2H), 4.75-4.57 (m, 1H), 2.68-2.52 (m, 1H), 2.45-2.27 (m, 1H), 2.07-1.92(m, 1H), 1.90-1.75 (m, 1H), 1.31-1.21 (m, 6H).

Compounds 268 and 269 were prepared according to the procedure of Compound 1, using Compound 247 and NaBD<sub>4</sub>, purified by flash column chromatography (eluting with PE/EA).

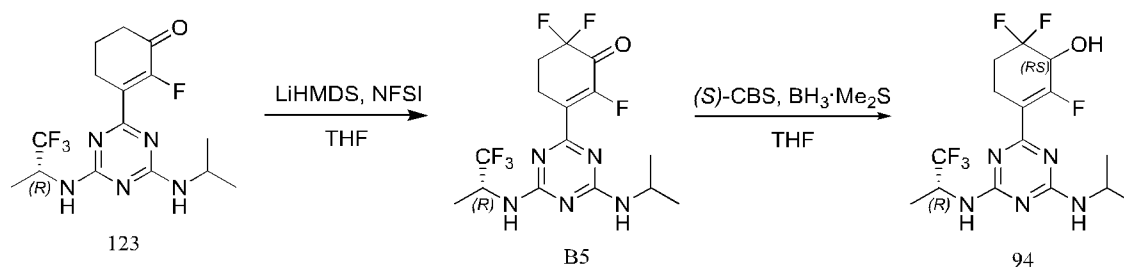
- 10 **Compound 268:** R<sub>f</sub> ≈ 0.55, MS (m/z): 437.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.93-4.80 (m, 2H), 4.71-4.55 (m, 1H), 2.54-2.40 (m, 2H), 1.97-1.83 (m, 2H), 1.30-1.22 (m, 6H).

**Compound 269:** R<sub>f</sub> ≈ 0.50, MS (m/z): 437.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.95-4.79 (m, 2H), 4.75-4.57 (m, 1H), 2.68-2.52 (m, 1H), 2.45-2.27 (m, 1H), 2.07-1.92 (m, 1H), 1.90-1.75 (m, 1H), 1.31-1.21 (m, 6H).

15

## Compound 94

### 2,6,6-Trifluoro-3-(4-(isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol



- 20 **(A) (R)-2,6,6-trifluoro-3-(4-(isopropylamino)-6-(((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one (B5)**

Under nitrogen atmosphere, to a solution of 1 mol/L LiHMDS in THF (14.85 mL, 14.85 mmol) was added a solution of Compound 123 (1.2 g, 3.30 mmol) in THF (20 mL) dropwise at -78 °C. The mixture was stirred at 0 °C for 2 hours. Then, to the mixture was added a solution of NFSI  
 25 (3.12 g, 9.90 mmol) in THF drop-wise, then the reaction was warmed to room temperature slowly and stirred for another 3 hours. After the reaction was completed, the mixture was quenched by the addition of saturated NH<sub>4</sub>Cl aqueous solution (30 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc. The organic layers were combined,

dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was condensed in vacuo and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give compound B5 as a white solid (25 mg, yield: 1.9%). MS (m/z): 398.1 [M+H]<sup>+</sup>

**(B) 2,6,6-Trifluoro-3-(4-(isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol**

Compound 94 was prepared according to the procedure of Compound 39, using compound B5 and corresponding reagents. MS (m/z): 400.2 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.97-4.88 (m, 1H), 4.33-4.19 (m, 1H), 4.19-4.07 (m, 1H), 2.78-2.61 (m, 1H), 2.59-2.40 (m, 1H), 2.21-2.00 (m, 2H), 1.37-1.30 (m, 3H), 1.21-1.12 (m, 6H).

10

The compounds in the below table were prepared according to the procedure of Compound 94 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

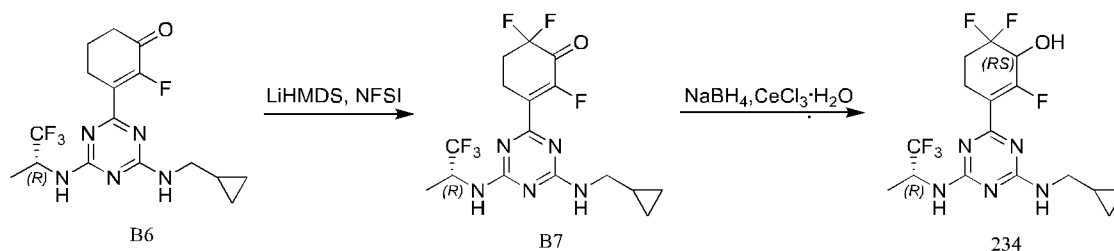
Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter- mediate
196		454.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.86 (m, 2H), 4.36-4.17 (m, 1H), 2.80-2.65 (m, 1H), 2.58-2.42 (m, 1H), 2.25-2.05 (m, 2H), 1.37-1.31 (m, 6H).	I-3
203		442.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.37-4.14 (m, 3H), 3.00-2.85 (m, 4H), 2.74-2.44 (m, 6H), 2.24-2.02 (m, 2H).	I-10
208		440.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.92 (m, 1H), 4.35-4.01 (m, 3H), 2.77-2.67 (br, 1H), 2.63-2.46 (m, 1H), 2.33-2.01 (m, 2H), 1.41-1.32 (m, 3H).	I-76
209		412.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.99-4.90 (m, 1H), 4.31-4.20 (m, 1H), 3.25-3.16 (m, 2H), 2.79-2.63 (m, 1H), 2.59-2.44 (m, 1H), 2.23-2.03 (m, 2H), 1.37-1.31 (m, 3H), 1.13-0.99 (m, 1H), 0.53-0.41 (m, 2H), 0.28-0.17 (m, 2H).	I-78



210		400.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.89 (m, 1H), 4.55-4.37 (m, 1H), 4.02-3.77 (m, 2H), 2.81-2.61 (m, 1H), 2.58-2.37 (m, 1H), 2.17-2.05 (m, 1H), 2.04-1.84 (m, 1H), 1.81-1.51 (m, 2H), 1.43-1.31 (m, 3H), 1.05-0.90 (m, 3H).	I-18
239		448.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.89 (m, 1H), 4.38-4.14 (m, 2H), 3.03- 2.86 (m, 2H), 2.78-2.44 (m, 4H), 2.30-2.01 (m, 2H), 1.42-1.30 (m, 3H).	I-54
245		440.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.92 (m, 1H), 4.35-4.01 (m, 3H), 2.77-2.67 (br, 1H), 2.63-2.46 (m, 1H), 2.33-2.01 (m, 2H), 1.41-1.32 (m, 3H).	I-76

### Compound 234

#### 3-(4-((Cyclopropylmethyl)amino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol



#### (A) (R)-3-(4-((cyclopropylmethyl)amino)-6-(((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-one (B7)

The title compound B7 was prepared according to the procedure of Step A of Compound 94 using compound B6 (prepared according to the procedure of Compound 1 using Intermediate I-77) and corresponding reagents.

#### (B) 3-(4-((Cyclopropylmethyl)amino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol

Compound 234 was prepared according to the procedure of Compound 1, using compound B7 and corresponding reagents. MS (m/z): 412.2 [M+H]<sup>+</sup>

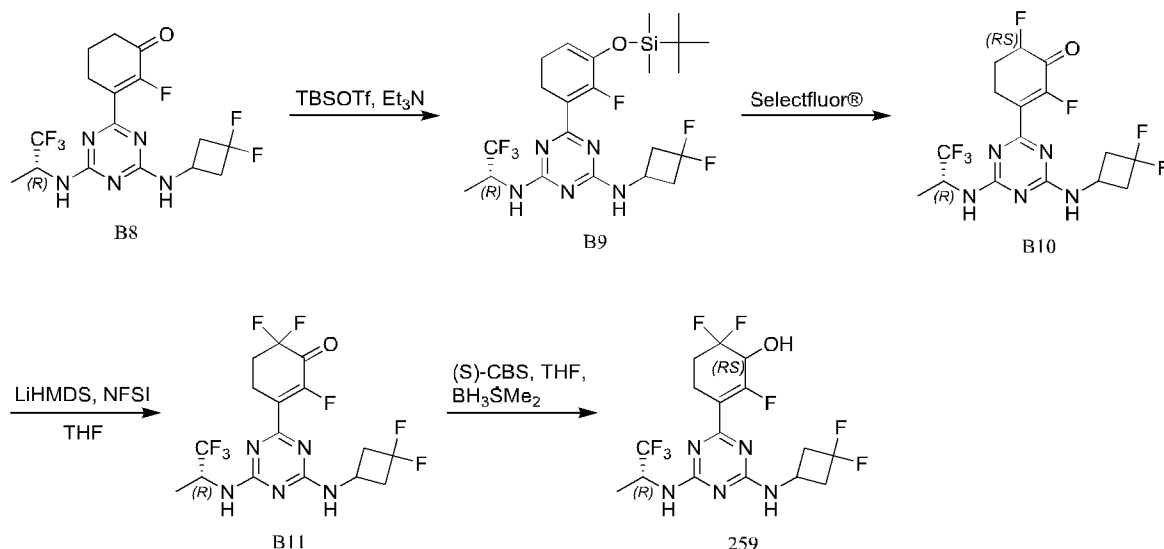
$^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  4.99-4.90 (m, 1H), 4.31-4.20 (m, 1H), 3.25-3.16 (m, 2H), 2.79-2.63 (m, 1H), 2.59-2.44 (m, 1H), 2.23-2.03 (m, 2H), 1.37-1.31 (m, 3H), 1.13-0.99 (m, 1H), 0.53-0.41 (m, 2H), 0.28-0.17 (m, 2H).

- 5 The compounds in the below table were prepared according to the procedure of Compound 234 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	$^1\text{H}$ NMR	Inter- mediate
211		455.1	$^1\text{H}$ NMR (400MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.03-4.87 (m, 2H), 2.82-2.66 (m, 1H), 2.62-2.45 (m, 1H), 2.27-2.02 (m, 2H), 1.40-1.29 (m, 6H).	I-3
235		462.2	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.02-4.88 (m, 1H), 4.54-4.39 (m, 1H), 4.33-4.17 (m, 1H), 2.79-2.64 (m, 1H), 2.61-2.44 (m, 2H), 2.29-2.00 (m, 6H), 1.90-1.67 (m, 1H), 1.39-1.31 (m, 3H).	I-82
238		398.0	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.05-4.91 (m, 1H), 4.31-4.20 (m, 1H), 2.86-2.60 (m, 2H), 2.59-2.43 (m, 1H), 2.24-2.04 (m, 2H), 1.38-1.31 (m, 3H), 0.78-0.66 (m, 2H), 0.57-0.44 (m, 2H).	I-16
248		400.0	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 4.98-4.90 (m, 1H), 4.32-4.19 (m, 1H), 3.38-3.23 (m, 2H), 2.80-2.61 (m, 1H), 2.60-2.41 (m, 1H), 2.28-2.02 (m, 2H), 1.64-1.52 (m, 2H), 1.38-1.30 (m, 3H), 0.99-0.87 (m, 3H).	I-18

### Compound 259

- 10 **3-(4-(((3,3-Difluorocyclobutyl)amino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol**



**(A) (R)-6-(3-(((tert-butyldimethylsilyl)oxy)-2-fluorocyclohexa-1,3-dien-1-yl)-N<sup>2</sup>-(3,3-difluorocyclobutyl)-N<sup>4</sup>-(1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine (B9)**

Under N<sub>2</sub>, to a mixture of compound B8 (prepared according to Compound 39 using  
 5 Intermediate I-9: 750 mg, 1.83 mmol) and Et<sub>3</sub>N (371 mg, 3.66 mmol) in dry DCM (15 mL) was added a solution of TBSOTf (726 mg, 2.75 mmol) in DCM (5 mL) at 0~5 °C. The mixture was stirred for 30 minutes. Then, it was poured into water and extracted with DCM. The organic layer was collected, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> condensed under reduced pressure and purified by flash column chromatography (eluting with PE/EA) to give compound B9 as a  
 10 yellow oil (958 mg, yield: 100%). MS (m/z): 524.1 [M+H]<sup>+</sup>

**(B) 3-(4-(((3,3-Difluorocyclobutyl)amino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6-difluorocyclohex-2-en-1-one (B10)**

Under N<sub>2</sub>, a solution of compound B9 (958 mg, 1.83 mmol) in dry MeCN (20 mL) was added to the suspension of Selectfluor® (778 mg, 2.20 mmol) in dry acetonitrile (20 mL) dropwise at 0~5  
 15 °C and stirred for 2 hours. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was collected, condensed under reduced pressure and purified by flash column chromatography (eluting with PE/EA) to give compound B10 as white solid (512 mg, yield: 66%). MS (m/z): 428.0 [M+H]<sup>+</sup>.

**(C) (R)-3-(4-(((3,3-difluorocyclobutyl)amino)-6-(((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-one (B11)**

Under N<sub>2</sub>, to a solution of compound B10 (512 mg, 1.12 mmol) in dry THF (10 mL) was added 1M LiHMDS/THF solution (3.47 mL, 3.47 mmol) dropwise at -78 °C and stirred for 30 minutes. Then to the mixture was added NFSI (388 mg, 1.23 mmol)/THF solution (10 mL) dropwise at -78 °C and the reaction was stirred for 2 hours. After the reaction was completed, saturated

NH<sub>4</sub>Cl aqueous solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic layer was collected, condensed under reduce pressure and purified by flash column chromatography (eluting with PE/EA) to give compound B11 as yellow solid (230 mg, yield: 46%). MS (m/z): 446.2 [M+H]<sup>+</sup>

5 **(D) 3-(4-(((3,3-Difluorocyclobutyl)amino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol**

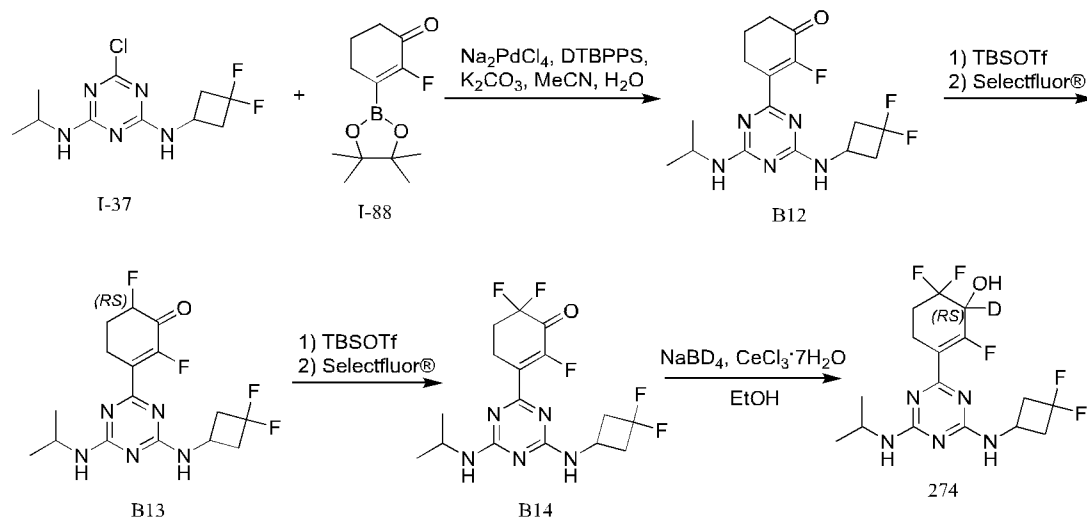
Compound 259 was prepared according to the procedure of Compound 39, using compound B11 and corresponding reagents. MS (m/z): 448.0 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.91-4.81 (s, 1H), 4.26-4.09 (m, 2H), 2.92-2.76 (m, 2H),  
10 2.72-2.33 (m, 4H), 2.18-1.96 (m, 2H), 1.30-1.22 (m, 3H).

The compounds in the below table were prepared according to the procedure of Compound 259 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
260		398.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.99-4.83 (m, 1H), 4.26-4.09 (m, 1H), 2.76-2.53 (m, 2H), 2.51-2.34 (m, 1H), 2.17-1.95 (m, 2H), 1.31-1.23 (m, 3H), 0.69-0.59 (m, 2H), 0.48-0.38 (m, 2H).	I-85
261		394.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.36-4.09 (m, 3H), 3.02-2.87 (m, 2H), 2.79-2.43 (m, 4H), 2.26-2.04 (m, 2H), 1.28-1.15 (m, 6H).	I-37
270		440.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 4.92-4.82 (m, 1H), 4.28-3.90 (m, 3H), 2.72-2.38 (m, 2H), 2.20-1.96 (m, 2H), 1.33-1.21 (m, 3H).	I-86
271		449.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.31-8.20 (m, 1H), 7.63-7.50 (m, 1H), 7.25-7.14 (m, 1H), 7.13-7.01 (m, 1H), 4.83-4.68 (m, 1H), 4.52-4.39 (m, 2H), 4.13-3.98 (m, 1H), 2.57-2.18 (m, 2H), 2.08-1.78 (m, 2H), 1.18 -1.00 (m, 3H).	I-87

## Compound 274

**3-(4-((3,3-difluorocyclobutyl)amino)-6-(isopropylamino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-D-1-ol**

5 **(A) 3-(4-((3,3-Difluorocyclobutyl)amino)-6-(isopropylamino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-one (B12)**

Under N<sub>2</sub>, a mixture of Intermediate I-37 (4.17 g, 15.0 mmol), Intermediate I-88 (4.32 g, 18.0 mmol), Na<sub>2</sub>PdCl<sub>4</sub> (221 mg, 0.75 mmol), DTBPPS (402 mg, 1.5 mmol), K<sub>2</sub>CO<sub>3</sub> (5.18 g, 37.5 mmol), MeCN (40 mL) and H<sub>2</sub>O (10 mL) was stirred at 60 °C for 2 hours. After the reaction was completed, the mixture was poured into water and extracted with DCM. The organic layer was collected, condensed and purified by flash column chromatography (eluting with PE/EA) to give Compound B12 as yellow solid (4.98 g, yield: 93%). MS (m/z): 356.1 [M+H]<sup>+</sup>

**(B) 3-(4-((3,3-Difluorocyclobutyl)amino)-6-(isopropylamino)-1,3,5-triazin-2-yl)-2,6-difluorocyclohex-2-en-1-one (B13)**

15 The title compound B13 was prepared according to the procedures of Steps A and B of Compound 259, using Compound B12 and corresponding reagents. MS (m/z): 374.1 [M+H]<sup>+</sup>

**(C) 3-(4-((3,3-Difluorocyclobutyl)amino)-6-(isopropylamino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-one (B14)**

20 The title compound B14 was prepared according to the procedures of Steps A and B of Compound 259, using compound B13 and corresponding reagents. MS (m/z): 392.0 [M+H]<sup>+</sup>

**(D) 3-(4-((3,3-Difluorocyclobutyl)amino)-6-(isopropylamino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-D-1-ol**

Compound 274 was prepared according to the procedure of Step B of Compound 1, using Compound B14, NaBD<sub>4</sub> and corresponding reagents. MS (m/z): 395.1 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.33-4.20 (m, 1H), 4.20-4.03 (m, 1H), 3.05-2.85 (m, 2H), 2.80-2.41 (m, 4H), 2.29-2.02 (m, 2H), 1.25-1.14 (m, 6H).

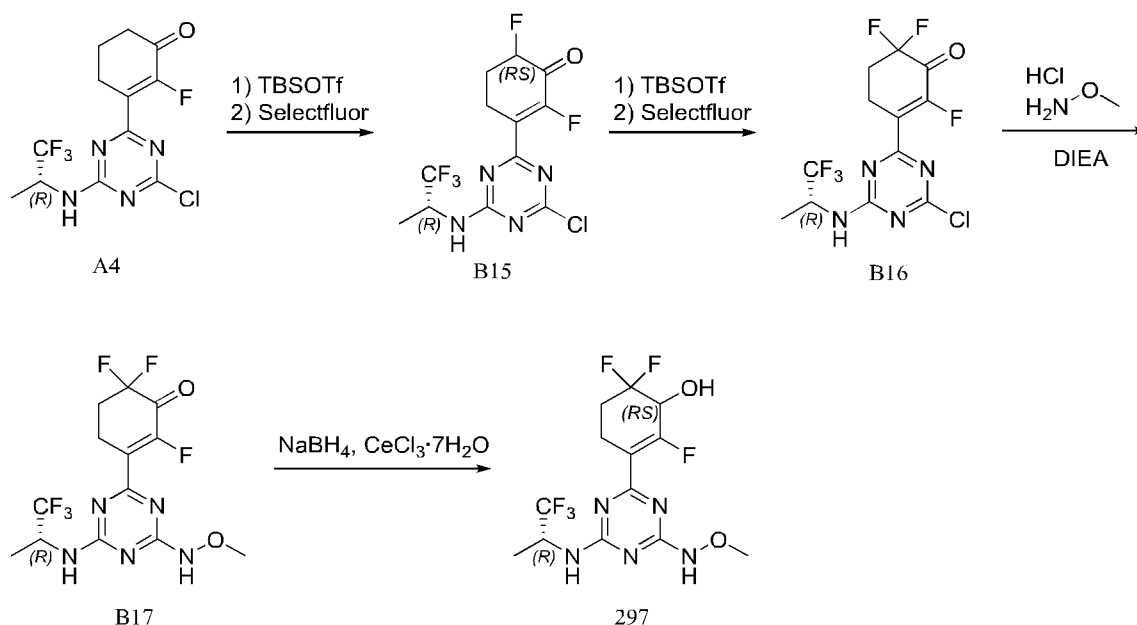
- 5 The compounds in the below table were prepared according to the procedure of Compound 274 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
275		479.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.67-8.30 (m, 2H), 8.06-7.80 (m, 1H), 4.45-4.23 (m, 1H), 2.93-2.75 (m, 1H), 2.69-2.50 (m, 1H), 2.33-2.06 (m, 2H), 1.42-1.20 (m, 9H).	I-63
276		480.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.67-8.32 (m, 2H), 8.08-7.80 (m, 1H), 2.91-2.75 (m, 1H), 2.69-2.52 (m, 1H), 2.32-2.08 (m, 2H), 1.42-1.26 (m, 9H).	I-63
277		454.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.05-4.91 (m, 2H), 4.38-4.16 (m, 1H), 2.83-2.66 (m, 1H), 2.62-2.45 (m, 1H), 2.29-2.03 (m, 2H), 1.44-1.26 (m, 6H).	I-89
278		399.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.14-4.92 (m, 1H), 2.88-2.64 (m, 2H), 2.59-2.43 (m, 1H), 2.32-1.99 (m, 2H), 1.45-1.28 (m, 3H), 0.82-0.66 (m, 2H), 0.58-0.45 (m, 2H).	I-85
279		399.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.13-4.93 (m, 1H), 2.90-2.64 (m, 2H), 2.61-2.41 (m, 1H), 2.33-1.99 (m, 2H), 1.49-1.24 (m, 3H), 0.86-0.67 (m, 2H), 0.62-0.46 (m, 2H).	I-16
281		436.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.87 (m, 1H), 5.10-4.91 (m, 2H), 4.49-4.21 (m, 1H), 2.90-2.54 (m, 2H), 2.34-1.98 (m, 2H), 1.50-1.20 (m, 6H).	I-3

282		437.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.87 (m, 1H), 5.10-4.91 (m, 2H), 2.90-2.54 (m, 2H), 2.34-1.98 (m, 2H), 1.50-1.20 (m, 6H).	I-3
283		454.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.05-4.90 (m, 2H), 4.40-4.19 (m, 1H), 2.84-2.66 (m, 1H), 2.62-2.45 (m, 1H), 2.30 -2.03 (m, 2H), 1.42-1.27 (m, 6H).	I-32
293		430.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.09-4.91 (m, 1H), 4.34-4.21 (m, 1H), 2.82-2.68 (m, 1H), 2.61-2.46 (m, 1H), 2.28-2.03 (m, 2H), 1.39-1.34 (m, 3H), 1.29-1.26 (m, 9H).	I-90
294		430.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.09-4.91 (m, 1H), 4.34-4.21 (m, 1H), 2.82-2.68 (m, 1H), 2.61-2.46 (m, 1H), 2.28-2.03 (m, 2H), 1.39-1.34 (m, 3H), 1.29-1.26 (m, 9H).	I-91
296		452.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.88 (m, 2H), 3.07-2.09 (m, 4H), 1.39-1.31 (m, 6H).	I-3
298		437.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.77-8.34 (m, 2H), 8.01-7.69 (m, 1H), 4.47-4.17 (m, 1H), 3.81 (s, 3H), 2.89-2.73 (m, 1H), 2.67-2.52 (m, 1H), 2.30-2.06 (m, 2H).	I-92

### Compound 297

**2,6,6-Trifluoro-3-(4-(methoxyamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol**



**(A) (R)-3-(4-chloro-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-one (B16)**

The title compound B16 was prepared according to the procedure of Steps B and C of Compound 274, using Intermediate A4 and corresponding reagents. MS (m/z): 375.1 [M+H]<sup>+</sup>

**(B) (R)-2,6,6-trifluoro-3-(4-(methoxyamino)-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one (B17)**

The title compound B17 was prepared according to the procedure of Compound 190, using Compound B16 and corresponding reagents. MS (m/z): 386.1 [M+H]<sup>+</sup>

**(C) 2,6,6-Trifluoro-3-(4-(methoxyamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol**

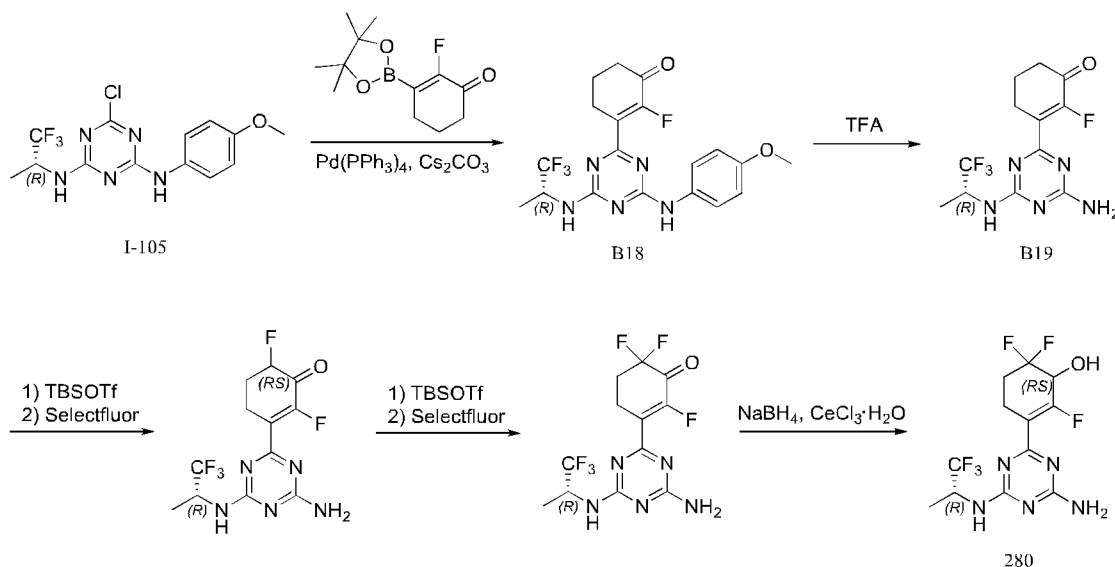
Compound 297 was prepared according to the procedure of Step B of Compound 1, using compound B17 and corresponding reagents. MS (m/z): 388.2 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 5.04-4.92 (m, 1H), 4.34-4.20 (m, 1H), 3.81-3.66 (m, 3H), 2.80-2.64 (m, 1H), 2.59- 2.44 (m, 1H), 2.31-2.04 (m, 2H), 1.41-1.32 (m, 3H).

**Compound 280**

**3-(4-Amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol**





**(A) (R)-2-fluoro-3-(4-((4-methoxyphenyl)amino)-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one (B18)**

The title compound B18 was prepared according to the procedure of Compound 1, using Intermediate I-105 and corresponding reagents. MS (m/z): 440.2 [M+H]<sup>+</sup>

**(B) (R)-3-(4-amino-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-one (B19)**

A mixture of Compound B18 (1.4 g, 3.19 mmol) in TFA (10 mL) was stirred at reflux for 2 hours. The solvent was removed under vacuo. The residue was dissolved in EtOAc and washed with saturated NaHCO<sub>3</sub> aqueous solution. The organic layer was collected, condensed under reduced pressure to give title compound B19 as yellow solid (800 mg, yield 79%), which was used for the next step without purification.

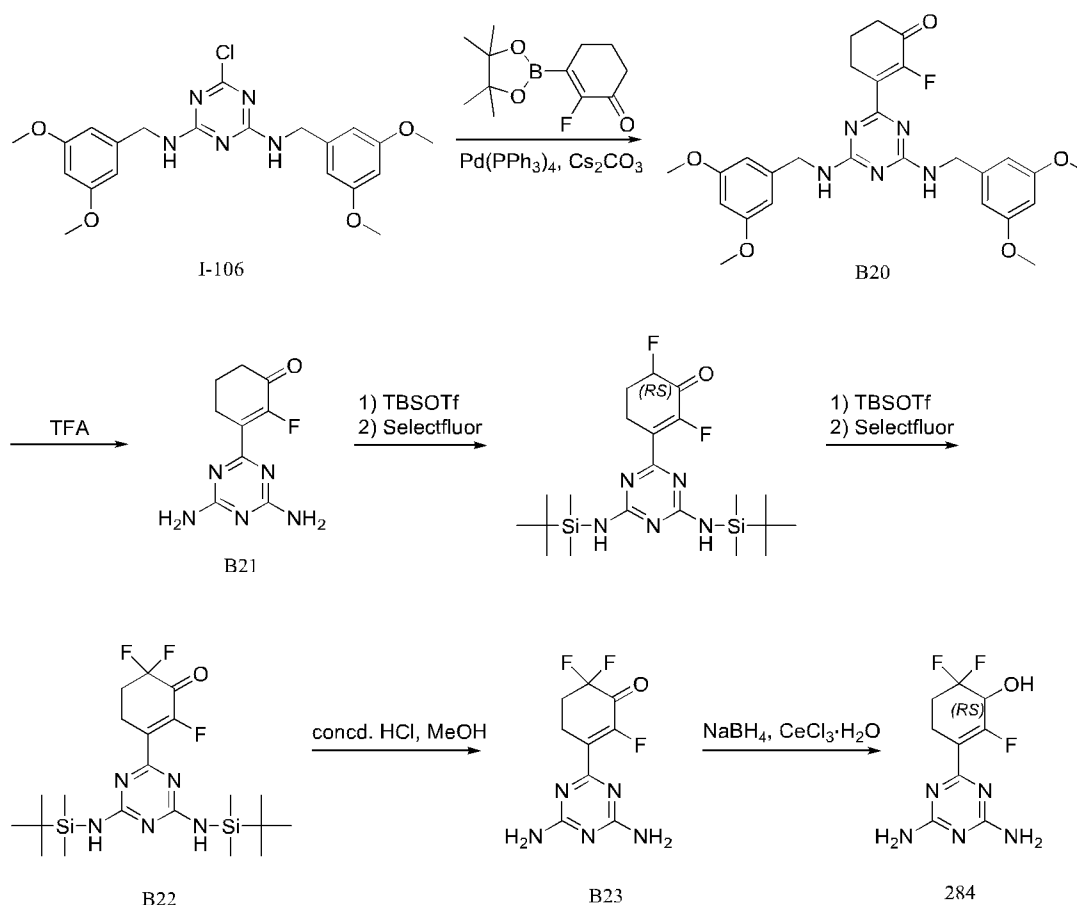
**(C) 3-(4-Amino-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol**

Compound 280 was prepared according to the procedure of Compound 274, using Compound B19 and corresponding reagents. MS (m/z): 358.1 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 5.00-4.92 (m, 1H), 4.38-4.18 (m, 1H), 2.80-2.61 (m, 1H), 2.61-2.44 (m, 1H), 2.31-2.10 (m, 2H), 1.50-1.23 (m, 3H).

**Compound 284**

**3-(4,6-Diamino-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol**



**(A) 3-(4,6-Bis((3,5-dimethoxybenzyl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-one (B20)**

The title compound B20 was prepared according to the procedure of Compound 1, using Intermediate I-106 and corresponding reagents. MS (m/z): 542.1 [M+H]<sup>+</sup>

**(B) 3-(4,6-Diamino-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-one (B21)**

The title compound B21 was prepared according to the procedure of Step B of Compound 280, using compound B20 and corresponding reagents. MS (m/z): 224.0 [M+H]<sup>+</sup>

**(C) 3-(4,6-Bis((tert-butyl(dimethyl)silyl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-one (B22)**

The title compound B22 was prepared according to the procedure of Steps B and C of Compound 274, using compound B21 and corresponding reagents. MS (m/z): 488.1 [M+H]<sup>+</sup>

**(D) 3-(4,6-Diamino-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-one (B23)**

A solution of Compound B22 (410 mg, 0.84 mmol) in concentrated HCl aqueous solution (1 mL) and MeOH (5 mL) was stirred at room temperature for 30 minutes. The mixture was diluted with EtOAc and adjusted to pH = 8 with saturated NaHCO<sub>3</sub> aqueous solution. The organic layer was

collected, concentrated to dryness under vacuo and purified by flash column chromatography (eluting with MeOH and water) to give the title compound B23 as white solid (150 mg, yield: 69%). MS (m/z): 260.0 [M+H]<sup>+</sup>

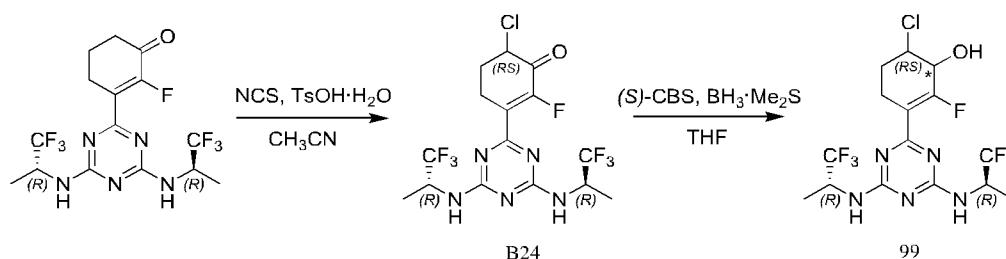
**(E) 3-(4,6-Diamino-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol**

5 Compound 284 was prepared according to the procedure of Step B of Compound 1, using Compound B23 and corresponding reagents. MS (m/z): 262.0 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 4.33-4.20 (m, 1H), 2.73-2.60 (m, 1H), 2.56-2.43 (m, 1H), 2.29-2.04 (m, 2H).

10 **Compound 99**

**3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-6-chloro-2-fluorocyclohex-2-en-1-ol**



15 **(A) 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-6-chloro-2-fluorocyclohex-2-en-1-one (B24)**

To a sealed tube was added 3-(4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2-fluorocyclohex-2-en-1-one (prepared according to the procedure of Compound 1 using Intermediate I-3, 700 mg, 1.69 mmol), NCS (224 mg, 1.69 mmol), TsOH·H<sub>2</sub>O (321 mg, 1.69 mmol) and MeCN (10 mL) in sequence. The mixture was heated to 80°C and stirred for 16 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give the title compound B24 as white solid (320 mg, yield 42.2%). MS (m/z): 450.1, 452.1 [M+H]<sup>+</sup>

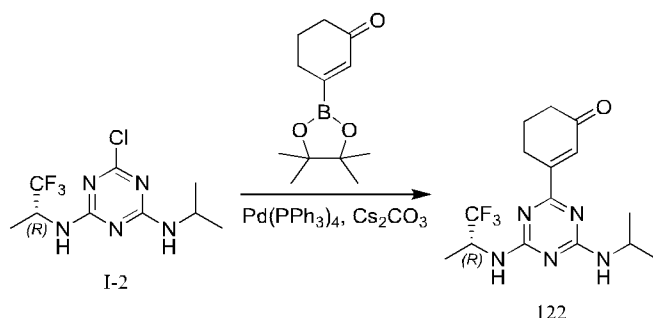
25 **(B) 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-6-chloro-2-fluorocyclohex-2-en-1-ol**

Compound 99 was prepared according to the procedure of Compound 39 using Compound B24 and corresponding reagents. MS (m/z): 452.1 [M+H]<sup>+</sup>

$^1\text{H}$  NMR (400MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  5.02-4.90 (m, 2H), 4.40-4.33 (m, 1H), 4.27-4.19 (m, 1H), 2.80-2.66 (m, 1H), 2.52-2.38 (m, 1H), 2.13-1.97 (m, 2H), 1.36-1.30 (m, 6H).

### Compound 122

5 **(R)-3-(4-(isopropylamino)-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one**

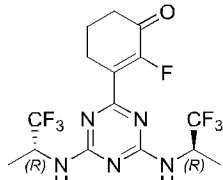


To a flask were added Intermediate I-2 (500 mg, 1.76 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-one (391 mg, 1.76 mmol),  $\text{Cs}_2\text{CO}_3$  (1144 mg, 3.52 mmol),  
 10  $\text{Pd}(\text{PPh}_3)_4$  (101 mg, 0.09 mmol), 1,4-dioxane (20 mL) and water (4 mL). The mixture was stirred at 80 °C for 2 hours under nitrogen atmosphere. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as a white solid (350 mg, yield 57.9%). MS (m/z): 344.1  $[\text{M}+\text{H}]^+$

15  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.00 (s, 1H), 5.05-4.86 (m, 1H), 4.26-4.04 (m, 1H), 2.87-2.74 (m, 2H), 2.48-2.41 (m, 2H), 2.11-2.02 (m, 2H), 1.39-1.32 (m, 3H), 1.23-1.17 (m, 6H).

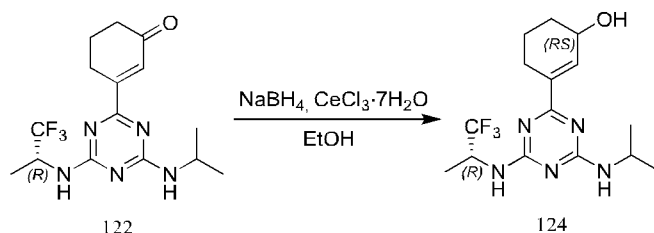
The compounds in the below table were prepared according to the procedure of Compound 122 using the corresponding intermediates and reagents under appropriate conditions that will be  
 20 recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	$^1\text{H}$ NMR	Inter-mediate
123		362.1	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.01-4.90 (m, 1H), 4.22-4.10 (m, 1H), 2.89-2.77 (m, 2H), 2.64-2.55 (m, 2H), 2.12-2.02 (m, 2H), 1.39-1.32 (m, 3H), 1.23-1.17 (m, 6H).	I-2

295		416.2	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 5.00-4.88 (m, 2H), 2.91-2.78 (m, 2H), 2.62-2.53 (m, 2H), 2.11-2.00 (m, 2H), 1.40-1.30 (m, 6H).	I-3
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### Compound 124

#### 3-(4-(Isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol



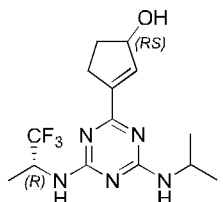
10 To a flask were added Compound 122 (250 mg, 0.73 mmol),  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (353 mg, 0.95 mmol) and EtOH (10 mL). The mixture was cooled to 0 °C,  $\text{NaBH}_4$  (36 mg, 0.95 mmol) was added and the reaction was stirred at 0 °C for 2 hours. After the reaction was completed, the mixture was quenched by the addition of saturated  $\text{NH}_4\text{Cl}$  aqueous solution (3 mL) and water (20 mL) and

15 extracted with EtOAc. The organic layer was collected, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as a white solid (210 mg, yield: 83.3%). MS (m/z): 346.0  $[\text{M}+\text{H}]^+$

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.19-6.92 (m, 1H), 5.10-4.87 (m, 1H), 4.37-4.26 (m, 1H), 4.25-4.07 (m, 1H), 2.51-2.30 (m, 2H), 2.01-1.82 (m, 2H), 1.71-1.49 (m, 2H), 1.38-1.30 (m, 3H),

15 1.23-1.12 (m, 6H).

The compounds in the below table were prepared according to the procedure of Compound 124 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

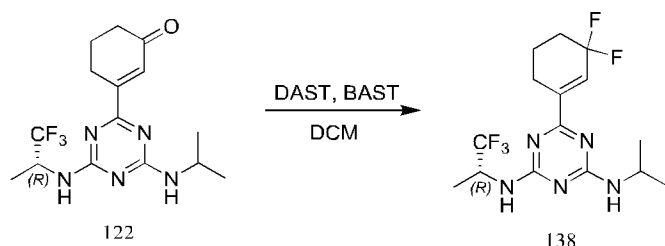
Comp.	Structure	MS (M+H) <sup>+</sup>	$^1\text{H}$ NMR	Inter-mediate
125		332.0	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ): $\delta$ 6.88-6.70 (m, 1H), 5.07-4.87 (m, 2H), 4.23-4.08 (m, 1H), 2.90-2.77 (m, 1H), 2.63-2.49 (m, 1H), 2.43-2.30 (m, 1H), 1.85-1.69 (m, 1H), 1.39-1.31 (m, 3H), 1.22-1.17 (m, 6H).	I-2

126		400.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.23-7.01 (m, 1H), 5.08-4.87 (m, 2H), 4.37-4.27 (m, 1H), 2.49-2.35 (m, 2H), 1.98-1.82 (m, 2H), 1.68-1.53 (m, 2H), 1.39-1.32 (m, 6H).	I-3
127		388.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.93 (m, 1H), 4.36-4.19 (m, 3H), 2.97-2.87 (m, 4H), 2.69-2.50 (m, 4H), 2.45-2.34 (m, 2H), 1.97-1.80 (m, 2H), 1.67-1.51 (m, 2H).	I-10
128		358.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.26-6.90 (m, 1H), 5.10-4.92 (m, 1H), 4.60-4.26 (m, 2H), 2.56-2.23 (m, 4H), 2.11-1.81 (m, 4H), 1.79-1.49 (m, 4H), 1.42-1.28 (m, 3H).	I-15
129		344.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.27-6.85 (m, 1H), 5.17-4.95 (m, 1H), 4.45-4.20 (m, 1H), 2.84-2.63 (m, 1H), 2.53-2.27 (m, 2H), 2.00-1.82 (m, 2H), 1.74-1.51 (m, 2H), 1.43-1.29 (m, 3H), 0.84-0.67 (m, 2H), 0.58-0.46 (m, 2H).	I-16
130		372.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.89 (m, 1H), 5.09-4.92 (m, 1H), 4.41-4.18 (m, 2H), 2.54-2.31 (m, 2H), 2.09-1.82 (m, 4H), 1.80-1.69 (m, 2H), 1.67-1.44 (m, 6H), 1.40-1.31 (m, 3H).	I-12
131		376.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.24-6.95 (m, 1H), 5.12-4.90 (m, 1H), 4.43-4.25 (m, 1H), 3.53-3.37 (m, 2H), 2.47-2.33 (m, 2H), 2.01-1.81 (m, 2H), 1.69-1.52 (m, 2H), 1.38-1.33 (m, 3H), 1.19 (s, 6H).	I-7
132		362.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.23-6.91 (m, 1H), 5.12-4.91 (m, 1H), 4.43-4.25 (m, 1H), 3.65-3.46 (m, 4H), 3.36 (s, 3H), 2.53-2.32 (m, 2H), 2.01-1.83 (m, 2H), 1.69-1.52 (m, 2H), 1.40-1.31 (m, 3H).	I-17
133		346.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.02-6.87 (m, 1H), 5.11-4.90 (m, 1H), 4.40-4.23 (m, 1H), 3.40-3.30 (m, 2H), 2.55-2.28 (m, 2H), 1.98-1.81 (m, 2H), 1.68-1.53 (m, 4H), 1.39-1.31 (m, 3H), 0.97-0.89 (m, 3H).	I-18
134		360.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.23-6.90 (m, 1H), 5.14-4.89 (m, 1H), 4.45-4.21 (m, 1H), 3.25-3.07 (m, 2H), 2.50-2.33 (m, 2H), 1.97-1.80 (m, 3H), 1.74-1.51 (m, 2H), 1.38-1.31 (m, 3H), 0.95-0.89 (m, 6H).	I-13

135		332.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.28-6.88 (m, 1H), 5.14-4.93 (m, 1H), 4.40-4.22 (m, 1H), 3.48-3.35 (m, 2H), 2.57-2.27 (m, 2H), 1.98-1.83 (m, 2H), 1.70-1.52 (m, 2H), 1.40-1.31 (m, 3H), 1.20-1.13 (m, 3H).	I-19
136		386.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.92 (m, 1H), 5.11-4.88 (m, 1H), 4.41-4.26 (m, 1H), 3.95-3.72 (m, 1H), 2.53-2.31 (m, 2H), 2.08-1.86 (m, 4H), 1.79-1.70 (m, 2H), 1.68-1.53 (m, 3H), 1.41-1.20 (m, 8H).	I-20
137		374.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.31-7.215 (m, 1H), 5.09-4.95 (m, 1H), 4.39-4.30 (m, 1H), 3.16-2.81 (m, 1H), 2.51-2.37 (m, 2H), 2.01-1.84 (m, 2H), 1.71-1.51 (m, 2H), 1.40-1.34 (m, 3H), 1.22-1.11 (m, 6H).	I-4

### Compound 138

**(R)-6-(3,3-difluorocyclohex-1-en-1-yl)-N<sup>2</sup>-isopropyl-N<sup>4</sup>-(1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine**



To a sealed tube were added Compound 122 (100 mg, 0.29 mmol), DAST (1 mL), BAST (1 mL) and DCM (10 mL). The mixture was stirred at 80 °C for 48 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as a white solid (40 mg, yield: 38.1%). MS (m/z): 366.1 [M+H]<sup>+</sup>

10

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.00-6.82 (m, 1H), 5.05-4.88 (m, 1H), 4.27-4.05 (m, 1H), 2.59-2.47 (m, 2H), 2.14-2.00 (m, 2H), 1.91-1.83 (m, 2H), 1.39-1.32 (m, 3H), 1.22-1.17 (m, 6H).

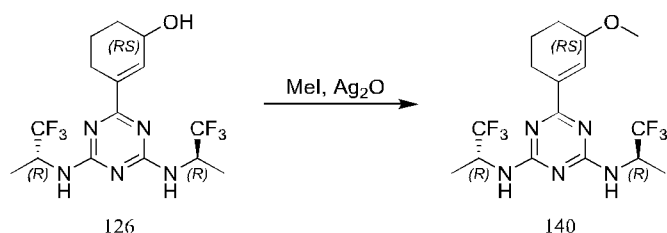
Compound 139 in the below table was prepared according to the procedure of Compounds 138 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

15

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter- mediate
139		394.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.12-6.83 (m, 1H), 5.07-4.92 (m, 1H), 4.64-4.41 (m, 1H), 4.03-3.88 (m, 2H), 3.87-3.76 (m, 1H), 3.72-3.60 (m, 1H), 2.64-2.46 (m, 2H), 2.34-2.18 (m, 1H), 2.13-2.00 (m, 2H), 1.95-1.82 (m, 3H), 1.42-1.30 (m, 3H).	I-8

### Compound 140

#### 6-(3-Methoxycyclohex-1-en-1-yl)-N<sup>2</sup>,N<sup>4</sup>-bis((R)-1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine



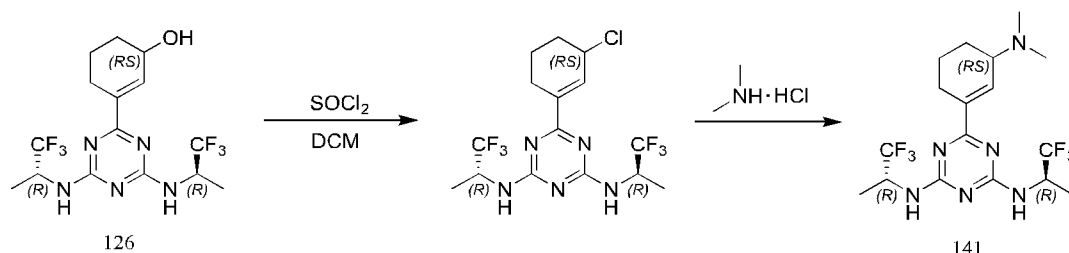
A mixture of Compound 126 (100 mg, 0.25 mmol) and Ag<sub>2</sub>O (115 mg, 0.5 mmol) in CH<sub>3</sub>I (4 mL) was stirred at reflux for 16 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as a white solid (60 mg, yield: 58.3%). MS (m/z): 414.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 7.27-7.08 (m, 1H), 5.05-4.87 (m, 2H), 4.03-3.91 (m, 1H), 3.42 (s, 3H), 2.51-2.34 (m, 2H), 1.98-1.80 (m, 2H), 1.69-1.56 (m, 2H), 1.38-1.29 (m, 6H).

10

### Compound 141

#### 6-(3-(Dimethylamino)cyclohex-1-en-1-yl)-N<sup>2</sup>,N<sup>4</sup>-bis((R)-1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine

15



To a solution of Compound 126 (50mg, 0.125mmol) in dry DCM (3 mL) was added SOCl<sub>2</sub> (16 mg, 0.137 mmol) under ice bath cooling<sup>o</sup>C, and the mixture was stirred in ice bath for 30

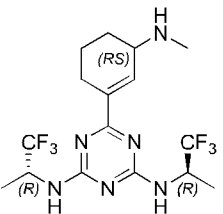


minutes. Then, the solution was charged into a sealed tube, dimethylamine hydrochloride (20 mg, 0.25 mmol) was added, and the mixture was stirred at reflux overnight. After the reaction was completed, the mixture was cooled to room temperature and partitioned between EtOAc and water. The organic layer was collected, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as a white solid (10 mg, yield: 18.9%). MS (m/z): 427.0 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.27-7.11 (m, 1H), 5.06-4.89 (m, 2H), 3.58-3.44 (m, 1H), 2.64-2.53 (m, 1H), 2.44-2.38 (m, 6H), 2.38-2.25 (m, 1H), 2.05-1.92 (m, 2H), 1.66-1.53 (m, 2H), 1.39-1.31 (m, 6H).

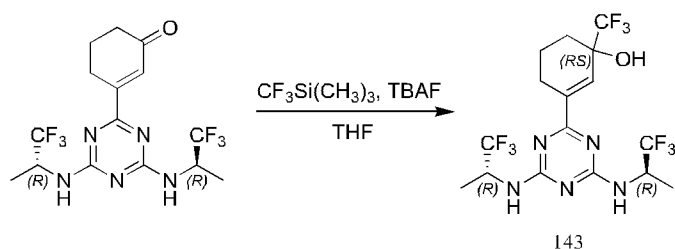
10

Compound 142 in the below table was prepared according to the procedure of Compound 141 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
142		413.1	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 7.26-7.06 (m, 1H), 5.08-4.91 (m, 2H), 3.89-3.73 (m, 1H), 2.74-2.66 (m, 3H), 2.63-2.44 (m, 2H), 2.19-2.07(m, 1H), 2.02-1.92 (m, 1H), 1.76-1.57(m, 2H), 1.38-1.33 (m, 6H).	Comp. 126

### 15 Compound 143

#### 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-1-(trifluoromethyl)-cyclohex-2-en-1-ol



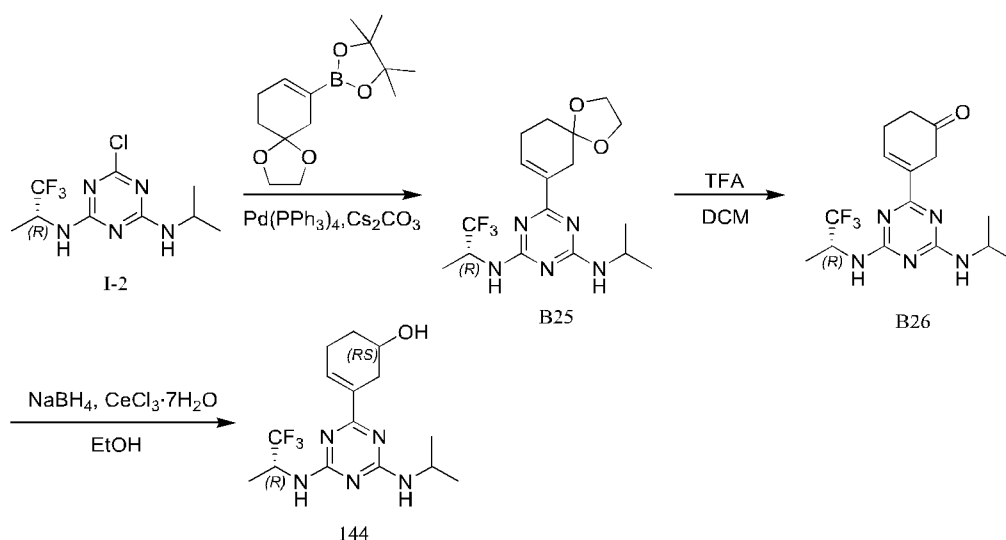
To a solution of 3-(4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-one (prepared according to the procedure of Compound 122 using corresponding intermediates and reagents, 100 mg, 0.25 mmol) and trimethyl(trifluoromethyl)silane (142 mg, 1.25 mmol) in dry THF (10 mL) was added TBAF (1M, 1.25 mL) under ice bath cooling 0°C. The mixture was stirred at reflux for 2 hours, quenched

by the addition of saturated  $\text{NH}_4\text{Cl}$  aqueous solution and extracted with EtOAc. The organic layer was collected, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as a white solid (10 mg, yield: 8.6%). MS (m/z): 468.0  $[\text{M}+\text{H}]^+$ ;

- 5  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.10 (s, 1H), 5.05-4.88 (m, 2H), 2.81-2.63 (m, 1H), 2.35-2.21 (m, 1H), 1.92-1.77 (m, 4H), 1.39-1.31 (m, 6H).

### Compound 144

- 10 **3-(4-(Isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-3-en-1-ol**



- (A) **(R)-N<sup>2</sup>-isopropyl-6-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)-N<sup>4</sup>-(1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine (B25)**

- 15 Under nitrogen atmosphere, to a flask were added Intermediate I-2 (320 mg, 1.13 mmol), 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-7-yl)-1,3,2-dioxaborolane (300 mg, 1.13 mmol),  $\text{Cs}_2\text{CO}_3$  (734 mg, 2.26 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (69 mg, 0.06 mmol), 1,4-dioxane (10 mL) and water (2 mL). The mixture was stirred at  $80^\circ\text{C}$  for 2 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound B25 as white solid.

- 20 (B) **(R)-3-(4-(Isopropylamino)-6-((1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-3-en-1-one (B26)**

To the solution of Compound B25 in dry DCM (3 mL) was added TFA (3 mL) and the mixture was stirred overnight at room temperature. After the reaction was completed, the reaction was

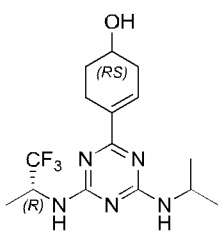
quenched by the addition of saturated NaHCO<sub>3</sub> aqueous solution and extracted with EtOAc. The organic layer was collected, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound B26 as yellow solid (200 mg, yield: 51.5%). MS (m/z): 344.3 [M+H]<sup>+</sup>

5 **(C) 3-(4-(Isopropylamino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-3-en-1-ol**

Compound 144 was prepared according to the procedure of Compound 124 using Compound B26 and corresponding reagents. MS (m/z): 346.3 [M+H]<sup>+</sup>

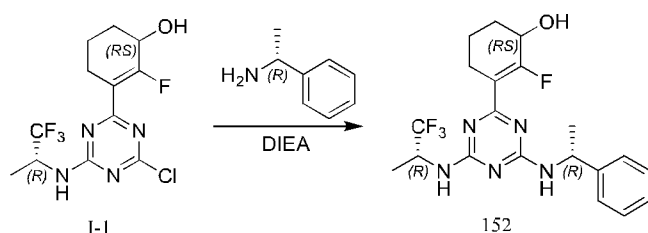
<sup>1</sup>H NMR (400MHz, CD<sub>3</sub>OD): δ 7.27-6.96 (m, 1H), ), 5.08-4.89 (m, 1H), 4.28-4.07 (m, 1H),  
10 4.02-3.83 (m, 1H), 2.91-2.72 (m, 1H), 2.47-2.20 (m, 3H), 1.93-1.80 (m, 1H), 1.65-1.53 (m, 1H),  
1.38-1.28 (m, 3H), 1.24-1.13 (m, 6H).

Compound 145 in the below table was prepared according to the procedure of Compound 144 using the corresponding intermediates and reagents under appropriate conditions that will be  
15 recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
145		346.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.1-6.90 (m, 1H), 5.04-4.88 (m, 1H), 4.25-4.07 (m, 1H), 3.97-3.85 (m, 1H), 2.74-2.60 (m, 1H), 2.57-2.48 (m, 1H), 2.46-2.33 (m, 1H), 2.21-2.09 (m, 1H), 1.97-1.87 (m, 1H), 1.70-1.58 (m, 1H), 1.36-1.29 (m, 3H), 1.21-1.14 (m, 6H).	I-2

**Compound 152**

**2-Fluoro-3-(4-(((R)-1-phenylethyl)amino)-6-(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)cyclohex-2-en-1-ol**



20 To a sealed tube was added Intermediate I-1 (50 mg, 0.15 mmol), (R)-1-phenylethylamine (36 mg, 0.30 mmol), DIEA (77 mg, 0.60 mmol) and 1,4-dioxane (3 mL) in sequence. The

mixture was stirred at 100 °C for 2 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as white solid (15 mg, yield: 23.4%). MS (m/z): 426.3 [M+H]<sup>+</sup>

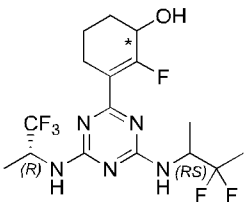
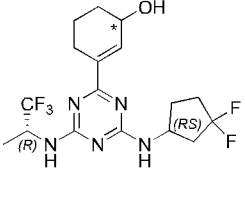
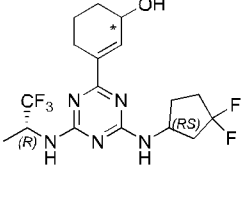
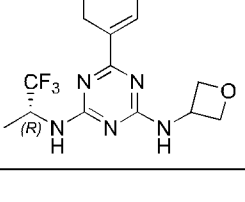
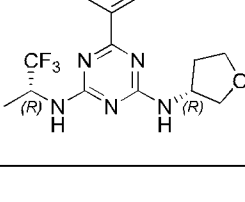
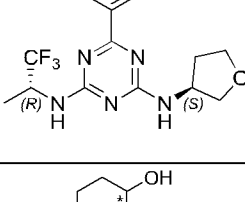
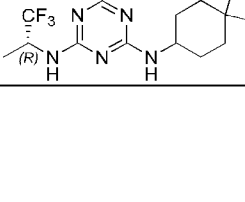
- 5 <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.35-7.15 (m, 5H), 5.22-4.60 (m, 2H), 4.33-4.21 (m, 1H), 2.62-2.23 (m, 2H), 1.89-1.73 (m, 3H), 1.67-1.58 (m, 1H), 1.50-1.44 (m, 3H), 1.34-1.28 (m, 2H), 1.16-1.07 (m, 1H).

10 The compounds in the below table were prepared according to the procedure of Compound 152 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
153		394.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.21-6.96 (m, 1H), 5.09-4.88 (m, 1H), 4.39-4.13 (m, 2H), 2.99-2.87 (m, 2H), 2.71-2.50 (m, 2H), 2.47-2.32 (m, 2H), 1.99-1.81 (m, 2H), 1.67-1.52 (m, 2H), 1.39-1.31 (m, 3H).	I-25
154		386.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.26-7.03 (m, 1H), 5.07-4.90 (m, 1H), 4.38-4.26 (m, 1H), 4.21-4.02 (m, 2H), 2.49-2.33 (m, 2H), 1.97-1.82 (m, 2H), 1.67-1.52 (m, 2H), 1.39-1.31 (m, 3H).	I-25
155		360.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.21-6.89 (m, 1H), 5.07-4.87 (m, 1H), 4.36-4.24 (m, 1H), 2.48-2.33 (m, 2H), 1.97-1.83 (m, 2H), 1.68-1.52 (m, 2H), 1.43 (s, 9H), 1.38-1.32 (m, 3H).	I-25
156		358.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.25-6.90 (m, 1H), 5.13-4.93 (m, 1H), 4.38-4.23 (m, 1H), 2.54-2.31 (m, 2H), 1.97-1.81 (m, 2H), 1.69-1.51 (m, 2H), 1.42-1.31 (m, 6H), 0.80-0.72 (m, 2H), 0.66-0.58 (m, 2H).	I-25
157		426.4	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.40-7.15 (m, 5H), 5.23-4.62 (m, 2H), 4.34-4.18 (m, 1H), 2.62-2.24 (m, 2H), 1.88-1.60 (m, 4H), 1.53-1.44 (m, 3H), 1.35-1.29 (m, 2H), 1.18-1.07 (m, 1H).	I-1

158		390.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.99-4.88 (m, 1H), 4.33-4.22 (m, 1H), 3.61- 3.40 (m, 1H), 2.65- 2.47 (m, 1H), 2.43-2.25 (m, 1H), 1.91-1.72 (m, 3H), 1.70- 1.59 (m, 1H), 1.36-1.31 (m, 3H), 1.27-1.21 (m, 3H), 1.03 – 0.86 (m, 1H), 0.56-0.30 (m, 3H), 0.26-0.15 (m, 1H).	I-1
159		416.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.97-4.88 (m, 1H), 4.35-4.13 (m, 2H), 2.60-2.47 (m, 1H), 2.44-2.26 (m, 3H), 2.10-2.02 (m, 2H), 1.97-1.76 (m, 9H), 1.70-1.60 (m, 1H), 1.38-1.29 (m, 3H).	I-1
160		452.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.97-4.89 (s, 1H), 4.43-4.22 (m, 2H), 2.68-2.43 (m, 7H), 2.37-2.25 (m, 1H), 2.121-2.06 (m, 2H), 1.91-1.73 (m, 3H), 1.73-1.58 (m, 1H), 1.37-1.29 (m, 3H).	I-1
161		418.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.97-4.88 (m, 1H), 4.78-4.71 (m, 2H), 4.64-4.55 (m, 2H), 4.37-4.14 (m, 2H), 2.70-2.48 (m, 3H), 2.38-2.12 (m, 3H), 1.90-1.61 (m, 4H), 1.38-1.29 (m, 3H).	I-1
162		362.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.10-4.89 (m, 1H), 4.33-4.20 (m, 1H), 2.79-2.67 (m, 1H), 2.64-2.48 (m, 1H), 2.40-2.22 (m, 1H), 1.89-1.72 (m, 3H), 1.70-1.59 (br, 1H), 1.40-1.31 (m, 3H), 0.77-0.67 (m, 2H), 0.55-0.48 (m, 2H).	I-1
163		392.3	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 4.98-4.89 (m, 1H), 4.33-4.22 (m, 1H), 4.00-3.86 (m, 1H), 2.62-2.47 (m, 1H), 2.41-2.23 (m, 1H), 1.89-1.72 (m, 4H), 1.71-1.60 (m, 1H), 1.38-1.30 (m, 3H), 1.15-1.07 (m, 3H), 0.96-0.88 (m, 6H).	I-1
164		378.3	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 4.97-4.90 (m, 1H), 4.34-4.22 (m, 1H), 4.03-3.91 (m, 1H), 2.63-2.48 (m, 1H), 2.40-2.24 (m, 1H), 1.90-1.73 (m, 3H), 1.69-1.61 (m, 1H), 1.58-1.47 (m, 2H), 1.39-1.30 (m, 3H), 1.19-1.11 (m, 3H), 0.97-0.88 (m, 3H).	I-1
165		378.3	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 4.97-4.90 (m, 1H), 4.34-4.22 (m, 1H), 4.03-3.91 (m, 1H), 2.63-2.48 (m, 1H), 2.40-2.24 (m, 1H), 1.90-1.73 (m, 3H), 1.69-1.61 (m, 1H), 1.58-1.47 (m, 2H), 1.39-1.30 (m, 3H), 1.19-1.11 (m, 3H), 0.97-0.88 (m, 3H).	I-1

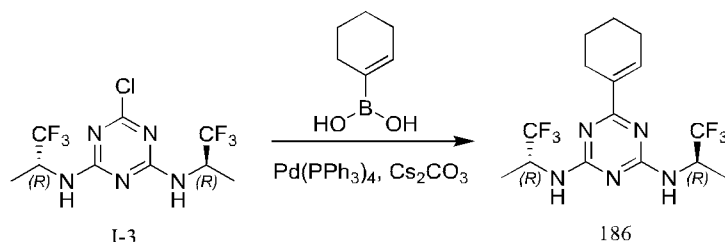
166		426.3	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 5.02-4.95 (m, 1H), 4.78-4.57 (m, 1H), 4.41-4.22 (m, 1H), 2.57-2.52 (m, 1H), 2.43-2.31 (m, 1H), 2.27-2.05 (m, 3H), 1.95-1.62 (m, 7H), 1.43-1.31 (m, 3H).	I-1
167		392.4	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.93 (m, 1H), 4.36-4.23 (m, 1H), 4.04-3.90 (m, 1H), 2.64-2.50 (m, 1H), 2.40-2.27 (m, 1H), 1.90-1.63 (m, 5H), 1.40-1.32 (m, 3H), 1.18-1.09 (m, 3H), 0.98-0.88 (m, 6H).	I-1
168		389.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.99-4.93 (m, 1H), 4.42-4.25 (m, 2H), 2.88-2.71 (m, 2H), 2.66-2.52 (m, 1H), 2.44-2.28 (m, 1H), 1.92-1.83 (m, 2H), 1.82-1.73 (m, 1H), 1.71-1.63 (m, 1H), 1.42-1.31 (m, 6H).	I-1
169		382.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.92 (m, 1H), 4.51-4.26 (m, 4H), 2.64-2.49 (m, 1H), 2.39-2.25 (m, 1H), 1.90-1.61 (m, 4H), 1.40-1.31 (m, 3H), 1.27-1.19 (m, 3H).	I-1
170		382.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.92 (m, 1H), 4.51-4.26 (m, 4H), 2.64-2.49 (m, 1H), 2.39-2.25 (m, 1H), 1.90-1.61 (m, 4H), 1.40-1.31 (m, 3H), 1.27-1.19 (m, 3H).	I-1
171		426.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.99-4.91 (m, 1H), 4.34-4.24 (m, 1H), 3.67-3.44 (m, 2H), 3.19-3.03 (m, 1H), 2.60-2.30 (m, 4H), 1.95-1.74 (m, 4H), 1.70-1.62 (m, 1H), 1.58-1.49 (m, 1H), 1.39-1.33 (m, 3H).	I-1
172		394.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.93 (m, 1H), 4.33-4.26 (m, 1H), 2.63-2.55 (m, 1H), 2.34-2.28 (m, 1H), 1.90-1.76 (m, 3H), 1.71-1.62 (m, 1H), 1.38-1.35 (m, 3H), 1.28 (s, 9H).	I-1
173		405.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.90 (m, 1H), 4.58-4.43 (m, 1H), 4.35-4.25 (m, 1H), 3.00-2.84 (m, 1H), 2.71-2.42 (m, 4H), 2.40-2.21 (m, 5H), 1.89-1.58 (m, 5H), 1.40-1.28 (m, 3H).	I-61
174		400.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 6.07-5.70 (m, 1H), 5.01-4.88 (m, 1H), 4.52-4.35 (m, 1H), 4.33-4.23 (m, 1H), 2.65-2.51 (m, 1H), 2.44-2.25 (m, 1H), 1.89-1.61 (m, 4H), 1.38-1.30 (m, 3H), 1.28-1.21 (m, 3H).	I-61

175		414.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.89 (m, 1H), 4.69-4.51 (m, 1H), 4.35-4.22 (m, 1H), 2.68-2.50 (m, 1H), 2.41-2.25 (m, 1H), 1.90-1.73 (m, 3H), 1.68-1.50 (m, 4H), 1.38-1.31 (m, 3H), 1.28-1.22 (m, 3H).	I-61
176		408.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.27-6.94 (m, 1H), 5.10-4.87 (m, 1H), 4.57-4.38 (m, 1H), 4.36-4.25 (m, 1H), 2.62-2.48 (m, 1H), 2.47-2.32 (m, 2H), 2.28-2.15 (m, 2H), 2.13-1.97 (m, 2H), 1.96-1.72 (m, 3H), 1.66-1.50 (m, 2H), 1.39-1.31 (m, 3H).	I-26
177		408.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.27-6.94 (m, 1H), 5.10-4.87 (m, 1H), 4.57-4.38 (m, 1H), 4.36-4.25 (m, 1H), 2.62-2.48 (m, 1H), 2.47-2.32 (m, 2H), 2.28-2.15 (m, 2H), 2.13-1.97 (m, 2H), 1.96-1.72 (m, 3H), 1.66-1.50 (m, 2H), 1.39-1.31 (m, 3H).	I-27
178		360.0	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 7.17-6.98 (m, 1H), 5.18-4.90 (m, 2H), 4.90-4.86 (m, 2H), 4.66-4.59 (m, 2H), 4.35-4.26 (m, 1H), 2.46-2.35 (m, 2H), 1.97-1.81 (m, 2H), 1.67-1.52 (m, 2H), 1.35-1.30 (m, 3H).	I-27
179		374	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.23-6.95 (m, 1H), 5.08-4.90 (m, 1H), 4.61-4.44 (m, 1H), 4.35-4.25 (m, 1H), 4.00-3.89 (m, 2H), 3.85-3.76 (m, 1H), 3.70-3.59 (m, 1H), 2.48-2.35 (m, 2H), 2.29-2.18 (m, 1H), 1.96-1.83 (m, 3H), 1.68-1.52 (m, 2H), 1.37-1.31 (m, 3H).	I-27
180		374	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.23-6.95 (m, 1H), 5.08-4.90 (m, 1H), 4.61-4.44 (m, 1H), 4.35-4.25 (m, 1H), 4.00-3.89 (m, 2H), 3.85-3.76 (m, 1H), 3.70-3.59 (m, 1H), 2.48-2.35 (m, 2H), 2.29-2.18 (m, 1H), 1.96-1.83 (m, 3H), 1.68-1.52 (m, 2H), 1.37-1.31 (m, 3H).	I-27
181		422.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.23-6.93 (m, 1H), 5.13-4.88 (m, 1H), 4.39-4.27 (m, 1H), 4.14-3.91 (m, 1H), 2.53-2.35 (m, 2H), 2.14-1.81 (m, 8H), 1.73-1.51 (m, 4H), 1.40-1.30 (m, 3H).	I-27

182		388.2	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 7.24-6.90 (m, 1H), 5.10-4.88 (m, 1H), 4.39-4.27 (m, 1H), 4.23-4.08 (m, 2H), 2.46-2.35 (m, 2H), 2.07-1.97 (m, 1H), 1.95-1.80 (m, 4H), 1.70-1.52 (m, 5H), 1.37-1.31 (m, 3H).	I-27
183		376.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.20-6.93 (m, 1H), 5.07-4.89 (m, 1H), 4.37-4.19 (m, 2H), 3.48-3.41 (m, 1H), 3.38-3.32 (m, 4H), 2.45-2.34 (m, 2H), 1.96-1.81 (m, 2H), 1.67-1.53 (m, 2H), 1.37-1.31 (m, 3H), 1.20-1.15 (m, 3H).	I-27
184		362.2	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 7.19-6.91 (m, 1H), 5.06-4.90 (m, 1H), 4.35-4.07 (m, 2H), 3.63-3.48 (m, 2H), 2.47-2.33 (m, 2H), 1.96-1.81 (m, 2H), 1.67-1.52 (m, 2H), 1.36-1.31 (m, 3H), 1.22-1.16 (m, 3H).	I-27

### Compound 186

#### 6-(Cyclohex-1-en-1-yl)-N<sup>2</sup>,N<sup>4</sup>-bis((R)-1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine



- 5 Under nitrogen atmosphere, to a flask was added Intermediate I-3 (150 mg, 0.44 mmol), cyclohex-1-en-1-ylboronic acid (85 mg, 0.66 mmol), Cs<sub>2</sub>CO<sub>3</sub> (290 mg, 0.88 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (26 mg, 0.022 mmol), 1,4-dioxane (10 mL) and water (2 mL) in sequence. The mixture was stirred at 100 °C for 16 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to
- 10 give the title compound as white solid (154 mg, yield: 90.4%). MS (m/z): 384.1 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.84-7.60 (m, 2H), 7.18 (s, 1H), 5.07-4.76 (m, 2H), 2.40-2.28 (m, 2H), 2.25-2.16 (m, 2H), 1.68-1.52 (m, 4H), 1.34-1.25 (m, 6H).

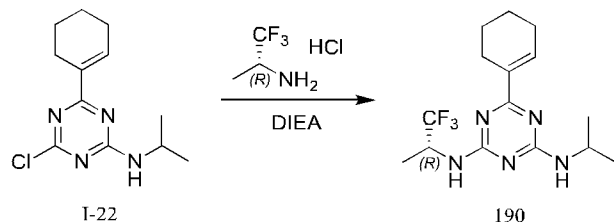
- The compounds in the below table were prepared according to the procedure of Compound 186
- 15 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:



Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
187		300.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.20-6.87 (m, 1H), 3.27-3.16 (m, 4H), 2.45-2.34 (m, 2H), 2.26-2.18 (m, 2H), 1.74-1.60 (m, 4H), 1.12-1.00 (m, 2H), 0.53-0.39 (m, 4H), 0.29-0.16 (m, 4H).	I-6
188		360.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.41-6.99 (m, 1H), 5.11-4.88 (m, 1H), 3.60-3.34 (m, 2H), 2.55-2.35 (m, 2H), 2.29-2.15 (m, 2H), 1.81-1.57 (m, 4H), 1.40-1.30 (m, 3H), 1.19 (s, 6H).	I-7
189		316.1	<sup>1</sup> H NMR (400MHz, CD <sub>3</sub> OD): δ 6.96-6.78 (m, 1H), 5.06-4.87 (m, 1H), 4.25-4.07 (m, 1H), 2.72-2.62 (m, 2H), 2.56-2.49 (m, 2H), 2.03-1.93 (m, 2H), 1.38-1.30 (m, 3H), 1.22-1.15 (m, 6H).	I-2

### Compound 190

**(R)-6-(cyclohex-1-en-1-yl)-N<sup>2</sup>-isopropyl-N<sup>4</sup>-(1,1,1-trifluoropropan-2-yl)-1,3,5-triazine-2,4-diamine**



A mixture of Intermediate I-22 (85 mg, 0.33 mmol), (R)-1,1,1-trifluoropropan-2-amine hydrochloride (201 mg, 1.34 mmol) and DIEA (0.47mL, 2.69 mmol) in 1,4-dioxane (3 mL) was stirred under microwave at 150 °C for 3 hours. After the reaction was completed, the mixture was cooled to room temperature, condensed and purified by flash column chromatography (eluting with PE/EA) to give the title compound as yellow solid (18 mg, yield 14%). MS (m/z): 330.1 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.32-6.94 (m, 1H), 4.66-4.52 (m, 1H), 4.32-4.02 (m, 1H), 2.52-2.33 (m, 2H), 2.29-2.16 (m, 2H), 1.79-1.60 (m, 4H), 1.40-1.29 (m, 3H), 1.24-1.14 (m, 6H).

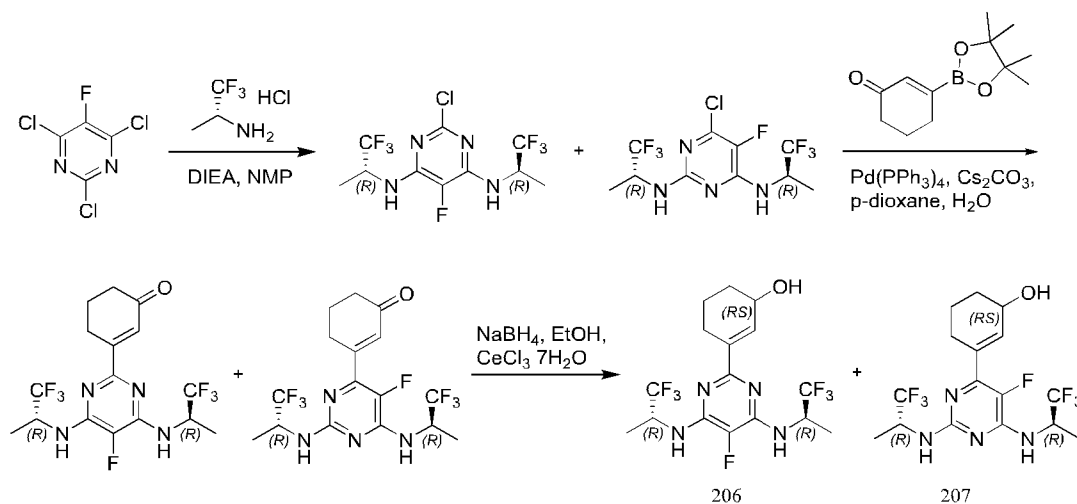
The compounds in the below table were prepared according to the procedure of Compound 190 using the corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter-mediate
191		328.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.19-6.85 (m, 1H), 3.60-3.40 (m, 2H), 2.46-2.29 (m, 2H), 2.25-2.16 (m, 2H), 1.73-1.60 (m, 4H), 1.23 (d, J = 6.6 Hz, 6H), 0.97-0.85 (m, 2H), 0.53-0.30 (m, 6H), 0.23-0.15 (m, 2H).	I-23
192		342.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.30-7.02 (m, 1H), 5.08-4.90 (m, 1H), 3.28-3.16 (m, 2H), 2.50-2.34 (m, 2H), 2.28-2.18 (m, 2H), 1.79-1.59 (m, 4H), 1.40-1.31 (m, 3H), 1.15-1.01 (m, 1H), 0.56-0.44 (m, 2H), 0.30-0.19 (m, 2H).	I-24
193		260.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.25-6.82 (m, 1H), 3.28-3.13 (m, 2H), 2.89 (s, 3H), 2.47-2.33 (m, 2H), 2.27-2.17 (m, 2H), 1.75-1.60 (m, 4H), 1.14-0.99 (m, 1H), 0.53-0.42 (m, 2H), 0.31-0.17 (m, 2H).	I-24
194		288.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.24-6.85 (m, 1H), 4.27-4.06 (m, 1H), 3.28-3.17 (m, 2H), 2.45-2.35 (m, 2H), 2.26-2.19 (m, 2H), 1.75-1.61 (m, 4H), 1.19 (d, J = 6.5 Hz, 6H), 1.12-1.01 (m, 1H), 0.53-0.43 (m, 2H), 0.29-0.18 (m, 2H).	I-24
195		318.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.26-6.89 (m, 1H), 3.45-3.35 (m, 2H), 3.27-3.16 (m, 2H), 2.45-2.35 (m, 2H), 2.26-2.19 (m, 2H), 1.75-1.61 (m, 4H), 1.20 (s, 6H), 1.10-1.02 (m, 1H), 0.52-0.43 (m, 2H), 0.26-0.19 (m, 2H).	I-24

## 5 Compounds 206 and 207

**3-(5-Fluoro-4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-2-yl)cyclohex-2-en-1-ol and**

**3-(5-fluoro-2,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl)cyclohex-2-en-1-ol**



**(A) A mixture of 2-chloro-5-fluoro- $N^4,N^6$ -bis((R)-1,1,1-trifluoropropan-2-yl)pyrimidine-4,6-diamine and 6-chloro-5-fluoro- $N^2,N^4$ -bis((R)-1,1,1-trifluoropropan-2-yl)pyrimidine-2,4-diamine**

- 5 Under nitrogen atmosphere, a mixture of 2,4,6-trichloro-5-fluoropyrimidine (1.12 g, 5.6 mmol), (R)-1,1,1-trifluoropropan-2-amine hydrochloride (2.51g, 16.8 mmol), DIEA (4.22g, 56mmol) and N-methylpyrrolidone (5 mL) was stirred under microwave at 200 °C for 1 hour. After cooled to room temperature, the mixture was directly injected into RP-C18 column and purified by flash column chromatography (eluting with gradient water/MeOH = 100:0-0:100) to give the product as white solid (80 mg, yield 4.2%). MS (m/z): 354.9 [M+H]<sup>+</sup>
- 10

**(B) A mixture of 3-(5-fluoro-4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino) pyrimidin-2-yl) cyclohex-2-en-1-one and 3-(5-fluoro-2,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino) pyrimidin-4-yl)cyclohex-2-en-1-one**

- Under nitrogen atmosphere, a mixture of the product obtained in step (A) (80mg, 0.23 mmol),
- 15 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-2-en-1-one (50mg, 0.23 mmol), Cs<sub>2</sub>CO<sub>3</sub> (150mg, 0.46mmol), 1,4-dioxane (5 mL) and water (1.5 mL) was stirred under microwave at 130 °C for 40 minutes. After cooled to room temperature, the mixture was condensed and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give the product as white solid (60 mg, yield: 63.2%). MS (m/z): 415.0 [M+H]<sup>+</sup>

- 20 **(C) 3-(5-Fluoro-4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-2-yl) cyclohex-2-en-1-ol and 3-(5-fluoro-2,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino)pyrimidin-4-yl) cyclohex-2-en-1-ol**

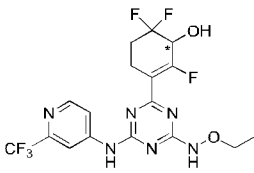
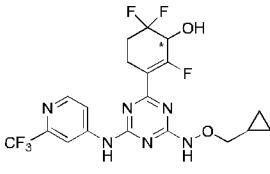
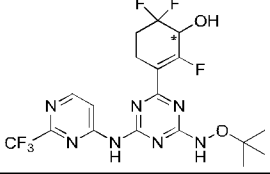
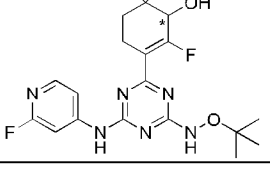
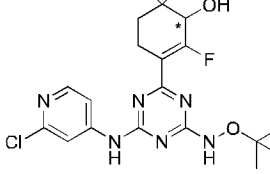
- Compounds 206 and 207 were prepared according to the procedure of Compound 124 using the mixture of 3-(5-fluoro-4,6-bis(((R)-1,1,1-trifluoropropan-2-yl)amino) pyrimidin-2-yl)cyclohex-2-en-1-one and 3-(5-fluoro-2,6-bis(((R)-1,1,1-trifluoro propan-2-yl)amino)pyrimidin-4-yl)
- 25

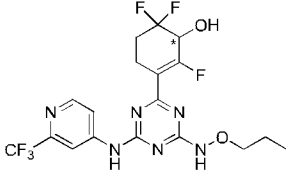
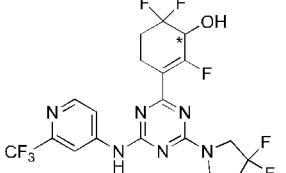
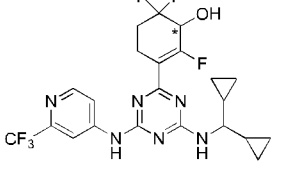
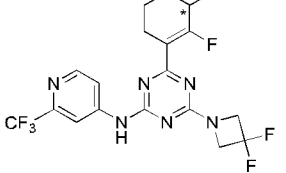
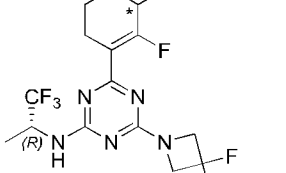
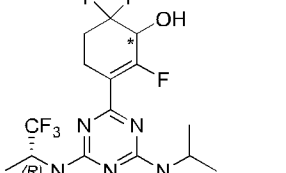
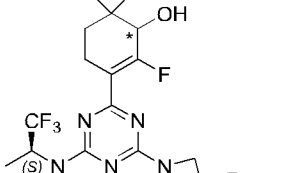
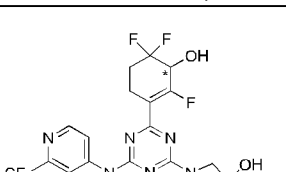
cyclohex-2-en-1-one obtained in step (B) and corresponding reagents, and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100).

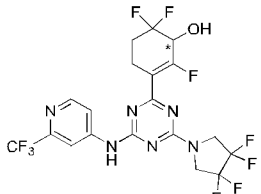
**Compound 206**, MS (m/z): 417.0 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 6.97-6.89 (m, 1H), 5.21-5.03 (m, 2H), 4.38-4.26 (m, 1H), 2.55-2.34 (m, 2H), 1.96-1.82 (m, 2H), 1.68-1.52 (m, 2H), 1.42-1.32 (m, 6H).

**Compound 207**, MS (m/z): 417.0 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 6.47-6.40 (m, 1H), 5.10-4.97(m, 1H), 4.82-4.72 (m, 1H), 4.35-4.26(m, 1H), 2.50-2.30 (m, 2H), 1.99-1.85 (m, 2H), 1.71-1.56 (m, 2H), 1.38 (d, J = 7.1 Hz, 3H), 1.32 (d, J = 7.0 Hz, 3H).

10 The compounds in the below table were prepared according to the procedure described above, using corresponding intermediates and reagents under appropriate conditions that will be recognized by POSITA:

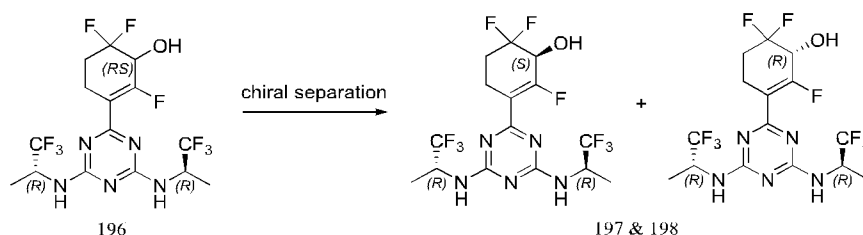
Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	Inter- mediate
212		451.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.54-8.35 (m, 2H), 7.98-7.78 (m, 1H), 4.37-4.24 (m, 1H), 4.10-3.94 (m, 2H), 2.89-2.72 (m, 1H), 2.66-2.52 (m, 1H), 2.33-2.05 (m, 2H), 1.33-1.24 (m, 3H).	I-93
213		477.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.50-8.31 (m, 2H), 8.00-7.88 (m, 1H), 4.41-4.24 (m, 1H), 3.78 (d, J = 7.2 Hz, 2H), 2.90-2.73 (m, 1H), 2.66-2.49 (m, 1H), 2.32-2.05 (m, 2H), 1.26-1.09 (m, 1H), 0.62-0.51 (m, 2H), 0.35-0.25 (m, 2H).	I-94
214		480.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.92-8.76 (m, 1H), 8.73-8.64 (m, 1H), 4.40- 4.26 (m, 1H), 2.93-2.77 (m, 1H), 2.71-2.55 (m, 1H), 2.34-2.07 (m, 2H), 1.31 (s, 9H).	I-95
215		429.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.05-7.88 (m, 2H), 7.47-7.43 (m, 1H), 4.34-4.30 (m, 1H), 2.85-2.77 (m, 1H), 2.65-2.55 (m, 1H), 2.31-2.06 (m, 2H), 1.32 (s, 9H).	I-65
216		445.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.31 (s, 1H), 8.13-8.02 (m, 1H), 7.64-7.47 (m, 1H), 4.38-4.23 (m, 1H), 2.89-2.71 (m, 1H), 2.66-2.50 (m, 1H), 2.32-2.03 (m, 2H), 1.32 (s, 9H).	I-96

217		465.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.61-8.28 (m, 2H), 8.07-7.76 (m, 1H), 4.42-4.16 (m, 1H), 4.03-3.82 (m, 2H), 2.88-2.72 (m, 1H), 2.67-2.50 (m, 1H), 2.31-2.06 (m, 2H), 1.80-1.63 (m, 2H), 1.10-0.90 (m, 3H).	I-97
218		497.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.61-8.26 (m, 2H), 7.91-7.74 (m, 1H), 4.45-4.21 (m, 1H), 3.98-3.77 (m, 4H), 2.90-2.75 (m, 1H), 2.65-2.41 (m, 3H), 2.30-2.05 (m, 2H).	I-98
220		501.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.77-7.63 (m, 2H), 7.68 (s, 1H), 4.39-4.18 (m, 1H), 3.27-3.16 (m, 1H), 2.89-2.45 (m, 2H), 2.33-2.02 (m, 2H), 1.17-0.98 (m, 2H), 0.60-0.47 (m, 2H), 0.44-0.27 (m, 6H).	I-99
221		483.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.50-8.37 (m, 2H), 7.88-7.80 (m, 1H), 4.60-4.40 (m, 4H), 4.34-4.27 (m, 1H), 2.85-2.75 (m, 1H), 2.65-2.55 (m, 1H), 2.31-2.05 (m, 2H).	I-100
243		434.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.86 (m, 1H), 4.49-4.34 (m, 4H), 4.30-4.20 (m, 1H), 2.75-2.65 (m, 1H), 2.55-2.45 (m, 1H), 2.27-2.02 (m, 2H), 1.45-1.33 (m, 3H).	I-101
244		400.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.90 (br, 1H), 4.37-4.20 (m, 1H), 4.19-4.03 (m, 1H), 2.85-2.39 (m, 2H), 2.32-2.02 (m, 2H), 1.43-1.29 (m, 3H), 1.23-1.09 (m, 6H).	I-2
299		434.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.04-4.86 (m, 1H), 4.50-4.34 (m, 4H), 4.31-4.20 (m, 1H), 2.78-2.65 (m, 1H), 2.59-2.44 (m, 1H), 2.29-1.98 (m, 2H), 1.41-1.31 (m, 3H).	I-102
300		545.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.60-8.47 (m, 1H), 8.43-8.38 (m, 1H), 7.86-7.70 (m, 1H), 4.38-4.23 (m, 1H), 4.01-3.66 (m, 4H), 2.89-2.73 (m, 1H), 2.69-2.51 (m, 1H), 2.41-2.06 (m, 4H).	I-103

301		533.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.51-8.43 (m, 1H), 8.42-8.38 (m, 1H), 7.91-7.84 (m, 1H), 4.40-4.29 (m, 1H), 4.24-4.12 (m, 4H), 2.93-2.77 (m, 1H), 2.69-2.55 (m, 1H), 2.36-2.06 (m, 2H).	I-104
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### Compounds 197 and 198

#### 3-(4,6-Bis(((R)-1,1,1-trifluoropropan-2-yl)amino)-1,3,5-triazin-2-yl)-2,6,6-trifluorocyclohex-2-en-1-ol, optically pure diastereoisomers



The Compound 196 was resolved by chiral HPLC to provide a pair of optically pure diastereoisomers, Compounds 197 and 198 (Chiral HPLC conditions: Preparation instrument: Shimadzu LC-10AD vp; Column: Daicel AD-H(250mm\*30mm, 5μm); mobile phase: n-heptane/isopropanol = 90/10; flow rate: 40 mL/min; column temperature: 40 °C). The first eluent (RT = 4.203 min) was concentrated and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give a compound named as Compound 197, de% = 99.27%, MS (m/z): 454.1 [M+1]<sup>+</sup>. The the second eluent (RT = 5.906 min) was concentrated and purified by flash column chromatography (eluting with gradient PE/EA = 100:0-0:100) to give a compound named as Compound 198, de% = 97.82%, MS (m/z): 454.2 [M+1]<sup>+</sup>.

15 **Compound 197:** <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 5.00-4.86 (m, 2H), 4.36-4.17 (m, 1H), 2.80-2.65 (m, 1H), 2.58-2.42 (m, 1H), 2.25-2.05 (m, 2H), 1.37-1.31 (m, 6H).

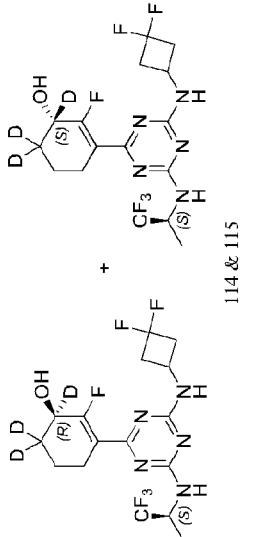
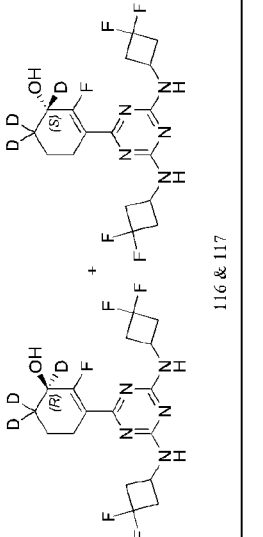
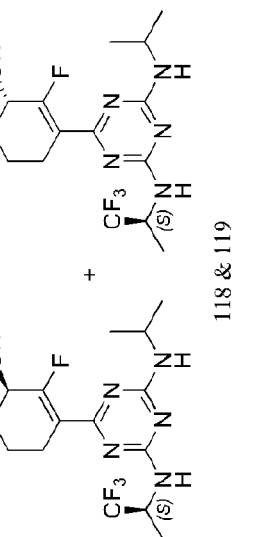
**Compound 198:** <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 5.00-4.86 (m, 2H), 4.36-4.17 (m, 1H), 2.80-2.65 (m, 1H), 2.58-2.42 (m, 1H), 2.25-2.05 (m, 2H), 1.37-1.31 (m, 6H).

20 The compounds in the below table were prepared according to the procedure of Compounds 197 and 198 using the corresponding compounds and under appropriate HPLC conditions (flow rate: 0.5 mL/min; detection wavelength: UV 254 nm):

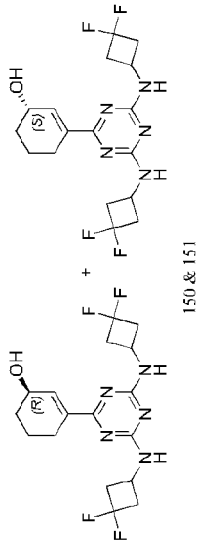
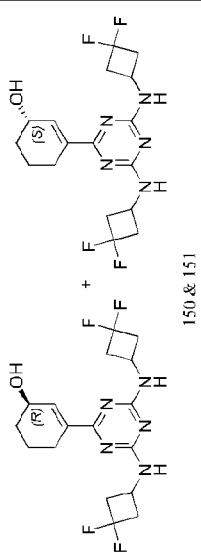
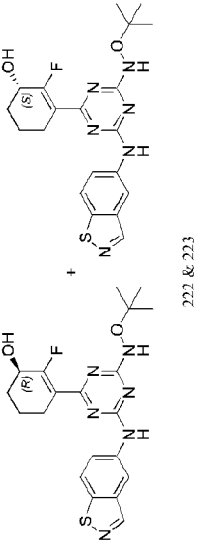
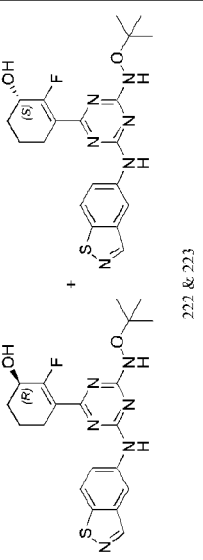
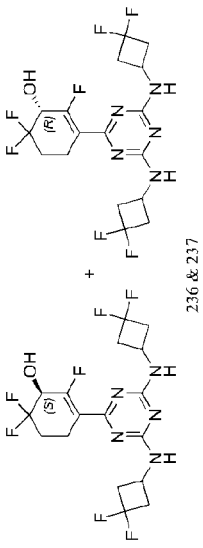
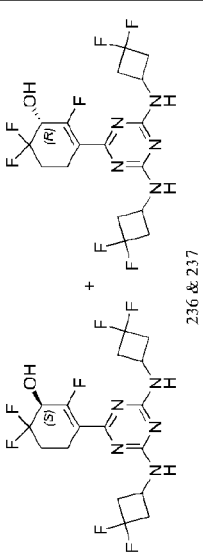
Comp.	Structure	MS (M+H) <sup>+</sup>	<sup>1</sup> H NMR	RT (min)	Purity	Chiral HPLC Condition	Comp. for separation
100		364.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.89 (m, 1H), 4.33-4.24 (m, 1H), 4.21-4.06 (m, 1H), 2.63-2.47 (m, 1H), 2.41-2.47 (br, 1H), 1.93-1.71 (m, 3H), 1.70-1.61 (m, 1H), 1.40-1.30 (m, 3H), 1.21-1.15 (m, 6H).	1.230	ee%=100%	Column: OJ-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol (0.1% Et <sub>2</sub> NH) = 90/10	1
101		364.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.90 (m, 1H), 4.34-4.24 (m, 1H), 4.20-4.06 (m, 1H), 2.65-2.48 (m, 1H), 2.43-2.23 (m, 1H), 1.92-1.72 (m, 3H), 1.68-1.59 (m, 1H), 1.40-1.31 (m, 3H), 1.21-1.14 (m, 6H).	1.316	ee%=100%		
102		418.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.88 (m, 2H), 4.34-4.25 (m, 1H), 2.68-2.51 (m, 1H), 2.41-2.26 (m, 1H), 1.90-1.74 (m, 3H), 1.70-1.58 (m, 1H), 1.37-1.31 (m, 6H).	1.899	de%=100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol (0.1% Et <sub>2</sub> NH) = 80/20	2
103		418.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.87 (m, 2H), 4.34-4.24 (m, 1H), 2.64-2.50 (m, 1H), 2.45-2.32 (m, 1H), 1.91-1.71 (m, 3H), 1.69-1.71 (m, 1H), 1.38-1.30 (m, 6H).	2.263	de%=100%		
104		406.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.37-4.22 (m, 3H), 3.02-2.86 (m, 4H), 2.73-2.50 (m, 5H), 2.41-2.25 (m, 1H), 1.91-1.72 (m, 3H), 1.72-1.62 (m, 1H).	3.608	ee%=100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol (0.1% Et <sub>2</sub> NH) = 70/30	5
105		406.3	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.37-4.22 (m, 3H), 3.02-2.86 (m, 4H), 2.73-2.50 (m, 5H), 2.41-2.25 (m, 1H), 1.91-1.72 (m, 3H), 1.72-1.62 (m, 1H).	3.871	ee%=100%		

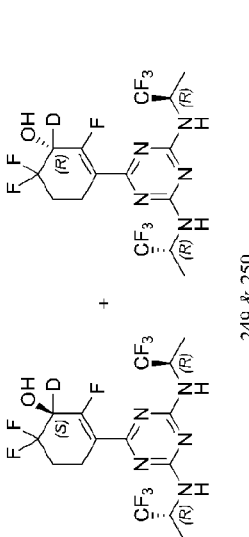
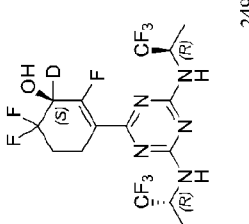
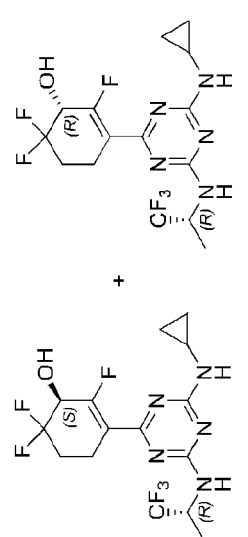
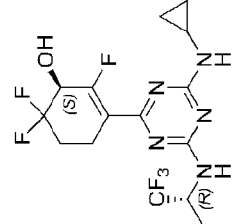
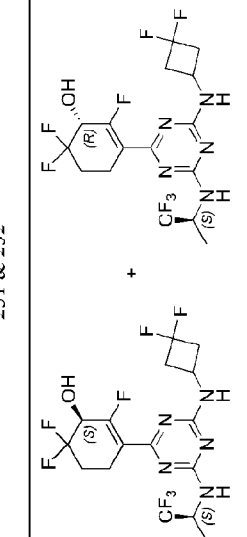
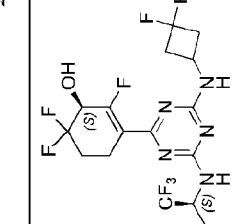
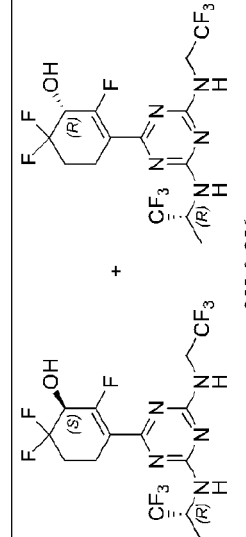
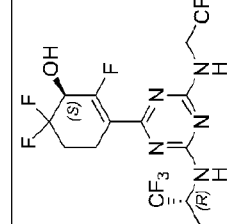
106			432.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.89 (m, 2H), 4.53-4.41 (m, 1H), 2.77-2.62 (m, 1H), 2.40-2.27 (m, 1H), 2.02-1.83 (m, 3H), 1.74-1.61 (m, 3H), 1.39-1.32 (m, 6H)	10.540	de% = 97.79%	Column: AS-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 90/10	19
107			432.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.89 (m, 2H), 4.53-4.41 (m, 1H), 2.77-2.62 (m, 1H), 2.40-2.27 (m, 1H), 2.02-1.83 (m, 3H), 1.74-1.61 (m, 3H), 1.39-1.32 (m, 6H)	18.120	de% = 97.84%		
108			407.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.38-4.15 (m, 2H), 3.05-2.85 (m, 4H), 2.72-2.48 (m, 5H), 2.40-2.26 (m, 1H), 1.90-1.61 (m, 4H)	4.596	de% = 99.8%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 70/30	
109			407.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.38-4.15 (m, 2H), 3.05-2.85 (m, 4H), 2.72-2.48 (m, 5H), 2.40-2.26 (m, 1H), 1.90-1.61 (m, 4H)	4.897	de% = 99.32%		
110			419.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.87 (m, 2H), 2.68-2.51 (m, 1H), 2.44-2.28 (m, 1H), 1.92-1.63 (m, 4H), 1.42-1.30 (m, 6H)	10.090	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 90/10	18
111			419.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.02-4.87 (m, 2H), 2.68-2.51 (m, 1H), 2.44-2.28 (m, 1H), 1.92-1.63 (m, 4H), 1.42-1.30 (m, 6H)	16.800	de% = 100%		
112			421.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.87 (m, 2H), 2.63-2.53 (m, 1H), 2.37-2.26 (m, 1H), 1.81-1.69 (m, 1H), 1.67-1.60 (m, 1H), 1.37-1.31 (m, 6H)	5.500	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane /isopropanol = 80/20	83
113			421.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.87 (m, 2H), 2.63-2.53 (m, 1H), 2.37-2.26 (m, 1H), 1.81-1.69 (m, 1H), 1.67-1.60 (m, 1H), 1.37-1.31 (m, 6H)	7.420	de% = 97.54%		



114	 <p>114 &amp; 115</p>	415.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.98-4.89 (m, 1H), 4.35-4.13 (m, 1H), 3.02-2.81 (m, 2H), 2.75-2.46 (m, 3H), 2.44-2.24 (m, 1H), 1.82-1.71 (m, 1H), 1.69-1.58 (m, 1H), 1.38-1.28 (m, 3H)	5.960	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	90
115		415.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.98-4.89 (m, 1H), 4.35-4.13 (m, 1H), 3.02-2.81 (m, 2H), 2.75-2.46 (m, 3H), 2.44-2.24 (m, 1H), 1.82-1.71 (m, 1H), 1.69-1.58 (m, 1H), 1.38-1.28 (m, 3H)	7.800	de% = 98.30%		
116	 <p>116 &amp; 117</p>	409.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.36-4.14 (m, 2H), 2.98-2.85 (m, 4H), 2.67-2.46 (m, 5H), 2.39-2.22 (m, 1H), 1.82-1.71 (m, 1H), 1.68-1.57 (m, 1H)	10.170	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	91
117		409.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.36-4.14 (m, 2H), 2.98-2.85 (m, 4H), 2.67-2.46 (m, 5H), 2.39-2.22 (m, 1H), 1.82-1.71 (m, 1H), 1.68-1.57 (m, 1H)	13.590	de% = 99.16%		
118	 <p>118 &amp; 119</p>	364.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.89 (m, 1H), 4.36-4.25 (m, 1H), 4.19-4.08 (m, 1H), 2.68-2.50 (m, 1H), 2.40-2.24 (m, 1H), 1.96-1.57 (m, 4H), 1.41-1.29 (m, 3H), 1.23-1.12 (m, 6H)	1.334	de% = 97.56%	Column: AS-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 90/10	33
119		364.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.01-4.89 (m, 1H), 4.32-4.25 (m, 1H), 4.20-4.07 (m, 1H), 2.64-2.48 (m, 1H), 2.42-2.26 (m, 1H), 1.93-1.59 (m, 4H), 1.38-1.31 (m, 3H), 1.22-1.15 (m, 6H)	1.403	de% = 100%		

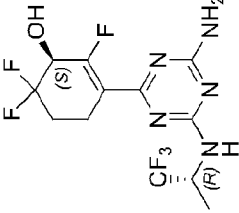
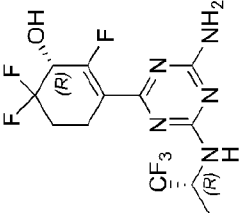
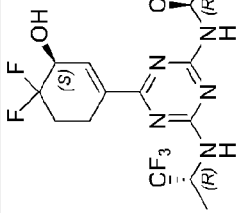
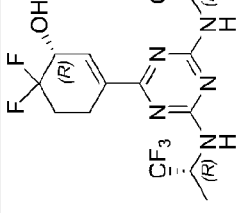
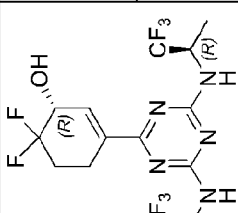
120		412.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.05-4.89 (m, 1H), 4.41-4.13 (m, 2H), 3.08-2.80 (m, 2H), 2.78-2.24 (m, 4H), 2.01-1.60 (m, 4H), 1.47-1.24 (m, 3H)	2.589	de% = 100%	Column: OJ-H (0.46 cm I.D. × 25 cm L); Mobile phase: n-heptane/ isopropanol (0.1% Et <sub>2</sub> NH) = 90/10	31
121		412.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.07-4.88 (m, 1H), 4.39-4.13 (m, 2H), 3.06-2.83 (m, 2H), 2.77-2.23 (m, 4H), 1.95-1.60 (m, 4H), 1.45-1.28 (m, 3H)	3.189	de% = 100%	Column: OJ-H (0.46 cm I.D. × 25 cm L); Mobile phase: n-heptane/ isopropanol (0.1% Et <sub>2</sub> NH) = 90/10	31
146		346.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.21-6.90 (m, 1H), 5.03-4.92 (m, 1H), 4.36-4.26 (m, 1H), 4.22-4.07 (m, 1H), 2.48-2.34 (m, 2H), 1.96-1.83 (m, 2H), 1.66-1.54 (m, 2H), 1.37-1.31 (m, 3H), 1.26-1.13 (m, 6H)	1.526	de% = 100%	Column: AS-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	124
147		346.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.18-6.93 (m, 1H), 5.06-4.91 (m, 1H), 4.37-4.25 (m, 1H), 4.24-4.06 (m, 1H), 2.51-2.28 (m, 2H), 1.98-1.79 (m, 2H), 1.69-1.49 (m, 2H), 1.38-1.30 (m, 3H), 1.22-1.15 (m, 6H)	1.995	de% = 99.774%	Column: AS-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	124
148		400.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-7.03 (m, 1H), 5.06-4.87 (m, 2H), 4.36-4.26 (m, 1H), 2.50-2.34 (m, 2H), 1.99-1.81 (m, 2H), 1.68-1.50 (m, 2H), 1.38-1.31 (m, 6H)	1.169	de% = 100%	Column: AS-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol (0.1% Et <sub>2</sub> NH) = 80/20	126
149		400.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-7.03 (m, 1H), 5.06-4.87 (m, 2H), 4.36-4.26 (m, 1H), 2.50-2.34 (m, 2H), 1.99-1.81 (m, 2H), 1.68-1.50 (m, 2H), 1.38-1.31 (m, 6H)	2.443	de% = 100%	Column: AS-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol (0.1% Et <sub>2</sub> NH) = 80/20	126

150		388.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.93 (m, 1H), 4.36-4.19 (m, 3H), 2.97-2.87 (m, 4H), 2.69-2.50 (m, 4H), 2.45-2.34 (m, 2H), 1.97-1.80 (m, 2H), 1.67-1.51 (m, 2H)	2.492	ee% = 100%	Column: AS-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 70/30	127
151		388.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.93 (m, 1H), 4.36-4.19 (m, 3H), 2.97-2.87 (m, 4H), 2.69-2.50 (m, 4H), 2.45-2.34 (m, 2H), 1.97-1.80 (m, 2H), 1.67-1.51 (m, 2H)	3.658	ee% = 100%		
222		431.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.93-8.78 (m, 2H), 7.98-7.93 (m, 1H), 7.84-7.77 (m, 1H), 4.37-4.30 (m, 1H), 2.70-2.61 (m, 1H), 2.48-2.36 (m, 1H), 1.92-1.86 (m, 2H), 1.85-1.76 (m, 1H), 1.73-1.65 (m, 1H), 1.33 (s, 9H)	5.097	ee% = 99.89%	Column: IC-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 60/40	34
223		431.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.93-8.75 (m, 2H), 7.98-7.93 (m, 1H), 7.83-7.77 (m, 1H), 4.37-4.30 (m, 1H), 2.71-2.61 (m, 1H), 2.48-2.36 (m, 1H), 1.92-1.86 (m, 2H), 1.85-1.77 (m, 1H), 1.73-1.66 (m, 1H), 1.33 (s, 9H)	6.651	ee% = 97.67%		
236		442.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.41-4.08 (m, 3H), 3.01-2.82 (m, 4H), 2.74-2.43 (m, 6H), 2.25-2.02 (m, 2H)	4.121	ee% = 100%	Column: AD-H (0.46 cm I.D. ×15 cm L); Mobile phase: n-heptane/ isopropanol (0.1% Et <sub>2</sub> NH) = 80/20	203
237		442.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.41-4.08 (m, 3H), 3.01-2.82 (m, 4H), 2.74-2.43 (m, 6H), 2.25-2.02 (m, 2H)	4.453	ee% = 100%		

249		455.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.87 (m, 2H), 2.82-2.66 (m, 1H), 2.62-2.45 (m, 1H), 2.27-2.02 (m, 2H), 1.40-1.29 (m, 6H)	2.293	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol (0.1% Et <sub>2</sub> NH) = 80/20	211
250		455.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.87 (m, 2H), 2.82-2.66 (m, 1H), 2.62-2.45 (m, 1H), 2.27-2.02 (m, 2H), 1.40-1.29 (m, 6H)	2.898	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol (0.1% Et <sub>2</sub> NH) = 80/20	211
251		398.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.14-4.92 (m, 1H), 4.33-4.19 (m, 1H), 2.81-2.60 (m, 2H), 2.60-2.41 (m, 1H), 2.25-2.05 (m, 2H), 1.38-1.32 (m, 3H), 0.77-0.69 (m, 2H), 0.55-0.48 (m, 2H)	2.179	de% = 100%	Column: OJ-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol = 90/10	238
252		398.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.04-4.94 (m, 1H), 4.32-4.19 (m, 1H), 2.83-2.61 (m, 2H), 2.58-2.42 (m, 1H), 2.23-2.05 (m, 2H), 1.39-1.32 (m, 3H), 0.77-0.69 (m, 2H), 0.57-0.47 (m, 2H)	2.465	de% = 99.76%	Column: OJ-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol = 90/10	238
253		448.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.04-4.89 (m, 1H), 4.38-4.16 (m, 2H), 3.05-2.85 (m, 2H), 2.81-2.43 (m, 4H), 2.31-1.96 (m, 2H), 1.42-1.30 (m, 3H)	3.225	de% = 100%	Column: OJ-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ethanol = 80/20	239
254		448.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.05-4.92 (m, 1H), 4.34-4.14 (m, 2H), 3.02-2.85 (m, 2H), 2.80-2.45 (m, 4H), 2.29-2.01 (m, 2H), 1.43-1.29 (m, 3H)	3.790	de% = 100%	Column: OJ-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ethanol = 80/20	239
255		440.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.97-4.83 (m, 1H), 4.29-3.90 (m, 3H), 2.77-2.58 (m, 1H), 2.51-2.37 (m, 1H), 2.26-1.93 (m, 2H), 1.37-1.20 (m, 3H)	3.119	de% = 100%	Column: OJ-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol = 80/20	245
256		440.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.82 (m, 1H), 4.27-3.84 (m, 3H), 2.75-2.58 (m, 1H), 2.52-2.35 (m, 1H), 2.21-1.95 (m, 2H), 1.39-1.23 (m, 3H)	3.644	de% = 100%	Column: OJ-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/isopropanol = 80/20	245

257		400.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.90-4.81 (m, 1H), 4.24-4.11 (m, 1H), 3.33-3.14 (m, 2H), 2.70-2.55 (m, 1H), 2.48-2.34 (m, 1H), 2.17-2.96 (m, 2H), 1.56- 1.44 (m, 2H), 1.29-1.23 (m, 3H), 0.88-0.80 (m, 3H)	3.436	de% = 99.24%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	248
258		400.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.90-4.83 (m, 1H), 4.25-4.10 (m, 1H), 3.34-3.13 (m, 2H), 2.70-2.54 (m, 1H), 2.54-2.33 (m, 1H), 2.19-1.96 (m, 2H), 1.56- 1.44 (m, 2H), 1.29-1.22 (m, 3H), 0.89-0.81 (m, 3H)	4.005	de% = 99.74%		
262		447.9	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.04-4.95 (m, 1H), 4.42-4.14 (m, 2H), 3.04-2.87 (m, 2H), 2.84-2.45 (m, 4H), 2.31-2.06 (m, 2H), 1.45-1.33 (m, 3H)	3.388	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	259
263		448.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.92-4.83 (m, 1H), 4.31-4.04 (m, 2H), 2.94-2.73 (m, 2H), 2.72-2.34 (m, 4H), 2.18-1.91 (m, 2H), 1.32-1.21 (m, 3H)	3.968	de% = 99.48%		
264		398.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.83 (m, 1H), 4.26-4.09 (m, 1H), 2.73-2.53 (m, 2H), 2.53-2.34 (m, 1H), 2.17-1.94 (m, 2H), 1.31-1.22 (m, 3H), 0.70-0.58 (m, 2H), 0.47-0.39 (m, 2H)	3.524	de% = 99.56%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	260
265		398.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.03-4.83 (m, 1H), 4.26-4.10 (m, 1H), 2.78-2.54 (m, 2H), 2.52-2.32 (m, 1H), 2.19-1.94 (m, 2H), 1.32-1.22 (m, 3H), 0.71-0.53 (m, 2H), 0.51-0.35 (m, 2H)	3.737	de% = 99.58%		

272	<p>272 &amp; 273</p>	394.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.36-4.09 (m, 3H), 3.02-2.87 (m, 2H), 2.79-2.43 (m, 4H), 2.26-2.04 (m, 2H), 1.28-1.15 (m, 6H)	4.176	ee% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 70/30	261
273		394.0	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 4.36-4.09 (m, 3H), 3.02-2.87 (m, 2H), 2.79-2.43 (m, 4H), 2.26-2.04 (m, 2H), 1.28-1.15 (m, 6H)	4.696	ee% = 100%		
285	<p>285 &amp; 286</p>	479.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.67-8.30 (m, 2H), 8.06-7.80 (m, 1H), 4.45-4.23 (m, 1H), 2.93-2.75 (m, 1H), 2.69-2.50 (m, 1H), 2.33-2.06 (m, 2H), 1.42-1.20 (m, 9H)	3.399	ee% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 70/30	275
286		479.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.67-8.30 (m, 2H), 8.06-7.80 (m, 1H), 4.45-4.23 (m, 1H), 2.93-2.75 (m, 1H), 2.69-2.50 (m, 1H), 2.33-2.06 (m, 2H), 1.42-1.20 (m, 9H)	4.089	ee% = 100%		
287	<p>287 &amp; 288</p>	480.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.67-8.32 (m, 2H), 8.08-7.80 (m, 1H), 2.91-2.75 (m, 1H), 2.69-2.52 (m, 1H), 2.32-2.08 (m, 2H), 1.42-1.26 (m, 9H)	3.400	ee% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 70/30	276
288		480.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 8.67-8.32 (m, 2H), 8.08-7.80 (m, 1H), 2.91-2.75 (m, 1H), 2.69-2.52 (m, 1H), 2.32-2.08 (m, 2H), 1.42-1.26 (m, 9H)	4.086	ee% = 100%		

289	  +   +  289 & 290 291 & 292	358.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.92 (m, 1H), 4.38-4.18 (m, 1H), 2.80-2.61 (m, 1H), 2.61-2.44 (m, 1H), 2.31-2.10 (m, 2H), 1.50-1.23 (m, 3H)	3.506	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	280
290		358.1	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 5.00-4.92 (m, 1H), 4.38-4.18 (m, 1H), 2.80-2.61 (m, 1H), 2.61-2.44 (m, 1H), 2.31-2.10 (m, 2H), 1.50-1.23 (m, 3H)	3.754	de% = 100%		
291		436.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.87 (m, 1H), 5.10-4.91 (m, 2H), 4.49-4.21 (m, 1H), 2.90-2.54 (m, 2H), 2.34-1.98 (m, 2H), 1.50-1.20 (m, 6H)	2.376	de% = 100%	Column: AD-H (0.46 cm I.D. × 15 cm L); Mobile phase: n-heptane/ isopropanol = 80/20	281
292		436.2	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD): δ 7.22-6.87 (m, 1H), 5.10-4.91 (m, 2H), 4.49-4.21 (m, 1H), 2.90-2.54 (m, 2H), 2.34-1.98 (m, 2H), 1.50-1.20 (m, 6H)	3.321	de% = 100%		

**Example 3 Fluorescent Determination of IDH2-R140Q Cell Activity****Materials:**

U87MGR140Q cells: U87MG cells were purchased from ATCC cell bank and then transfected with plasmid containing IDH2-R140Q mutation, and monoclonal cells stably expressing the R140Q mutation were isolated for experiments. The cells were cultured in MEM medium containing 10% FBS.

96-well plate a: Beckman Dickinson, Catalog No. 353072;

96-well plate b: Thermo, Catalog No. 249952;

96-well plate c: Greiner, Catalog No. 675076.

**10 Solution preparation:**

Enzyme reaction solution: 1 mM nicotinamide adenine dinucleotide (NAD), 0.6 ng/ $\mu$ L D-2-hydroxyglutarate dehydrogenase (D2HGDH), 0.8 U/mL lipoamidase dehydrogenase (Diaphorase) and 60  $\mu$ M Resazurin in 40 mM Tris.HCl pH 8.8 assay buffer.

Standard curve stock solution: The standard of 2-HG sodium salt was serially diluted in serum-free MEM medium to make a standard curve stock solution. The final gradient concentrations are: 500  $\mu$ M, 167  $\mu$ M, 56  $\mu$ M, 18.5  $\mu$ M, 6  $\mu$ M, 2  $\mu$ M, 0.7  $\mu$ M, 0.2  $\mu$ M.

**Methods:**

100  $\mu$ L of U87MGR140Q cells were seeded at a density of  $6 \times 10^4$  /mL per well in a 96-well plate a. The plate was incubated at 37°C with 5% CO<sub>2</sub> overnight, then 10  $\mu$ L per well of test compound solution diluted in serum-free MEM (final concentration of test compound: 10  $\mu$ M, 3.3  $\mu$ M, 1.1  $\mu$ M, 0.37  $\mu$ M, 0.12  $\mu$ M, 0.041  $\mu$ M, 0.014  $\mu$ M and 0.005  $\mu$ M, final DMSO concentration is 0.5%) or 10  $\mu$ L of control solution (serum-free MEM medium containing 0.5% DMSO in final concentration) was added and incubated for 72 hours.

From each well of 96-well plate a, 50  $\mu$ L of the culture supernatant was transferred to the corresponding well of 96-well plate b; at the same time, 50  $\mu$ L of standard curve stocking solution was added to other wells of 96-well plate b. Then 10  $\mu$ L of 360 mM hydrochloric acid was added to all the wells. After shaking and mixing, the plate was placed on ice for 10 minutes, and then 10  $\mu$ L of 420 mM Tris-base was added. After shaking and mixing, the plate was placed on ice for additional 5 minutes. Then the plate was centrifuged at 2500 rpm for 10 minutes.



After centrifuging, from each well of 96-well plate b, 20  $\mu$ L of the supernatant was transferred to 96-well plate c. An additional 80  $\mu$ L of the enzyme reaction solution was added to each well and incubated at 25°C for 90 minutes.

**Detection:**

- 5 The plate c was measured on Tecan Infinite F500 Reader instrument at 544 nm excitation and 590 nm emission. A standard curve of the fluorescence value vs. the corresponding 2-HG concentration was made, and the 2-HG concentration corresponding to each concentration point of the compound was calculated, then the inhibition ratio was calculated, and the data was analyzed using XLfit5 (ID Business Solutions Limited) software to obtain the IC<sub>50</sub> value.
- 10 The inhibition ratio was calculated as follows:

Inhibition Ratio (IH %) = (1 - 2-HG concentration of test compound treated cells / 2-HG concentration of control cells) x 100%.

The followings are the activity values of some of the compounds of the invention determined in this example.

Compound	IC <sub>50</sub> ( $\mu$ M)	Compound	IC <sub>50</sub> ( $\mu$ M)	Compound	IC <sub>50</sub> ( $\mu$ M)	Compound	IC <sub>50</sub> ( $\mu$ M)
1	0.097	73	0.064	148	1.558	221	0.487
2	0.137	74	0.034	149	0.177	222	0.065
3	0.866	75	0.218	150	0.541	224	0.137
4	0.080	78	0.069	151	0.039	225	0.036
5	0.093	79	0.106	152	0.300	226	0.361
6	0.115	80	0.079	153	0.099	227	0.048
7	0.087	81	0.099	154	0.202	228	0.417
8	0.216	82	0.075	155	0.319	229	0.383
9	0.571	83	0.203	156	0.657	230	0.658
10	0.113	84	0.048	157	0.141	231	0.037
11	0.284	85	0.035	158	0.278	232	0.040
12	0.199	86	0.021	159	0.205	233	0.368
13	0.373	87	0.205	160	0.180	234	0.078
14	0.230	89	0.057	162	0.177	235	0.130
15	0.259	90	0.065	163	0.162	236	0.045
16	0.326	91	0.058	164	0.176	237	1.492
17	1.616	92	0.143	165	0.198	238	0.139

18	0.110	94	0.131	166	0.180	239	0.046
19	0.083	95	0.043	167	0.327	240	0.984
20	0.232	96	0.675	169	0.738	241	0.100
21	0.099	97	0.052	170	1.382	242	0.802
22	0.336	98	0.344	171	0.268	243	1.175
23	0.192	99	0.553	172	0.344	244	0.053
24	0.197	100	2.905	174	0.096	245	0.102
25	0.665	101	0.080	175	0.291	248	0.093
27	0.148	102	0.051	176	0.612	249	0.072
28	0.123	103	1.002	177	0.046	250	2.473
29	0.177	104	2.079	178	0.934	252	0.050
30	0.228	105	0.040	179	0.598	254	0.025
31	0.110	106	0.106	180	0.531	255	0.078
32	0.080	107	0.554	181	0.177	257	0.056
34	0.145	108	2.226	182	1.231	259	0.057
35	0.591	109	0.057	183	0.507	260	0.094
36	0.181	110	0.070	184	3.779	261	0.094
37	1.911	111	2.257	186	0.677	262	0.056
38	1.619	112	0.098	187	0.742	263	1.394
39	0.164	113	2.059	188	5.015	264	0.084
40	0.106	114	1.716	189	1.415	266	0.033
41	0.297	115	0.059	190	0.413	267	1.327
42	0.152	116	2.620	191	0.999	268	0.349
43	0.328	117	0.095	192	0.314	269	0.137
44	3.149	118	0.106	196	0.094	270	0.109
47	0.059	119	3.393	197	0.041	272	0.051
49	0.210	120	2.397	198	0.845	273	1.228
50	0.072	121	0.068	199	1.504	274	0.084
51	0.125	122	1.340	200	0.632	275	0.062
52	0.229	124	0.137	201	0.045	276	0.081
53	0.131	125	1.671	202	0.383	277	0.156
54	0.015	126	0.086	203	0.098	278	0.148
55	0.103	127	0.064	204	0.209	279	0.170
56	0.093	128	0.092	205	0.803	280	>10

57	2.180	129	0.171	207	0.564	281	0.690
58	0.169	130	0.067	208	0.102	282	0.343
59	0.221	131	2.798	209	0.078	283	0.174
60	0.590	133	0.174	210	0.093	285	0.034
61	0.170	134	0.100	211	0.097	286	0.165
62	1.343	135	0.336	212	0.063	287	0.095
64	1.628	136	0.296	213	0.038	288	0.035
65	0.152	137	1.540	214	0.108	291	0.201
67	2.374	138	0.504	215	0.079	292	3.456
68	0.435	139	2.505	216	0.082	293	0.637
69	0.173	140	2.390	217	0.069	294	0.425
70	0.112	144	2.748	218	0.381	296	0.423
71	0.050	146	0.999	219	0.707	297	2.660
72	0.042	147	0.067	220	0.059	298	0.620

#### Example 4 Fluorescent Determination of IDH1-R132H Cell Activity

The 2-HG inhibitory activity of the compounds of the invention in U87MGR132H cells transfected with the IDH1-R132H mutant plasmid was determined according to the method of Example 3.

- 5 The followings are the activity values of some of the compounds of the invention determined in this example.

Compound	IC <sub>50</sub> (μM)	Compound	IC <sub>50</sub> (μM)	Compound	IC <sub>50</sub> (μM)	Compound	IC <sub>50</sub> (μM)
2	0.365	94	1.144	198	1.893	245	1.499
4	0.750	95	0.317	199	>10	248	4.338
5	0.869	96	2.703	200	>10	249	0.134
6	0.670	97	0.047	201	0.109	250	2.480
7	1.503	98	0.254	202	1.101	252	2.621
8	1.221	99	0.938	203	0.733	254	0.262
11	1.016	101	1.141	204	>10	255	0.715
13	2.076	102	0.232	205	>10	257	1.380
14	1.326	103	2.501	207	1.510	259	0.213
15	0.619	105	0.351	208	1.499	260	>10
18	0.219	106	0.272	209	1.763	261	2.231

19	0.421	107	1.751	210	4.338	262	0.182
21	0.234	109	0.279	211	0.175	263	3.513
24	0.769	110	0.160	212	>10	264	>10
31	0.280	118	2.141	213	>10	266	0.043
32	0.610	119	>10	214	>10	267	3.566
34	>10	121	0.186	215	>10	268	0.939
39	1.913	124	0.658	216	8.519	269	0.296
40	0.450	126	0.289	217	>10	270	2.853
41	1.627	127	0.203	218	>10	272	2.086
47	5.636	130	0.733	219	3.232	273	>10
51	6.042	134	2.472	220	2.878	274	3.284
52	2.245	136	1.342	221	>10	275	8.017
54	1.683	147	0.372	222	>10	276	8.367
60	>10	149	0.693	224	4.650	277	1.030
61	>10	151	0.256	225	0.917	278	>10
62	2.703	152	2.008	226	5.123	279	9.426
64	>10	153	0.447	227	0.081	280	>10
65	>10	155	2.245	228	0.705	281	0.455
67	>10	157	4.350	229	>10	282	0.444
71	3.054	158	1.520	230	>10	283	1.319
73	>10	159	2.717	231	1.528	285	3.587
74	7.441	163	0.809	232	0.070	286	>10
75	>10	166	1.347	233	0.628	287	>10
78	1.407	167	3.171	234	1.763	288	2.695
79	1.296	169	9.464	235	0.246	291	0.179
80	2.695	170	6.933	236	0.252	292	3.639
81	3.571	171	1.575	238	7.355	293	>10
82	0.181	174	0.343	239	0.344	294	9.184
83	0.282	175	0.495	240	>10	296	1.135
84	0.268	177	0.094	241	2.060	297	>10
85	0.207	181	0.476	242	3.523	298	>10
87	0.781	196	0.210	243	>10		
89	2.957	197	0.120	244	1.082		

**Example 5 Metabolic Stability Test in Liver Microsomes****Materials:**

Male CD1 mouse liver microsomes was supplied by Research Institute for Liver Diseases (Shanghai) Co., Ltd.. Male SD rat liver microsomes was supplied by BioreclamationIVT in US.

- 5 Phenacetin, glucose-6-phosphate (G-6-P), glucose-6-phosphate dehydrogenase (G-6-PD), and nicotinamide adenine dinucleotide phosphate (NADP) were supplied by Sigma-Aldrich (Missouri, USA).

**Solution preparation:**

- 10 mM stock solution of test compound: Certain amount of test compound was weighed and dissolved in certain volume of dimethylsulfoxide (DMSO) to get the stock solution of test compound at 10 mM.

Reaction termination solution: Certain amount of phenacetin as internal standard was weighed and dissolved in acetonitrile to get the reaction termination solution at 1000 ng/mL, and stored at room temperature for use.

**15 Experimental method:**

- The stock solution of test compound was diluted to the designated concentration with organic solution (usually the mixtures of acetonitrile, methanol and water with different portions depending on the compound solution) to make the final concentration to be 1  $\mu$ M and the contents of organic solvents no more than 1% (For DMSO, the controlled margin was 0.1%) in the final incubation system. 100 mM NADP, 500 mM G-6-P and 100 U/mL G-6-PDH were mixed and diluted with ultrapure water to provide the NADPH regenerating system containing 1 mM NADP, 5 mM G-6-P and 1U/mL G-6-PD, which was pre-incubated at 37 °C water-bath for 10 min and then cooled on ice until being added into the reaction system. 20 mg/mL liver microsomes was mixed with 200 mM PBS and diluted with ultrapure water to make the concentrations of liver microsomes and PBS to be 0.5 mg/mL and 50 mM in the final incubation system, respectively. After the diluted liver microsomes was mixed with the NADPH regenerating solution, certain volumes of 100 mM EDTA and 300 mM MgCl<sub>2</sub> (concentration of EDTA and MgCl<sub>2</sub> in the final incubation system is 1 mM and 3 mM, respectively) were added, and the incubation system was put into 37°C water bath. The incubation was commenced by adding the stock solution of test compound and maintained for 30 min. The incubation was terminated by adding the reaction termination solution. The 0 min sample was prepared by adding the reaction termination solution to the incubation system immediately prior to putting the system into the water bath with the addition of the stock solution of test

compound. The terminated incubation mixtures were vortexed and centrifuged at 4400 rpm for 10 min, and the supernatant was collected for LC-MS/MS analysis.

#### Analytical method:

5 The concentration of test compound was determined using LC-MS/MS method. Using the peak area ratio of the compound and the internal standard as an index, the percentage of remaining compound after incubation for 30 minutes as compared with the 0 minute sample was calculated, and the metabolic stability of the compound was evaluated.

According to the above tests, the compounds of the invention showed good metabolic stability. The metabolic stability of some exemplary compounds of the invention is as follows:

10

Compound	Rat liver microsome stability	Mouse liver microsome stability	Compound	Rat liver microsome stability	Mouse liver microsome stability
1	73.8%	83.5%	124	74.1%	44.1%
2	99.0%	83.8%	126	79.8%	58.2%
4	62.9%	82.1%	127	49.8%	28.7%
5	76.8%	58.6%	128	34.0%	15.9%
6	70.0%	76.3%	147	65.0%	48.1%
7	50.3%	49.8%	149	66.8%	59.7%
11	87.6%	80.3%	153	41.7%	46.9%
18	91.5%	82.7%	177	45.9%	31.0%
19	83.8%	66.2%	196	100.0%	95.2%
82	92.9%	93.1%	197	99.5%	98.4%
83	96.6%	83.7%	201	91.6%	79.3%
84	67.8%	78.9%	202	94.2%	96.4%
85	78.1%	64.0%	203	92.1%	91.3%
87	97.9%	88.5%	211	98.8%	99.7%
90	82.4%	80.9%	227	88.8%	81.4%
91	86.6%	70.5%	232	86.6%	76.3%
94	82.6%	65.4%	235	89.0%	75.5%
95	74.8%	80.1%	236	91.3%	83.9%
97	98.5%	89.5%	239	93.0%	91.8%
98	99.2%	83.7%	249	98.0%	100.0%

101	88.0%	84.6%	254	100.0%	90.9%
102	92.7%	86.2%	259	95.1%	86.9%
103	89.7%	78.5%	262	98.3%	92.2%
105	84.0%	67.3%	266	98.2%	91.5%
109	85.4%	58.8%	291	100.0%	98.9%

## Example 6 Determination of solubility

### 1. Preparation of sample solution

Sample standard solution: About 3-5 mg test compound was accurately weighed and added into a 5 mL sample tube, 5 mL DMSO was added. Shaking and sonicating for 1 hour.

pH 2.1 sample solution: About 1mg test compound was accurately weighed and added into a 1 mL sample tube, 1 mL pH 2.1 sodium phosphate buffer was added. Shaking. Adding test compound to the solution, if the solution is visually clear, till there is obvious insoluble in the solution. Sonicating for 1 hour.

pH 7.4 sample solution: About 1mg test compound was accurately weighed and added into a 1 mL sample tube, 1 mL pH 7.4 sodium phosphate buffer was added. Shaking. Adding test compound to the solution, if the solution is visually clear, till there is obvious insoluble in the solution. Sonicating for 1 hour.

### 2. Determination

1 mL sample standard solution was accurately pipetted into a HPLC tube. The peak area was determined by HPLC.

0.5 mL pH 2.1 sample solution was filtered by syringe filter and was accurately pipetted into a HPLC tube, and 0.5 mL pH 2.1 sodium phosphate buffer was accurately added. Shaking. The peak area was determined by HPLC.

0.5 mL pH 7.4 sample solution was filtered by syringe filter and was accurately pipetted into a HPLC tube, and 0.5 mL pH 7.4 sodium phosphate buffer was accurately added. Shaking. The peak area was determined by HPLC.

HPLC condition:

Instrument: Agilent 1200

Column: Agilent SB-C18 5u 4.6\*150mm

Mobile phase:

Phase A: Water (containing 0.1% formic acid)

Phase B: MeOH (containing 0.1% formic acid)

Gradient table

Time (min)	% A	% B
0	95	5
10	5	95
13	5	95
14	95	5
16	95	5

### 3. Calculation

5 The solubility of the test compound in pH 2.1 and pH 7.4 sodium phosphate buffers were calculated by the following formulae:

Sample solubility at pH 2.1 (mg/mL) =  $2 \times A \times Y \div X$

Sample solubility at pH 7.4 (mg/mL) =  $2 \times A \times Z \div X$

wherein:

10 A: The concentration of the test compound in sample standard solution, mg/mL;

X: The peak area of sample standard solution;

Y: The peak area of pH 2.1 sample solution;

Z: The peak area of pH 7.4 sample solution.

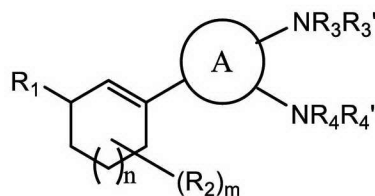
The solubilities of some exemplary compounds of the invention are as follows:

Compound	Solubility (mg/mL)		Compound	Solubility (mg/mL)	
	pH 2.1	pH 7.4		pH 2.1	pH 7.4
3	>1.000	0.716	125	0.448	0.019
9	>1.000	0.085	219	0.190	0.060
20	0.570	0.062	223	0.060	0.016
68	0.141	<0.005	243	0.055	<0.005
71	0.064	0.055	249	0.036	0.011
82	0.146	0.037	262	0.237	0.013
97	0.077	0.021	271	0.974	0.124
102	0.729	<0.005	284	0.789	0.818



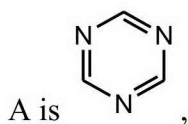
## Claims

1. A compound of formula (I):



(I)

and/or a pharmaceutically acceptable salt thereof, and/or solvates, racemic mixtures, enantiomers, diastereomers, and tautomers thereof, wherein



R<sub>1</sub> is chosen from H, -OH, halo, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1-4</sub> alkyl), -N(C<sub>1-4</sub> alkyl)<sub>2</sub>, oxo, or C<sub>3-8</sub> cycloalkyl;

each of R<sub>2</sub> is independently chosen from H, deuterium, halo, -OH, -NH<sub>2</sub>, -CN, -SH, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-8</sub> cycloalkyl, oxo, -OR<sub>5</sub>, -OCOR<sub>5</sub>, -NHR<sub>5</sub>, -N(R<sub>5</sub>)(C<sub>1-4</sub> alkyl), -COR<sub>5</sub>, -NHCOR<sub>5</sub>, or 3-8 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S; in which each of said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-8</sub> cycloalkyl or 3-8 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S is optionally substituted with one or more groups chosen from deuterium, halo, -CN, -OH, -SH, -NH<sub>2</sub>, -NH(C<sub>1-4</sub> alkyl), -N(C<sub>1-4</sub> alkyl)<sub>2</sub>, or C<sub>1-6</sub> alkoxy; or two R<sub>2</sub>, which attach to the same carbon atom, together with the carbon atom they are attached to form a 3-5 membered cycloalkyl which is optionally substituted with one or more halo or deuterium;

R<sub>3</sub>' and R<sub>4</sub>' are both H;

R<sub>3</sub> and R<sub>4</sub> are independently chosen from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, 5-12 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S, -C(O)R<sub>5</sub>, -OR<sub>5</sub>, or -NHR<sub>5</sub>, in which each of said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered

heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, or 5-12 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S is optionally substituted with one or more R<sub>6</sub>; provided that R<sub>3</sub> and R<sub>4</sub> are not H simultaneously; provided that when one of R<sub>3</sub> and R<sub>4</sub> is optionally substituted phenyl or optionally substituted 5-6 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S, the other one is -OR<sub>5</sub> or -NHR<sub>5</sub>;

or R<sub>3</sub> and R<sub>3</sub>' are independently chosen from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, 5-12 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S, -C(O)R<sub>5</sub>, -OR<sub>5</sub>, or -NHR<sub>5</sub>, in which each of said C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, or 5-12 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S is optionally substituted with one or more R<sub>6</sub>; R<sub>4</sub> and R<sub>4</sub>' together with the N atom they are attached to form a 3-8 membered heterocycl containing one or more heteroatoms independently chosen from N, O, and S optionally substituted by one or more R<sub>6</sub>;

R<sub>5</sub> is chosen from C<sub>1-6</sub> alkyl or C<sub>3-8</sub> cycloalkyl, each of which is optionally substituted with one or more groups independently chosen from halo, -CN, -OH, -SH, -NH<sub>2</sub>, or C<sub>1-6</sub> alkoxy;

each of R<sub>6</sub> is independently chosen from deuterium, halo, -CN, -OH, -SH, -NH<sub>2</sub>, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>3-8</sub> cycloalkyl, 3-8 membered heterocycl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, or 5-6 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S, in which each of said C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, 3-8 membered heterocycl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, or 5-6 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S is optionally substituted with one or more groups independently chosen from halo, -CN, -OH, -SH, -NH<sub>2</sub>, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkynyl, or C<sub>1-6</sub> alkyl;

m is 0, 1, 2, 3, 4, 5, or 6;

n is 0, 1, or 2;

wherein the term “cycloalkyl” as used herein refers to saturated or partially unsaturated cyclic hydrocarbon radical, which may have one or more rings.

2. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein,  $R_1$  is chosen from H, -OH or halo.
3. The compound of formula (I) according to claim 1 or claim 2, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein,  $R_1$  is -OH.
4. The compound of formula (I) according to any one of claims 1-3, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, each of  $R_2$  is independently chosen from H, deuterium, halo, -OH, -NH<sub>2</sub>, -CN, -SH, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>3-8</sub> cycloalkyl, oxo, -OR<sub>5</sub>, -OCOR<sub>5</sub>, -NHR<sub>5</sub>, -N(R<sub>5</sub>)(C<sub>1-4</sub> alkyl), -NHCOR<sub>5</sub>, or 3-8 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S.
5. The compound of formula (I) according to any one of claims 1-4, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, each of  $R_2$  is independently chosen from H, deuterium, halo, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl.
6. The compound of formula (I) according to any one of claims 1-5, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein,  $R_3$  and  $R_4$  are independently chosen from C<sub>1-6</sub> alkyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, 5-12 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S, -C(O)R<sub>5</sub>, -OR<sub>5</sub>, or -NHR<sub>5</sub>, in which each of said C<sub>1-6</sub> alkyl, C<sub>3-12</sub> cycloalkyl, 3-12 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, or 5-12 membered

heteroaryl containing one or more heteroatoms independently chosen from N, O, and S is optionally substituted with one or more R<sub>6</sub>.

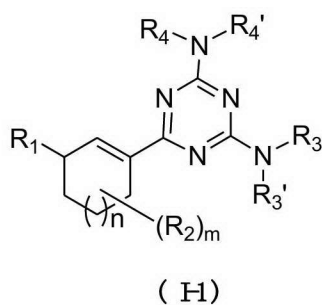
7. The compound of formula (I) according to any one of claims 1-6, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, R<sub>3</sub> and R<sub>4</sub> are independently chosen from C<sub>1-6</sub> alkyl substituted with one or more halo, 5-12 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S substituted with C<sub>1-6</sub> haloalkyl, or -OR<sub>5</sub>.

8. The compound of formula (I) according to any one of claims 1-7, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, R<sub>3</sub> and R<sub>4</sub> are C<sub>1-6</sub> alkyl substituted with one or more halo.

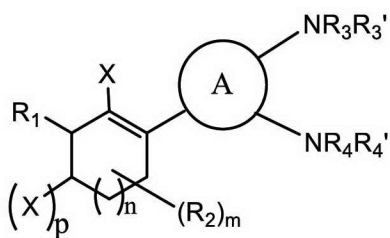
9. The compound of formula (I) according to any one of claims 1-8, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, R<sub>5</sub> is C<sub>1-6</sub> alkyl optionally substituted with one or more halo.

10. The compound of formula (I) according to any one of claims 1-9, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, each of R<sub>6</sub> is independently chosen from deuterium, halo, -CN, -OH, -NH<sub>2</sub>, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>3-8</sub> cycloalkyl, 3-8 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, or 5-6 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S, in which each of said C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkyl, C<sub>3-8</sub> cycloalkyl, 3-8 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S, phenyl, or 5-6 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S is optionally substituted with one or more halo.

11. The compound of formula (I) according to any one of claims 1-10, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, n is 1.
12. The compound of formula (I) according to any one of claims 1-5, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, R<sub>3</sub> is chosen from H, C<sub>1-6</sub> alkyl optionally substituted by C<sub>1-6</sub> haloalkyl, or 5-12 membered heteroaryl containing one or more heteroatoms independently chosen from N, O, and S optionally substituted by C<sub>1-6</sub> haloalkyl; R<sub>3</sub>' is H; R<sub>4</sub> and R<sub>4</sub>' together with the N atom they are attached to form a 3-8 membered heterocyclyl containing one or more heteroatoms independently chosen from N, O, and S optionally substituted by one or more groups chosen from halo, -OH, or C<sub>1-6</sub> haloalkyl.
13. The compound of formula (I) according to any one of claims 1-12, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, the compound of formula (I) has the structure of formula (I-1)

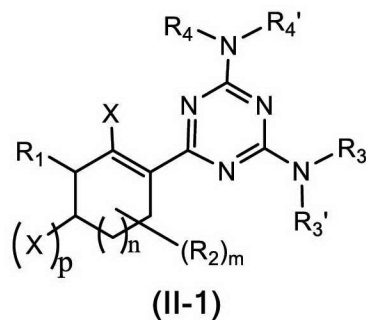


14. The compound of formula (I) according to any one of claims 1-12, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, the compound of formula (I) has the structure of formula (II); wherein X is halo; p is 0, 1, or 2; m is 0, 1, or 2;



(II).

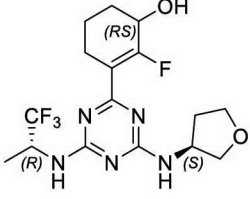
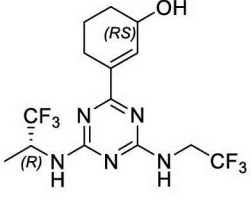
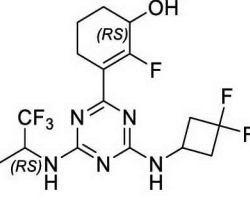
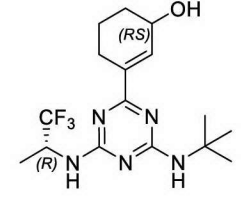
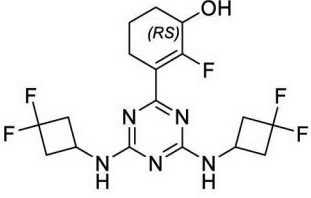
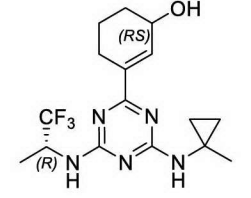
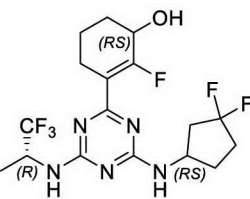
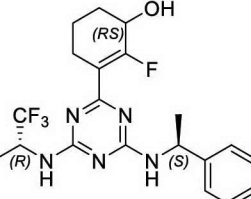
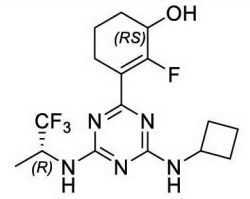
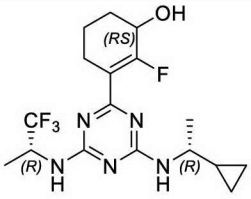
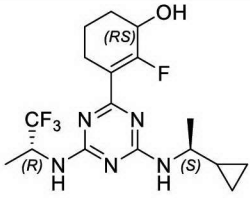
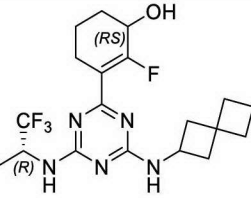
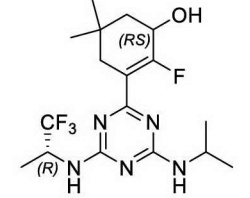
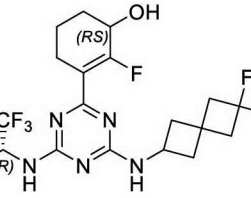
15. The compound of formula (I) according to claim 14, or a pharmaceutically acceptable salts thereof, and/or solvates, racemic mixture, enantiomers, diastereomers, and tautomers thereof, wherein, the compound of formula (I) has the structure of formula (II-1); wherein  $X$  is halo;  $p$  is 0, 1, or 2;  $m$  is 0, 1, or 2;

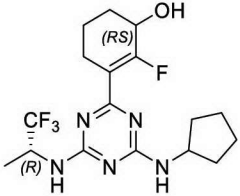
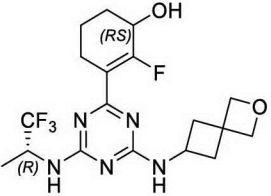
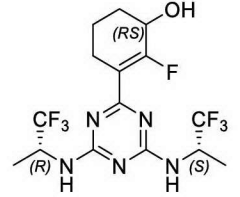
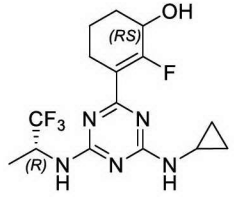
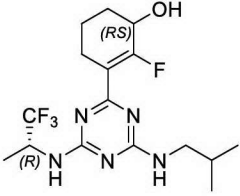
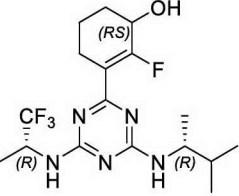
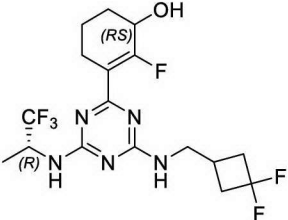
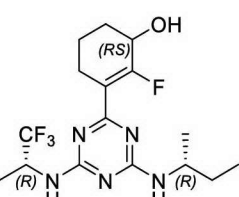
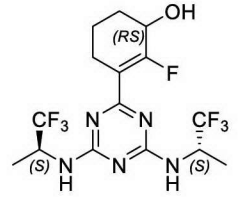
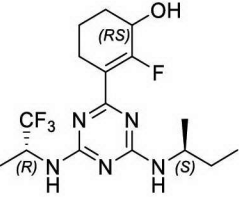
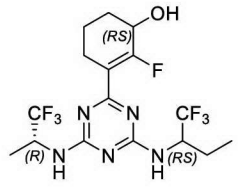
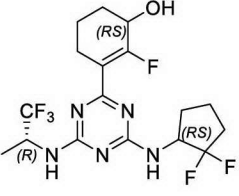
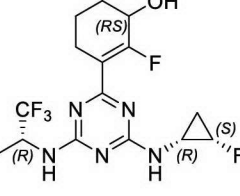
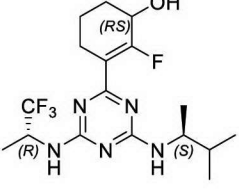


(II-1)

16. A compound, which is selected from:

Compound	Structure	Compound	Structure
1		152	
2		153	

3		154	
4		155	
5		156	
6		157	
7		158	
8		159	
9		160	

10		161	
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13		164	
14		165	
15		166	
16		167	

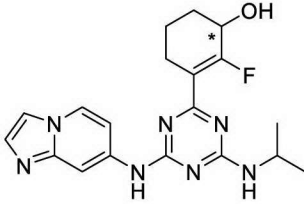
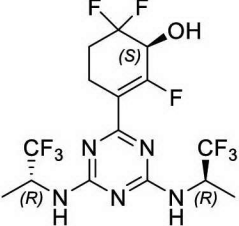
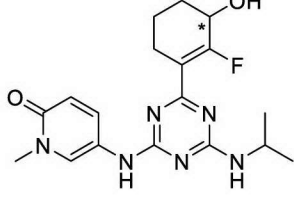
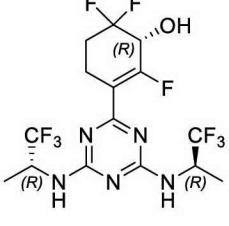

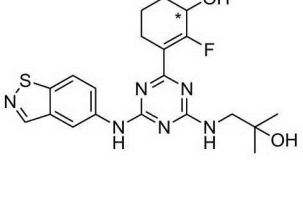
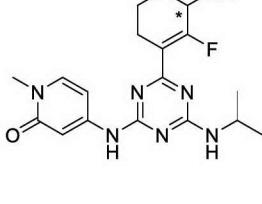
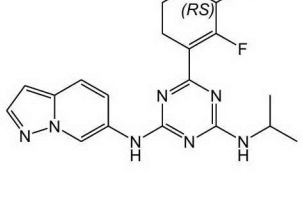
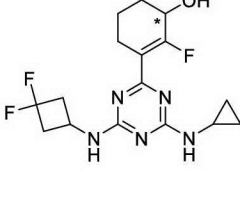
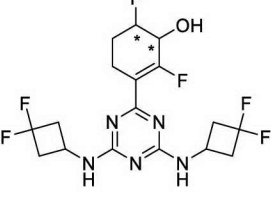
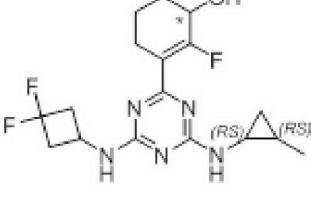
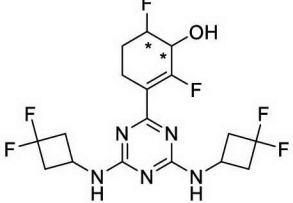


17		168	
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30		181	

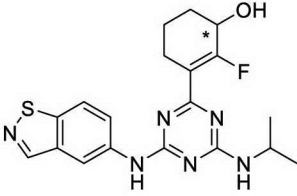
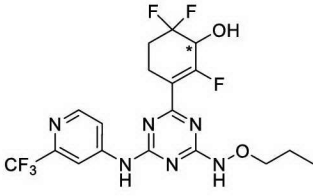
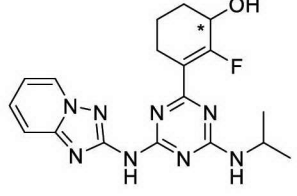
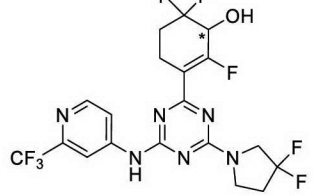
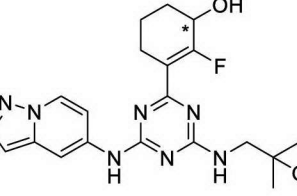
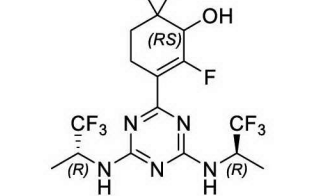
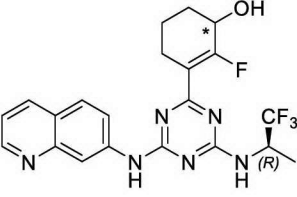
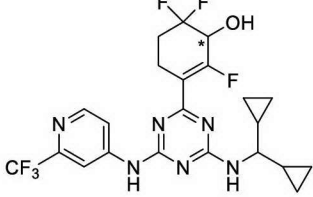
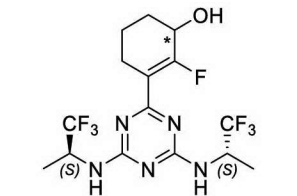
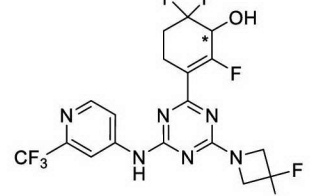
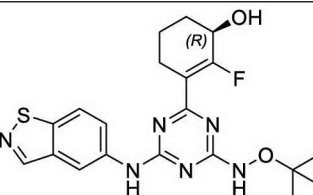
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49		201 & 202	
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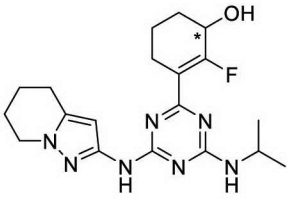
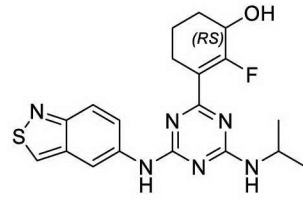
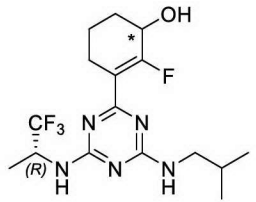
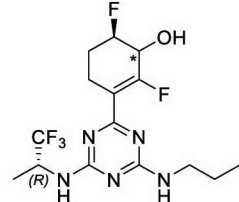
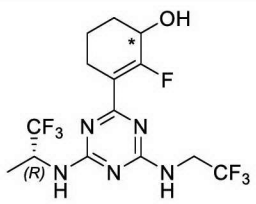
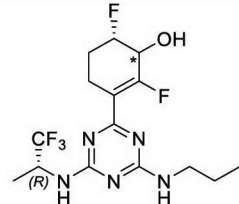
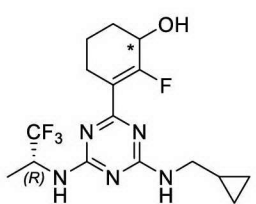
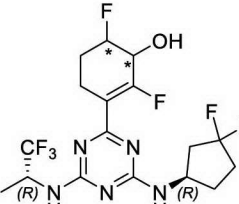
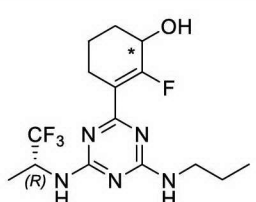
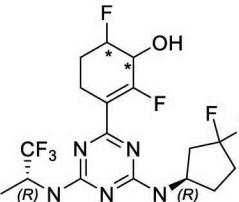
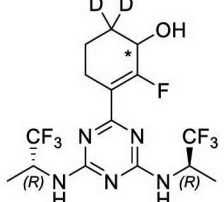
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68		220	
69		221	
		222 & 223	



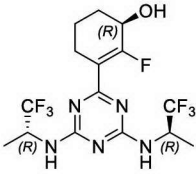
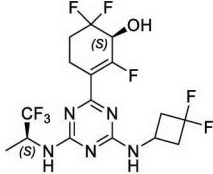
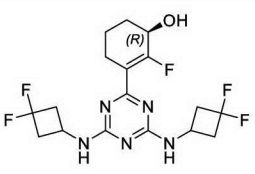
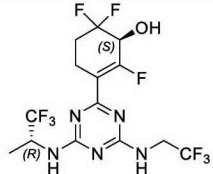
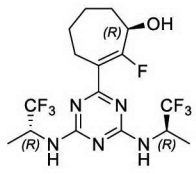
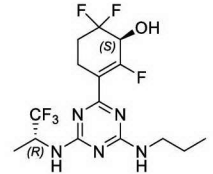
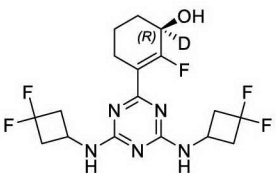
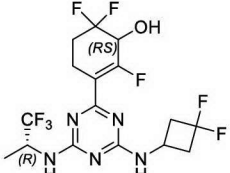
71			
72		224	
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75		227	
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78		230 & 231	
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80		232	
81		233	
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83		235	
84		236 & 237	
85			
		238	
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89		240	

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91		242	
92		243	
93		244	
94			
95 & 96		246 & 247	

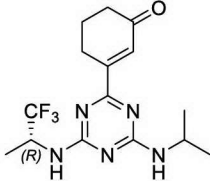
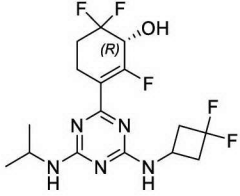
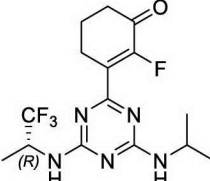
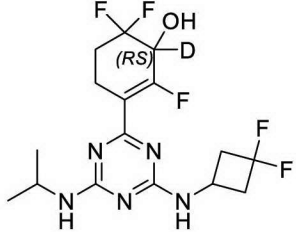
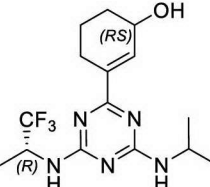
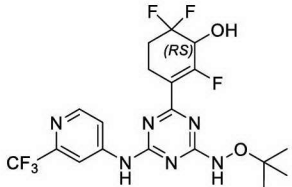
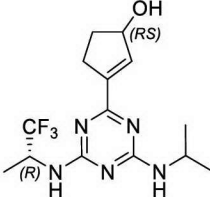
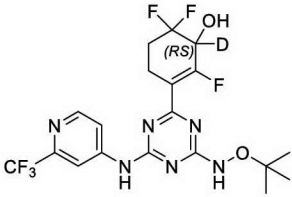
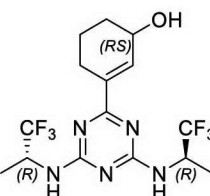
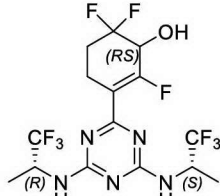
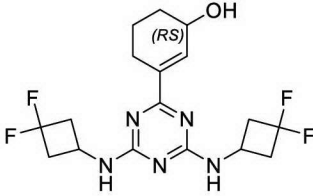
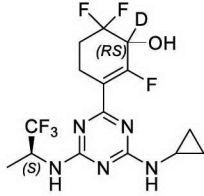
97 & 98			
		249 & 250	
99			
100 & 101		251 & 252	

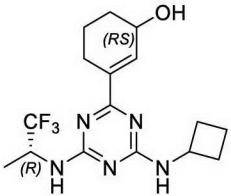
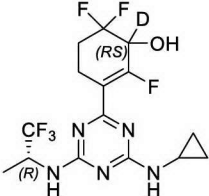
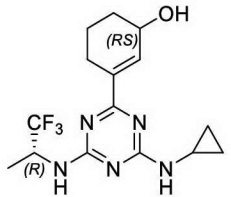
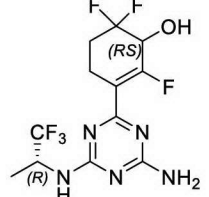
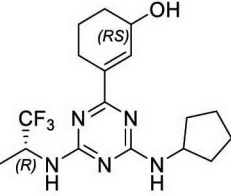
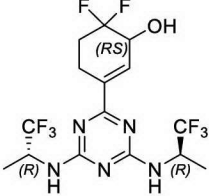
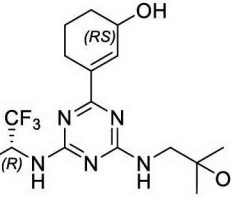
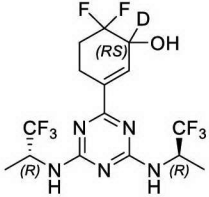
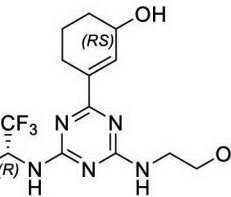
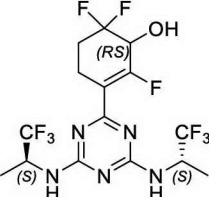
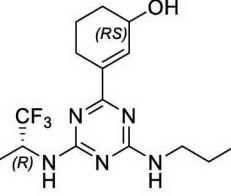
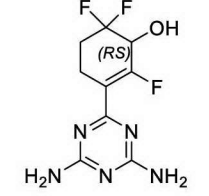
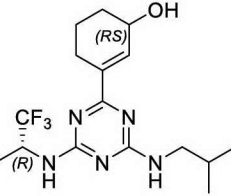
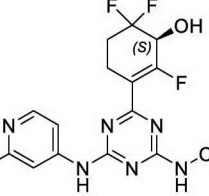
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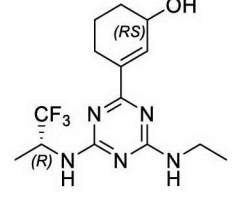
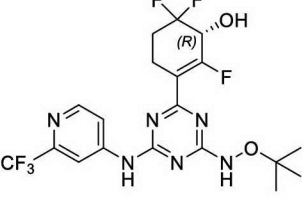
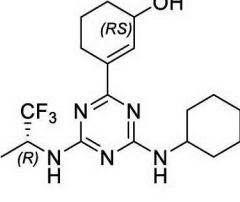
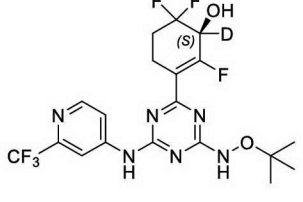
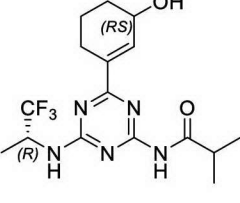
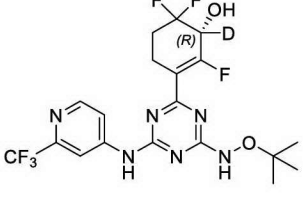
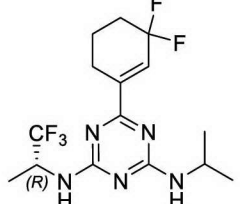

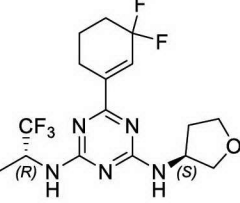
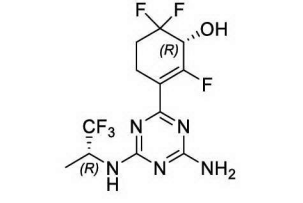
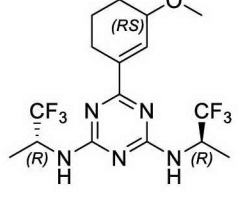
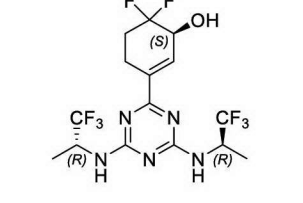
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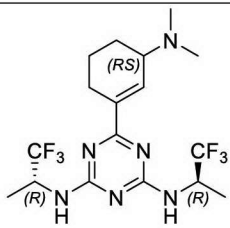
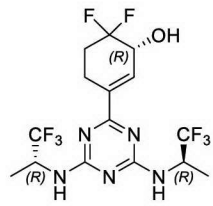
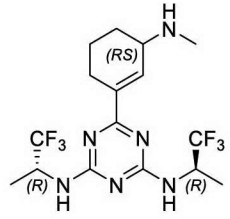
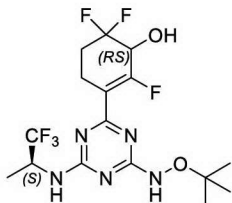
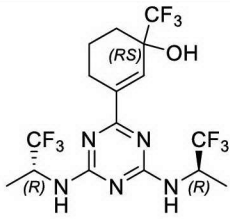
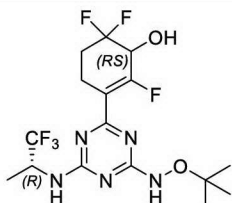
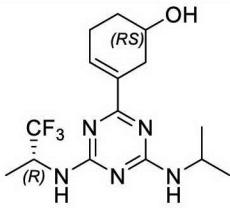
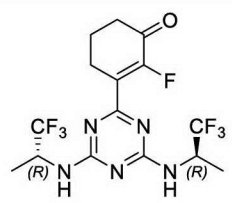
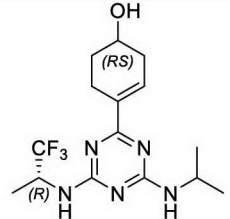
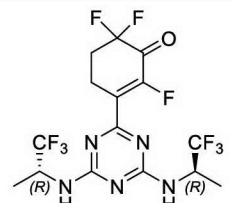
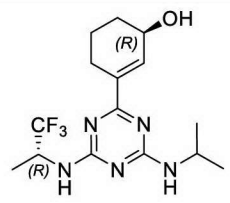
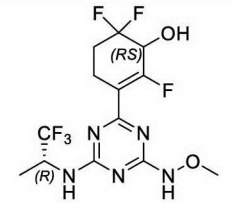




122			
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or a pharmaceutically acceptable salt thereof, wherein when a structure contains an asterisk '\*', it means that the chiral center of the compound marked by '\*' is in either an R-configuration or an S-configuration, and the content of the compound with the single configuration marked by '\*' is at least 90%.

17. A pharmaceutical composition comprising the compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, and optionally comprising at least one pharmaceutically acceptable excipient.

18. A use of a compound of any one of claims 1-16 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease induced by IDH mutation in a subject.

19. A method for treating a disease induced by IDH mutation, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-16 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 17.

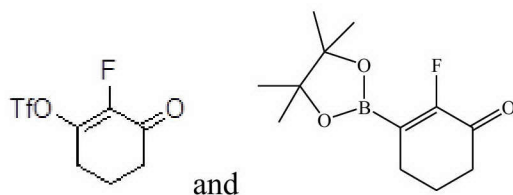
20. The use of claim 18 or the method of claim 19, wherein, the disease induced by IDH mutation is cancer, which is chosen from solid tumors, neurogliocytoma, or hematological malignant tumor.

21. The use or method of claim 20, wherein the cancer is leukaemia, lymphoma, or myeloma.

22. The use or method of claim 20, wherein, the cancer is chosen from acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), glioblastoma (GBM), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), cholangiocarcinoma, chondrosarcoma, giant cell tumor, intestinal cancer, melanoma, lung cancer, or non-Hodgkin's lymphoma (NHL).

23. The use or method of claim 20, wherein, the cancer is intrahepatic cholangiocarcinoma (IHCC).

24. A compound selected from:



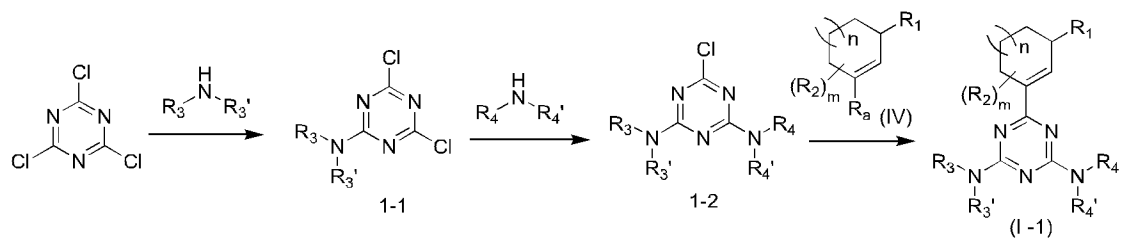


Fig.1

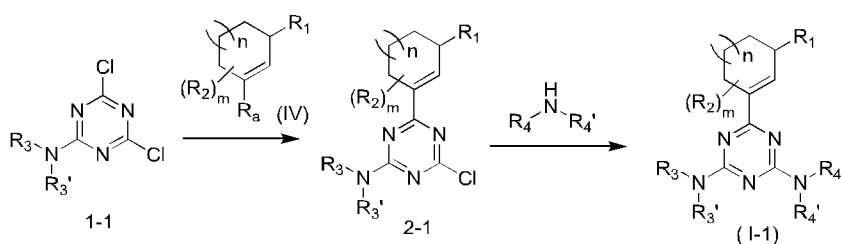


Fig.2

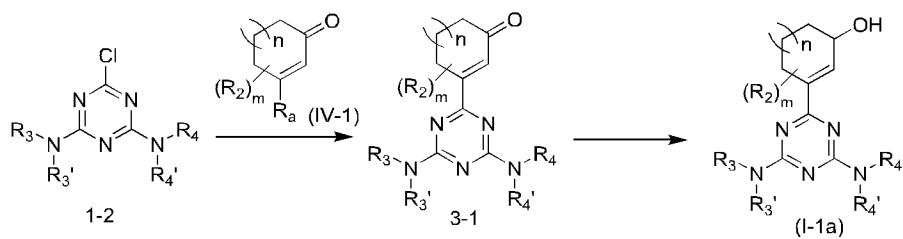


Fig.3

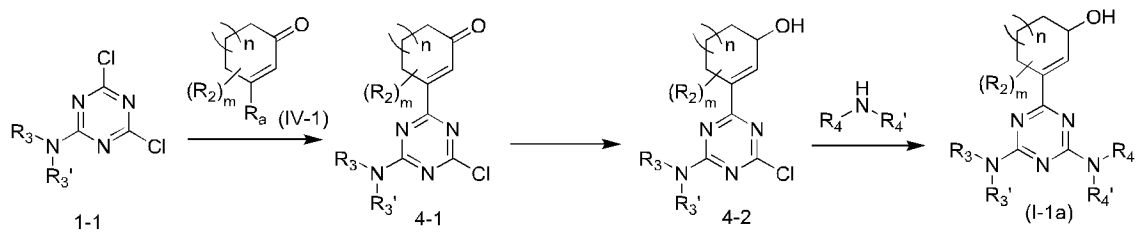


Fig.4

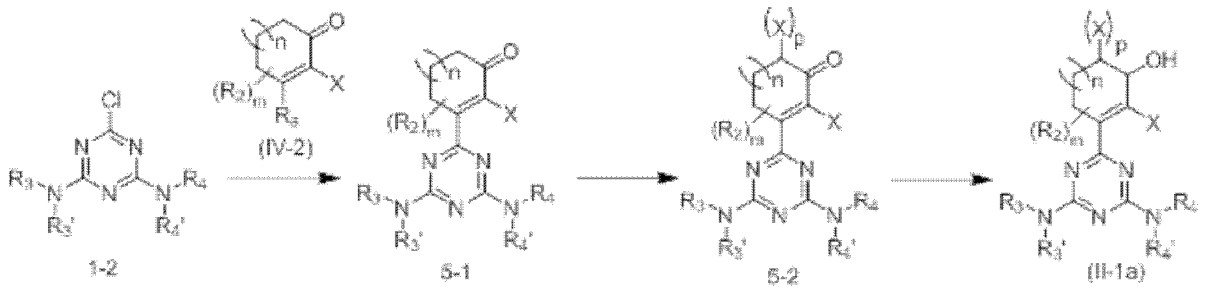


Fig.5

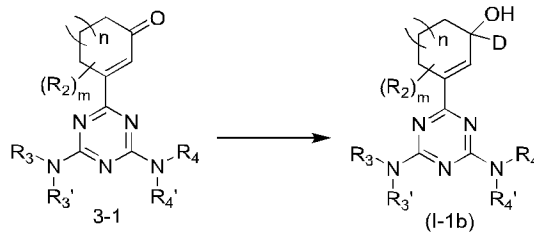


Fig.6