

DEUTERIUM AND ARYL AMINE COMPOUNDS AND USES THEREOF**RELATED APPLICATIONS**

[001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Applications, U.S.S.N. 63/583,710, filed September 19, 2023, and U.S.S.N. 63/681,004, filed August 8, 2024; the entire contents of each of which is incorporated herein by reference.

BACKGROUND

[002] Voltage-gated potassium channels, including the voltage-gated potassium channels Kv7.2 and Kv7.3 (Kv7.2/Kv7.3), are important in controlling neuronal excitability. Kv7.2/Kv7.3 underlie the neuronal “M-current,” named according to its initial characterization as a neuronal current decreased in response to muscarinic/cholinergic agonists (see Brown, D.A. *et al.*, *Nature* (1980), 283:673-676). The M-current is a non-inactivating, hyperpolarizing current known to act as a brake on neuronal hyperexcitability. Consequently, a decrease in the Kv7.2-mediated M-current, for example through genetic loss-of-function, can cause neuronal depolarization and an increase in membrane and neuronal excitability that can lead to action potential bursts that manifest as, *e.g.*, epileptic seizures. In contrast, an increase in the Kv7.2-mediated M-current can hyperpolarize the cell membrane and thereby reduce neuronal excitability and prevent the initiation and propagation of action potential bursts and the resultant seizures. Enhancing the open state of Kv7.2/Kv7.3 channels in neurons favors a hyperpolarized resting state, which reduces rapid action potential spiking (*i.e.*, burst firing). Such enhancement can provide a stabilizing effect on excitable, particularly hyper-excitable, neurons and can therefore be useful in treating certain seizure disorders. This enhancement has been clinically proven to be effective for treatment of seizure disorders, such as partial onset seizures in adults with epilepsy, with retigabine (ezogabine), a known Kv7.2/Kv7.3 potentiator.

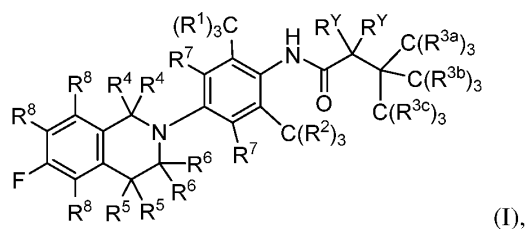
[003] While significant advances have been made in this field, there remains a substantial need for improved compounds and methods for potentiating voltage-gated potassium channels, including the voltage-gated potassium channels Kv7.2/Kv7.3. Such compounds and methods can be used to treat diseases, disorders, and conditions in which potassium channel dysfunction is implicated.

SUMMARY

[004] Provided herein are compounds, including compounds of any of the formulae described herein (*e.g.*, Formula (I)), and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, hydrates, and prodrugs thereof. Compounds provided herein can act as potentiators of voltage-gated potassium channels (*e.g.*, Kv7 potassium channels such as Kv7.2/Kv7.3) and are therefore useful in the treatment and/or prevention of diseases, disorders, and conditions (*e.g.*, diseases, disorders, and conditions associated with Kv7 potassium channel dysfunction). Also provided herein are pharmaceutical compositions comprising the compounds provided herein, and kits comprising the same. Additionally, the disclosure provides methods of preparing the compounds and pharmaceutical compositions described

herein, and intermediates useful thereto.

[005] Provided herein are compounds of Formula (I):

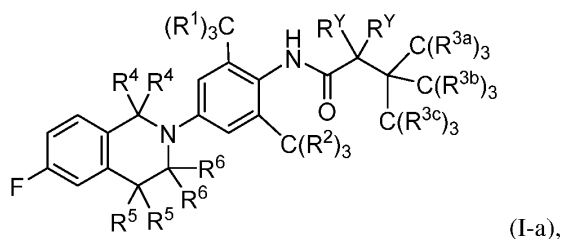


and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, wherein:

each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^6 , R^7 , R^8 , and R^Y is independently hydrogen or deuterium; and each instance of R^5 is independently hydrogen, -OH, or deuterium;

provided that at least one of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y is deuterium.

[006] In certain embodiments, the compound of Formula (I) is of Formula (I-a):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, provided that at least one of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y is deuterium.

[007] In certain embodiments, for example, a compound of Formula (I) is selected from those recited in **Table 1** (*infra*), and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

[008] In another aspect, provided herein are pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers and/or excipients. In certain embodiments, a pharmaceutical composition provided herein comprises an effective amount (*e.g.*, therapeutically effective amount) of a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof.

[009] As described, compounds and pharmaceutical compositions provided herein can potentiate voltage-gated potassium channels (*e.g.*, Kv7.2/Kv7.3 potassium channels) and are therefore useful for treating and/or preventing diseases, disorders, and conditions in a subject, including, *e.g.*, indications in which Kv7 potassium channel dysfunction is implicated.

[010] In other aspects, provided herein are methods and uses of the compounds and pharmaceutical compositions provided herein, including, but not limited to, the following:

- (a) Methods of potentiating a Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) in a subject comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical

composition thereof.

- (b) Methods of treating a disease, disorder, or condition associated with Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) dysfunction in a subject in need thereof comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof.
- (c) Method of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof.
- (d) Methods of potentiating a Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) in a cell *in vitro* comprising contacting the cell with a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof.

[011] In another aspect, provided herein are compounds disclosed herein, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, and pharmaceutical compositions thereof, for use in any of the methods provided herein. In another aspect, provided herein are compounds disclosed herein, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, and pharmaceutical compositions thereof, for use as medicaments and/or in the preparation of medicaments.

[012] In another aspect, provided herein are kits comprising a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof. The kits described herein may include a single dose or multiple doses of the compound or pharmaceutical composition thereof. The kits described herein are useful in any method or use provided herein, and optionally further comprise instructions for using the kit (*e.g.*, instructions for using the compound or composition included in the kit).

[013] Also provided herein are methods of preparing compounds disclosed herein, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, and pharmaceutical compositions thereof. Synthetic intermediates useful in the preparation of the compounds and compositions are also provided herein.

[014] The details of certain embodiments of the disclosure are set forth in the Detailed Description, as described below. Other embodiments of the disclosure will be apparent from the Definitions, Examples, Abstract, and Claims.

DEFINITIONS

Chemical Definitions

[015] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are

generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Michael B. Smith, *March's Advanced Organic Chemistry*, 7th Edition, John Wiley & Sons, Inc., New York, 2013; Richard C. Larock, *Comprehensive Organic Transformations*, John Wiley & Sons, Inc., New York, 2018; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[016] As used herein, the term "salt" refers to any and all salts and encompasses pharmaceutically acceptable salts. Salts include ionic compounds that result from the neutralization reaction of an acid and a base. A salt is composed of one or more cations (positively charged ions) and one or more anions (negative ions) so that the salt is electrically neutral (without a net charge). Salts of the compounds of the present disclosure include those derived from inorganic and organic acids and bases. Examples of acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid, or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate, hippurate, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further salts include ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[017] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of the present disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange.

Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4} \text{ alkyl})_4^-$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[018] Compounds described herein include one or more deuterium (D) atoms. Unless otherwise provided, formulae and structures depicted herein include compounds that include other isotopically enriched atoms in addition to deuterium (“isotopically labeled derivatives”). For example, compounds having the present structures except for the replacement of ^{19}F with ^{18}F , or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays. The term “isotopes” refers to variants of a particular chemical element such that, while all isotopes of a given element share the same number of protons in each atom of the element, those isotopes differ in the number of neutrons.

[019] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer, or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The present disclosure additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[020] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”.

[021] “Stereoisomers” that are not mirror images of one another are termed “diastereomers” and those

that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the *R*- and *S*-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+)- or (–)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture.”

[022] The term “tautomers” or “tautomeric” refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

[023] The term “solvate” refers to forms of a compound, including salts thereof, that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. “Solvate” encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[024] The term “hydrate” refers to a solvate wherein the compound is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \times x \text{ H}_2\text{O}$, wherein *R* is the compound, and *x* is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (*x* is 1), lower hydrates (*x* is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \times 0.5 \text{ H}_2\text{O}$)), and polyhydrates (*x* is a number greater than 1, *e.g.*, dihydrates ($R \times 2 \text{ H}_2\text{O}$) and hexahydrates ($R \times 6 \text{ H}_2\text{O}$)).

[025] The term “prodrugs” refers to compounds that have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active *in vivo*. See, *e.g.*, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985. Prodrugs include acid derivatives such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds described herein are

particular prodrugs. In some cases it is desirable to prepare double ester-type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer advantages of solubility, tissue compatibility, or delayed release in the subject.

[026] Use of the phrase “at least one instance” refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[027] Throughout the present disclosure, references to “the compound” and “a compound” provided herein are intended to encompass the compound or group of compounds, and also pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, isotopically labeled derivatives, and prodrugs thereof.

[028] The terms “composition” and “formulation” are used interchangeably.

[029] A “subject” to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. The term “patient” refers to a human subject in need of treatment of a disease, disorder, or condition.

[030] The term “administer,” “administering,” or “administration” refers to implanting, absorbing, ingesting, injecting, inhaling, providing or otherwise introducing a compound described herein, or a composition thereof, in, to or on a subject.

[031] The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[032] The term “prevent,” “preventing,” or “prevention” refers to a prophylactic treatment of a subject who is not and was not with a disease but is at risk of developing the disease or who was with a disease, is not with the disease, but is at risk of regression of the disease. In certain embodiments, the subject is at a higher risk of developing the disease or at a higher risk of regression of the disease than an average healthy member of a population.

[033] The terms “condition,” “disease,” and “disorder” are used interchangeably.

[034] An “effective amount” of a compound described herein refers to an amount sufficient to elicit the

desired biological response. An effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, severity of side effects, disease, or disorder, the identity, pharmacokinetics, and pharmacodynamics of the particular compound, the condition being treated, the mode, route, and desired or required frequency of administration, the species, age and health or general condition of the subject. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses. In certain embodiments, an effective amount is an amount sufficient for potentiating a Kv7 potassium channel (*e.g.*, in a subject or in a cell *in vitro*).

[035] A “therapeutically effective amount” of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, a therapeutically effective amount is an amount sufficient for treating a disease, disorder, or condition (*e.g.*, a disease, disorder, or condition associated with Kv7 potassium channel dysfunction) in a subject. In certain embodiments, a therapeutically effective amount is an amount sufficient for potentiating a Kv7 potassium channel in a subject.

[036] A “prophylactically effective amount” of a compound described herein is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent. In certain embodiments, a prophylactically effective amount is an amount sufficient for preventing a disease, disorder, or condition (*e.g.*, a disease, disorder, or condition associated with Kv7 potassium channel dysfunction) in a subject. In certain embodiments, a prophylactically effective amount is an amount sufficient for potentiating a Kv7 potassium channel in a subject.

[037] “Voltage-gated potassium channels” (VGKCs) are transmembrane channels specific for potassium and sensitive to voltage changes in a cell’s membrane potential. During action potentials, they play an important role in returning the depolarized cell to a resting state. In VGKCs, alpha subunits form the actual conductance pore. Based on sequence homology of the hydrophobic transmembrane cores, the alpha subunits of voltage-gated potassium channels are grouped into 12 families (Kv1-12), of which Kv7 is one family. The Kv7 family of voltage-gated potassium channels consists of five members (Kv7.1-7.5) which are encoded for by the *KCNQ1-5* genes, respectively. Of the five, Kv7.2/Kv7.3 is the active

heterotetramer that is the main active Kv7 current in neurons (M-current). A Kv7 potassium channel can be a member selected from Kv7.1, Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5.

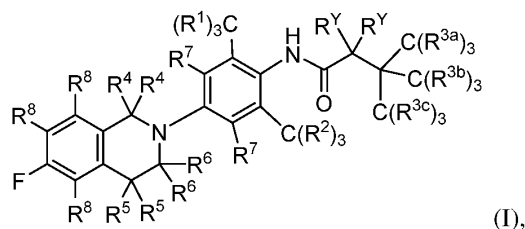
[038] “Potassium channel potentiator” and “potassium channel opener” are used interchangeably and refer to an agent that restores, enhances, or increases the activity of a potassium channel (*e.g.*, voltage-gated potassium channel, *e.g.*, Kv7 potassium channel), for example, by facilitating ion transmission through the potassium channel. “Potentiating,” “potentiation,” and the like, for the purposes of this disclosure, refer to restoring, enhancing, or increasing the activity or effect of a potassium channel.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[039] Provided herein are compounds, including compounds of any of the formulae described herein (*e.g.*, Formula (I)), and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, hydrates, and prodrugs thereof. Compounds provided herein can act as potentiators of voltage-gated potassium channels (*e.g.*, Kv7 potassium channels such as Kv7.2/Kv7.3) and can therefore be used in the treatment and/or prevention of diseases, disorders, and conditions (*e.g.*, diseases, disorders, and conditions associated with Kv7 potassium channel dysfunction). Also provided herein are pharmaceutical compositions comprising the compounds provided herein, and kits comprising the same. Additionally, the disclosure provides methods of preparing the compounds and pharmaceutical compositions described herein, and intermediates useful thereto.

Compounds

[040] Provided herein are compounds of Formula (I):

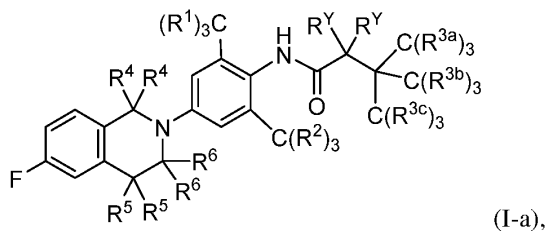


and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, wherein:

each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^6 , R^7 , R^8 , and R^Y is independently hydrogen or deuterium; and each instance of R^5 is independently hydrogen, -OH, or deuterium;

provided that at least one of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y is deuterium.

[041] In certain embodiments, the compound of Formula (I) is of Formula (I-a):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof; provided that at

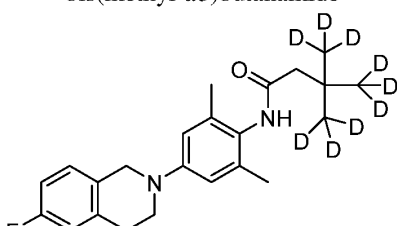
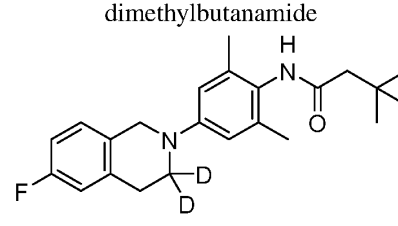
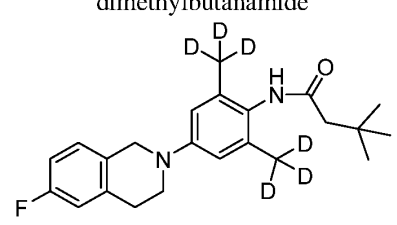
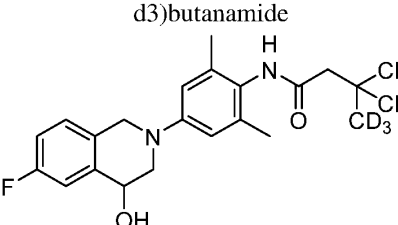
least one of R¹, R², R^{3a}, R^{3b}, R^{3c}, R⁴, R⁵, R⁶, and R^Y is deuterium.

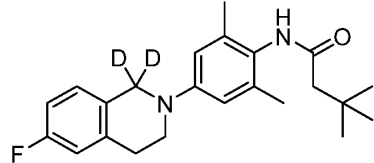
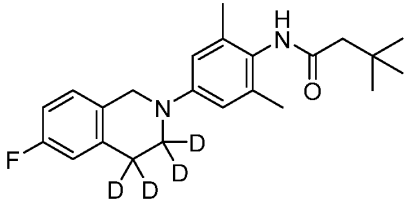
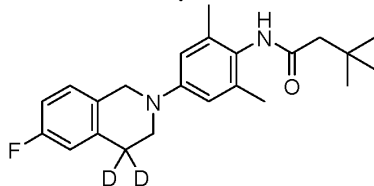
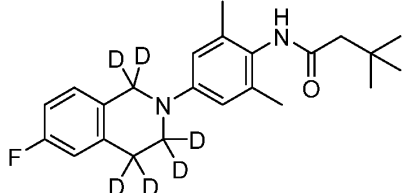
[042] In certain embodiments, a compound provided herein is a compound of Formula (I) or any species thereof, or a pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof. In certain embodiments, a compound provided herein is a compound of Formula (I) or any species thereof, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof. In certain embodiments, a compound provided herein is a compound of Formula (I) or any species thereof, or a pharmaceutically acceptable salt thereof. In certain embodiments, a compound provided herein is a compound of Formula (I) or any species thereof, as a free base.

[043] In the various aspects and embodiments disclosed herein, express reference to a compound of Formula (I) is understood to alternatively refer to a compound of any disclosed subgenus or species thereof, for example, to a compound of **Table 1**.

[044] In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1**, and pharmaceutically acceptable salts, stereoisomers, and tautomers thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1**, and pharmaceutically acceptable salts thereof. In certain embodiments, a compound disclosed herein is selected from the compounds recited in **Table 1** (in free base form).

Table 1

Ex.	Name and Structure	Ex.	Name and Structure
1	<i>N</i> -(4-(6-fluoro-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl- <i>d</i> 3)butanamide 	5	<i>N</i> -(4-(6-fluoro-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl-3,3- <i>d</i> 2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 
2	<i>N</i> -(4-(6-fluoro-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2,6-bis(methyl- <i>d</i> 3)phenyl)-3,3-dimethylbutanamide 	6	<i>N</i> -(4-(6-fluoro-4-hydroxy-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl- <i>d</i> 3)butanamide 

Ex.	Name and Structure	Ex.	Name and Structure
3	<i>N</i> -(4-(6-fluoro-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl-1,1- <i>d</i> 2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 	7	<i>N</i> -(4-(6-fluoro-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl-3,3,4,4- <i>d</i> 4)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 
4	<i>N</i> -(4-(6-fluoro-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl-4,4- <i>d</i> 2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 	8	<i>N</i> -(4-(6-fluoro-3,4-dihydroisoquinolin-2(1 <i>H</i>)-yl-1,1,3,3,4,4- <i>d</i> 6)-2,6-dimethylphenyl)-3,3-dimethylbutanamide 

[045] The following definitions and embodiments apply to all generic formulae comprising the relevant groups (*e.g.*, Formula (I)) provided herein. The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[046] As described herein for compounds of Formula (I), at least one instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y is deuterium (“D”). In certain embodiments, at least two instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least three instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least four instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least five instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least six instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least seven instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least eight instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least nine instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least ten instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least eleven instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y is deuterium D.

[047] As described herein for compounds of Formula (I-a), in certain embodiments, at least one instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y is D. In certain embodiments, at least two instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least three instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least four instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least five instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least six instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least seven instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least eight instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least nine instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least ten instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least eleven instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y is deuterium D.

R^5 , R^6 , and R^Y are D. In certain embodiments, at least five instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least six instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least seven instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least eight instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least nine instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y are D. In certain embodiments, at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 instances of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y are D. In certain embodiments, each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , and R^Y is D.

[048] As defined herein, each instance of R^1 is independently H or D. In certain embodiments, at least one instance of R^1 is H. In certain embodiments, at least one instance of R^1 is D. In certain embodiments, each instance of R^1 is H. In certain embodiments, each instance of R^1 is D.

[049] As defined herein, each instance of R^2 is independently H or D. In certain embodiments, at least one instance of R^2 is H. In certain embodiments, at least one instance of R^2 is D. In certain embodiments, each instance of R^2 is H. In certain embodiments, each instance of R^2 is D.

[050] In certain embodiments, each instance of R^1 and R^2 is D.

[051] As defined herein, each instance of R^{3a} is independently H or D. In certain embodiments, at least one instance of R^{3a} is H. In certain embodiments, at least one instance of R^{3a} is D. In certain embodiments, each instance of R^{3a} is H. In certain embodiments, each instance of R^{3a} is D.

[052] As defined herein, each instance of R^{3b} is independently H or D. In certain embodiments, at least one instance of R^{3b} is H. In certain embodiments, at least one instance of R^{3b} is D. In certain embodiments, each instance of R^{3b} is H. In certain embodiments, each instance of R^{3b} is D.

[053] As defined herein, each instance of R^{3c} is independently H or D. In certain embodiments, at least one instance of R^{3c} is H. In certain embodiments, at least one instance of R^{3c} is D. In certain embodiments, each instance of R^{3c} is H. In certain embodiments, each instance of R^{3c} is D.

[054] In certain embodiments, each instance of R^{3a} , R^{3b} , and R^{3c} is D.

[055] As defined herein, each instance of R^4 is independently H or D. In certain embodiments, at least one instance of R^4 is H. In certain embodiments, at least one instance of R^4 is D. In certain embodiments, each instance of R^4 is H. In certain embodiments, each instance of R^4 is D.

[056] As defined herein, each instance of R^5 is independently H, D, or -OH.

[057] In certain embodiments, at least one instance of R^5 is H. In certain embodiments, at least one instance of R^5 is D. In certain embodiments, each instance of R^5 is H. In certain embodiments, each instance of R^5 is D.

[058] In certain embodiments, at least one instance of R^5 is -OH. In certain embodiments, one instance of R^5 is -OH and the other is H.

[059] As defined herein, each instance of R^6 is independently H or D. In certain embodiments, at least one instance of R^6 is H. In certain embodiments, at least one instance of R^6 is D. In certain embodiments, each instance of R^6 is H. In certain embodiments, each instance of R^6 is D.

[060] As defined herein for compounds of Formula (I), each instance of R^7 is independently H or D. In

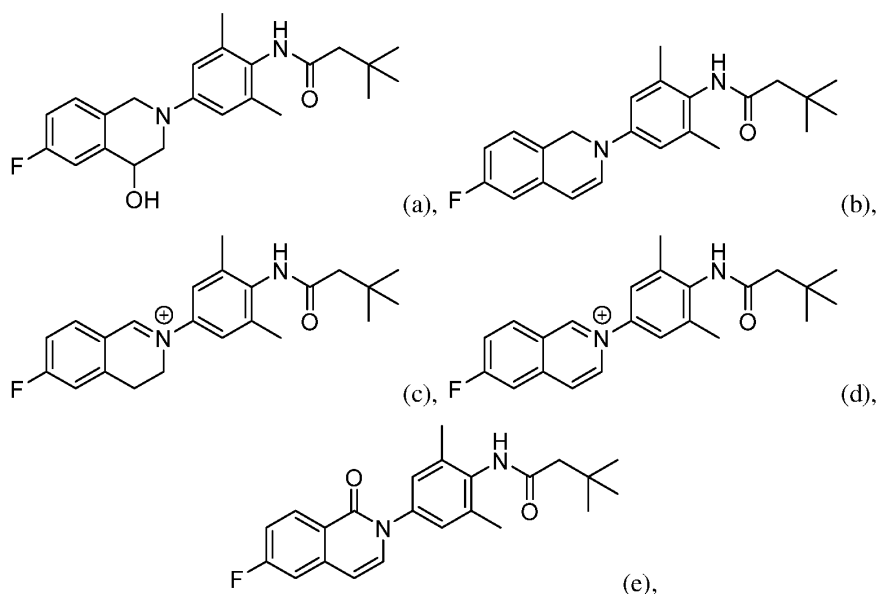
certain embodiments, at least one instance of R^7 is H. In certain embodiments, at least one instance of R^7 is D. In certain embodiments, each instance of R^7 is H. In certain embodiments, each instance of R^7 is D.

[061] As defined herein for compounds of Formula (I), each instance of R^8 is independently H or D. In certain embodiments, at least one instance of R^8 is H. In certain embodiments, at least one instance of R^8 is D. In certain embodiments, each instance of R^8 is H. In certain embodiments, each instance of R^8 is D.

[062] As defined herein, each instance of R^Y is independently H or D. In certain embodiments, at least one instance of R^Y is H. In certain embodiments, at least one instance of R^Y is D. In certain embodiments, each instance of R^Y is H. In certain embodiments, each instance of R^Y is D.

[063] In some embodiments, deuterium-containing compounds provided herein (*e.g.*, Examples 3-8) were designed based on the discovery of certain metabolites of the Kv7 potentiator azetukalner (*N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide). These metabolites (compounds (a)-(e) shown below) are also provided herein as embodiments of the disclosure. These compounds may be useful, *e.g.*, as tool compounds, reference standards, as Kv7 potentiators in their own right, *etc.*

[064] Provided herein are the following compounds (a)-(e):



and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof. In certain embodiments, the compound is of any one of (a)-(e), or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is of any one of (a)-(e), as a free base.

Pharmaceutical Compositions, Kits, and Administration

[065] The present disclosure provides pharmaceutical compositions comprising a compound provided herein (*e.g.*, a compound of Formula (I), or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof) and one or more pharmaceutically acceptable carriers and/or excipients. In certain embodiments, a compound described herein is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective

amount. In certain embodiments, the effective amount is a prophylactically effective amount.

[066] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include bringing the compound described herein (*i.e.*, the “active ingredient”) into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[067] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as one-half or one-third of such a dosage.

[068] Relative amounts of the active ingredient, the pharmaceutically acceptable carrier or excipient, and/or any additional ingredients in a pharmaceutical composition described herein will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered.

[069] Pharmaceutically acceptable carriers/excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, solvents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, oils, butters, and/or waxes. Excipients such as coloring agents, coating agents, sweetening agents, flavoring agents, and fragrances may also be present in the composition.

[070] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, intradermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, buccal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[071] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[072] Compounds provided herein are typically formulated in dosage unit form for ease of administration

and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[073] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. An effective amount may be included in a single dose (*e.g.*, single oral dose) or multiple doses (*e.g.*, multiple oral doses). In certain embodiments, when multiple doses are administered to a subject or applied to a tissue or cell, any two doses of the multiple doses include different or substantially the same amounts of a compound described herein.

[074] A compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, in reducing the risk to develop a disease in a subject in need thereof), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[075] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. In some embodiments, the pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form a single unit dosage form. Thus, in one aspect, provided are kits including a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, the kits are useful for treating and/or preventing a disease, disorder, or condition in a subject in need thereof.

[076] In certain embodiments, a kit described herein further includes instructions for using the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is

prescribing information. In certain embodiments, the kits provide instructions for treating a disease (*e.g.*, a seizure disorder, a depressive disorder, pain, or anhedonia) in a subject in need thereof. In certain embodiments, the kits provide instructions for preventing a disease in a subject in need thereof. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

Methods of Treatment and Uses

[077] As described in some aspects, compounds provided herein can act as voltage-gated potassium channel potentiators (*e.g.*, Kv7.2/Kv7.3 potentiators) and are therefore useful, *e.g.*, for the treatment of diseases, disorders, and conditions.

[078] In one aspect, provided herein are methods of potentiating a Kv7 potassium channel in a subject comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the Kv7 potassium channel is Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5. In certain embodiments, the Kv7 potassium channel is Kv7.2. In certain embodiments, the Kv7 potassium channel is Kv7.3. In certain embodiments, the Kv7 potassium channel is Kv7.2/Kc7.3. In certain embodiments, the compound or composition is selective for one or more of Kv7.2-Kv7.5 over Kv7.1. In certain embodiments, the compound or composition is selective for one or more of Kv7.2/Kv7.3 over Kv7.1.

[079] Also provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, and pharmaceutical compositions thereof, for use in potentiating a Kv7 potassium channel in a subject.

[080] In another aspect, provided herein are methods of treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject in need thereof comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the disease, disorder, or condition is associated with Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5 dysfunction. In certain embodiments, the disease, disorder, or condition is associated with Kv7.2 dysfunction. In certain embodiments, the disease, disorder, or condition is associated with Kv7.3 dysfunction. In certain embodiments, the disease, disorder, or condition is associated with Kv7.2/Kc7.3 dysfunction.

[081] Also provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, and pharmaceutical compositions thereof, for use in treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject.

[082] In another aspect, provided herein are methods of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof.

[083] Also provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts,

stereoisomers, tautomers, solvates, and prodrugs thereof, and pharmaceutical compositions thereof, for use in treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof.

[084] In certain embodiments, the disease, disorder, or condition is a seizure disorder. “Seizure disorders” refers to seizures and disorders associated with seizures such as partial onset seizures (also known as focal onset seizures), photosensitive epilepsy, self-induced syncope, intractable epilepsy, Angelman syndrome, benign rolandic epilepsy, CDKL5 disorder, childhood and juvenile absence epilepsy, Dravet syndrome, frontal lobe epilepsy, Glut1 deficiency syndrome, hypothalamic hamartoma, infantile spasms/West’s syndrome, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic-absences, Ohtahara syndrome, Panayiotopoulos syndrome, PCDH19 epilepsy, progressive myoclonic epilepsies, Rasmussen’s syndrome, ring chromosome 20 syndrome, reflex epilepsies, temporal lobe epilepsy, Lafora progressive myoclonus epilepsy, neurocutaneous syndromes, tuberous sclerosis complex, early infantile epileptic encephalopathy, early onset epileptic encephalopathy, generalized epilepsy with febrile seizures +, Rett syndrome, multiple sclerosis, Alzheimer’s disease, autism, ataxia, hypotonia, paroxysmal dyskinesia, generalized onset seizures, or primary generalized tonic-clonic seizures, or a combination thereof. In certain embodiments, the seizure disorder refers to generalized onset seizures. In some embodiments, the generalized onset seizures are primary generalized tonic-clonic seizures. In some embodiments, the seizure disorder is primary generalized tonic-clonic seizures.

[085] In certain embodiments, the term “seizure disorder” refers to focal onset epilepsy, also known as partial onset epilepsy. In some embodiments, the seizure disorder is photosensitive epilepsy. In some embodiments, the seizure disorder is self-induced syncope. In some embodiments, the seizure disorder is intractable epilepsy. In some embodiments, the seizure disorder is Angelman syndrome. In some embodiments, the seizure disorder is benign rolandic epilepsy. In some embodiments, the seizure disorder is CDKL5 disorder. In some embodiments, the seizure disorder is childhood and juvenile absence epilepsy. In some embodiments, the seizure disorder is Dravet syndrome. In some embodiments, the seizure disorder is frontal lobe epilepsy. In some embodiments, the seizure disorder is Glut1 deficiency syndrome. In some embodiments, the seizure disorder is hypothalamic hamartoma. In some embodiments, the seizure disorder is infantile spasms/West’s syndrome. In some embodiments, the seizure disorder is juvenile myoclonic epilepsy. In some embodiments, the seizure disorder is Landau-Kleffner syndrome. In some embodiments, the seizure disorder is Lennox-Gastaut syndrome (LGS). In some embodiments, the seizure disorder is epilepsy with myoclonic-absences. In some embodiments, the seizure disorder is Ohtahara syndrome. In some embodiments, the seizure disorder is Panayiotopoulos syndrome. In some embodiments, the seizure disorder is PCDH19 epilepsy. In some embodiments, the seizure disorder is progressive myoclonic epilepsies. In some embodiments, the seizure disorder is Rasmussen’s syndrome. In some embodiments, the seizure disorder is ring chromosome 20 syndrome. In some embodiments, the seizure disorder is reflex epilepsies. In some embodiments, the seizure disorder is temporal lobe epilepsy. In some embodiments, the seizure disorder is Lafora progressive myoclonus epilepsy. In some embodiments, the seizure disorder is neurocutaneous syndromes. In some

embodiments, the seizure disorder is tuberous sclerosis complex. In some embodiments, the seizure disorder is early infantile epileptic encephalopathy. In some embodiments, the seizure disorder is early onset epileptic encephalopathy. In some embodiments, the seizure disorder is generalized epilepsy. In some embodiments, the seizure disorder is generalized epilepsy with febrile seizures +. In some embodiments, the seizure disorder is Rett syndrome. In some embodiments, the seizure disorder is multiple sclerosis. In some embodiments, the seizure disorder is Alzheimer's disease. In some embodiments, the seizure disorder is autism. In some embodiments, the seizure disorder is ataxia. In some embodiments, the seizure disorder is hypotonia. In some embodiments, the seizure disorder is paroxysmal dyskinesia. In some embodiments, the seizure disorder is generalized onset seizures. In some embodiments, the seizure disorder is focal onset seizures (also known as partial onset seizures).

[086] In certain embodiments, the disease, disorder, or condition is a depressive disorder. "Depressive disorders" are mood disorders characterized by depressed mood. In certain embodiments, the depressive disorder is major depressive disorder (MDD), disruptive mood dysregulation disorder, persistent depressive disorder, bipolar spectrum disorder, postpartum depression, premenstrual dysphoric disorder (PMDD), seasonal affective disorder (SAD), atypical depression, treatment-resistant depression (TRD), depression associated with agitation or anxiety, adjustment disorder with depressed mood, prolonged depressive reaction, or a combination thereof. Also contemplated by the disclosure is treatment of obsessive-compulsive disorder (OCD), panic disorder, social anxiety disorder, social phobia, agoraphobia, agoraphobia with panic disorder, hypochondriasis, post-traumatic stress disorder (PTSD), treatment-resistant bipolar disorder, generalized anxiety disorder, attention-deficit/hyperactivity disorder (ADHD), bipolar I disorder, bipolar II disorder, manic disorder, cyclothymic disorder and bipolar disorder not otherwise specified, dysthymic disorder, depressive disorder not otherwise specified, minor depression, recurrent brief depressive disorder, depressive-type psychosis, impulse-control disorders, schizophrenia, schizophreniform disorder, schizoaffective disorder, Parkinson's disease, dementia, Alzheimer's disease, Huntington's disease, Tourette's syndrome, aggression, and substance use and/or abuse, or a combination thereof.

[087] In some embodiments, the depressive disorder is major depressive disorder (MDD). In some embodiments, the depressive disorder is disruptive mood dysregulation disorder. In some embodiments, the depressive disorder is persistent depressive disorder. In some embodiments, the depressive disorder is bipolar spectrum disorder. In some embodiments, the depressive disorder is postpartum depression. In some embodiments, the depressive disorder is premenstrual dysphoric disorder (PMDD). In some embodiments, the depressive disorder is seasonal affective disorder (SAD). In some embodiments, the depressive disorder is atypical depression. In some embodiments, the depressive disorder is treatment-resistant depression (TRD). In some embodiments, the depressive disorder is depression associated with agitation or anxiety. In some embodiments, the depressive disorder is adjustment disorder with depressed mood. In some embodiments, the depressive disorder is prolonged depressive reaction.

[088] In certain embodiments, the disease, disorder, or condition is pain. "Pain" as used herein refers to all categories of pain and includes, but is not limited to, neuropathic pain, inflammatory pain, nociceptive

pain, idiopathic pain, neuralgic pain, orofacial pain, burn pain, burning mouth syndrome, somatic pain, visceral pain, myofacial pain, dental pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, reflex sympathetic dystrophy, brachial plexus avulsion, neurogenic bladder, acute pain (*e.g.*, musculoskeletal and post-operative pain), chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, familial hemiplegic migraine, conditions associated with cephalic pain, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, pain following stroke, thalamic lesions, radiculopathy, HIV pain, post-herpetic pain, non-cardiac chest pain, chronic back pain, osteoarthritis (OA) pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia, and combinations thereof.

[089] In certain embodiments, the disease, disorder, or condition is anhedonia. “Anhedonia” as used herein refers to markedly diminished interest or pleasure in all, or almost all activities. Anhedonia of mild degree is sometimes referred to as hypohedonia. Social anhedonia is a type of anhedonia. “Social anhedonia” as used herein refers to a disinterest in social contact and a lack of pleasure in social situations. Social anhedonia is characterized by social withdrawal and typically manifests as an indifference to social interactions with other people. This trait is considered to be a central characteristic, as well as a predictor, of schizophrenia spectrum disorders.

[090] In another aspect, provided herein are compounds disclosed herein, and a pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof, and pharmaceutical compositions thereof, for use as medicaments. In certain embodiments, the medicament is for treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject (*e.g.*, Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5 dysfunction, *e.g.*, Kv7.2/Kc7.3 dysfunction). In certain embodiments, the medicament is for treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject.

[091] Also provided herein are methods of potentiating a Kv7 potassium channel in a cell *in vitro* comprising contacting the cell with a compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the Kv7 potassium channel is Kv7.2, Kv7.3, Kv7.4, and/or Kv7.5. In certain embodiments, the Kv7 potassium channel is Kv7.2. In certain embodiments, the Kv7 potassium channel is Kv7.3. In certain embodiments, the Kv7 potassium channel is Kv7.2/Kc7.3. In certain embodiments, the compound or composition is selective for one or more of Kv7.2-Kv7.5 over Kv7.1. In certain embodiments, the compound or composition is selective for one or more of Kv7.2/Kv7.3 over Kv7.1.

[092] Provided herein are methods of potentiating a Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) in a subject or in a cell *in vitro*. In certain embodiments, the activity of the Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) is increased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 100%, relative to control. In certain embodiments, the activity of the Kv7 potassium channel (*e.g.*, Kv7.2/Kv7.3) is increased by at least 1-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 100-fold, at least 200-fold, at least 300-fold, at least 400-

fold, at least 500-fold, or at least 1000-fold, relative to control.

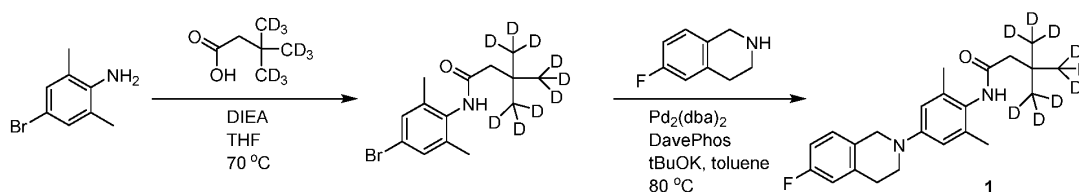
EXAMPLES

[093] In order that the present disclosure may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting in their scope.

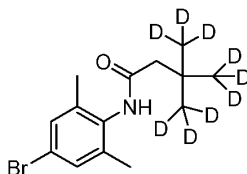
[094] The examples provided below include procedures, intermediates, and characterization data useful, *e.g.*, for the preparation of compounds provided herein. All synthetic steps, procedures, compounds (*e.g.*, synthetic intermediates), reaction conditions, reaction mixtures, reagents, *etc.* are included herein as aspects of the present disclosure.

Synthesis of Compounds

Example 1. *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl-*d*₃)butanamide

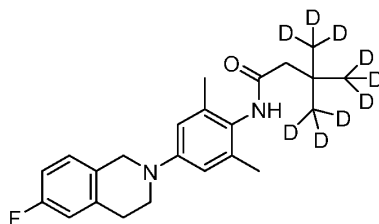


Step 1. Preparation of *N*-(4-bromo-2,6-dimethylphenyl)-3,3-bis(methyl-*d*₃)butanamide



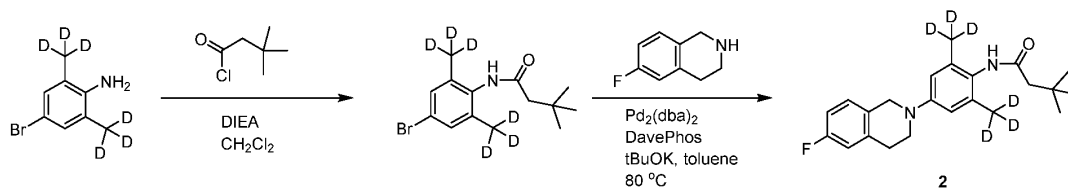
[095] To a solution 4,4,4-trideuterio-3,3-bis(trideuteriomethyl)butanoic acid (0.50 g, 3.99 mmol) in tetrahydrofuran (10 mL) was added 2-chloro-1-methylpyridinium iodide (1.53 g, 5.99 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.86 g, 14.40 mmol) at 25 °C. After being stirred at 25 °C for 2 h, 4-bromo-2,6-dimethyl-aniline (0.72 g, 3.59 mmol) was added. The reaction mixture was stirred at 70 °C for 12 h. After being cooled to room temperature, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate=10:1 to 1:1) to afford 0.328 g of *N*-(4-bromo-2,6-dimethylphenyl)-3,3-bis(methyl-*d*₃)butanamide (26% yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.19 (m, 2H), 6.80–6.51 (m, 1H), 2.30–2.26 (m, 2H), 2.23–2.18 (m, 6H).

Step 2. Preparation of *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl-*d*₃)butanamide

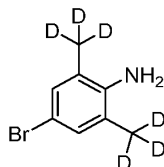


[096] To a solution of 2'-(dicyclohexylphosphaneyl)-*N,N*-dimethyl-[1,1'-biphenyl]-2-amine (0.922 g, 0.234 mmol) and bis(dibenzylideneacetone)-palladium(0) (0.045 g, 0.078 mmol) in toluene (1.0 mL) under nitrogen atmosphere. The reaction was stirred at 25 °C for 0.5 h. Potassium *tert*-butoxide (0.219 g, 1.95 mmol), *N*-(4-bromo-2,6-dimethylphenyl)-3,3-bis(methyl-*d*₃)butanamide (0.240 g, 0.781 mmol) and 6-fluoro-1,2,3,4-tetrahydroisoquinoline (0.176 g, 0.937 mmol) hydrogen chloride were added under nitrogen atmosphere. The reaction was stirred at 80 °C for 12 h. After being cooled to room temperature, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated in vitro. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate=5:1 to 1:1) followed by prep-HPLC (column: Waters Xbridge 150 mm × 25mm × 5 μm; mobile phase: [water (ammonia hydroxide)-acetonitrile]; B%:52–82%, 9 min) to afford 0.689 g of *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl-*d*₃)butanamide (99% purity, 23% yield) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.87 (s, 1H), 7.25 (dd, *J* = 5.6, 9.6 Hz, 1H), 7.00 (td, *J* = 3.2, 6.0 Hz, 2H), 6.70 (s, 2H), 4.31 (s, 2H), 3.47 (t, *J* = 5.6 Hz, 2H), 2.90 (t, *J* = 5.6 Hz, 2H), 2.15 (s, 2H), 2.10 (s, 6H); MS (ES+) *m/z* 378.4(*M* + 1).

Example 2. *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl)-2,6-bis(methyl-*d*₃)phenyl)-3,3-dimethylbutanamide



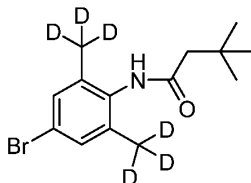
*Step 1. Preparation of 4-bromo-2,6-bis(methyl-*d*₃)aniline*



[097] To a solution of 2,6-bis(trideuteriomethyl)aniline (0.30 g, 2.36 mmol) in dimethyl formamide (5 mL) was added bromo-succinimide (0.42 g, 2.36 mmol) at 0 °C. The reaction was stirred at 25 °C for 12 h. After being cooled to room temperature, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel

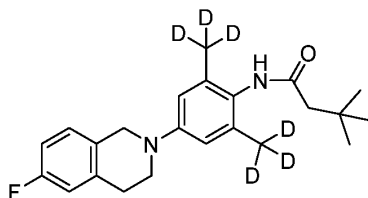
chromatography (petroleum ether: ethyl acetate=5:1 to 1:1) to afford 0.400 g of 4-bromo-2,6-bis(trideuteriomethyl)aniline (82% yield) as a light-yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 7.07 (s, 2H), 6.99–6.92 (m, 1H), 3.71–3.33 (m, 2H).

Step 2. Preparation of N-(4-bromo-2,6-bis(methyl- d_3)phenyl)-3,3-dimethylbutanamide



[098] To a solution of 4-bromo-2,6-bis(trideuteriomethyl)aniline (0.200 g, 0.970 mmol) in dichloromethane (2 mL) was added *N*-ethyl-*N*-isopropylpropan-2-amine (0.125 g, 0.970 mmol) followed by 3,3-dimethylbutanoyl chloride (0.130 mL, 0.970 mmol) at 0 °C. The reaction was stirred at 25 °C for 4 h. After being cooled to room temperature, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate=5:1 to 1:1) to afford 0.24 g of *N*-[4-bromo-2,6-bis(trideuteriomethyl)phenyl]-3,3-dimethyl-butnamide (80% yield) as a light-yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 7.22 (s, 2H), 6.61 (br s, 1H), 2.29 (s, 2H), 1.15 (s, 9H).

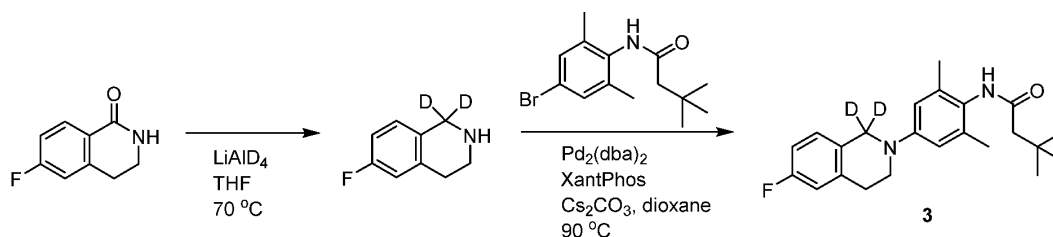
Step 3. Preparation of N-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,6-bis(methyl- d_3)phenyl)-3,3-dimethylbutanamide



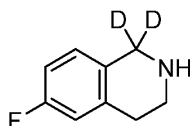
[099] To a solution of bis(dibenzylideneacetone)-palladium(0) (0.038 g, 0.066 mmol) and 2'-(dicyclohexylphosphaneyl)-*N,N*-dimethyl-[1,1'-biphenyl]-2-amine (0.078 g, 0.197 mmol) in toluene (5 mL) under nitrogen atmosphere. The reaction was stirred at 25 °C for 0.5 h. Potassium *tert*-butoxide (0.184 g, 1.640 mmol), *N*-[4-bromo-2,6-bis(trideuteriomethyl)phenyl]-3,3-dimethyl-butnamide (0.200 g, 0.657 mmol) and 6-fluoro-1,2,3,4-tetrahydroisoquinoline (0.148 g, 0.789 mmol, hydrogen chloride) were added under nitrogen atmosphere latter. The reaction was stirred at 80 °C for 12 h. After being cooled to room temperature, the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate=5:1 to 1:1) followed by prep-HPLC (column: Waters Xbridge 150 mm × 25 mm × 5 μm ; mobile phase: [water (ammonia hydroxide v/v)-acetonitrile]; B%: 52–82%, 9 min) to afford 0.087 g of *N*-[4-(6-fluoro-3,4-dihydro-1*H*-isoquinolin-2-yl)-2,6-bis(trideuteriomethyl)phenyl]-3,3-dimethyl-

butanamide (35% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.84 (s, 1H), 7.24 (dd, J = 6.0, 9.6 Hz, 1H), 7.04–6.93 (m, 2H), 6.68 (s, 2H), 4.29 (s, 2H), 3.46 (t, J = 5.8 Hz, 2H), 2.88 (t, J = 5.8 Hz, 2H), 2.15 (s, 2H), 1.03 (s, 9H); MS (ES+) m/z 375.4 ($M + 1$).

Example 3. *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-1,1- d_2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

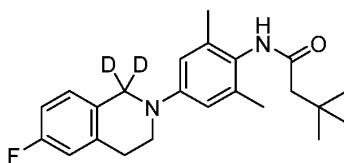


Step 1. Preparation of 6-fluoro-1,2,3,4-tetrahydroisoquinoline-1,1- d_2



[100] A solution of 6-fluoro-3,4-dihydro-2H-isoquinolin-1-one (0.50 g, 3.03 mmol) in tetrahydrofuran (4 mL) was added to a solution of lithium tetradeuterioaluminumide (0.75 g, 16.30 mmol) in tetrahydrofuran (2 mL) at 25 °C under nitrogen. The mixture was stirred at 70 °C for 4 h. The reaction mixture was cooled to room temperature. The reaction mixture was quenched by addition sodium sulfate decahydrate (20.0 g) at 25 °C, and the mixture was filtered and concentrated under reduced pressure to afford 0.50 g of 6-fluoro-1,2,3,4-tetrahydroisoquinoline-1,1- d_2 as a yellow oil that was used without further purification: ^1H NMR (400 MHz, CDCl_3) δ 7.03–6.92 (m, 1H), 6.85–6.78 (m, 2H), 3.69 (dt, J = 2.8, 5.6 Hz, 1H), 3.18–3.08 (m, 2H), 2.80 (q, J = 6.4 Hz, 2H).

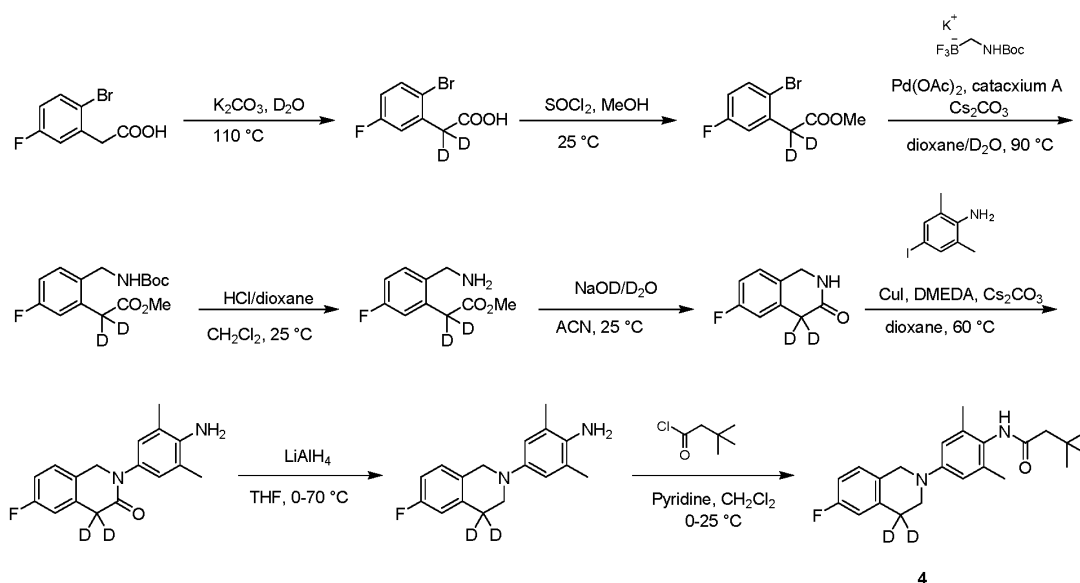
*Step 2. Preparation of *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-1,1- d_2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide*



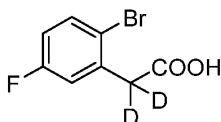
[101] A mixture of 6-fluoro-1,2,3,4-tetrahydroisoquinoline-1,1- d_2 (0.50 g, 3.26 mmol), *N*-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butnamide (0.97 g, 3.26 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.30 g, 0.33 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.38 g, 0.65 mmol) and cesium carbonate (3.19 g, 9.79 mmol) in dioxane (15 mL) was stirred at 90 °C for 12 h under nitrogen. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography (12 g SepaFlash® Silica Flash Column, eluent of 0–55% ethyl acetate/petroleum ether gradient at 80 mL/min)

and by prep-HPLC (column: Unisil 3-100 C18 Ultra 150 mm × 50 mm × 3 μm; mobile phase: [water(formic acid)- acetonitrile]; B%: 50%–80%, 7 min). The desired fraction was collected and lyophilized to afford 0.078 g of *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl-1,1-*d*₂)-2,6-dimethylphenyl)-3,3-dimethylbutanamide (6% yield, 95% purity) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.87 (s, 1H), 7.30–7.21 (m, 1H), 7.05–6.96 (m, 2H), 6.69 (s, 2H), 3.51–3.45 (m, 2H), 2.89 (t, *J* = 5.6 Hz, 2H), 2.16 (s, 2H), 2.09 (s, 6H), 1.05 (s, 9H); MS (ES+) *m/z* 371.2(*M* + 1).

Example 4. *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl-4,4-*d*₂)-2,6-dimethylphenyl)-3,3-dimethylbutanamide



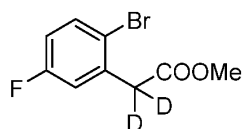
*Step 1. Preparation of 2-(2-bromo-5-fluorophenyl)acetic-2,2-*d*₂ acid*



[102] To a solution of 2-(2-bromo-5-fluorophenyl)acetic acid (5.0 g, 21.5 mmol) in deuterium oxide (50 mL) was added potassium carbonate (11.9 g, 85.8 mmol), then the mixture was stirred at 110 °C for 24 h. Cooled to room temperature, the reaction mixture was acidified with diluted hydrochloric (1.0 M) to adjust pH = 3, then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 5.0 g of 2-(2-bromo-5-fluorophenyl)acetic-2,2-*d*₂ acid (99% yield) as a white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.59 (s, 1H), 7.64 (dd, *J* = 8.8 5.2 Hz, 1H), 7.33 (dd, *J* = 9.6, 3.2 Hz, 1H), 7.14–7.09 (m, 1H).

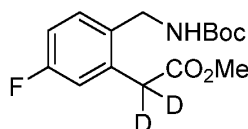
*Step 2. Preparation of methyl 2-(2-bromo-5-fluorophenyl)acetate-*d*₂*

25



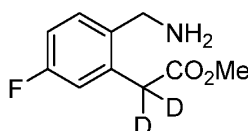
To a solution of 2-(2-bromo-5-fluorophenyl)acetic-2,2- d_2 acid (5.0 g, 21.2 mmol) in methanol (50 mL) was added thionyl chloride (7.6 g, 63.8 mmol), then the mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (3 × 100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0–30% ethyl acetate/petroleum ether gradient at 40 mL/min) to afford 4.7 g of methyl 2-(2-bromo-5-fluorophenyl)acetate- d_2 (86% yield) as colorless oil: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.66 (dd, J = 8.8, 5.2 Hz, 1H), 7.35 (dd, J = 9.6, 3.2 Hz, 1H), 7.16–7.11 (m, 1H), 3.64 (s, 3H).

Step 3. Preparation of methyl 2-(2-(((tert-butoxycarbonyl)amino)methyl)-5-fluorophenyl)acetate- d_2



[103] To a solution of methyl 2-(2-bromo-5-fluorophenyl)acetate- d_2 (1.20 g, 4.82 mmol), potassium (((tert-butoxycarbonyl)amino)methyl)trifluoroborate (2.29 g, 9.64 mmol), palladium acetate (0.11 g, 0.48 mmol), bis(1-adamantyl)-butyl-phosphane (0.35 g, 0.96 mmol) and cesium carbonate (4.71 g, 14.40 mmol) in dioxane (40 mL) and deuterium oxide (4 mL). The mixture was stirred at 90 °C under nitrogen for 16 h. Cooled to room temperature, the reaction was diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0–0% ethyl acetate/petroleum ether gradient at 20mL/min) to afford 1.13 g of methyl 2-(2-(((tert-butoxycarbonyl)amino)methyl)-5-fluorophenyl)acetate- d_2 (70% yield) as yellow oil: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.29–7.26 (m, 1H), 7.11–7.06 (m, 1H), 4.07 (d, J = 6.0 Hz, 2H), 3.62 (s, 3H), 1.38 (s, 9H).

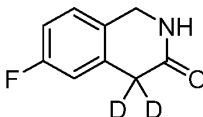
Step 4. Preparation of methyl 2-(2-(aminomethyl)-5-fluorophenyl)acetate- d_2



[104] To a solution of methyl 2-(2-(((tert-butoxycarbonyl)amino)methyl)-5-fluorophenyl)acetate- d_2 (1.10 g, 3.67 mmol) in dichloromethane (10 mL) was added hydrogen chloride (4 M in dioxane, 1.0 mL). The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give methyl 2-(2-(aminomethyl)-5-fluorophenyl)acetate- d_2 hydrochloride (1.16 g, crude) as a brown

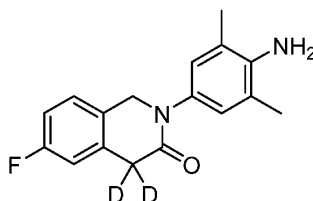
solid. The crude product was used in the next step without further purification: MS (ES+) m/z 200.2 (M + 1).

Step 5. Preparation of 6-fluoro-1,4-dihydroisoquinolin-3(2H)-one-4,4- d_2



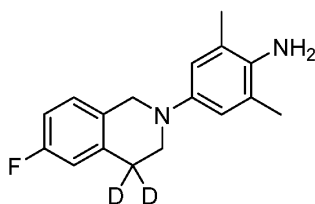
[105] To a solution of methyl 2-(2-(aminomethyl)-5-fluorophenyl)acetate- d_2 hydrochloride (1.80 g, 7.64 mmol) in acetonitrile (20 mL) was added sodium deuterioxide (3.05 g, 2 mL, 30% purity). The mixture was stirred at 25 °C for 2 h. The reaction was diluted with deuterium oxide (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (3 × 30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 1.10 g of 6-fluoro-1,4-dihydroisoquinolin-3(2H)-one-4,4- d_2 (85% yield, 99% purity) as a brown solid that was used without further purification: ^1H NMR (400 MHz, DMSO- d_6) δ 8.04 (s, 1H), 7.30 (dd, J = 8.0, 5.6 Hz, 1H), 7.09–7.01 (m, 2H), 4.30 (s, 2H).

Step 6. Preparation of 2-(4-amino-3,5-dimethylphenyl)-6-fluoro-1,4-dihydroisoquinolin-3(2H)-one-4,4- d_2



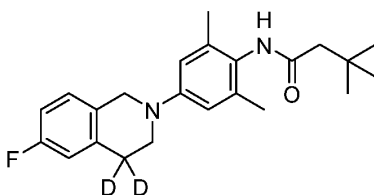
[106] To a solution of 6-fluoro-1,4-dihydroisoquinolin-3(2H)-one-4,4- d_2 (0.50 g, 2.99 mmol) and 4-iodo-2,6-dimethylaniline (0.89 g, 3.59 mmol) in dioxane (20 mL) were added *N,N'*-dimethylethane-1,2-diamine (0.26 g, 2.99 mmol), cesium carbonate (1.95 g, 5.98 mmol) and copper iodide (0.29 g, 1.50 mmol), the resulting mixture was stirred at 60 °C under nitrogen for 16 h. Then deuterium oxide (10 mL) was added to the mixture and stirred for another 2 h. After being cooled to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (3 × 20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0–100% ethyl acetate/petroleum ether gradient @ 30 mL/min) to afford 0.72 g of 2-(4-amino-3,5-dimethylphenyl)-6-fluoro-1,4-dihydroisoquinolin-3(2H)-one-4,4- d_2 (84% yield) as a brown solid: ^1H NMR (400 MHz, DMSO- d_6) δ 7.34 (dd, J = 8.4, 5.6 Hz, 1H), 7.16 (dd, J = 9.2, 2.4 Hz, 1H), 7.10–7.04 (m, 1H), 6.73 (s, 2H), 4.71 (s, 2H), 4.58 (s, 2H), 2.07 (s, 6H).

Step 7. Preparation of 4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-4,4- d_2)-2,6-dimethylaniline



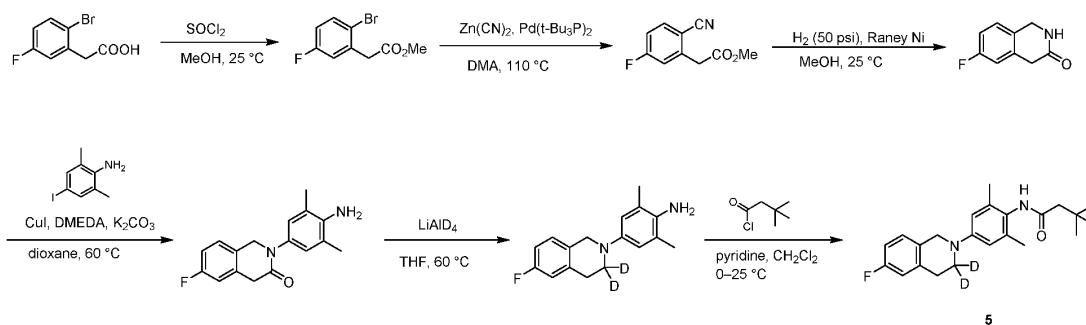
[107] To a solution of 2-(4-amino-3,5-dimethylphenyl)-6-fluoro-1,4-dihydroisoquinolin-3(2H)-one-4,4- d_2 (0.40 g, 1.40 mmol) in tetrahydrofuran (16 mL) was added lithium aluminium hydride (1.0 M in tetrahydrofuran, 2.79 mL) dropwise at 0 °C, then the mixture was stirred at 70 °C under nitrogen for 2 h. After being cooled to room temperature, the reaction was quenched with sodium sulfate decahydrate (0.200 g). The mixture was filtered off over *Celite*, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0–50% ethyl acetate/petroleum ether gradient at 15 mL/min) to afford 0.12 g of 4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-4,4- d_2)-2,6-dimethylaniline (32% yield) as a brown solid: ^1H NMR (400 MHz, DMSO- d_6) δ 7.19 (dd, J = 9.2, 5.6 Hz, 1H), 7.00–6.96 (m, 2H), 6.59 (s, 2H), 4.08 (s, 4H), 3.23 (s, 2H), 2.07 (s, 6H).

Step 8. Preparation of N-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-4,4- d_2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

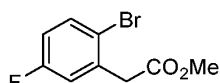


[108] To a solution of 4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-4,4- d_2)-2,6-dimethylaniline (0.085 g, 0.312 mmol) and pyridine (0.049 g, 0.624 mmol) in dichloromethane (5 mL) was added 3,3-dimethylbutanoyl chloride (0.050 g, 0.375 mmol) dropwise at 0 °C, then the mixture was stirred at 25 °C for 0.5 h. The reaction was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (3 × 30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0–50% ethyl acetate/petroleum ether gradient at 15 mL/min) to afford 0.056 g of N-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-4,4- d_2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide (48% yield, 95% purity) as a white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 8.87 (s, 1H), 7.26 (dd, J = 9.2, 5.6 Hz, 1H), 7.03–6.99 (m, 2H), 6.70 (s, 2H), 4.31 (s, 2H), 3.46 (s, 2H), 2.17 (s, 2H), 2.10 (s, 6H), 1.05 (s, 9H); MS (ES+) m/z 371.2 ($M + 1$).

Example 5. N-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-3,3- d_2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

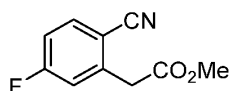


Step 1. Preparation of 2-methyl 2-(2-bromo-5-fluorophenyl)acetate



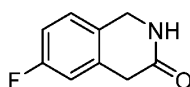
[109] To a solution of 2-(2-bromo-5-fluorophenyl)acetic acid (8.00 g, 34.30 mmol) in methanol (80 mL) was added thionyl chloride (12.30 g, 103.39 mmol) at 25 °C. The mixture was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0–30% ethyl acetate/petroleum ether gradient at 70 mL/min) to afford 8.40 g of methyl 2-(2-bromo-5-fluorophenyl)acetate (94% yield, 95% purity) as a colorless oil: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.35 (dd, *J* = 3.2, 9.6 Hz, 1H), 7.13 (dt, *J* = 3.2, 8.8 Hz, 1H), 3.84 (s, 2H), 3.64 (s, 3H).

Step 2. Preparation of methyl 2-(2-cyano-5-fluorophenyl)acetate



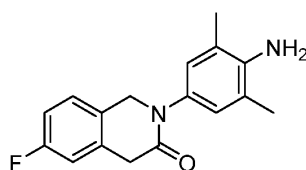
[110] Under nitrogen atmosphere, to a solution of methyl 2-(2-bromo-5-fluorophenyl)acetate (7.20 g, 29.10 mmol) in *N,N*-dimethylacetamide (70 mL) was added zinc(II) cyanide (5.14 g, 43.80 mmol) and palladium;tritylphosphane (1.49 g, 2.91 mmol) at 25 °C. Then the mixture was stirred at 110 °C for 12 h. The mixture was poured into saturated aqueous sodium carbonate (250 mL). The mixture was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were washed with brine (250 mL), dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent of 0–20% ethyl acetate/petroleum ether gradient at 70 mL/min) to afford 4.5 g of methyl 2-(2-cyano-5-fluorophenyl)acetate (76% yield, 95% purity) as a colorless oil: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.96 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.48 (dd, *J* = 2.8, 9.6 Hz, 1H), 7.38 (dt, *J* = 2.8, 8.8 Hz, 1H), 3.98 (s, 2H), 3.66 (s, 3H).

Step 3. Preparation of methyl 6-fluoro-1,4-dihydroisoquinolin-3(2H)-one



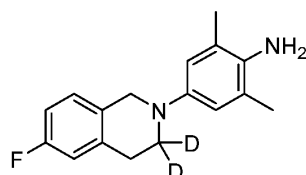
[111] To a solution of methyl 2-(2-cyano-5-fluorophenyl)acetate (4.50 g, 23.30 mmol) in methanol (200 mL) was added Raney-Nickel (4.50 g, 52.52 mmol) at 25 °C under nitrogen atmosphere. The suspension was degassed and purged with hydrogen three times. The mixture was stirred at 25 °C for 12 h under hydrogen (50 psi). After completion of the reaction, the resulting mixture was filtered over *Celite*. The filter cake was washed with methanol (20–30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase column (column: C18, 80 g; mobile phase: [water (0.1% formic acid)-acetonitrile]; B%: 0–30%) to afford 0.78 g of 6-fluoro-1,4-dihydroisoquinolin-3(2*H*)-one (19% yield, 95% purity) as a yellow solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.04 (s, 1H), 7.30 (dd, *J* = 6.0, 8.0 Hz, 1H), 7.12–6.97 (m, 2H), 4.30 (s, 2H), 3.45 (s, 2H).

Step 4. Preparation of 2-(4-amino-3,5-dimethylphenyl)-6-fluoro-1,4-dihydroisoquinolin-3(2*H*)-one



[112] Under nitrogen atmosphere, to a solution of 6-fluoro-1,4-dihydroisoquinolin-3(2*H*)-one (0.47 g, 2.85 mmol), 4-iodo-2,6-dimethylaniline (1.41 g, 5.71 mmol) and cesium carbonate (1.86 g, 5.70 mmol) in dioxane (10 mL) was added copper(I) iodide (0.27 g, 1.43 mmol) and *N*¹,*N*²-dimethylethane-1,2-diamine (0.25 g, 2.88 mmol) at 25 °C. Then the mixture was stirred at 60 °C for 12 h. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent of 0–100% ethyl acetate/petroleum ether gradient at 100 mL/min) to afford 0.66 g of 2-(4-amino-3,5-dimethylphenyl)-6-fluoro-1,4-dihydroisoquinolin-3(2*H*)-one (75% yield, 91% purity) as a brown solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.37–7.30 (m, 1H), 7.15 (dd, *J* = 2.4, 9.6 Hz, 1H), 7.06 (dt, *J* = 2.4, 8.8 Hz, 1H), 6.73 (s, 2H), 4.71 (s, 2H), 4.58 (s, 2H), 3.66 (s, 2H), 2.07 (s, 6H).

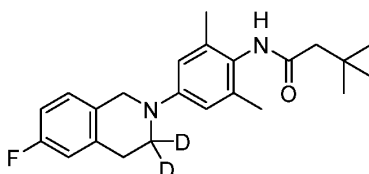
Step 4. Preparation of 4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl-3,3-*d*₂)-2,6-dimethylaniline



[113] Under nitrogen atmosphere, to a solution of 2-(4-amino-3,5-dimethylphenyl)-6-fluoro-1,4-dihydroisoquinolin-3(2*H*)-one (0.66 g, 2.31 mmol) in tetrahydrofuran (20 mL) was added lithium aluminum deuteride (0.34 g, 8.10 mmol) at 25 °C. The mixture was stirred at 70 °C for 2 h. The reaction mixture was cooled to room temperature and quenched by addition of sodium sulfate decahydrate until gas evolution ceased. The reaction mixture was filtered, washing with tetrahydrofuran (20 mL) and methanol (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, eluent of 0–35% ethyl acetate/petroleum

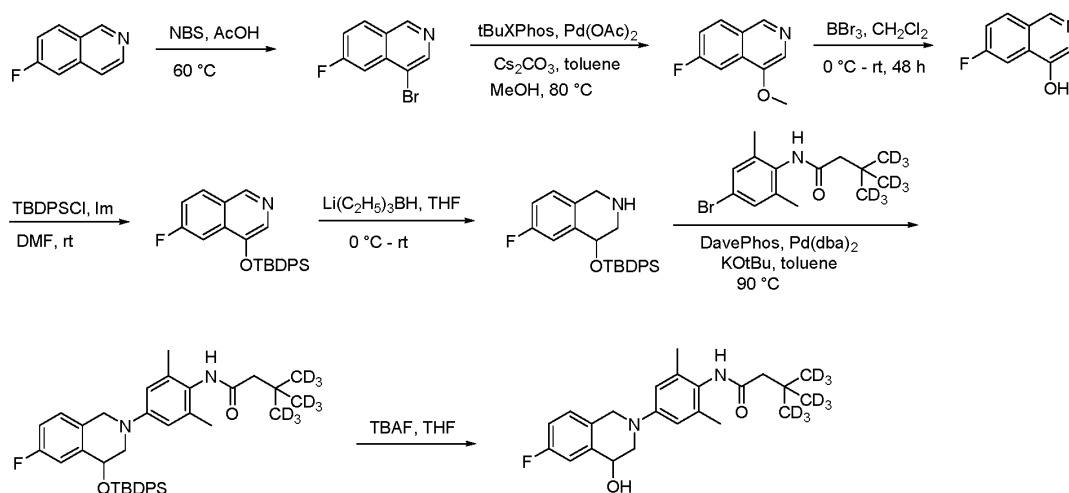
ether gradient at 70 mL/min) to afford 0.19 g of 4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-3,3- d_2)-2,6-dimethylaniline (27% yield, 90% purity) as a brown solid: ^1H NMR (400 MHz, DMSO- d_6) δ 7.19 (dd, J = 6.0, 9.6 Hz, 1H), 7.02–6.92 (m, 2H), 6.58 (s, 2H), 4.12–4.03 (m, 4H), 2.86 (s, 2H), 2.07 (s, 6H).

Step 5. Preparation of N-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-3,3- d_2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

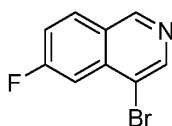


[114] To a solution of 4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-3,3- d_2)-2,6-dimethylaniline (0.190 g, 0.698 mmol) and pyridine (0.111 g, 1.40 mmol) in dichloromethane (3 mL) was added 3,3-dimethylbutanoyl chloride (0.103 g, 0.765 mmol) at 0 °C. Then the mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent of 0–30% ethyl acetate/petroleum ether gradient at 70 mL/min) to afford 0.075 g of *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl-3,3- d_2)-2,6-dimethylphenyl)-3,3-dimethylbutanamide (27% yield, 92% purity) as a yellow solid: ^1H NMR (400 MHz, DMSO- d_6) δ 8.86 (s, 1H), 7.25 (dd, J = 5.6, 9.2 Hz, 1H), 7.07–6.95 (m, 2H), 6.69 (s, 2H), 4.31 (s, 2H), 2.88 (s, 2H), 2.17 (s, 2H), 2.10 (s, 6H), 1.05 (s, 9H); MS (ES+) m/z 371.1 ($M + 1$).

Example 6. *N*-(4-(6-fluoro-4-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl- d_3)butanamide

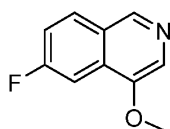


Step 1. Preparation of 2-methyl 2-(2-bromo-5-fluorophenyl)acetate



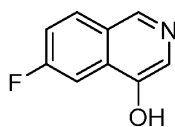
[115] A mixture of 6-fluoroisoquinoline (9.58 g, 65.09 mmol) and *N*-bromosuccinimide (17.38 g, 97.64 mmol) in acetic acid (100 mL) was stirred at 60 °C for 48 h. The mixture was concentrated in vacuo. The resulting residue was diluted with ethyl acetate and saturated aqueous sodium bicarbonate solution. Layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 70 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography, eluting with a gradient of 0% to 20% of ethyl acetate in heptanes, to afford 4.58 g of the title compound as a pale yellow solid (31% yield): ¹H NMR (300 MHz; CDCl₃): δ 9.16 (s, 1H), 8.73 (s, 1H), 8.04 (dd, *J* = 9.0, 5.4 Hz, 1H), 7.81 (dd, *J* = 9.9, 2.5 Hz, 1H), 7.46 (ddd, *J* = 8.9, 8.3, 2.5 Hz, 1H); MS (ES+) *m/z* 225.9, 227.9 (*M* + 1).

Step 2. Preparation of 6-fluoro-4-methoxyisoquinoline



[116] A mixture of 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.87 g, 2.05 mmol), palladium(II) acetate (0.23 g, 1.02 mmol) and cesium carbonate (8.35 g, 25.61 mmol) in anhydrous toluene (17 mL) was purged with argon for 20 min, heated to 80 °C for 10 min and cooled to ambient temperature. To the resulting mixture was added a solution of 4-bromo-6-fluoroisoquinoline (3.86 g, 17.08 mmol) in anhydrous methanol (17 mL). The reaction mixture was heated to 80 °C for 5 h, cooled to ambient temperature and filtered through a pad of diatomaceous earth. The pad was washed with ethyl acetate (2 × 50 mL) and the combined filtrate was washed with brine (60 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of 0% to 50% to 100% of ethyl acetate in heptanes, to afford 2.72 g of the title compound as a pale yellow solid (90% yield): ¹H NMR (300 MHz; CDCl₃): δ 8.87 (s, 1H), 8.07 (s, 1H), 7.96 (dd, *J* = 9.0, 5.4 Hz, 1H), 7.79 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.38 (td, *J* = 8.7, 2.6 Hz, 1H), 4.0 (s, 3H); MS (ES+) *m/z* 178.1 (*M* + 1).

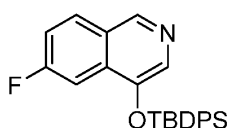
Step 3. Preparation of 6-fluoroisoquinolin-4-ol



[117] To a stirred solution of 6-fluoro-4-methoxyisoquinoline (2.00 g, 11.29 mmol) in anhydrous dichloromethane (50 mL) at 0 °C was added dropwise a solution of boron tribromide (10.9 mL, 112.9 mmol) in dichloromethane (30 mL). The mixture was allowed to warm to ambient temperature and stirred for 48 h. The reaction mixture was cooled to 0 °C and methanol (100 mL) was added slowly dropwise with vigorous stirring. The mixture was stirred at 0 °C for 2 h, warmed to ambient temperature

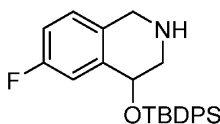
and stirred for 1 h, then concentrated in vacuo. The residue was cooled to 0 °C and diluted with saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (60 mL), brine (60 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to afford 1.84 g of the title compound as a pale yellow solid (100% yield): ¹H NMR (300 MHz; CD₃OD): δ 8.75 (s, 1H), 8.12 (dd, *J* = 9.0, 5.4 Hz, 1H), 7.94 (s, 1H), 7.82 (dd, *J* = 9.9, 2.3 Hz, 1H), 7.49 (td, *J* = 8.8, 2.6 Hz, 1H); MS (ES+) *m/z* 164.1 (*M* + 1).

Step 4. Preparation of 4-((tert-butyl diphenylsilyl)oxy)-6-fluoroisoquinoline



[118] To a stirred mixture of 6-fluoroisoquinolin-4-ol (1.84 g, 11.28 mmol) and imidazole (4.61 g, 67.68 mmol) in anhydrous *N,N*-dimethylformamide (56 mL) at 0 °C was added *tert*-butyl(chloro)diphenylsilane (8.8 mL, 33.83 mmol) dropwise. The mixture was stirred at ambient temperature for 24 h, diluted with water and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with water (2 × 150 mL), brine (100 mL), dried over magnesium sulfate and filtered. Concentration of the filtrate in vacuo and purification of the residue by column chromatography, eluting with a gradient of 0 to 10% of ethyl acetate in dichloromethane, afforded 3.74 g of the title compound as a colorless solid (83% yield): ¹H NMR (300 MHz; CD₃OD): δ 8.76 (s, 1H), 8.18 (dd, *J* = 9.1, 5.4 Hz, 1H), 7.97 (dd, *J* = 9.8, 2.5 Hz, 1H), 7.80-7.72 (m, 4H), 7.58-7.35 (m, 8H), 1.21 (s, 9H); MS (ES +) *m/z* 402.2 (*M* + 1).

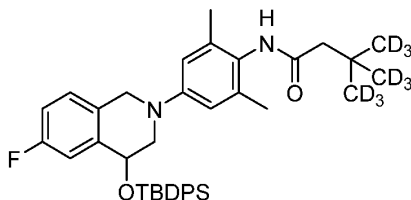
Step 5. Preparation of 4-((tert-butyl diphenylsilyl)oxy)-6-fluoro-1,2,3,4-tetrahydroisoquinoline



[119] To a solution of 4-((*tert*-Butyl diphenylsilyl)oxy)-6-fluoroisoquinoline (**5**, 1.5 g, 3.74 mmol) in anhydrous tetrahydrofuran (30 mL) was added a 1M solution of lithium triethylborohydride in tetrahydrofuran (20.2 mL, 20.2 mmol) dropwise with stirring at 0 °C. The mixture was stirred at ambient temperature for 19 h, cooled to 0 °C and anhydrous methanol (15 mL) was added dropwise under nitrogen atmosphere with stirring. The mixture was stirred at 0 °C for 15 minutes and at ambient temperature for 30 minutes. The mixture was diluted with cold saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with brine (70 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with a gradient of 0% to 100% of ethyl acetate in heptane, to afford 0.45 g of the title compound as a colorless oil (29% yield): ¹H NMR (300 MHz; CD₃OD): δ 7.75-7.62 (m, 4H), 7.54-7.34 (m, 6H), 7.11-7.01 (m, 1H), 6.92 (td, *J* = 8.6, 2.7 Hz, 1H), 6.77 (dd, *J* = 9.7,

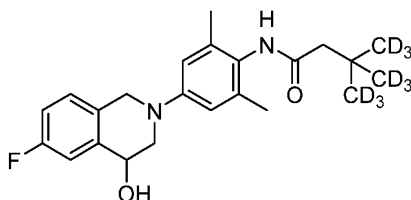
2.6 Hz, 1H), 4.73 (br t, $J = 4.8$, 1H), 4.03-3.74 (m, 2H), 3.03-2.86 (m, 2H), 1.08 (s, 9H); MS (ES +) m/z 406.2 ($M + 1$).

Step 6. Preparation of N-(4-(4-((tert-butyl)diphenylsilyl)oxy)-6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl- d_3)butanamide(4,4,4- d_3)



[120] A mixture of 4-((*tert*-Butyldiphenylsilyl)oxy)-6-fluoro-1,2,3,4-tetrahydroisoquinoline (0.45 g, 1.11 mmol), *N*-(4-bromo-2,6-dimethylphenyl)-3,3-bis(methyl- d_3)butanamide(4,4,4- d_3) (0.34 g, 1.11 mmol) and potassium *tert*-butoxide (0.19 g, 1.67 mmol) in anhydrous toluene (11 mL) was purged with argon for 20 minutes and then 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (0.10 g, 0.26 mmol) was added, followed by bis-(dibenzylideneacetone)palladium(0) (0.05 g, 0.09 mmol). The mixture was purged with argon for an additional 5 minutes and then heated to 90 °C for 22 h. The reaction mixture was cooled to ambient temperature and diluted with ethyl acetate and saturated aqueous sodium bicarbonate solution. Layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 60 mL). The combined organic layers were washed with brine (80 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 40% ethyl acetate in heptanes, to afford 0.49 g of the title compound as a colorless oil that solidified on standing (70% yield): ^1H NMR (300 MHz; CD_3OD): δ 7.79-7.72 (m, 4H), 7.54-7.39 (m, 6H), 7.23 (dd, $J = 8.5$, 5.6, Hz 1H), 7.18-7.11 (m, 1H), 6.99 (td, $J = 8.5$, 2.7 Hz, 1H), 6.34 (s, 2H), 5.05-4.96 (m, 1H), 4.36-4.18 (m, 2H), 3.47-3.36 (m, 1H), 3.15-3.03 (m, 1H), 2.26 (s, 2H), 2.12 (s, 6H), 1.11 (s, 9H); MS (ES +) m/z 632.3 ($M + 1$).

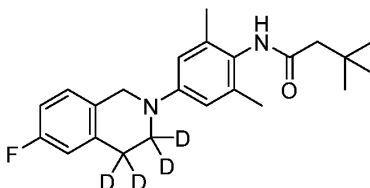
Step 7. Preparation of N-(4-(6-fluoro-4-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl- d_3)butanamide(4,4,4- d_3)



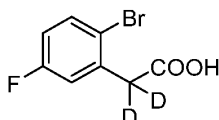
[121] To a solution of *N*-(4-(4-((*tert*-butyldiphenylsilyl)oxy)-6-fluoro-3,4-dihydroisoquinolin-2(1H)-yl)-2,6-dimethylphenyl)-3,3-bis(methyl- d_3)butanamide(4,4,4- d_3) (0.35 g, 0.55 mmol) in anhydrous tetrahydrofuran (6 mL) was added a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.83 mL, 0.83 mmol) dropwise with stirring. The mixture was stirred at ambient temperature for 2 h and then concentrated *in vacuo*. The residue was diluted with water and ethyl acetate. The layers were

separated and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine (60 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with a gradient of 0% to 50% of ethyl acetate in heptane, to afford 0.113 g of the title compound as a colorless solid (52% yield): ¹HNMR (300 MHz; CD₃OD): δ 7.31-7.18 (m, 2H), 7.09-6.95 (m, 1H), 6.79 (s, 2H), 4.85-4.75 (m, 1H), 4.30 (s, 2H), 3.69-3.62 (m, 1H), 3.39-3.35 (m, 1H), 2.28 (s, 2H), 2.21 (s, 6H).

Example 7. *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl-3,3,4,4-d₄)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

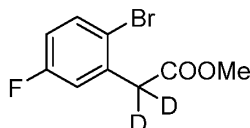


Step 1. Preparation of 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetic acid



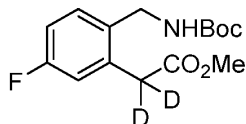
[122] To a solution of 2-(2-bromo-5-fluoro-phenyl) acetic acid (1.00 g, 4.29 mmol) in deuterium oxide (10.0 mL) was added potassium carbonate (2.37 g, 17.20 mmol). The mixture was stirred at 110 °C for 24 hrs. The reaction mixture was adjusted pH = 3 with dilute hydrochloric acid (1 M) at 0 °C, and then extracted with ethyl acetate (2 x 20.0 mL). The combined organic phases were washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 0.93 g of crude 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetic acid (92% yield) as a white solid that was used without further purification: ¹H NMR (400 MHz, deuterium oxide) δ 7.52 (dd, *J*₁ = 8.8 Hz, *J*₂ = 5.6 Hz, 1H), 7.02 (dd, *J*₁ = 9.6 Hz, *J*₂ = 3.2 Hz, 1H), 7.02 (td, *J*₁ = 8.8 Hz, *J*₂ = 3.2 Hz, 1H).

Step 2. Preparation of methyl 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetate



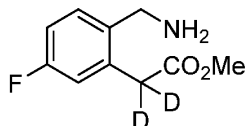
[123] To a solution of 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetic acid (0.93 g, 3.96 mmol) in methanol (10.0 mL) was added thionyl chloride (1.41 g, 11.90 mmol). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was quenched by the addition of water (50.0 mL) at 0 °C, and then extracted with ethyl acetate (2 x 20.0 mL). The combined organic phases were washed with brine (40.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 0.99 g crude of methyl 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetate (99% yield) as a colorless oil that was used without further purification: MS (ES+) *m/z* 250.8 (M+1).

Step 3. Preparation of methyl 2-[2-[(tert-butoxycarbonylamino)methyl]-5-fluoro-phenyl]-2,2-dideuterio-acetate



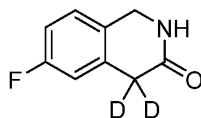
[124] A mixture of methyl 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetate (0.99 g, 3.95 mmol), potassium (*tert*-butoxycarbonylamino)methyl-trifluoro-boranide (1.88 g, 7.91 mmol), palladium acetate (0.09 g, 0.40 mmol), bis(1-adamantyl)-butyl-phosphane (0.28 g, 0.79 mmol) and cesium carbonate (3.87 g, 11.90 mmol) in dioxane (33.3 mL) and deuterium oxide (3.3 mL) was degassed and purged with N₂ 3 times. The mixture was stirred at 90 °C for 12 hrs under N₂ atmosphere. The reaction mixture was quenched by addition of water (40.0 mL) at 0 °C, and then extracted with ethyl acetate (2 x 20.0 mL). The combined organic phases were washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10: 1 to 4: 1, TLC: petroleum ether: ethyl acetate = 3: 1, R_f = 0.46 (P1)) to afford 1.0 g of methyl 2-[2-[(*tert*-butoxycarbonylamino)methyl]-5-fluoro-phenyl]-2,2-dideuterio-acetate (85% yield) as a yellow oil: MS (ES+) *m/z* 200.2 (M-99).

Step 4. Preparation of methyl 2-[2-(aminomethyl)-5-fluoro-phenyl]-2,2-dideuterio-acetate



[125] The solution of methyl 2-[2-[(*tert*-butoxycarbonylamino)methyl]-5-fluoro-phenyl]-2,2-dideuterio-acetate (1.00 g, 3.34 mmol) in hydrogen chloride solution (20.0 mL, 4.0 M in dioxane) was stirred at 25 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to afford 0.67 g of crude methyl 2-[2-(aminomethyl)-5-fluoro-phenyl]-2,2-dideuterio-acetate (99% yield) as a white solid that was used without further purification: MS (ES+) *m/z* 200.1 (M+1)

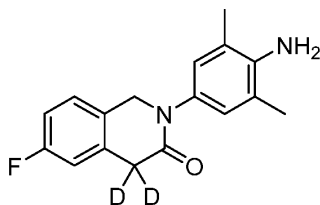
Step 5. Preparation of 4,4-dideuterio-6-fluoro-1,2-dihydroisoquinolin-3-one



[126] To a solution of methyl 2-[2-(aminomethyl)-5-fluoro-phenyl]-2,2-dideuterio-acetate (665 mg, 3.34 mmol) in acetonitrile (6.00 mL) was added sodium deuterioxide (1.11 g, 8.35 mmol, 30% purity). The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched by addition deuterium oxide (6.00 mL) at 0 °C, and then extracted with ethyl acetate (2 x 10.0 mL). The combined organic phases were washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under

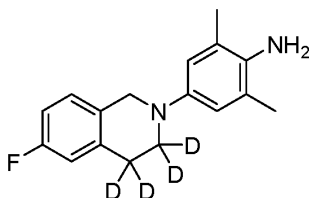
reduced pressure to afford 0.45 g of 4,4-dideuterio-6-fluoro-1,2-dihydroisoquinolin-3-one (80% yield) as a yellow solid that was used without further purification: ^1H NMR: (400 MHz, chloroform-*d*) δ 7.14 (dd, $J_1 = 8.4$ Hz, $J_2 = 5.6$ Hz, 1H), 6.98-6.87 (m, 2H), 4.49 (s, 2H); MS (ES+) m/z 166.2 (M+1).

Step 6. Preparation of 2-(4-amino-3,5-dimethyl-phenyl)-4,4-dideuterio-6-fluoro-1H-isoquinolin-3-one



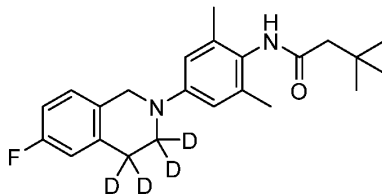
[127] A mixture of 4,4-dideuterio-6-fluoro-1,2-dihydroisoquinolin-3-one (450 mg, 2.69 mmol), 4-iodo-2,6-dimethyl-aniline (0.80 g, 3.23 mmol), cesium carbonate (1.75 g, 5.38 mmol), iodocopper (0.26 g, 1.35 mmol) and *N,N'*-dimethylethane-1,2-diamine (0.24 g, 2.69 mmol) in dioxane (20.0 mL) was degassed and purged with N_2 3 times. The mixture was stirred at 60 °C for 12 hrs under N_2 atmosphere. The reaction mixture was quenched by the addition of deuterium oxide (10.0 mL) at 60 °C for 2 hrs, and then quenched by addition water (10.0 mL) at 20 °C and extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10: 1 to 1: 1, TLC: petroleum ether: ethyl acetate = 0: 1, $R_f = 0.42$ (P1)) to afford 0.41 g of 2-(4-amino-3,5-dimethyl-phenyl)-4,4-dideuterio-6-fluoro-1H-isoquinolin-3-one (40% yield) as a yellow solid: MS (ES+) m/z 285.2 (M-1).

Step 7. Preparation of 2,6-dimethyl-4-(3,3,4,4-tetradeuterio-6-fluoro-1H-isoquinolin-2-yl)aniline



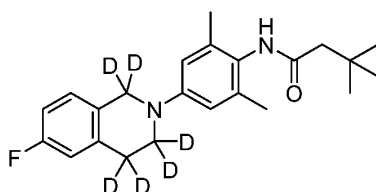
[128] To a solution of 2-(4-amino-3,5-dimethyl-phenyl)-4,4-dideuterio-6-fluoro-1H-isoquinolin-3-one (0.41 g, 1.07 mmol) in THF (10.0 mL) was added lithium aluminum deuteride (0.08 g, 2.14 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred at 70 °C for 2 hrs under N_2 atmosphere. The mixture was cooled to room temperature and the reaction was quenched with sodium sulfate decahydrate (200 mg). The mixture was filtered through celite and the resulting filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10: 1 to 5: 1, TLC: petroleum ether: ethyl acetate = 2: 1, $R_f = 0.52$ (P1)) to afford 0.07 g of 2,6-dimethyl-4-(3,3,4,4-tetradeuterio-6-fluoro-1H-isoquinolin-2-yl)aniline (23% yield) as a brown oil: ^1H NMR: EC23322-90-P1A1 (400 MHz, chloroform-*d*) δ 7.08 (dd, $J_1 = 8.0$ Hz, $J_2 = 5.6$ Hz, 1H), 6.93-6.82 (m, 2H), 6.71 (s, 2H), 4.20 (s, 2H), 3.35 (brs, 2H), 2.21 (s, 6H); MS (ES+) m/z 275.2 (M+1).

Step 8. Preparation of *N*-[2,6-dimethyl-4-(3,3,4,4-tetradeuterio-6-fluoro-1*H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

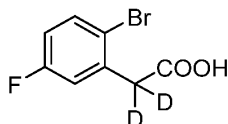


[129] To a solution of 2,6-dimethyl-4-(3,3,4,4-tetradeuterio-6-fluoro-1*H*-isoquinolin-2-yl)aniline (0.070 g, 0.250 mmol) in dichloromethane (1.00 mL) was added pyridine (0.040 g, 0.501 mmol) and 3,3-dimethylbutanoyl chloride (0.009 g, 0.070 mmol). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was quenched by the addition of water (2.00 mL) at 0 °C, and then extracted with dichloromethane (2 x 5.00 mL). The combined organic phases were washed with brine (10.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10: 1 to 3: 1, TLC: petroleum ether: ethyl acetate = 1: 1, R_f = 0.47 (P1)) to afford 0.040 g of *N*-[2,6-dimethyl-4-(3,3,4,4-tetradeuterio-6-fluoro-1*H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide (40% yield) as a yellow solid: ^1H NMR: EC23322-99-P1B (400 MHz, dimethyl sulfoxide- d_6) δ 8.86 (s, 1H), 7.25 (dd, J_1 = 9.2 Hz, J_2 = 6.0 Hz, 1H), 7.04-6.94 (m, 2H), 6.93 (s, 2H), 4.31 (s, 2H), 2.17 (s, 2H), 2.10 (s, 6H), 1.05 (s, 9H); MS (ES+) m/z 373.2 (M+1).

Example 8. *N*-(4-(6-fluoro-3,4-dihydroisoquinolin-2(1*H*)-yl-1,1,3,3,4,4- d_6)-2,6-dimethylphenyl)-3,3-dimethylbutanamide



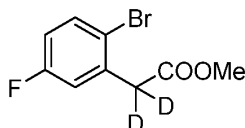
Step 1. Preparation of 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetic acid



[130] To a solution of 2-(2-bromo-5-fluoro-phenyl) acetic acid (2.00 g, 8.58 mmol) in deuterium oxide (20.0 mL) was added potassium carbonate (4.74 g, 34.30 mmol). The mixture was stirred at 110 °C for 12 hrs. The reaction mixture was adjusted to pH value of 3 with 1.0 M hydrochloric acid solution, and then extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with brine (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude residue was used directly for the next step without further purification. Compound 2-(2-

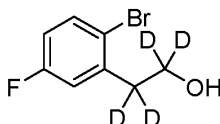
bromo-5-fluoro-phenyl)-2,2-dideuterio-acetic acid (1.7 g, 84% yield) was obtained as a white solid: ^1H NMR: (400 MHz, D_2O) δ 7.55 (dd, $J_1 = 8.4$ Hz, $J_2 = 5.2$ Hz, 1H), 7.02 (dd, $J_1 = 9.6$ Hz, $J_2 = 2.8$ Hz, 1H), 6.90 (td, $J_1 = 8.4$ Hz, $J_2 = 2.8$ Hz, 1H).

Step 2. Preparation of 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetate



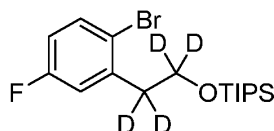
[131] To a solution of 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetic acid (1.70 g, 7.23 mmol) in methanol (17.0 mL) was added thionyl chloride (2.58 g, 21.70 mmol, 1.58 mL). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was quenched by the addition of water (50.0 mL) at 0 °C, and then extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with brine (40.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 1.75 g (97% yield) of crude methyl 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetate as a colorless oil that was used without further purification: ^1H NMR: (400 MHz, dimethyl sulfoxide- d_6) δ 7.65 (dd, $J_1 = 8.8$ Hz, $J_2 = 5.6$ Hz, 1H), 7.35 (dd, $J_1 = 9.6$ Hz, $J_2 = 3.2$ Hz, 1H), 7.13 (td, $J_1 = 8.8$ Hz, $J_2 = 3.2$ Hz, 1H), 3.64 (s, 3H).

Step 3. Preparation of 2-(2-bromo-5-fluoro-phenyl)-1,1,2,2-tetradeuterio-ethanol



[132] To a solution of methyl 2-(2-bromo-5-fluoro-phenyl)-2,2-dideuterio-acetate (1.35 g, 5.42 mmol) in tetrahydrofuran (15.0 mL) was added lithium;tetradeuterioalumanuide (0.41 g, 10.80 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 hrs. After cooling to room temperature, the reaction was quenched with sodium sulfate decahydrate (500 mg). The mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse-phase HPLC (0.1% HCl condition) to afford 0.60 g of 2-(2-bromo-5-fluoro-phenyl)-1,1,2,2-tetradeuterio-ethanol as a brown oil.

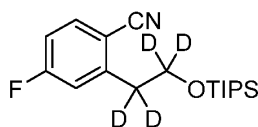
Step 4. Preparation of [2-(2-bromo-5-fluoro-phenyl)-1,1,2,2-tetradeuterio-ethoxy]-triisopropyl-silane



[133] To a solution of 2-(2-bromo-5-fluoro-phenyl)-1,1,2,2-tetradeuterio-ethanol (0.50 g, 2.24 mmol) in dimethylformamide (10.0 mL) was added imidazole (0.92 g, 13.50 mmol) and chlorotriisopropylsilane (2.59 g, 13.50 mmol). The mixture was stirred at 25 °C for 3 hrs. The reaction mixture was quenched by addition of water (10.0 mL) at 0 °C, and then extracted with ethyl acetate (3 x 10.0 mL). The combined

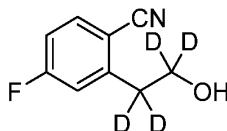
organic phases were washed with brine (2 x 10.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 1: 0 to 0: 1) to afford 0.80 g of [2-(2-bromo-5-fluoro-phenyl)-1,1,2,2-tetradeterio-ethoxy]-triisopropyl-silane (94% yield) as a colorless oil.

Step 5. Preparation of 4-fluoro-2-(1,1,2,2-tetradeterio-2-triisopropylsilyloxy-ethyl)benzonitrile



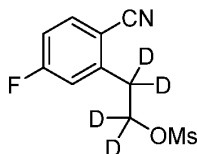
[134] To a solution of [2-(2-bromo-5-fluoro-phenyl)-1,1,2,2-tetradeterio-ethoxy]-triisopropyl-silane (0.80 g, 2.11 mmol) in methylpyrrolidone (10.0 mL) was added zinc cyanide (0.30 g, 2.53 mmol, 0.16 mL), zinc (0.011 g, 0.169 mmol) and palladium;tritet-butylphosphane (0.16 g, 0.32 mmol). The mixture was stirred at 120 °C for 2 hrs. The reaction mixture was diluted with water (10.0 mL) and extracted with ethyl acetate (3 x 10.0 mL). The combined organic phases were washed with brine (2 x 10.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 0.60 g of 4-fluoro-2-(1,1,2,2-tetradeterio-2-triisopropylsilyloxy-ethyl)benzonitrile (78% yield) was obtained as a brown oil and used in the next step without further purification: MS (ES-) m/z 326.3 (M+1).

Step 6. Preparation of 4-fluoro-2-(1,1,2,2-tetradeterio-2-hydroxy-ethyl)benzonitrile



[135] To a solution of 4-fluoro-2-(1,1,2,2-tetradeterio-2-triisopropylsilyloxy-ethyl)benzonitrile (0.60 g, 1.64 mmol) in tetrahydrofuran (10.0 mL) was added tetrabutylammonium fluoride (1.00 M, 3.28 mL) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. The reaction mixture was quenched by the addition of water (10.0 mL) at 0 °C, and then extracted with ethyl acetate (3 x 10.0 mL). The combined organic phases were washed with brine (2 x 10.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by reverse-phase HPLC (0.1% FA condition) to afford 0.24 g of 4-fluoro-2-(1,1,2,2-tetradeterio-2-hydroxy-ethyl)benzonitrile (83% yield) as a brown oil: MS (ES-) m/z 170.2 (M+1).

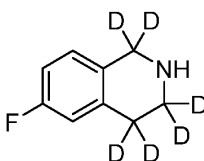
Step 7. Preparation of [2-(2-cyano-5-fluoro-phenyl)-1,1,2,2-tetradeterio-ethyl] methanesulfonate



[136] To a solution of 4-fluoro-2-(1,1,2,2-tetradeterio-2-hydroxy-ethyl)benzonitrile (0.24 g, 1.42 mmol)

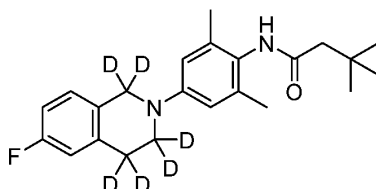
in dichloromethane (5.0 mL) was added methylsulfonyl methanesulfonate (0.37 g, 2.13 mmol) and triethylamine (0.29 g, 2.84 mmol). The mixture was stirred at 20 °C for 1 hr. The reaction mixture was quenched by the addition of water (30.0 mL) at 0 °C, and then extracted with dichloromethane (2 x 20.0 mL). The combined organic phases were washed with brine (2 x 10.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 10: 1 to 3: 1) to afford 0.25 g of [2-(2-cyano-5-fluoro-phenyl)-1,1,2,2-tetradeuterio-ethyl] methanesulfonate (71% yield) as a colourless oil: ¹H NMR: (400 MHz, chloroform-*d*) δ 7.70 (dd, J_1 = 8.8 Hz, J_2 = 5.6 Hz, 1H), 7.18-7.08 (m, 2H), 3.01 (s, 3H).

Step 8. Preparation of 1,1,3,3,4,4-hexadeuterio-6-fluoro-2H-isoquinoline



[137] To a solution of [2-(2-cyano-5-fluoro-phenyl)-1,1,2,2-tetradeuterio-ethyl] methanesulfonate (0.10 g, 0.40 mol) in deuteriooxymethane (2.0 mL) was added alumane:nickel (0.003 g, 0.040 mmol) under nitrogen atmosphere. The suspension was degassed and purged with deuterium for 3 times. The mixture was stirred under deuterium at 25 °C for 12 hrs. The reaction mixture was filtered and concentrated under reduced pressure to afford 0.06 g of 1,1,3,3,4,4-hexadeuterio-6-fluoro-2H-isoquinoline (94% yield) as a brown oil that was used in the next step without further purification: MS (ES-) m/z 158.1 (M+1).

Step 8. Preparation of N-[4-(1,1,3,3,4,4-hexadeuterio-6-fluoro-2-isoquinolyl)-2,6-dimethyl-phenyl]-3,3-dimethyl-butanamide



[138] This reaction was done in two batches. Second batch description is as follows. To a solution of 1,1,3,3,4,4-hexadeuterio-6-fluoro-2H-isoquinoline (0.040 g, 0.254 mmol) and *N*-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (0.091 g, 0.305 mmol) in dioxane (1.00 mL) was added cesium carbonate (0.249 g, 0.763 mmol) and [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (0.021 g, 0.025 mmol). The mixture was stirred at 100 °C for 3 hrs. The two crude reaction mixtures were combined for workup. The mixture was filtered and washed with ethyl acetate (3 x 20.0 mL). The filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 1: 0 to 0: 1) to afford 0.064 g of *N*-[4-(1,1,3,3,4,4-hexadeuterio-6-fluoro-2-isoquinolyl)-2,6-dimethyl-phenyl]-3,3-dimethyl-butanamide (65% yield) as a white solid: ¹H NMR: (400 MHz, DMSO-*d*₆) δ 8.86 (s, 1H), 7.28-7.23 (m, 1H), 7.04-6.97 (m, 2H), 6.69 (s, 2H), 2.17 (s, 2H), 2.10 (s,

6H), 1.05 (s, 9H); MS (ES-) m/z 375.3 (M+1).

Biological Activity

Kv7.2/Kv7.3 Potassium Channel Assay

[139] This potassium flux assay employs the cell-permeable, potassium-sensitive dye, IPG-2 AM, to quantify potassium ion flux through potassium channels. In general, TREX HEK 293 or HEK 293 cells were stably transfected with either an inducible or non-inducible expression vector containing the full-length cDNA coding for the desired human Kv7.2/Kv7.3 or in combination with another full-length cDNA for a second desired human Kv7 potassium channel. Potassium channel-expressing cell lines were induced with tetracycline (1 µg/mL), if required, and plated on 384-well poly-D-lysine (PDL)-coated plates in culture media (DMEM, containing 10% FBS and 1% L-glutamine). After overnight incubation, culture media was removed and cells were loaded with 5 µM IPG-2 AM dye for 1 hour in Assay buffer (140 mM NaCl, 20 mM RbCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer), 10 mM glucose, adjusted with Tris to pH 7.4). Excess dye was removed, and cells incubated at room temperature for 20 minutes with or without test compound. A Hamamatsu FDSS µCell was used to perform a 1:1 addition of K challenge buffer (150 mM NaCl, 10 mM HEPES, 2 mM CaCl₂, 10 mM KCl, 1 mM MgCl₂, 10 mM glucose, adjusted with Tris to pH 7.4 for human Kv7.2/Kv7.3, and simultaneously read plates at excitation wavelength of 530 nm and emission wavelength of 558 nm. Non-potassium channel-mediated potassium influx was determined in the presence of DMSO, and maximal influx was determined in the presence of a known Kv7.x channel modulator. For each test compound, a concentration response curve was generated with 16 concentrations points, 2-fold serial dilution starting at 30 µM and an EC₅₀ value was determined.

[140] Compounds provided herein are potentiators of Kv7.2/Kv7.3 potassium channels as shown in Table 3.

Table 3

EXAMPLE	Kv7.2/ Kv7.3 EC ₅₀ (µM)
1	++++
2	++++
3	++++
4	++++
5	++++
6	+++
7	++++
8	++++

For EC₅₀ values:
++++ indicates a value less than 1 µM
+++ indicates a value from 1 up to 10 µM

++ indicates a value from 10 up to 30 μM
+ indicates a value of 30 μM or more

EQUIVALENTS AND SCOPE

[141] In the claims, articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The present disclosure includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The present disclosure includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[142] Furthermore, the present disclosure encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the present disclosure, or aspects of the present disclosure, is/are referred to as comprising particular elements and/or features, certain embodiments of the present disclosure or aspects of the present disclosure consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the present disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[143] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the present disclosure can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

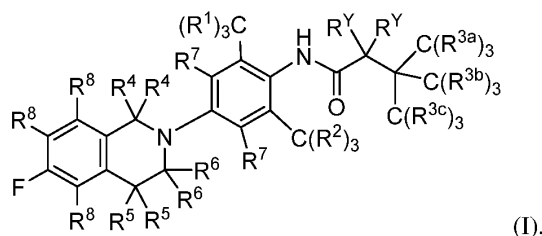
[144] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is

as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present disclosure, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound of Formula (I):



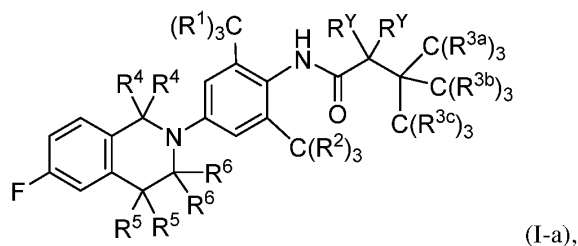
or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein:

each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^6 , R^7 , R^8 , and R^Y is independently hydrogen or

deuterium; and each instance of R^5 is independently hydrogen, -OH, or deuterium;

provided that at least one of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , R^8 , and R^Y is deuterium.

2. The compound of claim 1, wherein the compound is of Formula (I-a):



or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^1 is deuterium.

4. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^2 is deuterium.

5. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein each instance of R^1 and R^2 is deuterium.

6. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^{3a} , R^{3b} , and R^{3c} is deuterium.

7. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein each instance of R^{3a} , R^{3b} , and R^{3c} is

deuterium.

8. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^4 is deuterium.

9. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein each instance of R^4 is deuterium.

10. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^5 is deuterium.

11. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein each instance of R^5 is deuterium.

12. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein one instance of R^5 is -OH and the other is hydrogen.

13. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^6 is deuterium.

14. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein each instance of R^6 is deuterium.

15. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^7 is deuterium.

16. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein each instance of R^7 is deuterium.

17. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least one instance of R^8 is deuterium.

18. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein each instance of R^8 is deuterium.

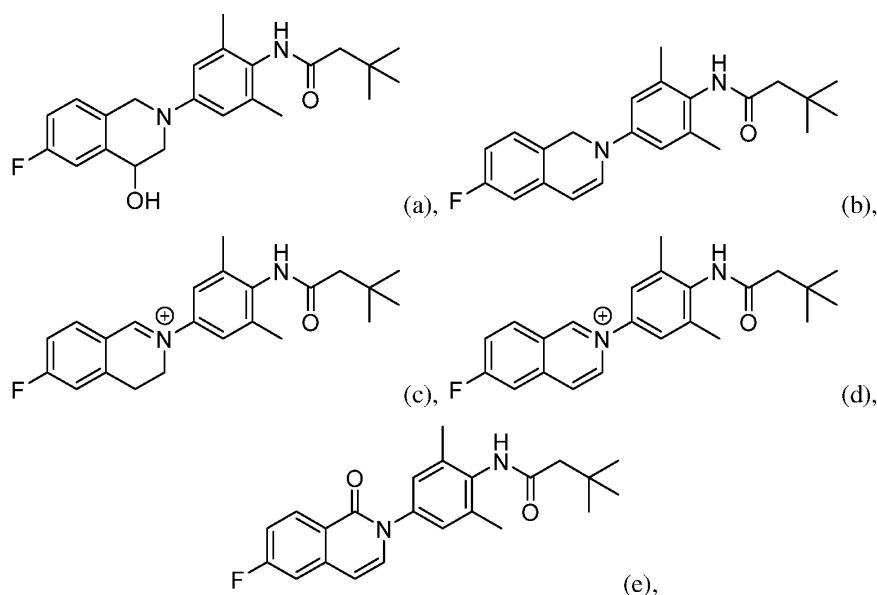
19. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least two instances, or at least three

instances, or at least four instances, or at least five instances, or at least six instances, or at least seven instances, or at least eight instances, or at least nine instances, or each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , and R^6 is deuterium.

20. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, wherein at least two instances, or at least three instances, or at least four instances, or at least five instances, or at least six instances, or at least seven instances, or at least eight instances, or at least nine instances, or each instance of R^1 , R^2 , R^{3a} , R^{3b} , R^{3c} , R^4 , R^5 , R^6 , R^7 , and R^8 is deuterium.

21. The compound of claim 1, wherein the compound is selected from those in **Table 1**, and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

22. A compound selected from:



and pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and prodrugs thereof.

23. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof.

25. A method of potentiating a Kv7 potassium channel in a subject comprising administering to the subject a compound of any one of claims 1-23, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof.

26. A method of treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-23, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof.
27. The method of claim 25 or 26, wherein the method enhances opening of a Kv7 potassium channel.
28. The method of any one of claims 25-27, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.
29. The method of any one of claims 25-28, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.
30. A method of treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject in need thereof comprising administering to the subject a compound of any one of claims 1-23, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof.
31. The method of any one of claims 25-30, wherein the subject is a human.
32. A compound of any one of claims 1-23, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof, for use in potentiating a Kv7 potassium channel in a subject.
33. A compound of any one of claims 1-23, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a disease, disorder, or condition associated with Kv7 potassium channel dysfunction in a subject.
34. The compound for use of claim 32 or 33, wherein the compound enhances opening of a Kv7 potassium channel.
35. The compound for use of any one of claims 32-34, wherein the Kv7 potassium channel is selected from one or more of Kv7.2, Kv7.3, Kv7.4, and Kv7.5.
36. The compound for use of any one of claims 32-35, wherein the Kv7 potassium channel is Kv7.2/Kv7.3.
37. A compound of any one of claims 1-23, or a pharmaceutically acceptable salt, stereoisomer,

tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof, for use in treating a seizure disorder, a depressive disorder, pain, or anhedonia in a subject.

38. The compound for use of any one of claims 32-37, wherein the subject is a human.

39. A compound of any one of claims 1-23, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or prodrug thereof, or a pharmaceutical composition thereof, for use as a medicament.