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(54) **Title:** COMPOUNDS AND METHODS OF DEUTERATED XANOMELINE FOR TREATING NEUROLOGICAL DISORDERS

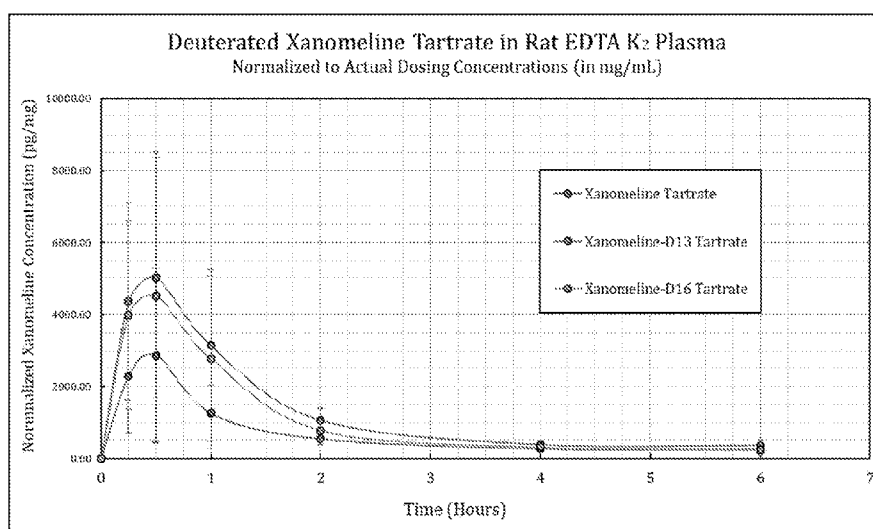
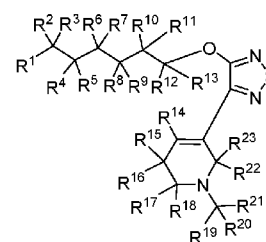


FIG. 1

Formula I



(57) **Abstract:** Provided herein are compounds of Formula I and/or salts thereof, wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}$ and R^{23} are independently chosen from H and D. At least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{22}$ and R^{23} is enriched with deuterium, and R^{19}, R^{20} , and R^{21} are independently chosen from H and D; or two of R^{19}, R^{20} , and R^{21} are enriched with deuterium. Also provided are medicaments comprising these compounds and methods for treating central nervous system disorders with the compounds and medicaments described herein.

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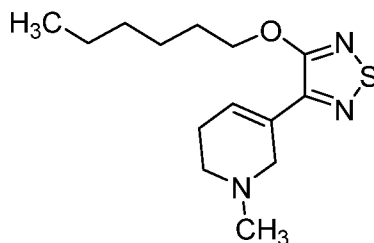
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COMPOUNDS AND METHODS OF DEUTERATED XANOMELINE FOR TREATING NEUROLOGICAL DISORDERS

[0001] This application claims the benefit of priority of United States Provisional Patent Application Serial No. 62/808,954 filed February 22, 2019, and also claims the benefit of priority of United States Provisional Patent Application Serial No. 62/936,358 filed November 15, 2019, the disclosure of which is incorporated by reference in its entirety for all purposes.

[0002] The present disclosure relates to new compounds and compositions, and their application as pharmaceuticals for treating disease. Methods of treating neurological disorders, such as psychosis and schizophrenia, in a human or animal subject are also provided.

[0003] Xanomeline [3-(hexyloxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole] is a mixed muscarinic partial agonist across all five muscarinic receptor subtypes:

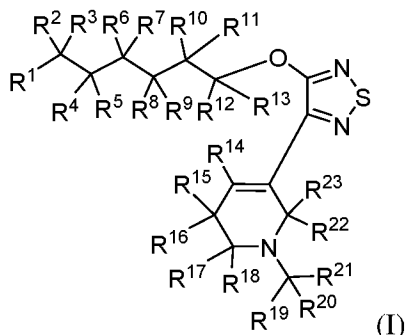


Activating the muscarinic system through muscarinic agonists may treat several diseases, including schizophrenia, Alzheimer's disease, Parkinson's disease, depression, movement disorders, drug addiction, pain, and neurodegeneration, such as tauopathies or synucleinopathies. Schizophrenia is characterized by a set of symptoms divided into positive symptoms (e.g., hallucinations, delusional thoughts, etc.), negative symptoms (e.g., social isolation, anhedonia, etc.), and cognitive symptoms (e.g., inability to process information, poor working memory, etc.). However, the metabolic profile in humans and lack of muscarinic receptor subtype selectivity has been problematic for the development of this drug. To reduce the peripheral side effects, xanomeline was reformulated as xanomeline in combination with the peripherally restricted broad spectrum antagonist, trospium, to block peripheral adverse events and is significantly better tolerated.

[0004] Thus, certain compounds disclosed herein provide deuterated xanomeline with improved pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles. Using these compounds reduces drug exposure variability and the incidence of metabolites. Without wishing to be bound by theory, first-pass metabolism is avoided via deuteration of

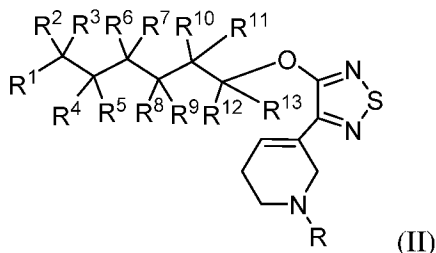
xanomeline at carbon positions susceptible to cytochrome p-450 mediated enzymatic oxidation.

[0005] Disclosed herein are compounds comprising structural Formula I:



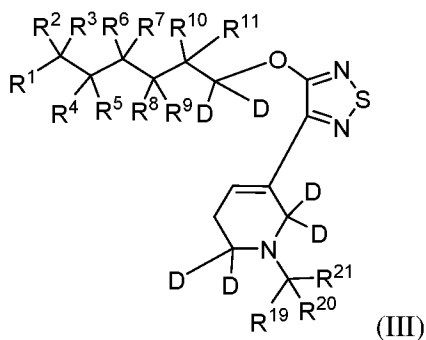
and/or salts thereof; wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}$ and R^{23} are independently chosen from H and D; and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{22}$ and R^{23} is enriched with deuterium and R^{19}, R^{20} , and R^{21} are independently chosen from H and D; or two of R^{19}, R^{20} , and R^{21} are enriched with deuterium.

[0006] In certain embodiments, the compound comprises Formula II



and/or salts thereof; wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$, and R^{13} are independently chosen from H and D; R is CH_3 or CD_3 ; and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$, or R^{13} is enriched with deuterium.

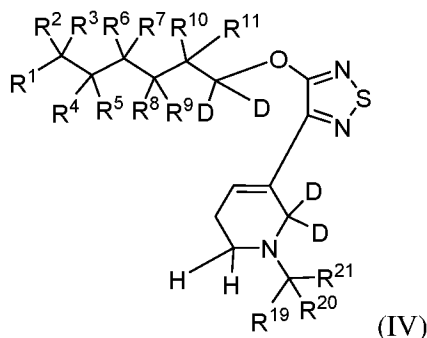
[0007] In certain embodiments, the compound comprises Formula III



and/or salts thereof, wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{19}, R^{20}$, and R^{21} are

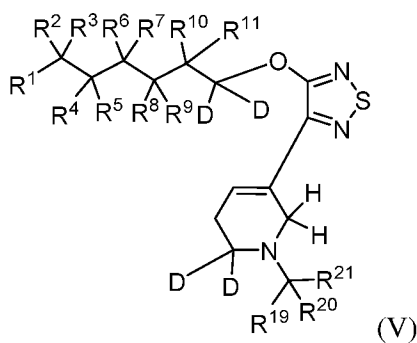
independently chosen from H or D.

[0008] In certain embodiments, the compound comprises Formula IV



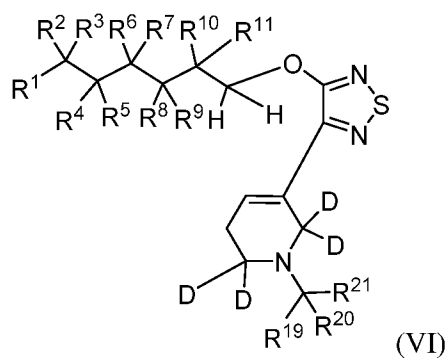
and/or salts thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

[0009] In certain embodiments, the compound comprises Formula V



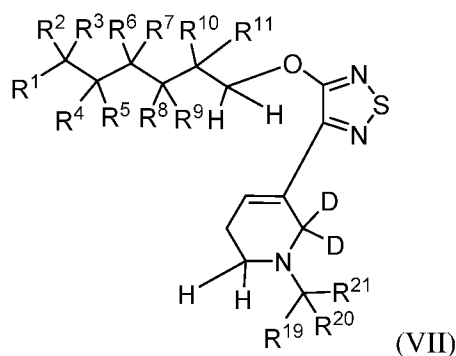
and/or salts thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

[0010] In certain embodiments, the compound comprises Formula VI



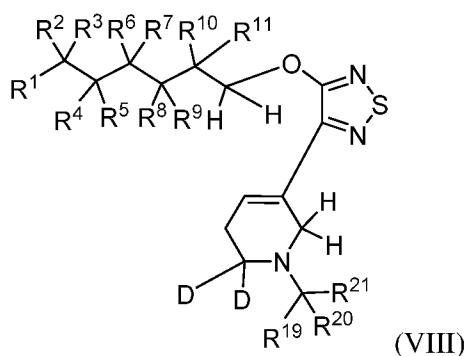
and/or salts thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

[0011] In certain embodiments, the compound comprises Formula VII



and/or salts thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

[0012] In certain embodiments, the compound comprises Formula VIII



and/or salts thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 depicts the normalized xanomeline concentration in pg/mg versus time in hours for rats dosed with xanomeline tartrate, xanomeline- d_{13} tartrate and xanomeline- d_{16} tartrate. Doses were normalized to actual dosing concentration in mg/mL.

[0014] FIG. 2 depicts the [3 H]-NMS specific binding (~ 14 nM) in CHO cells measured in counts per minute activity (CPMA).

[0015] FIG. 3 depicts the [3 H]-NMS specific binding (~ 14 nM) in CHO cells from FIG. 2 normalized to femtomoles per milligram protein (fmol/mg).

[0016] FIG. 4 depicts the pERK dose response (% FBS stimulation) experiments in CHO cells stably expressing the human muscarinic AChRs M1-M5 and treated with xanomeline- d_{13} tartrate (n = 3–4).

[0017] FIG. 5 depicts the pERK dose response (% FBS stimulation) experiments in CHO cells stably expressing the human muscarinic AChRs M1-M5 and treated with xanomeline- d_{16} tartrate (n = 3–4).

[0018] FIG. 6 depicts the pERK dose response (% FBS stimulation) experiments in CHO cells stably expressing the human muscarinic AChRs M1-M5 and treated with acetylcholine (n = 3–4).

DETAILED DESCRIPTION

[0019] To aid understanding of the disclosure set forth herein, several terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood in the art to which this disclosure belongs. If there is a plurality of definitions for a term used herein, those in this section prevail unless stated otherwise.

[0020] When introducing elements of the present disclosure or the embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are inclusive and mean that there may be additional elements other than the listed elements.

[0021] The term "and/or" when in a list of two or more items, means that any of the listed items can be employed by itself or in combination with one or more of the listed items. For example, the expression "A and/or B" means either or both of A and B, i.e. A alone, B alone or A and B in combination. The expression "A, B and/or C" is intended to mean A alone, B alone, C alone, A and B in combination, A and C in combination, B and C in combination or A, B, and C in combination.

[0022] When ranges of values are disclosed, and the notation "from n_1 ... to n_2 " or "between n_1 ... and n_2 " is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μ M (micromolar)," which is intended to include 1 μ M, 3 μ M, and everything in between to any number of significant figures (e.g., 1.255 μ M, 2.1 μ M, 2.9999 μ M, etc.).

[0023] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium

is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods, such as mass spectrometry and nuclear magnetic resonance spectroscopy.

[0024] The term “is/are deuterium,” when used to describe a given position in a molecule such as R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, and R₁₁ or the symbol “D,” when used to represent a given position in a drawing of a molecular structure, means that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. In an embodiment deuterium enrichment is of no less than about 1%, in another no less than about 5%, in another no less than about 10%, in another no less than about 20%, in another no less than about 50%, in another no less than about 70%, in another no less than about 80%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.

[0025] The term “isotopic enrichment” refers to the percentage of incorporation of a less prevalent isotope of an element at a given position in a molecule in the place of the more prevalent isotope of the element.

[0026] The term “non-isotopically enriched” refers to a molecule in which the percentages of the various isotopes are substantially the same as the naturally occurring percentages.

[0027] The terms “substantially pure” and “substantially homogeneous” mean sufficiently homogeneous to appear free of readily detectable impurities as determined by standard analytical methods, including, but not limited to, thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and mass spectrometry (MS); or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, or biological and pharmacological properties, such as enzymatic and biological activities, of the substance. In certain embodiments, “substantially pure” or “substantially homogeneous” refers to a collection of molecules, wherein at least about 50%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% of the molecules are a single compound, including a racemic mixture or single stereoisomer thereof, as determined by standard analytical methods.

[0028] The term “about” qualifies the numerical values that it modifies, denoting such a value as variable within a margin of error. When no margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term “about” means

that range which would encompass the recited value and the range which would be included by rounding up or down to that figure, considering significant figures.

[0029] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety chosen from hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which is optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and Rⁿ where n = (1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. For example, an unsymmetrical group such as -C(O)N(R)- may be attached to the parent moiety at either the carbon or the nitrogen.

[0030] The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder," "syndrome," and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0031] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single dosage having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0032] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treating a disease or disorder or on the effecting of a clinical endpoint.

[0033] The term "therapeutically acceptable" refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0034] As used herein, reference to "treatment" of a patient is intended to include prophylaxis. Treatment may also be preemptive in nature, i.e., it may include prevention of disease. Prevention of a disease may involve complete protection from disease, for example as in the case of prevention of infection with a pathogen or may involve prevention of disease progression. For example, prevention of a disease may not mean complete foreclosure of any effect related to the diseases at any level, but instead may mean prevention of the symptoms of a disease to a clinically significant or detectable level. Prevention of diseases may also mean prevention of progression of a disease to a later stage of the disease.

[0035] The term "patient" is generally synonymous with the term "subject" and includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

[0036] The term "prodrug" refers to a compound that is made more active *in vivo*. Certain compounds disclosed herein may also exist as prodrugs. Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0037] To eliminate foreign substances, such as therapeutic agents, from its circulation system, the animal body expresses various enzymes, such as the cytochrome P₄₅₀ enzymes or CYPs, esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C-H) bond to either a carbon-oxygen (C-O) or

carbon-carbon (C-C) π -bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For most drugs, such oxidations are generally rapid and ultimately lead to administration of multiple or high daily doses.

[0038] The relationship between the activation energy and the rate of reaction may be quantified by the Arrhenius equation, $k = Ae^{-E_{act}/RT}$, where E_{act} is the activation energy, T is temperature, R is the molar gas constant, k is the rate constant for the reaction, and A (the frequency factor) is a constant specific to each reaction that depends on the probability that the molecules will collide with the correct orientation. The Arrhenius equation states that the fraction of molecules that have enough energy to overcome an energy barrier, that is, those with energy at least equal to the activation energy, depends exponentially on the ratio of the activation energy to thermal energy (RT), the average amount of thermal energy that molecules possess at a certain temperature.

[0039] The transition state in a reaction is a short-lived state (on the order of 10^{-14} sec) along the reaction pathway during which the original bonds have stretched to their limit. The activation energy E_{act} for a reaction is the energy required to reach the transition state of that reaction. Reactions that involve multiple steps will necessarily have several transition states, and in these instances, the activation energy for the reaction is equal to the energy difference between the reactants and the most unstable transition state. Once the transition state is reached, the molecules can either revert, thus reforming the original reactants, or the new bonds form giving rise to the products. This dichotomy is possible because both pathways, forward and reverse, result in the release of energy. A catalyst facilitates a reaction process by lowering the activation energy leading to a transition state. Enzymes are examples of biological catalysts that reduce the energy necessary to achieve a transition state.

[0040] A carbon-hydrogen bond is by nature a covalent chemical bond. Such a bond forms when two atoms of similar electronegativity share some of their valence electrons, thereby creating a force that holds the atoms together. This force or bond strength can be quantified and is expressed in units of energy, and as such, covalent bonds between various atoms can be classified according to how much energy must be applied to the bond in order to break the bond or separate the two atoms.

[0041] The bond strength is directly proportional to the absolute value of the ground-state vibrational energy of the bond. This vibrational energy, which is also known as the zero-point

vibrational energy, depends on the mass of the atoms that form the bond. The absolute value of the zero-point vibrational energy increases as the mass of one or both atoms making the bond increases. Since deuterium (D) is two-fold more massive than hydrogen (H), it follows that a C-D bond is stronger than the corresponding C-H bond. Compounds with C-D bonds are frequently indefinitely stable in H₂O and have been widely used for isotopic studies. If a C-H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), then substituting a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect (DKIE) and can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small size of a hydrogen atom and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. A deuterium is larger and statistically has a much lower probability of undergoing this phenomenon. Substitution of tritium for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects.

[0042] Discovered in 1932 by Urey, deuterium (D) is a stable and non-radioactive isotope of hydrogen. It was the first isotope to be separated from its element in pure form and is twice as massive as hydrogen and makes up about 0.02% of the total mass of hydrogen (in this usage meaning all hydrogen isotopes) on earth. When two deuteriums bond with one oxygen, deuterium oxide (D₂O or “heavy water”) is formed. D₂O looks and tastes like H₂O, but has different physical properties. It boils at 101.41 °C and freezes at 3.79 °C. Its heat capacity, heat of fusion, heat of vaporization, and entropy are all higher than H₂O. It is also more viscous and is not as powerful a solvent as H₂O.

[0043] When pure D₂O is given to rodents, it is readily absorbed and reaches an equilibrium level that is usually about eighty percent of the concentration of what was consumed. The quantity of deuterium required to induce toxicity is extremely high. When 0% to as much as 15% of the body water has been replaced by D₂O, animals are healthy but are unable to gain weight as fast as the control (untreated) group. When about 15% to about 20% of the body water has been replaced with D₂O, the animals become excitable. When about 20% to about 25% of the body water has been replaced with D₂O, the animals are so excitable that they go into frequent convulsions when stimulated. Skin lesions, ulcers on the

paws and muzzles, and necrosis of the tails appear. The animals also become very aggressive; males becoming almost unmanageable. When about 30% of the body water has been replaced with D₂O, the animals refuse to eat and become comatose. Their body weight drops sharply, and their metabolic rates drop far below normal, with death occurring at about 30 to about 35% replacement with D₂O. The effects are reversible unless more than thirty percent of the previous body weight has been lost due to D₂O. Studies have also shown that the use of D₂O can delay the growth of cancer cells and enhance the cytotoxicity of certain antineoplastic agents.

[0044] Tritium (T) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Mixing tritium with a phosphor provides a continuous light source, a technique that is commonly used in wristwatches, compasses, rifle sights and exit signs. It was discovered by Rutherford, Oliphant and Harteck in 1934, and is produced naturally in the upper atmosphere when cosmic rays react with H₂ molecules. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T₂O, a colorless and odorless liquid. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level.

[0045] Deuteration of pharmaceuticals to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles, has been demonstrated previously with some classes of drugs. For example, DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching which may even give rise to an oxidative intermediate with a faster off-rate from an activating Phase I enzyme (e.g., cytochrome P₄₅₀ 3A4). The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations before the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart toxicity. Such

pitfalls are non-obvious and have not been heretofore sufficiently predictable *a priori* for any drug class.

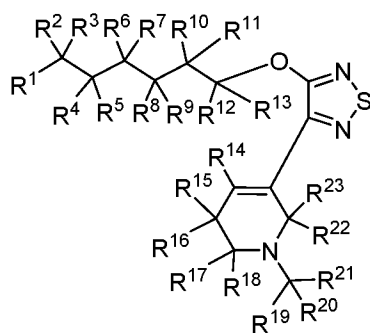
[0046] Xanomeline is a functionally selective M1/M4 agonist that has shown a promising therapeutic profile in preclinical trials (Shannon *et al.*, 1994)The carbon-hydrogen bonds of xanomeline contain a naturally occurring distribution of hydrogen isotopes, namely ^1H or protium (about 99.9844%), ^2H or deuterium (about 0.0156%), and ^3H or tritium (in the range between about 0.5 and 67 tritium atoms per 10^{18} protium atoms). Increased levels of deuterium incorporation may produce a detectable Kinetic Isotope Effect (KIE) that could affect the pharmacokinetic, pharmacologic and/or toxicologic profiles of such muscarinic agonists in comparison with the compound having naturally occurring levels of deuterium.

[0047] Xanomeline is likely metabolized in humans by liver (Nicholas D *et al.*, 2001). Other sites on the molecule may also undergo transformations leading to metabolites with as-yet-unknown pharmacology/toxicology. Limiting the production of these metabolites has the potential to decrease the danger of the administration of such drugs and may even allow increased dosage and concomitant increased efficacy. All these transformations can occur through polymorphically-expressed enzymes, thus exacerbating the interpatient variability. Further, disorders, such as multiple sclerosis, are best treated when the subject is medicated around the clock for an extended period. For the foregoing reasons, there is a strong likelihood that a longer half-life medicine will diminish these problems with greater efficacy and cost savings.

[0048] Various deuteration patterns can be used to a) reduce or eliminate unwanted metabolites, b) increase the half-life of the parent drug, c) decrease the number of doses needed to achieve a desired effect, d) decrease the amount of a dose needed to achieve a desired effect, e) increase the formation of active metabolites, if any are formed, and/or f) decrease the production of deleterious metabolites in specific tissues and/or create a more effective drug and/or a safer drug for polypharmacy, whether the polypharmacy be intentional or not. The deuteration approach has strong potential to slow the metabolism via various oxidative and racemization mechanisms.

[0049] In one aspect, disclosed herein is a compound having structural Formula I:

Formula I

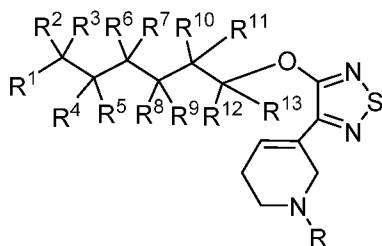


and/or salts thereof;

wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}$ and R^{23} are independently chosen from H and D; and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{22}$ and R^{23} is enriched with deuterium, and R^{19}, R^{20} , and R^{21} are independently chosen from H and D; or two of R^{19}, R^{20} , and R^{21} are enriched with deuterium.

[0050] In certain embodiments, the compound comprises f Formula II

Formula II

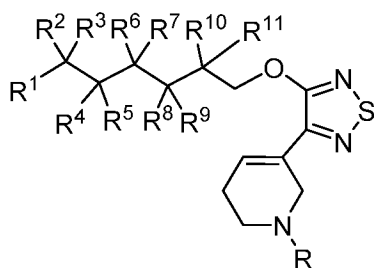


and/or salts thereof;

wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$, and R^{13} are independently chosen from H and D; R is CH_3 or CD_3 ; and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$, or R^{13} is enriched with deuterium.

[0051] In certain embodiments, the compound comprises Formula IIA

Formula IIA



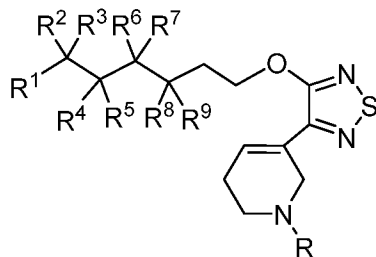
and/or salts thereof;

wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}$, and R^{11} are independently chosen from H and D; R is CH_3 or CD_3 ; and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}$ and R^{11} is enriched

with deuterium.

[0052] In certain embodiments, the compound comprises Formula IIB

Formula IIB

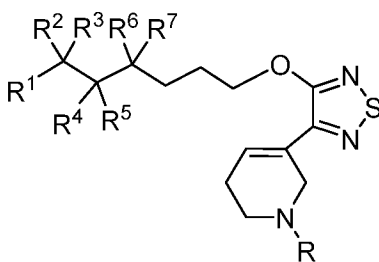


and/or salts thereof;

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently chosen from H and D; R is CH_3 or CD_3 ; and at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is enriched with deuterium.

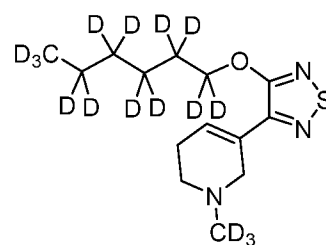
[0053] In certain embodiments, the compound comprises Formula IIC

Formula IIC

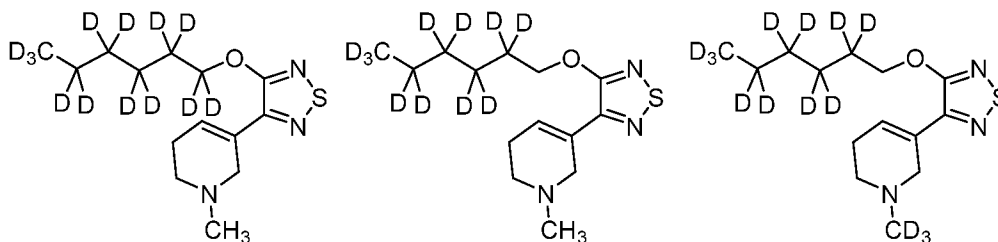


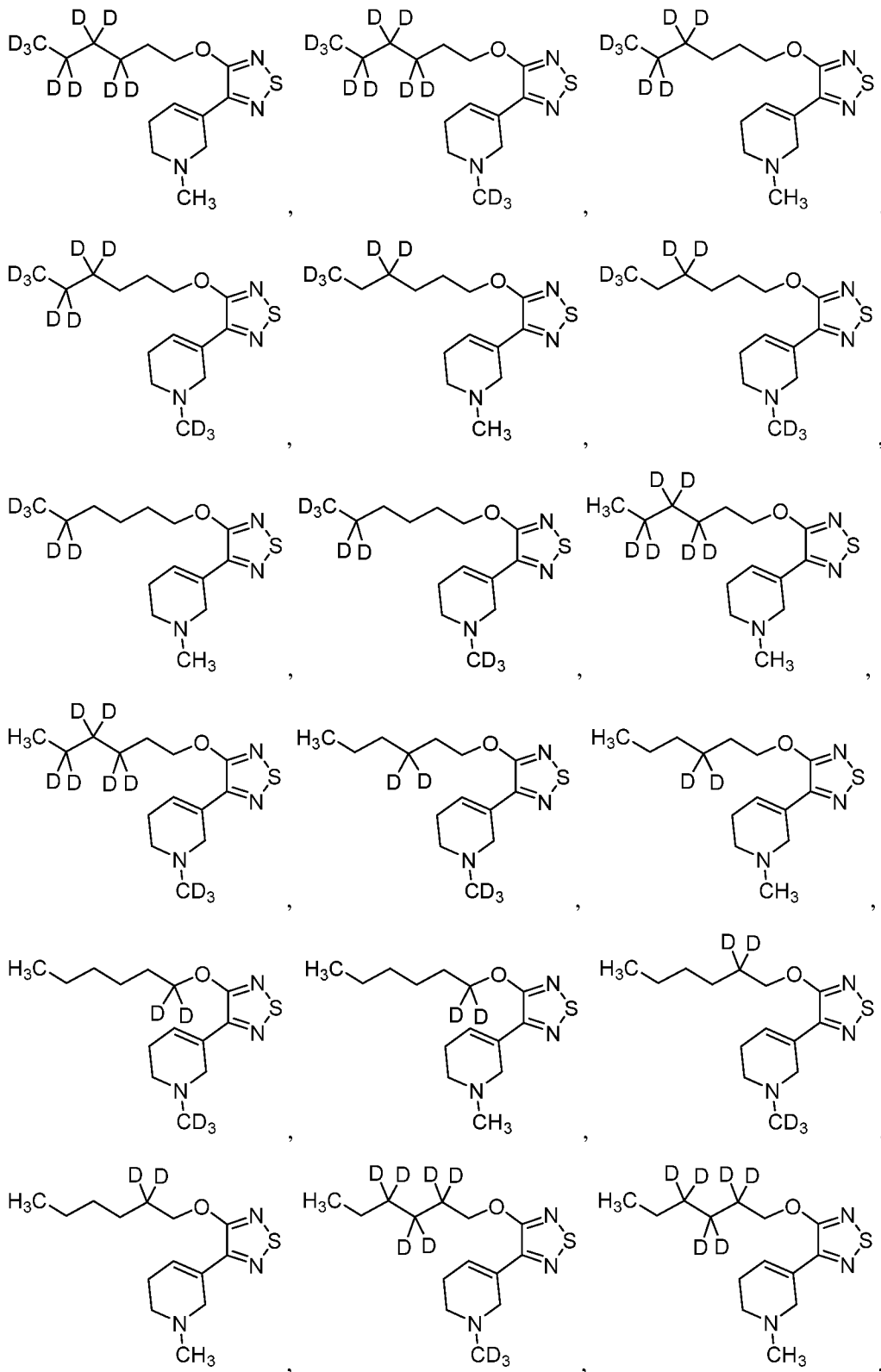
and/or salts thereof;

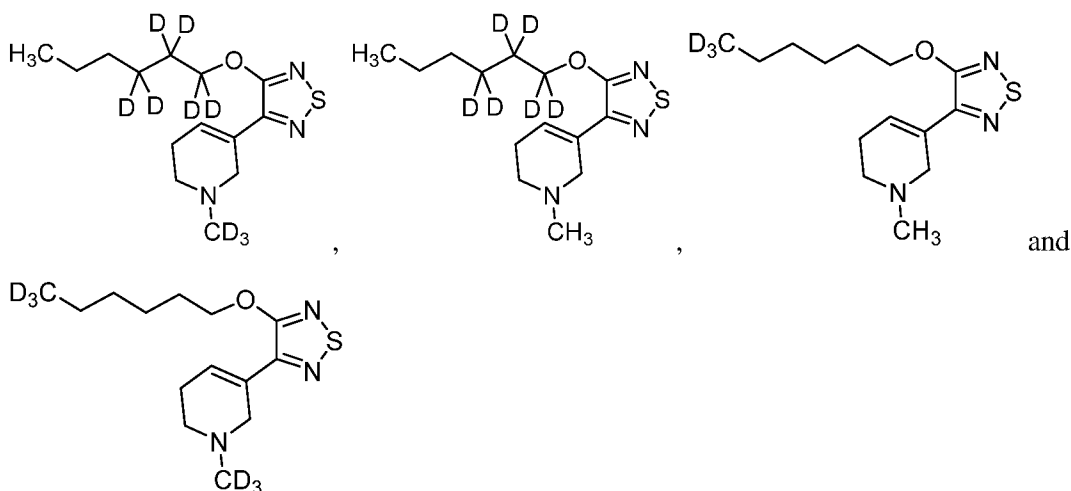
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are independently chosen from H and D; R is CH_3 or CD_3 ; and at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 is enriched with deuterium.



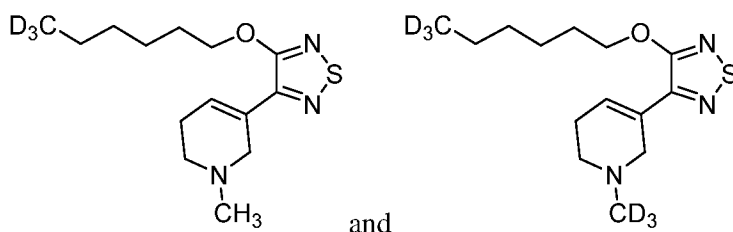
[0054] In certain embodiments, the compound is chosen from







[0055] In certain embodiments, the compound is chosen from



[0056] In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CH_3 . In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CD_3 . In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}$ and R^{11} , are each D, and R is CH_3 . In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}$ and R^{11} are each D, and R is CD_3 . In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$ and R^9 , are each D, and R is CH_3 . In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$ and R^9 are each D, and R is CD_3 . In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6$ and R^7 are each D, and R is CH_3 . In certain embodiments, $R^1, R^2, R^3, R^4, R^5, R^6$ and R^7 are each D, and R is CD_3 . In certain embodiments, R^1, R^2, R^3, R^4 and R^5 are each D, and R is CH_3 .

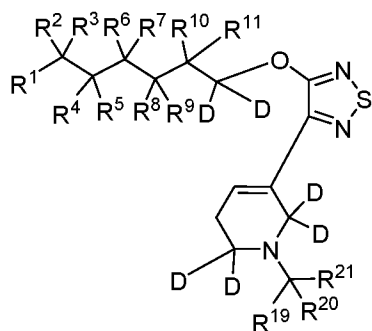
[0057] In certain embodiments, R^1, R^2, R^3, R^4 and R^5 are each D, and R is CD_3 . In certain embodiments, R^1, R^2 and R^3 are each D, and R is CH_3 . In certain embodiments, R^1, R^2 and R^3 are each D, and R is CD_3 . In certain embodiments, $R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CH_3 . In certain embodiments, $R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CD_3 . In certain embodiments, $R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CH_3 . In certain embodiments, $R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CD_3 . In certain embodiments, $R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CH_3 . In certain embodiments, $R^8, R^9, R^{10}, R^{11}, R^{12}$ and R^{13} are each D, and R is CD_3 . In certain embodiments, R^{10}, R^{11}, R^{12} and R^{13} are each D, and R is CH_3 . In certain embodiments,

R^{10} , R^{11} , R^{12} and R^{13} are each D, and R is CD_3 . In certain embodiments, R^{12} and R^{13} are each D, and R is CH_3 . In certain embodiments, R^{12} and R^{13} are each D, and R is CD_3 .

[0058] In certain embodiments, R^4 and R^5 are each D, and R is CH_3 . In certain embodiments, R^4 and R^5 are each D, and R is CD_3 . In certain embodiments, R^6 and R^7 are each D, and R is CH_3 . In certain embodiments, R^6 and R^7 are each D, and R is CD_3 . In certain embodiments, R^8 and R^9 are each D, and R is CH_3 . In certain embodiments, R^8 and R^9 are each D, and R is CD_3 . In certain embodiments, R^{10} and R^{11} are each D, and R is CH_3 . In certain embodiments, R^{10} and R^{11} are each D, and R is CD_3 .

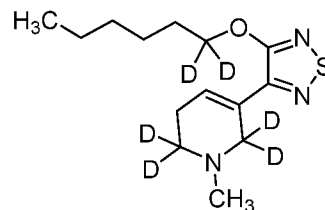
[0059] In certain embodiments, the compound comprises Formula III

Formula III

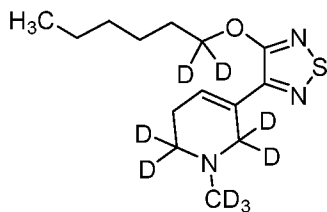


and/or salts thereof,

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.



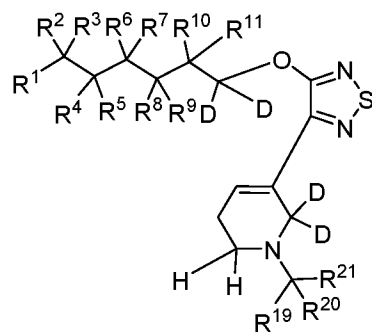
[0060] In certain embodiments, the compound is chosen from



and

[0061] In certain embodiments, the compound comprises Formula IV

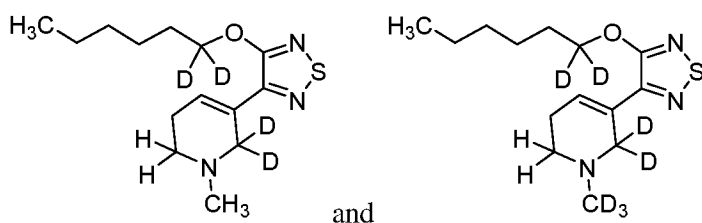
Formula IV



and/or salts thereof,

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

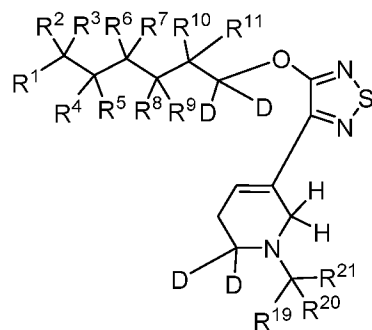
[0062] In certain embodiments, the compound is chosen from



and

[0063] In certain embodiments, the compound comprises Formula V

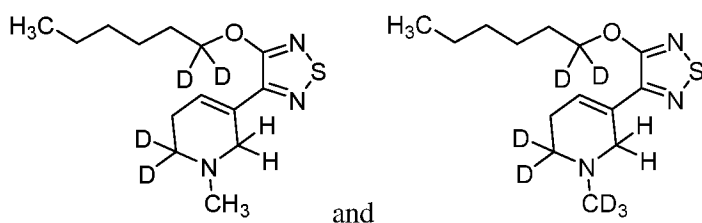
Formula V



and/or salts thereof,

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D; and at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} is enriched with deuterium.

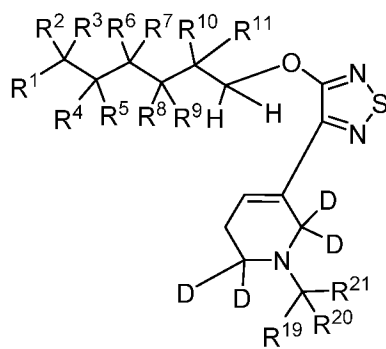
[0064] In certain embodiments, the compound is chosen from



and

[0065] In certain embodiments, the compound comprises Formula VI

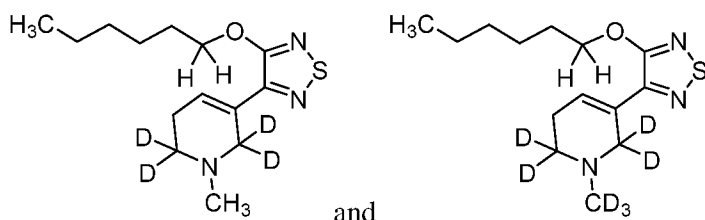
Formula VI



and/or salts thereof,

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

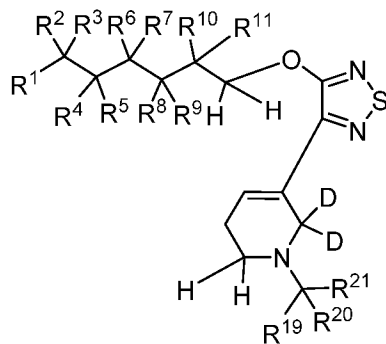
[0066] In certain embodiments, the compound is chosen from



and

[0067] In certain embodiments, the compound comprises Formula VII

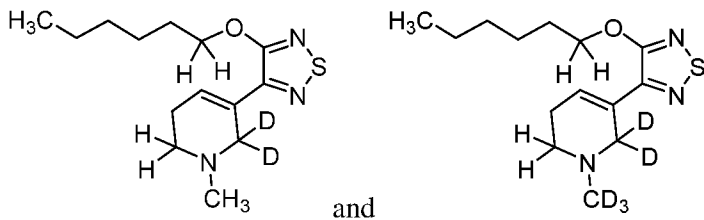
Formula VII



and/or salts thereof,

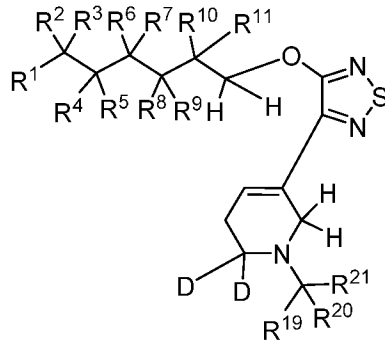
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

[0068] In certain embodiments, the compound is chosen from



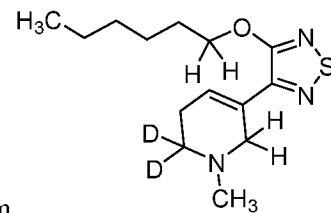
[0069] In certain embodiments, the compound comprises Formula VIII

Formula VIII

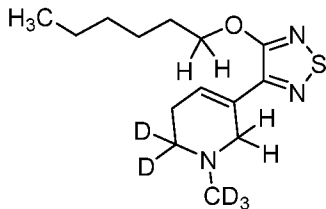


and/or salts thereof,

wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹⁹, R²⁰, and R²¹ are independently chosen from H or D.



[0070] In certain embodiments, the compound is chosen from



and

[0071] The present disclosure also provides a method of treating a central nervous system disorder in a patient in need thereof, the method comprising administering therapeutically effective amount of a medicament described herein to the patient in need thereof. In certain embodiments, the medicament is orally administered. In certain embodiments, use of the trospium chloride, when present, alleviates a side effect associated with use of a compound or composition described herein.

[0072] In another embodiment, at least one of the positions represented as D independently has deuterium enrichment of no less than about 1%, no less than about 5%, no

less than about 10%, no less than about 20%, no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, or no less than about 98%.

[0073] In a further embodiment, said compound is substantially a single enantiomer, a mixture of about 90% or more by weight of the (-)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (-)-enantiomer, substantially an individual diastereomer, or a mixture of about 90% or more by weight of an individual diastereomer and about 10% or less by weight of any other diastereomer.

[0074] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of the (-)-enantiomer of the compound and about 40% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of the (-)-enantiomer of the compound and about 30% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of the (-)-enantiomer of the compound and about 20% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of the (-)-enantiomer of the compound and about 10% or less by weight of the (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 95% or more by weight of the (-)-enantiomer of the compound and about 5% or less by weight of (+)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 99% or more by weight of the (-)-enantiomer of the compound and about 1% or less by weight of (+)-enantiomer of the compound.

[0075] In certain embodiments, the compound as disclosed herein contains about 60% or more by weight of the (+)-enantiomer of the compound and about 40% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 70% or more by weight of the (+)-enantiomer of the compound and about 30% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 80% or more by weight of the (+)-enantiomer of the compound and about 20% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 90% or more by weight of the (+)-enantiomer of the compound and about 10% or less by weight of the (-)-enantiomer of the compound. In certain embodiments, the compound as disclosed herein contains about 95% or more by weight of the (+)-enantiomer of the compound and about 5% or less by weight of (-)-enantiomer of the compound. In certain embodiments, the compound

as disclosed herein contains about 99% or more by weight of the (+)-enantiomer of the compound and about 1% or less by weight of (-)-enantiomer of the compound.

[0076] The deuterated compound as disclosed herein may also contain less prevalent isotopes for other elements, including, but not limited to, ^{13}C or ^{14}C for carbon, ^{15}N for nitrogen, and ^{17}O or ^{18}O for oxygen.

[0077] In one embodiment, the deuterated compounds disclosed herein maintain the beneficial aspects of the corresponding non-isotopically enriched molecules while substantially increasing the maximum tolerated dose, decreasing toxicity, increasing the half-life ($T_{1/2}$), lowering the maximum plasma concentration (C_{max}) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

[0078] Isotopic hydrogen can be introduced into a compound of a compound disclosed herein as disclosed herein by synthetic techniques that employ deuterated reagents, whereby incorporation rates are pre-determined; and/or by exchange techniques, wherein incorporation rates are determined by equilibrium conditions, and may be highly variable depending on the reaction conditions. Synthetic techniques, where tritium or deuterium is directly and specifically inserted by tritiated or deuterated reagents of known isotopic content, may yield high tritium or deuterium abundance, but can be limited by the chemistry required. In addition, the molecule being labeled may be changed, depending upon the severity of the synthetic reaction employed. Exchange techniques, on the other hand, may yield lower tritium or deuterium incorporation, often with the isotope being distributed over many sites on the molecule, but offer the advantage that they do not require separate synthetic steps and are less likely to disrupt the structure of the molecule being labeled. Isotopic hydrogen can be introduced into organic molecules by synthetic techniques that employ deuterated reagents whereby incorporation rates are pre-determined and/or by exchange techniques wherein incorporation rates are determined by equilibrium conditions and may be highly variable depending on the reaction conditions. Synthetic techniques, where tritium or deuterium is directly and specifically inserted by tritiated or deuterated reagents of known isotopic content, may yield high tritium or deuterium abundance, but can be limited by the chemistry required. In addition, the molecule being labeled may be changed, depending upon the severity of the synthetic reaction employed.

[0079] It is to be understood that the compounds disclosed herein may contain one or more chiral centers, chiral axes, and/or chiral planes, as described in "Stereochemistry of Carbon Compounds" Eliel and Wilen, John Wiley & Sons, New York, 1994, pp. 1119-1190.

Such chiral centers, chiral axes, and chiral planes may be of either the (R) or (S) configuration or may be a mixture thereof.

[0080] Another method for characterizing a composition containing a compound having at least one chiral center is by the effect of the composition on a beam of polarized light. When a beam of plane polarized light is passed through a solution of a chiral compound, the plane of polarization of the light that emerges is rotated relative to the original plane. This phenomenon is known as optical activity, and compounds that rotate the plane of polarized light are said to be optically active. One enantiomer of a compound will rotate the beam of polarized light in one direction, and the other enantiomer will rotate the beam of light in the opposite direction. The enantiomer that rotates the polarized light in the clockwise direction is the (+) enantiomer, and the enantiomer that rotates the polarized light in the counterclockwise direction is the (-) enantiomer. Included within the scope of the compositions described herein are compositions containing between 0 and 100% of the (+) and/or (-) enantiomer of compounds disclosed herein.

[0081] Where a compound as disclosed herein contains an alkenyl or alkenylene group, the compound may exist as one or mixture of geometric *cis/trans* (or *Z/E*) isomers. Where structural isomers are interconvertible *via* a low energy barrier, the compound disclosed herein may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the compound disclosed herein that contains for example, an imino, keto, or oxime group; or so-called valence tautomerism in the compound that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[0082] The compounds disclosed herein may be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, a racemic mixture, or a diastereomeric mixture. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[0083] The compounds disclosed herein can exist as therapeutically acceptable salts. The present disclosure includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such

acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable.

[0084] The term “therapeutically acceptable salt,” as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present disclosure contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0085] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine,

tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-phenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0086] A salt of a compound can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

[0087] The compound as disclosed herein may also be designed as a prodrug, which is a functional derivative of the compound as disclosed herein and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich *et al.* in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang *et al.*, *Curr. Pharm. Design* 1999, *5*, 265-287; Pauletti *et al.*, *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen *et al.*, *Pharm. Biotech.* **1998**, *11*, 345-365; Gagnault *et al.*, *Pract. Med. Chem.* **1996**, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon *et al.*, Ed., Marcell Dekker, 185-218, 2000; Balant *et al.*, *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Balimane and Sinko, *Adv. Drug Delivery Rev.* **1999**, *39*, 183-209; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Bundgaard, *Adv. Drug Delivery Rev.* **1992**, *8*, 1-38; Fleisher *et al.*, *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Fleisher *et al.*, *Methods Enzymol.* **1985**, *112*, 360-381; Farquhar *et al.*, *J. Pharm. Sci.* **1983**, *72*, 324-325; Freeman *et al.*, *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Gangwar *et al.*, *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Stella *et al.*, *Drugs* **1985**, *29*, 455-73; Tan *et al.*, *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148;

Valentino and Borchardt, *Drug Discovery Today* **1997**, 2, 148-155; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, 39, 63-80; Waller *et al.*, *Br. J. Clin. Pharmac.* **1989**, 28, 497-507.

[0088] While the disclosed compounds may be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0089] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound disclosed herein or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0090] Formulations of the compounds disclosed herein suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0091] Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0092] In certain embodiments, a single dosage form contains 50 mg xanomeline as the tartrate salt and 10 mg trospium chloride. Because 50 mg xanomeline as free base corresponds to about 76 mg xanomeline tartrate, the ratio of the active ingredients in such a formulation is about 7.6 to 1.

[0093] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately before use. Extemporaneous

injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0094] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0095] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0096] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[0097] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[0098] Certain compounds disclosed herein may be administered topically, that is by non-systemic administration. This includes the application of a compound disclosed herein externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[0099] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the

eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 1% w/w of the formulation.

[0100] For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds may be a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0101] Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

[0102] In addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0103] Before administering the claimed combinations, patients may have a lead-in period from one to fourteen days, during which lead-in period trospium chloride is given alone. In one embodiment, the trospium chloride is administered for one or more dose periods before administering xanomeline to accumulate trospium chloride in the body, or for the trospium chloride to reach or approach steady-state exposure levels. This accumulation, or higher exposure levels of the trospium chloride, increases the blockade of muscarinic receptors outside of the brain and reduces adverse events when xanomeline is administered. In another embodiment, the trospium chloride is administered for one or more days before xanomeline

[0104] Various time and resource intensive methods demonstrated the efficacy of the combination of xanomeline and trospium chloride. For example, animal models demonstrate the efficacy of new therapeutics for schizophrenia, including both pharmacological models (e.g., ketamine model) and genetic models (e.g., DISC1 mouse). Likewise, animal models

including rodents, dogs and non-human primates demonstrate the side effect profile of pharmacological agents. Animal models are an experimental proxy for humans but may suffer from deficiencies in the physiological differences between human and animals and thus may have limited predictive power for human experiments, particularly for central nervous system disorders. Alternatively, the disclosed combination can be tried in controlled clinical trials of people. Standard measures based on patient self-report can be used by those skilled in the art to assess various side effects such as GI discomfort. As another example, objective physiological measures (e.g., EKGs) may be used by those skilled in the art. A set of standard measures has also been developed to assess schizophrenia symptoms including the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), and Clinical Global Impression (CGI). Typically, clinical trials are double blinded, where one group of patients receives an inactive placebo and the other group the active intervention.

[0105] The present disclosure also provides a medicament comprising a compound described herein and/or a salt thereof and at least one pharmaceutically acceptable carrier. In certain embodiments, the medicament comprises between 5 mg and 300 mg of the compound, such as between 5 mg and 10 mg, between 10 mg and 15 mg, between 15 mg and 20 mg, between 20 mg and 25 mg, between 25 mg and 30 mg, between 30 mg and 35 mg, between 35 mg and 40 mg, between 40 mg and 45 mg, between 45 mg and 50 mg, between 50 mg and 55 mg, between 55 mg and 60 mg, between 60 mg and 65 mg, between 65 mg and 70 mg, between 70 mg and 75 mg, between 75 mg and 80 mg, between 80 mg and 85 mg, between 85 mg and 90 mg, between 90 mg and 95 mg, between 95 mg and 100 mg, between 100 mg and 105 mg, between 105 mg and 110 mg, between 110 mg and 115 mg, between 115 mg and 120 mg, between 120 mg and 125 mg, between 125 mg and 130 mg, between 130 mg and 135 mg, between 135 mg and 140 mg, between 140 mg and 145 mg, between 145 mg and 150 mg, between 150 mg and 155 mg, between 155 mg and 160 mg, between 160 mg and 165 mg, between 165 mg and 170 mg, between 170 mg and 175 mg, between 175 mg and 180 mg, between 180 mg and 185 mg, between 185 mg and 190 mg, between 190 mg and 195 mg, between 195 mg and 200 mg, between 200 mg and 205 mg, between 205 mg and 210 mg, between 210 mg and 215 mg, between 215 mg and 220 mg, between 220 mg and 225 mg, between 225 mg and 230 mg, between 230 mg and 235 mg, between 235 mg and 240 mg, between 240 mg and 245 mg, between 245 mg and 250 mg, between 250 mg and 255 mg, between 255 mg and 260 mg, between 260 mg and 265 mg, between 265 mg and 270 mg, between 270 mg and 275 mg, between 275 mg and 280 mg, between 280 mg and 285 mg, between 285 mg and 290 mg, between 290 mg and 295 mg, or between

295 mg and 300 mg of the compound.

[0106] In certain embodiments, the medicament further comprises a muscarinic inhibitor. In certain embodiments, the muscarinic inhibitor is trospium chloride. In certain embodiments, the medicament comprises between 5 mg and 150 mg of trospium chloride, such as between 5 mg and 10 mg, between 10 mg and 15 mg, between 15 mg and 20 mg, between 20 mg and 25 mg, between 25 mg and 30 mg, between 30 mg and 35 mg, between 35 mg and 40 mg, between 40 mg and 45 mg, between 45 mg and 50 mg, between 50 mg and 55 mg, between 55 mg and 60 mg, between 60 mg and 65 mg, between 65 mg and 70 mg, between 70 mg and 75 mg, between 75 mg and 80 mg, between 80 mg and 85 mg, between 85 mg and 90 mg, between 90 mg and 95 mg, between 95 mg and 100 mg, between 100 mg and 105 mg, between 105 mg and 110 mg, between 110 mg and 115 mg, between 115 mg and 120 mg, between 120 mg and 125 mg, between 125 mg and 130 mg, between 130 mg and 135 mg, between 135 mg and 140 mg, between 140 mg and 145 mg, or between 145 mg and 150 mg of trospium chloride.

[0107] In certain embodiments, the medicament is formulated as an immediate release formulation. In certain embodiments, the medicament is formulated as a controlled release formulation. In certain embodiments, the medicament is formulated as a controlled release formulation and the trospium chloride is formulated as an immediate release formulation.

[0108] In certain embodiments, the medicament comprises between 25 mg and 150 mg of the compound and between 10 mg and 40 mg trospium chloride in a single dosage form. In certain embodiments, the medicament comprises between 50 mg and 150 mg of the compound and between 10 mg and 40 mg trospium chloride in a single dosage form. In certain embodiments, the medicament comprises 50 milligrams of the compound. In certain embodiments, the medicament comprises 75 milligrams of the compound. In certain embodiments, the medicament comprises 10 milligrams trospium chloride. In certain embodiments, the medicament comprises 20 milligrams trospium chloride. In certain embodiments, the medicament is in the form of a single dosage formulation consisting essentially of 50 milligrams of the compound, 10 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier.

[0109] In certain embodiments, the medicament is in the form of a single dosage formulation consisting essentially of 75 milligrams of the compound, 20 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier. In certain embodiments, the medicament is in the form of a single dosage formulation consisting essentially of 50 milligrams of the compound, 20 milligrams trospium chloride, and at least one

pharmaceutically acceptable carrier. In certain embodiments, the medicament is in the form of a single dosage formulation consisting essentially of 75 milligrams of the compound, 10 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutically acceptable carrier comprises cellulose and lactose.

[0110] In certain embodiments, the medicament is in the form of a single dosage formulation consisting essentially of 125 milligrams of the compound, 30 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier. In certain embodiments, the medicament is in the form of a single dosage formulation consisting essentially of 100 milligrams of the compound, 20 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier. In certain embodiments, the medicament is in the form of a single dosage formulation consisting essentially of 125 milligrams of the compound, 20 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutically acceptable carrier comprises cellulose and lactose.

[0111] Before administering the claimed combinations, patients may have a lead-in period from one to fourteen days, during which lead-in period trospium chloride is given alone. In one embodiment, the trospium chloride is administered for one or more dose periods before administering deuterated xanomeline to accumulate trospium chloride in the body, or for the trospium chloride to reach or approach steady-state exposure levels. This accumulation, or higher exposure levels of the trospium chloride, increases the blockade of muscarinic receptors outside of the brain and reduces adverse events when deuterated xanomeline is administered. In another embodiment, the trospium chloride is administered for one or more days before deuterated xanomeline.

[0112] In one embodiment, deuterated xanomeline and trospium chloride are administered to a patient 6 times during a 24-hour period. In another embodiment, deuterated xanomeline and trospium chloride are administered to a patient 5 times during a 24-hour period. In another embodiment, deuterated xanomeline and trospium chloride are administered to a patient 4 times during a 24-hour period. In an embodiment, deuterated xanomeline and trospium chloride are administered to a patient 3 times during a 24-hour period. In another embodiment, deuterated xanomeline and trospium chloride are administered to a patient twice during a 24-hour period. In another embodiment, deuterated xanomeline and trospium chloride are administered to a patient once during a 24-hour period.

[0113] In one embodiment, an extended release formulation of trospium chloride is used in combination with deuterated xanomeline. In another embodiment, trospium chloride

extended release is administered to a patient from one time to five times during a 24-hour period. In an embodiment, trospium chloride extended release is administered from one to three times during a 24-hour period. In another embodiment, from five milligrams to 400 milligrams of trospium chloride extended release is used during a 24-hour period. In an embodiment, from 20 milligrams to 200 milligrams of trospium chloride extended release is used during a 24-hour period.

[0114] In one embodiment, 250 mg deuterated xanomeline and 60 mg trospium chloride are administered to a patient in a 24-hour period. In one embodiment, 225 mg deuterated xanomeline and 60 mg trospium chloride are administered to a patient in a 24-hour period. In one embodiment, 225 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 100 mg deuterated xanomeline and 20 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 125 mg deuterated xanomeline and 20 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 125 mg deuterated xanomeline and 30 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 125 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 200 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 200 mg deuterated xanomeline and 80 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 250 mg deuterated xanomeline and 60 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 250 mg deuterated xanomeline and 80 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 300 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 300 mg deuterated xanomeline and 80 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 300 mg deuterated xanomeline and 120 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 300 mg deuterated xanomeline and 150 mg trospium chloride are administered to a patient in a 24-hour period.

[0115] In one embodiment, 115 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 50 mg deuterated xanomeline and 20 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 60 mg deuterated xanomeline and 20 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 60 mg deuterated

xanomeline and 30 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 60 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 100 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 100 mg deuterated xanomeline and 80 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 125 mg deuterated xanomeline and 60 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 125 mg deuterated xanomeline and 80 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 150 mg deuterated xanomeline and 40 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 150 mg deuterated xanomeline and 80 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 150 mg deuterated xanomeline and 120 mg trospium chloride are administered to a patient in a 24-hour period. In another embodiment, 150 mg deuterated xanomeline and 150 mg trospium chloride are administered to a patient in a 24-hour period.

[0116] Treatment may be initiated with smaller dosages. Thereafter, the dosage may be increased by small increments until a balance between therapeutic effect and side effects is attained. While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including compound, amounts, times of administration and formulation, may be adjusted per such monitoring. The patient may be periodically reevaluated to determine improvement by measuring the same parameters. Adjustments to the disclosed compound administered and possibly to the time of administration may be made based on these reevaluations.

[0117] In certain embodiments, the single dosage form has a dosage strength of 50 mg deuterated xanomeline free base and 20 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 50 mg deuterated xanomeline free base and 10 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 75 mg deuterated xanomeline free base and 20 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 75 mg deuterated xanomeline free base and 10 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 125 mg deuterated xanomeline free base and 30 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 125 mg deuterated xanomeline free base and 40 mg trospium chloride.

[0118] In certain embodiments, the single dosage form has a dosage strength of 10 mg deuterated xanomeline and 30 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 10 mg deuterated xanomeline and 60 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 25 mg deuterated xanomeline and 30 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 25 mg deuterated xanomeline and 60 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 50 mg deuterated xanomeline and 30 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 50 mg deuterated xanomeline and 60 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 100 mg deuterated xanomeline and 30 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 100 mg deuterated xanomeline and 60 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 125 mg deuterated xanomeline and 30 mg trospium chloride. In certain embodiments, the single dosage form has a dosage strength of 125 mg deuterated xanomeline and 60 mg trospium chloride. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the mode of administration.

[0119] The compounds can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

[0120] In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant may only have minimal therapeutic benefit, but in combination with

another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[0121] In any case, the multiple therapeutic agents (at least one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few min to four weeks.

[0122] The present disclosure further provides a method of treating a central nervous system disorder in a patient in need thereof, the method comprising administering therapeutically effective amount of a compound described herein to the patient in need thereof. In certain embodiments, the compound is orally administered.

[0123] The term "muscarinic disorder" refers to any disease or condition ameliorated by activating the muscarinic system. Such diseases include ones in which direct activation of muscarinic receptors themselves or inhibition of cholinesterase enzymes has produced a therapeutic effect.

[0124] The terms "diseases related to schizophrenia" and "disorders related to schizophrenia" include, but are not limited to, schizo-affective disorder, psychosis, delusional disorders, psychosis associated with Alzheimer's disease, psychosis associated with Parkinson's disease, psychotic depression, bipolar disorder, bipolar with psychosis or any other disease with psychotic features.

[0125] The term "movement disorders" includes, but is not limited to, Gilles de la Tourette's syndrome, Friederich's ataxia, Huntington's chorea, restless leg syndrome and other diseases or disorders whose symptoms include excessive movements, ticks and spasms.

[0126] The term "mood disorders" includes major depressive disorder, dysthymia, recurrent brief depression, minor depression disorder, bipolar disorder, mania and anxiety.

[0127] The term "cognitive disorders" refers to diseases or disorders marked by cognitive deficit (e.g., having abnormal working memory, problem solving abilities, etc.). Diseases include but are not limited to Alzheimer's disease, Parkinson's Disease, dementia (including, but not limited to, AIDS related dementia, vascular dementia, age-related dementia, dementia associated with Lewy bodies and idiopathic dementia), Pick's disease, tauopathies, synucleinopathies, confusion, cognitive deficit associated with fatigue, learning disorders, traumatic brain injury, autism, age-related cognitive decline, and Cushing's Disease, a cognitive impairment associated with autoimmune diseases

[0128] The term "attention disorders" refers to diseases or conditions marked by having an abnormal or decreased attention span. Diseases include but are not limited to attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD), Dubowitz Syndrome, FG Syndrome, Down's Syndrome, growth delay due to insulin-like growth factor I (IGF1) deficiency, hepatic encephalopathy syndrome, and Strauss Syndrome.

[0129] The term "addictive disorders" refers to diseases or conditions marked by addiction or substance dependence as defined by the *Diagnostic & Statistical Manual V* (DSM-5). Such disorders are characterized by physical dependence, withdrawal and tolerance to a substance. Such substances include but are not limited to alcohol, cocaine, amphetamines, opioids, benzodiazepines, inhalants, nicotine, barbiturates, cocaine and cannabis. Addictive disorders also encompass behaviors that a patient does compulsively or continually despite clear negative consequences. For instance, ludomania (gambling addiction, or compulsive gambling) is recognized by those skilled in the art as being an addictive behavior that often has devastating consequences. In certain embodiments, the addictive behavior may be Internet Gaming Disorder (gaming addiction), as defined in the DSM-5.

[0130] The term "pain" refers to physical suffering or discomfort caused by illness or injury. Pain is a subjective experience and the perception of pain is performed parts of the central nervous system (CNS). Usually noxious (peripheral) stimuli are transmitted to the CNS beforehand, but pain is not always associated with nociception. A broad variety of clinical pain exists, derived from different underlying pathophysiological mechanisms and needing different treatment approaches. Three major types of clinical pain have been characterized: acute pain, chronic pain, and neuropathic pain. In certain embodiments, deuterated xanomeline potently and effectively reverses tactile allodynia and heat hyperalgesia associated with established neuropathic and inflammatory pain in both rat and mouse models. In certain embodiments, pain is treated, and the type of pain is chosen from allodynia, hyperalgesia, nociceptive pain, inflammatory pain, and neuropathic pain. In certain

embodiments, the pain is allodynia. In certain embodiments, the pain is hyperalgesia. In certain embodiments, the pain is nociceptive pain. In certain embodiments, the pain is inflammatory pain. In certain embodiments, the pain is neuropathic pain.

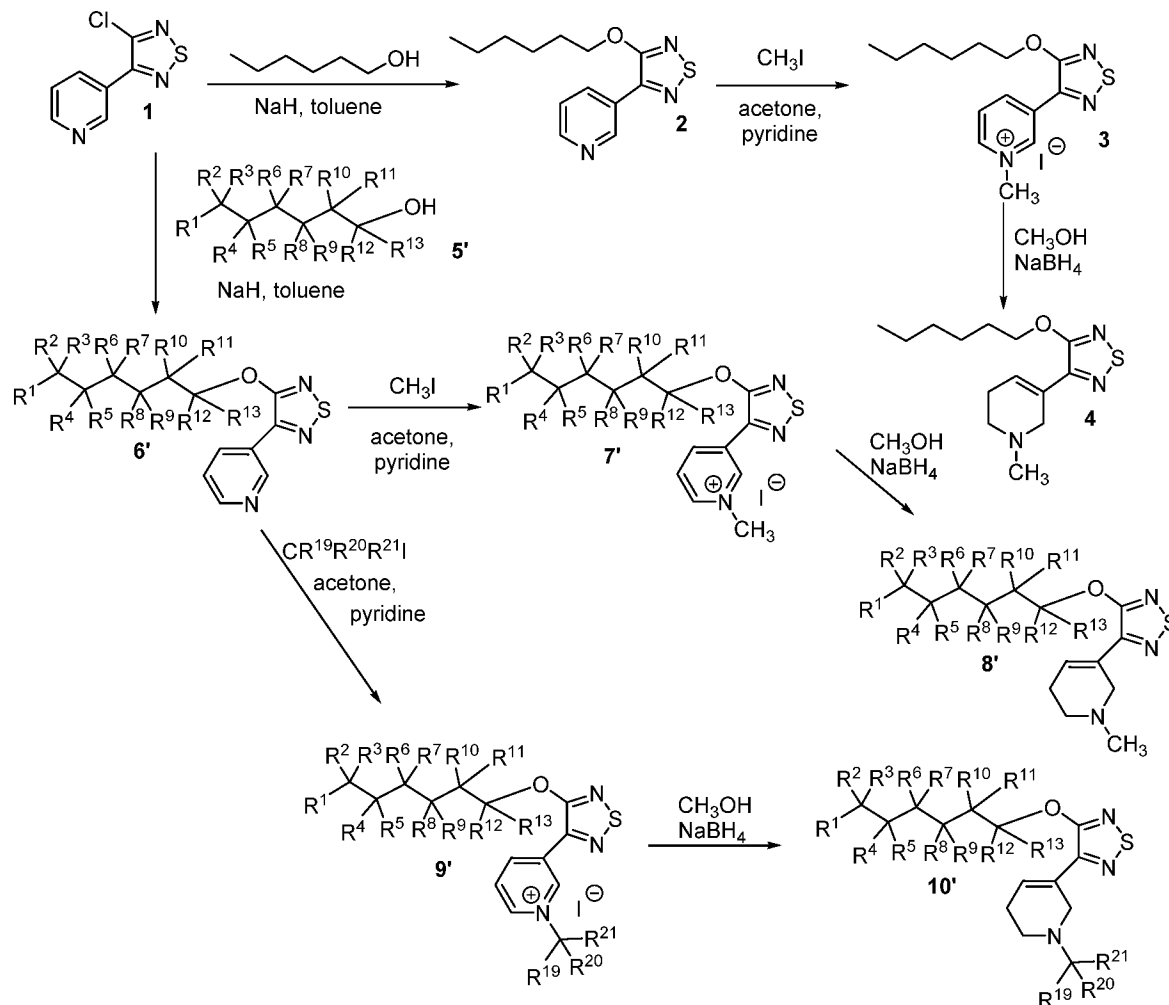
[0131] In certain embodiments, the central nervous system disorder is chosen from schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, Lewy Body dementia, psychosis and cognition deficit. In certain embodiments, the central nervous system disorder is schizophrenia. In certain embodiments, the central nervous system disorder is Alzheimer's disease. In certain embodiments, the central nervous system disorder is Huntington's disease. In certain embodiments, the central nervous system disorder is Parkinson's disease. In certain embodiments, the central nervous system disorder is Lewy Body dementia. In certain embodiments, the central nervous system disorder is psychosis. In certain embodiments, the central nervous system disorder is cognition deficit.

[0132] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. Additional examples of animals include horses, dogs, and cats.

General Synthetic Methods for Preparing Compounds

[0133] The following scheme can generally be used to practice the present disclosure:

Scheme I



[0134] Scheme I depicts a general synthesis for installing a deuterated ether chain and/or a deuteromethyl group in xanomeline. 3-Chloro-4-(pyridin-3-yl)-1,2,5-thiadiazole (**1**) was reacted in a Williamson ether synthesis with n-hexanol and sodium hydride in toluene to yield 3-(hexyloxy)-4-(pyridin-3-yl)-1,2,5-thiadiazole (**2**). Compound **2** was reacted with iodomethane in acetone and pyridine to yield 3-(4-(hexyloxy)-1,2,5-thiadiazol-3-yl)-1-methylpyridin-1-ium iodide (**3**), which was then reduced with sodium borohydride in methanol to yield xanomeline free base (**4**).

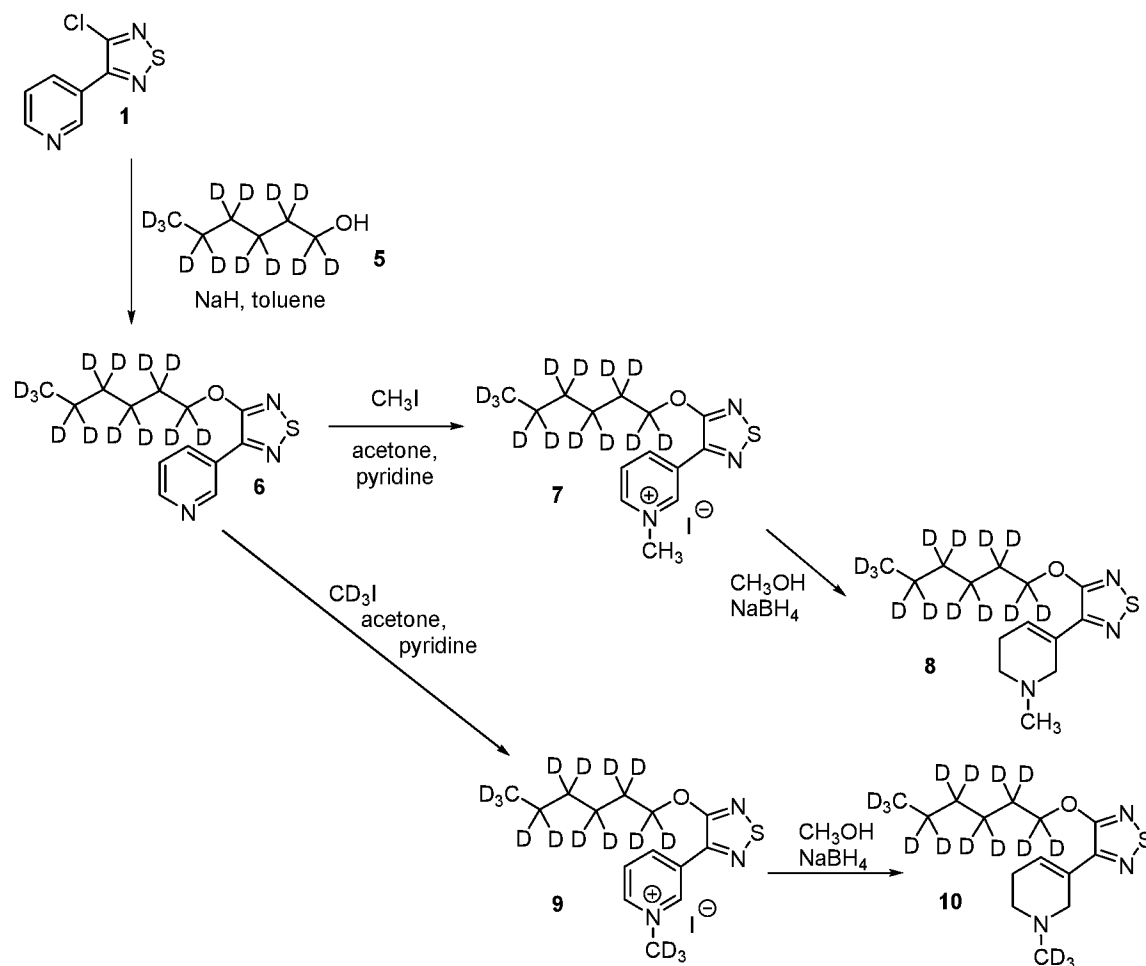
[0135] To install a deuterated ether chain, n-hexanol is substituted with a deuterated hexanol, (**5'**) to yield 3-((deutrohxyloxy)-4-(pyridin-3-yl)-1,2,5-thiadiazole (**6'**). When compound **6'** is reacted with iodomethane, 3-(4-(deutrohxyloxy)-1,2,5-thiadiazol-3-yl)-1-methylpyridin-1-ium iodide (**7'**) results and is then reduced to yield 3-(deutrohxyloxy)-4-(1-methyl-1,2,5,6-

tetrahydropyridin-3-yl)-1,2,5-thiadiazole (**8'**). When compound **6'** is reacted with deuteriodomethane, 3-(4-(deuterohexyloxy)-1,2,5-thiadiazol-3-yl)-1-(deuteromethylpyridin-1-ium iodide (**9'**) results and is then reduced to yield 3-(deuterohexyloxy)-4-(1-(deuteromethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole (**10'**).

[0136] In Scheme 2, each R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{19} , R^{20} , R^{21} is independently chosen from H and D, and at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{19} , R^{20} , and R^{21} is enriched with deuterium. Each free base product can be converted to a pharmaceutically acceptable salt, such as the tartrate, using methods available in the art.

[0137] Scheme II depicts the synthesis for installing a perdeuterated ether chain and/or a trideuteromethyl group in xanomeline.

Scheme II



[0138] To install a deuterated ether chain, n-hexanol was substituted with a deuterated hexanol, such as perdeuterohexanol (1,1,2,2,3,3,4,4,5,5,6,6,6-hexanol- d_{13} , **5**) to yield 3-((hexyl- d_{13})oxy)-4-(pyridin-3-yl)-1,2,5-thiadiazole (**6**). When compound **6** was reacted with

iodomethane, 3-(4-((hexyl- d_{13})oxy)-1,2,5-thiadiazol-3-yl)-1-methylpyridin-1-ium iodide (**7**) resulted and was then reduced to yield 3-((hexyl-1,1,2,2,3,3,4,4,5,5,6,6,6- d_{13})oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole (**8**, xanomeline- d_{13} , Ex. No. 1). When compound **6** was reacted with iodomethane- d_3 , 3-(4-((hexyl- d_{13})oxy)-1,2,5-thiadiazol-3-yl)-1-(methyl- d_3)pyridin-1-ium iodide (**9**) resulted and was then reduced to yield 3-((hexyl-1,1,2,2,3,3,4,4,5,5,6,6,6- d_{13})oxy)-4-(1-(methyl- d_3)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole (**10**, xanomeline- d_{16} , Ex. No. 2). Each free base product can be converted to a pharmaceutically acceptable salt, such as the tartrate, using methods available in the art.

Example 1: 3-((Hexyl-1,1,2,2,3,3,4,4,5,5,6,6,6- d_{13})oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole (8**)**

[0139] The title compound was prepared by the method described in Scheme 1. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 2.35 (m, 2H), 2.5 (s, 3H), 2.7 (m, 2H), 3.5 (m, 2H), 4.2 (s, 2H), 7.1 (m, 1H). MS: m/z calcd. for $\text{C}_{14}\text{H}_{10}\text{D}_{13}\text{N}_3\text{OS}$ ($M + 1$): 295.42, found 295.5.

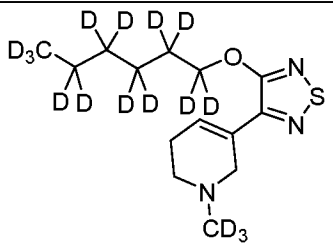
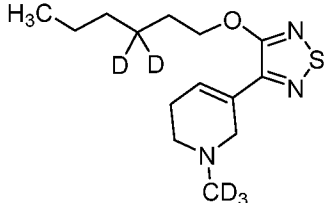
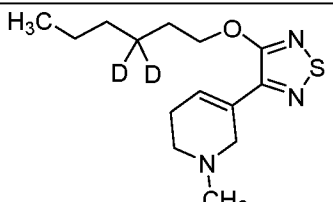
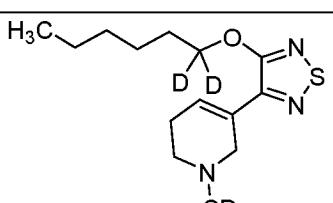
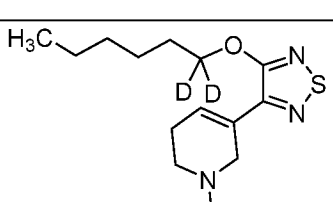
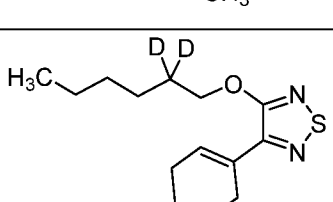
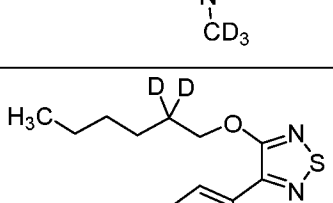
Example 2: 3-((Hexyl-1,1,2,2,3,3,4,4,5,5,6,6,6- d_{13})oxy)-4-(1-(methyl- d_3)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole (10**)**

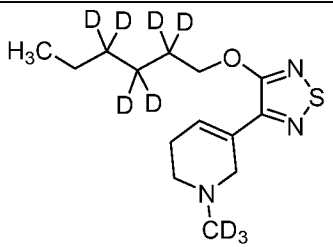
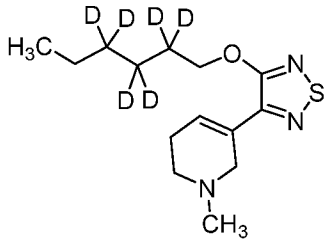
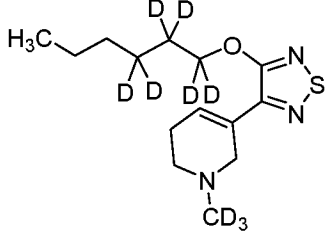
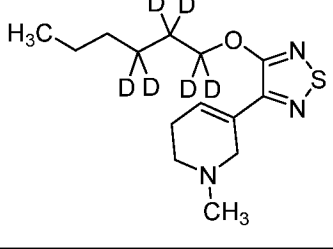
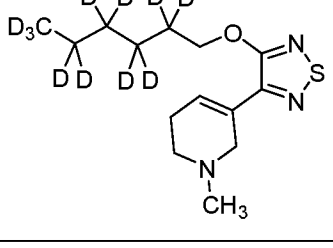
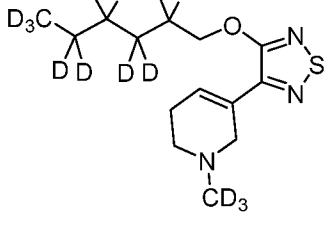
[0140] The title compound was prepared by the method described in Scheme 1. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6) δ : 2.4 (m, 2H), 2.8 (m, 2H), 3.6 (m, 2H), 4.2 (s, 2H), 7.1 (m, 1H). MS: m/z calcd. for $\text{C}_{14}\text{H}_7\text{D}_{16}\text{N}_3\text{OS}$ ($M + 1$): 298.42, found 298.4.

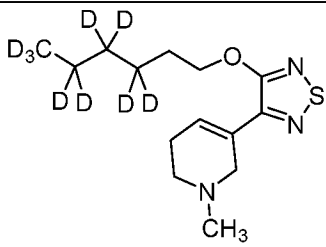
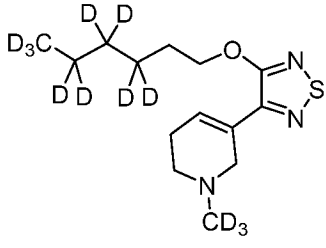
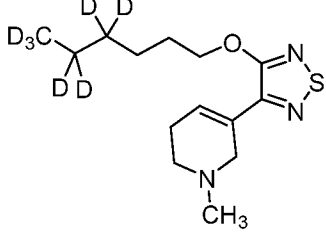
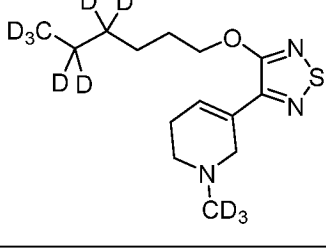
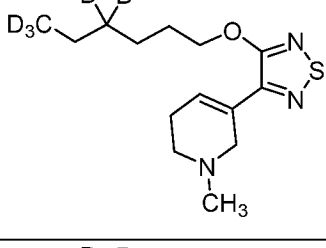
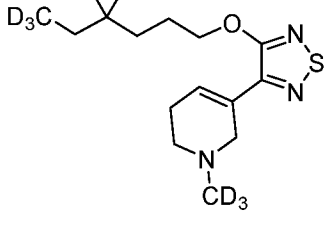
[0141] The following compounds in Table 1 have been made or prepared using the methods set forth above: Ex. No. 1 and 2. The other compounds in Table 1 can be prepared by the methods set forth above.

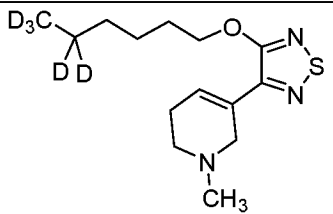
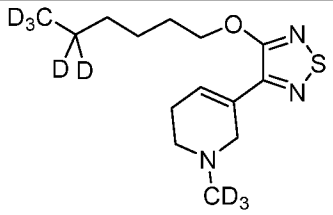
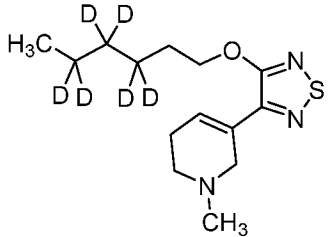
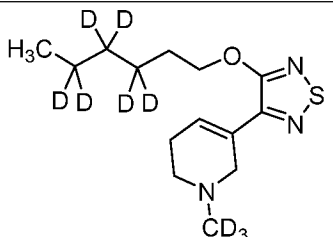
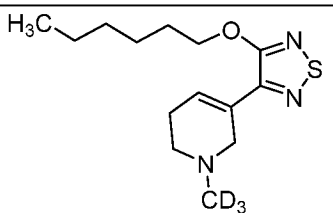
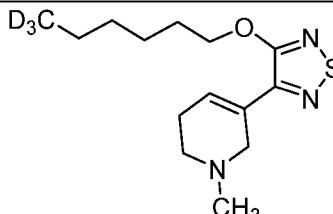
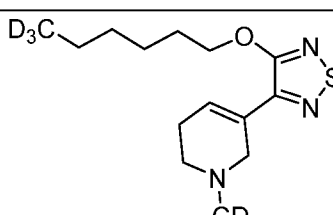
Table 1: Exemplary Compounds

Ex. No.	Structure	IUPAC Name	Chemical Formula	MW (g/mol)
1		3-((hexyl-1,1,2,2,3,3,4,4,5,5,6,6,6- d_{13})oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	$\text{C}_{14}\text{H}_{10}\text{D}_{13}\text{N}_3\text{OS}$	294.42

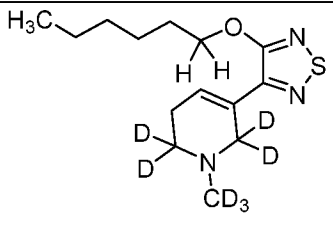
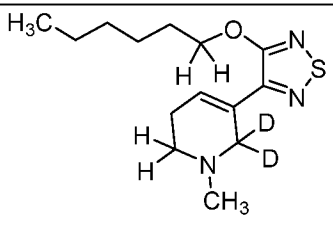
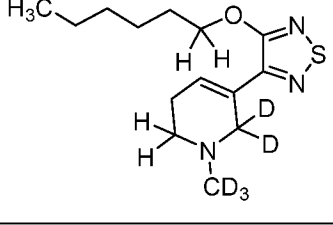
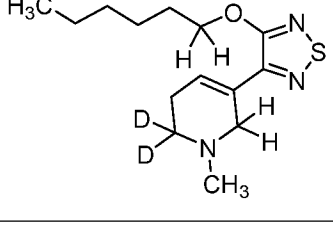
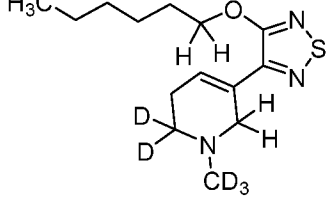
2		3-((hexyl-1,1,2,2,3,3,4,4,5,5,6,6,6- <i>d</i> ₁₃)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₇ D ₁₆ N ₃ OS	297.42
3		3-((hexyl-3,3- <i>d</i> ₂)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₅ N ₃ OS	286.42
4		3-((hexyl-3,3- <i>d</i> ₂)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₂₁ D ₂ N ₃ OS	283.42
5		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₅ N ₃ OS	286.42
6		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₂₁ D ₂ N ₃ OS	283.42
7		3-((hexyl-2,2- <i>d</i> ₂)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₅ N ₃ OS	286.42
8		3-((hexyl-2,2- <i>d</i> ₂)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₂₁ D ₂ N ₃ OS	283.42

9		3-((hexyl-2,2,3,3,4,4- <i>d</i> ₆)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₄ D ₉ N ₃ OS	290.42
10		3-((hexyl-2,2,3,3,4,4- <i>d</i> ₆)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₇ D ₆ N ₃ OS	287.42
11		3-((hexyl-1,1,2,2,3,3- <i>d</i> ₆)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₄ D ₉ N ₃ OS	290.42
12		3-((hexyl-1,1,2,2,3,3- <i>d</i> ₆)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₇ D ₆ N ₃ OS	287.42
13		3-((hexyl-2,2,3,3,4,4,5,5,6,6- <i>d</i> ₁₁)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₂ D ₁₁ N ₃ OS	292.42
14		3-((hexyl-2,2,3,3,4,4,5,5,6,6- <i>d</i> ₁₁)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₉ D ₁₄ N ₃ OS	295.42

15		3-((hexyl-3,3,4,4,5,5,6,6,6- <i>d</i> ₉)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₄ D ₉ N ₃ OS	290.42
16		3-((hexyl-3,3,4,4,5,5,6,6,6- <i>d</i> ₉)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₁ D ₁₂ N ₃ OS	293.42
17		3-((hexyl-4,4,5,5,6,6,6- <i>d</i> ₇)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₆ D ₇ N ₃ OS	288.42
18		3-((hexyl-4,4,5,5,6,6,6- <i>d</i> ₇)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₃ D ₁₀ N ₃ OS	291.42
19		3-((hexyl-4,4,6,6,6- <i>d</i> ₅)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₅ N ₃ OS	286.42
20		3-((hexyl-4,4,6,6,6- <i>d</i> ₅)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₅ D ₈ N ₃ OS	289.42

21		3-((hexyl-5,5,6,6,6- <i>d</i> ₅)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₅ N ₃ OS	286.42
22		3-((hexyl-5,5,6,6,6- <i>d</i> ₅)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₅ D ₈ N ₃ OS	289.42
23		3-((hexyl-3,3,4,4,5,5,6,6,6- <i>d</i> ₉)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₄ D ₉ N ₃ OS	290.42
24		3-((hexyl-3,3,4,4,5,5,6,6,6- <i>d</i> ₉)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₁ D ₁₂ N ₃ OS	293.42
25		3-(hexyloxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₂₀ D ₃ N ₃ OS	284.42
26		3-((hexyl-6,6,6- <i>d</i> ₃)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₃ N ₃ OS	284.42
27		3-((hexyl-6,6,6- <i>d</i> ₃)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-1,2,5-thiadiazole	C ₁₄ H ₁₅ D ₆ N ₃ OS	287.42

28		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-2,2,6,6- <i>d</i> ₄ -1,2,5-thiadiazole	C ₁₄ H ₁₇ D ₆ N ₃ OS	287.42
29		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-2,2,6,6- <i>d</i> ₄ -1,2,5-thiadiazole	C ₁₄ H ₁₄ D ₉ N ₃ OS	290.42
30		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-2,2- <i>d</i> ₂ -1,2,5-thiadiazole	C ₁₄ H ₁₉ D ₄ N ₃ OS	285.42
31		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-2,2- <i>d</i> ₂ -1,2,5-thiadiazole	C ₁₄ H ₁₆ D ₇ N ₃ OS	288.42
32		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-6,6- <i>d</i> ₂ -1,2,5-thiadiazole	C ₁₄ H ₁₉ D ₄ N ₃ OS	285.42
33		3-((hexyl-1,1- <i>d</i> ₂)oxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-6,6- <i>d</i> ₂ -1,2,5-thiadiazole	C ₁₄ H ₁₆ D ₇ N ₃ OS	288.42
34		3-(hexyloxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-2,2,6,6- <i>d</i> ₄ -1,2,5-thiadiazole	C ₁₄ H ₁₉ D ₄ N ₃ OS	285.42

35		3-(hexyloxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-2,2,6,6- <i>d</i> ₄)-1,2,5-thiadiazole	C ₁₄ H ₁₆ D ₇ N ₃ OS	288.42
36		3-(hexyloxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-2,2- <i>d</i> ₂)-1,2,5-thiadiazole	C ₁₄ H ₂₁ D ₂ N ₃ OS	283.42
37		3-(hexyloxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-2,2- <i>d</i> ₂)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₅ N ₃ OS	286.42
38		3-(hexyloxy)-4-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)-6,6- <i>d</i> ₂)-1,2,5-thiadiazole	C ₁₄ H ₂₁ D ₂ N ₃ OS	283.42
39		3-(hexyloxy)-4-(1-(methyl- <i>d</i> ₃)-1,2,5,6-tetrahydropyridin-3-yl)-6,6- <i>d</i> ₂)-1,2,5-thiadiazole	C ₁₄ H ₁₈ D ₅ N ₃ OS	286.42

[0142] Also provided are alkyl esters of the compounds disclosed above, which can be made by the methods above and may be useful as, *inter alia*, prodrugs. Ethyl esters are shown, and other esters, such as methyl, n-propyl, isopropyl, and so on, are also provided herein.

In-Vivo Assessment of Pharmacokinetics Following Oral Dose Administration in Male Sprague-Dawley Rats

[0143] The objective of this study was to assess the pharmacokinetics (PK) of xanomeline tartrate molecules (xanomeline, xanomeline-*d*₁₆ and xanomeline-*d*₁₃) following single oral dose administration of aqueous formulations to male Sprague-Dawley rats, as shown in Table 2.

Table 2: Xanomeline Concentration ($\mu\text{g/mL}$) in Rat Dosing Solution

Formulation	Sample ID	Concentration ($\mu\text{g/mL}$)	Mean Concentration (mg/mL)
Xanomeline Tartrate	01	2463.72	2.48
Xanomeline Tartrate	02	2495.72	
Xanomeline-D16 Tartrate*	03	1328.62	1.32
Xanomeline-D16 Tartrate*	04	1314.03	
Xanomeline-D13 Tartrate*	05	1532.88	1.55
Xanomeline-D13 Tartrate*	06	1564.53	

*Approximate concentrations were obtained by adding the precursor and product ion of d_{16} and d_{13} to the xanomeline MS-MS acquisition parameters.

[0144] Blood samples were collected from all animals in Groups 1–3 at 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post dose, with each animal bled at all time points. AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , and $T_{1/2}$ were calculated from the individual xanomeline, xanomeline- d_{16} or xanomeline- d_{13} plasma concentration data using standard noncompartmental methods, when possible. The slopes of the elimination phase of the concentrations vs. time curve used to calculate the $T_{1/2}$ were determined by log-linear regression.

[0145] Results from Groups 2 and 3, where xanomeline- d_{16} and xanomeline- d_{13} were measured respectively, were compared descriptively to the results from Group 1 (xanomeline). PK analyses were performed and validated using Phoenix® WinNonlin® version 8.0. To normalize the AUC across treatment groups, the xanomeline concentrations for each formulation was recalculated to account for bias, as shown in Table 3.

Table 3: Xanomeline Concentration ($\mu\text{g/mL}$) in Rat Dosing Solution from a target Concentration of 2.5 mg/mL

Formulation	Sample ID	Conc. ($\mu\text{g/mL}$)	% Bias	Mean Conc. ($\mu\text{g/mL}$)	Mean % Bias
Xanomeline Tartrate	01	2463.72	-1.45	2479.72	-0.81
Xanomeline Tartrate	02	2495.72	-0.17		
Xanomeline- d_{16} tartrate*	03	1328.62	-46.86	1321.33	-47.15
Xanomeline- d_{16} tartrate*	04	1314.03	-47.44		
Xanomeline- d_{13} tartrate*	05	1532.88	-38.68	1548.71	-38.05

Xanomeline- <i>d</i> ₁₃ tartrate*	06	1564.53	-37.42		
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*Approximate concentrations obtained by adding the precursor and product ions of *d*₁₆ or *d*₁₃ to the xanomeline MS/MS acquisition parameters.

[0146] Overall, deuterating xanomeline resulted in an average 1.76-fold increase in exposure. Xanomeline tartrate had a normalized AUC of 4210 h*pg/mg. Xanomeline-*d*₁₃ had a normalized AUC of 8070 h*pg/mg and xanomeline-*d*₁₆ a normalized AUC of 6780 h*pg/mg (FIG. 1). The mean peak xanomeline, xanomeline-*d*₁₆, and xanomeline-*d*₁₃ plasma concentrations were observed within 30 minutes post-dose independent of the treatment. Estimated elimination half-life (*t*_{1/2}) was also similar among treatment groups (ranged between 1.5 and 2.7 hours post-dose). Xanomeline levels following the oral administration of xanomeline tartrate 25 mg/kg were about mid-way between the levels of xanomeline-*d*₁₆ and xanomeline-*d*₁₃ obtained after administration of xanomeline-*d*₁₆ tartrate and xanomeline-*d*₁₃ tartrate at the same dosage.

In-Vitro Radioligand Binding Assays

[0147] Xanomeline-*d*₁₆ and xanomeline-*d*₁₃ were tested for their agonist capacity on FlpIn™ Chinese hamster ovary (CHO) cells stably expressing the muscarinic acetylcholine receptor (mAChRs) human M1–M5 (hM1-hM5). The Flp-In™ cell lines are designed for rapid generation of stable cell lines that express a protein of interest from a Flp-In™ expression vector. Targeted integration of a Flp-In™ expression vector ensured a high-level expression of the mAChRs hM1–hM5.

[0148] First, the expression of the mAChRs in each CHO cell line was analyzed by binding [³H]-*N*-methylscopolamine ([³H]-NMS; *see* FIGS. 2 and 3). FIG. 2 units are expressed on the Y axis as counts per minute activity (CPMA) and then normalized to femtomoles per mg protein in FIG. 3.

[0149] Next, pERK assays were performed using the different compounds or acetylcholine (10 μM) at different times (2.5–60 minutes). Extracellular signal-related kinase (ERK1/2 or p42/44) is a kinase in the mitogen-activated protein kinase (MAPK) family. Phosphorylation of ERK (pERK) can be used as a common end point measurement for the activation of many classes of G protein coupled receptors (GPCR) and beta-arrestin linked signaling.

[0150] For the pERK assay, cells were serum starved for 5 to 6 hours. Curves were normalized to the maximum response from the fetal bovine serum (FBS) medium corresponding to a 5-minute stimulation. A 5–minute incubation with the agonists was

selected for the dose response pERK assays (n=2).

[0151] pERK dose response experiments were performed to test the agonist capacity of xanomeline-*d*₁₆ and xanomeline-*d*₁₃ in CHO cells stably expressing hM2, hM3 and hM5 (n = 3). These pERK dose response experiments were repeated to test the agonist capacity of xanomeline-*d*₁₆ and xanomeline-*d*₁₃ in CHO cells stably expressing hM1 and hM4 (n = 4). As shown in FIGS. 4–6, values were normalized to the maximum FBS response. Nonlinear regression curves were calculated per the three parameters method with no constraints. Differences in drug potency were evaluated by comparing pEC₅₀ values and the differences in the compounds efficacy were analyzed by the maximal response (E_{max}). pEC₅₀ values are listed at Table 4.

Table 4

Receptor	Xanomeline- <i>d</i> ₁₃	Xanomeline- <i>d</i> ₁₆	Acetylcholine
M1	9.835	9.771	7.167
M2	6.177	6.134	7.522
M3	8.015	7.566	7.925
M4	11.41	11.096	7.600
M5	6.985	7.056	7.102

[0152] Overall, xanomeline-*d*₁₆ and xanomeline-*d*₁₃ were modestly potent partial agonists at mAChRs hM3 > hM5 > hM2, and were efficacious partial agonist at hM4 > hM1. These deuterated xanomeline derivatives have surprisingly low picomolar activity at M4 receptors. This activity is an order of magnitude greater than M1 receptors and several orders of magnitude greater than M2 receptors. Thus, these results showed that xanomeline-*d*₁₆ and xanomeline-*d*₁₃ have are selective for hM1 and hM4 over the other receptor subtypes.

In-Vitro Assessment of Metabolic Stability in Suspension of Cryopreserved Hepatocytes

[0153] The primary site of metabolism for many drugs is the liver. Intact hepatocytes contain the cytochrome P450s (CYPs), other non-P450 enzymes, and phase II enzymes such as sulfo- and glucuronosyltransferases, and thus represent a prime model system for studying drug disposition *in vitro*. Given that cryopreserved hepatocytes retain enzymatic activities similar to those of fresh hepatocytes, the utility of cryopreserved hepatocytes is advantageous compared to other model systems.

[0154] The incubation medium is prepared by combining a hepatocyte maintenance

supplement pack (serum-free) with Williams Medium E and warmed to 37 °C in a water bath. Compound stocks are prepared from test articles and positive controls dissolved in an organic solvent such as methanol or DMSO to desired concentration, such as 1 mM.

Hepatocytes are prepared immediately before assay, diluted to 1×10^6 viable cells/mL in Williams' Medium E supplemented with hepatocyte maintenance medium.

[0155] In separate conical tubes, the test compounds and positive controls are added and warmed with incubation medium to yield the desired working concentration. For example, a 2 μ M solution is prepared by adding 10 μ L of 1 mM test article stock solution to 5 mL incubation medium. When DMSO is a solvent, the concentration should not exceed 0.1%, with a maximum of 1% in the final incubation medium. The test article is a deuterated xanomeline described herein. Examples of positive controls include midazolam, phenacetin, testosterone, dextromethorphan, (S)-mephentoin, and 7-hydroxycoumarin.

[0156] Next 0.5 mL of incubation medium containing the test article or positive control is pipetted into respective wells of a 12-well non-coated plate. The final substrate concentration is 1 μ M. The plates are incubated on an orbital shaker to allow the substrates to warm for about 5–10 minutes before initiating reaction. For the negative control, 1.0×10^6 viable hepatocytes/mL are boiled for 5 minutes to eliminate enzymatic activity.

[0157] The 12-well non-coated plate containing the substrates is removed from the incubator. Reactions are started by adding 0.5 mL of 1.0×10^6 viable cells/mL in each well of the plate to yield a final cell density of 0.5×10^6 viable cells/mL. Next 0.5 mL of the inactivated hepatocytes are pipetted into the negative control wells. The plate is returned to the orbital shaker in the incubator and the shaker speed is adjusted to 90–120 rpm. Well contents are removed in 50- μ L aliquots at 0, 15, 30, 60, 90 and 120 minutes. Additional time points 180 min and 240 min may be included but may not be necessary for healthy and metabolically competent hepatocytes to detect high turnover compounds. Incubations are stopped by adding sample aliquots (e.g. 50 μ L) to tubes containing the appropriate quenching solvent and either freeze at -70 °C or by direct extraction.

[0158] *In-vitro* half-life ($t_{1/2}$) of the parent compound is determined by regression analysis of the percent parent disappearance vs. time curve. Intrinsic clearance *in vitro* is calculated per the equation: $Cl_{int} = kV/N$, where $k = 0.693/t_{1/2}$, V = incubation volume (1 mL) and N = number of hepatocytes per well (0.5×10^6 viable cells). Cl_{int} *in vitro* may be scaled to *in vivo* predictions

[0159] It can be predicted that the compounds as disclosed herein, when tested in this assay, will demonstrate an increase of at least 5% or more in the degradation half-life, as

compared to the non-isotopically enriched drug.

In-vitro metabolism using human cytochrome P₄₅₀ enzymes

[0160] The cytochrome P₄₅₀ enzymes are expressed from the corresponding human cDNA using a baculovirus expression system (BD Biosciences, San Jose, CA). A 0.25 milliliter reaction mixture containing 0.8 milligrams per milliliter protein, 1.3 millimolar NADP⁺, 3.3 millimolar glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3 millimolar magnesium chloride and 0.2 millimolar of a compound of the corresponding species, the corresponding non-isotopically enriched compound or standard or control in 100 millimolar potassium phosphate (pH 7.4) will be incubated at 37 °C for 20 min. After incubation, the reaction is stopped by the addition of an appropriate solvent (e.g., acetonitrile, 20% trichloroacetic acid, 94% acetonitrile/6% glacial acetic acid, 70% perchloric acid, 94% acetonitrile/6% glacial acetic acid) and centrifuged (10,000 g) for 3 min. The supernatant is analyzed by HPLC/MS/MS. The standards for each Cytochrome P₄₅₀ enzyme are listed below at Table 5.

Table 5: Standards for Cytochrome P₄₅₀ enzymes

Cytochrome P ₄₅₀	Standard
CYP1A2	Phenacetin
CYP2A6	Coumarin
CYP2B6	[¹³ C]-(<i>S</i>)-mephenytoin
CYP2C8	Paclitaxel
CYP2C9	Diclofenac
CYP2C19	[¹³ C]-(<i>S</i>)-mephenytoin
CYP2D6	(+/-)-Bufuralol
CYP2E1	Chlorzoxazone
CYP3A4	Testosterone
CYP4A	[¹³ C]-Lauric acid

[0161] It is expected that compounds disclosed herein will be effective in reducing symptoms such as hallucinations and delusional thoughts characterize as positive symptoms and negative symptoms such social isolation and anhedonia. Finally, other symptoms and diseases expected to have a decrease are cognitive symptoms such inability to process information and poor working memory and diseases, including schizophrenia, Alzheimer's, Parkinson's, depression, movement disorders, drug addiction, pain, and neurodegeneration.

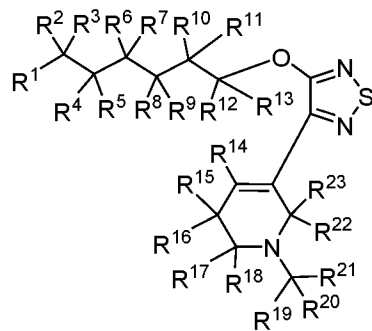
[0162] All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein in their entireties. Where any inconsistencies arise, material literally disclosed herein controls.

[0163] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

1. A compound of Formula I

Formula I



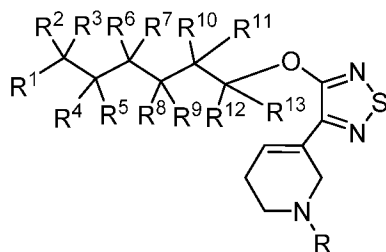
and/or salts thereof;

wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}$ and R^{23} are independently chosen from H and D; and

at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{22}$ and R^{23} is enriched with deuterium and R^{19}, R^{20} , and R^{21} are independently chosen from H and D; or two of R^{19}, R^{20} , and R^{21} are enriched with deuterium.

2. The compound of claim 1, comprising Formula II

Formula II

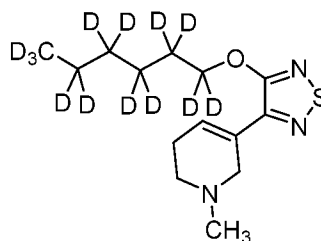


and/or salts thereof;

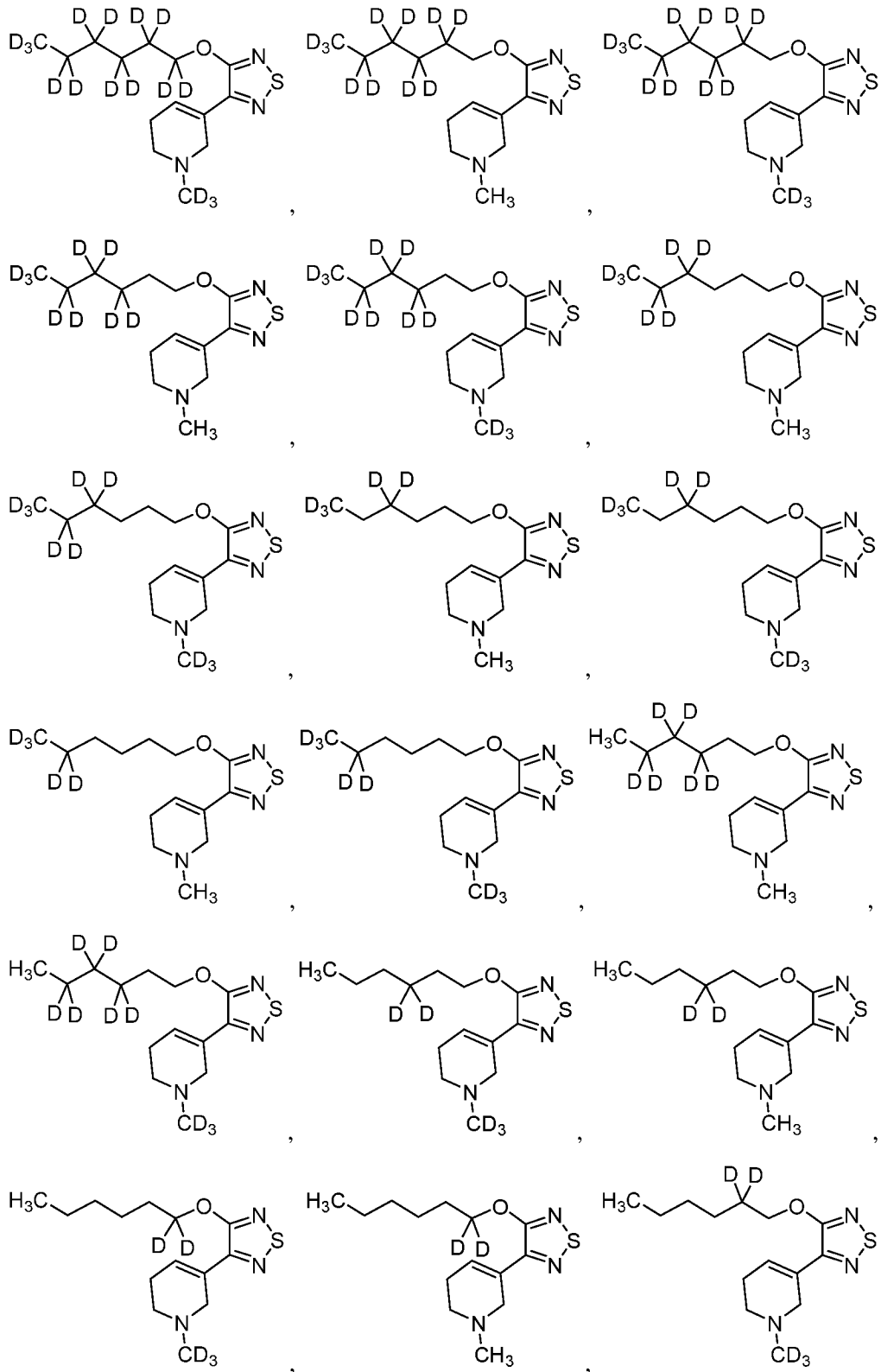
wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$, and R^{13} are independently chosen from H and D;

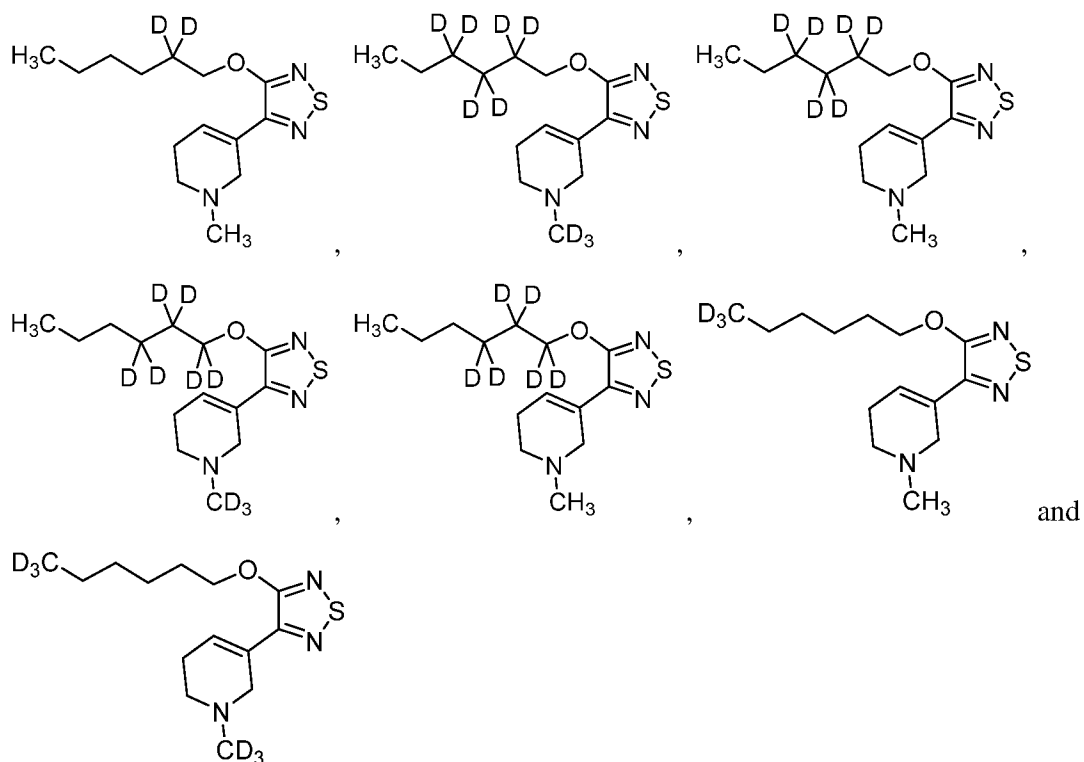
R is CH_3 or CD_3 ; and

at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}$, or R^{13} is enriched with deuterium.



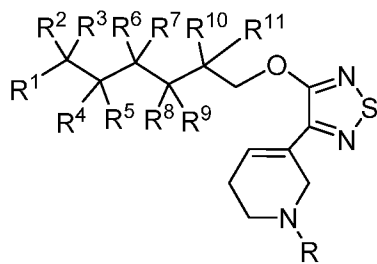
3. The compound of claim 2 chosen from





4. The compound of claim 1, comprising Formula IIA

Formula IIA

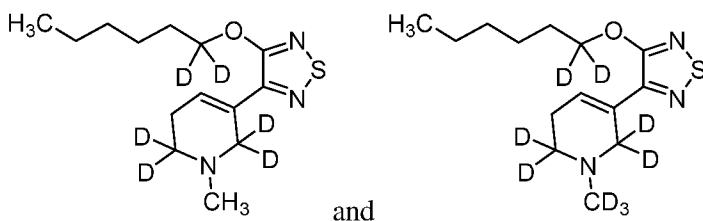


and/or salts thereof;

wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}$, and R^{11} are independently chosen from H and D;

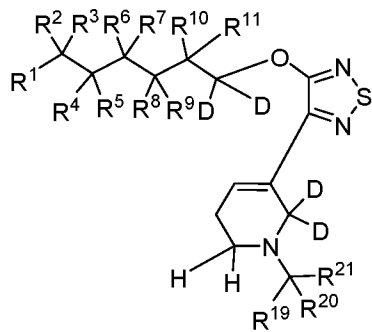
R is CH_3 or CD_3 ; and

at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}$ and R^{11} is enriched with deuterium.



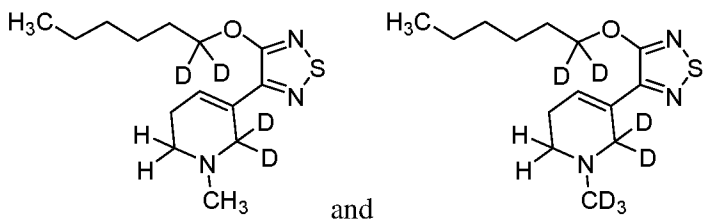
9. The compound of claim 1, comprising Formula IV

Formula IV



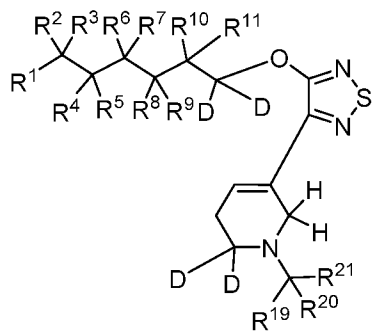
wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹⁹, R²⁰, and R²¹ are independently chosen from H or D.

10. The compound of claim 9 chosen from



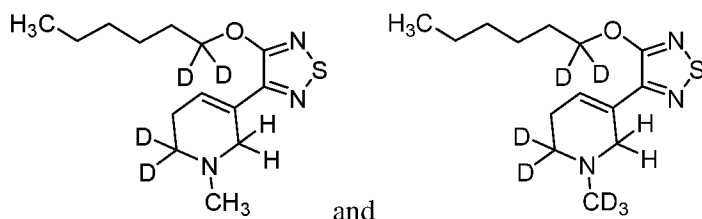
11. The compound of claim 1, comprising Formula V

Formula V



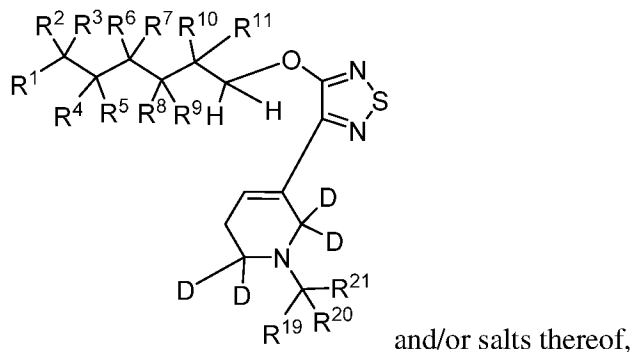
wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹⁹, R²⁰, and R²¹ are independently chosen from H or D.

12. The compound of claim 11 chosen from



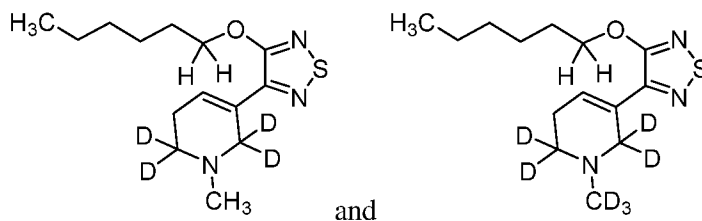
13. The compound of claim 1, comprising Formula VI

Formula VI



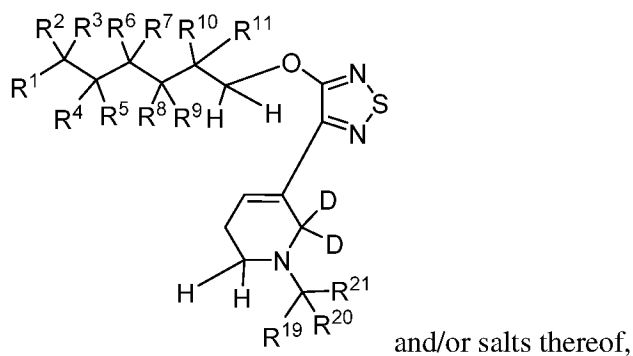
wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹⁹, R²⁰, and R²¹ are independently chosen from H or D.

14. The compound of claim 13 chosen from

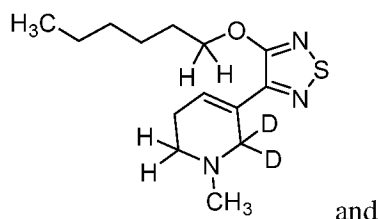


15. The compound of claim 1, comprising Formula VII

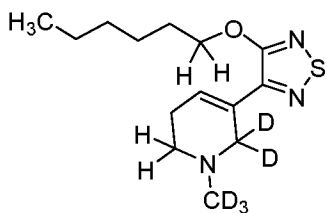
Formula VII



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹⁹, R²⁰, and R²¹ are independently chosen from H or D.

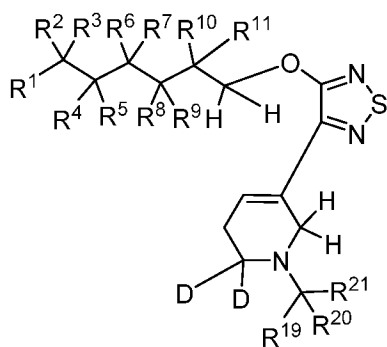


16. The compound of claim 15 chosen from



17. The compound of claim 1, comprising Formula VIII

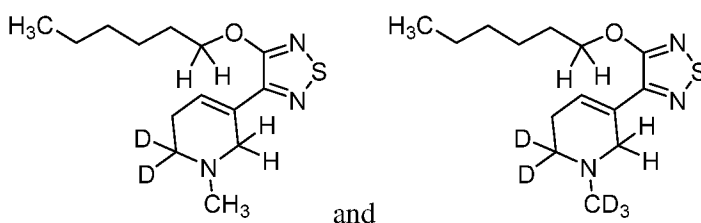
Formula VIII



and/or salts thereof,

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{19} , R^{20} , and R^{21} are independently chosen from H or D.

18. The compound of claim 17 chosen from



19. A medicament comprising a compound of any one of claims 1–18 and/or a salt thereof and at least one pharmaceutically acceptable carrier.

20. The medicament of claim 19, comprising between 5 mg and 300 mg of the compound.

21. The medicament of claim 20, further comprising a muscarinic inhibitor.

22. The medicament of claim 21, wherein the muscarinic inhibitor is trospium chloride.

23. The medicament of claim 22, comprising between 10 mg and 150 mg trospium chloride.

24. The medicament of any one of claims 19–23, formulated as an immediate release

- formulation.
25. The medicament of any one of claims 19–23, formulated as a controlled release formulation.
 26. The medicament of claim 21 or 22, wherein the compound is formulated as a controlled release formulation and the trospium chloride is formulated as an immediate release formulation.
 27. The medicament of claim 22, comprising between 5 mg and 300 mg of the compound and between 5 mg and 150 mg trospium chloride in a single dosage form.
 28. The medicament of any one of claims 19–27, comprising 10 milligrams of the compound.
 29. The medicament of any one of claims 19–27, comprising 20 milligrams of the compound.
 30. The medicament of any one of claims 19–27, comprising 30 milligrams of the compound.
 31. The medicament of any one of claims 19–27, comprising 40 milligrams of the compound.
 32. The medicament of any one of claims 19–27, comprising 50 milligrams of the compound.
 33. The medicament of any one of claims 19–27, comprising 75 milligrams of the compound.
 34. The medicament of any one of claims 19–27, comprising 125 milligrams of the compound.
 35. The medicament of any one of claims 19–27, comprising 200 milligrams of the compound.
 36. The medicament of any one of claims 19–27, comprising 300 milligrams of the compound.
 37. The medicament of claim 27, comprising 10 milligrams trospium chloride.
 38. The medicament of claim 27, comprising 20 milligrams trospium chloride.
 39. The medicament of claim 27, comprising 30 milligrams trospium chloride.
 40. The medicament of claim 27, comprising 40 milligrams trospium chloride.
 41. The medicament of claim 27, comprising 80 milligrams trospium chloride.
 42. The medicament of claim 27, comprising 120 milligrams trospium chloride.
 43. The medicament of claim 27, comprising 150 milligrams trospium chloride.
 44. The medicament of claim 22, in the form of a single dosage formulation comprising 50 milligrams of the compound, 10 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier.
 45. The medicament of claim 22, in the form of a single dosage formulation comprising 75 milligrams of the compound, 20 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier.
 46. The medicament of claim 22, in the form of a single dosage formulation comprising 50

- milligrams of the compound, 20 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier.
47. The medicament of claim 22, in the form of a single dosage formulation comprising 75 milligrams of the compound, 10 milligrams trospium chloride, and at least one pharmaceutically acceptable carrier.
 48. The medicament of any one of claims 19–47, wherein the pharmaceutically acceptable carrier comprises cellulose and lactose.
 49. A method of treating pain or a central nervous system disorder in a patient in need thereof, the method comprising administering therapeutically effective amount of a compound from any one of claims 1–18 to the patient in need thereof.
 50. The method of claim 49, wherein the compound is administered orally, intramuscularly, transdermally, buccally, or sublingually.
 51. The method of claim 49 or 50, wherein a central nervous system disorder is treated and is chosen from schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, Lewy Body dementia, psychosis, and cognition deficit.
 52. A method of treating pain or a central nervous system disorder in a patient in need thereof, the method comprising administering therapeutically effective amount of a medicament from any one of claims 19–48 to the patient in need thereof.
 53. The method of claim 52, wherein the medicament is administered orally, intramuscularly, transdermally, buccally, or sublingually.
 54. The method of claim 52 or 53, wherein a central nervous system disorder is treated and is chosen from schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, Lewy Body dementia, psychosis and cognition deficit.
 55. The method of any one of claims 49–54, wherein use of the trospium chloride, when present, alleviates a side effect associated with use of the compound from any one of claims 1–18.

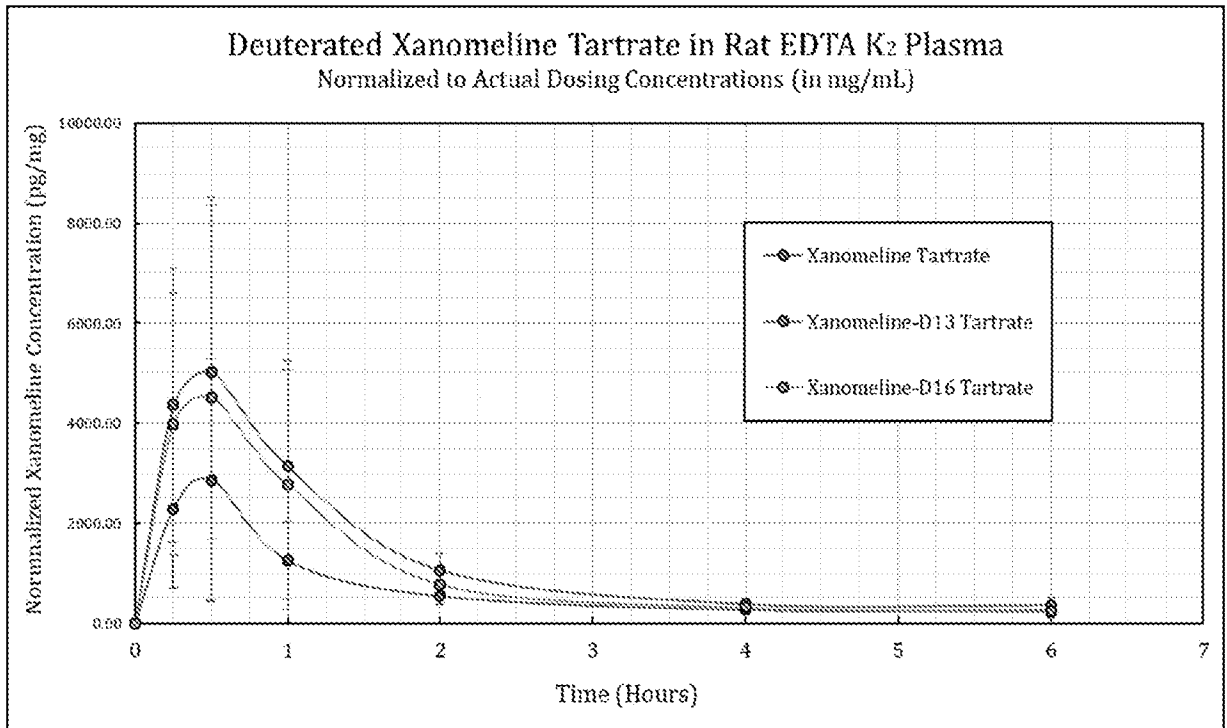


FIG. 1

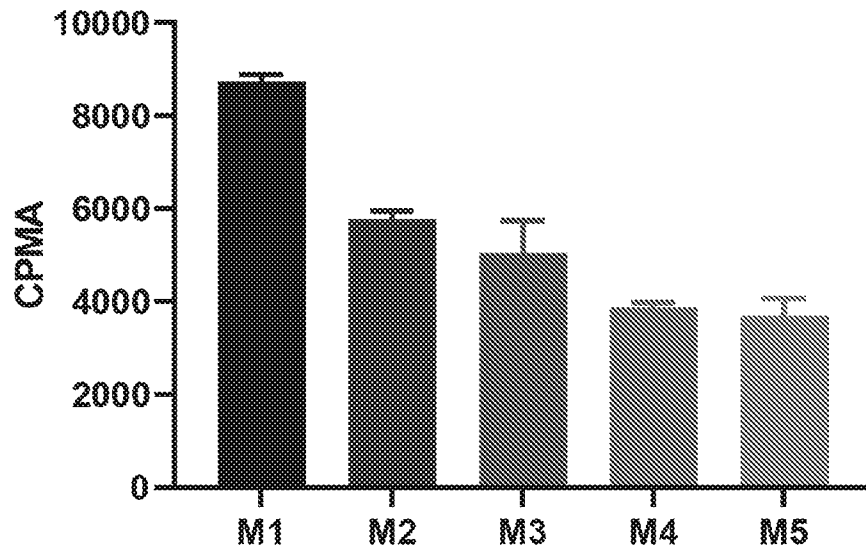


FIG. 2

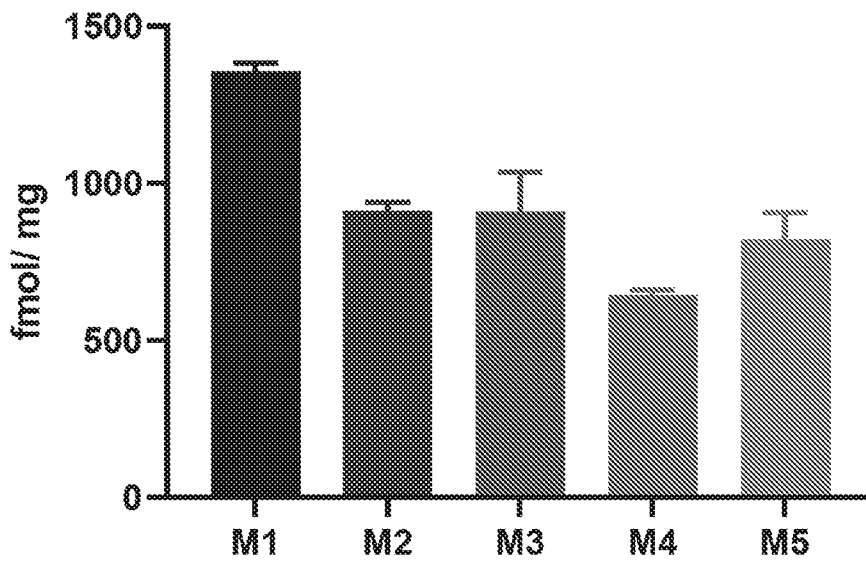


FIG. 3

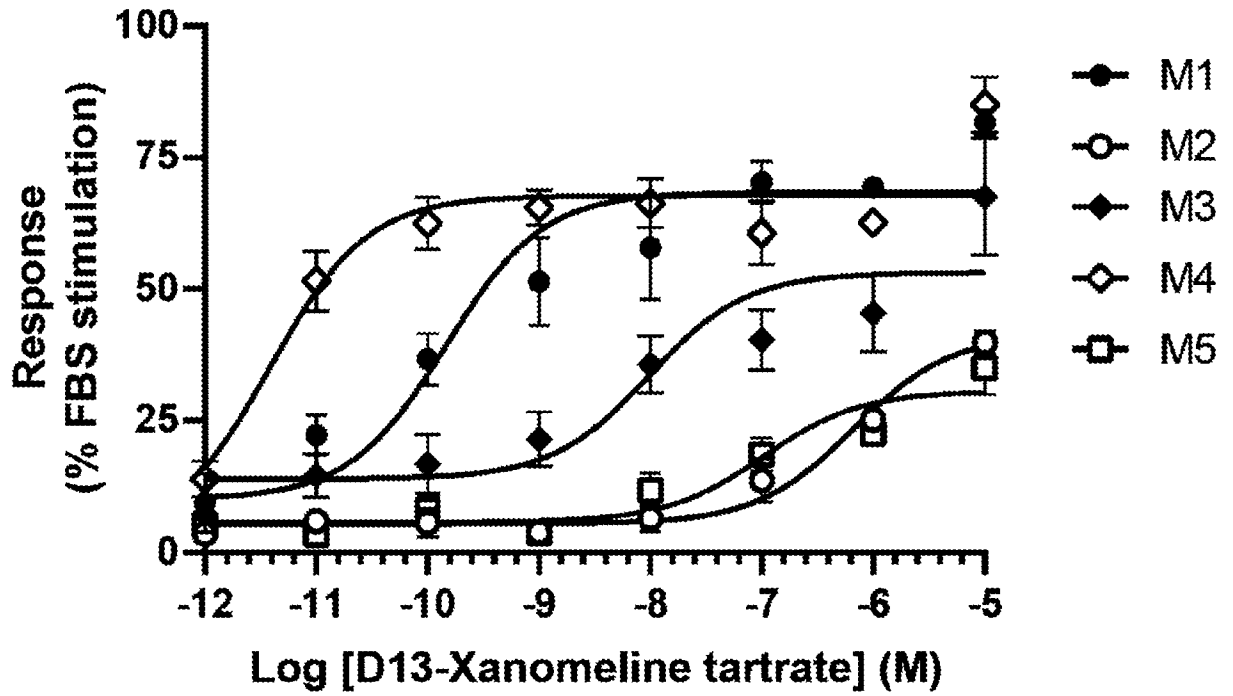


FIG. 4

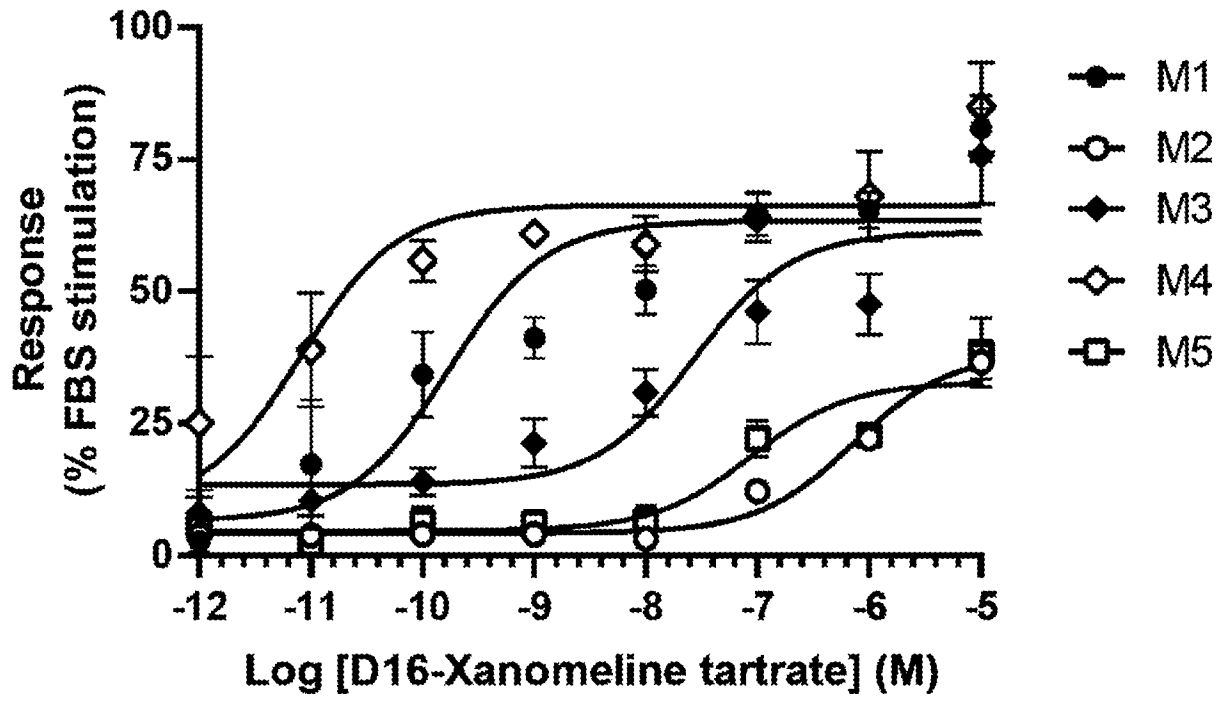


FIG. 5

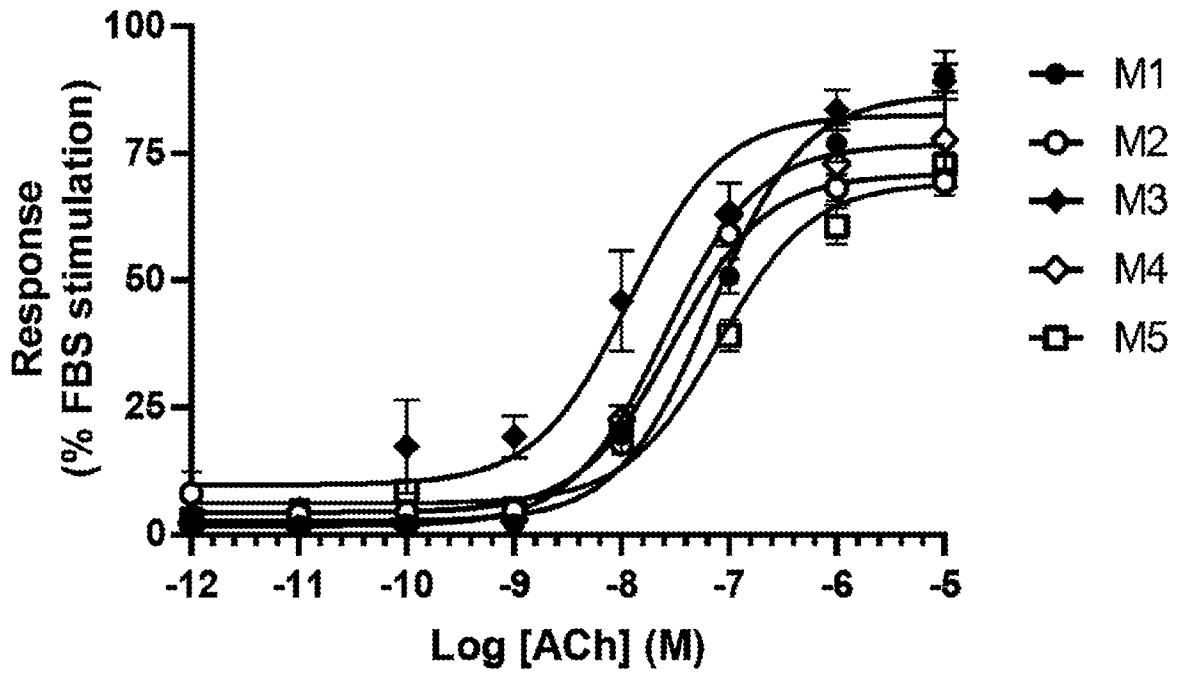


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/19193

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/433; A61P 25/28 (2020.01)

CPC - A61K 31/433; A61P 25/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2017/0112820 A1 (PURETECH HEALTH LLC) 27 April 2017; paragraphs [0009], [0013], [0051], [0054]-[0055], [0058]-[0060], [0079], [0085], [0093], [0121]	1-2, 4-6, 19/1-2, 19/4-6, 20/19/1-2, 20/19/4-6, 21/20/19/1-2, 21/20/19/4-6, 22/21/20/19/1-2, 22/21/20/19/4-6, 23/22/21/20/19/1-2, 23/22/21/20/19/4-6, 27/22/21/20/19/1-2, 27/22/21/20/19/4-6, 37/27/22/21/20/19/1-2, 37/27/22/21/20/19/4-6, 38/27/22/21/20/19/1-2, 38/27/22/21/20/19/4-6, 39/27/22/21/20/19/1-2, 39/27/22/21/20/19/4-6, 40/27/22/21/20/19/1-2, 40/27/22/21/20/19/4-6, 41/27/22/21/20/19/1-2, 41/27/22/21/20/19/4-6, 42/27/22/21/20/19/1-2, 42/27/22/21/20/19/4-6, 43/27/22/21/20/19/1-2, 43/27/22/21/20/19/4-6, 44/22/21/20/19/1-2,

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"D" document cited by the applicant in the international application	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"E" earlier application or patent but published on or after the international filing date	"&" document member of the same patent family
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
01 April 2020 (01.04.2020)

Date of mailing of the international search report

26 MAY 2020

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Shane Thomas
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/19193

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2018/0099956 A1 (NEUROSOLIS, INC.) 12 April 2018; paragraphs [0144]-[0147]	44/22/21/20/19/4-6, 45/22/21/20/19/1-2, 45/22/21/20/19/4-6, 46/22/21/20/19/1-2, 46/22/21/20/19/4-6, 47/22/21/20/19/1-2, 47/22/21/20/19/4-6, 49/1-2, 49/4-6, 50/49/1-2, 50/49/4-6 1-2, 4-6, 19/1-2, 19/4-6, 20/19/1-2, 20/19/4-6, 21/20/19/1-2, 21/20/19/4-6, 22/21/20/19/1-2, 22/21/20/19/4-6, 23/22/21/20/19/1-2, 23/22/21/20/19/4-6, 27/22/21/20/19/1-2, 27/22/21/20/19/4-6, 37/27/22/21/20/19/1-2, 37/27/22/21/20/19/4-6, 38/27/22/21/20/19/1-2, 38/27/22/21/20/19/4-6, 39/27/22/21/20/19/1-2, 39/27/22/21/20/19/4-6, 40/27/22/21/20/19/1-2, 40/27/22/21/20/19/4-6, 41/27/22/21/20/19/1-2, 41/27/22/21/20/19/4-6, 42/27/22/21/20/19/1-2, 42/27/22/21/20/19/4-6, 43/27/22/21/20/19/1-2, 43/27/22/21/20/19/4-6, 44/22/21/20/19/1-2, 44/22/21/20/19/4-6, 45/22/21/20/19/1-2, 45/22/21/20/19/4-6, 46/22/21/20/19/1-2, 46/22/21/20/19/4-6, 47/22/21/20/19/1-2, 47/22/21/20/19/4-6, 49/1-2, 49/4-6, 50/49/1-2, 50/49/4-6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/19193

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3. Claims Nos.: 24-26, 28-36, 48, 51-55
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

----Continued Within the Next Supplemental Box----

Claims 1-2, 4-6, 19/1-2, 19/4-6, 20/19/1-2, 20/19/4-6, 21/20/19/1-2, 21/20/19/4-6, 22/21/20/19/1-2, 22/21/20/19/4-6, 23/22/21/20/19/1-2, 23/22/21/20/19/4-6, 27/22/21/20/19/1-2, 27/22/21/20/19/4-6, 37/27/22/21/20/19/1-2, 37/27/22/21/20/19/4-6, 38/27/22/21/20/19/1-2, 38/27/22/21/20/19/4-6, 39/27/22/21/20/19/1-2, 39/27/22/21/20/19/4-6, 40/27/22/21/20/19/1-2, 40/27/22/21/20/19/4-6, 41/27/22/21/20/19/1-2, 41/27/22/21/20/19/4-6, 42/27/22/21/20/19/1-2, 42/27/22/21/20/19/4-6, 43/27/22/21/20/19/1-2, 43/27/22/21/20/19/4-6, 44/22/21/20/19/1-2, 44/22/21/20/19/4-6, 45/22/21/20/19/1-2, 45/22/21/20/19/4-6, 46/22/21/20/19/1-2, 46/22/21/20/19/4-6, 47/22/21/20/19/1-2, 47/22/21/20/19/4-6, 49/1-2, 49/4-6, 50/49/1-2, 50/49/4-6

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
- 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
----Please See Above----

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/19193

-***-Continued from Box No. III Observations where unity of invention is lacking -***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid. Groups I+, Claims 1-23, 27, 37-47, 49-50; and a compound of Formula I, wherein R1 is D; R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22 and R23 are H (compound structure); are directed toward compounds, medicaments comprising the compound; and a method associated therewith.

The compounds, medicaments, and methods will be searched to the extent they encompass a compound of Formula I, wherein R1 is D; R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22 and R23 are H (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure(s) thereof (e.g. no optional or variable atoms, isotopes, bonds, or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1-2 (in-part), 4-6 (in-part), 19-23 (in-part), 27 (in-part), 37-47 (in-part), and 49-50 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula I, wherein R1 is D; R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22 and R23 are H (compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula I wherein R1 is H; R2 is D; R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22 and R23 are H (compound structure).

Groups I+ share the technical features including: a compound of Formula I wherein R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22 and R23 are independently chosen from H and D; and at least one of R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R22 and R23 is enriched with deuterium and R19, R20, and R21 are independently chosen from H and D; or two of R19, R20, and R21 are enriched with deuterium (compound structure); a medicament comprising a compound and at least one pharmaceutically acceptable carrier; and a method of treating pain or a central nervous system disorder in a patient in need thereof, the method comprising administering therapeutically effective amount of a compound to the patient in need thereof.

However, these shared technical features are previously disclosed by US 2017/0112820 A1 (PURETECH HEALTH LLC) (hereinafter 'PureTech') in view of US 2018/0099956 A1 (NEUROSOLIS, INC.) (hereinafter 'NeuroSolis').

PureTech discloses a compound of Formula I wherein R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22 and R23 are H (method of treatment comprising administering a muscarinic activator and a muscarinic inhibitor, wherein the muscarinic activator is xanomeline (R2-R23 are H); paragraphs [0009], [0079]); a medicament comprising a compound and at least one pharmaceutically acceptable carrier (dose form (medicament) comprises a compound and one or more pharmaceutically-acceptable carriers; paragraph [0093]); and a method of treating pain or a central nervous system disorder in a patient in need thereof (method of treating a disorder that can be ameliorated by activation of the muscarinic system, such as Alzheimer's disease, in a human (patient); paragraphs [0051], [0054]-[0055]), the method comprising administering therapeutically effective amount of a compound to the patient in need thereof (method comprises administering to the human an effective amount of a compound; paragraphs [0051], [0055], [0058]-[0060]), but PureTech does not disclose wherein R1 is D. However, NeuroSolis discloses wherein R1 is D (compound of formula XIA wherein X is S and R1 is alkyl substituted by one D (R1 is D); paragraphs [0144]-[0147]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the compound, as previously disclosed by PureTech, in order to have provided wherein R1 is D, as previously disclosed by NeuroSolis, for providing muscarinic acetylcholine receptor modulators, such as xanomeline derivatives/analogs, useful in the treatment of CNS-related disorders (PureTech; abstract; NeuroSolis; abstract; paragraph [0137]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the PureTech and NeuroSolis references, unity of invention is lacking.