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(54) Title: PROPANEDIOL-DICARBAMATE DERIVATIVES

(57) Abstract: This disclosure relates to novel propanediol-dicarbamates, their derivatives, pharmaceutically acceptable salts thereof. This disclosure also provides compositions comprising a compound of this disclosure and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a dual *N*-methyl *D*-aspartic acid (NMDA) receptor antagonist and sodium channel blocker.

PROPANEDIOL-DICARBAMATE DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATION

[1] This application claims priority under 35 U.S.C. § 119 to U.S. Prov. Ser. No. 61/044,715, filed April 14, 2008, incorporated by reference in its entirety herein.

BACKGROUND

[2] Felbamate, also known as 2-phenyl-1,3-propanediol dicarbamate, has a weak inhibitory effect on gamma-aminobutyric acid (GABA) receptor binding sites. Although its precise mechanism of action in treating epilepsy is unknown, it is known as a mixed voltage-dependent sodium channel and NMDA receptor antagonist.

[3] Felbamate is currently approved for epilepsy and in particular for Lennox-Gastaut syndrome, and is in clinical trials for bipolar disorder. Post-approval, however, the US FDA recommended that felbamate be limited to second-line therapy of refractory epilepsy.

[4] Primary felbamate metabolism in humans has been found to proceed through 4 different pathways. CYP3A4 and CYP2E1 catalyze formation of a 2-hydroxypropyl metabolite and a 4'-hydroxyphenyl metabolite. Esterase-catalyzed carbamate hydrolysis leads to a monocarbamate hydroxyl metabolite which undergoes ALDH catalyzed reversible oxidation to a monocarbamate aldehyde metabolite. The fourth pathway leads directly to the monocarbamate aldehyde via oxidative elimination. Once formed, the monocarbamate aldehyde can undergo beta-elimination to form a toxic metabolite, atropaldehyde (ATPAL). Atropaldehyde has been found to inhibit ALDH and GST activities; to lead to loss of hepatocyte viability; and has been linked to hepatoxicity and aplastic anemia. (Kapetanovic, I.M. et al. Chem-Biol Interact, 2002, 142(1-2): 119).

[5] The most common adverse events observed in patients dosed with felbamate include, but are not limited to, somnolence, headache, fatigue, dizziness, nausea, anorexia, vomiting, and constipation. Postmarketing reports of aplastic anemia and acute liver failure lead to changes in the original label to include felbamate as a second line therapy in refractory epilepsy. Evidence suggests that the felbamate metabolite, ATPAL, may be responsible, at least in part, for the observed hepatoxicity

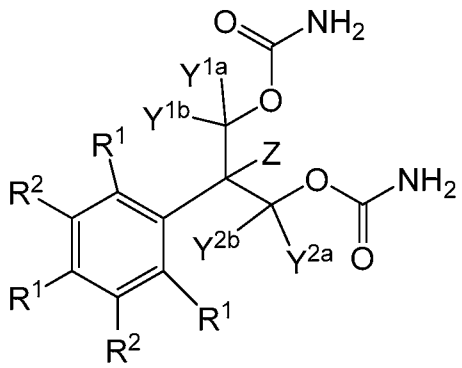
and aplastic anemia. (Kapetanovic, I.M. et al. Chem-Biol Interact, 2002, 142(1-2): 119).

[6] Despite the beneficial activities of felbamate, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

SUMMARY

[7] This disclosure relates to novel propanediol-dicarbamates and pharmaceutically acceptable salts thereof. This disclosure also provides compositions comprising a compound of this disclosure and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a dual *N*-methyl *D*-aspartic acid (NMDA) receptor antagonist and sodium channel blocker.

[8] Accordingly, provided herein is a compound of Formula I:



, or a pharmaceutically acceptable salt thereof, wherein:

each Y is independently selected from hydrogen and deuterium;

each of R^1 and R^2 is independently selected from hydrogen and deuterium;

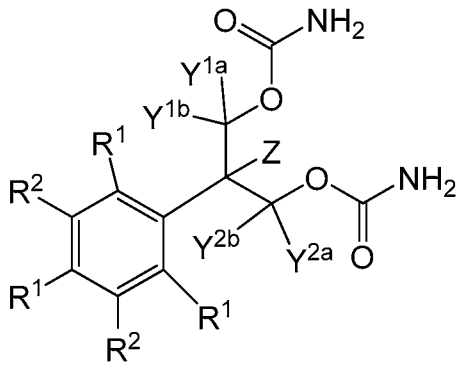
Z is selected from hydrogen, deuterium or fluorine; and

at least one Y, R, or Z is deuterium. In some embodiments, any atom not designated as deuterium is present at its natural isotopic abundance. In some embodiments, each Y is deuterium, and at least one R or Z is not hydrogen. In some embodiments, each R is the same. In some embodiments, each Y^1 is the same; and/or each Y^2 is the same.

In some embodiments, each Y is the same, the compound being selected from any one of the compounds set forth in the table below:

Compound	R^1	R^2	Each Y	Z
100	D	D	D	D
101	D	H	D	D
102	H	D	D	D
103	H	H	D	D
104	D	D	H	D
105	D	H	H	D
106	H	D	H	D
107	H	H	H	D
108	D	D	D	F
109	D	H	D	F
110	H	D	D	F
111	H	H	D	F
112	D	D	H	F
113	D	H	H	F
114	H	D	H	F
115	D	D	D	H
116	D	H	D	H
117	H	D	D	H
118	D	D	H	H
119	D	H	H	H
120	H	D	H	H

[9] Also provided is a pyrogen-free composition comprising:

a. a compound of Formula I: , or a pharmaceutically acceptable salt thereof, wherein:

each Y is independently selected from hydrogen and deuterium;

each of R^1 and R^2 is independently selected from hydrogen and deuterium;

Z is selected from hydrogen, deuterium or fluorine;

at least one Y, R or Z is deuterium; and

b. an acceptable carrier. In some embodiments, the composition is formulated for pharmaceutical administration, wherein the carrier is a pharmaceutically acceptable carrier. In some embodiments, the composition additionally comprises a second therapeutic agent useful in the treatment of a patient suffering from or susceptible to a disease or condition selected from epilepsy, bipolar disorder, hypoxic damage resulting from stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity.

[10] Also provided is a method of inhibiting activity at the NMDA receptor and/or blocking the voltage-dependent sodium channel of a cell of the central nervous system, comprising contacting the cell with a compound as described above.

[11] Further provided is a method of treating a patient suffering from, or susceptible to, a disease selected from epilepsy, bipolar disorder, hypoxic damage resulting from stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity, where the method comprises the step of administering to the patient in need thereof a compound or composition as described above. In some embodiments, the patient is suffering from or susceptible to a disease or condition selected from epilepsy and bipolar disorder. In some embodiments, the patient is suffering from or susceptible to Lennox-Gastaut syndrome.

[12] In some embodiments, any of the methods described herein also includes the step of co-administering to the patient in need thereof a second therapeutic agent useful to treat a disease or condition selected from epilepsy, bipolar disorder, hypoxic damage resulting from stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity.

DETAILED DESCRIPTION

Definitions

[13] The terms "ameliorate" and "treat" are used interchangeably and refer to therapeutic and/or prophylactic treatment. Both terms mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein).

[14] "Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[15] It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of felbamate will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this disclosure. See, for instance, Wada E et al., Seikagaku 1994, 66:15; Ganes LZ et al., Comp Biochem Physiol Mol Integr Physiol 1998, 119:725. In a compound of this disclosure, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of at least 3000 (45% deuterium incorporation) at each atom designated as deuterium in said compound.

[16] The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

[17] In other embodiments, a compound of this disclosure has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[18] In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless

otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition.

[19] The term "isotopologue" refers to a species that has the same chemical structure and formula as a specific compound of this invention, with the exception of the isotopic composition at one or more positions, e.g., H vs. D. Thus an isotopologue differs from a specific compound of this invention in the isotopic composition thereof.

[20] A salt of a compound of this disclosure is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

[21] The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

[22] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephathalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-

hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2- sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

[23] The compounds of the present disclosure (e.g., compounds of Formula I), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this disclosure can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present disclosure will include both racemic mixtures, and also individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers, or less than "X"% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are well known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[24] The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

[25] "D" refers to deuterium.

[26] "Stereoisomer" refers to both enantiomers and diastereomers.

[27] "Tert", "^{t}", and "t-" each refer to tertiary.

[28] "US" refers to the United States of America.

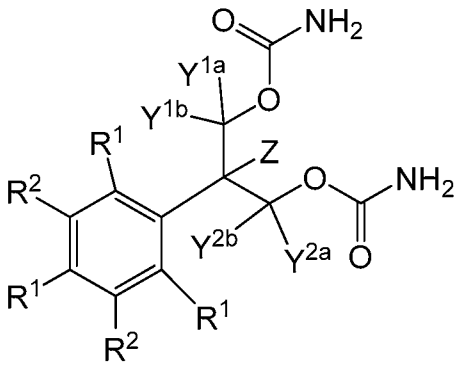
[29] "FDA" refers to Food and Drug Administration.

[30] "NDA" refers to New Drug Application.

[31] Throughout this specification, a variable may be referred to generally (e.g.,"each R") or may be referred to specifically (e.g., R^1, R^2, R^3, etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

Therapeutic Compounds

[32] The present disclosure provides a compound of Formula I:



, or a salt thereof, wherein:

each Y is independently selected from hydrogen and deuterium;

each of R^1 and R^2 is independently selected from hydrogen and deuterium;

Z is selected from hydrogen, deuterium or fluorine; and

wherein at least one Y, R or Z is deuterium.

[33] In certain embodiments of formula I:

a) when each Y^1 and each Y^2 is deuterium, at least one R or Z is not hydrogen.

b) each R is the same;

c) each Y^1 is the same; or

d) each Y^2 is the same.

[34] In a more specific embodiment a compound of formula I has the features set forth in at least two of a) through d), above.

[35] In yet another embodiment, the compound is selected from any one of the compounds (Cmpd) set forth in Table 1 (below):

Table 1: Exemplary Embodiments of Formula I

Compound	R^1	R^2	Each Y^1	Each Y^2	Z
100	D	D	D	D	D
101	D	H	D	D	D
102	H	D	D	D	D
103	H	H	D	D	D
104	D	D	H	H	D
105	D	H	H	H	D
106	H	D	H	H	D
107	H	H	H	H	D
108	D	D	D	D	F
109	D	H	D	D	F
110	H	D	D	D	F
111	H	H	D	D	F
112	D	D	H	H	F
113	D	H	H	H	F
114	H	D	H	H	F
115	D	D	D	D	H
116	D	H	D	D	H
117	H	D	D	D	H
118	D	D	H	H	H
119	D	H	H	H	H
120	H	D	H	H	H

[36] In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

[37] In another set of embodiments, the compound of Formula I is isolated or purified, e.g., the compound of Formula I is present at a purity of at least 50% by weight (e.g., at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 98.5%, 99%, 99.5% or 99.9%) of the total amount of isotopologues of Formula I present. Thus, in some embodiments, a composition comprising a compound of Formula I can include a distribution of isotopologues of the compound, provided at least 50% of the isotopologues by weight are the recited compound.

[38] In some embodiments, any position in the compound of Formula I designated as having D has a minimum deuterium incorporation of at least 45% (e.g., at least 52.5%, at least 60%, at least 67.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, at least 99%, or at least 99.5%) at the designated position(s) of the compound of Formula I. Thus, in some embodiments, a

composition comprising a compound of Formula I can include a distribution of isotopologues of the compound, provided at least 45% of the isotopologues include a D at the designated position(s).

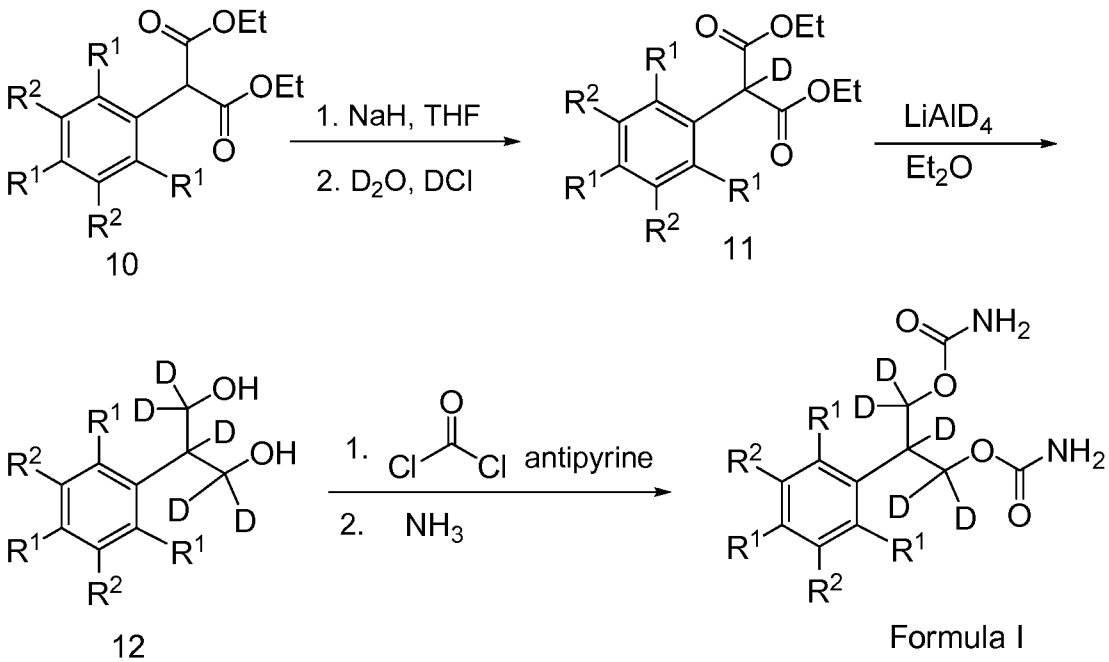
[39] In some embodiments, a compound of Formula I is "substantially free of" other isotopologues of the compound, e.g., less than 50%, less than 25%, less than 10%, less than 5%, less than 2%, less than 1%, or less than 0.5% of other isotopologues are present.

[40] The synthesis of compounds of Formula I can be readily achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance in US Patent Nos. 2,884,444, and 4,868,327; US Patent Publication No. 2006/0241298; and in Ludwig, BJ et al, J Med Chem 1969, 12:462.

[41] Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Synthesis

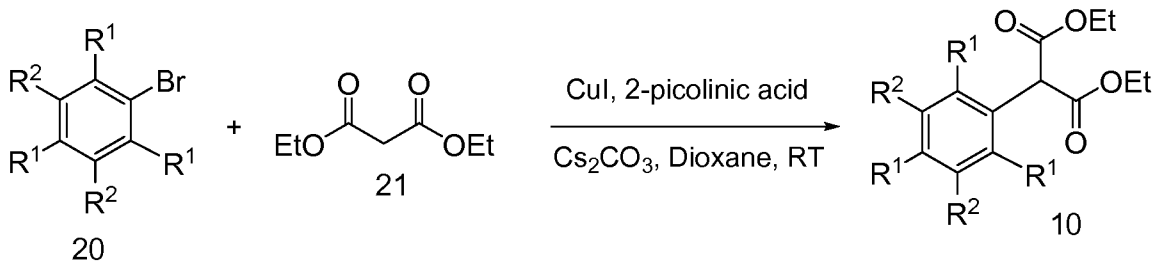
[42] Scheme 1.



[43] A convenient method for synthesizing compounds of Formula I, wherein each Y^1, each Y^2 and Z is deuterium is depicted in Scheme 1. Treatment of the appropriately deuterated diethyl phenylmalonate **10** with sodium hydride generates

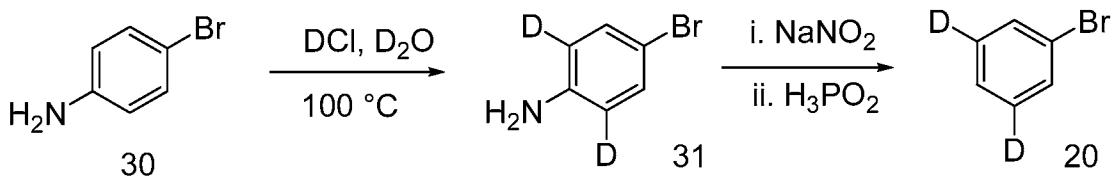
the corresponding sodium enolate which is trapped with deuterium chloride in deuterated water according to the procedure described by Matoishi, K et al., Chem Comm 2000:1519-1520 to afford the α-deuterated diethyl phenylmalonate **11**. Subsequent reduction of the diester with lithium aluminum deuteride according to the procedure described by Choi, YM et al, J Label Comp Radiopharm 1986, 23:785-789 affords the corresponding deuterated diol **12**. Using the protocol from the aforementioned reference, treatment of the deuterated diol **12** with phosgene in the presence of antipyrine followed by treatment with anhydrous ammonia gives the desired compound of Formula I. The replacement of lithium aluminum deuteride with lithium aluminum hydride in the reduction of diethyl phenylmalonate **11** to the corresponding deuterated diol **12** produces a compound of formula I, wherein each Y^1 and each Y^2 is hydrogen; and Z is deuterium.

[44] Scheme 2.



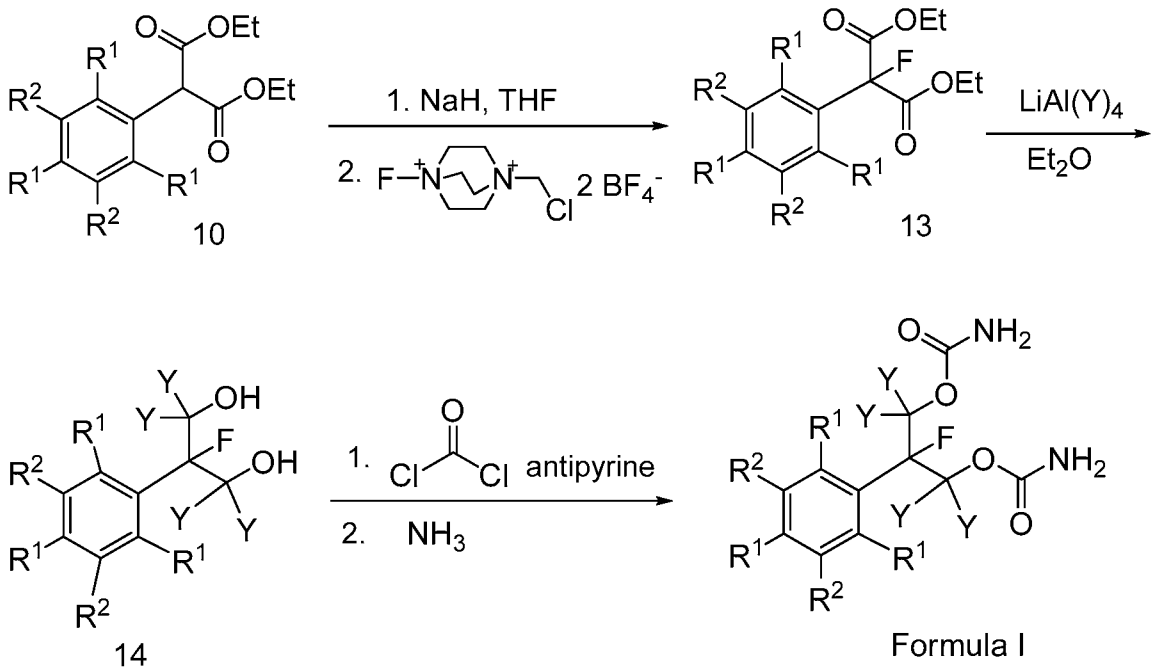
[45] The synthesis of the appropriately deuterated diethyl phenylmalonate building block **10** is shown in Scheme 2. Treatment of the appropriately deuterated bromobenzene **20** with diethylmalonate (**21**), catalytic copper(I) iodide, and 2-picolinic acid in the presence of cesium carbonate according to the procedure described by Kwong, FY et al, Org Lett 2007, 9:3469-3472 furnishes the desired deuterated intermediate **10**. Examples of appropriately deuterated bromobenzene that can be used as starting material in Scheme 2 include commercially available 2,4,6-trideutero-bromobenze, commercially available 2,3,4,5,6-pentadeutero-bromobenzene, and 3,5-dideutero-bromobenzene (see Scheme 3).

[46] Scheme 3.



[47] Treatment of commercially available 4-bromoaniline (**30**) with deuterium chloride in deuterated water at 100 °C according to the procedure described by Kuck, D et al, J Chem Soc, Perkin Trans II 1985, pp 689-696 affords the 2,6-dideutero-4-bromoaniline **31**. Using the protocol from the aforementioned paper, treatment of the dideuteroaniline with sodium nitrite in an aqueous hypophosphorous acid solution gives the desired 3,5-dideutero-bromobenzene **20**.

[48] Scheme 4.



[49] The production of a compound of formula I wherein Z is F and each Y is the same is depicted in Scheme 4. Treatment of the appropriately deuterated diethyl phenylmalonate **10** with sodium hydride in tetrahydrofuran generates the corresponding sodium enolate which is trapped with Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2.]octane bis(tetrafluoroborate)) according to the procedure described by Banks, RE et al, J Chem Soc, Chem Comm 1994, pp 343-344 to provide the α-fluorinated diethyl phenylmalonate **13**. The fluorinated compound **13** is reduced with either lithium aluminum deuteride or lithium aluminum hydride to produce a corresponding diol **14**, which is then treated with phosgene in the presence of antipyrine followed by treatment with anhydrous ammonia to produce the desired compound of Formula I.

[50] The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are

hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R^1, R^2, R^3, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

[51] Additional methods of synthesizing compounds of Formula I and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[52] Combinations of substituents and variables envisioned by this disclosure are only those that result in the formation of stable compounds.

Compositions

[53] The disclosure also provides pyrogen-free compositions comprising an effective amount of a compound of Formula I (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and an acceptable carrier. Preferably, a composition of this disclosure is formulated for pharmaceutical use ("a pharmaceutical composition"), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

[54] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or

electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[55] If required, the solubility and bioavailability of the compounds of the present disclosure in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

[56] Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this disclosure optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

[57] The pharmaceutical compositions of the disclosure include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA (17th ed. 1985).

[58] Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[59] In certain embodiments, the compound is administered orally. Compositions of the present disclosure suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

[60] In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[61] Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

[62] Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, 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. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[63] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-

butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

[64] The pharmaceutical compositions of this disclosure may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this disclosure with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[65] The pharmaceutical compositions of this disclosure may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

[66] Topical administration of the pharmaceutical compositions of this disclosure is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this disclosure include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this disclosure may also be topically applied to the

lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this disclosure.

[67] Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

[68] Thus, according to yet another embodiment, the compounds of this disclosure may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

[69] According to another embodiment, the disclosure provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

[70] According to another embodiment, the disclosure provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this disclosure. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

[71] According to another embodiment, the disclosure provides an implantable medical device coated with a compound or a composition comprising a compound of this disclosure, such that said compound is therapeutically active.

[72] According to another embodiment, the disclosure provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this disclosure, such that said compound is released from said device and is therapeutically active.

[73] Where an organ or tissue is accessible because of removal from the patient, such organ or tissue may be bathed in a medium containing a composition of this disclosure, a composition of this disclosure may be painted onto the organ, or a composition of this disclosure may be applied in any other convenient way.

[74] In another embodiment, a composition of this disclosure further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as felbamate. Such agents include those indicated as being useful in combination with felbamate, including but not limited to, those described in WO 2002003915.

[75] Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from epilepsy, bipolar disorder, hypoxic damage resulting from stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity.

[76] In one embodiment, the disclosure provides separate dosage forms of a compound of this disclosure and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

[77] In the pharmaceutical compositions of the disclosure, the compound of the present disclosure is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

[78] The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., (1966) Cancer Chemother. Rep 50: 219. Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

[79] In one embodiment, an effective amount of a compound of this disclosure can range from about 3 mg to about 9000 mg per treatment. In a more specific embodiment the range is from about 30 to 4500 mg, or from about 60 to 1800 mg, or most specifically from about 300 to 900 mg per treatment. Treatment typically is administered from two to four times daily.

[80] Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for felbamate.

[81] For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. *See*, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

[82] It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this disclosure. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this disclosure to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this disclosure, synergistic improvements in efficacy, improved ease of

administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

[83] In another embodiment, the disclosure provides a method of inhibiting activity at an NMDA receptor and/or blocking a voltage-dependent sodium channel in a cell of the central nervous system (e.g., in a cell of the central nervous system of a mammal), comprising contacting such a cell with one or more compounds of Formula I herein. A mammal can be any mammal, including humans, monkeys, horses, cows, pigs, sheep, dogs, cats, rats, and mice.

[84] According to another embodiment, the disclosure provides a method of treating a patient suffering from, or susceptible to, a disease that is beneficially treated by felbamate comprising the step of administering to said patient an effective amount of a compound or a composition of this disclosure. Such diseases are well known in the art and are disclosed in, but not limited to the diseases disclosed in the following patents and published applications: US 4978680, US 5055489, US 5082861, WO 2002003915, and EP 0531105. Such diseases include, but are not limited to, epilepsy, bipolar disorder, hypoxic damage resulting from stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity.

[85] In one particular embodiment, the method of this disclosure is used to treat a patient suffering from or susceptible to a disease or condition selected from epilepsy, in particular for Lennox-Gastaut syndrome, and for bipolar disorder.

[86] In another particular embodiment, the method of this disclosure is used to treat a patient suffering from or susceptible to a disease or condition selected from epilepsy, and in particular for Lennox-Gastaut syndrome.

[87] Methods delineated herein also include those wherein the patient is identified as in need of a particular stated treatment. Identifying a patient in need of such treatment can be in the judgment of a patient or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[88] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to said patient one or more second therapeutic agents. The choice of second therapeutic agent may be any second therapeutic agent known to be useful for co-administration with felbamate. The choice of second therapeutic

agent may be also dependent upon the particular disease or condition to be treated.

[89] The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this disclosure as part of a single dosage form (such as a composition of this disclosure comprising a compound of the disclosure and a second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this disclosure. In such combination therapy treatment, both the compounds of this disclosure and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this disclosure, comprising both a compound of the disclosure and a second therapeutic agent, to a patient does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this disclosure to said patient at another time during a course of treatment.

[90] Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

[91] In one embodiment of the disclosure, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this disclosure is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this disclosure is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

[92] In yet another aspect, the disclosure provides the use of a compound of Formula I alone or together with one or more of a second therapeutic agent in the manufacture of a medicament, either as a single composition or as separate dosage

forms, for treatment or prevention in a patient of a disease, disorder or symptom set forth above. Another aspect of the disclosure is a compound of Formula I for use in the treatment or prevention in a patient of a disease, disorder or symptom thereof delineated herein.

Diagnostic Methods and Kits

[93] The compounds and compositions of this disclosure are also useful as reagents in methods for determining the concentration or amount of felbamate in solution or biological sample such as plasma, in methods for examining the metabolism of felbamate, and for other analytical studies.

[94] According to one embodiment, the disclosure provides a method of determining the concentration, in a solution or a biological sample, of felbamate, comprising the steps of:

a) adding a known concentration of a compound of Formula I to the solution of biological sample;

b) subjecting the solution or biological sample to a measuring device that distinguishes felbamate from a compound of Formula I;

c) calibrating the measuring device to correlate the detected quantity of the compound of Formula I with the known concentration of the compound of Formula I added to the biological sample or solution; and

d) measuring the quantity of felbamate in the biological sample with said calibrated measuring device; and

e) determining the concentration of felbamate in the solution of sample using the correlation between detected quantity and concentration obtained for a compound of Formula I.

[95] Measuring devices that can distinguish felbamate from the corresponding compound of Formula I include any measuring device that can distinguish between two compounds that differ from one another in isotopic abundance. Exemplary measuring devices include a mass spectrometer, NMR spectrometer, or IR spectrometer.

[96] In another embodiment, a method for determining the amount of felbamate in a solution or a biological sample is provided, comprising:

a) adding a known amount of a compound of Formula I to the solution or biological sample;

b) detecting at least one signal for a compound of Formula I and at least one signal for felbamate in a measuring device that is capable of distinguishing the two compounds;

c) correlating the at least one signal detected for a compound of Formula I with the known amount of the compound of Formula I added to the solution or the biological sample; and

d) determining the amount of felbamate in the solution or biological sample using the correlation between the at least one signal detected of the compound of Formula I and the amount added to the solution or biological sample of a compound of Formula I.

[97] In another embodiment, the disclosure provides a method of evaluating the metabolic stability of a compound of Formula I comprising the steps of contacting the compound of Formula I with a metabolizing enzyme source for a period of time and comparing the amount of the compound of Formula I with the metabolic products of the compound of Formula I after the period of time.

[98] In a related embodiment, the disclosure provides a method of evaluating the metabolic stability of a compound of Formula I in a patient following administration of the compound of Formula I. This method comprises the steps of obtaining a blood, saliva, tissue, serum, urine or feces sample from the patient at a period of time following the administration of the compound of Formula I to the subject; and comparing the amount of the compound of Formula I with the metabolic products of the compound of Formula I in the blood, saliva, tissue, serum, urine or feces sample.

[99] The present disclosure also provides kits for use to treat epilepsy, in particular for Lennox-Gastaut syndrome, and for bipolar disorder. These kits comprise (a) a pharmaceutical composition comprising a compound of Formula I or a salt thereof, wherein said pharmaceutical composition is in a container; and (b) instructions describing a method of using the pharmaceutical composition to treat epilepsy, in particular for Lennox-Gastaut syndrome, and for bipolar disorder.

[100] The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition. Examples include bottles, ampules, divided or multi-chambered holders bottles, wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as

known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. In one embodiment, the container is a blister pack.

[101] The kits of this disclosure may also comprise a device to administer or to measure out a unit dose of the pharmaceutical composition. Such device may include an inhaler if said composition is an inhalable composition; a syringe and needle if said composition is an injectable composition; a syringe, spoon, pump, or a vessel with or without volume markings if said composition is an oral liquid composition; or any other measuring or delivery device appropriate to the dosage formulation of the composition present in the kit.

[102] In certain embodiment, the kits of this disclosure may comprise in a separate vessel of container a pharmaceutical composition comprising a second therapeutic agent, such as one of those listed above for use for co-administration with a compound of this disclosure.

Evaluation of Metabolic Stability

[103] Certain *in vitro* liver metabolism studies have been described previously in the following references, each of which is incorporated herein in its entirety: Obach, RS, Drug Metab Disp, 1999, 27:1350; Houston, JB et al., Drug Metab Rev, 1997, 29:891; Houston, JB, Biochem Pharmacol, 1994, 47:1469; Iwatsubo, T et al., Pharmacol Ther, 1997, 73:147; and Lave, T, et al., Pharm Res, 1997, 14:152.

[104] *Microsomal Assay:* The metabolic stability of test compounds of Formula I are tested using pooled liver microsomal incubations. Full scan LC-MS analysis is then performed to detect major metabolites of the test compounds. Samples of the test compounds, exposed to pooled human liver microsomes, are analyzed using HPLC-MS (or MS/MS) detection. For determining metabolic stability, multiple reaction monitoring (MRM) is used to measure the disappearance of the test compounds. For

metabolite detection, Q1 full scans are used as survey scans to detect the major metabolites.

[105] *Experimental Procedures:* Human liver microsomes are obtained from a commercial source (e.g., XenoTech, LLC (Lenexa, KS)). The incubation mixtures are prepared as follows:

Reaction Mixture Composition

Liver Microsomes	0.5-2.0 mg/mL
NADPH	1 mM
Potassium Phosphate, pH 7.4	100 mM
Magnesium Chloride	10 mM
Test Compound	0.1-1 μM.

[106] *Incubation of Test Compounds with Liver Microsomes:* The reaction mixture, minus cofactors, is prepared. An aliquot of the reaction mixture (without cofactors) is incubated in a shaking water bath at 37°C for 3 minutes. Another aliquot of the reaction mixture (without cofactors) is prepared as the negative control. The test compound is added into both the reaction mixture and the negative control at a final concentration of 1 μM. An aliquot of the reaction mixture (without cofactors) is prepared as a blank control, by the addition of plain organic solvent (no test compound added). The reaction is initiated by the addition of cofactors (not added to the negative controls), and then incubated in a shaking water bath at 37°C. Aliquots (200 μL) are withdrawn in triplicate at multiple time points (e.g., 0, 15, 30, 60, and 120 minutes) and combined with 800 μL of ice-cold 50/50 acetonitrile/dH_2O to terminate the reaction. The positive controls, testosterone and propranolol, as well as felbamate, are each run simultaneously with the test compounds in separate reactions.

[107] All samples are analyzed using LC-MS (or MS/MS). An LC-MRM-MS/MS method is used to evaluate metabolic stability. Also, Q1 full scan LC-MS methods are performed on the blank matrix and the test compound incubation samples. The Q1 scans serve as survey scans to identify any sample unique peaks that might represent possible metabolites. The masses of these potential metabolites can be determined from the Q1 scans.

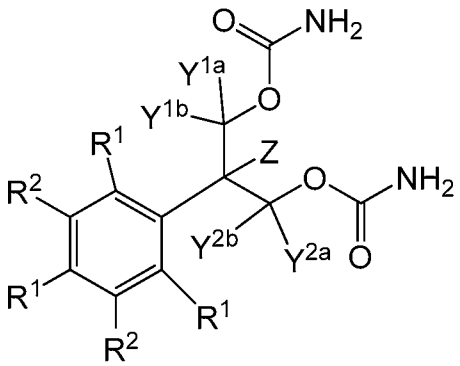
[108] *SUPERSOMES™ Assay.* Various human cytochrome P450-specific SUPERSOMES™ are purchased from GenTest (Woburn, MA, USA). A 1.0 mL reaction mixture containing 25 pmole of SUPERSOMES™, 2.0 mM NADPH, 3.0 mM MgCl, and 1 μM of a compound of Formula I in 100 mM potassium phosphate

buffer (pH 7.4) is incubated at 37 °C in triplicate. Positive controls contain 1 μM of felbamate instead of a compound of formula I. Negative controls used Control Insect Cell Cytosol (insect cell microsomes that lacked any human metabolic enzyme) purchased from GenTest (Woburn, MA, USA). Aliquots (50 μL) are removed from each sample and placed in wells of a multi-well plate at various time points (e.g., 0, 2, 5, 7, 12, 20, and 30 minutes) and to each aliquot is added 50μL of ice cold acetonitrile with 3μM haloperidol as an internal standard to stop the reaction.

[109] Plates containing the removed aliquots are placed in -20 °C freezer for 15 minutes to cool. After cooling, 100 μL of deionized water is added to all wells in the plate. Plates are then spun in the centrifuge for 10 minutes at 3000 rpm. A portion of the supernatant (100 μL) is then removed, placed in a new plate and analyzed using Mass Spectrometry.

[110] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present disclosure and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the disclosure. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WE CLAIM:

1. A compound of Formula I:  , or a pharmaceutically acceptable salt thereof, wherein:

each Y is independently selected from hydrogen and deuterium;

each of R^1 and R^2 is independently selected from hydrogen and deuterium;

Z is selected from hydrogen, deuterium or fluorine; and

at least one Y, R, or Z is deuterium.

2. The compound of claim 1, wherein when each Y is deuterium, at least one R or Z is not hydrogen.

3. The compound of claim 1 or 2, wherein each R is the same.

4. The compound of any one of claims 1 to 3, wherein each Y^1 is the same.

5. The compound of any one of claims 1 to 4, wherein each Y^2 is the same.

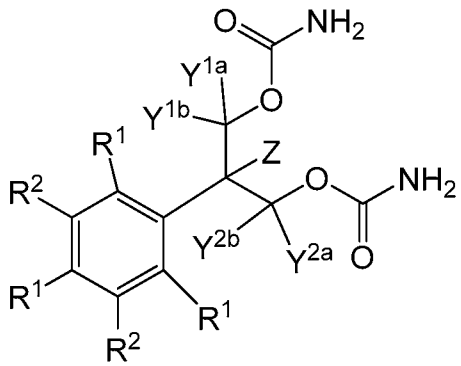
6. The compound of claim 1, wherein each Y is the same, the compound being selected from any one of the compounds set forth in the table below:

Compound	R^1	R^2	Each Y	Z
100	D	D	D	D
101	D	H	D	D
102	H	D	D	D
103	H	H	D	D
104	D	D	H	D
105	D	H	H	D
106	H	D	H	D
107	H	H	H	D
108	D	D	D	F
109	D	H	D	F
110	H	D	D	F

Compound	R^1	R^2	Each Y	Z
111	H	H	D	F
112	D	D	H	F
113	D	H	H	F
114	H	D	H	F
115	D	D	D	H
116	D	H	D	H
117	H	D	D	H
118	D	D	H	H
119	D	H	H	H
120	H	D	H	H

7. The compound of any one of claims 1 to 6, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

8. A pyrogen-free composition comprising

c. a compound of Formula I: 

, or a pharmaceutically acceptable salt thereof, wherein:

each Y is independently selected from hydrogen and deuterium;

each of R^1 and R^2 is independently selected from hydrogen and deuterium;

Z is selected from hydrogen, deuterium or fluorine;

at least one Y, R or Z is deuterium; and

d. an acceptable carrier.

9. The composition of claim 8 formulated for pharmaceutical administration, wherein the carrier is a pharmaceutically acceptable carrier.

10. The composition of claim 9, additionally comprising a second therapeutic agent useful in the treatment of a patient suffering from or susceptible to a disease or condition selected from epilepsy, bipolar disorder, hypoxic damage resulting from

stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity.

11. A method of inhibiting activity at the NMDA receptor and/or blocking the voltage-dependent sodium channel of a cell of the central nervous system, comprising contacting the cell with a compound of claim 1.

12. A method of treating a patient suffering from, or susceptible to, a disease selected from epilepsy, bipolar disorder, hypoxic damage resulting from stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity, comprising the step of administering to the patient in need thereof a composition of claim 9.

13. The method of claim 12, wherein the patient is suffering from or susceptible to a disease or condition selected from epilepsy and bipolar disorder.

14. The method of claim 13, wherein the patient is suffering from or susceptible to Lennox-Gastaut syndrome.

15. The method of any one of claims 12 to 14, comprising the step of co-administering to the patient in need thereof a second therapeutic agent useful to treat a disease or condition selected from epilepsy, bipolar disorder, hypoxic damage resulting from stroke or other ischemic event, neuropsychopharmacological disorders and neurodegenerative diseases resulting from excessive activation of the N-methyl-D-aspartate receptor complex, and obesity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/040369

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C271/12 C07C271/14 A61K31/27 A61P25/08

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)
C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/056827 A (UNIV VIRGINIA [US]; MACDONALD TIMOTHY L [US]) 25 July 2002 (2002-07-25) felbamate (page 1-3, scheme 1), example 1, page 23 (lines 29-32), page 24 (lines 1-4)	1-15
X	WO 01/85149 A (UNIV VIRGINIA [US]; MACDONALD TIMOTHY L [US]) 15 November 2001 (2001-11-15) example 1, page 27 (lines 9-15), felbamate (page 2, lines 1-8), fluoro felbamate 12 (page 33),	1-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2009	07/08/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bueno Torres, Pilar

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/040369

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	YONG M. CHOI ET AL: "Synthesis of deuterium-labeled felbamate from diethyl phenylmalonate" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS, vol. 23, no. 7, 1986, pages 785-789, XP002538611 cited in the application felbamate and felbamate-d4	1-15
X	ROBERT L. WOLEN: "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence" J. CLIN. PHARMACOL, vol. 26, 1986, pages 419-424, XP009120629 the whole document	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

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