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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING DEUTERIUM-ENRICHED PERILLYL ALCOHOL, ISOPERILLYL ALCOHOL AND DERIVATIVES THEREOF

(57) Abstract: The present invention, provides for a deuterium-enriched monoterpene or sesquiterpene such as perillyl alcohol, or a deuterium-enriched isomer or analog of monoterpenes or sesquiterpenes, such as isoperillyl alcohol. The present invention also provides for a deuterium-enriched derivative of a monoterpene or sesquiterpene, such as a perillyl alcohol carbamate, or a deuterium-enriched derivative of an isomer or analog of a monoterpene or sesquiterpene, such as an isoperillyl alcohol carbamate. The deuterium-enriched derivative may be perillyl alcohol or isoperillyl alcohol conjugated with a therapeutic agent such as a chemotherapeutic agent. The present invention also provides for a method of treating a disease such as cancer, comprising the step of delivering to a patient a therapeutically effective amount of a deuterium-enriched compound.

PHARMACEUTICAL COMPOSITIONS COMPRISING DEUTERIUM-ENRICHED PERILLYL ALCOHOL, ISO-PERILLYL ALCOHOL AND DERIVATIVES THEREOF

Cross Reference to Related Applications

This application claims priority to U.S. Provisional Application No. 61/562,105 (filed on November 21, 2011), and U.S. Application No. 13/566,731 (filed on August 3, 2012), each of which is incorporated herein by reference in its entirety.

Field of the Invention

The present invention relates to deuterium-enriched perillyl alcohol (POH), deuterium-enriched isoperillyl alcohol (iso-POH) and derivatives thereof.

Background of the Invention

Malignant gliomas, the most common form of central nervous system (CNS) cancers, are currently considered essentially incurable. Among the various malignant gliomas, anaplastic astrocytomas (Grade III) and glioblastoma multiforme (GBM; Grade IV) have an especially poor prognosis due to their aggressive growth and resistance to currently available therapies. The present standard of care for malignant gliomas consists of surgery, ionizing radiation, and chemotherapy. Despite recent advances in medicine, the past 50 years have not seen any significant improvement in prognosis for malignant gliomas. Wen et al. Malignant gliomas in adults, New England J Med., 359: 492-507, 2008. Stupp et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, New England J Med., 352: 987-996, 2005.

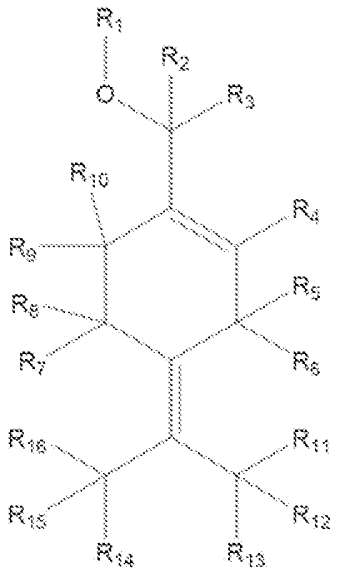
The poor response of tumors, including malignant gliomas, to various types of chemotherapeutic agents is often due to intrinsic drug resistance. Additionally, acquired resistance of initially well-responding tumors and unwanted side effects are other problems that frequently thwart long-term treatment using chemotherapeutic agents. Perillyl alcohol (POH), a naturally occurring monoterpene, has been suggested to be an effective agent against a variety of cancers, including CNS cancer, breast cancer, pancreatic cancer, lung cancer, melanomas and colon cancer. Gould, M., Cancer chemoprevention and therapy by monoterpenes, Environ. Health Perspect., 1997 June; 105 (Suppl 4): 977–979. Hybrid molecules containing both perillyl alcohol and retinoids were prepared to increase apoptosis-inducing activity. Das et al., Design

and synthesis of potential new apoptosis agents: hybrid compounds containing perillyl alcohol and new constrained retinoids, Tetrahedron Letters 2010, 51, 1462–1466.

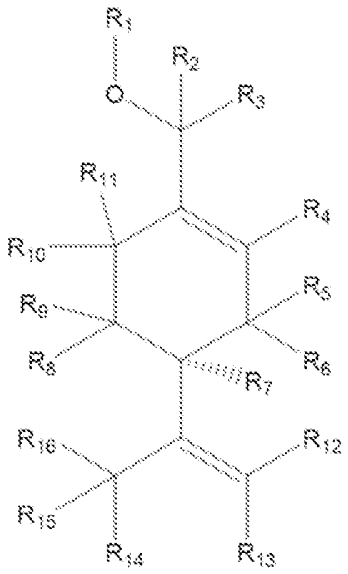
However, POH is rapidly metabolized. In order to improve performance over perillyl alcohol and its derivatives, e.g., using a lower dose, there is a need to prepare deuterated forms of perillyl alcohol, including isomers or analogs, such as perrillyl alcohol or isoperillyl alcohol conjugated with other therapeutic agents, and use this material in the treatment of cancers such as malignant gliomas, as well as other brain disorders such as Parkinson's and Alzheimer's disease.

Summary

The present disclosure provides for a deuterium-enriched compound of Formula I or Formula II



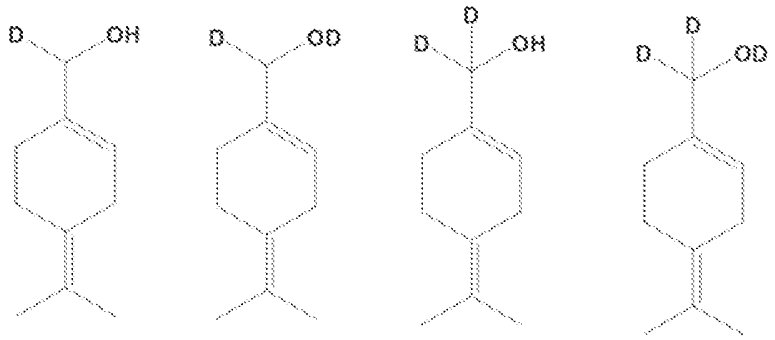
Formula I

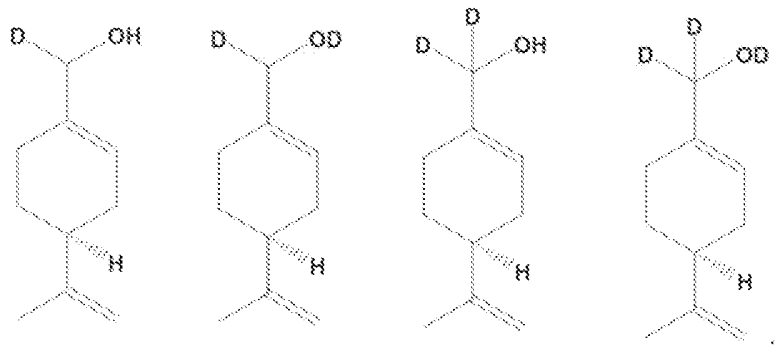


Formula II

or a pharmaceutically acceptable salt 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} and R_{16} are independently selected from the group consisting of hydrogen-1 and deuterium, 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} and R_{16} is deuterium.

For example, the deuterium-enriched compound may be the one of the following.





The present disclosure provides for a deuterium-enriched perillyl alcohol or isoperillyl alcohol.

The present deuterium-enriched compounds may be conjugated with a therapeutic agent to form a carbamate. The present disclosure also provides for a deuterium-enriched perillyl alcohol carbamate or isoperillyl alcohol carbamate. For example, perillyl alcohol or isoperillyl alcohol is conjugated with a therapeutic agent to form a carbamate. The therapeutic agent may be a chemotherapeutic agent, including, but not limited to, a DNA alkylating agent, a topoisomerase inhibitor, an endoplasmic reticulum stress inducing agent, a platinum compound, an antimetabolite, an enzyme inhibitor, and a receptor antagonist. For example, the therapeutic agent can be dimethyl celocoxib (DMC), temozolomide (TMZ) or rolipram.

In the deuterium-enriched compound, the abundance of deuterium may be at least about 10%, at least about 20% or at least about 30%.

The present disclosure also provides for a pharmaceutical composition comprising the present deuterium-enriched compound. The pharmaceutical composition may further comprise a chemotherapeutic agent selected from the group consisting of a DNA alkylating agent, a topoisomerase inhibitor, an endoplasmic reticulum stress inducing agent, a platinum compound, an antimetabolite, an enzyme inhibitor, and a receptor antagonist. For example, the pharmaceutical composition may further comprise a therapeutic agent such as dimethyl celocoxib (DMC), temozolomide (TMZ) and rolipram.

The present disclosure further provides for a method for treating a disease in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of a deuterium-enriched perillyl alcohol, a deuterium-enriched isoperillyl alcohol, a deuterium-enriched perillyl alcohol carbamate, and/or a deuterium-enriched isoperillyl alcohol carbamate.

The present disclosure provides for a method for treating a disease in a mammal, comprising the step of administering to the mammal a pharmaceutical composition disclosed in the present disclosure.

The methods may further comprise the step of treating the mammal with radiation, and/or the step of administering to the mammal a chemotherapeutic agent. The pharmaceutical composition or deuterium-enriched compound may be administered before, during or after radiation and/or the administration of a chemotherapeutic agent. The chemotherapeutic agent may be a DNA alkylating agent, a topoisomerase inhibitor, an endoplasmic reticulum stress inducing agent, a platinum compound, an antimetabolite, an enzyme inhibitor, or a receptor antagonist. For example, the chemotherapeutic agent may be dimethyl celocoxib (DMC), temozolomide (TMZ) or rolipram.

The disease may be cancer, such as a tumor of the nervous system (e.g., glioblastoma).

The pharmaceutical composition or deuterium-enriched compound may be administered by inhalation, intranasally, orally, intravenously, subcutaneously or intramuscularly.

The pharmaceutical composition or deuterium-enriched compound may be administered using a nasal delivery device, such as an intranasal inhaler, an intranasal spray device, an atomizer, a nebulizer, a metered dose inhaler (MDI), a pressurized dose inhaler, an insufflator, a unit dose container, a pump, a dropper, a squeeze bottle and a bi-directional device.

Detailed Description of the Invention

The present invention provides for deuterium-enriched compounds and pharmaceutical compositions comprising the deuterium-enriched compounds. Specifically, the present invention provides for deuterium-enriched monoterpenes or sesquiterpenes (e.g., deuterium-enriched perillyl alcohol) and deuterium-enriched isomers or analogs of monoterpenes or sesquiterpenes (e.g., deuterium-enriched isoperillyl alcohol).

The present invention also provides for deuterium-enriched derivatives of monoterpenes or sesquiterpenes, such as a deuterium-enriched perillyl alcohol derivative. For example, the deuterium-enriched perillyl alcohol derivative may be a deuterium-enriched perillyl alcohol carbamate. The perillyl alcohol derivative may be perillyl alcohol conjugated with a therapeutic agent such as a chemotherapeutic agent.

The present invention further provides for deuterium-enriched derivatives of isomers or analogs of monoterpenes or sesquiterpenes, such as a deuterium-enriched isoperillyl alcohol derivative. For example, the deuterium-enriched isoperillyl alcohol derivative may be a deuterium-enriched isoperillyl alcohol carbamate. The isoperillyl alcohol derivative may be isoperillyl alcohol conjugated with a therapeutic agent such as a chemotherapeutic agent.

Also encompassed by the present invention is a pharmaceutical composition comprising a therapeutically effective amount of a deuterium-enriched compound of the present invention (or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier.

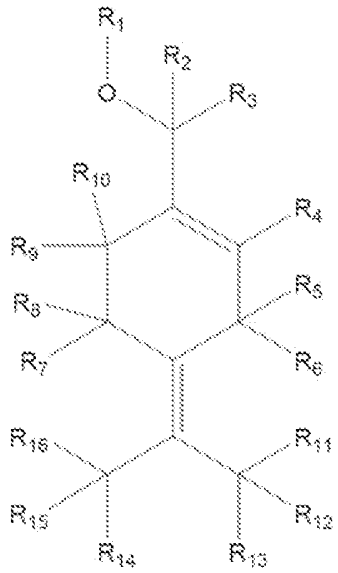
The invention provides for methods of using the deuterium-enriched compounds or the pharmaceutical compositions to treat a disease, such as cancer or other nervous system disorders. The compounds or pharmaceutical compositions of the present invention may be administered alone, or in combination with radiation, surgery or chemotherapeutic agents. The deuterium-enriched molecule may also be co-administered with antiviral agents, anti-inflammatory agents or antibiotics. The agents may be administered concurrently or sequentially. The compounds of the present invention can be administered before, during or after the administration of the other active agent(s).

One of ordinary skill in the art recognizes that in all chemical compounds with an H atom, the H atom represents a mixture of ^{1}H (hydrogen-1, protium) and D (deuterium, hydrogen-2, ^{2}H), with about 0.015% being D. Thus, a deuterium-enriched compound (or a deuterated

compound) has a level of deuterium greater than its natural abundance of 0.015%. As used herein, all percentages given for the abundance of deuterium are mole percentages.

The isomer or analog of monoterpene or sesquiterpene can be an isoperillyl alcohol (iso-POH). Isoperillyl alcohols include any isomers or analogs of perillyl alcohol. In one embodiment, the isoperillyl alcohol is (4-isopropylidene cyclohex-1-enyl)methanol. Other examples of isoperillyl alcohol include, but are not limited to, (4-isopropyl cyclohexa-1,3-dienyl)methanol, (4-isopropyl cyclohexa-1,4-dienyl)methanol, (4-isopropylphenyl)methanol and (4-isopropenylphenyl)methanol.

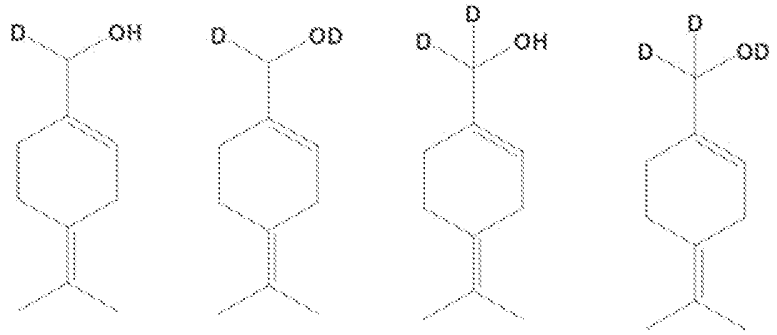
The present invention provides for deuterium-enriched isoperillyl alcohol where the compound is enriched with deuterium in at least one position. In one embodiment, the deuterium-enriched isoperillyl alcohol is represented by Formula I shown below:



Formula I

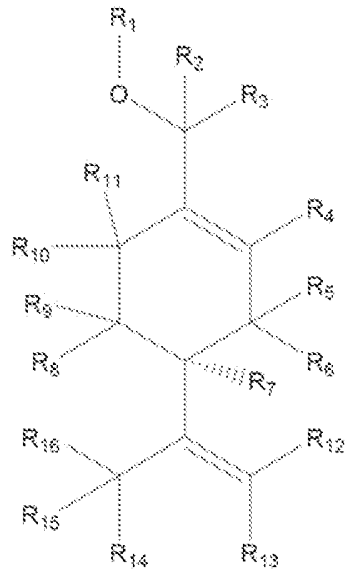
or a pharmaceutically acceptable salt thereof; wherein: R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} are independently selected from the group consisting of hydrogen-1 (^1H) and deuterium; and at least one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15} and R_{16} is deuterium.

Non-limiting examples of the deuterium-enriched isoperillyl alcohol are illustrated as follows.



The deuterium-enriched isoperillyl alcohol may be prepared by oxidation of commercially sourced perillyl alcohol or isoperillyl alcohol followed by reduction of the oxidized intermediates using deuterium-enriched hydride reducing agents or by use of deuterohydrogen gas with a suitable catalyst or by other means.

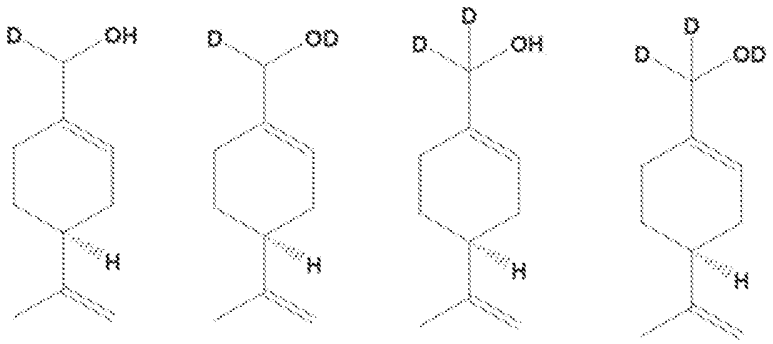
The present invention provides for deuterium-enriched perillyl alcohol, wherein the compound is enriched with deuterium in at least one position. In one embodiment, the deuterium-enriched perillyl alcohol is represented by Formula II, shown below.



Formula II

or a pharmaceutically acceptable salt 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} and R_{16} are independently selected from the group consisting of hydrogen-1 (^{1}H) and deuterium; 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} and R_{16} is deuterium.

Non-limiting examples of the deuterium-enriched perillyl alcohol are illustrated as follows.



The term "is/are deuterium," when used to describe a given position in a molecule such as 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} and R_{16} 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 greater than its natural abundance of 0.015%.

The term "abundance of deuterium" herein refers to the mole percentage of incorporation of deuterium (D, or ^{2}H) at a given position in a molecule in the place of hydrogen. For example, the abundance of deuterium of about 6% at a given position means that about 6% of molecules in a given sample contain deuterium at the specified position.

The abundance of deuterium in the present deuterium-enriched compound may be at least about 1%, at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, about 0.5% to about 100% , about 1% to about 100%, about 5% to about 100%, about 6% to about 100%, about 7% to about 100%, about 10% to about 100%, about 20% to about 100%, about 30% to about 100%, about 40% to about 100%, about 50% to about 100%, about 60% to about 100%, about 70% to about 100%, about 80% to about 100%, or about 90% to about 100%.

Deuterium enrichment can be determined using analytical methods, such as mass spectrometry, nuclear magnetic resonance spectroscopy and infrared spectrometry. In one embodiment, deuterium enrichment is determined by ^{1}H NMR.

The deuterium-enriched perillyl alcohol of the present invention may be synthesized with deuterium incorporated in place of hydrogen atoms. For example, the deuterium may be incorporated in place of hydrogen atoms at the carbinol side chain where metabolic degradation takes place *in vivo*. The deuterium atoms retard or slow down the metabolic processes when compared with the rate of metabolism for conventional perillyl alcohol or isoperillyl alcohol. Without being limited to any specific physiologic mechanism, it is believed that this slow-down is due to the kinetic isotope effects at the active site of perillyl alcohol dehydrogenase enzyme. Deuterium can also be incorporated at a number of different centers in the molecule. In an embodiment, deuterium is incorporated at the carbinol moiety where 1, 2 or 3 deuterium atoms can be incorporated in place of hydrogen atoms to give any of the isotopic analogs of perillyl alcohol or isoperillyl alcohol.

Because of its slower metabolism, the deuterated forms of perillyl alcohol or isoperillyl alcohol will demonstrate significant improvement in the therapeutic effectiveness as compared with conventional non-deuterated material.

The deuterium-enriched compounds described herein may contain one or more deuterium atoms. The compounds may be partially or fully deuterated. Any chemical compound described herein may be deuterium-enriched.

Monoterpenes include terpenes that consist of two isoprene units. Monoterpenes may be linear (acyclic) or contain rings. Derivatives of monoterpenoids are also encompassed by the present invention. Monoterpenoids may be produced by biochemical modifications such as oxidation or rearrangement of monoterpenes. Examples of monoterpenes and monoterpenoids include, perillyl alcohol (S(-)) and (R(+)), ocimene, myrcene, geraniol, citral, citronellol, citronellal, linalool, pinene, terpineol, terpinen, limonene, terpinenes, phellandrenes, terpinolene, terpinen-4-ol (or tea tree oil), pinene, terpineol, terpinen; the terpenoids such as *p*-cymene which

is derived from monocyclic terpenes such as menthol, thymol and carvacrol; bicyclic monoterpenoids such as camphor, borneol and eucalyptol.

Monoterpenes may be distinguished by the structure of a carbon skeleton and may be grouped into acyclic monoterpenes (e.g., myrcene, (Z)- and (E)-ocimene, linalool, geraniol, nerol, citronellol, myrcenol, geranial, citral a, neral, citral b, citronellal, etc.), monocyclic monoterpenes (e.g., limonene, terpinene, phellandrene, terpinolene, menthol, carveol, etc.), bicyclic monoterpenes (e.g., pinene, myrtenol, myrtenal, verbanol, verbanon, pinocarveol, carene, sabinene, camphene, thujene, etc.) and tricyclic monoterpenes (e.g. tricyclene). See Encyclopedia of Chemical Technology, Fourth Edition, Volume 23, page 834-835.

A specific example of a monoterpene is perillyl alcohol (POH).

Sesquiterpenes of the present invention include terpenes that consist of three isoprene units. Sesquiterpenes may be linear (acyclic) or contain rings. Derivatives of sesquiterpenoids are also encompassed by the present invention. Sesquiterpenoids may be produced by biochemical modifications such as oxidation or rearrangement of sesquiterpenes. Examples of sesquiterpenes include farnesol, farnesal, farnesylic acid and nerolidol. PCT Application Nos. PCT/US2011/027051 and PCT/US2011/049392. U.S. Application No. 13/040,059. All these applications are incorporated herein by reference in their entirety.

The present invention also provides for deuterium-enriched derivatives of monoterpenes or sesquiterpenes, such as a deuterium-enriched perillyl alcohol derivative. For example, the deuterium-enriched perillyl alcohol derivative may be a deuterium-enriched perillyl alcohol carbamate. The perillyl alcohol derivative may be perillyl alcohol conjugated with a therapeutic agent such as a chemotherapeutic agent.

The present invention further provides for deuterium-enriched derivatives of isomers or analogs of monoterpenes or sesquiterpenes, such as a deuterium-enriched isoperillyl alcohol derivative. For example, the deuterium-enriched isoperillyl alcohol derivative may be a deuterium-enriched isoperillyl alcohol carbamate. The perillyl alcohol derivative may be isoperillyl alcohol conjugated with a therapeutic agent such as a chemotherapeutic agent.

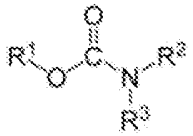
The derivatives may be deuterated at any desired atom position, including the atom positions of perillyl alcohol or isoperillyl alcohol, as well as the atom positions of the therapeutic agent conjugated with the perillyl alcohol or isoperillyl alcohol.

A deuterium-enriched compound can be prepared by, e.g., exchanging hydrogens with deuterium, or synthesizing the compound with deuterium-enriched starting materials or intermediates. In one embodiment, deuterium can be introduced by deuterium-containing reagents including, but not limited to, lithium aluminium deuteride, deuterium gas or other reagents. In another embodiment, depending on the desired sites of deuteration, deuterium from D_2O can be exchanged directly into finished drug compounds or into reagents that are used to synthesize drug molecules.

The deuterated derivatives of monoterpene or sesquiterpene (or deuterated derivatives of isomers or analogs of monoterpene or sesquiterpene) include, but are not limited to, carbamates, esters, ethers, alcohols and aldehydes of the monoterpene or sesquiterpene (or of isomers or analogs of monoterpene or sesquiterpene). The present invention also provides for derivatives and conjugates of a deuterium enriched perillyl alcohol or isoperillyl alcohol.

Derivatives include, but are not limited to, carbamates, esters, ethers, alcohols and aldehydes of a monoterpene or sesquiterpene (e.g., POH), or of the isomer or analog of a monoterpene or sesquiterpene (e.g., iso-POH). Alcohols may be derivatized to carbamates, esters, ethers, aldehydes or acids.

Carbamates refer to a class of chemical compounds sharing the functional group

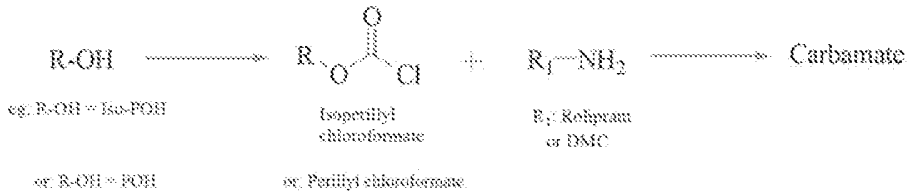


based on a carbonyl group flanked by an oxygen and a nitrogen. R^1, R^2 and R^3 can be a group such as alkyl, aryl, etc., which can be substituted. The R groups on the nitrogen and the oxygen may form a ring. R^1-OH may be a monoterpene, e.g., POH or iso-POH. The R^2-N-R^3 moiety may be a therapeutic agent.

Carbamates may be synthesized by reacting isocyanate and alcohol, or by reacting chloroformate with amine. Carbamates may be synthesized by reactions making use of phosgene or phosgene equivalents. For example, carbamates may be synthesized by reacting phosgene gas, diphosgene or a solid phosgene precursor such as triphosgene with two amines or an amine and an alcohol. Carbamates (also known as urethanes) can also be made from reaction of a urea

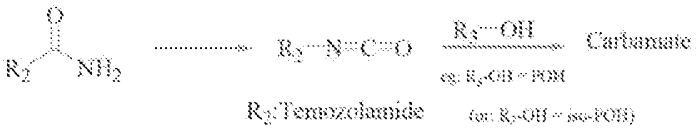
intermediate with an alcohol. Dimethyl carbonate and diphenyl carbonate are also used for making carbamates. Alternatively, carbamates may be synthesized through the reaction of alcohol and/or amine precursors with an ester-substituted diaryl carbonate, such as bismethylsalicylcarbonate (BMSC). U.S. Patent Publication No. 20100113819.

Carbamates may be synthesized by the following approach:



Suitable reaction solvents include, but are not limited to, tetrahydrofuran, dichloromethane, dichloroethane, acetone, and diisopropyl ether. The reaction may be performed at a temperature ranging from about -70°C to about 80°C, or from about -65°C to about 50°C. The molar ratio of isoperillyl chloroformate (or perillyl chloroformate) to the substrate R – NH_2 may range from about 1:1 to about 2:1, from about 1:1 to about 1.5:1, from about 2:1 to about 1:1, or from about 1.05:1 to about 1.1:1. Suitable bases include, but are not limited to, organic bases, such as triethylamine, potassium carbonate, N,N'-diisopropylethylamine, butyl lithium, and potassium-t-butoxide.

Alternatively, carbamates may be synthesized by the following approach:



Suitable reaction solvents include, but are not limited to, dichloromethane, dichloroethane, toluene, diisopropyl ether, and tetrahydrofuran. The reaction may be performed at a temperature ranging from about 25°C to about 110°C, or from about 30°C to about 80°C, or about 50°C. The molar ratio of isoperillyl alcohol to the substrate R-N=C=O may range from about 1:1 to about 2:1, from about 1:1 to about 1.5:1, from about 2:1 to about 1:1, or from about 1.05:1 to about 1.1:1.

Esters of a monoterpene or sesquiterpene alcohol, or esters of the alcohol of the isomers or analogs of a monoterpene or sesquiterpene, can be derived from an inorganic acid or an organic acid. Inorganic acids include, but are not limited to, phosphoric acid, sulfuric acid, and nitric acid. Organic acids include, but are not limited to, carboxylic acid such as benzoic acid, fatty acid, acetic acid and propionic acid, and any therapeutic agent bearing at least one carboxylic acid functional group. Examples of the esters of alcohols include, but are not limited to, carboxylic acid esters (such as benzoate esters, fatty acid esters (e.g., palmitate ester, linoleate ester, stearate ester, butyryl ester and oleate ester), acetates, propionates (or propanoates), and formates), phosphates, sulfates, and carbamates (e.g., N,N-dimethylaminocarbonyl).

The derivatives of perillyl alcohol include, perillyl alcohol carbamates, perillyl alcohol esters, perillic aldehydes, dihydroperillic acid, perillic acid, perillic aldehyde derivatives, dihydroperillic acid esters and perillic acid esters. The derivatives of perillyl alcohol may also include its oxidative and nucleophilic/electrophilic addition derivatives. U.S. Patent Publication No. 20090031455. U.S. Patent Nos. 6,133,324 and 3,957,856.

The derivatives of isoperillyl alcohol include isoperillyl alcohol carbamates, isoperillyl alcohol esters, isoperillyl alcohol ethers, isoperillic aldehydes, isoperillic acid, isoperillic aldehyde derivatives, and isoperillic acid esters. The derivatives of isoperillyl alcohol may also include its oxidative and nucleophilic/electrophilic addition derivatives. Few examples of derivatives of isoperillyl alcohol are reported in the chemistry literature. See U.S. Patent No. 5,994,598 and Japanese Patent No. 07048264A.

In certain embodiments, a POH carbamate (or an iso-POH carbamate) is synthesized by a process comprising the step of reacting a first reactant of perillyl chloroformate (or isoperillyl chloroformate) with a second reactant such as dimethyl celocoxib (DMC), temozolomide (TMZ) and rolipram. The reaction may be carried out in the presence of tetrahydrofuran and a base such as n-butyl lithium. Perillyl chloroformate (or isoperillyl chloroformate) may be made by reacting POH (or iso-POH) with phosgene. For example, POH (or iso-POH) conjugated with temozolomide through a carbamate bond may be synthesized by reacting temozolomide with oxalyl chloride followed by reaction with perillyl alcohol (or iso-POH). The reaction may be carried out in the presence of 1,2-dichloroethane.

POH carbamates encompassed by the present invention include, but not limited to, 4-(bis-N,N'-4-isopropenyl cyclohex-1-enylmethyloxy carbonyl [5-(2,5-dimethyl phenyl)-3-trifluoromethyl pyrazol-1-yl] benzenesulfonamide, 4-(3-cyclopentyloxy-4-methoxy phenyl)-2-oxo-pyrrolidine-1-carboxylic acid 4-isopropenyl cyclohex-1-enylmethyl ester, and (3-methyl 4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carbonyl)carbamic acid-4-isopropenyl cyclohex-1-enylmethyl ester.

Iso-POH carbamates encompassed by the present invention include, but are not limited to, (3-Methyl 4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carbonyl)-carbamic acid -4-isopropylidene cyclohex-1-enylmethyl ester, 4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-oxo-pyrrolidine-1-carboxylic acid 4-isopropylidene cyclohex-1-enylmethyl ester, 4-(Bis-N,N'-4-isopropylidene cyclohex-1-enylmethyloxy carbonyl [5-(2,5-dimethyl phenyl)-3-trifluoromethyl pyrazol-1-yl] benzenesulfonamide. The details of the chemical reactions generating these compounds are described in the Examples below.

In certain embodiments, perillyl alcohol derivatives may be perillyl alcohol fatty acid esters, such as palmitoyl ester of POH and linoleoyl ester of POH; iso-perillyl alcohol derivatives may be isoperillyl alcohol fatty acid esters, such as palmitoyl ester of iso-POH and linoleoyl ester of iso-POH.

The deuterium-enriched perillyl alcohol or isoperillyl alcohol may also be conjugated with other therapeutic moieties such as anti-cancer agents (such as temozolomide) by means of carbamate or other chemical linkage between the deuterated isoperillyl alcohol moiety and the other therapeutic moiety with net therapeutic advantage compared with either moiety or both moieties in their own right.

The monoterpene (or sesquiterpene) derivative may be a monoterpene (or sesquiterpene) conjugated with a therapeutic agent. A monoterpene (or sesquiterpene) conjugate encompassed by the present invention is a molecule having a monoterpene (or sesquiterpene) covalently bound via a chemical linking group to a therapeutic agent.

The derivative of an isomer or analog of monoterpene or sesquiterpene may be an isomer or analog of monoterpene or sesquiterpene conjugated with a therapeutic agent. A conjugate encompassed by the present invention may be a molecule having an isomer or analog of

monoterpene or sesquiterpene covalently bound via a chemical linking group to a therapeutic agent.

The molar ratio of the monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) to the therapeutic agent in the conjugate may be 1:1, 1:2, 1:3, 1:4, 2:1, 3:1, 4:1, or any other suitable molar ratios. The monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) and the therapeutic agent may be covalently linked through carbamate, ester, ether bonds, or any other suitable chemical functional groups. When the monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) and the therapeutic agent are conjugated through a carbamate bond, the therapeutic agent may be any agent bearing at least one carboxylic acid functional group, or any agent bearing at least one amine functional group. In a specific example, a perillyl alcohol (or an iso-POH) conjugate is perillyl alcohol (or iso-POH) covalently bound via a chemical linking group to a chemotherapeutic agent.

According to the present invention, the therapeutic agents that may be conjugated with a monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) include, but are not limited to, chemotherapeutic agents, therapeutic agents for treatment of CNS disorders (including, without limitation, primary degenerative neurological disorders such as Alzheimer's, Parkinson's, multiple sclerosis, Attention-Deficit Hyperactivity Disorder or ADHD, psychological disorders, psychosis and depression), immunotherapeutic agents, angiogenesis inhibitors, and anti-hypertensive agents. Anti-cancer agents that may be conjugated with a monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) can have one or more of the following effects on cancer cells or the subject: cell death; decreased cell proliferation; decreased numbers of cells; inhibition of cell growth; apoptosis; necrosis; mitotic catastrophe; cell cycle arrest; decreased cell size; decreased cell division; decreased cell survival; decreased cell metabolism; markers of cell damage or cytotoxicity; indirect indicators of cell damage or cytotoxicity such as tumor shrinkage; improved survival of a subject; or disappearance of markers associated with undesirable, unwanted, or aberrant cell proliferation. U.S. Patent Publication No. 20080275057.

Chemotherapeutic agents include, but are not limited to, DNA alkylating agents, topoisomerase inhibitors, endoplasmic reticulum stress inducing agents, a platinum compound,

an antimetabolite, vincalkaloids, taxanes, epothilones, enzyme inhibitors, receptor antagonists, tyrosine kinase inhibitors, boron radiosensitizers (i.e. velcade), and chemotherapeutic combination therapies.

Non-limiting examples of DNA alkylating agents are nitrogen mustards, such as Cyclophosphamide (Ifosfamide, Trofosfamide), Chlorambucil (Melphalan, Prednimustine), Bendamustine, Uramustine and Estramustine; nitrosoureas, such as Carmustine (BCNU), Lomustine (Semustine), Fotemustine, Nimustine, Ranimustine and Streptozocin; alkyl sulfonates, such as Busulfan (Mannosulfan, Treosulfan); Aziridines, such as Carboquone, Triaziquone, Triethylenemelamine; Hydrazines (Procarbazine); Triazenes such as Dacarbazine and Temozolomide; Altretamine and Mitobronitol.

Non-limiting examples of Topoisomerase I inhibitors include Campothecin derivatives including SN-38, APC, NPC, campothecin, topotecan, exatecan mesylate, 9-nitrocamptothecin, 9-aminocamptothecin, lurtotecan, rubitecan, silatecan, gimatecan, diflomotecan, extatecan, BN-80927, DX-8951f, and MAG-CPT as decribed in Pommier Y. (2006) Nat. Rev. Cancer 6(10):789-802 and U.S. Patent Publication No. 200510250854; Protoberberine alkaloids and derivatives thereof including berberrubine and coralyne as described in Li et al. (2000) Biochemistry 39(24):7107-7116 and Gatto et al. (1996) Cancer Res. 15(12):2795-2800; Phenanthroline derivatives including Benzo[i]phenanthridine, Nitidine, and fagaronine as described in Makhey et al. (2003) Bioorg. Med. Chem. 11 (8): 1809-1820; Terbenzimidazole and derivatives thereof as described in Xu (1998) Biochemistry 37(10):3558-3566; and Anthracycline derivatives including Doxorubicin, Daunorubicin, and Mitoxantrone as described in Foglesong et al. (1992) Cancer Chemother. Pharmacol. 30(2):123-]25, Crow et al. (1994) J. Med. Chem. 37(19):31913194, and Crespi et al. (1986) Biochem. Biophys. Res. Commun. 136(2):521-8. Topoisomerase II inhibitors include, but are not limited to Etoposide and Teniposide. Dual topoisomerase I and II inhibitors include, but are not limited to, Saintopin and other Naphthecenediones, DACA and other Acridine-4-Carboxamindes, Intoplicine and other Benzopyridoindoles, TAS-I03 and other 7H-indeno[2,1-c]Quinoline-7-ones, Pyrazoloacridine, XR 11576 and other Benzophenazines, XR 5944 and other Dimeric compounds, 7-oxo-7H-dibenz[f,ij]Isoquinolines and 7-oxo-7H-benzo[e]pyrimidines, and Anthracenyl-amino Acid Conjugates as described in Denny and Baguley (2003) Curr. Top. Med. Chem. 3(3):339-353. Some agents inhibit Topoisomerase II and have DNA intercalation activity such as, but not

limited to, Anthracyclines (Aclarubicin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin) and Antracenediones (Mitoxantrone and Pixantrone).

Examples of endoplasmic reticulum stress inducing agents include, but are not limited to, dimethyl-celecoxib (DMC), nelfinavir, celecoxib, and boron radiosensitizers (i.e. velcade (Bortezomib)).

Platinum based compounds are a subclass of DNA alkylating agents. Non-limiting examples of such agents include Cisplatin, Nedaplatin, Oxaliplatin, Triplatin tetranitrate, Satraplatin, Aroplatin, Lobaplatin, and JM-216. (see McKeage et al. (1997) J. Clin. Oncol. 201 :1232-1237 and in general, CHEMOTHERAPY FOR GYNECOLOGICAL NEOPLASM, CURRENT THERAPY AND NOVEL APPROACHES, in the Series Basic and Clinical Oncology, Angioli et al. Eds., 2004).

"FOLFOX" is an abbreviation for a type of combination therapy that is used to treat colorectal cancer. It includes 5-FU, oxaliplatin and leucovorin. Information regarding this treatment is available on the National Cancer Institute's web site, cancer.gov, last accessed on January 16, 2008.

"FOLFOX/BV" is an abbreviation for a type of combination therapy that is used to treat colorectal cancer. This therapy includes 5-FU, oxaliplatin, leucovorin and Bevacizumab. Furthennore, "XELOX/BV" is another combination therapy used to treat colorectal cancer, which includes the prodrug to 5-FU, known as Capecitabine (Xeloda) in combination with oxaliplatin and bevacizumab. Infonnation regarding these treatments are available on the National Cancer Institute's web site, cancer.gov or from 23 the National Comprehensive Cancer Network's web site, nccn.org, last accessed on May 27,2008.

Non-limiting examples of antimetabolite agents include Folic acid based, i.e. dihydrofolate reductase inhibitors, such as Aminopterin, Methotrexate and Pemetrexed; thymidylate synthase inhibitors, such as Raltitrexed, Pemetrexed; Purine based, i.e. an adenosine deaminase inhibitor, such as Pentostatin, a thiopurine, such as Thioguanine and Mercaptopurine, a halogenated/ribonucleotide reductase inhibitor, such as Cladribine, Clofarabine, Fludarabine, or a guanine/guanosine: thiopurine, such as Thioguanine; or Pyrimidine based, i.e. cytosine/cytidine: hypomethylating agent, such as Azacitidine and Decitabine, a DNA polymerase inhibitor, such as Cytarabine, a ribonucleotide reductase inhibitor, such as

Gemcitabine, or a thymine/thymidine: thymidylate synthase inhibitor, such as a Fluorouracil (5-FU). Equivalents to 5-FU include prodrugs, analogs and derivative thereof such as 5' -deoxy-5-fluorouridine (doxifluroidine), l-tetrahydrofuranyl-5-fluorouracil (ftorafur), Capecitabine (Xeloda), S-I (MBMS-247616, consisting of tegafur and two modulators, a 5-chloro-2,4-dihydroxypyridine and potassium oxonate), ralititrexed (tomudex), nolatrexed (Thymitaq, AG337), LY231514 and ZD9331, as described for example in Papamicheal (1999) The Oncologist 4:478-487.

Examples of vincalkaloids include, but are not limited to Vinblastine, Vincristine, Vinflunine, Vindesine and Vinorelbine.

Examples of taxanes include but are not limited to docetaxel, Larotaxel, Ortataxel, Paclitaxel and Tesetaxel. An example of an epothilone is iabepilone.

Examples of enzyme inhibitors include, but are not limited to farnesyltransferase inhibitors (Tipifarnib); CDK inhibitor (Alvocidib, Seliciclib); proteasome inhibitor (Bortezomib); phosphodiesterase inhibitor (Anagrelide; rolipram); IMP dehydrogenase inhibitor (Tiazofurine); and lipoxygenase inhibitor (Masoprocol). Examples of receptor antagonists include, but are not limited to ERA (Atrasentan); retinoid X receptor (Bexarotene); and a sex steroid (Testolactone).

Examples of tyrosine kinase inhibitors include, but are not limited to inhibitors to ErbB: HER1/EGFR (Erlotinib, Gefitinib, Lapatinib, Vandetanib, Sunitinib, Neratinib); HER2/neu (Lapatinib, Neratinib); RTK class III: C-kit (Axitinib, Sunitinib, Sorafenib), FLT3 (Lestaurtinib), PDGFR (Axitinib, Sunitinib, Sorafenib); and VEGFR (Vandetanib, Semaxanib, Cediranib, Axitinib, Sorafenib); bcr-abl (Imatinib, Nilotinib, Dasatinib); Src (Bosutinib) and Janus kinase 2 (Lestaurtinib).

"Lapatinib" (Tykerb®) is a dual EGFR and erbB-2 inhibitor. Lapatinib has been investigated as an anticancer monotherapy, as well as in combination with trastuzumab, capecitabine, letrozole, paclitaxel and FOLFIRI (irinotecan, 5-fluorouracil and leucovorin), in a number of clinical trials. It is currently in phase III testing for the oral treatment of metastatic breast, head and neck, lung, gastric, renal and bladder cancer.

A chemical equivalent of lapatinib is a small molecule or compound that is a tyrosine kinase inhibitor (TKI) or alternatively a HER-l inhibitor or a HER-2 inhibitor. Several TKIs have been found to have effective antitumor activity and have been approved or are in clinical trials.

Examples of such include, but are not limited to, Zactima (ZD6474), Iressa (gefitinib), imatinib mesylate (STI571; Gleevec), erlotinib (OSI-1774; Tarceva), canertinib (CI 1033), semaxinib (SU5416), vatalanib (PTK787/ZK222584), sorafenib (BAY 43- 9006), sutent (SUI 1248) and lefltmomide (SU10l).

PTK/ZK is a tyrosine kinase inhibitor with broad specificity that targets all VEGF receptors (VEGFR), the platelet-derived growth factor (PDGF) receptor, c-KIT and c-Fms. Drevs (2003) Idrugs 6(8):787-794. PTK/ZK is a targeted drug that blocks angiogenesis and lymphangiogenesis by inhibiting the activity of all known receptors that bind VEGF including VEGFR-I (Flt-1), VEGFR-2 (KDR/Flk-1) and VEGFR-3 (Flt-4). The chemical names of PTK/ZK are 1-[4-Chloroanilino]-4-[4-pyridylmethyl] phthalazine Succinate or 1-Phthalazinamine, N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-butanedioate (1:1). Synonyms and analogs of PTK/TK are known as Vatalanib, CGP79787D, PTK787/ZK 222584, CGP-79787, DE-00268, PTK-787, PTK787A, VEGFR-TK inhibitor, ZK 222584 and ZK.

Chemotherapeutic agents that can be conjugated with a monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) may also include amsacrine, Trabectedin, retinoids (Alitretinoin, Tretinoin), Arsenic trioxide, asparagine depleter Asparaginase/ Pegaspargase), Celecoxib, Demecolcine, Elesclomol, Elsamitrucin, Etoglucid, Lonidamine, Lucanthone, Mitoguazone, Mitotane, Oblimersen, Temsirolimus, and Vorinostat.

A monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) may be conjugated with angiogenesis inhibitors. Examples of angiogenesis inhibitors include, but are not limited to, angiostatin, angiozyme, antithrombin III, AG3340, VEGF inhibitors, batimastat, bevacizumab (avastin), BMS-275291, CAI, 2C3, HuMV833 Canstatin, Captopril, carboxyamidotriazole, cartilage derived inhibitor (CDI), CC-5013, 6-O-(chloroacetyl-carbonyl)-fumagillol, COL-3, combretastatin, combretastatin A4 Phosphate, Dalteparin, EMD 121974 (Cilengitide), endostatin, erlotinib, gefitinib (Iressa), genistein, halofuginone hydrobromide, Id1, Id3, IM862, imatinib mesylate, IMC-IC11 Inducible protein 10, interferon-alpha, interleukin 12, lavendustin A, LY317615 or AE-941, marimastat, mspin, medroxpregesterone acetate, Meth-1, Meth-2, 2-methoxyestradiol (2-ME), neovastat, oteopontin cleaved product, PEX, pigment epithelium growth factor (PEGF), platelet factor 4, prolactin fragment, proliferin-related protein (PRP), PTK787/ZK 222584, ZD6474, recombinant human platelet factor 4 (rPF4), restin, squalamine, SU5416, SU6668, SU11248 suramin, Taxol,

Tecogalan, thalidomide, thrombospondin, TNP-470, troponin-I, vasostatin, VEG1, VEGF-Trap, and ZD6474.

Non-limiting examples of angiogenesis inhibitors also include, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, pentosan polysulfate, angiotensin II antagonists, cyclooxygenase inhibitors (including non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen, as well as selective cyclooxygenase-2 inhibitors such as celecoxib and rofecoxib), and steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone).

Other therapeutic agents that modulate or inhibit angiogenesis include agents that modulate or inhibit the coagulation and fibrinolysis systems, including, but not limited to, heparin, low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]). U.S. Patent Publication No. 20090328239. U.S. Patent No. 7,638,549.

Non-limiting examples of the anti-hypertensive agents include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril etc.), angiotensin II antagonists (e.g., candesartan cilexetil, candesartan, losartan (or Cozaar), losartan potassium, eprosartan, valsartan (or Diovan), termisartan, irbesartan, tasosartan, olmesartan, olmesartan medoxomil etc.), calcium antagonists (e.g., manidipine, nifedipine, amlodipine (or Amlodin), efonidipine, nicardipine etc.), diuretics, renin inhibitor (e.g., aliskiren etc.), aldosterone antagonists (e.g., spironolactone, eplerenone etc.), beta-blockers (e.g., metoprolol (or Toporol), atenolol, propranolol, carvedilol, pindolol etc.), vasodilators (e.g., nitrate, soluble guanylate cyclase stimulator or activator, prostacycline etc.), angiotensin vaccine, clonidine and the like. U.S. Patent Publication No. 20100113780.

Other therapeutic agents that may be conjugated with a monoterpene or sesquiterpene (or an isomer or analog of monoterpene or sesquiterpene) include, but are not limited to, Sertraline (Zoloft), Topiramate (Topamax), Duloxetine(Cymbalta), Sumatriptan (Imitrex), Pregabalin (Lyrica), Lamotrigine (Lamictal), Valaciclovir (Valtrex), Tamsulosin (Flomax), Zidovudine (Combivir), Lamivudine (Combivir), Efavirenz (Sustiva), Abacavir (Epzicom), Lopinavir (Kaletra), Pioglitazone (Actos), Desloratidine (Clarinex), Cetirizine (Zyrtec), Pentoprazole

(Protonix), Lansoprazole (Prevacid), Rebeprazole (Aciphex), Moxifloxacin (Avelox), Meloxicam (Mobic), Dorzolamide (Truspot), Diclofenac (Voltaren), Enlapril (Vasotec), Montelukast (Singulair), Sildenafil (Viagra), Carvedilol (Coreg), Ramipril (Delix), and L-DOPA.

Also encompassed by the present invention are admixtures and/or coformulations of the present deuterium-enriched compound and at least one therapeutic agent discussed above.

The purity of the present compounds may be assayed by gas chromatography (GC) or high pressure liquid chromatography (HPLC). Other techniques for assaying purity and for determining the presence of impurities include, but are not limited to, mass spectrometry (MS), GC-MS, infrared spectroscopy (IR), nuclear magnetic resonance (NMR) spectroscopy, and thin layer chromatography (TLC). Chiral purity can be assessed by chiral GC or measurement of optical rotation.

The present compounds may be purified by methods such as crystallization, or by separating the compounds from impurities according to the unique physicochemical properties (e.g., solubility or polarity) of compounds. Accordingly, the present compound can be separated by suitable separation techniques known in the art, such as preparative chromatography, (fractional) distillation, or (fractional) crystallization.

The compounds and methods of the present invention may be used to inhibit the Ras protein. The Ras family is a protein family of small GTPases that are involved in cellular signal transduction. Activation of Ras signaling causes cell growth, differentiation and survival. Mtations in *ras* genes can permanently activate it and cause inappropriate transmission inside the cell even in the absence of extracellular signals. Because these signals result in cell growth and division, dysregulated Ras signaling can ultimately lead to oncogenesis and cancer. Activating mutations in Ras are found in 20-25% of all human tumors and up to 90% in specific tumor types. Goodsell DS (1999). Downward J., "The molecular perspective: the ras oncogene". Oncologist 4 (3): 263–4. (January 2003). "Targeting RAS signaling pathways in cancer therapy". Nat. Rev. Cancer 3 (1): 11–22. Ras family members include, but are not limited to, HRAS; KRAS; NRAS; DIRAS1; DIRAS2; DIRAS3; ERAS; GEM; MRAS; NKIRAS1; NKIRAS2; NRAS; RALA; RALB; RAP1A; RAP1B; RAP2A; RAP2B; RAP2C; RASD1; RASD2;

RASL10A; RASL10B; RASL11A; RASL11B; RASL12; REM1; REM2; RERG; RERGL; RRAD; RRAS; and RRAS. Wennerberg K, Rossman KL, Der CJ (March 2005). "The Ras superfamily at a glance". J Cell Sci. 118 (Pt 5): 843–6.

The present deuterium-enriched compounds may be formulated into a pharmaceutical composition. The deuterium-enriched compound may be present in the pharmaceutical composition in an amount ranging from about 0.01% (w/w) to about 100% (w/w), from about 0.1% (w/w) to about 80% (w/w), from about 1% (w/w) to about 70% (w/w), from about 10% (w/w) to about 60% (w/w), or from about 0.1% (w/w) to about 20% (w/w).

The present compounds or pharmaceutical compositions may be administered by any route known in the art, including, without limitation, inhalation, intranasal, oral, transdermal, ocular, intraperitoneal, inhalation, intravenous, ICV, intracisternal injection or infusion, subcutaneous, implant, vaginal, sublingual, urethral (e.g., urethral suppository), subcutaneous, intramuscular, intravenous, rectal, sub-lingual, mucosal, ophthalmic, spinal, intrathecal, intra-articular, intra-arterial, sub-arachinoid, bronchial and lymphatic administration. Intranasal formulation can be delivered as a spray or in a drop; inhalation formulation can be delivered using a nebulizer or similar device; topical formulation may be in the form of gel, ointment, cream, aerosol, etc; transdermal formulation may be administered via a transdermal patch or iontorphoresis. Compositions can also take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

To prepare such pharmaceutical compositions, one or more of compound of the present invention may be mixed with a pharmaceutical acceptable carrier, adjuvant and/or excipient, according to conventional pharmaceutical compounding techniques. Pharmaceutically acceptable carriers that can be used in the present compositions encompass any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. The compositions can additionally contain solid pharmaceutical excipients such as starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils,

including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols. For examples of carriers, stabilizers and adjuvants, see Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990). The compositions also can include stabilizers and preservatives.

The present invention also provides for a method of treating a disease comprising the step of administering to a patient a therapeutically effective amount of a deuterium-enriched compound, e.g., deuterium-enriched perillyl alcohol, deuterium-enriched isoperillyl alcohol, a deuterium-enriched perillyl alcohol carbamate or a deuterium-enriched isoperillyl alcohol carbamate.

As used herein, the term "therapeutically effective amount" is an amount sufficient to treat a specified disorder or disease or alternatively to obtain a pharmacological response treating a disorder or disease. Methods of determining the most effective means and dosage of administration can vary with the composition used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Treatment dosages generally may be titrated to optimize safety and efficacy. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician. Suitable dosage formulations and methods of administering the agents can be readily determined by those of skill in the art. For example, the composition are administered at about 0.01 mg/kg to about 200 mg/kg, about 0.1 mg/kg to about 100 mg/kg, or about 0.5 mg/kg to about 50 mg/kg. When the compounds described herein are co-administered with another agent or therapy, the effective amount may be less than when the agent is used alone.

Transdermal formulations may be prepared by incorporating the active agent in a thixotropic or gelatinous carrier such as a cellulosic medium, e.g., methyl cellulose or hydroxyethyl cellulose, with the resulting formulation then being packed in a transdermal device adapted to be secured in dermal contact with the skin of a wearer. If the composition is in the form of a gel, the composition may be rubbed onto a membrane of the patient, for example, the skin, preferably intact, clean, and dry skin, of the shoulder or upper arm and or the upper torso, and maintained thereon for a period of time sufficient for delivery of the present compound to the blood serum of the patient. The composition of the present invention in gel form may be

contained in a tube, a sachet, or a metered pump. Such a tube or sachet may contain one unit dose, or more than one unit dose, of the composition. A metered pump may be capable of dispensing one metered dose of the composition.

This invention also provides the compositions as described above for intranasal administration. As such, the compositions can further comprise a permeation enhancer. Southall et al. Developments in Nasal Drug Delivery, 2000. The present compound may be administered intranasally as an aerosol, in a liquid form such as a solution, an emulsion, a suspension, drops, or in a solid form such as a powder, gel, or ointment.

Devices to deliver intranasal medications are well known in the art. Nasal drug delivery can be carried out using devices including, but not limited to, intranasal inhalers, intranasal spray devices, atomizers, nasal spray bottles, unit dose containers, pumps, droppers, squeeze bottles, nebulizers, metered dose inhalers (MDI), pressurized dose inhalers, insufflators, and bi-directional devices. The nasal delivery device can be metered to administer an accurate effective dosage amount to the nasal cavity. The nasal delivery device can be for single unit delivery or multiple unit delivery. In a specific example, the ViaNase Electronic Atomizer from Kurve Technology (Bethell, Washington) can be used in this invention. The compounds of the present invention may also be delivered through a tube, a catheter, a syringe, a packtail, a pledget, a nasal tampon or by submucosal infusion. U.S. Patent Publication Nos. 20090326275, 20090291894, 20090281522 and 20090317377.

The present compound can be formulated as aerosols using standard procedures. The compound may be formulated with or without solvents, and formulated with or without carriers. The formulation may be a solution, or may be an aqueous emulsion with one or more surfactants. For example, an aerosol spray may be generated from pressurized container with a suitable propellant such as, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, hydrocarbons, compressed air, nitrogen, carbon dioxide, or other suitable gas. The dosage unit can be determined by providing a valve to deliver a metered amount. Pump spray dispensers can dispense a metered dose or a dose having a specific particle or droplet size. As used herein, the term "aerosol" refers to a suspension of fine solid particles or liquid solution droplets in a gas. Specifically, aerosol includes a gas-borne suspension of droplets of a monoterpene (or sesquiterpene), as may be produced in any suitable device, such as an MDI, a nebulizer, or a mist sprayer. Aerosol also includes a dry powder composition of the composition of the instant

invention suspended in air or other carrier gas. Gonda (1990) Critical Reviews in Therapeutic Drug Carrier Systems 6:273-313. Raeburn et al., (1992) Pharmacol. Toxicol. Methods 27:143-159.

The present compound may be delivered to the nasal cavity as an aerosol, such as a liquid aerosol, or a solid aerosol. The present compound may be delivered to the nasal cavity as a powder in a form such as microspheres delivered by a nasal insufflator. The present compound may be absorbed to a solid surface, for example, a carrier. The powder or microspheres may be administered in a dry, air-dispensable form. The powder or microspheres may be stored in a container of the insufflator. Alternatively the powder or microspheres may be filled into a capsule, such as a gelatin capsule, or other single dose unit adapted for nasal administration.

The pharmaceutical composition can be delivered to the nasal cavity by direct placement of the composition in the nasal cavity, for example, in the form of a gel, an ointment, a nasal emulsion, a lotion, a cream, a nasal tampon, a dropper, or a bioadhesive strip. In certain embodiments, it can be desirable to prolong the residence time of the pharmaceutical composition in the nasal cavity, for example, to enhance absorption. Thus, the pharmaceutical composition can optionally be formulated with a bioadhesive polymer, a gum (e.g., xanthan gum), chitosan (e.g., highly purified cationic polysaccharide), pectin (or any carbohydrate that thickens like a gel or emulsifies when applied to nasal mucosa), a microsphere (e.g., starch, albumin, dextran, cyclodextrin), gelatin, a liposome, carbamer, polyvinyl alcohol, alginate, acacia, chitosans and/or cellulose (e.g., methyl or propyl; hydroxyl or carboxy; carboxymethyl or hydroxylpropyl).

The composition containing the present compound can be administered by oral inhalation into the respiratory tract, i.e., the lungs.

Typical delivery systems for inhalable agents include nebulizer inhalers, dry powder inhalers (DPI), and metered-dose inhalers (MDI).

Nebulizer devices produce a stream of high velocity air that causes a therapeutic agent in the form of liquid to spray as a mist. The therapeutic agent is formulated in a liquid form such as a solution or a suspension of particles of suitable size. In one embodiment, the particles are micronized. The term "micronized" is defined as having about 90% or more of the particles with a diameter of less than about 10 μm. Suitable nebulizer devices are provided commercially, for example, by PARI GmbH (Starnberg, Germany). Other nebulizer devices include Respimat

(Boehringer Ingelheim) and those disclosed in, for example, U.S. Patent Nos. 7,568,480 and 6,123,068, and WO 97/12687. The present compound can be formulated for use in a nebulizer device as an aqueous solution or as a liquid suspension.

DPI devices typically administer a therapeutic agent in the form of a free flowing powder that can be dispersed in a patient's air-stream during inspiration. DPI devices which use an external energy source may also be used in the present invention. In order to achieve a free flowing powder, the present compound can be formulated with a suitable excipient (e.g., lactose). A dry powder formulation can be made, for example, by combining dry lactose having a particle size between about 1 μm and 100 μm with micronized particles of the present compound and dry blending. Alternatively, the compound can be formulated without excipients. The formulation is loaded into a dry powder dispenser, or into inhalation cartridges or capsules for use with a dry powder delivery device. Examples of DPI devices provided commercially include Diskhaler (GlaxoSmithKline, Research Triangle Park, N.C.) (see, e.g., U.S. Patent No. 5,035,237); Diskus (GlaxoSmithKline) (see, e.g., U.S. Patent No. 6,378,519; Turbuhaler (AstraZeneca, Wilmington, Del.) (see, e.g., U.S. Patent No. 4,524,769); and Rotahaler (GlaxoSmithKline) (see, e.g., U.S. Patent No. 4,353,365). Further examples of suitable DPI devices are described in U.S. Patent Nos. 5,415,162, 5,239,993, and 5,715,810 and references therein.

MDI devices typically discharge a measured amount of the stored composition using compressed propellant gas. Formulations for MDI administration include a solution or suspension of an active ingredient in a liquefied propellant. Examples of propellants include hydrofluoroalklanes (HFA), such as 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA 227), and chlorofluorocarbons, such as CCl_3F. Additional components of HFA formulations for MDI administration include co-solvents, such as ethanol, pentane, water; and surfactants, such as sorbitan trioleate, oleic acid, lecithin, and glycerin. (See, for example, U.S. Patent No. 5,225,183, EP 0717987, and WO 92/22286). The formulation is loaded into an aerosol canister, which forms a portion of an MDI device. Examples of MDI devices developed specifically for use with HFA propellants are provided in U.S. Patent Nos. 6,006,745 and 6,143,227. For examples of processes of preparing suitable formulations and devices suitable for inhalation dosing see U.S. Patent Nos. 6,268,533, 5,983,956, 5,874,063, and 6,221,398, and WO 99/53901, WO 00/61108, WO 99/55319 and WO 00/30614.

The present compound or pharmaceutical composition may be encapsulated in liposomes or microcapsules for delivery via inhalation. A liposome is a vesicle composed of a lipid bilayer membrane and an aqueous interior. The lipid membrane may be made of phospholipids, examples of which include phosphatidylcholine such as lecithin and lysolecithin; acidic phospholipids such as phosphatidylserine and phosphatidylglycerol; and sphingophospholipids such as phosphatidylethanolamine and sphingomyelin. Alternatively, cholesterol may be added. A microcapsule is a particle coated with a coating material. For example, the coating material may consist of a mixture of a film-forming polymer, a hydrophobic plasticizer, a surface activating agent or/and a lubricant nitrogen-containing polymer. U.S. Patent Nos. 6,313,176 and 7,563,768.

The present compound or pharmaceutical composition may also be used alone or in combination with other chemotherapeutic agents via topical application for the treatment of localized cancers such as breast cancer or melanomas. The present compound may also be used in combination with narcotics or analgesics for transdermal delivery of pain medication.

This invention also provides the compound or the compositions as described above for ocular administration. As such, the compositions can further comprise a permeation enhancer. For ocular administration, the compositions described herein can be formulated as a solution, emulsion, suspension, etc. A variety of vehicles suitable for administering compounds to the eye are known in the art. Specific non-limiting examples are described in U.S. Patent Nos. 6,261,547; 6, 197,934; 6,056,950; 5,800,807; 5,776,445; 5,698,219; 5,521,222; 5,403,841; 5,077,033; 4,882,150; and 4,738,851.

The present compound or pharmaceutical composition can be given alone or in combination with other drugs for the treatment of the above diseases for a short or prolonged period of time. The present compound or pharmaceutical compositions can be administered to a mammal, preferably a human. Mammals include, but are not limited to, murines, rats, rabbit, simians, bovines, ovine, porcine, canines, feline, farm animals, sport animals, pets, equine, and primates.

The present compounds or compositions can be administered alone, or may be co-administered together with radiation or another agent (e.g., a chemotherapeutic agent), to treat a disease such as cancer. Treatments may be sequential, with the present compounds or

compositions being administered before or after the administration of other agents. For example, a deuterium-enriched perillyl alcohol (or isoperillyl alcohol) may be used to sensitize a cancer patient to radiation or chemotherapy. Alternatively, agents may be administered concurrently.

The present deuterium-enriched compounds may be used in combination with radiation therapy. In one embodiment, the present invention provides for a method of treating tumor cells, such as malignant glioma cells, with radiation, where the cells are treated with an effective amount of a deuterium-enriched compound of the present invention (such as deuterium-enriched perillyl alcohol or deuterium-enriched isoperillyl alcohol), and then exposed to radiation. Treatment by the compounds of the present invention may be before, during and/or after radiation. For example, the compounds of the present invention may be administered continuously beginning one week prior to the initiation of radiotherapy and continued for two weeks after the completion of radiotherapy. U.S. Patent Nos. 5,587,402 and 5,602,184.

In one embodiment, the present invention provides for a method of treating tumor cells, such as malignant glioma cells, with chemotherapeutical agent, where the cells are treated with an effective amount of a deuterium-enriched compound of the present invention (such as deuterium-enriched perillyl alcohol or deuterium-enriched isoperillyl alcohol), and then exposed to chemotherapeutical agent. Treatment by the compounds of the present invention may be before, during and/or after chemotherapy.

The compounds or pharmaceutical compositions of the present invention may be used for the treatment of nervous system cancers, such as a malignant glioma (e.g., astrocytoma, anaplastic astrocytoma, glioblastoma multiforme), retinoblastoma, pilocytic astrocytomas (grade I), meningiomas, metastatic brain tumors, neuroblastoma, pituitary adenomas, skull base meningiomas, and skull base cancer.

Cancers that can be treated by the present compounds or pharmaceutical compositions include, but are not limited to, lung cancer, ear, nose and throat cancer, leukemia, colon cancer, melanoma, pancreatic cancer, mammary cancer, prostate cancer, breast cancer, hematopoietic cancer, ovarian cancer, basal cell carcinoma, biliary tract cancer; bladder cancer; bone cancer; breast cancer; cervical cancer; choriocarcinoma; colon and rectum cancer; connective tissue cancer; cancer of the digestive system; endometrial cancer; esophageal cancer; eye cancer; cancer of the head and neck; gastric cancer; intra-epithelial neoplasm; kidney cancer; larynx

cancer; leukemia including acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia; liver cancer; lymphoma including Hodgkin's and Non-Hodgkin's lymphoma; myeloma; fibroma, neuroblastoma; oral cavity cancer (e.g., lip, tongue, mouth, and pharynx); ovarian cancer; pancreatic cancer; prostate cancer; retinoblastoma; rhabdomyosarcoma; rectal cancer; renal cancer; cancer of the respiratory system; sarcoma; skin cancer; stomach cancer; testicular cancer; thyroid cancer; uterine cancer; cancer of the urinary system, as well as other carcinomas and sarcomas. U.S. Patent No. 7,601,355.

The present invention also provides methods of treating CNS disorders, including, without limitation, primary degenerative neurological disorders such as Alzheimer's, Parkinson's, psychological disorders, psychosis and depression. Autism may also be treated by the present compositions and methods. Treatment may consist of the use of a compound of the present invention alone or in combination with current medications used in the treatment of Parkinson's, Alzheimer's, or psychological disorders.

The present invention also provides a method of improving immunomodulatory therapy responses, comprising the steps of exposing cells to an effective amount of a compound (such as deuterium-enriched perillyl alcohol or deuterium-enriched isoperillyl alcohol) or pharmaceutical compositions of the present invention, before or during immunomodulatory treatment. Preferred immunomodulatory agents are cytokines, such interleukins, lymphokines, monokines, interfereons and chemokines.

The invention also provides a method for inhibiting the growth of a cell *in vitro*, *ex vivo* or *in vivo*, where a cell, such as a cancer cell, is contacted with an effective amount of the present compound as described herein.

Pathological cells or tissue such as hyperproliferative cells or tissue may be treated by contacting the cells or tissue with an effective amount of the compound or composition of this invention. The cells, such as cancer cells, can be primary cancer cells or can be cultured cells available from tissue banks such as the American Type Culture Collection (ATCC). The pathological cells can be cells of a systemic cancer, gliomas, meningiomas, pituitary adenomas, or a CNS metastasis from a systemic cancer, lung cancer, prostate cancer, breast cancer, hematopoietic cancer or ovarian cancer. The cells can be from a vertebrate, preferably a mammal, more preferably a human. U.S. Patent Publication No. 2004/0087651. Balassiano et

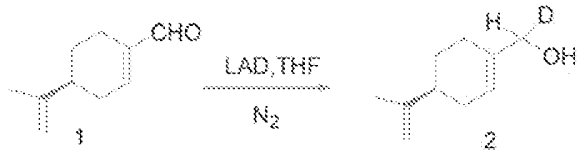
al. (2002) Intern. J. Mol. Med. 10:785-788. Thorne, et al. (2004) Neuroscience 127:481-496. Fernandes, et al. (2005) Oncology Reports 13:943-947. Da Fonseca, et al. (2008) Surgical Neurology 70:259267. Da Fonseca, et al. (2008) Arch. Immunol. Ther. Exp. 56:267-276. Hashizume, et al. (2008) Neuroncology 10:112-120.

Efficacy of the present composition can be determined using methods well known in the art. For example, the cytoxicity of the present compound may be studied by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] cytotoxicity assay. MTT assay is based on the principle of uptake of MTT, a tetrazolium salt, by metabolically active cells where it is metabolized into a blue colored formazon product, which can be read spectrometrically. J. of Immunological Methods 65: 55 63, 1983. The cytoxicity of the present compound may be studied by colony formation assay. Functional assays for inhibition of VEGF secretion and IL-8 secretion may be performed via ELISA. Cell cycle block by the present compound may be studied by standard propidium iodide (PI) staining and flow cytometry. Invasion inhibition may be studied by Boyden chambers. In this assay a layer of reconstituted basement membrane, Matrigel, is coated onto chemotaxis filters and acts as a barrier to the migration of cells in the Boyden chambers. Only cells with invasive capacity can cross the Matrigel barrier. Other assays include, but are not limited to, cell viability assays, apoptosis assays, and morphological assays.

The following are examples of the present invention and are not to be construed as limiting.

Example 1 Synthesis of Deuterated perillyl alcohol

Scheme-1:

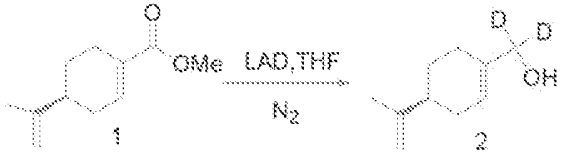


S-(-)Perillaldehyde

Synthesis of (S)-4-Isopropenyl-1-cyclohexene-1-methan-α-d1-ol (2)

Lithium aluminum deuteride (LAD, 1.0 M in THF, 21.2 mL, 21.3 mmol) was added slowly to a cold solution of (*S*)-Perilladehyde (**1**, 2.0g, 13.3 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture was slowly warmed to room temperature and then heated to reflux for 2.0 h. The reaction mixture was quenched with saturated sodium sulfate solution carefully and the resulting lithium salts were filtered and washed with ethyl acetate. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated and the resulting oil was passed through a Thomson single StEP 40 g column and eluted with 7% ethyl acetate/hexanes (120 mL). The clean fractions were combined and concentrated under vacuum to give compound **2** as colorless oil. Weight: 1.78 g. Yield: 88%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.48 (m, 1H), 1.73 (s, 3H), 1.84-1.99 (m, 2H), 2.11 (m, 4H), 3.99 (d, 1H), 4.71 (m, 2H), 5.71 (bs, 1H). MS (APCI +ve mode): Molecular ion peak was observed.

Scheme-2:

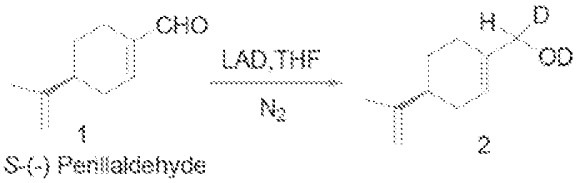


S-(-) Methyl Perillate

Synthesis of (S)-4-Isopropenyl-1-cyclohexene-1-methan-α,α'-d2-ol (2)

Lithium aluminum deuteride (LAD, 1.0 M in THF, 16.6 mL, 16.6 mmol) was added slowly to a cold solution of (*S*)-Methylperillate (**1**, 2.0g, 11 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture was slowly warmed to room temperature and then stirred at room temperature for 2.0 h. The reaction mixture was quenched with saturated sodium sulfate solution carefully and the resulting lithium salts were filtered and washed with ethyl acetate. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated and the resulting oil was passed through a Thomson single StEP 40 g column and eluted with 5% ethyl acetate/hexanes (150 mL). The clean fractions were combined and concentrated under vacuum to give compound **2** as colorless oil. Weight: 1.34 g. Yield: 79%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45-1.49 (m, 1H), 1.73 (s, 3H), 1.84-1.98 (m, 2H), 2.11-2.17 (m, 4H), 4.71 (m, 2H), 5.69 (bs, 1H). MS (APCI +ve mode): Molecular ion peak was observed.

Scheme-3:

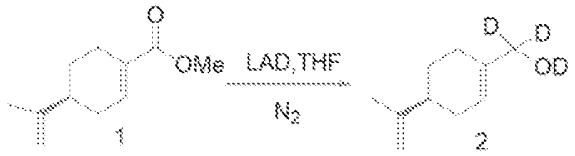


S-(-) Perillaldehyde

Synthesis of (S)-4-Isopropenyl-1-cyclohexene-1-deutero methan-α-d1-ol (2)

Lithium aluminum deuteride (LAD, 1.0 M in THF, 21.2 mL, 21.3 mmol) will be added slowly to a cold solution of (*S*)-Perilladehyde (**1**, 2.0g, 13.3 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture will be slowly warmed to room temperature and heated to reflux for 2.0 h. The reaction will be quenched with 5% sodium deuteroxide in D_2O (6.0 mL) carefully. The resulting lithium salts will be filtered and washed with ethyl acetate. The organic layer will be dried over sodium sulfate and filtered. The filtrate will be concentrated and the resulting oily residue will be passed through a Thomson single StEP 40 g column and will be eluted with 7% ethyl acetate/hexanes (120 mL). The clean fractions will be combined and concentrated under vacuum to give compound **2** as colorless oil.

Scheme-4:



S-(-) Methyl Perillate

Synthesis of (S)-4-Isopropenyl-1-cyclohexene-1-deutero methan-α,α'-d2-ol (2)

Lithium aluminum deuteride (LAD, 1.0 M in THF, 16.6 mL, 16.6 mmol) will be added slowly to a cold solution of (*S*)-Methylperillate (**1**, 2.0g, 11 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture will be slowly warmed to room temperature and then stirred at room temperature for 2.0 h. The reaction mixture will be quenched with 5% sodium deuteroxide in D_2O (6.0 mL) carefully. The resulting lithium salts will be filtered and washed with ethyl acetate. The organic layer will be dried over sodium

sulfate and filtered. The filtrate will be concentrated. The resulting oily residue will be passed through a Thomson single StEP 40 g column and will be eluted with 7% ethyl acetate/hexanes (120 mL). The clean fractions will be combined and concentrated under vacuum to give compound **2** as colorless oil.

Example 2 Synthesis of Deuterated iso-perillyl alcohol: 4-isopropylidene-1-cyclohexene-1-methan-α,α'-d2-ol

Scheme:

Synthesis of trifluoromethanesulfonic acid 4-isopropylidenecyclohex-1-enyl ester (2):

A 2.5 M solution of n-Butyl lithium in hexanes (5.6 mL, 14.1 mmol) was added to a solution of diisopropylamine (1.98 mL, 14.1 mmol) in dry THF (30 mL) at -78 °C over a period of 0.5 hr. After stirring for 1.0 h at -78 °C, a solution of ketone (**1**, 1.3g, 9.4 mmol) in dry THF (10 mL) was added over a period of 10 min while maintaining the temperature below -78°C. The reaction mixture was stirred for 1.0 h at -78 °C. A solution of phenyltriflimide (3.53g, 9.86 mmol) in dry THF (15 mL) was added slowly while maintaining the temperature below -78 °C. The reaction mixture was slowly warmed to 0 °C, maintained for 2.0 h at 0 °C and then quenched with saturated ammonium chloride solution. The separated organic layer was washed with water (15 mL), brine (15 mL) and dried over sodium sulfate. The filtered organic layer was concentrated under vacuum. The resulting residue was purified by column chromatography. [Column dimensions: diameter: 6.0 cm, height: 12 cm, silica: 200 mesh, eluted with hexanes (200 mL)] The similar fractions were combined and concentrated under vacuum which gave **2** as an oil. Weight: 0.9 g. Weight yield: 38%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.68 (s, 3H), 1.71 (s, 3H), 2.37 (m, 2H), 2.46 (m, 2H), 2.91 (m, 2H), 5.73 (m, 1H). MS (APCI +ve mode): Molecular ion peak was observed.

Synthesis of 4-isopropylidene cyclohex-1-ene carboxylic acid methyl ester (3):

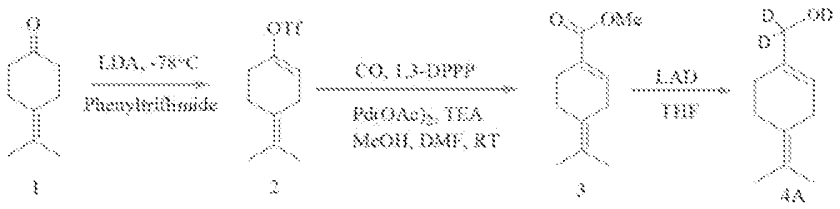
To a solution of compound **2** (0.2g, 0.74 mmol) in N'N-dimethylformamide (1.5 mL) were added methanol (1.0 mL), triethylamine (0.17 mL, 1.2 mmol), 1, 3-bis(diphenylphosphino)propane (0.03 g, 0.07 mmol) and palladium acetate (0.04g, 0.07 mmol). The reaction mixture was degassed and then stirred at room temperature under carbon monoxide (balloon pressure) for 5 h. The reaction mixture was diluted with ethyl acetate (15 mL) and washed with 0.5 N HCl (15 mL), brine (15 mL) and dried over sodium sulfate. The filtered organic layer was concentrated under vacuum and the resulting residue was purified by column chromatography. [Column dimensions: diameter: 6.0 cm, height: 12 cm, silica: 200 mesh, eluted with hexanes (100 mL) followed by ethyl acetate: hexanes (2%, 150 mL)]. The similar fractions were combined and concentrated under vacuum which gave an oil. Weight: 0.07 g. Yield: 52%.

Synthesis of 4-isopropylidene-1-cyclohexene-1-methan-α,α'-d2-ol (4)

Lithium aluminum deuteride (1.0 M in THF, 16.6 mL, 16.6 mmol) will be added slowly to a cold solution of methyl ester (3, 2.0g, 11 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture will be slowly warmed to room temperature and then stirred at room temperature for 2.0 h. The reaction mixture will be quenched with saturated sodium sulfate solution carefully. The resulting lithium salts will be filtered and washed with ethyl acetate. The organic layer will be dried over sodium sulfate and filtered. The filtrate will be concentrated and the resulting oil will be purified by column chromatography to obtain compound **4**.

Example 3 Synthesis of Deuterated iso-perillyl alcohol: 4-Isopropylidene-1-cyclohexene-1-deutero methan-α,α'-d2-ol

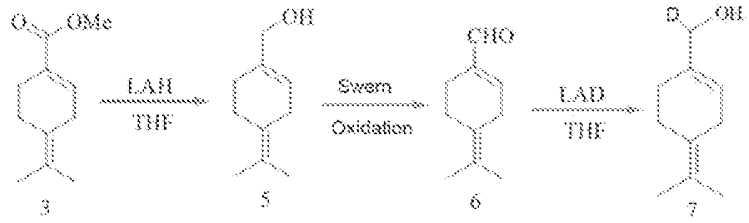
Scheme:



Lithium aluminum deuteride (1.0 M in THF, 16.6 mL, 16.6 mmol) will be added slowly to a cold solution of Methyl ester (3, 2.0g, 11 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture will be slowly warmed to room temperature and then it will be stirred at room temperature for 2.0 h. The reaction mixture will be quenched with 5% sodium deuteroxide in D_2O (6.0 mL) carefully. The resulting lithium salts will be filtered, and washed with ethyl acetate. The organic layer will be dried over sodium sulfate and filtered. The filtrate will be concentrated and the resulting oily residue will be purified by column chromatography to obtain compound 4A.

Example 4 Synthesis of Deuterated iso-perillyl alcohol: 4-Isopropylidene-1-cyclohexene-1-methan-α-d1-ol

Scheme:



Synthesis of 4-isopropylidene cyclohex-1-enyl methanol (5)

Methyl ester (**3**, 1.0 g, 5.54 mmoL) in dry THF (10 mL) was added to lithium aluminum hydride (0.25 g, 6.6 mmoL) in dry THF (20 mL) at 10 °C over a period of 5 min. The mixture was slowly heated to reflux and maintained for 2.0 h. The reaction mixture was cooled and quenched with saturated sodium sulfate solution (2.0 mL). The lithium salts were filtered and washed with hot ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to give a colorless oil. Weight: 0.67 g. Yield: 80%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.65 (s, 3H), 1.69 (s, 3H), 1.77 (bs, OH), 2.09 (m, 2H), 2.33 (t, 2H), 2.79 (br s, 2H); MS (APCI +ve mode): m/e: 152 (M^+, 3.5%), 135.07 (100 %), 107.12 (5%).

Synthesis of 4-isopropylidene-cyclohex-1-ene carbaldehyde (6):

Dry DMSO (0.5 ml) will be added to a cold solution of oxalyl chloride (0.67 mL, 7.8 mmol) in dichloromethane (15 mL) at -78 °C and the mixture will be stirred for 20 min. Alcohol

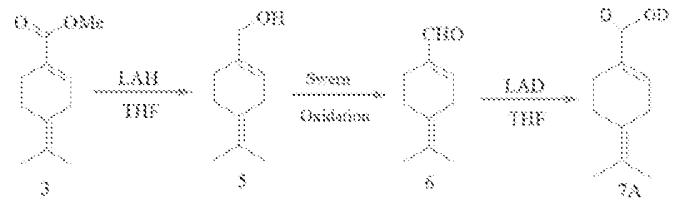
(**5**, 1.0g, 6.5 mmol), in 5 mL of DCM will be added over 10 min and the mixture will be stirred for 1.0 h followed by the addition of triethylamine (0.8 mL). The reaction mixture will be stirred for 0.5 h and then warmed to room temperature. Water (20 mL) will be added and the DCM layer will be separated. The aqueous layer will be extracted with DCM (20 mL) and separated. The combined DCM layer will be washed with water, separated, and will be dried over sodium sulfate. The filtered organic layer will be concentrated under vacuum and the resultant residue will be purified by column chromatography to obtain compound **6**.

Synthesis of 4-isopropylidene-1-cyclohexene-1-methan-α-d1-ol (7):

Lithium aluminum deuteride (1.0 M in THF, 21.2 mL, 21.3 mmol) will be added slowly to a cold solution of adehyde (**6**, 2.0g, 13.3 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture will be slowly warmed to room temperature and then heated to reflux for 2.0 h. The reaction mixture will be quenched with saturated sodium sulfate solution carefully. The resulting lithium salts will be filtered and washed with ethyl acetate. The organic layer will be dried over sodium sulfate and filtered. The filtrate will be concentrated and the resulting oil will be purified by column chromatography to obtain compound **7**.

Example 5 Synthesis of Deuterated iso-perillyl alcohol: 4-Isopropylidene -1-cyclohexene-1-deutero methan-α-d1-ol

Scheme:

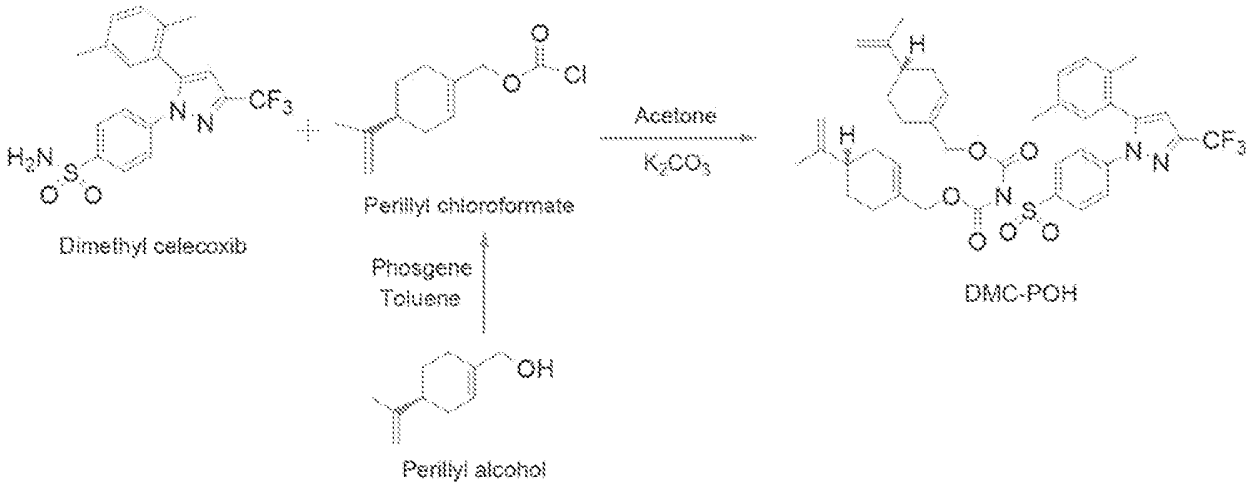


Lithium aluminum deuteride (1.0 M in THF, 21.2 mL, 21.3 mmol) will be added slowly to a cold solution of aldehyde (**6**, 2.0g, 13.3 mmol) in dry THF (20 mL) while maintaining the temperature below 10 °C under N_2. The reaction mixture will be slowly warmed to room temperature and then it will be heated to reflux for 2.0 h. The reaction will be quenched with

5% sodium deuteroxide in D_2O (6.0 mL) carefully and the resulting lithium salts will be filtered, washed with ethyl acetate. The organic layer will be dried over sodium sulfate and filtered. The filtrate will be concentrated and the resulting oily residue will be purified by column chromatography to obtain compound 7A.

Example 6 Synthesis of Dimethyl Celecoxib bisPOH Carbamate (4-(bis-N,N'-4-isopropenyl cyclohex-1-enylmethyloxy carbonyl [5-(2,5-dimethyl phenyl)-3-trifluoromethyl pyrazol-1-yl] benzenesulfonamide)

The reaction scheme is the following:



Phosgene (20% in toluene, 13 ml, 26.2 mmol) was added to a mixture of perillyl alcohol (2.0 grams, 13.1 mmol) and potassium carbonate (5.4 grams, 39.1 mmol) in dry toluene (30 mL) over a period of 30 minutes while maintaining the temperature between 10° C to 15° C. The reaction mixture was allowed to warm to room temperature and stirred for 8.0 hours under N_2. The reaction mixture was quenched with water (30 mL) and the organic layer was separated. The aqueous layer was extracted with toluene (20 mL) and the combined organic layer was washed with water (50 mL x 2), brine (15%, 30 mL) and dried over sodium sulfate (20 grams). The filtered organic layer was concentrated under vacuum to give perillyl chloroformate as an

oil. Weight: 2.5 grams; Yield: 89%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.5 (m, 1H), 1.7 (s, 3H), 1.8 (m, 1H), 2.0 (m, 1H), 2.2 (m, 4H), 4.7 (dd, 4H); 5.87 (m, 1H).

Perillyl chloroformate (0.11 grams, 0.55 mmol) was added slowly to a mixture of dimethyl celecoxib (0.2 grams, 0.50 mmol) and potassium carbonate (0.13 grams, 1.0 mmol) in dry acetone (10 mL) over a period of 5 minutes under N_2. The reaction mixture was heated to reflux and maintained for 3 hours. Since TLC analysis indicated the presence of dimethyl celecoxib (> 60%), another 1.0 equivalent of perillyl chloroformate was added and refluxed for an additional 5 hours. The reaction mixture was cooled and acetone was concentrated under vacuum to give a residue.

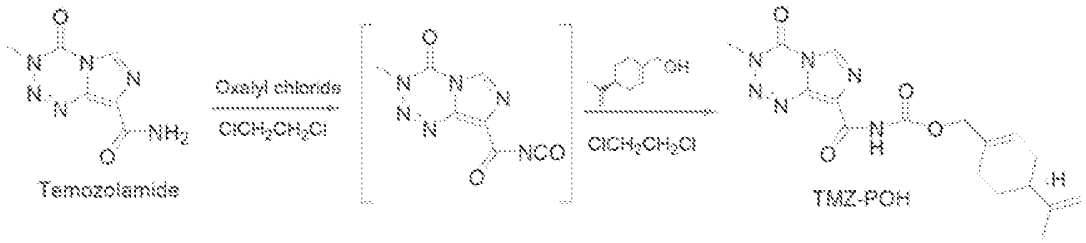
The resulting residue was suspended in water (15 mL) and extracted with ethyl acetate (3x15 mL). The combined organic layer was washed with water (20 mL) followed by brine (15%, 20 mL) and dried over sodium sulfate. The filtered organic layer was concentrated under vacuum to give a residue which was purified by column chromatography [column dimensions: diameter: 1.5 cm, height: 10 cm, silica: 230-400 mesh] and eluted with hexanes (100 mL) followed by a mixture of hexanes/ethyl acetate (95:5, 100 mL). The hexane/ethyl acetate fractions were combined and concentrated under vacuum to give a gummy mass.

The product POH carbamate exhibited a weight of 120 mg and a yield of 31%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.9 (m, 2H), 1.4 (m, 2H), 1.7 (m, 7H*), 1.95 (m, 8H*), 2.1 (m, 4H), 2.3 (s, 3H), 4.4 (d, 2H), 4.7 (dd, 2H), 5.6 (br d, 2H), 6.6 (s, 1H), 7.0 (br s, 1H), 7.12 (d, 1H), 7.19 (d, 1H), 7.4 (d, 2H), 7.85 (d, 2H); MS, m/e: 751.8 (M^+ 3%), 574.3 (100%), 530.5 (45%), 396 (6%).
* N.B. further 2H overlapping from presumed impurity discounted in NMR integration.

The product POH carbamate may be partially or fully deuterated. For example, one or more of the H atoms may be deuterium.

Example 7 Synthesis of Temozolomide POH Carbamate (3-methyl 4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carbonyl)-carbamic acid-4-isopropenyl cyclohex-1-enylmethyl ester)

The reaction scheme is the following:



Oxalyl chloride (0.13 grams, 1.0 mmol) was added slowly to a mixture of temozolomide (OChem Incorporation, 0.1 grams, 0.5 mmol) in 1,2-dichloroethane (10 mL) over a period of 2 minutes while maintaining the temperature at 10° C under N_2. The reaction mixture was allowed to warm to room temperature and then heated to reflux for 3 hours. The excess of oxalyl chloride and 1,2-dichloroethane were removed by concentration under vacuum. The resulting residue was re-dissolved in 1,2-dichlorethane (15 mL) and the reaction mixture was cooled to 10° C under N_2. A solution of perillyl alcohol (0.086 grams, 0.56 mmol) in 1,2-dichloroethane (3 mL) was added over a period of 5 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 14 hours. 1,2-dichloroethane was concentrated under vacuum to give a residue, which was triturated with hexanes. The resulting yellow solid was filtered and washed with hexanes. Weight: 170 mg; Yield: 89%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.4-2.2 (m, 10H), 4.06 (s, 3H), 4.6-4.8 (m, 4H), 5.88 (br s, 1H), 8.42 (s, 1H), 9.31 (br s, 1H); MS, no molecular ion peak was observed. m/e: 314 (100%), 286.5 (17%), 136 (12%).

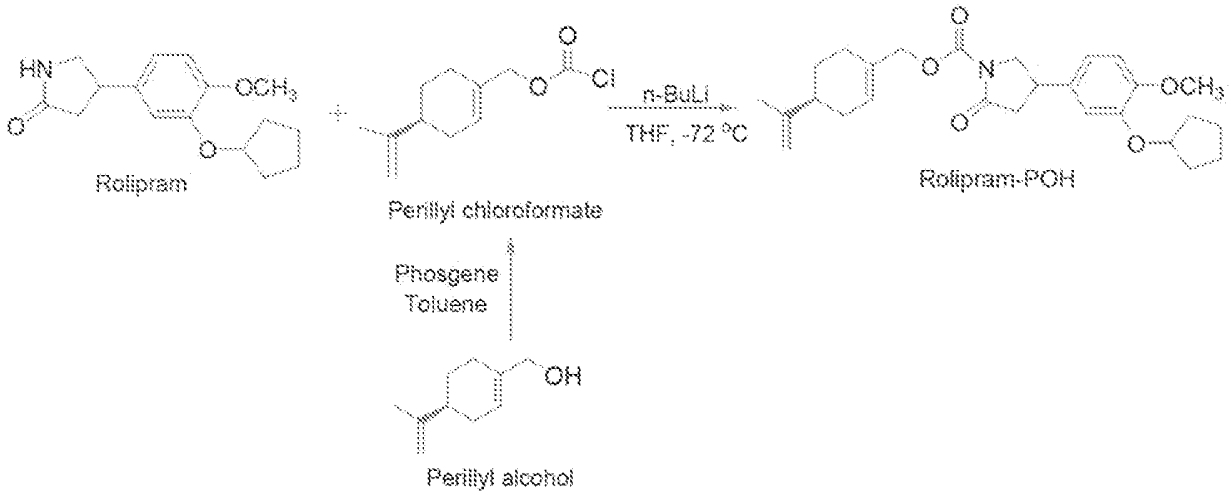
Alternatively, temozolomide POH carbamate was synthesized according to the following procedure. Oxalyl chloride (0.13 grams, 1.0 mmol) was added slowly to a mixture of temozolomide (OChem Incorporation, 0.1 grams, 0.5 mmol) in 1,2-dichloroethane (10 mL) over a period of 2 minutes while maintaining the temperature at 10 °C under N_2. The reaction mixture was allowed to warm to room temperature and then heated to reflux for 3 hours. The excess of oxalyl chloride and 1,2-dichloroethane were removed by concentration under vacuum. The resulting residue was re-dissolved in 1,2-dichlorethane (15 mL) and the reaction mixture was cooled to 10 °C under N_2. A solution of perillyl alcohol (0.086 grams, 0.56 mmol) in 1,2-dichloroethane (3mL) was added over a period of 5 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 14 hours. 1,2-Dichloroethane was concentrated under vacuum to give a residue, which was purified by a short silica-plug column (column dimensions: diameter: 2 cm, height: 3 cm, silica: 230-400 mesh) and eluted with a mixture of

hexanes/ethyl acetate (1:1, 100 mL). The hexane/ethyl acetate fractions were combined and concentrated under vacuum to give a white solid residue which was triturated with heptanes and filtered to obtain a white solid. Weight: 170 mg; Yield: 89%. ^{1}H-NMR (400 MHz, CDCl3): 1.4-2.2 (m, 10H), 4.06 (s, 3H), 4.6-4.8 (m, 4H), 5.88 (br s, 1H), 8.42 (s, 1H), 9.31 (br s, 1H); MS, no molecular ion peak was observed, m/e: 314 (100%), 286.5 (17%), 136 (12%).

The product POH carbamate may be partially or fully deuterated. For example, one or more of the H atoms may be deuterium.

Example 8 Synthesis of Rolipram POH Carbamate (4-(3-cyclopentyloxy-4-methoxy phenyl)-2-oxo-pyrrolidine-1-carboxylic acid 4-isopropenyl cyclohex-1-enylmethyl ester)

The reaction scheme is the following:



Phosgene (20% in toluene, 13 ml, 26.2 mmol) was added to a mixture of perillyl alcohol (2.0 grams, 13.1 mmol) and potassium carbonate (5.4 grams, 39.1 mmol) in dry toluene (30 mL) over a period of 30 minutes while maintaining the temperature between 10° C to 15° C. The reaction mixture was allowed to warm to room temperature and stirred for 8.0 hours under N_2. The reaction mixture was quenched with water (30 mL) and the organic layer separated. The aqueous layer was extracted with toluene (20 mL) and the combined organic layer washed with water (50 mL x 2), brine (15%, 30 mL) and dried over sodium sulfate (20 grams). The filtered organic layer was concentrated under vacuum to give perillyl chloroformate as an oil. Weight:

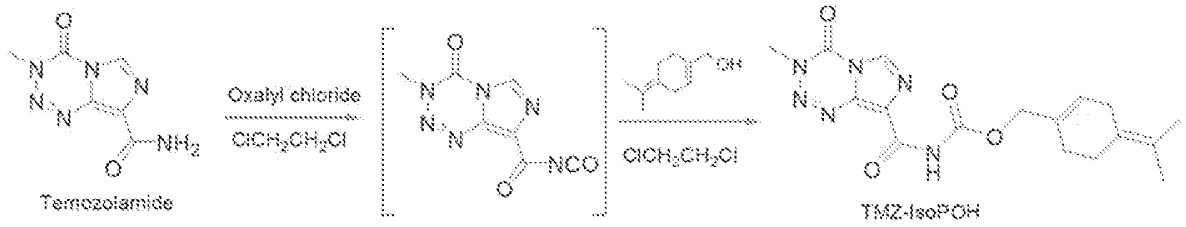
2.5 grams; Yield: 89%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.5 (m, 1H), 1.7 (s, 3H), 1.8 (m, 1H), 2.0 (m, 1H), 2.2 (m, 4H), 4.7 (dd, 4H); 5.87 (m, 1H).

Butyl lithium (2.5 M, 0.18 mL, 0.45 mmol) was added to a solution of rolipram (GL synthesis, Inc., 0.1 grams, 0.36 mmol) in dry THF at -72° C over a period of 5 minutes under N_2. After the reaction mixture was stirred for 1.0 hours at -72° C, perillyl chloroformate (dissolved in 4 mL THF) was added over a period of 15 minutes while maintaining the temperature at -72° C. The reaction mixture was stirred for 2.5 hours and quenched with saturated ammonium chloride (5 mL). The reaction mixture was allowed to warm to room temperature and extracted with ethyl acetate (2x15 mL). The combined organic layer was washed with water (15 mL), brine (15%, 15 mL), and then dried over sodium sulfate. The filtered organic layer was concentrated to give an oil which was purified by column chromatography [column dimensions: diameter: 1.5 cm, height: 10 cm, silica: 230-400 mesh] and eluted with a mixture of 8% ethyl acetate/hexanes (100 mL) followed by 12% ethyl acetate/hexanes (100 mL). The 12% ethyl acetate /hexanes fractions were combined and concentrated under vacuum to yield a gummy solid. Weight: 142 mg; Yield: 86%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.5 (m, 1H), 1.6 (m, 2H), 1.7 (s, 3H), 1.9 (m, 6H), 2.2 (m, 5H), 2.7 (m, 1H), 2.9 (m, 1H), 3.5 (m, 1H), 3.7 (m, 1H), 3.8 (s, 3H), 4.2 (m, 1H), 4.7 (m, 6H), 5.8 (br s, 1H), 6.8 (m, 3H); MS, m/e: 452.1 (M^{+1} 53%), 274.1 (100%), 206.0 (55%).

The product POH carbamate may be partially or fully deuterated. For example, one or more of the H atoms may be deuterium.

Example 9 Synthesis of Iso-POH Conjugated with Temozolamide (TMZ)

The reaction scheme is the following:



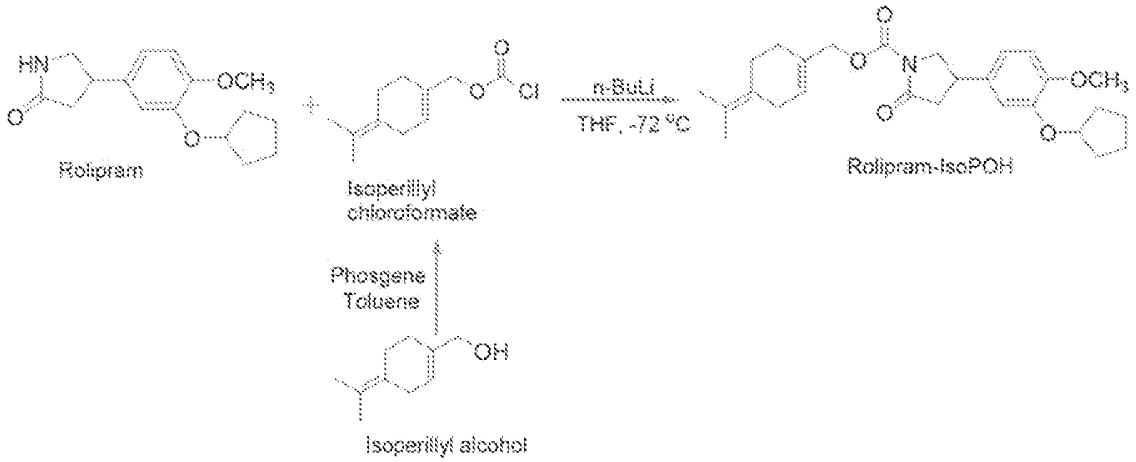
Preparation of (3-Methyl 4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carbonyl)-carbamic acid -4-isopropylidene cyclohex-1-enylmethyl ester:

Oxalyl chloride (0.26 g, 2.0 mmol) will be added slowly to a mixture of Temozolamide (Source: OChem Incorporation, Lot # 0711185A; 0.2 g, 1.0 mmol) in 1,2-dichloroethane (15 mL) over a period of 5 min while maintaining the temperature at 10 °C under N_2. The reaction mixture will be allowed to warm to room temperature and then heated to reflux for 2.5 h. The excess of oxalyl chloride and 1,2-dichloroethane will be removed by concentration under vacuum. The resulting residue will be redissolved in 1,2-dichloroethane (20 mL) and the reaction mixture cooled to 5°C under N_2. A solution of isoperillyl alcohol (0.17 g, 1.12 mmol) in 1,2-dichloroethane (5 mL) will be added over a period of 10 min. The reaction mixture will be allowed to warm to room temperature and stirred for 12 h. 1,2-Dichloroethane will be concentrated under vacuum to give a residue which will be triturated with hexanes. The resulting pale yellow solid will be filtered and washed with hexanes.

The product iso-POH carbamate may be partially or fully deuterated. For example, one or more of the H atoms may be deuterium.

Example 10 Synthesis of Iso-POH Conjugated with Rolipram

The reaction scheme is as follows.



Preparation of 4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-oxo-pyrrolidine-1-carboxylic acid 4-isopropylidene cyclohex-1-enylmethyl ester:

Phosgene (20% in toluene, 19.5 ml, 39.4 mmol) will be added to a mixture of isoperillyl alcohol (3.0 g, 19.7 mmol) and potassium carbonate (8.1 g, 58.6 mmol) in dry toluene (45 mL) over a period of 45 min while maintaining the temperature between 10-12 °C. The reaction

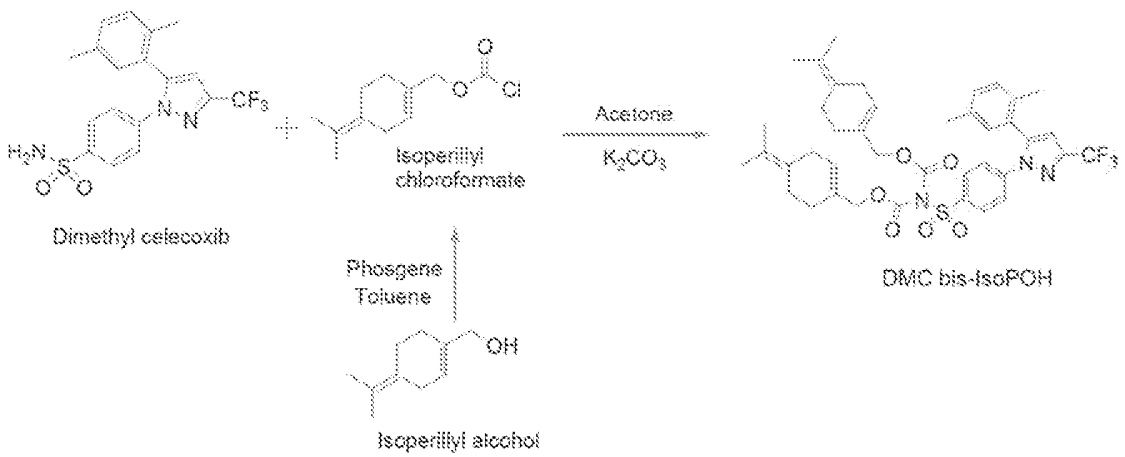
mixture will be allowed to warm to room temperature and stirred for 10 h under N_2. The reaction mixture will be quenched with water (40 mL) and the organic layer separated. The aqueous layer will be extracted with toluene (30 mL) and the combined organic layer washed with water (40 mL x 2), brine (10%, 40 mL), and dried over sodium sulfate (25 g). The filtered organic layer will be concentrated under vacuum to give isoperillyl chloroformate as an oil.

Butyl lithium (2.5 M, 0.36 mL, 0.90 mmol) will be added to a solution of rolipram (Source: GL synthesis, Inc. Lot # GLS-SH-110809; 0.2g, 0.72 mmol) in dry THF (8 mL) at -72 °C over a period of 10 min under N_2. After the reaction mixture being stirred for 1.0 h at -72 °C, isoperillyl chloroformate (0.16 g, 0.76 mmol, dissolved in 4 mL THF) will be added over a period of 10 min while maintaining the temperature at -72 °C. The reaction mixture will be stirred for 3 h and quenched with saturated ammonium chloride (10 mL). The reaction mixture will be allowed to warm to room temperature and extracted with ethyl acetate (2x20 mL). The combined organic layer will be washed with water (20 mL), brine (10%, 25 mL), and dried over sodium sulfate. The filtered organic layer will be concentrated to give an oil which will be purified by column chromatography [Column dimensions: dia: 1.5 cm, height: 15 cm, silica: 230-400 mesh] and eluted with a mixture of 5% ethyl acetate/hexanes (120 mL) followed by 10% ethyl acetate/hexanes (150 mL). The 10% ethyl acetate /hexanes fractions will be combined and concentrated under vacuum to give a gummy solid.

The product iso-POH carbamate may be partially or fully deuterated. For example, one or more of the H atoms may be deuterium.

Example 11 Synthesis of Dimethyl Celecoxib bis iso-POH carbamate conjugate

The reaction scheme is as follows.



Preparation of 4-(Bis-N,N'-4-isopropylidene cyclohex-1-enylmethyloxy carbonyl [5-(2,5-dimethyl phenyl)-3-trifluoromethyl pyrazol-1-yl] benzenesulfonamide:

Phosgene (20% in toluene, 19.5 ml, 39.4 mmol) will be added to a mixture of isoperillyl alcohol (3.0 g, 19.7 mmol) and potassium carbonate (8.1 g, 58.6 mmol) in dry toluene (45 mL) over a period of 45 min while maintaining the temperature between 10-12 °C. The reaction mixture will be allowed to warm to room temperature and stirred for 10 h under N_2. The reaction mixture will be quenched with water (40 mL) and the organic layer separated. The aqueous layer will be extracted with toluene (30 mL) and the combined organic layer washed with water (40 mL x 2), brine (10%, 40 mL), and dried over sodium sulfate (25 g). The filtered organic layer will be concentrated under vacuum to give isoperillyl chloroformate as an oil.

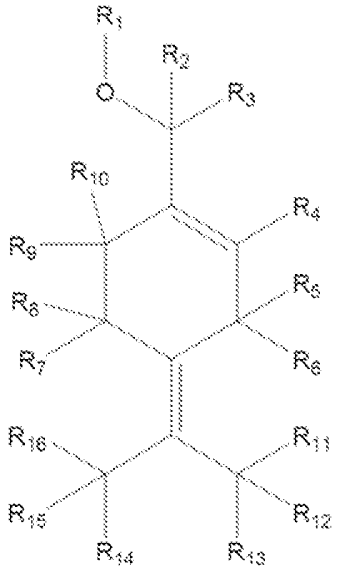
Isoperillyl chloroformate (0.22 g, 1.0 mmol) will be added slowly to a mixture of dimethyl celecoxib (0.2 g, 0.50 mmol) and potassium carbonate (0.14 g, 1.0 mmol) in dry acetone (25 mL) over a period of 5 min under N_2. The reaction mixture will be heated to reflux and maintained for 4 h. The reaction mixture will be cooled and the acetone concentrated under vacuum. The resulting residue will be suspended in water (25 mL) and extracted with ethyl acetate (3x20 mL). The combined organic layer will be washed with water (40 mL), followed by brine (10%, 30 mL), and dried over sodium sulfate. The filtered organic layer will be concentrated under vacuum to give a residue which will be purified by column chromatography [Column dimensions: dia: 1.5 cm, height: 15 cm, silica: 230-400 mesh] and eluted with hexanes (100 mL) followed by a mixture of hexanes/ethyl acetate (95:5, 100 mL). The hexane/ethyl acetate fractions will be combined and concentrated under vacuum to give a gummy mass.

The product iso-POH carbamate may be partially or fully deuterated. For example, one or more of the H atoms may be deuterium.

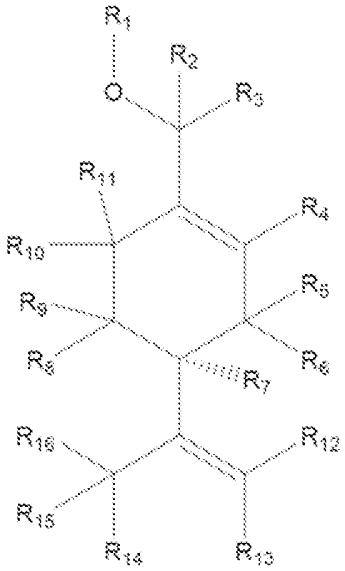
The scope of the present invention is not limited by what has been specifically shown and described hereinabove. Those skilled in the art will recognize that there are suitable alternatives to the depicted examples of materials, configurations, constructions and dimensions. Numerous references, including patents and various publications, are cited and discussed in the description of this invention. The citation and discussion of such references is provided merely to clarify the description of the present invention and is not an admission that any reference is prior art to the invention described herein. All references cited and discussed in this specification are incorporated herein by reference in their entirety. Variations, modifications and other implementations of what is described herein will occur to those of ordinary skill in the art without departing from the spirit and scope of the invention. While certain embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications may be made without departing from the spirit and scope of the invention. The matter set forth in the foregoing description and accompanying drawings is offered by way of illustration only and not as a limitation.

What is claimed is:

1. A deuterium-enriched compound of Formula I or Formula II



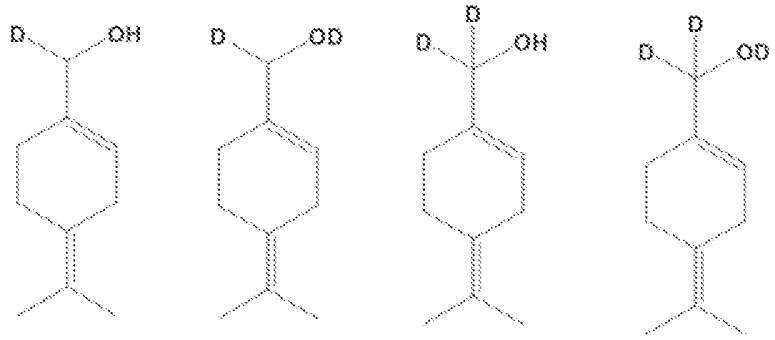
Formula I

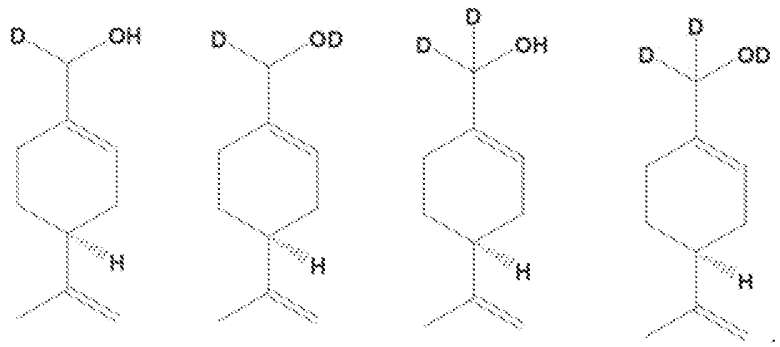


Formula II

or a pharmaceutically acceptable salt 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} and R_{16} are independently selected from the group consisting of hydrogen-1 and deuterium, 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} and R_{16} is deuterium; and wherein the abundance of deuterium is at least about 10%.

2. The deuterium-enriched compound of claim 1, selected from the group consisting of:





3. A deuterium-enriched perillyl alcohol or isoperillyl alcohol, wherein the abundance of deuterium is at least about 10%.

4. The deuterium-enriched compound of claims 1, 2 or 3, conjugated with a therapeutic agent to form a carbamate.

5. A deuterium-enriched perillyl alcohol carbamate or isoperillyl alcohol carbamate, wherein the abundance of deuterium is at least about 10%.

6. The deuterium-enriched compound of any of claims 1 - 5, wherein the abundance of deuterium is at least about 20% or at least about 30%.

7. The deuterium-enriched compound of claim 5, wherein perillyl alcohol or isoperillyl alcohol is conjugated with a therapeutic agent to form a carbamate.

8. The deuterium-enriched compound of claims 4 or 7, wherein the therapeutic agent is a chemotherapeutic agent selected from the group consisting of a DNA alkylating agent, a topoisomerase inhibitor, an endoplasmic reticulum stress inducing agent, a platinum compound, an antimetabolite, an enzyme inhibitor, and a receptor antagonist.

9. The deuterium-enriched compound of claims 4 or 7, wherein the therapeutic agent is selected from the group consisting of dimethyl celocoxib (DMC), temozolomide (TMZ) and rolipram.

10. A pharmaceutical composition comprising the deuterium-enriched compound of any of claims 1 – 3.

11. The pharmaceutical composition of claim 10, further comprising a chemotherapeutic agent selected from the group consisting of a DNA alkylating agent, a topoisomerase inhibitor, an endoplasmic reticulum stress inducing agent, a platinum compound, an antimetabolite, an enzyme inhibitor, and a receptor antagonist.

12. The pharmaceutical composition of claim 10, further comprising a therapeutic agent selected from the group consisting of dimethyl celocoxib (DMC), temozolomide (TMZ) and rolipram.

13. A pharmaceutical composition comprising the deuterium-enriched compound of any of claims 4 – 9.

14. A method for treating a disease in a mammal, comprising the step of administering to the mammal a pharmaceutical composition comprising a therapeutically effective amount of a deuterium-enriched perillyl alcohol, a deuterium-enriched isoperillyl alcohol, a deuterium-enriched perillyl alcohol carbamate, and/or a deuterium-enriched isoperillyl alcohol carbamate.

15. A method for treating a disease in a mammal, comprising the step of administering to the mammal a pharmaceutical composition of any of claims 10 - 13.

16. The method of claims 14 or 15, wherein the disease is cancer.

17. The method of claim 16, wherein the cancer is a tumor of the nervous system.

18. The method of claim 17, wherein the disease is glioblastoma.

19. The method of claims 14 or 15, wherein the pharmaceutical composition is administered by inhalation, intranasally, orally, intravenously, subcutaneously or intramuscularly.

20. The method of claims 14 or 15, further comprising the step of treating the mammal with radiation.

21. The method of claim 20, wherein the pharmaceutical composition is administered before, during or after radiation.

22. The method of claims 14 or 15, further comprising the step of administering to the mammal a chemotherapeutic agent.

23. The method of claim 22, wherein the pharmaceutical composition is administered before, during or after the administration of a chemotherapeutic agent.

24. The method of claim 22, wherein the chemotherapeutic agent is selected from the group consisting of a DNA alkylating agent, a topoisomerase inhibitor, an endoplasmic reticulum stress inducing agent, a platinum compound, an antimetabolite, an enzyme inhibitor, and a receptor antagonist.

25. The method of claim 22, wherein the chemotherapeutic agent is selected from the group consisting of dimethyl celocoxib (DMC), temozolomide (TMZ) and rolipram.

26. The method of claims 14 or 15, wherein the pharmaceutical composition is administered using a nasal delivery device.

27. The method of claim 26, wherein the nasal delivery device is selected from the group consisting of an intranasal inhaler, an intranasal spray device, an atomizer, a nebulizer, a metered dose inhaler (MDI), a pressurized dose inhaler, an insufflator, a unit dose container, a pump, a dropper, a squeeze bottle and a bi-directional device.

摘要

本发明提供了富含氘的单萜或倍半萜，例如紫苏醇；或者富含氘的单萜或倍半萜的异构体或类似物，例如异紫苏醇 。本发明还提供了富含氘的单萜或倍半萜的衍生物，例如紫苏醇氨基甲酸酯；或者富含氘的单萜或倍半萜的异构体或类似物的衍生物，例如异紫苏醇氨基甲酸酯 。富含氘的衍生物可以是与诸如化疗剂的治疗剂缀合的紫苏醇或异紫苏醇 。本发明还提供了治疗诸如癌症的疾病的方法，其包括向患者递送治疗有效量的富含氘的化合物的步骤 。