US 20070088075A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0088075 A1**

Chou et al. (43) **Pub. Date: Apr. 19, 2007**

(54) **DEUTERATED AMINOCYCLOHEXYL ETHER COMPOUNDS AND PROCESSES FOR PREPARING SAME**

(75) Inventors: **Doug Ta Hung Chou**, Vancouver (CA); **Bertrand M. C. Plouvier**, Vancouver (CA); **Peter Pang**, Richmond (CA); **James Gee Ken Yee**, Vancouver (CA); **Jeffery Jerome Wheeler**, Surrey (CA); **Aregahegn S. Yifru**, Somerville, MA (US); **Allen W. Davidoff**, Calgary (CA)

Correspondence Address:
SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104 (US)

(73) Assignee: **Cardiome Pharma Corp.**, Vancouver (CA)

(21) Appl. No.: **11/581,225**

(22) Filed: **Oct. 13, 2006**

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/US06/23668, filed on Jun. 15, 2006.
Continuation-in-part of application No. PCT/US05/11124, filed on Mar. 31, 2005.

(60) Provisional application No. 60/748,248, filed on Dec. 7, 2005. Provisional application No. 60/690,989, filed on Jun. 15, 2005. Provisional application No. 60/586,922, filed on Jul. 12, 2004. Provisional application No. 60/559,405, filed on Apr. 1, 2004.

Publication Classification

(51) **Int. Cl.**
A61K 31/4015 (2006.01)

(52) **U.S. Cl.** **514/424**; 548/541

(57) **ABSTRACT**

This invention is directed to deuterated aminocyclohexyl ether compounds and processes for preparing same and methods of using same.

DEUTERATED AMINOCYCLOHEXYL ETHER COMPOUNDS AND PROCESSES FOR PREPARING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of PCT Patent Application No. PCT/US06/23668, filed Jun. 15, 2006, now pending, which claims priority to U.S. Provisional Patent Application No. 60/690,989, filed Jun. 15, 2005, and U.S. Provisional Patent Application No. 60/748,248, filed Dec. 7, 2005, which applications are incorporated herein by reference in their entireties.

[0002] This application is also a continuation-in-part of PCT Patent Application No. PCT/US05/11124, filed Mar. 31, 2005, now pending, which claims priority to U.S. Provisional Patent Application No. 60/559,405, filed Apr. 1, 2004, and U.S. Provisional Patent Application No. 60/586,992, filed Jul. 8, 2004, which applications are incorporated herein by reference in their entireties.

[0003] This application also claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 60/748,248, filed Dec. 7, 2005; of U.S. which application is incorporated herein by reference in its entirety.

FIELD OF INVENTION

[0004] The present invention is generally directed towards deuterated aminocyclohexyl ether compounds and methods for their preparation. In particular, this invention is directed to deuterated-trans-(1R,2R)-aminocyclohexyl ether compounds, deuterated-trans-(1S,2S)-aminocyclohexyl ether compounds, deuterated cis-(1R,2S)-aminocyclohexyl ether compounds, and deuterated cis-(1S,2R)aminocyclohexyl ether compounds, as well as various intermediates, substrates and stereoisomers and methods for their preparation. The deuterated compounds of the invention are useful as standards in determining the biological efficacy of the corresponding non-deuterated compounds. The deuterated compounds of the invention are also useful in treating arrhythmia in humans.

BACKGROUND OF THE INVENTION

[0005] Deuterated drugs are widely used in studies of metabolism of drugs and toxic substances in humans and other animals. The deuterated forms of drugs often have different actions than the protonated forms. Some deuterated drugs show different transport processes. Most are more resistant to metabolic changes, especially those changes mediated by cytochrome P450 systems. Deuteration may also change the pathway of drug metabolism (metabolic switching). Changed metabolism may lead to increased duration of action and lower toxicity. It may also lead to lower activity, if the drug is normally changed to the active form in vivo. Deuteration can also lower the genotoxicity of the anticancer drug tamoxifen and other compounds. Deuteration increases effectiveness of long-chain fatty acids and fluoro-D-phenylalanine by preventing their breakdown by target microorganisms.

[0006] Deuterium (D) is a nonradioactive isotope which

Deuterium behaves similarly to ordinary hydrogen, but it can be distinguished from ordinary hydrogen by its mass using mass spectrometry or infrared spectrometry. Consequently, deuterated compounds have been long used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action and metabolic-pathway of the non deuterated parent compound. Such metabolic studies are important in the design of safe, effective therapeutic drugs.

[0007] Incorporation of deuterium for a hydrogen atom in a drug can give rise to an isotope effect that can alter the pharmacokinetics of the drug. This effect is usually insignificant if the label is placed in a molecule at the metabolically inert position of the molecule. For instance, deuteration, as exemplified by deuterated Rapamycin (see U.S. Pat. No. 6,503,921), Cyclosporine (see U.S. Pat. No. 6,613,739) or Nifedipine (see U.S. Pat. No. 5,846,514) has been reported to alter the pharmacokinetics of a drug. Forster et al. (Isotechnica, AB) have shown that deuteration can enhance duration of action.

[0008] Deuterium-labeling of a drug can alter its physicochemical properties such as pKa and lipid solubility. These changes may influence the fate of the drug at different steps along its passage through the body. Absorption, distribution, metabolism or excretion can be changed. Absorption and distribution are processes that depend primarily on the molecular size and the lipophilicity of the substance.

[0009] Drug metabolism can give rise to large isotopic effect if the breaking of a chemical bond to a deuterium atom is the rate limiting step in the process. While some of the physical properties of a deuterium-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. In any reaction in which the breaking of this bond is the rate limiting step, the reaction will proceed slower for the molecule with the heavy isotope due to kinetic isotope effect. A reaction involving breaking a C-D bond can be up to 700 percent slower than a similar reaction involving breaking a C—H bond.

[0010] More caution has to be observed when using deuterium-labeled drugs. If the C-D bored is not involved in any of the steps leading to the metabolite, there may not be any effect to alter the behavior of the drug. If deuterium is placed at a site involved in the metabolism of a drug, an isotope effect will be observed only if breaking of the C-D bond is the rate limiting step. There are evidences to suggest that whenever cleavage of an aliphatic C—H bond occurs, usually by oxidation catalyzed by a mixed-function oxidase, replacement of the hydrogen by deuterium will lead to observable isotope effect. It is also important to understand that the incorporation of deuterium at the site of metabolism slows its rate to the point where another metabolite produced by attack at a carbon atom not substituted by deuterium becomes the major pathway by a process called "metabolic switching".

[0011] It is also observed that one of the most important metabolic pathways of compounds containing aromatic sys-

involves cleavage of the C—H bond, it is often not accompanied by an isotope effect, because the cleavage of this bond is mostly not involved in the rate-limiting step. The substitution of hydrogen by deuterium at the stereo center will induce a greater effect on the activity of the drug.

[0012] Clinically relevant questions with respect to deuterium-labeled drugs include the toxicity of the drug and its metabolite derivatives, the changes in distribution or elimination (enzyme induction), lipophilicity which will have an effect on absorption of the drug. Replacement of hydrogen by deuterium at the site involving the metabolic reaction will lead to increased toxicity of the drug. Replacement of hydrogen by deuterium at the aliphatic carbons will have an isotopic effect to a larger extent. Deuterium placed at an aromatic carbon atom, which will be the site of hydroxylation, may lead to an observable isotope effect, although this is less often the case than with aliphatic carbons. In few cases, such as in penicillin, the substitution on the aromatic ring will induce the restriction of rotation of the ring around the C—C bond leading to a favorable stereo-specific situation to enhance the activity of the drug.

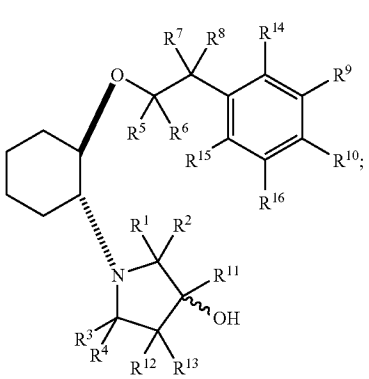
[0013] Side-effects with acute deuterium dosing have been shown to be transitory with no demonstrated evidence of permanent deleterious action. The threshold of deuterium toxicity has been defined in animals and is far in excess of concentrations conceivably used in human studies. The possibility that deuterium may have additional beneficial pharmacological applications can therefore not be excluded.

[0014] PCT Published Patent Application, WO 2004/099137 discloses a class of aminocyclohexyl ether compounds as being useful in the treatment of arrhythmias. One class of compounds disclosed therein are particularly effective in the treatment and/or prevention of arrhythmia, particularly atrial fibrillation.

[0015] There exists, therefore, a need to prepare deuterated compounds which can be used, inter alia, as standards or tracer molecules in biological or bioanalytical assays in order to determine the biological effectiveness and metabolic pathway for a class of compounds disclosed in PCT Published Patent Application WO 99/50225.

SUMMARY OF THE INVENTION

[0016] In one aspect, this invention is directed to compounds of formula (I):



(I)

wherein:

[0017] R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently hydrogen or deuterium;

[0018] R^9 and R^{10} are each independently hydroxy, methoxy or —OCD_3; and

[0019] at least one deuterium is present;

[0020] as an isolated stereoisomer or as a mixture of stereoisomers;

[0021] or a pharmaceutically acceptable salt thereof.

[0022] In another aspect, this invention is directed to compounds of formula (I), as described above, wherein:

[0023] R^1 and R^2 are both hydrogen or are both deuterium;

[0024] R^3 and R^4 are both hydrogen or are both deuterium;

[0025] R^5 and R^6 are both hydrogen or are both deuterium;

[0026] R^7 and R^8 are both hydrogen or are both deuterium;

[0027] R^9 and R^{10} are each independently hydroxy, methoxy or —OCD_3;

[0028] R^{11} is hydrogen or deuterium;

[0029] R^{12} and R^{13} are both hydrogen or are both deuterium; and

[0030] R^{14}, R^{15} and R^{16} are each hydrogen;

[0031] wherein at least one of the following applies:

[0032] a) R^1 and R^2 are both deuterium;

[0033] b) R^3 and R^4 are both deuterium;

[0034] c) R^5 and R^6 are both deuterium;

[0035] d) R^7 and R^8 are both deuterium;

[0036] e) R^9 is —OCD_3;

[0037] f) R^{10} is —OCD_3;

[0038] g) R^{11} is deuterium; or

[0039] h) R^{12} and R^{13} are both deuterium;

[0040] as an isolated stereoisomer or as a mixture of stereoisomers;

[0041] or a pharmaceutically acceptable salt thereof.

[0042] In another aspect, this invention is directed to pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound of formula (I), as described above, as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

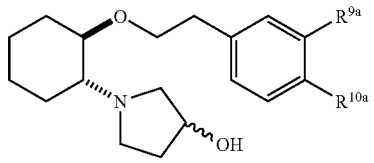
[0043] In another aspect, this invention is directed to methods of treating arrhythmia in a human, wherein the methods comprise administering to the human in need thereof a therapeutically effective amount of a compound of formula (I), as described above, as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0044] In another aspect, this invention is directed to

as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0045] In another aspect, this invention is directed to methods of determining the concentration of a compound in a biological matrix, wherein the method comprises contacting a compound of formula (I), as described above, where R^{14}, R^{15} and R^{16} are each hydrogen, as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, with a biological matrix containing a compound of formula (1):

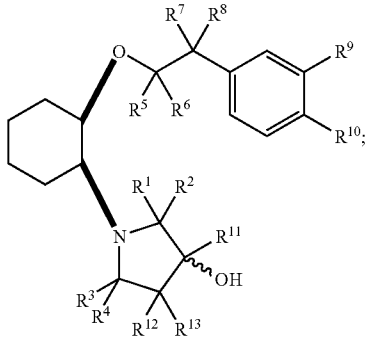
(1)



wherein each R^{9a} and R^{10a} are independently hydroxy or methoxy; as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof; and determining the concentration of the compound of formula (1) in the biological matrix.

[0046] In another aspect, this invention is directed to compounds of formula (II):

(II)



wherein:

[0047] R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{11}, R^{12} and R^{13} are each independently hydrogen or deuterium;

[0048] R^9 and R^{10} are each independently hydroxy, methoxy or —OCD_3; and

[0049] at least one deuterium is present;

[0050] as an isolated stereoisomer or as a mixture of stereoisomers;

[0051] or a pharmaceutically acceptable salt thereof.

[0052] In another aspect, this invention is directed to compounds of formula (II) described above, wherein:

[0053] R^1 and R^2 are both hydrogen or are both deuterium;

[0054] R^3 and R^4 are both hydrogen or are both deuterium;

[0056] R^7 and R^8 are both hydrogen or are both deuterium;

[0057] R^9 and R^{10} are each independently hydroxy, methoxy or —OCD_3;

[0058] R^{11} is hydrogen or deuterium; and

[0059] R^{12} and R^{13} are both hydrogen or are both deuterium;

[0060] wherein at least one of the following applies:

[0061] a) R^1 and R^2 are both deuterium;

[0062] b) R^3 and R^4 are both deuterium;

[0063] c) R^5 and R^6 are both deuterium;

[0064] d) R^7 and R^8 are both deuterium;

[0065] e) R^9 is —OCD_3;

[0066] f) R^{10} is —OCD_3;

[0067] g) R^{11} is deuterium; or

[0068] h) R^{12} and R^{13} are both deuterium;

[0069] as an isolated stereoisomer or as a mixture of stereoisomers;

[0070] or a pharmaceutically acceptable salt thereof.

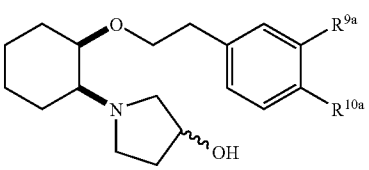
[0071] In another aspect, this invention is directed to pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound of formula (II), as described above, as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0072] In another aspect, this invention is directed to methods of treating arrhythmia in a human, wherein the methods comprise administering to the human in need thereof a therapeutically effective amount of a compound of formula (II), as described above, as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0073] In another aspect, this invention is directed to methods of preparing compounds of formula (II), as described above, as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof.

[0074] In another aspect, this invention is directed to methods of determining the concentration of a compound in a biological matrix, wherein the method comprises contacting a compound of formula (II), as described above, as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof, with a biological matrix containing a compound of formula (2):

(2)



wherein each R^{9a} and R^{10a} are independently hydroxy or methoxy; as an isolated stereoisomer or as a mixture of stereoisomers, or a pharmaceutically acceptable salt thereof; and determining the concentration of the compound of formula (2) in the biological matrix.

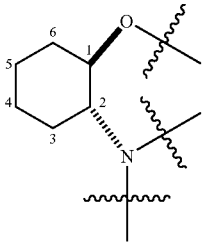
[0075] These and other aspects of the invention will be apparent upon reference to the following detailed description. To this end, various references are set forth herein which describe in more detail certain background information, procedures, compounds and/or compositions, and are each hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

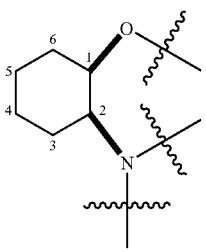
[0076] An understanding of the present invention may be aided by reference to the following explanation of conventions used herein and definitions:

[0077] The compounds of formula (I) and the compounds of formula (II) have an ether oxygen atom at position 1 of a cyclohexane ring, and an amine nitrogen atom at position 2 of the cyclohexane ring, with other positions numbered in corresponding order as shown below in Structure (Aa) and Structure (Ab), respectively, below:

(Aa)



(Ab)



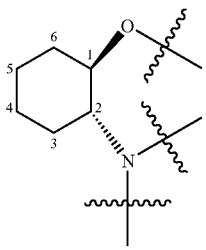
[0078] The bonds from the cyclohexane ring to the 1-oxygen and 2-nitrogen atoms in the Structure (Aa) above are disposed in the trans relationship. Therefore, the stereochemistry of the amine and ether substituents of the cyclohexane ring in Structure (Aa) is (1R,2R)-trans or (1S,2S)-trans. The bonds from the cyclohexane ring to the 1-oxygen and 2-nitrogen atoms in the Structure (Ab) above are disposed in the cis relationship. Therefore, the stereochemistry of the amine and ether substituents of the cyclohexane ring in Structure (Ab) is (1R,2S)-cis or (1R,2S)-cis.

[0079] Following the standard chemical literature description practice and as used in this specification, a dashed full bond, as illustrated above in Structure (Aa) and a dashed full bond, as illustrated above in Structure (Aa), means that the substituents, in this case the amine and ether substituents, are in a trans-configuration with respect to the plane of the ring.

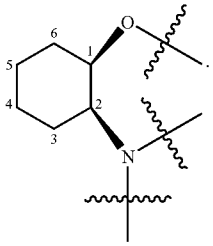
[0080] Following the standard chemical literature description practice and as used in this specification, a solid full bond, as illustrated above in Structure (Ab) and a solid full bond, as illustrated above in Structure (Ab), means that the substituents, in this case the amine and ether substituents, are in a cis-configuration with respect to the plane of the ring.

[0081] Following the standard chemical literature description practice and as used in this specification, a full wedge bond, as exemplified below in Structure (Ac), means that the substituent bonded to the ring by this bond, in this case the ether substituent, is above the ring plane as illustrated on the page in a two dimensional representation, and a dashed wedge bond, as exemplified below in Structure (Ac), means that the substituent bonded to the ring by this bond, in this case the amine substituent, is below the ring plane as shown on the page in a two dimensional representation. In contrast, two full wedge bonds, as exemplified below in Structure (Ad), means that both substituents bonded to the ring by these bonds, in this case both the ether and the amino substituent, are above the ring plane as illustrated on the page in a two dimensional representation:

(Ac)



(Ad)



[0082] In a similar manner, as exemplified below in Structure (Ae), the ether substituent is below the ring plane and the amino substituent is above the ring plane, as shown on the page in a two dimensional representation. In contrast, as exemplified below in Structure (Af), both the ether and the

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.