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(54) **Synthesis of deuterated benzodioxoles**

Synthese deuterierter Benzodioxole

Synthèse de benzodioxoles deutériés

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(56) References cited:
WO-A-2007/016361 **WO-A-2007/016431**
WO-A-2007/058998 **US-A1- 2007 191 381**

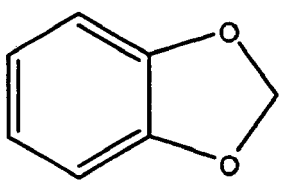
- **IWASA K ET AL: "Biotransformations of protoberberines in cell cultures of dicentra spectablis" PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 46, no. 8, 1 December 1997 (1997-12-01), pages 1359-1363, XP004293606 ISSN: 0031-9422**

EP 2 200 997 B9

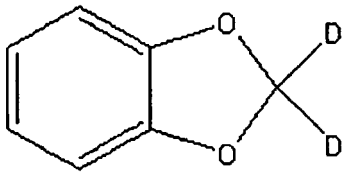
Description

BACKGROUND OF THE INVENTION

[0001] It has been reported that improvements in drug performance can be achieved by incorporating deuterium into specific sites of the active agent of certain approved pharmaceuticals. Examples include paroxetine (see WO 2007/016431 and US2007/0112031) and tadalafil (see US2007/0191381). The above-mentioned drugs all comprise benzo[*d*][1,3]dioxole groups. The methylenedioxy carbon of the benzo[*d*][1,3]dioxole group in paroxetine and tadalafil is one of the positions where deuterium incorporation is reported to provide for improved drug performance. The structures of benzo[*d*][1,3]dioxole and d_2-benzo[*d*][1,3]dioxole (i.e., benzo[*d*][1,3]dioxole with two deuteriums at the methylenedioxy carbon) are shown below:

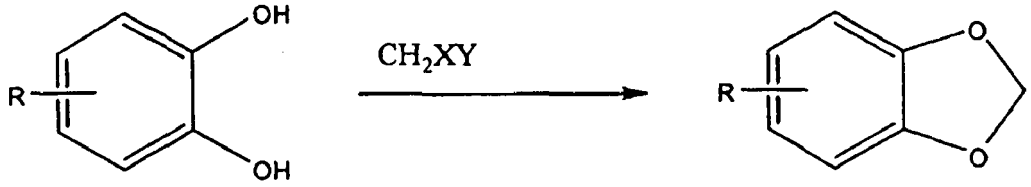


Benzo[*d*][1,3]dioxole

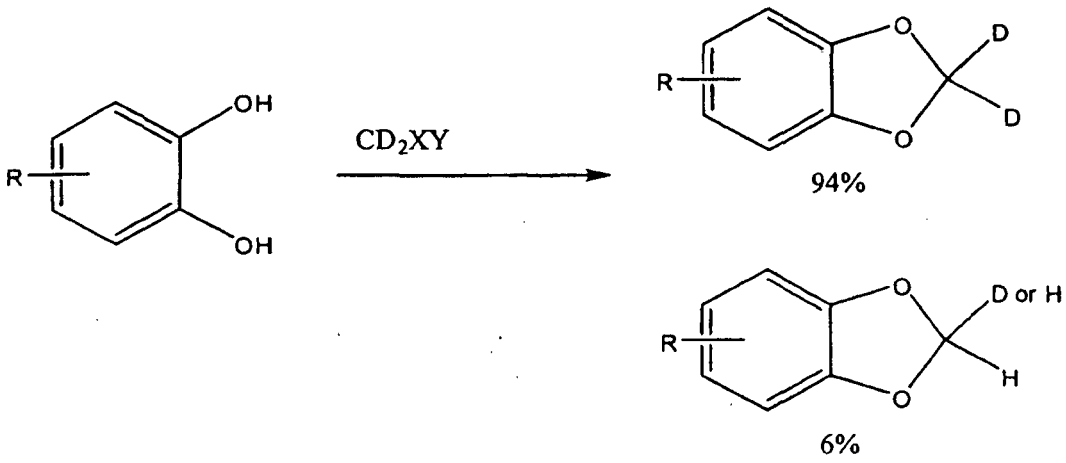


d_2-Benzo[*d*][1,3]dioxole

[0002] However, site-specific deuterium incorporation adds another level of complexity in developing suitable commercial syntheses. Specifically, reactions used to incorporate the deuterium should use reagents that are economical and that result in both a high chemical and isotopic yield. Total syntheses of paroxetine, tadalafil and the natural product berberine typically utilize benzo[*d*][1,3]dioxole derivatives as synthetic intermediates. Benzo[*d*][1,3]dioxole derivatives are typically made by reacting 1,2-catechols with dihalomethanes (CH_2XY, wherein X and Y are halides that are the same or different):



Using deuterated dihalomethanes (CD_2XY) to prepare d_2-benzo[*d*][1,3]dioxole results in low incorporation of deuterium into the benzo[*d*][1,3]dioxole product, i.e., typically no greater than about 94% deuterium incorporation at each labeled site:



[0003] The low isotopic yield is less than desired for commercial syntheses of deuterated analogues of paroxetine, tadalafil and berberine comprising d_2-benzo[*d*][1,3]dioxole groups.

[0004] WO 2007/058998 describes substituted phenylpiperidines with serotoninergic activity and enhanced therapeutic properties.

[0005] WO 2007/016361 discloses derivatives of tadalafil optionally further substituted with deuterium atoms in place of normally abundant hydrogen.

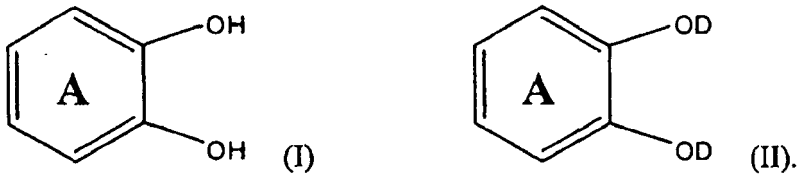
[0006] Iwasa et al (Phytochemistry, Vol. 46, no. 8, 1 December 1997, pp. 1359-1363) describes biotransformations of protoberberines in cell cultures of *Dicentra spectablis.*

SUMMARY OF THE INVENTION

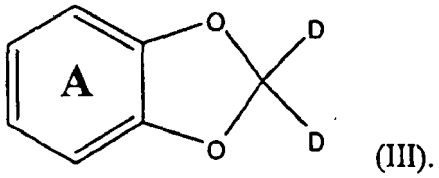
[0007] The invention relates to the process of the appended claims.

[0008] It has now been found that reacting deuterated dihalomethanes with catechols comprising deuterated phenolic groups increases the isotopic yield of the resulting d_2- benzo[*d*][1,3]dioxole to greater than 99.0% (see Examples 1-7). Based on this discovery, a novel two-step method for preparing d_2-benzo[*d*][1,3]dioxoles in high isotopic and chemical yield using inexpensive reagents is disclosed herein.

[0009] In one embodiment, the first step of the process for preparing d_2-benzo[*d*][1,3]dioxole comprises reacting a catechol represented by Structural Formula (I) with a source of deuterium cation (also referred to herein as "D^+") to form a deuterated catechol having an isotopic enrichment of deuterium of at least 75% and represented by Structural Formula (II):



[0010] The second step of the process comprises reacting the deuterated catechol represented by Structural Formula (II) with base and a dihalodideuteromethane to form a d_2-benzo[*d*][1,3]dioxole represented by Structural Formula (III):



[0011] Ring A in the deuterated catechol and d_2-benzo[*d*][1,3]dioxole is substituted with one or more groups, provided that the substituent group(s) do not undergo significant reaction with the D^+ source, the base or the dihalodideuteromethane.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

FIG. 1 depicts the drug-drug interaction potential between Test Compound A and tamoxifen.
FIGS. 2A and 2B depicts the inactivation of CYP2D6 of Test Compound A compared to paroxetine.
FIG. 3 provides the k_{INACT} curve for paroxetine.
FIG..4 depicts the metabolic stability of paroxetine and Test Compound A in rat liver microsomes.
FIG. 5 depicts the metabolic stability of paroxetine and Test Compound A in human liver microsomes.

DETAILED DESCRIPTION OF THE INVENTION

[0013] A source of D^+ is utilized when converting the catechol represented by Structural Formula (I) to the deuterated catechol represented by Structural Formula (II). This reaction is hereinafter referred to as the "Deuterium/Proton Exchange Reaction".

[0014] A source of deuterium cation is a compound having an exchangeable D^+, typically a compound having a pK_a less than about 17 and which donates D^+ in place of a proton (H^+). Suitable examples include: i) solvents such as D_2O; ii) deuterated alcoholic solvents (ROD, where R is, for example, a C_1-C_5 straight or branched alkyl group) such as

CH_3OD and CH_3CH_2OD; and iii) acids such as DCl, D_2SO_4, DNO_3 and deuterated sulfonic acids (e.g., CH_3SO_3D). D_2O, CH_3OD and DCl are most commonly used.

[0015] When the source of D^+ has a high pK_a (e.g., D_2O and CH_3OD), it is commonly used as the solvent. Other reagents can be added to increase the reaction rate. In one example, the other reagent is both a source of deuterium cation and a strong acid (e.g. DCl, D_2SO_4, DNO_3 and deuterated sulfonic acids such as CH_3SO_3D). Alternatively, the other reagent is a base that can deprotonate a phenolic group; to prevent isotopic dilution, potentially exchangeable protons in the base are preferably replaced with deuterium. Examples of suitable bases include NaH, MOD, $X(OD)_2$, MOR and $X(OR)_2$, wherein M is a monovalent cation such as Li^+, Na^+ or K^+; X is a divalent cation such as Mg^{+2} and Ca^{+2}; and R is a C_1-C_5 straight or branched alkyl. Optionally, aprotic solvents that are miscible with D_2O or CH_3OD are added as co-solvents. Examples include tetrahydrofuran, *N*-methylpyrrolidinone, dimethylsulfoxide, acetonitrile and dioxane.

[0016] The Deuterium/Proton Exchange Reaction is commonly carried out at temperatures between room temperature and reflux for two to 48 hours (h); more commonly at room temperature for about 24 h.

[0017] The source of D^+ and the starting catechol are combined along with any other desired reagents either stepwise or in a single step to form a reaction mixture, thereby reacting the starting catechol and the D^+ source. Following completion of the reaction, the deuterated catechol product is isolated or separated from the D^+ source. The resulting composition comprises the deuterated catechol and is substantially free of the D^+ source, i.e., less than 10%, preferably less than 5%, more preferably less than 2% and even more preferably less than 1% by weight of the isolated composition is D^+ source. The deuterated catechol can be separated from the D^+ source by any suitable means, including by evaporation *in vacuo* when the D^+ source is a liquid or solvent. The resulting deuterated catechol in the composition can, if desired, be further purified by any suitable means, including crystallization or chromatography. The purity of the composition typically is at least 90%, 95%, 98% or 99% by weight deuterated catechol.

[0018] The reaction between the deuterated catechol and the deuterated dihalodeuteromethane is referred to herein as the "Alkylation Reaction". The Alkylation Reaction utilizes a deuterated catechol starting material represented by structural Formula (II) that has a deuterium isotope enrichment of at least 75%, preferably at least 80%, more preferably at least 85%, even more preferably at least 90% and even more preferably at least 95%. Deuterium enrichments corresponding to these levels can be obtained using the Deuterium/Proton Exchange Reaction (see Example 2). The percent deuterium isotope enrichment is defined as the actual number of moles of deuterium present at those positions designated as being labeled with deuterium divided by the theoretical maximum number of moles of deuterium that can be present at those positions. For example, in the benzo[*d*][1,3]dioxole represented by Structural Formula (III), theoretically, there are two moles of deuterium for every mole of benzo[*d*][1,3]dioxole. A deuterium enrichment of 85% means that there are 1.7 moles of deuterium for every mole of benzo[*d*][1,3]dioxole. Isotopic enrichment is routinely determined by ^1H NMR analysis.

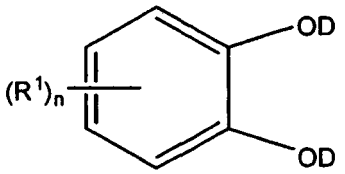
[0019] Dihalodeuteromethane is represented by CD_2XY, wherein X and Y are halides and can be the same or different. Examples include CD_2Cl_2, CD_2Br_2, CD_2I_2 or $BrCD_2Cl$. CD_2Cl_2 and CD_2Br_2 are more commonly used; and CD_2Cl_2 is most commonly used. The reaction is typically carried out in polar aprotic solvents such as *N*-methylpyrrolidinone, dimethylformamide, acetonitrile, hexamethylphosphoramide or *N,N*-dimethylpropyleneurea. In one embodiment, *N*-methylpyrrolidinone and dimethylformamide are used; in another embodiment dimethylformamide is used; and in another embodiment a mixture of *N*-methylpyrrolidinone and D_2O is used. Between 5 and 20 volumes of solvent relative to catechol are commonly used; typically between 10 and 20 volumes are used.

[0020] The Alkylation Reaction is carried out in the presence of a base. Examples include carbonate bases (e.g., K_2CO_3 and Cs_2CO_3), alkoxide bases (e.g., $NaOCH_3$ and potassium *tert*-butoxide), hydride bases (e.g., NaH) and fluoride bases (e.g., KF and CsF). Between 2 and 4 equivalents of base relative to the catechol are typically used, more commonly between 2.0 and 2.2 equivalents are used.

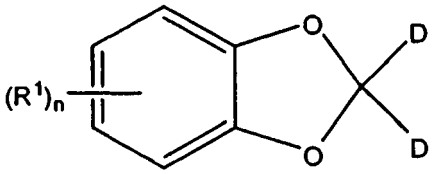
[0021] The Alkylation Reaction is commonly carried out at a temperature between room temperature and 130 °C for 1 to 24 h. More commonly, the temperature is between 90 and 110 °C for between 1 and 4 h; and most commonly, the temperature is 110 °C for about 1.5 h.

[0022] The deuterium isotope enrichment in the deuterated benzo[*d*][1,3]dioxoles disclosed herein is typically greater than 99.0%, more commonly greater than 99.5% and even more commonly greater than 99.9%.

[0023] In a specific embodiment, the deuterated catechol starting material used and the deuterated benzo[*d*][1,3]dioxole formed in the Alkylation Reaction are represented by Structural Formula (IV) and Structural Formula (V), respectively. The deuterated catechol starting material has a deuterium isotope enrichment of at least 75%, preferably at least 80%, more preferably at least 85%, even more preferably at least 90% and even more preferably at least 95%:



(IV)



(V).

n is 1, 2 or 3.

[0024] Each R^1 is independently halo; -OR^a; OR'; -CHO; -$COOR^b$; -COOR'; C(O)R'; -CN; -$OC(O)NH_2$; -$OC(O)NHR'$; -$OC(O)N(R')_2$; -$CR^4{=}C(R^4)_2$; -$C{\equiv}CR^4$; or an aryl group optionally substituted with one or more groups represented by R^5.

[0025] Each R^4 is independently -H or a group represented by R';

[0026] Each R^5 is independently selected from halo; alkyl, -OR^a; alkoxy; haloalkoxy; -CHO; -$COOR^b$; -COOR"; C(O)R"; -NO_2; haloalkyl; -CN; NHR^c; -NR^cR"; -$N(R")_2$; -NHC(O)R"; -$NHC(O)NH_2$; -NHC(O)NHR"; -$NHC(O)N(R")_2$; -$OC(O)NH_2$; -OC(O)NHR"; -$OC(O)N(R")_2$; -NHC(O)H; -NHC(O)R"; -NHC(O)OR"; -S(O)R"; -$S(O)_2$R"; -SO_2NH_2; -SO_2NHR"; -$SO_2N(R")_2$; -$NHSO_2NH_2$; -$NHSO_2$NHR"; -$NHSO_2N(R")_2$; and -$NHSO_2$R".

[0027] R' is alkyl or aryl, each of which is optionally and independently substituted with one or more groups selected from halo; -OR^a; alkoxy; haloalkoxy; -CHO; -$COOR^b$; -COOR"; C(O)R"; -NO_2; alkyl; haloalkyl; -CN; -NHR^c; -NR^cR"; -$N(R")_2$; -NHC(O)R"; -$NHC(O)NH_2$; -NHC(O)NHR"; -$NHC(O)N(R")_2$; -$OC(O)NH_2$; -OC(O)NHR"; -$OC(O)N(R")_2$; -NHC(O)H; -NHC(O)R"; -NHC(O)OR"; -S(O)R"; -$S(O)_2$R"; -SO_2NH_2; -SO_2NHR"; -$SO_2N(R")_2$; -$NHSO_2NH_2$; -$NHSO_2$NHR"; -$NHSO_2N(R")_2$; and -$NHSO_2$R".

[0028] R" is alkyl.

[0029] R^a is a phenol protecting group.

[0030] R^b is a carboxylic acid protecting group.

[0031] R^c is an amine protecting group.

[0032] Preferably for Structural Formulas (IV) and (V):

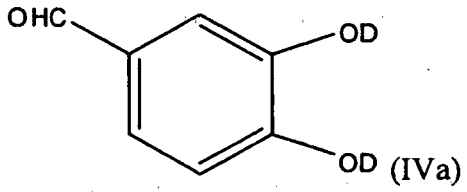
n is 1.

R^1 is halo; -OR^a; -OR'; -CHO; -$COOR^b$; -COOR'; C(O)R'; -CN; -$CH{=}CHR^4$; -C≡CH; -$C{\equiv}CR^4$; or a phenyl group optionally substituted with one or more groups represented by R^5.

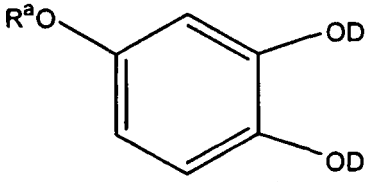
[0033] Each R^5 is independently selected from halo; alkyl; -OR^a; alkoxy; haloalkoxy; -CHO; -$COOR^b$; -COOR"; C(O)R"; -NO_2; haloalkyl; and -CN.

[0034] R' is an alkyl; or a phenyl group optionally substituted with halo; -OR^a; alkoxy; haloalkoxy; -CHO; -$COOR^b$; -COOR"; C(O)R"; -NO_2; alkyl; haloalkyl; or -CN; and the remainder of the variables are as described above.

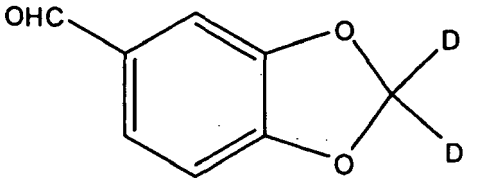
[0035] In another embodiment, the deuterated catechol starting material used in the Alkylation Reaction is represented by Structural Formula (IVa) or (IVb) and the deuterated benzo[*d*][1,3]dioxole formed in the Alkylation Reaction is represented by Structural Formula (Va) or (Vb), respectively. The deuterated catechol starting material has a deuterium isotope enrichment of at least 75%, preferably at least 80%, more preferably at least 85%, even more preferably at least 90% and even more preferably at least 95%.



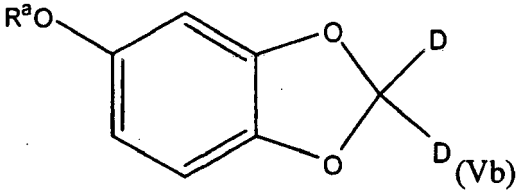
(IVa)



(IVb)



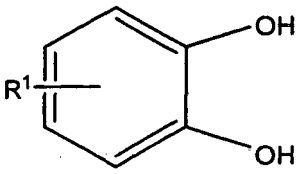
(Va)



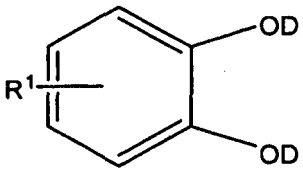
(Vb)

R^a in Structural Formula (IVb) and (Vb) is a phenol protecting group.

[0036] In another specific embodiment, the catechol starting material and the deuterated catechol product in the Deuterium/Proton Exchange Reaction are represented by Structural Formula (VI) and Structural Formula (VII), respectively.



(VI)



(VII)

[0037] R^1 is halo; -OR^a; alkoxy; -CHO; -$COOR^b$; -COOR'; C(O)R'; -CN; -CH=CHR^4; -C≡CH; -C≡CR^4; or a phenyl group optionally substituted with one or more groups represented by R^5;

R^4 is -H or a group represented by R';

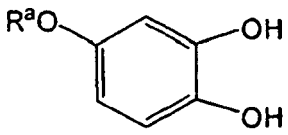
each R^5 is independently selected from halo; alkyl; -OR^a; alkoxy; haloalkoxy; -CHO; -$COOR^b$; -COOR"; C(O)R"; -NO_2; haloalkyl; and -CN;

R' is alkyl; or a phenyl group optionally substituted with halo; -OR^a; alkoxy; haloalkoxy; -CHO; -$COOR^b$; -COOR"; C(O)R"; -NO_2; haloalkyl; or -CN;

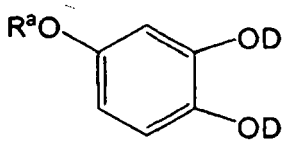
R^a is a phenol protecting group; and

R^b is a carboxylic acid protecting group.

[0038] In another embodiment, catechol starting material and the deuterated catechol product in the Deuterium/Proton Exchange Reaction are represented by Structural Formula (VIII) and Structural Formula (IX), respectively:



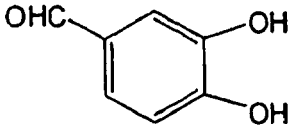
(VIII)



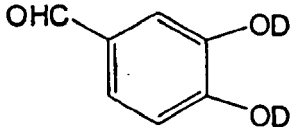
(IX)

wherein R^a is a protecting group for a phenol.

[0039] In another embodiment, catechol starting material and the deuterated catechol product in the Deuterium/Proton Exchange Reaction are represented by Structural Formula (X) and Structural Formula (XI), respectively.



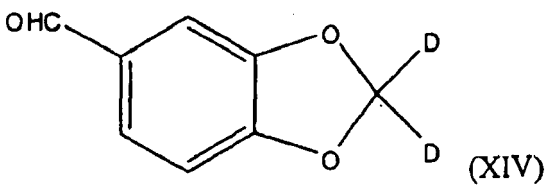
(X)



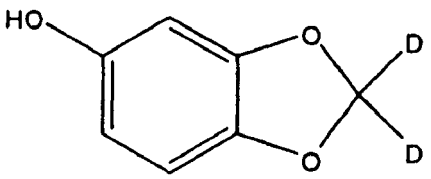
(XI)

[0040] The deuterated catechol represented by Structural Formula (VII), (IX) or (XI) is separated from the source of D^+, thereby resulting in a composition that comprises by weight less than 10%, preferably less than 5%, more preferably less than 2% and even more preferably less than 1% D^+ source. The purity of the composition by weight is at least 90%, preferably 95%, more preferably 98% and even more preferably 99% deuterated catechol and the deuterated catechol has an isotopic enrichment of at least 75%, preferably at least 80%, more preferably at least 85%, even more preferably at least 90% and even more preferably at least 95%.

[0041] The structures of two particularly useful d_2-benzo[*d*][1,3]dioxoles prepared by the disclosed method are shown below:



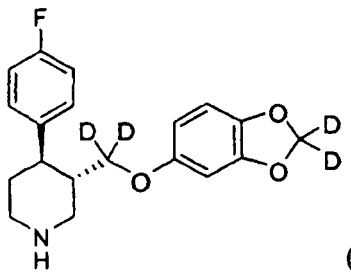
(XIV)



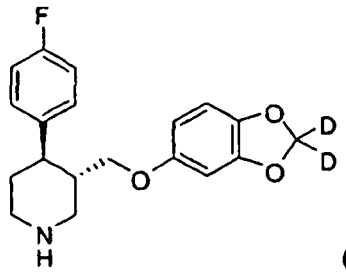
(XV).

The d_2-benzo[*d*][1,3]dioxole represented by Structural Formula (XIV) may be used in the preparation of deuterated tadalafil (XIX , R^1 = H, R^2 = CD_3) and of deuterated berberine (XXI, X = Cl) (see Scheme 3); and the d_2-benzo[*d*][1,3]dioxole represented by Structural Formula (XV) may be used in the preparation of deuterated paroxetines XVII (see Scheme 1) and XVIII (see Scheme 7). Details of suitable experimental conditions follow.

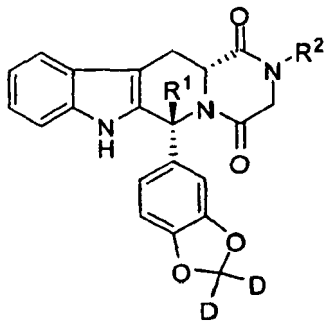
[0042] Examples of deuterated paroxetine and deuterated tadalafil are represented by Structural Formulas (XVII)-(XIX):



(XVII)



(XVIII)



(XIX).

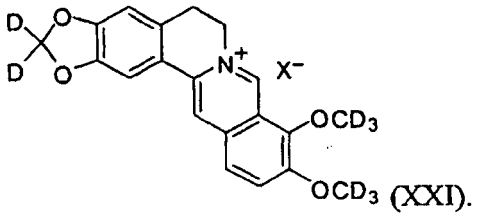
R^1 is H or D and R^2 is -CH_3 or -CD_3. Pharmaceutically acceptable salts of deuterated paroxetine represented by Structural Formulas (XVII) and (XVIII) and deuterated tadalafil represented by Structural Formula (XIX) are also included.

[0043] In an alternative embodiment, the isotopic enrichment of the compounds represented by Structural Formulas (XIV), (XV), (XVII), (XVIII), (XIX), and (XXI) is at least 96%, such as at least 97% and at least 98%, and all of the structural variables are as described above for the given Structural Formula.

[0044] In a particular set of embodiments, any atom not designated as deuterium in Structural Formulas: II, III, IV, IVa, IVb, V, Va, Vb, VII, IX, XI, XIV, XV, XVII, XVIII, XIX, and XXI, is present at its natural isotopic abundance.

[0045] Synthetic details for incorporating deuterium into the labeled sites shown in Structural Formulas (XVII)-XIX) that are outside of the benzo[d][1,3]dioxole group are provided in WO 2007/016431, US2007/0112031 and US2007/0191381.

[0046] An example of a deuterated berberine is represented by Structural Formula (XXI):



(XXI).

wherein X^- is a pharmaceutically acceptable anion.

[0047] When a deuterated compound is designated as having deuterium at a position other than at the benzo[d][1,3]dioxole group (e.g., the methoxy groups in Structural Formula (XXI)), the isotopic enrichment for each deuterium present at the designated site designated site is at least 15%, at least 22.5%, at least 30%, at least 37.5%, at least 45%, at least 52.5%, at least 60% deuterium, at least 67.5%, at least 75%, at least 82.5%, at least 90%, at least 95%, at least 97%, at least 99.0%, or at least 99.5%. It is understood that the isotopic enrichment of each deuterium present at a site designated as a site of deuteration is independent of other deuterated sites.

[0048] Included are pharmaceutically acceptable salts of the deuterated paroxetine and deuterated tadalafil compounds disclosed herein. These disclosed compounds have basic amine groups and therefore can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds include salts of inorganic acids (such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic, and tartaric acids). Compounds with a quaternary ammonium group (such as berberine) also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like or the anion of any one of the aforementioned acids. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

[0049] The term "alkyl" as used herein means a saturated straight-chain or branched hydrocarbon having one to ten carbon atoms, more typically one to six; or a saturated cyclic hydrocarbon having three to eight carbon atoms.

[0050] The term "aryl group" means carbocyclic aromatic rings have only carbon ring atoms (typically six to fourteen) and include monocyclic aromatic rings such as phenyl and fused polycyclic aromatic ring systems in which two or more carbocyclic aromatic rings are fused to one another. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl.

[0051] Ring A in Structural Formulas (I) and (II) comprises substituents which do not interfere with the reactions described therein. Specifically, substituents that are sufficiently acidic that they react with the base used in the Alkylation Reaction are desirably derivatized with a suitable protecting group. Examples of substituents of this type include carboxylic acids, sulfonic acids, alcohols and phenols. Additionally, substituents that are sufficiently nucleophilic that they can react with the dihalodideuteromethane are also desirably derivatized with a suitable protecting group. Examples of substituents of this type include primary and secondary amines, phenols and alcohols.

[0052] "Protecting groups" and reactions and conditions for protecting and deprotecting the phenol group are well known in the art and are disclosed, for example, in Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (2007), Chapter 2 and references cited therein.

[0053] Suitable protecting groups protect the phenol group as ethers, examples of such protecting groups include methyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, [3,4-dimethoxybenzyl)oxy]methyl, *p*-nitrobenzyloxymethyl, *o*-nitrobenzyloxymethyl, [(R)-1-(2-nitrophenyl)ethoxy]methyl, (4-methoxyphenoxy)methyl, guaiacolmethyl, [(*p*-phenylphenyl)oxy]methyl, *t*-butoxymethyl, 4-pentenyloxymethyl, siloxymethyl, 2-methoxyethoxymethyl, 2-cyanoethoxymethyl, bis(2-chloroethoxy)methyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, menthoxymethyl, *o*-bis(2-acetoxyethoxy)methyl, tetrahydropyranyl, fluorous tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl, *S,S*-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl, 1-(4-chlorophenyl)-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3*a*,4,5,6,7,7*a*-octahyrdo-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-hydroxyethyl, 2-bromoethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxyethyl, 2,2,2-trichloroethyl, 1,1,-dianisyl-2,2,2,-trichloroethyl, 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl, 1-(2-cyanoethoxy)ethyl, 2-trimethylsilylethyl, 2-(benzylthio)ethyl, 2-(phenylselenyl)ethyl, t-butyl, cyclohexyl, 1-methyl-1'-cyclopropylmethyl, allyl, prenyl, cinnamyl, 2-phenallyl, propargyl, *p*-chlorophenyl, *p*-methoxyphenyl, *p*-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, 2,6-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, pentadienylnitrobenzyl, pentadienylnitropiperonyl, halobenzyl, 2,6-dichlorobenzyl, 2,4-dichlorobenzyl, 2,6-difluorobenzyl, *p*-cyanobenzyl, fluoros benzyl, 4-fluorousalkoxybenzyl, trimethylsilylxylyl, *p*-phenylbenzyl, 2-phenyl-

2-propyl (cumyl), *p*-acylaminobenzyl, *p*-azidobenzyl, 4-azido-3-chlorobenzyl, 2-and 4-trifluoromethylbenzyl, *p*-(methylsulfinyl)benzyl, *p*-siletanylbenzyl, 4-acetoxybenzyl, 4-(2-trimethylsilyl)ethoxymethoxybenzyl, 2-naphthylmethyl, 2- and 4-picolyl, 3-methyl-2-picolyl *N*-oxido, 2-quinolinylmethyl, 6-methoxy-2-(4-methylpheny)-4-quinolinemethyl, 1-pyrenylmethyl, diphenylmethyl, 4-methoxydiphenylmethyl, 4-phenyldiphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, tris(4-*t*-butylphenyl)methyl, α-naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl)methyl, 4,4',4"tris(benzoyloxyphenyl)methyl, 4,4'-dimethoxy-3"-[*N*-(imidazolylmethyl)trityl, 4,4'-dimethoxy-3"-[*N*-(imidazolylethyl)carbamoyl]trityl, bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenzo[*a,c,g,i*]fluorenylmethyl)-4,4"-dimethoxytrityl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-phenylthioxanthyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodithiolan-2-yl, 4,5-bis(ethoxycarbonyl-[1,3]-dioxolan-2-yl, benzisothiazolyl *S,S'*-dioxido,_trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsiyl, diethylisopropylsilyl, dimethylthexylsilyl, 2-norbornyldimethylsily, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-*t*-butylmethylsilyl, bis(*t*-butyl)-1-pyrenylmethoxysilyl, tris(trimethylsilyl)silyl, sisyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl and 1,1,3,3-tetraisopropyl-3-[2-(triphenylmethoxy)ethoxy]disiloxane-1-yl.

[0054] Alternatively, suitable protecting groups protect the phenol group as esters, for example, formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trichloroacetamidate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, phenylacetate, *p*-phenylacetate, diphenylacetate, 3-phenylpropionate, bisfluorous chain type propanoyl (Bfp-OR), 4-pentenoate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate, 5-[3-Bis(4-methoxyphenyl)hydroxymethylphenoxy]levulinate, pivaloate, 1-adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), 4-bromobenzoate, 2,5-difluorobenzoate, *p*-nitrobenzoate, picolinate, nicotinate, 2-(azidomethyl)benzoate, 4-azidobutyrate, (2-azidomethyl)phenylacetate, 2-{[(tritylthio)oxy]methyl}benzoate, 2-{[(4-methoxytritylthio)oxy]methyl}benzoate,2-{[methyl(tritylthio)amino]methyl}benzoate, 2{{[4-methoxytrityl)thio]methylamino}-methyl}benzoate, 2-(allyloxy)phenylacetate, 2-(prenyloxymethyl)benzoate, 6-(levulinyloxymethyl)-3-methoxy-2- and 4-nitrobenzoate, 4-benzyloxybutyrate, 4-trialkylsiloxybutrate, 4-acetoxy-2,2-dimethylbutyrate, 2,2-dimethyl-4-pentenoate, 2-iodobenzoate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 4-methylthiomethoxy)butyrate, 2-methylthiomethoxymethyl)benzoate, 2-(chloroacetoxymethyl)benzoate, 2[(2-chloroacetoxy)ethyl]benzoate, 2-[2-(benzyloxy)ethyl]benzoate, 2-[2-(4-methoxybenzyloxy)ethyl]benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-imethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenoate tigloate), *o*-(methoxycarbonyl)benzoate, *p*-benzoate, α-naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, 2-chlorobenzoate, as sulfonates, sulfenates and sulfinates such as sulfate, allylsulfonate, ethanesulfonate (mesylate), benzylsulfonate, tosylate, 2-[(4-nitrophenyl)ethyl]sulfonate, 2-trifluoromethylsulfonate, 4-monomethoxytritylsulfenate, alkyl 2,4-initrophenylsulfenate, 2,2,5,5-tetramethylpyrrolidin-3-one-1-sulfinate, borate, dimethylphosphinothioyl, as carbonates such as alkyl methyl carbonate, methoxymethyl carbonate, 9-fluorenylmethyl carbonate, ethyl carbonate, bromoethyl carbonate, 2-(methylthiomethoxy)ethyl carbonate, 2,2,2-trichloroethyl carbonate, 1,1-dimethyl-2,2,2-trichloroethyl carbonate, 2-(trimethylsilyl)ethyl carbonate, 2-[dimethyl(2-naphthylmethyl)silyl]ethyl carbonate, 2-(phenylsulfonyl)ethyl carbonate, 2-(triphenylphosphonio)ethyl carbonate, *cis*-[4-[[(-methoxytrityl)sulfenyl]oxy] tetraydrofuran-3-yl]oxy carbonate, isobutyl carbonate, *t*-butyl carbonate, vinyl carbonate, allyl carbonate, cinnamyl carbonate, propargyl carbonate, *p*-chlorophenyl carbonate, *p*-nitrophenyl carbonate, 4-ethoxyl-1-naphthyl carbonate, 6-bromo-7-hydroxycoumarin-4-ylmethyl carbonate, benzyl carbonate, *o*-nitrobenzyl carbonate, *p*-nitrobenzyl carbonate, *p*-methoxybenzyl carbonate, 3,4-dimethoxybenzyl carbonate, anthraquinon-2-ylmethyl carbonate, 2-dansylethyl carbonate, 2-(4-nitrophenyl)ethyl, 2-(2,4-nitrophenyl)ethyl, 2-(2-nitrophenyl)propyl, 2-(3,4-methylenedioxy-6-nitrophenylpropyl, 2-cyano-1-phenylethyl carbonate, 2-(2-pyridyl)amino-1-phenylethyl carbonate, 2-[*N*-methyl-*N*-(2-pyridyl)]amino-1-phenylethyl carbonate, phenacyl carbonate, 3',5'-dimethoxybenzoin carbonate, methyl dithiocarbonate, *S*-benzyl thiocarbonate, and carbamates such as dimethylthiocarbamate, *N*-phenylcarbamate, and *N*-methyl-*N*-(*o*-nitrophenyl) carbamate.

[0055] Examples of suitable protecting groups for amino groups include carbamates (*e.g*, methyl, ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 17-tetrabenzo[*a,c,g,i*]fluoernylthmethyl, 2-chloro-3-indenylmethyl, benz[*f*]inden-3-ylmethyl-2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 1,1-dioxobenzo[*b*]thiophene-2-ylmethyl, 2,2,2-tricholoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 2-chloroethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2-dibromethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, *t*-butyl, 1-adamantyl, 2-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, *m*-nitrophenyl, 3,5-dimethoxybenzyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, α-methylnitropiperonyl, o-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, and phenyl(*o*-nitrophenyl)methyl), amides (*e.g.*, *n*-formyl, *n*-acetyl, *n*-chloroacetyl, *n*-trichloroacetyl, *n*-trifluoroacetyl, *n*-phenylacetyl, and *n*-3-phenylpropionyl), *N*-alkyl and *N*-aryl amines (*e.g.*, *n*-methyl, *n*-*t*-butyl, *n*-allyl, *n*-benzyl, *n*-4-methoxybenzyl, *n*-2,4-dimethoxybenzyl, and *n*-2-hydroxybenzyl).

[0056] Examples of suitable protecting groups for carboxylic acid groups include 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, pivaloyloxymethyl, phenylacetoxymethyl, triisopropylsilylmethyl, cyanomethyl, acetol, *p*-bromophenacyl, α-methylphenacyl, p-methoxyphenacyl, desyl, carboxamidomethyl, *p*-azobenzenecarboxamidomethyl, *N*-phthalimidomethyl, 2,2,2-trichloroethyl, 2-haloethyl, ω-chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2-(*p*-nitropheylsulfenyl)ethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-2'-pyridyl)ethyl, 2-(*p*-methoxyphenyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, 2-(4-acetyl-2-nitrophenyl)ethyl, 2-cyanoethyl, *t*-butyl, 3-methyl-3-pentyl, dicyclopropylmethyl, 2,4-dimethyl-3-pentyl, cyclopentyl, cyclohexyl, allyl, methallyl, 2-methylbut-3-en-2-yl, 3-methylbut-2-(Prenyl), 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl, α-methylcinnamyl, prop-2-ynyl (Propargyl), phenyl, 2,6-dimethylphenyl, 2,6-diisopropylphenyl, 2,6-di-*t*-butyl-4-methylphenyl, 2,6-di-*t*-butyl-4-methoxyphenyl, p-(methylthio)phenyl, pentafluoropheynyl, benzyl, triphenylmethyl, diphenylmethyl, bis(*o*-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl, 5-dibenzosuberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl, 2,4,6-trimethylbenzyl, *p*-bromobenzyl, o-nitrobenzyl, *p*-nitrobenzyl, *p*-methoxybenzyl, 2,6-dimethoxybenzyl, 4-(methylsulfinyl)benzyl, 4-sulfobenzyl, 4-azidomethoxybenzyl, 4-{*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl, piperonyl, 4-picolyl, *p*-benzyl, trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, *i*-propyldimethylsilyl, phenyldimethylsilyl, di-*t*-butylmethylsilyl and triisopropylsilyl.

[0057] The structural formulas depicted herein designate certain atoms as sites enriched with deuterium (e.g., the phenolic groups in Structural Formula (II)), but do not designate other positions. In a most general embodiment, when a structural formula is silent with respect to whether a particular position is isotopically enriched, it is to be understood that the stable isotopes at the particular position are present either at natural abundance, or, alternatively, that the particular position is isotopically enriched with one or more naturally occurring stable isotopes. In a more specific embodiment, the stable isotopes are present at natural abundance at all positions in a compound not designated as potential sites of isotopic enrichment (referred to herein as "non-designated atoms).

[0058] While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

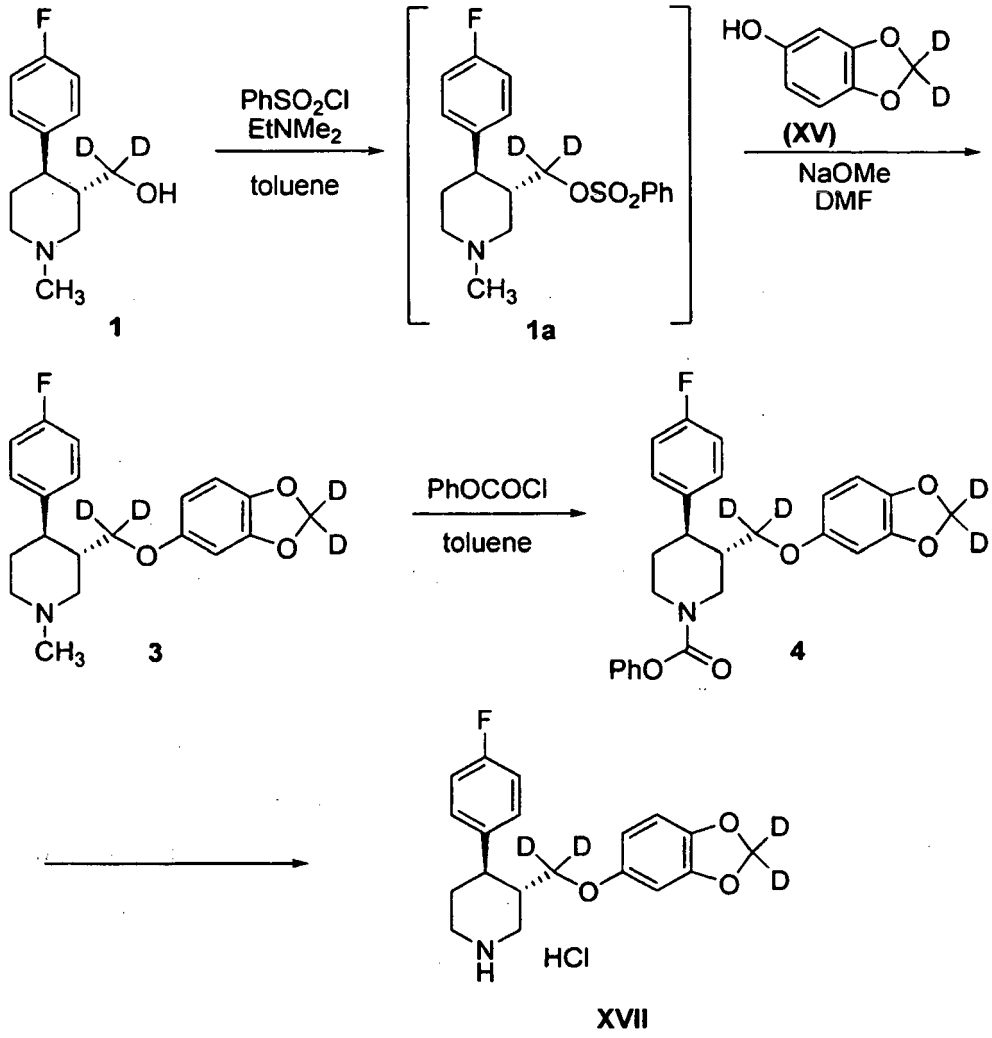
EXEMPLARY SYNTHESES USING DIDEUTERO BENZO[*d*][1,3]DIOXOLES

[0059] The following schemes outlining the preparation of d_4-paroxetine, d_2- and d_3-tadalafil, and d_8-berberine are given as examples where the dideutero benzo[d][1,3]dioxole intermediates XIV and XV could be used.

D_4-Paroxetine Synthesis

[0060] The synthesis of d_4-paroxetine (XVII) also known as (3S,4R)-3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl-d_2)-4-(4-fluorophenyl)piperidine hydrochloride using intermediate XV is outlined in Scheme 1 below. Details of the synthetic procedure are provided and are based on the actual preparation of d_4-paroxetine, that was performed without the benefit of the high isotopically enriched intermediate XV. One of ordinary skill in the art would recognize that the same procedures can be performed using an intermediate XV of this invention to provide d_4-paroxetine having high isotopic enrichment of the methylenedioxy carbon position.

Scheme 1.



[0061] Synthesis of (3S,4R)-3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl-d_2)-4-(4-fluorophenyl)-1-methylpiperidine (3). To a solution of ((3S, 4R)-4-(-4-fluorophenyl)-1-methylpiperidin-3-yl)methanol-d_2 (**1**) in toluene at 5 °C, can be added dimethylethylamine with stirring. A nitrogen purge can be attached and the mixture can be further cooled to 0 °C. A mixture of benzenesulphonyl chloride in toluene can be added slowly over 70 minutes (min), maintaining the temperature at around 0 °C. The resulting mixture can be stirred for 20 minutes, allowing the temperature to rise to 10 °C. A mixture of saturated brine and aqueous sodium hydroxide can be added over 10 min and the resulting mixture can be stirred for 15 min at 10 °C. The aqueous phase can be separated, and extracted with toluene. The combined toluene phases can be dried over anhydrous magnesium sulfate, filtered and approximately one third of the solvent can be removed *in vacuo.* This solution of intermediate **1a** can be diluted with N,N'-dimethylformamide, the resulting mixture can be warmed to 50 °C, and a solution of **XV** and sodium methoxide (9.33 g) in N, N'-dimethylformamide can be added over 20 min. Water can be added and the mixture can be heated to 70 °C, then stirred at that temperature for 1 hour (h). After cooling to 50 °C, more water can be added, and stirring can be continued for 15 minutes. The aqueous phase can be separated and extracted with toluene. The combined toluene phases are washed with 2.5 molar aqueous sodium hydroxide solution (2 times) and water (1 times). The resulting toluene phase can be then dried over anhydrous magnesium sulfate (10.4 g) and filtered. Toluene can be removed by distillation at reduced pressure to form **3** as a pale yellow solid, which can be dried in a vacuum oven (40 °C) overnight.

[0062] Synthesis of (3S,4R)-phenyl-3-((2,2-d_2-benzo[*d*][1,3]dioxolo-5-yloxy)methyl-d_2)-4-(4-fluorophenyl)piperidine-1-carboxylate (4). A solution of the methylpiperidine **(3)** in dry toluene can be heated to 60-65 °C and phenyl chloroformate can be added over 15 minutes with stirring. The resulting mixture can be stirred for 1 h at 60-65 °C, then can be cooled to 20 °C and washed with 10% aqueous (aq) sulphuric acid. The combined acid washes are extracted with toluene and the combined organic phases are washed with water, dried over magnesium sulfate, and filtered over Celite. The filtrate can be concentrated *in vacuo* followed by the addition of propan-2-ol; this concentration/redissolution

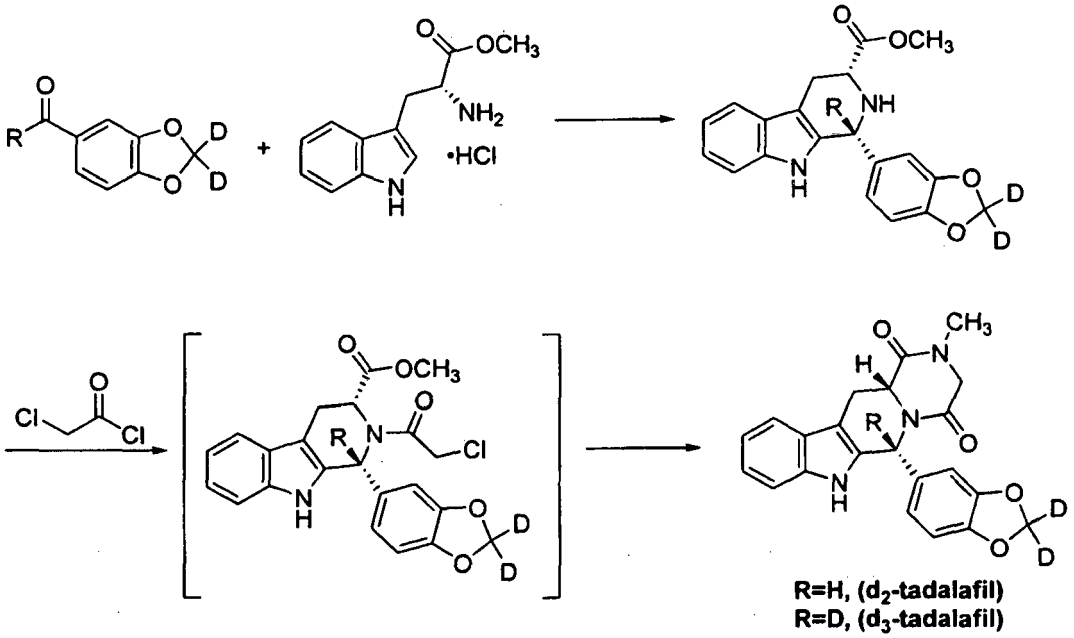
step can be repeated 2 times. After the last dissolution with propan-2-ol, the solution can be slowly cooled to 0 to 5 °C over 2 h and then stirred at this temperature for about 1 h, to provide the product as crystals. The crystals are isolated by filtration, and dried to yield product 4.

[0063] Synthesis of (3S,4R)-3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl-d_2)-4-(4-fluorophenyl)piperidine hydrochloride (XVII). A suspension of **4** (0.8 mmol) in 3 N KOH (0.37 mL) can be heated at reflux for 4 h. The mixture can be cooled and partitioned between 10 mL each of water and methylene chloride. The aqueous portion can be separated, extracted with methylene chloride and the combined organic layers are washed with 50 % brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue can be taken up in 2 mL of isopropyl alcohol and treated with 0.9 mmol of anhydrous HCl as a 4.2 N solution in dioxane. The resulting solid can be filtered, washed with a small amount of isopropyl alcohol, then with ether, and dried to yield the desired product **XVII.**

Deuterated-Tadalafil Synthesis

[0064] The synthesis of d_2- or d_3-tadalafil using intermediate XIV can be carried out as outlined in Scheme 2 below.

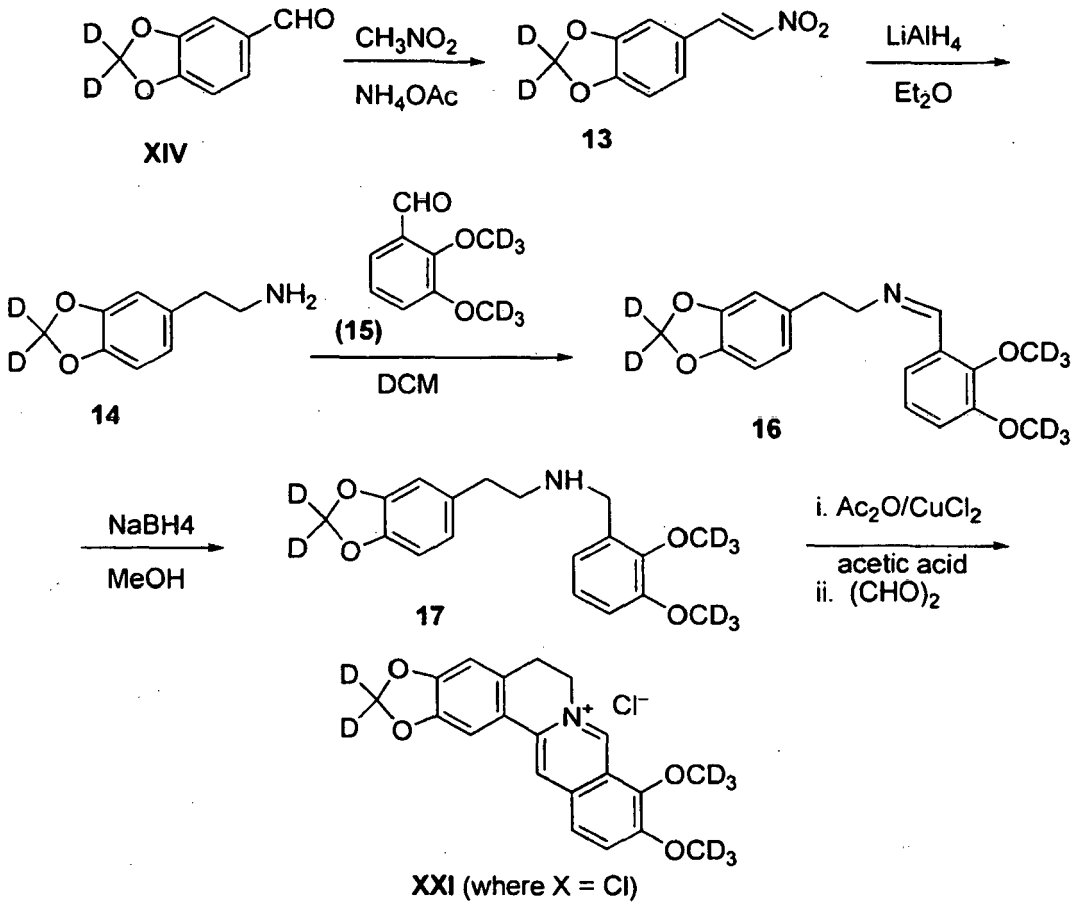
Scheme 2.



D_8-Berberine Synthesis

[0065] The synthesis of d_8-berberine (XXI, where X=Cl) also known as 5,6-dihydro-9,10-(dimethoxy-d_6)-benzo[g]-(2,2-d_2-benzo[d][1,3]dioxolo[5,6-a]quinolizinium chloride using intermediate XIV is outlined in Scheme 3 below. Details of a synthetic procedure are provide and are based on the actual preparation of d_8-berberine that was performed without the benefit of the high isotopically enriched intermediate XIV. One of ordinary skill in the art would recognize that the same procedures can be performed using an intermediate XIV of this invention to provide d_4-paroxetine having high isotopic enrichment of the methylenedioxy carbon position.

Scheme 3.



[0066] Synthesis of (E)-5-(2-nitrovinyl)-2,2-d_2-benzo[d][1,3]dioxole (13). A mixture of **XIV** (85.4 g, 0.562 mol, 1.0 eq.), nitromethane (91.0 mL, 1.68 mol, 3.0 eq.) and ammonium acetate (108.2 g, 1.40 mol, 2.5 eq.) in acetic acid (500 mL) can be stirred under reflux conditions for 4 h. After cooling to rt, the mixture can be poured into ice-water (500 mL) and extracted with dichloromethane (DCM) (3 x 1.4 L). The dichloromethane solution can be washed with water (2 x 1.4 L) and brine (2 x 1.4 L), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product as a brown oil which can be purified by column chromatography, (SiO_2; 1:1 DCM/hexane) to give **13.**

[0067] Synthesis of 2-(2,2-d_2-benzo[d][1,3]dioxol-5-yl)ethanamine (14). A solution of **13** (62.1 g, 0.318 mol, 1 eq.) in THF (1.28 L) can be added dropwise to a well stirred suspension of $LiAlH_4$ (45.9 g, 1.21 mol, 3.8 eq.) in Et_2O (1.9 L). The mixture can be heated to reflux for 2 h, after which time the reaction should be complete. The solution can be cooled in an ice bath and quenched by the dropwise addition of water (46 mL), followed by the addition of a 15% aqueous NaOH solution (46 mL) and more water (138 mL). The mixture can be allowed to stir for 30 min. then filtered and the organic solvents removed *in vacuo.* The aqueous residue can be extracted with DCM (3 x 900 mL) and the combined organics extracted with 5% aqueous HCl (640 mL). The acidic aqueous layer can be basified to pH 9 with 5% aqueous NH_4OH (640 mL), extracted with DCM (3 x 900 mL) and the combined organics washed with water (2 x 900 mL) and brine (2 x 900 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **14.**

[0068] Synthesis of (Z)-2-(2,2-d_2-benzo[d][1,3]dioxol-5-yl)-N-(2,3-(dimethoxy-d_6)-benzylidene)ethanamine (16). A mixture of the amine **14** (21.55 g, 0.129 mol, 1.0 eq.), the aldehyde **15** (22.20 g, 0.129 mol, 1.0 eq.) and 4Å molecular sieves (63.0 g) in anhydrous DCM (600 mL) can be stirred at room temperature for 16 h, until the reaction can be complete. The mixture can be filtered through Celite (100 g) and the DCM removed *in vacuo* to give the crude product **16.**

[0069] Synthesis of 2-(2,2-d_2-benzo[d][1,3]dioxol-5-yl)-N-(2,3-(dimethoxy-d_6)benzyl)ethanamine (17). A mixture of the imine **16** (40.4 g, 0.126 mol, 1.0 eq.) and sodium borohydride (7.15 g, 0.189 mol, 1.5 eq.) in methanol (450 mL) can be heated at reflux with stirring for 2 h. The reaction can be cooled to 0 and 5 °C (icebath), and water (450 mL) can be added. The mixture can be extracted with DCM (2 x 900mL), and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the product **17**.

[0070] The free base (38.2 g, 0.118 mol, 1.0 eq.) can be dissolved in methanol (240 mL) and conc. HCl (10 mL) can

be added until pH 4 is obtained. The solvents can be removed *in vacuo* to give a brown oil which can be cooled to 0 °C with stirring and cold Et_2O/MeOH (4:1, 48 mL) can be added. The mixture can be stirred for 30 min resulting in the formation of a solid which can be filtered off. Further cold Et_2O/MeOH (4:1, 48 mL) can be added to the filtrate which can be stirred for 20 min, resulting in the formation of additional solid. The solid can be removed by filtration and the combined solids are washed with cold Et_2O and dried to give the HCl salt **17.**

[0071] Synthesis of 5,6-dihydro-9,10-(dimethoxy-d6)-benzo[g]-(2,2-d_2-benzo[d][1,3]dioxolo[5,6-a]quinolizinium chloride (XXI, where X=Cl). A 250 mL dry three-necked flask can be charged with acetic anhydride (13.9 g, 0.136 mol, 2.5 eq), acetic acid (100 mL), $CuCl_2$ (14.7 g, 0.109 mol, 2.0 eq) and NaCl (13.8 g, 0.240 mol, 4.4 eq). The mixture can be heated to 80 and 90 °C, glyoxal (40% in water, 13.4 g, 0.725 mol, 1.5 eq) can be added and the mixture can be heated at reflux for 20 minutes. The mixture can be cooled to less than 90°C, and the amine HCl salt **17** (19.7 g, 0.055 mol, 1.0 eq) can be added, and the mixture heated to reflux (112-114 °C) with stirring overnight. The reaction mixture can be cooled to 50 °C and the acetic acid can be distilled off under reduced pressure. The residue can be charged with water (170 mL) and the mixture heated to 80 °C with stirring for 20 minutes. The salt **XXI** can be obtained by filtration, then can be added to aqueous ammonium hydroxide (0.72 M, 550 mL) and the mixture can be stirred at 25 to 30 °C for 2.5 h. The solid can be again filtered, washed with cold water (110 mL), and dried overnight *in vacuo* at 40 °C to afford crude product.

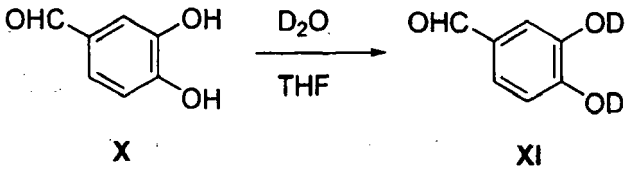
[0072] The crude product can be dissolved in MeOH (800 mL), stirred at reflux for 30 min then filtered hot to give a dark brown solid (12.1 g). The solid can be suspended in MeOH (1 L), stirred at reflux for 30 min then filtered hot to give a dark brown solid (10.2 g). The two filtrates are combined, charcoal (12.0 g) can be added and the mixture heated at just below reflux for 20 min then the hot suspension can be filtered through Celite. The filtrate can be concentrated *in vacuo* to give an orange solid which can be recrystallised from MeOH (104 mL, 16 vols), yielding **XXI.**

[0073] Because deuterated paroxetine, as described herein, or a pharmaceutically acceptable salt thereof shows reduced inhibition of cytochrome P450 2D6 (CYP2D6) as compared to paroxetine, the contraindication of co-dosing paroxetine with therapeutic agents that are metabolized by CYP2D6 can be avoided. The replacement of paroxetine with deuterated paroxetine, as described herein, or a pharmaceutically acceptable salt thereof in the treatment of a patient who is also being administered a therapeutic agent that is metabolized by CYP2D6 represents an improvement in a method of treating a patient suffering from of susceptible to both: a condition that is treatable with paroxetine (e.g., one or more disease or disorder described above); and a condition that is treatable by a therapeutic agent that is metabolized by CYP2D6. Therapeutics that are CYP2D6 substrates are known in the art (see http://medicine.iupui.edu/flockhart/2D6.htm#2D6sub), as are the diseases and conditions which they are used to treat.

EXAMPLES

[0074] Example 1. Synthesis of 3,4-Dideuteroxybenzaldehyde **(XI).** Compound XI was prepared as outlined in Scheme 4 below. Details of the conversion are set forth below.

Scheme 4.



X XI

[0075] Synthesis of 3,4-dideuteroxybenzaldehyde (XI). To a solution of 3,4-dihydroxybenzaldehyde **(X)** (40 g) in THF (160 mL) was added D_2O (160 mL) with stirring. The resulting mixture was stirred overnight at room temperature (rt) under nitrogen. The solvent was removed *in vacuo* and the residue dried *in vacuo* at 40 °C overnight to provide **XI** as a solid (40 g). Analysis by 300 MHz ^1H NMR (d_6-DMSO) showed an H/D exchange level of approximately 85%.

[0076] Example 2. Alternate synthesis of 3,4-Dideuteroxybenzaldehyde **(XI).** Compound XI was prepared as generally outlined in Scheme 4 above. Details of the conversion are set forth below.

[0077] Synthesis of 3,4-dideuteroxybenzaldehyde (XI). To a solution of 3,4-dihydroxybenzaldehyde **(X)** (10 g) in acetonitrile (200 mL) was added D_2O (40 mL) and the resulting mixture was stirred for 4 days at rt. The solvent was removed in *vacuo* to provide **XI** as a solid. Analysis by 300 MHz ^1H NMR (d_6-DMSO) showed an H/D exchange level of approximately 85%.

[0078] Example 3. Alternate synthesis of 3,4-Dideuteroxybenzaldehyde **(XI).** Compound XI was prepared as generally outlined in Scheme 4 above. Details of the conversion are set forth below.

[0079] Synthesis of 3,4-dideuteroxybenzaldehyde (XI). To a solution of 3,4-dihydroxybenzaldehyde **(X)** (25 g) in

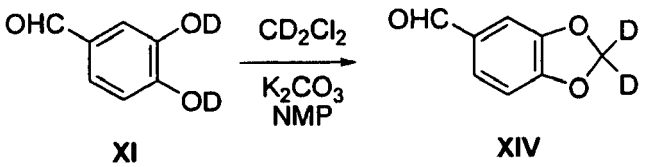
CH_3OD (100 mL) was added DCl (0.4 mL) with stirring. The resulting mixture was stirred overnight at rt and the solvent was removed *in vacuo.* The residue was re-dissolved in CH_3OD (100 mL), DCl (0.4 mL) was added, and the mixture was stirred again overnight at rt. The solvent was removed *in vacuo* to provide **XI** as a solid. Analysis by 300 MHz ^1H NMR (d_6-DMSO) showed an H/D exchange level of approximately 85%.

[0080] **Example 4.** Alternate synthesis of 3,4-Dideuteroxybenzaldehyde **(XI).** Compound XI was prepared as generally outlined in Scheme 4 above. Details of the conversion are set forth below.

[0081] **Synthesis of 3,4-dideuteroxybenzaldehyde (XI).** A 50-L, jacketed reactor equipped with a temperature probe, nitrogenous atmosphere, and reflux condenser was charged with 3,4-dihydroxybenzaldehyde (3.5 kg) and THF (14.0 L). Deuterium oxide (14.0 L) was added and the reaction mixture was stirred for 18 hours (h) at ambient temperature. EtOAc (14 L) was added, and the phases were separated. The aqueous phase was then extracted with EtOAc (14 L). The combined organic layers were concentrated to about 14 L. Toluene was added (14 L) and the suspension was concentrated back down to 14 L. This solvent-swap procedure was repeated two additional times with toluene (14 L each). The solid was collected, and the resulting cake was washed with toluene (10 L). The batch was then dried under high vacuum (40 °C) for 20 h. 3,4-Dideuteroxybenzaldehyde was isolated as a tan solid (3480 g, 98% yield, greater than 99.9% AUC by HPLC, 300 MHz ^1H NMR indicated a deuteration level of approximately 91 %).

[0082] **Example 5**. Synthesis of 2,2-d_2-Benzo[d][1,3]dioxole-5-carbaldehyde **(XIV)**. Compound XIV was prepared as outlined in Scheme 5 below. Details of the synthesis are set forth below.

Scheme 5.



XI **XIV**

[0083] **Synthesis of 2,2-d2-benzo[d][1,3]dioxole-5-carbaldehyde (XIV).** A suspension of K_2CO_3 (29.6 g, 0.22 mol) in *N*-methylpyrrolidinone (NMP) (270 mL) was heated to 110 °C and stirred under N_2. A solution of 3,4-dideuteroxybenzaldehyde **(XI)** (15 g, 0.11 mol) in CD_2Cl_2 (68 mL, 1.1 mol) and NMP (30 mL) was added dropwise over 45 minutes (min). The reaction mixture was stirred at 110 °C for an additional 90 min. The mixture was allowed to cool, was filtered, and the filtrate was poured into water (900 mL) and extracted with EtOAc (3 x 600 mL). The combined organics were washed with water (2 x 600 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was purified by silica-gel chromatography (4:1 Hexane/EtOAc) to give 14.2 g (87%) of **XIV** as a pale brown oil that solidified on standing. The level of CHD and CH_2 present was determined to be approximately 0.5% and approximately 0.03% respectively. (See below).

[0084] Quantification of the Amount of the Monodeutero-product in 2,2-d_2-Benzo[d][1,3]dioxole-5-carbaldehyde (XIV). Due to the very low levels of the CHD present in XIV, routine procedures such as the use of an external standard for comparison of NMR integration values do not allow sufficient accuracy of measurement. The procedure employed here makes use of ^{13}C-^1H coupling of the aldehyde signal (a consistent internal comparison) to measure the amount of the CHD present in a sample of **XIV.** As the natural abundance of ^{13}C in carbon is 1.11%, the integration for each signal in the doublet pattern of the aldehyde signal at about 9.75 ppm (^{13}C-^1H doublet signals at 9.46 ppm and 10.15 ppm) in the ^1H NMR spectrum equates to about 0.56% each. Comparison of the integration value of one of the doublet peaks versus the CHD signal at 6.03 ppm indicates approximately equal value and therefore the level of CHD in the **XIV** sample is determined to be about 0.5%. Similarly, the CH_2 peak at 6.05 ppm has a level of about 0.03%. 300 MHz ^1HNMR **(XIV)** ($CDCl_3$) δ = 6.89, 6.92 (d, 1H); 7.30, 7.31, 7.37, 7.38, 7.40, 7.41 (m, 2H); and 9.79 (s, 1H). For the corresponding d_2-benzo[d][1,3]dioxole prepared from dihydroxybenzaldehyde **(X)** the level of the CHD peak was determined to be 6%. The level of the CH2 peak was determined to be at the limit of quantification by 300 MHz ^1H NMR.

[0085] **Example 6.** Alternate synthesis of 2,2-d_2-Benzo[d][1,3]dioxole-5-carbaldehyde **(XIV).** Compound XIV was prepared as generally outlined in Scheme 5 above. Details of the synthesis are set forth below.

[0086] **Synthesis of 2,2-d_2-benzo[d][1,3]dioxole-5-carbaldehyde (XIV).** A solution of 3,4-dideuteroxybenzaldehyde **(XI)** (5g, 1eq) in *N*-methylpyrrolidinone (NMP) (10 mL) and CD_2Cl_2 (22.3 mL, 10 eq) was added over 1 h to a stirring suspension of K_2CO_3 (4.9 g, 2 eq) in NMP (100 mL) and D_2O (1.5 mL, 2.1 eq) at 110 °C under nitrogen. Stirring was continued at 110 °C for 1.5 h after which time the reaction mixture was cooled to rt, filtered and the solid was washed with ethyl acetate (10 mL). The combined reaction mixture and wash was partitioned between water (50 mL) and ethyl acetate/heptane (4:1, 50 mL). The aqueous layer was separated and extracted with ethyl acetate/heptane (4:1, 3 x 50 mL). The organic extracts were combined and washed with water (3 x 60 mL), dried over magnesium sulfate and concentrated *in vacuo* to a brown oil. The residue was purified by chromatography using ethyl acetate/heptane (1:8) to afford 1.99g of **XIV** with a CHD level of 0.59% by 300 MHz ^1H NMR. The level of the CH2 peak was determined to be

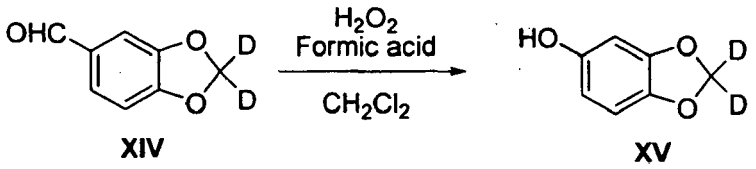
at the limit of quantification by 300 MHz ^{1}H NMR.

[0087] **Example 7.** Alternate synthesis of 2,2-d_2-Benzo[d][1,3]dioxole-5-carbaldehyde (**XIV**). Compound XIV was prepared as generally outlined in Scheme 5 above. Details of the synthesis are set forth below.

[0088] **Synthesis of 2,2-d_2-benzo[d][1,3]dioxole-5-carbaldehyde (XIV).** A 100-L, jacketed reactor equipped with a temperature probe, nitrogenous atmosphere, and reflux condenser was charged with powdered potassium carbonate (4236 g) and NMP (38.7 L). The resulting suspension was heated to 110°C. A pre-mixed solution of 3,4-dideuteroxybenzaldehyde (2150 g), d_2-methylene chloride (13.33 Kg) and NMP (4.3 L) was added via an addition funnel. The solution was added over 20 min via subsurface addition. The temperature of the batch had decreased from 110 °C to 100.6 °C over the course of the addition. The batch was allowed to warm back to 110°C, and after 90 min HPLC indicated less than 1% of 3,4-dideuteroxybenzaldehyde. The green-gray suspension was cooled to ambient temperature for 18 h (overnight), and then filtered over a pad of celite. The pad was washed with 4:1 EtOAc/heptane (21.5 L), and the combined filtrates were added to deionized water (54 L). The resulting aqueous mixture was extracted with 4:1 EtOAc/heptane twice (1 × 32 L, 1 × 54 L). The combined organic layers were washed with deionized water (3 × 43 L) and brine (43 L), dried ($MgSO_4$), filtered over celite, and concentrated *in vacuo.* Crude **XIV** was isolated as an orange oil which solidified upon standing (2340 g, quantitative yield, 97.6% AUC by HPLC, CHD impurity as determined by 300 MHz ^{1}H NMR was 0.41%). The material was further was purified via column chromatography (10.0 kg SiO_2 gel, 10 to 20% EtOAc/heptane). The product-containing fractions were concentrated to provide d_2-piperonal as light yellow solid (1775 g, 82% yield from 3,4-dideuteroxybenzaldehyde, greater than 99.9% AUC by HPLC, CHD impurity as determined by 300 MHz ^{1}H NMR was 0.50%). The level of the CH2 peak was determined to be at the limit of quantification by 300 MHz ^{1}H NMR.

[0089] **Example 8.** Synthesis of 2,2-d_2-Benzo[d][1,3]dioxol-5-ol (**XV**). Compound XV was prepared as outlined in Scheme 6 below. Details of the synthesis are set forth below.

Scheme 6.



[0090] **Synthesis of 2,2-d_2-benzo[d][1,3]dioxol-5-ol (XV).** To a stirred solution of **XIV** (165 g, 1.08 mol, 1.0 eq) in CH_2Cl_2 (5.5 L) was added 30% hydrogen peroxide (343 mL, 3.01 mol, 2.75 eq) and 96% formic acid (182 mL, 4.63 mol, 4.3 eq) and the resulting mixture was stirred overnight at reflux. The reaction mixture was cooled to 0-5 °C, 1.5 M NaOH (5.9 L, 8.85 mol, 8.2 eq) was added portionwise over 30 min (exotherm to 25-30 °C) and the mixture was stirred for an additional 30 min. The organic layer was separated and concentrated *in vacuo.* The residue was dissolved in MeOH (3.6 L), added to the aqueous layer and the resulting mixture stirred at room temperature for 30 min. MeOH was removed *in vacuo* and the remaining aqueous mixture was extracted with CH_2Cl_2 (2 L then 1.5 L), acidified to pH 3 with concentrated aq. HCl then extracted again with CH_2Cl_2 (2 L then 2 x 1.5 L). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was combined with material from another 165 g batch and purified by column chromatography (hexane/EtOAc 4/1) to give **XV** (185 g, 61% combined yield) as a white solid with a purity of greater than 95% by 300 MHz ^{1}H NMR and 99% by LC. The level of CHD impurity as determined by ^{1}H NMR was 1.0%. The level of the CH_2 peak was determined to be at the limit of quantification by 300 MHz ^{1}H NMR.

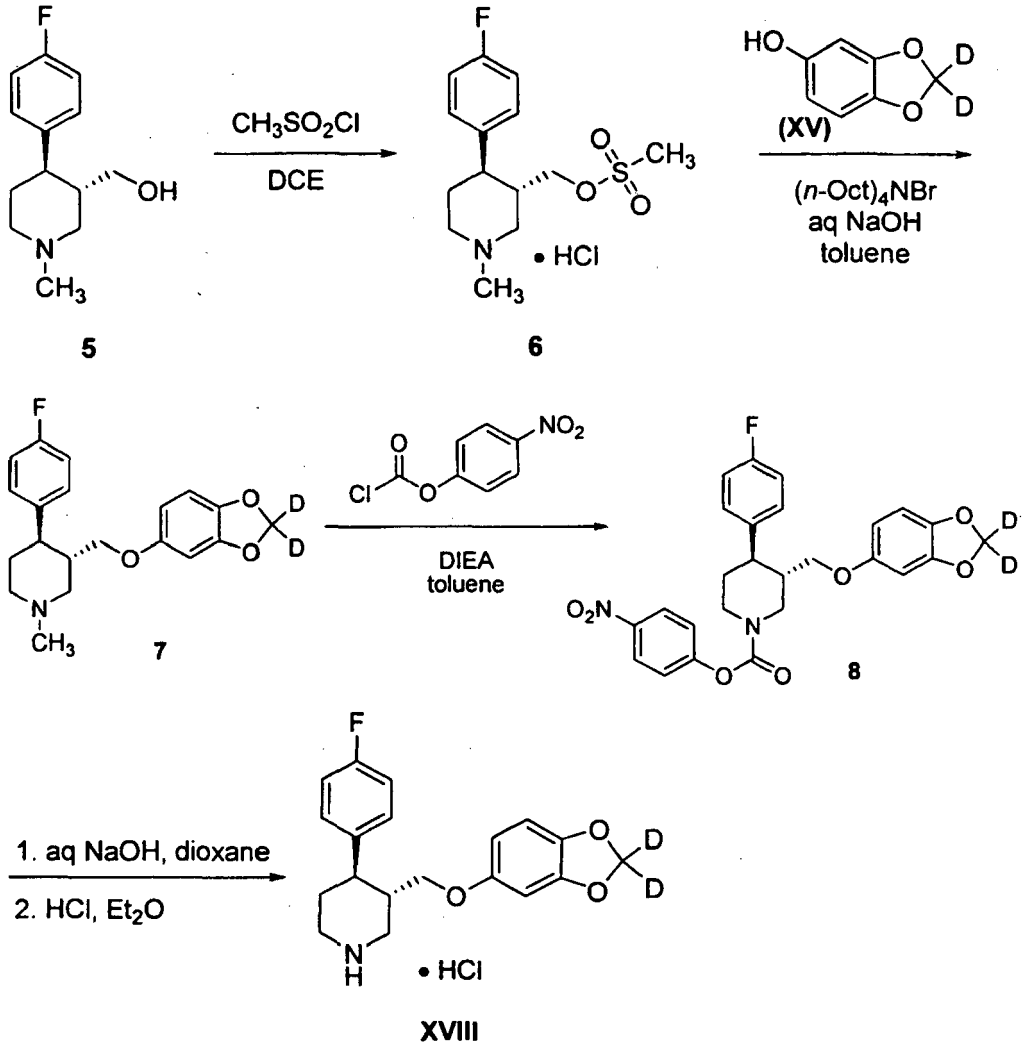
[0091] **Example 9.** Alternate synthesis of 2.2-d_2-Benzo[d][1,3]dioxol-5-ol (**XV**). Compound XV was prepared as outlined in Scheme 6 above. Details of the synthesis are set forth below.

[0092] **Synthesis of 2,2-d_2-benzo[d][1,3]dioxol-5-ol (XV).** To a 100-L jacketed reactor equipped with a temperature probe, nitrogenous atmosphere, and reflux condenser was added **XIV** (1990 g) and DCM (20 L). The mixing of these reagents resulted in an endotherm from 20.2 °C to 15.2 °C. Formic acid (2720 mL, 4.5 equiv) was added, and the batch was warmed to 25-27 °C. Hydrogen peroxide (3874 mL of a 30 wt % solution in water, 2.9 equiv) was then added so as to maintain the internal temperature below 30 °C. This addition required 3 h and 15 min. Upon completion of the addition, the batch was stirred for 18 h at 20 to 25 °C. HPLC indicated 4.1 % **XIV** remaining. The phases were separated and the organic phase was washed with 25 wt % sodium metabisulfite in water (7.5 L). The organic phase was then cooled to 10-15 °C, and an 8.8 wt % solution of sodium hydroxide and water (12 L) was added. This addition was carried out so as to maintain the internal temperature below 20 °C. The biphasic mixture was stirred for 30 min at 10-20 °C, and then HPLC indicated less than 1% of the intermediate sesamyl formate remaining. The phases were separated, and the aqueous phase was returned to the reactor. MTBE (6 L) was added, followed by 3 N HCl (10 L). The biphasic mixture was stirred for 15 min, and then the phases were separated. The aqueous phase was extracted with MTBE (2 × 8 L).

The combined organic phases were washed with water (8 L) and brine (8 L), dried ($MgSO_4$), filtered over celite, and concentrated to 6 L. Heptane (6 L) was added, and the mixture was concentrated back down to 6 L. This solvent-swap procedure was repeated two additional times with heptane (6 L each time). The resulting off-white suspension was cooled to ambient temperature. The solid was collected, washed with heptane (1 bed volume), and dried under high vacuum. Crude **XV** was isolated as a yellow solid (1350 g, 74% yield, 97.3% AUC by HPLC, CHD impurity as determined by 300 MHz ^{1}H NMR was 0.42%). A portion of the crude material (540 g) was purified via column chromatography (4.4 kg SiO_2 gel, 10 to 20% EtOAc/heptane). The product-containing fractions were concentrated to provide **XV** as an off-white solid (525 g, 69% yield from **XIV,** greater than 99.9% AUC by HPLC, CHD impurity as determined by ^{1}H NMR was 0.55%). The level of the CH_2 peak was determined to be at the limit of quantification by 300 MHz ^{1}H NMR.

[0093] **Example 10.** Synthesis of (3S,4R)-3-((2,2-d_2-Benzo[d][1,3]dioxol-5-yloxy)-methyl-4-(4-fluorophenyl)piperidine hydrochloride (**XVIII**). Compound XVIII was prepared as outlined in Scheme 7 below. Details of the synthesis are set forth below.

Scheme 7.



[0094] **Synthesis ((3S,4R)-4-(4-fluorophenyl)-1-methylpiperidin-3-yl)methyl methanesulfonate, HCl salt (6).** ((3S,4R)-4-(4-fluorophenyl)-1-methylpiperidin-3-yl)methanol (**5**) (2.00 g, 8.96 mmol) was dissolved in dichloroethane (20 mL) and methanesulfonyl chloride (0.73 mL) was added. The reaction was stirred for 6 h at rt. The reaction mixture was concentrated on a rotary evaporator to afford **6** as a white solid residue which was suitable for use in crude form. **MS** m/z: 302.1 (M+H).

[0095] **Synthesis of (3S,4R)-3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)-1-methylpiperidine (7).** To a flask containing crude **6** (approximately 8.96 mmol) was added toluene (45 mL), 2,2-d_2-benzo[d][1,3]dioxol-5-ol (**XV**, 99.7% isotopic purity, 1.26 g, 8.96 mmol), tetra-n-octylammonium bromide (245 mg, 0.448 mmol), and 3M

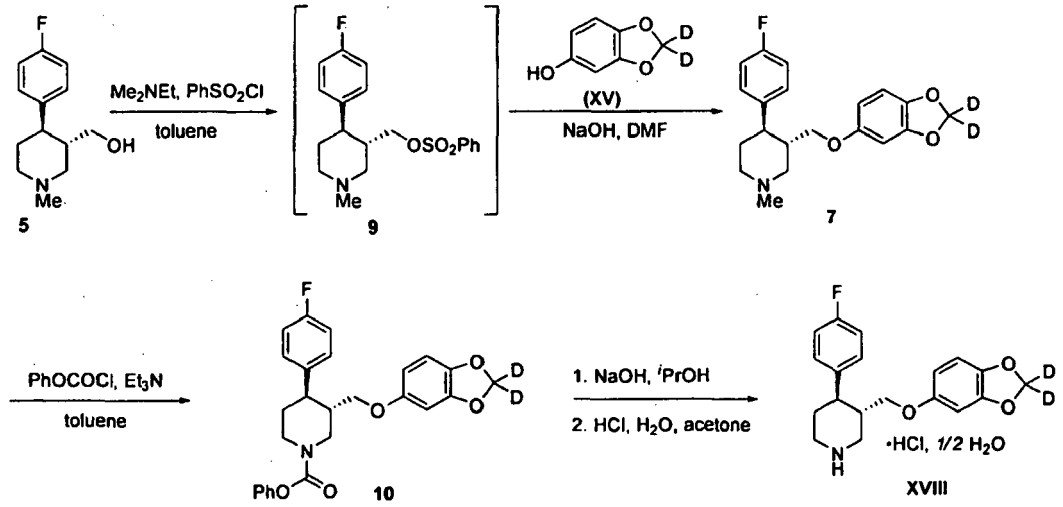
aqueous NaOH (22.4 mL, 67.2 mmol) with stirring. The resulting pale yellow turbid bilayer was stirred and heated in a 90 °C oil bath under a vented air condenser for 5 h. The reaction mixture was cooled to rt and diluted with water (100 mL) and toluene (50 mL). The mixture was poured into a separatory funnel and shaken, and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and with brine, then dried over magnesium sulfate, filtered and concentrated on a rotary evaporator to afford approximately 4 g of **7** which contained some residual toluene. This material was suitable for use in crude form. **MS** m/z: 346.3 (M+H).

[0096] Synthesis of (3S,4R)-4-nitrophenyl 3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (8). To a flask containing crude **7** (approximately 8.96 mmol) was added toluene (60 mL), diisopropylethylamine (0.312 mL, 1.79 mmol) and 4-nitrophenylchloroformate (1.81 g, 8.96 mmol). The mixture was stirred and heated in an 80 °C oil bath under a vented air condenser for 5 h. The reaction mixture was cooled to rt and diluted with toluene (50 mL). The mixture was poured into a separatory funnel and the flask was rinsed with an additional 50 mL of toluene. A 100-mL portion of water was added to the separatory funnel and the layers were shaken and separated. The aqueous layer was extracted with an additional 25 mL of toluene. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated on a rotary evaporator to afford an amber oil. The material was purified via column chromatography (5% to 30% EtOAc/hexanes) to provide 2.16 g of **8.**

[0097] Synthesis of (3S,4R)-3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine, HCl salt (XVIII). To a solution of **8** (2.16 g, 4.35 mmol) in dioxane (29 mL) was added 2M aqueous NaOH (43.5 mL, 87.0 mmol) and the mixture was stirred and heated in a 70 °C oil bath under a vented air condenser for 3 h. The reaction mixture was cooled to rt and concentrated on a rotary evaporator to remove the majority of the dioxane. The aqueous residue was poured into a separatory funnel and extracted three times with Et_2O. The combined organic layers were washed with 1N aqueous NaOH, then dried over magnesium sulfate, filtered and concentrated on a rotary evaporator to afford the free base **of XVIII** as a pale yellow oil (1.2 g). This material was purified via preparative HPLC/MS to provide 710 mg of the free base of **XVIII,** which was then taken up in a minimal volume of acetone and added slowly to a stirred solution of 1M HCl/Et_2O (5 mL), Et_2O (15 mL), and hexanes (60 mL). The resulting cloudy white mixture was held at 0 °C for 1 h, then concentrated to a reduced volume on a rotary evaporator. The resulting white solids were filtered, washed with hexanes/Et_2O, and dried in a vacuum oven at 35 to 40 °C overnight to provide 651 mg of the HCl salt of **XVIII.** **^{1}H-NMR** (300 MHz, DMSO-d_6): δ 9.04 (br s, 2H), 7.25 - 7.14 (m, 4H), 6.74 (d, 1H, *J*= 8.3), 6.48 (d, 1H, *J* = 2.9), 6.18 (dd, 1H, *J* = 2.4, 8.3), 3.58 (dd, 1H, *J*= 3.4, 10.2), 3.52 - 3.47 (m, 2H), 3.39-3.35 (m, 1H), 3.01 - 2.91 (m, 2H), 2.86 (dt, 1H, *J*= 3.4, 12.2), 2.47 -2.39 (m, 1H), 2.05 - 1.94 (m, 1H), 1.88 -1.85 (m, 1H). **MS** (M+H): 332.0.

[0098] Example 11. Alternative Synthesis of (3S,4R)-3-((2,2-d_2-Benzo[d][1,3]dioxol-5-yloxy)-methyl-4-(4-fluorophenyl)piperidine hydrochloride (**XVIII**). Compound XVIII was prepared as outlined in Scheme 8 below. Details of the synthesis are set forth below.

Scheme 8.



[0099] Alternative Synthesis of (3S,4R)-3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)-1-methylpiperidine (7). A solution of 50 g of compound **5** (224 mmol) in toluene (230 mL) was cooled to ≤ 5°C and then 48.8 mL (450 mmol, 2.0 equiv) dimethylethylamine was added. To the reaction mixture was charged a solution of 48.23 g (0.273 mmol, 1.22 eq) benzenesulfonyl chloride in toluene (37.1 mL), keeping the temperature of the reaction mixture at less than or equal to 10 °C. The mixture was stirred at 0-5 °C for 110 min. The reaction mixture was then quenched with a solution of 30.5% NaOH (7.5 mL, 37 mmol, 0.34 equiv) and water (140 mL). After stirring for 15 min, the aqueous

layer was removed and discarded. The solution of compound **9** was stored at 0 °C overnight. To the organic layer was added 31.4 g of **XV** (1.0 equiv, 224 mmol), DMF (230 mL) and 10.75 g NaOH (1.2 equiv, 67.2 mmol). The reactor was heated to 71 °C and stirred for 3h. The reaction mixture was cooled to 50 °C and quenched with water (149 mL). The aqueous layer was extracted with toluene (100 mL) at 50 °C. Then the aqueous layer was removed, and the two organic layers were combined. This organic layer was washed with sodium hydroxide solution (prepared by mixing 53 mL of 30.5% sodium hydroxide and 141 mL water) at 50 °C. The aqueous layer was removed, and the organic layer was again washed with purified water (149 mL) at 50 °C. The organic layer was concentrated at 50-55 °C. under vacuum to 2 volumes and then isopropyl alcohol (IPA) (225 mL) was added. The mixture was heated and concentrated at constant volume with introduction of fresh IPA until the refractive index of the distillate was 1.377 (consistent with pure IPA). At this point the mixture was cooled to 45 °C, seeded and aged for 90 min. At this point crystallization occurred. The temperature was lowered to 0 °C over 2 h and 30 min and the mixture was held at that temperature for 3 h. The solid was filtered and washed with cold isopropyl alcohol (36 mL). The solid was vacuum dried for 4 h at 40 °C to afford 55.7 g of compound **7** (72% yield).

[0100] Synthesis of (35,4R)-4-phenyl 3-((2,2-d_2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (10). A solution of 50 g (0.145 mmol) of compound **7** in toluene (365 mL) was heated to 90 °C and then 40.4 g (257 mmol, 1.79 equiv) of phenylchloroformate was charged over approximately 37 minutes. The reaction mixture was heated to 105 °C and stirred for 8 h. The reaction mixture was then cooled to 60 °C and triethylamine (20.9 mL) was added. The reaction mixture was stirred at 60 °C for 1 h, and then cooled to rt. The toluene solution was washed with 10% aqueous sodium hydroxide solution (prepared by mixing 76.5 mL water and 29 mL 30.5% NaOH). The layers were separated and the organic layer was washed with a mixture of water (98.4 mL) and sodium chloride (10 g). After separating the layers, water (105 mL) was added to the toluene solution and the pH was adjusted to ≤ 2 using concentrated hydrochloric acid. The aqueous layer was removed and the organic layer was washed three times with 105 mL of water. The organic layer was concentrated at 55-65 °C under vacuum to 2 volumes and then isopropyl alcohol (IPA) (165 mL) was added. The mixture was heated and concentrated to 3 volumes and at this point the refractive index of the distillate was 1.377. IPA (111 mL) was added and the mixture was heated to 70 °C. At this temperature the mixture was a pale yellow solution. The mixture was cooled to 64 °C, at which temperature crystallization occurred and the mixture was aged for 90 min. Then the mixture was cooled to 0 °C over 150 min and held at that temperature for 120 min. The solids were filtered and washed with cold IPA (35 mL) and then vacuum dried at 40 °C to afford 60.4 g (92%) of compound **10.**

[0101] Synthesis of (3S,4R)-3-((2,2-d2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine, HCl salt (XVIII). A mixture of 40 g (88.6 mmol) of compound **10** and isopropyl alcohol (840 mL) was heated to 79 °C and to the hot reaction mixture was charged a solution of 30.5% sodium hydroxide (131 g, 11.3 equiv) over a period of approximately 45 min. After the addition was completed, the mixture was heated to reflux for 8 h. The reaction mixture was cooled to rt. To the stirring reactor was charged 277 mL water (6.92 vol). This mixture was extracted two times with toluene (123 mL). The toluene extracts were combined and washed three times with 5% aqueous sodium hydroxide solution (114 mL) to remove residual phenol. The toluene solution was then washed with water (123 mL). The organic layer was concentrated to an oil. The oil was dissolved in acetone (229 mL) and this solution was heated to 55 °C and at this point water (7.2 mL) and hydrochloric acid (7.2 mL) were introduced. Then the mixture was cooled to 35 °C, seeded, and aged for 2 h. The mixture was further cooled to 20-25 °C in 1 h and n-heptane (95 mL) was added .The mixture was cooled to 0 to 5 °C and held at that temperature for 2 h. The solids were filtered and washed with cold acetone (42 mL). The product was dried under vacuum at 40 °C to give 26.1 g (80%) of the title compound.

Example 12. Investigation of the Drug-Drug Interaction (DDI) Potential between Deuterated Paroxetine (Test Compound A) and Tamoxifen.

[0102] Tamoxifen's activity against breast cancer is primarily mediated through its 4-hydroxy metabolites, which are formed by the action of cytochrome P450 isozyme CYP2D6. The 4-hydroxy metabolites act as estrogen receptor antagonists in breast tissue. Because tamoxifen conversion to its active metabolites requires CYP2D6, tamoxifen has limited efficacy in phenotypes that are poor CYP2D6 metabolizers and should not be used with other drugs that inactivate the enzyme.

[0103] Tamoxifen therapy has been implicated in the occurrence of severe hot flashes. A promising treatment for hot flashes - paroxetine - is also a mechanism-based inactivator of CYP2D6. Since paroxetine-mediated CYP2D6 inactivation would inhibit the formation of the active metabolite endoxifen, its use in breast cancer patients on tamoxifen therapy should be avoided.

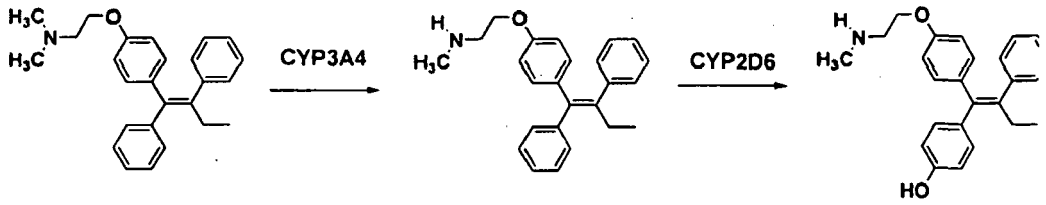
[0104] Deuterated paroxetine is being developed for the treatment of postmenopausal and tamoxifen-induced hot flashes.

[0105] ***Objective:*** The objective of this study was to determine the potential for the deuterated paroxetine, (3S,4R)-3-((2,2-d2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine, HCl salt-hemihydrate, to inhibit the formation of endoxifen using human cDNA-expressed CYP2D6 as compared with paroxetine. The deuterated paroxetine,

(3S,4R)-3-((2,2-d2-benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine, HCl salt-hemihydrate, will be referred to as "Test Compound A" in the following examples and the figures.

[0106] Tamoxifen (TAM), an antagonist of the estrogen receptor, is metabolized to N-desmethyl TAM by CYP3A4 which in turn is hydroxylated to endoxifen by CYP2D6 (Scheme 9). Endoxifen is an active metabolite with 30-100-fold higher activity than TAM and is the major circulating metabolite in humans.

Scheme 9. Metabolism of N-Desmethyl Tamoxifen to Endoxifen by CYP2D6



[0107] ***Method:*** Test Compound A was pre-incubated for 20 min at various concentrations with human cDNA-expressed CYP2D6 (500 pmol/mL) in the presence of NADPH, after which aliquots of the reaction mixture were diluted 1:10 in buffer containing NADPH. N-desmethyl TAM (50 μM) was then added to the diluted pre-incubation mixtures. After 45 min of incubation, endoxifen concentrations were determined by LC-MS/MS. Similar incubations with paroxetine (reference compound) were performed in parallel.

[0108] ***Results:*** There was little to no change in the formation of endoxifen from *N*-desmethyl tamoxifen over the range of Test Compound A concentrations tested (0-25 μM). Conversely, as concentrations of paroxetine exceeded 5 μM, the rate of endoxifen formation dropped dramatically (Figure 1). At the highest concentration (25 μM), there was 12-fold more endoxifen produced in the presence of Test Compound A than in the presence of paroxetine. These results confirm that deuterated paroxetine, Test Compound A, is a poor CYP2D6 mechanism-based inactivator and subsequently has a greatly reduced drug-drug interaction potential.

[0109] ***Conclusion:*** The maximum plasma concentration of Test Compound A in humans, for vasomotor symptoms (VMS), is not expected to be greater than 30 nM. In this study, Test Compound A had little or no effect on metabolism of *N*-desmethyl tamoxifen to endoxifen and hence Test Compound A would not be expected to cause clinically relevant drug-drug interactions when co-administered with tamoxifen.

Example 13. Inactivation of CYP2D6 in human liver microsomes by Test Compound A.

[0110] ***Objective:*** The objective of this study was to evaluate the potential of Test Compound A to inactivate CYP2D6 in human liver microsomes: comparison with paroxetine.

[0111] ***Method:*** This study was conducted according to the procedure established by Bertelsen et al for paroxetine. *See* Bertelsen KM, Venkatakrishnan K, von Moltke LL, Obach S, Greenblatt, DJ. Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. Drug Met Disp 2003;31:289-293. Briefly, the test articles were pre-incubated with human liver microsomes for various times followed by the addition of dextromethorphan, a CYP2D6 substrate. The formation of dextrorphan, a CYP2D6-specific metabolite of dextromethorphan, was monitored as a measure of CYP2D6 activity.

[0112] ***Results:*** As previously shown, paroxetine (reference compound) produced a concentration- and time-dependent inhibition of CYP2D6, expressed as the percentage of dextrorphan formation relative to control (FIG. 2). Deuteration appears to significantly diminish this effect, as CYP2D6 activity for Test Compound Aremained similar to that of control in the 0-10 μM concentration range. Some inhibition of CYP2D6 occurred as the concentration of Test Compound A approached 25 μM. These results were confirmed by determination of K_I and k_{INACT} for paroxetine-mediated CYP2D6 inactivation (Figure 3). Paroxetine showed a significant inactivation of CYP2D6 with K_I and k_{INACT} values of 1.96 μM and 0.08 min^{-1} respectively, whereas due to the modest inhibition of CYP2D6, the k_{INACT} of Test Compound A could not be calculated.

[0113] ***Conclusion:*** Test Compound A does not exhibit mechanism-based inactivation of CYP2D6 at concentrations up to 10 μM.

Example 14. Metabolic Stability of Deuterated Paroxetine (Test Compouond A) in Rat and Human Liver Microsomal Preparations.

[0114] ***Objective:*** The objective of this study was to evaluate the *in vitro* metabolic clearance of Test Compound A in rat and human liver microsomes: comparison with paroxetine.

[0115] ***Method:*** Test Compound A was evaluated at a concentration of 1 μM for apparent metabolic stability by the *in vitro* $t_{1/2}$ method described by Obach et al. *See* Obach RS, Baxter JG, Liston TE, Silber BM, Jones BC, MacIntyre F, et al. The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. JPET 1997;283:46-58.

[0116] ***Results:*** Following incubation in rat, and human hepatic microsomes (0.5 mg/mL) the mean relative amounts of Test Compound A remaining at the end of 30 minutes incubation were 25.5 ± 4.3% and 37.2 ± 3.9% (n=4), respectively. The $t_{1/2}$ values, calculated from the LN (% parent remaining) versus time relationship, were 15.5 ± 1.6 and 20.9 ± 2.0 min in rat and human hepatic microsomes, respectively (FIGS. 4 and 5). The metabolic stability of paroxetine was also assessed similarly in parallel and the corresponding $t_{1/2}$, values are shown in Table 1.

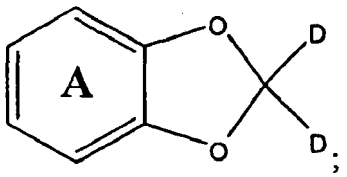
Table 1.

Species	Test Article	$t_{1/2}$ (min)
Rat	Test Compound A	15.5 ±1.6
	Paroxetine	20.4 ±2.1
Human	Test Compound A	20.9 ±2.0
	Paroxetine	49.0 ±7.8

[0117] ***Conclusion:*** Under the *in vitro* conditions tested, Test Compound A was readily cleared by metabolic pathways in rat and human liver microsomal preparations. The $t_{1/2}$ values of Test Compound A were approximately 24% and 57% less in rat and human liver microsomes, respectively, than the corresponding values for paroxetine. These data suggest that Test Compound A does not inhibit its own clearance as has been reported for paroxetine. *See* Bertelsen KM, Venkatakrishnan K, von Moltke LL, Obach S, Greenblatt, DJ. Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. Drug Met Disp 2003;31:289-293; and Heydom WE. Paroxetine: a review of its pharmacology, pharmacokinetics and utility in the treatment of a variety of psychiatric disorders. Exp Opin Invest Drugs 1999;8(4):417-441. The greater variability observed in the $t_{1/2}$ values of paroxetine in human liver microsomal preparations is likely due the inactivation of its own metabolism.

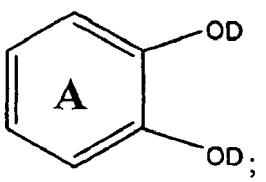
Claims

1. A process for the preparation of a deuterated benzo[*d*][1,3]dioxole represented by the following structural formula:



comprising the step of reacting a deuterated catechol with base and a dihalodideuteromethane to form the deuterated benzo[*d*][1,3]dioxole, wherein:

the deuterated catechol is represented by the following structural formula:

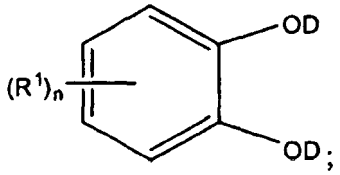


wherein:

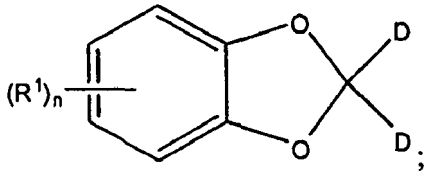
the isotopic enrichment of the deuterated catechol with deuterium is at least 75%; and
Ring **A** of the deuterated catechol and deuterated benzo[*d*][1,3]dioxole is substituted with one or more groups, provided that the substituent group(s) do not react with the base or with the dihalodeuteromethane.

2. The process of Claim 1 wherein the isotopic enrichment of the deuterated catechol with deuterium is at least 85%, or wherein the isotopic enrichment of the deuterated catechol with deuterium is at least 95%.

3. The process of Claim 1 wherein the deuterated catechol is represented by the following structural formula:



and the deuterated benzo[*d*][1,3]dioxole is represented by the following structural formula:



wherein:

n is 1, 2 or 3;
each R^1 is independently halo; -OR^a; -OR'; -CHO; -$COOR^b$, -COOR'; C(O)R'; -CN; -$OC(O)NH_2$; -OC(O)NHR'; -$OC(O)N(R')_2$; -$CR^4{=}C(R^4)_2$; -$C{\equiv}CR^4$; or an aryl group optionally substituted with one or more groups represented by R^5;
each R^4 is independently -H or a group represented by R';
each R^5 is independently selected from halo; alkyl, -OR^a; alkoxy; haloalkoxy, -CHO; -$COOR^b$, -COOR"; C(O)R"; -NO_2; haloalkyl; -CN; -NHR^c, -NR^cR", -$N(R")_2$; -NHC(O)R"; -$NHC(O)NH_2$; -NHC(O)NHR"; -$NHC(O)N(R")_2$; -$OC(O)NH_2$; -OC(O)NHR"; -$OC(O)N(R")_2$; -NHC(O)H; -NHC(O)R"; -NHC(O)OR"; -S(O)R"; -$S(O)_2R$"; -SO_2NH_2; -SO_2NHR"; -$SO_2N(R")_2$; -$NHSO_2NH_2$; -$NHSO_2NHR$"; -$NHSO_2N(R")_2$; and -$NHSO_2R$" ;
R' is alkyl or aryl, each optionally and independently substituted with one or more groups selected from halo; -OR^a; alkoxy; haloalkoxy, -CHO; -$COOR^b$, -COOR"; C(O)R"; -NO_2; alkyl; haloalkyl; -CN; -NHR^c, -NR^cR", -$N(R")_2$; -NHC(O)R"; -$NHC(O)NH_2$; -NHC(O)NHR"; -$NHC(O)N(R")_2$; -$OC(O)NH_2$; -OC(O)NHR"; -$OC(O)N(R")_2$; -NHC(O)H; -NHC(O)R"; -NHC(O)OR"; -S(O)R"; -$S(O)_2R$"; -SO_2NH_2; -SO_2NHR"; -$SO_2N(R")_2$; -$NHSO_2NH_2$; -$NHSO_2NHR$"; -$NHSO_2N(R")_2$; and -$NHSO_2R$";
R" is alkyl;
R^a is a phenol protecting group;
R^b is a carboxylic acid protecting group; and
R^c is an amine protecting group.

4. The process of Claim 3 wherein:

n is 1; and
R^1 is halo; -OR^a; -OR'; -CHO; -$COOR^b$, -COOR'; C(O)R'; -CN; -$CH{=}CHR^4$; -$C{\equiv}CH$; -$C{\equiv}CR^4$; or a phenyl group optionally substituted with one or more groups represented by R^5; and
each R^5 is independently selected from halo; alkyl, -OR^a; alkoxy; haloalkoxy, -CHO; -$COOR^b$, -COOR"; C(O)R"; -NO_2; alkyl; haloalkyl; and -CN;
R' is alkyl; or a phenyl optionally substituted with halo; -OR^a; alkoxy; haloalkoxy, -CHO; -$COOR^b$, -COOR"; C(O)R"; -NO_2; haloalkyl; and -CN.

5. The process of Claim 1 wherein the dihalodideuteromethane is CD_2Cl_2, CD_2Br_2, CD_2I_2 or $BrCD_2Cl$.

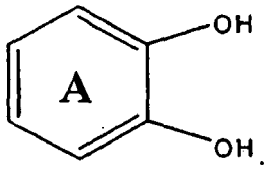
6. The process of Claim 1 wherein the base is K_2CO_3, Cs_2CO_3, $NaOCH_3$, NaH, KF, CsF or potassium *tert*-butoxide.

7. The process of Claim 1 wherein the reaction is carried out in a dipolar aprotic solvent, or wherein the reaction is carried out in a D_2O/*N*-methylpyrrolidinone co-solvent.

8. The process of Claim 7 wherein the dipolar aprotic solvent is *N*-methylpyrrolidinone, dimethylformamide, acetonitrile, hexamethylphosphoramide or *N,N*-dimethylpropyleneurea.

9. The process of Claim 1 wherein: i) the dihalodideuteromethane is CD_2Cl_2, CD_2Br_2, CD_2I_2 or $BrCD_2Cl$; ii) the base is K_2CO_3, Cs_2CO_3, $NaOCH_3$, NaH, KF, CsF or potassium *tert*-butoxide; and iii) the reaction is carried out in a solvent selected from *N*-methylpyrrolidinone, dimethylformamide, acetonitrile, hexamethylphosphoramide and *N,N*-dimethylpropyleneurea.

10. The process of Claim 1 wherein the deuterated catechol is prepared by reacting a catechol with a source of D^+, wherein the catechol is represented by the following structural formula:

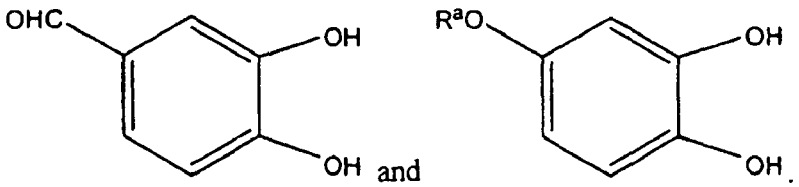


11. The process of Claim 10 wherein the source of D^+ is CH_3OD, D_2O or DCl.

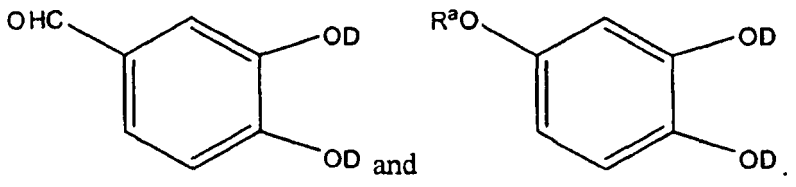
12. The process of Claim 10 wherein the reaction to form the deuterated catechol is carried out in a solvent that is selected from CH_3OD and D_2O, or
wherein the reaction to form the deuterated catechol is carried out in a co-solvent comprising: i) tetrahydrofuran, *N*-methylpyrrolidinone, dimethylsulfoxide acetonitrile or dioxane; and ii) - CH_3OD or D_2O.

13. The process of Claim 10 wherein the reaction is carried out in the presence of NaH, NaOD or DCl.

14. The process of Claim 10 wherein the catechol is represented by a structural formula selected from:

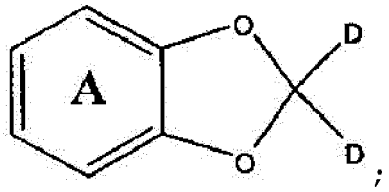


15. The process of Claim 1 wherein the deuterated catechol is represented by a structural formula selected from:



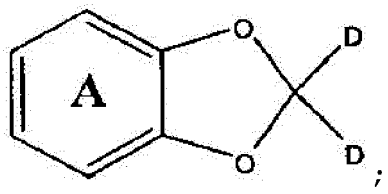
Patentansprüche

1. Verfahren zur Herstellung eines deuterierten Benzo[d][1,3]dioxols der folgenden Strukturformel:



wobei das Verfahren die Stufe der Umsetzung eines deuterierten Brenzkatechins mit einer Base und einem Dihalogendideuteromethan unter Bildung des deuterierten Benzo[d][1,3]dioxols umfasst, wobei:

das deuterierte Brenzkatechin durch die folgende Strukturformel dargestellt wird:

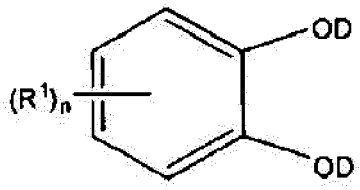


wobei:

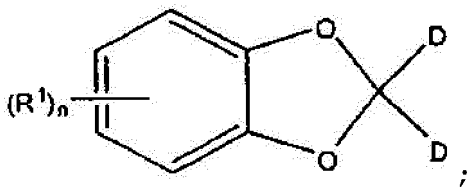
die Isotopenanreicherung des deuterierten Brenzkatechins mit Deuterium mindestens 75 % beträgt; und
der Ring A des deuterierten Brenzkatechins und des deuterierten Benzo[d][1,3]dioxols mit einer oder mehreren Gruppen substituiert ist, mit der Maßgabe, dass die Substituentengruppe(n) mit der Base oder mit dem Dihalogendideuteromethan nicht reagieren.

2. Verfahren nach Anspruch 1, wobei die Isotopenanreicherung des deuterierten Brenzkatechins mit Deuterium mindestens 85 % beträgt oder
wobei die Isotopenanreicherung des deuterierten Brenzkatechins mit Deuterium mindestens 95 % beträgt.

3. Verfahren nach Anspruch 1, wobei das deuterierte Brenzkatechin durch die folgende Strukturformel dargestellt wird:



und das deuterierte Benzo[d][1,3]dioxol durch die folgende Strukturformel dargestellt wird:



worin:
n für 1, 2 oder 3 steht;
jedes R^1 unabhängig voneinander für Halogen; -OR^a; -OR'; -CHO; -$COOR^b$, -COOR'; C(O)R'; -CN; -$OC(O)NH_2$; -OC(O)NHR'; -$OC(O)N(R')_2$; -$CR^4{=}C(R^4)_2$; -$C{\equiv}CR^4$; oder eine Arylgruppe, die optional mit einer oder mehreren Gruppen R^5 substituiert ist, steht;
jedes R^4 unabhängig voneinander für -H oder eine Gruppe R' steht;

jedes R^5 unabhängig voneinander ausgewählt ist aus Halogen; Alkyl, -OR^a; Alkoxy; Halogenalkoxy, -CHO; -$COOR^b$, -COOR"; C(O)R"; -NO_2; Halogenalkyl; -CN; -NHR^c, -NR^cR", -$N(R")_2$; -NHC(O)R"; -$NHC(O)NH_2$; -NHC(O)NHR"; -$NHC(O)N(R")_2$; -$OC(O)NH_2$; -OC(O)NHR"; -$OC(O)N(R")_2$; -NHC(O)H; -NHC(O)R"; -NHC(O)OR"; -S(O)R"; -$S(O)_2R$"; -SO_2NH_2; -SO_2NHR"; -$SO_2N(R")_2$; -$NHSO_2NH_2$; -$NHSO_2NHR$"; -$NHSO_2N(R")$ und -$NHSO_2R$"; R' für Alkyl oder Aryl steht, die jeweils optional und unabhängig voneinander mit einer oder mehreren Gruppen substituiert sind, die ausgewählt sind aus Halogen; -OR^a; Alkoxy; Halogenalkoxy, -CHO; -$COOR^b$, -COOR"; C(O)R"; -NO_2; Alkyl; Halogenalkyl; -CN; -NHR^c, -NR^cR", -$N(R")_2$; -NHC(O)R"; -$NHC(O)NH_2$; -NHC(O)NHR"; -$NHC(O)N(R")_2$; -$OC(O)NH_2$; - OC(O)NHR"; -$OC(O)N(R")_2$; -NHC(O)H; -NHC(O)R"; -NHC(O)OR"; -S(O)R"; -$S(O)_2R$"; -SO_2NH_2; -SO_2NHR"; -$SO_2N(R")_2$; -$NHSO_2NH_2$; -$NHSO_2NHR$"; -$NHSO_2N(R")$ und -$NHSO_2R$";
R" für Alkyl steht;
R^a für eine Phenol-Schutzgruppe steht;
R^b für eine Carbonsäure-Schutzgruppe steht und
R^c für eine Amin-Schutzgruppe steht.

4. Verfahren nach Anspruch 3, wobei:

n 1 ist; und
R^1 für Halogen; -OR^a; -OR'; -CHO; -$COOR^b$, -COOR'; C(O)R'; -CN; -CH=CHR^4; -C≡CH; -C≡CR^4; oder eine Phenylgruppe, die optional mit einer oder mehreren Gruppen R^5 substituiert ist, steht; und
jedes R^5 unabhängig voneinander ausgewählt ist aus Halogen; Alkyl, -OR^a; Alkoxy; Halogenalkoxy, -CHO; -$COOR^b$, -COOR";
C(O)R"; -NO_2; Alkyl; Halogenalkyl; und -CN;
R' für Alkyl oder ein Phenyl steht, die optional mit Halogen; -OR^a; Alkoxy; Halogenalkoxy, -CHO; -$COOR^b$, -COOR";
C(O)R"; -NO_2; Halogenalkyl; und -CN substituiert sind.

5. Verfahren nach Anspruch 1, wobei das Dihalogendideuteromethan CD_2Cl_2, CD_2Br_2, CD_2I_2 oder $BrCD_2Cl$ ist.

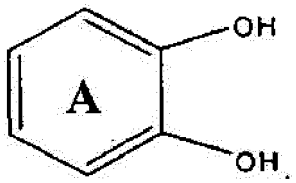
6. Verfahren nach Anspruch 1, wobei die Base K_2CO_3, Cs_2CO_3, $NaOCH_3$, NaH, KF, CsF oder Kalium-tert-butoxid ist.

7. Verfahren nach Anspruch 1, wobei die Umsetzung in einem dipolaren aprotischen Lösemittel durchgeführt wird oder wobei die Umsetzung in einem D_2O/N-Methylpyrrolidinon-Co-Lösemittel durchgeführt wird.

8. Verfahren nach Anspruch 7, wobei das dipolare aprotische Lösemittel N-Methylpyrrolidinon, Dimethylformamid, Acetonitril, Hexamethylphosphoramid oder N,N-Dimethylpropylenharnstoff ist.

9. Verfahren nach Anspruch 1, wobei: i) das Dihalogendideuteromethan CD_2Cl_2, CD_2Br_2, CD_2I_2 oder $BrCD_2Cl$ ist; ii) die Base K_2CO_3, Cs_2CO_3, $NaOCH_3$, NaH, KF, CsF oder Kalium-tert-butoxid ist; und iii) die Umsetzung in einem Lösemittel durchgeführt wird, das aus N-Methylpyrrolidinon, Dimethylformamid, Acetonitril, Hexamethylphosphoramid und N,N-Dimethylpropylenharnstoff ausgewählt ist.

10. Verfahren nach Anspruch 1, wobei das deuterierte Brenzkatechin durch Umsetzung eines Brenzkatechins mit einer Quelle für D^+ hergestellt wird, wobei das Brenzkatechin durch die folgende Strukturformel dargestellt wird:



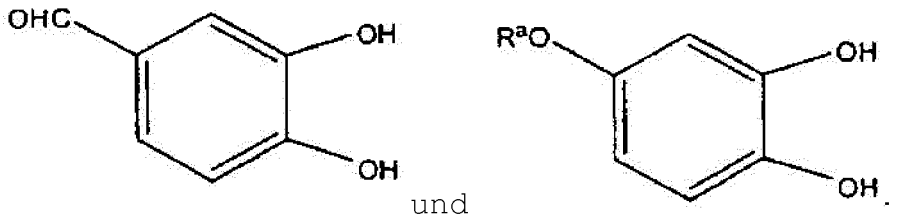
11. Verfahren nach Anspruch 10, wobei die Quelle für D^+ CH_3OD, D_2O oder DCl ist.

12. Verfahren nach Anspruch 10, wobei die Umsetzung zur Bildung des deuterierten Brenzkatechins in einem Lösemittel durchgeführt wird, das aus CH_3OD und D_2O ausgewählt ist,
oder
wobei die Umsetzung zur Bildung des deuterierten Brenzkatechins in einem Co-Lösemittel durchgeführt wird, das

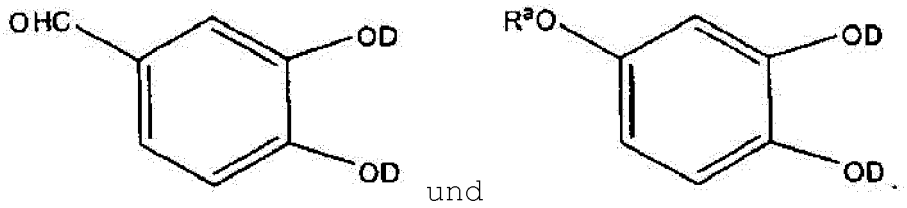
umfasst: i) Tetrahydrofuran, N-Methylpyrrolidinon, Dimethylsulfoxid, Acetonitril oder Dioxan und ii) CH_3OD oder D_2O.

13. Verfahren nach Anspruch 10, wobei die Umsetzung in Gegenwart von NaH, NaOD oder DCl durchgeführt wird.

14. Verfahren nach Anspruch 10, wobei das Brenzkatechin durch eine Strukturformel dargestellt wird, die ausgewählt ist aus:

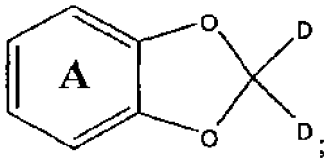


15. Verfahren nach Anspruch 1, wobei das deuterierte Brenzkatechin durch eine Strukturformel dargestellt wird, die ausgewählt ist aus:



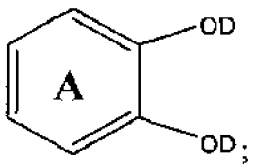
Revendications

1. Procédé de préparation d'un benzo[*d*][1,3]-dioxole deutéré représenté par la formule structurale suivante :



comprenant l'étape de réaction d'un catéchol deutéré avec une base et un dihalogéno-dideutéro-méthane pour former le benzo[*d*][1,3]dioxole deutéré, dans lequel :

le cachétol deutéré est représenté par la formule structurale suivante :

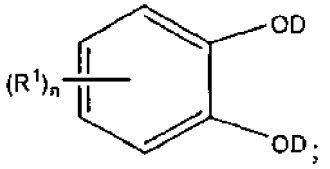


dans laquelle :

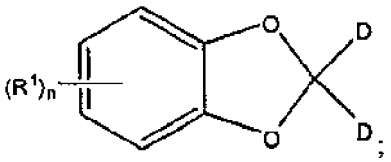
l'enrichissement isotopique du catéchol deutéré en deutérium est d'au moins 75 % ; et
le Cycle A du catéchol deutéré et du benzo[*d*]-[1,3]dioxole deutéré est substitué par un ou plusieurs groupes, à condition que le ou les groupes de substitution ne réagissent pas avec la base ou avec le dihalogénodeutérométhane.

2. Procédé selon la revendication 1 dans lequel l'enrichissement isotopique du catéchol deutéré en deutérium est d'au moins 85 % ; ou
dans lequel l'enrichissement isotopique du catéchol deutéré en deutérium est d'au moins 95 %.

3. Procédé selon la revendication 1 dans lequel le catéchol deutéré est représenté par la formule structurale suivante :



et le benzo[*d*][1,3]dioxole deutéré est représenté par la formule structurale suivante :



dans lesquelles :

n est 1, 2 ou 3 ;
chaque R^1 est indépendamment halogéno ; $-OR^a$; -OR' ; -CHO ; $-COOR^b$; -COOR' ; C(O)R' ; -CN ; $-OC(O)NH_2$; -OC(O)NHR' ; $-OC(O)N(R')_2$; $-CR^4=C(R^4)_2$; $-C\equiv CR^4$; ou un groupe aryle éventuellement substitué par un ou plusieurs groupes représentés par R^5 ;
chaque R^4 est indépendamment -H ou un groupe représenté par R' ;
chaque R^5 est indépendamment choisi parmi halogéno ; alkyle, $-OR^a$; alcoxy ; halogénoalcoxy ; -CHO ; $-COOR^b$; -COOR" ; C(O)R" ; $-NO_2$; halogénoalkyle ; -CN ; $-NHR^c$, $-NR^cR"$, $-N(R")_2$; -NHC(O)R" ; $-NHC(O)NH_2$; -NHC(O)NHR" ; $-NHC(O)N(R")_2$; $-OC(O)NH_2$; -OC(O)NHR" ; $-OC(O)N(R")_2$; -NHC(O)H ; -NHC(O)R" ; -NHC(O)OR" ; -S(O)R" ; $-S(O)_2R"$; $-SO_2NH_2$; $-SO_2NHR"$; $-SO_2N(R")_2$; $-NHSO_2NH_2$; $-NHSO_2NHR"$; $-NHSO_2N(R")_2$; et $-NHSO_2R"$;
R' est alkyle ou aryle, chacun éventuellement et indépendamment substitué par un ou plusieurs groupes choisis parmi halogéno ; $-OR^a$; alcoxy ; halogénoalcoxy ; -CHO ; $-COOR^b$, -COOR" ; C(O)R" ; $-NO_2$; alkyle ; halogénoalkyle ; -CN ; $-NHR^c$; $-NR^cR"$; $-N(R")_2$; -NHC(O)R" ; $-NHC(O)NH_2$; -NHC(O)NHR" ; $-NHC(O)N(R")_2$; $-OC(O)NH_2$; -OC(O)NHR" ; $-OC(O)N(R")_2$; -NHC(O)H ; -NHC(O)R" ; -NHC(O)OR" ; -S(O)R" ; $-S(O)_2R"$; $-SO_2NH_2$; $-SO_2NHR"$; $-SO_2N(R")_2$; $-NHSO_2NH_2$; $-NHSO_2NHR"$; $-NHSO_2N(R")_2$; et $-NHSO_2R"$;
R" est alkyle ;
R^a est un groupe protecteur du phénol ;
R^b est un groupe protecteur de l'acide carboxylique ; et
R^c est un groupe protecteur d'amine.

4. Procédé selon la revendication 3 dans lequel :

n est 1 ; et
R^1 est halogéno ; $-OR^a$; -OR' ; -CHO ; $-COOR^b$; -COOR' ; C(O)R' ; -CN ; $-CH=CHR^4$; $-C\equiv CH$; $-C\equiv CR^4$; ou un groupe phényle éventuellement substitué par un ou plusieurs groupes représentés par R^5 ; et
chaque R^5 est indépendamment choisi parmi halogéno ; alkyle, $-OR^a$; alcoxy ; halogénoalcoxy ; -CHO ; $-COOR^b$; -COOR" ; C(O)R" ; $-NO_2$; alkyle ; halogénoalkyle ; et -CN ;
R' est alkyle ; ou un phényle éventuellement substitué par un halogéno ; $-OR^a$; alcoxy ; halogénoalcoxy, -CHO ; $-COOR^b$, -COOR" ; C(O)R" ; $-NO_2$; halogénoalkyle ; et -CN.

5. Procédé selon la revendication 1 dans lequel le dihalogéno-dideutéro-méthane est CD_2Cl_2, CD_2Br_2, CD_2I_2 ou $BrCD_2Cl$.

6. Procédé selon la revendication 1 dans lequel la base est K_2CO_3, Cs_2CO_3, $NaOCH_3$, NaH, KF, CsF ou un tert-

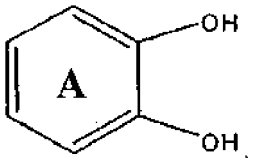
butoxyde de potassium.

7. Procédé selon la revendication 1 dans lequel la réaction est mise en oeuvre dans un solvant aprotique dipolaire, ou dans lequel la réaction est mise en oeuvre dans un co-solvant D_2O/*N*-méthylpyrrolidinone.

8. Procédé selon la revendication 7 dans lequel le solvant aprotique dipolaire est la *N*-méthylpyrrolidinone, le diméthylformamide, l'acétonitrile, l'hexaméthylphosphoramide ou la *N*,*N*-diméthylpropylène-urée.

9. Procédé selon la revendication 1 dans lequel : i) le dihalogéno-dideutéro-méthane est CD_2Cl_2, CD_2Br_2, CD_2I_2 ou $BrCD_2Cl$; ii) la base est K_2CO_3, Cs_2CO_3, $NaOCH_3$, NaH, KF, CsF ou un *tert*-butoxyde de potassium ; et iii) la réaction est mise en oeuvre dans un solvant choisi parmi la *N*-méthylpyrrolidinone, le diméthyl-formamide, l'acétonitrile, l'hexaméthylphosphoramide et la *N,N*-diméthylpropylène-urée.

10. Procédé selon la revendication 1 dans lequel le catéchol deutéré est préparé par réaction d'un catéchol avec une source de D^+, le catéchol étant représenté par la formule structurale suivante :

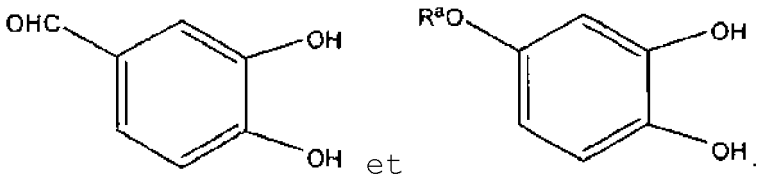


11. Procédé selon la revendication 10 dans lequel la source de D^+ est CH_3OD, D_2O ou DCl.

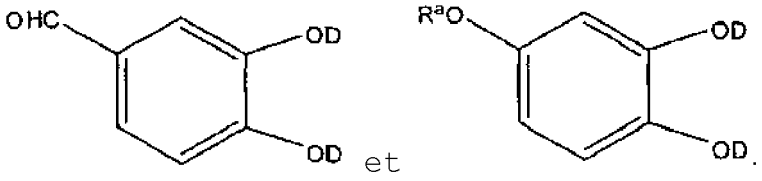
12. Procédé selon la revendication 10 dans lequel la réaction pour former le catéchol deutéré est mise en oeuvre dans un solvant qui est choisi parmi CH_3OD et D_2O, ou dans lequel la réaction pour former le catéchol deutéré est mise en oeuvre dans un co-solvant comprenant : i) du tétrahydrofurane, une *N*-méthylpyrrolidinone, du diméthylsulfoxyde, de l'acétonitrile ou du dioxane ; et ii) CH_3OD ou D_2O.

13. Procédé selon la revendication 10 dans lequel la réaction est mise en oeuvre en présence de NaH, NaOD ou DCl.

14. Procédé selon la revendication 10 dans lequel le catéchol est représenté par une formule structurale choisie parmi :



15. Procédé selon la revendication 1 dans lequel le catéchol deutéré est représenté par une formule structurale choisie parmi .



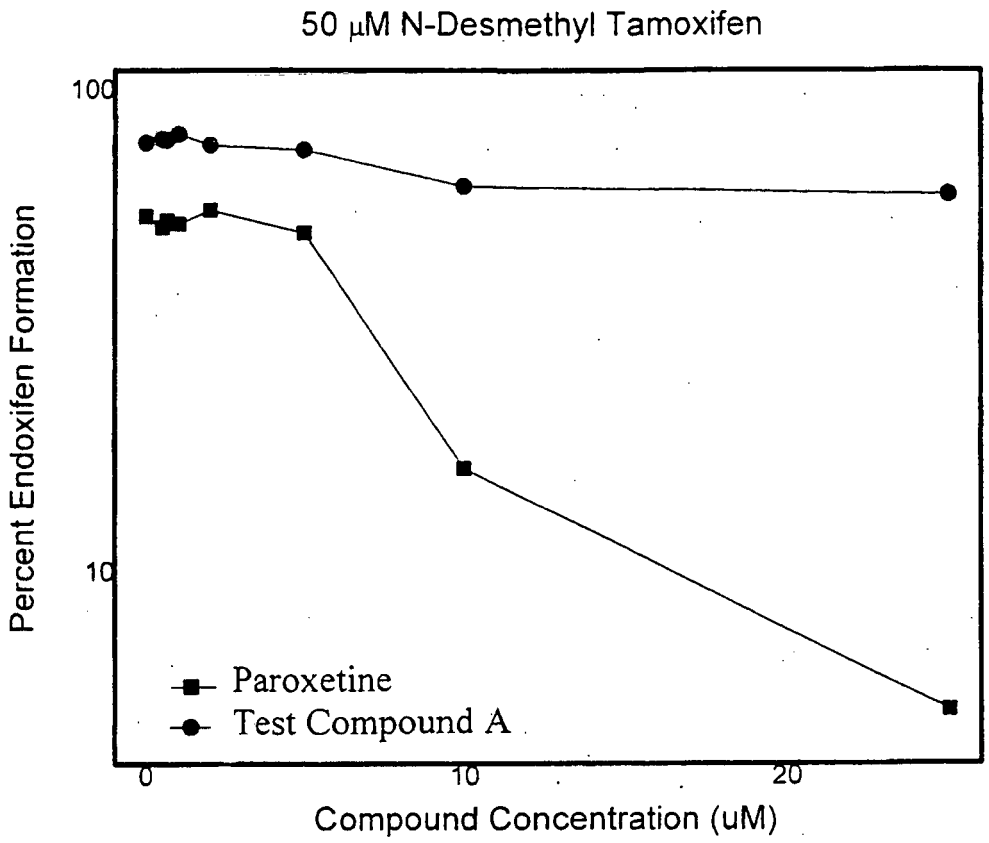

50 μM N-Desmethyl Tamoxifen
100
10
Percent Endoxifen Formation
Paroxetine
Test Compound A
0
10
20
Compound Concentration (uM)

FIG. 1

Test Compound A

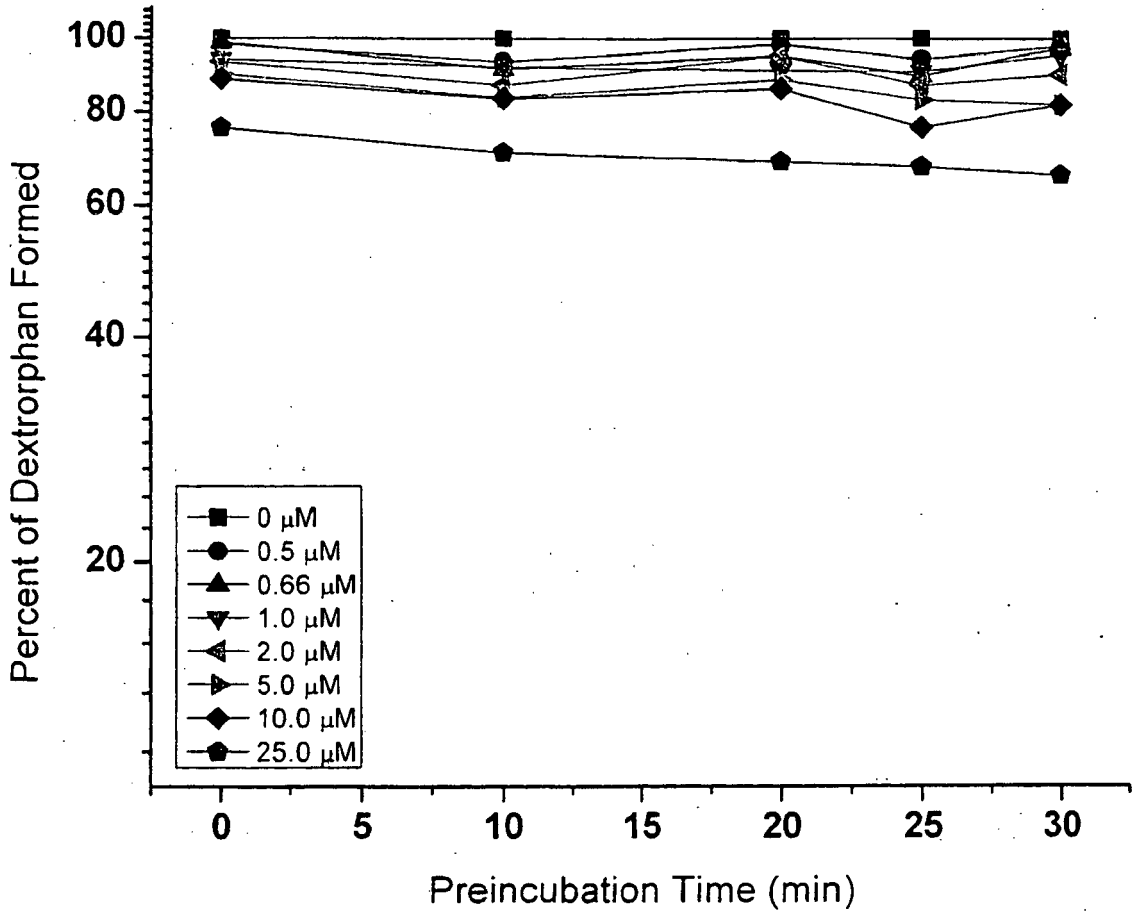


FIG. 2A

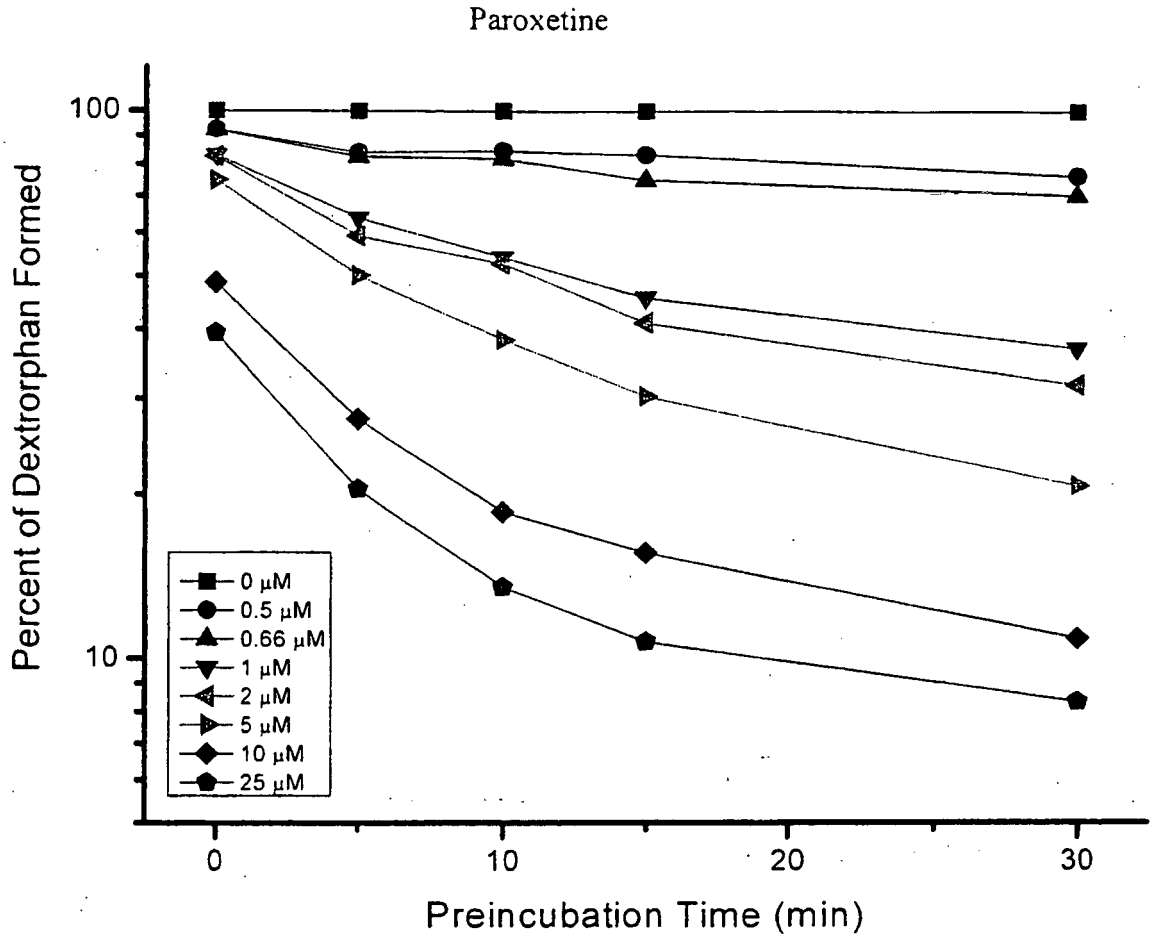

Paroxetine
Percent of Dextrorphan Formed
100
10
0
10
20
30
Preincubation Time (min)
0 µM
0.5 µM
0.66 µM
1 µM
2 µM
5 µM
10 µM
25 µM

FIG. 2B

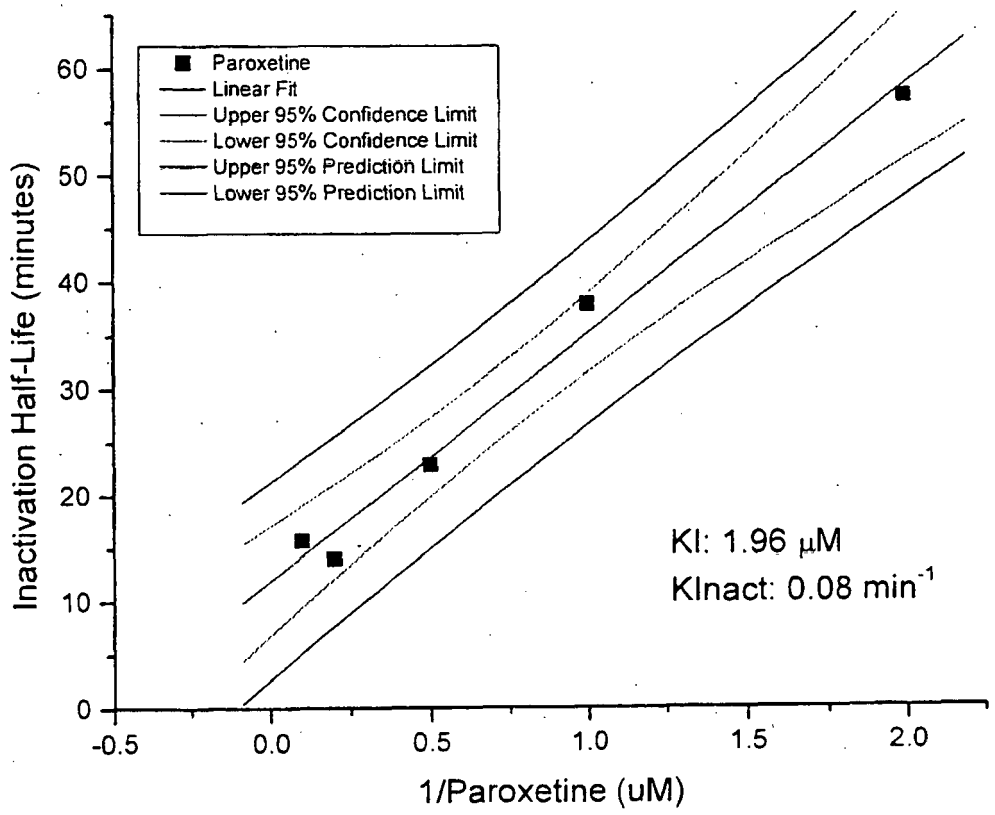

Paroxetine
Linear Fit
Upper 95% Confidence Limit
Lower 95% Confidence Limit
Upper 95% Prediction Limit
Lower 95% Prediction Limit
KI: 1.96 μM
KInact: 0.08 min-1
Inactivation Half-Life (minutes)
1/Paroxetine (uM)
0
10
20
30
40
50
60
-0.5
0.0
0.5
1.0
1.5
2.0

FIG. 3

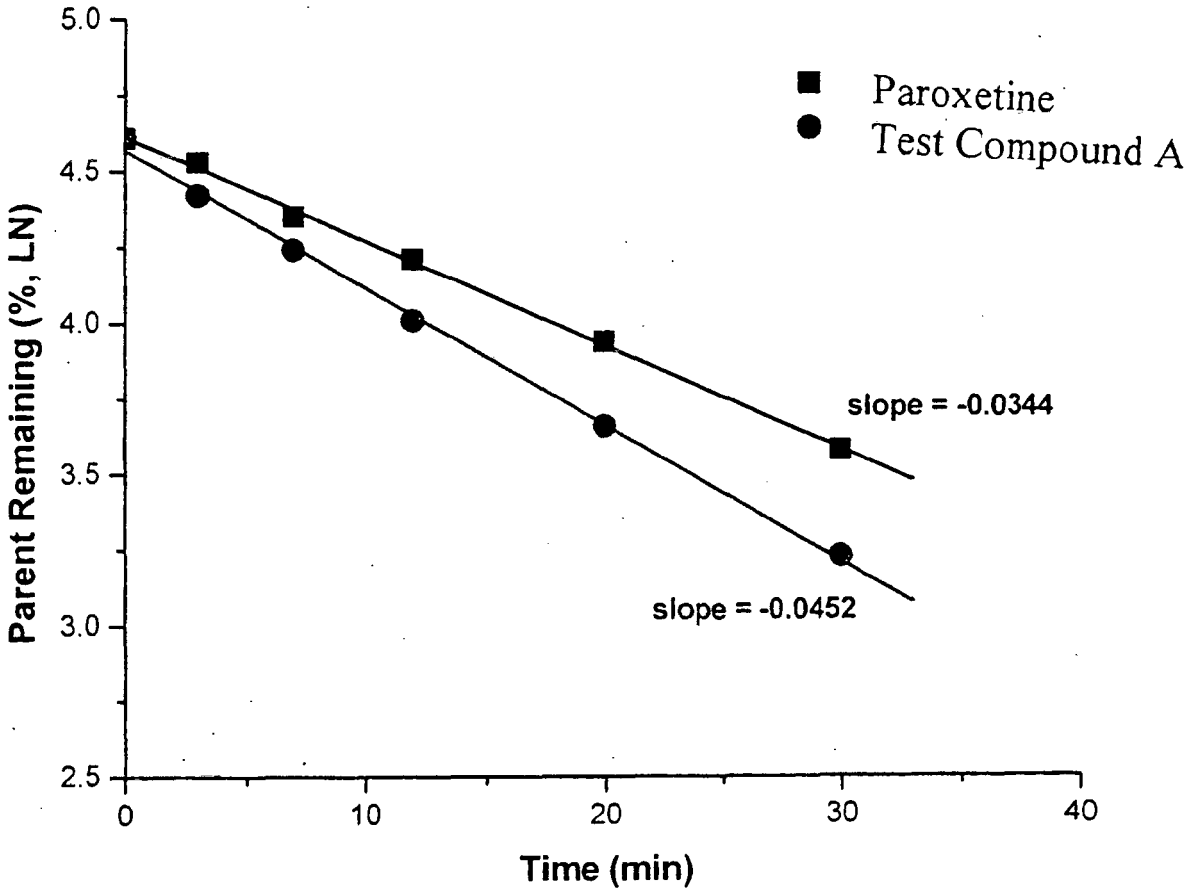

5.0
4.5
4.0
3.5
3.0
2.5
Parent Remaining (%, LN)
0
10
20
30
40
Time (min)
Paroxetine
Test Compound A
slope = -0.0344
slope = -0.0452

FIG. 4

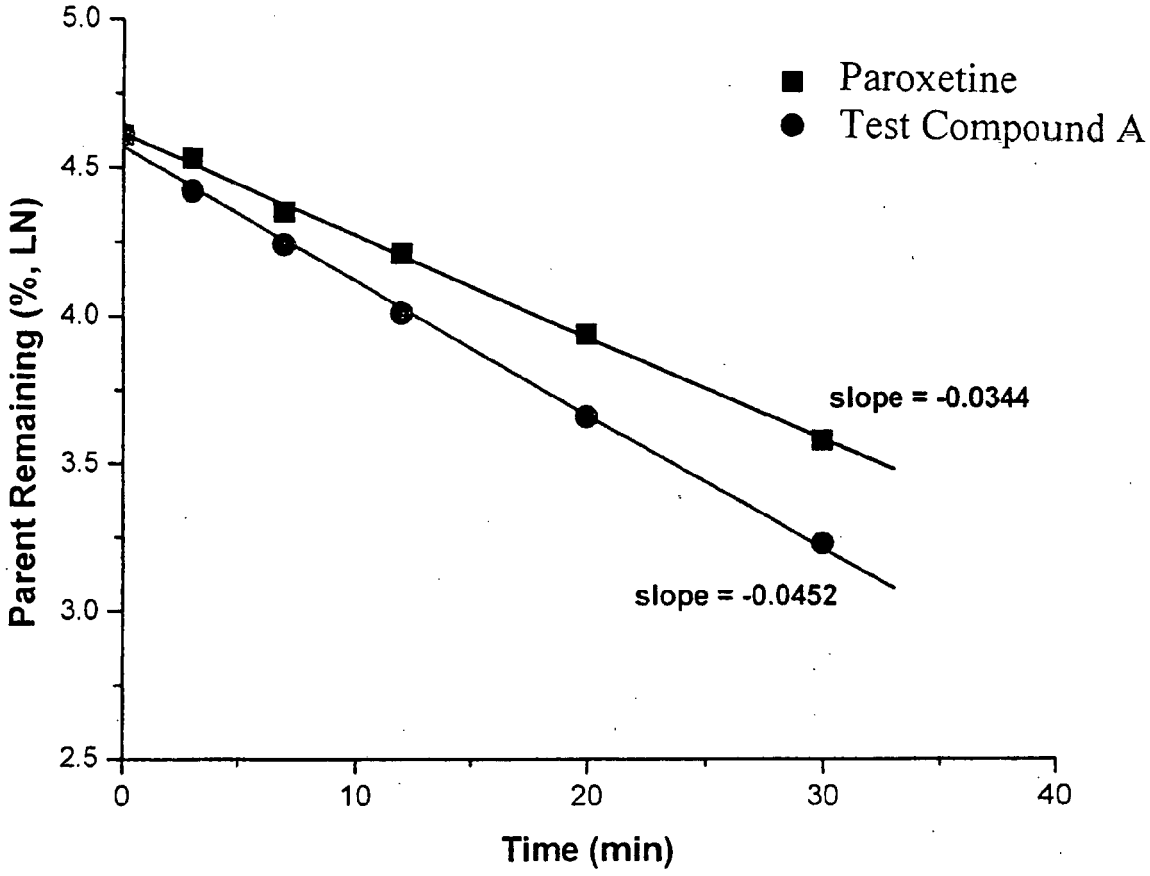

5.0
4.5
4.0
3.5
3.0
2.5
Parent Remaining (%, LN)
0
10
20
30
40
Time (min)
Paroxetine
Test Compound A
slope = -0.0344
slope = -0.0452

FIG. 5

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 2007016431 A **[0001] [0045]**
- US 20070112031 A **[0001] [0045]**
- US 20070191381 A **[0001] [0045]**
- WO 2007058998 A **[0004]**
- WO 2007016361 A **[0005]**

Non-patent literature cited in the description

- **IWASA et al.** *Phytochemistry,* 01 December 1997, vol. 46 (8), 1359-1363 **[0006]**
- **GREENE ; WUTS.** Protective Groups in Organic Synthesis. John Wiley & Sons, 2007 **[0052]**
- **BERTELSEN KM ; VENKATAKRISHNAN K ; VON MOLTKE LL ; OBACH S ; GREENBLATT, DJ.** Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. *Drug Met Disp,* 2003, vol. 31, 289-293 **[0111] [0117]**
- **OBACH RS ; BAXTER JG ; LISTON TE ; SILBER BM ; JONES BC ; MACINTYRE F et al.** The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. *JPET,* 1997, vol. 283, 46-58 **[0115]**
- **HEYDOM WE.** Paroxetine: a review of its pharmacology, pharmacokinetics and utility in the treatment of a variety of psychiatric disorders. *Exp Opin Invest Drugs,* 1999, vol. 8 (4), 417-441 **[0117]**