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(54) **DEUTERATED BENZO[*D*][1,3]-DIOXOL DERIVATIVES**

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(63) Continuation-in-part of application No. 11/498,334, filed on Jul. 31, 2006.

(60) Provisional application No. 60/704,073, filed on Jul. 29, 2005.

(51) **Int. Cl.**
C07D 211/22 (2006.01)
A01N 43/62 (2006.01)

(52) **U.S. Cl.** **546/197**; 514/321

(58) **Field of Classification Search** 546/197; 514/321

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to an isotopologue of Compound 1 substituted with deuterium at the methylene carbon of the benzodioxol ring. The isotopologues of this invention selective serotonin reuptake inhibitors (SSRIs) and possess unique biopharmaceutical and metabolic properties compared to Compound 1. They may also be used to accurately determine the concentration of Compound 1 in biological fluids and to determine metabolic patterns of Compound 1 and its isotopologues. The invention further provides compositions comprising these deuterated isotopologues and methods of treating diseases and conditions that are responsive to increased neuronal serotonin transmission, alone and in combination with additional agents.

4 Claims, No Drawings

DEUTERATED BENZO[*D*][1,3]-DIOXOL DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 11/498,334, filed Jul. 31, 2006, which claims benefit of U.S. provisional application 60/704,073, filed Jul. 29, 2005, the contents of each is incorporated by reference herein.

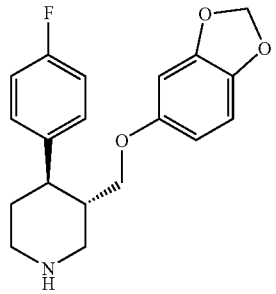
TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel isotopologues of Compound 1, its acceptable acid with additional deuterium and ^{13}C atoms in place of the normally abundant hydrogen and ^{12}C, respectively addition salts, solvates, hydrates and polymorphs thereof, substituted with deuterium on the methylene carbon atom situated between the oxygens of the benzodioxol ring, and optionally substituted. The compounds of this invention are selective serotonin reuptake inhibitors (SSRIs) and are poorer substrates for metabolism by cytochrome 2D6, and possess unique pharmacokinetic and biopharmaceutical properties compared to the corresponding non-isotopically substituted compounds. The invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions beneficially treated by SSRIs, particularly those relating to major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, post-traumatic stress disorder, and premenstrual dysphoric disorder. The invention further provides methods for the use of a compound of this invention to determine concentrations of Compound 1, particularly in biological fluids, and to determine metabolism patterns of Compound 1.

BACKGROUND OF THE INVENTION

Compound 1, chemically described variously as (−)-trans-4R-(4'-fluorophenyl)-3S-[(3',4'-methylenedioxyphenoxy) methyl]piperidine; (3S,4R)-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine; trans-(−)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl) piperidine, and its pharmaceutically acceptable

Compound 1



addition salts, hydrates, and polymorphs thereof, are known as a useful selective serotonin reuptake inhibitor (SSRI). This compound and pharmaceutical compositions comprising it

major depression, panic disorder, social phobia, premenstrual syndrome, cardiac disorders, non-cardiac chest pain, smoking (both to cause cessation and prevent relapses), reducing platelet activation states, alcoholism and alcohol dependence, psychiatric syndromes (including anger, rejection sensitivity, and lack of mental or physical energy), late luteal phase dysphoric disorder, premature ejaculation, senile dementia, obesity, Parkinson's Disease, and canine affective aggression. See US Food and Drug Administration product label for New Drug Application (NDA) Nos. 020031, 020710, and 020936; Christensen J A and Squires R F, U.S. Pat. No. 4,007,196, to Ferrosan; Lassen J B, U.S. Pat. No. 4,745,122 to Ferrosan; Johnson A M U.S. Pat. No. 5,371,092 to Beecham Group; Crenshaw R T and Wiesner M G, U.S. Pat. No. 5,276,042; Dodman N H, U.S. Pat. Nos. 5,788,986 and 5,554,383 to Trustees of Tufts College; Norden M J U.S. Pat. No. 5,789,449; Gleason M, U.S. Pat. No. 6,121,291 to SmithKline Beecham; Cook L, U.S. Pat. No. 6,071,918 to DuPont Pharmaceuticals; Serebruany V L, U.S. Pat. No. 6,245,782 to Heartdrug Research; Steiner M X, U.S. Pat. No. 6,300,343 to SmithKline Beecham; Krishnan K R et. al., U.S. Pat. No. 6,316,469 to Duke University; Jenner P N, U.S. Pat. No. 6,372,763 to SmithKline Beecham.

Additionally disclosed uses for Compound 1 include methods of inhibiting cancer cell growth, stimulating bone formation by osteoblast stimulation, treatment of dermatological diseases or disorders such as hyperproliferative or inflammatory skin diseases, and treatment of premature female orgasm: see US Patent Applications 20040127573 (Telerman A et. al.); 20040127573 (Stashenko P and Battaglino R); 20050013853 and 20040029860 (Gil-Ad I and Weizman A); and 20050054688 (May K E and Quinn P).

Definitions and descriptions of these conditions are known to the skilled practitioner and are further delineated, for instance, in the above patents and patent applications and references contained therein. See also: Harrison's Principles of Internal Medicine 16th Edition, Kasper D L et. al. Eds., 2004, McGraw-Hill Professional; and Robbins & Cotran Pathologic Basis of Disease, Kumar V et. al. Eds., 2004, W.B. Saunders.

The combination of Compound 1 with additional agents extends or enhances its utility in the treatment or prevention of depression, hypertension, generalized anxiety disorder, phobias, posttraumatic stress syndrome, avoidant personality disorder, sexual dysfunction, eating disorders (including bulimia, anorexia nervosa, and binge eating), obesity, chemical dependencies, cluster headache, migraine, pain (including neuropathic pain, diabetic nephropathy, post-operative pain, psychogenic pain disorders, and chronic pain syndrome), Alzheimer's disease, obsessive-compulsive disorder, panic disorder with or without agoraphobia, memory disorders, Parkinson's diseases, endocrine disorders, vasospasm, cerebellar ataxia, gastrointestinal tract disorders, negative symptoms of schizophrenia, premenstrual syndrome, Fibromyalgia Syndrome, urinary incontinence (including stress incontinence), Tourette's syndrome, trichotillomania, kleptomania, male impotence, cancer, chronic paroxysmal hemicrania and headache in a mammal, sleep-related breathing disorders, cognitive deficits due to aging, stroke, head trauma, neurodegenerative diseases, schizophrenia, anxiety, aggression, stress, disorders of thermoregulation, respiratory disease, bipolar disorder, psychosis, sleep disorders, mania (including acute mania), bladder disorder, genitourinary disorder, cough, emesis, nausea, psychotic disorders such as paranoia and manic-depressive illness, tic disorder, diabetic

syndrome, premature ejaculation, dysphoria, post partum depression, social phobia, disruptive behavior disorders, impulse control disorders, borderline personality disorder, attention deficit disorders without hyperactivity, Shy-Drager Syndrome, cerebral ischemia, spinal cord trauma, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, convulsions, perinatal hypoxia, hypoxia, cardiac arrest, hypoglycemic neuronal damage, ocular damage and retinopathy, brain edema, tardive dyskinesia, cerebral deficits subsequent to cardiac bypass surgery and grafting, affective disorders, mood disorders, agoraphobia without history of panic disorder, and acute stress disorders. These additional agents are also useful for reducing the side effects of Compound 1, enhancing or potentiating its activity, or increasing its duration of pharmacological action. U.S. Pat. Nos. 5,776,969 (James S P) to Eli Lilly; 5,877,171 (McLeod M N); 5,977,099 (Nickolson V J) to Akzo Nobel; 5,962,514 and 6,169,098 (Evenden J and Thorberg S-O) to Astra; 5,958,429 (Wong D T) to Eli Lilly; 5,945,416 (Shannon H E and Womer D E) to Eli Lilly; 6,066,643 (Perry K W) to Eli Lilly; 5,817,665 and 6,034,091 (Dante L G) to Nagle J S; 5,990,159 (Meulemans A L G et. al.) to Janssen Pharmaceutica; 6,001,848 (Noble E P) to The Regents of the University of California; 6,011,054 (Oxenkrug G F and Requintina P J) to St. Elizabeth's Medical Center of Boston; 6,080,736 (Landry D W and Klein D F) to Janus Pharmaceuticals; 6,162,805 (Hefti F F) to Merck Sharp & Dohme; 6,136,861 (Chenard B L) to Pfizer; 6,147,072 (Bymaster F P et. al.) to Eli Lilly; 6,218,395 (Swartz C M); 6,169,105 (Wong D T and Oguiza J I) to Eli Lilly; 6,191,133 (Coppen A J) to Scarista; 6,239,126 and 6,242,448 (Kelly M G et. al.) to American Home Products; 6,372,919 (Lippa A S and Epstein J W) to DOV; 6,369,051 (Jenkins S N) to American Home Products; 6,358,944 (Lederman S et. al.) to Vela Pharmaceuticals; 6,121,259; 6,174,882; 6,348,455; 6,352,984; and 6,468,997 (Yelle W E) to Sepracor; 6,403,597 (Wilson L F et. al.) to Vivus; 6,395,788 and 6,541,523 (Iglehart I W III) to Vela Pharmaceuticals; 6,127,385 and 6,395,752 (Midha K K et. al.) to Pharmaquest Limited; 6,380,200 (Mylari B L) to Pfizer; 6,387,956 (Shapira N A et. al.) to University of Cincinnati; 6,444,665 (Helton D R et. al.) to Eli Lilly; 6,541,478 (O'Malley S et. al.) to Yale University; 6,541,043 (Lang P C) to DexGen Pharmaceuticals; 6,562,813 (Howard H R) to Pfizer; 6,579,899 (Wurtman J J and Wurtman R J) to Massachusetts Institute of Technology; 6,627,653 (Plata-Salaman C R et. al.) to Ortho-McNeil; 6,649,614 (Carlson E J and Rupniak N M) to Merck Sharp & Dohme; 6,667,329 (Maj J) to Boehringer Ingelheim; 6,727,242 (Radulovacki M and Carley D W) to The Board of Trustees of the University of Illinois; 6,656,951; 6,780,860; 6,815,448; 6,821,981; and 6,861,427 (Stack; Gary P et. al.) to Wyeth; 6,878,732 (Wrobleski M L) to Schering Corporation; and 6,894,053 (Childers W E et. al.) to Wyeth.

Further disclosed are additional combinations of Compound 1 with other agents extending or enhancing its utility in the treatment or prevention of autism, dyskinesia, disthymic disorder; obesity due to genetic or environmental causes, polycystic ovary disease, craniopharyngeoma, Prader-Willi Syndrome, Frohlich's Syndrome, Type II diabetes, growth hormone deficiency, Turner's Syndrome; pro-inflammatory cytokine secretion or production, jet lag, insomnia, hypersomnia, nocturnal enuresis, restless-legs syndrome, vaso-occlusive events, hyperglycemia, hyperinsulinaemia, hyperlipidaemia, hypertriglyceridemia, diabetes, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting glucose, angina pectoris, vascular restenosis, endothelial dysfunction, impaired vascular compliance, or congestive heart failure; or to increase the onset of action of Compound 1. US Patent Applications 20020032197, 20020002137, 20020086865, 20020077323, 20020103249, 20020094960, 20030109544, 20030092770, 20030144270, 20030158173, 20030139395, 20030055070, 20030139429, 20040044005, 20010014678, 20040044005, 20030235631, 20030027817, 20030229001, 20030212060, 20040132797, 20040204469, 20040204401, 20040171664, 20040229940, 20040229941, 20040229942, 20040229911, 20040224943, 20040229866, 20040224942, 20040220153, 20040229849, 20050069596, 20050059654, 20050014848, 20050026915, 20050026946, 20050143350, 20020035105, 20050143314, 20050137208, 20040010035, 20040013741, 20050136127, 20050119248, 20050119160, 20050085477, 20050085475, 20010003749, 20050009815, 20040248956, 20050014786, 20050009870, 20050054659, 20050143381, 20050080087, 20050070577, and 20050080084.

Compound 1 has been characterized by in vitro studies of binding to rat cortical membranes, wherein radiolabeled Compound 1 was found to bind to a single, high affinity, saturable site. See e.g. Habert E et. al., Eur. J. Pharmacol. 1985 118: 107.

Compound 1 has also been characterized in a number of animal model systems. For instance, in models of depression, obesity, and anxiety, treatment with Compound 1 accurately produced results that are correlated with human clinical effects. See, e.g. Akegawa Y et. al. Methods Find Exp Clin Pharmacol 1999 21: 599; Lassen J B, U.S. Pat. No. 4,745,122 to Ferrosan; and Hascoet M et. al., Pharmacol. Biochem. Behav. 2000 65: 339.

In human clinical studies, Compound 1 demonstrated good tolerability and statistical efficacy in patients suffering from major depression, minor depression and dysthymia, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and post-traumatic stress disorder. Compound 1 is highly effective, for instance demonstrating superior antidepressant effects to other compounds with the same mechanism of action in a number of direct comparison studies. See, e.g. US Food and Drug Administration product label for New Drug Application (NDA) Nos. 020031, 020710, and 020936; Wagstaff A J et. al., Drugs 2002 62: 655; Katona C and Livingston G, J. Affect. Disord. 2002 69: 47.

Following oral administration to humans, Compound 1 is well absorbed, after which it undergoes extensive oxidative and phase II metabolism. Its major metabolic pathway proceeds by oxidative cleavage of the benzodioxol ring to forming a catechol metabolite. Subsequent phase II metabolism involves mainly methylation, glucuronidation and sulfation. See Scheme I. In vitro measurements indicate that these metabolites possess <2% of the potency of Compound 1 and therefore do not contribute pharmacodynamically to its action. During a 10-day post-dosing period following a 30 mg oral solution dose of radiolabeled Compound 1 in healthy volunteers, approximately 64% of Compound 1 was found to be excreted in the urine, comprising 2% as the parent compound and 62% as metabolites. About 36% was excreted in the feces, mostly as metabolites and less than 1% as the parent

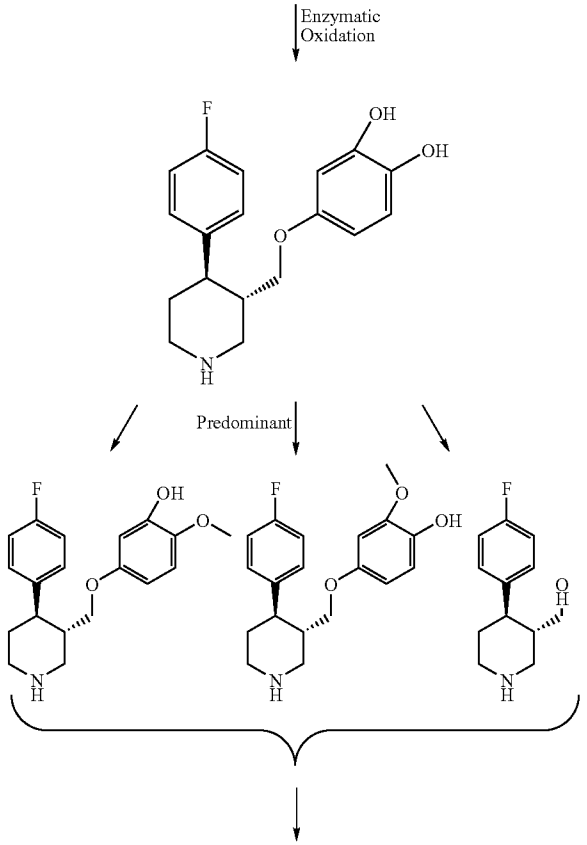
The benzodioxol ring scission is carried out in significant part by cytochrome 2D6 (CYP2D6), which acts as a high affinity, but relatively low capacity, oxidant. Compound 1 also acts as a highly potent, mechanism based inactivator of CYP2D6, possibly through formation of a carbene intermediate during the metabolic oxidation step or by formation of an ortho-quinone and subsequent reaction with active-site nucleophiles. Bertelsen K M et. al., Drug Metab. Dispos. 2003 31: 289; Murray M, Curr. Drug Metab. 2000 1: 67; Ortiz de Montellano and Correi M A in "*Cytochrome P450 Structure, Mechanism and Biochemistry*" (Ortiz de Montellano P R ed) pp 305-366, 1995 Plenum Press, New York; Wu et. al., Biochem. Pharmacol. 1997 53: 1605; Bolton J L et. al., 1994 Chem. Res. Toxicol. 7: 443.

Clinically, this mechanism-based inactivation manifests in several ways. For instance, Compound 1 displays significantly non-linearity pharmacokinetics, with steady state doses several times the levels expected from a single dose as a result of auto-inhibition of its metabolism. Compound 1 also causes a dose-dependent, highly significant reduction in CYP2D6 activity. CYP2D6 comprises the main metabolic pathway for a number of other clinically important drugs, including for instance anti-cancer agents, other anti-depressants, and antipsychotics; as well as drugs of abuse such as the widely used drug "Ecstasy". Co-dosing Compound 1 with those agents causes clinically significant increases in their blood levels, leading to the potential for increased toxicity. Jeppesen U et. al., Eur. J. Clin. Pharmacol. 1996 51: 73; US FDA approved label for NDA # 020935, approved Jan. 12, 2005; Laugesen S et. al., Clin Pharmacol Ther. 2005 77: 312; Jin Y et. al., J. Natl. Cancer Inst. 2005 97: 30; Joos A A B et al., Pharmacopsychiat. 1997 30, 266; Segura M et. al., Clin Pharmacokinet. 2005 44: 649.

Compound 1 is subject to substantial inter-patient variation. Patients possessing relatively low and relatively high levels of CYP2D6 activity have been shown to metabolize Compound 1 at substantially different rates, leading to an approximately 3-fold longer half-life in a European cohort of poor metabolizers (PMs) with low CYP2D6-mediated oxidative efficiency versus extensive metabolizers (EMs) with higher CYP2D6 activity; Sindrup S H et. al., Clin. Pharmacol. 1992 51: 278. Even when measured at steady state, at which time variability is substantially less than on initial dosing, high variability of Compound 1 was observed in a test population (about 30-70% coefficients of variability across maximal and minimal plasma concentrations (Cmax and Cmin) and overall exposure measured as area under the plasma concentration-time curve (AUC_{∞})). Kaye C M et. al., Acta Psychiatr. Scand. 80(Suppl. 350): 60.

CYP2D6 is the source of substantial variability in the pharmacokinetics of a number of drugs due to well-known polymorphisms resulting in low CYP2D6 activity in a substantial percentage of the population, including about 2% of Asians and 7-8% of Caucasians (Wolf C R and Smith G, IARC Sci. Publ. 1999 148: 209 (chapter 18); Mura C et. al., Br. J. Clin. Pharmacol. 1993 35: 161; Shimizu T et. al., Drug Metab. Pharmacokinet. 2003 18: 48). Notably, different CYP2D6 polymorphisms exist across racial types, and it is possible that the even greater variability may exist in other patient popu-

Scheme I

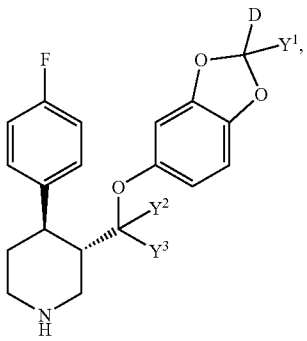


It is therefore desirable to create a compound displaying the beneficial activities of Compound 1, but with a decreased metabolic liability for CYP2D6, to further extend its pharmacological effective life in extensive metabolizers, decrease population pharmacokinetic variability and/or decrease its potential for dangerous drug-drug interactions.

SUMMARY OF THE INVENTION

The present invention solves the problems set forth above by providing an isolated compound of Formula I:

Formula I



or a salt thereof; or a prodrug, or a salt of a prodrug thereof; or a hydrate, solvate, or polymorph thereof; wherein:

D is deuterium;

each Y is independently selected from deuterium or hydrogen;

each hydrogen is independently optionally replaced with deuterium; and

each carbon is independently optionally replaced with ^{13}C.

A compound of Formula I reduces the efficiency of benzodioxol ring cleavage by CY2D6 and beneficially decreases the rate of mechanism-based CYP2D6 inhibition relative to Compound 1.

The decreased CYP2D6 inhibition is important in reducing the pharmacokinetic interactions between Compound 1 and other drugs metabolized by that enzyme. This provides increased safety as compared to Compound 1.

In particular, this would produce benefits in the treatment of co-morbidities and the use of combinations of medications, which is common in patients suffering from depression, anxiety and other psychiatric disorders. Moreover, it would be useful in patients taking Compound 1, while being treated by different healthcare providers without disclosing all of their medications to each of them. It would also be beneficial in patients who are using drugs of abuse while taking Compound 1 without the knowledge of their physician.

The decreased substrate efficiency for CYP2D6 at the methylenedioxy portion of the benzodioxol ring demonstrated by the compounds of this invention will provide the further benefit of reducing inter-patient pharmacokinetic variability observed for Compound 1.

The compounds of the present invention comprising additional deuterium for hydrogen replacement at the methylenedioxy carbon demonstrate the added benefit of reduced metabolism by other cytochrome P450 enzymes. This is important for poor metabolizers of Compound 1, wherein the main metabolic pattern of Compound 1 proceeds largely by scission of the benzodioxol ring, likely due to oxidative attack by another cytochrome enzyme. Also, a relatively minor amount of ring scission (complete cleavage of the benzodioxol ring, forming 4-(4-fluorophenyl)-3-hydroxymethylpiperidine) observed in normal metabolizers, which could result from oxidation of the methylene carbon attached to the piperidine ring, may become more predominant if the benzodioxol ring is metabolically stabilized. Therefore, compounds of this invention that are deuterated at that carbon will also be beneficial to the clearance rate of the compound.

The compounds of this invention, and compositions comprising them, are useful for treating or lessening the severity of disorders characterized by reduced serotonin-dependent neurological activity. Preferred applications for compounds of formula I include methods of use in treating depression, anxiety, stress, phobias, panic, dysphoria, and other psychiatric disorders, and pain.

The compounds and compositions of this invention are also useful as analytical reagents for determining the concentration of the Compound 1 in solution. "Compound 1" as used herein refers to a compound wherein all hydrogen and all carbon atoms are present at their natural isotopic abundance percentages. It is recognized that some variation of natural isotopic abundance occurs depending upon the origin of chemical materials. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial with respect to the degree of stable isotopic substitution of compounds of this invention. See for instance Wada E and Hanba Y, Seikagaku 1994 66: 15;

Incorporation of deuterium in place of hydrogen is known in certain instances to have significant effects on the physiological and pharmacological activities of the substituted compound. For instance, N-nitrosamines substituted with deuterium can display increased, decreased, or unchanged carcinogenicity depending on where in the compound hydrogen is replaced with deuterium and on the identity of the compound to which substitutions are made (Lijinsky W et. al., Food Cosmet. Toxicol. 1982 20: 393; Lijinsky W et. al., JCNI 1982 69: 1127). Similarly, both increases and decreases in bacterial mutagenicity of deuterium-substituted aza-amino acids are known, depending on the identity of the amino acid derivative and position of substitution (Mangold J B et. al., Mutation Res. 1994 308: 33). Reduced hepatotoxicity of certain deuterium-substituted compounds is known (Gordon W P et. al., Drug Metab. Dispos. 1987 15: 589; Thompson D C et. al., Chem. Biol. Interact. 1996 101: 1). Deuterium substitution can affect compound's odors (Turin L, Chem. Senses 1996 21: 773) and plasma protein binding (Echmann M L et. al., J. Pharm. Sci. 1962 51: 66; Cherrah Y. et. al., Biomed. Environm. Mass Spectrom. 1987 14: 653; Cherrah Y. et. al., Biochem. Pharmacol. 1988 37: 1311). Changes in the biodistribution and clearance of certain deuterium-substituted compounds suggests changes in their recognition by active transport mechanisms (Zello G A et. al., Metabolism 1994 43: 487; Gately S J et. al., J. Nucl. Med. 1986 27: 388; Wade D, Chem. Biol. Interact. 1999 117: 191).

Replacement of hydrogen with deuterium at sites subject to oxidative metabolism by, for instance, heme proteins such as cytochrome P450 and peroxidase enzymes, is known in certain, but not all, cases to produce a significant reduction in the rate of metabolism due to the primary isotope effect of breaking the C—^{1}H versus C—^{2}H bond (see, e.g., Guengerich F P et. al., J. Biol. Chem. 2002 277: 33711; Kraus, J A and Guengerich, F P, J. Biol. Chem. 2005 280: 19496; Mitchell K H et. al., Proc. Natl. Acad. Sci. USA 2003 109: 3784; Nelson S D and Trager W F, Drug Metab. Dispos. 2003 31: 1481; Hall L R and Harzlik R P, J. Biol. Chem. 1990 265: 12349; Okazaki 0 and Guengerich F P, J. Biol. Chem. 268, 1546; Iwarnura S et. al., J. Pharmacobio-Dyn. 1987 10: 229). If the C—H bond breaking step is rate-limiting, a substantial isotope effect can be observed. If other steps determine the overall rate of reaction, the isotope effect may be insubstantial. In cases where a rate-limiting step of a reaction involves rehybridization of the attached carbon from sp2 to sp3, deuterium substitution often creates a negative isotope effect, speeding up the reaction rate. Introducing deuterium into a compound at a site subject to enzymatic oxidation does not predictably produce a significant pharmacokinetic change. See for instance Mamada K et. al., Drug Metab. Dispos. 1986 14: 509; Streeter A J et. al., Arch. Toxicol. 1990 64: 109; Morgan D S et. al., Int. Arch. Occup. Environ. Health 1993 65(1 Suppl.): S139.

Although incorporation of deuterium into specific organic compounds can change their pharmacological properties, general exposure to and incorporation of deuterium is safe within levels potentially achieved by use of compounds of this invention as medicaments. For instance, the weight percentage of hydrogen in a mammal (approximately 9-10%) and natural abundance of deuterium (approximately 0.015%) indicates, for instance that an average adult US male normally contains approximately 1.2 grams of deuterium (see e.g. Harper V W et. al. "*Review of Physiological Chemistry*" 16th Edition, 1977 Lange Medical Publications; Ogden C L et. al.

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