(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 September 2012 (27.09.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/129381 A1

(51) International Patent Classification:
C07D 487/14 (2006.01) *A61P 25/16* (2006.01)
A61K 31/505 (2006.01) *C07B 59/00* (2006.01)

(21) International Application Number:
PCT/US2012/030081

(22) International Filing Date:
22 March 2012 (22.03.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/466,310 22 March 2011 (22.03.2011) US

(71) Applicant *(for all designated States except US)*: **CONCERT PHARMACEUTICALS INC.** [US/US]; 99 Hayden Avenue, Suite 100, Lexington, Massachusetts 02421 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **PANDYA, Bhaumik A.** [US/US]; 28 Silk Street, Arlington, Massachusetts 02474 (US).

(74) Agent: **LAVOIE, Teresa A.**; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2012/129381 A1

(54) Title: DEUTERATED PRELADENANT

(57) Abstract: This invention relates to novel 5 -amino-pyrazolo- [4,3-e] - 1, 2, 4 - triazolo [1, 5 - c] pyrimidines and pharmaceutic - ally acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating Parkinson's diseases, other Parkinsonian disorders, anxiety, and other conditions that are benefi - cially treated by administering an adenosine A2A antagonist.

DEUTERATED PRELADENANT

Cross-Reference to Related Applications

[1] This application claims priority to U.S. Application Serial No. 61/466,310, filed on March 22, 2011, which is incorporated by reference in its entirety.

Background of the Invention

[2] Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use or limit their use in certain indications. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems such as poor patient compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment. A rapidly metabolized drug may also expose patients to undesirable toxic or reactive metabolites.

[3] Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving the drug may experience toxicities, or the safe dosing of such drugs may be limited such that patients receive a suboptimal amount of the active agent. In certain cases, modifying dosing intervals or formulation approaches can help to reduce clinical adverse effects, but often the formation of such undesirable metabolites is intrinsic to the metabolism of the compound.

[4] In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically responsible for their metabolism (see Kempf, D.J. et al., Antimicrobial agents and

chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6 metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L et al., Clinical Pharmacology and Therapeutics, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at www.accessdata.fda.gov).

[5] In general, combining drugs with cytochrome P450 inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme's activity can affect the metabolism and clearance of other drugs metabolized by that same enzyme. CYP inhibition can cause other drugs to accumulate in the body to toxic levels.

[6] A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

[7] Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, MI et al, J Pharm Sci, 1975, 64:367-91; Foster, AB, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, DJ et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, MB et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 ("Fisher")). The results have been variable and unpredictable. For some compounds deuteration caused decreased metabolic clearance *in vivo*. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also

led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

[8] The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. *See,* for example, Fukuto et al. (J. Med. Chem. 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

[9] This invention relates to novel 5-amino-pyrazolo-[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines and pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating Parkinson's disease, other Parkinsonian disorders, anxiety, and other conditions that are beneficially treated by administering an adenosine A2A antagonist.

[10] Preladenant also known as 2-(2-Furyl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]piperazin-1-yl]ethyl]-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine is a potent, selective and orally active adenosine A2A agonist.

[11] Preladenant is currently in Phase III clinical trials for the prevention and treatment of Parkinson's disease.

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

Definitions

[13] The term "treat" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

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

[15] It will be recognized that some variation of natural isotopic abundance occurs in a

synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of Preladenant will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada, E et al., Seikagaku, 1994, 66:15; Gannes, LZ et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

[16] In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 45% incorporation of deuterium).

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

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

[19] The term "isotopologue" refers to a species in which the chemical structure differs from a specific compound of this invention only in the isotopic composition thereof.

[20] The term "compound," when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure

containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues *in toto* will be less than 55% of the compound. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 50%, less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

[21] The invention also provides salts of the compounds of the invention.

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

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

[24] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic

acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

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

[26] Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

[27] The term "mammal" as used herein includes a human or a non-human animal, such as mouse, rat, guinea pig, dog, cat, horse, cow, pig, monkey, chimpanzee, baboon,

or rhesus. In one embodiment, the mammal is a non-human animal. In another embodiment, the mammal is a human.

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

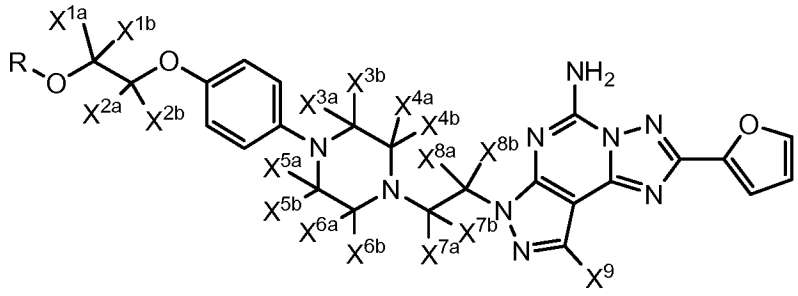
[29] "D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert" and "t-" each refer to tertiary. "US" refers to the United States of America.

[30] "Substituted with deuterium" refers to the replacement of one or more hydrogen atoms with a corresponding number of deuterium atoms.

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

Therapeutic Compounds

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



(I), wherein:

each X is independently selected from hydrogen and deuterium;

R is selected from CH_3 and CD_3; and

when R is CH_3, at least one X is deuterium.

[33] In one embodiment, X^{1a} and X^{1b} are the same; X^{2a} and X^{2b} are the same; X^{3a} and X^{3b} are the same; X^{4a} and X^{4b} are the same; X^{5a} and X^{5b} are the same; X^{6a} and X^{6b} are the

same; X^{7a} and X^{7b} are the same; and X^{8a} and X^{8b} are the same. In one aspect of this embodiment, X^{3a}, X^{3b}, X^{5a} and X^{5b} are the same; and X^{4a}, X^{4b}, X^{6a} and X^{6b} are the same. In an even more specific aspect X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b} X^{6a} and X^{6b} are the same. In one aspect of this embodiment, X^{1a} and X^{1b} are each deuterium. In one aspect of this embodiment, X^{2a} and X^{2b} are each deuterium. In one aspect of this embodiment, X^{1a}, X^{1b}, X^{2a} and X^{2b} are each deuterium. In an example of this aspect, X^{7a}, X^{7b}, X^{8a} and X^{8b} are each hydrogen. In one aspect of this embodiment, X^{7a} and X^{7b} are each deuterium. In one aspect of this embodiment, X^{8a} and X^{8b} are each deuterium. In one aspect of this embodiment, X^{7a}, X^{7b}, X^{8a} and X^{8b} are each deuterium. In an example of this aspect, X^{1a}, X^{1b}, X^{2a} and X^{2b} are each deuterium. In another example of this aspect, X^{1a}, X^{1b}, X^{2a} and X^{2b} are each hydrogen. In one aspect of this embodiment, X^{3a} and X^{3b} are each deuterium. In one aspect of this embodiment, X^{5a} and X^{5b} are each deuterium. In one aspect of this embodiment, X^{3a}, X^{3b}, X^{5a} and X^{5b} are each deuterium. In an example of this aspect, X^{4a}, X^{4b}, X^{6a} and X^{6b} are each hydrogen. In one aspect of this embodiment, X^{4a} and X^{4b} are each deuterium. In one aspect of this embodiment, X^{6a} and X^{6b} are each deuterium. In one aspect of this embodiment, X^{4a}, X^{4b}, X^{6a} and X^{6b} are each deuterium. In one example of this aspect, X^{3a}, X^{3b}, X^{5a} and X^{5b} are each deuterium. In another example of this aspect, X^{3a}, X^{3b}, X^{5a} and X^{5b} are each hydrogen. In one example of any of the foregoing aspects or examples, R is CD_3. In one example of any of the foregoing aspects or examples, R is CH_3.

[34] In another embodiment R is CD_3; and X^{1a} and X^{1b} are the same; X^{2a} and X^{2b} are the same; X^{3a} and X^{3b} are the same; X^{4a} and X^{4b} are the same; X^{5a} and X^{5b} are the same; X^{6a} and X^{6b} are the same; X^{7a} and X^{7b} are the same; and X^{8a} and X^{8b} are the same. In one aspect of this embodiment, X^{3a}, X^{3b}, X^{5a} and X^{5b} are the same; and X^{4a}, X^{4b}, X^{6a} and X^{6b} are the same. In an even more specific aspect X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b} X^{6a} and X^{6b} are the same.

[35] In still another embodiment R is CH_3; and X^{1a} and X^{1b} are the same; X^{2a} and X^{2b} are the same; X^{3a} and X^{3b} are the same; X^{4a} and X^{4b} are the same; X^{5a} and X^{5b} are the same; X^{6a} and X^{6b} are the same; X^{7a} and X^{7b} are the same; and X^{8a} and X^{8b} are the same. In one aspect of this embodiment, X^{3a}, X^{3b}, X^{5a} and X^{5b} are the same; and X^{4a}, X^{4b}, X^{6a}

and X^{6b} are the same. In an even more specific aspect X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b} X^{6a} and X^{6b} are the same.

[36] In one example of the aspect wherein X^{1a} and X^{1b} are the same; X^{2a} and X^{2b} are the same; X^{3a}, X^{3b}, X^{5a} and X^{5b} are the same; X^{4a}, X^{4b}, X^{6a} and X^{6b} are the same; X^{7a} and X^{7b} are the same; and X^{8a} and X^{8b} are the same, the compound is selected from any one of the compounds (Cmpd) set forth in Table 1 (below):

Table 1: Exemplary Embodiments of Formula I

Cmpd#	X^{1a}/ X^{1b}	X^{2a}/ X^{2b}	X^{3a}/X^{3b}/ X^{5a}/X^{5b}	X^{4a}/X^{4b}/ X^{6a}/X^{6b}	X^{7a}/ X^{7b}	X^{8a}/ X^{8b}	X^{9}	R
100	D	D	D	D	D	D	D	CD_3
101	D	D	D	D	D	D	H	CD_3
102	D	D	D	D	H	H	D	CD_3
103	D	D	H	H	D	D	D	CD_3
104	H	H	D	D	D	D	D	CD_3
105	D	D	D	D	H	H	H	CD_3
106	D	D	H	H	D	D	H	CD_3
107	H	H	D	D	D	D	H	CD_3
108	D	D	D	D	D	D	D	CH_3
109	D	D	D	D	D	D	H	CH_3
110	D	D	D	D	H	H	D	CH_3
111	D	D	H	H	D	D	D	CH_3
112	H	H	D	D	D	D	D	CH_3
113	D	D	D	D	H	H	H	CH_3
114	D	D	H	H	D	D	H	CH_3
115	H	H	D	D	D	D	H	CH_3
116	H	H	D	D	H	H	D	CH_3
117	H	H	D	D	H	H	H	CH_3
118	D	H	D	D	D	D	D	CD_3
119	D	H	D	D	D	D	H	CD_3
120	D	H	D	D	H	H	D	CD_3
121	D	H	H	H	D	D	D	CD_3
122	D	H	D	D	H	H	H	CD_3
123	D	H	H	H	D	D	H	CD_3
124	H	D	D	D	D	D	H	CD_3
125	D	H	D	D	D	D	D	CH_3
126	D	H	D	D	D	D	H	CH_3
127	D	H	D	D	H	H	D	CH_3
128	D	H	H	H	D	D	D	CH_3
129	H	D	D	D	D	D	D	CH_3
130	D	H	D	D	H	H	H	CH_3
131	D	H	H	H	D	D	H	CH_3
132	H	D	D	D	D	D	H	CH_3

Cmpd#	X^{1a}/ X^{1b}	X^{2a}/ X^{2b}	X^{3a}/X^{3b}/ X^{5a}/X^{5b}	X^{4a}/X^{4b}/ X^{6a}/X^{6b}	X^{7a}/ X^{7b}	X^{8a}/ X^{8b}	X^{9}	R
133	H	D	D	D	H	H	D	CH_3
134	H	D	D	D	H	H	H	CH_3
135	H	D	H	D	D	D	D	CD_3
136	D	D	H	D	D	D	D	CD_3
137	D	D	H	D	D	D	H	CD_3
138	D	D	H	D	H	H	D	CD_3
139	D	D	D	H	D	D	D	CD_3
140	H	H	H	D	D	D	D	CD_3
141	D	D	H	D	H	H	H	CD_3
142	D	D	D	H	D	D	H	CD_3
143	H	H	H	D	D	D	H	CD_3
144	D	D	H	D	D	D	D	CH_3
145	D	D	H	D	D	D	H	CH_3
146	D	D	H	D	H	H	D	CH_3
147	D	D	D	H	D	D	D	CH_3
148	H	H	H	D	D	D	D	CH_3
149	D	D	H	D	H	H	H	CH_3
150	D	D	D	H	D	D	H	CH_3
151	H	H	H	D	D	D	H	CH_3
152	H	H	H	D	H	H	D	CH_3
153	H	H	H	D	H	H	H	CH_3
154	D	D	D	H	H	H	D	CD_3
155	H	H	D	H	D	D	D	CD_3
156	D	D	D	H	H	H	H	CD_3
157	H	H	D	H	D	D	H	CD_3
158	D	D	D	H	H	H	D	CH_3
159	H	H	D	H	D	D	D	CH_3
160	D	D	D	H	H	H	H	CH_3
161	H	H	D	H	D	D	H	CH_3
162	H	H	D	H	H	H	D	CH_3
163	H	H	D	H	H	H	H	CH_3
164	D	D	D	D	D	H	D	CD_3
165	D	D	D	D	D	H	H	CD_3
166	D	D	D	D	H	D	D	CD_3
167	D	D	H	H	D	H	D	CD_3
168	H	H	D	D	D	H	D	CD_3
169	D	D	D	D	H	D	H	CD_3
170	D	D	H	H	D	H	H	CD_3
171	H	H	D	D	D	H	H	CD_3
172	D	D	D	D	D	H	D	CH_3
173	D	D	D	D	D	H	H	CH_3
174	D	D	D	D	H	D	D	CH_3
175	D	D	H	H	D	H	D	CH_3

Cmpd#	X^{1a}/ X^{1b}	X^{2a}/ X^{2b}	X^{3a}/X^{3b}/ X^{5a}/X^{5b}	X^{4a}/X^{4b}/ X^{6a}/X^{6b}	X^{7a}/ X^{7b}	X^{8a}/ X^{8b}	X^{9}	R
176	H	H	D	D	D	H	D	CH_3
177	D	D	D	D	H	D	H	CH_3
178	D	D	H	H	D	H	H	CH_3
179	H	H	D	D	D	H	H	CH_3
180	H	H	D	D	H	D	D	CH_3
181	H	H	D	D	H	D	H	CH_3
182	D	D	H	H	H	D	D	CD_3
183	H	H	D	D	H	D	D	CD_3
184	D	D	H	H	H	D	H	CD_3
185	H	H	D	D	H	D	H	CD_3
186	D	D	H	H	H	D	D	CH_3
187	D	D	H	H	H	D	H	CH_3

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

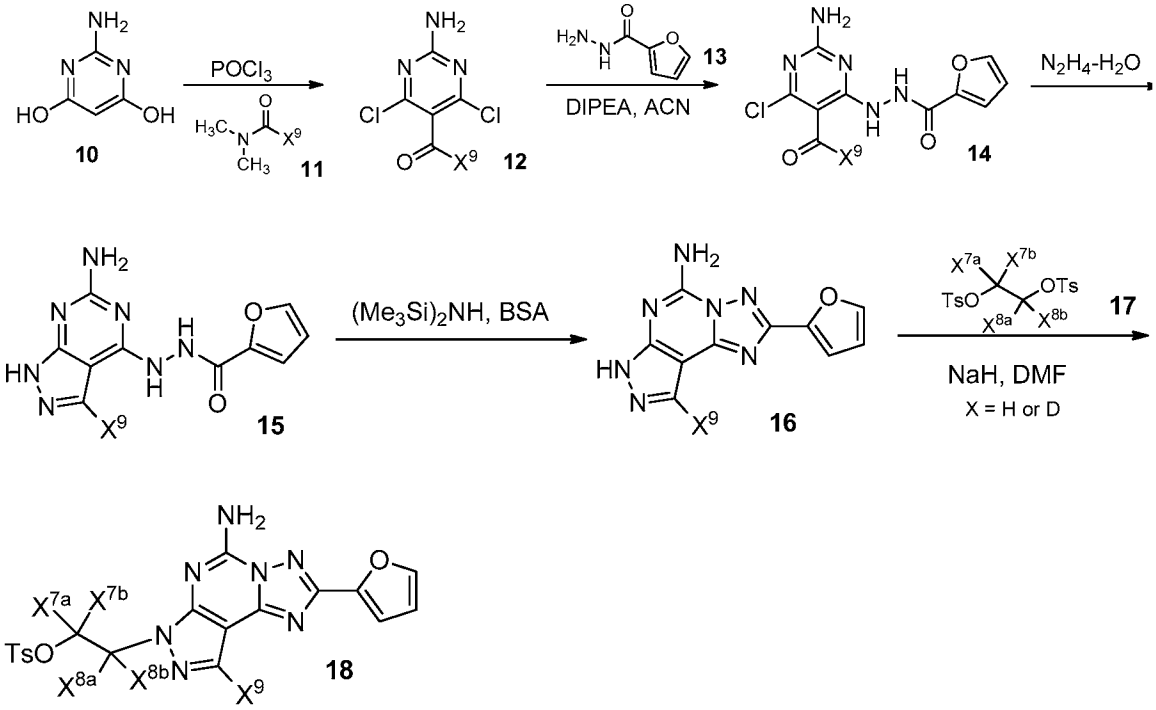
[38] In another set of embodiments, the compound of this invention has an isotopic enrichment factor of at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), or at least 98% deuterium incorporation at the position corresponding to each of variables X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b}, X^{6a}, and X^{6b}.

[39] The synthesis of compounds of Formula I may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis and Examples disclosed herein. Relevant procedures analogous to those of use for the preparation of compounds of Formula I and intermediates thereof are disclosed, for instance in PCT patent publication WO2005/054245; Urgaonkar, S. and Verkade, J. G. Adv Synth Catal, 2004, 346(6), 611-616; and in Bird, I., Farmer, P. B. J Label Comp Radiopharm, 1989, 27, 199-216. Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

Exemplary Synthesis

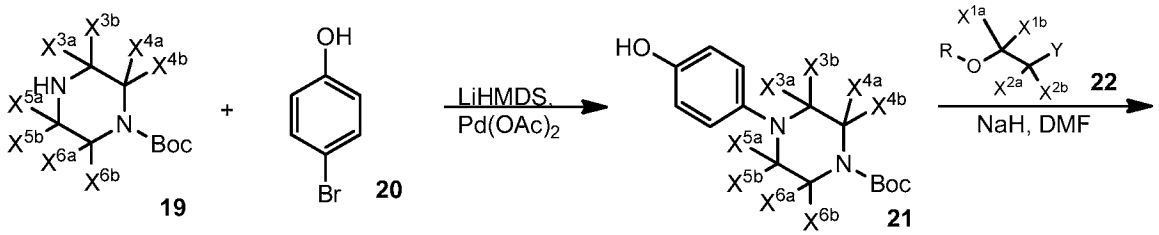
[40] A convenient method for synthesizing compounds of Formula I is depicted in Schemes 1-3.

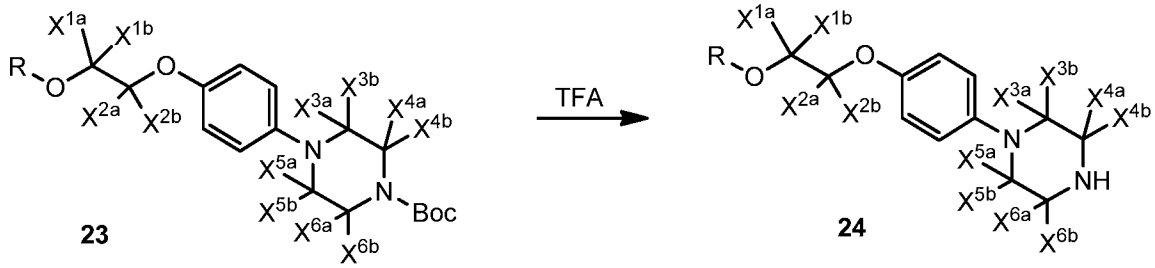
[41] Scheme 1: Synthesis of 5-amino-1,2,4-triazolo[1,5-c]pyrimidine intermediates **18**



[42] 2-aminopyrimidine-4,6-diol **10** is acylated and concurrently chlorinated with dimethyl formamide or its deuterated equivalent and phosphorous oxychloride ($POCl_3$) to provide bis-chlorinated intermediate **12**. Nucleophilic aromatic substitution with hydrazide **13** yield intermediate **14** which is then condensed with hydrazine to produce bicycle **15**. A second annulation reaction mediated by base yields the fused triazolo pyrimidine **16**. Alkylation with an appropriately deuterated bis-electrophilic synthons **17** yields the extended triazolo pyrimidine **18**.

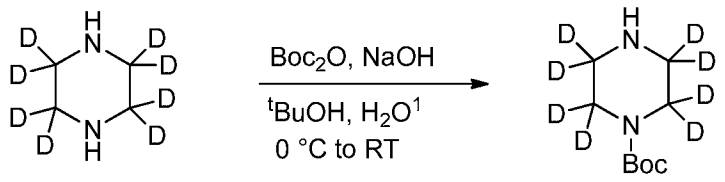
[43] Scheme 2: Synthesis of phenyl-piperazine Intermediate **24**.





, wherein Y (in reagent **22**) is a leaving group (e.g., tosylate, mesylate, bromo, etc.)

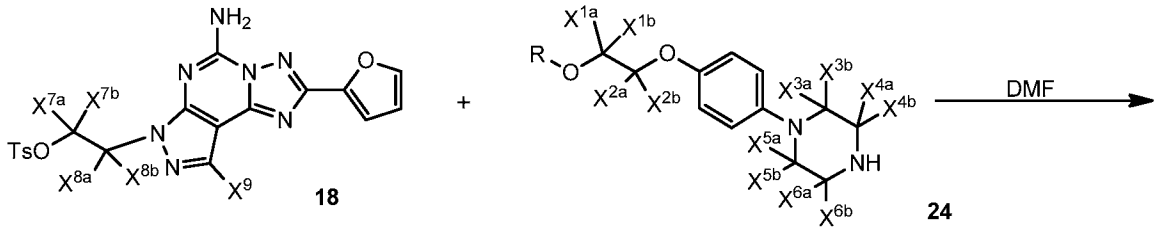
[44] Appropriately deuterated substituted piperazine **24** is prepared from the corresponding protected piperazine **19**. As an example, d^8- piperazine (available from CDN isotopes with 98% deuterium enrichment) may be protected according to the following scheme, analoagously to what is described in WO 2006/099474:

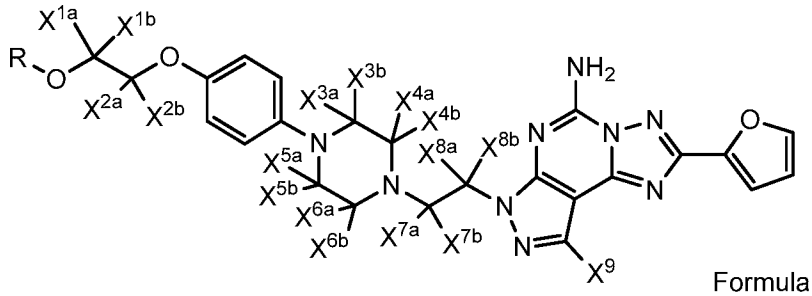


d_8-piperazine

[45] Palladium mediated cross coupling with *para*-bromophenol (**20**) provides phenol **21**. Alkylation of the phenol under basic conditions with appropriately deuterated ether **22** yields protected piperazine **23**. Removal of the *tert*-butylcarbamate masking group provides secondary amine **24**.

[46] Scheme 3: Synthesis of Compounds of Formula I.



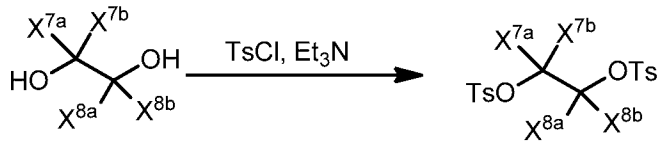


Formula I

[47] The union of substituted piperazine **24** and triazolo pyrimidine **18** Occurs spontaneously following dissolution of the two substances in appropriate solvents such as dimethylformamide to yield compounds such as Formula I.

[48] Schemes 4-8 detail the preparation of substituted ethane synthons containing various levels of isotopic abundance.

[49] Scheme 4. Synthesis of Appropriately Deuterated Ethane-1,2-diyl bis(4-methylbenzenesulfonate) **17**.



25 **17**

Appropriately deuterated,2-ethylene glycol **25** is converted to the corresponding bis-tosylate **17** by reaction with *para*-toluene sulfonyl chloride and triethylamine.

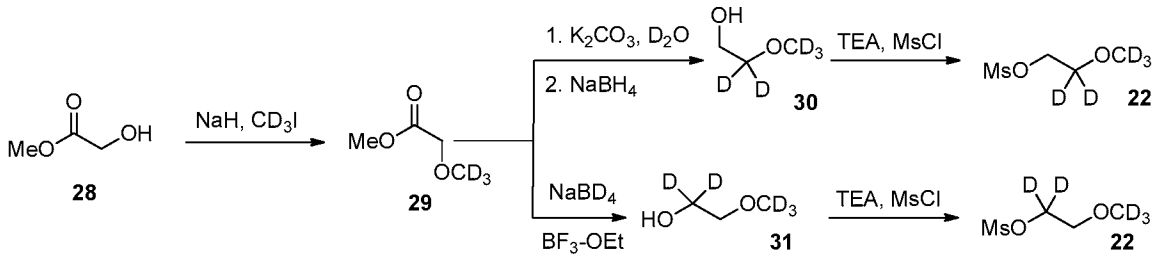
[50] Scheme 5. Synthesis of Appropriately Deuterated 2-bromoethyl methyl ether useful as Reagent **22**.

26 **22**

Monoalkylation of appropriately deuterated alcohols **27** with an appropriately deuterated dibromoethane **26** is accomplished by reaction of the alcohol **27** with sodium hydride followed by introduction of the appropriate electrophile to yield **22**.

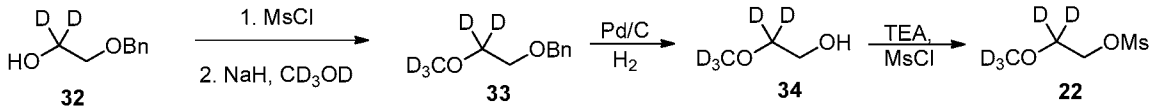
[51] Scheme 6. Syntheses of Various Deuterated d_3-methoxyethyl methanesulfonates useful as Reagent **22**.

A.



Methyl 2-hydroxyacetate **28** is alkylated with an appropriately deuterated iodomethane to yield ether **29**. Hydrogen-deuterium exchange of **29** under alkaline conditions followed by reduction with sodium borohydride yields primary alcohol **30**. Treatment of **30** with methanesulfonyl chloride yields **22** deuterated at X^{1a} and X^{1b}. Alternatively ether **29** is reduced with sodium borodeuteride and converted to the corresponding mesylate to yield **22** deuterated at X^{2a} and X^{2b}.

B.



Conversion of primary alcohol **32**, previously disclosed in Bird, I., Farmer, P. B. J Label Comp Radiopharm, 1989, 27, 199-216, to the mesylate followed by displacement with an appropriately deuterated alcohol, such as d_4-methanol, yields bis-ether **33**. Removal of the benzyl protecting group yields **34**, which is converted mesylate **22** deuterated at X^{1a} and X^{1b}.

[52] The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., X^1, X^2, X^3, etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

[53] Additional methods of synthesizing compounds of Formula I and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry

transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene, TW et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser, L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette, L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

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

Compositions

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

[56] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[57] If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral

Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

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

[59] The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000).

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

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

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

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

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

[65] Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural

pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

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

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

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

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

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

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

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

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

[74] According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising

a compound of this invention, such that said compound is released from said device and is therapeutically active.

[75] In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as Preladenant. Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of Parkinson's disease or other Parkinsonian disorders or symptoms thereof.

[76] In one embodiment, the second therapeutic agent is a dopaminergic agent. In one aspect of this embodiment, the second therapeutic agent is L-dopa.

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

[78] In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat the target disorder.

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

[80] In one embodiment, an effective amount of a compound of this invention is between about 0.1 - 20 mg, which is typically administered in oral form BID. In certain

aspects, an effective amount of a compound of this invention can range from 1 - 5 mg BID, which is typically administered in oral form BID.

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

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

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

Methods of Treatment

[84] In another embodiment, the invention provides a method of treating a disease selected from Parkinson's disease, other Parkinsonian disorders, and anxiety disorders, such as panic disorder, agoraphobia, obsessive-compulsive disorder, social phobia, post-traumatic stress disorder and specific phobia. In one embodiment the subject is a patient in need of such treatment.

[85] In one particular embodiment, the method of this invention is used to treat Parkinson's disease in a subject in need thereof.

[86] Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[87] In another embodiment, any of the above methods of treatment comprise the further step of co-administering to the subject in need thereof one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with an adenosine A2A receptor antagonist. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. In one particular aspect of this embodiment, the second therapeutic agent is an agent useful in the treatment of Parkinson's disease, Parkinsonian disorders, or symptoms of any of the foregoing. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention and a second therapeutic agent.

[88] In particular, the combination therapies of this invention include co-administering a compound of Formula I and L-dopa to a subject in need thereof for treatment of Parkinson's disease.

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

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

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

[92] In yet another aspect, the invention provides the use of a compound of Formula I alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

Example X. Evaluation of Metabolic Stability

[93] ***Microsomal Assay:*** Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

[94] ***Determination of Metabolic Stability:*** 7.5 mM stock solutions of test compounds

are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 12.5-50 μM test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37 °C, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 °C for 20 minutes after which 100 μL of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for the non-deuterated counterpart of the compound of Formula I and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

[95] ***Data analysis:*** The *in vitro* $t_{1/2}$s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

in vitro $t_{½}$ = 0.693/k

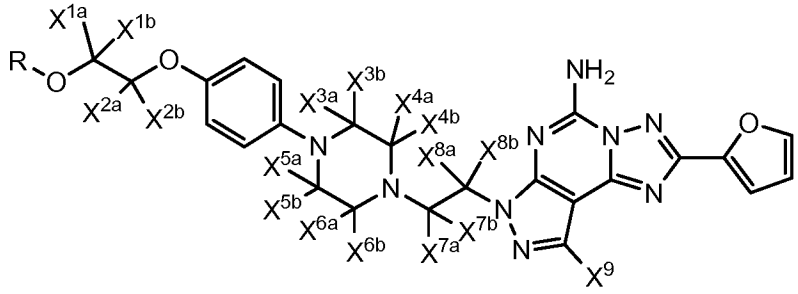
k = -[slope of linear regression of % parent remaining(ln) vs incubation time]

[96] Data analysis is performed using Microsoft Excel Software.

[97] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

We claim:

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



(I), wherein:

each X is independently selected from hydrogen and deuterium;

R is selected from CH_3 and CD_3; and

when R is CH_3, at least one X is deuterium.

2. The compound of claim 1, wherein:

X^{1a} and X^{1b} are the same;

X^{2a} and X^{2b} are the same;

X^{3a} and X^{3b} are the same;

X^{4a} and X^{4b} are the same;

X^{5a} and X^{5b} are the same;

X^{6a} and X^{6b} are the same;

X^{7a} and X^{7b} are the same; and

X^{8a} and X^{8b} are the same.

3. The compound of claim 2, wherein:

X^{3a}, X^{3b}, X^{5a} and X^{5b} are the same; and

X^{4a}, X^{4b}, X^{6a} and X^{6b} are the same.

4. The compound of claim 3, wherein X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b} X^{6a} and X^{6b} are the same.

5. The compound of claim 2, wherein X^{1a} and X^{1b} are each deuterium.

6. The compound of claim 2 or 5, wherein X^{2a} and X^{2b} are each deuterium.

7. The compound of claim 6, wherein X^{7a}, X^{7b}, X^{8a} and X^{8b} are each hydrogen.

8. The compound of claim 2, wherein X^{7a} and X^{7b} are each deuterium.

9. The compound of claim 2 or 8, wherein X^{8a} and X^{8b} are each deuterium.

10. The compound of claim 9, wherein X^{1a}, X^{1b}, X^{2a} and X^{2b} are each deuterium.

11. The compound of claim 9, wherein X^{1a}, X^{1b}, X^{2a} and X^{2b} are each hydrogen.

12. The compound of claim 2, wherein X^{3a} and X^{3b} are each deuterium.

13. The compound of claim 2 or 12, wherein X^{5a} and X^{5b} are each deuterium.

14. The compound of claim 13, wherein X^{4a}, X^{4b}, X^{6a} and X^{6b} are each hydrogen.

15. The compound of claim 2, wherein X^{4a} and X^{4b} are each deuterium.

16. The compound of claim 2 or 15, wherein X^{6a} and X^{6b} are each deuterium.

17. The compound of claim 16, wherein X^{3a}, X^{3b}, X^{5a} and X^{5b} are each deuterium.

18. The compound of claim 16, wherein X^{3a}, X^{3b}, X^{5a} and X^{5b} are each hydrogen.

19. The compound of any one of claims 1-18, wherein R is CD_3.

20. The compound of any one of claims 1-18, wherein R is CH_3.

21. The compound of claim 1, wherein: X^{1a} and X^{1b} are the same; X^{2a} and X^{2b} are the same; X^{3a}, X^{3b}, X^{5a} and X^{5b} are the same; X^{4a}, X^{4b}, X^{6a} and X^{6b} are the same; X^{7a} and X^{7b} are the same; X^{8a} and X^{8b} are the same; and the compound is selected from any one of the compounds set forth in the table below:

Cmpd#	X^{1a}/ X^{1b}	X^{2a}/ X^{2b}	X^{3a}/X^{3b}/ X^{5a}/X^{5b}	X^{4a}/X^{4b}/ X^{6a}/X^{6b}	X^{7a}/ X^{7b}	X^{8a}/ X^{8b}	X^9	R
100	D	D	D	D	D	D	D	CD_3
101	D	D	D	D	D	D	H	CD_3
102	D	D	D	D	H	H	D	CD_3
103	D	D	H	H	D	D	D	CD_3
104	H	H	D	D	D	D	D	CD_3
105	D	D	D	D	H	H	H	CD_3
106	D	D	H	H	D	D	H	CD_3
107	H	H	D	D	D	D	H	CD_3
108	D	D	D	D	D	D	D	CH_3
109	D	D	D	D	D	D	H	CH_3
110	D	D	D	D	H	H	D	CH_3
111	D	D	H	H	D	D	D	CH_3
112	H	H	D	D	D	D	D	CH_3
113	D	D	D	D	H	H	H	CH_3

Cmpd#	X^{1a}/ X^{1b}	X^{2a}/ X^{2b}	X^{3a}/X^{3b}/ X^{5a}/X^{5b}	X^{4a}/X^{4b}/ X^{6a}/X^{6b}	X^{7a}/ X^{7b}	X^{8a}/ X^{8b}	X^{9}	R
114	D	D	H	H	D	D	H	CH_3
115	H	H	D	D	D	D	H	CH_3
116	H	H	D	D	H	H	D	CH_3
117	H	H	D	D	H	H	H	CH_3
118	D	H	D	D	D	D	D	CD_3
119	D	H	D	D	D	D	H	CD_3
120	D	H	D	D	H	H	D	CD_3
121	D	H	H	H	D	D	D	CD_3
122	D	H	D	D	H	H	H	CD_3
123	D	H	H	H	D	D	H	CD_3
124	H	D	D	D	D	D	H	CD_3
125	D	H	D	D	D	D	D	CH_3
126	D	H	D	D	D	D	H	CH_3
127	D	H	D	D	H	H	D	CH_3
128	D	H	H	H	D	D	D	CH_3
129	H	D	D	D	D	D	D	CH_3
130	D	H	D	D	H	H	H	CH_3
131	D	H	H	H	D	D	H	CH_3
132	H	D	D	D	D	D	H	CH_3
133	H	D	D	D	H	H	D	CH_3
134	H	D	D	D	H	H	H	CH_3
135	H	D	H	D	D	D	D	CD_3
136	D	D	H	D	D	D	D	CD_3
137	D	D	H	D	D	D	H	CD_3
138	D	D	H	D	H	H	D	CD_3
139	D	D	D	H	D	D	D	CD_3
140	H	H	H	D	D	D	D	CD_3
141	D	D	H	D	H	H	H	CD_3
142	D	D	D	H	D	D	H	CD_3
143	H	H	H	D	D	D	H	CD_3
144	D	D	H	D	D	D	D	CH_3
145	D	D	H	D	D	D	H	CH_3
146	D	D	H	D	H	H	D	CH_3
147	D	D	D	H	D	D	D	CH_3
148	H	H	H	D	D	D	D	CH_3
149	D	D	H	D	H	H	H	CH_3
150	D	D	D	H	D	D	H	CH_3
151	H	H	H	D	D	D	H	CH_3
152	H	H	H	D	H	H	D	CH_3
153	H	H	H	D	H	H	H	CH_3
154	D	D	D	H	H	H	D	CD_3
155	H	H	D	H	D	D	D	CD_3
156	D	D	D	H	H	H	H	CD_3

Cmpd#	X^{1a}/ X^{1b}	X^{2a}/ X^{2b}	X^{3a}/X^{3b}/ X^{5a}/X^{5b}	X^{4a}/X^{4b}/ X^{6a}/X^{6b}	X^{7a}/ X^{7b}	X^{8a}/ X^{8b}	X^{9}	R
157	H	H	D	H	D	D	H	CD_3
158	D	D	D	H	H	H	D	CH_3
159	H	H	D	H	D	D	D	CH_3
160	D	D	D	H	H	H	H	CH_3
161	H	H	D	H	D	D	H	CH_3
162	H	H	D	H	H	H	D	CH_3
163	H	H	D	H	H	H	H	CH_3
164	D	D	D	D	D	H	D	CD_3
165	D	D	D	D	D	H	H	CD_3
166	D	D	D	D	H	D	D	CD_3
167	D	D	H	H	D	H	D	CD_3
168	H	H	D	D	D	H	D	CD_3
169	D	D	D	D	H	D	H	CD_3
170	D	D	H	H	D	H	H	CD_3
171	H	H	D	D	D	H	H	CD_3
172	D	D	D	D	D	H	D	CH_3
173	D	D	D	D	D	H	H	CH_3
174	D	D	D	D	H	D	D	CH_3
175	D	D	H	H	D	H	D	CH_3
176	H	H	D	D	D	H	D	CH_3
177	D	D	D	D	H	D	H	CH_3
178	D	D	H	H	D	H	H	CH_3
179	H	H	D	D	D	H	H	CH_3
180	H	H	D	D	H	D	D	CH_3
181	H	H	D	D	H	D	H	CH_3
182	D	D	H	H	H	D	D	CD_3
183	H	H	D	D	H	D	D	CD_3
184	D	D	H	H	H	D	H	CD_3
185	H	H	D	D	H	D	H	CD_3
186	D	D	H	H	H	D	D	CH_3
187	D	D	H	H	H	D	H	CH_3

22. The compound of any one of claims 1-21, wherein any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

23. A pharmaceutical composition comprising a compound of any one of claims 1-22; and a pharmaceutically acceptable carrier.

24. A method of treating a disease or condition selected from Parkinson's disease, other Parkinsonian disorders, and anxiety disorders in a subject comprising the step of administering to the subject in need thereof the composition of claim 23.

25. The method of claim 24, wherein the disease is Parkinson's disease.

26. The method of claim 25, additionally comprising administering to the subject in need thereof L-dopa.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/030081

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/14 A61K31/505 A61P25/16 C07B59/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/92264 A1 (SCHERING CORP [US]; NEUSTADT BERNARD R [US]; LINDO NEIL A [US]; GREENL) 6 December 2001 (2001-12-06) claims 14, 15; examples 1-62 -----	1-4,7, 11,14, 18,20, 22-26
Y	LI-KANG ZHANG ET AL: "Characterization of major degradation products of an adenosine A 2A receptor antagonist under stressed conditions by LC-MS and FT tandem MS analysis", JOURNAL OF MASS SPECTROMETRY, vol. 45, no. 2, 1 February 2010 (2010-02-01), pages 146-156, XP55027274, ISSN: 1076-5174, DOI: 10.1002/jms.1695 the whole document -----	5,6, 8-10,12, 13, 15-17, 19,21
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2012	05/06/2012

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/030081

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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PCT/US2012/030081

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