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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 March 2012 (08.03.2012)

PCT

(10) International Publication Number
WO 2012/028635 A1

(51) International Patent Classification:
C07B 59/00 (2006.01) *A61K 31/445* (2006.01)
C07D 211/24 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/EP2011/064954

(22) International Filing Date:
31 August 2011 (31.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2010 70385 3 September 2010 (03.09.2010) DK
61/380,851 8 September 2010 (08.09.2010) US

(71) Applicant *(for all designated States except US)*: **NSAB, FILIAL AF NEUROSEARCH SWEDEN AB, SVERIGE** [DK/DK]; c/o NeuroSearch A/S, Pederstrupvej 93, DK-2750 Ballerup (DK).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **SONESSON, Clas** [SE/SE]; c/o NeuroSearch Sweden AB, Arvid Wallgrens Backe 20, S-41346 Göteborg (SE).

(74) Agent: **ABILDGREN, Michael**; NeuroSearch A/S, Intellectual Property Rights, Pederstrupvej 93, DK-2750 Ballerup (DK).

(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, 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))*

Published:

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

WO 2012/028635 A1

(54) **Title**: DEUTERATED ANALOGS OF PRIDOPIDINE USEFUL AS DOPAMINERGIC STABILIZERS

(57) **Abstract**: The present invention provides novel deuterated analogs of Pridopidine, i.e. 4-(3-methanesulfonyl-phenyl)-1 -propyl-piperidine. Pridopidine is a drug substance currently in clinical development for the treatment of Huntington's disease. In other aspects the invention relates to pharmaceutical compositions 10 comprising a deuterated analog of Pridopidine of the invention, and to therapeutic applications of these analogs.

DEUTERATED ANALOGS OF PRIDOPIDINE USEFUL AS DOPAMINERGIC STABILIZERS

FIELD OF THE INVENTION

The present invention provides novel deuterated analogs of Pridopidine, i.e. 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine. Pridopidine is a drug substance currently in clinical development for the treatment of Huntington's disease.

In other aspects the invention relates to pharmaceutical compositions comprising a deuterated analog of Pridopidine of the invention, and to therapeutic applications of these analogs.

BACKGROUND OF THE INVENTION

Deuterium, also called "heavy hydrogen", is a stable isotope of hydrogen with a natural abundance in the oceans of Earth of approximately one atom in 6,500 of hydrogen (~154 ppm). Deuterium thus accounts for approximately 0.0154% (alternately, on a mass basis: 0.0308%) of all naturally occurring hydrogen in the oceans on Earth. The nucleus of deuterium, called a deuteron, contains one proton and one neutron, whereas the hydrogen nucleus contains no neutron.

Deuterium forms bonds with carbon that vibrate at a lower frequency and are thus stronger than C-H bonds. Therefore "heavy hydrogen" versions of drugs may be more stable towards degradation and last longer in the organism. Incorporating deuterium in place of hydrogen thus may improve the pharmacodynamic and pharmacokinetic profiles of drugs, thus modifying the metabolic fate, while retaining the pharmacologic activity and selectivity of physiologically active compounds. Deuterated drugs thus may positively impact safety, efficacy and/or tolerability.

Pridopidine, i.e. 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine, a dopaminergic stabilizer currently in clinical development for the treatment of Huntington's disease. The compound is described in e.g. WO 01/46145, and in e.g. WO 2006/040155 an alternative method for its synthesis is described.

SUMMARY OF THE INVENTION

The object of the present invention is to provide analogs of Pridopidine with improved pharmacodynamic and pharmacokinetic profiles.

Therefore, in its first aspect the invention provides a partially or fully deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine as represented by Formula 1, below.

In another aspect the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine of the invention, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

Viewed from another aspect the invention relates to the use of the deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine of the invention as a medicament, or for the manufacture of a medicament.

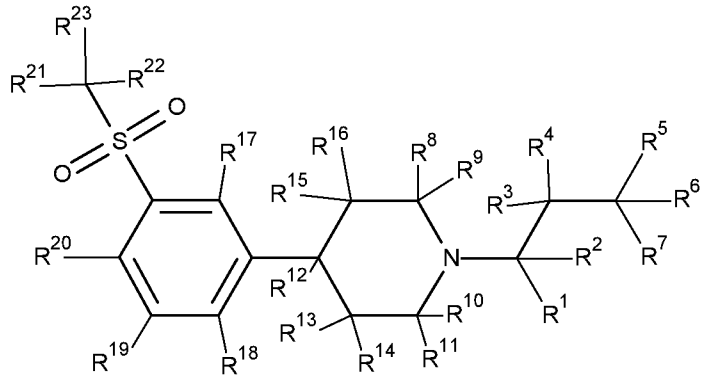
In a further aspect the invention provides a method for treatment, prevention or alleviation of a dopamine mediated disorder of a living animal body, including a human, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine according to the invention, or a pharmaceutically acceptable salt thereof.

Other aspects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DESCRIPTION OF THE INVENTION

Deuterated analogs of Pridopidine

In its first aspect the present invention provides deuterated analogs of Pridopidine. The deuterated analog of the invention may be a fully or partially deuterium substituted derivative. The deuterated analog of the invention may in particular be characterised by Formula I



(I)

or a pharmaceutically acceptable salt thereof, wherein

at least one of R^1 - R^{23} represents deuterium (D); and

the remaining of R^1 - R^{23} represent hydrogen (H).

In the context of this invention, when a particular position is designated as holding deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is about 0.015%.

In a preferred embodiment the abundance of deuterium at that position is at least 3340 times greater (i.e. at least 50.1% incorporation of deuterium) than the natural abundance of deuterium. In other preferred embodiments of the invention the abundance of deuterium at that position is at least 3500 (52.5% deuterium incorporation), 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).

In a preferred embodiment the deuterated analog of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

R^1 - R^2 represent deuterium (D); and

all of R^3 - R^{23} represent hydrogen (H).

In another preferred embodiment the deuterated analog of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

at least one of R^1 - R^7 represents deuterium (D); and

the remaining of R^1 - R^{23} represent hydrogen (H).

In a third preferred embodiment the deuterated analog of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

all of R^1 - R^7 represent deuterium (D); and

all of R^8 - R^{23} represent hydrogen (H).

In a fourth preferred embodiment the deuterated analog of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

R^8, R^9, R^{10} and R^{11} represent deuterium (D); and

all of R^1 - R^7 and R^{12} - R^{23} represent hydrogen (H).

In a fifth preferred embodiment the deuterated analog of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

R^{12} represents deuterium (D); and

all of R^1 - R^{11} and R^{13} - R^{23} represent hydrogen (H).

In a sixth preferred embodiment the deuterated analog of the invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein

R^{17} - R^{20} represent deuterium (D); and

all of R^1 - R^{16} and R^{21} - R^{23} represent hydrogen (H).

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Pharmaceutically Acceptable Salts

The deuterated analog of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the deuterated analog of the invention.

Examples of pharmaceutically acceptable salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a deuterated analog of the invention and its pharmaceutically acceptable acid addition salt.

Examples of pharmaceutically acceptable cationic salts of a deuterated analog of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysinium, and the ammonium salt, and the like, of a deuterated analog of the invention

containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

The deuterated analog of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvent such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Methods of Preparation

The deuterated analog of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention may be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological activity

WO 01/46145, WO 01/46146, WO 2005/121087, WO 2007/042295 WO 2008/127188 and WO 2008/155357 all describe substituted 4-phenyl-N-alkyl-piperazines and 4-phenyl-N-alkyl-piperidines, reported to be modulators of dopamine neurotransmission, and to be useful in treatment of symptoms of various disorders of the central nervous system. The deuterated analog of the invention is considered useful for the same medical indications as described in these publications, and these publications therefore are incorporated by reference.

Neurological indications contemplated according to these publications include the treatment of Huntington's disease and other movement disorders, as well as movement disorders induced by drugs.

Therefore, in a preferred embodiment, the invention relates to the use of the deuterated analog of the invention for use as a medicament for the treatment of Huntington's disease.

Pharmaceutical Compositions

Viewed from another aspect the invention provides deuterated analogs for use as medicaments. Therefore, in another aspect, the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the compound of the invention.

While a deuterated analog of the invention for use in therapy may be administered in the form of the raw compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

Pharmaceutical compositions of the invention may in particular be formulated as described in WO 01/46145.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depends on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 1 to about 500 mg of active ingredient per individual dose, preferably of from about 10 to about 100 mg, most preferred of from about 25 to about 50 mg, are suitable for therapeutic treatments. The daily dose will preferably be administered in individual dosages 1 to 4 times daily.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a dopamine mediated disorder of a living animal body, including a human, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of the deuterated analog of the invention.

In a preferred embodiment the dopamine mediated disorder is Huntington's disease.

EXAMPLES

The invention is further illustrated in the examples below, which in no way are intended to limit the scope of the invention.

Example 1

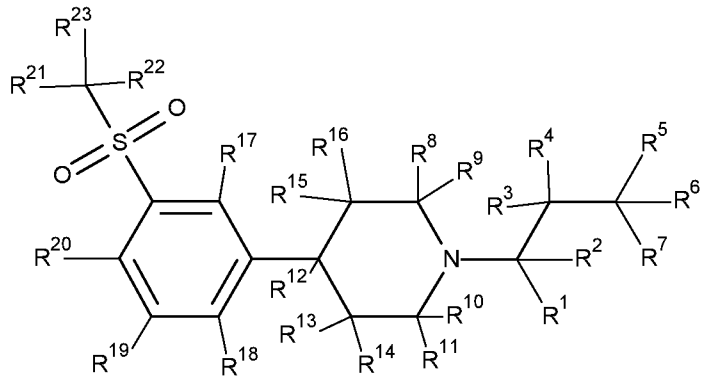
Preparatory example

4-(3-Methanesulfonyl-phenyl)-1-propyl-d7-piperidine x HCl

4-(3-Methanesulfonyl-phenyl)-piperidine (0.43 g), CH3CN (4 ml), K_2CO_3 (0.49 g), and 1-Iodopropane-d7 (0.19 g) are mixed and heated in microwave oven for 30 min at 120°C. The mixture is filtered and evaporated to dryness and purified on silica column using iso-octane:EtOAc (1:1) containing 5% NEt_3 as eluent. After evaporation of the fractions with pure product, the residue is re-dissolved in EtOAc and washed with a 10% Na_2CO_3 solution. The organic phase is separated and dried with Na_2SO_4, filtered and evaporated to yield pure product (0.33 g). The amine is then converted to the HCl salt, and re-crystallized from EtOH:Et_2O. M.p. 198-199°C.

CLAIMS

1. A fully or partially deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine represented by Formula 1



(I)

or a pharmaceutically acceptable salt thereof, wherein
at least one of R^1 - R^{23} represents deuterium (D); and
the remaining of R^1 - R^{23} represent hydrogen (H).

2. The deuterated analog according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
R^1 - R^2 represent deuterium (D); and
all of R^3 - R^{23} represent hydrogen (H).

3. The deuterated analog according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
at least one of R^1 - R^7 represents deuterium (D); and
the remaining of R^1 - R^{23} represent hydrogen (H).

4. The deuterated analog according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
all of R^1 - R^7 represent deuterium (D); and
all of R^8 - R^{23} represent hydrogen (H).

5. The deuterated analog according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^8, R^9, R^{10} and R^{11} represent deuterium (D); and
all of R^1 - R^7 and R^{12} - R^{23} represent hydrogen (H).

6. The deuterated analog according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
R^{12} represents deuterium (D); and
all of R^1 - R^{11} and R^{13} - R^{23} represent hydrogen (H).

7. The deuterated analog according to claim 1, or a pharmaceutically acceptable salt thereof, wherein
R^{17} - R^{20} represent deuterium (D); and
all of R^1 - R^{16} and R^{21} - R^{23} represent hydrogen (H).

8. A pharmaceutical composition, comprising a therapeutically effective amount of a deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

9. The deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, for use as a medicament.

10. Use of the deuterated analog according to any one of claims 1-7, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.

11. A method for treatment, prevention or alleviation of a dopamine mediated disorder of a living animal body, including a human, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a deuterated analog of 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine according to any one of the claims 1-7, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/064954

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07B59/00 C07D211/24 A61K31/445 A61P25/00
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)
C07B 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 practical, 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.
A	WO 01/46145 A1 (CARLSSON A RESEARCH AB [SE]; SVAN INGELA MARIANNE LF [SE]; CARLBERG JE) 28 June 2001 (2001-06-28) cited in the application example 6	1-11
E	WO 2011/107583 A1 (NSAB AF NEUROSEARCH SWEDEN AB SVERIGE [DK]; WATERS NICHOLAS [SE]; WATE) 9 September 2011 (2011-09-09) claims	1-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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
7 October 2011	17/10/2011

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	Diederen, Jeroen

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/064954

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0146145 A1	28-06-2001	AT 254601 T	15-12-2003
		AT 307113 T	15-11-2005
		AT 491697 T	15-01-2011
		AU 2570401 A	03-07-2001
		AU 778422 B2	02-12-2004
		AU 2570501 A	03-07-2001
		BG 106841 A	31-01-2003
		BR 0016611 A	03-09-2002
		CA 2394602 A1	28-06-2001
		CN 1420869 A	28-05-2003
		CN 1765890 A	03-05-2006
		CZ 20022070 A3	16-10-2002
		DE 60006717 D1	24-12-2003
		DE 60006717 T2	12-08-2004
		DE 60023345 T2	24-05-2006
		DK 1240142 T3	06-02-2006
		EE 200200344 A	16-06-2003
		EE 200900004 A	15-04-2009
		EP 1240141 A1	18-09-2002
		EP 1240142 A1	18-09-2002
		EP 1428822 A2	16-06-2004
		ES 2208461 T3	16-06-2004
		ES 2246926 T3	01-03-2006
		HK 1054229 A1	22-09-2006
		HK 1091482 A1	15-02-2008
		HR 20020540 A2	31-12-2004
		HR 20050784 A2	28-02-2006
		HU 0203872 A2	28-03-2003
		IL 150351 A	29-12-2008
		JP 2003518095 A	03-06-2003
		JP 2009007358 A	15-01-2009
		KR 20060006979 A	20-01-2006
		MX PA02006320 A	14-05-2004
		NO 20022878 A	21-08-2002
		NO 324874 B1	27-12-2007
		NZ 519595 A	28-05-2004
		NZ 531680 A	28-10-2005
		PL 362253 A1	18-10-2004
		WO 0146144 A1	28-06-2001
		SI 1240142 T1	28-02-2006
		SK 8672002 A3	04-03-2003
		UA 73338 C2	15-10-2002
		US 2003139423 A1	24-07-2003
		US 2003109532 A1	12-06-2003
		ZA 200204812 A	29-10-2003
WO 2011107583 A1	09-09-2011	NONE	