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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2013 (12.12.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/184732 A1

(51) International Patent Classification:
C07D 213/63 (2006.01) *A61P 25/00* (2006.01)
A61K 31/4412 (2006.01)

(21) International Application Number:
PCT/US2013/044191

(22) International Filing Date:
5 June 2013 (05.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/656,127 6 June 2012 (06.06.2012) US

(71) Applicant: **TARGACEPT, INC.** [US/US]; 100 North Main Street, Suite 1510, Winston-Salem, North Carolina 27701 (US).

(72) Inventors; and
(71) Applicants : **BOHLIN, Martin** [SE/SE]; AstraZeneca R&D, SE-15185 Sodertalje (SE). **SEBHATU, Tesfai** [SE/SE]; AstraZeneca R&D, S-15185 Sodertalje (SE).

(74) Agent: **FIX, Amy H.**; P.O. Box 7037, Atlanta, Georgia 30357 (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, BN, 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, 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, PA, 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, 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, KM, 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 2013/184732 A1

(54) **Title**: CRYSTALLINE (2S)-(4E)-N-METHYL-5-[3-(5-ISOPROPOXYPYRIDIN)YL]4-PENTEN-2-AMINE 1,5-NAPHTHALENEDISULFONATE

(57) **Abstract**: Substantially pure, stable and crystalline (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate, and pharmaceutical compositions that include such as salt, methods for treating a wide variety of conditions and disorders with such a salt, and treatment of conditions and disorders associated with dysfunction of the central and autonomic nervous systems using the salt.

CRYSTALLINE (2S)-(4E)-N-METHYL-5-[3-(5-ISOPROPOXYPYRIDIN)YL]4-PENTEN-2-AMINE 1,5-NAPHTHALENEDISULFONATE

FIELD OF THE INVENTION:

The present invention relates to substantially pure, stable and crystalline (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate, and with pharmaceutical compositions that include the salt. This invention also relates to the treatment of central nervous system disorders and particularly to the treatment of such disorders with the salt, and particularly to treatment using the salt of conditions and disorders associated with dysfunction of the central and autonomic nervous systems.

BACKGROUND OF THE INVENTION:

The compound (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine is known to provide benefits in the area of the treatment and/or prevention of central nervous system disorders. The compound, its synthesis, and its use in methods of medical treatment, is described, for example, in PCT WO 99/65876 to Caldwell et al., and in US application 11/270,018, the contents of which are hereby incorporated by reference in their entirety.

The commercial development of a drug candidate such as (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine involves many steps, including scaling up the chemical synthesis and purification, finding optimal salt forms, and the like. In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially-viable manufacturing process, but also for the subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of drug compositions, chemical stability, solid state stability, and "shelf life" of the active ingredients are very important factors. The drug substance, and compositions containing it, should preferably be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics. For example, its chemical composition should be stable, its chemical form should not change and it should not absorb water from the environment. Moreover, it is also important to be able to provide the drug in a form, which is as

chemically pure as possible. The skilled person will appreciate that, typically, if a drug can be readily obtained in a stable form, such as a stable crystalline form, advantages are provided in terms of ease of handling, ease of preparation of suitable pharmaceutical compositions, and an improved solubility profile.

SUMMARY OF THE INVENTION

The present invention relates to a stable, non-hygroscopic and crystalline 1,5-naphthalenedisulfonic acid salt of (2S)-(4E)-N- methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine. This salt is obtained in a substantially pure form. The invention also relates to the preparation of this salt. In one embodiment the stoichiometric ratio of the acid to the amine is 1:1. In another embodiment the stoichiometric ratio of the acid to the amine is 1:2. A stoichiometric ratio of acid to amine of 1:2 is preferred.

The present invention also relates to therapeutic methods for treating and/or preventing a wide variety of conditions or disorders, and particularly those disorders characterized by dysfunction of nicotinic cholinergic neurotransmission including disorders involving neuromodulation of neurotransmitter release, such as dopamine release.

Disorders for which the salt described herein is contemplated to provide a benefit are age-associated memory impairment, mild cognitive impairment, pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Lewy body dementia, vascular dementia, Alzheimer's disease, Cognition in Down's Syndrome , Huntington's Disease, Parkinsonism, and Parkinson's Disease, stroke, AIDS dementia complex, attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, cognitive deficits of schizophrenia, and schizoaffective disorder.

Particular Disorders for which the salt described herein is contemplated to provide a benefit are Alzheimer's Disease and ADD/ADHD.

The present invention further relates to therapeutic methods for treating and/or preventing disorders, such as central nervous system (CNS) disorders, which are characterized by an alteration in normal neurotransmitter release, and also for treating certain conditions, for example alleviating pain.

Such therapeutic methods involve administering to a subject an effective amount of the salt described herein or pharmaceutical compositions including the salt. The salt can be

provided in the form of a pharmaceutical composition that includes an effective amount of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate as described herein.

Pharmaceutical compositions suitable for use in therapeutic methods described herein include a therapeutically effective amount of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate.

Pharmaceutical compositions described herein provide therapeutic benefit to individuals suffering from disorders described herein, and, when employed in effective amounts, (i) exhibit nicotinic pharmacology and affect relevant nicotinic receptors sites (e.g., act as a pharmacological agonist to activate nicotinic receptors), and/or (ii) elicit neurotransmitter secretion, and hence prevent and suppress the symptoms associated with those diseases.

Pharmaceutical compositions described herein are believed to be safe and effective with regards to prevention and treatment of a wide variety of conditions and disorders. The foregoing and other aspects of the present invention are explained in detail in the detailed description and examples set forth below.

DETAILED DESCRIPTION

(2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate, pharmaceutical compositions including this salt, methods of preparing the salt, and methods of treatment and/or prevention using the salt, are described in detail herein.

Preparation of the salt:

Generally the free base or a solution of the free base of suitably pure (2S)-(4E)-N-methyl-5-[3(5-isopropoxypyridin)yl]-4-penten-2-amine in a suitable solvent is mixed with pure solid 1,5-naphthalenedisulfonic acid or a solution of 1,5-naphthalenedisulfonic acid in a suitable solvent (preferably using 0.5 equivalent of the acid) with stirring. The resulting mixture is then (a) cooled if necessary to cause precipitation, or (b) precipitated by use of a suitable anti-solvent, or (c) evaporated to remove the first solvent followed by dissolution in a new solvent, repeating steps (a), (b) or (c) and filtering and collecting the salt.

The stoichiometry, solvent mix, solute concentration and temperature employed may vary. Representative solvents that can be used to prepare and/or recrystallize the salt form

include, without limitation, ethanol, methanol, isopropyl alcohol, acetone, ethyl acetate, and acetonitrile.

The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used.

Examples:

Example 1. Preparation of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine-hemi-1,5-naphthalene disulfonate:

(2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine free base (18.6 g) was dissolved in 359 mL acetone and transferred to a reactor. Then, water (0.6 mL) was added. The inner temperature was adjusted to 40 °C. 1,5-naphthalene disulfonic acid tetrahydrate (14.7 g, 97%) was added in solid form to the solution. Crystallization started immediately. The temperature was increased to 52 °C and kept there for a short time before starting a cooling profile down to 20 °C in 4 hours. The slurry was then left overnight at 20 °C before filtration. The crystals were washed with acetone (3x20 mL) and dried under vacuum at 40 °C. A total of 28.5 g salt was obtained. The identity of the salt was verified by NMR and the stoichiometric ratio was determined to be 1:0.5 (base:acid). The NMR-shifts were: ^{1}H NMR (500 MHz, D_2O) δ ppm 8.77 (1H, d, *J* 8.5 Hz), 8.10 (1H, d, *J* 7.4 Hz), 7.97 (1H, d, *J* 1.4 Hz), 7.94 (1H, d, *J* 2.6 Hz), 7.59 (1H, dd, *J* 8.5, 7.4 Hz), 7.24 (1H, dd, *J* 2.6, 1.4 Hz), 6.38 (1H, d, *J* 15.9 Hz), 6.13 (1H, dt, *J* 15.9, 7.4 Hz), 4.57 (1H, sept, *J* 6.0 Hz), 3.26 (1H, m), 2.63 (3H, s), 2.50 (1H, m), 2.39 (1H, m), 1.24 (6H, d, *J* 6.0 Hz), 1.23 (3H, d, *J* 8.5 Hz),

Example 2. Preparation of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine-hemi-1,5-naphthalene disulfonate:

(2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine free base (15.0 g) was dissolved in acetone (290 mL). Then water (0.485 mL) was added. The temperature was adjusted to 40 °C. 1,5-naphthalene disulfonic acid tetrahydrate (in total 11.9 g, 97%) was weighed to a beaker and added in portions over a period of 2 hours. Crystallization started immediately after the first portion was added. The beaker was finally rinsed with 5 mL acetone

which was added to the slurry. The slurry was left for 1 hour and then a small amount of water (0.67 mL) was added. The slurry was then cooled to 20 °C over 4 hours. After three hours cooling 2 mL water was added and the slurry left overnight with stirring. Water was added (3x5 mL) to the slurry. After 3 hours slurrying, the crystals were filtered off and washed with 20 mL acetone. The crystals were dried under vacuum at 40 °C. A total of 7.3 g salt was obtained.

XRPD Analysis:

X-ray powder diffraction analysis (XRPD) was performed on samples prepared according to standard methods, for example those described in Giacovazzo, C. et al., (1995), Fundamentals of Crystallography, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-ray Diffraction Procedures, John Wiley and Sons, New York. X-ray diffraction analyses were performed using a PANanlytical X'Pert PRO MPD diffractometer for 96 minutes from 1 to 60° 2θ. XRPD distance values (d values) may vary in the range ±2 on the last decimal place.

Crystalline (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate was analyzed using X-ray powder diffraction (XRPD) as described above: The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from a diffractogram of the crystalline salt. The main peaks that are the most characteristic, significant, distinct and/or reproducible, occur with d-values of 27.55, 6.94, 5.97, 4.29 and 3.77 Å. The presence of these main peaks is reproducible and within the error limit, is for most circumstances sufficient to establish the presence of the crystalline salt. Additional peaks can be extracted, using conventional methods, from a diffractogram and are presented in Table 1. The relative intensity of peaks may be very strong (vs), strong (s), medium (m), weak (w), or very weak (vw).

Table 1: (2S)-(4E)-N- methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine hemi-1.5 naphthalenedisulfonate Form A X-ray powder diffraction peak d values (Å) comprising:

Corrected angles	d- (Å)	Relative intensity
3.20	27.55	vs

5.37	16.44	vw
8.69	10.17	vw
9.57	9.23	vw
9.90	8.92	w
10.94	8.08	vw
12.33	7.17	vw
12.75	6.94	vs
14.01	6.31	vw
14.65	6.04	w
14.82	5.97	s
15.45	5.73	m
16.06	5.51	w
16.69	5.31	m
16.87	5.25	w
18.41	4.81	w
18.58	4.77	w
19.74	4.49	m
20.52	4.32	m
20.69	4.29	s
21.61	4.11	w
21.96	4.04	m
22.21	4.00	m
22.38	3.97	m
23.02	3.86	m
23.56	3.77	s
24.13	3.68	m
24.64	3.61	w
25.10	3.55	w
25.64	3.47	m
26.67	3.34	vw
28.16	3.17	w
28.38	3.14	w
29.01	3.08	w
29.82	2.99	m
30.93	2.89	vw
32.19	2.78	vw
35.46	2.53	w
37.19	2.42	vw
38.87	2.32	vw
40.33	2.23	w
43.16	2.09	vw

Stability:

The term "stability" as defined herein includes chemical stability and solid state stability. By "chemical stability", we include that it may be possible to store the salt of the invention in an isolated form, or in the form of a formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of chemical degradation or decomposition. By "solid state stability", we include that it may be possible to store the salt of the invention in an isolated solid form, or in the form of a solid formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallization, recrystallization, solid state phase transition, hydration, dehydration, solvatization or desolvatization).

Examples of storage conditions can include temperatures from minus 80 to plus 50 °C or between minus 80 and plus 50 °C preferably from 0 to 40 °C or between 0 and 40 °C and more preferably room temperatures, such as from 15 to 30 °C or between 15 and 30 °C, pressures from 0.1 to 2 bars or between 0.1 and 2 bars and preferably at atmospheric pressure, relative humidity from 5 to 95% or between 5 and 95% preferably, from 10 to 60%, and/or exposure to 460 lux of UV/visible light, for prolonged periods e.g., for more than six months. The skilled person will appreciate that the above-mentioned temperatures, pressures and relative humidity represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage which would be at a temperature of 50 °C and a pressure of 1 bar.

DVS Analysis:

Tendency of (2S)-(4E)-N- methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine hemi-1.5 naphthalenedisulfonate to absorb water under humid conditions was tested using standard procedures. For comparison purposes the tendency of (2S)-(4E)-N- methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine para hydroxy-benzoate to absorb water under the same conditions was tested. A DVS instrument (Surface Measurement systems, UK) was used for moisture uptake studies. The relative humidity (RH) was increased from 0 to 90% in 10%

steps and the temperature was maintained at a constant 25 °C +/- 0.1 °C. The sorption isotherms were calculated from the equilibrium mass values. Results are presented in Table 2.

Table 2: Mass increase (water absorption) at different relative humidities (RH) for (2S)-(4E)-N- methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine para hydroxybenzoate (PHB) and (2S)-(4E)-N- methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine hemi-1.5 naphthalenedisulfonate (NDS). Data is presented to two decimal places:

Target RH %	Change In Mass (%) Sorption (PHB)	Change In Mass (%) Sorption (NDS)
0.0	0.00	0.00
10.0	0.01	0.01
20.0	0.29	0.02
30.0	0.53	0.03
40.0	0.92	0.04
50.0	1.80	0.06
60.0	12.81	0.07
70.0	19.00	0.09
80.0	27.86	0.12
90.0	32.10	0.24

It can readily be seen that the naphthalene disulfonate salt does not absorb water appreciably at any tested humidity up to 90%, whereas the hydroxybenzoate salt absorbs water at as low as 20% humidity and increasing amounts of water as the humidity is increased.

A further aspect of the present invention comprises processes for the preparation of the salt. The precise conditions under which the salts are formed may be empirically determined. The salt may be obtained in crystal form by crystallization under controlled conditions.

Medical Uses:

Determination of Binding to Relevant Receptor Sites.

Binding of the compounds to relevant receptor sites may be determined in accordance with the techniques described in U.S. Patent No. 6,953,855 to Mazurov et al. Inhibition constants (Ki values), reported in nM, can be calculated from the IC_{50} values using the method of Cheng et al., *Biochem, Pharmacol.* 22:3099 (1973). Low binding constants indicate that the

compounds of the present invention exhibit good high affinity binding to certain CNS nicotinic receptors.

One embodiment of the invention relates to the ability of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate to express nicotinic pharmacology, and in particular, to act as a nicotinic partial agonist. Receptor binding constants provide a measure of the ability of the compound to bind to half of the relevant receptor sites of certain brain cells of the patient. See, Cheng, et al., Biochem. Pharmacol. 22:3099 (1973). The (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4penten-2-amine compound used to prepare the salt has extremely high affinity for the relevant receptors, with a binding affinity in the low nM range. The compound has the ability to demonstrate a nicotinic function by effectively modulating neurotransmitter secretion from neurons. As such, the compound has the ability to affect relevant the release of acetylcholine, dopamine, and other neurotransmitters by neurons.

(2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate when employed in effective amounts, is selective to certain relevant nicotinic receptors, and does not cause significant activation of receptors associated with undesirable side effects at concentrations required for modulation of CNS neuronal activity. The selectivity of the compound against ganglia-type receptors responsible for cardiovascular side effects is demonstrated by a lack of the ability of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine to activate nicotinic function of adrenal chromaffin tissue at concentrations greater than those required for modulation of CNS neuronal activity. Thus, administration of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine provides a therapeutic window in which treatment of certain CNS disorders may be achieved, and certain side effects avoided. That is, an effective dose of the compound is sufficient to provide the desired effects on the CNS, but is insufficient (i.e., is not at a high enough level) to yield undesirable side effects. The salt described herein may be used to achieve these desirable effects.

Thus, the present invention relates to the (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate for use in therapy. The present invention further relates to the use of said salt in the manufacture of a medicament for treatment of a central nervous system disorder.

Also provided is a method for treatment of a central nervous system disorder, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate of the present invention.

Further provided is a method for treatment of disorders selected from the group consisting of age-associated memory impairment, mild cognitive impairment, pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Lewy body dementia, vascular dementia, Alzheimer's disease, Cognition in Down's Syndrome , Huntington's Disease, Parkinsonism, and Parkinson's Disease, stroke, AIDS dementia complex, attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, cognitive deficits of schizophrenia, and schizoaffective disorder.

Particular Disorders for which treatment is provided are Alzheimer's Disease and ADD/ADHD.

Pharmaceutical Compositions:

Pharmaceutical compositions containing (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate are therefore contemplated to be useful in the treatment of a variety of CNS disorders, including but not limited to neurodegenerative disorders, neuropsychiatric disorders, neurologic disorders, and addictions. Such pharmaceutical compositions can be used to treat cognitive deficits (age-related and otherwise), attentional disorders and dementias (including but not limited to those due to infectious agents or metabolic disturbances); to provide neuroprotection; to treat convulsions and multiple cerebral infarcts; to treat mood disorders, compulsions and addictive behaviors; to provide analgesia; and to control inflammation (such as mediated by cytokines and nuclear factor kappa B) and treat inflammatory disorders. Among the disorders, diseases and conditions, that pharmaceutical compositions of the present invention can be used to treat, are: age-associated memory impairment, mild cognitive impairment, pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Lewy body dementia, vascular dementia, Alzheimer's disease, Cognition in Down's Syndrome , Huntington's Disease, Parkinsonism, and Parkinson's Disease, stroke, AIDS dementia complex,

attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, cognitive deficits of schizophrenia, and schizoaffective disorder.

Particular Disorders which the pharmaceutical compositions described herein can be used to treat are Alzheimer's Disease and ADD/ADHD.

According to one embodiment of the present invention there is provided a pharmaceutical composition comprising as active ingredient a therapeutically effective amount of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate, in association with one or more pharmaceutically acceptable diluents, excipients and/or inert carriers.

The manner in which pharmaceutical compositions are administered can vary. The compositions can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al); topically (e.g., in lotion form); orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid; intravenously (e.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids); intrathecally; intracerebroventricularly; or transdermally (e.g., using a transdermal patch or by powder injection). Although it is possible to administer the compositions in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition for efficient and effective administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compositions can be administered in the form of a tablet, a hard gelatin capsule or as a time release capsule. The administration of the pharmaceutical compositions described herein can be intermittent, or at a gradual, continuous, constant or controlled rate to an animal, (e.g., a mammal such as a mouse, rat, cat, rabbit, dog, pig, cow, or monkey); but particularly is administered to a human subject.

The time of day and the number of times per day that a pharmaceutical composition as described herein is administered can vary. Administration preferably is such that the active ingredients of the pharmaceutical composition interact with receptor sites within the body of the subject that effect the functioning of the CNS. More specifically, in treating a CNS disorder administration preferably is such so as to optimize the effect upon those relevant receptor subtypes, which have an effect upon the functioning of the CNS, while minimizing the effects

upon muscle-type receptor subtypes. The appropriate dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. By "effective amount", "therapeutic amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disorder. Thus, when treating a CNS disorder, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject, and to modulate the activity of relevant nicotinic receptor subtypes (e.g., modulate neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder).

Prevention of a disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the reoccurrence of the symptoms of the disorder. The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount sufficient to modulate relevant receptors to affect neurotransmitter (e.g., dopamine) release, but the amount should be insufficient to induce effects on skeletal muscles and ganglia to any significant degree. The effective dose of compounds will of course differ from patient to patient but in general includes amounts starting where CNS effects or other desired therapeutic effects occur, but below the amount where muscular and ganglionic effects are observed. Typically, the effective dose of compounds may require administering the compound in an amount of less than 5 mg/kg of patient weight. Often, the compounds may be administered in an amount from less than about 1 mg/kg patent weight to less than about 100 μg/kg of patient weight, and occasionally from about 10 μg/kg to less than 100 μg/kg of patient weight. The foregoing effective doses typically represent that amount administered as a single dose, or as one or more doses administered over a 24 hours period. For human patients, the effective dose of the compounds may require administering the compound in an amount of at least about 1 mg, but not more than about 1000 mg, often not more than about 500 mg/ 24 hr. / patient.

In another embodiment the amount of the salt described herein effective to prevent or treat said central nervous system disorder disease is at least about 10 mg/patient/24 hours and does not exceed about 400 mg/patient/24 hours.

In yet a further embodiment the amount of the salt described herein administered is such that the subject does not experience a concentration of compound in plasma which exceeds 500 ng/ml.

(2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate can also can be administered in formulation compositions that incorporate other ingredients, such as those types of ingredients that are useful in formulating a diagnostic composition. Compositions useful as diagnostics can be employed as set forth in U.S. Patent Nos. 5,853,696 to Elmaleh et al., and 5,969,144 to London et al.

(2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine 1,5-naphthalenedisulfonate can also be formulated and/or administered in combination with other therapeutic compounds, such as those used in the treatment and or prevention of CNS disorders.

The examples are provided to illustrate the present invention, and should not be construed as limiting it. In the examples, all parts and percentages are by weight, unless otherwise noted.

Claims:

1. Substantially pure, stable and crystalline 1,5-naphthalenedisulfonate salt of (2S)-(4E)-N-methyl-5-[3-(5-isopropoxypyridin)yl]-4-penten-2-amine.

2. A salt according to claim 1 having XRPD diffraction peaks having d-values of 27.55, 6.94, 5.97, 4.29 and 3.77 Å.

3. A pharmaceutical composition comprising a salt according to claim 1 together with at least one pharmaceutically acceptable carrier, diluent or adjuvant.

4. A pharmaceutical composition comprising a salt according to claim 2 together with at least one pharmaceutically acceptable carrier, diluent or adjuvant.

5. A method of treating conditions and disorders associated with dysfunction of the central and autonomic nervous systems comprising administering to a subject in need thereof therapeutically effective amount of a compound according to claim 1.

6. Use of a compound according to claim 1 in the treatment of conditions and disorders associated with dysfunction of the central and autonomic nervous systems.

7. The method according to claim 6, wherein the central nervous system disorder is selected from the group consisting of age-associated memory impairment, mild cognitive impairment, pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Lewy body dementia, vascular dementia, Alzheimer's disease, Cognition in Down's Syndrome , Huntington's Disease, Parkinsonism, and Parkinson's Disease, stroke, AIDS dementia complex, attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, cognitive deficits of schizophrenia, and schizoaffective disorder.

8. The method according to claim 7, wherein the disorder is Alzheimer's disease or attention deficit hyperactivity disorder.

9. The method according to claim 6, wherein the amount effective to prevent or treat said central nervous system disorder disease is at least about 1 mg/patient/24 hours and does not exceed about 500 mg/patient/24 hours.

10. The method according to claim 6, wherein the amount effective to prevent or treat said central nervous system disorder disease is at least about 10 mg/patient/24 hours and does not exceed about 400 mg/patient/24 hours.

11. The method according to claim 6, wherein the amount administered is such that the subject does not experience a concentration of compound in plasma which exceeds 500 ng/ml.

12. A compound of claim 1 or 2 for use in therapy.

13. A compound according to claim 1 or 2, for use in treating of cognitive disorder(s) or indications with deficit(s) in cognition such as: age-associated memory impairment, mild cognitive impairment, pre-senile dementia, early onset Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, Lewy body dementia, vascular dementia, Alzheimer's disease, Cognition in Down's Syndrome , Huntington's Disease, Parkinsonism, and Parkinson's Disease, stroke, AIDS dementia complex, attention deficit disorder, attention deficit hyperactivity disorder, dyslexia, schizophrenia, schizophreniform disorder, cognitive deficits of schizophrenia, and schizoaffective disorder.

14. The use of claim 13 wherein the central nervous system disorder is Alzheimer Disease or attention deficit hyperactivity disorder.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/044191

A. CLASSIFICATION OF SUBJECT MATTER

C07D 213/63(2006.01)i, A61K 31/4412(2006.01)i, A61P 25/00(2006.01)i

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 213/63; A61K 31/554; C07D 213/38; A61K 31/55; A61K 31/44; C07D 213/62; A61K 31/4412; A61P 25/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: N-methyl-5-(3-(5-isopropoxypyridin)yl)-4-penten-2-amine, TC-1734, ispronicline, naphthalen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010-0234349 A1 (OLSEN GUNNAR M. et al.) 16 September 2010 See whole document	1-4,12-13
A	US 2007-0265314 A1 (GARY DULL et al.) 15 November 2007 See whole document	1-4,12-13
A	WO 99-65876 A1 (R.J. REYNOLDS TOBACCO COMPANY) 23 December 1999 See whole document	1-4,12-13

☐ 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 application or patent 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 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
25 September 2013 (25.09.2013)	**25 September 2013 (25.09.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
CHOI Won Chul
Telephone No. +82-42-481-5578

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/044191

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5~11, 14
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 5~11, 14 pertain to methods for treatment of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) and Rule 39.1(iv) of the Regulations under the PCT.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/044191

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0234349 A1	16/09/2010	EP 2083921 A2	05/08/2009
		EP 2255848 A2	01/12/2010
		EP 2255848 A3	06/04/2011
		WO 2008-028903 A2	13/03/2008
		WO 2008-028903 A3	14/08/2008
US 2007-0265314 A1	15/11/2007	AU 2007-249485 A1	22/11/2007
		AU 2007-249485 B2	01/11/2012
		BR PI0709781 A2	26/07/2011
		CA 2649961 A1	22/11/2007
		CN101472893 A	01/07/2009
		EP 2021326 A1	11/02/2009
		EP 2418201 A1	15/02/2012
		IL194833D0	03/08/2009
		JP 04-477097 B2	09/06/2010
		JP 2009-531465 A	03/09/2009
		KR 10-2009-0005369 A	13/01/2009
		US 2010-0048643 A1	25/02/2010
		US 8461344 B2	11/06/2013
		WO 2007-134034 A1	22/11/2007
WO 99-65876 A1	23/12/1999	AU 1997-27332 B2	04/01/2001
		AU 1999-42307 A1	05/01/2000
		AU 1999-46291 A1	07/02/2000
		AU 1999-46291 B2	26/09/2002
		AU 2000-44719 A1	02/11/2000
		AU 2000-53261 A1	28/12/2000
		AU 2003-282908 A1	23/04/2004
		AU 2003-282908 B2	28/05/2009
		CA 2252515 A1	30/10/1997
		CA 2252515 C	07/11/2006
		CA 2334923 A1	23/12/1999
		CA 2334923 C	29/09/2009
		CA 2337849 A1	27/01/2000
		CA 2337849 C	17/03/2009
		CA 2370206 A1	26/10/2000
		CA 2370206 C	27/09/2011
		CA 2376061 A1	14/12/2000
		CA 2501335 A1	15/04/2004
		CA 2501335 C	28/02/2012
		CA 2677519 A1	23/12/1999
		CA 2709735 A1	23/12/1999
		EP 0900200 A1	02/01/2003
		EP 0900200 B1	03/12/2008
		EP 0900200 B9	21/10/2009
		EP 1086082 A1	28/03/2001
		EP 1086082 B1	18/08/2004
		EP 1086082 B9	02/03/2005
		EP 1098888 A1	16/05/2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/044191

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EP 1171127 A2	16/01/2002
		EP 1171127 B1	14/09/2005
		EP 1185514 A1	13/03/2002
		EP 1556352 A1	27/07/2005
		EP 1997806 A1	03/12/2008
		EP 2253616 A1	24/11/2010
		ES2228054 T3	01/04/2005
		JP 04-240815 B2	18/03/2009
		JP 04-357001 B2	04/11/2009
		JP 04-896923 B2	14/03/2012
		JP 04-972608 B2	11/07/2012
		JP 2000-509041 A	18/07/2000
		JP 2002-518373 A	25/06/2002
		JP 2002-520401 A	09/07/2002
		JP 2002-542188 A	10/12/2002
		JP 2003-501416 A	14/01/2003
		JP 2006-511482 A	06/04/2006
		JP 2008-247903 A	16/10/2008
		JP 2008-255122 A	23/10/2008
		JP 2008-260774 A	30/10/2008
		JP 2010-229149 A	14/10/2010
		JP 2011-144192 A	28/07/2011
		KR 10-0568997 B1	15/12/2006
		KR 10-0593433 B1	28/06/2006
		KR 10-0816898 B1	26/03/2008
		US 06166048 A	26/12/2000
		US 2002-0032206 A1	14/03/2002
		US 2002-0052497 A1	02/05/2002
		US 2003-0087915 A1	08/05/2003
		US 2003-0125345 A1	03/07/2003
		US 2004-0214835 A1	28/10/2004
		US 2005-0131034 A1	16/06/2005
		US 2005-0148611 A1	07/07/2005
		US 2005-0282846 A1	22/12/2005
		US 2006-0264445 A1	23/11/2006
		US 2006-0293289 A1	28/12/2006
		US 2008-0139809 A1	12/06/2008
		US 2008-0214628 A1	04/09/2008
		US 2010-0121061 A1	13/05/2010
		US 2010-0160390 A1	24/06/2010
		US 2010-0204481 A1	12/08/2010
		US 2010-0222395 A1	02/09/2010
		US 6232316 B1	15/05/2001
		US 6344456 B1	05/02/2002
		US 6455554 B1	24/09/2002
		US 6489349 B1	03/12/2002
		US 6492399 B1	10/12/2002
		US 6555684 B2	29/04/2003
		US 6603011 B1	05/08/2003
		US 6958399 B2	25/10/2005

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/044191

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 6979695 B2	27/12/2005
		US 7045538 B2	16/05/2006
		US 7060826 B2	13/06/2006
		US 7307092 B2	11/12/2007
		US 7790757 B2	07/09/2010
		US 8288420 B2	16/10/2012
		WO 00-04000 A1	27/01/2000
		WO 00-62767 A2	26/10/2000
		WO 00-62767 A3	08/03/2001
		WO 00-75110 A1	14/12/2000
		WO 2004-031151 A1	15/04/2004
		WO 97-40011 A1	30/10/1997
		WO 99-65876 A1	23/12/1999