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(54) **Title**: METHOD OF TREATMENT OF DEPRESSION

(57) **Abstract**: The invention comprises a method of treatment of depression or depression- related disorders by a pharmaceutical agent exhibiting combined serotonergic or noradrenergic reuptake transporters and monoamine receptor activity.

METHOD OF TREATMENT OF DEPRESSION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to US Provisional Application No. 61/174,084, filed April 30, 2009, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Viloxazine (Emovit®, Vivalan®, Vivarint®, Vicilan®) is a bicyclic antidepressant morpholine derivative that inhibits the reuptake of norepinephrine. It is a racemic compound with two isomers, the S(-)-isomer being five times more pharmacologically active than the R(+)-isomer. Viloxazine hydrochloride has been approved in Italy, Belgium, the United States, England, Ireland, Germany, Portugal, Spain, the former Yugoslavia, France, Slovakia, for the treatment of clinical depression.

[0003] The principle pharmacology of viloxazine is believed to be the inhibition of noradrenergic reuptake transporters (155 nM) with very weak activity at the serotonin reuptake inhibitor (17.3 μm) (Tatsumi et al [1997] Eur J Pharmacol 340 (2-3): 249-58). The dose in adults varies from 150 to 800 mg per day. However, unlike the tricyclic antidepressants, viloxazine does not have marked antimuscarinic, cardiotoxic, or sedative properties. Side effects of viloxazine include nausea, vomiting, insomnia, loss of appetite, increased erythrocyte sedimentation, EKG and EEG anomalies, epigastric pain, diarrhea, constipation, vertigo, orthostatic hypotension, edema of the lower extremities, dysarthria, tremor, psychomotor agitation, mental confusion, inappropriate secretion of antidiuretic hormone, increased transaminases, seizure, and increased libido (Chebili S, Abaoub A, Mezouane B, Le Goff JF (1998). "Antidepressants and sexual stimulation: the correlation" L'Encephale 24 (3): 180-4.)

[0004] The current invention discloses a method of treatment of depression with viloxazine that enhances clinical response while minimizing incidence and severity of side effects.

SUMMARY OF THE INVENTION

[0005] The invention provides a method of identifying compounds for the treatment of depression and/or similar disorders, comprising (1) selecting one or a combination of active agents with known activity inhibiting either serotonin or noradrenergic reuptake transporters; (2) conducting a receptor screening assay on the selected agent(s) to identify activity on at least one dopaminergic, serotonergic or gabaergic receptor where the activity is known to inhibit depression or where the opposite activity is associated with depression (e.g., where a compound is determined to be a receptor antagonist and if stimulation (agonism) of that receptor is associated with the onset or worsening of depression); (3) determining if said activity is agonistic or antagonistic; (4) selecting among the screened active agents at least one that targets the most diverse types of depression-associated receptors; and (5) optimizing the total dosage of the selected active agent(s).

[0006] Identification of monoamine agonist / antagonist activity in agents that inhibit serotonin or noradrenergic reuptake is important, since it allows for selection of drugs that have more than one therapeutic target (e.g. both 5HT7 and noradrenergic reuptake transporter). This is superior to taking a combination of therapies to achieve multiple targets because of the enhanced patient compliance with the reduced pill load. It also can lead to a lower dose, since different receptor activities may be additive, or even synergistic, in their effect.

[0007] Use of molecules that target a specific class of receptors with a limited distribution in the brain is also potentially beneficial in that it limits the potential for side effects. This restricted set of neural pathways is less likely to have “off-target” effect in the systems not involved in the desired activity.

[0008] In one embodiment, the invention comprises a method of treatment of depression and depression-related disorders including, but not limited, to mood disorders such as bipolar disorder or disorders where depression may be a co-morbid syndrome, including but not limited to, fibromyalgia, by a pharmaceutical agent exhibiting both serotonin or noradrenergic reuptake activity and 5-HT7 antagonistic activity.

[0009] In another embodiment, the invention provides a method of treatment of depression and depression related disorders by a pharmaceutical agent exhibiting combined serotonin or noradrenergic reuptake activity and 5-HT7 antagonistic activity, wherein the total dosage of the pharmaceutical agent is smaller than the dosage anticipated on the premise of the serotonin or noradrenergic reuptake activity only.

[0010] In yet another embodiment of the invention, the pharmaceutical agent is viloxazine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] **Figure 1** shows a competition curve obtained with compound SPN-809V with human 5-HT7 receptor.

[0012] **Figure 2** shows the agonist effect of the compound SPN-809V with human 5HT7 receptor.

[0013] **Figure 3** shows the antagonist effect of the compound SPN-809V with human 5HT7 receptor.

DETAILED DESCRIPTION OF THE INVENTION

[00014] Unless otherwise specified, "a" or "an" means "one or more." Notwithstanding the well-documented conventional understanding in the art that viloxazine exerts its pharmaceutical activity by inhibiting noradrenergic reuptake, the present invention is based on the unexpected discovery that viloxazine also has specific antagonist activity at the 5-HT7 (serotonin) receptor. Without being held to or bound by theory, the present invention is thought to take advantage of this discovery. In one embodiment, for example, the present invention provides a

method of treating depression using a dose of viloxazine that is substantially below what is currently deemed therapeutic. Significantly, lower daily dosing of the viloxazine can result in the diminishing frequency and severity, if at all, of the adverse effects commonly associated with the treatment of depression using viloxazine.

[0015] In a preferred embodiment, the invention provides a method of treatment of depression or depression-related disorders in human subjects by administering viloxazine in the total daily dose that is at least 10% lower than the current minimally effective dose of 2.14 mg/kg. In other embodiments, the dose is 15% lower, 25% lower, 35% lower, and 50% lower than the current dose. Dosage ranges of 1.1 mg/kg/day to 9.7 mg/kg/day or approximately 20 to 800 mg for pediatric (aged 6 to 17) and adult population are also provided.

[0016] According to the invention, viloxazine can be administered in the amount of from 100 to 600 mg/day. In another embodiment, the daily dose of viloxazine constitutes from 150 to 400 mg/day. In yet further embodiment of the invention, viloxazine is administered in the amount of up to 300 mg/day.

[0017] In another embodiment, the invention encompasses a method of treatment of depression or depression-related disorders with viloxazine that is characterized by an improved adverse effect profile. The adverse effects that are diminished by the method of the present invention include, but are not limited to, nausea, vomiting, insomnia, loss of appetite, increased erythrocyte sedimentation, EKG and EEG anomalies, epigastric pain, diarrhea, constipation, vertigo, orthostatic hypotension, edema of the lower extremities, dysarthria, tremor, psychomotor agitation, mental confusion, inappropriate secretion of antidiuretic hormone, increased transaminases, seizure, and increased libido. Hence, the inventive method provides for the treatment of depression without, or at least with far less frequency than with conventional viloxazine-treatment, one, two, six or more of these listed side effects. The efficacy and the adverse effect profile of the lower dose treatment of the current invention are evaluated in a randomized, placebo controlled trial.

Viloxazine activity on 5-HT receptors

[0018] A heterologous competition assay was to determine the relative affinity of viloxazine for 5-HT receptors. Briefly, recombinant 5-HT7 receptors were expressed in a CHO cell line. The receptors were then saturated with a tritiated receptor-specific ligand at concentrations known to be saturating. Thereupon, 10 µm viloxazine was added to the cells in the presence of non-specific ligand and incubated. In this way, viloxazine is allowed to "compete" with the receptor-specific ligand, such that greater displacement (i.e., % inhibition) is indicative to greater binding strength of viloxazine at a given receptor. "Specific binding" refers here to the difference in the binding of the ligand to the receptors in the presence and absence of an excess of the viloxazine. The conditions and results of the assay are summarized in the **Table 1**.

[0019] **Table 1.** Conditions of the displacement assay at select serotonin receptors for viloxazine

Receptor	Ligand	Conc.	Non-specific	Incubation	% Inhib.	Detection method
5-HT1A *(h)*	[^{3}H]8-OH-DPAT	0.3 nM	8-OH-DPAT (10 µM)	60 min/22°C	66	Scintillation counting
5-HT1B	[^{125}I]CYP (+ 30 µM (-)propranolol)	0.1 nM	serotonin (10 µM)	120 min/37°C	78	Scintillation counting
5-HT1D	[^{3}H]serotonin	1 nM	serotonin (10 µM)	60 min/22°C	18	Scintillation counting
5-HT2A *(h)*	[^{3}H]ketanserin	0.5 nM	ketanserin (1 µM)	60 min/22°C	-17*	Scintillation counting
5-HT2C *(h)*	[^{3}H]mesulergine	1 nM	RS-102221 (10 µM)	60 min/37°C	56	Scintillation counting
5-HT3 *(h)*	[^{3}H]BRL 43694	0.5 nM	MDL 72222 (10 µM)	120 min/22°C	18	Scintillation counting
5-HT4e *(h)*	[^{3}H]GR 113808	0.3 nM	serotonin (100 µM)	60 min/37°C	16	Scintillation counting
5-HT5A *(h)*	[^{3}H]LSD	1 nM	serotonin (100 µM)	60 min/37°C	15	Scintillation counting
5-HT6 *(h)*	[^{3}H]LSD	2 nM	serotonin (100 µM)	120 min/37°C	6	Scintillation counting

5-HT7 *(h)*	[^{3}H]LSD	4 nM	serotonin (10 μM)	120 min/22°C	70	Scintillation counting

* A negative number reflects 0% inhibition. Since % inhibition equals (100 minus measured specific binding in the presence of SPN809V) / control specific binding), a negative number represents a condition where the binding of the radioactive test ligand was greater in the presence of SPN-809V. This reflects either the variability in the radioactive control ligand binding or facilitation by the test ligand.

[0020] The affinity of viloxazine for 5-HT7 receptors was further characterized by determining the IC50 (i.e., the concentration of viloxazine that can inhibit 50% of control specific binding). For this experiment, a range of viloxazine concentrations was selected for the ligand blocking assay. The IC50 was determined using non-linear regression analysis of the competition curves using Hill equation curve fitting. The inhibition constants Ki were calculated using Cheng Prusoff equation. Ki is defined as the concentration of the competing ligand (viloxazine) that bound to half the binding sites at equilibrium in the absence of radioligand or other competitors, The results of the affinity assay are summarized in T**ables 2** and **3**, and in **Fig.1**.

Table 2. IC_{50} Determination Data

Receptor	Concentration(M)	% of Control Specific Binding		
		1st	2nd	Mean
5-HT_{1A} *(h)*	3.0E-08	97.8	99.8	98.8
	1.0E-07	93.8	96.9	95.4
	3.0E-07	104.7	110.3	107.5
	1.0E-06	104.8	109.1	107.0
	3.0E-06	76.5	71.4	73.9
	1.0E-05	32.5	41.3	36.9
	3.0E-05	21.9	19.6	20.7
	1.0E-04	5.3	5.8	5.5
5-HT_{1B}	3.0E-08	102.0	99.9	101.0
	1.0E-07	97.6	92.4	95.0
	3.0E-07	92.4	82.7	87.6
	1.0E-06	77.7	79.0	78.4
	3.0E-06	61.5	52.6	57.1
	1.0E-05	36.6	27.1	31.9
	3.0E-05	13.7	4.5	9.1
	1.0E-04	-10.4	-12.4	-11.4
5-HT_{2C} *(h)*	3.0E-08	97.9	125.8	111.9
	1.0E-07	116.6	111.5	114.0
	3.0E-07	92.9	102.7	97.8
	1.0E-06	108.2	104.2	106.2
	3.0E-06	90.6	91.9	91.3
	1.0E-05	61.6	63.1	62.3
	3.0E-05	33.1	36.6	34.8
	1.0E-04	8.4	14.3	11.4
5-HT_{7} *(h)*	3.0E-08	90.6	92.7	91.7
	1.0E-07	102.9	94.2	98.5
	3.0E-07	80.4	85.1	82.7
	1.0E-06	73.5	66.5	70.0
	3.0E-06	48.2	60.2	54.2
	1.0E-05	27.3	27.9	27.6
	3.0E-05	15.3	13.2	14.3
	1.0E-04	6.5	8.1	7.3

Table 3. Summary of IC50 determination at select serotonin receptors for Viloxazine.

Assay	Reference compound	IC_{50} (M)	K_i (M)	$n_{(H)}$
5-HT_{1A} *(h)*	8-OH-DPAT	7.1E-06	4.5E-06	1.3
5-HT_{1B}	serotonin	3.8E-06	2.3E-06	1.0
5-HT_{2C} *(h)*	RS-102221	1.4E-05	6.4E-06	1.0
5-HT_7 *(h)*	serotonin	3.2E-06	1.2E-06	0.8

[0021] The nature of the binding (i.e., agonist or antagonist) was next determined. Briefly, an assay was designed that examined the agonist effect on the 5HT7 receptor, i.e., the generation of cAMP or the blockade of this effect when stimulated by a 5HT7 agonist, serotonin. This was also done with a range of concentrations to determine the relative agonist versus antagonist binding Ki. The EC_{50} values (concentration producing a half-maximal specific response) and IC_{50} values (a concentration causing a half-maximal inhibition of the control-specific agonist response) were determined by a non-linear regression analysis of the concentration-response curves generated with mean replicate values using Hill equation curve fitting. The apparent dissociation constants for antagonists K_b were calculated using the modified Cheng Prusoff equation.

[0022] The conditions of the screening are represented in **Table 4**. Results of the functional assays are seen in **Figures 2** (agonist assay) and **3** (antagonist assay). The agonist assay demonstrated no measurable response (**Figure 2**). The antagonist assay yielded a weak response with an IC_{50} greater than 3.0×10^{-5} M.

Table 4. Conditions for 5HT7 Functional Assay

Assay	Reference compound	Incubation conditions	Reaction product	Method of detection
5-HT_7 *(h)* *(agonist effect)*	none	45 min/37° C	cAMP	HTRF
5-HT_7 *(h)* *(antagonist effect)*	serotonin	45 min/37° C	cAMP	HTRF

[0023] All of the publications, patent applications and patents cited in this specification, including the following references, are incorporated herein by reference in their entirety.

1. Vanhoenacker P, Haegeman G, Leysen JE. 5-HT7 receptors: current knowledge and future prospects. Trends Pharmacol Sci 2000;21(2):70-7.
2. Lucchelli A, Santagostino-Barbone MG, D'Agostino G, Masoero E, Tonini M. The interaction of antidepressant drugs with enteric 5-HT7 receptors. Naunyn Schmiedebergs Arch Pharmacol 2000;362(3):284-9.
3. Hedlund PB, Huitron-Resendiz S, Henriksen SJ, Sutcliffe JG. 5-HT7 receptor inhibition and inactivation induce antidepressant like behavior and sleep pattern. Biol Psychiatry 2005;58 (10):831-7.

[0024] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

WHAT IS CLAIMED IS:

1. A method of treating depression or depression-related disorders in a patient, comprising administering to the patient a dose of viloxazine that less than about 1.95 mg/kg/day, wherein the treatment diminishes the frequency or severity of adverse effects of doses of viloxazine greater than about 1.95 mg/kg/day.
2. A method of treating depression or depression-related disorders comprising:
    a. selecting several active agents with known activity inhibiting either serotonin or noradrenergic reuptake transporters;
    b. conducting a receptor screening assay on these same agents to identify activity for at least one dopaminergic, serotonergic or gabaergic receptor where the activity is known to inhibit depression or opposite activity is associated with depression;
    c. determining if said activity is agonistic or antagonistic in nature;
    d. by the results of steps b) and c), choosing among the screened active agents at least one that targets the most diverse types of depression-associated receptors;
    e. optimizing the total dosage of the active agent(s), taking into account results of steps b)-d).
3. A method of treating depression and/or or depression-related disorders by a pharmaceutical agent exhibiting combined serotonin or noradrenergic reuptake inhibition and 5-HT7 antagonistic activity, wherein the total dosage of the pharmaceutical agent is less than the dosage anticipated on the basis of only noradrenergic reuptake transporter activity.
4. The method of claim 2, wherein the pharmaceutical agent is viloxazine.
5. The method of claim 3, wherein the pharmaceutical agent is administered in a dose range of from 20 to 800 mg/day.
6. The method of claim 3, wherein the pharmaceutical agent is administered in a dose range of from 1.1 mg/kg/day to 9.7 mg/kg/day.
7. The method of claim 3, wherein the pharmaceutical agent has a dose that is 15% lower, 25% lower, 35% lower, or 50% lower than 2.14mg/kg.

8. The method of claim 3, wherein there is a decrease in the side effects associated with viloxazine administration.
9. A pharmaceutical composition for the treatment depression or a depressive disorder in a patient comprising less than about 10 mg of viloxazine and a pharmaceutical carrier.

Figure 1

COMPETITION CURVE OBTAINED WITH COMPOUND SPN-809V
AT THE HUMAN 5-HT7 RECEPTOR

IC50 = 3.2E-06 M
nH = 0.8

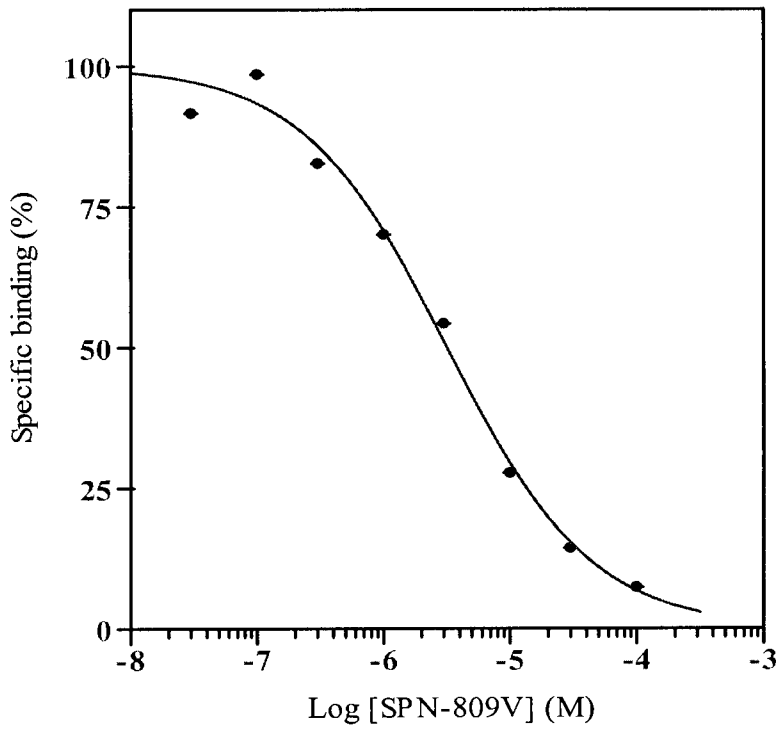


Figure 2

AGONIST EFFECT OF COMPOUND SPN-809V
AT THE HUMAN 5-HT7 RECEPTOR

EC50 not calculable

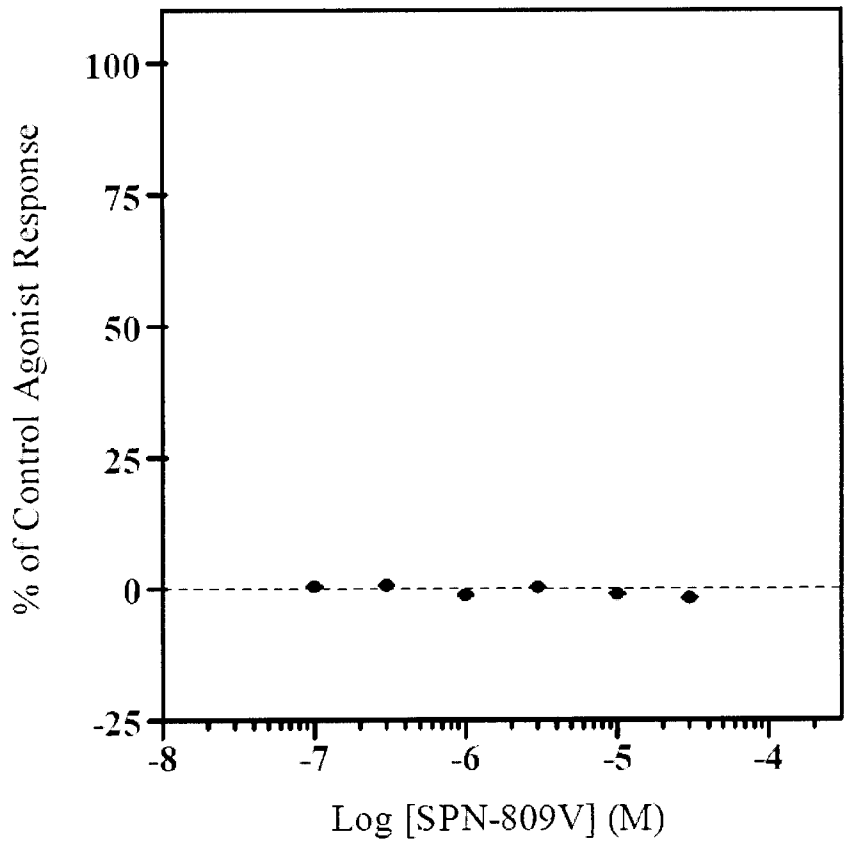
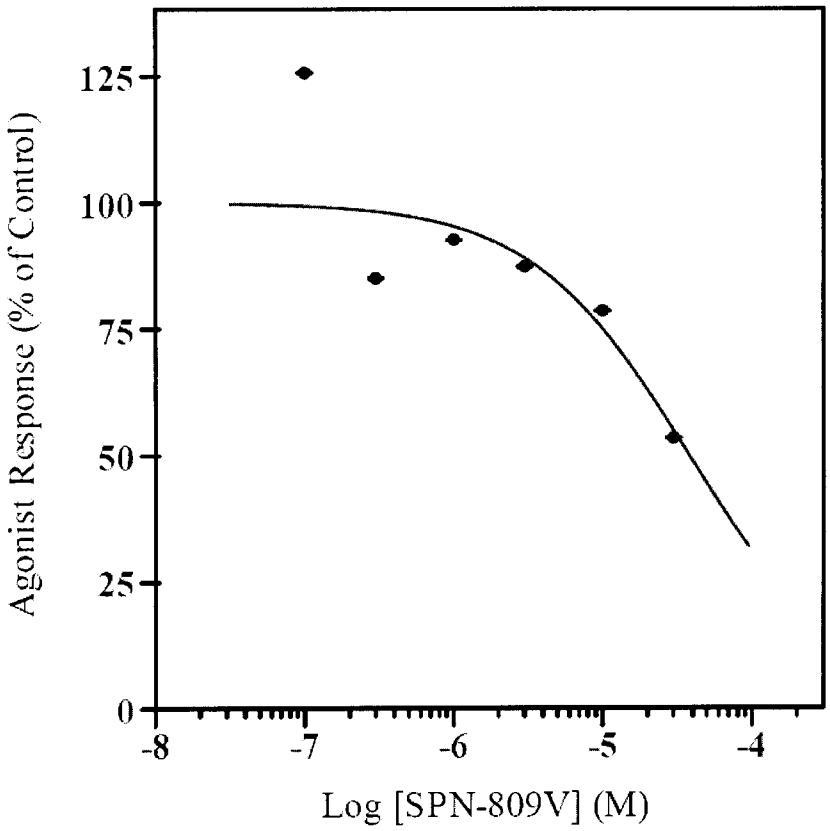


Figure 3

ANTAGONIST EFFECT OF COMPOUND SPN-809V
AT THE HUMAN 5-HT7 RECEPTOR

IC50 > 3.0E-05 M



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/32974

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/535 (2010.01)
USPC - 514/231.2
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)
USPC - 514/231.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/231.5, 238.8, 239.2 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used: viloxazine, mg/kg, dose, 5-HT7, receptor, antagonist, noradrenergic, reuptake/transporter, antidepressant, side effect

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Bayliss et al. Blood level studies with viloxazine hydrochloride in man. Br. J. Clin. Pharmacol., 1975, Jun; 2(3):209-14. Esp: p 209, left col, ln 7-16 & right col, 4th para; p 210, left col, 1st - 4th para; p 211, Figure 1	1, 9 --- 2-8
Y	Lucchelli et al. The interaction of antidepressant drugs with enteric 5-HT7 receptors. Naunyn-Schmiedebergs Arch. Pharmacol., 2000, 362(3):284-289. Esp: p 285, left col, 2nd - 4th para; p 287, right col, 1st para to p 288, left col, 3rd para 5-ht7 receptor antidepressant	2-8
A	Hedlund et al. 5-HT7 receptor inhibition and inactivation induce antidepressant like behavior and sleep pattern. Biol. Psychiatry, 2005, 58(10):831-837. Entire disclosure	2-3
A	Tatsumi et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur. J. Pharmacol., 1997, 340(2-3):249-258. Entire disclosure,esp: pp 252-253, Table 1 2-3	2-3
A	US 4,260,606 A (Cale, Jr. et al.) 07 April 1981 (07.04.1981) entire disclosure, esp: col 7, Table 1	1, 6, 7
A	US 2006/0003992 A1 (Wong et al.) 05 January 2006 (05.01.2006) entire disclosure, para [0010], [0029], [0034], [0042] 3-8 side same vilo, vilo+dose	3-8
A/P	US 2010/0069390 A1 (Breder) 18 March 2010 (18.03.2010) entire disclosure	1-8

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

* 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 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
23 June 2010 (23.06.2010)	05 AUG 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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