



HU000031070T2

(19) **HU****MAGYARORSZÁG****Szellemi Tulajdon Nemzeti Hivatala**(11) Lajstromszám: **E 031 070**(13) **T2**

EURÓPAI SZABADALOM SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 08 732084**(22) A bejelentés napja: **2008. 03. 13.**

(96) Az európai bejelentés bejelentési száma:

EP 20080732084

(97) Az európai bejelentés közzétételi adatai:

EP 2125698 A1 **2008. 11. 20.**

(97) Az európai szabadalom megadásának meghirdetési adatai:

EP 2125698 B1 **2016. 08. 31.**(51) Int. Cl.: **C07C 217/74** (2006.01)**C07B 59/00** (2006.01)**C07C 211/64** (2006.01)**C07D 265/16** (2006.01)**C07C 215/64** (2006.01)

(86) A nemzetközi (PCT) bejelentési szám:

PCT/US 08/056780

(87) A nemzetközi közzétételi szám:

WO 08140859

(30) Elsőbbségi adatok:

895049 P **2007. 03. 15.** **US****944399 P** **2007. 06. 15.** **US**

(73) Jogosult(ak):

**Auspex Pharmaceuticals, Inc., La Jolla, CA
92037 (US)**

(72) Feltaláló(k):

GANT, Thomas, G., Vista, CA 92081-8356 (US)**SEPEHR, Sarshar, Vista, CA 92081-8356 (US)****WOO, Soon, Hyung, Vista, CA 92081-8356 (US)**

(74) Képviselő:

**Danubia Szabadalmi és Jogi Iroda Kft.,
Budapest**

(54)

Deuterált d9-venlafaxin

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

A fordítást a szabadalmas az 1995. évi XXXIII. törvény 84/H. §-a szerint nyújtotta be. A fordítás tartalmi helyességét a Szellemi Tulajdon Nemzeti Hivatala nem vizsgálta.



(11)

EP 2 125 698 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
31.08.2016 Bulletin 2016/35

(51) Int Cl.:
C07C 217/74 ^(2006.01) **C07C 215/64** ^(2006.01)
C07D 265/16 ^(2006.01) **C07B 59/00** ^(2006.01)
C07C 211/64 ^(2006.01)

(21) Application number: **08732084.2**

(86) International application number:
PCT/US2008/056780

(22) Date of filing: **13.03.2008**

(87) International publication number:
WO 2008/140859 (20.11.2008 Gazette 2008/47)

(54) **DEUTERATED d9-VENLAFAXINE**
DEUTERIERTES d9-VENLAFAXINE
d9-VENLAFAXINE DEUTERE

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HR HU IE IS IT LI LT LU LV MC MT NL NO PL PT
RO SE SI SK TR**

(30) Priority: **15.03.2007 US 895049 P**
15.06.2007 US 944399 P

(43) Date of publication of application:
02.12.2009 Bulletin 2009/49

(60) Divisional application:
12176584.6 / 2 514 740
16179352.6

(73) Proprietor: **Auspex Pharmaceuticals, Inc.**
Vista, CA 92081-8356 (US)

(72) Inventors:
• **GANT, Thomas, G.**
Vista, CA 92081-8356 (US)
• **SEPEHR, Sarshar**
Vista, CA 92081-8356 (US)
• **WOO, Soon, Hyung**
Vista, CA 92081-8356 (US)

(74) Representative: **Smaggasgale, Gillian Helen**
WP Thompson
138 Fetter Lane
London EC4A 1BT (GB)

(56) References cited:
WO-A-2007/064697 US-A1- 2007 149 622

- **B. R. DENT: "Certificate of Analysis Venlafaxine-d6 HCl"[Online] 26 April 2006 (2006-04-26), XP002489186 BDG Synthesis, Wellington, NZ Retrieved from the Internet: URL: http://www.bdg.co.nz/uploads/tx_chem/OA_venlafaxine-d6.pdf [retrieved on 2008-07-18]**
- **B. R. DENT: "Certificate of Analysis O-Desmethylvenlafaxine-d6 HCl"[Online] 26 April 2006 (2006-04-26), XP002489187 BDG Synthesis, Wellington, NZ Retrieved from the Internet: URL: http://www.bdg.co.nz/uploads/tx_chem/OA_Odesmethylvenlafaxine-d6.pdf [retrieved on 2008-07-18]**
- **BASAPPA KAVITHA C V ET AL: "Simple and an efficient method for the synthesis of 1-[2-dimethylamino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol hydrochloride: (+/-) venlafaxine racemic mixtures" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 12, 21 June 2004 (2004-06-21), pages 3279-3281, XP004841389 ISSN: 0960-894X cited in the application**
- **LIU ET AL: "Simultaneous stereoselective analysis of venlafaxine and O-desmethylvenlafaxine enantiomers in human plasma by HPLC-ESI/MS using a vancomycin chiral column" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL SCIENCES & APPLICATIONS, ELSEVIER, AMSTERDAM, NL, vol. 850, no. 1-2, 30 November 2006 (2006-11-30), pages 183-189, XP022044059 ISSN: 1570-0232**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 125 698 B1

- FRANCOIS DESCHAMPS: "Catalog 2007-08"
[Online] October 2007 (2007-10), SYNTHÈSE
APTOCHEM , MONTRÉAL, CANADA ,
XP002490781 Retrieved from the Internet:
URL:<http://www.aptochem.com/Catalog.pdf>>
[retrieved on 2008-07-17] page 44
- FOSTER A B: "Deuterium isotope effects in the
metabolism of drugs and xenobiotics:
implications for drug design", ADVANCES IN
DRUG RESEARCH, ACADEMIC PRESS,
LONDON, GB, vol. 14, 1 January 1985
(1985-01-01), pages 1-40, XP009086953, ISSN:
0065-2490

Remarks:

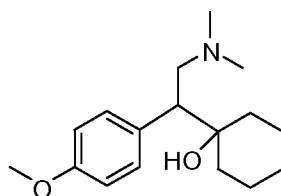
The file contains technical information submitted after
the application was filed and not included in this
specification

Description**FIELD**

[0001] The present invention is directed to inhibitors of the uptake of monoamine neurotransmitters and pharmaceutically acceptable salts and prodrugs thereof, the chemical synthesis thereof, and the medical use of such compounds for the treatment and/or management of psychotropic disorders, anxiety disorder, generalized anxiety disorder, depression, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, hot flashes, senile dementia, migraine, hepatopulmonary syndrome, chronic pain, nociceptive pain, neuropathic pain, painful diabetic retinopathy, bipolar depression, obstructive sleep apnea, psychiatric disorders, premenstrual dysphoric disorder, social phobia, social anxiety disorder, urinary incontinence, anorexia, bulimia nervosa, obesity, ischemia, head injury, calcium overload in brain cells, drug dependence, attention deficit hyperactivity disorder, fibromyalgia, irritable bowel syndrome, and/or premature ejaculation.

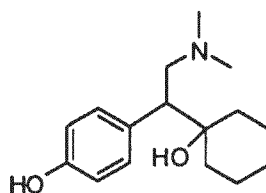
BACKGROUND

[0002] Venlafaxine (Effexor®) (1-[2-dimethylamino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol) is a therapeutic agent whose efficacy is hypothesized to act through inhibition of serotonin reuptake and, potentially, norepinephrine reuptake in neuronal cells. Norepinephrine activity modulation is purported to occur at higher doses of venlafaxine than those required for serotonin activity modulation. Venlafaxine also has the potential to modulate dopamine activity, though the interaction *in vitro* is weak and the clinical relevance of this interaction is unknown. The drug substance is sold as a 50/50 racemic mixture of R and S-enantiomers.



Venlafaxine

[0003] Venlafaxine is converted *in vivo* by oxidative and conjugative degradation to multiple metabolites, at least 48 of which are documented. The major metabolic pathways include phase I metabolism leading to demethylation at the oxygen and/or nitrogen centers and cyclohexyl ring hydroxylation, as well as phase II metabolism including glucuronidation of the hydroxylated metabolites. Because venlafaxine is metabolized by polymorphically-expressed isozymes of cytochrome P₄₅₀ including CYPs 2C19 and 2D6, and because it can act as an inhibitor of CYP2D6, its application in polypharmacy is necessarily complex and has potential for adverse events. These CYPs are involved in the metabolism of medications that are typically prescribed concurrently with venlafaxine. This phenomenon increases interpatient variability in response to polypharmacy. An example of the critical need for improvement of venlafaxine is the observed interpatient variability in "poor metabolizers" having either defective CYP2D6 alleles or total lack of CYP2D6 expression. These patients fail to convert venlafaxine to its equipotent metabolite, O-desmethylvenlafaxine. Venlafaxine also suffers from a short half-life relative to the majority of serotonin reuptake inhibitors. The half-life of venlafaxine in humans is ~5 hours, while its active metabolite has a T_{1/2} of ~11 hours. As a consequence of its 5 - 11 hour pharmacological half-life, those taking venlafaxine are at significant risk of SRI discontinuation symptoms if the drug is abruptly discontinued. Furthermore, in order to overcome its short half-life, the drug must be taken 2 (BID) or 3 (TID) times a day. An extended release formulation of Venlafaxine is also available; however, it does not significantly increase the carryover of drug to the next day. Most other serotonin reuptake inhibitors (SRIs) have half-lives ≥ 24 hours. The half-life of the primary active metabolite, O-desmethylvenlafaxine ("ODV"), is longer than that of the parent compound; however, it is still desirable and beneficial to increase the half-life of ODV.



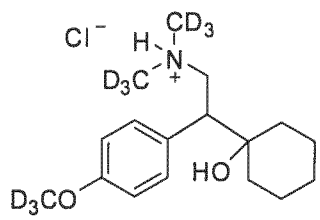
O-desmethylvenlafaxine

Commercially available deuterated venlafaxine derivatives are described in B.R. Dent, "Certificate of Analysis Venlafaxine-d6 HCl", [Online] 26 April 2006, XP002489186, BDG Synthesis, Wellington, NZ; http://www.bdg.co.nz/uploads/tx_chem/COA_venlafaxine-d6.pdf. B.R. Dent, "Certificate of Analysis of O-Desmethylvenlafaxine-d6 HCl", [Online] 26 April 2006, XP002489187, BDG Synthesis, Wellington, NZ; http://www.bdg.co.nz/uploads/tx_chem/COA_Odesmethylvenlafaxine-d6.pdf, and Francois Dechamps, "Catalog 2007-08", [Online] October 2007 (2007-10), Synthese Aptochem, Montreal, Canada, XP002490781, <http://www.aptochem.com/catalog.pdf>. WO2007/064697 and its US equivalent, US2007/149622, describe substituted phenethylamines with serotonergic and/or norepinephrinergic activity which are deuterium enriched.

The effects of the deuterium isotope effect on the metabolism of drugs and xenobiotics is described in Foster, A.B., "Deuterium isotope effects in the metabolism of drugs and xenobiotics: implications for drug design", Advances in Drug Research, Academic Press, London, GB, Vol. 14, 1 January 1985, pages 1-40, XP009086953, ISSN: 0065-2490.

SUMMARY OF INVENTION

[0004] Disclosed herein is a polymorph of the hydrochloride salt of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride having the structural formula:



wherein said polymorph exhibits high-intensity diffraction peaks at diffraction angles (2θ) of 6.683, 10.201, 13.441, 15.517, 18.198, 19.719, 20.258, 21.68, 22.658, 25.543, 28.022, and 35.02 in X-ray powder diffraction analysis. Also disclosed herein is a polymorph as described above wherein said polymorph has an x-ray diffraction spectrum substantially the same as shown in Figure 2.

Further disclosed herein is a polymorph as described wherein said polymorph has an X-ray powder diffraction spectrum having characteristic peaks expressed in degrees (2θ) at approximately:

2-theta	RI	2 -theta	RI	2-theta	RI
6.683	15.5	22.658	24.8	31.379	8.2
10.201	93.6	23.923	2.7	31.978	9.1
13.441	27.8	25.322	9.6	32.28	10.5
15.014	7.6	25.543	22.4	32.701	6.5
15.517	66.2	26.502	6.7	32.981	2.3
16.458	1.5	27.122	9.5	34.12	9.1
16.84	10.3	27.557	5.5	35.02	33.4
17.206	2.7	28.022	20.9	36.024	3.1
18.198	41	28.64	4.4	36.842	2.6
19.719	34.1	29.241	10.6	37.5	6.7

(continued)

2-theta	RI	2 -theta	RI	2-theta	RI
20.258	100	29.659	7.1	38.341	3.9
21.68	71.2	31.079	11.9	38.753	1.2

[0005] The polymorph of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug thereof may be provided as a pharmaceutical composition, in combination with one or more pharmaceutically acceptable excipients or carriers.

[0006] The polymorph of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug thereof may be used in a method for treating, preventing, or ameliorating one or more symptoms of a monoamine-mediated disorder, which comprises administering to a subject a therapeutically effective amount of at least the polymorph of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0007] The polymorph of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug thereof may be used in a method for treating, preventing, or ameliorating one or more symptoms of the following disorders, including, but not limited to: psychotropic disorders, anxiety disorders, generalized anxiety disorder, depression, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, hot flashes, senile dementia, migraine, hepatopulmonary syndrome, chronic pain, nociceptive pain, neuropathic pain, painful diabetic retinopathy, bipolar depression, obstructive sleep apnea, psychiatric disorders, premenstrual dysphoric disorder, social phobia, social anxiety disorder, urinary incontinence, anorexia, bulimia nervosa, obesity, ischemia, head injury, calcium overload in brain cells, drug dependence, Gilles de la Tourette syndrome, Shy Drager syndrome, vasomotor flushing, chronic fatigue syndrome, cognition enhancement, attention deficit hyperactivity disorder, fibromyalgia, irritable bowel syndrome, and/or premature ejaculation, which comprises administering to a subject a therapeutically effective amount of the polymorph of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[0008] The polymorph of the present invention or a pharmaceutically acceptable salt, solvate, or prodrug thereof may be used in methods of modulating a target selected from the group consisting of a serotonin receptor, a norepinephrine receptor, a serotonin transporter, and a norepinephrine transporter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009]

FIGURE 1 is an X-ray powder diffraction spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form A) which was prepared and isolated according to the process disclosed in Example 34.

FIGURE 2 is an X-ray powder diffraction spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form B) which was prepared and isolated according to the process disclosed in Example 35.

FIGURE 3 is an X-ray powder diffraction spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form C) which was prepared and isolated according to the process disclosed in Example 36.

FIGURE 4 is an X-ray powder diffraction spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form D) which was prepared and isolated according to the process disclosed in Example 37.

FIGURE 5 is an X-ray powder diffraction spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form E) which was prepared and isolated according to the process disclosed in Example 38.

FIGURE 6 is an X-ray powder diffraction spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form F) which was prepared and isolated according to the process disclosed in Example 39.

FIGURE 7 is a solid state infrared absorption spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form A) which was prepared and isolated according to the process disclosed in Example 34.

FIGURE 8 is a solid state infrared absorption spectrum of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride, Form B) which was prepared and isolated according to the process disclosed in Example 35.

FIGURE 9 is a solid state infrared absorption spectrum of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₉-venlafaxine hydrochloride, Form C) which was prepared and isolated according to the process disclosed in Example 36.

FIGURE 10 is a solid state infrared absorption spectrum of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₉-venlafaxine hydrochloride, Form D) which was prepared and isolated according to the process disclosed in Example 37.

FIGURE 11 is a solid state infrared absorption spectrum of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₉-venlafaxine hydrochloride, Form E) which was prepared and isolated according to the process disclosed in Example 38.

FIGURE 12 is a solid state infrared absorption spectrum of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₉-venlafaxine hydrochloride, Form F) which was prepared and isolated according to the process disclosed in Example 39.

FIGURE 13 is a thermogravimetric analysis (TGA) of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₉-venlafaxine hydrochloride, Form B) which was prepared and isolated according to the process disclosed in Example 35, heated at 10°C/min from ambient temperature to approximately 700°C and then in regular mode to 1000°C, in a nitrogen atmosphere (25 cc/min).

FIGURE 14 is a thermogravimetric analysis (TGA) of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₉-venlafaxine hydrochloride, Form C) which was prepared and isolated according to the process disclosed in Example 36, heated at 10°C/min from ambient to approximately 700°C and then in regular mode to 1000°C, in a nitrogen atmosphere (25 cc/min).

FIGURE 15 is a thermogravimetric analysis (TGA) spectrum of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₉-venlafaxine hydrochloride, Form E) which was prepared and isolated according to the process disclosed in Example 38, heated at 10°C/min from ambient to approximately 700°C and then in regular mode to 1000°C, in a nitrogen atmosphere (25 cc/min).

[0010] With respect to any similar or identical terms found in the publications referenced herein and those explicitly put forth or defined in this document, then those terms definitions or meanings explicitly put forth in this document shall control in all respects.

DETAILED DESCRIPTION

[0011] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. In the event that there is a plurality of definitions for a term used herein, those in this section prevail unless stated otherwise.

[0012] As used herein, the singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise.

[0013] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0014] The term "is/arc deuterium," when used to describe a given position in a molecule such as R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅ and R₂₆ or the symbol "D," when used to represent a given position in a drawing of a molecular structure, means that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. The deuterium enrichment is of no less than 1%, no less than 5%, no less than 10%, no less than 20%, no less than 50%, no less than 70%, no less than 80%, no less than 90%, and no less than 98% of deuterium at the specified position.

[0015] The term "about" or "approximately" means an acceptable error for a particular value, which depends in part on how the value is measured or determined. In certain embodiments, "about" can mean 1 or more standard deviations.

[0016] The term "monoamine-mediated disorder" refers to a disorder that is characterized by abnormal serotonin and/or norepinephrine levels, and when the levels of these neurotransmitters are modified, leads to the amelioration of other abnormal biological processes. A monoamine-mediated disorder may be completely or partially mediated by abnormal serotonin, and/or norepinephrine receptors and/or transporters. In particular, a monoamine-mediated disorder is one in which modulation of serotonin-norepinephrine reuptake activity results in some effect on the underlying condition, disorder, or disease, e.g., administration of an SNRI results in some improvement in at least some of the patients being treated.

[0017] The term "halogen", "halide" or "halo" includes fluorine, chlorine, bromine, and iodine.

[0018] The term "leaving group" (LG) refers to any atom (or group of atoms) that is stable in its anion or neutral form after it has been displaced by a nucleophile and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "leaving group" includes but is not limited to: water, methanol, ethanol, chloride, bromide, iodide, an alkyl sulfonate, for example methanesulfonate, ethane sulfonate and the like, an arylsulfonate, for example benzenesulfonate, tolylsulfonate and the like, a perhaloalkanesulfonate, for example trifluoromethanesulfonate, trichloromethanesulfonate and the like, an alkylcarboxylate, for example acetate and the like, a perhaloalkylcarboxylate, for example trifluoroacetate, trichloroacetate and the like, an arylcarboxylate, for example benzoate and the like, an N-hydroxyimide anion, for example N-hydroxyrnamide anion, N-hydroxysuccinimide anion, N-hydroxyphthalimide anion, N-hydroxysulfosuccinimide anion and the like.

[0019] The term "protecting group" or "removable protecting group" refers to a group which, when bound to a functionality, such as the oxygen atom of a hydroxyl or carboxyl group, or the nitrogen atom of an amino group, prevents reactions from occurring at that functional group, and which can be removed by a conventional chemical or enzymatic step to reestablish the functional group (Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999).

Deuterium Kinetic Isotope Effect

[0020] In an attempt to eliminate foreign substances, such as therapeutic agents, from its circulation system, the animal body expresses various enzymes, such as the cytochrome P₄₅₀ enzymes or CYPs, esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C-H) bond to either a carbon-oxygen (C-O) or carbon-carbon (C-C) π -bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For most drugs, such oxidations are generally rapid and ultimately lead to administration of multiple or high daily doses.

[0021] The relationship between the activation energy and the rate of reaction may be quantified by the Arrhenius equation, $k = Ae^{-E_{act}/RT}$, where E_{act} is the activation energy, T is temperature, R is the molar gas constant, k is the rate constant for the reaction, and A (the frequency factor) is a constant specific to each reaction that depends on the probability that the molecules will collide with the correct orientation. The Arrhenius equation states that the fraction of molecules that have enough energy to overcome an energy barrier, that is, those with energy at least equal to the activation energy, depends exponentially on the ratio of the activation energy to thermal energy (RT), the average amount of thermal energy that molecules possess at a certain temperature.

[0022] The transition state in a reaction is a short lived state (on the order of 10^{-14} sec) along the reaction pathway during which the original bonds have stretched to their limit. By definition, the activation energy E_{act} for a reaction is the energy required to reach the transition state of that reaction. Reactions that involve multiple steps will necessarily have a number of transition states, and in these instances, the activation energy for the reaction is equal to the energy difference between the reactants and the most unstable transition state. Once the transition state is reached, the molecules can either revert, thus reforming the original reactants, or new bonds form giving rise to the products. This dichotomy is possible because both pathways, forward and reverse, result in the release of energy. A catalyst facilitates a reaction process by lowering the activation energy leading to a transition state. Enzymes are examples of biological catalysts that reduce the energy necessary to achieve a particular transition state.

[0023] A carbon-hydrogen bond is by nature a covalent chemical bond. Such a bond forms when two atoms of similar electronegativity share some of their valence electrons, thereby creating a force that holds the atoms together. This force or bond strength can be quantified and is expressed in units of energy, and as such, covalent bonds between various atoms can be classified according to how much energy must be applied to the bond in order to break the bond or separate the two atoms.

[0024] The bond strength is directly proportional to the absolute value of the ground-state vibrational energy of the bond. This vibrational energy, which is also known as the zero-point vibrational energy, depends on the mass of the atoms that form the bond. The absolute value of the zero-point vibrational energy increases as the mass of one or both of the atoms making the bond increases. Since deuterium (D) has twice the mass of hydrogen (H), it follows that a C-D bond is stronger than the corresponding C-H bond. Compounds with C-D bonds are frequently indefinitely stable in H₂O, and have been widely used for isotopic studies. If a C-H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest transition state energy), then substituting a deuterium for that hydrogen will cause a decrease in the reaction rate and the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect (DKIE). The magnitude of the DKIE can be expressed as the ratio between the rates of a given reaction in which a C-H bond is broken, and the same reaction where deuterium is substituted for hydrogen. The DKIE can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or

more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small mass of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. Because deuterium has more mass than hydrogen, it statistically has a much lower probability of undergoing this phenomenon. Substitution of tritium for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects

[0025] Discovered in 1932 by Urey, deuterium (D) is a stable and non-radioactive isotope of hydrogen. It was the first isotope to be separated from its element in pure form and has twice the mass of hydrogen, and makes up about 0.02% of the total mass of hydrogen (in this usage meaning all hydrogen isotopes) on earth. When two deuterium atoms bond with one oxygen, deuterium oxide (D₂O or "heavy water") is formed. D₂O looks and tastes like H₂O, but has different physical properties. It boils at 101.41 °C and freezes at 3.79 °C. Its heat capacity, heat of fusion, heat of vaporization, and entropy are all higher than H₂O. It is more viscous and has different solubilizing properties than H₂O.

[0026] When pure D₂O is given to rodents, it is readily absorbed and reaches an equilibrium level that is usually about eighty percent of the concentration of what was consumed. The quantity of deuterium required to induce toxicity is extremely high. When 0% to as much as 15% of the body water has been replaced by D₂O, animals are healthy but are unable to gain weight as fast as the control (untreated) group. When about 15% to about 20% of the body water has been replaced with D₂O, the animals become excitable. When about 20% to about 25% of the body water has been replaced with D₂O, the animals are so excitable that they go into frequent convulsions when stimulated. Skin lesions, ulcers on the paws and muzzles, and necrosis of the tails appear. The animals also become very aggressive; males becoming almost unmanageable. When about 30%, of the body water has been replaced with D₂O, the animals refuse to eat and become comatose. Their body weight drops sharply and their metabolic rates drop far below normal, with death occurring at about 30 to about 35% replacement with D₂O. The effects are reversible unless more than thirty percent of the previous body weight has been lost due to D₂O. Studies have also shown that the use of D₂O can delay the growth of cancer cells and enhance the cytotoxicity of certain antineoplastic agents.

[0027] Tritium (T) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Mixing tritium with a phosphor provides a continuous light source, a technique that is commonly used in wristwatches, compasses, rifle sights and exit signs. It was discovered by Rutherford, Oliphant and Harteck in 1934, and is produced naturally in the upper atmosphere when cosmic rays react with H₂ molecules. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T₂O, a colorless and odorless liquid. Tritium decays slowly (half-life = 12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk. As compared with deuterium, a lesser amount of tritium must be consumed before it reaches a hazardous level.

[0028] Deuteration of pharmaceuticals to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles, has been demonstrated previously with some classes of drugs. For example, the DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching. The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and rebound in a variety of conformations prior to the chemical reaction (e.g., oxidation). This hypothesis is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity. Such pitfalls are non-obvious and are not predictable *a priori* for any drug class.

Deuterated Phenethylamine Derivatives

[0029] Venlafaxine is a substituted phenethylamine-based SNRI. The carbon-hydrogen bonds of venlafaxine contain a naturally occurring distribution of hydrogen isotopes, namely 1H or protium (about 99.9844%), 2H or deuterium (about 0.0156%), and 3H or tritium (in the range between about 0.5 and 67 tritium atoms per 1018 protium atoms). Increased levels of deuterium incorporation may produce a detectable Kinetic Isotope Effect (KIE) that could affect the pharmacokinetic, pharmacologic and/or toxicologic profiles of such SNRIs in comparison with the compound having naturally occurring levels of deuterium.

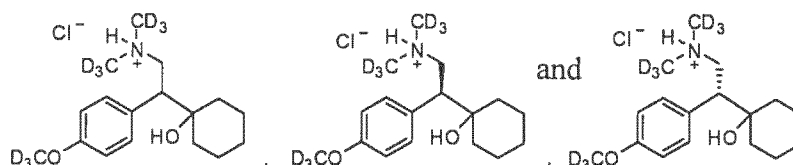
[0030] The novel approach to designing and synthesizing new analogs of venlafaxine and related compounds through incorporation of deuterium disclosed herein may generate novel monoamine reuptake inhibitors with unexpected and non-obvious improvements of pharmacological, pharmacokinetic and toxicological properties in comparison to the non-isotopically enriched monoamine reuptake inhibitors.

[0031] Both N-methyl groups, the single O-methyl, and several sites on the cyclohexyl ring of venlafaxine are now known to be sites of cytochrome P₄₅₀ metabolism. The toxicities of all resultant metabolites are not known. Furthermore,

because polymorphically expressed CYPs such as 2C19 and 2D6 oxidize venlafaxine, and because venlafaxine inhibits the polymorphically expressed CYP2D6, the prevention of such interactions decreases interpatient variability, decreases drug-drug interactions, increases $T_{1/2}$, decreases the necessary C_{max} , and improves several other ADMET parameters. For example, the half-life of venlafaxine ranges from 3 - 7 hours. The equipotent metabolite, O-demethylated venlafaxine (ODV), has a half-life averaging 11 hours. Various deuteration patterns can be used to a) alter the ratio of active metabolites, b) reduce or eliminate unwanted metabolites, c) increase the half-life of the parent drug, and/or d) increase the half-life of active metabolites and create a more effective drug and a safer drug for polypharmacy, whether the polypharmacy be intentional or not. High doses of venlafaxine are often prescribed in order to reach levels capable of inhibiting norepinephrine reuptake. Unfortunately, high doses are also associated with hypertension. Since these phenomena are linked by the pharmaceutical agent rather than the pharmacological target, they are theoretically separable by increasing the half-life, thus allowing dosing in a range that lowers the C_{max} and thus may avoid triggering the mechanism leading to hypertension. Further illustrating this point, venlafaxine is known to display linear kinetics at the low end of the dose range, 75 mg/day, but displays non-linear kinetics at the high end of the dose range, ~400 mg/day, as a result of the saturation of clearance mechanisms. This non-linearity produces an ascending, rather than a flat, dose-response curve for venlafaxine. The deuteration approach has strong potential to slow metabolism through the previously saturated mechanism allowing linear, more predictable ADMET responses throughout the dose range (which would also be lower via this invention). This leads to lesser interpatient variability of the type that can lead to the hypertensive effects.

[0032] The compounds disclosed herein have the potential to uniquely maintain the beneficial aspects of the non-isotopically enriched drugs while substantially increasing the half-life ($T_{1/2}$), lowering the maximum plasma concentration (C_{max}) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions. These drugs also have strong potential to reduce the cost-of-goods (COG) owing to the ready availability of inexpensive sources of deuterated reagents combined with previously mentioned potential for lowering the therapeutic dose. It has been discovered that deuteration at the N-methyl and the O-methyl groups alone, deuteration at the N-methyl and the O-methyl groups in combination, or deuteration of additional sites found to be labile as a result of metabolic switching are effective in achieving some of the objectives disclosed herein.

[0033] In another embodiment, a pharmaceutically acceptable acid addition salt of a compound has a structural formula selected from the group consisting of:



[0034] In certain embodiments, without being bound by any theory, a compound of the present invention may expose a patient to a maximum of about 0.000005% D_2O or about 0.00001% DHO, assuming that all of the C-D bonds in the compound as disclosed herein are metabolized and released as D_2O or DHO. This quantity is a small fraction of the naturally occurring background levels of D_2O or DHO in circulation. The levels of D_2O shown to cause toxicity in animals is much greater than even the maximum limit of exposure because of the deuterium enriched compound as disclosed herein. Thus, the deuterium-enriched compound of the present invention should not cause any additional toxicity because of the use of deuterium.

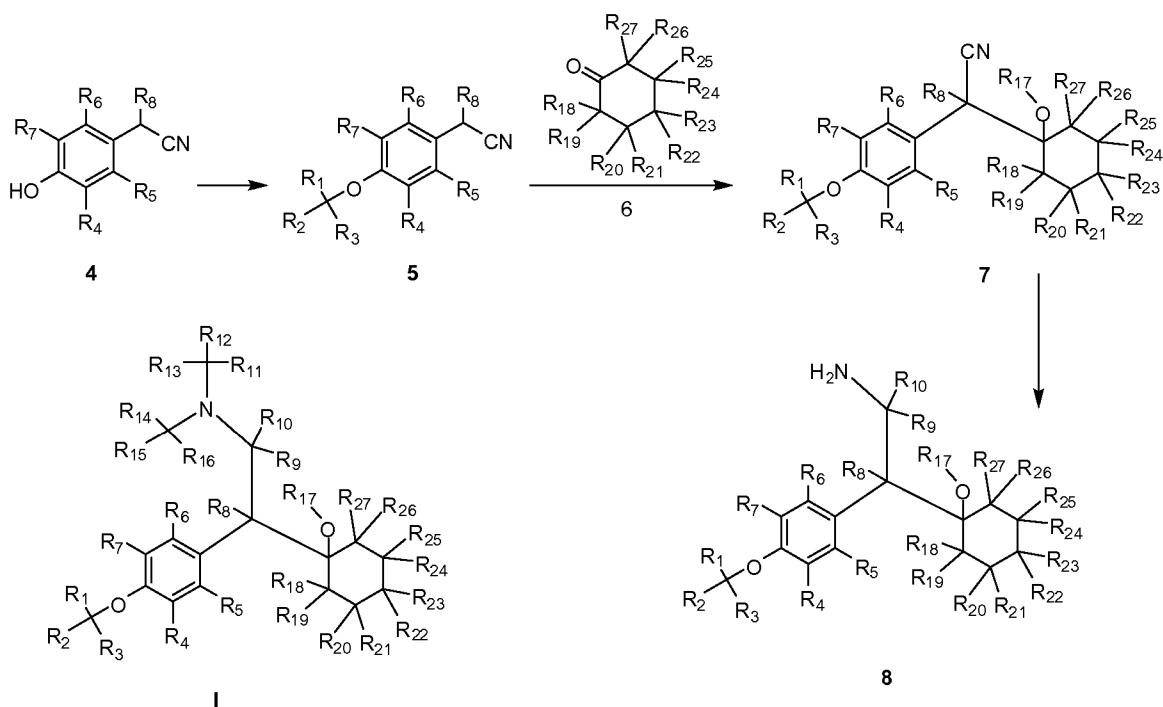
[0035] The deuterated compound of the present invention maintains the beneficial aspects of the corresponding non-isotopically enriched molecules while substantially increasing the maximum tolerated dose, decreasing toxicity, increasing the half-life ($T_{1/2}$), lowering the maximum plasma concentration (C_{max}) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

[0036] Isotopic hydrogen can be introduced into a compound as disclosed herein by synthetic techniques that employ deuterated reagents, whereby incorporation rates are predetermined; and/or by exchange techniques, wherein incorporation rates are determined by equilibrium conditions, and may be highly variable depending on the reaction conditions. Synthetic techniques, where tritium or deuterium is directly and specifically inserted by tritiated or deuterated reagents of known isotopic content, may yield high tritium or deuterium abundance, but can be limited by the chemistry required. Exchange techniques, on the other hand, may yield lower tritium or deuterium incorporation, often with the isotope being distributed over many sites on the molecule.

[0037] Compounds having the structural formulae below can be prepared by methods known to one of skill in the art or following procedures similar to those described in the Example section herein and routine modifications thereof. In the Schemes below, deuterated intermediates are either commercially available or can be prepared by methods known

to one of skill in the art or following procedures similar to those described in the Example section herein and routine modifications thereof.

[0038] For example, a compound having structural formula I can be prepared as shown in Scheme 1.

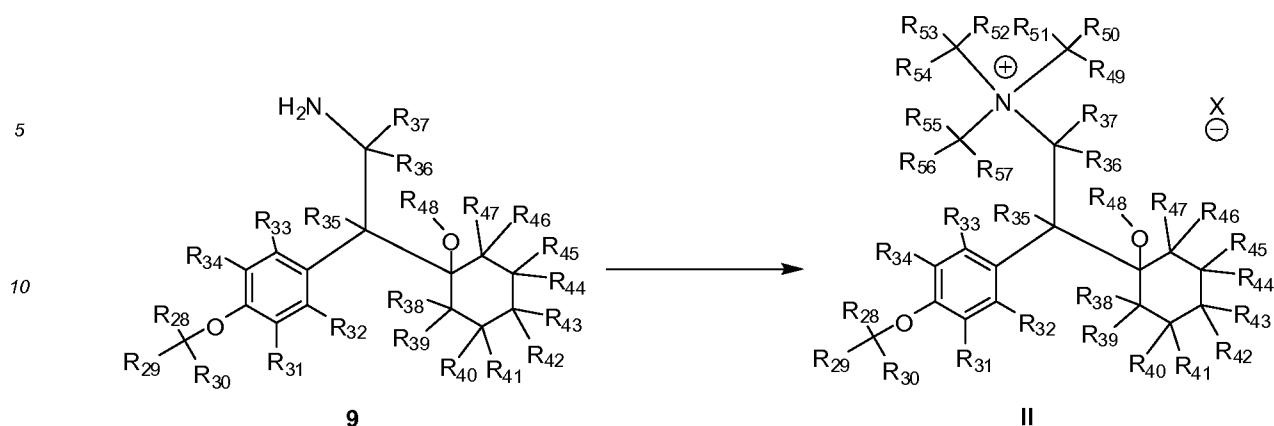


Scheme 1

[0039] Phenol **4** reacts with methyl iodide and a deprotonating agent, such as potassium carbonate, to give ether **5**, which reacts with cyclohexanone **6** in the presence of a deprotonating agent, such as sodium hydroxide, and a phase transfer catalyst, such tetra-*n*-butyl ammonium hydrogen sulfate, to give nitrile **7**. Compound **7** is reduced to aminoalcohol **8** under a hydrogen atmosphere in the presence of a catalyst, such as rhodium on alumina. Alternatively, alcohol **7** is dissolved in ammonia in methanol and reduced to aminoalcohol **8** using a continuous flow hydrogenation reactor equipped with a Raney Ni catalyst cartridge. Compound **8** reacts with excess methyl iodide to give the corresponding quaternary salt II (similar to the reaction step shown in scheme 2) which is demethylated with a nucleophile, such as 2-aminoethanol or 3-aminopropanol, at an elevated temperature to produce the compound of formula I as the free base. The hydrochloride salt of the compound of Formula I can be prepared by methods known in the art.

[0040] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 1, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions selected from R₁, R₂, R₃, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, and R₁₆, methyl iodide with the corresponding deuterium substitutions can be used.

[0041] By way of another example, a compound having structural formula II can be prepared as shown in Scheme 2.

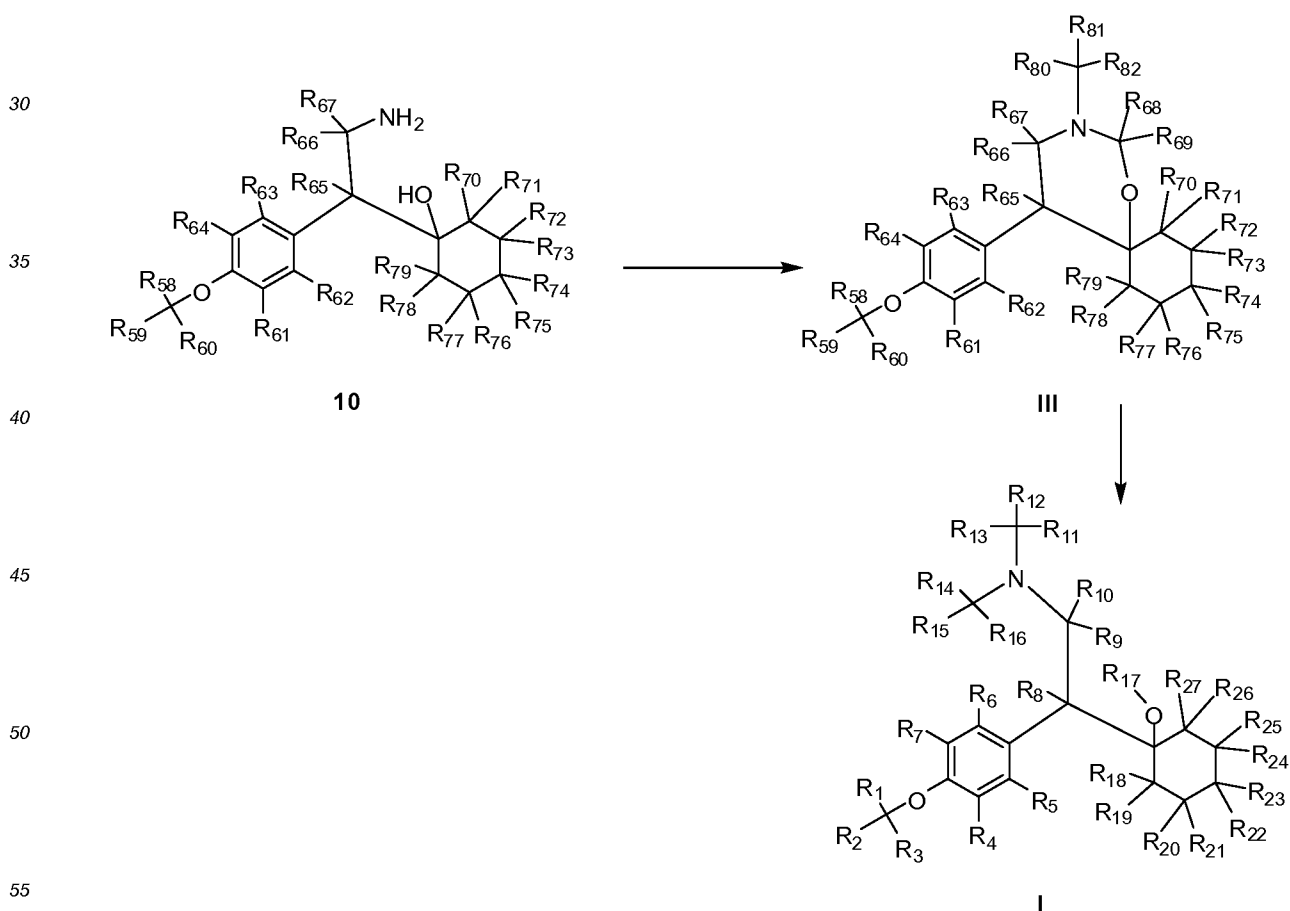


Scheme 2

[0042] Compound **9** is prepared as in Scheme 1 and reacts with excess methyl iodide to produce the compound of formula II as the iodide salt.

[0043] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 1, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions selected from R₂₈, R₂₉, R₃₀, R₄₉, R₅₀, R₅₁, R₅₂, R₅₃, R₅₄, R₅₅, R₅₆, and R₅₇ methyl iodide with the corresponding deuterium substitutions can be used.

[0044] By way of another example, a compound having structural formula III or structural formula I can be prepared as shown in Scheme 3.

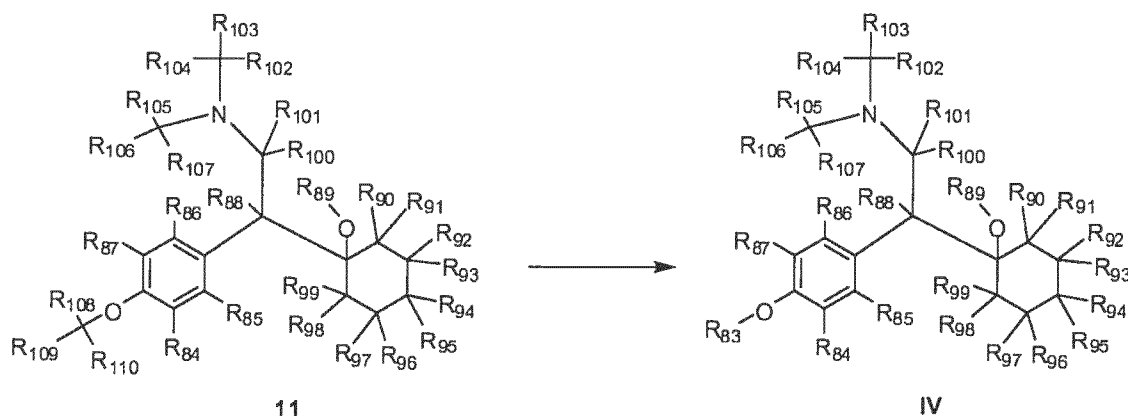


Scheme 3

[0045] Compound **10** is prepared as in Scheme 1 and reacts with formic acid and formaldehyde at an elevated temperature to produce the compound of formula III. The compound of formula III reacts with formic acid and a deprotonating agent, such as sodium hydroxide or sodium formate, to produce the compound of formula I. The hydrochloride salt of the compound of formula I can be prepared by methods known in the art.

[0046] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 3, by using appropriate deuterated intermediates. For example, to introduce deuterium at one or more positions selected from R₆₈, R₆₉, R₈₀, R₈₁, and R₈₂, formic acid and formaldehyde with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions selected from R₅₈, R₅₉, and R₆₀, methyl iodide with the corresponding deuterium substitutions can be used.

[0047] By way of example, a compound having structural formula IV or structural formula can be prepared as shown in Scheme 4.



Scheme 4

[0048] Compound **11** is prepared as in Scheme 1-3 and reacts with a demethylating agent to produce the compound of formula IV.

[0049] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 4, by using appropriate deuterated intermediates as described in Schemes 1-3.

[0050] It is to be understood that the compounds disclosed herein may contain one or more chiral centers, chiral axes, and/or chiral planes, as described in "Stereochemistry of Carbon Compounds" Eliel and Wilen, John Wiley & Sons, New York, 1994, pp. 1119-1190. Such chiral centers, chiral axes, and chiral planes may be of either the (R) or (S) configuration, or may be a mixture thereof.

[0051] Another method for characterizing a composition containing a compound having at least one chiral center is by the effect of the composition on a beam of polarized light. When a beam of plane polarized light is passed through a solution of a chiral compound, the plane of polarization of the light that emerges is rotated relative to the original plane. This phenomenon is known as optical activity, and compounds that rotate the plane of polarized light are said to be optically active. One enantiomer of a compound will rotate the beam of polarized light in one direction, and the other enantiomer will rotate the beam of light in the opposite direction. The enantiomer that rotates the polarized light in the clockwise direction is the (+) enantiomer and the enantiomer that rotates the polarized light in the counterclockwise direction is the (-) enantiomer. Included within the scope of the compositions described herein are compositions containing between 0 and 100% of the (+) and/or (-) enantiomer of compound of the present invention.

[0052] Where a compound contains an alkenyl or alkenylene group, the compound may exist as one or mixture of geometric *cis/trans* (or *Z/E*) isomers. Where structural isomers are interconvertible via a low energy barrier, the compound may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the compound that contains for example, an imino, keto, or oxime group; or so-called valence tautomerism in the compound that contains an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

[0053] The compound of the present invention may be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, a racemic mixture, or a diastereomeric mixture. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[0054] When the compound of the present invention contains an acidic or basic moiety, it may also disclosed as a

pharmaceutically acceptable salt (See, Berge et al., J. Pharm. Sci. 1977, 66, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002).

[0055] Suitable acids for use in the preparation of pharmaceutically acceptable acid addition salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α -oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, ($\pm$)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, ($\pm$)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[0056] Suitable bases for use in the preparation of pharmaceutically acceptable basic addition salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[0057] The compound of the present invention may also be designed as a prodrug, which is a functional derivative of the compound and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, Progress in Drug Research 1962, 4, 221-294; Morozowich et al. in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang et al., Curr. Pharm. Design 1999, 5, 265-287; Pauletti et al., Adv. Drug. Delivery Rev. 1997, 27, 235-256; Mizen et al., Pharm. Biotech. 1998, 11, 345-365; Gagnault et al., Pract. Med. Chem. 1996, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon et al., Ed., Marcell Dekker, 185-218, 2000; Balant et al., Eur. J. Drug Metab. Pharmacokinet. 1990, 15, 143-53; Balimane and Sinko, Adv. Drug Delivery Rev. 1999, 39, 183-209; Browne, Clin. Neuropharmacol. 1997, 20, 1-12; Bundgaard, Arch. Pharm. Chem. 1979, 86, 1-39; Bundgaard, Controller Drug Delivery 1987, 17, 179-96; Bundgaard, Adv. Drug Delivery Rev. 1992, 8, 1-38; Fleisher et al., Adv. Drug Delivery Rev. 1996, 19, 115-130; Fleisher et al., Methods Enzymol. 1985, 112, 360-381; Farquhar et al., J. Pharm. Sci. 1983, 72, 324-325; Freeman et al., J. Chem. Soc., Chem. Commun. 1991, 875-877; Friis and Bundgaard, Eur. J. Pharm. Sci. 1996, 4, 49-59; Gangwar et al., Des. Biopharm. Prop. Prodrugs Analogs, 1977, 409-421; Nathwani and Wood, Drugs 1993, 45, 866-94; Sinhababu and Thakker, Adv. Drug Delivery Rev. 1996, 19, 241-273; Stella et al., Drugs 1985, 29, 455-73; Tan et al., Adv. Drug Delivery Rev. 1999, 39, 117-151; Taylor, Adv. Drug Delivery Rev. 1996, 19, 131-148; Valentino and Borchardt, Drug Discovery Today 1997, 2, 148-155; Wiebe and Knaus, Adv. Drug Delivery Rev. 1999, 39, 63-80; Waller et al., Br. J. Clin. Pharmac. 1989, 28, 497-507.

Pharmaceutical Compositions

[0058] Disclosed herein are pharmaceutical compositions comprising a compound of the present invention as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in combination with one or more pharmaceutically acceptable excipients or carriers.

[0059] Disclosed herein are pharmaceutical compositions in modified release dosage forms, which comprise a compound of the present invention and one or more release controlling excipients or carriers as described herein. Suitable modified release dosage vehicles include, but are not limited to, hydrophilic or hydrophobic matrix devices, water-soluble separating layer coatings, enteric coatings, osmotic devices, multiparticulate devices, and combinations thereof. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[0060] Further disclosed herein are pharmaceutical compositions in enteric coated dosage forms, which comprise a compound of the present invention and one or more release controlling excipients or carriers for use in an enteric coated

dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[0061] Further disclosed herein are pharmaceutical compositions in effervescent dosage forms, which comprise a compound of the present invention and one or more release controlling excipients or carriers for use in an effervescent dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients or carriers.

[0062] Additionally disclosed are pharmaceutical compositions in a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 up to 24 hours. The pharmaceutical compositions comprise a compound of the present invention and one or more release controlling and non-release controlling excipients or carriers, such as those excipients or carriers suitable for a disruptable semi-permeable membrane and as swellable substances.

[0063] Disclosed herein also are pharmaceutical compositions in a dosage form for oral administration to a subject, which comprise a compound of the present invention and one or more pharmaceutically acceptable excipients or carriers, enclosed in an intermediate reactive layer comprising a gastric juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer.

[0064] Pharmaceutical compositions are provided herein which comprise about 0.1 to about 1000 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg of the compound of the present invention.

[0065] The pharmaceutical compositions may be in the form of immediate-release capsules for oral administration, and may further comprise cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

[0066] The pharmaceutical compositions may be in the form of delayed-release capsules for oral administration, and may further comprise cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.

[0067] The pharmaceutical compositions may be in the form of enteric coated delayed-release tablets for oral administration, and may further comprise carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow ferric oxide.

[0068] The pharmaceutical compositions may be in the form of enteric coated delayed-release tablets for oral administration, and may further comprise calcium stearate, crospovidone, hydroxypropyl methylcellulose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

[0069] The compound of the present invention may be administered alone or in combination with one or more other active ingredients. Pharmaceutical compositions comprising a compound of the present invention may be formulated in various dosage forms for oral, parenteral, and topical administration. The pharmaceutical compositions may also be formulated as a modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (see, *Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2002; Vol. 126).

[0070] The pharmaceutical compositions disclosed herein may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[0071] In the case wherein the patient's condition does not improve, upon the doctor's discretion the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[0072] In the case wherein the patient's status does improve, upon the doctor's discretion the compounds may be given continuously or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday").

[0073] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disorder is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[0074] Any of the pharmaceutical formulations described herein can comprise (as the active component) at least one of the hydrochloride salt Forms A-F of formula I, or further contain (as the active component) substantially only one or more of the hydrochloride, salt Forms A-F of formula I.

Polymorphs of Compounds of d₉-venlafaxine (d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol

[0075] The hydrochloride salt Forms A-F of the compound of d₉-venlafaxine have been characterized using X-ray powder diffractometry.

[0076] These provide X-ray powder diffraction patterns substantially the same as shown in FIGURES 1-6.

[0077] The hydrochloride salt Form A of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol (d₉-venlafaxine) of the present disclosure is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of 2-theta (2θ) in a X-ray powder diffraction spectrum of about 6.703, 8.321, 12.681, 13.5, 15.54, 18.918, 20.359, 21.161, 21.762, 25.04, and 28.518.

[0078] The hydrochloride salt Form B of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol (d₉-venlafaxine) of the present disclosure is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of 2-theta (2θ) in a X-ray powder diffraction spectrum of about 6.683, 10.201, 13.441, 15.517, 18.198, 19.719, 20.258, 21.68, 22.658, 25.543, 28.022, and 35.02.

[0079] The hydrochloride salt Form C of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol (d₉-venlafaxine) of the present disclosure is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of 2-theta (2θ) in a X-ray powder diffraction spectrum of about 6.718, 8.335, 12.68, 13.5, 15.539, 16.282, 18.902, 19.737, 20.34, 21.161, 21.758, 25.02, 25.601, 26.261, 28.518, 31.54, 33.198, 33.937, and 35.159.

[0080] The hydrochloride salt Form D of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol (d₉-venlafaxine) of the present disclosure is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of 2-theta (2θ) in a X-ray powder diffraction spectrum of about 6.74, 7.421, 8.341, 10.219, 12.7, 13.502, 17.9, 15.541, 20.36, 21.221, 21.761, 25.078, 31.04, 34.018, and 35.139.

[0081] The hydrochloride salt Form E of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol (d₉-venlafaxine) of the present disclosure is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of 2-theta (2θ) in a X-ray powder diffraction spectrum of about 5.597, 7.182, 9.078, 9.557, 11.201, 14.46, 14.76, 16.86, 17.497, 19.201, 19.619, 20.241, 20.66, 21.76, 22.596, 23.06, 24.4, 25.02, 26.519, 26.842, 31.52, and 35.438.

[0082] The hydrochloride salt Form F of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol (d₉-venlafaxine) of the present disclosure is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of 2-theta (2θ) in a X-ray powder diffraction spectrum of about 5.581, 7.186, 11.22, 14.499, 14.802, 16.882, 19.242, 20.317, 21.798, 22.637, and 35.445.

[0083] In the infrared absorption spectra FIGURES 7-12 the horizontal axis shows the wavenumber in cm⁻¹ and the vertical axis shows the transmittance in percent (%).

[0084] The hydrochloride salt of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d₉-venlafaxine) has been characterized by X-ray powder diffractometry.

[0085] The hydrochloride crystals of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d₉-venlafaxine, Forms A-F) provide powder X-ray diffraction spectra substantially the same as the powder X-ray diffraction spectra shown in FIGURES 1-6, respectively. However, it is known that a powder X-ray diffraction spectrum may be obtained with a measurement error depending on measurement conditions. In particular, it is generally known that intensities in a powder X-ray diffraction spectrum may fluctuate depending on measurement conditions. Therefore, it should be understood that the salts of the present disclosure are not limited to the crystals that provide X-ray powder diffraction spectrum completely identical to the X-ray powder diffraction spectra shown in FIGURES 1-6, and that any crystals providing X-ray powder diffraction spectra substantially the same as the aforementioned X-ray powder diffraction spectra fall within the scope of the present disclosure. Those skilled in the field of X-ray powder diffractometry can readily judge the substantial identity of X-ray powder diffraction spectra.

[0086] Generally, a measurement error of diffraction angle for a usual X-ray powder diffractometry is about 5% or less, and such degree of a measurement error should be taken into account as to diffraction angles. Furthermore, it should be understood that intensities may fluctuate depending on experimental conditions.

[0087] The hydrochloride salt Form A of d₉-venlafaxine is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of about 2-theta, [% relative intensity]: 6.703 [29.3], 8.321 [19], 12.681 [77.5], 13.5 [47.9], 15.54 [17.7], 18.918 [24.4], 20.359 [100], 21.161 [38.3], 21.762 [26.1], 25.04 [27.8], and 28.518 [18.2]. The hydrochloride salt Form A of the present disclosure provides a X-ray powder diffraction spectrum substantially the same as the X-ray diffraction spectrum shown in FIGURE 1.

[0088] The characteristic 2-theta (2θ) values and relative intensity (RI) in percentage for the diffraction spectrum of the hydrochloride salt Form A of d₉-venlafaxine is shown in Table 1. Thus, described herein is a polymorph of the hydrochloride salt of d₉-venlafaxine having at least four of the most intense peaks presented in Table 1.

TABLE 1

2-theta	RI	2-theta	RI	2-theta	RI	2-theta	RI
6.703	29.3	16.762	8.1	25.04	27.8	31.539	10.5
7.399	9	17.318	4.6	25.34	5.3	32.456	2.1
8.321	19	18.5	4.2	25.641	8	32.758	3.3
8.52	2.7	18.918	24.4	26.261	6.4	33.162	7.3
10.195	3.6	19.757	6.1	26.481	4.9	33.957	10.4
12.681	77.5	20.359	100	26.866	1.6	35.181	15.5
13.5	47.9	21.161	38.3	27.265	6.7	36.024	1.8
14.863	9.3	21.762	26.1	28.518	18.2	36.399	1.6
15.54	17.7	22.196	2	28.822	6.2	36.814	2
15.92	3.8	22.92	2.8	30.419	2.5	37.76	3
16.299	11.4	24.084	1.7	31.001	7.9	38.68	5.1
						39.159	2.2

[0089] The compound of the present invention is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of about 2-theta, [% relative intensity]: 6.683 [15.5], 10.201 [93.6], 13.441 [27.8], 15.517 [66.2], 18.198 [41], 19.719 [34.1], 20.258 [100], 21.68 [71.2], 22.658 [24.8], 25.543 [22.4], 28.022 [20.9], and 35.02 [33.4]. The compound of the present invention provides a x-ray powder diffraction spectrum substantially the same as the X-ray diffraction spectrum shown in FIGURE 2.

[0090] The characteristic 2-theta (2 θ) values and relative intensity (RI) in percentage for the diffraction spectrum of the compound of the present invention is shown in Table 2. Thus, described herein is a polymorph of the hydrochloride salt of formula I having at least four of the most intense peaks presented in Table 2.

TABLE 2

2-theta	RI	2-theta	RI	2-theta	RI
6.683	15.5	22.658	24.8	31.379	8.2
10.201	93.6	23.923	2.7	31.978	9.1
13.441	27.8	25.322	9.6	32.28	10.5
15.014	7.6	25.543	22.4	32.701	6.5
15.517	66.2	26.502	6.7	32.981	2.3
16.458	1.5	27.122	9.5	34.12	9.1
16.84	10.3	27.557	5.5	35.02	33.4
17.206	2.7	28.022	20.9	36.024	3.1
18.198	41	28.64	4.4	36.842	2.6
19.719	34.1	29.241	10.6	37.5	6.7
20.258	100	29.659	7.1	38.341	3.9
21.68	71.2	31.079	11.9	38.753	1.2

[0091] The hydrochloride salt Form C of d₉-venlafaxine is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of about 2-theta, [% relative intensity]: 6.718 [21.4], 8.335 [20.6], 12.68 [80], 13.5 [40.7], 15.539 [20.2], 16.282 [24.3], 18.902 [48.9], 19.737 [17.4], 20.34 [100], 21.161 [79.4], 21.758 [30.5], 25.02 [31.5], 25.601 [18.9], 26.261 [15.2], 28.518 [30.2], 31.54 [18.7], 33.198 [14.2], 33.937 [16.5], and 35.159 [21.3]. The hydrochloride salt Form C of d₉-venlafaxine provides a X-ray powder diffraction spectrum substantially the same as the X-ray diffraction spectrum shown in FIGURE 3.

EP 2 125 698 B1

[0092] The characteristic 2-theta (2 θ) values and relative intensity (RI) in percentage for the diffraction spectrum of the hydrochloride salt Form C of d₉-venlafaxine is shown in Table 3. Thus, described herein is a polymorph of the hydrochloride salt of d₉-venlafaxine having at least four of the most intense peaks presented in Table 3.

TABLE 3

2-theta	RI	2-theta	RI	2-theta	RI	2-theta	RI
6.718	21.4	18.182	4.2	25.36	11.1	33.198	14.2
8.335	20.6	18.4	3	25.601	18.9	33.937	16.5
10.18	9.1	18.902	48.9	26.261	15.2	35.159	21.3
12.68	80	19.737	17.4	26.856	3.2	36.076	3.1
13.5	40.7	20.34	100	27.258	8.8	36.438	2.7
15.539	20.2	21.161	79.4	28.518	30.2	36.765	3.9
15.68	11.5	21.758	30.5	28.839	11.6	37.66	5.6
15.938	9.4	22.151	3.6	30.42	2.4	38.207	2.2
16.282	24.3	22.659	2.1	30.962	11.7	38.658	6.7
16.778	9.9	22.955	2.4	31.54	18.7	39.2	3.6
16.916	9.5	24.073	1.7	32.478	4.6		
17.302	8.2	25.02	31.5	32.775	3.9		

[0093] The hydrochloride salt Form D of d₉-venlafaxine is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of about 2-theta, [% relative intensity]: 6.74 [21.2], 7.421 [14], 8.341 [35.5], 10.219 [23], 12.7 [99.5], 13.502 [40.7], 17.9 [17.5], 15.541 [37.3], 20.36 [100], 21.221 [23.7], 21.761 [41], 25.078 [26.3], 31.04 [17.7], 34.018 [14.8], and 35.139 [22.7]. The hydrochloride salt Form D of the d₉-venlafaxine provides a X-ray powder diffraction spectrum substantially the same as the X-ray diffraction spectrum shown in FIGURE 4.

[0094] The characteristic 2-theta (2 θ) values and relative intensity (RI) in percentage for the diffraction spectrum of the hydrochloride salt Form D of the compound of formula I is shown in Table 4. Thus, described herein is a polymorph of the hydrochloride salt of d₉-venlafaxine having at least four of the most intense peaks presented in Table 4.

TABLE 4

2-theta	RI	2-theta	RI	2-theta	RI	2-theta	RI
6.74	21.2	18.54	7.2	25.604	9.7	32.742	4
7.421	14	18.96	12.1	26.303	6	33.239	5.4
8.341	35.5	19.741	12	26.483	8.9	34.018	14.8
10.219	23	20.36	100	26.959	6.9	35.139	22.7
12.7	99.5	21.221	23.7	27.258	7.1	36.1	2.5
13.502	40.7	21.761	41	28.223	7.3	36.388	1.8
17.9	17.5	22.279	2.2	28.518	11.9	36.839	2.2
15.541	37.3	22.719	4.9	28.919	4.8	37.719	3.5
16.361	9.9	23.039	3	29.322	3.2	38.681	5.5
16.764	13	24.024	3.2	30.419	3.2	39.198	3.8
17.424	3	25.078	26.3	31.04	17.7		
18.276	10.2	25.383	5.9	31.66	10.6		

[0095] The hydrochloride salt Form E of d₉-venlafaxine is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of about 2-theta, [% relative intensity]: 5.597 [28], 7.182 [36.2], 9.078 [24.1], 9.557

EP 2 125 698 B1

[14.9], 11.201 [100], 14.46 [40.2], 14.76 [40.4], 16.86 [71.7], 17.497 [15.7], 19.201 [66.5], 19.619 [19.6], 20.241 [35.2], 20.66 [19.6], 21.76 [22.5], 22.596 [26.4], 23.06 [13.2], 24.4 [15.3], 25.02 [12.1], 26.519 [13.5], 26.842 [18.7], 31.52 [12.6], and 35.438 [17.9]. The hydrochloride salt Form E of d₉-venlafaxine provides a X-ray powder diffraction spectrum substantially the same as the X-ray diffraction spectrum shown in FIGURE 5.

[0096] The characteristic 2-theta (2θ) values and relative intensity (RI) in percentage for the diffraction spectrum of the hydrochloride salt Form E of d₉-venlafaxine I is shown in Table 5. Thus, described herein is a polymorph of the hydrochloride salt of d₉-venlafaxine having at least four of the most intense peaks presented in Table 5.

TABLE 5

2-theta	RI	2-theta	RI	2-theta	RI	2-theta	RI
5.597	28	15.721	11.2	23.06	13.2	30.98	7.7
7.182	36.2	16.041	8.4	23.994	2	31.52	12.6
9.078	24.1	16.86	71.7	24.4	15.3	32.362	6.4
9.557	14.9	17.497	15.7	25.02	12.1	32.721	6
10.663	9	17.866	3	25.643	3.9	33.162	2.1
11.201	100	18.398	12.8	25.861	6.7	34.461	9.6
12.104	2.4	19.201	66.5	26.519	13.5	35.438	17.9
12.361	1.2	19.619	19.6	26.842	18.7	35.899	5.6
13.422	2.1	20.241	35.2	27.502	5.1	36.779	4.7
13.921	4.4	20.66	19.6	28.422	6.1	37.4	4.5
14.46	40.2	20.879	11.2	28.859	7.2	37.984	2
14.76	40.4	21.76	22.5	29.937	3.1	38.962	3.6
15.366	3.2	22.596	26.4				

[0097] The hydrochloride salt Form F of d₉-venlafaxine is characterized in that the crystal provides high-intensity diffraction peaks at diffraction angles of about 2-theta, [% relative intensity]: 5.581 [26.1], 7.186 [18.3], 11.22 [100], 14.499 [18.8], 14.802 [20.5], 16.882 [63.9], 19.242 [38.4], 20.317 [51.6], 21.798 [17.5], 22.637 [26.3], and 35.445 [16.2]. The hydrochloride salt Form F of d₉-venlafaxine provides a X-ray powder diffraction spectrum substantially the same as the X-ray diffraction spectrum shown in FIGURE 6.

[0098] The characteristic 2-theta (2θ) values and relative intensity (RI) in percentage for the diffraction spectrum of the hydrochloride salt Form F of d₉-venlafaxine I is shown in Table 6. Thus, described herein is a polymorph of the hydrochloride salt of d₉-venlafaxine having at least four of the most intense peaks presented in Table 6.

TABLE 6

2-theta	RI	2-theta	RI	2-theta	RI	2-theta	RI
5.581	26.1	15.559	5.1	23.101	9	31.597	9.1
6.688	6.4	15.796	6.1	24.425	11.9	32.374	1.6
7.186	18.3	16.087	3.6	25.042	7.1	33.32	1.3
9.079	7.7	16.882	63.9	25.921	7.7	34.524	6.3
9.576	9.1	17.519	10.6	26.587	5.4	35.112	4.7
10.206	2.4	18.407	5.6	26.939	10.1	35.445	16.2
10.735	4.4	19.242	38.4	27.194	5.3	35.88	1.3
11.22	100	19.68	11.8	27.579	2.5	36.727	2.3
12.133	3	20.317	51.6	28.435	3.9	36.981	3.2
13.447	9	20.72	8.8	28.921	3.5	37.464	2.9
13.963	2.2	20.923	6.3	29.4	1.6	39.023	1.9

(continued)

2-theta	RI	2-theta	RI	2-theta	RI	2-theta	RI
14.499	18.8	21.798	17.5	29.808	2.6	38.962	3.6
14.802	20.5	22.637	26.3	31.064	3.7		

[0099] X-ray powder diffraction pattern is only one of many ways to characterize the arrangement of atoms comprising the hydrochloride salt of d_9 -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d_9 -venlafaxine, Forms A-F). Other methods are well known in the art, such as, single X-ray crystal diffraction, may be used to identify aforementioned salt forms of d_9 -venlafaxine

[0100] The hydrochloride salt Forms A-F have high crystallinity, i.e., substantially free of amorphous material. Such salts provide more reproducible dosing results. The hydrochloride salt Forms A-F are substantially hygroscopically stable, which alleviates potential problems associated with weight changes of the active ingredient during the manufacture of capsules or tablets. The hydrochloride Forms A-F also have a low tendency for concentrated aqueous solution to form viscous mixtures upon standing. The hydrochloride salt Forms A-F have rapid kinetic aqueous solubility which simplifies aqueous dosing and make them suitable for injectable dosage forms. Furthermore, the hydrochloride salt Forms A-F with enhanced solubility characteristics facilitate the dissolution of solid dosage forms in a timely manner.

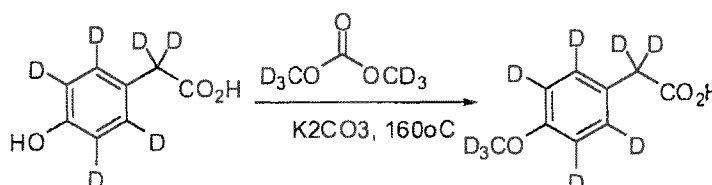
[0101] The hydrochloride salt Forms A-F have greater kinetic solubility than the free base of the compound d_9 -venlafaxine. Additionally, the hydrochloride salt Forms A-F of the compound d_9 -venlafaxine are more stable in air and can be used without deliquescence. Form B is the compound of the present invention. The other forms are for reference only.

[0102] Steps involved in obtaining the compound of the present invention and similar deuterated compounds are illustrated in the following examples. Any examples relating to a reaction leading to compounds not falling within the scope of the present claims are for reference only.

EXAMPLE

Example 1 - d_9 -2-(4-Methoxyphenyl)-acetic acid

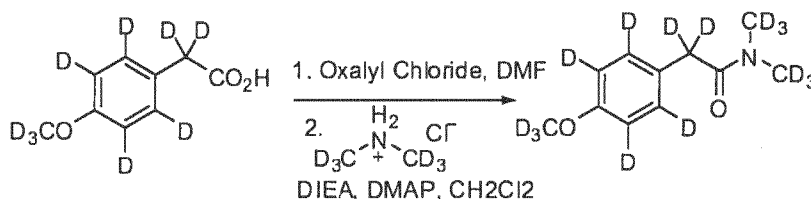
[0103]



[0104] d_9 -(4-Methoxyphenyl)-acetic acid can be prepared according to known literature procedures Ouk et al., Green Chemistry, 2002, 4(5), 431-435, by reacting d_6 -(4-hydroxyphenyl)-acetic acid (1 equiv, Cambridge Isotopes Laboratories), K_2CO_3 (0.04 equiv) and d_6 -carbonic acid dimethyl ester (1.25 equiv, Cambridge Isotopes Laboratories) at 160°C until completion.

Example 2 - d_{15} -2-(4-Methoxyphenyl)-N,N-dimethyl-acetamide

[0105]

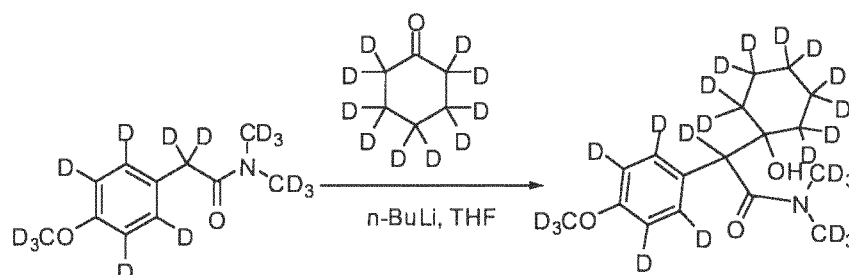


[0106] The title compound is prepared according to the procedure described in Yardley et al, Journal of Medicinal

Chemistry 1990, 33(10), 2899-2905. A solution of d_9 -(4-methoxyphenyl)-acetic acid (1 equiv) in methylene chloride is treated with oxalyl chloride (1.22 equiv) and DMF (catalytic amount) and then stirred at room temperature until all acid is converted to the acid chloride. The solvent is removed under reduced pressure and the residue is taken up in methylene chloride and treated with d_6 -dimethylamine hydrochloride (1 equiv, Cambridge Isotopes Laboratories), ethyl diisopropylamine (2.1 equiv), and DMAP (0.2 equiv). The mixture is stirred overnight, the solvent is removed under reduced pressure and the crude residue is purified by silica gel column chromatography.

Example 3 - d_{24} -2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)-N,N-dimethylacetamide

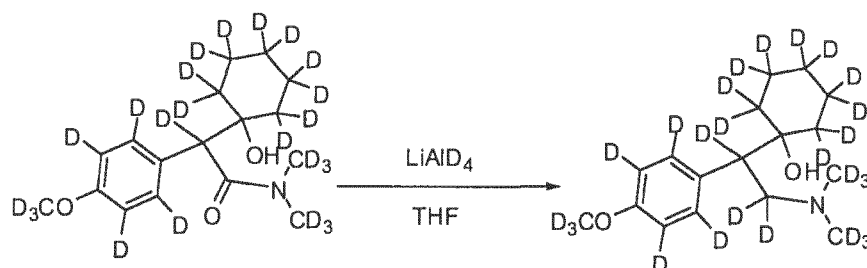
[0107]



[0108] The title compound is prepared according to the procedure described in Yardley et al., Journal of Medicinal Chemistry 1990, 33(10), 2899-2905. A solution of d_{15} -2-(4-methoxyphenyl)-N,N-dimethyl-acetamide (1 equiv) in THF is treated with *n*-butyllithium (1 equiv) at -78°C . The mixture is stirred for 90 minutes at -78°C ; a THF solution of d_{10} -cyclohexanone (1.2 equiv, Sigma-Aldrich) is added, and stirring is maintained until completion. The reaction is quenched by addition of D_2O (2 equiv), the mixture is warmed to room temperature and the solvent is removed under reduced pressure and the crude residue is purified by silica gel column chromatography.

Example 4 - d_{26} -1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol

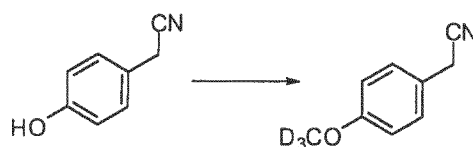
[0109]



[0110] The title compound is prepared according to the procedure described in Yardley et al., Journal of Medicinal Chemistry 1990, 33(10), 2899-2905; d_{24} -2-(1-Hydroxycyclohexyl)-2-(4-methoxyphenyl)-N,N-dimethyl-acetamide (1 equiv) in THF is added dropwise to a mixture of lithium aluminum deuteride (1.6 equiv) at 0°C and stirred until completion. The reaction is quenched with D_2O , and worked up under standard conditions known to one skilled in the art. The mixture is then filtered and the precipitate is washed several times with THF. The combined filtrates are evaporated, and the residue is recrystallized from a suitable solvent.

Example 5 - d_3 -(4-Methoxyphenyl)-acetonitrile

[0111]



[0112] d_3 -iodomethane (8.70 g, 60 mmol) was added to a stirred solution of (4-hydroxyphenyl)-acetonitrile (4.50 g, 30 mmol) in acetone (30 mL) containing potassium carbonate (6.21 g, 45 mmol) at ambient temperature, and the mixture was heated at reflux overnight, cooled to ambient temperature, filtered, and concentrated to give the crude product, which was purified by flash chromatography using hexanes-ethyl acetate to afford the desired product, d_3 -(4-methoxyphenyl)-acetonitrile, as a light yellow oil.

[0113] Yield: 3.99 g (89%). $^1\text{H-NMR}$ (CDCl_3) δ ppm: 3.67(s, 2H), 6.88(d, 2H, $J = 8.7\text{Hz}$), 7.22(d, 2H, $J = 8.7\text{Hz}$).

Example 6 - d_3 -(1-Hydroxycyclohexyl)-(4-methoxyphenyl)-acetonitrile

[0114]

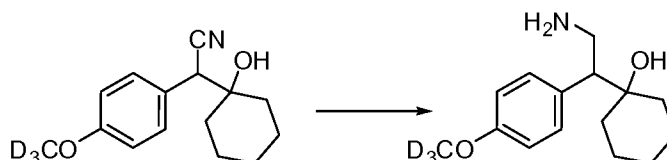


[0115] Tetra-*n*-butyl ammonium hydrogen sulfate (0.10 g, 0.29 mmol) and 2N NaOH (1.2 mL) were added sequentially to a vigorously stirred d_3 -(4-methoxyphenyl)-acetonitrile (0.85 g, 5.66 mmol) at 0°C , and stirring was maintained for 30 minutes. Cyclohexanone (0.67 g, 6.8 mmol) was added to this mixture at $0-5^\circ\text{C}$ over 10 minutes. The reaction mixture was allowed to warm to ambient temperature and vigorous stirring was continued for an additional 1 hour. The white precipitate was filtered and washed with water and hexanes to afford the desired product, d_3 -(1-hydroxycyclohexyl)-(4-methoxyphenyl)-acetonitrile, as a white solid.

[0116] Yield: 1.28g (91%). $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.05-1.80 (m, 10H), 3.73 (s, 1H), 6.90 (d, 2H, $J = 8.7\text{Hz}$), 7.27 (d, 2H, $J = 8.7\text{Hz}$).

Example 7 - d_3 -1-[2-Amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol

[0117]

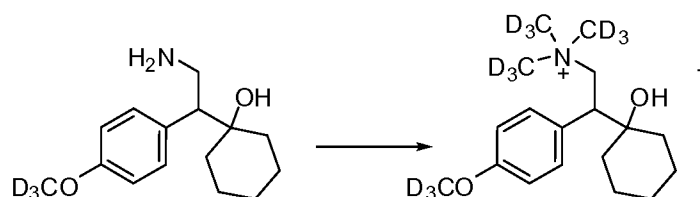


[0118] d_3 -(1-Hydroxycyclohexyl)-(4-methoxyphenyl)-acetonitrile (400.0 mg, 1.61 mmol) was reduced on an H-CubeTM continuous-flow hydrogenation reactor (Thales Nanotechnology, Budapest, Hungary) equipped with a Raney Ni catalyst cartridge (eluent: 2.0M ammonia in methanol, flow rate: 1 mL/min, temperature: 80°C , pressure: 80 bar) to yield the desired product, d_3 -1-[2-amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol, as a clear colorless oil.

[0119] Yield: 280 mg (69%). $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.05-1.80 (m, 10H), 2.59 (br s, 2H), 2.68 (t, 1H, 6.9Hz), 3.21 (m, 2H), 6.83 (d, 2H, $J = 9.0\text{Hz}$), 7.17 (d, 2H, $J = 9.0\text{Hz}$).

Example 8 - d_{12} -1-[2-Trimethylammonium-1-(4-methoxyphenyl)-ethyl]-cyclohexanol iodide

[0120]

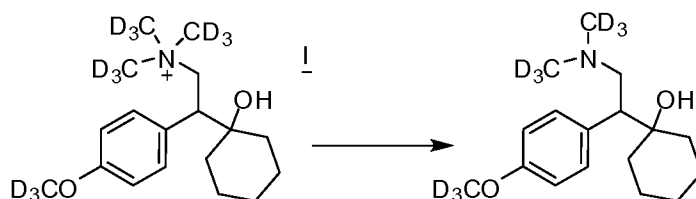


[0121] D_3 -iodomethane (0.4 mL, 6.34 mmol) and potassium carbonate (424 mg, 3.0 mmol) were added at ambient temperature to a solution of d_3 1-[2-amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (252 mg, 1.0 mmol) in anhydrous

tetrahydrofuran (1.5 ml.), and stirred at ambient temperature for 20 hours. The reaction mixture was diluted with tetrahydrofuran, filtered, and the filtrate was concentrated in vacuo to provide the product, d_{12} -1-[2-trimethylammonium-1-(4-methoxyphenyl)-ethyl]-cyclohexanol iodide, as a beige solid. $^1\text{H-NMR}$ (CD_3OD) δ ppm: 0.90-1.80 (m, 10H), 3.19 (m, 1H), 4.00 (m, 2H), 6.93 (d, $J = 8.1\text{Hz}$, 2H), 7.43 (d, $J = 8.1\text{Hz}$, 2H).

Example 9 - d_9 -1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d_9 -venlafaxine)

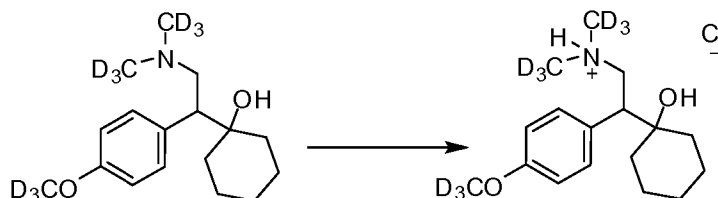
[0122]



[0123] A solution of d_{12} -1-[2-trimethylammonium-1-(4-methoxyphenyl)-ethyl]-cyclohexanol iodide in 3-amino-1-propanol (1 mL) was heated at 170°C for 4 hours, cooled to ambient temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and concentrated under reduced pressure. The resulting residue was dissolved in 6N hydrochloric acid (5 mL), washed with ether. The aqueous layer was basified with 30% aqueous sodium hydroxide to pH = 11-12 and extracted with ethyl acetate. The organic extract was washed with brine, dried, and concentrated to afford d_9 -venlafaxine (208 mg, 73%). $^1\text{H-NMR}$ (CDCl_3) δ ppm: 0.78-1.80 (m, 10H), 2.33 (dd, 1H, $J = 12.0, 3.3\text{ Hz}$), 2.96 (dd, 1H, $J = 12.0, 3.3\text{ Hz}$), 3.31 (t, 1H, $J = 12.0\text{ Hz}$), 6.81 (d, 2H, $J = 9.0\text{ Hz}$), 7.17 (d, 2H, $J = 9.0\text{ Hz}$). MS (m/z): 287 ($M+1$).

Example 10 - d_9 -1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d_9 -venlafaxine hydrochloride)

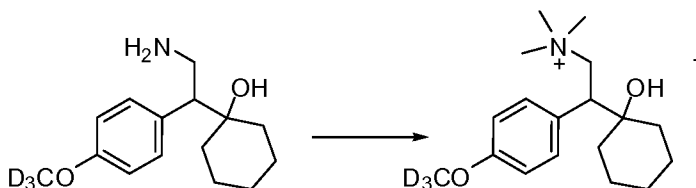
[0124]



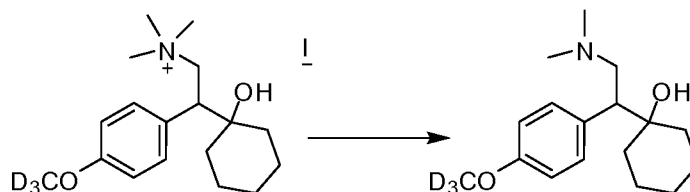
[0125] A solution of d_9 -venlafaxine (63mg, 0.22 mmol) in ether (10 mL) was treated with 2N hydrochloric acid in ether (0.2 mL) at 0°C for 10 minutes. The white precipitate was collected by filtration, washed with ether, and dried in vacuo to provide d_9 -venlafaxine hydrochloride salt (60mg, 85%). $^1\text{H-NMR}$ (CD_3OD) δ ppm: 0.95-1.80 (m, 10H), 2.83 (s, 6H), 3.04 (dd, 1H, $J = 9.9, 5.4\text{ Hz}$), 3.68 (m, 2H), 6.96 (d, 2H, $J = 9.0\text{ Hz}$), 7.30 (d, 1H, $J = 9.0\text{ Hz}$).

Example 11 - d_3 -1-[2-Trimethylammonium-1-(4-methoxyphenyl)-ethyl]-cyclohexanol iodide

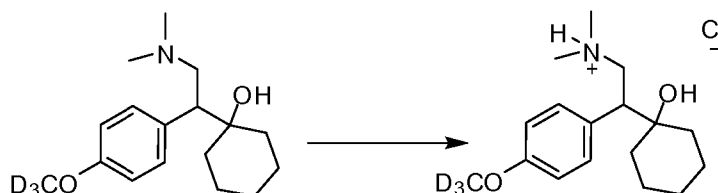
[0126]



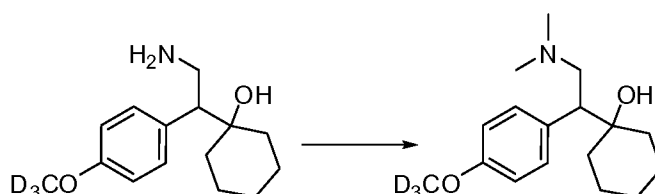
[0127] Prepared according to Example 8 by substituting methyl iodide for d_3 -methyl iodide. $^1\text{H-NMR}$ (CD_3OD) δ ppm: 0.90-1.80 (m, 10H), 3.05 (s, 9H), 3.12 (m, 1H), 3.96 (m, 2H), 6.94 (d, $J = 8.1\text{Hz}$, 2H), 7.39 (d, $J = 8.1\text{Hz}$, 2H).

Example 12 - d₃-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d₃-venlafaxine)**[0128]**

[0129] Prepared according to Example 9. ¹H-NMR (CD₃OD) δ ppm: 0.84-1.54 (m, 10H), 2.42 (s, 6H), 2.84-2.92 (m, 2 H), 3.26-3.36 (m, 1H), 6.87 (d, 2H), 7.18 (d, 2H).

Example 13 - d₃-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₃-venlafaxine hydrochloride)**[0130]**

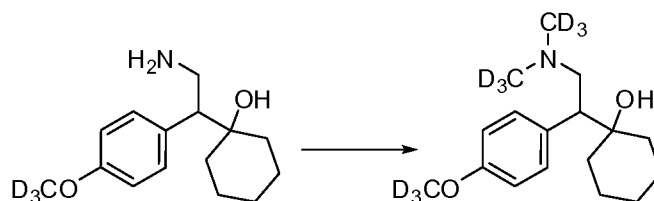
[0131] Prepared according to Example 10.

Example 14 - d₃-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d₃-venlafaxine)**[0132]**

[0133] d₃-1-[2-Amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (207 mg, 0.82 mmol), 37% aqueous formaldehyde (0.3 mL), formic acid (0.3 mL) and water (2 mL) were stirred at 80-90°C for 12 hours, concentrated *in vacuo* to a volume of 1.5 mL, made basic by the dropwise addition of aqueous 20% sodium hydroxide, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give a crude residue which was purified by silica gel chromatography (ethyl acetate-methanol-ammonium hydroxide) to give the desired product, d₃-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol.

[0134] Yield: 24.4 mg (11%). ¹H-NMR (methanol-d₄) δ ppm: 0.84-1.54 (m, 10 H), 2.42 (s, 6 H), 2.84-2.92 (m, 2 H), 3.26-3.36 (m, 1 H), 6.87 (d, 2 H), 7.18 (d, 2 H).

Example 15 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d₉-venlafaxine)**[0135]**

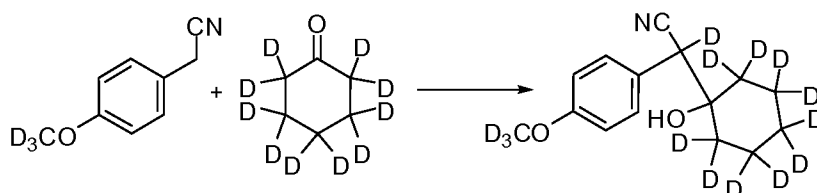


[0136] A solution of d_3 -1-[2-amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (0.126 g, 0.5 mmol), d_2 -formic acid (0.3 mL), and d_2 -formaldehyde (20 wt% in D_2O , 0.25 mL) in D_2O (1.5 mL) was heated at $100^\circ C$ for 16 hours, cooled to ambient temperature, diluted with water (5 mL), neutralized with 35% aqueous ammonia, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to yield a crude residue which was purified by flash chromatography (ethyl acetate-methanol- NH_4OH) to give the desired product, d_9 -1-[2-methylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol, as a light yellow semi-solid.

[0137] Yield: 0.024 g (20%). ^1H -NMR ($CDCl_3$) δ ppm: 0.78-1.80 (m, 10H), 2.33 (dd, 1H, $J = 12.0, 3.3$ Hz), 2.96 (dd, 1H, $J = 12.0, 3.3$ Hz), 3.31 (t, 1H, $J = 12.0$ Hz), 6.81 (d, 2H, $J = 9.0$ Hz), 7.17 (d, 2H, $J = 9.0$ Hz). MS (m/z): 287 ($M+1$).

Example 16 - d_{14} -(1-Hydroxycyclohexyl)-(4-methoxyphenyl)-acetonitrile

[0138]

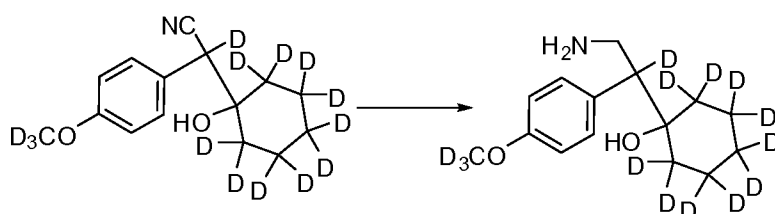


[0139] The title compound was prepared as in Example 6 by substituting d_{10} -cyclohexanone (Sigma-Aldrich) for cyclohexanone and 2N NaOD in D_2O for 2N NaOH in water. The final product was purified by recrystallization from ethyl acetate-hexanes.

[0140] Yield (60%). ^1H -NMR ($CDCl_3$) δ ppm: 1.60 (br s, 1H), 6.90 (d, 2H, $J = 8.4$ Hz), 7.26 (d, 2H, $J = 8.4$ Hz).

Example 17 - d_{14} -1-[2-Amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol

[0141]

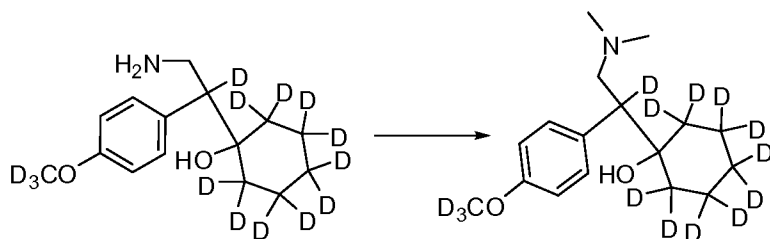


[0142] d_{14} -(1-Hydroxycyclohexyl)-(4-methoxyphenyl)-acetonitrile (570.0 mg, 2.21 mmol) was reduced on an H-CubeTM continuous-flow hydrogenation reactor (Thales Nanotechnology, Budapest, Hungary) equipped with a Raney Ni catalyst cartridge (eluent: 2.0M ammonia in methanol, flow rate: 1 mL/min, temperature: $80^\circ C$, pressure: 80 bar) to yield the desired product, d_{14} -1-[2-amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol, as a clear colorless oil.

[0143] Yield: 530 mg (92%). ^1H -NMR ($CDCl_3$) δ ppm: 2.62 (br s, 3H), 3.21 (dd, 2H), 6.83 (d, 2H), 7.17 (d, 2H).

Example 18 - d_{14} -1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d_{14} -venlafaxine)

[0144]

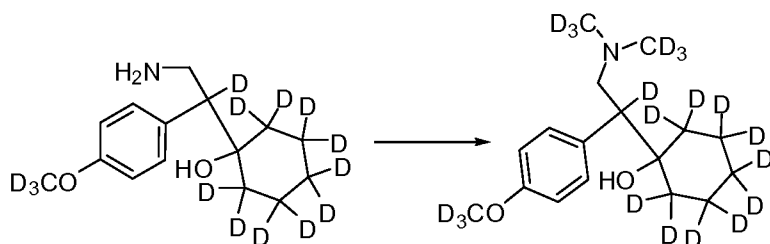


[0145] A solution of d_{14} -1-[2-amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (257.0 mg, 0.98 mmol), formic acid (0.334 mL), and formaldehyde (37% in water, 0.146 mL) in water (2.32 mL) was stirred at room temperature for 45 minutes. Formaldehyde (37% in water, 0.146 mL) was added and the mixture was heated to reflux for 17 hours, cooled to room temperature, washed with ethyl acetate, made basic with 20% aqueous sodium hydroxide and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude residue which was purified by column chromatography (ethyl acetate-methanol-ammonium hydroxide) to give the desired product, d_{14} -1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol, as a clear colorless oil.

[0146] Yield: 154.4 mg (54%), $^1\text{H-NMR}$ (methanol- d_4) δ ppm: 2.25 (s, 6 H), 2.55 (d, 1 H), 3.14 (d, 1 H), 6.84 (d, 2 H), 7.13 (d, 2 H).

Example 19 - d_{20} -1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d_{20} -venlafaxine)

[0147]

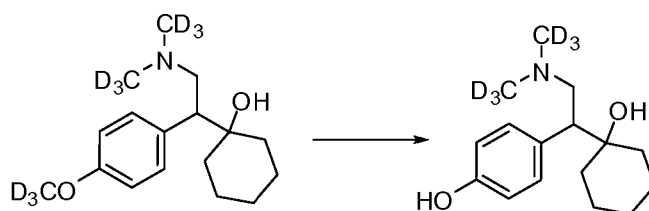


[0148] The title compound was prepared as in Example 15.

[0149] Yield (31%). $^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.33 (d, 1H, $J = 12.6\text{Hz}$), 3.30 (d, 1H, $J = 12.6\text{Hz}$), 6.81 (d, 2H, $J = 9.0\text{Hz}$), 7.05 (d, 2H, $J = 9.0\text{Hz}$). MS (m/z): 298 ($M+1$).

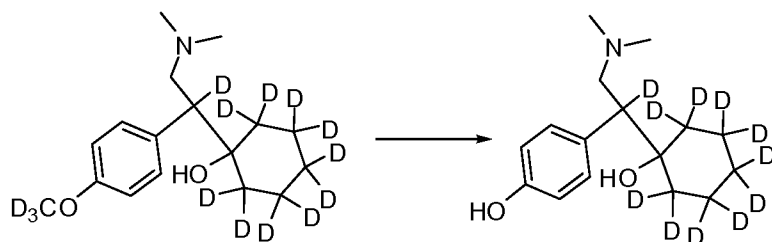
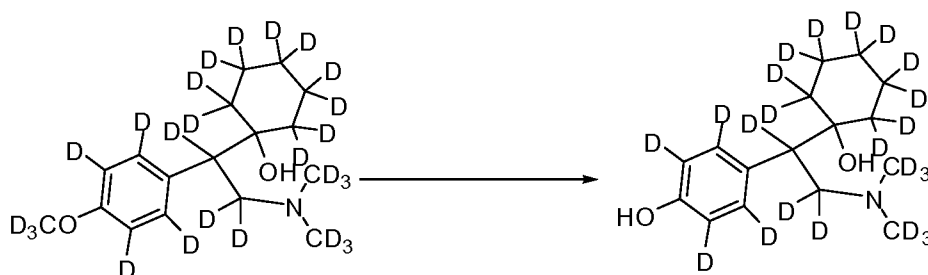
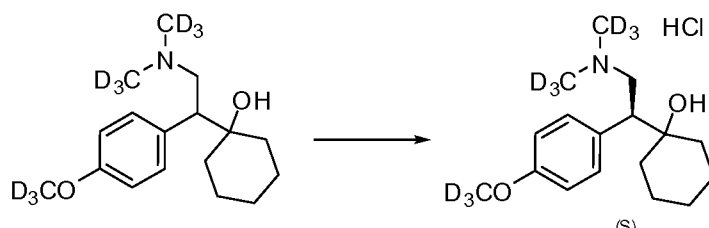
Example 20 - d_6 -4-[2-Dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol (d_6 -O-desmethylvenlafaxine)

[0150]



[0151] A 1.0 M solution of boron tribromide in methylene chloride (0.125 mL, 0.125 mol) was added at -40°C to a stirred solution of d_6 -venlafaxine (17 mg, 0.059 mmol) in methylene chloride (0.5 mL) over 5 minutes, and the mixture was allowed to warm to 0°C over 30 minutes. After being stirred for additional 3 hours at 0°C , the reaction was quenched at 0°C with aqueous 2N NaOH (0.35 mL) and the mixture was slowly allowed to warm to ambient temperature overnight with stirring. The solvent was removed under reduced pressure and the resulting residue was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound as a beige solid.

[0152] Yield: 75%. $^1\text{H-NMR}$ (CDCl_3) δ : 0.75-1.80 (m, 10H), 2.52 (dd, 1H, $J = 12.3, 4.2\text{ Hz}$), 2.99 (dd, 1H, $J = 10.2, 4.2\text{ Hz}$), 3.39 (t, 1H, $J = 10.8\text{ Hz}$), 6.75 (d, 2H, $J = 8.7\text{ Hz}$), 6.99 (d, 1H, $J = 8.7\text{ Hz}$). MS: m/z 270.1 (M^++1).

Example 21 - d₁₁-4-[2-Dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol (d₁₁-O-desmethyivenlafaxine)**[0153]****[0154]** The title compound is prepared from d₁₄-venlafaxine according to Example 20.**Example 22 - d₂₃-4-[2-Dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol (d₂₃-O-desmethyivenlafaxine)****[0155]****[0156]** The title compound is prepared from d₂₆-venlafaxine according to Example 20.**Example 23 -(S)-d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol Hydrochloride Salt ((S)-d₉-venlafaxine HCl)****[0157]**

[0158] A solution of (-)-di-*p*-toluoyl-L-tartaric acid (3.60 mmol) in ethyl acetate (10mL) was added at once at room temperature to a solution of d₉-venlafaxine (7.22 mmol) in ethyl acetate (20 mL), and the mixture was stirred at room temperature for 4 hours. The resulting precipitate was collected by filtration, dried and recrystallized from a mixture of methanol and ethyl acetate to afford d₉-(S)-venlafaxine di-*p*-toluoyl-L tartarate salt as white crystals (optical purity > 99.5% by a chiral HPLC). The filtrate was used to provide d₉-(R)-venlafaxine (see Example 18). Chiral separation was performed at ambient temperature on an Agilent 1100 HPLC equipped with a Chirobiotic V chiral column (Astec), 250 x 4.6 mm column. Isocratic gradient: 5 mM ammonium acetate in water (60%) and tetrahydrofuran (40%); Flowrate: 1 mL/min; Run time: 30 minutes; Injection volume: 10 μL injection (1 mg/mL). UV wavelength: 229 nm. All samples were dissolved in acetonitrile-water (1:1).

[0159] d₉-(S)-venlafaxine di-*p*-toluoyl-L tartarate salt was suspended in dichloromethane (25 mL) and treated with 2N NaOH until pH 13. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give d₉-(S)-venlafaxine as a white solid Yield: 0.71g. ¹H-NMR (CDCl₃) δ: 0.75-1.80 (m, 10H), 2.37(s, 6H), 2.40(m, 1H), 3.01 (dd, 1H, J = 11.1,

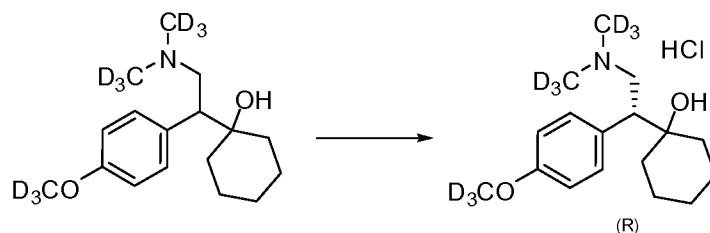
3.3 Hz), 3.39 (t, 1H, J = 12.0 Hz), 6.81 (d, 2H, J = 8.7 Hz), 7.05 (d, 1H, J = 8.7 Hz). MS: m/z 281.3 (M⁺+1).

[0160] d₉-(S)-venlafaxine (0.69g, 2.46 mol) was dissolved in ether (30 mL) and treated with a solution of 2N HCl in ether (1.7mL) at 0-5 °C for 10 minutes. The precipitate was filtered, washed with ether, and recrystallized from a mixture of ether and methanol to give d₉-(S)-venlafaxine HCl salt as a white solid (optical purity > 99.5% by chiral HPLC).

[0161] Yield: 0.55g. ¹H-NMR (CD₃OD) δ: 0.95-1.80 (m, 10H), 2.83(s, 6H), 3.04 (dd, 1H, J = 9.9, 5.4 Hz), 3.68 (m, 2H), 6.96 (d, 2H, J = 9.0 Hz), 7.30 (d, 1H, J = 9.0 Hz). Chiral HPLC: RT = 23.45 min.

Example 24 - (R)-d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol Hydrochloride Salt ((R)-d₉-venlafaxine HCl)

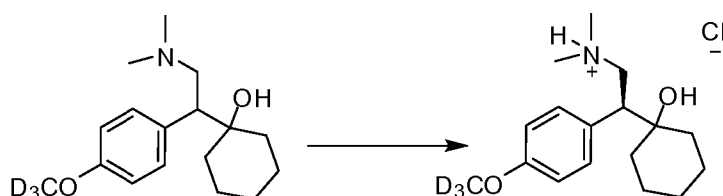
[0162]



[0163] The filtrate obtained in Example 23 was concentrated under reduced pressure, and the resulting residue (1.80g) was dissolved in dichloromethane and treated with 2N aqueous sodium hydroxide as in Example 23, washed with brine, and concentrated to give a white solid (1.01g), which was dissolved in ethyl acetate (15mL) and treated with (+)-di-*p*-toluoyl-D-tartaric acid in ethyl acetate (10 mL). The mixture was stirred at room temperature for 4 hours. The resulting white precipitate was collected by filtration and recrystallized from a mixture of ethyl acetate and methanol to provide d₉-(R)-venlafaxine di-*p*-toluoyl-D tartarate salt (optical purity > 99.5% by chiral HPLC). The corresponding free base of d₉-(R)-venlafaxine (optical purity > 99.5% by chiral HPLC) were prepared as in Example 23.

Example 25 - (S)-d₃-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride ((S)-d₃-venlafaxine HCl)

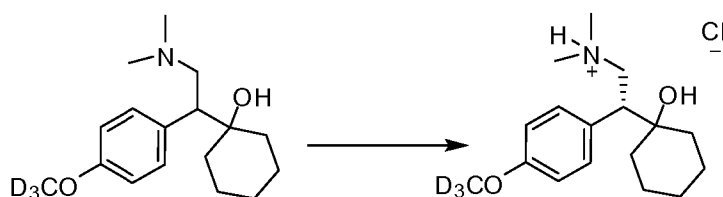
[0164]



[0165] Prepared according to Example 23.

Example 26 - (R)-d₃-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride ((R)-d₃-venlafaxine HCl)

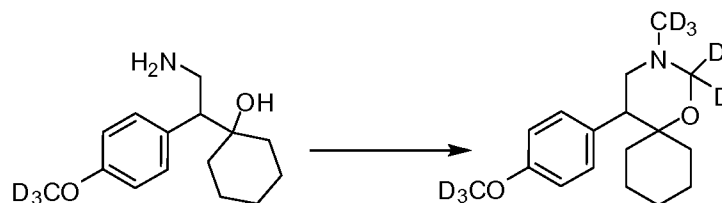
[0166]



[0167] Prepared according to Example 23.

Example 27 - d₈-5-(4-Methoxy-phenyl)-3-methyl-1-oxa-3-aza-spiro[5.5]undecane

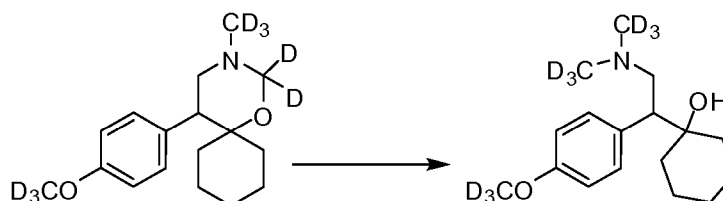
[0168]



[0169] A solution of d₃-1-[2-amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (0.126 g, 0.5 mmol), d₂ formic acid (0.3 mL), and d₂-formaldehyde (20 wt% in deuterium oxide, 0.25 mL) in deuterium oxide (1.5 mL) was heated at 100°C for 16 hours, cooled to ambient temperature, diluted with water (5 mL), neutralized with 35% aqueous ammonia, and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to yield a crude residue which was purified by flash chromatography (ethyl acetate-methanol-ammonium hydroxide) to give the desired product, d₈-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-aza-spiro[5.5]undecane. ¹H-NMR (CDCl₃) δ: 0.75-1.80 (m, 9H), 2.28 (br d, 1H), 2.70 (dd, 1H, J = 12.3, 3.6 Hz), 3.03 (dd, 1H, J = 12.3, 3.6 Hz), 3.21 (t, 1H, J = 12.3 Hz), 6.81 (d, 2H, J = 8.7 Hz), 7.05 (d, 2H, J = 8.7 Hz). MS: m/z 284 (M+1).

Example 28 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d₉-venlafaxine)

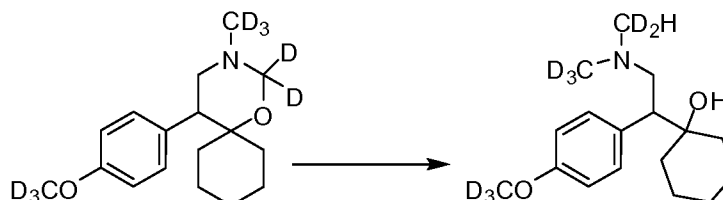
[0170]



[0171] A stirred emulsion of d₈-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-aza-spiro[5.5]undecane (1.93 g, 6.82 mmol) in deuterium oxide (25 mL) was treated with d₂-formic acid (1.96g, 40.92 mmol), and 30% sodium deuterioxide in deuterium oxide (2.8 mL, 20.46 mmol) at ambient temperature. The resulting clear solution was heated at 100°C for 20 hours, cooled to ambient temperature, diluted with water, basified to pH = 11 with 2N aqueous sodium hydroxide, and extracted with ethyl acetate. The combined organic extracts were dried and concentrated under reduced pressure to give a crude residue, which was purified by flash column chromatography to afford d₉-venlafaxine (1.21 g, 62%) as a white solid.

Example 29 - d₈-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol (d₈-venlafaxine)

[0172]

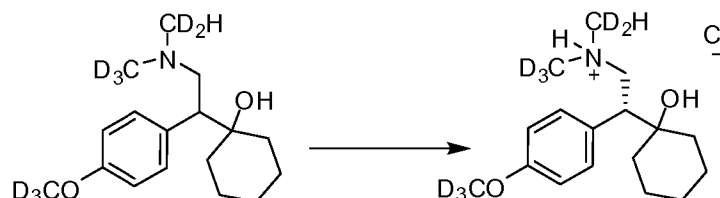


[0173] A stirred emulsion of d₈-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-aza-spiro[5.5]undecane (123 mg, 0.434 mmol) in water (1 mL) was treated with formic acid (100 mg, 2.17 mmol), and sodium formate at 100°C for 18 hours, cooled to ambient temperature, diluted with water, basified to pH = 11 with 2N aqueous sodium hydroxide, and extracted with

ethyl acetate. The combined organic extracts were dried and concentrated under reduced pressure to give a crude residue, which was purified by flash column chromatography to afford d₈-venlafaxine (68 mg, 55%) as a white solid. ¹H-NMR (CDCl₃) δ: 0.75-1.80 (m, 10H), 2.28 (s, 1H), 2.32 (dd, 1H, J = 12.3, 3.3 Hz), 2.96 (dd, 1H, J = 12.3, 3.3 Hz), 3.31 (t, 1H, J = 12.3 Hz), 6.81 (d, 2H, J = 8.7 Hz), 7.05 (d, 2H, J = 8.7 Hz). MS: m/z 286.4 (M+1).

Example 30 - d₈-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride (d₈-venlafaxine hydrochloride)

[0174]



[0175] Prepared according to Example 23. ¹H-NMR (CD₃OD) δ: 0.85-1.80 (m, 10H), 2.80 (s, 1H), 3.04 (dd, 1H, J = 9.9, 5.4 Hz), 3.59-3.75 (m, 2H), 6.96 (d, 2H, J = 8.4 Hz), 7.30 (d, 2H, J = 8.4 Hz).

Example 31 - d₅-1-[2-Amino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol

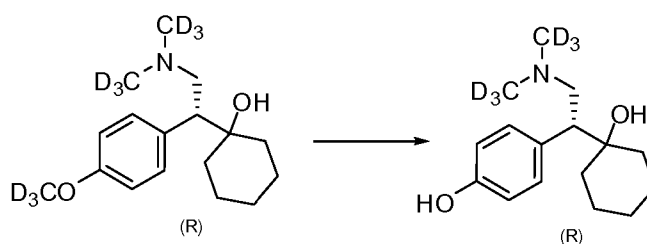
[0176]



[0177] The title compound can be prepared according to the procedure of Example 7, by substituting the water reservoir with a deuterium oxide reservoir for the generation of deuterium gas.

Example 32 - (R)-d₆-4-[2-Dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol ((R)-d₆-O-desmethylvenlafaxine)

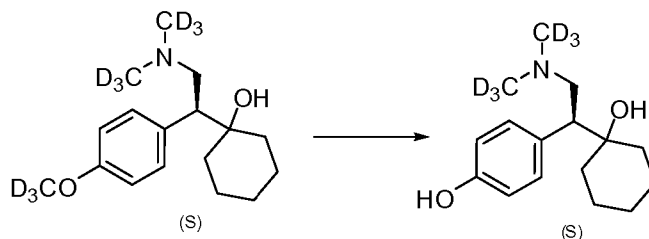
[0178]



[0179] The title compound was prepared from (R)-d₉-venlafaxine according to Example 20.

Example 33 - (S)-d₆-4-[2-Dimethylamino-1-(1-hydroxycyclohexyl)-ethyl]-phenol ((S)-d₆-O-desmethylvenlafaxine)

[0180]



[0181] The title compound was prepared from (S)-d₉-venlafaxine according to Example 20.

Example 34 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride Form A (d₉-venlafaxine hydrochloride Form A)

[0182] d₉-Venlafaxine hydrochloride (500mg) was dissolved in isopropanol (8 mL) at about 60°C, and subsequently cooled to 0-5°C in ice-water bath and kept at that temperature for about 3 hours. The solid was filtered, washed with cold isopropanol and dried under high vacuum to give d₉-venlafaxine hydrochloride Form A (248mg). Characteristic X-ray powder diffraction peaks (2-theta, [% relative intensity]): 6.703 [29.3], 8.321 [19], 12.681 [77.5], 13.5 [47.9], 15.54 [17.7], 18.918 [24.4], 20.359 [100], 21.161 [38.3], 21.762 [26.1], 25.04 [27.8], 28.518 [18.2], and 35.181 [15.5]. A sample of d₉-venlafaxine hydrochloride Form A was analyzed by infrared spectroscopy. The results are shown in FIGURE 7.

Example 35 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride Form B (d₉-venlafaxine hydrochloride Form B)

[0183] d₉-Venlafaxine hydrochloride (150mg) was triturated in a vial with acetone at about 60°C for about 1 hour and cooled to 0-5°C for about 1 hour. The solid was filtered, washed with cold acetone and dried at 50°C on rotary evaporator to a constant weight to give ds-venlafaxine hydrochloride Form B (102mg). Characteristic X-ray powder diffraction peaks (2-theta, [% relative intensity]): 6.683 [15.5], 10.201 [93.6], 13.441 [27.8], 15.517 [66.2], 18.198 [41], 19.719 [34.1], 20.258 [100], 21.68 [71.2], 22.658 [24.8], 25.543 [22.4], 28.022 [20.9], and 35.02 [33.4]. A sample of d₉-venlafaxine hydrochloride Form B was analyzed by infrared spectroscopy. The results are shown in FIGURE 8. A sample of d₉-venlafaxine hydrochloride Form B was heated at 10°C/min from ambient to approximately 700°C and then in regular mode to 1000°C, in a nitrogen atmosphere (25 cc/min). The results are shown in FIGURE 13.

Example 36 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride Form C (d₉-venlafaxine hydrochloride Form C)

[0184] A slurry of d₉-venlafaxine hydrochloride Form A (70mg) in isopropanol (0.56 mL) was stirred in a vial at ambient temperature for 3 days. The solid was filtered, washed with cold isopropanol and dried under high vacuum to give d₉-venlafaxine hydrochloride Form C (30mg). Characteristic X-ray powder diffraction peaks (2-theta, [% relative intensity]): 6.718 [21.4], 8.335 [20.6], 12.68 [80], 13.5 [40.7], 15.539 [20.2], 16.282 [24.3], 18.902 [48.9], 19.737 [17.4], 20.34 [100], 21.161 [79.4], 21.758 [30.5], 25.601 [18.9], 26.261 [15.2], 28.518 [30.2], 31.54 [18.7], 33.937 [16.5], and 35.159 [21.3]. A sample of d₉-venlafaxine hydrochloride Form C was analyzed by infrared spectroscopy. The results are shown in FIGURE 9. A sample of d₉-venlafaxine hydrochloride Form C was heated at 10°C/min from ambient to approximately 700°C and then in regular mode to 1000°C, in a nitrogen atmosphere (25 cc/min). The results are shown in FIGURE 14.

Example 37 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride Form D (d₉-venlafaxine hydrochloride Form D)

[0185] A suspension of d₉-venlafaxine hydrochloride (1.45g) in ether (40 mL) was heated under reflux at 65°C. Methanol was added dropwise to the mixture until it became homogeneous and the solution was cooled to ambient temperature, and kept at that temperature for 1 hour and at 0-5°C for an additional 3 hours. The solid was filtered and dried under high vacuum to provide d₉-venlafaxine hydrochloride Form D (1.08g). Characteristic X-ray powder diffraction peaks (2-theta, [% relative intensity]): 6.74 [21.2], 7.421 [14], 8.341 [35.5], 10.219 [23], 12.7 [99.5], 13.502 [40.7], 17.9 [17.5], 15.541 [37.3], 20.36 [100], 21.221 [23.7], 21.761 [41], 25.078 [26.3], 31.04 [17.7], and 35.139 [22.7]. A sample of d₉-venlafaxine hydrochloride Form D was analyzed by infrared spectroscopy. The results are shown in FIGURE 10.

Example 38 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride Form E (d₉-venlafaxine hydrochloride Form E)

[0186] d₉-Venlafaxine hydrochloride Form D (98mg) was heated in a sealed tube for 1.5 hours at 200-200°C and cooled to ambient temperature. Characteristic X-ray powder diffraction peaks (2-theta, [% relative intensity]): 5.597 [28], 7.182 [36.2], 9.078 [24.1], 9.557 [14.9], 11.201 [100], 14.46 [40.2], 14.76 [40.4], 16.86 [71.7], 17.497 [15.7], 19.201 [66.5], 19.619 [19.6], 20.241 [35.2], 20.66 [19.6], 21.76 [22.5], 22.596 [26.4], 23.06 [13.2], 24.4 [15.3], 26.842 [18.7], 31.52 [12.6], and 35.438 [17.9]. A sample of d₉-venlafaxine hydrochloride Form E was analyzed by infrared spectroscopy. The results are shown in FIGURE 11. A sample of d₉-venlafaxine hydrochloride Form E was heated at 10°C/min from ambient to approximately 700°C and then in regular mode to 1000°C, in a nitrogen atmosphere (25 cc/min). The results are shown in FIGURE 15.

Example 39 - d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride Form F (d₉-venlafaxine hydrochloride Form F)

[0187] d₉-Venlafaxine hydrochloride Form A (68mg) was heated at 205°C for 2 hours and cooled to ambient temperature. The crystals that formed at the top of the flask were collected. Characteristic X-ray powder diffraction peaks (2-theta, [% relative intensity]): 5.581 [26.1], 7.186 [18.3], 11.22 [100], 14.499 [18.8], 14.802 [20.5], 16.882 [63.9], 19.242 [38.4], 20.317 [51.6], 21.798 [17.5], 22.637 [26.3], and 35.445 [16.2]. A sample of d₉-venlafaxine hydrochloride Form F was analyzed by infrared spectroscopy. The results are shown in FIGURE 12.

Example 40 - In vitro Liver Microsomal Stability Assay

[0188] Liver microsomal stability assays were conducted at 1 mg per mL liver microsome protein with an NADPH-generating system in 2%NaHCO₃ (2.2 mM NADPH, 25.6 mM glucose 6-phosphate, 6 units per mL glucose 6-phosphate dehydrogenase and 3.3 mM MgCl₂). Test compounds were prepared as solutions in 20% acetonitrile-water and added to the assay mixture (final assay concentration 5 microgram per mL) and incubated at 37°C. Final concentration of acetonitrile in the assay were <1%. Aliquots (50 μL) were taken out at times 0, 15, 30, 45, and 60 minutes, and diluted with ice cold acetonitrile (200 μL) to stop the reactions. Samples were centrifuged at 12000 RPM for 10 minutes to precipitate proteins. Supernatants were transferred to microcentrifuge tubes and stored for LC/MS/MS analysis of the degradation half-life of the test compounds. It has thus been found that the compounds as disclosed herein that have been tested in this assay showed an increase of 10% or more in the degradation half-life, as compared to the non-isotopically enriched drug. For example, the degradation half-life of (±)-d₃-venlafaxine, (R)-d₃-venlafaxine, (S)-d₃-venlafaxine, (±)-d₈-venlafaxine, (±)-d₉-venlafaxine, (R)-d₉-venlafaxine, (S)-d₉-venlafaxine, d₁₄-venlafaxine, and d₂₀-venlafaxine were increased by 50-300% as compared to non-isotopically enriched venlafaxine.

Example 41 - In vitro metabolism using human cytochrome P₄₅₀ enzymes

[0189] The cytochrome P₄₅₀ enzymes are expressed from the corresponding human cDNA using a baculovirus expression system (BD Biosciences). A 0.25 milliliter reaction mixture containing 0.8 milligrams per milliliter protein, 1.3 millimolar NADP⁺, 3.3 millimolar glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3 millimolar magnesium chloride and 0.2 millimolar of a compound of Formula I, the corresponding non-isotopically enriched compound or standard or control in 100 millimolar potassium phosphate (pH 7.4) is incubated at 37°C for 20 min. After incubation, the reaction is stopped by the addition of an appropriate solvent (e.g. acetonitrile, 20% trichloroacetic acid, 94% acetonitrile/6% glacial acetic acid, 70% perchloric acid, 94% acetonitrile/6% glacial acetic acid) and centrifuged (10,000 g) for 3 minutes. The supernatant is analyzed by HPLC/MS/MS.

Cytochrome P ₄₅₀	Standard
CYP1A2	Phenacetin
CYP2A6	Coumarin
CYP2B6	[¹³ C]-(S)-mephenytoin
CYP2C8	Paclitaxel
CYP2C9	Diclofenac
CYP2C19	[¹³ C]-(S)-mephenytoin

(continued)

Cytochrome P ₄₅₀	Standard
CYP2D6	(+/-)-Bufuralol
CYP2E1	Chlorzoxazone
CYP3A4	Testosterone
CYP4A	[¹³ C]-Lauric acid

Example 42 - Monoamine Oxidase A Inhibition and Oxidative Turnover

[0190] The procedure is carried out as described in Weyler, Journal of Biological Chemistry 1985, 260, 13199-13207. Monoamine oxidase A activity is measured spectrophotometrically by monitoring the increase in absorbance at 314 nm on oxidation of kynuramine with formation of 4-hydroxyquinoline. The measurements are carried out, at 30°C, in 50mM NaP_i buffer, pH 7.2, containing 0.2% Triton X-100 (monoamine oxidase assay buffer), plus 1 mM kynuramine, and the desired amount of enzyme in 1 mL total volume.

Example 43 - Monoamine Oxidase B Inhibition and Oxidative Turnover

[0191] The procedure is carried out as described in Uebelhack, Pharmacopsychiatry 1998,31,187-192.

Pharmacology

[0192] The pharmacological profile of compounds as described herein or the non-isotopically enriched compounds or standards or controls can be demonstrated as follows. The preferred exemplified compounds exhibit a K_i value less than 1 micromolar, more preferably less than 500 nanomolar at the Serotonin transporter as determined using the scintillation proximity assay (SPA) described below. See WO 2005/060949. Furthermore, the preferred exemplified compounds selectively inhibit the Serotonin transporter relative to the Norepinephrine and dopamine transporters by a factor of at least five using such SPAs.

Example 44 - Generation of stable cell lines expressing the human dopamine, norepinephrine and serotonin transporters

[0193] Standard molecular cloning techniques are used to generate stable cell-lines expressing the human dopamine, norepinephrine and serotonin transporters. The polymerase chain reaction (PCR) is used in order to isolate and amplify each of the three full-length cDNAs from an appropriate cDNA library. PCR Primers for the following neurotransmitter transporters are designed using published sequence data. The PCR products are cloned into a mammalian expression vector, such as for example pcDNA3.1 (Invitrogen), using standard ligation techniques, followed by co-transfection of HEK293 cells using a commercially available lipofection reagent (Lipofectamine™ - Invitrogen) following the manufacturer's protocol.

- Human Dopamine transporter: GenBank M95167. Vandenberg et al, Molecular Brain Research 1992, 15, 161-166,
- Human Norepinephrine transporter: GenBank M65105. Pacholczyk et al, Nature 1991, 350, 350-354.
- Human Serotonin transporter: GenBank L05568. Ramamoorthy et al, Proceedings of the National Academy of Sciences of the USA 1993, 90, 2542-2546.

Example 45 - In vitro SPA binding assay for the norepinephrine transporter

[0194] The assay is performed according to the procedure described in Gobel et al, Journal of Pharmacological and Toxicological Methods 1999, 42(4), 237-244. Compounds as described herein or the corresponding non-isotopically enriched compounds are serotonin/norepinephrine reuptake inhibitors; ³H-nisoxetine binding to norepinephrine re-uptake sites in a cell line transfected with DNA encoding human norepinephrine transporter binding protein has been used to determine the affinity of ligands at the norepinephrine transporter.

Membrane Preparation

[0195] Cell pastes from large scale production of HEK-293 cells expressing cloned human norepinephrine transporters

are homogenized in 4 volumes of 50 millimolar Tris-HCl containing 300 millimolar NaCl and 5 millimolar KCl, pH 7.4. The homogenate is centrifuged twice (40,000g, 10 minutes, 4°C) with pellet re-suspension in 4 volumes of Tris-HCl buffer containing the above reagents after the first spin, and 8 volumes after the second spin. The suspended homogenate is centrifuged (100g, 10 minutes, 4°C), the supernatant is kept and re-centrifuged (40,000g, 20 minutes, 4°C). The pellet is re-suspended in Tris-HCl buffer containing the above reagents along with 10% w/v sucrose and 0.1 millimolar phenylmethylsulfonyl fluoride (PMSF). The membrane preparation is stored in aliquots (1.0 milliliter) at -80°C until required. The protein concentration of the membrane preparation is determined using a Bicinchoninic acid (BCA) protein assay reagent kit (available from Pierce).

[³H]-Nisoxetine Binding Assay

[0196] Each well of a 96 well microtiter plate is set up to contain 50 microliters of 2 nanomolar [N-methyl-³H]-Nisoxetine hydrochloride (70-87 Ci/millimole, from NEN Life Science Products), 75 microliters Assay buffer (50 millimolar Tris-HCl pH 7.4 containing 300 millimolar NaCl and 5 millimolar KCl), 25 microliter of diluted compounds of Formula I or the corresponding non-isotopically enriched compounds, assay buffer (total binding) or 10 micromolar Desipramine HCl (non-specific binding), 50 microliter wheat germ agglutinin coated poly (vinyltoluene) (WGA PVT) SPA Beads (Amersham Biosciences RPNQ0001) (10 milligram/milliliter), 50 microliter membrane (0.2 milligram protein per milliliter). The microtiter plates are incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results are analyzed using an automatic spline-fitting program (Multicalc, Packard, Milton Keynes, UK) to provide K_i values for each of the test compounds.

Example 46 - In vitro SPA binding assay for the Serotonin transporter

[0197] The assay is preformed according to the procedure described in Ramamoorthy et al, J. Biol. Chem. 1998, 273(4), 2458-2466.

[0198] The ability of a compound as described herein or the corresponding non-isotopically enriched compound to compete with [³H]-Citalopram for its binding sites on cloned human Serotonin transporter containing membranes has been used as a measure of test compound ability to block Serotonin uptake via its specific transporter.

Membrane preparation

[0199] Membrane preparation is essentially similar to that for the norepinephrine transporter containing membranes as described above. The membrane preparation is stored in aliquots (1 milliliter) at -70°C until required. The protein concentration of the membrane preparation is determined using a BCA protein assay reagent kit.

[³H]-Citalopram binding assay

[0200] Each well of a 96 well microtiter plate is set up to contain 50 microliters of 2 nanomolar [³H]-citalopram (60-86Ci/millimole, Amersham Biosciences), 75 microliters Assay buffer (50 millimolar Tris-HCl pH 7.4 containing 150 millimolar NaCl and 5 millimolar KCl), 25 microliters of diluted compounds of Formula 1 or the corresponding non-isotopically enriched compounds, assay buffer (total binding) or 100 micromolar fluoxetine (non-specific binding), 50 microliters WGA PVT SPA Beads (40 milligram/milliliter), 50 microliters membrane preparation (0.4 milligram protein per milliliter). The microtiter plates are incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results are analyzed using an automatic spline-fitting program (Multicalc, Packard, Milton Keynes, UK) to provide K_i (nanomolar) values for each of the test compounds.

Example 47 - In vitro SPA binding assay for the dopamine transporter

[0201] The assay is preformed according to the procedure described in Ramamoorthy et al, J. Biol. Chem. 1998, 273(4), 2458-2466.

[0202] The ability of a test compound to compete with [³H]-WIN35,428 for its binding sites on human cell membranes containing cloned human dopamine transporter has been used as a measure of the ability of such test compounds to block dopamine uptake via its specific transporter.

Membrane Preparation

[0203] Membrane preparation is performed in the same manner as membranes containing cloned human Serotonin transporter as described above.

[³H]-WIN35,428 Binding Assay

[0204] Each well of a 96 well microtiter plate is set up to contain 50 microliters of 4 nanomolar [³H]-WIN35,428 (84-87 Ci/millimole, from NEN Life Science Products), 5 microliters Assay buffer (50 millimolar Tris-HCl pH 7.4 containing 150 millimolar NaCl and 5 millimolar KCl), 25 microliters of diluted compounds as described herein or the corresponding non-isotopically enriched compounds, assay buffer (total binding) or 100 micromolar nomifensine (non-specific binding), 50 microliters WGA PVT SPA Beads (10 milligram/milliliter), 50 microliters membrane preparation (0.2 milligram protein per milliliter). The microtiter plates are incubated at room temperature for 120 minutes prior to reading in a Trilux scintillation counter. The results are analyzed using an automatic spline-fitting program (Multicalc, Packard, Milton Keynes, UK) to provide K_i values for each of the test compounds.

Example 48 - In vivo assay for behavioral despair in rats

[0205] The assay is performed according to the procedure described in Porsolt et al, Archives Internationales de Pharmacodynamie et de Therapie, 1977, 229(2), 327-336.

[0206] After intraperitoneal administration of test compound in rats, animals are put in a cylinder containing water for 6 minutes. Immobility time is measured during the last 4 minutes. Diminished time of immobility is indicative of increased efficacy.

[0207] The examples set forth above are disclosed to give a complete disclosure and description of how to make and use various deuterated compounds, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious, are intended to be within the scope of the claims.

[0208] With respect to any similar or identical terms found in both the publications, references, patent or patent applications referenced herein and those explicitly put forth or defined in this document, then those terms definitions or meanings explicitly put forth in this document shall control in all respects.

Patent Documents**[0209]**

US 4,069,346 February 14, 1977 McCarty
 US 5,386,032 January 31, 1995 Brandstrom
 EP0654264 May 24, 1995 Thor
 US 5,846,514 December 8, 1998 Foster
 US 6,221,335 April 24, 2001 Foster
 US 6,333,342 December 25, 2001 Foster
 US 6,334,997 January 1, 2002 Foster
 US 6,342,507 January 29, 2002 Foster
 US 6,476,058 November 5, 2002 Foster
 US 6,503,921 January 7, 2003 Naicker
 US 6,605,593 August 12, 2003 Naicker
 US 6,613,739 September 2, 2003 Naicker
 US 6,710,053 March 23, 2004 Naicker
 US 6,818,200 November 16, 2004 Foster
 US 6,884,429 April 26, 2005 Koziak
 WO 2002064543 August 22, 2002 Hadfield

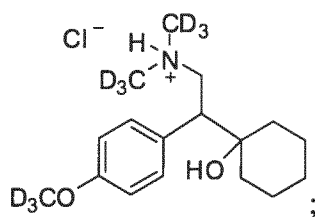
Other References**[0210]**

Altermatt, Cancer 1988, 62(3), 462-466.
 Altermatt, International Journal of Cancer 1990, 45(3), 475-480.
 Baldwin, International Journal of Neuropsychopharmacology 2005, 8(2), 293-302.
 Baselt, Disposition of Toxic Drugs and Chemicals in Man, 2004, 7th Edition.
 Bassapa et al, Bioorganic & Medicinal Chemistry Letters 2004, 14, 3279-3281.
 Browne, Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 7th, Dresden, Germany, June 18-22, 2000, 519-532.
 Browne, Pharmacochemistry Library, 1997, 26.

- Browne, Pharmacochemistry Library, 1997, 26, 13-18.
- Browne, Clinical Pharmacology & Therapeutics, 1981, 29(4), 511-515.
- Browne, Journal of Clinical Pharmacology 1982, 22(7), 309-315.
- Browne, Synth. Appl. Isot. Labeled Compd., Proc. Int. Symp. 1983, Meeting Date 1982, 343-348.
- 5 Browne, Therapeutic Drug Monitoring 1984, 6(1), 3-9.
- Chavan et al, Tetrahedron Letters 2004, 45, 7291-7295.
- Davies et al, Journal of the Chemical Society, Abstracts 1945, 352-354.
- Ding et al Journal of Neurochemistry 1995, 65(2), 682-690.
- Eap et al, Pharmacogenetics 2002, 13, 39-47.
- 10 Foster, Trends in Pharmacological Sciences 1984, 5(12), 524-527.
- Garland, Synth. Appl. Isot. Labeled Compd. Proc. Int. Symp. 2nd, 1986, Meeting Date 1985, 283-284.
- Gobel et al, Journal of Pharmacological and Toxicological Methods 1999, 42(4), 237-244 Goeringer, Journal of Forensic Sciences 2000, 45(3), 633-648.
- Katzman, Expert Review of Neurotherapeutics, 2005, 5(1), 129-139.
- 15 Kaufman, Phys. Rev. 1954, 93, 1337-1344.
- Ko et al British Journal of Clinical Pharmacology 2000, 49(4), 343-351.
- Kritchevsky, Annals of the New York Academy of Science 1960, vol. 84, article 16.
- Kushner, Can. J. Physiol. Pharmacol. 1999, 77, 79-88.
- Lamprect, European Journal of Cell Biology 1990, 51(2), 303-312.
- 20 Lessard et al, Pharmacogenetics 1999, 9(4), 435-443.
- Lewis, J. Am. Chem. Soc. 1968, 90, 4337.
- Li et al Rapid Communications in Mass Spectrometry 2005, 19(14), 1943-1950 Liu et al, Journal of Chromatography B: Biomedical Sciences & Applications, 2006, Vol.850, no.1-2, pages 183-189 March, Advanced Organic Chemistry 1992, 4th edition, 226-230.
- 25 Morton et al, Annals of Pharmacotherapy 1995, 29(4), 387-395.
- Ouk et al Green Chemistry, 2002, 4(5), 431-435.
- Pacher, Current Medicinal Chemistry 2004, 11(7), 925-943.
- Pachcr et al, Current Pharmaceutical Design 2004, 10(20), 2463-2475.
- Pacholczyk et al, Nature 1991, 350, 350-354.
- 30 Phelps et al, Annals of Pharmacotherapy 2005, 39(1), 136-140.
- Physicians Desk Reference, 2003.
- Porsolt et al, Archives Internationales de Pharmacodynamie et de Therapie, 1977, 229(2), 327-336.
- Pohl, Drug Metabolism Reviews 1985 (Volume Date 1984), 15(7), 1335-1351.
- Preskorn et al, Handbook of Experimental Pharmacology. Antidepressants: Past, Present and Future, 2004, Volume 157.
- 35 Raggi, Current Topics in Medicinal Chemistry 2003, 3, 203-220.
- Ramamoorthy et al, J. Biol. Chem. 1998, 273(4), 2458-2466.
- Ramamoorthy et al, Proceedings of the National Academy of Sciences of the USA 1993, 90, 2542-2546.
- Reis et al, Therapeutic Drug Monitoring 2002, 24, 545-553.
- 40 Roecker, J. Am. Chem. Soc. 1987, 109, 746.
- Schroeter, European Journal of Cell Biology 1992, 58(2), 365-370.
- Sicat et al, Pharmacotherapy 2004, 24(1), 79-93.
- Silverstone, Journal of Clinical Psychiatry 2004, 65(Suppl. 17), 19-28.
- Tolonen, European Journal of Pharmaceutical Sciences 2005, 25, 155-162.
- 45 Thomson, International Series of Monographs on Pure and Applied Biology, Modern trends in Physiological Sciences, 1963, "Biological Effects of Deuterium".
- Urey, Phys. Rev. 1932, 39, 164 "A Hydrogen Isotope of Mass 2".
- Vandenbergh et al, Molecular Brain Research 1992, 15, 161-166.
- Yardley et al, Journal of Medicinal Chemistry 1990, 33(10), 2899-2905.

Claims

1. A polymorph of the hydrochloride salt of d₉-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol hydrochloride having the structural formula:



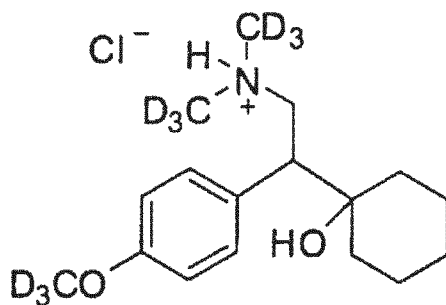
wherein said polymorph exhibits high-intensity diffraction peaks at diffraction angles (2θ) of 6.683, 10.201, 13.441, 15.517, 18.198, 19.719, 20.258, 21.68, 22.658, 25.543, 28.022, and 35.02 in X-ray powder diffraction analysis.

2. A polymorph according to Claim 1 wherein the polymorph has an x-ray diffraction spectrum substantially the same as shown in Figure 2.
3. A polymorph according to Claim 1 wherein said polymorph has an X-ray powder diffraction spectrum having characteristic peaks expressed in degrees (2θ) at approximately:

2-theta	RI	2-theta	RI	2-theta	RI
6.683	15.5	22.658	24.8	31.379	8.2
10.201	93.6	23.923	2.7	31.978	9.1
13.441	27.8	25.322	9.6	32.28	10.5
15.014	7.6	25.543	22.4	32.701	6.5
15.517	66.2	26.502	6.7	32.981	2.3
16.458	1.5	27.122	9.5	34.12	9.1
16.84	10.3	27.557	5.5	35.02	33.4
17.206	2.7	28.022	20.9	36.024	3.1
18.198	41	28.64	4.4	36.842	2.6
19.719	34.1	29.241	10.6	37.5	6.7
20.258	100	29.659	7.1	38.341	3.9
21.68	71.2	31.079	11.9	38.753	1.2

Patentansprüche

1. Polymorph des Hydrochloridsalzes von d₉-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexanol-hydrochlorid mit der Strukturformel:



EP 2 125 698 B1

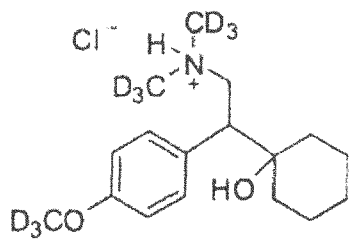
wobei das Polymorph Beugungspeaks hoher Intensität bei Beugungswinkeln (2θ) aufweist von 6,683, 10,201, 13,441, 15,517, 18,198, 19,719, 20,258, 21,68, 22,658, 25,543, 28,022 und 35,02 in Pulver-Röntgenbeugungsanalyse.

2. Polymorph nach Anspruch 1, wobei das Polymorph ein im Wesentlichen gleiches Röntgenbeugungsspektrum aufweist wie in Abbildung 2 gezeigt.
3. Polymorph nach Anspruch 1, wobei das Polymorph ein Pulver-Röntgenbeugungsspektrum aufweist mit charakteristischen Peaks angegeben in Grad (2θ) bei annähernd:

2-theta	RI	2-theta	RI	2-theta	RI
6,683	15,5	22,658	24,8	31,379	8,2
10,201	93,6	23,923	2,7	31,978	9,1
13,441	27,8	25,322	9,6	32,28	10,5
15,014	7,6	25,543	22,4	32,701	6,5
15,517	66,2	26,502	6,7	32,981	2,3
16,458	1,5	27,122	9,5	34,12	9,1
16,84	10,3	27,557	5,5	35,02	33,4
17,206	2,7	28,022	20,9	36,024	3,1
18,198	41	28,64	4,4	36,842	2,6
19,719	34,1	29,241	10,6	37,5	6,7
20,258	100	29,659	7,1	38,341	3,9
21,68	71,2	31,079	11,9	38,753	1,2

Revendications

1. Polymorphe du sel chlorhydrate du chlorhydrate de d_9 -1-[2-diméthylamino-1-(4-méthoxyphényl)-éthyl]-cyclohexanol ayant la formule structurale :



dans laquelle ledit polymorphe présente des pics de diffraction de haute intensité à des angles de diffraction (2θ) de 6,683, 10,201, 13,441, 15,517, 18,198, 19,719, 20,258, 21,68, 22,658, 25,543, 28,022, et 35,02 dans une analyse de diffraction des rayons X sur poudre.

2. Polymorphe selon la revendication 1, dans lequel le polymorphe présente un spectre de diffraction des rayons X sensiblement identique à celui représenté sur la figure 2.
3. Polymorphe selon la revendication 1, dans lequel ledit polymorphe présente un spectre de diffraction des rayons X sur poudre ayant des pics caractéristiques exprimés en degrés (2θ) à approximativement :

EP 2 125 698 B1

5

10

15

20

25

30

35

40

45

50

55

2-thêta	IR	2-thêta	IR	2-thêta	IR
6,683	15,5	22,658	24,8	31,379	8,2
10,201	93,6	23,923	2,7	31,978	9,1
13,441	27,8	25,322	9,6	32,28	10,5
15,014	7,6	25,543	22,4	32,701	6,5
15,517	66,2	26,502	6,7	32,981	2,3
16,458	1,5	27,122	9,5	34,12	9,1
16,84	10,3	27,557	5,5	35,02	33,4
17,206	2,7	28,022	20,9	36,024	3,1
18,198	41	28,64	4,4	36,842	2,6
19,719	34,1	29,241	10,6	37,5	6,7
20,258	100	29,659	7,1	38,341	3,9
21,68	71,2	31,079	11,9	38,753	1,2

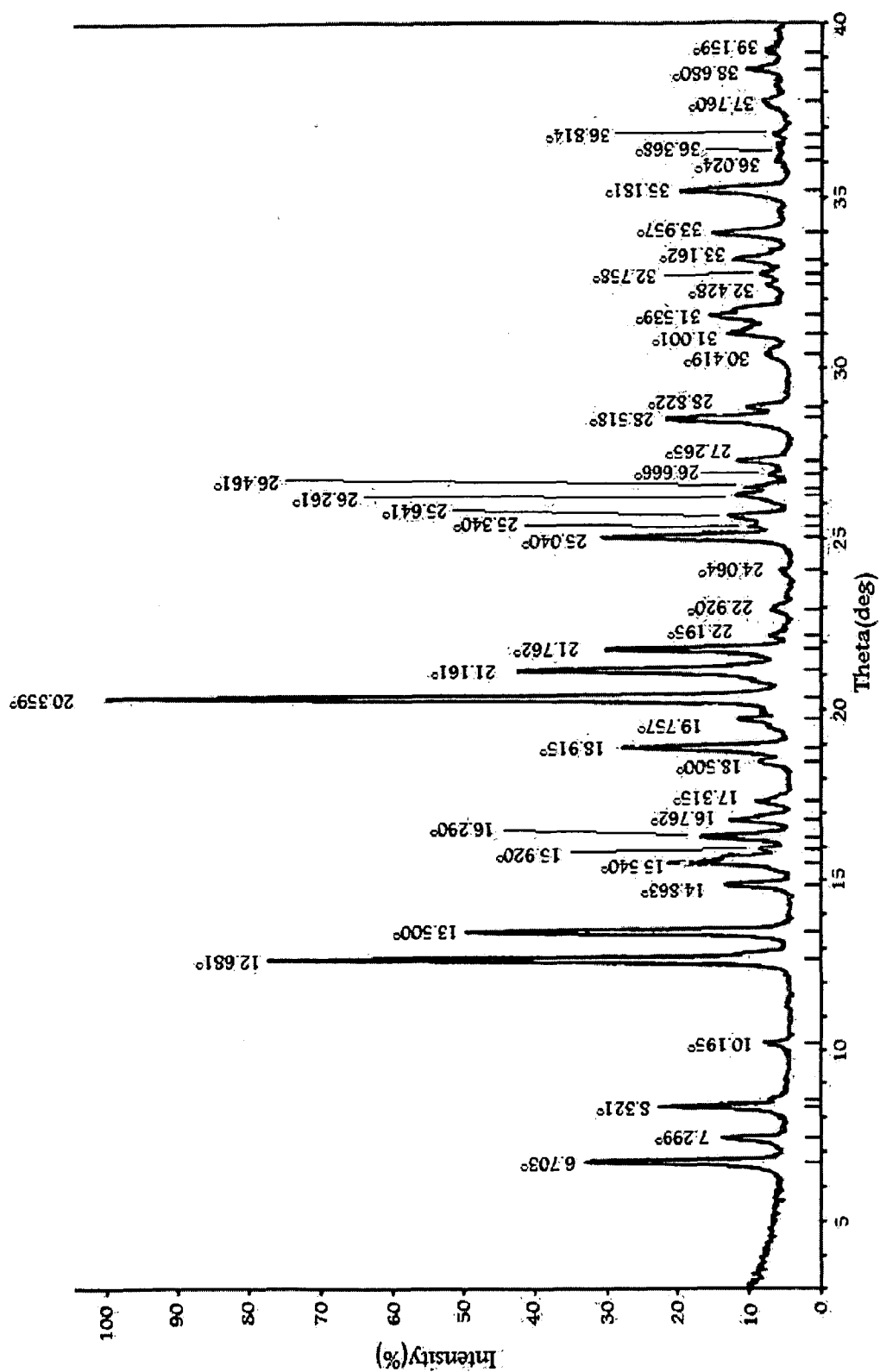
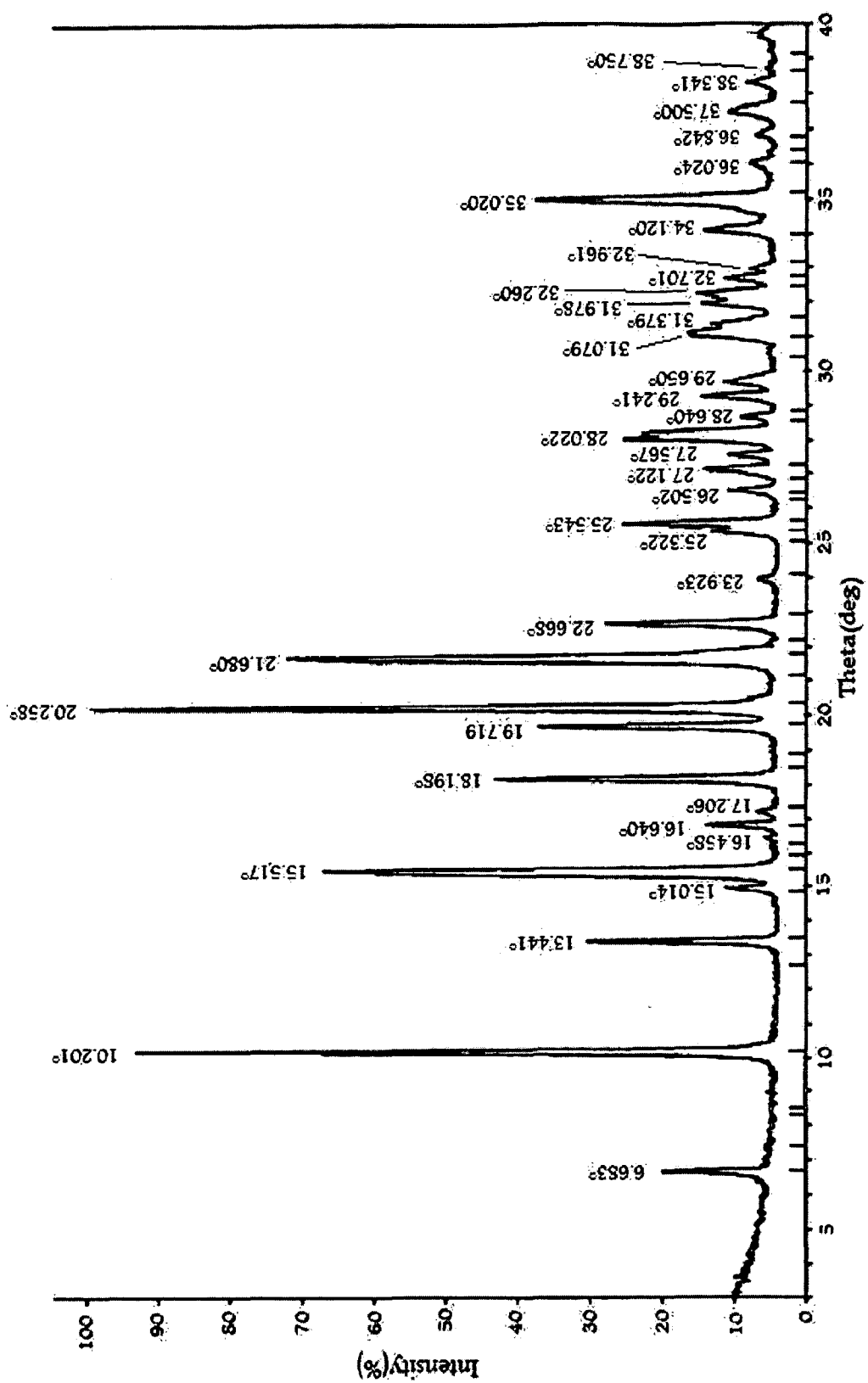


FIGURE 1



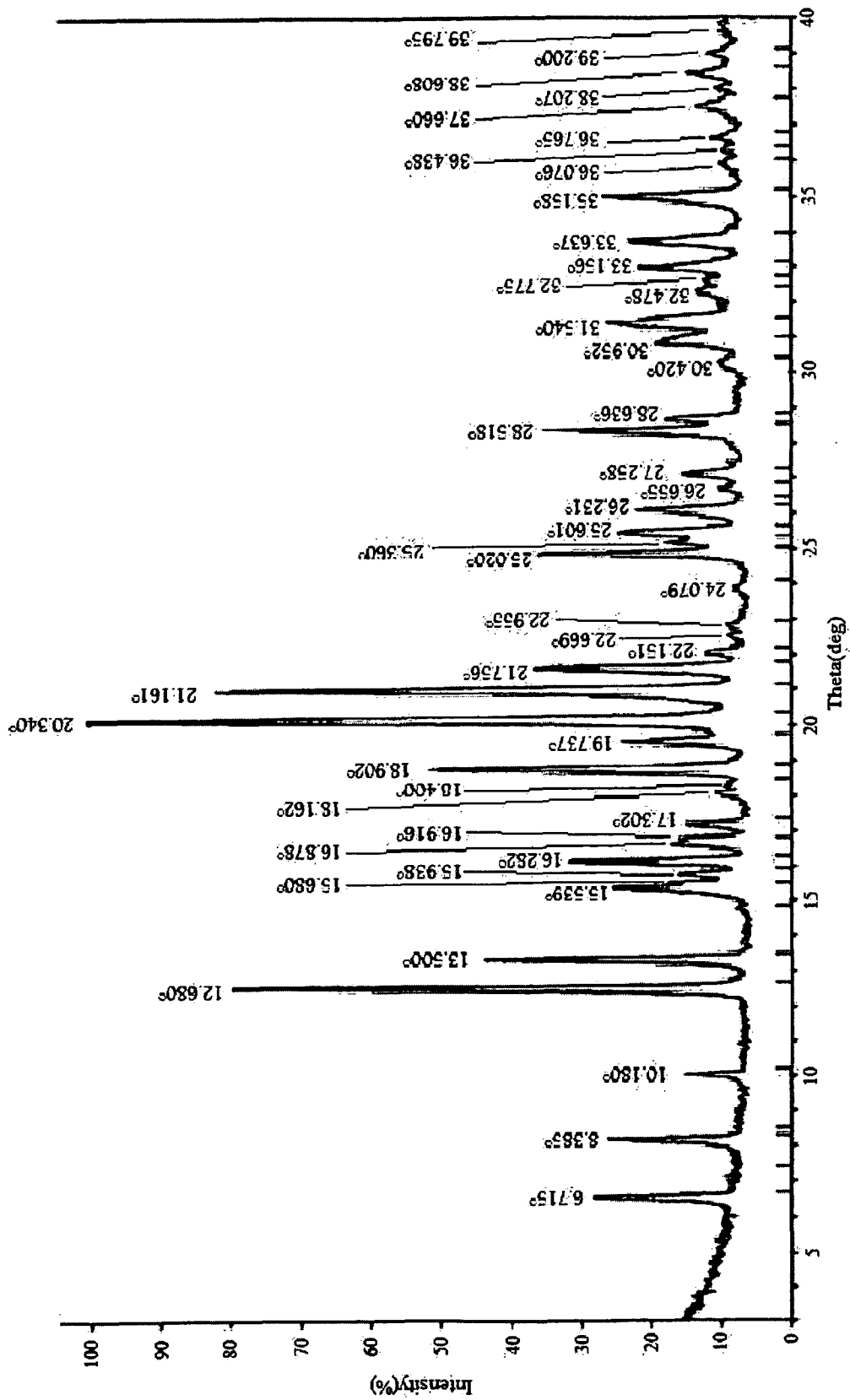


FIGURE 3

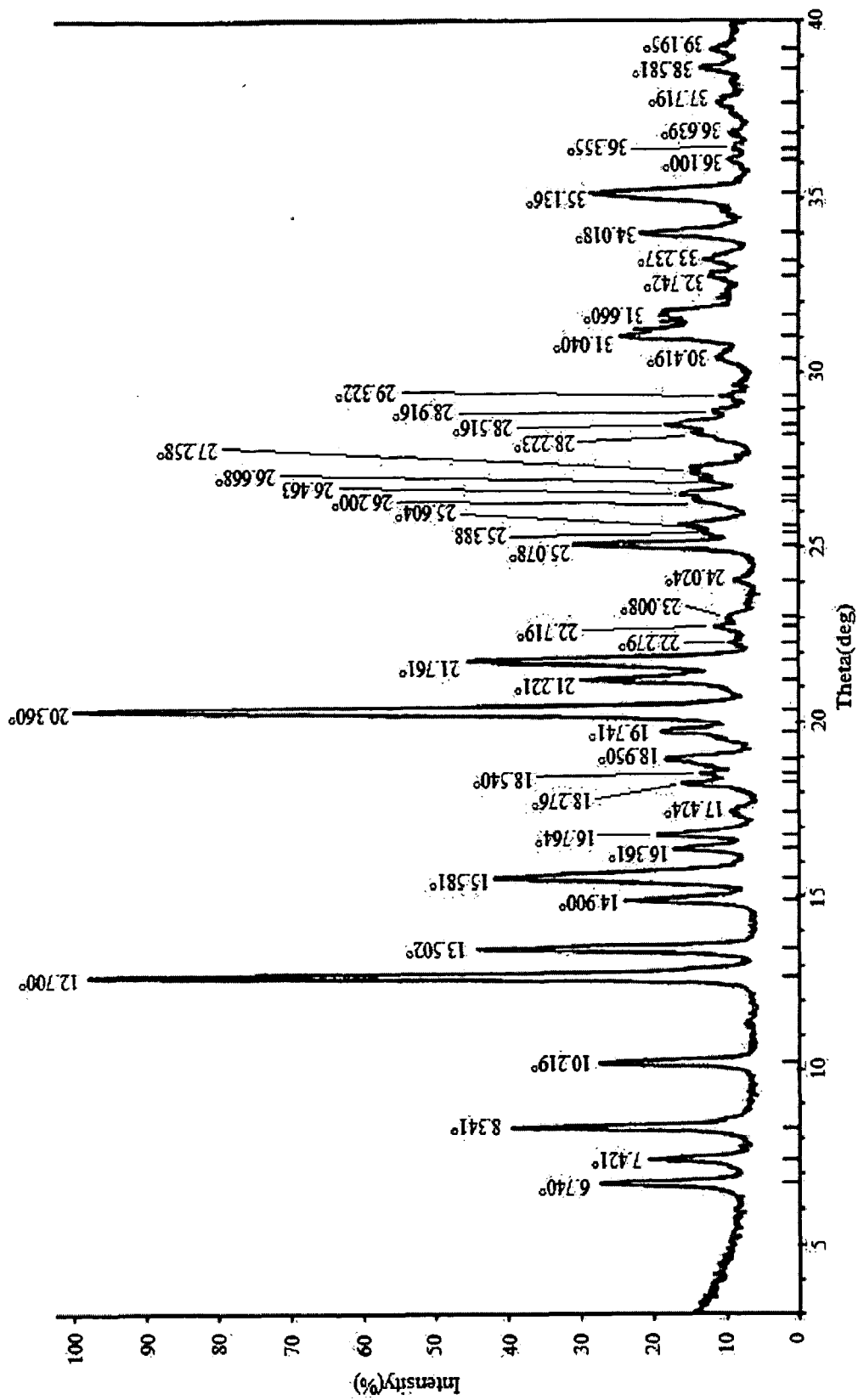


FIGURE 4

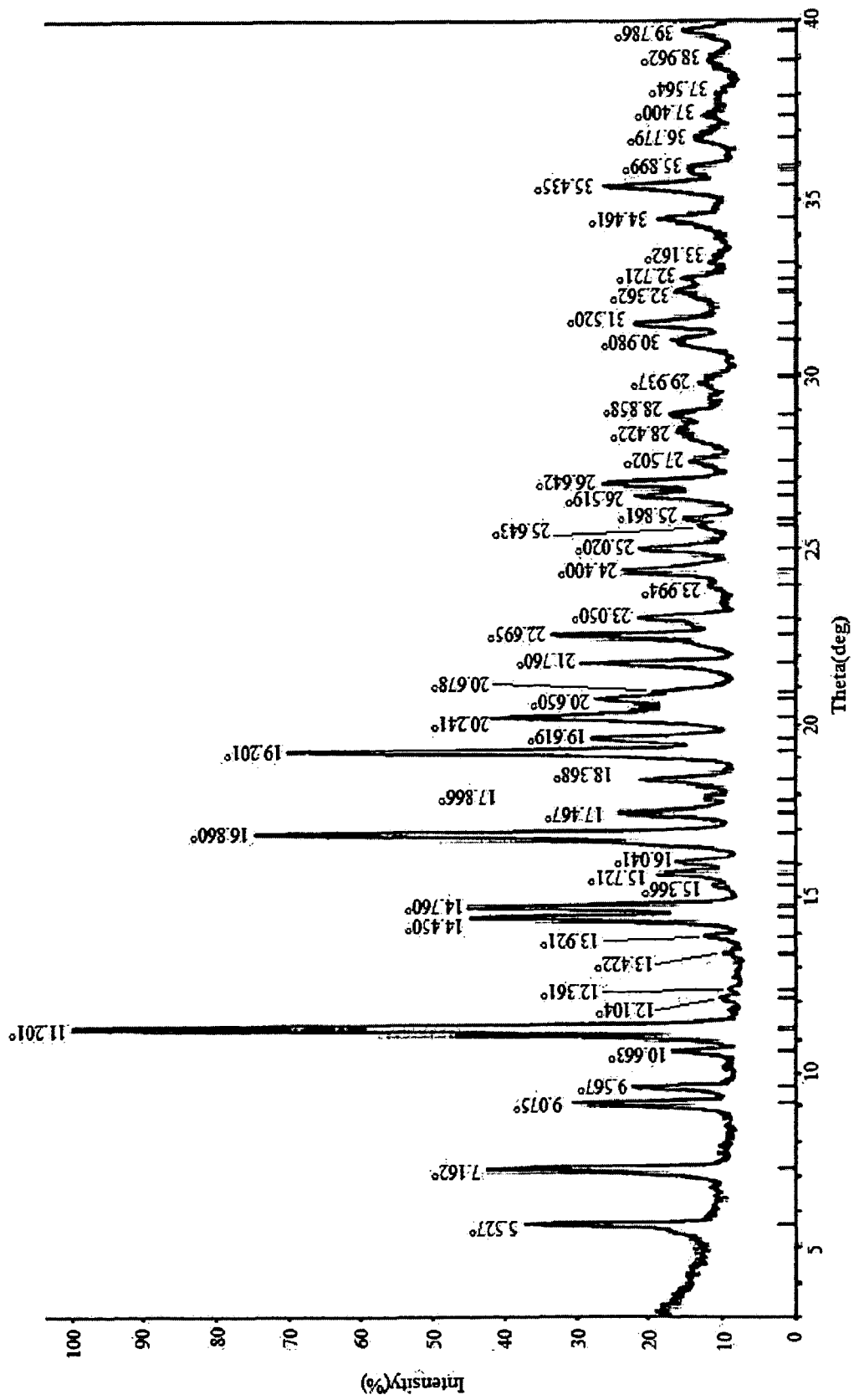
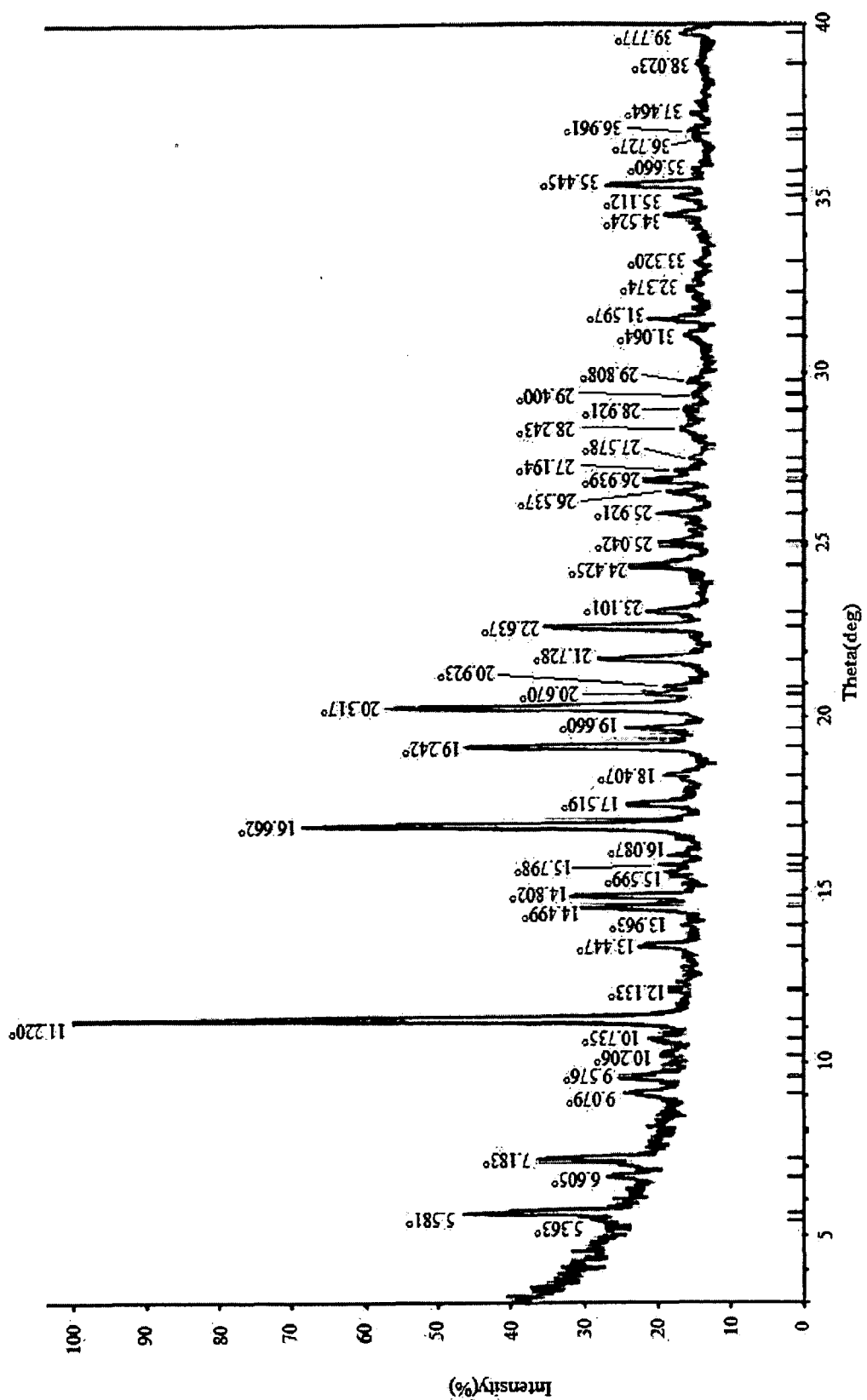


FIGURE 5



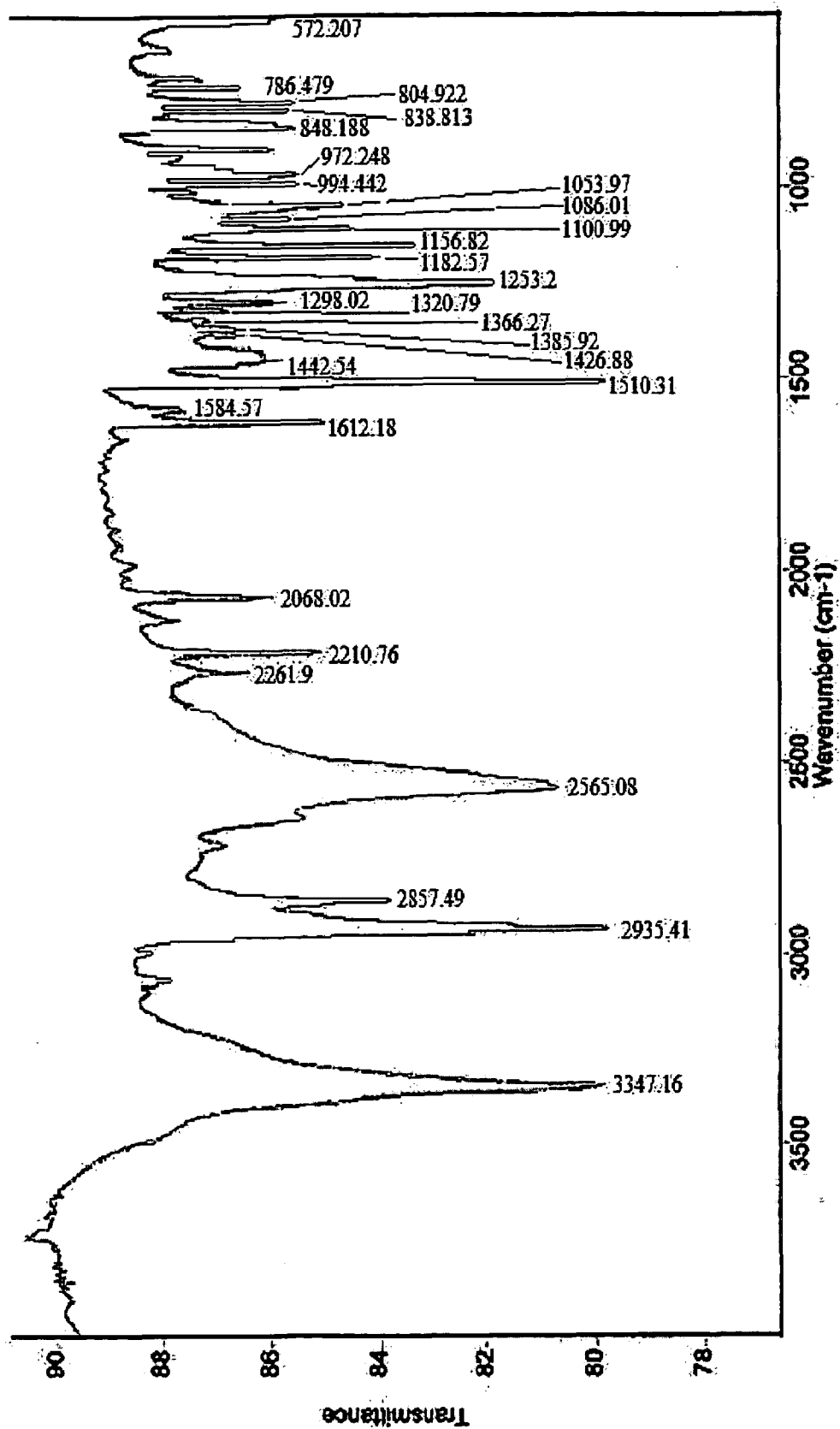


FIGURE 7

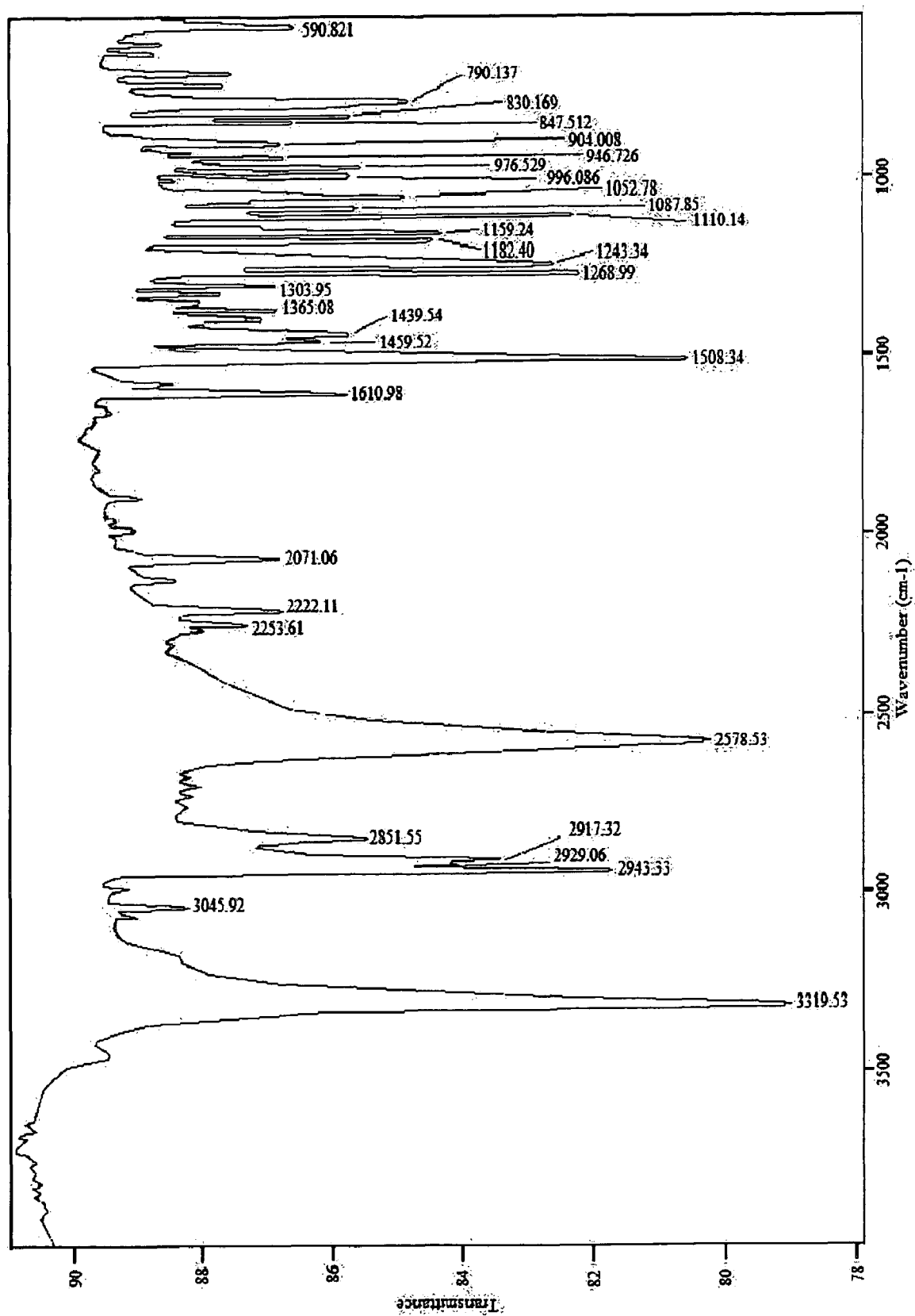


FIGURE 8

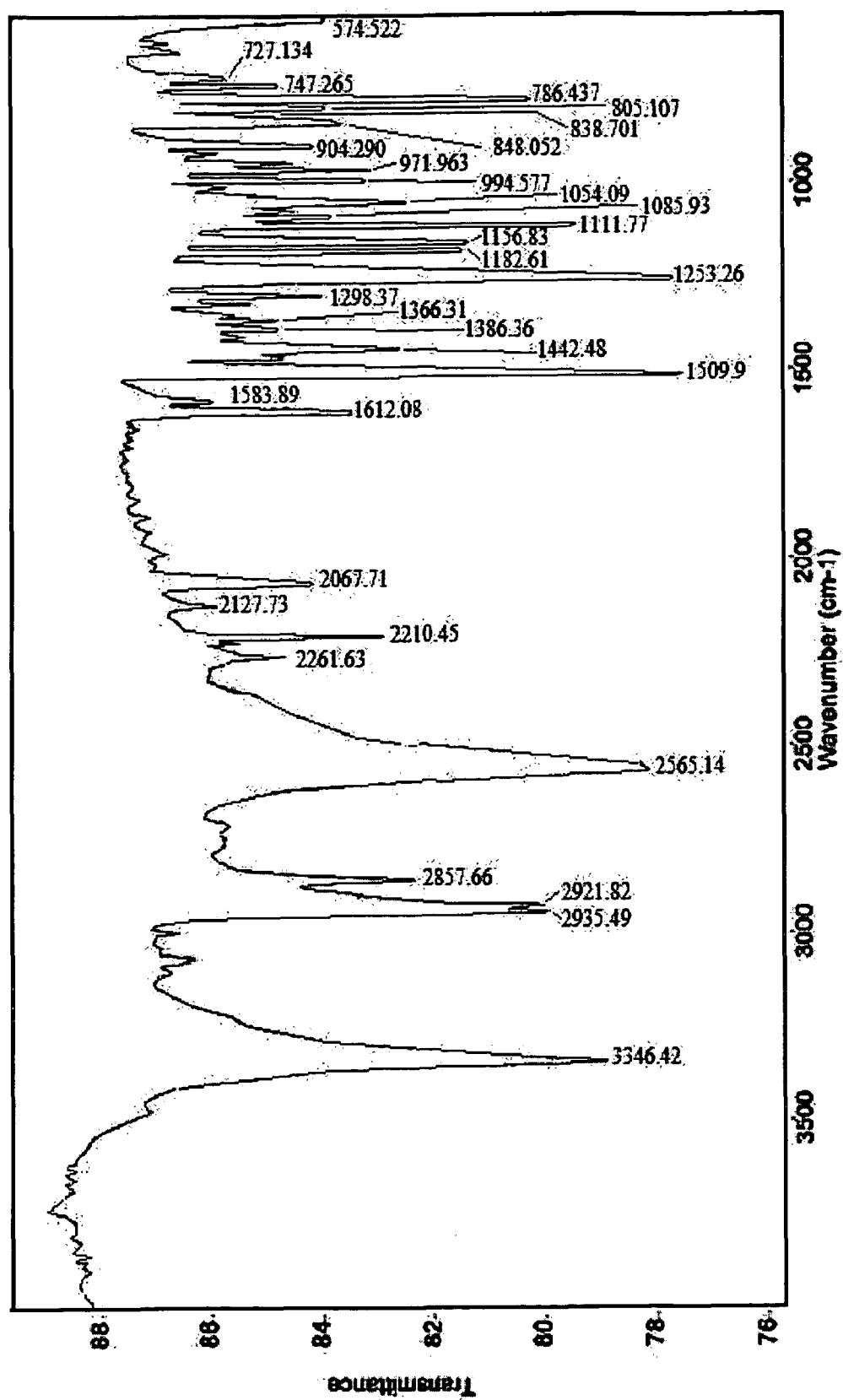


FIGURE 9

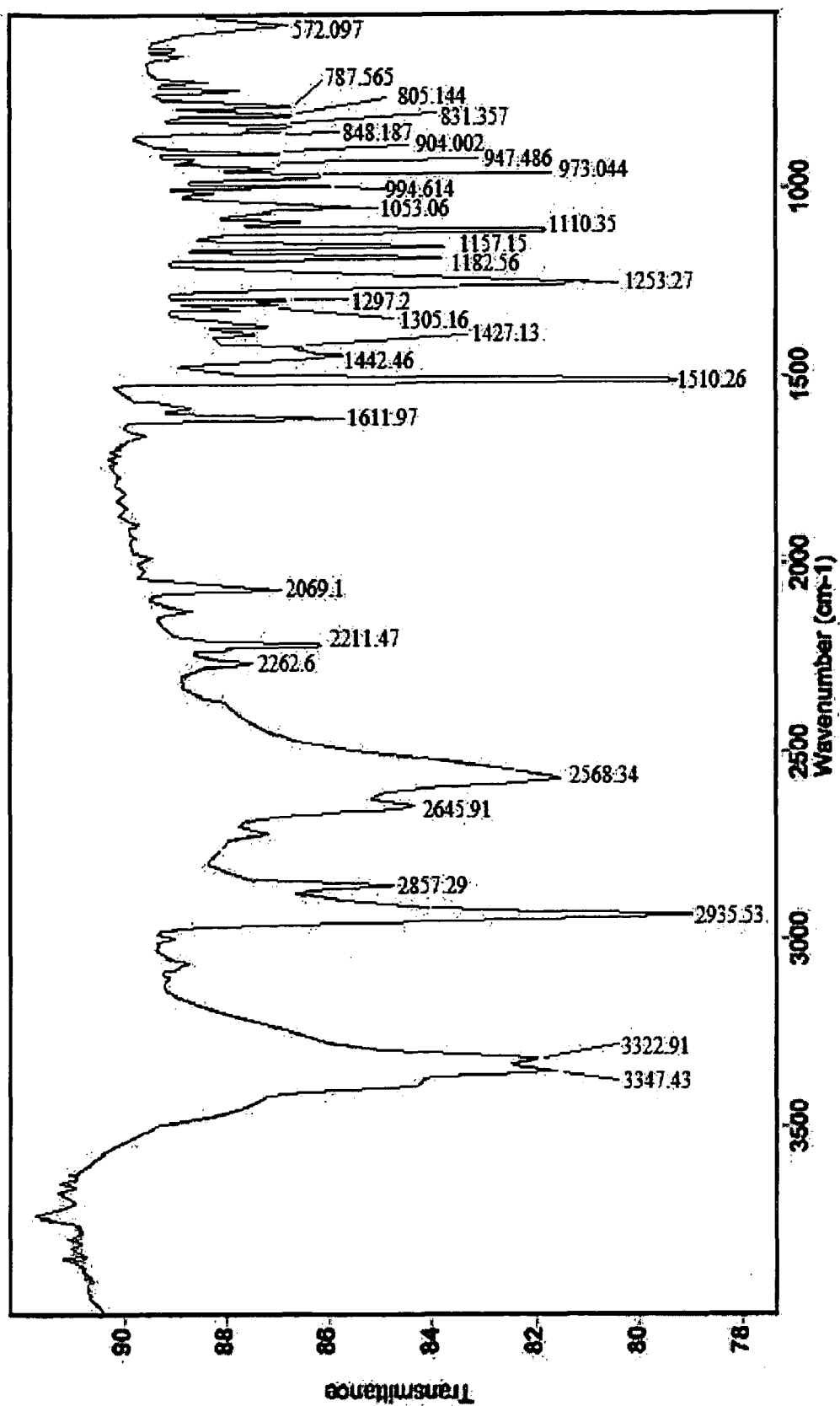


FIGURE 10

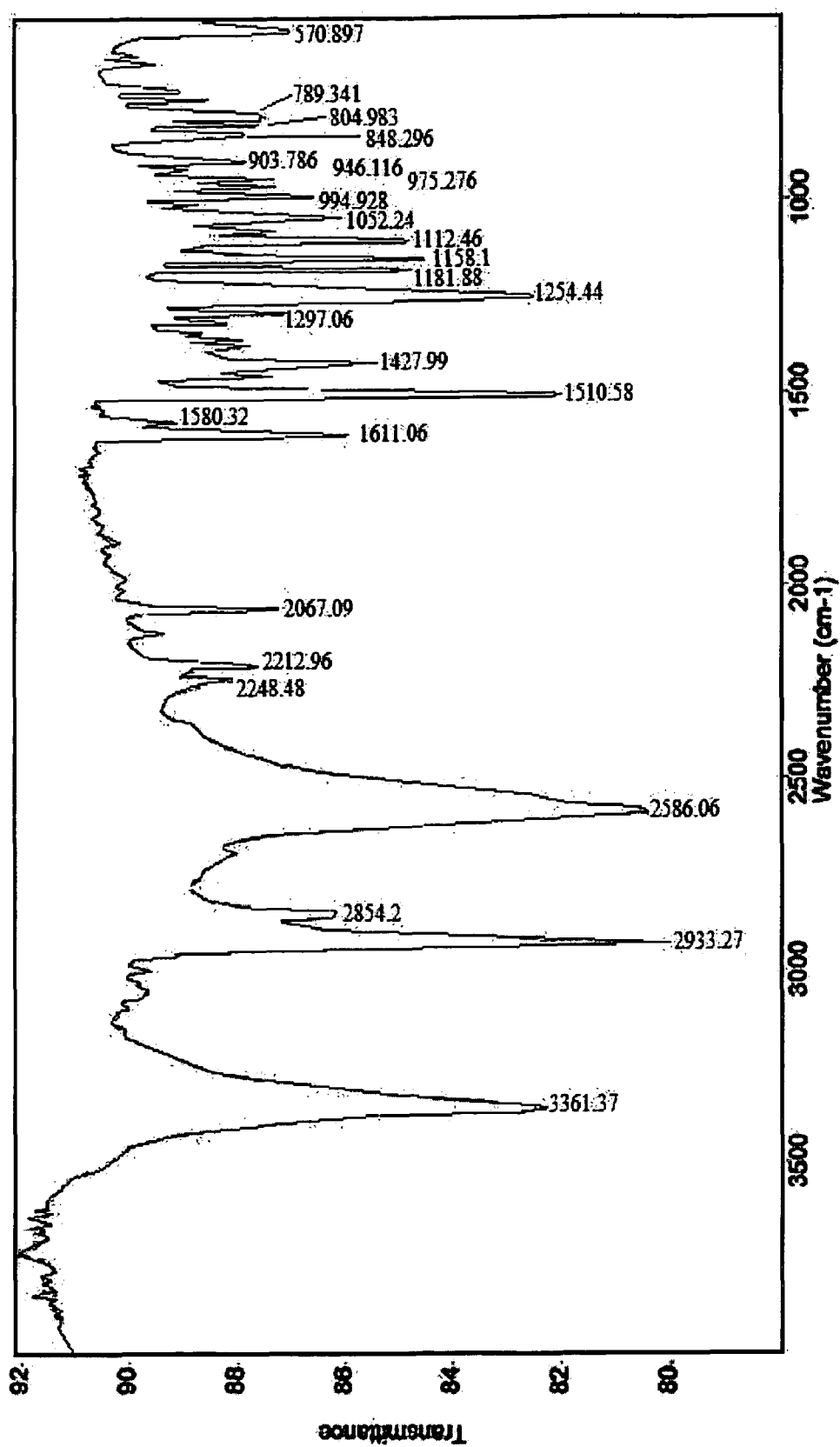


FIGURE 11

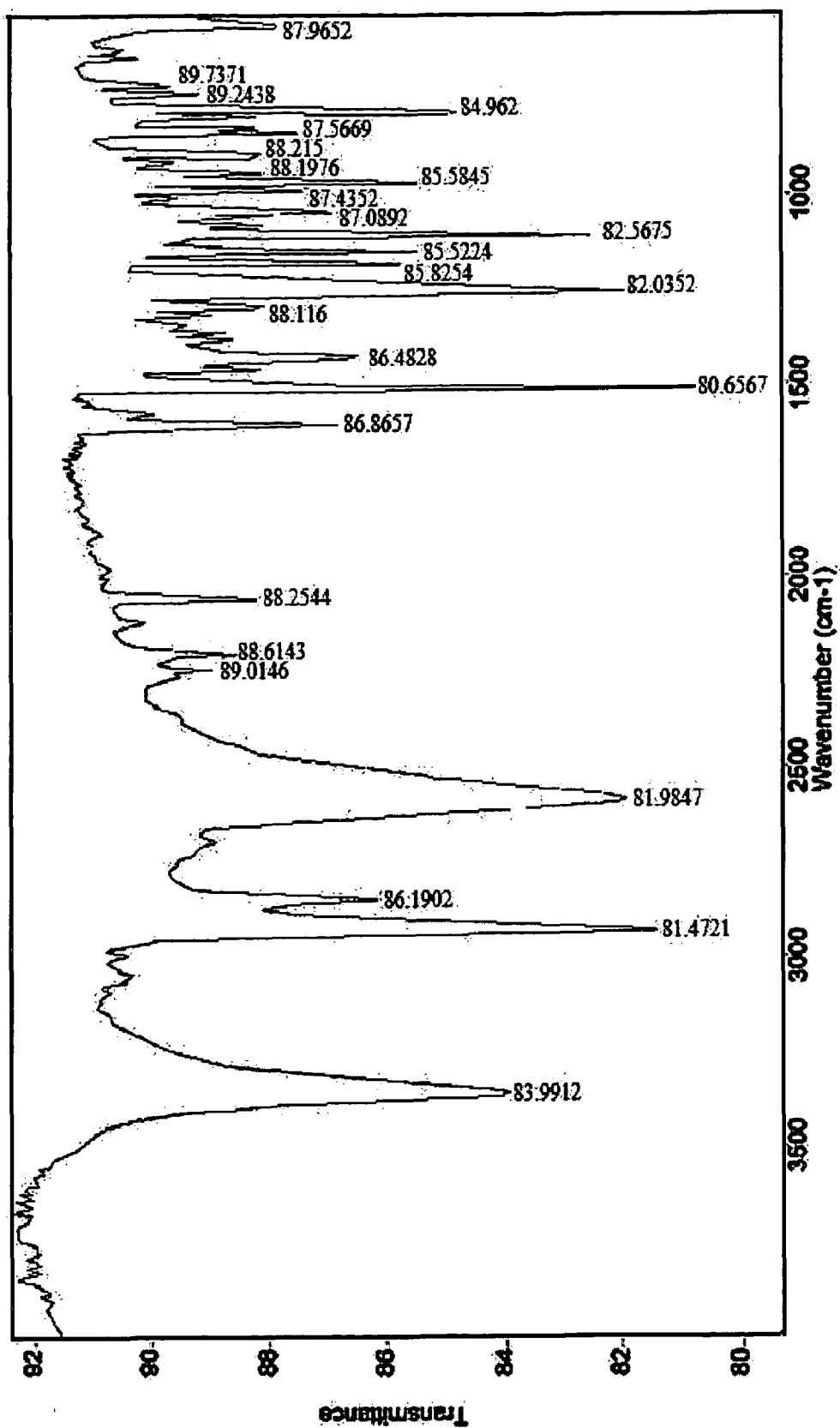


FIGURE 12

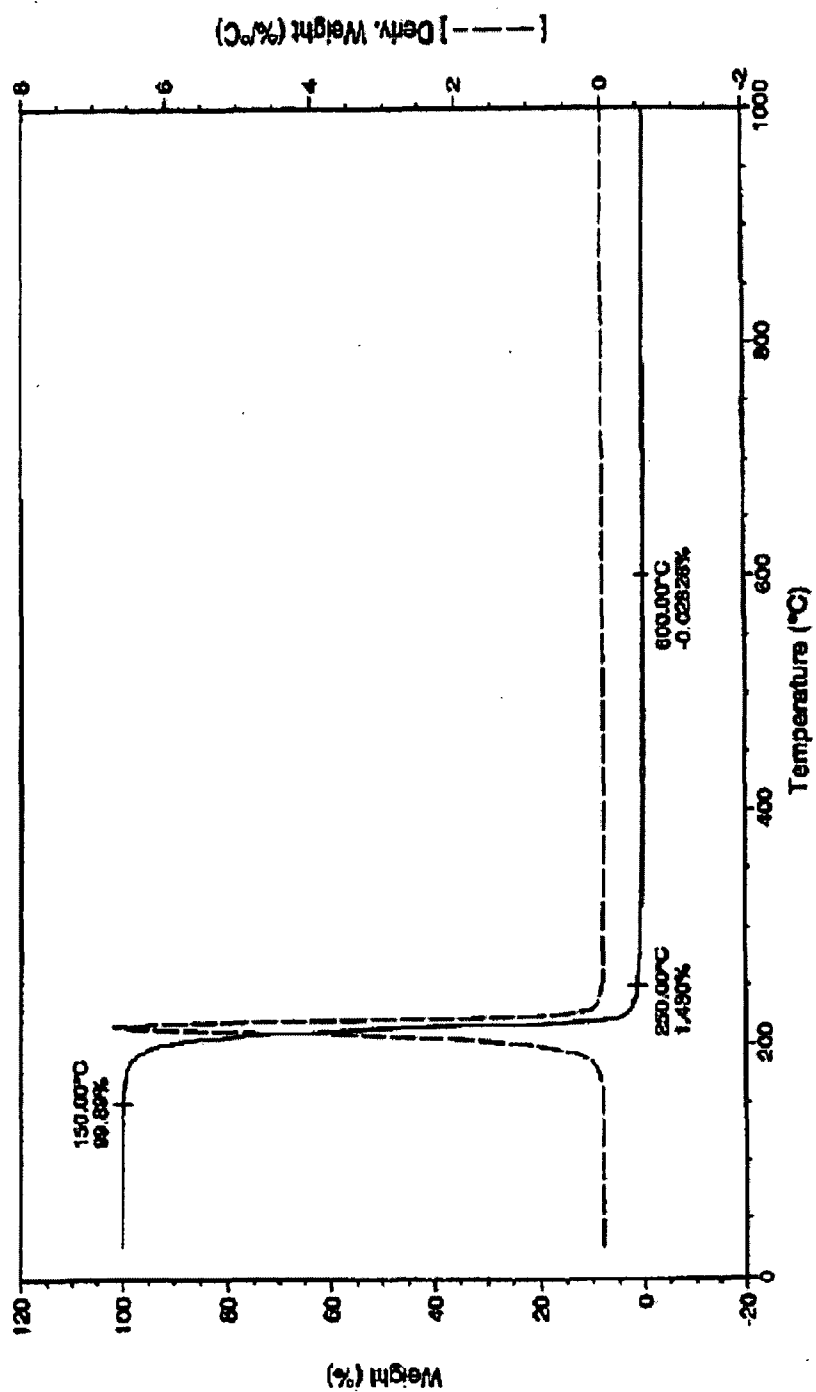


FIGURE 13

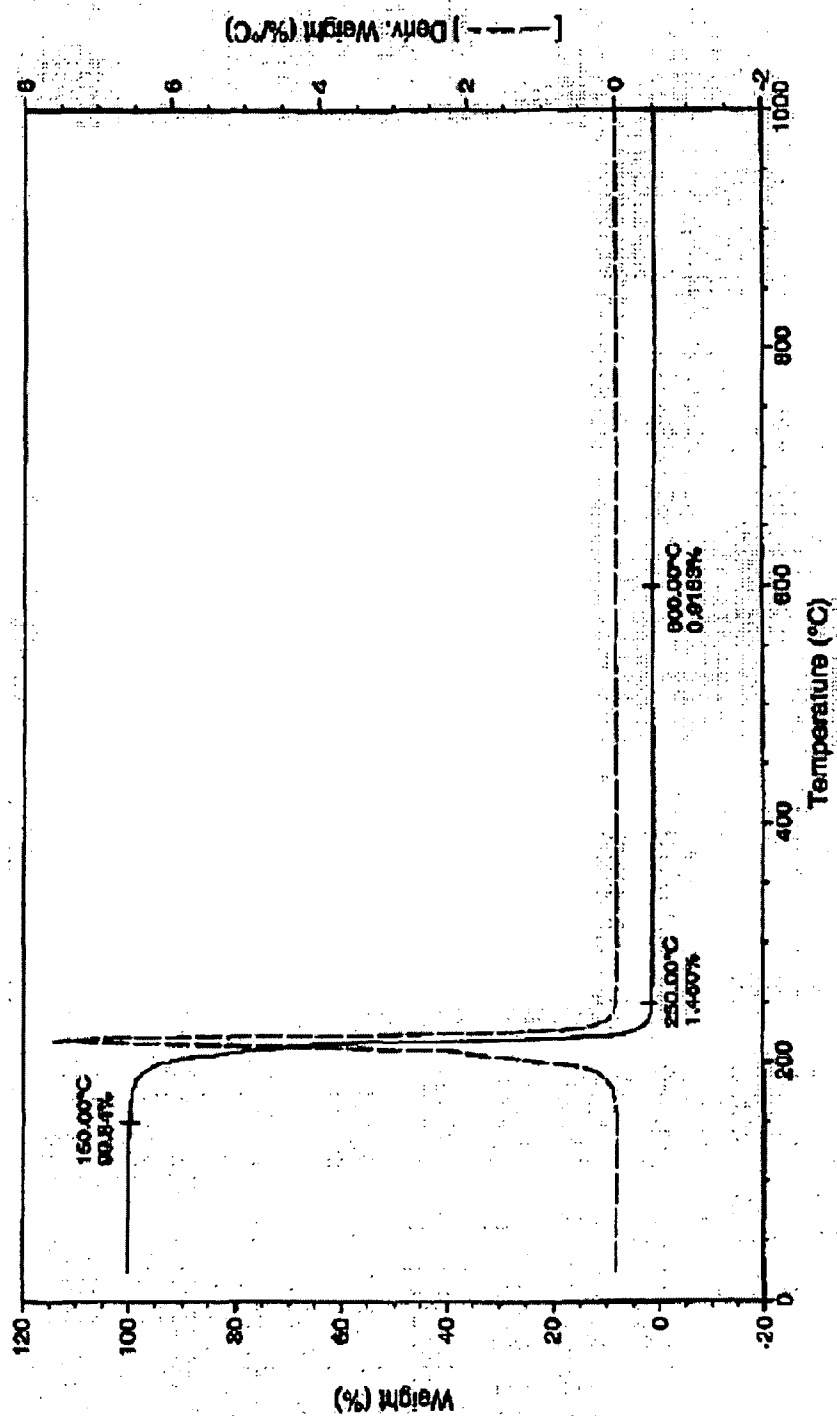


FIGURE 14

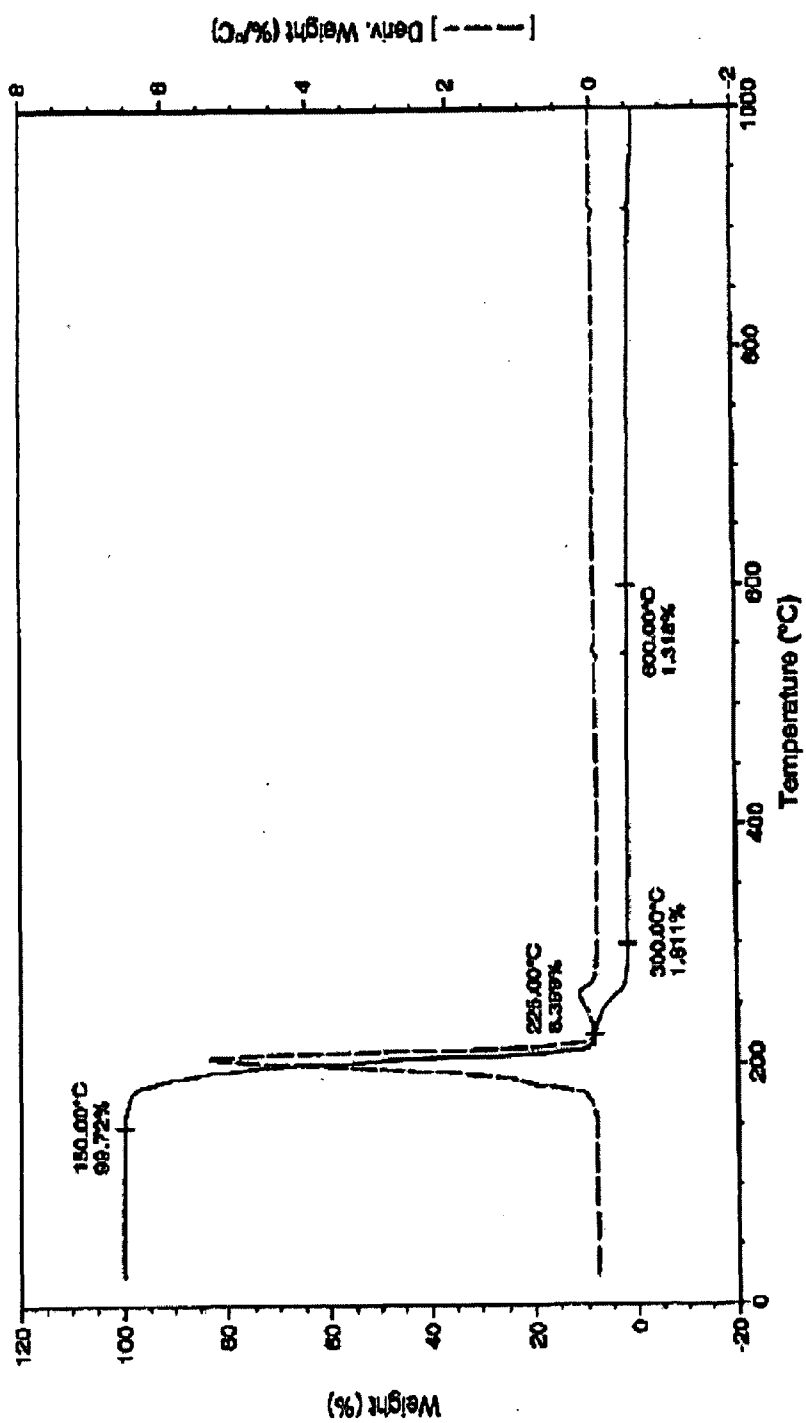


FIGURE 15

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 2007064697 A [0003]
- US 2007149622 A [0003]
- WO 2005060949 A [0192]
- US 4069346 A, McCarty [0209]
- US 5386032 A, Brandstrom [0209]
- EP 0654264 A, Thor [0209]
- US 5846514 A, Foster [0209]
- US 6221335 B, Foster [0209]
- US 6333342 B, Foster [0209]
- US 6334997 B, Foster [0209]
- US 6342507 B, Foster [0209]
- US 6476058 B, Foster [0209]
- US 6503921 B, Naicker [0209]
- US 6605593 B, Naicker [0209]
- US 6613739 B, Naicker [0209]
- US 6710053 B, Naicker [0209]
- US 6818200 B, Foster [0209]
- US 6884429 B, Koziak [0209]
- WO 2002064543 A, Hadfield [0209]

Non-patent literature cited in the description

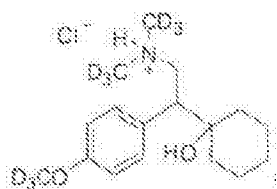
- **B.R. DENT.** Certificate of Analysis Venlafaxine-d6 HCl. *Synthesis*, 26 April 2006, http://www.bdg.co.nz/uploads/tx_chem/COA_venlafaxne-d6.pdf [0003]
- **B.R. DENT.** Certificate of Analysis of O-Desmethylvenlafaxine-d6 HCl. *BDG Synthesis*, 26 April 2006, http://www.bdg.co.nz/uploads/tx_chem/COA_Odesmethylenlafaxine-d6.pdf [0003]
- **FRANCOIS DECHAMPS.** Catalog 2007-08. *Synthese Aptochem*, October 2007, <http://www.aptochem.com/catalog.pdf> [0003]
- Deuterium isotope effects in the metabolism of drugs and xenobiotics: implications for drug design. **FOSTER, A.B.** *Advances in Drug Research*. Academic Press, 01 January 1985, vol. 14, 1-40 [0003]
- **GREENE ; WUTS.** *Protective Groups in Organic Synthesis*. John Wiley & Sons, 1999 [0019]
- **ELIEL ; WILEN.** *Stereochemistry of Carbon Compounds*. John Wiley & Sons, 1994, 1119-1190 [0050]
- **BERGE et al.** *J. Pharm. Sci.*, 1977, vol. 66, 1-19 [0054]
- *Handbook of Pharmaceutical Salts, Properties, and Use*. Wiley-VCH and VHCA, 2002 [0054]
- **HARPER.** *Progress in Drug Research*, 1962, vol. 4, 221-294 [0057]
- **MOROZOWICH et al.** *Design of Biopharmaceutical Properties through Prodrugs and Analogs*. APHA Acad. Pharm. Sci, 1977 [0057]
- *Bioreversible Carriers in Drug Design, Theory and Application*. APHA Acad. Pharm. Sci, 1987 [0057]
- **BUNDGAARD.** *Design of Prodrugs*. Elsevier, 1985 [0057]
- **WANG et al.** *Curr. Pharm. Design*, 1999, vol. 5, 265-287 [0057]
- **PAULETTI et al.** *Adv. Drug. Delivery Rev.*, 1997, vol. 27, 235-256 [0057]
- **MIZEN et al.** *Pharm. Biotech.*, 1998, vol. 11, 345-365 [0057]
- **GAIGNAULT et al.** *Pract. Med. Chem.*, 1996, 671-696 [0057]
- **ASGHARNEJAD et al.** *Transport Processes in Pharmaceutical Systems*. Marcell Dekker, 2000, 185-218 [0057]
- **BALANT et al.** *Eur. J. Drug Metab. Pharmacokinet.*, 1990, vol. 15, 143-53 [0057]
- **BALIMANE ; SINKO.** *Adv. Drug Delivery Rev.*, 1999, vol. 39, 183-209 [0057]
- **BROWNE.** *Clin. Neuropharmacol.*, 1997, vol. 20, 1-12 [0057]
- **BUNDGAARD.** *Arch. Pharm. Chem.*, 1979, vol. 86, 1-39 [0057]
- **BUNDGAARD.** *Controller Drug Delivery*, 1987, vol. 17, 179-96 [0057]
- **BUNDGAARD.** *Adv. Drug Delivery Rev.*, 1992, vol. 8, 1-38 [0057]
- **FLEISHER et al.** *Adv. Drug Delivery Rev.*, 1996, vol. 19, 115-130 [0057]
- **FLEISHER et al.** *Methods Enzymol.*, 1985, vol. 112, 360-381 [0057]
- **FARQUHAR et al.** *J. Pharm. Sci.*, 1983, vol. 72, 324-325 [0057]
- **FREEMAN et al.** *J. Chem. Soc., Chem. Commun.*, 1991, 875-877 [0057]
- **FRIIS ; BUNDGAARD.** *Eur. J. Pharm. Sci.*, 1996, vol. 4, 49-59 [0057]
- **GANGWAR et al.** *Des. Biopharm. Prop. Prodrugs Analogs*, 1977, 409-421 [0057]
- **NATHWANI ; WOOD.** *Drugs*, 1993, vol. 45, 866-94 [0057]

- **SINHABABU ; THAKKER.** *Adv. Drug Delivery Rev.*, 1996, vol. 19, 241-273 [0057]
- **STELLA et al.** *Drugs*, 1985, vol. 29, 455-73 [0057]
- **TAN et al.** *Adv. Drug Delivery Rev.*, 1999, vol. 39, 117-151 [0057]
- **TAYLOR.** *Adv. Drug Delivery Rev.*, 1996, vol. 19, 131-148 [0057]
- **VALENTINO ; BORCHARDT.** *Drug Discovery Today*, 1997, vol. 2, 148-155 [0057]
- **WIEBE ; KNAUS.** *Adv. Drug Delivery Rev.*, 1999, vol. 39, 63-80 [0057]
- **WALLER et al.** *Br. J. Clin. Pharmacol.*, 1989, vol. 28, 497-507 [0057]
- Modified-Release Drug Delivery Technology. *Drugs and the Pharmaceutical Science*. Marcel Dekker, Inc, 2002, vol. 126 [0069]
- **OUK et al.** *Green Chemistry*, 2002, vol. 4 (5), 431-435 [0104] [0210]
- **YARDLEY et al.** *Journal of Medicinal Chemistry*, 1990, vol. 33 (10), 2899-2905 [0106] [0108] [0210]
- **YARDLEY.** *Journal of Medicinal Chemistry*, 1990, vol. 33 (10), 2899-2905 [0110]
- **WEYLER.** *Journal of Biological Chemistry*, 1985, vol. 260, 13199-13207 [0190]
- **UEBELHACK.** *Pharmacopsychiatry*, 1998, vol. 31, 187-192 [0191]
- **VANDENBERGH et al.** *Molecular Brain Research*, 1992, vol. 15, 161-166 [0193] [0210]
- **PACHOLCZYK et al.** *Nature*, 1991, vol. 350, 350-354 [0193] [0210]
- **RAMAMOORTHY et al.** *Proceedings of the National Academy of Sciences of the USA*, 1993, vol. 90, 2542-2546 [0193] [0210]
- **GOBEL et al.** *Journal of Pharmacological and Toxicological Methods*, 1999, vol. 42 (4), 237-244 [0194] [0210]
- **RAMAMOORTHY et al.** *J. Biol. Chem.*, 1998, vol. 273 ((4)), 2458-2466 [0197] [0210]
- **RAMAMOORTHY.** *J. Biol. Chem.*, 1998, vol. 273 ((4)), 2458-2466 [0201]
- **PORSOLT et al.** *Archives Internationales de Pharmacodynamie et de Therapie*, 1977, vol. 229 ((2)), 327-336 [0205]
- **ALTERMATT.** *Cancer*, 1988, vol. 62 (3), 462-466 [0210]
- **ALTERMATT.** *International Journal of Cancer*, 1990, vol. 45 (3), 475-480 [0210]
- **BALDWIN.** *International Journal of Neuropsychopharmacology*, 2005, vol. 8 (2), 293-302 [0210]
- **BASELT.** *Disposition of Toxic Drugs and Chemicals in Man*. 2004 [0210]
- **BASSAPA et al.** *Bioorganic & Medicinal Chemistry Letters*, 2004, vol. 14, 3279-3281 [0210]
- **BROWNE.** *Synthesis and Applications of Isotopically Labelled Compounds. Proceedings of the International Symposium*, 18 June 2000, 519-532 [0210]
- **BROWNE.** *Pharmacochemistry Library*, 1997, 26 [0210]
- **BROWNE.** *Pharmacochemistry Library*, 1997, vol. 26, 13-18 [0210]
- **BROWNE.** *Clinical Pharmacology & Therapeutics*, 1981, vol. 29 (4), 511-515 [0210]
- **BROWNE.** *Journal of Clinical Pharmacology*, 1982, vol. 22 (7), 309-315 [0210]
- **BROWNE.** *Synth. Appl. Isot. Labeled Compd., Proc. Int. Symp.*, 1983, 343-348 [0210]
- **BROWNE.** *Therapeutic Drug Monitoring*, 1984, vol. 6 (1), 3-9 [0210]
- **CHAVAN et al.** *Tetrahedron Letters*, 2004, vol. 45, 7291-7295 [0210]
- **DAVIES et al.** *Journal of the Chemical Society*, 1945, 352-354 [0210]
- **DING et al.** *Journal of Neurochemistry*, 1995, vol. 65 ((2)), 682-690 [0210]
- **EAP et al.** *Pharmacogenetics*, 2002, vol. 13, 39-47 [0210]
- **FOSTER.** *Trends in Pharmacological Sciences*, 1984, vol. 5 (12), 524-527 [0210]
- **GARLAND.** *Synth. Appl. Isot. Labeled Compd. Proc. Int. Symp. 2.* 1986, 283-284 [0210]
- **GOERINGER.** *Journal of Forensic Sciences*, 2000, vol. 45 (3), 633-648 [0210]
- **KATZMAN.** *Expert Review of Neurotherapeutics*, 2005, vol. 5 (1), 129-139 [0210]
- **KAUFMAN.** *Phys. Rev.*, 1954, vol. 93, 1337-1344 [0210]
- **KO et al.** *British Journal of Clinical Pharmacology*, 2000, vol. 49 (4), 343-351 [0210]
- **KRITCHEVSKY.** *Annals of the New York Academy of Science*. 1960, vol. 84 [0210]
- **KUSHNER.** *Can. J. Physiol. Pharmacol.*, 1999, vol. 77, 79-88 [0210]
- **LAMPRECT.** *European Journal of Cell Biology*, 1990, vol. 51 ((2)), 303-312 [0210]
- **LESSARD.** *Pharmacogenetics*, 1999, vol. 9 (4), 435-443 [0210]
- **LEWIS.** *J. Am. Chem. Soc.*, 1968, vol. 90, 4337 [0210]
- **LI et al.** *Rapid Communications in Mass Spectrometry*, 2005, vol. 19 ((14)), 1943-1950 [0210]
- **LIU et al.** *Journal of Chromatography B: Biomedical Sciences & Applications*, 2006, vol. 850 (1-2), 183-189 [0210]
- **MARCH.** *Advanced Organic Chemistry*. 1992, 226-230 [0210]
- **MORTON et al.** *Annals of Pharmacotherapy*. 1995, vol. 29, 387-395 [0210]
- **PACHER.** *Current Medicinal Chemistry*, 2004, vol. 11 (7), 925-943 [0210]
- **PACHCR.** *Current Pharmaceutical Design*, 2004, vol. 10 (20), 2463-2475 [0210]
- **PHELPS et al.** *Annals of Pharmacotherapy*. 2005, vol. 39, 136-140 [0210]
- *Physicians Desk Reference*, 2003 [0210]

- **PORSOLT.** *Archives Internationales de Pharmacodynamie et de Therapie*, 1977, vol. 229 ((2)), 327-336 [0210]
- **POHL.** *Drug Metabolism Reviews*, 1985, vol. 15 (7), 1335-1351 [0210]
- **PRESKORN et al.** *Handbook of Experimental Pharmacology. Antidepressants: Past, Present and Future*. 2004, vol. 157 [0210]
- **RAGGI.** *Current Topics in Medicinal Chemistry*, 2003, vol. 3, 203-220 [0210]
- **REIS et al.** *Therapeutic Drug Monitoring*, 2002, vol. 24, 545-553 [0210]
- **ROECKER.** *J. Am. Chem. Soc.*, 1987, vol. 109, 746 [0210]
- **SCHROETER.** *European Journal of Cell Biology*, 1992, vol. 58 (2), 365-370 [0210]
- **SICAT et al.** *Pharmacotherapy*, 2004, vol. 24 (1), 79-93 [0210]
- **SILVERSTONE.** *Journal of Clinical Psychiatry*, 2004, vol. 65 (17), 19-28 [0210]
- **TOLONEN.** *European Journal of Pharmaceutical Sciences*, 2005, vol. 25, 155-162 [0210]
- **THOMSON.** *Biological Effects of Deuterium. International Series of Monographs on Pure and Applied Biology, Modern trends in Physiological Sciences*, 1963 [0210]
- **UREY.** *A Hydrogen Isotope of Mass 2. Phys. Rev.*, 1932, vol. 39, 164 [0210]

Szabadalmi igénypontok

1. A d_3 -1-[2-Dimetilamino-1-(4-metoxifenil)-etil]-ciklohexanol-hidroklorid hidroklorid só polimorfja, amely a következő képlettel rendelkezik:



ahol a polimorf nagy intenzitású diffrakciós csúcsokat mutat a következő (2 θ) diffrakciós szögekneként röntgen pordiffrakciós analízisben: 6,683, 10,201, 13,441, 15,517, 18,198, 19,719, 20,258, 21,68, 22,658, 25,543, 28,022 és 35,02.

2. Az 1. igénypont szerinti polimorf, ahol a polimorf röntgen pordiffrakciós spektruma alapvetően megegyezik a 2. ábrán láthatóval.

3. Az 1. igénypont szerinti polimorf, ahol a polimorf röntgen pordiffrakciós spektruma a következő körülbelüli értékekneként (2 θ) szögekben kifejezett karakterisztikus csúcsokkal rendelkezik:

2-theta	relatív intenzitás (RI)	2-theta	RI	2-theta	RI
6,683	15,5	22,658	24,8	31,379	8,2
10,201	93,6	23,923	2,7	31,978	9,1
13,441	27,8	25,323	9,6	32,28	10,5
15,014	7,6	25,543	22,4	32,701	6,5
15,517	66,2	26,502	6,7	32,981	2,3
16,458	1,5	27,122	9,5	34,12	9,1
16,84	10,3	27,557	5,5	35,02	33,4
17,206	2,7	28,022	20,9	36,024	3,1
18,198	41	28,64	4,4	36,842	2,6
19,719	34,1	29,241	10,6	37,5	6,7
20,258	100	29,659	7,1	38,341	3,9
21,68	21,2	31,079	11,9	38,753	1,2