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Department, C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **TULP, Martinus Th.M.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department, C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).

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(74) **Agent: VERHAGE, Marinus**; Octrooibureau Zoan B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

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(71) **Applicant (for all designated States except US): SOLVAY PHARMACEUTICALS B.V.** [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

(75) **Inventors/Applicants (for US only): TURSKI, Lechoslaw A.** [DE/DE]; c/o Solvay Pharmaceuticals B.V., IPSI Department, C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **STOIT, Axel** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department, C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **KRUSE, Cornelis G.** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI Department, C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL). **VADER, Sander** [NL/NL]; c/o Solvay Pharmaceuticals B.V., IPSI

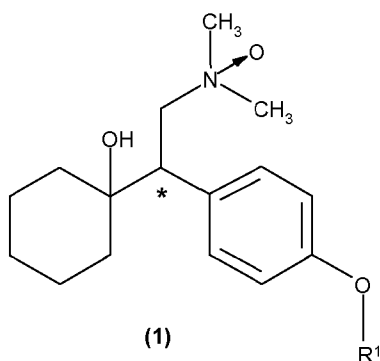
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(54) **Title:** N-OXIDES OF VENLAFAXINE AND O-DESMETHYLVENLAFAXINE AS PRODRUGS



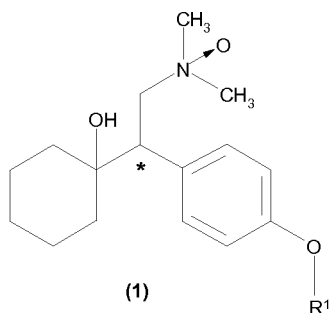
(57) **Abstract:** The invention concerns venlafaxine-N-oxide and O-desmethylvenlafaxine-N-oxide as prodrugs of venlafaxine and its major (active) metabolite O-desmethylvenlafaxine respectively, to pharmaceutical compositions containing these N-oxides, to methods for preparing them, and methods for preparing compositions. The invention relates to N-oxide, having formula (1), wherein R¹ is H or CH₃, and tautomers, stereoisomers, hydrates and solvates thereof. The invention also relates to the uses of the N-oxides and compositions, particularly for the manufacture of medicaments useful in the treatment of affections or diseases effectively treatable - albeit with side effects - with venlafaxine.

N-OXIDES OF VENLAFAXINE AND O-DESMETHYLVENLAFAXINE AS PRODRUGS**INDEX**

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TECHNICAL FIELD

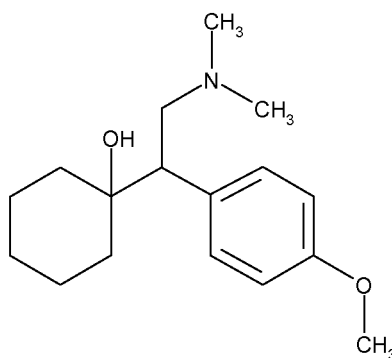
This invention relates to the fields of pharmaceutical and organic chemistry, and provides venlafaxine-N-oxide and O-desmethylenlafaxine-N-oxide, having formula (1):



wherein the asterisk (*) marks the asymmetric carbon atom, R^1 is H or CH_3 , and tautomers, stereoisomers, hydrates and solvates thereof, as prodrugs of venlafaxine and its major (active) metabolite O-desmethylenlafaxine respectively, as well as pharmaceutical compositions containing this compound, methods for preparing it, and methods for preparing compositions.

BACKGROUND ART

Venlafaxine is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents. It has been reported that its (-)-enantiomer is a more potent inhibitor of norepinephrine synaptosomal uptake while its (+)-enantiomer is more selective in inhibiting serotonin uptake (*Howell, 1994*). Venlafaxine is marketed as racemate.



(±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol, venlafaxine
(U.S. Pat. No. 4,761,501; Pento, 1988)

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine, are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. O-desmethylvenlafaxine is the only major active metabolite. Other metabolites are N-desmethylvenlafaxine, and N,O-didesmethylvenlafaxine (*Klamerus, 1992*). O-desmethylvenlafaxine succinate is in a late stage of its development, and recently received an approvable letter from the FDA for the treatment of Major Depressive Disorder. The compound is also in development as treatment of vasomotor symptoms associated with menopause.

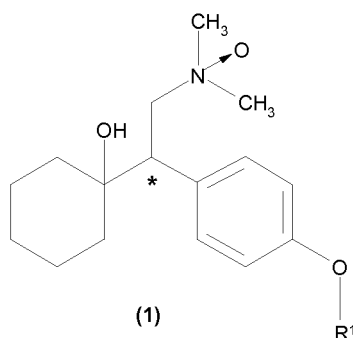
N-oxides are known since 1894. By now it is very well known that N-oxides are metabolites of many tertiary amines, and in most cases are also intermediates between tertiary amines and their N-dealkylated analogs. Most, but not all, tertiary amine drugs give rise to N-oxides. This is for instance the case with morphine, imipramine, promazine, cinnarizine and nicotine. How much N-oxidation takes place varies from trace amounts to a nearly quantitative conversion. Some N-oxides were shown to be more potent than their corresponding tertiary amines. The most famous example of these is chlordiazepoxide (Librium[®]), one of the most frequently used drugs in psychiatric and general medicine. In many more cases however, N-oxides were found to be less potent than their corresponding tertiary amines, and N-oxidation is most commonly regarded to be metabolic deactivation. Whilst N-oxides are easily reduced to their corresponding tertiary amines by chemical means, in the human body this happens to varying degrees. Some N-oxides undergo nearly quantitative reductive conversion to the corresponding tertiary amines and in other cases the conversion is a mere trace reaction or even completely absent (*Bickel, 1969*). Thus, the formation of N-oxides and their corresponding tertiary amines is unpredictable. Once formed, N-oxides may be *more active* than their corresponding tertiary

amines, *less active* or even completely *inactive*. N-oxides may be reduced to the corresponding tertiary amines or not. When they are, the reaction may be a mere trace or nearly quantitative.

Since Paracelsus ('*Sola dosis facit venenum*') it is generally accepted that therapeutic as well as toxic effects of drugs are related to their concentration at the relevant target sites. Because generally speaking the latter are not easily accessible, blood plasma levels are used as approximations of relevant drug concentrations. During drug development a window of suitable plasma concentrations are defined providing a lower limit or range for efficacy, and an upper range at which side effects start to become apparent. In ideal situations the two concentrations are so far apart that it is easy to administer the drug in such a way that it is effective, yet does not give rise to side effects. In reality, situations are hardly ever ideal, and most drugs show side effects. In most cases the occurrence of side effects can be linked to peak plasma concentrations exceeding the lower level associated with the occurrence of side effects. Venlafaxine produces peak plasma concentrations resulting in side effects. The most commonly observed adverse events associated with the use of venlafaxine (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., incidence for venlafaxine at least twice that for placebo), include sustained hypertension, headache, asthenia, sweating, nausea, constipation, somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, blurred or blurry vision, and abnormal ejaculation/orgasm or impotence in males (*Physicians' Desk Reference, 1999; Sinclair, 1998*). These adverse effects can significantly limit the dose level, frequency, and duration of drug therapy. Adverse events can be attenuated using extended-release formulations (venlafaxine XR), but different compounds can solve the problem, too. It would thus be desirable to find a compound with the advantages of venlafaxine while avoiding its disadvantages. Prodrugs have an identical pharmacological profile, but a more favourable pharmacokinetic profile.

DISCLOSURE

When administrated orally, venlafaxine-N-oxide and O-desmethylenlafaxine-N-oxide act as prodrugs: they are rapidly converted to their parent compounds venlafaxine and O-desmethylenlafaxine respectively. The invention relates to N-oxides having formula (1):



wherein the asterisk (*) marks the asymmetric carbon atom, R¹ is H or CH₃, and to tautomers, stereoisomers, hydrates and solvates thereof. The N-oxides of the invention may be substantially free of venlafaxine and O-desmethylvenlafaxine, and tautomers, stereoisomers, salts, hydrates and solvates thereof. Venlafaxine N-oxide and O-des-methylvenlafaxine N-oxide can be prepared by oxidizing venlafaxine or O-desmethylvenlafaxine with a suitable oxidizing agent, for instance with m-CPBA. The invention relates to racemates, mixtures of diastereomers and the individual stereoisomers of the N-oxides of the invention, as well as to hydrates and solvates thereof.

The invention particularly relates to N-oxides having formula (1) wherein R¹ is CH₃.

Another preferred embodiment of the invention are N-oxides having formula (1) wherein R¹ is H.

Yet other preferred embodiments are (S)- and (R)-enantiomers of N-oxides having formula (1).

Venlafaxine-N-oxide and compositions comprising them are useful in treating affections or diseases effectively treatable—albeit with side effects—with venlafaxine: depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and vasomotor symptoms associated with menopause, a.k.a. 'hot flashes'.

The invention also comprises:

pharmaceutical compositions for treating, for example, a disorder or condition treatable by venlafaxine, the compositions comprising an N-oxide of formula (1), and a pharmaceutically acceptable carrier;

methods of treating a disorder or condition treatable by venlafaxine, the methods comprising administering to a mammal in need of such treating an N-oxide of formula (1);

methods of treating a disorder or condition treatable by venlafaxine, the methods comprising administering to a mammal in need of such treating an N-oxide of formula (1);

pharmaceutical compositions for treating a disorder or condition treatable by venlafaxine, the compositions comprising an N-oxide of formula (1), and a pharmaceutically acceptable carrier;

methods for treating a disorder or condition treatable by venlafaxine, the methods comprising administering to a patient in need of such treating an N-oxide of formula (1).

The invention also provides the use of an N-oxide of formula (1), for the manufacture of medicament.

The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with

another therapeutic agent or agents, for instance venlafaxine or O-desmethyl-venlafaxine, for treating one or more of the conditions listed. Such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the compounds of the invention.

5 The invention also provides compounds, pharmaceutical compositions, kits and methods for treating a disorder or condition treatable by venlafaxine, the method comprising administering to a patient in need of such treating an N-oxide of formula (1).

 The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

10 The compounds of the present invention contain an asymmetric center. This will produce two optical isomers. All of the possible optical isomers and diastereomers, in mixtures and as pure or partially purified compounds, belong to this invention. The present invention comprehends all such isomeric forms of these compounds. Formula (1) shows the structure of the class of compounds without preferred stereochemistry. The independent syntheses of these
15 diastereomers, or their chromatographic separations, may be achieved as known in the art by appropriate modification of the methodology disclosed therein. Their absolute stereochemistry may be determined by the X-ray crystallography of crystalline products or crystalline intermediates, which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. Racemic mixtures of the compounds can be separated
20 into the individual enantiomers by methods well-known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture
25 of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases: Methods well-known in the art. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well-known in the art.

 Some of the crystalline forms for the compounds may exist as polymorphs: as such
30 intended to belong to the invention. In addition, some of the compounds may form solvates with water (i.e. hydrates), or common organic solvents. Such solvates also fall within the scope of this invention.

 Isotopically-labeled N-oxides of formula (1), detectable by PET or SPECT, also fall within the scope of the invention. The same applies to N-oxides of formula (1) labeled with [¹³C]-, [¹⁴C]-
35 , [³H]-, [¹⁸F]-, [¹²⁵I]- or other isotopically enriched atoms, suitable for receptor binding or metabolism studies.

The chance finding that N-oxides of venlafaxine and O-desmethylvenlafaxine are useful as prodrugs of their respective parent compounds, offers possibilities to use these compounds as alternatives, with the clinical benefits of an extended duration of action and a blunted peak plasma concentration, leading to an enhanced side-effect profile. Thus in some embodiments of the present invention, compounds of the present invention may be provided substantially free of parent compound 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol, venlafaxine, or O-desmethylvenlafaxine. By substantially free is meant that compound of the present invention contains less than about 50%, 40%, 30%, 20%, 10%, 1%, 0.5% or is, within detectable limits, free of venlafaxine or O-desmethylvenlafaxine as an impurity. Pharmaceutical compositions containing N-oxides of venlafaxine and/or O-desmethylvenlafaxine which are substantially free of venlafaxine and/or O-desmethylvenlafaxine are envisioned in accordance with the present invention.

DEFINITIONS

As used herein, the term "venlafaxine" means the racemic compound (R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol.

Any compound metabolized *in vivo* to provide the bioactive agent (i.e., the compound of formula (1)) is a **prodrug** within the scope and spirit of the application. Prodrugs are therapeutic agents, inactive per se but transformed into one or more active metabolites. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass treating the various disorders described with the compound specifically disclosed, or with a compound that not specifically disclosed, but that converts to the specified compound *in vivo* after administration to the patient. Prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism and targeting limitations (*Bundgaard, 1985; King, 1994; Stella, 2004; Ettmayer, 2004; Järvinen, 2005*). Prodrugs, i.e. compounds that when administered to humans by any known route, are metabolised to compounds having formula (1), belong to the invention. In particular this relates to the hydroxy group, which can be reacted with organic acids to yield compounds having formula (1) wherein an additional group is present that is easily removed after administration, for instance, but not limited to amidine, enamine, a Mannich base, a hydroxyl-methylene derivative, an O-(acyloxymethylene carbamate) derivative, carbamate, ester, amide or enaminone.

The term "**polymorphism**" is defined as the ability of a compound to exist in more than one crystal form, a so-called polymorph. Polymorphism is a frequently occurring phenomenon. Polymorphism is affected by several crystallization conditions such as temperature, level of supersaturation, the presence of impurities, polarity of solvent, rate of cooling. Polymorphs can

be characterized by several methods such as solid state NMR, solubility tests, DSC or melting point determination, IR or Raman spectroscopy.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "**about**". It is understood that whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value. Throughout the description and the claims of this specification the word "**comprise**" and variations of the word, such as "comprising" and "comprises" is not intended to exclude other additives, components, integers or steps. The term "**composition**" as used herein encompasses a product comprising specified ingredients in predetermined amounts or proportions, as well as any product that results, directly or indirectly, from combining specified ingredients in specified amounts. In relation to pharmaceutical compositions, this term encompasses a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product that results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. The pharmaceutical composition includes enough of the active object compound to produce the desired effect upon the progress or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

Within the context of this application, the term '**combination preparation**' comprises both true combinations, meaning an N-oxide of formula (1), and other medicaments physically combined in one preparation such as a tablet or injection fluid, as well as '**kit-of-parts**', comprising an N-oxide of formula (1), and venlafaxine or another medicament in separate dosage forms, together with instructions for use, optionally with further means for facilitating compliance with the administration of the component compounds, e.g. label or drawings. With true combinations, the pharmacotherapy by definition is simultaneous. The contents of 'kit-of-parts', can be administered either simultaneously or at different time intervals. Therapy being either concomitant or sequential will be dependant on the characteristics of the other medicaments used, characteristics like onset and duration of action, plasma levels, clearance, etc., as well as on the disease, its stage, and characteristics of the individual patient.

By "**pharmaceutically acceptable**" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Dose: recommended treatment dose is the same as for venlafaxine: 75 mg per day, administered in two or three divided doses, taken with food. Pharmacokinetic, pharmacodynamic, and other considerations may alter the dose actually administered to a higher or lower value. The dose of the compound to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will preferably be in the range of from 0.01 mg/kg to 10 mg/kg. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician. In general, oral and parenteral dosages will be in the range of 0.1 to 1,000 mg per day of total active ingredients.

The term "**therapeutically effective amount**" as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administering a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic, preventative or ameliorative response in a tissue system, animal or human. The effect may include, for example, treating or preventing the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician (researcher, veterinarian, medical doctor or other clinician), and the therapeutics, or combination of therapeutics, selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

The term "**treatment**" as used herein refers to any treatment of a mammalian, preferably human condition or disease, and includes: (1) preventing the disease or condition from occurring in a subject predisposed to the disease, but not yet diagnosed as having it, (2) inhibiting the disease or condition, i.e., arresting its development, (3) relieving the disease or condition, i.e., causing the condition to regress, or (4) stopping the symptoms of the disease. As used herein, the term "**medical therapy**" intendeds to include prophylactic, diagnostic and therapeutic regimens carried out *in vivo* or *ex vivo* on humans or other mammals. The term "**subject**" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

EXAMPLE 1: ANALYTICAL METHODS

Nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR, APT) were determined in the indicated solvent using a Bruker DRX 600 (^1H : 600 MHz, ^{13}C : 150 MHz) at 300 K, unless indicated otherwise. The spectra were determined in deuterated DMSO, obtained from Cambridge Isotope Laboratories Ltd. Chemical shifts (δ) are given in ppm downfield from

tetramethylsilane (^1H). Coupling constants J are given in Hz. Peak shapes in the NMR spectra are indicated with the symbols 'q' (quartet), 'dq' (double quartet), 't' (triplet), 'dt' (double triplet), 'd' (doublet), 'dd' (double doublet), 's' (singlet), 'bs' (broad singlet) and 'm' (multiplet). NH and OH signals were identified after mixing the sample with a drop of D_2O .

5

Melting points were recorded on a Büchi B-545 melting point apparatus.

Flash chromatography refers to purification using the indicated eluent and silica gel (either Acros: 0.030-0.075 mm or Merck silica gel 60: 0.040-0.063 mm).

10

Reactions were monitored by using **thin-layer chromatography** (TLC) on silica coated plastic sheets (Merck precoated silica gel 60 F254) with the indicated eluent. Spots were visualised by UV light (254 nm) or I_2 .

15

Liquid Chromatography- Mass Spectrometry (LC-MS) was performed using a system consisting of 2 Perkin Elmer series 200 micro pumps. The pumps are connected to each other by a 50 μl tee mixer, connected to a Gilson 215 auto sampler. The method is as follows:

	step	total time	flow ($\mu\text{l}/\text{min}$)	A(%)	B(%)
20	0	0	2000	95	5
	1	1.8	2000	0	100
	2	2.5	2000	0	100
	3	2.7	2000	95	5
	4	3.0	2000	95	5

25

A= 100% Water with 0.025% HCOOH and 10mmol NH_4HCOO pH= +/- 3

B= 100% ACN with 0.025% HCOOH

30

The auto sampler has a 2 μl injection loop. The auto sampler is connected to a Waters Atlantis C18 30*4.6 mm column with 3 μm particles. The column is thermo stated in a Perkin Elmer series 200 column oven at 40° C. The column is connected to a Perkin Elmer series 200 UV meter with a 2.7 μl flowcel. The wavelength is set to 254 nm. The UV meter is connected to a Sciex API 150EX mass spectrometer. The mass spectrometer has the following parameters:

35

Scanrange:150-900 a.m.u.; polarity: positive; scan mode: profile ; resolution Q1: UNIT ; step size: 0.10 a.m.u.; time per scan: 0.500 sec; NEB: 10; CUR: 10 IS: 5200; TEM: 325; DF: 30; FP: 225 and EP: 10. The light scattering detector is connected to the Sciex API 150. The light scattering detector is a Sedere Sedex 55 operating at 50° C and 3 bar N_2 . The complete system is controlled by a G3 powermac.

Venlafaxine and its N-oxide were analyzed in mouse plasma and brain samples using a generic bioanalytical method comprising protein precipitation and HPLC with MS/MS detection.

Proteins in 100 µl plasma were precipitated with acetonitrile, and 5 µl samples of the obtained solutions were analyzed. Complete brains were homogenized and centrifuged, and 10 µl samples of the supernatant were analyzed.

Liquid Chromatography – Tandem Mass Spectrometry (LC-MS/MS) was performed using a Sciex API4000 LC-MS/MS. Samples were quantified using extracted calibration samples, treated the same as the study samples, in the range of 1 – 5000 ng/ml and 5.0 – 5000 ng/brain for plasma and brain samples, respectively. Compound peak area was used for quantification. Calibration curves were fitted to the model $y = A + Bx + Cx^2$ (y is the peak area of the analyte, x is the nominal calibration level in ng/ml (plasma) or ng/g (brain), A is the intercept, B is the slope and C is the description of the curvature). $1/x^2$ weighing was used. LC-MS/MS system performance was monitored using a reference solution injected at standard intervals. The method was not validated in detail, therefore the reported concentrations were good estimations. The Lower Limit Of Quantification (LLOQ) was established at 1.00 ng/ml and 5.00 ng/brain, for plasma and brain samples, respectively. Values below the LLOQ were given as best estimate. Reversed phase HPLC was performed using gradient elution by a Hypersil BDS C18 100 x 4.6 mm 3 µm analytical column, at 45 °C and with a flow of 1.00 ml/min:

Time (min)	Solvent			
	% A	% B	% C	% D
0.00	10.0	70.0	0.0	20.0
1.00	10.0	70.0	0.0	20.0
2.00	10.0	10.0	0.0	80.0
4.00	10.0	10.0	0.0	80.0
4.10	10.0	70.0	0.0	20.0
7.00	10.0	0.0	0.0	20.0

Solvent A	100 mM NH ₄ FA/ 1% FA
Solvent B	Milli-Q water
Solvent C	methanol
Solvent D	acetonitrile

Detection on MS/MS was done using positive MRM ionization. Measured ions were:

	venlafaxine	venlafaxine-N-oxide
Q1	278.3	294.5
Q3	121.1	121.1

EXAMPLE 2: SYNTHESSES OF SPECIFIC COMPOUNDS

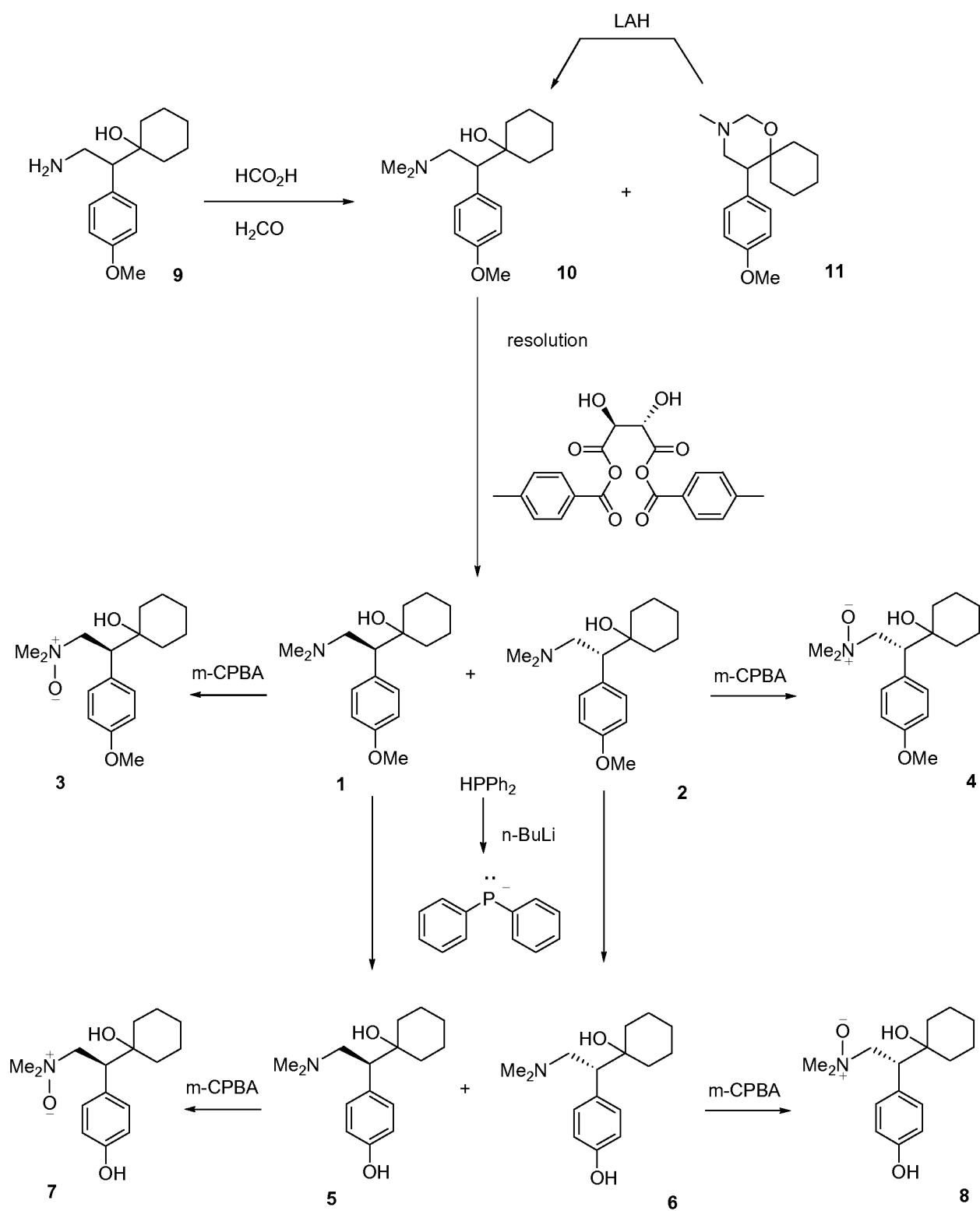
(R,S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol (venlafaxine), and
(R,S)-1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]-cyclohexanol (O-desmethylvenla-
5 faxine) were synthesized as described in EP 1 721 889. An alternative to the latter is given below.

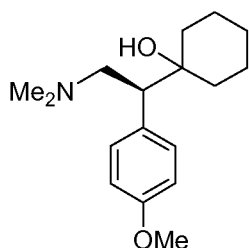
(R,S)-1-[2-oxido-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol (venlafaxine N-oxide):

10 Venlafaxine (0.28 g, 1.02 mmol) was dissolved in 20 ml DCM and cooled to -10°C. To the reaction mixture was added meta-chloroperbenzoic acid (m-CPBA, 0.8 g, 2.02 mmol) and the solution was stirred at -10°C for 30 minutes. Solid K₂CO₃ (2 g) was added and the resulting mixture was stirred for another 30 minutes at 0°C. The reaction mixture was filtrated (glass
15 funnel), and the precipitate was washed carefully with DCM. The resulting solution was concentrated and purified by flash chromatography (SiO₂, DCM/MeOH (95/5 followed by 9/1) to yield the title compound as a solid (0.22 g, 74%). mp 145 °C. LCMS ; R_t : 1.12 min, ([M+H]⁺ = 294). ¹H- NMR (600 MHz, D₆DMSO) : δ 7.12 (bd, J = 8 Hz, 2H), 6.86 (bd, J = 8 Hz, 2H), 3.95-3.89 (m, 1H), 3.73 (s, 3H), 3.56-3.52 (m, 1H), 3.28-3.25 (m, 1H), 3.14 (s, 3H), 2.95 (s, 3H), 1.69-
20 1.53 (m, 3H), 1.47-1.42 (m, 1H), 1.38-1.32 (m, 2H), 1.31-1.25 (m, 1H), 1.02 (dt, J = 11 Hz, 4 Hz, 1H), 0.87 (dt, J = 11 Hz, 4 Hz, 1H), 0.77-0.69 (m, 1H).

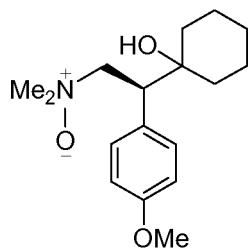
(R,S)-1-[2-oxido-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]-cyclohexanol (O-desmethylvenlafaxine N-oxide) can be prepared by the same method.

25 (S)- and (R)- enantiomers of venlafaxine, their respective N-oxides, and the O-desmethyl analogues were synthesized as depicted in the scheme below.

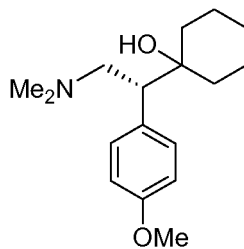




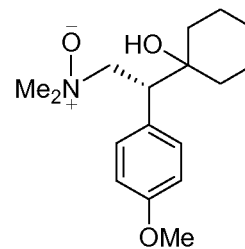
(S)-venlafaxine



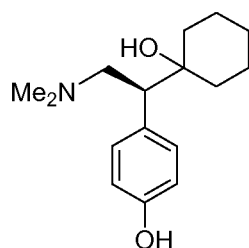
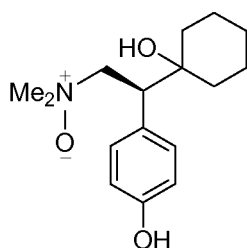
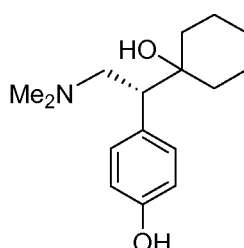
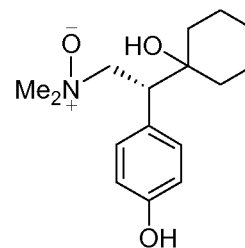
(S)-venlafaxine oxide



(R)-venlafaxine



(R)-venlafaxine oxide

O-desmethyl-
(S)-venlafaxineO-desmethyl-
(S)-venlafaxine oxideO-desmethyl-
(R)-venlafaxineO-desmethyl-
(R)-venlafaxine oxide**(R,S)-1-(2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (venlafaxine, **10**):**

Cyclohexanol (33g, 0.13 mol) was dissolved in formic acid (99%, 54 mL, 1.43 mol) and water (330 mL) by addition of formaldehyde (37%, 41 mL, 1.48 mol). The mixture was refluxed for 2 h.

- 5 Reaction mixture was concentrated to 150 mL (pH ~ 1.0), water (100 mL) was added and the mixture was extracted with ethyl acetate (4x 100 mL). The aqueous layer was cooled in an ice bath and basified to pH ~ 10 by addition of 50% NaOH. The mixture was extracted with ethyl acetate (3 x 100 mL), dried over Na₂SO₄ and concentrated. Yield:

- 10 This material (23.8 g, mainly compound **11**) was suspended in diethyl ether (500 mL) and treated with lithium aluminum hydride (3.8g, 0.1 mol). The suspension was stirred for 18 h at rt. 5 N KOH (16 mL) was added carefully, and the mixture was stirred for 15 min. Solids were removed by filtering over Celite, and washed (diethyl ether, 300 mL). The filtrates were dried (sodium sulfate) and concentrated. Yield: 21.4 g of compound **10** (60 %) as a white solid.

- 15 ¹H-NMR (300 MHz, CDCl₃): δ 7.05 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.8 Hz), 3.79 (s, 3H), 3.27 (t, 1H, J = 12.6), 2.93 (dd, 1H, ²J = 3.2 Hz, ³J = 12.5 Hz), 2.32 (s, 6H), 2.30 (dd, 1H, ²J = 3.2 Hz, ³J = 12.5 Hz), 1.82-1.61 (m, 3H), 1.60-1.45 (m, 3H), 1.42-1.22 (m, 2H), 1.01-0.78 (m, 2H).

R-venlafaxine (compound 2 in the scheme above):

- 20 (R,S)-Venlafaxine (23.4 g, 84 mmol) was dissolved in ethyl acetate (160 mL). To the solution was added a solution of *D*-ditoluyl-tartaric acid (18.7g, 48 mmol) in ethyl acetate (130 mL). Within 10 min. the salt started to precipitate. The mixture was stirred for 4 hours at rt. The precipitate was collected by filtering over a glass filter, and washed with ethyl acetate (2 x 100

mL). White crystalline solid. This solid was recrystallized from ethyl acetate:methanol (6:1, 100 mL). The solids were collected on a glass filter. Yield: 14.0 g. This material was treated with 2N NaOH (cold, 180 mL). The aqueous phase was extracted with ethyl acetate (3 x 200 mL). The organic phase was washed with 2 N NaOH (cold, 75 mL) then with water until washings were neutral (pH 7). The organic phase was dried (sodium sulfate) and concentrated. Yield: 8.1 g of *R*-Venlafaxine (**2**) as white crystalline solid. m.p.: 106°C - 109.5°C. $[\alpha]_D^{23} = -8.0$ (c = 1.5, MeOH). Chiral HPLC: 99 % e.e. ¹H-NMR (CDCl₃): see above.

S-Venlafaxine (1):

The mother liquor of the resolution (see above) was freed by washing with 1 N NaOH (4 x 100 mL), with water (3 x 200 mL) and with brine (100 mL). The organic phase was dried (sodium sulfate) and concentrated. Oil, solidifies quickly. This material was re-dissolved in ethyl acetate (75 mL). A solution of *L*-ditoluy tartaric acid (11.3 g, 29 mmol) in ethyl acetate (75 mL) was added. Precipitation started within 5 minutes. Ethyl acetate (50 mL) was added and the mixture was stirred for 72 hours at room temperature. Solids were collected on a glass filter. Yield: 14.2 g. This material was treated with 2N NaOH (cold, 180 mL). The aqueous phase was extracted with ethyl acetate (3 x 200 mL). The organic phase was washed with 2 N NaOH (cold, 75 mL) then with water until washings were neutral (pH 7). The organic phase was dried (sodium sulfate) and concentrated. Yield: 6.7 g of *S*-Venlafaxine (**1**) as white crystalline solid. m.p. 104.5°C - 106°C. $[\alpha]_D^{23} = +13.9$ (c = 1.6, MeOH). Chiral HPLC: 98 % e.e. ¹H-NMR (CDCl₃): see above

S-Venlafaxine N-oxide (3)

Crude material (2.2 g, 7.5 mmol) has been obtained by FAI (106796), according to the procedure described for **4**. Pure **3** was obtained by column chromatography (gradient dichloromethane:methanol, 9:1 → dichloromethane: 3.5 M ammonia in methanol, 9:1). Yield: 1.70 g (5.8 mmol, 78 %) of **3** as a slightly yellow solid. $[\alpha]_D^{23} = -20.8$ (c = 1.0, MeOH). ¹H-NMR (300 MHz, CDCl₃): δ 7.09 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.5 Hz), 4.16 (m, 1H), 3.79 (s, 3H), 3.51 (dd, 1H, ²J = 3.8 Hz, ³J = 12.7 Hz), 3.41 (m, 1H), 3.27 (s, 3H), 3.07 (s, 3H), 1.78-1.60 (m, 3H), 1.60-1.35 (m, 4H), 1.29-1.01 (m, 2H), 0.95-0.76 (m, 1H).

R-Venlafaxine N-oxide (4)

R-Venlafaxine (**2**, 1.0 g, 3.4 mmol) was dissolved in dichloromethane (60 mL). The solution was cooled to -10°C. *m*-CPBA (fresh, 2.9 g, 7.3 mmol) was added. The suspension was stirred for 30 min. at -10°C. TLC check revealed full conversion. K₂CO₃ (5.0 g, 36 mmol.) was added, and the mixture was stirred for 30 min. at 0°C. Dichloromethane (50 mL) was added and the suspension was filtered. The filtrate was dried and concentrated. The crude product was purified

as above. YIELD: 0.9 g (3.0 mmol, 90 %) as a white solid. $[\alpha]_D^{23}$: not determined. $^1\text{H-NMR}$ (300 MHz, CDCl_3): see above.

O-desmethyl-S-Venlafaxine (5)

5 A solution of diphenylphosphine (18 mL, 0.1 mol) in dry tetrahydrofuran (120 mL) was, under N_2 , cooled to -10°C . $n\text{-BuLi}$ (2.5 M in hexanes, 50 mL) and additional tetrahydrofuran (40 mL) were added. The mixture was stirred for 30 min. at -10°C , then the temperature was allowed to raise to 0°C . At this temperature a solution of S-venlafaxine (**1**, 6.2 g, 23 mmol) in tetrahydrofuran (60 mL) was added. The mixture was stirred for 2 hours, while the temperature
10 was allowed to raise to room temperature, and subsequently at reflux temperature for 16 hours. The reaction mixture was cooled to room temperature, poured into 2N HCl (cold, 300 mL) and stirred for 10 min. The aqueous phase was washed (ethyl acetate, 3 x 300 mL), then neutralized (pH 7) by means of slow (!) addition of NaHCO_3 (s), and extracted (ethyl acetate, 6 x 300 mL). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was suspended
15 in ethyl acetate (100 mL) and stirred for 30 min. Solids were collected on a glass filter, and washed with ethyl acetate, until the smell of diphenylphosphine could no longer be detected. White solid. Yield: 4.6 g (17.5 mmol, 76 %). m.p. $237.3^\circ\text{C} - 237.9^\circ\text{C}$. $[\alpha]_D^{23} = +17.0$ ($c = 0.88$, MeOH). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): δ 9.12 (br, 1H), 6.94 (d, 2H, $J = 8.3$ Hz), 6.62 (d, 2H, $J = 8.3$ Hz), 5.37 (br, 1H), 2.98 (m, 1H), 2.71 (t, 1H, $J = 5.8$ Hz), 2.34 (m, 1H), 2.14 (s, 6H), 1.64-1.22 (m,
20 7H), 1.20-0.78 (m, 3H).

O-desmethyl-R-Venlafaxine (6)

As above, starting with R-Venlafaxine (5.0 g, 18 mmol), using diphenylphosphine (14 mL) and $n\text{-BuLi}$ in hexanes (2.5 M, 41 mL). Yield: 3.8 g (14.5 mmol, 80 %). m.p. $235.5^\circ\text{C} - 237.1^\circ\text{C}$.
25 $[\alpha]_D^{23} = -21.3$ ($c = 0.9$, MeOH). $^1\text{H-NMR}$ (300 MHz, DMSO-d_6): see above.

O-desmethyl-S-venlafaxine N-oxide (7)

O-desmethyl-S-Venlafaxine (**5**, 1.5 g, 5.7 mmol) was suspended in dichloromethane (100 mL). The suspension was cooled to -10°C . m-CPBA (4.8 g, 12 mmol) was added. The suspension
30 was stirred for 60 min. at -10°C . TLC check revealed full conversion. K_2CO_3 (7.5 g, 54 mmol.) was added, and the mixture was stirred for 30 min. at 0°C . Dichloromethane (100 mL) was added and the suspension was filtered. The residue was stirred in methanol (300 mL), and filtered again. The combined filtrates were concentrated *in vacuo* (Yield: 7.1 g).

This material was purified by column chromatography: the crude product was dissolved in
35 methanol (20 mL), brought on the column (silica in dichloromethane), eluted with dichloromethane (200 mL) and subsequently with dichloromethane: 7M NH_3 in methanol, 9: 1. YIELD: 1.15 g (4.1 mmol, 72 %) of compound **7** as a slightly yellow solid. $[\alpha]_D^{23} = -26.8$ ($c =$

0.8, MeOH). ¹H-NMR (300 MHz, DMSO-d⁶): δ 9.66 (br, 1H), 6.98 (d, 2H, J = 8.3 Hz), 6.69 (d, 2H, J = 8.3 Hz), 3.88 (m, 1H), 3.55 (dd, ²J = 2.4 Hz, ³J = 12.7 Hz, 1H), 3.34 (br, 1H), 3.20 (dd, ²J = 2.4 Hz, ³J = 12.7 Hz, 1H), 3.14 (s, 3H), 2.95 (s, 3H), 1.69-1.20 (m, 6H), 1.11-0.66 (m, 4H).

5 O-Desmethyl-R-venlafaxine N-oxide (8)

As above, starting with O-desmethyl-R-Venlafaxine (6, 1.5 g, 5.7 mmol). Yield: 1.20 g (4.3 mmol, 75 %) as a slightly yellow solid. $[\alpha]_D^{23} = +16.3$ (c = 0.8, MeOH). ¹H-NMR (300 MHz, DMSO-d⁶): see above.

10 EXAMPLE 3: PHARMACOLOGICAL METHODS

In vitro affinity for neurotransmitter reuptake sites were either obtained by CEREP (128, rue Danton, 92500 Reuil-Malmaison, France) or at Solvay Pharmaceuticals B.V. (C.J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands), using well documented procedures.

15 Measured were affinities for serotonin (*Tatsumi, 1999*), norepinephrine (*Pacholczyk, 1991*) and dopamine reuptake sites (*Pristupa, 1994*).

In vitro functional inhibition of [³H]-serotonin reuptake: Male rats (Wistar Hsd/Cpb: WU; 175-200 g) were decapitated, the cerebral hemispheres were rapidly removed, and a P2-synaptosomal fraction was prepared. Synaptosomes were pre-incubated in absence or presence of the test compound for 15 min at 37°C, in a medium containing the MAO inhibitor pargyline (7 μM). Subsequently, the synaptosomes were exposed to [³H]-serotonin (0.2 mM final concentration) for 10 min. [³H]-Serotonine uptake was stopped by filtration with a harvester and the non-incorporated radioactivity was removed by extensive washing. Filterplates with synaptosomes were dehydrated, and the amount of [³H]-serotonin present was determined by Betaplate liquid scintillation counting. Inhibitory effects on the uptake of the [³H]-serotonin were expressed as pIC₅₀ value, that is the negative logarithm of the concentration at which half maximal inhibition of radiolabeled neurotransmitter uptake is achieved. pIC₅₀ values given are mean values of 2-9 experiments performed in duplicate. Testcompounds, 10⁻² M dissolved in DMSO, were diluted in Krebs Ringer buffer to the testconcentrations of 10⁻⁸ to 10⁻⁵ M. Further experimental details were as described (*Coyle, 1969*).

In vitro functional inhibition of [³H]-norepinephrine reuptake: Male rats (Wistar Hsd/Cpb: WU; 175-200 g) were decapitated, the hypothalamus was rapidly removed and a crude synaptosomal fraction was prepared. Synaptosomes were pre-incubated in absence or presence of the test compound for 10 min at 37°C, in a medium containing the MAO inhibitor pargyline (7 μM). Subsequently, the synaptosomes were exposed to [³H]-norepinephrine (0.4

mM final concentration) for 15 min. [³H]- Norepinephrine uptake was stopped by filtration with a harvester and the non-incorporated radioactivity was removed by an extensive washing programme. The filterplates with synaptosomes were dehydrated and the amount of [³H]- norepinephrine present was determined by Betaplate liquid scintillation counting. Inhibitory effects on the uptake of the [³H]- norepinephrine were expressed as pIC₅₀ value, that is the negative logarithm of the concentration at which half maximal inhibition of radiolabeled neurotransmitter uptake is achieved. pIC₅₀ values given are mean values of 2-9 experiments performed in duplicate. Testcompounds, 10⁻² M dissolved in DMSO, were diluted in Krebs Ringer buffer to testconcentrations of 10⁻⁸ - 10⁻⁵ M. Further experimental details were as described (Coyle, 1969).

***In vitro* functional inhibition of [³H]-dopamine reuptake:** Male rats (Wistar Hsd/Cpb: WU; 175-200 g) were decapitated; the striatum was rapidly removed and a crude synaptosomal fraction (P2) was prepared by homogenization and centrifugation. Synaptosomes were pre-incubated in absence or presence of the test compound for 15 min at 37°C, in a medium containing the monoamine oxidase inhibitor pargyline (7x10⁻⁶ M) (Coyle, 1969). Subsequently, [³H]-dopamine (2x10⁻⁷ M final concentration) was added and incubation was continued for 10 min. [³H]-dopamine uptake was stopped by filtration and the synaptosomes were washed four times with phosphate buffered saline. The amount of [³H]-dopamine in the synaptosomes was determined by Betaplate liquid scintillation counting. Compounds were tested in a concentration range of 10⁻⁹ to 10⁻⁵ M. Inhibitory effects on the uptake of [³H]-dopamine were expressed using the pIC₅₀ value (the negative logarithm of the concentration at which the drug caused 50% uptake inhibition). Inhibition of DA uptake was performed in duplicate.

The human colon model TIM2 (TNO Intestinal Model 2): is a dynamic model for the human large intestine that simulates in vivo conditions. It is an artificial digestive system that has been validated by many studies (Minekus, 1999).

Venlafaxine-N-oxides are prodrugs of the parent compound. They are useful in the treatment of diseases effectively treatable—albeit with side effects—with venlafaxine: depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and vasomotor symptoms associated with menopause, a.k.a. 'hot flashes'.

EXAMPLE 4: PHARMACOKINETIC AND PHARMACOLOGICAL TEST RESULTS

Venlafaxine and its N-oxide, formulated in 40% HP β CD or 1% methylcellulose, respectively, were individually administered (intravenously (i.v.) or orally (p.o.)) to male NMRI mice (3 animals per time point), after which their plasma and brain were analyzed by LC-MS (*method see above*) for both compounds. Data were averaged (n=3), and collected in table 1.

Table 1: plasma and brain concentrations of venlafaxine and its N-oxide					
		venlafaxine		venlafaxine-N-oxide	
		plasma	brain	plasma	brain
administered	Time (h)	[ng/ml]	[ng/g]	[ng/ml]	[ng/g]
venlafaxine 1.0 mg/kg i.v.	0.17	250	710	0.32	0.19
	0.5	97	289	0.12	0
	1	49	200	0.10	0
	3	4.7	15	0	0
	7	0.30	1.7	0	0
	24	0.37	0	0	0
venlafaxine 10 mg/kg p.o.	0.17	630	1133	2.5	0
	0.5	543	2267	7.0	0.37
	1	523	1800	3.0	0.09
	3	38	137	0.31	0
	7	3.6	15	0.06	0
	24	0	0	0	0
venlafaxine-N-oxide 1.0 mg/kg i.v.	0.17	42	56	623	3.3
	0.5	22	52	173	58
	1	8.0	26	39	8.1
	3	0.59	3.0	7.3	0.44
	7	0	0.85	0.16	0.15
	24	0	0	0	0
venlafaxine-N-oxide 10 mg/kg p.o.	0.17	82	55	1040	14
	0.5	72	167	840	33
	1	117	353	183	6.7
	3	77	280	38	1.8
	7	3.3	12	0.75	1.6
	24	0.63	0	0.12	0

In mice, venlafaxine is only marginally metabolized to its N-oxide: The concentration thereof in the plasma never exceeds 1 – 2% of that of the parent compound, and in brain only traces can be found. When venlafaxine-N-oxide itself is administered it is reduced to the parent compound. Approximately one hour after i.v. administration of venlafaxine-N-oxide, venlafaxine concentrations in plasma and brain exceed those of the N-oxide. The effects are more pronounced after oral administration: Venlafaxine concentrations in both plasma and brain rise to levels that are a factor 10 to 100 higher than those of the N-oxide.

Suspended in 1% methylcellulose, venlafaxine-N-oxide (1 mg) was inserted into the lumen (120 ml) of the TIM2 model (see above, Minekus, 1999). Samples from the lumen and the dialysate (the latter being a model for the vascular bed of the intestines) were taken at various time intervals, and analyzed for venlafaxine-N-oxide and venlafaxine: Table 2:

5

Table 2 reduction of venlafaxine N-oxide in the human colon model TIM2				
	venlafaxine-N-oxide		venlafaxine	
	lumen	dialysate	lumen	dialysate
Time (h)	[ng/ml]	[ng/ml]	[ng/ml]	[ng/ml]
0	< 1.0	< 1.0	< 1.0	< 1.0
2	2.0	7.4	5,400	320
4	2.0	1.2	4,700	470
6	2.0	1.0	4,600	430
8	1.9	< 1.0	3,900	370
24	< 1.0	< 1.0	970	210

Form the results above it is clear that already within 2 hours after dosing venlafaxine N-oxide was nearly quantitatively reduced to venlafaxine. Because many studies validated TIM2 as an *in vitro* model with high predictive value for the gastrointestinal conditions in living human beings, it is predicted that also in man, after oral administration, venlafaxine N-oxide will be reduced to venlafaxine: that it will be a prodrug.

10

Table 3: plasma pharmacokinetics of venlafaxine and its N-oxide				
	venlafaxine		Venlafaxine-N-oxide	
Route of administration:	i.v.	p.o.	i.v.	p.o.
Dose (mg/kg)	1	10	1	10
C_{max} (ng/ml)	407.9 (C_0)*	630.0	1205.2 (C_0)*	1040.0
T_{max} (hr)	0.0	0.2	0.0	0.2
$t_{1/2}$ (hr)	0.8	0.9	0.8	3.1
$AUC_{0 \rightarrow end}$ (ng/ml x hr)	194.3	943.4	361.6	841.6
→ remark	$T_{end} = 24$ hrs	$T_{end} = 7$ hrs	$T_{end} = 7$ hrs	$T_{end} = 24$ hrs
$AUC_{0 \rightarrow \infty}$ (ng/ml x hr)	194.8	948.0	361.7	842.2
→ remark	$T_{end} = \infty$	$T_{end} = \infty$	$T_{end} = \infty$	$T_{end} = \infty$
Clearance (ml/min/kg)	85.6	-	46.1	-
V_D (ml/kg)	6200.0	-	3000.0	-
Bioavailability (%)	48.7	-	23.3	-
Brain/plasma ratio	3.1	3.4	0.1	0.0

15

* For i.v. administration, C_{max} values were extrapolated to T_0 (time zero)

From the data given above it is evident that clearance, volume of distribution and bioavailability of venlafaxine are twice as high as those of its pyridine N-oxide. Clearly, the two compounds have different pharmacokinetic properties. As is also clear from the data given in Table 1, venlafaxine-N-oxide hardly penetrates the brain: Hence dramatically different brain/plasma ratio's.

<i>in vitro</i> pharmacology of (O-desmethyl)venlafaxine, their N-oxides, and enantiomers						
	dopamine		noradrenaline		serotonin	
	binding	inhibition	binding	inhibition	binding	inhibition
compound	pK _i	pIC ₅₀	pK _i	pIC ₅₀	pK _i	pIC ₅₀
(R,S)-venlafaxine	5.4	5.3	5.2	6.2	7.9	7.2
(S)-venlafaxine	4.8	5.0	< 4.5	6.1	8.0	7.3
(R)-venlafaxine	5.6	5.5	5.4	6.8	7.5	7.1
(S)-O-desmethyl-venlafaxine	4.9	5.0	4.6	6.4	8.0	7.3
(R)-O-desmethyl-venlafaxine	5.2	5.3	5.2	6.4	7.6	7.1
(R,S)-venlafaxine-N-oxide	< 4.5	4.5	< 4.5	4.9	5.5	4.9
(S)-venlafaxine-N-oxide	< 4.5	< 4.5	< 4.5	< 4.5	5.2	4.8
(R)-venlafaxine-N-oxide	< 4.5	< 4.5	< 4.5	4.4	5.1	4.7
(S)-O-desmethyl-venlafaxine-N-oxide	< 4.5	< 4.5	< 4.5	< 4.5	4.9	4.6
(R)-O-desmethyl-venlafaxine-N-oxide	< 4.5	< 4.5	< 4.5	< 4.5	5.0	4.4

The *in vitro* pharmacological data compiled in the table above clearly indicate that venlafaxine is most potent as inhibitor of serotonin reuptake. Its (R)- and (S)-enantiomers showed only marginal differences. The major metabolite, O-desmethylvenlafaxine, was found to be equipotent with venlafaxine, both as racemate, and in the form of its individual enantiomers. The N-oxides of venlafaxine and O-desmethyl-venlafaxine, as racemates as well as individual (R)- or (S)-enantiomers were found to be virtually devoid of activity.

EXAMPLE 5: PHARMACEUTICAL PREPARATIONS

For clinical use, N-oxides of formula (1) are formulated into pharmaceutical compositions that are important and novel embodiments of the invention because they contain the compounds, more particularly specific compounds disclosed herein. Types of pharmaceutical compositions that may be used include: tablets, chewable tablets, capsules (including microcapsules), solutions, parenteral solutions, ointments (creams and gels), suppositories, suspensions, and other types disclosed herein, or are apparent to a person skilled in the art from the specification and general knowledge in the art. The active ingredient for instance, may also be in the form of an inclusion complex in cyclodextrins, their ethers or their esters. The compositions are used for

oral, intravenous, subcutaneous, tracheal, bronchial, intranasal, pulmonary, transdermal, buccal, rectal, parenteral or other ways to administer. The pharmaceutical formulation contains at least one N-oxide of formula (1) in admixture with at least one pharmaceutically acceptable adjuvant, diluent and/or carrier. The total amount of active ingredients suitably is in the range of
5 from about 0.1% (w/w) to about 95% (w/w) of the formulation, suitably from 0.5% to 50% (w/w) and preferably from 1% to 25% (w/w). In some embodiments, the amount of active ingredient is greater than about 95% (w/w) or less than about 0.1% (w/w).

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances such as liquid or solid, powdered
10 ingredients, such as the pharmaceutically customary liquid or solid fillers and extenders, solvents, emulsifiers, lubricants, flavorings, colorings and/or buffer substances. Frequently used auxiliary substances include magnesium carbonate, titanium dioxide, lactose, saccharose, sorbitol, mannitol and other sugars or sugar alcohols, talc, lactoprotein, gelatin, starch, amylopectin, cellulose and its derivatives, animal and vegetable oils such as fish liver oil,
15 sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets. A tablet is prepared using the ingredients below:

20	<u>Ingredient</u>	<u>Quantity (mg/tablet)</u>
	venlafaxine N-oxide	10
	Cellulose, microcrystalline	200
	Silicon dioxide, fumed	10
	<u>Stearic acid</u>	<u>10</u>
25	Total	230

The components are blended and compressed to form tablets each weighing 230 mg.

The active ingredients may be separately premixed with the other non-active ingredients,
30 before being mixed to form a formulation. The active ingredients may also be mixed with each other, before being mixed with the non-active ingredients to form a formulation.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active ingredients of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active ingredients. Hard gelatin capsules
35 may also contain the active ingredients together with solid powdered ingredients such as

lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories that contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatin rectal capsule that contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations may be prepared in the form of syrups, elixirs, concentrated drops or suspensions, e.g. solutions or suspensions containing the active ingredients and the remainder consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, preservatives, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations may also be prepared in the form of a dry powder, reconstituted with a suitable solvent prior to use. Solutions for parenteral administration may be prepared as a solution of a formulation of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients, preservatives and/or buffering ingredients. Solutions for parenteral administration may also be prepared as a dry preparation, reconstituted with a suitable solvent before use.

Also provided according to the present invention are formulations and 'kits of parts' comprising one or more containers filled with one or more of the ingredients of a pharmaceutical composition of the invention, for use in medical therapy. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals products, which notice reflects approval by the agency of manufacture, use, or sale for human or veterinary administration. The use of formulations of the present invention in the manufacture of medicaments for use in treating depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and vasomotor symptoms associated with menopause, a.k.a. 'hot flashes', and methods of medical treatment or comprising the administration of a therapeutically effective total amount of at least one N-oxide of formula (1), either as such or, in the case of prodrugs, after administration, to a patient suffering from depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and vasomotor symptoms associated with menopause, a.k.a. 'hot flashes'.

By way of example and not of limitation, several pharmaceutical compositions are given, comprising preferred active compounds for systemic use or topical application. Other compounds of the invention or combinations thereof, may be used in place of (or in addition to) said compounds. The concentration of the active ingredient may be varied over a wide range as discussed herein. The amounts and types of ingredients that may be included are well known in the art.

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To the extent in which the following references are useful to one skilled in the art, or to more fully describe this invention, they are incorporated herein by reference. Neither these, nor any other documents or quotes cited herein, nor citations to any references, are admitted to be prior art documents or citations.

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10 **PATENTS AND PATENT APPLICATIONS:**

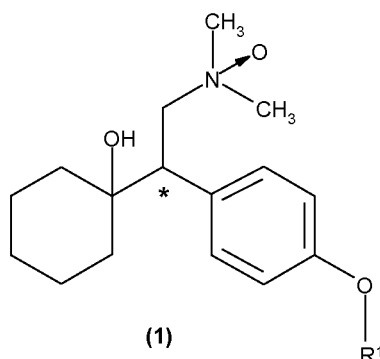
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U.S. 4,761,501

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CLAIMS:

1. N-oxide having formula (1):

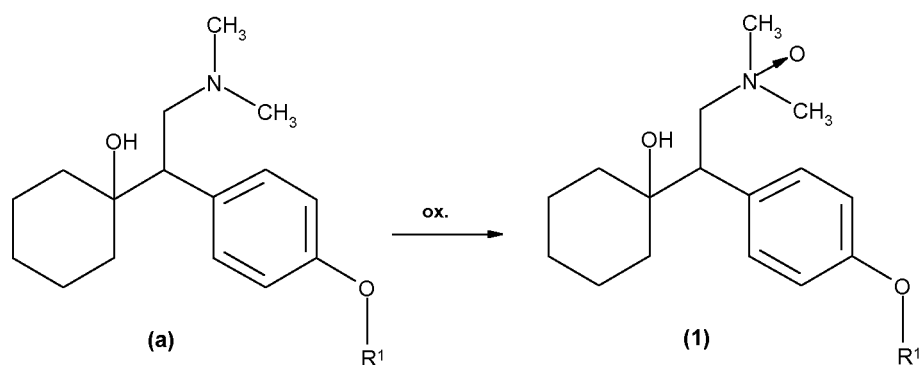


wherein the asterisk (*) marks the asymmetric carbon atom, R^1 is H or CH_3 , and tautomers, stereoisomers, hydrates and solvates thereof.

2. N-oxide as claimed in claim 1, substantially free of 1-[2-(dimethylamino)-1-(4-methoxy-phenyl)ethyl]-cyclohexanol and 1-[2-(dimethylamino)-1-(4-hydroxy-phenyl)ethyl]-cyclohexanol, and tautomers, stereoisomers, salts, hydrates and solvates thereof.
3. N-oxide as claimed in claim 1 wherein R^1 is CH_3 , and tautomers, stereoisomers, hydrates and solvates thereof.
4. N-oxide as claimed in claim 3 substantially free of 1-[2-(dimethylamino)-1-(4-methoxy-phenyl)ethyl]-cyclohexanol, and tautomers, stereoisomers, salts, hydrates and solvates thereof.
5. N-oxide as claimed in claim 1 wherein R^1 is H, and tautomers, stereoisomers, hydrates and solvates thereof.
6. N-oxide as claimed in claim 5 substantially free of 1-[2-(dimethylamino)-1-(4-hydroxy-phenyl)ethyl]-cyclohexanol, and tautomers, stereoisomers, salts, hydrates and solvates thereof.
7. N-oxide as claimed in any one of the claims 1-6, or a pharmacologically acceptable salt, hydrate or solvate of any of the foregoing, said compound being an optically active enantiomer.

8. N-oxide as claimed in claim 7 or a pharmacologically acceptable salt, hydrate or solvate of any of the foregoing, which is the (R)-enantiomer.
9. N-oxide as claimed in claim 7 or a pharmacologically acceptable salt, hydrate or solvate of any of the foregoing, which is the (S)-enantiomer.
10. N-oxide as claimed in claim 8, substantially free of (S)-1-[2-(dimethylamino)-1-(4-methoxy-phenyl)ethyl]-cyclohexanol and (S)-1-[2-(dimethylamino)-1-(4-hydroxy-phenyl)-ethyl]-cyclohexanol, and pharmacologically acceptable salts, hydrates and solvates thereof.
11. N-oxide as claimed in claim 9 substantially free of (R)-1-[2-(dimethylamino)-1-(4-methoxy-phenyl)ethyl]-cyclohexanol and (R)-1-[2-(dimethylamino)-1-(4-hydroxy-phenyl)-ethyl]-cyclohexanol, and pharmacologically acceptable salts, hydrates and solvates thereof.
12. A medicament, comprising a compound according to any one of the claims 1-11, or hydrate or solvate thereof.
13. A pharmaceutical composition comprising, apart from a pharmaceutically acceptable carrier and/or at least one pharmaceutically acceptable auxiliary substance, a pharmacologically active amount of at least one compound of any one of the claims 1-11, or hydrate or solvate thereof, as an active ingredient.
14. Combination pharmaceutical preparation comprising (i) an N-oxide of formula (1), or hydrates or solvates thereof, and (ii) another therapeutic agent, for simultaneous, separate or sequential use in therapy of depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and 'hot flashes'.
15. Combination pharmaceutical preparation as claimed in claim 14, wherein said other therapeutic agent is venlafaxine or O-demethylvenlafaxine.
16. A compound as claimed in any of the claims 1-11, for treating depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and 'hot flashes'.

17. Use of a compound as claimed in any of the claims 1-11, for the preparation of a pharmaceutical composition for the treatment of depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and 'hot flashes'.
18. Use of a combination preparation as claimed in claim 15 to prepare a pharmaceutical composition for treating depression, including major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, social anxiety disorder, panic disorder, general depressive disorders, diabetic neuropathy, migraine and 'hot flashes'.
19. Process for the preparation of compounds as claimed in claim 1, characterized in that a compound of the general formula (a) is oxidized with an oxidizing agent to yield a compound of the general formula (1)



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/057939

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C291/04 A61K31/135 A61P25/24

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	BICKEL M H: "THE PHARMACOLOGY AND BIOCHEMISTRY OF N-OXIDES" 1969, PHARMACOLOGICAL REVIEWS, WILLIAMS AND WILKINS INC., BALTIMORE, MD., US, PAGE(S) 325-355, XP000984853 ISSN: 0031-6997 page 348 - page 349	1-19
A	US 4 535 186 A (HUSBANDS G E MORRIS [US] ET AL) 13 August 1985 (1985-08-13) column 12, line 22 - line 33; claims	1-19
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☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

& document member of the same patent family

Date of the actual completion of the international search

11 September 2008

Date of mailing of the international search report

23/09/2008

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zervas, Brigitte

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No

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