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**Ethers of O-desmethyl venlafaxine**

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WO 01/38293 A1

(54) Title: ETHERS OF O-DESMETHYL VENLAFAXINE

(57) Abstract: This invention provides O- $\alpha$ -acyloxyalkyl ethers of the venlafaxine metabolite 4-[2-(Dimethylamino-1-(1-hydroxy-cyclohexyl)ethyl]phenol, represented by Formula (I); wherein the configuration at the stereogenic center (\*) may be R, S, or RS (the racemate); R<sub>1</sub> is selected from C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or the moiety: (a); R<sub>2</sub> is selected from H, or C<sub>1</sub>-C<sub>6</sub> alkyl; or, R<sub>1</sub> and R<sub>2</sub> may be concatenated such that (i), form a moiety having formula (b); R<sub>3</sub> is selected from H or C<sub>1</sub>-C<sub>6</sub> alkyl; and R<sub>4</sub> and R<sub>5</sub> are independently selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> thioalkoxy, -CN, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, halogen, -NH<sub>2</sub>, -NO<sub>2</sub>, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, or pharmaceutically acceptable salts or hydrates thereof, R, S, or RS forms thereof; as well as pharmaceutical compositions and methods treating central nervous system disorders.

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**ETHERS OF O-DESMETHYL VENLAFAXINE**

This invention relates to ethers of O-desmethyl venlafaxine, more particularly to O- $\alpha$ -acyloxyalkyl ethers of 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl)-phenol, processes for preparing them as well as pharmaceutical compositions and uses thereof.

**Background of the Invention**

10 Various patents and literature references describe the biological activities of venlafaxine, and its salts and analogs. Venlafaxine hydrochloride tablets are marketed by Wyeth-Ayerst Laboratories as EFFEXOR.

15 The absolute configuration of the (+) enantiomer of venlafaxine was established as S by a single crystal X-ray analysis of the hydrobromide salt and the anomalous dispersion technique (Yardley et al., J. Med. Chem., 1990, 33, 2899).

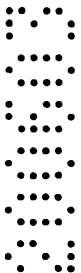
(R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and its metabolites 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol and 1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol are disclosed and claimed in 20 U.S. Patent No. 4,535,186 (Husbands et al.). U.S. Patent No. 5,530,013 (Husbands et al.) claims the use of venlafaxine in the inducement of cognition enhancement. U.S. Patent No. 5,506,270 (Upton et al.) claims venlafaxine's use in methods of treating hypothalamic amenorrhea in non-depressed women.

25

U.S. Patents Nos. 5,788,986 (Dodman) and 5,554,383 (Dodman) teaches and claims the use of serotonin reuptake inhibitors in modifying the behavior of dogs.

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

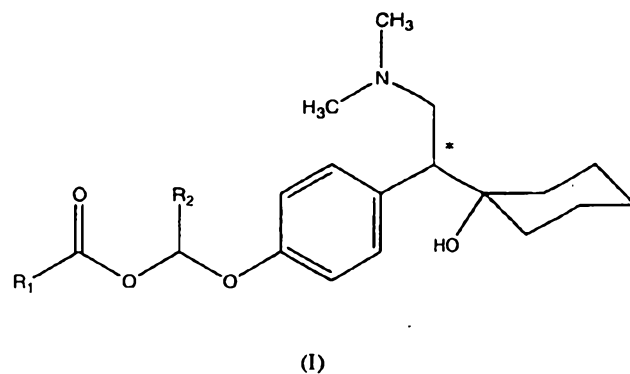
Throughout the description and the claims of this specification the word “comprise” and variations of the word, such as “comprising” and “comprises” is not intended to exclude other additives, components, integers or steps.



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**Detailed Description of the Invention**

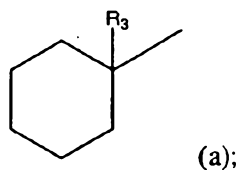
This invention provides pharmaceutically active O- $\alpha$ -acyloxyalkyl ethers of the venlafaxine metabolite 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol ("O-Desmethyl venlafaxine" or "ODV") having the structural formula I



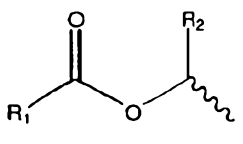
wherein

the configuration at the stereogenic center (\*) may be R, S, or RS (the racemate);

10  $R_1$  is selected from  $C_1 - C_6$  alkyl,  $C_1 - C_6$  alkoxy,  $C_3 - C_6$  cycloalkyl, or the moiety:

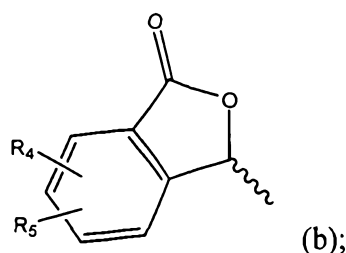


$R_2$  is selected from H, or  $C_1 - C_6$  alkyl; or,

$R_1$  and  $R_2$  may be concatenated such that , form a moiety

15 having formula (b):

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R<sub>3</sub> is selected from H or C<sub>1</sub> – C<sub>6</sub> alkyl; and

R<sub>4</sub> and R<sub>5</sub> are independently selected from H, C<sub>1</sub> – C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub>

5 cycloalkyl, C<sub>1</sub> – C<sub>6</sub> alkoxy, C<sub>1</sub> – C<sub>6</sub> thioalkoxy, -CN, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, halogen, -NH<sub>2</sub>, -NO<sub>2</sub>, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, for example, -N(CH<sub>3</sub>)<sub>2</sub>, or pharmaceutically acceptable salts or hydrates thereof.

In some preferred embodiments of the present invention R<sub>1</sub> is t-butyl,  
10 methoxy, or isobenzofuranone.

In other preferred embodiments of the invention R<sub>2</sub> is C<sub>1</sub> – C<sub>3</sub> alkyl and in still more preferred embodiments of the invention R<sub>2</sub> is methyl.

Specific examples of compounds of Formula I include:

15 {4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate;

1-{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}ethyl propionate; and

20 3-{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}-2-benzofuran-1(3H)-one.

Particularly, this invention provides compounds and/or compositions of both the O- $\alpha$ -acyloxyalkyl R-ether of Formula I and the O- $\alpha$ -acyloxyalkyl S-ether of Formula I, both being substantially free of the other. In addition, the invention

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provides the O- $\alpha$ -acyloxyalkyl RS-ether of 4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]-phenol of Formula I.

Substantially free, as used herein means the compound or composition is made up of significantly greater proportion of the desired isomer than of the optical antipode. In a preferred embodiment of the invention, "substantially free" means that the compound or composition is made up of at least about 90% of the desired isomer and about 10% or less of the optical antipode. In still more preferred embodiments of the present invention, the compound or composition is made up of at least about 95% of the desired isomer and about 5% or less of the optical antipode. In yet further embodiments of the present invention the compound or composition is made up of at least about 99% of the desired isomer and about 1% or less of the optical antipode. Preferably the characterized or separated enantiomer will exhibit physical properties of a fully characterized compound, i.e. a uniform melting point and a uniform rotation of plane-polarized light in a polarimeter. Most preferably, the enantiomers will be recrystallized to analytical purity.

C<sub>1</sub> - C<sub>6</sub> alkyl as used herein, such as in the definition of R<sub>1</sub>, includes straight or branched chain alkyl groups within the specified range of carbon atoms, eg methyl, ethyl, propyl, n-butyl or t-butyl.

Halogen, as used herein refers to chlorine, bromine, iodine and fluorine.

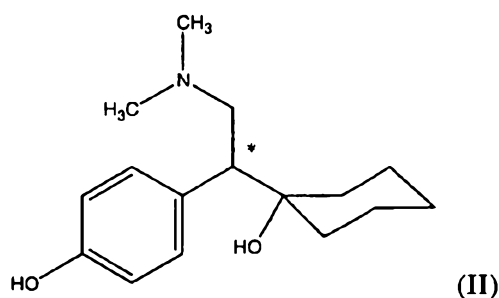
Pharmaceutically acceptable salts refer to salts prepared from pharmaceutically acceptable acids, including inorganic acids and organic acids, such as, but not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and the like.

Compounds of the invention are readily prepared by methods known in the art, for instance, as described by Bodor, et al., *J. Org. Chem.*(48) 5280-5284 (1983). Where necessary any reactive substituent group or atom may be protected prior to any reaction and deprotected afterwards.

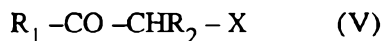
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Accordingly this invention provides a process for preparing a compound of formula (I) as defined herein, or a pharmaceutically acceptable salt or hydrate thereof, which process comprises one of the following:

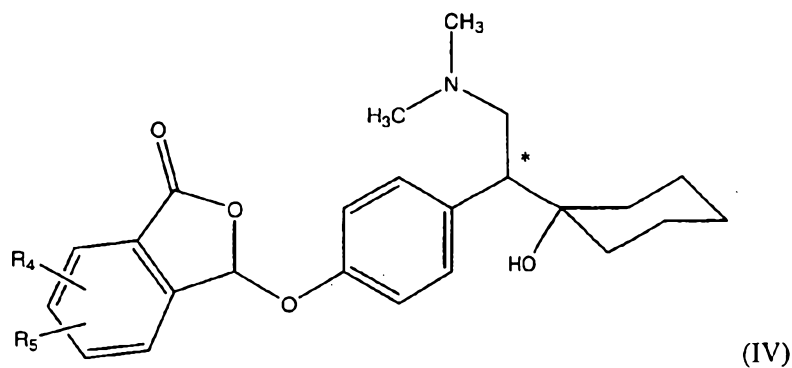
- 5 (i) reacting R-, S-, or (R/S)- 4-[2-(dimethylamino-1-(1-hydroxycyclohexyl)ethyl)-phenol of formula:



or a salt thereof, with a compound having the formula (V)



- 10 where  $R_1$  and  $R_2$  are as defined above subject to the proviso that a reactive substituent group, eg an -OH or -NH<sub>2</sub> substituent on the concatenated  $R_1$  and  $R_2$  group may be protected by a protecting group that is subsequently removed and X is a leaving group for example a halogen atom such as chlorine, bromine or preferably iodine; or
- 15 (ii) subjecting a compound having formula (IV)





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wherein:

the configuration at the stereogenic center (\*) may be R, S, or RS (the racemate) and

$R_4$  and  $R_5$  are independently selected from H,  $C_1 - C_6$  alkyl,  $C_1 - C_6$  alkoxy,

$C_1 - C_6$  thioalkoxy, -CN, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, halogen, -NH<sub>2</sub>, -NO<sub>2</sub>, or

- 5    -N(CH<sub>3</sub>)<sub>2</sub> subject to the proviso that at least one of is  $R_4$  and  $R_5$  is -NO<sub>2</sub>, or a pharmaceutically acceptable salt or salt hydrate of such a compound to reduction to give a compound having formula (IV) wherein  $R_4$  and  $R_5$  are as defined above subject to the proviso that at least one of is  $R_4$  and  $R_5$  is -NH<sub>2</sub>, or a pharmaceutically acceptable salt or salt hydrate of such a compound;

10   or

(iii) separating a compound having formula (I) wherein  $R_1$  and  $R_2$  are as defined under formula (I) in the form of an enantiomeric mixture so as to isolate a particular enantiomeric form;

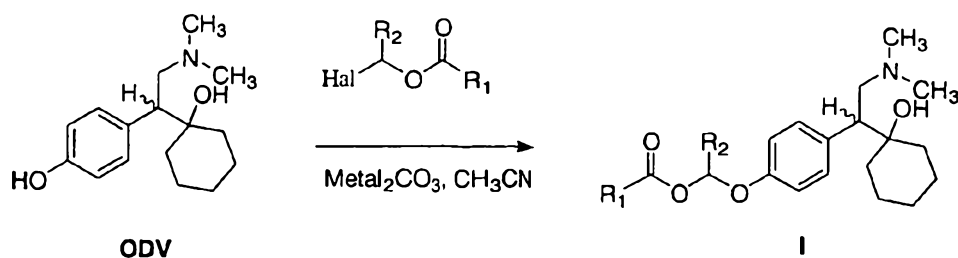
or

- 15   (iv) converting a compound having formula (I) wherein  $R_1$  and  $R_2$  are as defined under formula (I) into a pharmaceutically acceptable salt or salt hydrate thereof by addition of an acid.

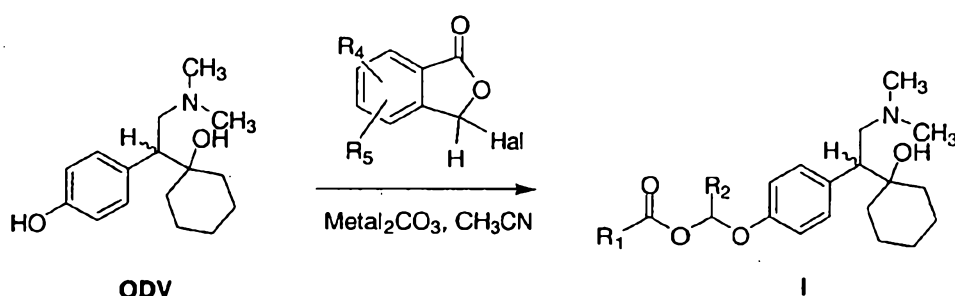
With regard to process (i) above the appropriate R-, S-, or (R/S)- 4-[2-(Dimethylamino-1-(1-hydroxy-cyclohexyl)ethyl)]phenol is reacted with the  
20   appropriate O- $\alpha$ -acyloxyalkyl halide (examples: pivaloyloxymethyl chloride, 3-bromophthalide, iodomethyl pivalate) (Scheme Ia) or (acyloxy)benzyl  $\alpha$ -halide (Scheme Ib) in an inert solvent (acetonitrile, tetrahydrofuran, dimethylformamide) in the presence of an alkali metal carbonate (sodium or potassium carbonate) or transition metal carbonate (silver carbonate) in accordance with Schemes Ia and Ib.

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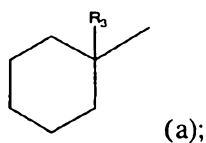


Scheme Ia



Scheme Ib

wherein  $\text{R}_1$  is selected from  $\text{C}_1 - \text{C}_6$  alkyl,  $\text{C}_1 - \text{C}_6$  alkoxy,  $\text{C}_3 - \text{C}_6$  cycloalkyl, or the moiety:



$\text{R}_2$  is selected from H, or  $\text{C}_1 - \text{C}_6$  alkyl;

or  $\text{R}_2$  and  $\text{R}_3$  are concatenated to form a moiety having formula (b);

$\text{R}_3$  is selected from H or  $\text{C}_1 - \text{C}_6$  alkyl; and

$\text{R}_4$  and  $\text{R}_5$  are independently selected from H,  $\text{C}_1 - \text{C}_6$  alkyl,  $\text{C}_3 - \text{C}_6$

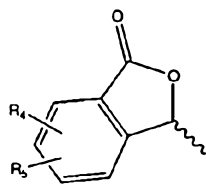
cycloalkyl,  $\text{C}_1 - \text{C}_6$  alkoxy,  $\text{C}_1 - \text{C}_6$  thioalkoxy,  $-\text{CN}$ ,  $-\text{OH}$ ,  $-\text{CF}_3$ ,  $-\text{OCF}_3$ , halogen, -

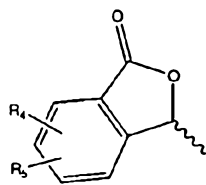
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NH<sub>2</sub>, -NO<sub>2</sub>, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms.

In some preferred embodiments of the invention increased yield may be obtained by reacting the appropriate R-, S-, or (R/S)- 4-[2-(Dimethylamino-1-(1-hydroxycyclohexyl)ethyl]phenol with the appropriate O- $\alpha$ -acyloxyalkyl iodide in an inert solvent (acetonitrile, tetrahydrofuran, dimethylformamide) in the presence of alkali metal carbonate such as potassium carbonate, or transition metal carbonate such as silver carbonate. Most preferred is the use of O- $\alpha$ -acyloxyalkyl iodide in the presence of silver carbonate at low temperatures in the range of approximately 0-5° C.

In a minor modification, compounds of formula I wherein R<sub>1</sub> and R<sub>2</sub> are



concatenated to form , and one or both of R<sub>4</sub> and R<sub>5</sub> are NH<sub>2</sub>, can be obtained by catalytic reductions, such as with palladium catalysts, from corresponding analogs wherein R<sub>4</sub> or R<sub>5</sub> are NO<sub>2</sub>.

Racemic 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol can be produced as described in Example 26 of U.S. Patent No. 4,535,186 (Husbands et al.), which is incorporated herein by reference. It will be understood that the enantiomers may be separated from each other by standard resolution techniques known in the art.

Alternatively, these R and S enantiomers may be obtained by O-demethylation of the separated enantiomers of venlafaxine using either boron tribromide or ethane thiol anion.

O- $\alpha$ -acyloxyalkyl ethers of Formula I and their pharmaceutically useful salts and hydrates are useful for the biological and pharmacological activities for which venlafaxine and its salts are known in the art. These O- $\alpha$ -acyloxyalkyl

ethers may be used in treating or inhibiting central nervous system disorders, including depression, (including but not limited to major depressive disorder, bipolar disorder, and dysthymia), fibromyalgia, anxiety, panic disorder, agoraphobia, post-traumatic stress disorder, premenstrual dysphoric disorder (also  
5 known as pre-menstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction (including premature  
10 ejaculation), borderline personality disorder, chronic fatigue syndrome, urinary incontinence, pain (including but not limited to migraine, chronic back pain, phantom limb pain, central pain, neuropathic pain such as diabetic neuropathy and postherpetic neuropathy), Raynaud's syndrome, and others. These compounds are also useful in the inducement of cognition enhancement and in regimens for cessation of smoking  
15 or other tobacco uses.

This invention also includes methods of treating, preventing, inhibiting or alleviating each of the maladies listed above in a mammal, preferably in a human, the methods comprising providing a pharmaceutically effective amount of a compound of this invention to the mammal in need thereof.

20 "Providing" as used herein with respect to providing a compound or substance covered by the invention, means either directly administering such a compound or substance, or administering a prodrug, derivative or analog which forms an equivalent amount of the compound or substance within the body.

A pharmaceutically effective dose will include those doses which provide the  
25 relief or prevention sought for the malady in question. The compounds of this invention may be provided in the dosages and pharmaceutical formulations known in the art as useful for venlafaxine hydrochloride (such as those doses known for the venlafaxine hydrochloride products marketed by Wyeth-Ayerst Laboratories under the Effexor® trademark). It will be understood that the initial dose, increases  
30 therefrom and final daily administration will be determined by a medical professional considering the needs and conditions for each recipient. For instance, a daily dose for

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an adult human may be from about 75 mg to about 450 mg per day, preferably between about 75 and about 225 mg per day. An initial dose of 75 mg per day may be administered, with increases as determined by a medical professional.

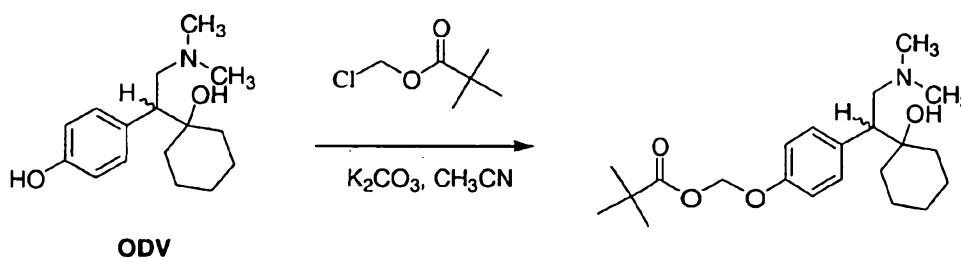
This invention also includes pharmaceutical compositions comprising a pharmaceutically effective amount of a compound of this invention and one or more pharmaceutically acceptable carriers or excipients. A preferred method of administration includes the use of the present compounds in extended release formulations of the type described in published PCT application WO 99/22724 (Sherman et al.), which is incorporated herein by reference.

10

The present invention is exemplified, but not limited by, the following specific examples.

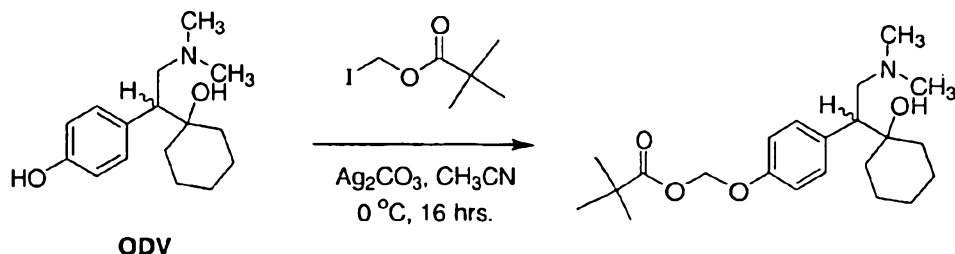
#### Example 1

15 {4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy} methyl pivalate.



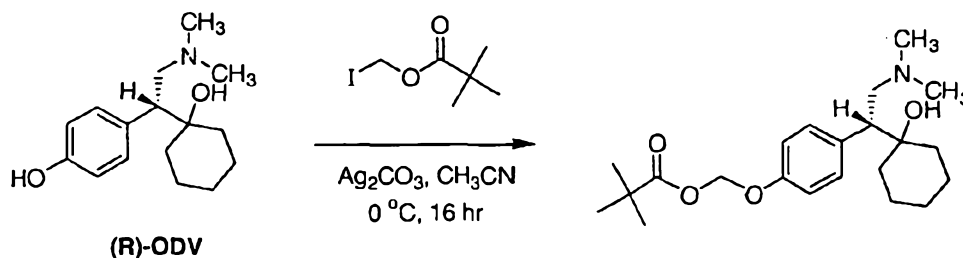
4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl) ethyl]phenol (1g, 3.79mmol),  
 20 chloromethyl pivalate (0.75g, 5mmol), anhydrous  $K_2CO_3$  (0.7 g, 5 mmol) and KI (75mg, 0.5 mmol) were stirred in acetonitrile (50mL) and refluxed overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The ethyl acetate was dried ( $MgSO_4$ ) and evaporated to give the title compound as a minor component. IR (KBr)  $1758cm^{-1}$ .  
 25 MS(+)FAB[M+H]<sup>+</sup> 378.3 calcd. For  $C_{22}H_{35}NO_4$  377.

## Example 2

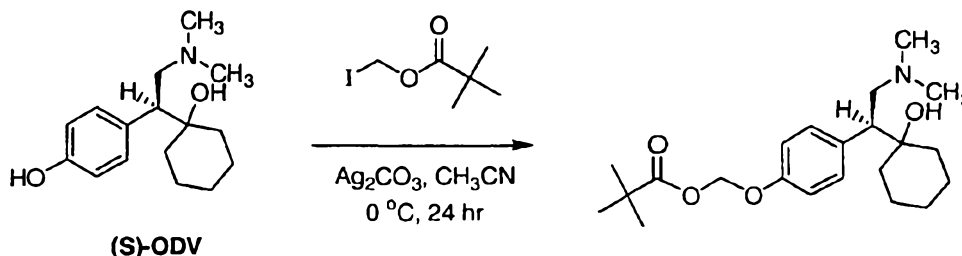
{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate

- 5 To a solution of ODV (2.0 g, 7.6 mmol) and silver carbonate (8.4 g, 30.4 mmol) in acetonitrile (60 mL) at 0 °C was added a solution of iodomethyl pivalate (prepared as described by Bodor, et al., *J. Org. Chem.* 1983, 48, 5280-5284.) (3.4 g, 14.0 mmol) in acetonitrile (100 mL) dropwise over 4 hr. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then
- 10 absorbed onto a activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company). and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (0.87 g, 45 %, based on 68 % conversion) as a yellow tinted semi-solid: <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5
- 15 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, J = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); MS (ESI) m/z 378 (M+H)<sup>+</sup>; further characterized as the maleate salt. Anal. (C<sub>26</sub>H<sub>39</sub>NO<sub>8</sub>·0.25H<sub>2</sub>O) Calc: C: 62.69,
- 20 H: 7.99, N: 2.81, Found: C: 62.68, H: 7.68, N: 2.65.

The celite cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 0.65 g (33%) recovered ODV.

**Example 3****4-[(1R)-2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenyl pivalate**

- 5 To a solution of ODV (3.0 g, 11.4 mmol) and silver carbonate (12.6 g, 45.6 mmol) in acetonitrile (300 mL) at 0 °C was added a solution of iodomethyl pivalate (prepared as described by Bodor, et al., *J. Org. Chem.* 1983, 48, 5280-5284.) (6.9 g, 28.5 mmol) in acetonitrile (40 mL) in eight equal portions over 16 hr. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation,
- 10 Lompoc, CA), then absorbed onto activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company) and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (1.15 g, 39 %, based on 60 % conversion) as a white foam: <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, J = 11.2 Hz, 1H), 5.7 (s, 2H),
- 15 6.95 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); [α]<sub>D</sub><sup>20</sup> -5.95° (c 1.00, MeOH); MS (ESI) m/z 378 (M+H)+.
- 20 The CELITE cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 1.2 g (40%) recovered ODV.

**Example 4****4-[(1S)-2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenyl pivalate**

5

To a solution of ODV (4.0 g, 15.2 mmol) and silver carbonate (16.8 g, 60.8 mmol) in acetonitrile (400 mL) at 0 °C was added a solution of iodomethyl pivalate (prepared as described by Bodor, et al., *J. Org. Chem.* 1983, 48, 5280-5284.) (8.3 g, 34.3 mmol) in acetonitrile (150 mL) over a 9 hr period. The reaction mixture was filtered through diatomaceous earth (CELITE, Celite Corporation, Lompoc, CA), then absorbed onto activated magnesium silicate (60-100 mesh) (FLORISIL, U.S. Silica Company). and purified by column chromatography (FLORISIL, ethyl acetate: acetonitrile 9:1) to afford the title compound (1.58 g, 48 %, based on 57 % conversion) as a clear viscous oil: <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 0.78-1.0 (m, 2H), 1.19 (s, 9H), 1.15-1.35 (m, 4H), 1.4-1.7 (m, 4H), 2.2 (s, 6H), 2.25 (dd, J = 11.2, 4.5 Hz, 1H), 2.94 (dd, J = 11.2, 4.5 Hz, 1H), 3.22 (t, J = 11.2 Hz, 1H), 5.7 (s, 2H), 6.95 (d, J = 8.7 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H); <sup>13</sup>C-NMR (CD<sub>3</sub>CN) δ 22.22, 22.44, 26.91, 27.10 (t), 32.83, 38.78 (t), 39.55 (s), 45.71 (q), 52.58, 61.74, 74.45 (d), 86.78 (t), 116.54, 131.48 (d), 136.68, 156.44, 178.05 (s); [α]<sub>D</sub><sup>20</sup> +7.23° (c 1.00, MeOH); MS (ESI) m/z 378 (M+H)<sup>+</sup>.

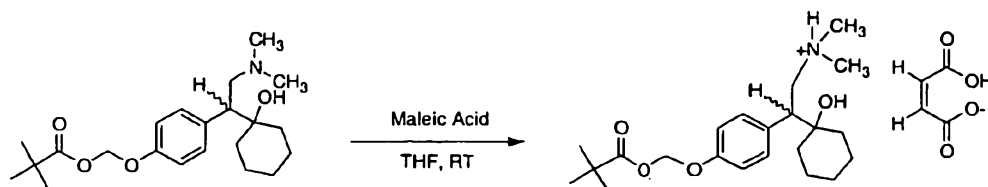
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The CELITE cake was taken up in brine and extracted with ethyl acetate. Evaporation of the solvent affords 1.7 g (43%) recovered ODV.



**Example 5****{4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}methyl pivalate****Maleate salt**

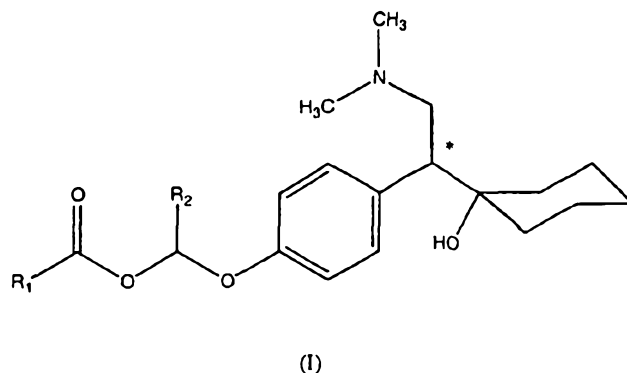
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To a solution of {4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenoxy}-methyl pivalate (0.032 g, 0.085 mmol) prepared as described in Example 1, in THF (1.0 mL) at RT was added a solution of maleic acid (0.007 g, 0.06 mmol) in THF (1.0 mL). The mixture was warmed and diluted with hexane. The solution was cooled and the resulting crystals filtered off giving the desired maleate salt as a white solid: mp 112-113 °C, <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 0.9-1.6 (m, 10H), 1.13 (s, 9H), 2.7 (br.s, 6H), 2.97 (m, 1H), 3.55 (m, 2H), 4.59 (br.s, 1H), 5.78 (s, 2H), 6.02 (s, 2H), 7.03 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 8.4 (br.s, 1H); MS (ESI) *m/z* 378 (M+H)<sup>+</sup>; (C<sub>26</sub>H<sub>39</sub>NO<sub>8</sub>·0.25H<sub>2</sub>O) Calc: C: 62.69, H: 7.99, N: 2.81, Found: C: 62.68, H: 7.68, N: 2.65.

**CLAIMS:**

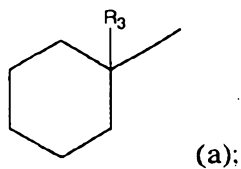
1. A compound of the Formula (I):



wherein

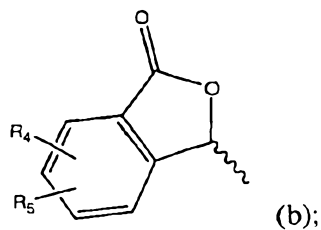
the configuration at the stereogenic center (\*) may be R, S, or RS (the racemate);

$R_1$  is selected from  $C_1 - C_6$  alkyl,  $C_1 - C_6$  alkoxy,  $C_3 - C_6$  cycloalkyl, or the moiety:



$R_2$  is selected from H, or  $C_1 - C_6$  alkyl; or,

$R_1$  and  $R_2$  may be concatenated such that  $R_1-C(=O)-O-CH(R_2)-$ , form a moiety having formula (b):

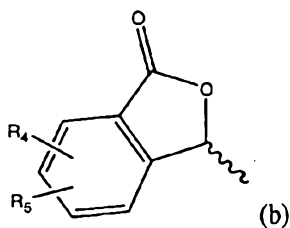
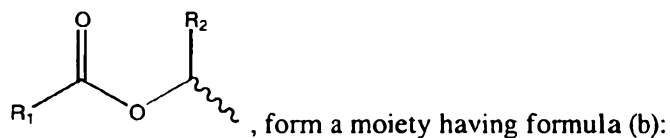


- 16 -

$R_3$  is selected from H or  $C_1 - C_6$  alkyl; and

$R_4$  and  $R_5$  are independently selected from H,  $C_1 - C_6$  alkyl,  $C_3 - C_6$  cycloalkyl,  $C_1 - C_6$  alkoxy,  $C_1 - C_6$  thioalkoxy, -CN, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, halogen, -NH<sub>2</sub>, -NO<sub>2</sub>, or mono or dialkylamino wherein each alkyl group has 1 to 6 carbon atoms, or a pharmaceutically acceptable salt or hydrate thereof.

2. A compound of Claim 1 wherein  $R_1$  is  $C_1 - C_6$  alkyl or  $C_1 - C_6$  alkoxy.
3. A compound of Claim 1 or Claim 2 wherein  $R_2$  is  $C_1 - C_6$  alkyl.
4. A compound of Claim 1 wherein  $R_1$  and  $R_2$  are concatenated such that



and  $R_4$  and  $R_5$  are hydrogen.

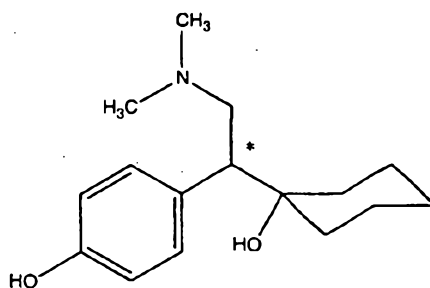
5. A compound of Claim 1 which is {4-[2-(Dimethylamino)-1-(1-hydroxy cyclohexyl)ethyl]phenoxy} methyl pivalate, or a pharmaceutically acceptable salt or hydrate thereof.

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6. A compound of Claim 1 which is 1-{4-[2-(dimethylamino)-1-(1-hydroxy-cyclohexyl)ethyl]phenoxy}ethyl propionate, or a pharmaceutically acceptable salt or hydrate thereof.
7. A compound of Claim 1 which is 3-{4-[2-(dimethylamino)-1-(1-hydroxy-cyclohexyl)ethyl]phenoxy}-2-benzofuran-1(3H)-one, or a pharmaceutically acceptable salt or hydrate thereof.
8. A pharmaceutical composition comprising a compound of Formula I as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt or hydrate thereof; and a pharmaceutically acceptable carrier or excipient.
9. A method of treating disorders of the central nervous system in a mammal, the method comprising providing to a mammal in need thereof a pharmaceutically effective amount of a compound of Formula I as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt or hydrate thereof.
10. The method of Claim 9 wherein the central nervous system disorder is selected from one or more of the following:  
depression; generalized anxiety disorder; panic disorder; post traumatic stress disorder; attention deficit disorder, with and without hyperactivity; anxiety; schizophrenia; cocaine addiction; alcohol addiction; premenstrual dysphoric disorder and autism.
11. The method of Claim 9 wherein the central nervous system disorder is anorexia nervosa, bulimia nervosa, vasomotor flushing, and chronic fatigue syndrome.
12. The method of Claim 9 wherein the central nervous system disorder is urinary incontinence.

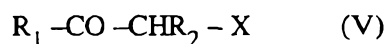
13. The method of Claim 9 wherein the central nervous system disorder is pain.
14. The method of Claim 9 wherein the central nervous system disorder is sexual dysfunction.
15. A method of enhancing cognition in a mammal, the method comprising providing to a mammal in need thereof a pharmaceutically effective amount of a compound of Formula I as claimed in any one of claims 1 to 7, or a pharmaceutically acceptable salt or hydrate thereof.
16. A process for the preparation of a compound having the formula I as claimed in claim 1, or a pharmaceutically acceptable salt or hydrate thereof, which process comprises one of the following:

- (i) reacting R-, S-, or (R/S)- 4-[2-(dimethylamino-1-(1-hydroxycyclohexyl)-ethyl)]-phenol of formula:



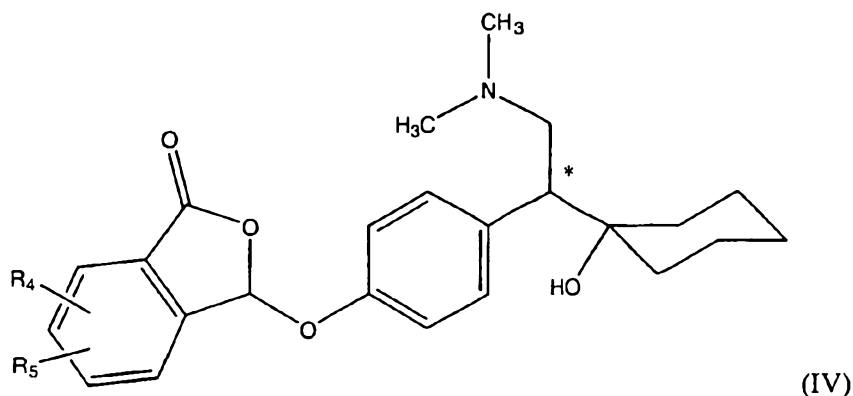
(II)

with a compound having the formula (V)



where  $R_1$  and  $R_2$  are as defined above subject to the proviso that an -OH or -NH<sub>2</sub> substituent on the concatenated  $R_1$  and  $R_2$  group may be protected by a protecting group that is subsequently removed and X is a leaving group; or

(ii) reducing a compound having formula (IV)



wherein the configuration at the stereogenic center (\*) may be R, S, or RS (the racemate) and  $R_4$  and  $R_5$  are independently selected from H,  $C_1 - C_6$  alkyl,  $C_1 - C_6$  alkoxy,  $C_1 - C_6$  thioalkoxy, -CN, -OH, -CF<sub>3</sub>, -OCF<sub>3</sub>, halogen, -NH<sub>2</sub>, -NO<sub>2</sub>, or -N(CH<sub>3</sub>)<sub>2</sub> subject to the proviso that at least one of  $R_4$  and  $R_5$  is -NO<sub>2</sub>, or a pharmaceutically acceptable salt or salt hydrate of such a compound, to give a compound having formula (IV) wherein  $R_4$  and  $R_5$  are as defined above, with the proviso that at least one of  $R_4$  and  $R_5$  is -NH<sub>2</sub>, or a pharmaceutically acceptable salt or salt hydrate of such a compound;  
or

(iii) separating a compound having formula (I) wherein  $R_1$  and  $R_2$  are as defined under formula (I) in the form of an enantiomeric mixture so as to isolate a particular enantiomeric form;  
or

- (iv) converting a compound having formula (I) wherein R1 and R2 are as defined under formula (I) into a pharmaceutically acceptable salt or salt hydrate thereof by addition of an acid.

5

17. A compound having the Formula (I) produced by a process according to claim 16.

18. A compound according to claim 1, substantially as hereinbefore described with reference to any of the Examples.

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Dated: 17 June 2003

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