

is to provide a method for treating a mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer in a pharmaceutically acceptable carrier and a composition comprising at least one mood stabilizer in a pharmaceutically acceptable carrier.

It is another object of the present invention to provide a method for treating a mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer and at least one mood stabilizer together in a pharmaceutically acceptable carrier, wherein the carbostyryl derivative is aripiprazole or a metabolite thereof.

Yet another object of the present invention is to provide a method for treating a mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer in a pharmaceutically acceptable carrier, wherein the carbostyryl derivative is aripiprazole or a metabolite thereof, and a composition comprising at least one mood stabilizer in a pharmaceutically acceptable carrier.

Still another object of the present invention is to provide a method for treating a mood disorder

comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer and at least one mood stabilizer in a
5 pharmaceutically acceptable carrier, wherein the carbostyryl derivative is a metabolite of aripiprazole and is dehydroaripiprazole (OPC-14857), DM-1458, DM-1451, DM-1452, DM-1454 or DCPD.

Yet another object of the present invention
10 is to provide a method for treating a mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer in a pharmaceutically acceptable carrier,
15 wherein the carbostyryl derivative is a metabolite of aripiprazole and is dehydroaripiprazole (OPC-14857), DM-1458, DM-1451, DM-1452, DM-1454 or DCPD, and a composition comprising at least one mood stabilizer in a pharmaceutically acceptable carrier.

20 Yet another object of the present invention is to provide a method for treating mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system
25 stabilizer and at least one mood stabilizer in a pharmaceutically acceptable carrier, wherein the mood disorder is bipolar disorder.

Yet another object of the present invention

is to provide a method for treating a mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer in a pharmaceutically acceptable carrier and a composition comprising at least one mood stabilizer in a pharmaceutically acceptable carrier, wherein the mood disorder is bipolar disorder.

Yet another object of the present invention is to provide a method for treating mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer and at least one mood stabilizer in a pharmaceutically acceptable carrier, wherein the mood disorder is mania.

Yet another object of the present invention is to provide a method for treating a mood disorder comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer in a pharmaceutically acceptable carrier and a composition comprising at least one mood stabilizer in a pharmaceutically acceptable carrier, wherein the mood disorder is mania.

It is another object of the present invention to provide a method for treating mood disorder comprising administration to a patient with a mood

disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer and at least one mood stabilizer in a pharmaceutically acceptable carrier.

5 It is another object of the present invention to provide a method for treating mood disorder comprising separate administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system
10 stabilizer in a pharmaceutically acceptable carrier, and a composition comprising at least one mood stabilizer in a pharmaceutically acceptable carrier.

 It is another object of the present invention to provide a method for treating mood disorder
15 comprising administration to a patient with a mood disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer and at least one mood stabilizer together with a pharmaceutically acceptable carrier, wherein the
20 carbostyryl derivative is aripiprazole or a metabolite thereof.

 Still another object of the present invention is to provide a method for treating mood disorder comprising administration to a patient with a mood
25 disorder of a composition comprising a carbostyryl derivative with activity as a dopamine-serotonin system stabilizer and at least one mood stabilizer in a pharmaceutically acceptable carrier, wherein the

carbostyryl derivative wherein the carbostyryl derivative is a metabolite of aripiprazole and is OPC-14857, DM-1458, DM-1451, DM-1452, DM-1454 or DCPD.

These and other objects, advantages, and uses of the present invention will reveal themselves to one of ordinary skill in the art after reading the detailed description of the preferred embodiments and the attached claims.

BRIEF DESCRIPTION OF THE DRAWINGS

10 Figure 1 is the thermogravimetric/differential thermogram of the aripiprazole hydrate A obtained in Reference Example 4.

 Figure 2 is the ^1H -NMR spectrum ($\text{DMSO}-d_6$, TMS) of the aripiprazole hydrate A obtained in Reference
15 Example 4.

 Figure 3 is the powder X-ray diffraction diagram of the aripiprazole hydrate A obtained in Reference Example 4.

 Figure 4 is the ^1H -NMR spectrum ($\text{DMSO}-d_6$, TMS) of the aripiprazole anhydride crystals B obtained in
20 Example 1.

 Figure 5 is the powder X-ray diffraction diagram of the aripiprazole anhydride crystals B obtained in Example 1.

25 Figure 6 is the thermogravimetric/differential thermogram of the aripiprazole hydrate obtained in Reference Example 3.

Figure 7 is the powder X-ray diffraction diagram of aripiprazole hydrate obtained in Reference Example 3.

Figure 8 is a schematic representation of the chemical structures of aripiprazole and metabolites thereof. Some of the metabolites may be formed through other possible pathways; for example, DM-1431 could be formed by N-dealkylation of DM-1451 and DM-1459.

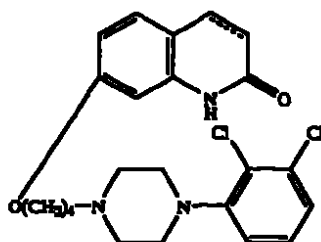
DETAILED DESCRIPTION

10 The pharmaceutical composition of the present invention comprises a first ingredient comprising a carbostyryl derivative active as a dopamine-serotonin system stabilizer and a second ingredient comprising a mood stabilizer, in a pharmaceutically acceptable
15 carrier. The pharmaceutical compositions of the present invention are useful in treating mood disorders, including bipolar disorder and mania.

The pharmaceutical composition: the first ingredient

 The first ingredient comprises a carbostyryl
20 derivative active as a dopamine-serotonin system system stabilizer. Such carbostyryl derivative has activity as an agonist or partial agonist at some serotonin receptors and some dopamine receptors, preferably as an agonist or partial agonist at the serotonin 5HT_{1A}
25 receptor and as an agonist or partial agonist at the dopamine D₂ receptor. Carbostyryl derivatives are

described in U.S. Patent 5,006,528 and U.S. published patent application 2002/0173513A1. In one embodiment of the present invention, the carbostyrl derivatives represented by the following formula (1) are used:



5

wherein the carbon-carbon bond between 3- and 4-positions in the carbostyrl skeleton is a single or a double bond.

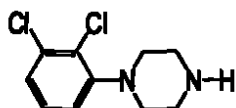
In a preferred embodiment, this activity of the carbostyrl derivative is as an agonist or partial agonist at the 5HT_{1A} receptor and an agonist or partial agonist at the dopamine D₂ receptor subtype. In another preferred embodiment, the carbostyrl derivative to be used as a first component in the present invention is aripiprazole, or a metabolic derivative thereof.

Metabolic derivatives of aripiprazole include but are not limited to dehydroaripiprazole, also called OPC-14857. Other metabolic derivatives of aripiprazole include but are not limited to the chemical structures shown in Figure 8 as OPC-14857, DM-1458, DM-1451, DM-1452, DM-1454 and DCPD.

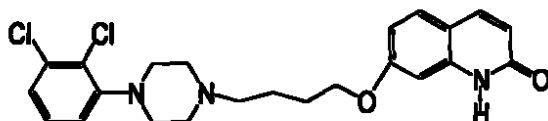
Structures and names of aripiprazole metabolites shown in Figure 8 are provided below.

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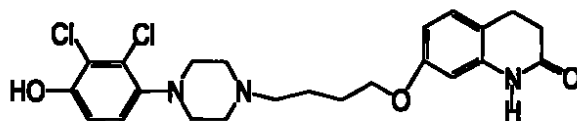
16



DCPP: 1-(2,3-dichlorophenyl)piperazine, and N-2,3-dichlorophenylpiperazine

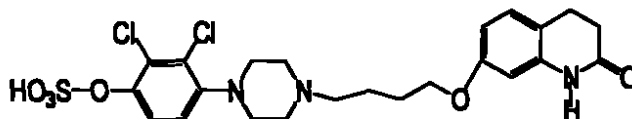


5 DM-14857, OPC-14857: 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-2-(1H)-quinolinone, also called dehydroaripiprazole



DM-1451: 7-{4-[4-(2,3-dichloro-4-hydroxyphenyl)-1-piperazinyl]butoxy}-3,4-dihydro-

10 2-(1H)-quinolinone, and hydroxyaripiprazole

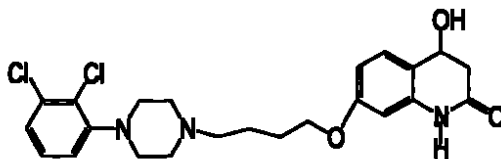


DM-1458: 2,3-dichloro-4-{4-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)-butyl] -

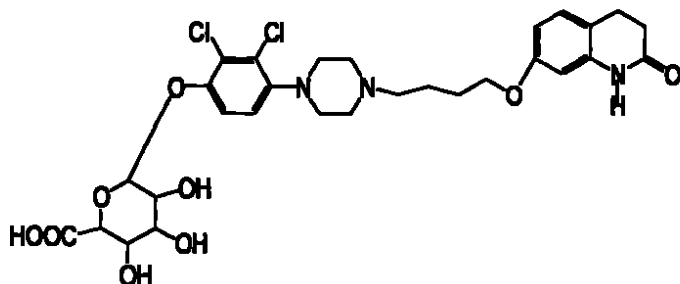
piperazin-1-yl}-phenyl sulfate, and sulfated

15 hydroxyaripiprazole

17



DM-1452: 7-(4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy)-3,4-dihydro-4-hydroxy-2-(1H)-quinolinone, and benzyl hydroxyaripiprazole



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DM-1454: DM-1454 is the glucuronide of DM-1451. This structure is also know by the following names:

1β-(2,3-dichloro-4-{4-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)-butyl] -

10 piperazin-1-yl}-phenoxy)-D-glucopyranuronic acid,

1β-(2,3-dichloro-4-{4-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)-butyl]-piperazin-1-yl}-phenyl-beta)-D-glucopyranosiduronic acid,

15 1β-(2,3-dichloro-4-{4-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)-butyl]-piperazin-1-yl}-phenyl)-beta)-D-Glucuronide,

1 β -(2,3-dichloro-4-{4-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)-butyl]-piperazin-1-yl}-phenyl-beta)-D-glucuronic acid, and glucuronide aripiprazole.

- 5 All of the aforementioned carbostyryl derivatives may be used as a first component in the practice of the present invention.

Aripiprazole, also called 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydro-
10 2(1H)-quinolinone, is a carbostyryl compound useful as the effective ingredient for treating schizophrenia (JP-A-2-191256, U.S. Patent 5,006,528). Aripiprazole is also known as 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl, Abilify,
15 OPC-14597, OPC-31 and BMS-337039. Aripiprazole possesses 5-HT_{1A} receptor agonist activity, and is known as a useful compound for treating types of depression and refractory depression, such as endogenous depression, major depression, melancholia and the like
20 (WO 02/060423A2; Jordan et al. U.S. Patent Application 2002/0173513A1). Aripiprazole has activity as an agonist at serotonin receptors and dopamine receptors, and acts as an agonist or partial agonist at the serotonin 5HT_{1A} receptor and as an agonist or partial
25 agonist at the dopamine D₂ receptor.

Aripiprazole is an antipsychotic drug having new mechanism of action which is different from that of

other atypical antipsychotic drugs. The available typical and atypical antipsychotic drugs act as antagonists at the dopamine-D₂ receptors. In contrast, aripiprazole acts as a partial agonist at the dopamine
5 D₂ receptor (Ishigooka Jyunya and Inada Ken: RINSHO SEISHIN YAKURI, Vol. 4, pp 1653-1664, (2001); Burris, K. D. et al.: J. Pharmacol. Exp. Ther., 302, pp 381-389, (2002)). In addition to the partial agonist action at dopamine-D₂ receptors, aripiprazole has
10 activity as a partial agonist at the serotonin 5-HT_{1A} receptor, as well as antagonist action serotonin 5-HT_{2A} receptors. Accordingly, aripiprazole is a drug belonging to new category defined as a dopamine-serotonin system stabilizer (dopamine-serotonin nervous
15 system stabilizer (Burris, K. D. et al., J. Pharmacol. Exp. Ther., 302, pp 381-389, 2002; Jordan, S. et al., Eur. J. Pharmacol. 441, pp 137-140, 2002)).

Methods of Preparing Aripiprazole

Aripiprazole and aripiprazole metabolites to
20 be used in the present invention may be any of form, for example, free bases, polymorphisms of every type of crystal, hydrate, salt (acid addition salts, etc.) and the like. Among of these forms, aripiprazole anhydride crystals B is a preferred form.

25 As to method for preparing the aripiprazole anhydride crystals B, for example it is prepared by heating aripiprazole hydrate A as follows.

Aripiprazole Hydrate A

The aripiprazole hydrate A having the physicochemical properties shown in (1) - (5) as follows:

- 5 (1) It has an endothermic curve which is substantially identical to the thermogravimetric/differential thermal analysis (heating rate 5°C/min) endothermic curve shown in Figure 1. Specifically, it is characterized by the
10 appearance of a small peak at about 71°C and a gradual endothermic peak around 60°C to 120°C.
- (2) It has an ¹H-NMR spectrum which is substantially identical to the ¹H-NMR spectrum (DMSO-d₆, TMS) shown in Figure 2. Specifically, it has
15 characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H),
6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-
20 7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).
- (3) It has a powder x-ray diffraction spectrum which is substantially identical to the powder
25 x-ray diffraction spectrum shown in Figure 3. Specifically, it has characteristic peaks at 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° and 24.8°.

(4) It has clear infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

(5) It has a mean particle size of 50 μm or less.

Method for Preparing Aripiprazole Hydrate A

Aripiprazole hydrate A is prepared by milling conventional aripiprazole hydrate. Conventional milling methods can be used to mill conventional aripiprazole hydrate. For example, conventional aripiprazole hydrate can be milled in a milling machine. A widely used milling machine such as an atomizer, pin mill, jet mill or ball mill can be used. Among of these, the atomizer is preferably used.

Regarding the specific milling conditions when using an atomizer, a rotational speed of 5000-15000 rpm could be used for the main axis, for example, with a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

The mean particle size of the aripiprazole hydrate A obtained by milling may be normally 50 μm or less, preferably 30 μm or less. Mean particle size can be ascertained by the particle size measuring method described hereinafter.

25 Aripiprazole Anhydride Crystals B

Aripiprazole anhydride crystals B of the

present invention have the physicochemical properties given in (6)-(10) below.

(6) They have an ^1H -NMR spectrum which is substantially identical to the ^1H -NMR spectrum ($\text{DMSO}-d_6$, TMS) shown in Figure 4. Specifically, they have characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, $J = 7.4$ Hz, 2H), 2.97 ppm (brt, $J = 4.6$ Hz, 4H), 3.92 ppm (t, $J = 6.3$ Hz, 2H), 6.43 ppm (d, $J = 2.4$ Hz, 1H), 6.49 ppm (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H), 7.04 ppm (d, $J = 8.1$ Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

(7) They have a powder x-ray diffraction spectrum which is substantially identical to the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they have characteristic peaks at $2\theta = 11.0^\circ$, 16.6° , 19.3° , 20.3° and 22.1° .

(8) They have clear infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

(9) They exhibit an endothermic peak near about 141.5°C in thermogravimetric/differential thermal analysis (heating rate $5^\circ\text{C}/\text{min}$).

(10) They exhibit an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate $5^\circ\text{C}/\text{min}$).

When the small particle size is required for

solid preparation, such as tablets and other solid dose formulations including for example flash melt formulations, the mean particle size is preferably 50 μm or less.

5 Method for Preparing Aripiprazole Anhydride Crystals B

The aripiprazole anhydride crystals B of the present invention are prepared, for example, by heating the aforementioned aripiprazole hydrate A at 90-125°C. The heating time is generally about 3-50 hours, but
10 cannot be stated unconditionally, because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example when the heating time is longer, then the heating temperature is lower, and when the heating
15 temperature is higher then the heating time is shorter. Specifically, if the heating temperature of aripiprazole hydrate A is 100°C, the heating time may be 18 hours or more, or preferably about 24 hours. If the heating temperature of aripiprazole hydrate A is
20 120°C, on the other hand, the heating time may be about 3 hours. The aripiprazole anhydride crystals B of the present invention can be prepared with certainty by heating aripiprazole hydrate A for about 18 hours at 100°C, and then heating it for about 3 hours at 120°C.
25 The aripiprazole anhydride crystals B of the present invention can also be obtained if the heating time is extended still further, but this method may not be

economical.

When small particle size is not required for the formulation, e.g., when drug substance is being prepared for injectable or oral solution formulations, 5 aripiprazole anhydride crystals B can be also obtained by the following process.

Aripiprazole anhydride crystals B of the present invention are prepared for example by heating conventional aripiprazole anhydride crystals at 90- 10 125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example if the heating time is longer, the heating 15 temperature is lower, and if the heating time is shorter, the heating temperature is higher. Specifically, if the heating temperature of the aripiprazole anhydride crystals is 100°C, the heating time may be about 4 hours, and if the heating 20 temperature is 120°C the heating time may be about 3 hours.

Furthermore, aripiprazole anhydride crystals B of the present invention are prepared for example, by heating conventional aripiprazole hydrate at 90-125° C. 25 The heating time is generally about 3-50 hours, but cannot be stated unconditionally because it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for

example, if the heating time is longer, the heating temperature is lower, and if the heating time is shorter, the heating temperature is higher.

Specifically, if the heating temperature of the
5 aripiprazole hydrate is 100°C, the heating time may be about 24 hours, and if the heating temperature is 120°C the heating time may be about 3 hours.

The aripiprazole anhydride crystals which are the raw material for preparing the aripiprazole
10 anhydride crystals B of the present invention are prepared for example by Method A or B below.

Method A: Process for Preparing Crude Crystals of Aripiprazole

Conventional aripiprazole anhydride crystals
15 are prepared by well-known methods, as described in Example 1 of Japanese Unexamined Patent Publication No. 191256/1990. 7-(4-bromobutoxy)-3,4-dihydrocarbostyryl, is reacted with 1-(2,3-dichlorophenyl)piperazine and the thus obtained crude aripiprazole crystals are re-
20 crystallized from ethanol.

Method B: Process for Preparing Conventional Aripiprazole Anhydride

The Method B is described in the Proceedings of the 4th Joint Japanese-Korean Symposium on
25 Separation Technology (October 6-8, 1996). The aripiprazole hydrate which is the raw material for

preparing the aripiprazole anhydride crystals B of the present invention is prepared for example by Method C below.

Method C: Method for Preparing Conventional

5 Aripiprazole Hydrate

Aripiprazole hydrate is easily obtained by dissolving the aripiprazole anhydride crystals obtained by Method A above in a hydrous solvent, and heating and then cooling the resulting solution. Using this
10 method, aripiprazole hydrate is precipitated as crystals in the hydrous solvent.

An organic solvent containing water is usually used as the hydrous solvent. The organic solvent may be preferable one which is miscible with
15 water, for example an alcohol such as methanol, ethanol, propanol or isopropanol, a ketone such as acetone, an ether such as tetrahydrofuran, dimethylformamide, or a mixture thereof, ethanol is particularly desirable. The amount of water in the
20 hydrous solvent may be 10-25% by volume of the solvent, or preferably close to 20% by volume.

Aripiprazole can easily form an acid addition salt with a pharmaceutically acceptable acid. As to such acid, for example, an inorganic acid, such as
25 sulfuric acid, nitric acid, hydrochloric acid, phosphoric acid, hydrobromic acid, etc.; an organic acid such as, acetic acid, p-toluenesulfonic acid,

methanesulfonic acid, oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, etc. can be exemplified. Similar to aripiprazole of free forms, these acid addition salts can also be
5 used as the active ingredient compounds in the present invention.

The objective compound thus obtained through each one of production steps, is separated from the reaction system by usual separation means, and can be
10 further purified. As to the separation and purification means, for example, distillation method, solvent extraction method, dilution method, re-crystallization method, column chromatography, ion-exchange chromatography, gel chromatography, affinity
15 chromatography, preparative thin-layer chromatography and the like can be exemplified.

The pharmaceutical composition: the second ingredient

In the composition of the present invention, a mood stabilizer is used as the second ingredient.
20 Compounds which function as mood stabilizers can be widely used as the mood stabilizers and are known to one of ordinary skill in the art.

A non-limiting list of mood stabilizers which may be used in the present invention includes, lithium,
25 valproic acid, divalproex sodium, carbamazapine, oxcarbamazapine, zonisamide, lamotragine, topiramate, gabapentin, levetiracetam and clonazepam.

The mood stabilizer may be either in the form of a free base or a salt (an acid addition salt or the like). Further, the mood stabilizer may be either a racemic modifications or R and S enantiomers. The mood stabilizers may be either a single use of one mood stabilizer, and in case of need, two or more of the mood stabilizers may be used in combination. Use of one mood stabilizer is preferred.

The mood stabilizer can easily form an acid addition salt with a pharmaceutically acceptable acid. As to such acid, for example, an inorganic acid, such as sulfuric acid, nitric acid, hydrochloric acid, phosphoric acid, hydrobromic acid, etc.; an organic acid such as, acetic acid, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, etc. can be exemplified. Similar to the reuptake inhibitor of free forms, these acid addition salts can also be used as the active ingredient compounds in the present invention.

Among the mood stabilizers, a compound having an acidic group can easily form salt by reacting with a pharmaceutically acceptable basic compound. As to such basic compound, a metal hydroxide, for example, sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide and the like; an alkali metal carbonate or bicarbonate, for example sodium carbonate, potassium carbonate, sodium hydrogencarbonate,

potassium hydrogencarbonate and the like; a metal alcoholate, for example sodium methyllate, potassium ethyllate and the like can be exemplified.

The thus obtained salt form of mood
5 stabilizer is separated from the reaction system by usual separation means, and can be further purified. As to the separation and purification means, for example, distillation method, solvent extraction method, dilution method, recrystallization method,
10 column chromatography, ion-exchange chromatography, gel chromatography, affinity chromatography, preparative thin-layer chromatography and the like can be exemplified.

Combination of the first ingredient with the second
15 ingredient

As to pharmaceutical compositions comprising a combination of carbostyryl derivatives with activity as dopamine-serotonin stabilizers, and mood stabilizers, non-limiting examples of aripiprazole and
20 dehydroaripiprazole are described herein. It is to be understood that the present invention also comprises a combination of carbostyryl derivatives with activity as dopamine-serotonin stabilizers, and mood stabilizers, wherein the carbostyryl derivatives are other
25 metabolites of aripiprazole described herein.

When aripiprazole is combined with at least one mood stabilizer, the following are non-limiting

examples of such combinations: aripiprazole/lithium, aripiprazole/valproic acid, aripiprazole/divalproex sodium, aripiprazole/carbamazapine, aripiprazole/oxcarbamazapine, aripiprazole/zonisamide, 5 aripiprazole/lamotragine, aripiprazole/topiramate, aripiprazole/gabapentin, aripiprazole/levetiracetam and aripiprazole/clonazepam. Among these combinations, the following are particularly preferable: aripiprazole/carbamazapine, 10 aripiprazole/oxcarbamazapine, aripiprazole/zonisamide, aripiprazole/lamotragine, aripiprazole/topiramate, aripiprazole/gabapentin, aripiprazole/levetiracetam and aripiprazole/clonazepam. The pharmaceutical composition comprising the above preferable combination 15 possesses excellent efficacy. Therefore such composition has fewer side-effects and an excellent safety profile.

In another embodiment of the present invention, aripiprazole, or a metabolite thereof may be 20 combined with more than one mood stabilizer. Metabolites of aripiprazole that may be used in the present invention include, but are not limited to, OPC-14857, DM-1458, DM-1451, DM-1452, DM-1454 and DCPD as shown in Figure 8. Any one of these metabolites may be 25 used in the present invention. The following sentences describe a combination of dehydroaripiprazole with specific mood stabilizers, however it is to be understood that any one of DM-1458, DM-1451, DM-1452,

DM-1454 or DCPD, as shown in Figure 8, could be substituted for dehydroaripiprazole in these disclosed combinations. Dehydroaripiprazole (also called OPC-14857 in Figure 8) is a preferred metabolite of

5 aripiprazole. As to the combination of dehydroaripiprazole with one or more mood stabilizers, the following are non-limiting examples of such combinations: dehydroaripiprazole/lithium, dehydroaripiprazole/valproic acid,

10 dehydroaripiprazole/divalproex sodium, dehydroaripiprazole/carbamazapine, dehydroaripiprazole/oxcarbamazapine, dehydroaripiprazole/zonisamide, dehydroaripiprazole/lamotragine,

15 dehydroaripiprazole/topiramate, dehydroaripiprazole/gabapentin, dehydroaripiprazole/levetiracetam and dehydroaripiprazole/clonazepam. Among these combinations, the following are particularly

20 preferable: dehydroaripiprazole/carbamazapine, dehydroaripiprazole/oxcarbamazapine, dehydroaripiprazole/zonisamide, dehydroaripiprazole/lamotragine, dehydroaripiprazole/topiramate,

25 dehydroaripiprazole/gabapentin, dehydroaripiprazole/levetiracetam and dehydroaripiprazole/clonazepam. The pharmaceutical composition comprising the above preferable combination

possesses excellent efficacy. Therefore such composition has fewer side-effects and an excellent safety profile.

Method of Treating a Mood Disorder, Especially Bipolar

5 Disorder or Mania

Patients with mood disorders may be treated with the compositions of the present invention. Such mood disorders include but are not limited to bipolar disorder, bipolar disorder I, bipolar disorder II,
10 bipolar disorder with and without psychotic features, mania, acute mania, bipolar depression or mixed episodes. Preferred disorders treated with the method and compositions of the present invention are bipolar disorder and mania. Treatment comprises administration
15 of the compositions of the present invention to a patient with a mood disorder such as bipolar disorder or mania, with or without psychotic features, in an amount and dose regimen effective to treat the mood disorder. The present invention includes treatment of
20 mood disorders wherein both the carbostyryl derivative with the previously stated activity and the mood stabilizer are combined together with a pharmaceutically acceptable carrier in a composition. The present invention further includes treatment of
25 mood disorders wherein both the carbostyryl derivative with the previously stated activity is combined with a pharmaceutically acceptable carrier in one composition,

the mood stabilizer is combined with a pharmaceutically acceptable carrier in a second composition, and the two compositions are administered at the same or different times to provide the desired treatment.

5 Dosage

Dosage of the drug used in the present invention is decided by considering the properties of each constituting drug to be combined, the properties of drugs after combination and symptoms of the patient.

10 As stated above, the carbostyryl derivatives and mood stabilizers may be administered separately and not combined in one composition. General outlines of the dosage are provided in the following guidelines.

Aripiprazole or a metabolite, such as
15 dehydroaripiprazole, DM-1458, DM-1451, DM-1452, DM-1454 or DCPD: generally about 0.1 to about 100 mg/once a day (or about 0.05 to about 50 mg/twice a day), preferably about 1 to about 30 mg/once a day (or about 0.5 to about 15 mg/twice a day).

20 The aripiprazole, or metabolite thereof, may be combined with at least one of any of the following mood stabilizers at the dose ranges indicated, or administered separately:

Lithium: generally about 300 to about
25 2400 mg/day, 300 mg to 1200 mg twice per day, preferably until the plasma lithium concentration is about 0.8-1.2 mmol/L.

Valproic acid: generally about 750 mg to 2000 mg/day, or 10 to 20 mg/kg/day.

Divalproex sodium: generally about 500 to 2500 mg/day.

5 Carbamazepine: generally about 100 to 1000 mg/day, preferably until plasma levels reach between about 6.0 to 9.0 mg/L.

Oxcarbamazepine: generally about 600 to 2100 mg/day.

10 Zonisamide: generally about 100 to 500 mg/day.

Lamotragine: generally about 50 to 500 mg/day, preferably 100 to 400 mg/day.

Topiramate: generally, about 25 to about 15 500 mg/day.

Gabapentin: generally, about 600 to 2400 mg/once a day.

Levetiracetam: generally, about 250 to about 3000 mg/day.

20 Clonazepam: generally, about 0.1 to 60 mg/day.

Generally, the weight ratio of the first ingredient to the second ingredient is selected in accordance with the above-mentioned guideline. As to 25 the ratio of the first ingredient and the second ingredient, if the first ingredient is about 1 part by weight of the former, the second ingredient is used at about 0.01 to about 500 parts by weight, preferably

about 0.1 to about 100 parts by weight.

Pharmaceutically Acceptable Carriers

Pharmaceutically acceptable carriers include diluents and excipients generally used in pharmaceutical preparations, such as fillers, extenders, binders, moisturizers, disintegrators, surfactant, and lubricants.

The pharmaceutical composition of the present invention may be formulated as an ordinary pharmaceutical preparation, for example in the form of tablets, flash melt tablets, pills, powder, liquid, suspension, emulsion, granules, capsules, suppositories or injection (liquid, suspension, etc.), troches, intranasal spray percutaneous patch and the like.

In case of shaping to tablet formulation, a wide variety of carriers that are known in this field can be used. Examples include lactose, saccharose, sodium chloride, glucose, urea, starch, xylitol, mannitol, erythritol, sorbitol, calcium carbonate, kaolin, crystalline cellulose, silic acid and other excipients; water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinyl pyrrolidone and other binders; dried starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters,

sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose and other disintegrators; white sugar, stearin, cacao butter, hydrogenated oil and other disintegration inhibitors; quaternary ammonium salt, 5 sodium lauryl sulfate and other absorption accelerator; glycerine, starch and other moisture retainers; starch, lactose, kaolin, bentonite, colloidal silic acid and other adsorbents; and refined talc, stearate, boric acid powder, polyethylene glycol and other lubricants 10 and the like. Tablets can also be formulated if necessary as tablets with ordinary coatings, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets and film coated tablets, as well as double tablets and multilayered tablets.

15 In case of shaping to pills, a wide variety of carriers that are known in this field can be used. Examples include glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and other excipients; gum arabic powder, traganth powder, 20 gelatin, ethanol and other binders; and laminaran, agar and other disintegrators and the like.

 In case of shaping to a suppository formulation, a wide variety of carriers that are known in the field can be used. Examples include 25 polyethylene glycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin semi-synthetic glyceride and the like.

 Capsules are prepared according to ordinary

methods by mixing aripiprazole anhydride crystals as the first ingredient and the second ingredient, and the various carriers described above and packing them in hard gelatin capsules, soft capsules

5 hydroxypropylmethyl cellulose capsules (HPMC capsules) and the like.

In addition, colorants, preservatives, perfumes, flavorings, sweeteners and the like as well as other drugs may be contained in the pharmaceutical
10 composition.

The amounts of the first ingredient and the second ingredient to be contained in the pharmaceutical composition of the present invention are suitably selected from a wide range depending on the diseases to
15 be treated. Generally, about 1 to 70 parts by weight, preferably about 1 to 30 parts by weight of the first ingredient and the second ingredient are combined in the total amount on the basis of the pharmaceutical composition.

20 The methods for administration of the pharmaceutical composition of the present invention are not specifically restricted. The composition is administered depending on each type of preparation form, and the age, gender and other condition of the
25 patient (degree and conditions of the disease, etc.). For example, tablets, pills, liquids, suspensions, emulsions, granules and capsules are administered orally. In case of injection preparation, it is

administered intravenously either singly or mixed with a common auxiliary liquid such as solutions of glucose or amino acid. Further, if necessary, the injection preparation is singly administered intradermally, 5 subcutaneously or intraperitoneally. In case of a suppository, it is administered intrarectally.

Administration forms of the pharmaceutical composition of the present invention may be any type by which the effective levels of both aripiprazole and 10 mood stabilizers can be provided in vivo at the same time. In one embodiment, aripiprazole together with a mood stabilizer are contained in one pharmaceutical composition and this composition may be administered. On the other hand, each one of aripiprazole and a mood 15 stabilizer are contained individually in a pharmaceutical preparation respectively, and each one of these preparations may be administered at the same or at different times.

Dosage of the pharmaceutical composition of 20 the present invention for treating and improving mood disorders may be used relatively in a small amount, because the composition possesses excellent efficacy. Therefore the composition has fewer side-effects and an excellent safety profile.

25 The pharmaceutical composition of the present invention can be manifest in a wide range of neurotransmission accommodation actions. As a result, the composition of the present invention establishes

pseudo-homeostatic dopaminergic and serotonergic neurotransmission (as a result of partial agonism), which, as a result of neuropathophysiological processes has ceased to function normally. The mood disorders which can be treated by the pharmaceutical composition of the present invention includes the mood disorders classified in "Diagnostic and Statistical Manual of Mental Disorders" Fourth Edition (DSM-IV) published by the American Psychiatric Association. These mood disorders include, for example, bipolar disorder such as bipolar disorder I or II, bipolar disorder with or without psychotic features, mania, acute mania, bipolar depression or mixed episodes.

In addition, the pharmaceutical composition of the present invention is effective on schizophrenia and other psychotic disorders. These disorders include, for example, depressive disorders such as major depressive disorder, endogenous depression, melancholia, depression in combination with psychotic episodes, refractory depression, dementia of the Alzheimer's disease with depressive symptoms, Parkinson's disease with depressive symptoms, senile dementia, mood disorder associated with cerebral blood vessels, mood disorder following head injury and the like; anxiety disorders such as panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, social phobia, specific phobia and the like; eating disorders;

sleep disorders; adjustment disorders; personality disorders; mental retardations; learning disorders; pervasive developmental disorders; attention-deficit and disruptive behavior disorders; tic disorders; 5 delirium; dementia; amnesic disorders; other cognitive disorders; alcohol-related disorders; amphetamine-related disorders; cocaine-related disorders; nicotine-related disorders; sedative-, hypnotic-, or anxiolytic-related disorders; sexual and gender identity 10 disorders. These disorders are classified in "Diagnostic and Statistical Manual of Mental Disorders" Fourth Edition (DSM-IV) published by the American Psychiatric Association.

The present invention will be explained more 15 in detail by illustrating Reference Examples, Example and Formulation Sample Examples. First, analytical methods are explained.

Analytical Methods

(1) The ^1H -NMR spectrum was measured in DMSO- 20 d_6 by using TMS as the standard.

(2) Powder X-ray Diffraction

By using RAD-2B diffraction meter manufactured by Rigaku Denki, the powder x-ray diffraction pattern was measured at room temperature by 25 using a Cu Ka filled tube (35 kV 20mA) as the x-ray source with a wide-angle goniometer, a 1° scattering

slit, an 0.15 mm light-intercepting slit, a graphite secondary monochromator and a scintillation counter. Data collection was done in 2 θ continuous scan mode at a scan speed of 5°/minute in scan steps of 0.02° in the range of 3° to 40°.

(3) The IR spectrum was measured by the KBr method.

(4) Thermogravimetric/Differential Thermal Analysis

10 Thermogravimetric/differential thermal analysis was measured by using SSC 5200 control unit and TG/DTA 220 simultaneous differential thermal/thermogravimetric measuring unit manufactured by Seiko Corp. Samples (5 - 10 mg) were placed in open
15 aluminum pans and heated at from 20°C to 200°C in a dry nitrogen atmosphere at a heating rate of 5°C/minute. α -Alumina was used as the standard substance.

(5) Differential Scanning Calorimetry

Thermogravimetric/differential thermal
20 analysis was measured by using SSC 5200 control unit and DSC 220C differential scanning calorimeter manufactured by Seiko Corp. Samples (5 - 10 mg) were placed in crimped aluminum pans and heated from 20°C to 200°C in a dry nitrogen atmosphere at a heating rate of
25 5°C/minute. α -Alumina was used as the standard substance.

(6) Particle Size Measurement

The particles (0.1 g) to be measured were

suspended in a 20 ml n-hexane solution of 0.5 g soy lecithin, and particle size was manufactured by using a size distribution measuring meter (Microtrack HRA, manufactured by Microtrack Co.).

5 Reference Example 1

7-(4-Chlorobutoxy)-3,4-dihydrocarbostyryl (19.4 g) and monohydrochloride 16.2 g of 1-(2,3-dichlorophenyl) piperadine 1 hydrochloride were added to a solution of 8.39 g of potassium carbonate dissolved in 140 ml of water, and refluxed for 3 hours under agitation. After the reaction was complete, the mixture was cooled and the precipitated crystals collected by filtration. These crystals were dissolved in 350 ml of ethyl acetate, and about 210 ml of water/ethyl acetate azeotrope was removed under reflux. The remaining solution was cooled, and the precipitated crystals were collected by filtration. The resulting crystals were dried at 60°C for 14 hours to obtain 20.4 g (74.2%) of crude product of aripiprazole.

20 The crude product of aripiprazole (30 g) obtained above was re-crystallized from 450 ml of ethanol according to the methods described in Japanese Unexamined Patent Publication No. 191256/1990, and the resulting crystals were dried at 80°C for 40 hours to obtain aripiprazole anhydride crystals. The yield was 29.4 g (98.0%).

The melting point (mp) of these aripiprazole

anhydride crystals was 140°C, which is identical to the melting point of the aripiprazole anhydride crystals described in Japanese Unexamined Patent Publication No. 191256/1990.

5 Reference Example 2

The crude product of aripiprazole (6930 g) obtained in Reference Example 1 was heat dissolved by heating in 138 liters of hydrous ethanol (water content 20% by volume) according to the method presented at the
10 4th Joint Japanese-Korean Symposium on Separation Technology, the solution was gradually (2-3 hours) cooled to room temperature, and then was chilled to near 0°C. The precipitated crystals were collected by filtration, about 7200 g of aripiprazole hydrate (wet-
15 state).

The wet-state aripiprazole hydrate crystals obtained above were dried at 80°C for 30 hours to obtain 6480 g (93.5%) of aripiprazole hydrate crystals. The melting point (mp) of these crystals was 139.5°C.

20 The water content of the crystals were confirmed by the Karl Fischer method, the moisture value was 0.03%, thus the crystals were confirmed as anhydrous product.

Reference Example 3

25 The aripiprazole hydrate (820 g) in wet state obtained from Reference Example 2 was dried at 50°C for

2 hours to obtain 780 g of aripiprazole hydrate crystals. The moisture value of the crystals had a moisture value was 3.82% measured according to the Karl Fischer method. As shown in Figure 6,

5 thermogravimetric/differential thermal analysis revealed endothermic peaks at 75.0, 123.5 and 140.5°C. Because dehydration began near at 70°C, there was no clear melting point (mp) was observed.

As shown in Figure 7, the powder x-ray
10 diffraction spectrum of aripiprazole hydrate obtained by this method exhibited characteristic peaks at $2\theta = 12.6^\circ, 15.1^\circ, 17.4^\circ, 18.2^\circ, 18.7^\circ, 24.8^\circ$ and 27.5° .

The powder x-ray diffraction spectrum of this aripiprazole hydrate was identical to the powder x-ray
15 diffraction spectrum of aripiprazole hydrate presented at the 4th Joint Japanese-Korean Symposium on Isolation Technology.

Reference Example 4

The aripiprazole hydrate crystals (500.3 g)
20 obtained in Reference Example 3 were milled by using a sample mill (small size atomizer). The main axis rotation rate was set to 12,000 rpm and the feed rotation rate to 17 rpm, and a 1.0 mm herringbone screen was used. Milling was finished in 3 minutes,
25 and obtained 474.6 g (94.9%) of aripiprazole hydrate A.

The aripiprazole hydrate A (powder) obtained in this way had a mean particle size of 20-25 μm . The

melting point (mp) was undetermined because dehydration was observed beginning near at 70°C.

The aripiprazole hydrate A (powder) obtained above exhibited an ^1H -NMR ($\text{DMSO}-d_6$, TMS) spectrum which was substantially identical to the ^1H -NMR spectrum shown in Figure 2. Specifically, it had characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, $J = 7.4$ Hz, 2H), 2.97 ppm (brt, $J = 4.6$ Hz, 4H), 3.92 ppm (t, $J = 6.3$ Hz, 2H), 6.43 ppm (d, $J = 2.4$ Hz, 1H), 6.49 ppm (dd, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H), 7.04 ppm (d, $J = 8.1$ Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

The aripiprazole hydrate A (powder) obtained above had a powder x-ray diffraction spectrum which was substantially identical to the powder x-ray diffraction spectrum shown in Figure 3. Specifically, it had characteristic peaks at $2\theta = 12.6^\circ$, 15.4° , 17.3° , 18.0° , 18.6° , 22.5° and 24.8° . This pattern is different from the powder x-ray spectrum of unmilled Aripiprazole hydrate shown in Figure 7.

The aripiprazole hydrate A (powder) obtained above had infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

As shown in Figure 1, the aripiprazole hydrate A (powder) obtained above had a weak peak at 71.3°C in thermogravimetric/differential thermal

analysis and a broad endothermic peak (weight loss observed corresponding to one molecule of water) between 60-120°C which was clearly different from the endothermic curve of unmilled aripiprazole hydrate (see 5 Figure 6).

It will be appreciated that other embodiments and uses will be apparent to those skilled in the art and that the invention is not limited to these specific illustrative examples.

10 Example 1

The aripiprazole hydrate A (powder) (44.29 kg) obtained in the Reference Examples was dried at 100°C for 24 hours by using a hot air dryer and further heated at 120°C for 3 hours, to obtain 42.46 kg (yield; 15 99.3 %) of aripiprazole anhydride Crystals B. These aripiprazole anhydride crystals B had a melting point (mp) of 139.7°C.

The aripiprazole anhydride crystals B obtained above had an ¹H-NMR spectrum (DMSO-d₆, TMS) 20 which was substantially identical to the ¹H-NMR spectrum shown in Figure 4. Specifically, they had characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm 25 (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-

7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

The aripiprazole anhydride crystals B obtained above had a powder x-ray diffraction spectrum which was substantially the identical to the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they had characteristic peaks at $2\theta = 11.0^\circ$, 16.6° , 19.3° , 20.3° and 22.1° .

The aripiprazole anhydride crystals B obtained above had remarkable infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum. The aripiprazole anhydride crystals B obtained above exhibited an endothermic peak near about at 141.5°C in thermogravimetric/differential thermal analysis. The aripiprazole anhydride crystals B obtained above exhibited an endothermic peak near about at 140.7°C in differential scanning calorimetry.

Example 2

20 Receptor Binding at the 5HT_{1A} Receptor

1. Materials and Methods

1.1 Test Compound

7-(4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy-3,4-dihydrocarbostyryl (aripiprazole) was used as test compound.

1.2 Reference Compounds

Serotonin (5-HT) and WAY-100635 (N-[2-[4-(2-

methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)-cyclohexanecarboxamide, a 5-HT_{1A} receptor antagonist, manufactured by RBI (Natick, Mass.) were used as reference compounds.

5 1.3 Vehicle

Dimethyl sulfoxide (DMSO) manufactured by Sigma Chemical Co. (St. Louis, Mo.) was used as vehicle.

1.4 Preparation of Test and Reference Compounds

10 Test compound was dissolved in 100% dimethyl sulfoxide (DMSO) to yield 100 µM stock solutions (final concentration of DMSO in all tubes containing test compound was 1%, v/v). All other reference compounds were prepared by the same method using double-distilled
15 water rather than DMSO.

1.5 Experimental Procedure for the [³⁵S]GTPγS Binding Assay

Test and reference compounds were studied in triplicate at 10 different concentrations (0.01, 0.1, 20 1, 5, 10, 50, 100, 1000, 10000 and 50000 nM) for their effects upon basal [³⁵S]GTPγS binding to h5-HT_{1A} CHO cell membranes. Reactions were performed in 5 ml glass test tubes containing 8 µl of test/reference drug mixed with 792 µl of buffer (25 mM Tris HCl, 50 mM NaCl, 5 mM
25 MgCl₂, 0.1 mM EGTA, pH=7.4) containing GDP (1 µM), [³⁵S]GTPS (0.1 nM) and h5-HT_{1A} CHO cell membranes (10 µg protein/reaction; NEN Life Science Products, Boston, Mass.; catalog #CRM035, lot #501-60024, GenBank #

X13556). Reactions proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper, using a Brandel harvester and 4x3 ml ice-cold buffer washes. S

5 radioactivity bound to the filter paper was measured using liquid scintillation counting (1272 Clinigamma, LKB/Wallach).

1.6 Experimental Procedure to Determine the Binding Affinity of the Test compound Aripiprazole at the h5-

10 HT_{1A} Receptor

Test compound was studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 10, 50, 100, 500, 1000, 5000 and 10000 nM) to determine its displacement of [³H]8-OH-DPAT (1 nM; NEN Life Sciences; catalog #NET 929, lot #3406035, Specific Activity =124.9 Ci/mmol) binding to h5-HT_{1A} receptors in CHO cell membranes (15-20 µg protein; NEN Life Science Products, catalog #CRM035, lot #501-60024). Membranes (396 µl) were incubated in 5 ml glass tubes containing [³H]8-OH-DPAT (396 µl), test compound or vehicle (8 µl) and buffer A (50 mM Tris.HCl, 10 mM MgSO₄, 0.5 mM EDTA, 0.1% (w/v) ascorbic acid, pH =7.4). All assays proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper (presoaked in buffer B; 50 mM Tris.HCl, pH=7.4), using a Brandel harvester and 4x1 ml ice-cold washes with buffer B. Non-specific binding was determined in the presence of 10 µM (+)8-OH-DPAT.

1.7 Parameters Determined

Serotonin (5-HT) is a full 5-HT_{1A} receptor agonist which stimulates increases in basal [³⁵S]GTPγS binding to h5-HT_{1A} receptors in recombinant CHO cell membranes. The test compound was studied at 10 concentrations to determine effects upon basal [³⁵S]GTPγS binding relative to that produced by 10 μM 5-HT. The relative potency (EC₅₀, 95% confidence interval) and intrinsic agonist activity (% of E_{max} for 10 μM 5-HT) was calculated for each compound by computerized non-linear regression analysis of complete concentration-effect data. The binding affinity of test compound at the h5-HT_{1A} receptor was determined by its ability to prevent [³H]8-OH-DPAT binding to CHO cell membranes that express this receptor. Non-linear regression analysis of the competition binding data was used to calculate an inhibition constant (IC₅₀, 95% confidence interval), which is the concentration of test compound that occupies half of the h5-HT_{1A} sites specifically bound by [³H]8-OH-DPAT. The affinity of h5-HT_{1A} receptors for test compound (K_i, 95% confidence interval) was calculated by the equation, $K_i = (IC_{50}) / (1 + ([^3H]8-OH-DPAT) / K_d)$, where the K_d for [³H]8-OH-DPAT at h5-HT_{1A} = 0.69 nM (NEN Life Sciences). All estimates of drug binding affinity, potency and intrinsic efficacy at the h5-HT_{1A} receptor were calculated using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, Calif.).

2. Results

The test compound and 5-HT produced concentration-dependent increases above basal [^{35} S]GTPyS binding. 1% DMSO tested alone had no effect upon basal or drug-induced [^{35} S]GTPyS binding.

The test compound (EC_{50} =2.12 nM), 5-HT (EC_{50} =3.67 nM), potently stimulated basal [^{35} S]GTPyS binding. Potency and intrinsic agonist efficacy estimates were derived by non-linear regression analysis with correlation coefficients (r^2)>0.98 in each case (Table 1). The test compound exerted partial agonist efficacies in the 65-70% range. WAY-100635 produced no significant change (unpaired Student's t-test) in basal [^{35} S]GTPyS binding at all concentrations tested (Table 1). WAY-100635 did, however, completely inhibit the effects of 5-HT and test compound upon [^{35} S]GTPyS binding to h5-HT $_{1A}$ receptors in CHO cell membranes (Table 2). Tables 1 and 2 are shown below.

The test compound demonstrated high affinity binding to h5-HT $_{1A}$ receptors in CHO cell membranes (IC_{50} 4.03 nM, 95% confidence interval=2.67 to 6.08 nM; K_i =1.65 nM, 95% confidence interval=1.09 to 2.48).

Table 1

Potency (EC_{50}) and Intrinsic Agonist Efficacy (E_{max}) of Test compound and Reference Drugs in a $h5-HT_{1A}$ [^{35}S]GTPyS CHO-cell Membrane Binding Assay.			
Drug	EC_{50} , nM (95% Confidence Interval)	E_{max} (% $\pm$ SEM)	Goodness of Fit (r^2)
Test Compound	2.12 (0.87 to 5.16)	68.13 $\pm$ 3.16	0.986
5-HT	3.67 (1.56 to 8.63)	98.35 $\pm$ 4.47	0.986
WAY-100635	-----	-----	-----

Table 2

Inhibitory Potency (IC_{50}) of WAY-100635 versus 1 μ M Concentration of 5-HT and Test compound in a $h5-HT_{1A}$ [^{35}S]GTPyS CHO-cell Membrane Binding Assay.		
Drug Combination	WAY-100635 Inhibition Potency, IC_{50} , nM (95% Confidence Interval)	Goodness of Fit (r^2)
5-HT + WAY-100635	217.1 (127.4 to 369.7)	0.988
Test Compound + WAY-100635	392.2 (224.1 to 686.2)	0.989

Example 3

Formulation Examples

- 5 Several non-limiting formulation examples of aripiprazole or dehydroaripiprazole with mood stabilizers are presented below.

53

Formulation Sample Example 1

	Aripiprazole Anhydride Crystals B	5 mg
	Lithium	600 mg
	Starch	131 mg
5	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	800 mg

According to a preparation method which is well-known to a person having an ordinary skill in the art, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 2

	Aripiprazole Anhydride Crystals B	5 mg
	Valproic Acid	1000 mg
15	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	1200 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 3

	Aripiprazole Anhydride Crystals B	5 mg
	Divalproex sodium	750 mg
	Starch	131 mg
25	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	950 mg

According to a common method, the tablet

containing the above mentioned formulation is prepared.

Formulation Sample Example 4

	Aripiprazole Anhydride Crystals B	5 mg
	Carbamazepine	500 mg
5	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	700 mg

According to a common method, the tablet
10 containing the above mentioned formulation is prepared.

Formulation Sample Example 5

	Aripiprazole Anhydride Crystals B	5 mg
	Oxcarbamazepine	800 mg
	Starch	131 mg
15	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	1000 mg

According to a common method, the tablet
containing the above mentioned formulation is prepared.

20 Formulation Sample Example 6

	Aripiprazole Anhydride Crystals B	5 mg
	Zonisamide	300 mg
	Starch	131 mg
	Magnesium stearate	4 mg
25	<u>Lactose</u>	<u>60 mg</u>
	Total	500 mg

According to a common method, the tablet

containing the above mentioned formulation is prepared.

Formulation Sample Example 7

	Aripiprazole Anhydride Crystals B	5 mg
	Lamotragine	250 mg
5	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	450 mg

According to a common method, the tablet
10 containing the above mentioned formulation is prepared.

Formulation Sample Example 8

	Aripiprazole Anhydride Crystals B	5 mg
	Topiramate	250 mg
	Starch	131 mg
15	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	450 mg

According to a common method, the tablet
containing the above mentioned formulation is prepared.

20 Formulation Sample Example 9

	Aripiprazole Anhydride Crystals B	5 mg
	Gabapentin	800 mg
	Starch	131 mg
	Magnesium stearate	4 mg
25	<u>Lactose</u>	<u>60 mg</u>
	Total	1000 mg

According to a common method, the tablet

containing the above mentioned formulation is prepared.

Formulation Sample Example 10

	Aripiprazole Anhydride Crystals B	5 mg
	Levetiracetam	600 mg
5	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	800 mg

According to a common method, the tablet
10 containing the above mentioned formulation is prepared.

Several non-limiting formulation examples of
dehydroaripiprazole and mood stabilizers are presented
below. It is to be understood that any one of DM-1458,
DM-1451, DM-1452, DM-1454 or DCPD, as shown in Figure
15 8, could be substituted for dehydroaripiprazole in
these disclosed formulations.

Formulation Sample Example 11

	Dehydroaripiprazole	5 mg
	Lithium	600 mg
20	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	800 mg

According to a preparation method which is
25 well-known to a person having an ordinary skill in the
art, the tablet containing the above mentioned
formulation is prepared.

Formulation Sample Example 12

	Dehydroaripiprazole	5 mg
	Valproic Acid	1000 mg
	Starch	131 mg
5	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	1200 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

10 Formulation Sample Example 13

	Dehydroaripiprazole	5 mg
	Divalproex sodium	750 mg
	Starch	131 mg
	Magnesium stearate	4 mg
15	<u>Lactose</u>	<u>60 mg</u>
	Total	950 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 14

20	Dehydroaripiprazole	5 mg
	Carbamazepine	500 mg
	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
25	Total	700 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 15

	Dehydroaripiprazole	5 mg
	Oxcarbamazepine	800 mg
	Starch	131 mg
5	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	1000 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

10 Formulation Sample Example 16

	Dehydroaripiprazole	5 mg
	Zonisamide	300 mg
	Starch	131 mg
	Magnesium stearate	4 mg
15	<u>Lactose</u>	<u>60 mg</u>
	Total	500 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 17

20	Dehydroaripiprazole	5 mg
	Lamotragine	250 mg
	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
25	Total	450 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 18

	Dehydroaripiprazole	5 mg
	Topiramate	250 mg
	Starch	131 mg
5	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	450 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

10 Formulation Sample Example 19

	Dehydroaripiprazole	5 mg
	Gabapentin	800 mg
	Starch	131 mg
	Magnesium stearate	4 mg
15	<u>Lactose</u>	<u>60 mg</u>
	Total	1000 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 20

20	Dehydroaripiprazole	5 mg
	Levetiracetam	600 mg
	Starch	131 mg
	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
25	Total	800 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Formulation Sample Example 21

	Aripiprazole Anhydride Crystals B	5 mg
	clonazepam	600 mg
	Starch	131 mg
5	Magnesium stearate	4 mg
	<u>Lactose</u>	<u>60 mg</u>
	Total	800 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

10 Formulation Sample Example 22

	Dehydroaripiprazole	5 mg
	clonazepam	600 mg
	Starch	131 mg
	Magnesium stearate	4 mg
15	<u>Lactose</u>	<u>60 mg</u>
	Total	800 mg

According to a common method, the tablet containing the above mentioned formulation is prepared.

Example 4

- 20 Method of Treatment of Patients with a New Diagnosis, Recurrent or Refractory Episode of Bipolar Disorder (I or II) with or without psychotic features, manic or mixed episode as defined by DSM -IV-R criteria.

A combination of aripiprazole, or an
25 aripiprazole metabolite, and at least one mood stabilizer is evaluated as a therapy for patients with

a new diagnosis, recurrent or refractory episode of bipolar disorder (I or II), acute mania, or bipolar depression. Patients ranging in age from 18 to 65 years who are diagnosed with bipolar disorder (I or 5 II), acute mania, or bipolar depression are evaluated to ensure that they have a baseline Young Mania Rating Scale (YMRS) score of greater than 24. Only patients with this YMRS score receive treatment. These patients are interviewed to obtain a complete medical and 10 psychiatric history. Aripiprazole, or an aripiprazole metabolite, is first administered at a dose of 10 mg/day and increased to 30 mg/day as needed in the opinion of the monitoring psychiatrist. Aripiprazole, or an aripiprazole metabolite, is administered to these 15 patients at a dose of from 10 mg/day to 30 mg/day for a period of at least four weeks, and up to eight weeks for patients who respond well to this treatment during the first four weeks. The aripiprazole, or the aripiprazole metabolite, is administered together with 20 at least one mood stabilizer, wherein the mood stabilizer is lithium, valproic acid, divalproex sodium, carbamazepine, oxcarbamazepine, zonisamide, lamotrigine, topiramate, gabapentin, levetiracetam or clonazepam.

25 The aripiprazole, or the aripiprazole metabolite, can be administered in one dosage form, for example a tablet, and the mood stabilizer may be administered in a separate dosage form, for example a

tablet. The administration may occur at about the same time or at different times during the day. Dosages may be within the ranges provided above for each of aripiprazole, an aripiprazole metabolite and for the mood stabilizer.

Alternatively, a dosage form containing aripiprazole, or an aripiprazole metabolite, in administered in combination with at least one mood stabilizer and a pharmaceutically acceptable carrier.

Such combinations include without limitation the following: aripiprazole/lithium, aripiprazole/valproic acid, aripiprazole/divalproex sodium, aripiprazole/carbamazepine, aripiprazole/oxcarbamazepine, aripiprazole/zonisamide, aripiprazole/lamotrigine, aripiprazole/topiramate, aripiprazole/gabapentin, aripiprazole/levetiracetam and aripiprazole/clonazepam. An improvement in alleviation of symptoms of bipolar disorder (I or II), acute mania, or bipolar depression is observed in these patients following administration of aripiprazole, or aripiprazole metabolite, and the one or more mood stabilizers, as shown by results of testing performed during and after the duration of administration of aripiprazole, or an aripiprazole metabolite, and the mood stabilizer. The YMRS and other measures such as CGI, AIMS, SAS, Simpson & Angus and Barnes, commonly known to one of ordinary skill in the art, are administered to these patients. Results demonstrate a

normalization of mood.

Example 5

Efficacy of Aripiprazole in combination with valproate or lithium in the treatment of mania in patients
5 partially nonresponsive to valproate or lithium monotherapy.

A 6-week double-blind, randomized, placebo-controlled trial is conducted to determine the efficacy of combined therapy with aripiprazole and either
10 valproate or lithium compared with valproate or lithium alone in treating acute manic or mixed bipolar episodes. The methods used are generally as described in Tohen et al., (Arch. Gen. Psychiatry, 2002 Jan;59(1):62-9). The objective is to evaluate the
15 efficacy of aripiprazole (1-30 mg/day) vs placebo when added to ongoing mood-stabilizer therapy as measured by reductions in Young Mania Rating Scale (YMRS) scores. Patients with bipolar disorder, manic or mixed episode, who are inadequately responsive to more than 2 weeks of
20 lithium (600 mg/day) or valproate (500 mg/day) therapy, are randomized to receive cotherapy (aripiprazole + mood-stabilizer) or monotherapy (placebo + mood-stabilizer). The results indicate that aripiprazole cotherapy improves patients' YMRS total scores more
25 than monotherapy. Clinical response rates ($>$ or $=$ 50% improvement on YMRS) are higher with cotherapy. Aripiprazole cotherapy improves 21-item Hamilton

Depression Rating Scale (HAMD-21) total scores more than monotherapy. In patients with mixed-episodes with moderate to severe depressive symptoms (DSM-IV mixed episode; HAMD-21 score of $>$ or $=$ 20 at baseline),

5 aripiprazole cotherapy improves HAMD-21 scores compared to monotherapy. Extrapyramidal symptoms (Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale) are not significantly changed from baseline to end point in either treatment group.

10 Compared with the use of valproate or lithium alone, the addition of aripiprazole provided superior efficacy in the treatment of manic and mixed bipolar episodes.

Example 6

Efficacy of Dehydroaripiprazole in combination with

15 valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy.

A 6-week double-blind, randomized, placebo-controlled trial is conducted to determine the efficacy

20 of combined therapy with dehydroaripiprazole and either valproate or lithium, compared with valproate or lithium alone, in treating acute manic or mixed bipolar episodes. The methods used are generally as described in Tohen et al., (Arch. Gen. Psychiatry, 2002

25 Jan;59(1):62-9). The objective is to evaluate the efficacy of dehydroaripiprazole (1-30 mg/day) vs placebo when added to ongoing mood-stabilizer therapy

as measured by reductions in Young Mania Rating Scale (YMRS) scores. Patients with bipolar disorder, manic or mixed episode, who are inadequately responsive to more than 2 weeks of lithium (600 mg/day) or valproate (500 mg/day) therapy, are randomized to receive cotherapy (dehydroaripiprazole + mood-stabilizer) or monotherapy (placebo + mood-stabilizer). The results indicate that dehydroaripiprazole cotherapy improves patients' YMRS total scores more than monotherapy.

10 Clinical response rates ($>$ or $=$ 50% improvement on YMRS) are higher with cotherapy. Dehydroaripiprazole cotherapy improves 21-item Hamilton Depression Rating Scale (HAMD-21) total scores more than monotherapy. In patients with mixed-episodes with moderate to severe

15 depressive symptoms (DSM-IV mixed episode; HAMD-21 score of $>$ or $=$ 20 at baseline), dehydroaripiprazole cotherapy improves HAMD-21 scores compared to monotherapy. Extrapyramidal symptoms (Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary

20 Movement Scale) are not significantly changed from baseline to end point in either treatment group. Compared with the use of valproate or lithium alone, the addition of dehydroaripiprazole provided superior efficacy in the treatment of manic and mixed bipolar

25 episodes.

Example 7

A double-blind, randomized, placebo-controlled study of

Aripiprazole as adjunctive treatment for adolescent mania.

This randomized, double-blind, placebo-controlled study examines the efficacy and tolerability of aripiprazole in combination with divalproex (DVP) for acute mania in adolescents with bipolar disorder. The methods employed are essentially as described by Delbello et al., (J. Am. Acad. Child Adolesc. Psychiatry, 2002 Oct;41(10):1216-23). It is hypothesized that DVP in combination with aripiprazole is more effective than DVP alone for treating mania associated with adolescent bipolar disorder. Thirty manic or mixed bipolar I adolescents (12-18 years) receive an initial DVP dose of 20 mg/kg and are randomly assigned to 6 weeks of combination therapy with aripiprazole, about 10 mg/day or placebo. Primary efficacy measures are change from baseline to endpoint in Young Mania Rating Scale (YMRS) score and YMRS response rate. Safety and tolerability are assessed weekly. The DVP + aripiprazole group demonstrates a greater reduction in YMRS scores from baseline to endpoint than the DVP + placebo group. Moreover, YMRS response rate is significantly greater in the DVP + aripiprazole group than in the DVP + placebo group. No significant group differences from baseline to endpoint in safety measures are noted. Sedation, rated as mild or moderate, is more common in the DVP + aripiprazole group than in the DVP + placebo group. The results

indicate that aripiprazole in combination with DVP is more effective for the treatment of adolescent bipolar mania than DVP alone. In addition, the results suggest that aripiprazole is well tolerated when used in
5 combination with DVP for the treatment of mania.

Example 8

A double-blind, randomized, placebo-controlled study of Dehydroaripiprazole as adjunctive treatment for adolescent mania.

10 This randomized, double-blind, placebo-controlled study examines the efficacy and tolerability of dehydroaripiprazole in combination with divalproex (DVP) for acute mania in adolescents with bipolar disorder. The methods employed are essentially as
15 described by Delbello et al., (J. Am. Acad. Child Adolesc. Psychiatry, 2002 Oct;41(10):1216-23). It is hypothesized that DVP in combination with dehydroaripiprazole is more effective than DVP alone for treating mania associated with adolescent bipolar
20 disorder. Thirty manic or mixed bipolar I adolescents (12-18 years) receive an initial DVP dose of 20 mg/kg and are randomly assigned to 6 weeks of combination therapy with dehydroaripiprazole, about 10 mg/day or placebo. Primary efficacy measures are change from
25 baseline to endpoint in Young Mania Rating Scale (YMRS) score and YMRS response rate. Safety and tolerability are assessed weekly. The DVP + dehydroaripiprazole

group demonstrates a greater reduction in YMRS scores from baseline to endpoint than the DVP + placebo group. Moreover, YMRS response rate is significantly greater in the DVP + dehydroaripiprazole group than in the DVP + placebo group. No significant group differences from baseline to endpoint in safety measures are noted. Sedation, rated as mild or moderate, is more common in the DVP + dehydroaripiprazole group than in the DVP + placebo group. The results indicate that dehydroaripiprazole in combination with DVP is more effective for the treatment of adolescent bipolar mania than DVP alone. In addition, the results suggest that aripiprazole is well tolerated when used in combination with DVP for the treatment of mania.

All patents, patent applications, scientific and medical publications mentioned herein are hereby incorporated in their entirety. It should be understood, of course, that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the invention as set forth in the appended claims.

CLAIMS

1. A composition comprising at least one carbostyryl derivative in combination with at least one mood stabilizer.
2. The composition of Claim 1 wherein the carbostyryl derivative is a dopamine-serotonin system stabilizer.
3. The composition of Claim 2 wherein the carbostyryl derivative is aripiprazole or a metabolite thereof.
4. The composition of Claim 3 wherein the metabolite of aripiprazole is dehydroaripiprazole, DM-1458, DM-1451, DM-1452, DM-1454 or DCPD.
5. The composition of any one of Claims 1 to 4, wherein the at least one mood stabilizer is lithium, valproic acid, divalproex sodium, carbamazepine, oxcarbamazepine, zonisamide, lamotrigine, topiramate, gabapentin, levetiracetam or clonazepam, or a salt thereof.
6. The composition of any one of Claims 1 to 5, wherein the at least one mood stabilizer is carbamazepine, oxcarbamazepine, zonisamide, lamotrigine, topiramate, gabapentin, levetiracetam or clonazepam, or a salt thereof.
7. The composition of any one of Claims 1 to 6, further comprising at least one pharmaceutically acceptable carrier.
8. Use of the compositions of any one of Claims

1 to 7 in the preparation of a medicament useful for treatment of mood disorders.

9. Use of the compositions of any one of Claims 1 to 7, in the preparation of a medicament useful for treatment of bipolar disorder.

10. Use of the compositions of any one of Claims 1 to 7, in the preparation of a medicament useful for treatment of mania.

11. A method of treating a mood disorder in a patient comprising administration of an amount of any of the compositions of Claims 1 to 7 in a pharmaceutically acceptable carrier, wherein the amount is effective to treat the mood disorder in the patient.

12. A method of treating a mood disorder in a patient comprising separate administration of a first amount of a carbostyryl derivative and a second amount of mood stabilizer, wherein the administration is effective to treat the mood disorder in the patient.

13. The method of Claim 12, wherein the carbostyryl derivative is aripiprazole or a metabolite thereof.

14. The composition of Claim 13 wherein the metabolite of aripiprazole is dehydroaripiprazole, DM-1458, DM-1451, DM-1452, DM-1454 or DCPD.

15. The method of Claim 12, wherein the mood stabilizer is lithium, valproic acid, divalproex sodium, carbamazepine, oxcarbamazepine, zonisamide, lamotrigine, topiramate, gabapentin, levetiracetam or

clonazepam, or a salt thereof.

16. The method of Claim 15, wherein the mood stabilizer is carbamazepine, oxcarbamazepine, zonisamide, lamotrigine, topiramate, gabapentin, levetiracetam or clonazepam, or a salt thereof.

ABSTRACT

The pharmaceutical composition of the present invention comprises a carbostyryl derivative which is a dopamine-serotonin system stabilizer and a mood stabilizer in a pharmaceutically acceptable carrier. The carbostyryl derivative may be aripiprazole or a metabolite thereof. The mood stabilizer may include but is not limited to lithium, valproic acid, divalproex sodium, carbamazapine, oxcarbamazapine, zonisamide, lamotragine, topiramate, gabapentin, levetiracetam or clonazepam. These compositions are used to treat patients with mood disorders, particularly bipolar disorder with or without psychotic features, mania or mixed episodes. Methods are provided for separate administration of a carbostyryl derivative and a mood stabilizer to a patient with a mood disorder.

FIG 1

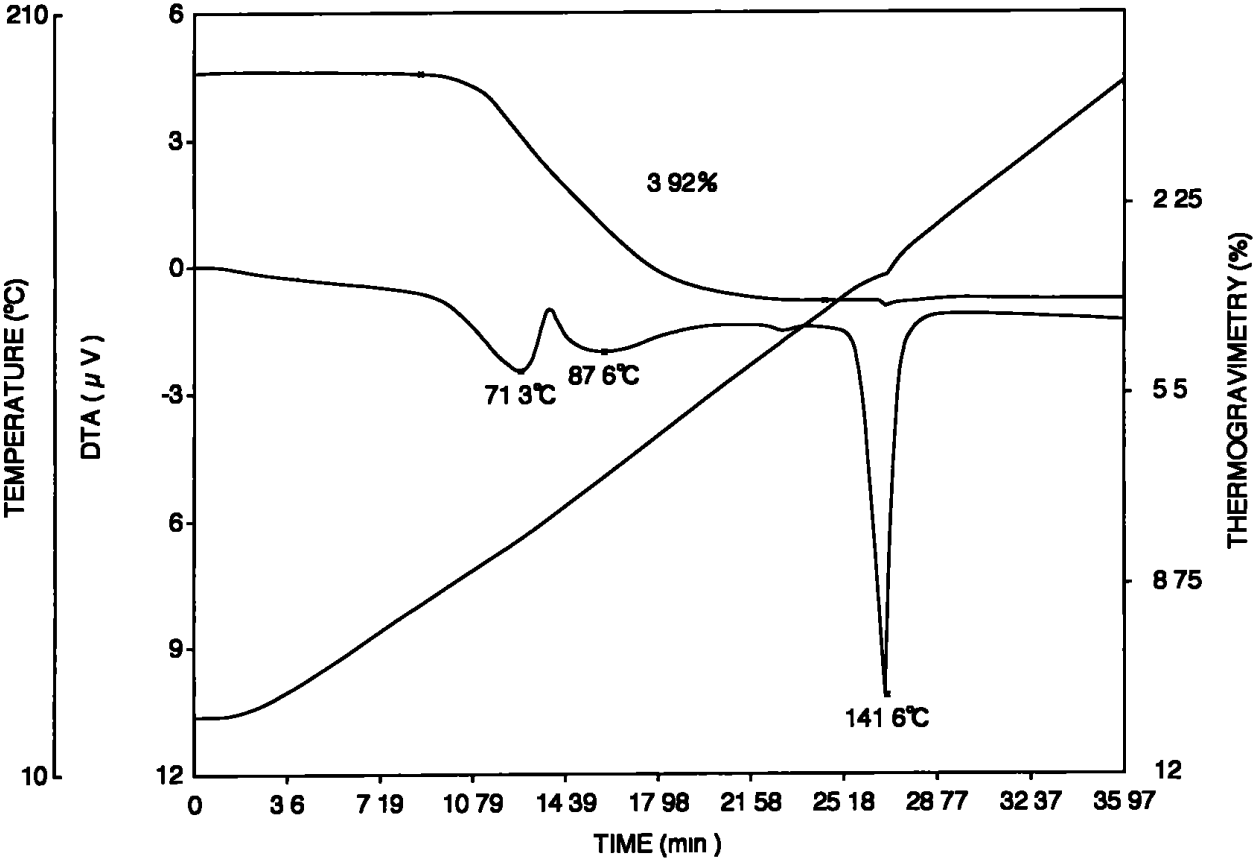
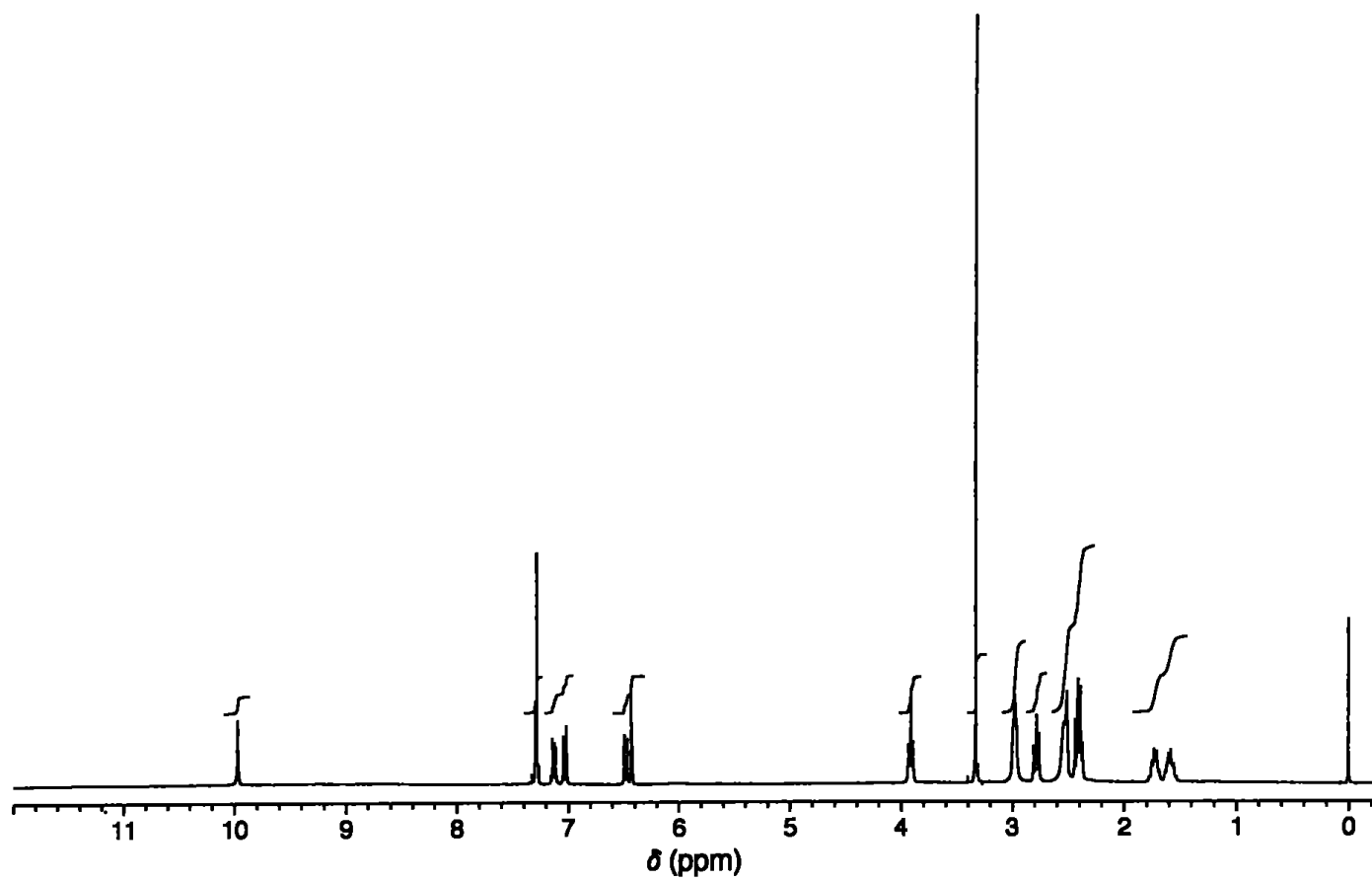


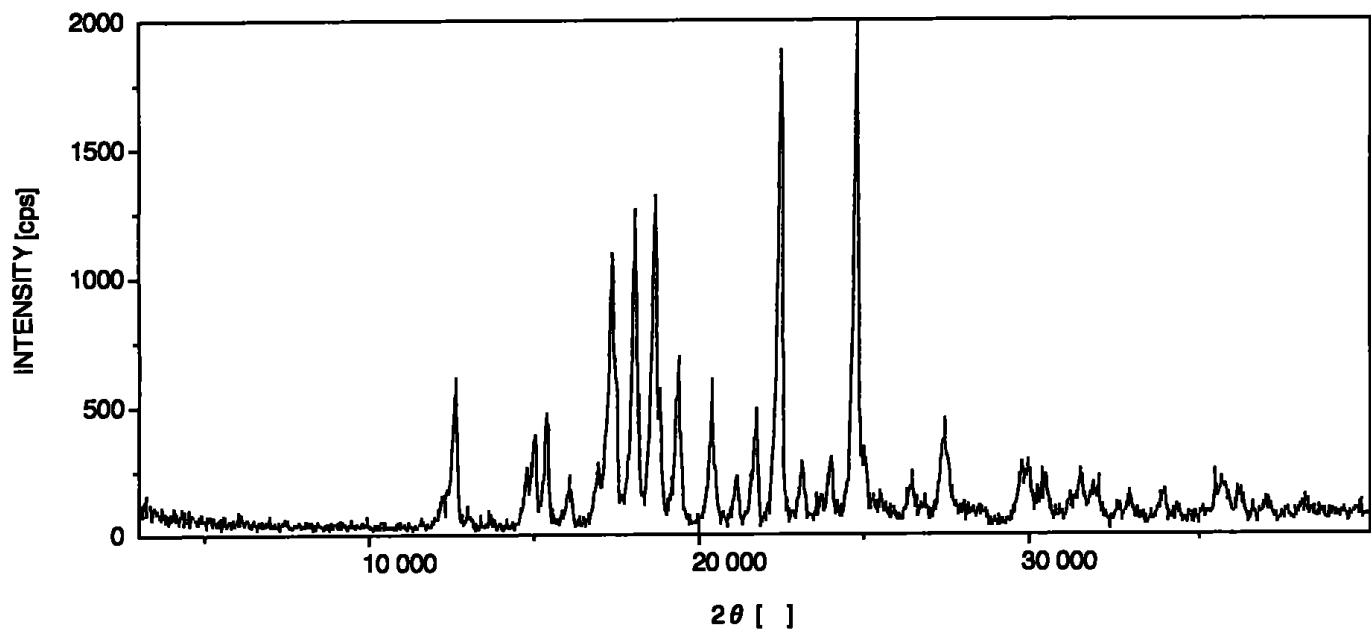
FIG 2



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FIG 3



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FIG 4

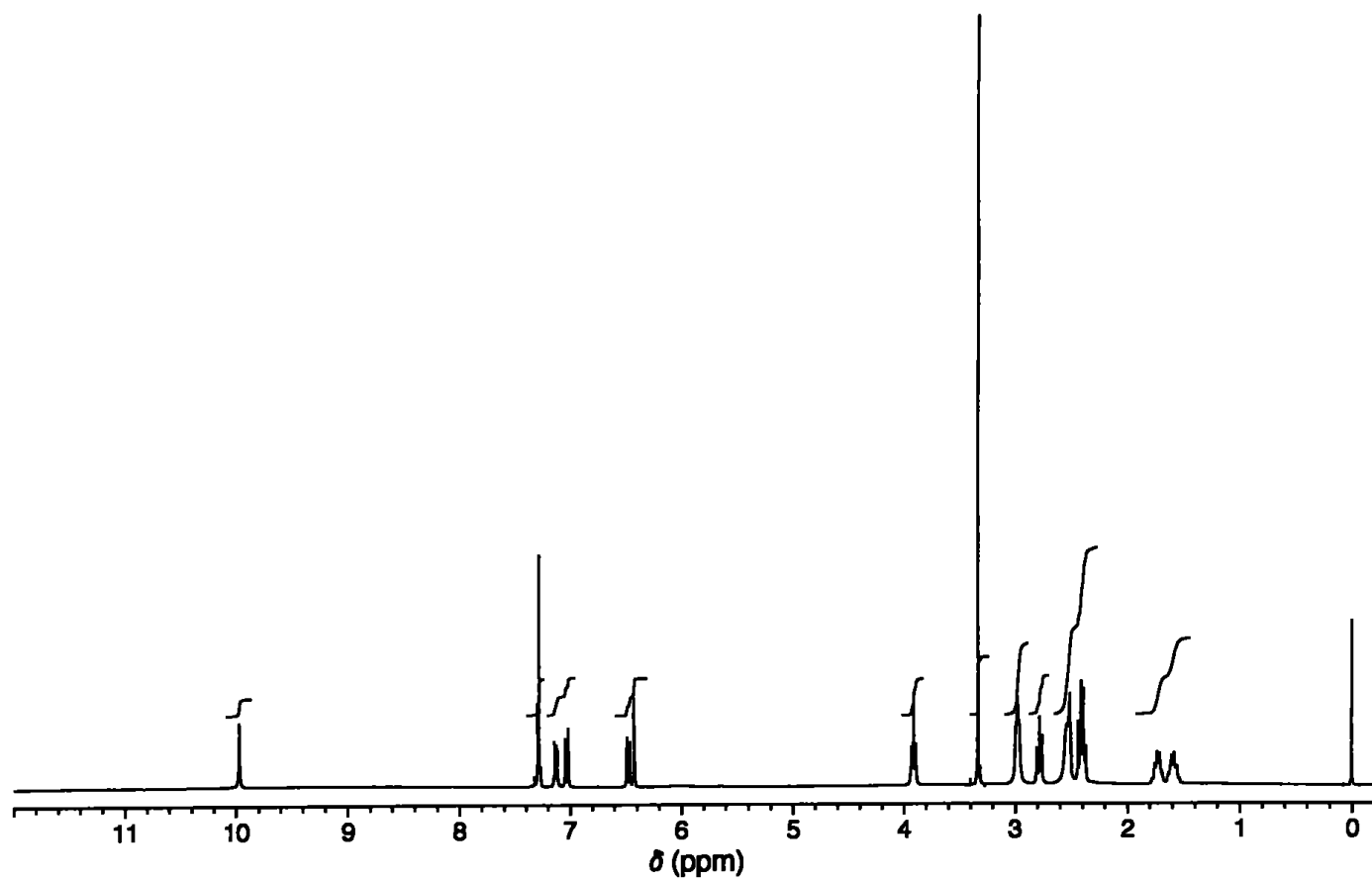
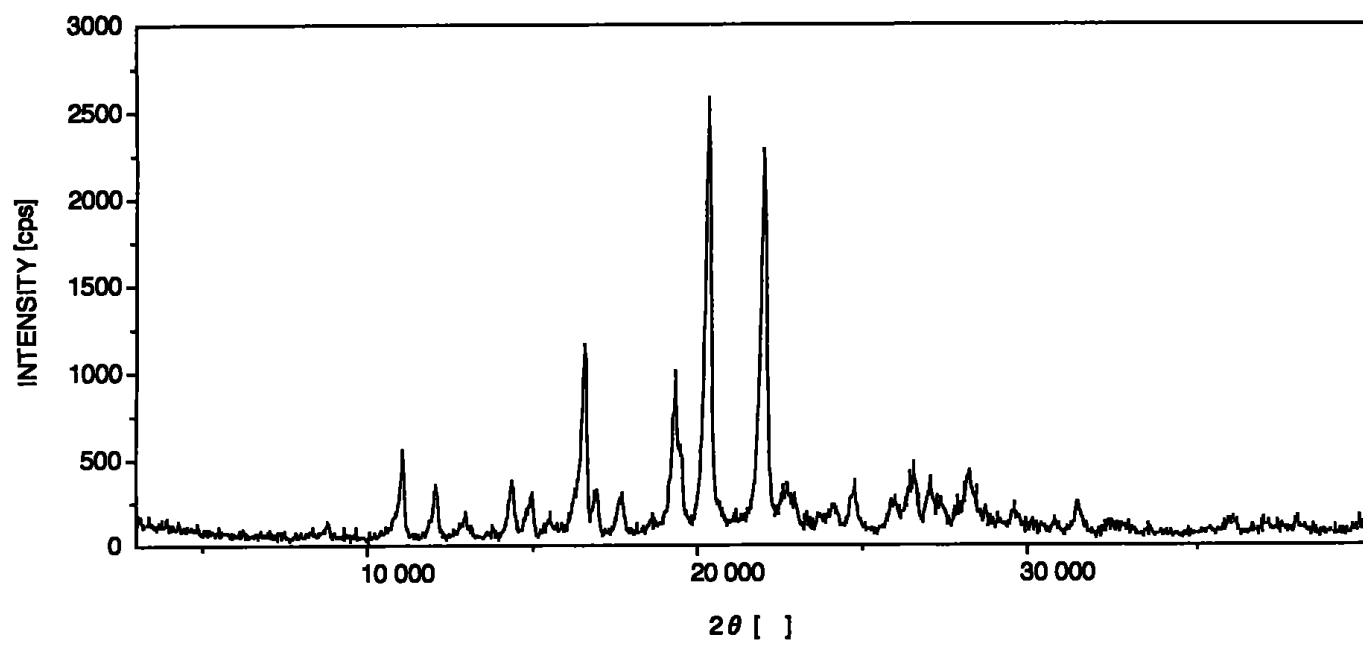


FIG 5



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FIG 6

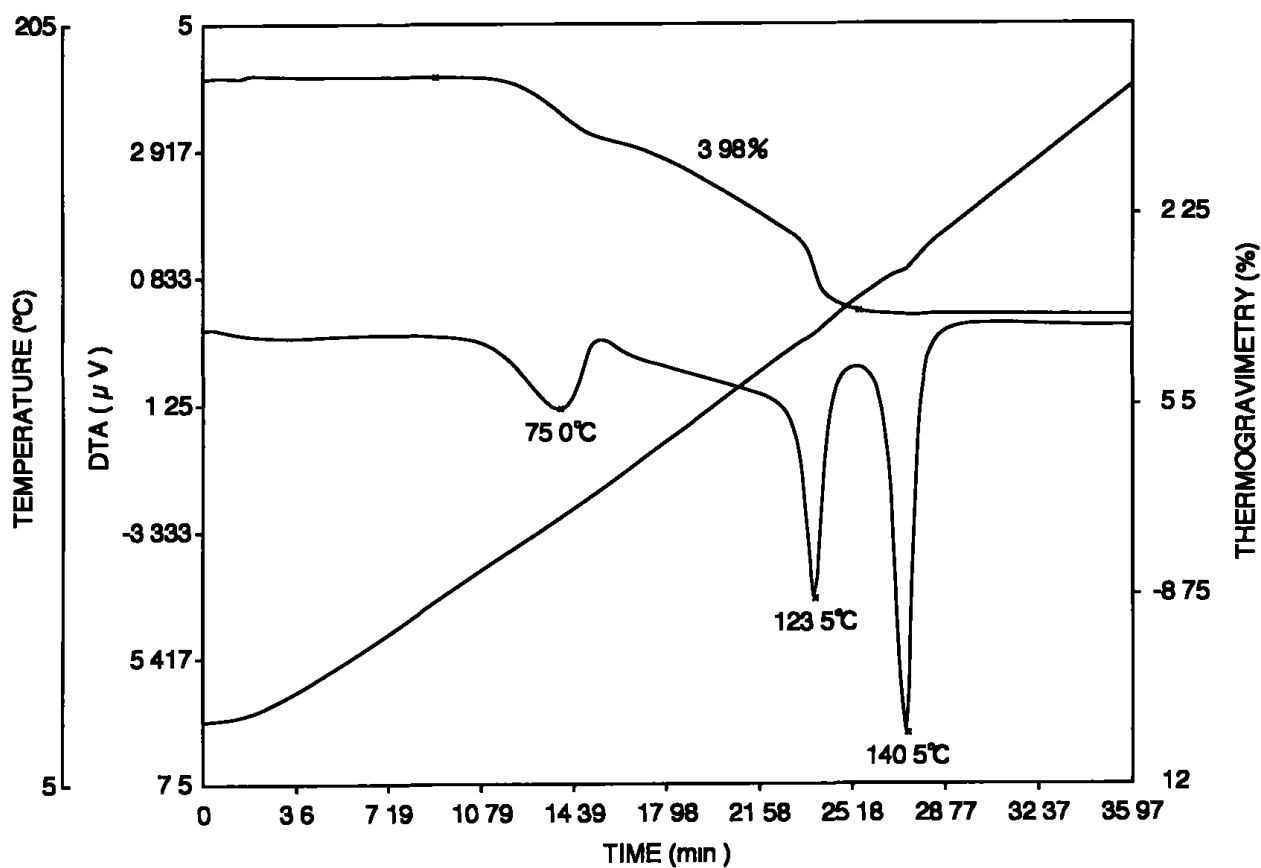
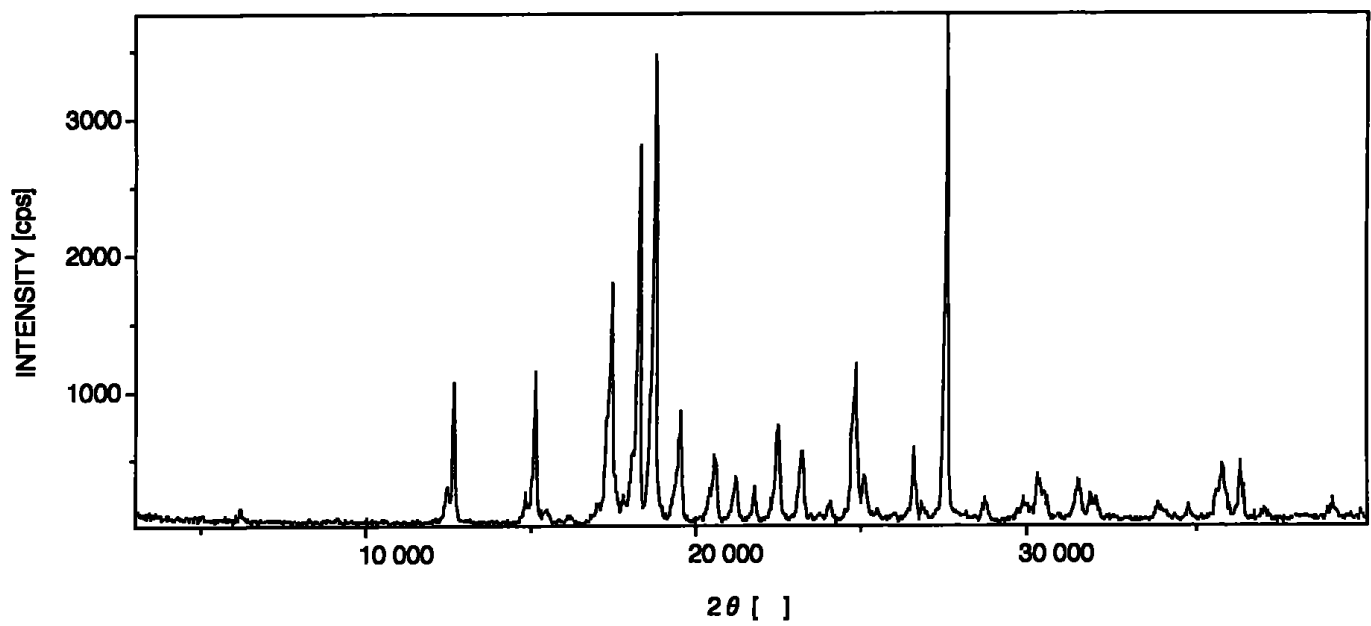


FIG 7



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The diagram illustrates the chemical synthesis of various compounds starting from Aripiprazole (OPC-14597). The scheme shows the following pathways:

- Top Pathway:** Aripiprazole (OPC-14597) is converted to DM-1451 via 3A4/2D6 metabolism. DM-1451 is then converted to DM-1454 (with GluO- addition) and DM-1458 (with HO₂SO- addition).
- Right Pathway:** Aripiprazole (OPC-14597) is converted to OPC-14857 via 3A4/2D6 metabolism. OPC-14857 is then converted to DM-1459, which is further converted to DM-1460.
- Central Pathway:** Aripiprazole (OPC-14597) is converted to DM-1452 via 3A4/2D6 metabolism. DM-1452 is then converted to DCPP, which is further converted to DM-1431.
- Bottom Pathway:** Aripiprazole (OPC-14597) is converted to OPC-3373 via 3A4/2D6 metabolism. OPC-3373 is then converted to DM-1457.
- Other Compounds:** DM-1431 is converted to the Glucuronide of DM-1431 and the Sulfate of DM-1431.

The chemical structures shown include various derivatives of the piperazine ring system, such as DM-1454, DM-1458, DM-1451, DM-1452, DM-1459, DM-1460, OPC-14857, OPC-3373, DM-1457, DCPP, DM-1431, and their respective glucuronide and sulfate conjugates.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference F178422	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US04/13308	International filing date (day/month/year) 19 May 2004 (19.05.2004)	(Earliest) Priority Date (day/month/year) 23 May 2003 (23.05.2003)
Applicant OTSUKA PHARMACEUTICAL, CO., LTD.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)3. ☐ Unity of invention is lacking (See Box No. III)

4. With regard to the title,

☒

the text is approved as submitted by the applicant.

☐

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒

the text is approved as submitted by the applicant.

☐

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. I

☒

as suggested by the applicant.

☐

as selected by this Authority, because the applicant failed to suggest a figure.

☐

as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6-11
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/13308

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/47; A61K 31/19; A61K 31/519
 US CL : 514/310

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)
 U.S. : 514/310; 514/557; 514/299

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 practicable, search terms used)
 CAPLUS; MEDLINE; EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/067390 A1 (ORTHO-MCNEIL PHARMACEUTICAL, INC.) 7 November 2002 (07.11.2002) page 4, lines 17-21; page 5 lines 5-10, 31-32; page 8, lines 4-11.	1-5, 12-16
X	US 2003/0109546 A1 (FENTON) 12 June 2003 (12.06.2003), see entire document, page 2 [0013]; [0017]; [0032].	1-5, 12-16
— P		
X	WO 03/066039 A1 (ABBOT LABORATORIES) 14 August 2003 (14.08.2003), page 5, lines 33-35; page 16 lines 40-42; page 15, lines 10-13.	1-5, 12-16
— P		
Y	WO 00/59489 A2 (SEPRACOR, INC.) 12 October 2000 (12.10.2000), page 4, lines 7-12; page 6, lines 14-18; page 7, lines 5-10	1-5, 12-16
Y	WO 99/62522 A1 (ELI LILLY AND COMPANY) 9 December 1999 (09.12.1999), page 3, line 6-page 4; line 30, page 7, line 12-17.	1-5, 12-16
Y	GORDON et al. Mood Stabilization and weight loss with Topiramate, American Journal of Psychiatry, June 1999, Vol. 156, No. 6, pages 968-969, see pages 1 and 2.	1-5, 12-16
Y	WO 97/33584 A1 (ELI LILLY AND COMPANY) 2 October 1997 (02.10.1997), see page 2, lines 9-15, and lines 34-36	1-5, 12-16

☒ 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

"B" earlier application or patent 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 understate 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

"Z"

document member of the same patent family

Date of the actual completion of the international search

05 December 2004 (05.12.2004)

Date of mailing of the international search report

17 FEB 2005

Name and mailing address of the ISA/US

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 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 Facsimile No. (703) 305-3230

Authorized officer

Sreeni Padmanathan

Telephone No. 571-272-1600

J. Roberts for

INTERNATIONAL SEARCH REPORT

PCT/US04/13308

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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.
A	BALDESSARINI et al. Hospital Use of Antipsychotic Agents in 1989 and 1993: Stable Dosing with Decreased Length of Stay, American Journal of Psychiatry, July 1995, Vol. 152, No. 7, pages 1038-1044, see pages 1-8.	1-5, 12-16

TRATADO DE C O P E R A C I O N E N M A T E R I A D E P A T E N T E S
PCT
REPORTE DE BÚSQUEDA INTERNACIONAL
(PCT Artículo 18 y Reglas 43 y 44)

176

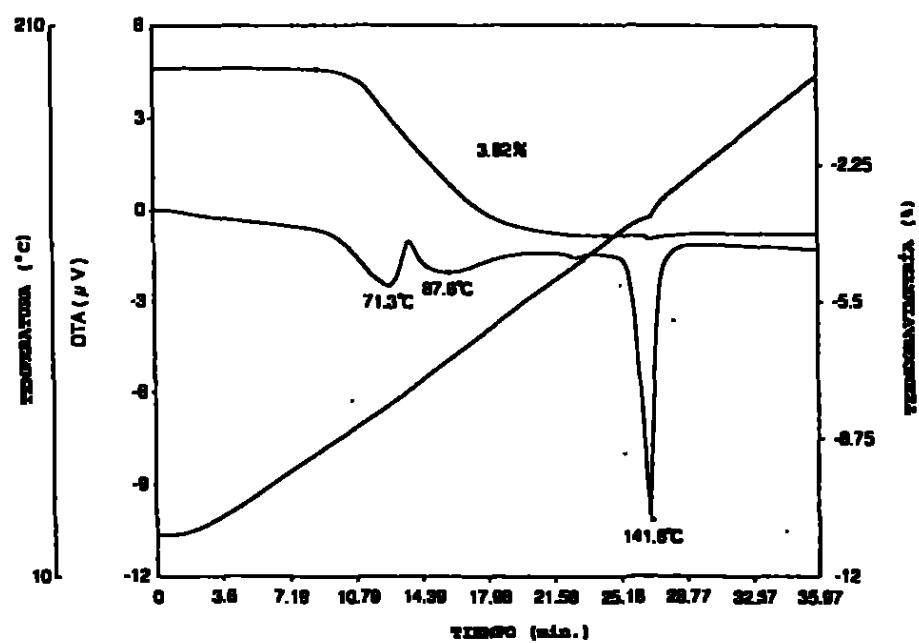
Referencia del archivo del solicitante o del agente F178422	Para ACCIONES ADICIONALES véase (Forma PCT/ISA/220) así como, cuando se aplicable, el inciso 5 abajo		
Solicitud Internacional No.	Fecha de presentación Internacional (día/mes/año)	(Primera) Fecha de prioridad (día/mes/año)	
PCT/US04/13308	19 de mayo del 2004 (19.05.2004)	23 de mayo del 2003 (23.05.2003)	
Solicitante: OTSUKA PHARMACEUTICAL, CO., LTD.			
Este reporte de búsqueda internacional se ha preparado por esta Autoridad Examinadora Internacional y es transmitida al solicitante de acuerdo con el Artículo 18. Se transmite una copia a la Oficina Internacional.			
Este reporte de búsqueda internacional consiste de un total de <u>4</u> hojas.			
☐ También está acompañado de una copia de cada documento de la técnica anterior mencionada en este reporte.			
1. Bases del reporte			
a. Con respecto al idioma, la búsqueda internacional se ha llevado a cabo en base en la solicitud internacional en el idioma en el cual se depositó, a menos que se indique de otra manera en este inciso.			
☐ La búsqueda internacional se ha llevado a cabo en base en una traducción de la solicitud internacional proporcionada a esta autoridad (Regla 23.1(b)).			
b. ☒ Con respecto a cualquier secuencia nucleotídica y/o aminoácidos descrita en la solicitud internacional, véase cuadro No. I.			
2. ☒ Ciertas reivindicaciones no se pueden investigar (véase Cuadro I).			
3. ☐ Se carece de unidad de invención (véase Cuadro II.)			
4. Con respecto al título,			
☒ el texto es aprobado como se envía por el solicitante.			
☐ el texto ha sido establecido por esta autoridad para que se lea como sigue:			
5. Con respecto al extracto,			
☒ el texto es aprobado como se envía por el solicitante.			
☐ el texto ha sido establecido de acuerdo con la Regla 38.2(b), por esta autoridad, para que aparezca en el Cuadro III. El solicitante puede enviar comentarios a esta autoridad, en el mes siguiente a partir de la fecha de envío por correo de este reporte de búsqueda internacional.			
6. Con respecto a los dibujos			
a. la figura de los dibujos que se van a publicar es la figura No. <u>1</u> .			
☒ como se sugiere por el solicitante			
☐ debido a que el solicitante no sugiere una figura.			
☐ debido a que esta figura caracteriza mejor la invención.			
b. ☐ ninguna de las figuras se ha publicado con el extracto			

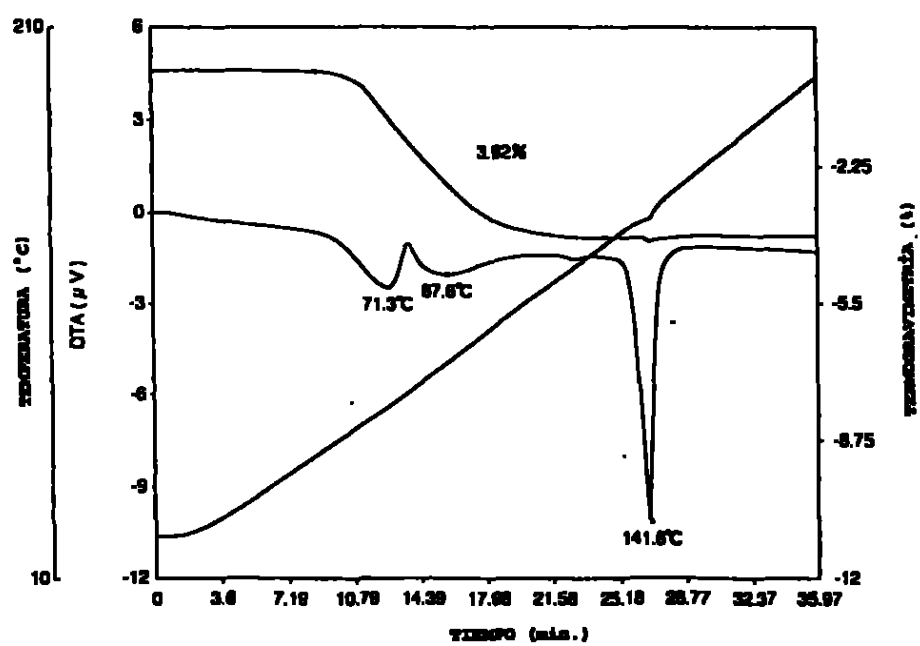
Forma PCT/ISA/210 (primera hoja) (Enero del 2004)

REPORTE DE BÚSQUEDA INTERNACIONAL	Solicitud Internacional No. PCT/US04/13308
Cuadro No. II. Observaciones en las que ciertas reivindicaciones se encontraron no examinables (Continuación del Inciso 2 de la primera hoja)	
Este reporte de búsqueda internacional no se ha establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2)(a) por las siguientes razones:	
1. ☐ Reivindicaciones Números: debido a que se relacionan con materia objeto la cual no se requiere investigar por esta autoridad, específicamente:	
2. ☐ Reivindicaciones Números: debido a que se relacionan con partes de la solicitud internacional que no cumplen con los requerimientos prescritos en la medida en que no se puede llevar a cabo un examen internacional con sentido, específicamente:	
3. ☒ Reivindicaciones Números: 8-11 debido a que son reivindicaciones dependientes y no están redactadas de acuerdo con el segundo y tercero párrafos de la Regla 6.4(a).	
Cuadro III Observaciones en las que se carece de unidad de la invención (continuación del Inciso 3 de la primera hoja)	
Esta Autoridad de Búsqueda Internacional encontró invenciones múltiples en esta solicitud internacional, como sigue:	
1. ☐ En la medida en que todos los derechos de búsqueda adicional requeridos fueron pagados oportunamente por el solicitante, este reporte de búsqueda internacional cubre todas las reivindicaciones susceptibles de examen.	
2. ☐ En la medida en que todas las reivindicaciones susceptibles de examen fueron examinadas sin esfuerzo que justifique un derecho adicional, esta Autoridad no solicita el pago de ningún derecho adicional	
3. ☐ En la medida en que únicamente parte de los derechos de búsqueda adicional requeridos fueron pagados oportunamente por el solicitante, este reporte de búsqueda internacional abarca únicamente aquellas reivindicaciones para las cuales se pagaron los derechos, específicamente, las reivindicaciones números:	
4. ☐ No se pagaron oportunamente los derechos de búsqueda internacional requeridos por el solicitante. En consecuencia, este reporte de búsqueda internacional se restringe a la invención mencionada primero en las reivindicaciones; que está cubierta por las reivindicaciones números:	
Observación bajo protesta	
☐ Los derechos de examen adicional están acompañados por la protesta del solicitante. ☐ No hay protesta que acompañe el pago de derecho de examen adicional.	

INFORME DE BÚSQUEDA INTERNACIONAL		Solicitud Internacional No. PCT/US04/13308
A. CLASIFICACIÓN DE LA MATERIA OBJETO IPC(7): A61K 31/47; A61K 31/19; A61K 31/519 US CL: 514/310 Conforme con la Clasificación Internacional de Patentes (IPC) o bien, tanto con la clasificación nacional como la IPC.		
B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA Documentación mínima consultada (sistema de clasificación seguido por símbolos de clasificación) U.S.: 514/310; 514/557; 514/299 Otros documentos consultados además de la documentación mínima, en la medida en que tales documentos forman parte de los sectores comprendidos por la búsqueda		
Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y términos de búsqueda utilizados, CAPLUS; MEDLINE; EAST		
C. DOCUMENTOS CONSIDERADOS PERTINENTES		
Categoría*	Cita del documento con indicación, cuando sea apropiado de los pasajes pertinentes	No. de las reivindicaciones a las que se refieren
X	WO 02/087590 A1 (ORTHO-MCNEIL PHARMACEUTICAL, INC.), 7 de noviembre del 2002 (07.11.2002) página 4, líneas 17-21; página 5, líneas 5-10, 31-32; página 8, líneas 4-11.	1-5, 12-16
X	US 2003/0109546 A1 (FENTON) 12 de junio del 2003 (12.06.2003), véase la totalidad del documento, página 2 [0013]; [0017]; [0032].	1-5, 12-16
P		
X	WO 03/086039 A1 (ABBOT LABORATORIES) 14 de agosto del 2003 (14.08.2003), página 5, líneas 33-35; página 16, líneas 40-42; página 15, líneas 10-13.	1-5, 12-16
P		
Y	WO 00/59489 A2 (SEPRACOR, INC.) 12 de octubre del 2000 (12.10.2000), página 4, líneas 7-12; página 8, líneas 14-18; página 7, líneas 5-10/	1-5, 12-16
Y	WO 99/62522 A1 (ELI LILLY AND COMPANY) 9 de diciembre de 1999 (09.12.1999), página 3, línea 6-página 4; línea 30, página 7, líneas 12-17.	1-5, 12-16
Y	GORDON et al. Mood Stabilization and weight with Topiramate, American Journal of Psychiatry, junio de 1999, Vol. 156, No. 6, páginas 988-989, véanse páginas 1 y 2.	1-5, 12-16
Y	WO 97/35584 A1 (ELI LILLY AND COMPANY) 2 de octubre de 1997 (02.10.1997), véase página 2, líneas 9-15 y líneas 34-36	1-5, 12-16
☒ Se anexan documentos adicionales en la continuación del cuadro C		☐ Véase anexo de familia de patentes
*Categorías especiales de documentos citados: "A" documento que define el estado general de la técnica, no considerado como particularmente pertinente "E" documento anterior, publicado ya sea en la fecha de presentación internacional o con posterioridad a la misma "I" documento que puede plantear dudas sobre una reivindicación de esta o por una razón especial (como la indicada) "O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro tipo de medio "P" documento publicado antes de la fecha de presentación internacional, pero con posterioridad a la fecha de prioridad reivindicada		"I" documento anterior publicado con posterioridad a la fecha de solicitud internacional o fecha de prioridad y que se le contraponga con la solicitud mencionada para comprender el principio o la teoría que constituya la base de la invención "X" documento particularmente pertinente: la invención reivindicada no puede considerarse como nueva si que implique una actividad inventiva cuando el documento se toma solo. "Y" documento particularmente pertinente: la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otros documentos de la misma naturaleza, cuya combinación resulta evidente para un experto en la materia "A" documento que forma parte de la misma familia de patentes
Fecha en que se ha concluido efectivamente la búsqueda internacional		Fecha de expedición del presente informe de búsqueda internacional
06 de diciembre del 2004 (06.12.2004)		17 de febrero del 2005
Nombre y dirección postal de la ISA Buzón PCT, Attn: ISA/US Comisionado para Patentes Apartado Postal 1450 Alexandria, Virginia 22313-1450 Facsimil No. (703) 305-3230		Firma del Funcionario que autoriza Sreeni Padmanabban (firmado) Teléfono No. 571-272-1600

REPORTE DE BÚSQUEDA INTERNACIONAL		Solicitud Internacional No. PCT/US04/13308
C. (Continuación) DOCUMENTOS CONSIDERADOS PERTINENTES		
Categoría*	Identificación del documento con indicación, en caso necesario, de los pasajes pertinentes	Número de reivindicaciones relevantes
A	BALDESSARINI et al. Hospital Use of Antipsychotic Agents in 1989 and 1993; Stable Dosing with Decreased length of Stay, American Journal of Psychiatry, Julio de 1995, Vol. 152, No. 7, páginas 1038-1044, véase páginas 1-8.	1-5, 12-16,





SEÑOR MINISTRO DE COMERCIO INDUSTRIA Y TURISMO
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E S D

SUPERINDUSTRIA Y COMERCIO
Rad. accion 05117551 00000001 Folios 28
Fecha (MM) 2006-01-05 17 12 17
Tramite 011 PCT-PATENT 379 FASE NNCI 329 COMPLEMEN
Dependencia 2009 DIVISION DE NUEVAS CREACIONES

REF
EXPEDIENTE 05 117551
PATENTE DERIVADOS DE CARBOSTIRILO Y ESTABILIZANTES
DEL ESTADO DE ÁNIMO PARA TRATAR TRASTORNOS
DEL MISMO
SOLICITANTE OTSUKA PHARMACEUTICAL CO LTD
TRAMITE 002
EVENTO 001
ACTUACIÓN 329- COMPLEMENTO DE INFORMACIÓN

El suscrito GERMAN ALONSO CUBILLOS MENDOZA abogado titulado e inscrito cedula en Bogotá bajo el No 19'397 479 portador de la Tarjeta Profesional No 38 422 del C Superior de la Judicatura y codificado ante esa División bajo el No 3667 en mi calidad de apoderado de la sociedad OTSUKA PHARMACEUTICAL CO LTD sociedad domiciliada en Tokio Japón allego los siguientes documentos a saber

- 1 Presento el poder para actuar y conforme a la ley debidamente Apostillado y traducido oficialmente
- 2 La certificación del Cónsul General de Colombia en Tokio Japón atestando que tuvo a la vista el certificado del registro mercantil de la sociedad solicitante OTSUKA PHARMACEUTICAL CO LTD
- 3 La presentación personal del poder y de la cesión de derechos ante Notario Publico (NOTARIAL CERTIFICATE) de los inventores de la patente de la referencia

Cordialmente


GERMAN ALONSO CUBILLOS MENDOZA
C C No 19 397 479 de Bogotá
T P No 38 422 del C S de la Judicatura
Código No 3667

183
~~402~~

Japanese Name Tate KIKUCHI, T
IBAMOTO v Tsuyoshi HIROSE.

done re por present GERMAN ALONSO
CUBILLOS MENDOZA de Calle 17 N 8-49
f 408 Bogotá, Colombia

recomendaciones son por el aspecto tanto para
solicitar y obtener de las cinas y autoridades
nacionales y de COLOMBIA

patente de invención por
DERIVADOS DE CARBOSTIRILO Y
ESTABILIZANTES DEL ESTADO DE ANIMO PARA
TRATAR TRASTORNOS DEL MISMO

OTSUKA PHARMACEUTICAL CO., LTD., una
compañi rra da bai l l ye d
J pō d 29 K d T k cho,
Chiyoda ku T ki pō

COLUMBIA

[illegible]

Dado y firmado en

2001

2005

~~Toshihiro Hirose~~
Toshihiro HIROSE

2005-1
FEB DE BOG
LA BA
DE COLOMBI

4 ENE 2006

2005

DR. DANIEL VELA PRIETO
NOTARIO 14 ENCARGADO

Yoshio SAMEZAWA,
Director of Intellectual Property Department

ASSIGNMENT OF PRIORITY RIGHT

We, the undersigned, Tetsuro KIKUCHI, Taro IWAMOTO and Tsuyoshi HIROSE, all citizens of Japan, residing at 157-13, Kawauchicho Komatsunishi, Tokushima-shi, Tokushima, Japan and 36 ~~Boulevard~~ ^{Boulevard T.I. 10/17/2015} Street, Princeton, New Jersey 08540, United States of America and 8-9-502, Sakoichibancho, Tokushima-shi, Tokushima, Japan, hereby declare that we filed the patent applications in U.S.A. on May 23, 2003 under No. 60/473378 for the invention relating to

"CARBOSTYRIL DERIVATEVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS"

And that we have assigned to OTSUKA PHARMACEUTICAL CO., LTD., a corporation organized under the laws of Japan, located at 2-9, Kanda-Tsukasacho, Chiyoda-ku, Tokyo, Japan, the entire rights of our priority right derived from the above-mentioned U.S. Patent Application pursuant to provisions of the International Convention for the Protection of Industrial Property so that said OTSUKA PHARMACEUTICAL CO., LTD., may apply for and obtain a patent in Corombia in their own names for the said invention claiming the priority right therefrom.

DATE

Tetsuro Kikuchi

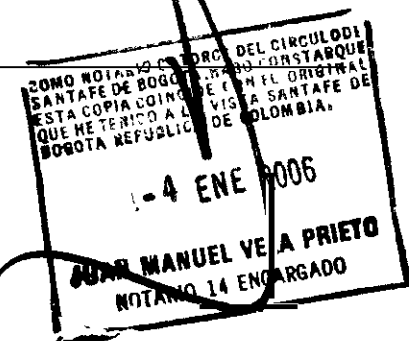
Tetsuro KIKUCHI

April 16, 2004Taro IWAMOTO

Taro IWAMOTO

October 17, 2005Tsuyoshi Hirose

Tsuyoshi HIROSE

April 16, 2004



185

004

Registration No 1161 of 2005

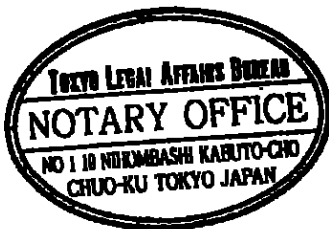
NOTARIAL CERTIFICATE

This is to certify that Katsuh sa MEREN
an attorney in fact of Tetsuro KIKUCHI Tsuyoshi HIROSE
Taro IWAMOTO and Yoshio SAMEZAWA (Director of Intellectual
Property Department of OTSUKA PHARMACEUTICAL CO LTD and
who is authori ed to sign to the attached document on behalf
of said company)

declared in my very presence that said Tetsuro KIKUCHI
T uyoshi HIROSE Taro IWAMOTO and Yo hio SAMEZAWA

had signed to the attached document and so the signatures
were true and genuine

Dated this 2nd day of December 2005

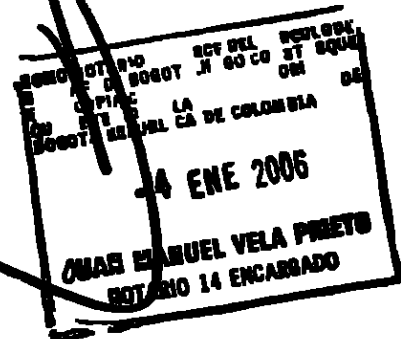


Masakazu Watanabe



Masakazu Watanabe

Notary attached to
The Tokyo Legal Affairs Bureau
No 1-10 Nihombashi Kabuto-cho
Chuo ku Tokyo Japan





囑託人 菊地哲朗 廣瀬毅 岩本太郎及び大塚製薬株式会社のため署名する権限を
付与されている門社 知的財産部部長 鮫澤由夫は 別添文書における署名が自己の
ものに相違ない旨 それぞれ代理人目連勝久を通し 本公証人に対し自認した

よって これを認証する

平成17年 12月 2日 本公証人役場において

東京都中央区日本橋兜町1番10号

東京法務局所属

公証人
Notary

後部
Masakazu

二
Watanabe
Masakazu Watanabe



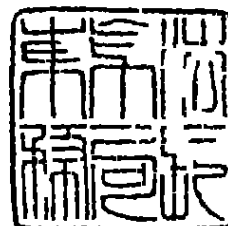
証 明

上記 名は 東京法務局所属公証人の署名に相違ないものであり かつ その押印は
真実のものであることを証明する

平成17年 12月 2日

東京法務局長

戸田信久



APOSTILLE
(Convention de La Haye du 5 octobre 1961)

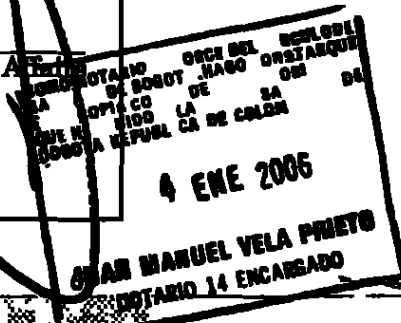
1 Country JAPAN
This public document
2 has been signed by Masakazu Watanabe
3 acting in the capacity of Notary of the Tokyo Legal Affairs Bureau
4 bears the seal/stamp of

Certified
6 DEC 2 2005

5 at Tokyo
7 by the Ministry of Foreign Affairs
8 05 No 036860
9 Seal/stamp

10 Signature
Kazutoyo OYABE

For the Minister for Foreign Affairs



ASIGNACIÓN, DERECHO DE PRIORIDAD

Nosotros los abajo firmantes Tetsuro KIKUCHI Taro IWAMOTO y Tsuyoshi HIROSE todos ciudadanos del Japón residentes en 157 13 Kawauchicho Komatsunishi Tokushima-shi Tokushima Japón y 36 Boudinot (Tl 10/17/2005) Street Princeton New Jersey 08540 Estados Unidos de América y 8-9-502 Sakoichibancho Tokushima-shi Tokushima Japón declaramos que la aplicación de la patente fue registrada en U S A el 23 de Mayo de 2003 bajo el No 60/473378 para la invención que se relaciona a

DERIVADOS DE CARBOSTIRIL Y ESTABILIZADORES DE HUMOR PARA TRATAR EL DESORDEN DE HUMOR

Y que hemos asignado a OTSUKA PHARMACEUTICAL CO LTD Corporación organizada bajo las leyes del Japón ubicada en 2 9 Kanda Tsukasacho Chiyoda ku Tokio Japón los completos Derechos de Prioridad derivados de dicha Aplicación de Patente Americana según la Convención Internacional para la Protección de la Propiedad Industrial para que OTSUKA PHARMACEUTICAL CO LTD pueda solicitar y obtener la patente en Colombia en sus propios nombres para dicha invención que exige el derecho de prioridad

Firmado por

Tetsuro KIKUCHI

Taro IWAMOTO

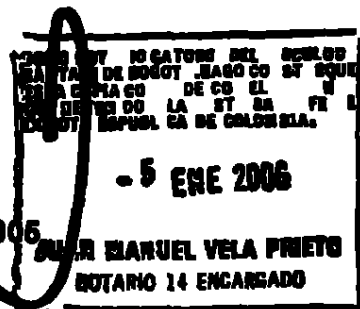
Tsuyoshi HIROSE

Fecha

16 de abril de 2004

17 de octubre de 2005

16 de abril de 2004



CARTEL NÚMERO 14

Registro N° 1161 de 2005

CERTIFICADO NOTARIAL

Este es para certificar que Katsuhisa MEREN es Abogado de Katsuhisa KIKUCHI Tsuyoshi HIROSE Taro IWAMOTO y Yoshio SAMEZAWA (Director del Departamento de Propiedad Intelectual de OTSUKA PHARMACEUTICAL CO LTD y quién está autorizado para firmar el documento adjunto en nombre de dicha compañía)

Declarado en mi presencia por los suscritos Tetsuro KIKUCHI Tsuyoshi
HIROSE Taro IWAMOTO y Yoshio SAMEZAWA

Han firmado el documento adjunto y que las firmas son reales y originales

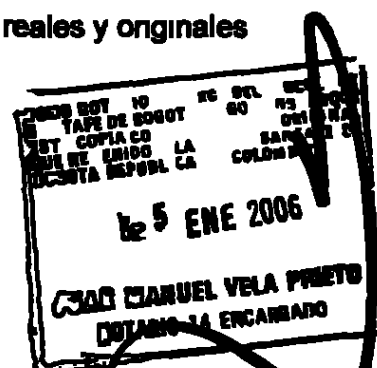
Fechado el 2 de Diciembre de 2005

Firmado por

Masakazu Watanabe

Notario adjunto a la Oficina de Asuntos Legales de Tokio.

No 1 10 Nihombashi Kabuto-cho Chuo-ku Tokio Japon



11 *E*

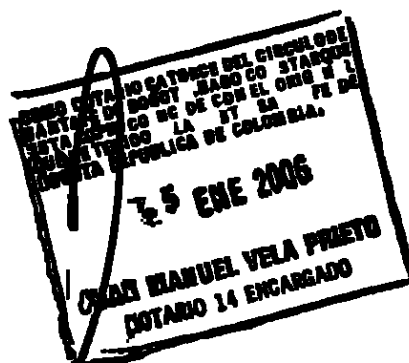
APOSTILLE

(Convention de La Haye du 5 de Octobre 1961)

- 1 País **JAPÓN**
- 2 Este documento publico
Ha sido firmado por **Masakazu Watanabe**
- 3 Actuando en su calidad de **Notario de la Oficina de Asuntos Legales de Tokio**
- 4 Lleva la firma y sello de

Certificado

- 5 En **TOKIO**
- 6 El **2 de Diciembre de 2005**
- 7 Por El **Ministro de Relaciones Exteriores**
- 8 **05 No 036860**
- 9 Sello **MINISTERIO DE RELACIONES EXTERIORES DE JAPON**
- 10 **Firmado y sellado por KAZUTOYO OYABE**
Por el Ministro de Relaciones Exteriores



**LA ANTERIOR TRADUCCIÓN FUE ELABORADA FIEL Y
CORRECTAMENTE DE SU ORIGINAL EN IDIOMA INGLES POR GABRIEL
RUEDA CHADID TRADUCTOR E INTERPRETE OFICIAL**

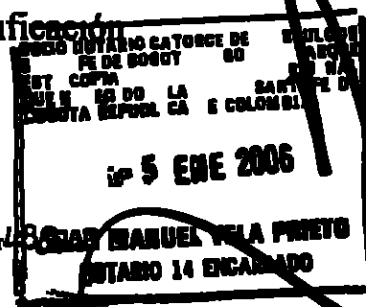
7 3 1
100 100
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En Español aparece la certificación de la EMBAJADA DE
COLOMBIA en Tokio – Japón de fecha 1 de mayo de 2003
donde se certifica que la compañía OTSUKA PHARMACEUTICAL CO
LTD está conformada de acuerdo a las leyes Japonesas y que se tuvo a la
vista el documento original traducido al español además que el objeto
social de la mencionada compañía se encuentra descrito en el certificado
que también se tuvo a la vista y hace la atestación de la conformación de la
Junta Directiva

Firma SERGIO SUAREZ ROA como Primer Secretario Encargado de
Funciones Consulares

El Jefe de la División de legalizaciones del Ministerio de Relaciones
Exteriores de Colombia certifica que la firma del Primer Secretario
Encargado de Las Funciones Consulares en Tokio Sr SERGIO SUAREZ
ROA es la registrada y que este funcionario se encontraba
desempeñando esas funciones para la época de la certificación

CORRESPONDE A LA LEGALIZACION N° 21648



Fu: *Manuel Vela Prieto*
Attorney at Law
Official Interpreter & Translator
Resolución 1029 Ministry of Justice
1997

**NO SE ASUME
RESPONSABILIDAD DEL TEXTO**

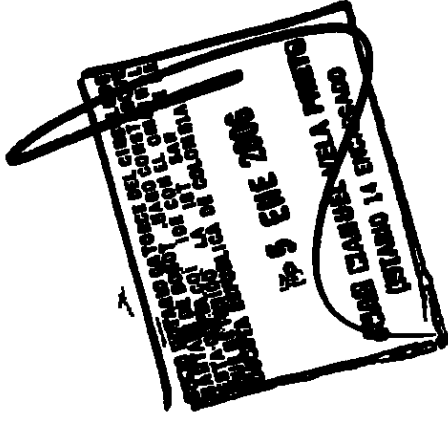
2003 MAY 15 P 1 14

**JEFES DE LEGALIZACIONES
SANTAFE DE BOGOTA D C**

**MINISTERIO DE RELACIONES
EXTERIORES**

18081

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FIRMAS



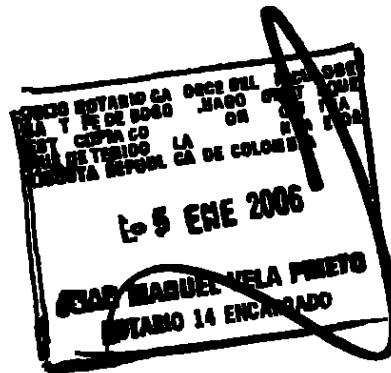
DECLARACION

Yo Katsuhisa MEREN de No 1359 5 1 511 Yonamoto Yachryo-shi
Chiba Ken Japón hago solemne y sinceramente esta declaración que
yo entiendo perfectamente las lenguas Japonesa e Inglesa y que el
documento anexo en versión española es una traducción parcial verdadera
y completamente fiel hecha por mí al undécimo (11) día de abril de 2003
del documento anexo

y que yo hago esta solemne declaración concientemente creyéndolo por ser la misma verdadera

Aparece firma ilegible

Katsuhisa MEREN



CERTIFICADO NOTARIAL

**Registro No 372 de 2003 suscrito y afirmado ante mí al undécimo (11) día
de abril de 2003**

Fu **Hernando Lopez Z**
Attorney at Law
Official Interpreter & Translator
Resolución 1025 Ministry of Justice
991

MASAKAZU WATANABE

Notario adjunto a la Oficina de Asuntos Legales de Tokio

No 1-10 Nihombashi Kabuto-cho

Chuo-ku Tokio Japon

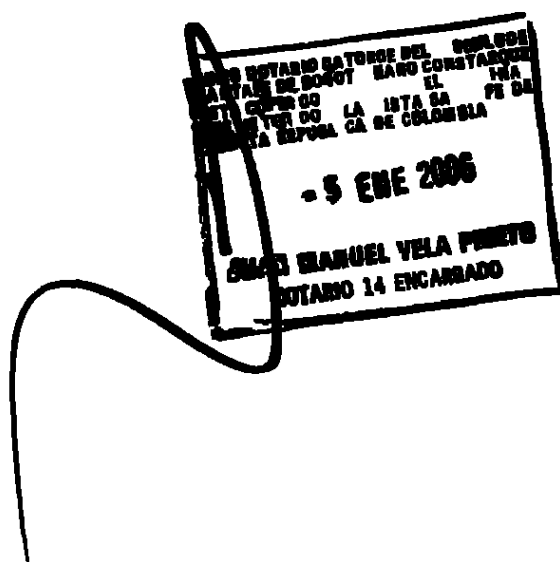
Aparece sello ovalado húmedo

Oficina de Asuntos Legales de Tokio

Oficina del Notario

No 1-10 Nihombashi Kabuto-cho

Chuo-ku Tokio Japon



Enis Hernández López Z.
 Attorney at Law
 Official Interpreter & Translator
 Resolution 1029 Ministry of Justice
 1991



EMBAJADA DE COLOMBIA
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No 19/2003

Tokio 1 de mayo de 2003



Suscrito Encargado de las Funciones Consulares en la Embajada de Colombia en
Tokio

CERTIFICA

Que la compañía OTSUKA PHARMACEUTICAL CO LTD está constituida de acuerdo con las leyes japonesas desde el 10 de agosto de 1984 y tiene su sede principal en la ciudad de Tokio - Japón según consta en la certificación de inscripción y registro de la Oficina de Asuntos Legales de Tokio número de registro de personería jurídica 0199-01-012988 documento cuyo original y traducción al español tuvo a la vista

Que el objeto social de la compañía OTSUKA PHARMACEUTICAL CO LTD se encuentra descrito en el certificado de inscripción y registro anexo a la presente

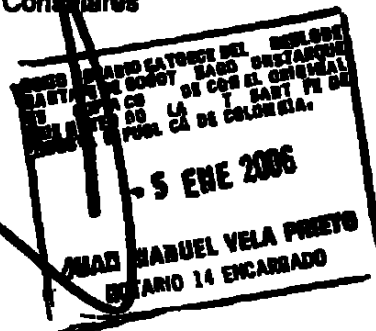
Que la junta directiva de la compañía OTSUKA PHARMACEUTICAL CO LTD está constituida por las siguientes personas: YUJIRO OTSUKA, en calidad de Director ICHIRO OTSUKA, en calidad de Director TATSUO HIGUCHI en calidad de director YUKIO KOBAYASHI en calidad de Director AKIHIKO OTSUKA, en calidad de Director TETSUO ARASHI en calidad de Director NAKAIMA OKABAYASHI en calidad de Director HIROMI YOSHIKAWA, en calidad de Director TADASU TOBA, en calidad de Director TATSUO HIGUCHI en calidad de Director Representante NAKAIMA OKABAYASHI en calidad de Director Representativo, MASAHIKO KATO en calidad de Auditor ISAO OTSUKA en calidad de Auditor TATSUYA OTSUKA, en calidad de Auditor

En constancia de lo anterior se firma en la ciudad de Tokio Japón a los un (1) día del mes de mayo de dos mil tres (2003)

SERGIO SUAREZ ROA
Primer Secretario

Encargado de Funciones Consulares

Fondo Rotatorio US\$ 100 00
Impuesto de Timbre US\$ 8 00
Total Derechos Cancelados US\$ 108 00



EMBAJADA DE COLOMBIA
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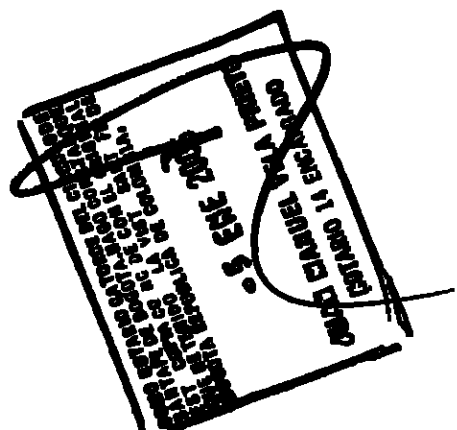
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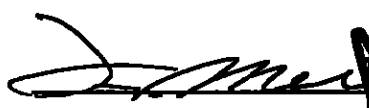
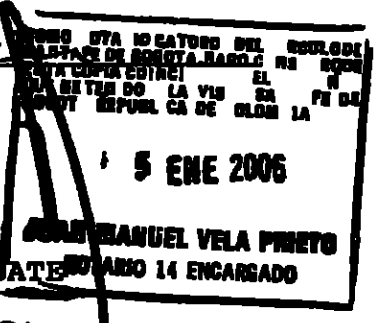
20-7 194
813



DECLARATION

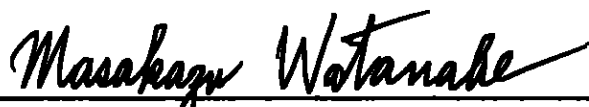
I Katsuhisa MEREN of No 1359 5-1-511 Yonamoto
Yachiyo shi Chiba ken Japan do solemnly and sincerely
declare that I well understand the Japanese language and
Spanish language and that the attached Spanish version
is partial true and faithful translation made by me
this 11th day of April 2003 of the attached document

And I made this solemn declaration conscientiously
believing the same to be true


Katsuhisa MEREN


NOTARIAL CERTIFICATE
Registration No 372 of 2003
Subscribed and affirmed before me
on the 11th day of April 2003




Masakazu Watanabe


Notary
No 1 10 Nihombashi Kabuto-cho
Chuo ku Tokyo Japan

Certificado de todos asuntos actuales

Otsuka Pharmaceutical Co Ltd
2 9 Kanda Tsukasacho Chiyoda ku, Tokio Japón
Número de corporación, etc 0199-01-012986

| | | |
|---|--|-----------------------------------|
| Razón social | Otsuka Pharmaceutical Co Ltd | |
| Oficina principal | 2-9 Kanda Tsukasacho Chiyoda ku, Tokio Japón | |
| Método de anuncio oficial | publicar en el boletín oficial | |
| Fecha de fundación de la corporación | 10 de agosto de 1964 | |
| Objetos | 1 Producción, venta, exportación e importación de productos farmacéuticos, productos farmacéuticos para animales cuasi drogas, examen clínico equipo médico insecticida agrícola, cosméticos, bebida alcohólica, productos alimenticios, y artículos de uso diario y en general
2 Todos los negocios relacionados a los negocios arriba mencionados | |
| Número total de las acciones que se emiten | 48 000 000 | |
| Número total clases y respectivos números de de las acciones emitidas | Número total de las acciones emitidas 12 000 000 | |
| Capital | 6 000 000 000 yenes | |
| Estipulación sobre la restricción de la transferencia de las acciones | La transferencia de las acciones requiere la aprobación de la junta directiva. | |
| Asuntos sobre directores | Director Yujiro Otsuka | Registrado
29 de junio de 2001 |
| | Director Ichiro Otsuka | Registrado
29 de junio de 2001 |
| | Director Tatsuo Higuchi | Registrado
29 de junio de 2001 |
| | Director Yukio Kobayashi | Registrado
29 de junio de 2001 |

COPIA NOT. EN LA OFICINA DEL GUB. DE
BARTAR DE BOGOT. J. RAMO GONZALEZ
EST. COPIA CO. HEIDE CON EL GUB. DE
EST. DE 1980 LA 1ST. SAN
GOBIERNO REPUBLICA DE COLOMBIA
25 JUN 2005
JUAN MANUEL VELAZQUEZ
NOTARIO 14 ENCARGADO

| | | |
|--|---|-----------------------------------|
| | Director Akihiko Otsuka | Registrado
29 de junio de 2001 |
| | Director Tetsuo Arashi | Registrado
29 de junio de 2001 |
| | Director Nakaima Okabayashi | Registrado
29 de junio de 2001 |
| | Director Hiromi Yoshikawa | Registrado
29 de junio de 2001 |
| | Director Tadasu Toba | Registrado
29 de junio de 2001 |
| | Director Representativo Tatsuo Higuchi | Registrado
29 de junio de 2001 |
| | Director Representativo
Nakaima Okabayashi | Registrado
29 de junio de 2001 |
| | Auditor Masahiko Kato | Registrado
29 de junio de 2001 |
| | Auditor Isao Otsuka | Registrado
29 de junio de 2001 |
| | Auditor Tatsuya Otsuka | Registrado
29 de junio de 2001 |
| | | |
| | | |

Va omitido lo demás

Este documento es el que certifica que los asuntos arriba mencionados son el
total registrado en el registro y válido actualmente
14 de enero de 2003

ESTADO DE CUENTA DEL CIERRE
DEL REGISTRO DE BANCOS
DEL SUPLENTE CON EL CIERRE
DEL REGISTRO LA VENTA EN
DEL REGISTRO DE BANCOS
5 ENE 2006
SADATOSHI KATANO
OFICIAL ENCARGADO DEL REGISTRO
OFICINA DE ASUNTOS LEGALES DE
TOKIO

現在事項全部証明書

東京都千代田区神田司町二丁目9番地
大塚製薬株式会社
会社法人等番号 0199-01-012986

| | | |
|----------------------|---|---------------|
| 商号 | 大塚製薬株式会社 | |
| 本店 | 東京都千代田区神田司町二丁目9番地 | |
| 公告をする方法 | 官報に掲載して之を為すものとする | |
| 会社成立の年月日 | 昭和39年8月10日 | |
| 目的 | 1. 医薬品、動物用医薬品、医薬部外品、臨床検査 医療用具、農業、化粧品
酒類、食料品、日用品雑貨の製造 販売、輸出並びに輸入
2. 上記に附帯関連する一切の事業 | |
| 発行する株式の総数 | 4800万株 | |
| 発行済株式の総数
並びに種類及び数 | 発行済株式の総数
1200万株 | |
| 資本の額 | 金60億円 | |
| 株式の譲渡制限に関する規定 | 株式の譲渡は取締役会の承認を要する | |
| 役員に関する事項 | 取締役 | 大塚 雄 二 郎 |
| | | 平成13年 6月27日重任 |
| | | 平成13年 6月29日登記 |
| | 取締役 | 大塚 一 郎 |
| | | 平成13年 6月27日重任 |
| | | 平成13年 6月29日登記 |
| | 取締役 | 樋口 達 夫 |
| | | 平成13年 6月27日重任 |
| | | 平成13年 6月29日登記 |
| | 取締役 | 上 林 幸 雄 |
| | | 平成13年 6月27日重任 |
| | | 平成13年 6月29日登記 |
| | 取締役 | 大塚 明 彦 |
| | | 平成13年 6月27日重任 |
| | | 平成13年 6月29日登記 |

NOTARIO DEL CIRCULO DE
LA VISTA-SANTAFE DE
BOGOTA-BOGOTA
5 ENE 2008
JOSE MANUEL VELA PIRETO
NOTARIO 14 ENCARGADO

代田区神田司町二丁目9番地
株式会社
法人番号 0199-01-012986

| | | |
|--|-----------------------------------|--------------------------------|
| | 取締役 嵐 哲夫 | 平成13年 6月27日就任
平成13年 6月29日登記 |
| | 取締役 岡 林中 今 | 平成13年 6月27日就任
平成13年 6月29日登記 |
| | 取締役 吉 川 博 巳 | 平成13年 6月27日就任
平成13年 6月29日登記 |
| | 取締役 鳥 羽 董 | 平成14年 6月26日就任
平成14年 7月2日登記 |
| | 東京都世田谷区松原三丁目25番19号
代表取締役 樋口 達夫 | 平成13年 6月27日就任
平成13年 6月29日登記 |
| | 東京都文京区根津一丁目16番9号
代表取締役 岡 林 中 今 | 平成14年 6月26日就任
平成14年 7月2日登記 |
| | 監査役 加 藤 昌 彦 | 平成13年 6月27日就任
平成13年 6月29日登記 |
| | 監査役 大 塚 公 | 平成13年 6月27日就任
平成13年 6月29日登記 |
| | 監査役 大 塚 達 也 | 平成13年 6月27日就任
平成13年 6月29日登記 |
| | 支店 | |
| | 1 札幌市中央区南一条西七丁目12番 | |
| | 2 名古屋市中区丸ノ内三丁目13番2号 | |
| | 3 福岡市博多区奈良屋町13番13号 | |
| | 5 横浜市本山三丁目3番89号 | |
| | 6 仙台市青葉区上杉五丁目3番36号 | 平成11年 7月 8日移転
平成11年 7月 8日登記 |

整理番号 エ754876

下線のあるものは抜粋事項である とを示す

2/3

千代田区 田司町二丁目9番地
株式会社
法人番号 0199-01-012986

| | | |
|----|---------------------------|--------------------------------|
| 7 | 千葉市中央区祐光一丁目5番2号 | |
| 8 | 静岡市西中原一丁目2番11号 | |
| 9 | 大阪市北区中之島一丁目2番40号 | |
| 10 | 京都市下京区烏丸通仏光寺下ノ大政所町680番地の1 | |
| 11 | 広島市西区楠木町一丁目14番31号 | |
| 12 | 神戸市中央区磯辺通三丁目1番7号 | 平成11年 6月14日移転
平成11年 6月15日登記 |
| 13 | 埼玉県上尾市大字瓦葺字観ヶ谷戸929番地1 | |
| 14 | 横浜市西区北幸二丁目15番1号 | |
| 15 | 東京都千代田区神田司町二丁目9番地 | |
| 16 | 新潟県新潟市近江260番地1の2 | |
| 17 | 石川県金沢市階江町中丁160-1 | 平成13年 4月 1日設置
平成13年 4月 3日登記 |

GOBIERNO GENERAL DEL DEPARTAMENTO DE BOYOTÁ, MAGD. CONSTANCIA
DE LOS ACTOS DE QUEL USU NAT
HA REVISADO A LA VISTA DE LA FE DE
LA REPUBLICA DE COLOMBIA.
6-8 ENE 2006
JUAN MANUEL YEJA-PINERO
NOTARIO LA ENCARRADO

これは登記簿に記載されている現効力を有する事項の全部であることを証明した書面である

平成15年 1月14日
東京法務局
登記官

片岡 貞



整理番号 エ754876

下線のあるものは抹消事項である とを示す