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

Reference Example 4

Preparation of 15 mg tablets containing type I crystals of aripiprazole anhydride obtained in Reference Example 2.

Type-I crystals of aripiprazole anhydride (525 g), lactose (1,995 g), corn starch (350 g) and crystalline cellulose (350 g) were charged in a fluidized bed granulating dryer (Flow coater FLO-5, manufactured by FREUND INDUSTRIAL CO., LTD.), and these granulating ingredients were mixed by fluidizing for about 3 minutes with an inlet air temperature at 70°C and air flow rate of 3 m^3/min. Further, the granulating ingredients were upon continued fluidizing under the same condition and sprayed about 1,400 g of the aqueous solution to obtained wet granules. The wet granules were dried under inlet air at temperature at 80°C, for about 15 minutes. The obtained dried granules contained 4.3% of water. (Yield: 99%). The dried granules were subjected to sizing by passing to a sieve of 710 μm.

About 1% by weight of magnesium stearate was added to the sized granules and mixed, then the granules were supplied to a tablet machine (Rotary

single tablet press 12HUK: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), there were obtained tablets, each having 95 mg of weight.

Water content of the tablets was measured according to volumetric titration method (Karl-Fischer method) described in water content measuring method in Japanese Pharmacopoea or the electrical quantity titration method.

Water content measuring method:

Sample (0.1 to 0.5 g) (in case of a tablet, 1 tablet was used) was weighed precisely, and the water content was measured by use of a water content measuring equipment.

Volumetric titration:

Automated water content measuring equipment

Model: KF-06 (manufacture by MITSUBISHI CHEMICAL CORP.)

Electrical quantity titration method:

Automated micro-water content measuring equipment

Model: AQ-7F (manufactured by HIRANUMA SANGYO CO., LTD.)

Automated water vaporization equipment Model: LE-20S (manufactured by HIRANUMA SANGYO CO., LTD.)

Heating temperature: 165±10°C

Nitrogen gas flow rate: about 150 ml/min.

Reference Example 5

Preparation of 15 mg tablets containing type B crystals of aripiprazole anhydride

Type B crystals of aripipraole anhydride (4,500 g), lactose (17,100 g), corn starch (3,000 g) and crystalline cellulose (3,000 g) were charged in a fluidized bed granulating dryer (NEW-MARUMERIZER Model: NQ-500, manufactured by FUJI PAUDAL CO., LTD.), and these granulating ingredients were mixed by fluidizing for about 3 minutes with an inlet air temperature at 70°C, air flow rate of 10 to 15 m^3/min. Further, the granulating ingredients were upon continued fluidizing under the same condition, and sprayed about 12,000 g of 5% aqueous solution of hydroxypropyl celulose to obtained wet granules. The wet granules were dried under inlet air at temperature at 85°C, for about 28 minutes. The thus obtained dried granules contained 3.8% of water (measured by the method according to Reference Example 4). (Yield: 96%). The dried granules were subjected to sizing by passing to a sieve of 850 μm.

About 1% by weight of magnesium stearate was added to the sized granules and mixed, then the granules were supplied to a tablet machine (Rotary single tablet press 12HUK: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), there were obtained tablets, each having 95 mg of weight.

Example 1

500.3 g of the aripiprazole hydrate crystals obtained in Reference Example 3 were milled using a sample mill (small 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 completed in 3 minutes, resulting in 474.6 g (94.9%) of Aripiprazole Hydrate A powder.

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 70°C.

The Aripiprazole Hydrate A (powder) obtained above exhibited an ^{1}H-NMR (DMSO-d_6, TMS) spectrum which was substantially the same as the ^{1}H-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 the same as the powder x-ray diffraction spectrum shown in Figure 3. Specifically, it had characteristic peaks at 2θ = 12.6°, 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 water molecule) between 60-120°C--clearly different from the endothermic curve of unmilled aripiprazole hydrate (see Figure 6).

Example 2

450 g of the Aripiprazole Hydrate A (powder) obtained in Example 1 was dried for 24 hours at 100°C using a hot air dryer to produce 427 g (yield 98.7%) 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 ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially the same as the ^{1}H-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 (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 same as the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they had characteristic peaks at 2θ = 11.0°, 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 141.5°C in thermogravimetric/differential thermal analysis.

The Aripiprazole Anhydride Crystals B obtained above exhibited an endothermic peak near about 140.7°C in differential scanning calorimetry.

Even when the Aripiprazole Anhydride Crystals B obtained above were left for 24 hours in a dessicator set at humidity 100%, temperature 60°C, they did not exhibit hygroscopicity exceeding 0.4% (See Table 1 below).

Example 3

44.29 kg of the Aripiprazole Hydrate A (powder) obtained in Example 1 was dry heated for 18 hours in a 100°C hot air dryer and then heated for 3 hours at 120°C to produce 42.46 kg (yield 99.3%) of Aripiprazole Anhydride Crystals B.

The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way did not exhibit hygroscopicity of more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Example 4

40.67 kg of the Aripiprazole Hydrate A (powder) obtained in Example 1 was dry heated for 18 hours in a 100°C hot air dryer and then heated for 3 hours at 120°C to produce 38.95 kg (yield 99.6%) of Aripiprazole Anhydride Crystals B.

The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way did not exhibit hygroscopicity of more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Examples 5-10 are useful for injectable or oral solution formulations but not solid dose formulations since they were made by heating Conventional Anhydride or Conventional Hydrate instead of Hydrate A.

Example 5

The hygroscopic aripiprazole anhydride crystals obtained in Reference Example 1 were heated for 50 hours at 100°C using the same methods as in Example 2. The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way did not exhibit hygroscopicity of more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Example 6

The hygroscopic aripiprazole anhydride

crystals obtained in Reference Example 1 were heated for 3 hours at 120°C using the same methods as in Example 2. The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way did not exhibit hygroscopicity of more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Example 7

The hygroscopic aripiprazole anhydride crystals obtained in Reference Example 2 were heated for 50 hours at 100°C using the same methods as in Example 2. The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way did not exhibit hygroscopicity of more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Example 8

The hygroscopic aripiprazole anhydride crystals obtained in Reference Example 2 were heated for 3 hours at 120°C using the same methods as in Example 2. The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way did not exhibit hygroscopicity of more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Example 9

The aripiprazole hydrate crystals obtained in Reference Example 3 were heated for 50 hours at 100°C using the same methods as in Example 2. The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way did not exhibit hygroscopicity of more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Example 10

The aripiprazole hydrate crystals obtained in Reference Example 3 were heated for 3 hours at 120°C using the same methods as in Example 2. The physicochemical properties of the resulting Aripiprazole Anhydride Crystals B were the same as the physicochemical properties of the Aripiprazole Anhydride Crystals B obtained in Example 2.

The Aripiprazole Anhydride Crystals B obtained in this way exhibited hygroscopicity of no more than 0.4% even when left for 24 hours in a dessicator set at humidity 100%, temperature 60°C (see Table 1 below).

Example 11 (Preparation of type C crystals of aripiprazole anhydride)

100 Miligrams of type-I crystals of aripiprazole anhydride obtained in Reference Example 2 were heated about 145°C (±3°C). In this occasion, there was observed the phenomena that the crystals were once melted, then again crystallized. After that, 100 mg (yield: 100%) of Type C crystals of aripiprazole anhydride were obtained. The melting point of the crystals was 150°C. The crystals were colorless prism form.

The type C crystals of aripiprazole anhydride obtained above had an endothermic curve which was substantially identical to the endothermic curve of

thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) shown in Figure 8. Specifically, it showed the endothermic curve around 150.2°C.

The type C crystals of aripiprazole anhydride thus obtained exhibited an ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 9. Specifically, it had the 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 type C crystals of aripiprazole anhydride obtained above had a powder X-ray diffraction spectrum which was substantially identical to the powder X-ray diffraction spectrum shown in Figure 10. Specifically, it had the characteristic peaks at 2θ = 12.6°, 13.7°, 15.4°, 18.1°, 19.0°, 20.6°, 23.5° and 26.4°.

The type C crystals of aripiprazole anhydride obtained above had an IR spectrum which was substantially identical to the IR (KBr) spectrum shown in Figure 11. Specifically, it had the characteristic infrared absorption bands at 2939, 2804, 1680, 1375 and 780 cm^{-1}.

The type C crystals of aripiprazole anhydride obtained above exhibited a solid ^{13}C-NMR spectrum, which was substantially identical to the solid ^{13}C-NMR spectrum shown in Figure 12. Specifically, it had the characteristic peaks at 32.8 ppm, 60.8 ppm, 74.9 ppm, 104.9 ppm, 152.2 ppm, 159.9 ppm and 175.2 ppm.

According to the above-mentioned data on endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) and powder X-ray diffraction spectrum, the formation of the type C crystals of aripiprazole anhydride was confirmed.

When the type C crystals of aripiprazole anhydride crystals obtained above were left for 24 hours in a dessicator where the conditions were set at humidity 100%, and temperature 60°C, then the crystals did not exhibit hygroscopicity higher than 0.4% (see, Table 1 below).

Example 12 (Preparation of type D crystals of aripiprazole anhydride)

The type-I crystals of aripiprazole anhydride obtained in Reference Example 2 were added in 200 ml of toluene, and dissolved by heating at 74°C. After confirmed that it was dissolved completely, the toluene solution was cooled to 7°C, and the precipitated crystals were collected by filtration. The crystals were subjected to air-drying as they were so as to obtain 17.9 g (yield: 89.5%) of type D crystals of

aripiprazole anhydride.

The type D crystals of aripiprazole anhydride obtained above had an endothermic curve substantially identical to the endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) shown in Figure 13. Specifically, it had the endothermic peaks at about 136.8°C and about 141.6°.

The type D crystals of aripiprazole anhydride obtained above exhibited ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 14. Specifically, they had the 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 type D crystals of aripiprazole anhydride obtained above had a powder X-ray diffraction spectrum which was substantially identical to the powder X-ray diffraction spectrum shown in Figure 15. Specifically, it had the characteristic peaks at 2θ = 8.7°, 11.6°, 16.3°, 17.7°, 18.6°, 20.3°, 23.4° and 25.0°.

The type D crystals of aripiprazole anhydride obtained above had an IR spectrum which was substantially identical to the IR (KBr) spectrum shown

in Figure 16. Specifically, it had the characteristic infrared absorption bands at 2946, 1681, 1375, 1273, 1175 and 862 cm^{-1}.

The type D crystals of aripiprazole anhydride obtained above exhibited a solid ^{13}C-NMR spectrum which was substantially identical to the solid ^{13}C-NMR spectrum shown in Figure 17. Specifically, it had the characteristic peaks at 32.1 ppm, 62.2 ppm, 66.6 ppm, 104.1 ppm, 152.4 ppm, 158.5 ppm and 174.1 ppm.

According to the above-mentioned data on the endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) and powder X-ray diffraction spectrum, the formation of type D crystals of aripiprazole anhydride was confirmed.

When the type D crystals of aripiprazole anhydride crystals obtained above were left for 24 hours in a dessicator where the conditions were set at humidity 100%, and temperature 60°C, the crystals did not have hygroscopicity higher than 0.4% (see, Table 1 below).

Example 13 (Preparation of type D crystals of aripiprazole anhydride)

1,200 Grams of the type-I crystals of aripiprazole anhydride obtained in Reference Example 2 were dissolved in 18 liters of toluene, with heating. This toluene solution was cooled to 40°C, and 36 g of type-D crystals of aripiprazole anhydride obtained in

Example 12 were added as seed crystals, then the solution was cooled to 10°C and allowed to stand as it is. The precipitated crystals were collected by filtration, dried at 60°C for 18 hours to obtain 1,073 g (yield: 86.8%) of type D crystals of aripiprazole anhyride (purity: 100%). The crystals were colorless plate form.

The type D crystals of aripiprazole anhydride had an endothermic curve substantially identical to the endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) shown in Figure 13. Specifically, it had the endothermic peaks around about 136.8°C and about 141.6°.

The type D crystals of aripiprazole anhydride obtained above exhibited an ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 14. Specifically, it had the 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 type D crystals of aripiprazole anhydride obtained above had a powder X-ray diffraction spectrum which was substantially identical to the powder X-ray

diffraction spectrum shown in Figure 15. Specifically, it had the characteristic peaks at 2θ = 8.7°, 11.6°, 16.3°, 17.7°, 18.6°, 20.3°, 23.4° and 25.0°.

The type D crystals of aripiprazole anhydride obtained above had an IR spectrum which was substantially identical to the IR (KBr) spectrum shown in Figure 16. Specifically, it had characteristic infrared absorption bands at 2946, 1681, 1375, 1273, 1175 and 862 cm^{-1}.

The type D crystals of aripiprazole anhydride obtained above had a solid ^{13}C-NMR spectrum which was substantially identical to the solid ^{13}C-NMR spectrum shown in Figure 17. Specifically, it had the characteristic peaks at 32.1 ppm, 62.2 ppm, 66.6 ppm, 104.1 ppm, 152.4 ppm, 158.5 ppm and 174.1 ppm.

According to the above-mentioned data on the endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) and powder X-ray diffraction spectrum, the formation of type D crystals of aripiprazole anhydride was confirmed.

When the type D crystals of aripiprazole anhydride crystals obtained above were left for 24 hours in a dessicator where the conditions were set at humidity 100%, and temperature 60°C, the crystals did not exhibit hygroscopicity higher than 0.4% (see, Table 1 below).

Example 14 (Preparation of type E crystals of aripiprazole anhydride)

40 Grams of type-I crystals of aripiprazole anhydride obtained in Reference Example 2 was dissolved in 1000 ml of acetonitrile with heating at 80°C. This acetonitrile solution was cooled to about 70°C by taking for about 10 minutes, and was kept at this temperature for about 30 minutes to precipitate the seed crystals. Next, the temperature of said solution was slowly risen to 75°C, and the crystals were grown up by keeping this temperature for 1 hour. Then, the solution was cooled to 10°C by taking about 4 hours, and the precipitated crystals were collected by filtration. Thus obtained crystals were subjected to air-drying overnight, there were obtained 37.28 g (yield: 93.2%) of type E crystals of aripiprazole anhydride (purity: 100%). The melting point of these crystals was 145°C, and the crystals were colorless needle form.

The type E crystals of aripiprazole anhydride had an endothermic curve substantially identical to the endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) shown in Figure 18. Specifically, it had endothermic peak at about 146.5°.

The type E crystals of aripiprazole anhydride obtained above exhibited an ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially identical to the ^{1}H-NMR

spectrum (DMSO-d_6, TMS) shown in Figure 19. Specifically, it had the 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 type E crystals of aripiprazole anhydride obtained above had a powder X-ray diffraction spectrum which was substantially identical to the powder X-ray diffraction spectrum shown in Figure 20. Specifically, it had the characteristic peaks at 2θ = 8.0°, 13.7°, 14.6°, 17.6°, 22.5° and 24.0°.

The type E crystals of aripiprazole anhydride obtained above had an IR spectrum which was substantially identical to the IR (KBr) spectrum shown in Figure 21. Specifically, it had the characteristic infrared absorption bands at 2943, 2817, 1686, 1377, 1202, 969 and 774 cm^{-1}.

According to the data on the endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) and powder X-ray diffraction spectrum, the formation of type E crystals of aripiprazole anhydride was confirmed.

When the type E crystals of aripiprazole anhydride obtained above were left for 24 hours in a

dessicator where the conditions were set at humidity 100%, and temperature 60°C, the crystals did not exhibit hygroscopicity higher than 0.4% (see, Table 1 below).

Example 15 (Preparation of type F crystals of aripiprazole anhydride)

140 Grams of type-I crystals of aripiprazole anhydride obtained in Reference Example 2 were suspended in 980 ml of acetone and continued to reflux for 7.5 hours with stirring. Next, the suspension was filtered in hot condition, and crystals separated out were subjected to air-drying for 16 hours at room temperature, there was obtained 86.19 g (yield: 61.6%) of type F crystals of aripiprazole anhydride (purity: 100%). The crystals were colorless prism form.

The type F crystals of aripiprazole anhydride had an endothermic curve substantially identical to the endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) shown in Figure 22. Specifically, it had the exothermic peaks at about 137.5°C and about 149.8°C.

The type F crystals of aripiprazole anhydride obtained above exhibited an ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 23. Specifically, it had the 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 type F crystals of aripiprazole anhydride obtained above had a powder X-ray diffraction spectrum which was substantially identical to the powder X-ray diffraction spectrum shown in Figure 24. Specifically, it had the characteristic peaks at 2θ = 11.3°, 13.3°, 15.4°, 22.8°, 25.2° and 26.9°.

The type F crystals of aripiprazole anhydride obtained above had an IR spectrum which was substantially identical to the IR (KBr) spectrum shown in Figure 25. Specifically, it had the characteristic infrared absorption bands at 2940, 2815, 1679, 1383, 1273, 1177, 1035, 963 and 790 cm^{-1}

According to the data on endothermic curve of thermogravimetric/differential thermal analysis (heating rate: 5°C/minute) and powder X-ray diffraction spectrum, the formation of type F crystals of aripiprazole anhydride was confirmed.

When the type F crystals of aripiprazole anhydride crystals obtained above were left for 24 hours in a dessicator where the conditions were set at humidity 100%, and temperature 60°C, the crystals did

not exhibit hygroscopicity higher than 0.4% (see, Table 1 below).

Table 1

Sample	Initial Moisture Content (%)	Moisture Content After 24 hrs (%)
Reference Example 1	0.04	3.28
Reference Example 2	0.04	1.78
Example 2	0.04	0.04
Example 3	0.02	0.02
Example 4	0.02	0.02
Example 5	0.04	0.04
Example 6	0.04	0.04
Example 7	0.04	0.03
Example 8	0.04	0.03
Example 9	0.03	0.01
Example 10	0.05	0.05
Example 11	0.03	0.03
Example 12	0.04	0.03
Example 13	0.04	0.03
Example 14	0.06	0.09
Example 15	0.04	0.04

Example 16

a) Type I crystals of aripiprazole anhydride (10 g) obtained in Reference Example 2 was charged in a stainless steel round tray (diameter: 80 mm), and heated to about 170°C so as to melted completely. When this melted liquid was cooled, then it solidified

clarity with pale brawn in color, the solid was peeled off from the stainless steel round tray, there was obtained 9.8 g (yield: 98%) of glassy state of aripiprazole anhydride. The obtained glassy state product was characterized by having no significant peak observed in a powder X-ray determination. (cf. Figure 31).

According to the thermogravimetric/ differental thermal analysis (heating rate: 5°C/ minute), as shown in Figure 30, an exothermic peak of type B crystals of aripiprazole anhydride was observed at around 86.5°C. While, an endothermic peak of type B crystals of aripiprazole anhydride owing to melting was observed at around 140.1°C.

b) When the glassy state of aripiprazole anhydride obtained in Example 16-a) were charged in a sealed vessel and left to stand at room temperature for about 6 months, then type G crystals of aripiprazole anhydride having white in color was obtained by changing the color from pale brown (25 g, yield: 100%). Melting point: 138 to 139°C.

The type G crystals of aripiprazole anhydride had an endothermic curve which was substantially identical to the thermogravimetric/differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 26, more particulaly, it has an endothermic peak around 141.0°C and an exothermic peak around 122.7°C.

The type G crystals of aripiprazole anhydride obtained as above exhibited an ^{1}H-NMR spectrum which was substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 27. Specifically, it has 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 type G crystals of aripiprazole anhydride obtained as above had a powder X-ray diffraction spectrum which was substantially identical to the powder X-ray diffraction spectrum shown in Figure 28. Specifically, it has characteristic peak at 2θ = 10.1°, 12.8°, 15.2°, 17.0°, 17.5°, 19.1°, 20.1°, 21.2°, 22.4°, 23.3°, 24.5° and 25.8°.

The type G crystals of aripiprazole anhydride obtained above had an IR spectrum which was substantially identical to the IR (KBr) spectrum shown in Figure 29. Specifically, it has clear infrared absorption bands at 2942, 2813, 1670, 1625, 1377, 1195, 962 and 787 cm^{-1}.

Example 17

a) Preparation of granules of 30 mg tablets containing

type B crystals of aripiprazole anhydride for additional drying

Type B crystals of aripiprazole anhydride (1,500 g), lactose (5,700 g), corn starch (1,000 g) and crystalline cellulose (1,000 g) were charged in a fluidized bed granulating dryer (Flow Coater Model FLO-5M; manufactured by FROINT SANGYO KABUSHIKI KAISHA), and these granulating ingredients were mixed by fluidizing for about 3 minutes with an inlet air temperature at 60°C, air flow rate of 3 to 4 m^3/min. Further, the granulating ingredients were continued fluidizing under the same condition, and sprayed with about 4,000 g of 5% aqueous solution of hydroxypropyl celulose to obtain wet granules. The wet granules were dried under an inlet air temperature at 85°C, for about 20 minutes. The obtained dried granules contained 3.8% of water (measured by the method according to Reference Example 4).

b) The dried granules (4 kg) obtained in Example 17-a) were sized by use of a mill (FIORE F-0: manufactured by TOKUJU CORPORATION).

The sized granules (3 kg) were charged in a fluidized bed granulating dryer (Flow Coater Model FLO-5M; manufactured by FREUND INDUSTRIAL CO., LTD.), and these granulating ingredients were dried under an inlet air temperature at 85°C, and air flow rate of 2 m^3/min for 2 hours. The obtained dried granules contained 3.6% of water (measured by the method according to

Reference Example 4).

About 1% by weight of of magnesium stearate was added to the sized granules and mixed, then the granules were supplied to a tabletting machine (a Rotary single tablet press, Model VIRGO: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), and there were obtained tablets, each having 190 mg of weight.

c) The dried granules (3 kg) obtained in Example 17-a) were charged in a vacuum dryer (vacuum granulating dryer model; VG-50: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), and dried at 70°C of a jacket temperature, under a reduced pressure at 5 torr of degree of vacumm for 1 hour. The thus obtained dried granules contained 3.1% of water (measured by the method according to Reference Example 4). The dried granules were subjected to sizing by passing to a sieve of 850 μm.

About 1% by weight of magnesium stearate was added to the sized granules and mixed, then the granules were supplied to a tablet machine (Rotary single tablet press, Model VIRGO: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), and there were obtained tablets, each having 190 mg of weight.

Example 18

a) Preparation of 30 mg tablets containing type B crystals of aripiprazole anhydride

Aripiprazole anhydride (type B crystals)

(4,500 g), lactose (17,100 g), corn starch (3,000 g) and crystalline cellulose (3,000 g) were charged in a fluidized bed granulating dryer (NEW-MARUMERIZER Model: NQ-500, manufactured by FUJI PAUDAL CO., LTD.), and these granulating ingredients were mixed by fluidizing for about 3 minutes with an inlet air temperature at 70°C, air flow rate of 10 - 15 m^3/min. Further, the granulating ingredients were continued fluidizing under the same condition, and were sprayed with about 12,000 g of 5% aqueous solution of hydroxypropyl celulose to obtain wet granules. The wet granules were dried under inlet air at temperature of 85°C, for about 30 minutes. The obtained dried granules contained 3.6% of water (measured by the method according to Reference Example 4). (Yield: 96%). The dried granules were sized by passing to a mill (FIOLE F-0: manufactured by TOKUJU CORPORATION).

About 1% by weight of magnesium stearate was added to the sized granules and mixed, then the granules were supplied to a tablet machine (a Rotary single tablet press, VIRGO: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), and there were obtained tablets, each having 190 mg of weight.

b) The tablets (5 kg) obtained in Example 18-a) were charged in a fan dryer (AQUA COATER AQC-48T, manufactured by FREUND INDUSTRIAL CO., LTD.), and dried under inlet air at temperature of 90°C, air flow rate of 2 m^3/min for 6 hours. The obtained dried granules

contained 3.3% of water (measured by the method according to Reference Example 4).

c) The dreid tablets (3 kg) obtained in Example 18-a) were charged in a vacuum dryer (vacuum granulating dryer, VG-50: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), and dried at 80°C of a jacket temperature, under reduced pressure of 5 torr of degree of vacumm for 4 hours. The obtained dried tablets contained 2.7% of water (measured by the method according to Reference Example 4).

Example 19

a) By the procedures similar to those of Example 18-a), there were obtained tablets (containing type I crystals of aripiprazole anhydride obtained in Reference Example 2), each having 190 mg of weight,

b) The tablets were dried by the procedures similar to those of Example 18-b), except that air inlet temperature was 100°C and dried for 1 hour.

c) The tablets were dried by the procedures similar to those of Example 18-b), except that inlet air temperature was 100°C and dried for 3 hours.

Example 20

By the procedures similar to those of Example 18-a), there were obtained tablets, each having 190 mg of weight, containing type C crystals of aripiprazole anhydride.

Example 21

By the procedures similar to those of Example 18-a), there were obtained tablets, each having 190 mg of weight, containing type D crystals of aripiprazole anhydride.

Example 22

a) Aripiprzole hydrate crystals (156 g) obtained in Reference Example 3, lactose (570 g), corn starch (100 g) and crystalline cellulose (100 g) were charged in a fluidized bed granulating dryer (NEW-MARUMERIZER, NQ-160: manufactured by FUJI POWDAL CO., LTD.), and these granulating ingredients were mixed under fluidizing for about 3 minutes with an inlet air temperature at 60°C, air flow rate of 1.0 to 1.5 m^3/min, and rotating disc with rotary speed of 400 rpm. Further, the granulating ingredients were continued fluidizing under the same condition, and sprayed about 500 g of 4% aqueous solution of hydroxypropyl celulose to obtain wet granules. The inlet air temperature was elevated up to 85°C, and dried until the temperature of the product was reatched to 46°C. The obtained dried granules were sized by passing to a sieve of 850 μm. The dried granules contained 4.37% of water (measured by the method according to Reference Example 4).

b) The dried granules (200 g) obtained in Example 22-a) were charged in a fluidized bed dryer (multiplex, MP-01: manufactured by POWREX CORPORATION),

and dried at 85°C of inlet air temperature, air flow rate of 0.5 m^3/min for 2 hours. The dried granules contained 3.50% of water (measured by the method according to Reference Example 4).

c) The dried granules (100 g) obtained in Example 22-a) were charged in a vacuum dryer (vacuum granulating dryer LCV-232: manufactured by TABAI CO., LTD.), and dried 80°C of tray temperature, about 760 mmHg of degree of vacuum for 2 hours. The dried granules were further dried similarly for 6 hours. The dried granules contained 3.17% of water (the product being dried for 2 hours: measured by the method according to Reference Example 4). The further dried granules contained 2.88% of water (the product being dried for 6 hours: measured by the method according to Reference Example 4).

d) About 1% by weight of magnesium stearate was added to the sized granules being obtained in Example 22-b) and mixed, then the mixed granules were supplied to a tablet machine (Single type Tablet machine No. 2B: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), and tabletted with punch, there were obtained tablets, each having 191 mg of weight.

e) About 1% by weight of magnesium stearate was added to the sized granules being obtained in Example 22-c) and mixed, then the mixed granules were supplied to a tablet machine (Single type Tablet machine No. 2B: manufactured by KIKUSUI SEISAKUSHO CO., LTD.), and

tabletted with punch, there were obtained tablets, each having 191 mg of weight.

Dissolution Test

Each tablets of the pharmaceutical solid oral preparations obtained previously was kept, repectively under the open at 25°C/60% RH for 6 months, and at 40°C/75% RH for 1 week, then their dissolution rates were measured by the following methods. The dissolution rates obtained from 60 minutes after the exposure are shown in Tables 2 and 3. The dissolution rates after 60 minutes, using the tablets kept under the open at 40°C/75% RH for 2 weeks, are shown in Tables 4 and 5. The dissolution rates after 60 minutes, using the tablets kept under the open condition at 40°C/75% RH for 1 week, are shown in Table 6.

Dissolution test equipment: USP

Model: NTR-6100 (manufactured by TOYAMA SANGYO CO., LTD.)

Model: DT-610(manufactured by JASCO CORPORATION)

a) Method of dissolution test of the 15 mg tablet

One tablet (containing 15 mg each of aripiprazole anhydride or hydrate) was tested by using 900 ml of acetic acid buffer solution (pH 5.0) (Note: 1) as the test solution, and by rotating a paddle at 100 rpm according to the method of USP (United States Pharmacopoea) (Note: 2).

The test solutions obtained respectively from 10 minutes, 20 minutes, 30 minutes, 45 minutes and 60 minutes after the start of test are named as T10, T20, T30, T45 and T60.

On the other hand, about 0.05 g of standard sample of aripiprazole was weighed accurately, dissolved in ethanol (95%) so as to make exactly 50 ml of ethanol solution. Twenty (20) ml of this ethanol solution was taken accurately, and to prepared exactly 1000 ml of the standard solution by adding 0.01 mol/ liter of hydrochloric acid reagent solution (Note: 3).

The test solutions and the standard solution were subjected to filtration, respectively by using a filter having micropores of 10 to 20 μm in diameters, then each of the filtrates were introduced to a spectrophotometer installed with flow cell (cell length: 10 mm), and to measure the absorbance of wave length at 249 nm and absorbance of wave length at 325 nm and determined the differences between absorbances to named as At10, At20, At30, At45, At60 and As, respectively.

After the measurements, the test solutions of T10, T20, T30 and T45 were put back to the test vessels respectively. Further, similar procedures were conducted to other 5 samples of the test solutions.

Dissolution rate (%) relating to the indicated amount of aripiprazole =

Amount of the standard sample of aripiprazole (mg) × At × As × 9/5 × 20/C

wherein, At: At10, At20, At30, At45 or At60

As: standard solution

C: Indicated amount of aripiprazole (mg)

(Note:1) Water was added to 1.97 g of acetic acid (100) and 9.15 g of sodium acetate·trihydrate to make 1000 ml of solution (0.1 mol/l).

(Note:2) Paddle method

(Note:3) Water was added to 100 ml of 0.1 mol/l hydrochloric acid (Note:4) to make 1000 ml of solution.

(Note:4) Water was added to 0.9 ml of hydrochloric acid to make 1000 ml of solution.

b) Method of dissolution test of the 30 mg tablet

One tablet each of the pharmaceutical solid oral preparations (containing 30 mg each of aripiprazole ~~anhydride or hydrate~~) was tested by using 900 ml of acetic acid buffer solution (pH 4.5) (Note: 5) as the test solution, and to conduct the test by rotating a paddle at 75 rpm in accordance with the method of USP (United States Pharmacopoea)(Note: 6).

The test solutions obtained respectively from 10 minutes, 20 minutes, 30 minutes 45 minutes and 60 minutes after the start of test, were named as T10, T20, T30, T45 and T60.

On the other hand, about 0.05 g of the

standard sample of aripiprazole was weighed accurately, and dissolved in ethanol (95%) so as to made exactly 50 ml of the ethanol solution. Twenty (20) ml of the ethanol solution was taken accurately, and prepared exactly 1000 ml of the standard solution by adding 0.01 mol/liter of hydrochloric acid reagent solution (Note: 7).

The test solutions and standard solution were subjected to filtration, respectively by using a filter having micropores of 10 to 20 μm in diameters, then each of the filtrates were introduced to a spectrophotometer in which a flow cell (cell length: 10 mm) was installed, and measured the absorbance of wave length at 249 nm and absorbance of wave length at 325 nm, and the difference between these absorbances were named as At10, At20, At30, At45, At60 and As, respectively.

After the measurements, the test solutions of T10, T20, T30 and T45 were put back respectively to the test vessels. Further, similar procedures were conducted to other 5 samples of the test solutions.

Dissolution rate (%) relating to the indicated amount of aripiprazole =

Amount of the standard sample of aripiprazole (mg) × At × As × 9/5 × 20/C

wherein, At: At10, At20, At30, At45 or At60

As: standard solution

C: Indicated amount of aripiprazole (mg)

(Note:5) Water was added to 1.91 g of acetic acid (100) and 2.99 g of sodium acetate·trihydrate to made 1000 ml of solution (0.05 mol/l).

(Note:6) Paddle method

(Note:7) Water is added to 100 ml of 0.1 mol/l hydrochloric acid (Note:8) to made 1000 ml of solution.

(Note:8) Water was added to 0.9 ml of hydrochloric acid to make 1000 ml of solution.

Table 2

Samples used	Open at 25°C/60% RH		Open at 40°C/75% RH	
	Initial	After 6 months	Initial	After 1 week
Tablet(15 mg) of Reference Example 4	83.4%	44.3%	83.4%	44.1%
Tablet(15 mg) of Reference Example 5	90.1%	61.9%	90.1%	65.2%

Table 3

Samples used	Open at 25°C/60% RH		Open at 40°C/75% RH	
	Initial	After 6 months	Initial	After 1 week
Tablet (30 mg) of Example 18-a)	96.7%	77.1%	96.7%	75.9%
Tablet (30 mg) of Example 17-b)	96.5%	93.6%	95.0%	92.2%
Tablet(30 mg) of Example 17-c)	97.0%	96.3%	94.7%	94.8%
Tablet (30 mg) of Reference Example 18-b)	97.2%	95.3%	97.2%	97.8%
Tablet(30 mg) of Reference Example 18-c)	97.8%	96.3%	97.8%	96.9%

Table 4

Samples used	Initial	After 2 weeks
Samples used Tablet (30 mg) of Example 19-a)	89.8%	66.9%
Tablet (30 mg) of Example 19-b)	-	79.8%
Tablet (30 mg) of Example 19-c)	-	85.9%

Table 5

Samples used	Initial	After 2 weeks
Tablet (30 of Example 18-a)	94.8%	94.7%
Tablet (30 mg) of Example 20	93.7%	93.1%
Tablet (30 mg) of Example 21	94.8%	90.9%

Table 6

Samples used	Initial	After 1 weeks
Tablet (30 mg) of Example 22-d)	96.5%	84.5%
Tablet (30 mg) of Example 22-e) (dreid for 2 hours)	92.5%	74.4%
Tablet (30 mg) of Example 22-e) (dreid for 6 hours)	96.2%	83.4%

(Note: Dissolution tests in Table 5 were conducted similarly to the procedures in the above-mentioned "b) Method of dissolution test of the 30 mg tablet" except that by using 900 ml of acetic acid buffer solution (pH 4.0) as the test solution, and by rotating a paddle at 50 rpm.

As can be seen clearly from the data shown in Table 2, in comparison with the 15 mg tablet containing conventional aripiprazole anhydride crystals (Reference Example 4), the 15 mg tablet containing type B crystals of aripiprazole anhydride (Reference Example 5) had the dissolution rate to maintain maximum drug concentration (Cmax), at pH 5.0 after 60 minutes, even though such tablet was kept under the open at 25°C/60%RH for 6 months and under the open at 40°C/75%RH for 1 week.

As can be seen clearly from the data shown in Table 3, even though 30 mg tablets (Examples 17-b) and 17-c)) prepared from twice dried granules of type B crystals of aripiprazole anhydride, and 30 mg tablets (Examples 18-b) and 18-c)) prepared from further dried pharmaceutical solid oral preparation containing type B crystals of aripiprazole anhydride were subjected to keep under the open at 25°C/60%RH for 6 months or 40°C/75%RH for 1 week, the dissolution rates of these tablets obtained 60 minutes after the test at pH 4.5 were not substantially lowered.

As can be seen clearly from the data shown in Table 4, when 30 mg tablets (Examples 19-a), 19-b) and 19-c)) containing conventional aripiprazole anhydride crystals were further dried and subjected to keep under open at 40°C/75%RH for 2 weeks, then the dissolution rates of the tablets obtained 60 minutes after the test at pH 4.5 were the dissolution rates to maintain

maximum drug concentration (Cmax).

As can be seen clearly from the data shown in Table 5, when 30 mg tablet (Example 18-a)) containing type B crystals of aripiprazole anhydride, 30 mg tablet (Example 20) containing type C crystals of aripiprazole anhydride and 30 mg tablet (Example 21) containing type D crystals of aripirazole anhydride were subjected to keep under open at 40°C/75%RH for 2 weeks, then the dissolution rates of the tablets obtained 60 minutes after the test at pH 4.0 were not substantially lowered.

As can be seen clearly from the data shown in Table 6, when 30 mg tablets (Examples 22-d) and 22-e)) prepared from granules of conventional aripiprazole hydrate being twice dried, and subjected to keep under open at 40°C/75%RH for 1 week, then the dissolution rates of the tablets obtained 60 minutes after the test at pH 4.5 were the dissolution rates to maintain maximum drug concentration (Cmax).

Sample Preparation 1

Aripiprazole anhydride crystals B	5 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	200 mg

Tablets containing the above ingredients in each tablet were prepared by formulation methods known to one skilled in the art of pharmaceutical formulation.

Sample Preparation 2

Type C crystals of aripiprazole anhydride	5 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	200 mg

In accordance with an ordinary method, tablet preparation, containing the above-mentioned ingredients per 1 tablet was prepared.

Sample Preparation 3

Type D crystals of aripiprazole anhydride	5 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	200 mg

In accordance with an ordinary method, tablet preparation, containing the above-mentioned ingredients per 1 tablet was prepared.

Sample Preparation 4

Type E crystals of aripiprazole anhydride	5 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	200 mg

In accordance with an ordinary method, tablet preparation, containing the above-mentioned ingredients per 1 tablet was prepared.

Sample Preparation 5

Type F crystals of aripiprazole anhydride	5 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	200 mg

In accordance with an ordinary method, tablet preparation, containing the above-mentioned ingredients per 1 tablet was prepared.

Sample Preparation 6

Type G crystals of aripiprazole anhydride	5 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	200 mg

In accordance with an ordinary method, tablet preparation, containing the above-mentioned ingredients per 1 tablet was prepared.

Formulation Example

The following examples used aripiprazole drug substance made by first milling or pulverizing the conventional hydrate of aripiprazole and then heating it to form the anhydrous form (anhydride B).

Formulation Example 1

Flash-melt tablets were prepared as follows:

Intragranulation:

Ingredient	Percent w/w	Mg. per tablet
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate	43.35	86.7
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was then added and the mixture blended for an additional three minutes. The blended formulation was compacted at a pressure of 30-35 kgF/cm^2 in a commercial compactor equipped with an orifice such that the compacts therefrom are in the form of ribbons. The ribbons were passed through a 30 mesh (600 microns) screen to form stable granules of about 150 to 400 microns.

Extragranulation Ingredients:

Ingredient	Percent w/w	Mg. per tablet
Intragranulation	92.75	185.5
Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU) and disintegrated in 10 seconds in 5

ml of water. The final blend formulation demonstrated excellent flow and was free of other problems such as chipping, capping and sticking. It has been found that utilizing Avicel® PH 102 for the intragranulation and Avicel® PH 200 for the extragranulation ingredient enhanced the quality of the resultant tablets.

Formulation Example 2

Flash-melt tablets containing a combination of two grades of calcium silicate were prepared as follows:

Intragranulation:

Ingredient	Percent w/w	Mg. per tablet
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate (crystalline, alpha triclinic)	33.35	66.7
Hubersorb 600 NF (amorphous calcium silicate)	10	20
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Formulation Example 1.

Extragranulation Ingredients:

Ingredient	Percent w/w	Mg. per tablet
Intragranulation	92.75	185.5
Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.0 kP (3.1 SCU) and disintegrated in 10 seconds in 5 ml of water.

Formulation Example 3

Flash-melt tablets containing aripiprazole, an antischizophrenic drug, were prepared as follows:

Intragranulation

Ingredient	Percent w/w	Mg. per tablet
Aripiprazole	15	30
Xylitol (300) Xylisorb	25	50
Avicel® PH 102	6	12
Calcium Silicate	37	74
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	94.4	188.8

The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Formulation Example 1.

Extragranulation Ingredients:

Ingredient	Percent w/w	Mg. per tablet
Intragranulation	94.4	188.8
Avicel® PH 200	1.1	2.2
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.0 kP (3.1 SCU) and disintegrated in 10 seconds in 5 ml of water.

Formulation Example 4

Flash-melt tablets containing aripiprazole were prepared as follows:

Intragranulation:

Ingredient	Percent w/w	Mg. per tablet
Aripiprazole	0.5	1
Xylitol (300) Xylisorb	27	54
Avicel® PH 102	12	24
Calcium Silicate	42	84
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.9	185.8

The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Formulation Example 1.

Extragranulation Ingredients:

Ingredient	Percent w/w	Mg. per tablet
Intragranulation	92.9	185.8
Avicel® PH 200	2.6	5.2
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU) and disintegrated in 10 seconds in 5 ml of water.

CLAIMS

1. Hydrate A of aripiprazole wherein said Hydrate has a powder x-ray diffraction spectrum which is substantially the same as the following powder x-ray diffraction spectrum shown in Figure 3.

2. Hydrate A of aripiprazole wherein said Hydrate has powder x-ray diffraction characteristic peaks at 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° and 24.8°.

3. Hydrate A of aripiprazole wherein said Hydrate has particular infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

4. Hydrate A of aripiprazole wherein said Hydrate has an endothermic curve which is substantially the same as the thermogravimetric/differential thermal analysis (heating rate 5°C/min) endothermic curve shown below shown in Figure 1.

5. Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 50 μm or less.

6. Hydrate A of aripiprazole wherein said Hydrate has a mean particle size range of 36 to 14 μm.

7. Hydrate A of aripiprazole wherein said Hydrate has

a powder x-ray diffraction spectrum which is substantially the same as the following powder x-ray diffraction spectrum shown in Figure 3;

particular infrared absorption bands at 2951,

2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum;

an endothermic curve which is substantially the same as the thermogravimetric/differential thermal analysis (heating rate 5°C/min) endothermic curve shown below shown in Figure 1; and

a mean particle size of 50 μm or less.

8. A process for the preparation of Hydrate A wherein said process comprises milling Conventional Hydrate to a mean particle size of 50 μm or less.

9. A process according to claim 8, wherein said milling is performed by an atomizer using a rotational speed of 5000-15000 rpm for the main axis, a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

10. The Hydrate A according to claim 8 made by a process comprising milling Conventional Hydrate to a mean particle size of 50 μm or less.

11. The Hydrate A according to claim 8 made by a process comprising milling Conventional Hydrate to a mean particle size of 50 μm or less wherein said milling is performed by an atomizer using a rotational speed of 5000-15000 rpm for the main axis, a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

12. Aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.40% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

13. Aripiprazole Anhydride Crystals B having low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.40% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

14. Aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.10% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

15. Aripiprazole Anhydride Crystals B having low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.10% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

16. Aripiprazole Anhydride Crystals B having a powder x-ray diffraction spectrum which is substantially the same as the following powder x-ray diffraction spectrum shown in Figure 5.

17. Aripiprazole Anhydride Crystals B having a powder x-ray diffraction spectrum having characteristic peaks at 2θ = 11.0°, 16.6°, 19.3°, 20.3° and 22.1°.

18. Aripiprazole Anhydride Crystals B having a particular infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

19. Aripiprazole Anhydride Crystals B exhibiting an endothermic peak near about 141.5°C in

thermogravimetric/differential thermal analysis (heating rate 5°C/min).

20. Aripiprazole Anhydride Crystals B exhibiting an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate 5°C/min).

21. Aripiprazole Anhydride Crystals B wherein said Crystals will not substantially convert to a hydrous form of aripiprazole when properly stored under a relative humidity (RH) of 60 % and at a temperature of 25°C, even for an extended period being not less than 4 years.

22. Aripiprazole Anhydride Crystal B wherein said crystals has a mean particle size of 50 μm or less.

23. Aripiprazole Anhydride Crystal B wherein said crystals has a mean particle size of 30 μm or less.

24. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 16 and 18 to 22.

25. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 17 to 22.

26. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 13, 16, 18 to 20 and 22.

27. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 15, 16, 18 to 20 and 22.

28. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 13, 17 to

20 and 22.

29. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 15, 17 to 20 and 22.

30. A process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A.

31. A process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 90-125°C for about 3-50 hours.

32. A process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 100°C for about 18 hours.

33. A process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 100°C for about 24 hours.

34. A process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 120°C for about 3 hours.

35. A process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A for about 18 hours at 100°C followed by additional heating for about 3 hours at 120°C.

36. The Aripiprazole Anhydride Crystals B according to any one of claims 24-29 made by a process comprising heating Aripiprazole Hydrate A for about 18 hours at 100°C followed by additional heating for about 3 hours at 120°C.

37. The Aripiprazole Anhydride Crystals B according to any one of claims 24-29 formulated with one or more pharmaceutically acceptable carriers.

38. The Aripiprazole Anhydride Crystals B according to any one of claims 24-29 formulated with one or more pharmaceutically acceptable carriers to form a solid oral tablet.

39. The Aripiprazole Anhydride Crystals B according to any one of claims 24-29 formulated with one or more pharmaceutically acceptable carriers to form an oral flashmelt tablet.

40. A process for the pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals B defined in claim 26 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7.

41. A process for the pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals B defined in claim 26 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7 at 90-125°C for about 3-50 hours.

42. A process for the pharmaceutical solid oral

preparation comprising Aripiprazole Anhydride Crystals B defined in claim 27 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7.

43. A process for the pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals B defined in claim 27 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7 at 90-125°C for about 3-50 hours.

44. A process for the pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals B defined in claim 28 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7.

45. A process for the pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals B defined in claim 28 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7 at 90-125°C for about 3-50 hours.

46. A process for the pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals B defined in claim 29 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7.

47. A process for the pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals

B defined in claim 29 and one or more pharmaceutically acceptable carriers, wherein said process comprises heating Aripiprazole Hydrate A defined in claim 7 at 90-125°C for about 3-50 hours.

48. Aripiprazole Anhydride Crystals B wherein said Crystals will not substantially convert to a hydrous form of aripiprazole when properly stored under a relative humidity (RH) of 60 % and at a temperature of 25°C, even for an extended period being not less than 1 year.

49. Aripiprazole Anhydride Crystals B wherein said Crystals will not substantially convert to a hydrous form of aripiprazole when properly stored under a relative humidity (RH) of 75 % and at a temperature of 40°C, even for an extended period being not less than 0.5 year.

50. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 16, 18 to 20, 22 and 48.

51. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 17 to 20, 22 and 48.

52. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 16, 18 to 20, 22 and 49.

53. Aripiprazole Anhydride Crystals B having all physicochemical properties defined in claims 17 to 20, 22 and 49.

54. The Aripiprazole Anhydride Crystals B according to any one of claims 50-53 formulated with one or more pharmaceutically acceptable carriers.

55. The Aripiprazole Anhydride Crystals B according to any one of claims 50-53 formulated with one or more pharmaceutically acceptable carriers to form a solid oral tablet.

56. The Aripiprazole Anhydride Crystals B according to any one of claims 50-53 formulated with one or more pharmaceutically acceptable carriers to form an oral flashmelt tablet.

57. The use of aripiprazole anhydride crystals B for the treatment of central system disorder.

58. The use of aripiprazole anhydride crystals B for the treatment of schizophrenia.

59. The use of aripiprazole anhydride crystals B for the treatment of bipolar disorder.

60. The use of aripiprazole anhydride crystals B for the treatment of intractable (drug-resistent, chronic) schizophrenia with cognitive impairment or intractable (drug-resistant, chronic) schizophrenia without cognitive impairment.

61. The use of aripiprazole anhydride crystals B for the treatment of autism, Down's syndrome or attention deficit hyperactivity disorder (ADHD).

62. The use of aripiprazole anhydride crystals B for the treatment of Alzheimer's disease, Parkinson's disease or other neurodegenerative diseases.

63. The use of aripiprazole anhydride crystals B for the treatment of panic, obsessive compulsive disorder (OCD), sleep disorders, sexual dysfunction, alcohol and drug dependency, vomiting, motion sickness, obesity, miparticlee headache or cognitive impairment.

64. The use of aripiprazole anhydride crystals B for the treatment of anxiety, depression or mania.

65. The use of aripiprazole anhydride crystals B to prepare a medicament to treat or prevent schizophrenia and the symptoms associated with schizophrenia.

66. A drug for treating schizophrenia or symptoms associated with schizophrenia, which comprises aripiprazole anhydride crystals B in an amount effective to treat schizophrenia or the symptoms thereof, in admixture with a pharmaceutically acceptable diluent.

67. The drug as claimed in claim 66, which is contained in a commercial package carrying instructions that the drug should be used for treating schizophrenia, or symptoms thereof.

68. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals B defined in claim 26, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

69. A process for the preparation of granules, characterized by wet granulating the Aripiprazole

Anhydride Crystals B defined in claim 27, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

70. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals B defined in claim 28, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

71. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals B defined in claim 29, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

72. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals B defined in claim 26 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

73. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals B defined in claim 27 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

74. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole

Anhydride Crystals B defined in claim 28 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

75. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals B defined in claim 29 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

76. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals B defined in claim 26 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

77. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals B defined in claim 27 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

78. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals B defined in claim 28 and one or more pharmaceutically

acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

79. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals B defined in claim 29 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

80. Aripiprazole Anhydride Crystals C having a powder X-ray diffraction spectrum shown in Figure 10.

81. Aripiprazole Anhydride Crystals C having a powder X-ray diffraction spectrum having characteristics peaks at 2θ = 12.6°, 13.7°, 15.4°, 18.1°, 19.0°, 20.6°, 23.5° and 26.4°.

82. Aripiprazole Anhydride crystals C having a particular infrared absorption bands at 2939, 2804, 1680, 1375 and 780 cm^{-1} on the IR (Kbr) spectrum.

83. Aripiprazole Anhydride crystals C exhibitng an endothermic peak near about 150.2°C in thermogravimetric/differential thermal analysis (heating rate 5°C/min).

84. Aripiprazole Anhydride crystals C having a solid ^{13}C-NMR spectrum having characteristic peaks at

32.8 ppm, 60.8 ppm, 74.9 ppm, 104.9 ppm, 152.2 ppm and 175.2 ppm.

85. Aripiprazole Anhydride crystals C having all physicochemical properties defined in claims 80, 82 to 84.

86. Aripiprazole Anhydride crystals C having all physicochemical properties defined in claims 81 to 84.

87. Aripiprazole Anhydride crystals D having a powder x-ray diffraction spectrum shown in Figure 15.

88. Aripiprazole Anhydride crystals D having a powder x-ray diffraction spectrum having characteristic peaks at 2θ = 8.7°, 11.6°, 16.3°, 17.7°, 18.6°, 20.3°, 23.4° and 25.0°.

89. Aripiprazole Anhydride crystals D having a particular infrared absorption bands at 2946, 1681, 1375, 1273, 1175 and 862 cm^{-1} on the IR (Kbr) spectrum.

90. Aripiprazole Anhydride crystals D exhibiting an endothermic peak near about 136.8°C and 141.6°C in thermogravimetric/differential thermal analysis (heating rate 5°C/min).

91. Aripiprazole Anhydride crystals D having a solid ^{13}C-NMR spectrum having characteristic peaks at 32.1 ppm, 62.2 ppm, 66.6 ppm, 104.1 ppm, 152.4 ppm, 158.4 ppm, and 174.1 ppm.

92. Aripiprazole Anhydride crystals D having all physicochemical properties defined in claims 87, 89 to 91.

93. Aripiprazole Anhydride crystals D having all

physicochemical properties defined in claims 88 to 91.

94. Aripiprazole Anhydride crystals E having a powder x-ray diffraction spectrum shown in Figure 20.

95. Aripiprazole Anhydride crystals E having a powder x-ray diffraction spectrum having characteristic peaks at 2θ = 8.0°, 13.7°, 14.6°, 17.6°, 22.5° and 24.0°.

96. Aripiprazole Anhydride crystals E having a particular infrared absorption bands at 2943, 2817, 1686, 1377, 1202, 969 and 774 cm^{-1} on the IR (Kbr) spectrum.

97. Aripiprazole Anhydride crystals E exhibiting an endothermic peak near about 146.5°C in thermogravimetric/differential thermal analysis (heating rate 5°C/min).

98. Aripiprazole Anhydride crystals E having all physicochemical properties defined in claims 94, 96 to 97.

99. Aripiprazole Anhydride crystals E having all physicochemical properties defined in claims 95 to 97.

100. Aripiprazole Anhydride crystals F having a powder x-ray diffraction spectrum shown in Figure 24.

101. Aripiprazole Anhydride crystals F having a powder x-ray diffraction spectrum having characteristic peaks at 2θ = 11.3°, 13.3°, 15.4°, 22.8°, 25.2° and 26.9°.

102. Aripiprazole Anhydride crystals F having a particular infrared absorption bands at 2940, 2815,

1679, 1383, 1273, 1177, 1035, 963 and 790 cm^{-1} on the IR (Kbr) spectrum.

103. Aripiprazole Anhydride crystals F exhibiting an endothermic peak near about 137.5°C and 149.8°C in thermogravimetric/differential thermal analysis (heating rate 5°C/min).

104. Aripiprazole Anhydride crystals F having all physicochemical properties defined in claims 100, 102 to 103.

105. Aripiprazole Anhydride crystals F having all physicochemical properties defined in claims 101 to 103.

106. Aripiprazole Anhydride crystals G having a powder x-ray diffraction spectrum shown in Figure 28.

107. Aripiprazole Anhydride crystals G having a powder x-ray diffraction spectrum having characteristic peaks at 2θ = 10.1°, 12.8°, 15.2°, 17.0°, 17.5°, 19.1°, 20.1°, 21.2°, 22.4°, 23.3°, 24.5° and 25.8°.

108. Aripiprazole Anhydride crystals G having a particular infrared absorption bands at 2942, 2813, 1670, 1625, 1377, 1195, 962 and 787 cm^{-1} on the IR (Kbr) spectrum.

109. Aripiprazole Anhydride crystals G exhibiting an endothermic peak near about 141.0°C and an exothermic peak around 122.7°C in thermogravimetric/ differential thermal analysis (heating rate 5°C/min).

110. Aripiprazole Anhydride crystals G having all physicochemical properties defined in claims 106, 108

to 109.

111. Aripiprazole Anhydride crystals G having all physicochemical properties defined in claims 107 to 109.

112. A process for preparing aripiprazole anhydride crystals C according to claim 85 or 86, characterized by heating aripiprazole anhydride crystals at a temperature higher than 140°C and lower than 150°C.

113. A process for preparing aripiprazole anhydride crystals D according to claim 92 or 93, characterized by recrystallizing it from toluene.

114. A process for preparing aripiprazole anhydride crystals E according to claim 98 or 99, characterized by heating and dissolving aripiprazole anhydride crystals in acetonitrile, then cooling it.

115. A process for preparing aripiprazole anhydride crystals F according to claim 104 or 105, characterized by heating a suspension of aripiprazole anhydride in acetone.

116. A process for preparing aripiprazole anhydride crystals G according to claim 110 or 111, characterized by leaving to stand aripiprazole anhydride glassy state in a sealed vessel at room temperature for at least 2 weeks.

117. A pharmaceutical composition comprising at least one aripiprazole anhydride crystals selected from the group consisting of the aripiprazole anhydride

crystals C according to claim 85, the aripiprazole anhydride crystals D according to Claim 92, the aripiprazole anhydride crystals E according to Claim 98, the aripiprazole anhydride crystals F according to Claim 104 and the aripiprazole anhydride crystals G according to Claim 110, together with pharmaceutically acceptable carriers.

118. A pharmaceutical composition comprising at least one aripiprazole anhydride crystals selected from the aripiprazole anhydride crystals C according to claim 86, the aripiprazole anhydride crystals D according to claim 93, the aripiprazole anhydride crystals E according to claim 99, the aripiprazole anhydride crystals F according to Claim 105, and the aripiprazole anhydride crystals G according to Claim 111, together with pharmaceutically acceptable carriers.

119. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals C defined in claim 85, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

120. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals C defined in claim 86, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

121. A process for the preparation of granules,

characterized by wet granulating the Aripiprazole Anhydride Crystals D defined in claim 92, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

122. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals D defined in claim 93, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

123. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals E defined in claim 98, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

124. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals E defined in claim 99, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

125. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals F defined in claim 104, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

126. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals F defined in claim 105, drying the obtained granules at 70 to 100°C and sizing it, then

drying the sized granules at 70 to 100°C again.

127. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals G defined in claim 110, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

128. A process for the preparation of granules, characterized by wet granulating the Aripiprazole Anhydride Crystals G defined in claim 111, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

129. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals C defined in claim 85 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

130. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals C defined in claim 86 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

131. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals D defined in claim 92 and one or more pharmaceutically acceptable carriers at 70 to

100°C.

132. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals D defined in claim 93 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

133. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals E defined in claim 98 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

134. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals E defined in claim 99 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

135. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals F defined in claim 104 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

136. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole

Anhydride Crystals F defined in claim 105 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

137. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals G defined in claim 110 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

138. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals G defined in claim 111 and one or more pharmaceutically acceptable carriers at 70 to 100°C.

139. A process for the preparation of granules, characterized by wet granulating conventional Aripiprazole Anhydride Crystals, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

140. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising conventional Aripiprazole Anhydride Crystals and one or more pharmaceutically acceptable carriers at 70 to 100°C.

141. A pharmaceutical solid oral preparation having at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30

minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

142. The pharmaceutical solid oral preparation prepared by the process of claim 139, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

143. The pharmaceutical solid oral preparation prepared by the process of claim 140, wherein said pharmaceutical solid oral preparation having at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

144. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals C defined in claim 85 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

145. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals C defined in claim 86 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid

oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

146. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals D defined in claim 92 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

147. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals D defined in claim 93 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

148. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals E defined in claim 98 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

149. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals E defined in claim 99 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

150. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals F defined in claim 104 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

151. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals F defined in claim 105 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

152. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals G defined in claim 110 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid

oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

153. The pharmaceutical solid oral preparation comprising the Aripiprazole Anhydride Crystals G defined in claim 111 and one or more pharmaceutically acceptable carriers, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

154. A process for the preparation of granules, characterized by wet granulating conventional Aripiprazole Hydrate Crystals, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

155. A process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising conventional Aripiprazole Hydrate Crystals and one or more pharmaceutically acceptable carriers at 70 to 100°C.

156. The pharmaceutical solid oral preparation prepared by the process of claim 154, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after

60 minutes.

157. The pharmaceutical solid oral preparation prepared by the process of claim 155, wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

FIG.1

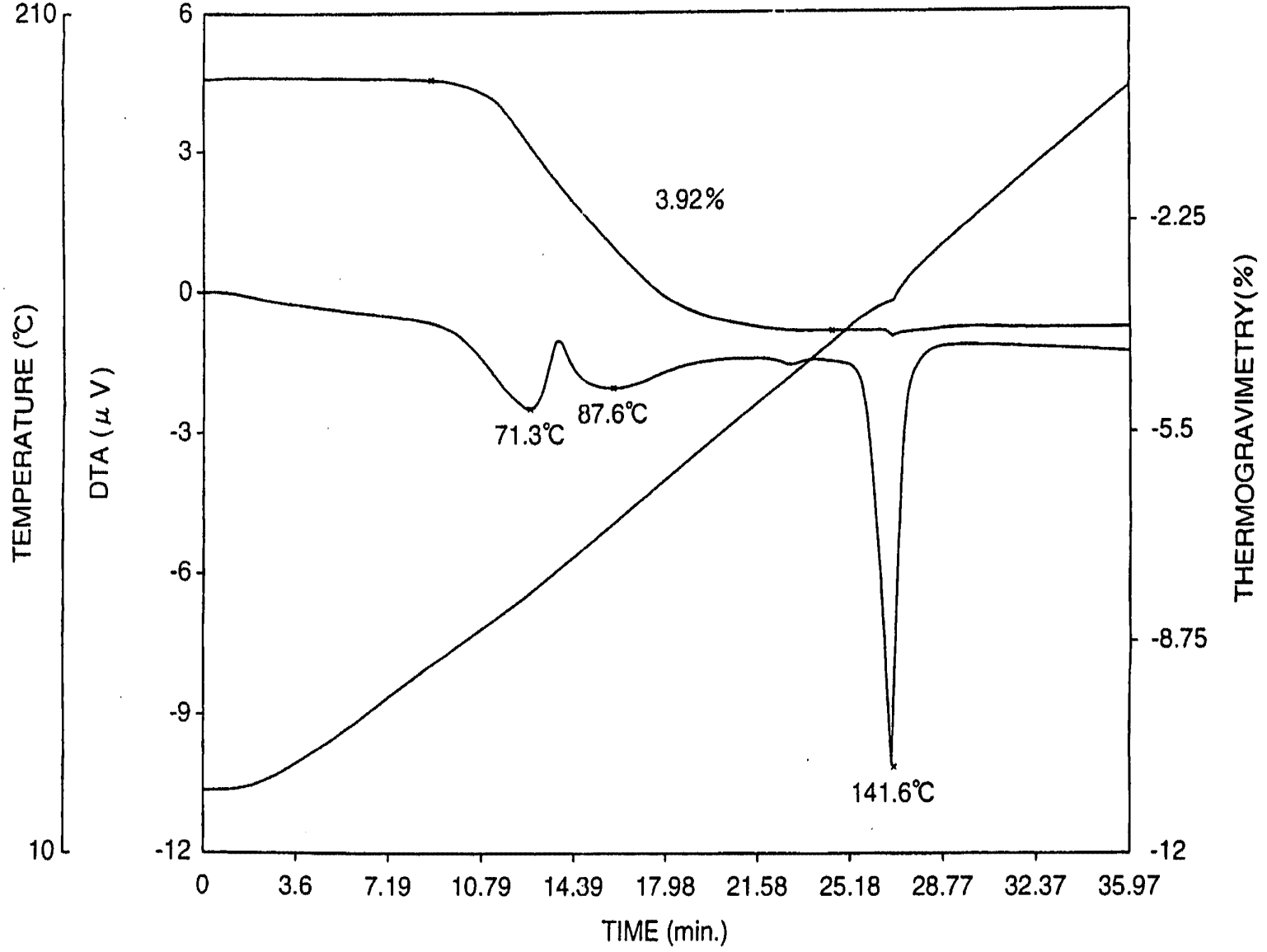


FIG.2

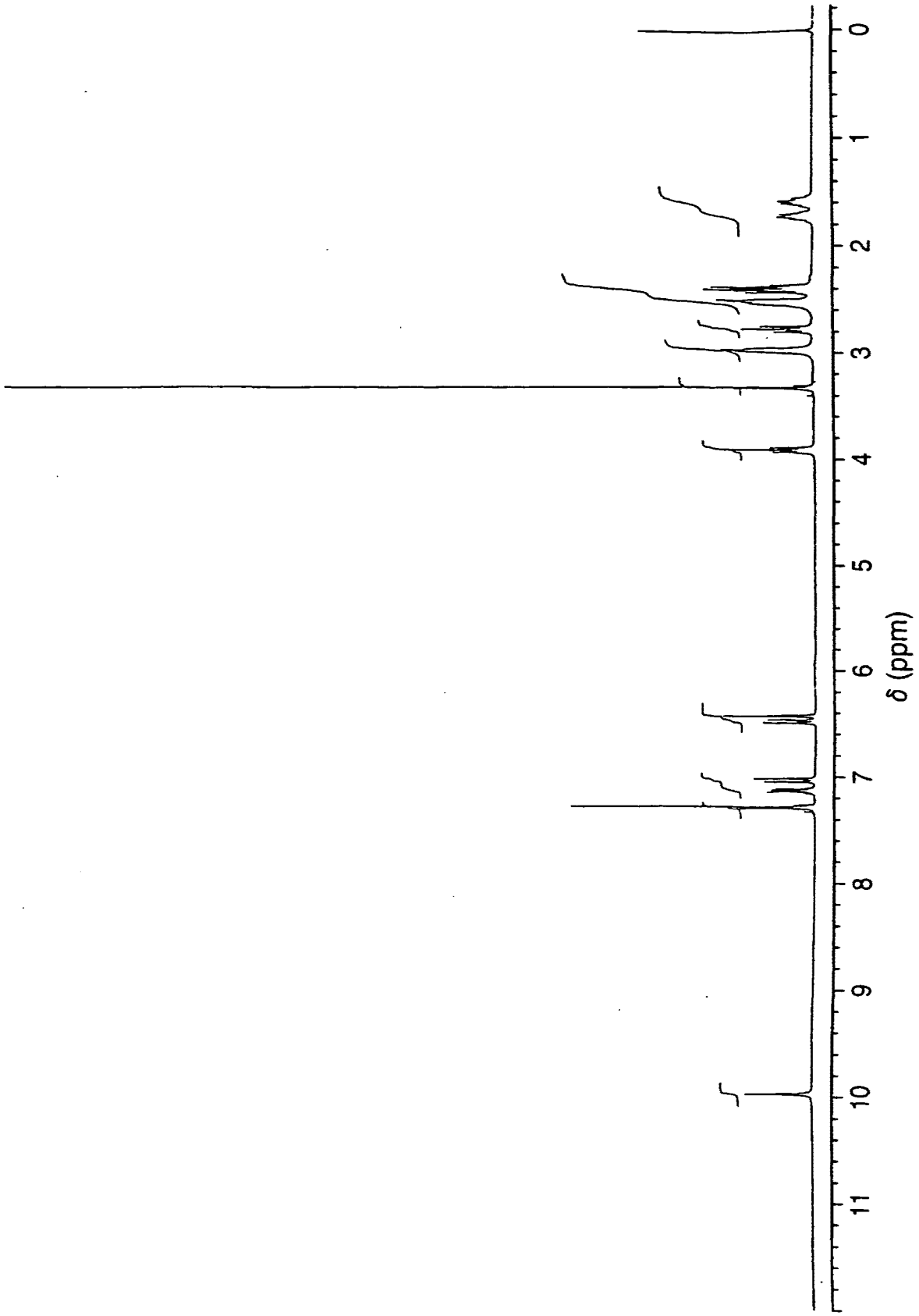


FIG.3

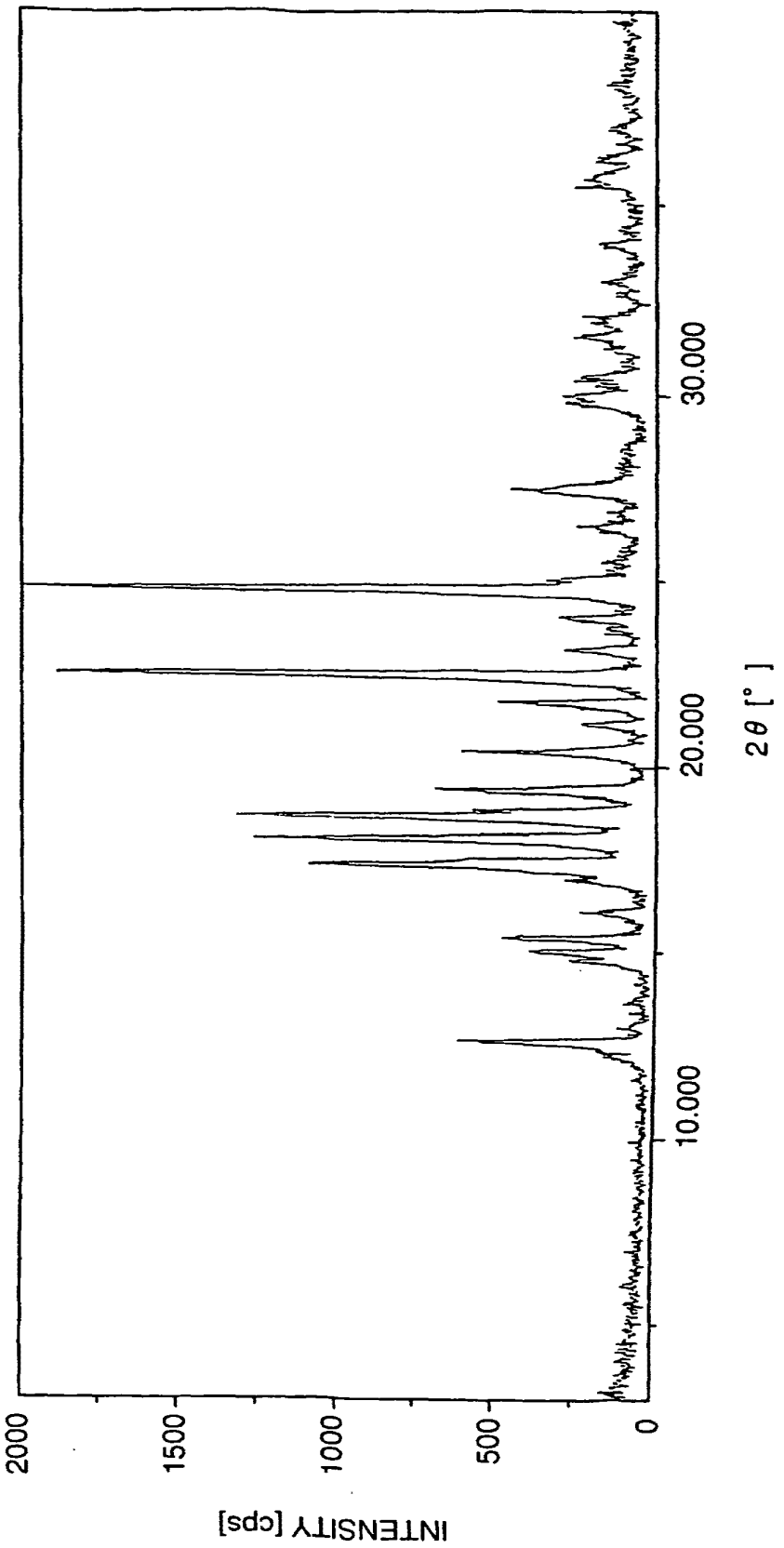


FIG.4

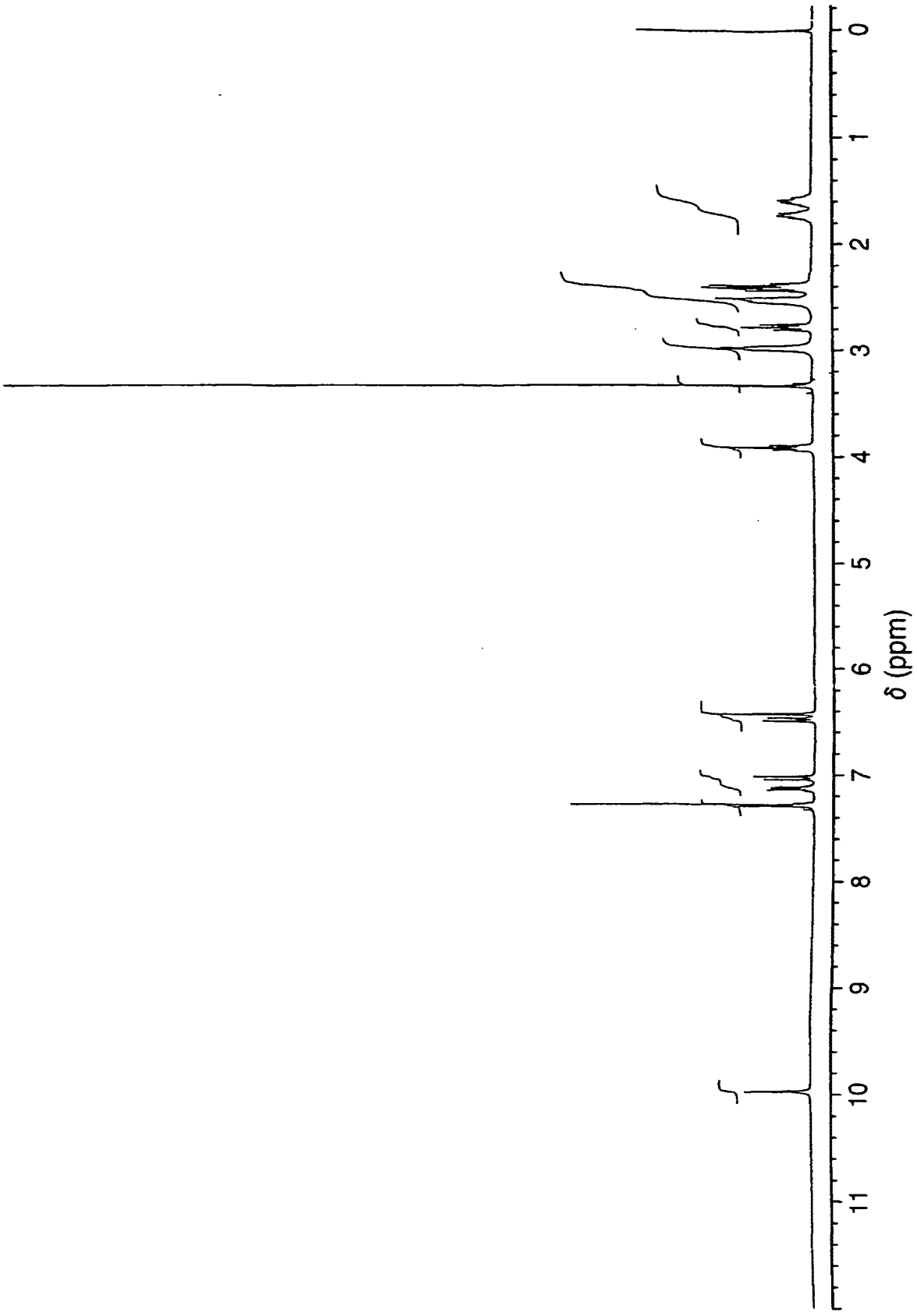


FIG.5

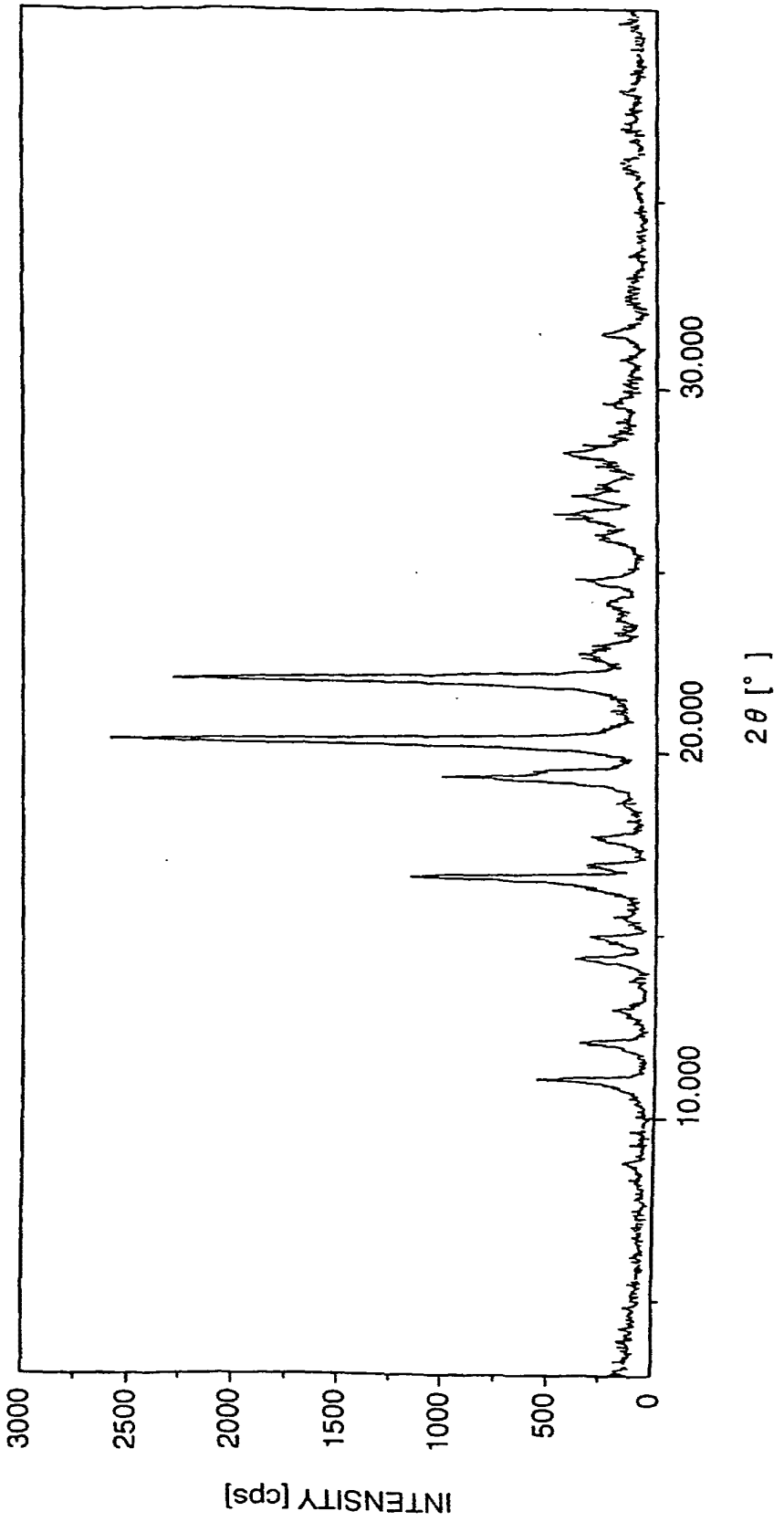

INTENSITY [cps]
3000
2500
2000
1500
1000
500
0
10.000
20.000
30.000
2θ [°]

FIG.6

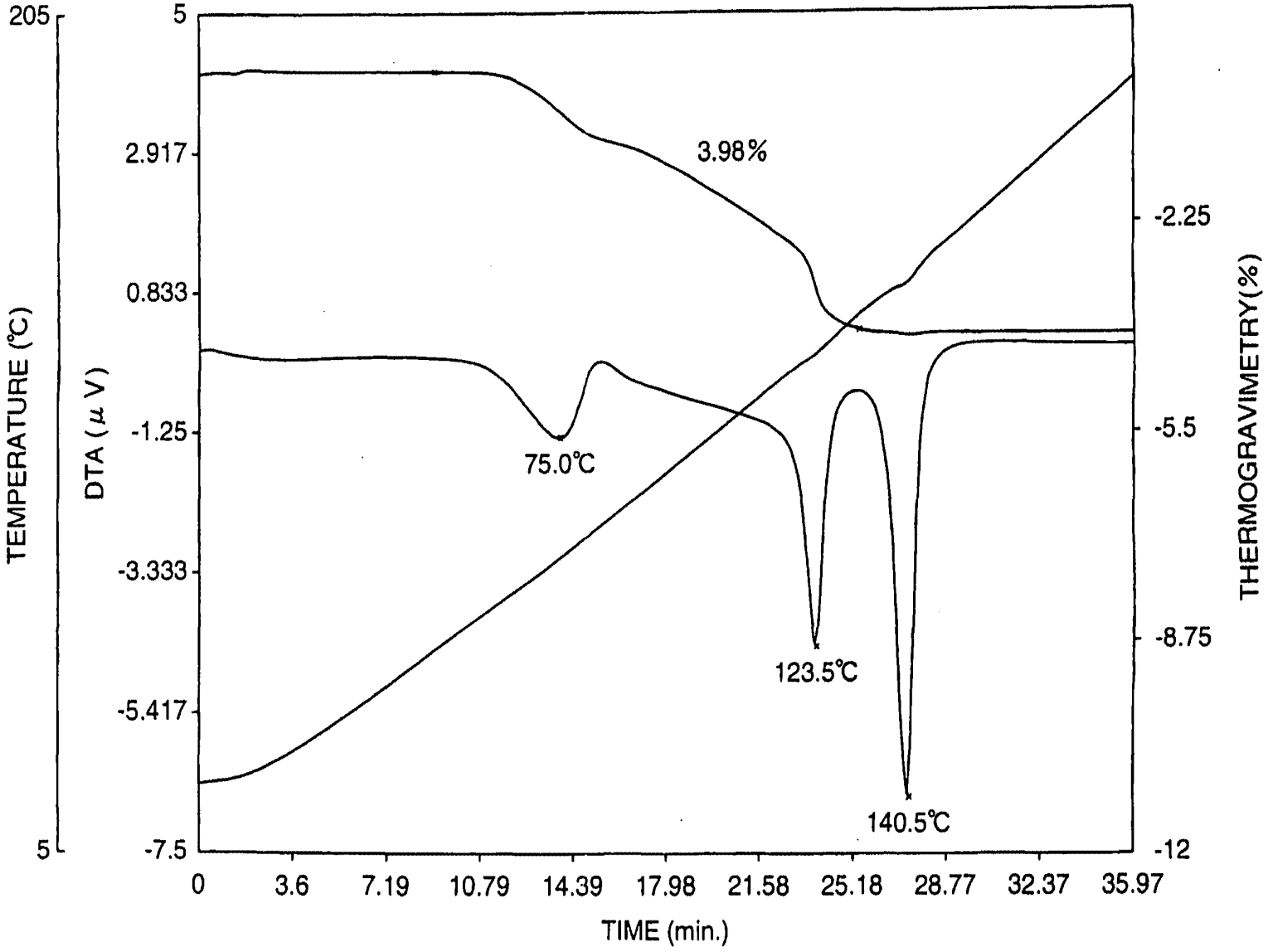


FIG.7

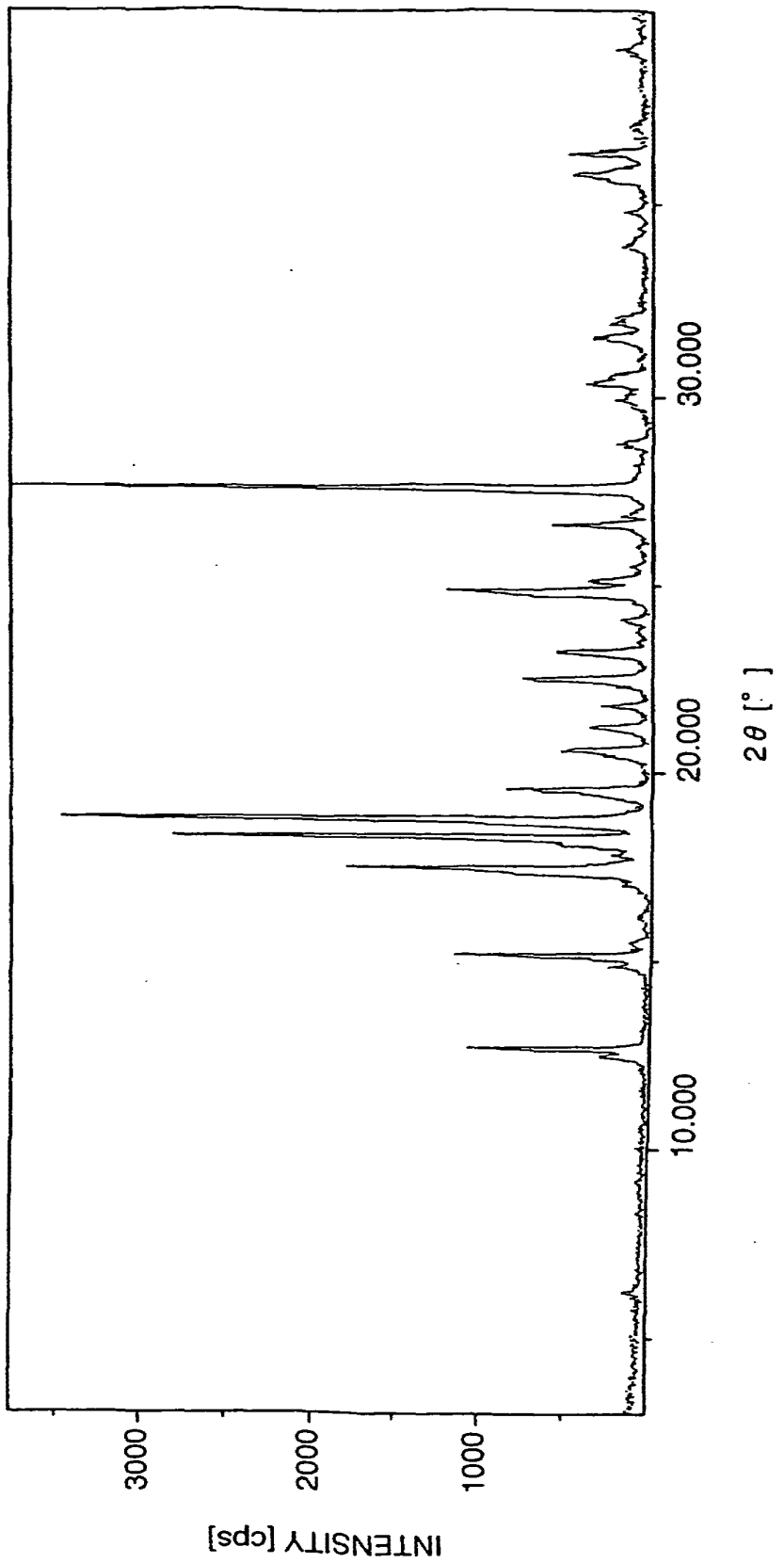


FIG.8

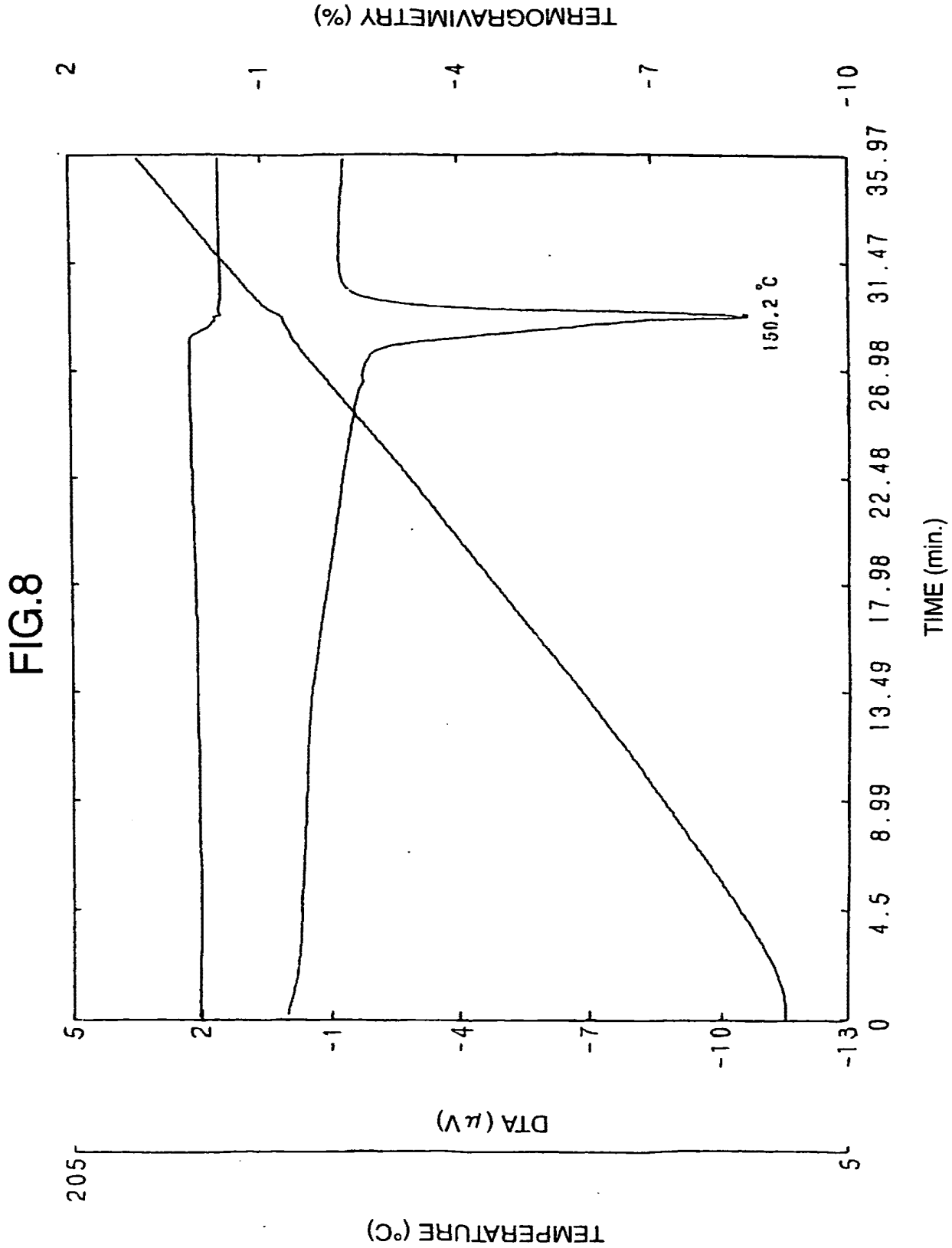

TERMOGRAVIMETRY (%)
2
-1
-4
-7
-10
150.2 ℃
35.97
31.47
26.98
22.48
17.98
13.49
8.99
4.5
0
TIME (min.)
5
2
-1
-4
-7
-10
-13
DTA (μV)
205
5
TEMPERATURE (℃)

FIG.9

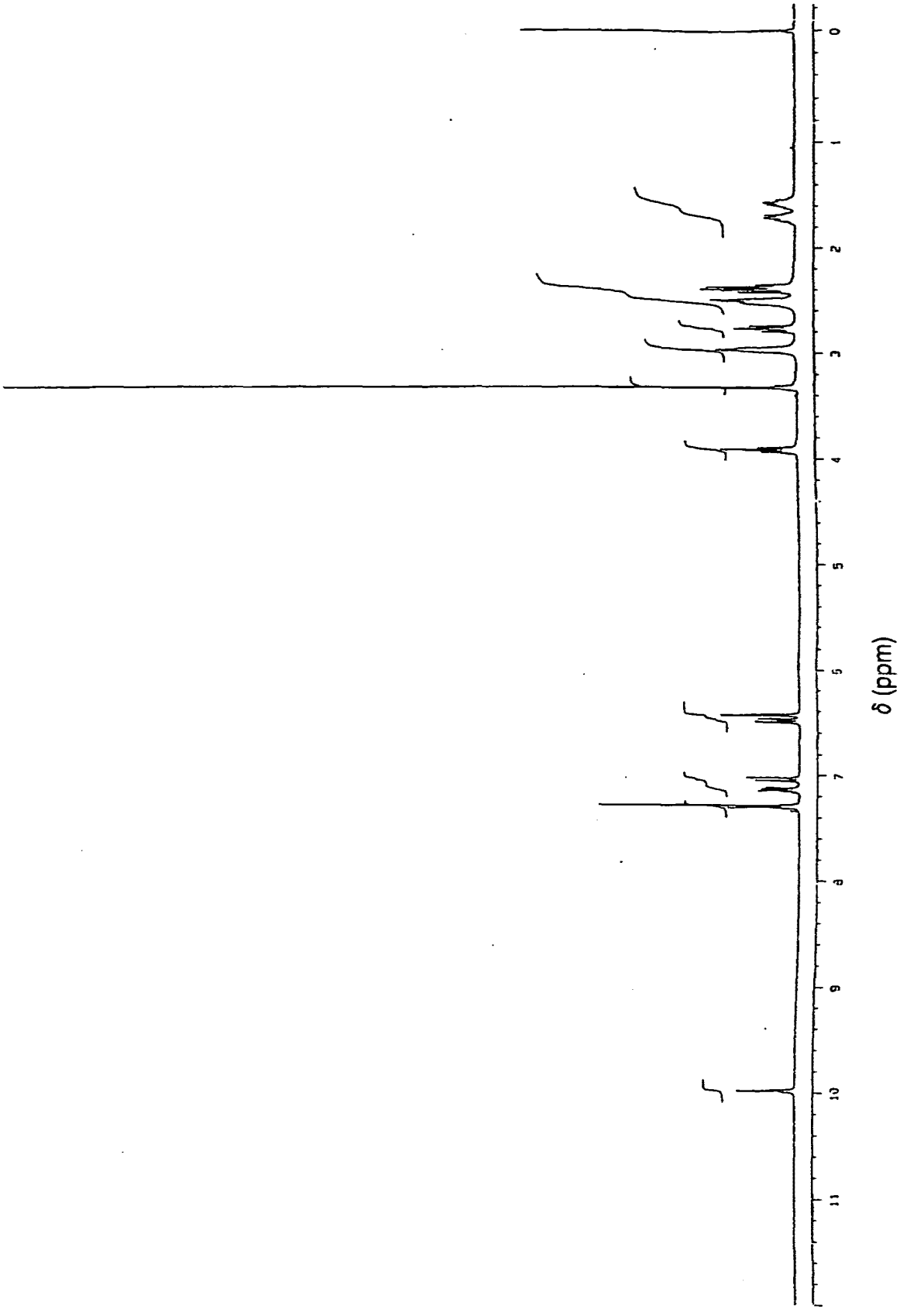


FIG.10

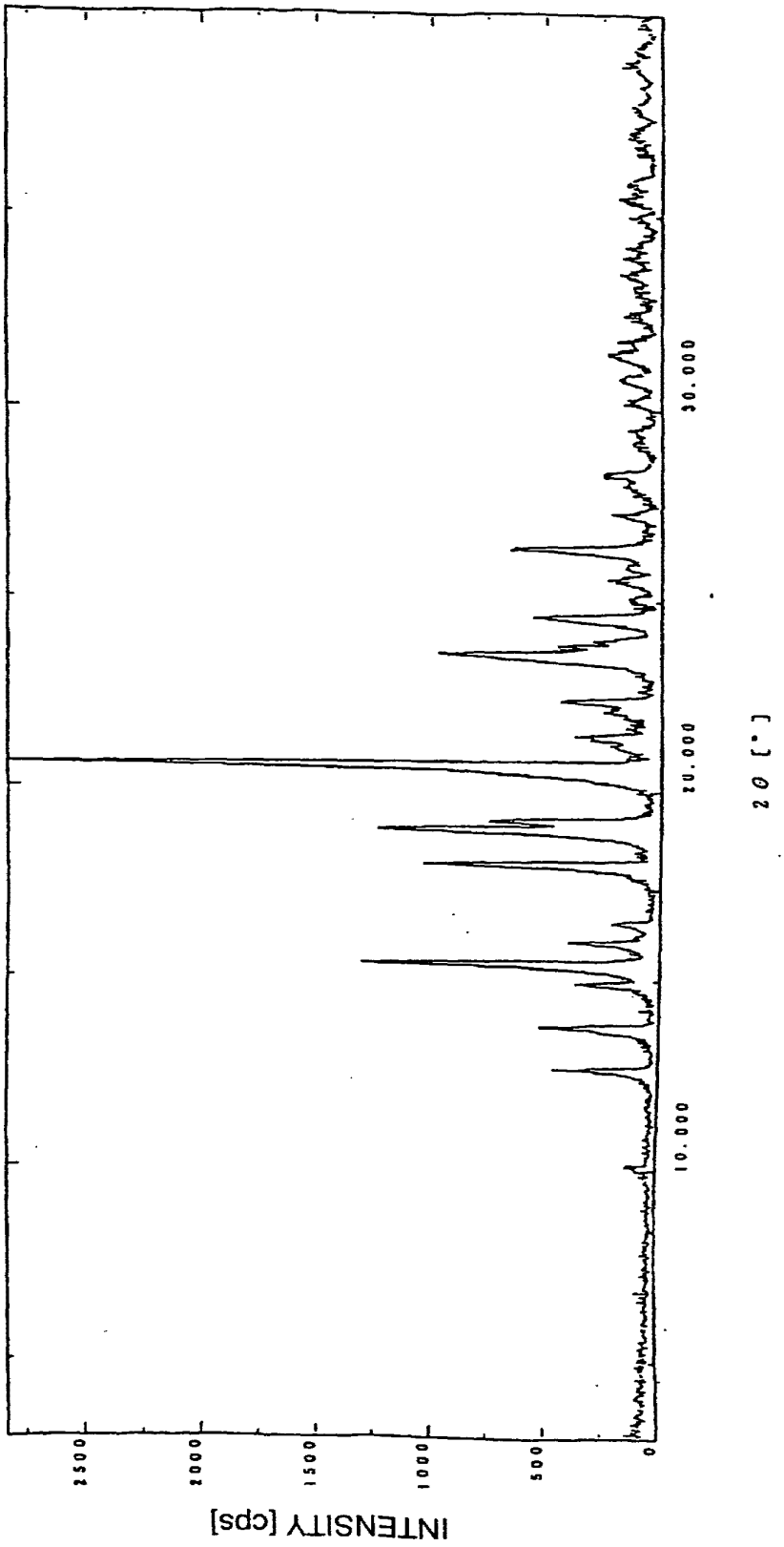


FIG.11

FIG.12

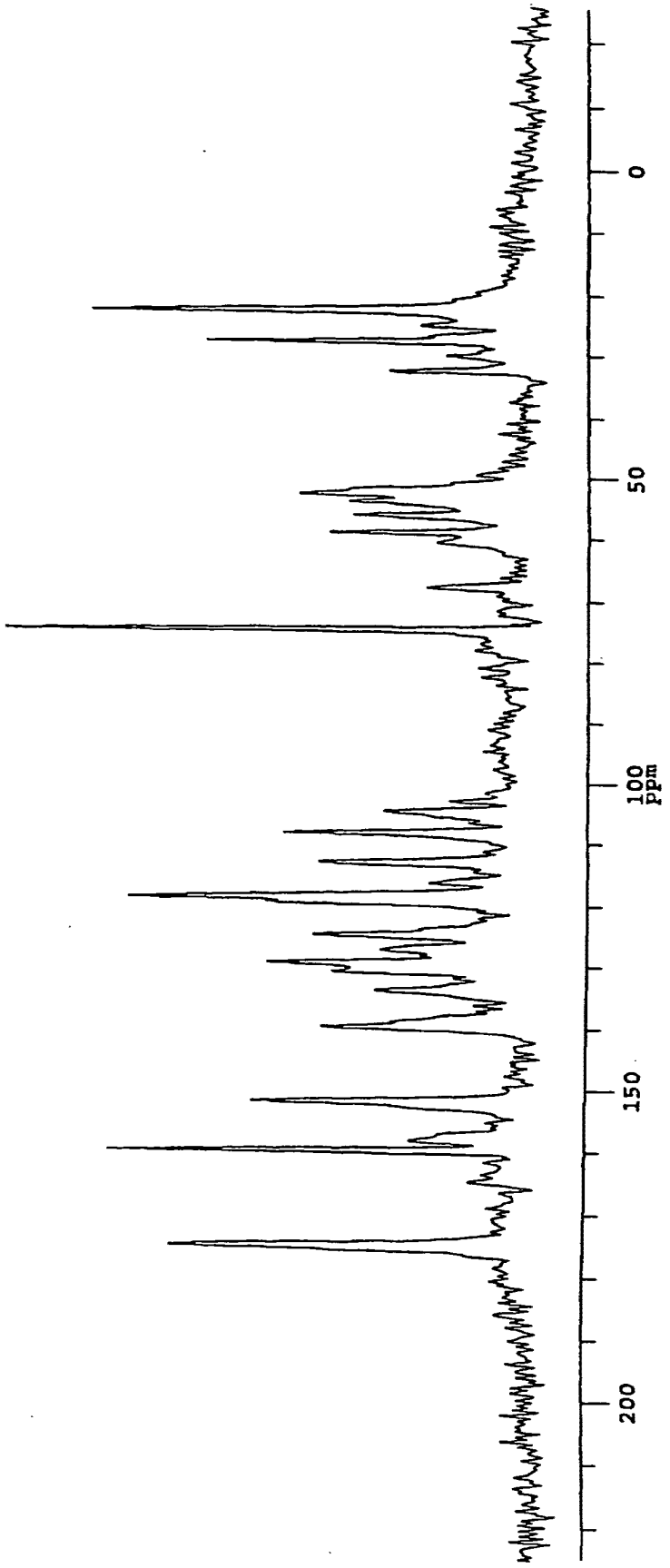


FIG.13

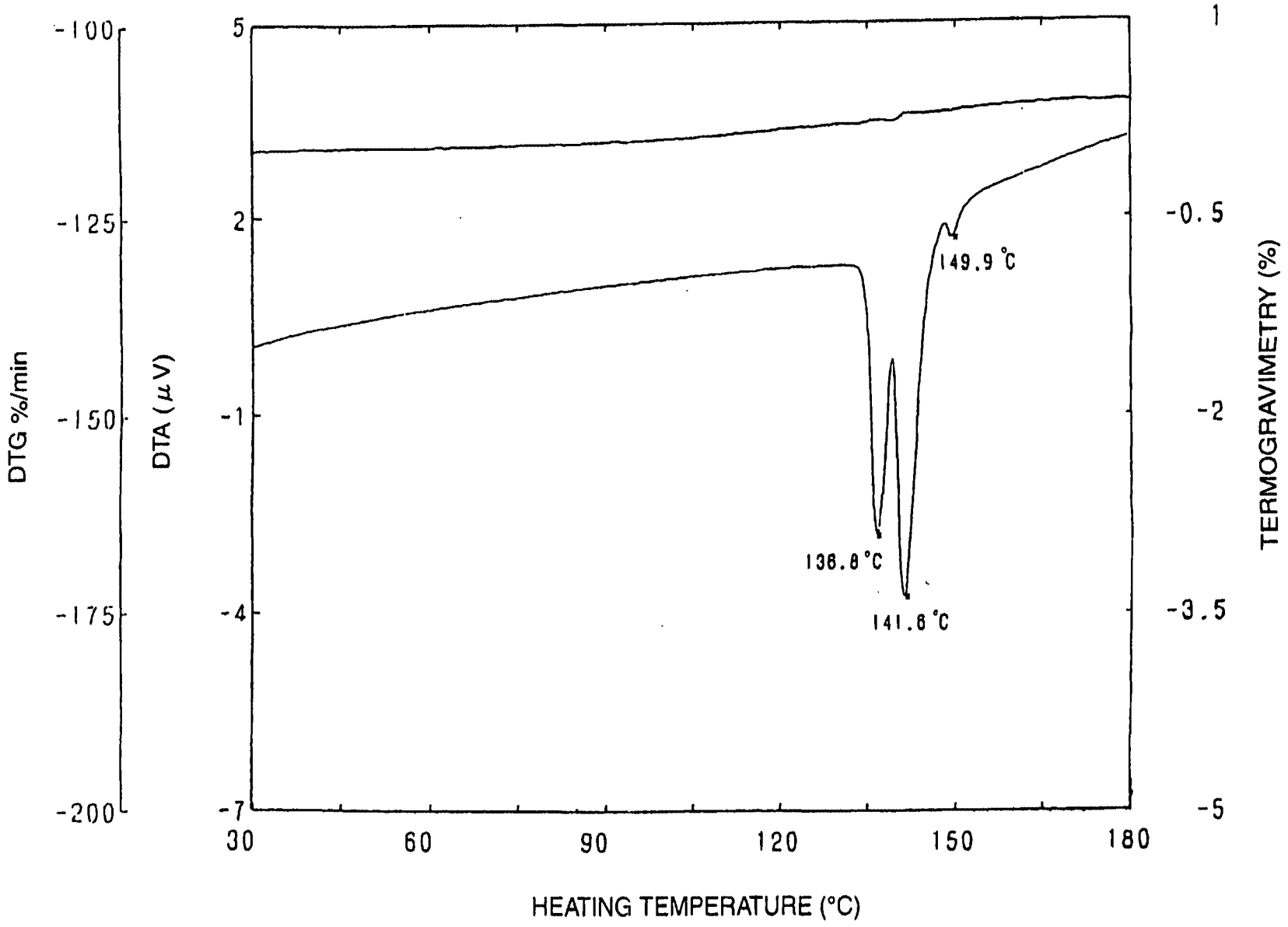


FIG.14

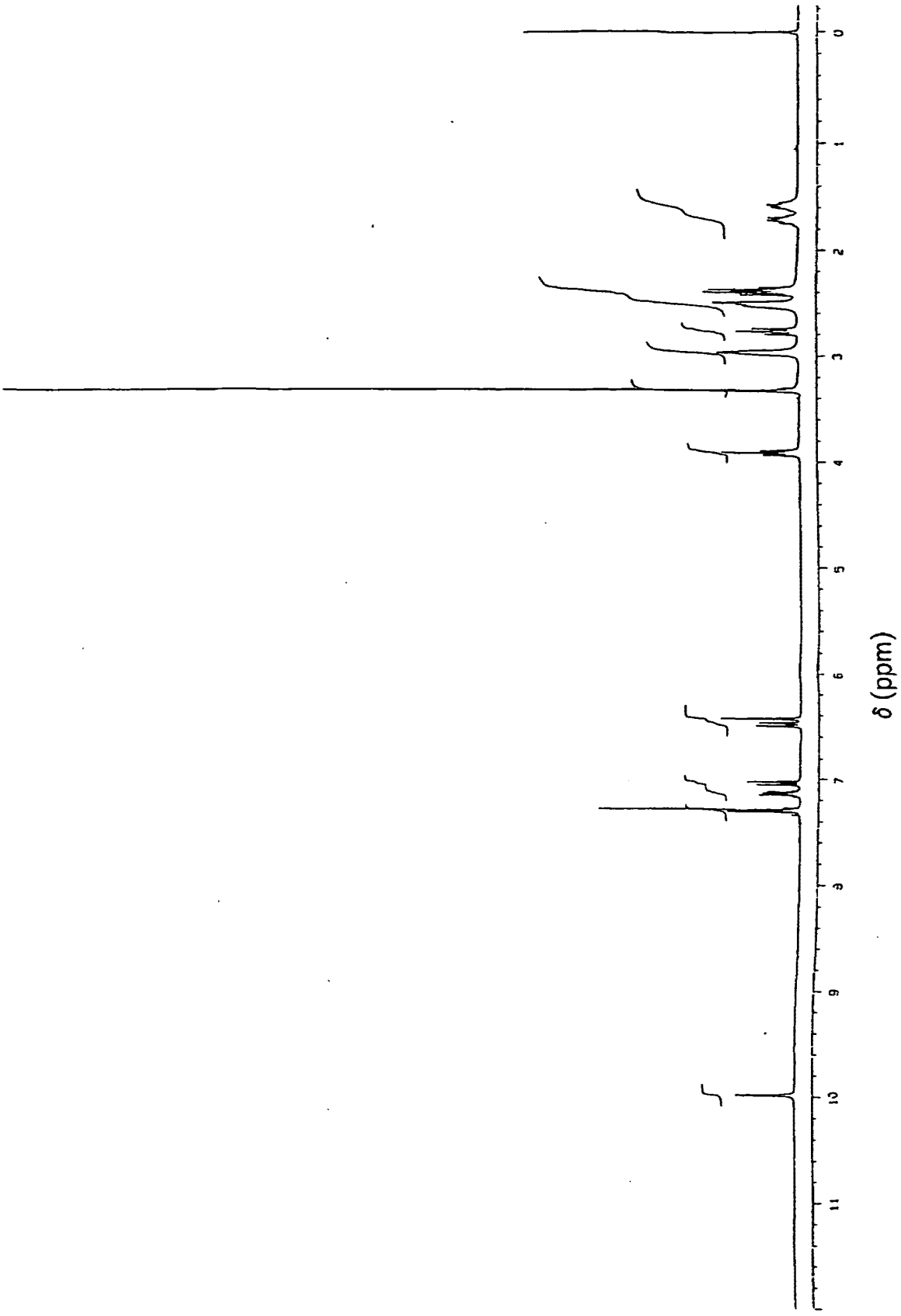
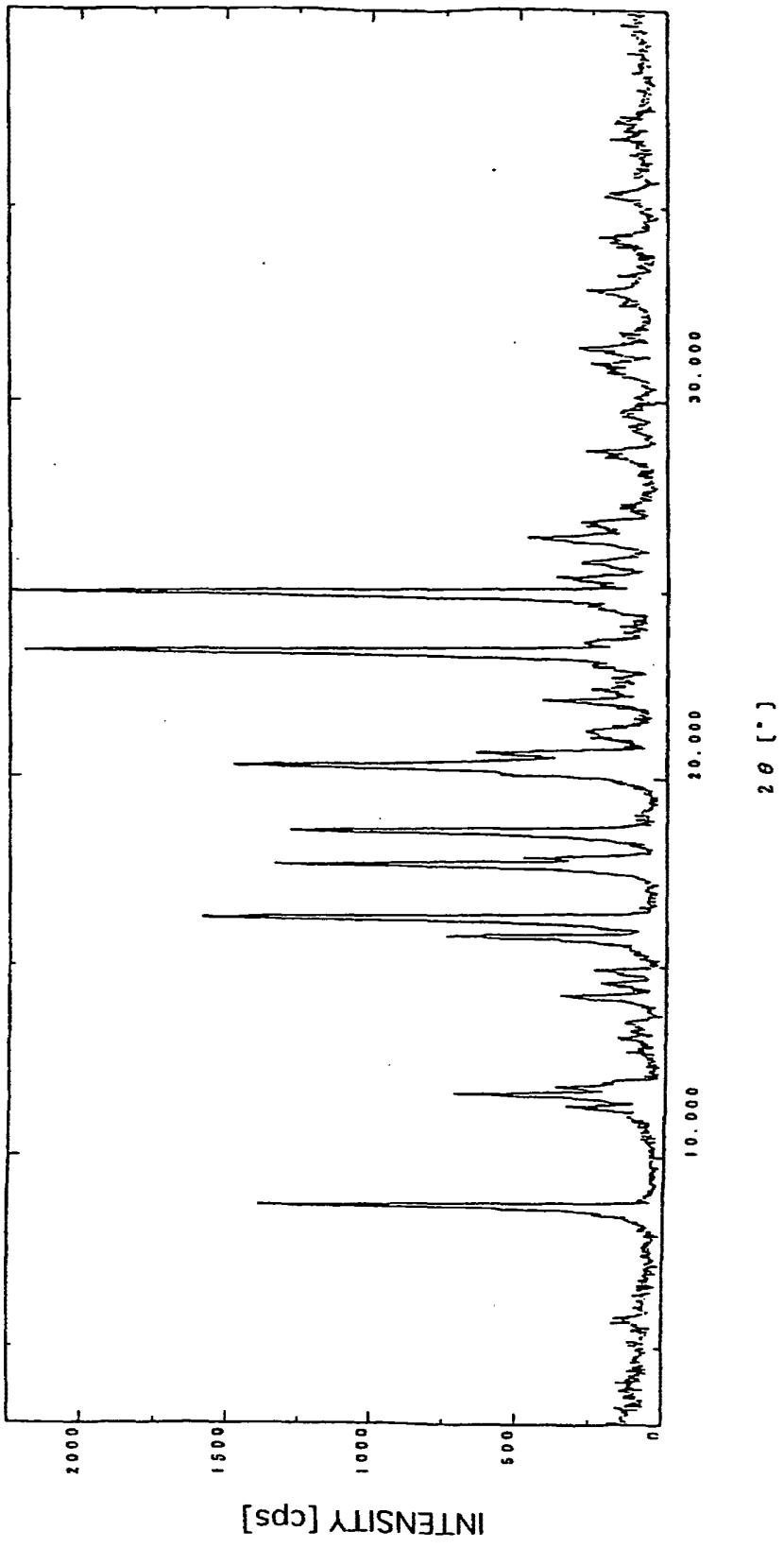


FIG.15



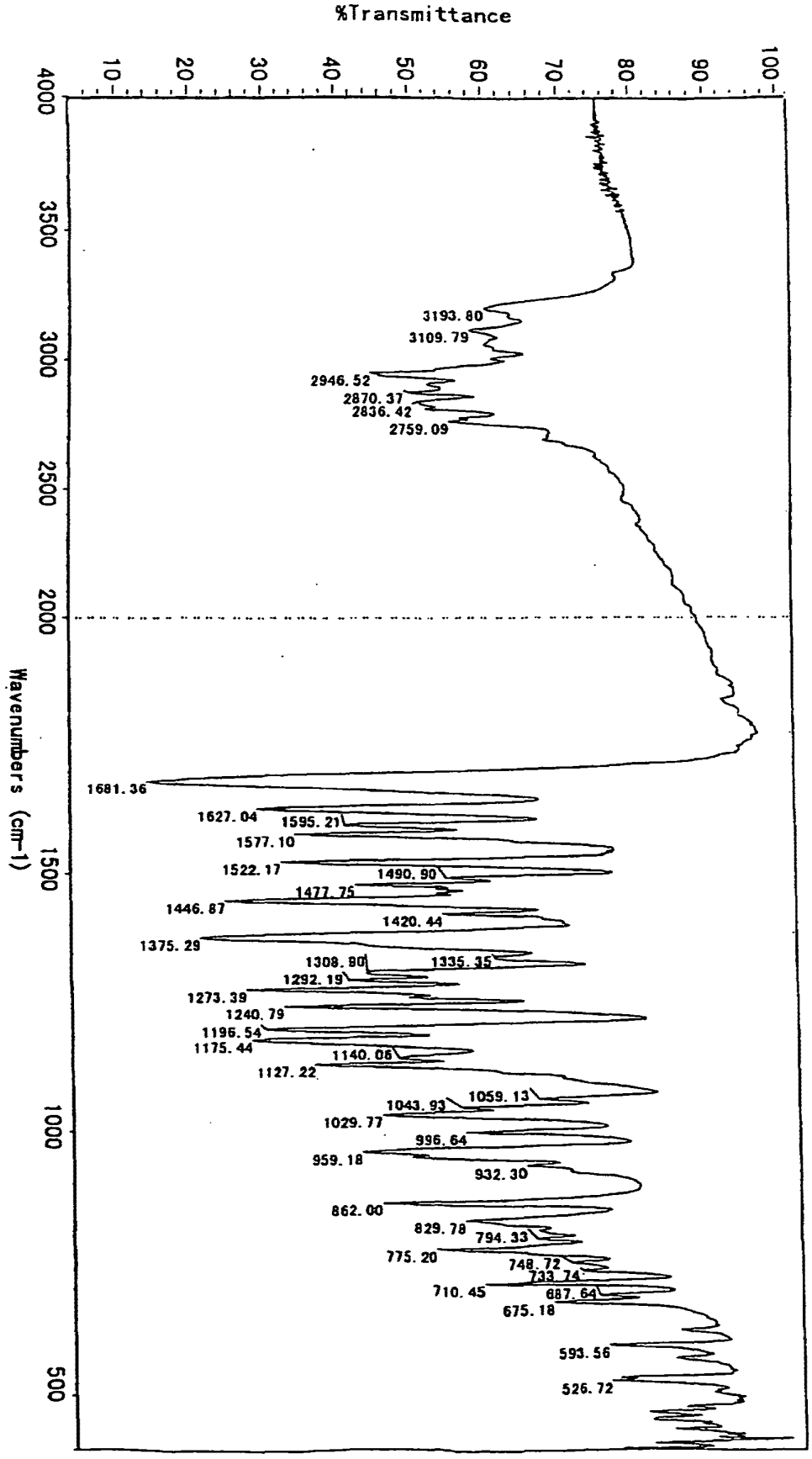
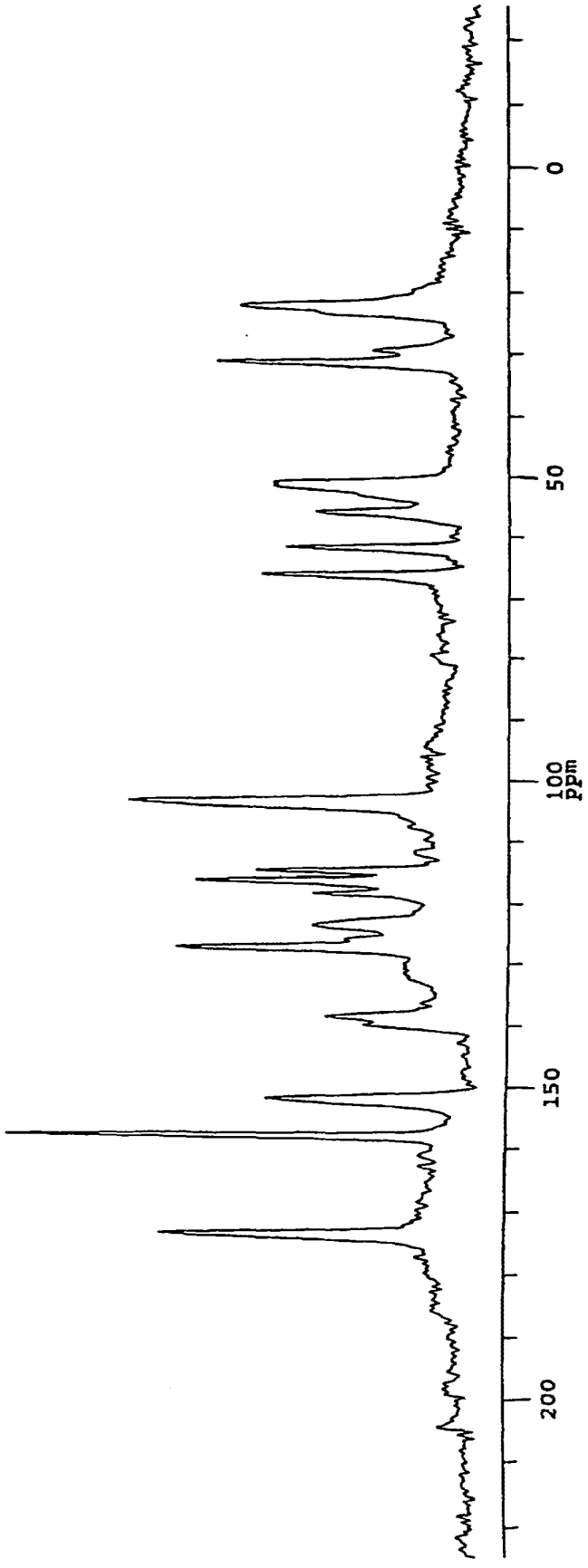


FIG.16

FIG.17



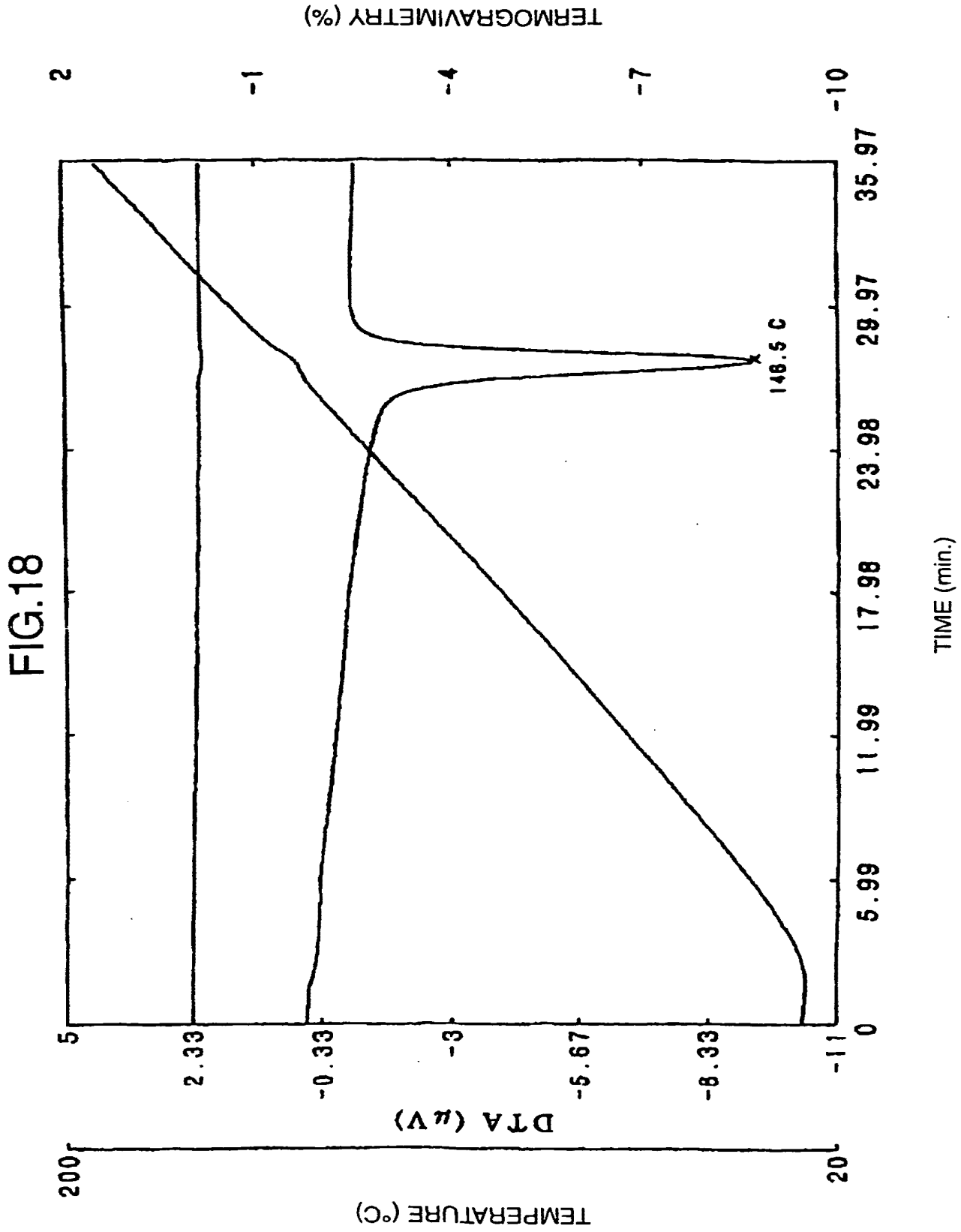

TERMOGRAVIMETRY (%)
2
-1
-4
-7
-10
146.5 C
35.97
29.97
23.98
17.98
11.99
5.99
0
TIME (min.)
5
2.33
-0.33
-3
-5.67
-8.33
-11
DTA (μV)
200
20
TEMPERATURE (°C)

FIG.18

FIG.19

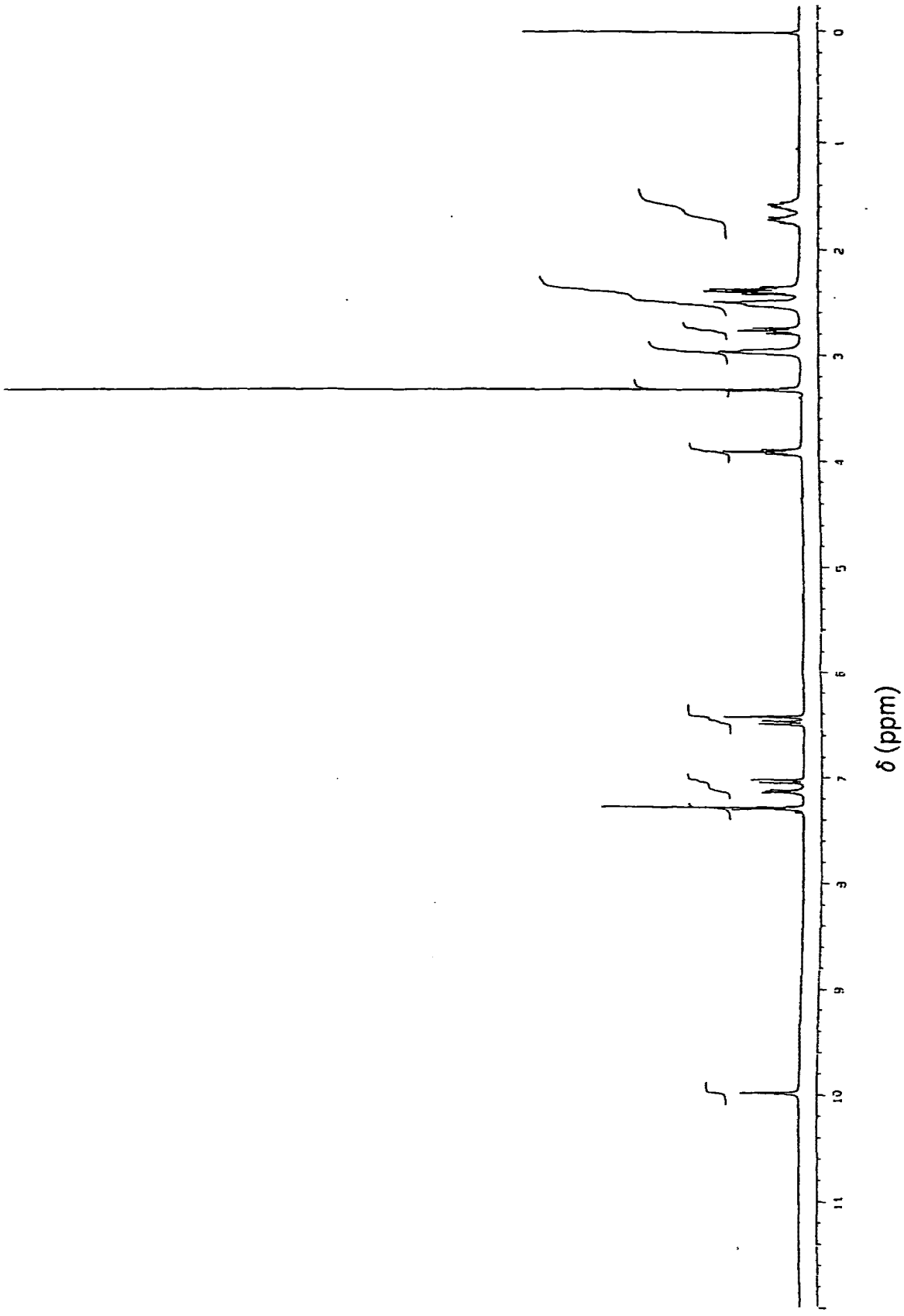
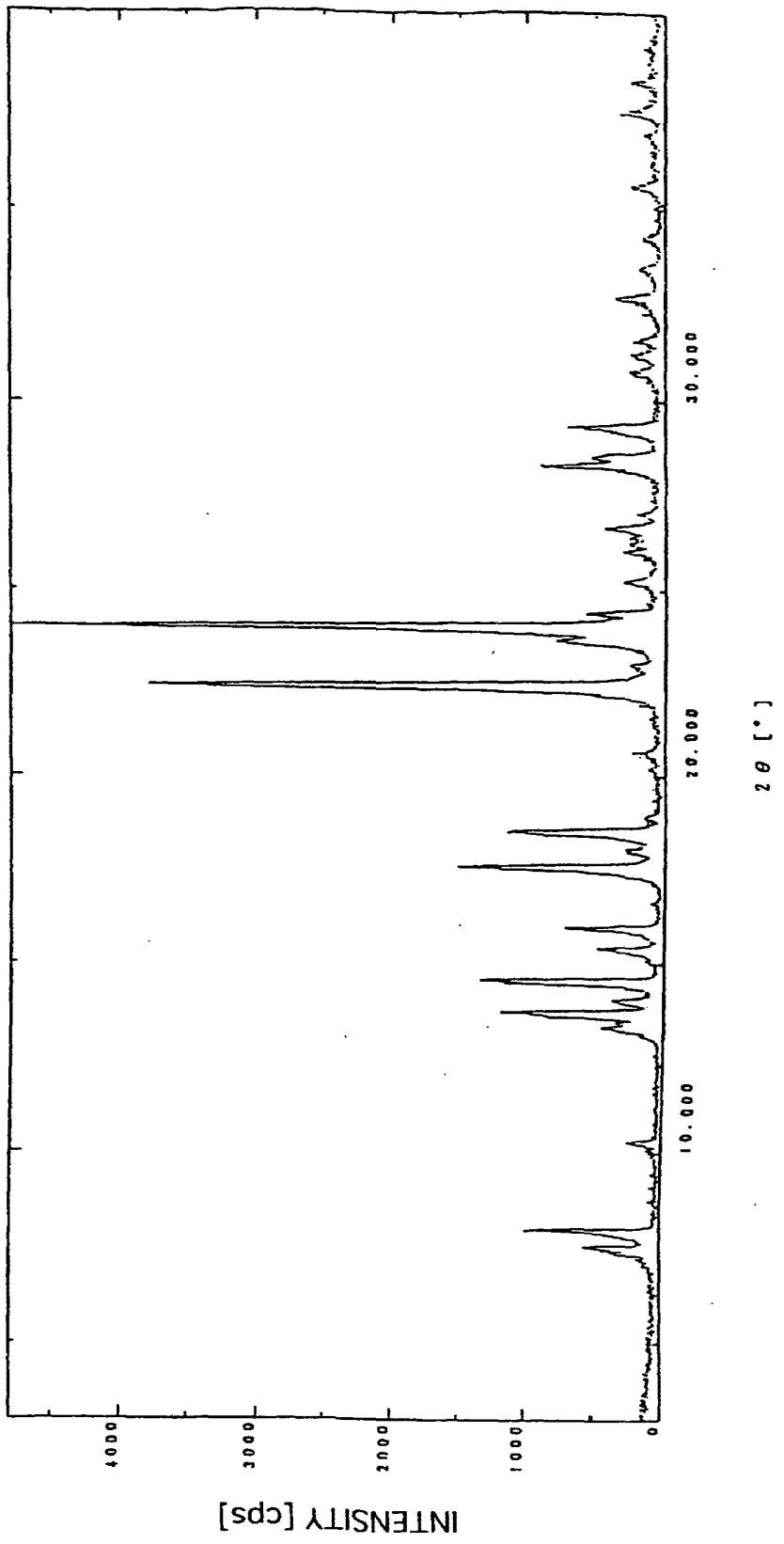


FIG.20



%Transmittance
30
40
50
60
70
80
90
100
110
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3059.71
2943.01
2866.17
2817.14
2766.84
1688.33
1626.91
1593.22
1577.85
1514.91
1488.49
1474.16
1448.82
1420.81
1404.93
1376.81
1334.33
1282.50
1256.94
1241.81
1201.99
1168.33
1138.92
1045.58
998.71
982.99
969.19
946.90
922.14
908.49
882.23
833.45
773.58
734.97
710.72
695.73
687.91
549.44
524.29
469.15
449.90

FIG.21

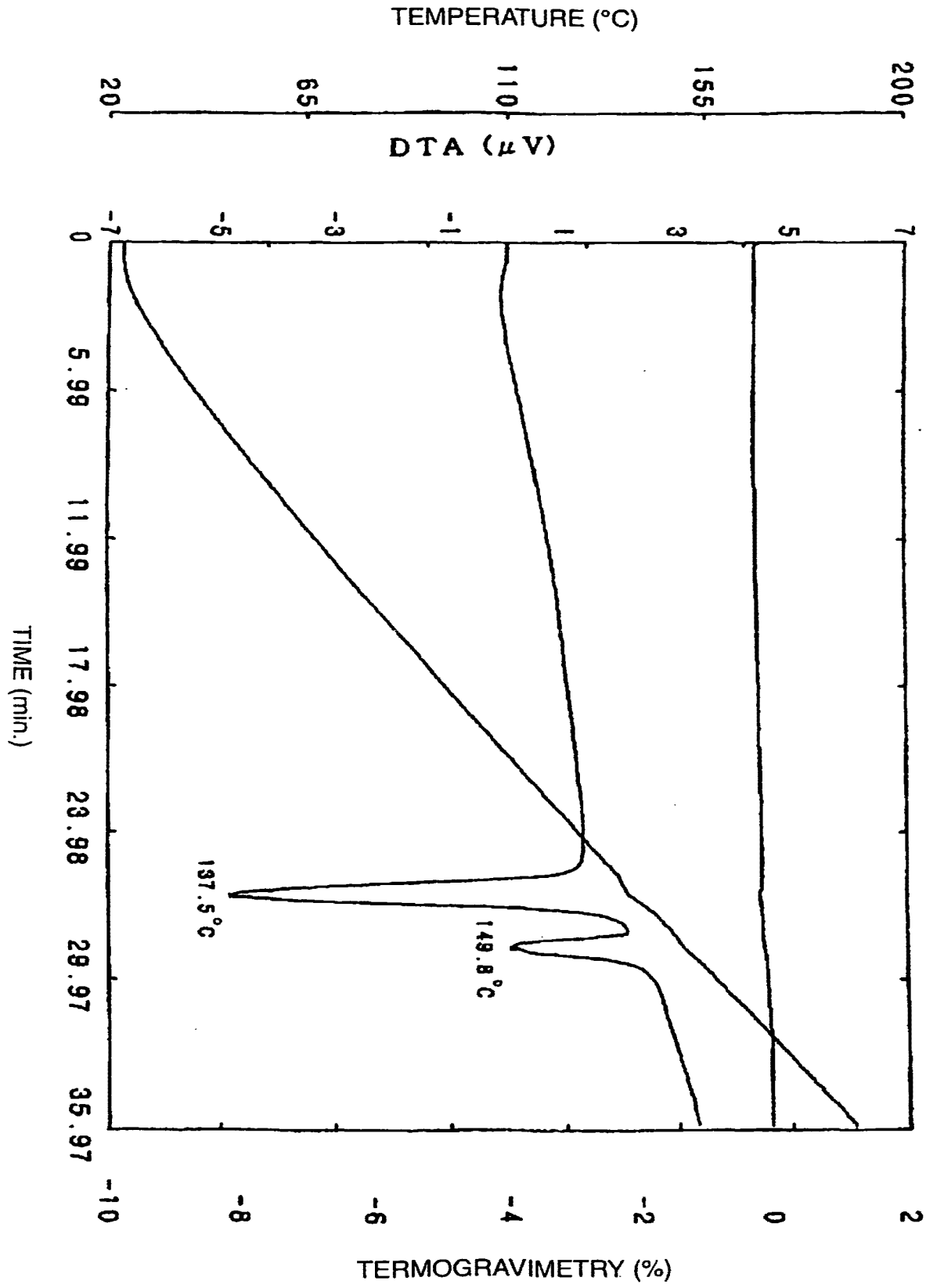


FIG.22

FIG.23

FIG.24

FIG.25

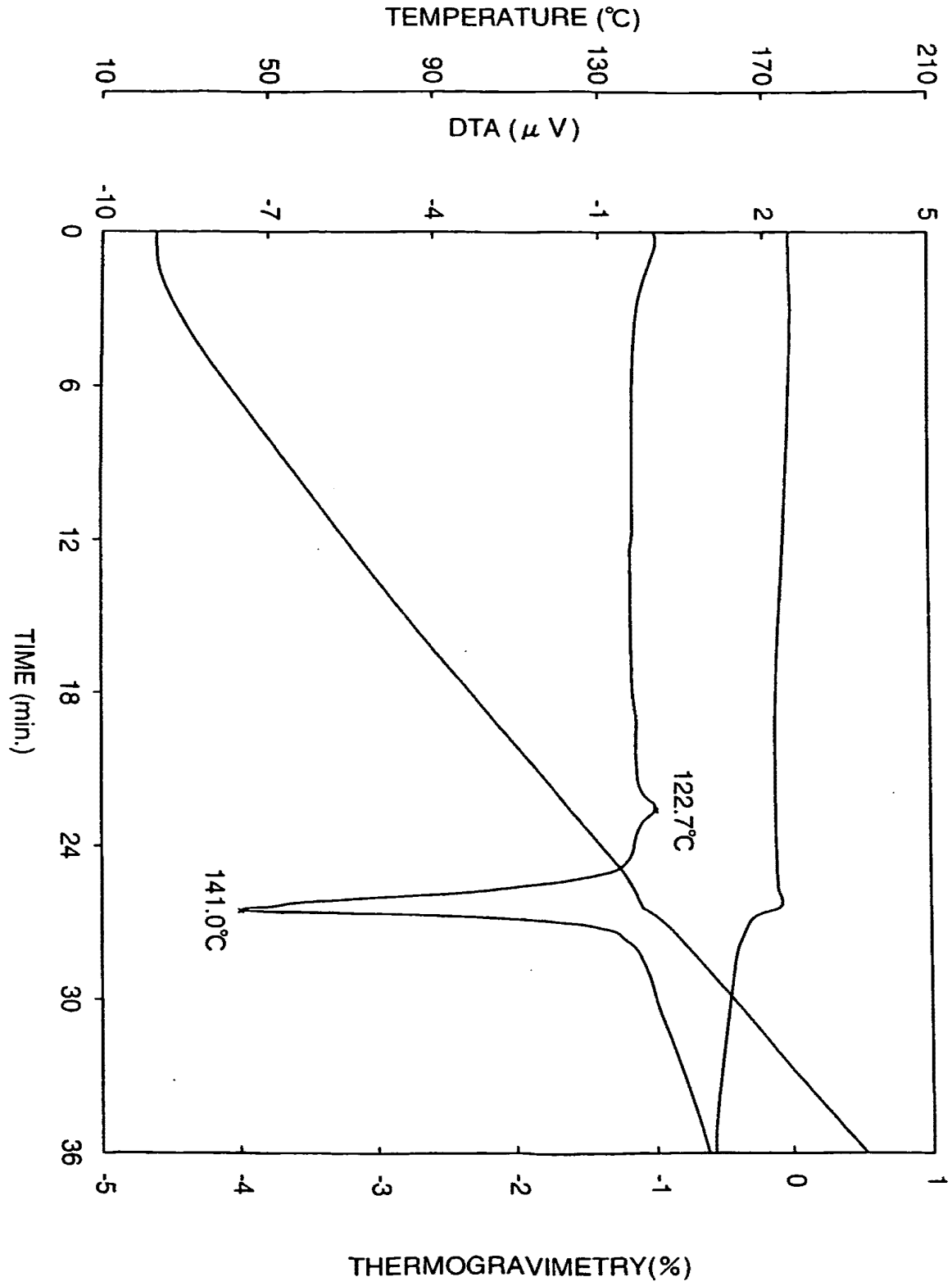


FIG.26

FIG.27

FIG.28

%Transmittance
10
20
30
40
50
60
70
80
90
100
110
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3202.69
3110.26
3055.50
2941.48
2812.81
1670.48
1624.69
1593.11
1575.63
1519.21
1477.18
1446.02
1420.65
1377.00
1334.69
1308.32
1274.11
1241.41
1194.65
1168.90
1136.47
1045.74
1030.17
962.05
947.25
857.60
786.53
736.35
713.59
674.96
620.48
587.92
572.62
526.10
480.43
465.22
432.16

FIG.29

FIG.30

FIG.31

INTERNATIONAL SEARCH REPORT

Internation: pplication No
PCT/JP 02/09858

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/496 C07D215/22 A61P25/18

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)
IPC 7 A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YASUO OSHIRO ET AL: "Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-'4-(4-Phenyl-1-piperazinyl)butoxy!-3,4-dihydro-2(1H)-quinolinone Derivatives" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 41, no. 5, 26 February 1998 (1998-02-26), pages 655-657, XP002948810 ISSN: 0022-2623 see compound 28 page 661 ---	1-140, 142-157
X	EP 0 367 141 A (OTSUKA PHARMA CO LTD) 9 May 1990 (1990-05-09) cited in the application example 1 -----	1-140, 142-157

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

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2002	21/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/09858

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 57-65 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 141
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:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 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

Information on patent family members

International application No
PCT/JP 02/09858

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0367141 A	09-05-1990	BR 1100204 A3	01-08-2000
		CN 1042537 A ,B	30-05-1990
		DE 68925405 D1	22-02-1996
		DE 68925405 T2	27-06-1996
		DK 539789 A	01-05-1990
		EP 0367141 A2	09-05-1990
		ES 2084594 T3	16-05-1996
		HK 1002706 A1	11-09-1998
		JP 2893175 B2	17-05-1999
		JP 10045717 A	17-02-1998
		JP 2976282 B2	10-11-1999
		JP 10045718 A	17-02-1998
		JP 7165720 A	27-06-1995
		JP 2191256 A	27-07-1990
		JP 2608788 B2	14-05-1997
		KR 138529 B1	15-05-1998
		MX 9202934 A1	30-06-1992
		US 5006528 A	09-04-1991

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 141

Present claim 141 relates to a product defined by reference to a desirable characteristic or property, namely having a specific dissolution rate.
The claim covers all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only one of such products . In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to aripiprazole.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 966 967 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
29.12.1999 Bulletin 1999/52

(21) Application number: **99303968.4**

(22) Date of filing: **21.05.1999**

(51) Int Cl.[6]: **A61K 31/55**, A61K 31/135, A61K 33/00, A61K 31/19, A61K 31/195

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **29.05.1998 US 87126 P**

(71) Applicant: **ELI LILLY AND COMPANY**
Indianapolis, Indiana 46285 (US)

(72) Inventor: **Tollefson, Gary Dennis**
Indianapolis, Indiana 46236 (US)

(74) Representative: **Hudson, Christopher Mark et al**
Eli Lilly and Company Limited,
Lilly Research Centre,
Erl Wood Manor
Windlesham Surrey GU20 6PH (GB)

(54) Combination therapy of olanzapine (zyprexa) and fluoxetine (prozac) for treatment of bipolar disorder

(57) The invention provides methods and compositions for the treatment of Bipolar Disorder, Bipolar Depression or Unipolar Depression, all with or without psychotic features. This method employs a compound having activity as an atypical antipsychotic and a serotonin reuptake inhibitor.

EP 0 966 967 A2

Description

[0001] The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides methods and compositions for treating Bipolar Disorder, Bipolar Depression or Unipolar Depression.

[0002] Bipolar Disorder is a psychiatric condition which is prevelant across cultures and age groups. The lifetime prevalence of Bipolar Disorder can be as high as 1.6%. DSM-IV, p. 353 (American Psychiatric Association, Washington, D.C. 1997). Bipolar Disorder is a recurrent disorder characterized by one or more Manic Episodes immediately before or after a Major Depressive Episode or may be characterized by one or more Major Depressive Episodes accompanied by at least one Hypomanic Episode. Additionally, the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

[0003] In some cases the Hypomanic Episodes themselves do not cause impairment; however, the impairment may result from the Major Depressive Episodes or from a chronic pattern of unpredictable mood episodes and fluctuating unreliable interpersonal and occupational functioning. The symptoms of Bipolar Disorder must not be better accounted for by a psychotic condition or due to the direct physiological effects of a medication, other somatic treatments for depression, drugs of abuse, or toxin exposure.

[0004] Bipolar Disorder is associated with a significant risk of completed suicide. Further, the patient suffering from Bipolar Disorder is likely to suffer from school truancy, school failure, occupational failure, or divorce.

[0005] Therefore, Bipolar Disorder is a serious, fairly prevelant, psychological condition which is clearly distinguished from psychotic conditions such as schizophrenia. DSM-IV, p. 353 (American Psychiatric Association, Washington, D. C. 1994).DSM-IV, p. 353 (American Psychiatric Association, Washington, D.C. 1994).

[0006] There remains a long felt need for treatments which provide a favorable safety profile and effectively provide relief for the patient suffering from Bipolar Disorder.

[0007] The invention provides a method for treating a patient suffering from or susceptible to Bipolar Disorder, Bipolar Depression or Unipolar Depression with or without psychotic features comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium.

[0008] As used herein, the term "Bipolar Disorder" shall refer to a condition characterized as a Bipolar Disorder, in the DSM-IV-R. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994) as catagory 296.xx. To further clarify, Applicants contemplate the treatment of both Bipolar Disorder I and Bipolar disorder II as described in the DSM-IV-R. The DSM-IV-R was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic catagories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

[0009] In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

[0010] As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

The Compounds

[0011] In the genieral expressions of the present invention, the first component is a compound which acts as an atypical antipsychotic. The essential feature of an atypical antipsychotic is less acute extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; (2) greater efficacy in the treatment of negative symptoms of schizophrenia; and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al., Neuropsychopharmacology, **14**(2), 111-123 , (1996)). Atypical antipsychotics include, but are not limited to:

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Patent No. 5,229,382 is herein incorporated by reference in its entirety;

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Patent No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., **24**, 62 (1988));

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663, which is herein incorporated by reference in its entirety;

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patent Nos. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety;

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt; and

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031. U.S. Patent Nos. 4,831,031 and 5,312,925 are herein incorporated by reference in their entirety.

[0012] Similarly, when the invention is regarded in its broadest sense, the second component compound is a compound which functions as a serotonin reuptake inhibitor, an anticonvulsant or lithium. The measurement of a compound's activity as an SSRI is now a standard pharmacological assay. Wong, et al., Neuropsychopharmacology 8, 337-344 (1993). Many compounds, including those discussed at length above, have such activity, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the protocol described by Wong *supra*. Serotonin reuptake inhibitors include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Patent 4,314,081 is an early reference on the compound. Robertson et al., J. Med. Chem. 31, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers;

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent;

Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., Neuropharmacology 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake;

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U.S. Patent 4,136,193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen et al., Eur. J. Pharmacol. 41, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour et al., Int. Clin. Psychopharmacol . 2, 225 (1987), and Timmerman et al., ibid., 239;

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U.S. Patent 4,085,225. Scientific articles about the drug have been published by Claassen et al., Brit. J. Pharmacol. 60, 505 (1977); and De Wilde et al., J. Affective Disord. 4, 249 (1982); and Benfield et al., Drugs 32, 313 (1986);

Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Patents 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, Eur. J. Pharmacol. 47, 351 (1978); Hassan et al., Brit. J. Clin. Pharmacol. 19, 705 (1985); Laursen et al., Acta Psychiat. Scand. 71, 249 (1985); and Battegay et al., Neuropsychobiology 13, 31 (1985);

Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor which is marketed as an antidepressant. It is disclosed by U.S. Patent 4,536,518;

Anticonvulsants contemplated as the second component include, but are not limited to, carbamezepine, valproic acid, lamotrigine, gabapentin and topiramate;

Carbamezepine, 5H-dibenz [b,f] azepine-5-carboxamide is an anticonvulsant and analgesic marketed for trigeminal neuralgia; U.S. Patent 2,948,718 (herein incorporated by reference in their entirety), discloses carbamezepine and methods of use;

Valproic Acid, 2-propylpentanoic acid or dispropylacetic acid is a well known antiepileptic agent which dissociates

to the valproate ion in the gastrointestinal tract; various pharmaceutically acceptable salts are disclosed in U.S. Patent 4,699,927.

Lamotrigine, 6-(2,3-dichlorophenyl)-1,2,4-trizine-3,5-diamine is an antiepileptic drug indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. Lamotrigine and its uses is disclosed in U.S. Patent 4,486,354, herein incorporated by reference in its entirety;

Gabapentin, 1-(aminomethyl)cyclohexane acetic acid, is an anticonvulsant indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin and its methods of use is described in U.S. Patents 4,024,175 and 4,087,544 herein incorporated by reference in their entirety;

Topiramate, 2,3:4,5-di-O-(1-isopropylidine)-3-D-fructopyranose sulphamate is an antiepileptic indicated for the treatment of refractory partial seizures, with or without secondary generalization and disclosed in U.S. Patent 4,513,006 herein incorporated by reference in its entirety; and

Lithium, preferably lithium carbonate, is indicated in the treatment of manic episodes of manic depressive illness.

[0013] All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

[0014] It will be understood that while the use of a single atypical antipsychotic as a first component compound is preferred, combinations of two or more atypical antipsychotics may be used as a first component if necessary or desired. Similarly, while the use of a single serotonin reuptake inhibitor as a second component compound is preferred, combinations of two or more serotonin reuptake inhibitors may be used as a second component if necessary or desired.

[0015] While all combinations of first and second component compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

olanzapine/fluoxetine
olanzapine/venlafaxine
olanzapine/citralopram
olanzapine/fluvoxamine
olanzapine/paroxetine
olanzapine/sertraline
olanzapine/milnacipran
olanzapine/duloxetine
clozapine/fluoxetine
risperidone/fluoxetine
sertindole/fluoxetine
quetiapine/fluoxetine
ziprasidone/fluoxetine

[0016] In general, combinations and methods of treatment using olanzapine as the first component are preferred. Furthermore, combinations and methods of treatment using fluoxetine as the second component are preferred. Especially preferred are combinations and methods of treatment using olanzapine as the first component and fluoxetine as the second component.

[0017] It is especially preferred that when the first component is olanzapine, it will be the Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665

(continued)

d
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

[0018] A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72
4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45

(continued)

d	I/I_1
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

[0019] The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper K_a radiation source of wavelength, 1 =1·541Å.

[0020] It is further preferred that the Form II olanzapine polymorph will be administered as the substantially pure Form II olanzapine polymorph.

[0021] As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II should contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005% content of acetonitrile. Additionally, the polymorph of the invention should contain less than 0.5% of associated water.

[0022] The polymorph obtainable by the process taught in the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein d represents the interplanar spacing:

d
9.9463
8.5579
8.2445
6.8862
6.3787
6.2439
5.5895
5.3055
4.9815
4.8333
4.7255
4.6286
4.533
4.4624
4.2915
4.2346
4.0855
3.8254
3.7489
3.6983
3.5817
3.5064
3.3392
3.2806
3.2138
3.1118
3.0507

(continued)

d
2.948
2.8172
2.7589
2.6597
2.6336
2.5956

[0023] A typical example of an x-ray diffraction pattern for Form I is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
9.9463	100.00
8.5579	15.18
8.2445	1.96
6.8862	14.73
6.3787	4.25
6.2439	5.21
5.5895	1.10
5.3055	0.95
4.9815	6.14
4.8333	68.37
4.7255	21.88
4.6286	3.82
4.533	17.83
4.4624	5.02
4.2915	9.19
4.2346	18.88
4.0855	17.29
3.8254	6.49
3.7489	10.64
3.6983	14.65
3.5817	3.04
3.5064	9.23
3.3392	4.67
3.2806	1.96
3.2138	2.52
3.1118	4.81
3.0507	1.96
2.948	2.40
2.8172	2.89
2.7589	2.27
2.6597	1.86
2.6336	1.10
2.5956	1.73

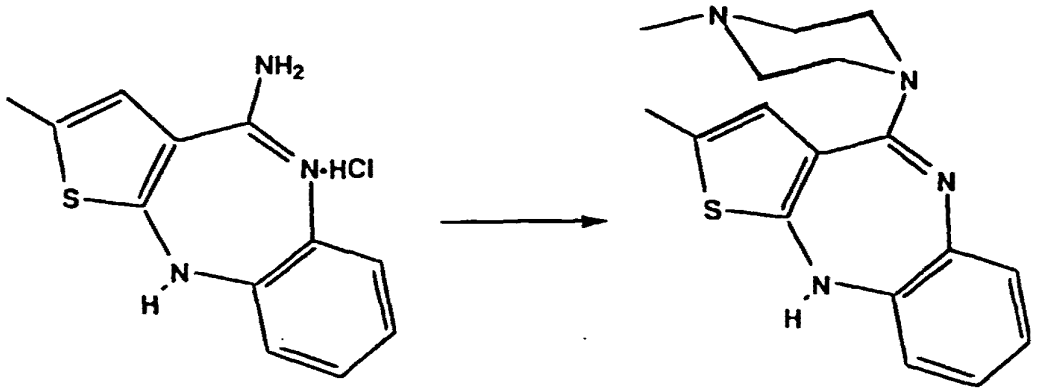
[0024] The x-ray powder diffraction patterns herein were obtained with a copper K_a of wavelength 1 = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I_1".

[0025] Though Form II olanzapine is preferred it will be understood that as used herein, the term "olanzapine" embraces all solvate and polymorphic forms unless specifically indicated.

Preparation 1

Technical Grade olanzapine

[0026]



Intermediate 1

[0027] In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical)	6 volumes
Intermediate 1	75 g
N-Methylpiperazine (reagent) equivalents	6

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the above-referenced '382 patent.

[0028] A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until = 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.
Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II olanzapine polymorph

[0029] A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.
Yield: 197 g.

[0030] The process described above for preparing Form II provides a pharmaceutically elegant product having potency ≥ 97%, total related substances < 0.5% and an isolated yield of > 73%.

[0031] It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above

as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

[0032] Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, b-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

Administration

[0033] The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Olanzapine: from about 0.25 to 100 mg, once/day; preferred, from 1 to 30 mg, once/day; and most preferably 1 to 25 mg once/day;
Clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;
Risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;
Sertindole: from about .0001 to 1.0 mg/kg daily;
Quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;
Ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily;
Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;
Duloxetine: from about 1 to about 160 mg once/day; or up to 80 mg twice daily; preferred, from about 5 to about 20 mg once/day;
Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day;
Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day;
Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day;
Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day;
Paroxetine: from about 20 to about 50 mg once/day; preferred, from about 20 to about 30 mg once/day;
Sertraline: from about 20 to about 500 mg once/day; preferred, from about 50 to about 200 mg once/day;
Lithium: from about 600 to 2100 mg/day; preferably 1200 mg/day;
Carbamezepine: from about 200 to 1200 mg/day; preferably 400 mg/day;
Valproic Acid: from about 250 to 2500 mgday; preferably 1000 mg/day;
Lamotrigine: from about 50 to 600mg/day in 1 to 2 doses; preferably 200 to 400 mg; most preferably 200 mg;
Gabapentin: from about 300 to 3600 mg/day in 2 to 3 divided doses; preferably 300 to 1800 mg/day; most preferably 900 mg/day;
Topiramate: from about 200 to 600 mg/day divided in 2 doses; most preferably 400 mg/day.

[0034] In more general terms, one would create a combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

[0035] Preferred ratios of olanzapine/fluoxetine by weight include:

1/5 6/25 12.5/25 25/50 17.5/50 25/75	olanzapine: fluoxetine

[0036] The adjunctive therapy of the present invention is carried out by administering a first component together with the second component in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

[0037] However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

[0038] The adjunctive combination may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

[0039] The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

[0040] Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[0041] Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

[0042] A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

[0043] Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, meth-

ylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

[0044] Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

[0045] A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. This enteric formulation is described in U.S. Patent No. 5,508,276, herein incorporated by reference in its entirety.

[0046] Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

[0047] When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

[0048] Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

[0049] The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

[0050] Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Olanzapine	25 mg
Fluoxetine, racemic, hydrochloride	20
Starch, dried	150
Magnesium stearate	10
Total	210 mg

Formulation 2

[0051] A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Olanzapine	10
Fluoxetine, racemic, hydrochloride	10
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total	310 mg

The components are blended and compressed to form tablets each weighing 465 mg.

Formulation 3

[0052] An aerosol solution is prepared containing the following components:

	Weight
Risperidone	5 mg
(+)-Duloxetine, hydrochloride	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	60.00
Total	100.75 mg

[0053] The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to-30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

[0054] Tablets, each containing 80 mg of active ingredient, are made as follows:

Sertindole	60 mg
(+)-Duloxetine, hydrochloride	20 mg
Starch	30 mg
Microcrystalline cellulose	20 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	140 mg

[0055] The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

Formulation 5

[0056] Capsules, each containing 130 mg of active ingredient, are made as follows:

Quetiapine	70 mg
Fluoxetine, racemic, hydrochloride	30 mg
Starch	39 mg
Microcrystalline cellulose	39 mg
Magnesium stearate	2 mg
Total	180 mg

[0057] The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 250 mg quantities.

Formulation 6

[0058] Suppositories, each containing 45 mg of active ingredient, are made as follows:

Ziprasidone	75 mg
(+)-Duloxetine, hydrochloride	5 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,080 mg

[0059] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

[0060] Suspensions, each containing 70 mg of active ingredient per 5 ml dose, are made as follows:

Olanzapine	20 mg
Sertraline	100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

[0061] The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

[0062] An intravenous formulation may be prepared as follows:

Olanzapine	20 mg
Paroxetine	25 mg
Isotonic saline	1,000 ml

Microdialysis assays of monoamines

[0063] Sprague-Dawley rats (Harlan or Charles River) weighing 270-300 grams are surgically implanted with microdialysis probes under chloral hydrate/pentobarbital anesthesia (170 and 36 mg/kg i.p. in 30% propylene glycol, 14% ethanol) (Perry and Fuller, Effect of fluoxetine on serotonin and dopamine concentration in rat hypothalamus after administration of fluoxetine plus L-5-hydroxytryptophan, Life Sci., 50, 1683-90 (1992)). A David Kopf stereotaxic instrument is used to implant the probe unilaterally in the hypothalamus at coordinates rostral -1.5 mm, lateral -1.3 mm, and ventral -9.0 mm (Paxinos and Watson, 1986). After a 48 hour recovery period, rats are placed in a large plastic bowl with a mounted liquid swivel system (CMA/120 system for freely moving animals, Bioanalytical Systems, West Lafayette, IN). Filtered artificial cerebrospinal fluid (CSF) (150 mM NaCl, 3.0 mM KCl, 1.7 mM CaCl2, and 0.9 mM MgCl2) is perfused through the probe at a rate of 1.0 ml/min. The output dialysate line is fitted to a tenport HPLC valve with a 20 ml loop. At the end of each 30 minute sampling period, dialysate collected in the loop is injected on an analytical column (Spherisorb 3 m ODS2, 2X150 mm, Keystone Scientific).

[0064] The method used to measure monoamines is as described by Perry and Fuller (1992). Briefly, dialysate collected in the 20 ml loop is assayed for 5-HT, NE and DA. The 20 ml injection goes onto the column with a mobile phase which resolves NE, DA, and 5-HT: 75 mM potassium acetate, 0.5 mM ethylenediaminetetraacetic acid, 1.4 mM sodium octanesulfonic acid and 8% methanol, pH 4.9. The mobile phase for the amine column is delivered with a flow programmable pump at an initial flow rate of 0.2 ml/min increasing to 0.3 ml/min at 5 min then decreasing back to 0.2 ml/min at 26 min with a total run time of 30 min. Flow programming is used to elute the 5-HT within a 25 min time period. The electrochemical detector (EG&G, Model 400) for the amine column is set at a potential of 400 mV and a sensitivity

of 0.2 nA/V. Basal levels are measured for at least 90 minutes prior to drug administration. The drugs are prepared in filtered deionized water (volume 0.25-0.3 ml) for administration at the desired doses.

Clinical Trials

[0065] The usefulness of the compound for treating a Bipolar Disorder can be supported by the following studies as described.

Clinical observations.

[0066] A double-blind multicenter clinical trial is designed to assess the safety and efficacy of an atypical antipsychotic in combination with an SSRI, such as fluoxetine for treatment of Bipolar Disorder, Bipolar Depression or Unipolar Depression. Patients are randomized to an atypical antipsychotic, such as olanzapine, an SSRI, such as fluoxetine or an atypical antipsychotic plus an SSRI.

[0067] In one such study, an 8-week, double blind trial, 28 patients diagnosed with treatment-resistant major depression were randomized to one of three treatment arms: (1) fluoxetine (20-60 mg/day) and placebo; (2) olanzapine (5-20 mg/day) and placebo; or (3) fluoxetine plus olanzapine (20-60 mg/day and 5-20 mg/day, respectively). The efficacy of the treatment was monitored using the HAMD-21 (Hamilton M. *Journal of Neurology, Neurosurgery & Psychiatry.* 1960.23:56-62, and Hamilton M. *Development of a rating scale for primary depressive illness.* British Journal of Social and Clinical Psychology. 1967;6:278-296), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery SA, Asberg M. A *new depression scale designed to be sensitive to change.* British Journal of Psychiatry. 1979;134:382-389), and the Clinical Global Impression (CGI) - Severity of Depression rating scale (Guy, W. ECDEU Assessment Manual for Psychopharmacology. Revised ed. US Dept of Health, Education and Welfare, Bethesda, MD. 1976). The olanzapine plus fluoxetine group experienced a greater improvement on the HAMD-21 total score that either of the monotherapy groups. Similar results were obtained using the CGI scale.

[0068] The antidepressant effect of olanzapine plus fluoxetine was evident within seven days of beginning the therapy. This is significantly earlier than is generally seen with a monotherapy using a serotonin uptake inhibitor alone, with no evidence of significant adverse interaction between-the antipsychotic and the serotonin reuptake inhibitor.

Claims

1. A method for treating a patient suffering from or susceptible to Bipolar Disorder, Bipolar Depression or Unipolar Depression comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium.

2. A method of **Claim 1** where the first component is chosen from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone; and the second component is selected from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine.

3. A method of **Claim 1** wherein the first component compound is olanzapine.

4. A method of **Claim 2** wherein the second component compound is fluoxetine.

5. A method of **Claim 1** where administration of the compounds is oral.

6. A method of Claim 1 wherein the Bipolar Disorder is Bipolar Disorder I.

7. A method of **Claim 1** wherein the Bipolar Disorder is Bipolar Disorder II.

8. A method of **Claim 1** wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577

(continued)

d
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

9. A method of **Claim 1** wherein the effective amount of olanzapine is from about 1 mg to about 25 mg per day.

10. A method of **Claim 9** wherein the effective amount of olanzapine is from about 1 mg to about 20 mg per day.

11. A method of any one of **Claims 1 to 8** wherein the ratio of olanzapine to fluoxetine by weight is selected from the group consisting of 1/5, 6/25,. 12.5/25, 25/50, 17.5/50 and 25/75.

12. A method of **Claim 1** where the first component is selected from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine and ziprasidone; and the second component is selected from the group consisting of lithium, carbamezepine, valproic acid, lamotrigine, gabapentin and topiramate.

13. The use of an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium, for the manufacture of a medicament for the treatment of bipolar disorder, bipolar depression or unipolar depression.

14. A pharmaceutical composition adapted for the treatment of a patient suffering from, or susceptible to bipolar disorder, bipolar depression or unipolar depression, comprising as the active ingredients a combination of an atypical antipsychotic and a second component selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

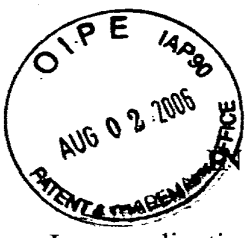
APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/556,600		1617	05P0

Correspondence Address / Fee Address Change

The following fields have been set to Customer Number 23373 on 07/06/2006

- Correspondence Address

The address of record for Customer Number 23373 is:
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON,DC 20037



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, et al.

Docket No: Q81665

Appln. No.: 10/556,600

Group Art Unit: Unknown

Confirmation No.: Unknown

Examiner: Unknown

Filed: November 14, 2005

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

SUBMISSION OF EXECUTED DECLARATION

MAIL STOP PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In view of the application filed on November 14, 2005 without the appropriate executed documents, and since Applicant's attorney has not yet received the "Notification of Missing Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office (DO/EO/US)," for the above-identified application, Applicant submits herewith a copy of the Declaration, properly executed by the inventors.

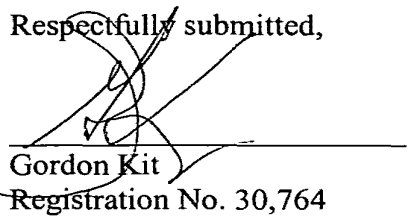
A check for the statutory fee of $130.00 is attached. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A

08/07/2006 ATRAN1 00000125 10556600
01 FC:1617 130.00 OP

Submission of Executed Declaration
U.S. application No. 10/556,600

duplicate copy of this paper is attached.

Respectfully submitted,



Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: August 2, 2006

Declaration and Power of Attorney for Patent Application
特許出願宣言書および委任状

Japanese Language Declaration

私は下記発明者として以下の通り宣言します：

As a below named inventor, I hereby declare that:

私の住所、郵送先、および国籍は私の氏名の後に記載された通りです。

My residence, mailing address and citizenship are as stated next to my name.

下記名称の発明に関し請求範囲に記載され特許出願がされている発明内容につき、私が最初、最先かつ唯一の発明者（下記氏名が一つのみの場合）であるか、あるいは最初、最先かつ共同発明者（下記氏名が複数の場合）であると信じます。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

下記項目に x 印が付いている場合を除き、上記発明の明細書は本書に添付されます。

the specification of which is attached hereto unless the following box is checked:

☐ 上記発明は米国出願番号あるいは PCT 国際出願番号_____（確認番号_____）として_____年__月__日に出願され、_____年__月__日に補正されました（該当する場合）。

☒ was filed on May 19, 2004 as United States Application Number or PCT International Application Number PCT/US04/13308 (Conf. No. _____) and was amended on _____ (if applicable).

私は特許請求範囲を含み上述の補正で補正された前記明細書の内容を検討し、理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は連邦規則法典第 37 編 1 条 56 項に定義される特許性に肝要な情報について開示義務があることを認めます。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Japanese Language Declaration

私は米国法典第 35 編 119 条(a)-(d)あるいは 365 条(b)に基づき特許あるいは発明者証書の下記外国出願、または 365 条(a)に基づき米国以外の少なくとも 1 ヶ国を指定した下記 PCT 外国出願についての外国優先権をここに主張するとともに、下記項目に x 印を付けることにより優先権を主張する出願以前の出願日を有する特許あるいは発明者証書の外国出願あるいは PCT 外国出願を示します。

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior foreign application(s) 外国での先行出願			Priority Claimed 優先権の主張
			Yes 有り / No 無し
(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	
(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	

私は米国法典第 35 編 119 条(e)に基づき下記の米国仮特許の利益をここに主張します。

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

		60/473378	23/May/2003
(Application No.) (出願番号)	(Filing Date) (出願日)	(Application No.) (出願番号)	(Filing Date) (出願日)
(Application No.) (出願番号)	(Filing Date) (出願日)	(Application No.) (出願番号)	(Filing Date) (出願日)

私は米国法典第 35 編 120 条に基づき下記米国特許出願、あるいは 365 条(c)に基づき米国を指定する下記 PCT 国際特許出願の利益をここに主張し、本特許出願内特許請求範囲の各項目の内容が米国法典第 35 編 112 条の最初の項に規定される方法により先行米国あるいは PCT 国際特許出願で開示されていない限りにおいて連邦規則法典第 37 編 1 条 56 項に定義される特許性に肝要で、先行特許出願の出願日から本特許出願の国内あるいは PCT の出願日までの間に入手された情報について開示義務があることを認めます。

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: patented, pending, abandoned) (状態：特許成立済、係属中、放棄済)
(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: patented, pending, abandoned) (状態：特許成立済、係属中、放棄済)

私は本宣言書内で私自身の知識に基づいてなされたすべての陳述が真実であり、情報および信ずるところに基づいてなされたすべての陳述が真実であると信じられていることをここに宣言し、さらに故意になされた虚偽の陳述等々は米国法典第 18 編 1001 条に基づき罰金あるいは拘禁または両方による処罰にあたり、またかような故意による虚偽の陳述はそれに基づく特許出願あるいは成立特許の有効性を危うくする可能性があることを認識した上でこれらの陳述をなしたことを宣言します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration

委任状：私は下記の米国特許商標局（USPTO）顧客番号のもとに記載されるSUGHRUE MION法律事務所のすべての弁護士を、同顧客番号のもとに記載される個々の弁護士は Sughrue Mion 法律事務所のみの自由裁量に基づき変更され得ることを認識した上で、本特許出願の手続きおよびそれに関わる特許商標局との業務を遂行する弁護士として指名し、本特許出願に関するすべての通信が同 USPTO 顧客番号のもとに提出された住所宛に送付されることを要請します。

POWER OF ATTORNEY: I hereby appoint all attorneys of SUGHRUE MION, PLLC who are listed under the USPTO Customer Number shown below as my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, recognizing that the specific attorneys listed under that Customer Number may be changed from time to time at the sole discretion of Sughrue Mion, PLLC, and request that all correspondence about the application be addressed to the address filed under the same USPTO Customer Number.

23373

23373

PATENT TRADEMARK OFFICE

電話連絡は下記へ：（名前および電話番号）

SUGHRUE MION, PLLC
+1 (202) 293-7060

Direct Telephone Calls to: (name and telephone number)

SUGHRUE MION, PLLC
(202) 293-7060

唯一あるいは第一の発明者名	**Full name of sole or first inventor** Tetsuro KIKUCHI
発明者の署名　日付	Inventor's signature　Date Tetsuro Kikuchi　Sepbember 30, 2005
住所	Residence Tokushima, Japan
国籍	Citizenship Japan
郵送先	Mailing Address 157-13, Kawauchicho Komatsunishi, Tokushima-shi, Tokushima, Japan
第二の共同発明者（該当する場合）	**Full name of second joint inventor if any** Taro IWAMOTO
第二発明者の署名　日付	Second inventor's signature　Date October 7, 2005
住所	Residence Princeton, United States of America
国籍	Citizenship Japan
郵送先	Mailing Address Boudinot T.I. 10/17/2005 36, ~~Boundinot~~ Street, Princeton, NJ 08540, United States of America

第三の共同発明者（該当する場合）	**Full name of third joint inventor, if any** Tsuyoshi HIROSE
第三発明者の署名　日付	Third inventor's signature　Date Tsuyoshi Hirose　Sepbember 30, 2005
住所	Residence Tokushima, Japan
国籍	Citizenship Japan
郵送先	Mailing Address 8-9-502, Sakoichibancho, Tokushima-shi, Tokushima, Japan
第四の共同発明者（該当する場合）	**Full name of fourth joint inventor, if any**
第四発明者の署名　日付	Fourth inventor's signature　Date
住所	Residence
国籍	Citizenship
郵送先	Mailing Address
第五の共同発明者（該当する場合）	**Full name of fifth joint inventor, if any**
第五発明者の署名　日付	Fifth inventor's signature　Date
住所	Residence
国籍	Citizenship
郵送先	Mailing Address
第六の共同発明者（該当する場合）	**Full name of sixth joint inventor, if any**
第六発明者の署名　日付	Sixth inventor's signature　Date
住所	Residence
国籍	Citizenship
郵送先	Mailing Address

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, et al.

Docket No: Q81665

Appln. No.: 10/556,600

Group Art Unit: Unknown

Confirmation No.: Unknown

Examiner: Unknown

Filed: November 14, 2005

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.97 and 1.98

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the documents which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

One copy of each of the listed documents is submitted herewith, except for the following: U.S. patents and/or U.S. patent publications; and co-pending non-provisional U.S. applications filed after June 30, 2003.

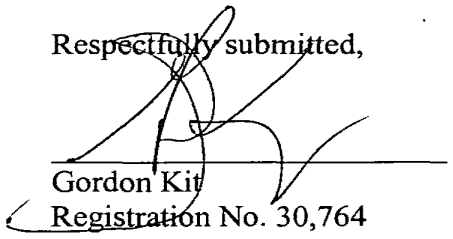
The present Information Disclosure Statement is being filed: (1) No later than three months from the application's filing date; (2) Before the mailing date of the first Office Action on the merits (whichever is later); or (3) Before the mailing date of the first Office Action after

filing a request for continued examination (RCE) under §1.114, and therefore, no Statement under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

The submission of the listed documents is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Gordon Kit
Registration No. 30,764

Date: August 2, 2006

Substitute for Form 1449 A & B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/556,600
Confirmation Number	Unknown
Filing Date	November 14, 2005
First Named Inventor	Tetsuro KIKUCHI
Art Unit	Unknown
Examiner Name	Unknown
Attorney Docket Number	Q81665

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US 2005/0004106	A1	01-06-2005	S. J. ROMANO
		US			
		US			
		US			
		US			
		US			
		US			
		US			
		US			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Number[4]	Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]
		WO	2004/100992	A2	11-25-2004	PFIZER PRODUCTS INC.	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]See Kind Codes of USPTO Patent Documents at www.uspto.gov, MPEP 901.04 or follow the hyperlink from the title of the document to the intranet. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST. 3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to indicate here if English language Translation is attached.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 November 2004 (25.11.2004)

PCT

(10) International Publication Number
WO 2004/100992 A2

(51) International Patent Classification[7]: A61K 45/06, A61P 25/18, 25/22, 25/24

(21) International Application Number: PCT/IB2004/001517

(22) International Filing Date: 3 May 2004 (03.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/471,188 16 May 2003 (16.05.2003) US

(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **ROMANO, Steven, Joseph** [US/US]; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(74) Agents: **FULLER, Grover, J., Fr.** et al.; c/o Lawrence, Jackie, Pfizer Inc., MS8260-1615, Eastern Point Road, Groton, CT 06340 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC COMBINATIONS OF ATYPICAL ANTIPSYCHOTICS WITH GABA MODULATORS AND/OR ANTICONVULSANT DRUGS

(57) Abstract: This invention relates to combinations of an atypical antipsychotic, and a GABA modulator, a benzodiazepine, and/or an anticonvulsant drug, kits containing such combinations, pharmaceutical compositions comprising such combinations, and methods of using such combinations to treat patients suffering from treatment-resistant anxiety disorders, psychotic disorders or conditions, or mood disorders or conditions.

WO 2004/100992 A2

THERAPEUTIC COMBINATIONS OF ATYPICAL ANTIPSYCHOTICS WITH GABA MODULATORS AND/OR ANTICONVULSANT DRUGS

Field of the Invention

The present invention relates to pharmaceutical compositions comprising combinations of ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt of ziprasidone or said prodrug and a GABA modulator, a prodrug thereof or a pharmaceutically acceptable salt of a GABA modulator or said prodrug, or an anticonvulsant drug, a prodrug thereof or a pharmaceutically acceptable salt of an anticonvulsant drug or said prodrug and/or a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of a benzodiazepine or said prodrug, kits containing such combinations and methods of using such combinations to treat patients, including humans, suffering from treatment resistant anxiety disorders, psychotic disorders or conditions, or mood disorders or conditions. This invention also relates to additive and synergistic combinations of ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt of ziprasidone and a GABA modulator, a prodrug thereof or a pharmaceutically acceptable salt of said GABA modulator or said prodrug, whereby those additive and synergistic combinations are useful in treating patients, including humans, suffering from treatment-resistant anxiety disorders, psychotic disorders or conditions, and/or mood disorders or conditions.

Background of the Invention

Schizophrenia is a common and serious mental disorder characterized by loss of contact with reality (psychosis), hallucinations (false perceptions), delusions (false beliefs), abnormal thinking, flattened affect, diminished motivation, and disturbed work and social functioning.

Atypical antipsychotics offer several clinical benefits over the conventional antipsychotics, which were the mainstays of care until the past decade. The principal mechanism underlying the many clinical benefits of the atypical agents is their ability to separate the antipsychotic effect from the extrapyramidal side effect (EPS). The distinct advantages over traditional antipsychotic medications include greater improvement in negative and cognitive symptoms, better antidepressant and mood stabilization effects, lower risk of parkinsonian side effects and tardive dyskinesia, and greater efficacy in otherwise refractory or treatment-resistant patients.

The clinical profile of the atypical and conventional antipsychotics can be understood in terms of their different pharmacological profiles. The conventional antipsychotics are antagonists of dopamine (D_2) receptors. The atypical antipsychotics also have D_2 antagonistic properties, but possess different binding kinetics to these receptors and activity at other receptors, particularly 5-HT_{2A} , 5-HT_{2c} and 5-HT_{1D} (Schmidt B et al, Soc. Neurosci. Abstr. 24:2177, 1998).

The class of atypical antipsychotics includes clozapine (clozaril®), risperidone (risperdal®), olanzapine (zyprexa®), quetiapine (seroquel®), aripiprazole (abilify®) and ziprasidone (geodon®). Ziprasidone is an atypical antipsychotic whose efficacy in the treatment of schizophrenia has been examined in an extensive clinical trial program that includes both short term and long term studies. Ziprasidone is indicated for the treatment of schizophrenia or psychotic disorders and is widely used in a variety of mood disorders, psychiatric medical syndromes and severe personality disorders.

Commonly assigned U.S. Pat. Nos. 4,831,031, 4,883,795, 6,245,766 and 6,126,373, which are hereby incorporated by reference, each disclose that ziprasidone has utility in the treatment of treatment-resistant anxiety disorders, psychotic disorders, and mood disorders.

The term "ziprasidone", as used herein, unless otherwise indicated, encompasses the free base of the compound ziprasidone and all pharmaceutically acceptable salts thereof.

GABA is the major inhibitory neurotransmitter in the patient in the central nervous system (CNS). GABA receptors can be found in 60-80% of CNS neurons. Allosteric facilitation of GABA receptors occurs at several distinct sites; the compounds which bind there are used as sedatives and anxiolytics.

GABA modulators have been disclosed to be useful in antiseizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia and spasticity. GABA agonists have also been disclosed to be useful antidepressants, anxiolytics and antipsychotics.

Commonly assigned U.S. Pat. No. 4,024,175, which is hereby incorporated by reference, discloses that GABA modulators have utility in the treatment of treatment-resistant anxiety, psychotic disorders and conditions, and mood disorders and conditions.

GABA modulators well known in the art include muscimol, progabide, riluzole, baclofen, gabapentin (Neurontin®), vigabatrin, valproic acid, (Depakene®, Depakote®) tiagabine (Gabitril®), lamotrigine (Lamictal®), pregabalin, topiramate (Topamax®) and analogs, derivatives, prodrugs and pharmaceutically acceptable salts of those GABA modulators.

Benzodiazepines have been used for several decades in connection with a broad spectrum of diseases. The major known effects of benzodiazepines are anticonvulsant, muscle relaxing, sedative, hypnotic, anxiolytic, and antipsychotic. The mechanism underlying the effect of the benzodiazepine drugs is unknown but it is believed to relate to the GABA system of the CNS.

When any of the anxiolytic or antipsychotic effects are desired, it is often a problem that the sedative and hypnotic effects of benzodiazepines prohibit the use of high dosages of benzodiazepines, or, when such high dosages are nevertheless necessary to get a reasonable effect of the treatment, make it necessary to hospitalize the patient. Even in the

dosages used against disorders or conditions, e.g. anxiety, the sedative effect of benzodiazepines may be disadvantageous.

According to DSM-IV, Generalized Anxiety Disorder is characterized by persistent and excessive anxiety and worry about a number of events and activities occurring on more days than not, for at least 6 months. Anxiety disorders are the most common form of mental illness in the United States affecting more than 19 million adults yearly. Treatments for anxiety disorders include the Selective Serotonin Reuptake Inhibitors (SSRIs), buspirone, venlafaxine and benzodiazepines. Typical and atypical antipsychotics investigated as therapeutic agents with utility for anxiety have demonstrated a more tolerable side effect profile, and a lower incidence of tardive dyskinesia. The serotoninergic properties of ziprasidone may make it useful in the treatment of anxiety disorders.

There remains a low rate of complete remission reported with benzodiazepines and antidepressants, thereby warranting alternative augmentation strategies to reduce disability and suffering in this chronic disorder.

Posttraumatic stress disorder (PTSD) is a severe and often chronic mental illness. PTSD has lifetime population prevalence of about 10% in the U.S., making it among the most prevalent of psychiatric disorders. The most common traumatic stressors are rape, domestic violence, child abuse, assault, accidents, and disasters. PTSD is characterized by symptoms in three clusters, intrusive, avoidant, and arousal. The intrusive symptom cluster (flashbacks, nightmares, intrusive thoughts, physiological and psychological arousal upon reminders of trauma) is considered unique to PTSD, and is not seen in any other psychiatric condition. Though classified as an anxiety disorder in DSM-IV, PTSD is accompanied by psychotic symptoms in almost half of patients. Treatment consists of the Selective Serotonin Reuptake Inhibitors (SSRIs) such as sertraline, GABA modulators, and benzodiazepines. The psychotic symptoms are treated as add-on therapy with antipsychotic agents. Therefore, a combination product would have utility in this patient population.

Mood disorders, also known as affective disorders, are a group of heterogeneous, typically recurrent illnesses including unipolar (depressive) and bipolar (manic-depressive) disorders, dysthymic disorder, and cyclothymic disorder that are characterized by pervasive mood disturbances, psychomotor dysfunction, and vegetative symptoms. Mood disorders may affect 20% of women and 12% of men during their lifetime. They are the most prevalent of psychiatric disorders, accounting for as many as 65% of psychiatric outpatients, and 10% of all patients seen in nonpsychiatric medical settings (The Merck Manual, 17th ed., Merck & Co. 1999, p. 1526).

Lithium, the standard of care for mood disorder has a response rate of only 50% and is associated with side effects. Anticonvulsants have been used in mood disorders as mood stabilizers and are indicated for use in bipolar disorders. For example, valproic acid and

derivatives, e.g. divalproex sodium or carbamazepine at doses of 500 to 2000 mg daily have shown limited efficacy. Antipsychotic agents are also clinically used in this patient population. A combination product containing anticonvulsants and atypical antipsychotics will have significant utility in the treatment of these patients.

Mental illness is particularly difficult to treat in that not all patients react similarly to the same treatment regimen. Patients often require multiple drug therapies. There also exists a large number of untreated individuals and treatment-resistant patients in need of effective therapy.

Exacerbating this is the problem of patient noncompliance. For example, it is conventionally thought that substantial numbers of patients with mental illnesses are not or only partially compliant with their medication. Poor compliance can cause relapses thereby negating whatever benefits were achieved through treatment in the first place.

Simplification of the regimen by combining several therapeutic agents, reduces the opportunity for patient noncompliance as occurs with a more rigorous schedule. There is a need for pharmaceutical combinations and pharmaceutical kits which employ atypical antipsychotics efficacious for the treatment of, e.g. treatment-resistant anxiety, psychotic disorders and conditions and mood disorders.

The present invention is directed to compositions which reduce or overcome these disadvantages in novel pharmaceutical combinations of ziprasidone and GABA modulators, anticonvulsants and benzodiazepines for the treatment of treatment-resistant anxiety, psychotic disorders and symptoms, and mood disorders and conditions.

Summary of the Invention

The present invention is directed to pharmaceutical compositions, therapeutic methods of treatment, and kits which employ an atypical antipsychotic together with a GABA modulator, an anticonvulsant or a benzodiazepine.

According to the invention, it has surprisingly been found that the pharmaceutical combinations of the present invention can provide synergistic and additive effects with less side effects and a reduction in use of concomitant psychotropic medications such as antidepressants, sedatives and mood stabilizers such as lithium.

Thus according to one aspect, the present invention provides a combination of an atypical antipsychotic agent and a GABA modulator, or an anticonvulsant or a benzodiazepine. Atypical antipsychotics which may be used in the present invention include olanazapine, clozapine, risperidone, sertindole, quetiapine, aripiprazole, amisulpride and ziprasidone. In general, pharmaceutical combinations and methods of treatment using ziprasidone as the first therapeutic agent are preferred.

A further feature of the present invention is a method of reducing the amount of the atypical antipsychotic agent required to produce an anti-anxiety, antipsychotic and mood

stabilizing effect which comprises treating a patient with a therapeutically effective amount of a drug combination according to the present invention.

It is also a feature of this invention that the use of such drug combinations will enhance the effect of the atypical antipsychotic agent to be used and therefore allow reduced quantities of the antipsychotic agent to be used and, therefore allow better management of drug-related toxicity and side effects.

The invention offers advantages over previous methods for treating neuropsychiatric disorders. For example, in the method of treatment of the present invention, the atypical antipsychotic counteracts the typical sedative and hypnotic effects of the benzodiazepine. Other features and advantages of the invention will be apparent from the following detailed description and from the claims.

Detailed Description of the Invention

The present invention is directed to pharmaceutical compositions comprising: an amount of ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt of ziprasidone or said prodrug; and an amount of a GABA modulator, an anticonvulsant drug and/or a benzodiazepine, prodrugs thereof or pharmaceutically acceptable salts of said GABA modulator, anticonvulsant drug or benzodiazepine; and a pharmaceutically acceptable vehicle, carrier or diluent.

The present invention is directed to a therapeutic method and pharmaceutical compositions comprising ziprasidone and a GABA modulator useful for treating treatment-resistant anxiety disorders; ziprasidone and an anticonvulsant drug useful in the treatment of mood disorders or psychotic disorders or treatment; and ziprasidone and a benzodiazepine effective in the treatment of treatment-resistant anxiety and/or psychotic disorders or conditions.

The present invention is also directed to a therapeutic method and a pharmaceutical composition comprising ziprasidone and a GABA modulator useful for treatment of treatment-resistant anxiety disorders.

The present invention is further directed to a therapeutic method and a pharmaceutical composition comprising ziprasidone and a benzodiazepine useful for treatment of psychotic disorders or conditions or treatment-resistant anxiety disorders.

The present invention is still further directed to a therapeutic method and a pharmaceutical composition comprising ziprasidone and an anticonvulsant drug useful for treating mood disorders or conditions, psychotic disorders or conditions, or psychotic symptoms.

This invention is also directed to kits for achieving a therapeutic effect in a patient comprising an amount of ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt of said ziprasidone and a pharmaceutically acceptable vehicle, carrier or diluent in a first unit

dosage form; and an amount of a GABA modulator or an anticonvulsant drug or a benzodiazepine, prodrugs thereof or pharmaceutically acceptable salts of said GABA modulator, anticonvulsant drug or benzodiazepine and a pharmaceutically acceptable vehicle, carrier or diluent in a second unit dosage form and a container.

This invention is also directed to methods of treating a patient in need of therapy comprising administering to said patient an amount of a first drug, the first drug being ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt of ziprasidone, and an amount of a second compound, the second compound being a GABA modulator, an anticonvulsant drug or a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of the GABA modulator, anticonvulsant drug or benzodiazepine.

This invention is further directed to methods for treating a patient in need of therapy comprising administering to said patient

an amount of a first compound, the first compound being ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt of ziprasidone or the prodrug; and

an amount of a second compound, the second compound being a GABA modulator, an anticonvulsant drug or a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of the GABA modulator, anticonvulsant drug or benzodiazepine or said prodrug;

wherein said first compound and said second compound are each optionally and independently administered together with a pharmaceutically acceptable vehicle, carrier or diluent.

This invention is also directed to methods for treating a patient in need of therapy comprising administering to the patient a pharmaceutical composition comprising

a) an amount of a first compound, the first compound being ziprasidone, a pharmaceutically salt of ziprasidone, a prodrug of ziprasidone, or a pharmaceutically acceptable salt of a ziprasidone prodrug; and

b) an amount of a second compound, the second compound being a GABA modulator, an anticonvulsant drug, a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of the GABA modulator, or anticonvulsant drug, or benzodiazepine or the prodrug; and, optionally,

a pharmaceutically acceptable vehicle, carrier or diluent.

The methods of this invention include therapeutic treatment of treatment-resistant anxiety. Treatment-resistant anxiety which may be treated by the methods of this invention includes, inter alia, treatment-resistant obsessive compulsive disorder or treatment-resistant post-traumatic stress disorder.

The methods of this invention include therapeutic treatment of psychotic disorders or conditions. Psychotic disorders which can be treated by the methods of this invention include,

inter alia, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder.

The methods of this invention include therapeutic treatment of mood disorders or conditions. Mood disorders are a group of heterogeneous illnesses including unipolar (depressive) and bipolar (manic-depressive) disorders that are characterized by pervasive mood disturbances, psychomotor dysfunction, and vegetative symptoms. While depression and elation are the core affective components, anxiety and irritability are equally common, explaining the continued popularity of the broader rubric "affective disorders", the previous official designation.

Preferred GABA modulators for use in the combinations, pharmaceutical compositions, methods and kits of this invention include: muscimol, progabide, riluzole, baclofen, gabapentin (Neurontin®), vigabatrin, valproic acid, tiagabine (Gabitril®), lamotrigine (Lamictal®), pregabalin, phenytoin (Dilantin®), carbamazepine (Tegretol®), topiramate (Topamax®), prodrugs thereof and pharmaceutically acceptable salts of the GABA modulators and the prodrugs.

More preferred GABA modulators for use in the combinations, pharmaceutical compositions, methods and kits of this invention include gabapentin, tiagabine, lamotrigine, topiramate, pregabalin, prodrugs thereof and pharmaceutically acceptable salts of the GABA modulators and the prodrugs.

A particularly preferred GABA modulator for use in the combinations, pharmaceutical compositions, methods and kits of this invention is pregabalin, a prodrug thereof or a pharmaceutically acceptable salt of pregabalin or a prodrug thereof.

Another particularly preferred GABA modulator for use in the combinations, pharmaceutical compositions, methods and kits of this invention is gabapentin (Neurontin®), a prodrug thereof or a pharmaceutically acceptable salt of gabapentin (Neurontin®) or prodrug thereof.

Preferred anticonvulsants for use in the combinations, pharmaceutical compositions, methods and kits of this invention include: hydantoins such as phenytoin (Dilantin®), mephenytoin (Mesantoin®); succinimides such as ethosuximide (Zarontin®), oxazolidinediones such as trimethadione (Tridione®), carbamazepine (Tegretol®), primadone (Mysoline®), valproic acid (Depakote®), prodrugs thereof and pharmaceutically acceptable salts of the anticonvulsants and prodrugs thereof.

More preferred anticonvulsants for use in the combinations, pharmaceutical compositions, methods and kits of this invention include phenytoin and valproic acid, prodrugs thereof and pharmaceutically acceptable salts of the anticonvulsants and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs.

A particularly preferred anticonvulsant for use in the combinations, pharmaceutical compositions, methods and kits of this invention is valproic acid, a prodrug thereof or a pharmaceutically acceptable salt of valproic acid or prodrug thereof.

Another particularly preferred anticonvulsant for use in the combinations, pharmaceutical compositions, methods and kits of this invention is phenytoin, a prodrug thereof or a pharmaceutically acceptable salt of phenytoin or prodrug thereof.

Preferred benzodiazepines for use in the combinations, pharmaceutical compositions, methods and kits of this invention include: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, halazepam, lorazepam, temazepam and oxaxepam, prodrugs thereof and pharmaceutically acceptable salts of benzodiazepines and prodrugs thereof.

More preferred benzodiazepines for the use in combinations, pharmaceutical compositions, methods and kits of this invention include clonazepam, diazepam and lorazepam, prodrugs thereof and pharmaceutically acceptable salts of anticonvulsants and prodrugs thereof.

A particularly preferred benzodiazepine for the use in combinations, pharmaceutical compositions, methods and kits of this invention is clonazepam, a prodrug thereof or a pharmaceutically acceptable salt of clonazepam or a prodrug thereof.

Another particularly preferred benzodiazepine for the use in combinations, pharmaceutical compositions, methods and kits of this invention is lorazepam, a prodrug thereof or a pharmaceutically acceptable salt of lorazepam or a prodrug thereof.

The combinations of this invention comprise at least two active components: ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt, and a GABA modulator, a prodrug thereof or a pharmaceutically acceptable salt of the GABA modulator; or ziprasidone, a prodrug thereof or a pharmaceutically acceptable salt, and an anticonvulsant, a prodrug thereof or a pharmaceutically acceptable salt of an anticonvulsant or a prodrug; or ziprasidone, a prodrug or pharmaceutically acceptable salt and a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of a benzodiazepine. The combinations of this invention include a pharmaceutically acceptable vehicle, carrier or diluent.

The combinations result in synergistic action allowing a lower dose of the atypical antipsychotic to be administered while achieving the same psychotropic effect. The dosage of the atypical antipsychotic may be reduced by about 25-90%, for example, about 40-80% and typically about 50-70%. The reduction in amount of antipsychotic required will be dependent on the amount of second therapeutic agent given.

The selection of the dosage of the first and second therapeutic agents is that which can provide relief to the patient as measured by a reduction or amelioration of symptoms associated with the disorder or condition of the patient. As is well known, the dosage of each component depends on several factors such as the potency of the selected specific

compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. This is considered to be within the skill of the artisan and one can review the existing literature regarding each component to determine optimal dosing. To the extent necessary for completeness, the synthesis of the components of the compositions and dosages are as described in the listed patents or the Physicians' Desk Reference, 57th ed., Thompson, 2003 which are expressly incorporated herein by reference. Desirably, when ziprasidone is selected as the active agent, the daily dose contains from about 5 mg to about 460 mg. More preferably, each dose of the first component contains about 20 mg to about 320 mg of the ziprasidone, and even more preferably, each dose contains from about 20 mg to about 160 mg of ziprasidone. Pediatric dosages may be less. This dosage form permits the full daily dosage to be administered in one or two oral doses, for example.

General outlines of the dosages for the atypical antipsychotics, GABA modulators, anticonvulsants, and benzodiazepines, and some preferred dosages, are provided herein. This list is not intended to be complete but is merely a guideline for any of the desired combinations of the present invention.

Olanzapine: from about 0.25 to about 100 mg, once/day; preferred, from about 1 to about 30 mg, once/day; and most preferably about 1 to about 25 mg once/day;

Clozapine: from about 12.5 to about 900 mg daily; preferred, from about 150 to about 450 mg daily;

Risperidone: from about 0.25 to about 16 mg daily; preferred from about 2-8 mg daily;

Sertindole: from about 0.0001 to about 1.0 mg/kg daily;

Quetiapine: from about 1.0 to about 40 mg/kg given once daily or in divided doses;

Asenapine: from about 0.005 to about 60 mg total per day, given as a single dose or in divided doses;

Carbamezepine: from about 200 to about 1200 mg/day; preferably about 400 mg/day;

Valproic Acid: from about 250 to about 2500 mgday; preferably about 1000 mg/day;

Lamotrigine: from about 50 to about 600 mg/day in 1 to 2 doses; preferably about 200 to about 400 mg; most preferably about 200 mg;

Gabapentin: from about 300 to about 3600 mg/day in 2 to 3 divided doses; preferably 300 to about 1800 mg/day; most preferably about 900 mg/day;

Tiagabine: from about 2 to about 56 mg/day in 2 to 4 divided doses; preferably about 32 to about 56 mg/day; most preferably about 56 mg/day.

Topiramate: from about 200 to about 600 mg/day divided in 2 doses; most preferably about 400 mg/day.

The Table below provides additional dosage ranges:

Drug Name		Dosage Range
Brand name	Generic Name	
Klonopin	Clonazepam	Minimum: 0.25 mg Maximum: 20mg
Tranxene	Clorazepate Dipotassium	Minimum: 3.75 mg. Maximum: 60 mg
Valium	Diazepam	Minimum: 1 mg. Maximum: 40 mg.
Xanax	Alprazolam	Minimum: 0.25 mg Maximum: 4 mg
Gabitril	Tiagabine	Minimum: 4 mg Maximum: 56 mg
Neurontin	Gabapentin	Minimum: 100 mg Maximum: 2400 mg
Dilantin	Phenytoin	Minimum: 50 mg Maximum: 1200 mg
Carbatrol Capsules	Carbamazepine ER	Minimum: 200 mg Maximum: 1200 mg
Depakote	Valproic acid	Minimum: 250 mg Maximum: 2000 mg
Felbatol	Felbamate	Minimum: 1200 mg Maximum: 3600 mg
Keppra	Levetiracetam	Minimum : 1000 mg Maximum : 3000 mg
Tegretol	Carbamazepine	Minimum: 200 mg Maximum: 1200 mg
Topamax	Topiramate	Minimum: 25 mg Maximum: 400 mg
Celontin	Methoximide	Minimum: 150 mg Maximum : 1200 mg
Trileptal	Oxcarbazepine	Minimum: 300 mg Maximum: 2400 mg

Drug Name		Dosage Range
Brand name	Generic Name	
Zonegran	Zonisamide	Minimum: 100 mg Maximum: 600 mg
Lamictal	Lamotrigine	Minimum: 200 mg Maximum: 400 mg
Zarontin Capsules	Ethosuximide	Minimum : 250 mg Maximum : 1500 mg

In more general terms, one would create a drug combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

The atypical antipsychotics of the present invention are useful in treating schizophrenia, bipolar disorders, and dementia.

The presently preferred atypical antipsychotic used according to the invention is ziprasidone. Ziprasidone (5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloroindolin-2-one hydrochloride hydrate) is a benzisothiazolyl piperazine-type atypical antipsychotic with in vitro activity as a 5-HT_{1A} receptor agonist and an inhibitor of serotonin and norepinephrine reuptake (See e.g. U.S. Pat. No. 4,831,031). The postsynaptic 5-HT_{1A} receptor has been implicated in both depressive and anxiety disorders (NM Barnes, T Sharp, 38 Neuropharmacology 1083-152,1999). Oral bioavailability of ziprasidone taken with food is approximately 60%, half-life is approximately 6-7 hours, and protein binding is extensive.

Ziprasidone is efficacious for the treatment of patients with schizophrenia and schizomood disorders, refractory schizophrenia, cognitive impairment in schizophrenia, affective and anxiety symptoms associated with schizoaffective disorder and bipolar disorder. The drug is considered a safe and efficacious atypical antipsychotic (Charles Caley & Chandra Cooper, 36 Ann. Pharmacother. 839-51, 2002).

The present invention is useful in treating mental disorders and conditions, the treatment of which is facilitated by the administration of ziprasidone. Thus, the present invention has application where ziprasidone use is indicated as, e.g., in U.S. Pat. Nos. 6,245,766; 6,245,765; 6,387,904; 5,312,925; 4,831,031; and European EP 0901789 published March 17, 1999, all of which are incorporated herein by reference.

Other atypical antipsychotics which can be used include, but are not limited to: Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Pat. No. 5,229,382 as being useful for the

treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Pat. No. 5,229,382 is herein incorporated by reference in its entirety;

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Pat. No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., 24, 62 (1988));

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Pat. No. 4,804,663, which is herein incorporated by reference in its entirety;

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Pat. No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Pat. Nos. 5,112,838 and 5,238,945. U.S. Pat. Nos. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety;

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl -1-piperazinyl) ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Pat. No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt;

Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3-,4-dihydro carbostyril or 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro -2(1H)-quinolinone, is an atypical antipsychotic agent used for the treatment of schizophrenia and described in U.S. Pat. No. 4,734,416 and U.S. Pat. No. 5,006,528, which are herein incorporated by reference in their entirety;

Amisulpride is described in U.S. Pat. No. 4,401,822;

Asenapine, *trans*-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole. Preparation and use of asenapine is described in U.S. Patent Nos. 4,145,434 and 5,763,476, which are incorporated herein in their entireties by reference.

A preferred combination is ziprasidone with a GABA modulator. The term "GABA", where used in the description and the appendant claims, is synonymous with the term "gamma-aminobutyric acid." These terms are used interchangeably throughout the description and appendant claims.

The term "GABA modulator" as used herein refers to a compound that either is structurally related to the neurotransmitter GABA but does not interact with the GABA receptor (e.g. gabapentin), or interacts with the GABA receptors, or is converted metabolically into GABA or a GABA agonist; or is an inhibitor of GABA uptake or degradation; or is a GABA

receptor subtype-selective antagonist and/or agonist. This definition includes pharmaceutically acceptable salts, prodrugs or pharmaceutically acceptable salts of said prodrugs.

The GABA modulators suitable for use herein include, but are not limited to, muscimol, progabide, riluzole baclofen, gabapentin (Neurontin®), vigabatrin, tiagabine (Gabitril®), lamotrigine (Lamictal®), pregabalin; topiramate (Topamax®), a prodrug thereof or a pharmaceutically acceptable salt of the GABA modulator or prodrug thereof. It will be recognized by those skilled in the art in light of this disclosure that other GABA agonists are also useful in the combinations, pharmaceutical compositions, methods and kits of this invention.

The GABA modulators disclosed herein are prepared by methods well known to those skilled in the art. Specifically, the following patents and patent applications, each of which is hereby incorporated herein by reference, exemplify GABA modulators which can be used in the combinations, pharmaceutical compositions, methods and kits of this invention, and refer to methods of preparing those GABA modulators: U.S. Pat. No. 3,242,190 (specifically, muscimol); U.S. Pat. No. 4,094,992 (specifically, progabide); U.S. Pat. No. 4,370,338 (specifically, riluzole); U.S. Pat. No. 3,471,548 (specifically, baclofen); U.S. Pat. No. 4,024,175 (specifically, gabapentin); U.S. Pat. No. 3,960,927 (specifically, vigabatrin); U.S. Pat. No. 5,010,090 (specifically, tiagabine); U.S. Pat. No. 4,602,017 (specifically, lamotrigine); U.S. Pat. No. 6,028,214 (specifically, pregabalin); and U.S. Pat. No. 4,513,006 (specifically, topiramate).

Gabapentin, 1-(aminomethyl)cyclohexane acetic acid, is an anticonvulsant indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin and its methods of use is described in U.S. Pat. Nos. 4,024,175 and 4,087,544 incorporated herein by reference in their entirety.

It will be recognized that certain of the GABA modulators used in the pharmaceutical compositions, methods and kits of this invention contain either a free carboxylic acid or a free amine group as part of the chemical structure. Thus, this invention includes pharmaceutically acceptable salts of those carboxylic acids or amine groups.

For use in medicine, pharmaceutically acceptable salts may be useful in the preparation of the compounds according to the invention. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts

thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Where the GABA modulators of use in the invention have at least one asymmetric center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention. Gabapentin may be in the form of the crystalline monohydrate as described in EP340677 which is incorporated herein by reference or the anhydrous crystalline form as described in WO 03031391.

The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

The pharmaceutically-acceptable cationic salts of GABA modulators containing free carboxylic acids may be readily prepared by reacting the free acid form of the GABA modulator with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (e.g., sodium or potassium ethylhexanoate, magnesium oleate), employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The pharmaceutically acceptable acid addition salts of GABA modulators containing free amine groups may be readily prepared by reacting the free base form of the GABA modulator with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a

dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However, when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The anticonvulsants disclosed herein are prepared by methods well known to those skilled in the art. Specifically, the following patents and patent applications, each of which is hereby incorporated herein by reference, exemplify anticonvulsants which can be used in the combinations, pharmaceutical compositions, methods and kits of this invention, and refer to methods of preparing those anticonvulsants:

Anticonvulsants contemplated as the second component include, but are not limited to, phenytoin, carbamezepine, valproic acid, lamotrigine and topiramate;

Carbamezepine, 5H-dibenz [b,f]azepine-5 -carboxamide is an anticonvulsant and analgesic marketed for trigeminal neuralgia; U.S. Pat. No. 2,948,718 (herein incorporated herein by reference in its entirety), discloses carbamezepine and methods of use;

Phenytoin, 5,5-diphenyl – 2,4-imidazolidinedione, is a well-known anticonvulsant; U.S. Patent No. 2,409,654 discloses phenytoin and methods of use; incorporated herein by reference in its entirety.

Valproic Acid, 2-propylpentanoic acid or dispropylacetic acid is a well known antiepileptic agent which dissociates to the valproate ion in the gastrointestinal tract; various pharmaceutically acceptable salts are disclosed in U.S. Pat. No. 4,699,927; Valproic acid is prepared as disclosed in Carraz et al., Therapie, 1965, 20, 419) incorporated herein by reference in its entirety;

Lamotrigine, 6-(2,3-dichlorophenyl)-1,2,4-trizine-3,5-diamine is an antiepileptic drug indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. Lamotrigine and its uses is disclosed in U.S. Pat. No. 4,486,354, incorporated herein by reference in its entirety; and

Topiramate, 2,3:4,5-di-O-(1-isopropylidine)-3-D-fructopyranose sulphamate is an antiepileptic indicated for the treatment of refractory partial seizures, with or without secondary generalization and disclosed in U.S. Pat. No. 4,513,006 incorporated herein by reference in its entirety.

The benzodiazepines are used as antianxiety agents and in psychiatric disorders in which anxiety is a prominent feature. For example, combination treatment with a benzodiazepine plus a typical antipsychotic (often haloperidol IM 5-10 mg plus lorazepam 1-2 mg) is commonly employed. However, this combination may be associated with intolerable

side effects, particularly acute dystonia with conventional antipsychotics and excessive sedation with benzodiazepines. Also, some clinicians avoid benzodiazepines in agitation associated with intoxication.

Benzodiazepines are also associated with excessive sedation, confusion, disinhibition, ataxia, nausea and vomiting, respiratory depression, asymptomatic tachypnea, and tachycardia (J. Modell, J Clin Psychopharmacol. 6:385-387, 1986). According to the invention it has surprisingly been found that an atypical antipsychotic counteracts the typical sedative and hypnotic effects of benzodiazepines.

Thus, by administering, in accordance with the principle of the present invention, an atypical antipsychotic such as ziprasidone to patients treated with benzodiazepines, it will be possible, because of the counteraction of the sedative and hypnotic effects, to use effective dosages of the benzodiazepines even where high dosages are necessary to obtain an effect, without disabling the patients from living a normal daily life.

In the present context, the term "a benzodiazepine" or "benzodiazepines" designate benzodiazepine as well as derivatives thereof which are normally classified as benzodiazepines in pharmaceutical textbooks such as, e.g., Ernst Mutschler, Arzneimittelwirkungen, Lehrbuch der Pharmaceutical makologie and Toxikologie, Aug. 5, 1986, Wissenschaftliche Verlagsgasellschaft mbk, Stuttgart, including, e.g., diazepam, dipotassium chlorazepate, chlorasepate, chlordiazapide, medazepam, flurazepam, clobasam, clonazepam, nitrasepam, flunitrasepam, astazolam, bromazepam, alprazolam, lorazepam, lormetasepam, oxazepam, temazepam, brotizolam, triazolam, chlordiazepam, halazepam, or prazepam. As defined herein the term benzodiazepines also refers to benzodiazepine receptor subtype compounds as well as pharmaceutically acceptable salts of benzodiazepines, prodrugs of benzodiazepines and pharmaceutically acceptable salts of benzodiazepine prodrugs.

Some benzodiazepines are used for their sedative or hypnotic effect; these benzodiazepines are typically those having a short half life. Other benzodiazepines are used for other effects where the sedative or the hypnotic effects are considered undesirable or even side effects of the benzodiazepine. These benzodiazepines are, e.g., diazepam, dipotassium chlorazepate, chlorazepate, chlordiazepide, medazepam, clobazam, clonazepam, estazolam, bromasepam, alprazolam, lorazepam, lormetazepam, oxazepam, brotizolam, chlordiazepam, halazepam, or prazepam.

The diseases treated with benzodiazepines constitute a broad spectrum of diseases because of the many effects of the benzodiazepines. Diseases where the sedative or hypnotic effects of the benzodiazepines are undesirable are diseases in connection with which the principle of the present invention is particularly important. Especially the treatment of the following diseases is accomplished by the drug combinations of the present invention:

treatment-resistant anxiety, psychotic disorders or conditions, psychotic symptoms. These diseases may benefit from the use of both a benzodiazepine and an atypical antipsychotic in accordance with the principle of the invention, as these diseases are known to require high dosages of benzodiazepine in order to obtain the benefit of the benzodiazepine therapy. However, the high dosages, on the other hand, incur the above-mentioned severe disadvantages due to the sedative and hypnotic effects if no administration of the atypical antipsychotic is performed in connection with the benzodiazepine treatment.

Psychotic disorders or conditions, such as schizophrenia, schizoaffective disorder, schizophreniform disorder, and schizotypical disorder are conditions in which benzodiazepine therapy, such as treatment with clonazepam, is important. According to the present invention, these conditions can now also be treated with an atypical antipsychotic in combination with a benzodiazepine.

The atypical antipsychotic can be administered simultaneously with the benzodiazepine, either as separate dosage forms in a kit product, or as one combined dosage form containing both the atypical antipsychotic and the benzodiazepine.

The effects of a pharmaceutical composition comprising ziprasidone and a GABA modulator, or ziprasidone and a benzodiazepine of the present invention can be examined by using one or more of the published models of anxiety well known in the art. The effects of a pharmaceutical composition comprising ziprasidone and a benzodiazepine, or ziprasidone and an anticonvulsant of the present invention can be examined by using one or more of the published models of psychotic disorders or conditions well known in the art. The effects of a pharmaceutical composition comprising ziprasidone and an anticonvulsant of the present invention can be examined by using one or more of the published models of mood disorders such as bipolar disorder which are well known in the art.

The pharmaceutical compositions containing ziprasidone and a GABA modulator or ziprazidone and a benzodiazepine of the present invention are particularly useful for the prevention of, reducing the development of, or reversal of, treatment-resistant anxiety disorders and are therefore particularly useful in the treatment of obsessive-compulsive disorder or post-traumatic stress disorder. This effect can be demonstrated, for example, by measuring markers such the Clinician Administered PTSD Scale or the Eysenck Personality Inventory and has been shown in clinical studies (MI Butterfield et al, 16 Int'l Clin Psychopharmacol 197-203, 2001).

The pharmaceutical compositions containing ziprasidone and an anticonvulsant or ziprazidone and a benzodiazepine of the present invention are particularly useful for the prevention of, reducing the development of, or reversal of, psychotic disorders, conditions or symptoms and are therefore particularly useful in the treatment of schizophrenia, schizophreniform disorder, schizoaffective disorder or delusional disorder. This can be

demonstrated, for example, by measuring markers such Positive or Negative Syndrome Scale (PANSS) and Scales for the Assessment of Negative Symptoms (SANS) or BPRS scores (Kay et al, Schizophrenia Bulletin 13:261-276, 1987), or in various animal models such as PCP or methamphetamine induced locomotor test or the conditioned avoidance response test.

The pharmaceutical compositions containing ziprasidone and an anticonvulsant are particularly useful for the prevention of, reducing the development of, or reversal of, mood disorders and are therefore particularly useful in the treatment of bipolar disorder, bipolar depression or unipolar depression. This can be demonstrated, for example, by measuring the symptomatic picture and using various animal models such as the "mouse behavioral despair test."

In general, ziprasidone employed in the combinations, pharmaceutical compositions, methods and kits of this invention, will be administered at dosages between about 20 and about 460 mg per day, preferably from about 40 mg to about 200 mg, and most preferably 40 mg to 160 mg together with therapeutically effective amounts of the second therapeutic agent in single or divided doses.

The term "therapeutically effective amount" as used herein refers to a sufficient amount of the compound to treat treatment-resistant anxiety disorders, mood disorders and psychotic disorders or conditions at a reasonable benefit/risk ratio applicable to any medical treatment.

The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The following dosage amounts and other dosage amounts set forth elsewhere in this description and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject. All doses set forth herein, and in the appendant claims, are daily doses.

In general, in accordance with this invention, the above GABA modulators used in the combinations, pharmaceutical compositions, methods and kits of this invention will be administered in a dosage amount of about 4 mg/kg body weight of the subject to be treated per day to about 60 mg/kg body weight of the subject to be treated per day, in single or divided doses. However, some variation in dosage will necessarily occur depending upon the

condition, age as well as factors which may alter pharmacokinetics of absorption, distribution, metabolism and excretion in the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject In particular, when used as the GABA modulator in this invention, pregabalin will be dosed at about 100 mg to about 1500 mg per day; and preferably about 300 mg to about 1200 mg per day; gabapentin will be dosed at about 100 mg to about 4000 mg per day, and preferably about 600 mg to about 3600 mg per day.

In general, in accordance with this invention, the above anticonvulsants used in the combinations, pharmaceutical compositions, methods and kits of this invention will be administered in a dosage amount of about 1 mg/kg body weight of the subject to be treated per day to about 10 mg/kg body weight of the subject to be treated per day, in single or divided doses. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual patient. In particular, when used as the anticonvulsant in this invention, phenytoin will be dosed at about 10 mg to about 1500 mg per day and preferably about 50 mg to about 1200 mg per day or doses to achieve serum levels in the range of about 10-20 mcg/mL; valproic acid will be dosed at about 1 mg/kg/day to about 100 mg/kg/day, and preferably about 5 mg/kg/day to about 70 mg/kg/day.

In general, in accordance with this invention, the above benzodiazepines used in the combinations, pharmaceutical compositions, methods and kits of this invention will be administered in a dosage amount of about 0.001 mg to about 200mg, in single or divided doses. However, some variation in dosage will necessarily occur depending upon the condition, age and pharmacokinetic altering physiology of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual patient. In particular, when used as the benzodiazepine in this invention, diazepam will be dosed at about 1 mg to about 40 mg per day; clonazepam will be dosed at about 0.001 mg/kg/day to about 1 mg/kg/day, and more preferably at about 0.01 mg/kg/day to about 0.2 mg/kg/day.

The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain therapeutic effects

It will be recognized by a skilled person that the free base form or other salt forms of the above GABA modulators, anticonvulsants and benzodiazepines may be used in this invention. Calculation of the dosage amount for these other forms of the free base form or other salt forms of a particular GABA modulator, anticonvulsant or benzodiazepine is easily

accomplished by performing a simple ratio relative to the molecular weights of the species involved.

The products of the present invention are of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include treatment-resistant anxiety disorders, such as obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder.

The products of the present invention have the advantage that they surprisingly provide relief from anxiety more rapidly than would be expected from administration of either compound alone. They are useful in reducing the complications associated with treatment-resistant anxiety disorders, including premature mortality and suicide.

The term "treatment-resistant", as in "a method of treating a disorder", refers to reversing, alleviating, or inhibiting the progress of the disorder to which such term applies, or one or more symptoms of the disorder. For example, in some clinical studies it is defined as patients with a principal DSM-IV diagnosis of generalized anxiety disorder who have not responded sufficiently after an adequate trial (4-8 weeks) of first-line anti-anxiety agents such as SSRIs, buspirone or a benzodiazepine. As used herein, the term also encompasses, depending on the condition of the patient, preventing the disorder, including preventing onset of the disorder or of any symptoms associated therewith, as well as reducing the severity of the disorder or any of its symptoms prior to onset, or to preventing a recurrence of a disorder.

Examples of treatment-resistant anxiety disorders that can be treated according to the present invention include, but are not limited to, treatment-resistant obsessive-compulsive disorder, treatment-resistant posttraumatic stress disorder, generalized or substance-induced anxiety disorder; neuroses and panic disorder.

The meanings attributed to the different types and subtypes of anxiety disorders are as stated in DSM-IV-TR the contents of which are incorporated by reference herein. (Diagnostic and Statistical Manual of Mental Disorders", 4th ed, American Psychiatric Assoc., Washington, DC, 2002, p. 429-484). Though classified as an anxiety disorder in DSM-IV, PTSD is accompanied by psychotic symptoms in almost half of patients.

Examples of psychotic disorders that can be treated according to the present invention include, but are not limited to, schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition; substance-induced psychotic disorder, for example psychosis

induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; personality disorder of the schizoid type; psychotic disorder not otherwise specified.

The meanings attributed to the different types and subtypes of psychotic disorders are as stated in DSM-IV-TR the contents of which are incorporated by reference herein. (Diagnostic and Statistical Manual of Mental Disorders", 4th ed, American Psychiatric Assoc., Washington, DC, 2002, p. 297-343).

Schizophrenia as used herein refers to a disorder that lasts for at least 6 months and includes at least one month of active-phase symptoms (i.e., two [or more] of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms) (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Schizoaffective disorder is defined as a disorder in which a mood episode and the active-phase symptoms of schizophrenia occur together and were preceded or are followed by at least 2 weeks of delusions or hallucinations without prominent mood symptoms (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Schizophreniform disorder is defined as a disorder characterized by a symptomatic presentation that is equivalent to schizophrenia except for its duration (i.e., the disturbance lasts from 1 to 6 months) and the absence of a requirement that there be a decline in functioning (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Schizotypical disorder is defined as a lifetime pattern of social and interpersonal deficits characterized by an inability to form close interpersonal relationships, eccentric behavior, and mild perceptual distortions.

The combinations of ziprasidone with anticonvulsant drugs or ziprasidone and benzodiazepines in the present invention can be used to treat other psychotic disorders such as delusional disorder; brief psychotic disorder; shared psychotic disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; psychotic disorder due to a general medical condition; personality disorder of the paranoid type; personality disorder of the schizoid type; and psychotic disorder not otherwise specified.

For example, "treating schizophrenia, or schizophreniform or schizoaffective disorder" as used herein also encompasses treating one or more symptoms (positive, negative, and other associated features) of said disorders, for example treating, delusions and/or hallucination associated therewith. Other examples of symptoms of schizophrenia and schizophreniform and schizoaffecctive disorders include disorganized speech, affective

flattening, alogia, anhedonia, inappropriate affect, dysphoric mood (in the form of, for example, depression, anxiety or anger), and some indications of cognitive dysfunction.

Delusional disorder as referred to herein is characterized by at least 1 month of nonbizarre delusions without other active-phase symptoms of schizophrenia. (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Brief psychotic disorder is a disorder that lasts more than 1 day and remits by 1 month. (Diagnostic and Statistical Manual of Mental Disorders , DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Shared psychotic disorder is characterized by the presence of a delusion in an individual who is influenced by someone else who has a longer-standing delusion with similar content. (Diagnostic and Statistical Manual of Mental Disorders , DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Psychotic disorder due to a general medical condition is characterized by psychotic symptoms judged to be a direct physiological consequence of a general medical condition. (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR, 4th ed, American Psychiatric Assoc., Washington, DC, 2002).

Psychotic disorder not otherwise specified is a psychotic presentation that does not meet the criteria for any of the specific psychotic disorders defined in the DSM-IV-TR (American Psychiatric Assoc., Washington, DC, 2002).

In another embodiment, the compounds used in the present invention are useful to treat other disorders that may present with psychotic symptoms as associated features such as dementia of the Alzheimer's type; substance-induced delirium; and major depressive disorder with psychotic features.

In a preferred embodiment, the compounds used in the present invention are useful for treating schizophrenia, a schizoaffective disorder, schizophreniform disorder, or a schizotypical disorder.

The combinations of ziprasidone and an anticonvulsant may be used to treat mood disorders, formerly designated as "affective disorders." Although mood disorders are not a clearly delineated group of illnesses they include unipolar and bipolar depression, generalized anxiety disorder, and more specific anxiety disorders such as agoraphobia, panic disorder and social phobia, obsessive-compulsive disorder and post traumatic stress disorder (PTSD). There is a high level of similarity and co-morbidity between these illnesses and clinicians may consider them as a single group.

The meanings attributed to the different types and subtypes of mood disorders are as stated in DSM-IV-TR under depressive disorders ("unipolalar depression") and bipolar disorders, generalized anxiety disorder, and more specific anxiety disorders such

as agoraphobia, panic disorder and social phobia, obsessive-compulsive disorder and post traumatic stress disorder (PTSD), the contents of which are incorporated by reference herein. (Diagnostic and Statistical Manual of Mental Disorders", 4th ed, American Psychiatric Assoc., Washington, DC, 2002, p. 345-484).

The term "affective disorder" as used herein is interchangeable with the term "mood disorders" and refers to disorders that are characterized by changes in mood as the primary clinical manifestation, for example, depression.

The expression "prodrug" refers to compounds that are drug precursors which, following administration, release the drug in vivo via a chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

The present invention includes within its scope the use of prodrugs of ziprasidone, GABA modulators, benzodiazepines or anticonvulsant drugs. In general, such prodrugs will be functional derivatives of these compounds which are readily convertible in vivo. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985 and can be achieved using methods well known to those skilled in the art. All such prodrugs are within the scope of the combinations, pharmaceutical compositions, methods and kits of this invention.

The chemist of ordinary skill in the art will also recognize that certain compounds within the scope of this invention can exist in zwitterionic form, i.e., that certain compounds contain an amine portion and a carboxylic acid portion, which, depending upon the pH of the solution, may exist as a free amine and a free carboxylic acid or as a zwitterion in which the amine is protonated to form an ammonium ion and the carboxylic acid is deprotonated to form a carboxylate ion. All such zwitterions are included in this invention.

The chemist of ordinary skill in the art will also recognize that the pharmaceutical combinations contemplated by the present invention can exist in different stereoisomers. Specific stereoisomers may exhibit an ability to treat mental disorders with a more favorable efficacy or safety profile. The present invention includes all possible stereoisomers and geometric isomers of the active ingredients of each pharmaceutical combination, and includes not only racemic compounds but also optical isomers as well. In situations where tautomers, i.e. that an equilibrium exists between two isomers which are in rapid equilibrium with each other are possible, the present invention is intended to include all tautomeric forms.

The combinations of the present invention can be administered in a standard manner for the treatment of treatment-resistant anxiety disorders, psychotic disorders, or mood disorders such as orally, parenterally, transmucosally (e.g., sublingually or via buccal administration), topically, transdermally, rectally, via inhalation (e.g., nasal or deep lung inhalation). Parenteral administration includes, but is not limited to intravenous, intraarterial,

intraperitoneal, subcutaneous, intramuscular, intrathecal, and intraarticular, or via a high pressure technique, like Powderject.™

For buccal administration, the composition can be in the form of tablets or lozenges formulated in conventional manner. For example, tablets and capsules for oral administration can contain conventional excipients such as binding agents (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate), or wetting agents (for example, sodium lauryl sulfate). The tablets can be coated according to methods well known in the art.

Such preparations can also be formulated as suppositories, e.g., containing conventional suppository bases, such as cocoa butter or other glycerides. Compositions for inhalation typically can be provided in the form of a solution suspension, or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant, such as dichlorodifluoromethane or trichlorofluoromethane. Typical topical and transdermal formulations comprise conventional aqueous or nonaqueous vehicles, such as eye drops, creams, ointments, lotions, and pastes, or are in the form of a medicated plaster, patch, or membrane.

Additionally, compositions of the present invention can be formulated for parenteral administration by injection or continuous infusion. Formulations for injection can be in the form of suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulation agents, such as suspending, stabilizing, and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle (e.g., sterile, pyrogen-free water) before use.

A composition in accordance with the present invention also can be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, the compounds of the invention can be formulated with suitable polymeric or hydrophobic materials (e.g., an emulsion in an acceptable oil), ion exchange resins, or as sparingly soluble derivatives (e.g., a sparingly soluble salt).

Solubilized forms of aryl-heterocyclics such as zirpasidone, pharmaceutically acceptable salts there, or prodrugs thereof, or pharmaceutically acceptable salts of prodrugs thereof, associated with (or at levels even greater than) immediate release can be fabricated into depot formulations. For example, a pharmaceutical kit comprising ziprazidone, ziprasidone salts or prodrugs thereof, or pharmaceutically acceptable salts of ziprasidone prodrugs, which can be solubilized or unsolubilized; and a constituting liquid vehicle

comprised of a viscosity agent with the proviso that when the ziprasidone compound is unsolubilized, the aqueous liquid further comprises a solubilizer.

Ziprazidone depot formulation in the form of a suspension are described in U.S. Patent Application Serial No. 60/42195, filed October 25, 2002 and incorporated herein by reference in its entirety. Novel injectable depot formulations of ziprasidone are described in U.S. Patent Application Serial No. 60/421473, filed October 25, 2002 and incorporated herein by reference in its entirety.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols.

Alternatively, the compounds of the present invention can be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, for example. Moreover, formulations containing these compounds can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can contain conventional additives, such as suspending agents, such as sorbitol syrup, synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin, glucose/sugar syrup, gelatin, hydroxyethylcellulose, hydroxypropylmethylcellulose, aluminum stearate gel, emulsifying agents, such as lecithin, sorbitan monooleate, or acacia; nonaqueous vehicles (which can include edible oils), such as almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol; and preservatives, such as methyl or propyl p-hydroxybenzoate and sorbic acid. The liquid forms in which the compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

Suitable dispersing or suspending agents for aqueous suspersions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

The combinations of this invention can also be administered in a controlled release formulation such as a slow release or a fast release formulation. Such controlled release formulations of the combinations of this invention may be prepared using methods well known to those skilled in the art. The method of administration will be determined by the attendant physician or other person skilled in the art after an evaluation of the patient's condition and requirements.

The pharmaceutical compositions of the present invention can consist of a combination of immediate release and controlled release characteristics. Such compositions can take the form of combinations of the active ingredients that range in size from nanoparticles to microparticles or in the form of a plurality of pellets with different release rates. The tablet or capsule composition of the present invention can contain an atypical antipsychotic in sustained or controlled release form and, a second therapeutic agent in an immediate release form. Alternatively, the atypical antipsychotic can be in immediate release form and the second therapeutic agent can be in sustained or controlled release form.

The combinations of this invention can also be administered in parenteral form. For parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions can be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, methods of preparing pellets are described in Remington: The Science and Practice of Pharmacy, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Prolonged release pellets are prepared by either coating immediate release pellets or via matrix systems. Coating may be carried out, for example, in coating pans or in fluid bed coater-driers. Extrusion and subsequent spheronization is a long-known method for the preparation of pharmaceutical pellets (J. W. Conine et al., Drug & Cosmetic Ind. 106, 38-41 (1970)). However, other methods such as pelletization may be utilized. Particles may be agglomerated to form spherical granules or pellets, in a high speed mixer granulator, or rotary fluid bed agglomerator. These methods are described by K. W. Olson and A. M. Mehta, Int.J.Pharm.Tech&.Prod.Mfr. 6 18-24, 1985. Pellets may be also prepared by extrusion of wet

masses or melts followed by spheronisation, for example as described in C. Vervaet, L. Baert & J. P. Remon Int.J.Pharm. 116 (1995) 131-146. Excipients used are typically those with plastic qualities such as microcrystalline cellulose, but also mannitol. Small quantities of a polymeric binder are generally added. Surfactants such as sodium dodecyl sulphate may also be incorporated to give easier extrusion.

Pharmaceutical compositions according to the invention can contain 0.1%-95% of the therapeutic agents of this invention, preferably 1%-70%. In any event, the composition or formulation to be administered will contain a quantity of therapeutic agent(s) according to the invention in an amount effective to treat the condition or disease of the subject being treated.

The two different compounds of this invention can be co-administered simultaneously or sequentially in any order, or as a single pharmaceutical composition comprising, for example, ziprasidone and a GABA modulator, or ziprasidone and an anticonvulsant, or ziprasidone and a benzodiazepine as described above.

Since the present invention has an aspect that relates to the treatment of the disease/conditions described herein with a combination of active ingredients which canbe administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: ziprasidone and a GABA modulator, a prodrug thereof or a pharmaceutically acceptable salt of said GABA modulator or prodrug; or ziprasidone and an anticonvulsant, a prodrug thereof or a pharmaceutically acceptable salt of said GABA modulator or prodrug; ziprasidone and a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of said GABA modulator or prodrug. The kit includes a container for containing the separate compositions such as a divided bottle or a divided foil packet. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from

the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, . . . etc . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent to the skilled practitioner. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of the ziprasidone can consist of one tablet or capsule while a daily dose of the anticonvulsant, benzodiazepine or GABA modulator can consist of several tablets or capsules or vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

In another embodiment of the present invention, the treatment of treatment-resistant anxiety disorder in a patient the method of the present invention can include administering a triple combination pharmaceutical composition containing an amount of a first therapeutic agent, said first therapeutic agent being ziprasidone;

an amount of a second therapeutic agent, said second therapeutic agent being a GABA modulator, a prodrug thereof or a pharmaceutically acceptable salt of said GABA modulator or said prodrug; and

an amount of a third therapeutic agent, said third therapeutic agent being a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of said benzodiazepine or said prodrug.

In still another embodiment of the present invention, for the treatment of psychotic disorders or conditions in a subjects, the method of the present invention can include administering a triple combination pharmaceutical composition containing

an amount of a first therapeutic agent, said first therapeutic agent being ziprasidone;

an amount of a second therapeutic agent, said second therapeutic agent being a benzodiazepine, a prodrug thereof or a pharmaceutically acceptable salt of said benzodiazepine modulator or said prodrug; and

an amount of a third therapeutic agent, said third therapeutic agent being an anticonvulsant, a prodrug thereof or a pharmaceutically acceptable salt of said anticonvulsant or said prodrug.

It will be understood that while the use of a single atypical antipsychotic as a first component compound is preferred, combinations of two or more atypical antipsychotics may be used as a first component if necessary or desired. Similarly, while the use of a single GABA modulator, anticonvulsant or benzodiazepine as a second component compound is preferred, combinations of two or more of these agents may be used as a second component if necessary or desired.

The atypical antipsychotic of the present invention is useful alone or in combination with a second antipsychotic agent, for example, an atypical antipsychotic such as ziprasidone mesylate, a typical antipsychotic such as haloperidol, or a dopamine system stabilizer antipsychotic such as aripiprazole. In addition, the combinations of the present invention may be used in combination with other therapeutic agents for anxiety, i.e. SSRIs , or buspirone or agents for psychotic or mood disorders, i.e. lithium, tricyclic antidepressants. It is preferred that if a second antipsychotic agent is used that they both administered to the patient in synergistic effective amounts. It is preferred that the total amount ranges from about 0.0001 to about 1000 mg/kg per day, more preferably from about 0.01 to about 100 mg/kg per day and most preferably from about 0.1 to about 60 mg/kg per day.

Pharmaceutical compositions of use in the present invention will comprise one or both active compound(s) in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampyules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredients are mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

When referring to these preformulation compositions as homogeneous, it is meant that the active ingredients is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as

tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 2000 mg of each of the active ingredients of the present invention. Typical unit dosage forms contain from 1 to 300 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

When administered in combination, either as a single or as separate pharmaceutical composition(s), the ziprasidone and the GABA modulator, anticonvulsant or benzodiazepine are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of ziprasidone to the GABA receptor modulator will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

The pharmaceutical combinations may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day, and most especially once daily.

As used herein the term "subject" includes animals of economic importance such as bovine, ovine, and porcine animals, especially those that produce meat, as well as domestic animals (e.g. cats and dogs), sports animals (e.g. horses), zoo animals, and humans, the latter being most preferred.

EXAMPLE 1

A pharmaceutical composition could be prepared by combining ziprasidone with a GABA modulator which is either: (a) gabapentin, (b) pregabalin or (c) lamotrigine in a pharmaceutically acceptable carrier. The composition contains respective amounts of ziprasidone and gabapentin, pregabalin or lamotrigine to deliver on a daily basis between about 20mg to about 160 mg ziprasidone and between about (a) 100 to 400 mg gabapentin; or (b) 1 to 500 mg pregabalin; or (c) 2 to 200 mg lamotrigine. The composition could be administered to a patient for the treatment of schizophrenia on a daily, twice daily, three times daily, or four times daily basis.

It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

CLAIMS:

1. A pharmaceutical composition for use in treating a psychiatric condition selected from the group consisting of a treatment-resistant anxiety disorder, a psychotic disorder or condition, or a mood disorder in a mammal comprising (i) a first therapeutic agent which is an atypical antipsychotic and (ii) a second therapeutic agent selected from the group consisting of GABA modulators, anticonvulsants, and benzodiazepines, wherein the amounts of (i) and (ii) are together effective in treating said psychiatric condition.

2. The pharmaceutical composition of claim 1 where the first therapeutic agent is selected from the group consisting of olanzapine, aripiprazole, clozapine, risperidone, sertindole, quetiapine, amisulpride, asenapine, and ziprasidone or a pharmaceutically acceptable salt or a prodrug thereof or a pharmaceutically acceptable salt of said prodrug; and the second therapeutic agent is selected from the group consisting of muscimol, progabide, riluzole, baclofen, gabapentin, vigabatrin, tiagabine, lamotrigine, pregabalin, topiramate, diazepam, lorazepam, clonazepam, oxazepam, dipotassium chlorazepate, chlorasepate, chlordiazepoxide, mediazepam, flurazepam, clobasam, nitrasepam, flunitrasepam, astazolam, bromazepam, alprazolam, lormetasepam, temazepam, brotizolam, triazolam, chlorodiazepam, halazepam, prazepam,valproate, phenytoin, carbamazepine, felbamate, levetiracetam, zonisamide, methoximide, oxycarbazepine, nemotrizine, ethosuximide, nemotrizine or a pharmaceutically acceptable salt or a prodrug thereof or a pharmaceutically acceptable salt of said prodrug.

3. The pharmaceutical composition of claim 1, wherein the first therapeutic agent is ziprasidone, a prodrug or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt of said prodrug.

4. A method for treating in a mammal in need thereof a disorder selected from treatment-resistant anxiety disorder, a psychotic disorder or condition, or a mood disorder, comprising administering to said mammal

i) an amount of a first therapeutic agent which is an atypical antipsychotic; and

ii) an amount of a second therapeutic agent which is selected from the group consisting of GABA modulators, anticonvulsants, and benzodiazepines, wherein the amounts of (i) and (ii) are together effective in treating said disorder.

5. A method according to claim 4, wherein said method is for treating a treatment-resistant anxiety disorder selected from the group consisting of treatment-resistant obsessive-compulsive disorder, treatment-resistant acute stress disorder, treatment-resistant generalized anxiety disorder, treatment-resistant substance-induced anxiety disorder, and treat-resistant anxiety disorder not otherwise specified.

6. A method according to claim 4, wherein said method is for treating a psychotic disorder or condition is selected from the group consisting of treatment-resistant

schizophrenia, treatment-resistant schizophreniform disorder, treatment-resistant schizoaffective disorder, treatment-resistant delusional disorder, treatment-resistant brief psychotic disorder, treatment-resistant shared psychotic disorder, treatment-resistant psychotic disorder due to a medical condition, and treatment-resistant psychotic disorder not otherwise specified.

7. A method according to claim 4, wherein said method is for treating a mood disorder or condition selected from the group consisting of unipolar disorders, bipolar disorders, dysthymic disorder, and cyclothymic disorder.

8. A method according to claim 4, wherein the affliction to be treated is a psychotic disorder or condition.

9. A method according to claim 4, further comprising an amount of a third therapeutic agent which is a benzodiazepine; wherein the amounts (i), (ii) and the benzodiazepine are together effective.

10. The method of any of the preceding claims wherein the atypical antipsychotic is ziprasidone.

11. The method of claims any of claims 1-9 wherein the atypical antipsychotic is ziprasidone and said ziprasidone is administered in dosages of about 5 mg to about 460 mg daily.

12. The method of any of claims 1-9 wherein the atypical antipsychotic is ziprasidone and said ziprasidone is administered in dosages of about 20 mg to about 200 mg daily.

13. The method of any of the preceding claims wherein the atypical antipsychotic is ziprasdione and the administration is oral.

14. The method of any of the preceding claims wherein the atypical antipsychotic is ziprasidone and the ziprasidone is administered parenterally.

15. The method of any of the preceding claims wherein the atypical antipsychotic is asenapine or a pharmaceutically acceptable salt thereof.

DO/ EO WORKSHEET

Patricia Booker **Paralegal/ National Stage Division**

U.S. Appl. No. 10/556600 **International Appl. No.** US2004/13308

Application filed by : ☐ 20 months ☑ 30 months

WIPO PUBLICATION INFORMATION :

Publication No.: WO2004/105682 **Publication Language :** ☐ English ☐ German ☐ Japanese ☐ Chinese ☐ Korean ☐ French ☐ Spanish ☐ Russian ☐ Other : _____

Publication Date : 2 Dec 2004 **Not Published :** ☐ U.S. only designated ☐ EP request **Published :** ☐ EP request

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE :

- ☑ **International Application** *(RECORD COPY)*
- ☐ **Article 19 Amendments**
- ☐ **PCT/IPEA/409 IPER :** ☐ EP ☐ JP ☐ SE ☐ AU ☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ ___ ☐ PCT/IPEA/409 IPER was NOT AVAILABLE at the time of paralegal review
- ☐ **Annexes to 409**
- ☑ **Priority Document (s) No.** 1
- ☐ **PCT/IB/331**
- ☐ **Request form PCT/RO/101**
- ☑ **PCT/ISA/210 - Search Report :** ☐ EP ☐ JP ☐ SE ☐ AU ☐ US ☐ FR ☐ CN ☐ ES ☐ RU ☐ AT ☐ KR ☐ OTHER ___ ☐ NONE
- ☐ **Search Report References**
- ☑ **Other :** 304

RECEIPTS FROM THE APPLICANT *(other than checked above) :*

- ☑ **Basic National Fee** *(or authorization to charge)*
- ☑ **Description** ☐ **Claims** ☑ **Abstract** 16/2
- ☑ **Drawing Figure(s) - (# of drwgs.** 8 **)**
- ☐ **Translation of Article 19 Amendments** ☐ entered ☐ not entered : ☐ not a page for page substitution ☐ replaced by Article 34 Amendment
- ☐ **Annexes to 409** ☐ entered ☐ not entered : ☐ not a page for page substitution ☐ no translation ☐ other : _____
- ☐ **Application Data Sheet**
- ☐ **Power of Attorney/ Change of Address**
- ☑ **Preliminary Amendment(s) Filed on :** 1. _____ 2. _____ 3. _____
- ☑ **Information Disclosure Statement(s) Filed on :** 1. 14 Nov 05 2. 02 Aug 06
- ☐ **Assignment Document** (forwarded to Assignment Branch) 1. _____
- ☐ **Assignee PG Publication Notice**
- ☑ **Substitute Specification Filed on :** 1. _____ 2. _____
- ☐ **Verified Small Status Statement**
- ☑ **Oath/ Declaration (executed)** 02 Aug 06 ☐ unsigned ☐ no citizenship
- ☐ **DNA Diskette** ☐ **Sequence Listing**
- ☐ **Other :** _____

NOTES : ☐ I.A. used as Specification ☐ Other :

35 U.S.C. 371 - Receipt of Request (PTO-1390) Express processing Sprint
Date Acceptable Oath/ Declaration Received
Date of Completion of requirements under 35 U.S.C. 371
Date of Completion of ALL requirements
Date of Completion of DO/ EO 903 - Notification of Acceptance
Date of Completion of DO/ EO 905 - Notification of Missing Requirements
Date of Completion of DO/ EO 909 - Notification of Abandonment
Date of Completion of DO/ EO 916 - Notification of Defective Response
Date of Completion of DO/ EO 922 - Notification to Comply w/ Requirements for Patent Applications Containing Nucleotide and/or Amino Acid Sequence Disclosures
Date of Completion of DO/ EO 923

Spec 68 drawings 8 total
Claims 3
Abst 2
81

Pat Booker

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 10/556602

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY TYPE ☐ RATE	FEE	OR	OTHER THAN SMALL ENTITY RATE	FEE
U.S. NATIONAL STAGE FEES							
BASIC FEE	SMALL ENT. = $ 150	LARGE ENT. = $ 300	BASIC FEE		OR	BASIC FEE	300
EXAMINATION FEE	Satisfies PCT Article 33(1)-(4) = $ 50 / $ 100	All other situations = $ 100 / $ 200	EXAM. FEE			EXAM. FEE	200
SEARCH FEE	U.S. is ISA = $ 50 / $ 100 ALL other countries = $ 200 / $ 400	All other situations = $ 250 / $ 500	SEARCH FEE			SEARCH FEE	100
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =	X $ 125 =			X $ 250 =	
TOTAL CHARGEABLE CLAIMS	16 minus 20 =	*	X $ 25 =		OR	X $ 50 =	
INDEPENDENT CLAIMS	2 minus 3 =	*	X $ 100 =		OR	X $ 200 =	
MULTIPLE DEPENDENT CLAIM PRESENT		☐	+ $ 180 =		OR	+ $ 360 =	
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL		OR	TOTAL	600

CLAIMS AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	ADDI-TIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	ADDI-TIONAL FEE
AMENDMENT A	Total	*	Minus	**	=	X $ 25 =		OR	X $ 50 =	
	Independent	*	Minus	***	=	X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐					+ $ 180 =		OR	+ $ 360 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDI-TIONAL FEE	OR	RATE	ADDI-TIONAL FEE
AMENDMENT B	Total	*	Minus	**	=	X $ 25 =		OR	X $ 50 =	
	Independent	*	Minus	***	=	X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐					+ $ 180 =		OR	+ $ 360 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

1 Dunken

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO: 10/556600

FILING DATE:

APPLICANT(S):

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1			1			
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12			1			
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						
32						
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						
44						
45						
46						
47						
48						
49						
50						
TOTAL IND.			2			
TOTAL DEP			14			
TOTAL CLAIMS			16			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
53						
54						
55						
56						
57						
58						
59						
60						
61						
62						
63						
64						
65						
66						
67						
68						
69						
70						
71						
72						
73						
74						
75						
76						
77						
78						
79						
80						
81						
82						
83						
84						
85						
86						
87						
88						
89						
90						
91						
92						
93						
94						
95						
96						
97						
98						
99						
100						
TOTAL IND.						
TOTAL DEP						
TOTAL CLAIMS						

PTO - 1360 (REV. 11/04)

U.S. DEPARTMENT of COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/556,600	08/02/2006	1617	730	Q81665	8	16	2

CONFIRMATION NO. 3822

FILING RECEIPT

23373
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC20037

Date Mailed: 11/01/2006

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Tetsuro Kikuchi, Tokushima, JAPAN;
Taro Iwamoto, Princeton, NJ;
Tsuyoshi Hirose, Tokushima, JAPAN;

Power of Attorney: The patent practitioners associated with Customer Number 23373

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US04/13308 05/19/2004

Foreign Applications

UNITED STATES OF AMERICA 60473378 05/23/2003

If Required, Foreign Filing License Granted: 10/28/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US10/556,600**

Projected Publication Date: 02/08/2007

Non-Publication Request: No

Early Publication Request: No

Title

Carbostyril derivatives and mood stabilizers for treating mood disorders

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/556,600	Tetsuro Kikuchi	Q81665

INTERNATIONAL APPLICATION NO.	
PCT/US04/13308	
I.A. FILING DATE	PRIORITY DATE
05/19/2004	05/23/2003

23373
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

CONFIRMATION NO. 3822

371 ACCEPTANCE LETTER

OC000000021026501

Date Mailed: 11/01/2006

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

08/02/2006	08/02/2006
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 11/14/2005
- Copy of the International Search Report filed on 11/14/2005
- Preliminary Amendments filed on 11/14/2005
- Information Disclosure Statements filed on 11/14/2005
- Oath or Declaration filed on 08/02/2006
- Request for Immediate Examination filed on 11/14/2005
- U.S. Basic National Fees filed on 11/14/2005
- Substitute Specification filed on 11/14/2005
- Priority Documents filed on 11/14/2005

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

PATRICIA A BOOKER
Telephone: (703) 308-9140 EXT 204

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

IFW

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Docket No: **Q81665**
Tetsuro KIKUCHI et al	Conf. No.: **3822**
Appln. No.: **10/556,600**	Group Art Unit: **1617**
Filed: **November 14, 2005**	Examiner: **Unassigned**

For: **CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS**

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §§ 1.97 and 1.98

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicants hereby notify the U.S. Patent and Trademark Office of the documents which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

One copy of each of the listed documents is submitted herewith.

The present Supplemental Information Disclosure Statement is being filed after three months from the application's filing date, but before the mailing date of the first Office Action on the merits. Therefore, no Statement under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT
U.S. Appln. No. 10/556,600

The submission of the listed documents is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicants do not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

Respectfully submitted,

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Gordon Kit
Registration No. 30,764

Date: November 17, 2006

MODIFIED PTO/SB/08 A & B (08-03)

Substitute for Form 1449 A & B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	10/556,600
Confirmation Number	3822
Filing Date	November 14, 2005
First Named Inventor	Tetsuro KIKUCHI et al
Art Unit	1617
Examiner Name	Unassigned
Attorney Docket Number	Q81665

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Document Number: Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Foreign Patent Document: Number[4]	Foreign Patent Document: Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		Merck Index 13, the Merck & Co. NJ. USA document, No. 791, 1788, 5368, 9625, 4342 and 2413	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]See Kind Codes of USPTO Patent Documents at www.uspto.gov, MPEP 901.04 or follow the hyperlink from the title of the document to the intranet. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST. 3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to indicate here if English language Translation is attached.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, et al.

Docket No: Q81665

Appln. No.: 10/556,600

Group Art Unit: 1617

Confirmation No.: 3822

Examiner: Unknown

Filed: November 14, 2005

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

REQUEST FOR CORRECTED OFFICIAL FILING RECEIPT

ATTN: Office of Initial Patent Examination
Filing Receipt Correction
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We enclose a copy of the Official Filing Receipt for the above-identified application and request the following correction:

Assignment for Published patent Application

OTSUKA PHARMACEUTICALS CO., LTD.

Verification for the requested correction is indicated on the Assignment and Recordation Document filed August 2, 2006.

Respectfully submitted,

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Gordon Kit
Registration No. 30,764

Date: November 27, 2006

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY.DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
10/556,600	08/02/2006	1617	730	Q81665	8	16	2

CONFIRMATION NO. 3822

23373
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

FILING RECEIPT

OC000000021026500

Date Mailed: 11/01/2006

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Tetsuro Kikuchi, Tokushima, JAPAN;
Taro Iwamoto, Princeton, NJ;
Tsuyoshi Hirose, Tokushima, JAPAN;

ASSIGNMENT FOR PUBLISHED PATENT APPLICATION
OTSUKA PHARMACEUTICAL CO., LTD

Power of Attorney: The patent practitioners associated with Customer Number **23373**.

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US04/13308 05/19/2004

Foreign Applications

UNITED STATES OF AMERICA 60473378 05/23/2003

If Required, Foreign Filing License Granted: 10/28/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is US10/556,600

Projected Publication Date: 02/08/2007

Non-Publication Request: No

Early Publication Request: No

Title

Carbostyril derivatives and mood stabilizers for treating mood disorders

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Q81665

MODIFIED Form PTO-1595
(Rev. 10/02)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

To the Director of the U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Tetsuro KIKUCHI
Taro IWAMOTO
Tsuyoshi HIROSE

Additional name(s) of conveying party(ies) attached? ☐ Yes ☑ No

2. Name and address of receiving party(ies):
OTSUKA PHARMACEUTICAL CO., LTD.
2-9, Kanda-Tsukasacho, Chiyoda-ku, Tokyo, Japan

Additional name(s) & address(es) attached? ☐ Yes ☑ No

3. Nature of conveyance:
☑ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date: September 30, 2005, October 7, 2005, and September 30, 2005

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
10/556,600

B. Patent No.(s)
Unknown

Additional numbers attached? ☐ Yes ☑ No

5. Name and address of party to whom correspondence concerning document should be mailed:
SUGHRUE MION, PLLC
WASHINGTON OFFICE
23373
CUSTOMER NUMBER

6. Total number of applications and patents involved:
1

7. Total fee (37 CFR 3.41): $40.00
☑ Enclosed.
☐ Authorized to be charged to Deposit Account No. 19-4880.
The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

8. Deposit Account Number:
19-4880
(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Gordon Kit — Reg. No. 30,764 — August 2, 2006
Date

Total number of pages including cover sheet, attachments, and documents: 2

Mail documents to be recorded with required cover sheet information to:
MAIL STOP ASSIGNMENT RECORDATION SERVICES
Director of the U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

ASSIGNMENT

As a below named inventor, I hereby declare that:

IN CONSIDERATION of the sum of One Dollar($1.00) or the equivalent thereof, and other good and valuable consideration paid to me citizen of Japan by OTSUKA PHARMACEUTICAL CO., LTD., a corporation organized under the laws of Japan, located at 2-9, Kanda-Tsukasacho, Chiyoda-ku, Tokyo, Japan, receipt of which is hereby acknowledged I do hereby sell and assign to said OTSUKA PHARMACEUTICAL CO., LTD., its successors and assigns, all my right, title and interest, in and for the United States of America, in and to

CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

invented by me (if only one is named below) or us (if plural inventors are named below) and described in the application for United States Letters Patent therefor, executed on even date herewith,

and all United States Letters Patent which may be granted therefor, and all divisions, continuations and extensions thereof, the said interest being the entire ownership of the said Letters Patent when granted, to be held and enjoyed by said OTSUKA PHARMACEUTICAL CO., LTD., its successors, assigns or other legal representatives, to the full end of term for which said Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by me or us if this assignment and sale had not been made;

And I hereby agree to sign and execute any further documents or instruments which may be necessary, lawful, and proper in the prosecution of the above-named application or in the preparation and prosecution of any continuing, continuation-in-part, substitute, divisional, renewal, reviewed or reissue applications or in any amendment, extension, or interference proceedings, or otherwise to secure the title thereto in said assignee;

And I do hereby authorize and request the Commissioner of Patents to issue said Letters Patent to said OTSUKA PHARMACEUTICAL CO., LTD.

Signed on the date(s) indicated aside signatures:

	INVENTOR(S) (発明者フルネームサイン)	Date Signed (署名日)	WITNESSES (立会人サイン)
1)	Tetsuro Kikuchi Tetsuro KIKUCHI	September 30, 2005	Jun Shimada
2)	Taro IWAMOTO	October 7, 2005	
3)	Tsuyoshi HIROSE	September 30, 2005	Jun Shimada
4)			
5)			
6)			
7)			
8)			
9)			

Electronic Acknowledgement Receipt

EFS ID:	1335047
Application Number:	10556600
International Application Number:	
Confirmation Number:	3822
Title of Invention:	Carbostyril derivatives and mood stabilizers for treating mood disorders
First Named Inventor/Applicant Name:	Tetsuro Kikuchi
Customer Number:	23373
Filer:	Brian Kenneth Shelton/Mussie Beyene
Filer Authorized By:	Brian Kenneth Shelton
Attorney Docket Number:	Q81665
Receipt Date:	27-NOV-2006
Filing Date:	02-AUG-2006
Time Stamp:	16:32:45
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	ReqCOROFR.pdf	248512	no	6
Warnings:					

Information:	
Total Files Size (in bytes):	248512

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

IFW

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, *et al.*

Docket No: Q81665

Appln. No.: 10/556,600

Group Art Unit: 1617

Confirmation No.: 3822

Examiner: *Unassigned*

Filed: November 14, 2005

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.97 and 1.98

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the document which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

One copy of each of the listed documents is submitted herewith, except for the following: U.S. patents and/or U.S. patent publications; and co-pending non-provisional U.S. applications filed after June 30, 2003.

The present Information Disclosure Statement is being filed: (1) No later than three months from the application's filing date; (2) Before the mailing date of the first Office Action on the merits (whichever is later); or (3) Before the mailing date of the first Office Action after filing a request for continued examination (RCE) under § 1.114, and therefore, no Statement under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

In compliance with the concise explanation requirement under 37 C.F.R. § 1.98(a)(3) for foreign language documents, Applicant encloses herewith a copy of a Communication from a foreign patent office in a counterpart application citing such document, together with an English-language version (if not already included) of at least that portion of the Communication indicating the degree of relevance found by the foreign patent office.

The submission of the listed document is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Gordon Kit
Registration No. 30,764

Date: December 8, 2006

MODIFIED PTO/SB/08 A & B (08-03)

Substitute for Form 1449 A & B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	10/556,600
Confirmation Number	3822
Filing Date	November 14, 2005
First Named Inventor	Tetsuro KIKUCHI *et al.*
Art Unit	1617
Examiner Name	*Unassigned*
Attorney Docket Number	Q81665

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Document Number: Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Foreign Patent Document: Number[4]	Foreign Patent Document: Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 791	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 1788	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 5368	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 9625	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 4342	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 2413	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]See Kind Codes of USPTO Patent Documents at www.uspto.gov, MPEP 901.04 or follow the hyperlink from the title of the document to the intranet. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST. 3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to indicate here if English language Translation is attached.

IFW

PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, *et al.*

Docket No: Q81665

Appln. No.: 10/556,600

Group Art Unit: 1617

Confirmation No.: 3822

Examiner: *Unassigned*

Filed: November 14, 2005

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.97 and 1.98

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the document which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

One copy of each of the listed documents is submitted herewith, except for the following: U.S. patents and/or U.S. patent publications; and co-pending non-provisional U.S. applications filed after June 30, 2003.

The present Information Disclosure Statement is being filed: (1) No later than three months from the application's filing date; (2) Before the mailing date of the first Office Action on the merits (whichever is later); or (3) Before the mailing date of the first Office Action after filing a request for continued examination (RCE) under § 1.114, and therefore, no Statement under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

In compliance with the concise explanation requirement under 37 C.F.R. § 1.98(a)(3) for foreign language documents, Applicant encloses herewith a copy of a Communication from a foreign patent office in a counterpart application citing such document, together with an English-language version (if not already included) of at least that portion of the Communication indicating the degree of relevance found by the foreign patent office.

The submission of the listed document is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Gordon Kit
Registration No. 30,764

Date: December 8, 2006

MODIFIED PTO/SB/08 A & B (08-03)

Substitute for Form 1449 A & B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	10/556,600
Confirmation Number	3822
Filing Date	November 14, 2005
First Named Inventor	Tetsuro KIKUCHI *et al.*
Art Unit	1617
Examiner Name	*Unassigned*
Attorney Docket Number	Q81665

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Document Number: Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Foreign Patent Document: Number[4]	Foreign Patent Document: Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 791	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 1788	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 5368	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 9625	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 4342	
		THE MERCK INDEX, An Encyclopedia of Chemicals, Drugs and Biologicals, Thirteenth Edition, Merck Index & Co., NJ, USA document, number 2413	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]See Kind Codes of USPTO Patent Documents at www.uspto.gov, MPEP 901.04 or follow the hyperlink from the title of the document to the intranet. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST. 3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to indicate here if English language Translation is attached.

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, et al.

Docket No: Q81665

Appln. No.: 10/556,600

Group Art Unit: 1617

Confirmation No.: 3822

Examiner: Unknown

Filed: November 14, 2005

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §§ 1.97 and 1.98

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the documents which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

One copy of each of the listed documents is submitted herewith, along with a copy of the corresponding Communication from a Foreign Patent Office, except for the following: U.S. patents and/or U.S. patent publications; and co-pending non-provisional U.S. applications filed after June 30, 2003.

The present Information Disclosure Statement is being filed: (1) No later than three months from the application's filing date; (2) Before the mailing date of the first Office Action

on the merits (whichever is later); or (3) Before the mailing date of the first Office Action after filing a request for continued examination (RCE) under §1.114, and therefore, no Statement under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

In compliance with the concise explanation requirement under 37 C.F.R. § 1.98(a)(3) for foreign language documents, Applicant encloses herewith a copy of a Communication from a foreign patent office in a counterpart application citing such documents, together with an English-language version (if not already included) of at least that portion of the Communication indicating the degree of relevance found by the foreign patent office.

The submission of the listed documents is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted.

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Gordon Kit
Registration No. 30,764

Date: January 5, 2007

Substitute for Form 1449 A & B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	10/556,600
Confirmation Number	3822
Filing Date	November 14, 2005
First Named Inventor	Tetsuro KIKUCHI
Art Unit	1617
Examiner Name	Unknown
Attorney Docket Number	Q81665

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number	Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US			
		US			
		US			
		US			
		US			
		US			
		US			
		US			
		US			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Number[4]	Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]
		WO	2004060374	A1	07-22-2004	OTSUKA PHARMACEUTICAL CO., LTD.	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		Copy of RU Search Report dated November 8, 2006 issued in Patent Application No. 2004 009073	Yes

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] See Kind Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04 or follow the hyperlink from the title of the document to the intranet. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST. 3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to indicate here if English language Translation is attached.

CARBOSTYRIL DERIVATIVES AND SEROTONIN REUPTAKE INHIBITORS FOR TREATMENT OF MOOD DISORDERS

Publication number: WO2004060374

Publication date: 2004-07-22

Inventor: KIKUCHI TETSURO (JP); IWAMOTO TARO (US); HIROSE TSUYOSHI (JP)

Applicant: OTSUKA PHARMA CO LTD (JP); KIKUCHI TETSURO (JP); IWAMOTO TARO (US); HIROSE TSUYOSHI (JP)

Classification:

- international: ***A61K31/135; A61K31/15; A61K31/165; A61K31/343; A61K31/381; A61K31/4525; A61K31/496; A61P25/24;*** **A61K31/135; A61K31/15; A61K31/165; A61K31/343; A61K31/381; A61K31/4523; A61K31/496; A61P25/00;** (IPC1-7): A61K31/496; A61K31/135; A61K31/15; A61K31/343; A61K31/381; A61K31/4525; A61P25/24

- european: A61K31/135; A61K31/15; A61K31/165; A61K31/343; A61K31/381; A61K31/4525; A61K31/496

Application number: WO2003JP16724 20031225

Priority number(s): JP20020379003 20021227; US20030470481P 20030514

Also published as:

- EP1575590 (A1)
- RU2005123808 (A)
- MXPA05006857 (A
- EP1575590 (A0)
- CA2511619 (A1)
- AU2003295235 (A

less <<

Cited documents:

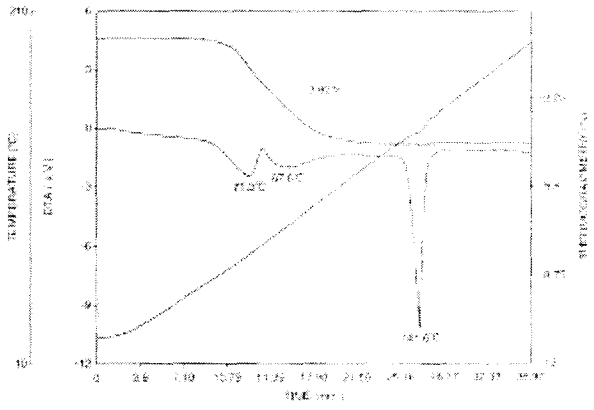
- US2002156067
- WO02060423
- WO2004010932
- XP002205416
- XP001087706
- XP002279121
- XP008029355
- XP008029340

less <<

Report a data error he

Abstract of **WO2004060374**

The pharmaceutical composition of the present invention comprises (1) a carbostyril derivative and (2) a serotonin reuptake inhibitor in a pharmaceutically acceptable carrier. The carbostyril derivative may be aripiprazole or a metabolite thereof, which is a dopamine-serotonin system stabilizer. The serotonin reuptake inhibitor may be fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline or escitalopram. The pharmaceutical composition of the present invention is useful for treating patients with mood disorders, particularly depression or major depressive disorder.

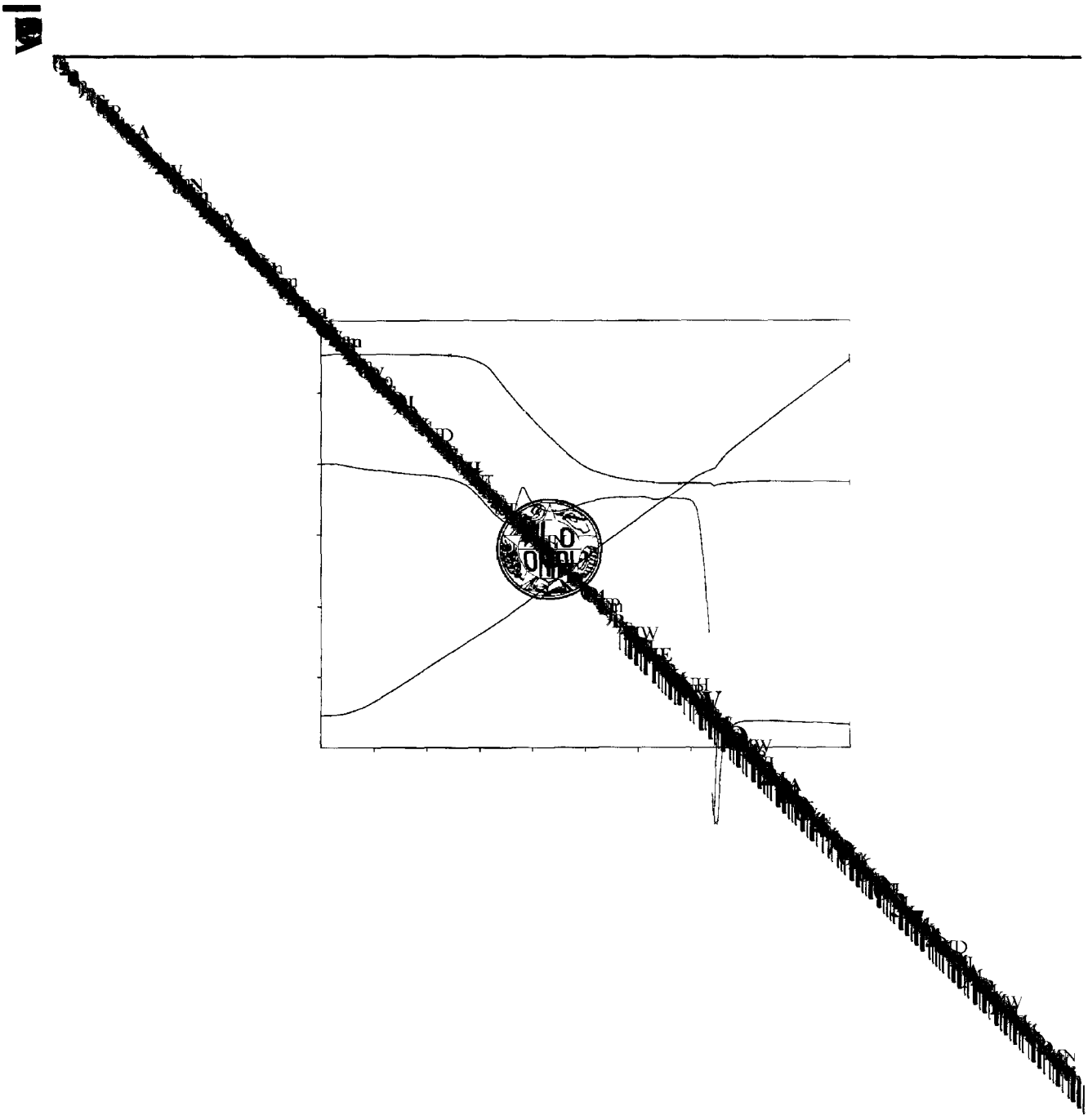


WO2004060374

Title:
CARBOSTYRIL DERIVATIVES AND SEROTONIN REUPTAKE INHIBITORS FOR TREATMENT OF MOOD DISORDERS

Abstract:

The pharmaceutical composition of the present invention comprises (1) a carbostyril derivative and (2) a serotonin reuptake inhibitor in a pharmaceutically acceptable carrier. The carbostyril derivative may be aripiprazole or a metabolite thereof, which is a dopamine-serotonin system stabilizer. The serotonin reuptake inhibitor may be fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline or escitalopram. The pharmaceutical composition of the present invention is useful for treating patients with mood disorders, particularly depression or major depressive disorder.



Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DESCRIPTION

CARBOSTYRIL DERIVATIVES AND SEROTONIN REUPTAKE INHIBITORS FOR TREATMENT OF MOOD DISORDERS

TECHNICAL FIELD

The present invention provides pharmaceutical compositions comprising carbostyril derivatives that act as dopamine-serotonin system stabilizers in combination with serotonin reuptake inhibitors in a pharmaceutically acceptable carrier. Further, the present invention provides methods of using the compositions of the present invention to treat mood disorders such as depression and major depressive disorder.

BACKGROUND ART

The number of people with mood disorders such as major depressive disorder, and exhibiting various symptoms of depressions is increasing every year for numerous reasons such as social stress, unemployment, disease, and poverty. Depression is a major social problem throughout the world. For example, in Japan the occurrence rate of depression in the generation older than 65 years is 5% or more, including major depressive disorder. Some of the depression in this population is associated with mental disturbances representing senile diseases associated with dementia

and neurosis. Many depressed patients show high recurrence rate, and severe depressive symptoms are major causes of suicide and drug abuse (Nishimura Ken, "NIPPON RONEN IGAKUZASSHI", Vol. 33, pp 503-504 (1996)).

Since the period of 1950, tricyclic antidepressant drugs (e.g., imipramine, desipramine, amitriptyline, etc.) have been developed that act to inhibit monoamine reuptake. They are frequently used for treating patients suffering from mood disorders, such as depression and major depressive disorder. However, these drugs have side-effects such as the following: dry mouth, hazy eyes, dysuria, constipation, recognition disturbance and the like due to anticholinergic activity; cardiovascular side-effects such as, orthostatic hypotension, tachycardia and the like on the basis of α_1-adrenoreceptor antagonist activity; side-effects such as, sedation, increase in the body weight and the like on the basis of histamine-H_1 receptor antagonist activity.

Since 1980, serotonin reuptake inhibitors have been developed, including but not limited to fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, escitalopram, fluvoxamine, paroxetine and sertraline, and these inhibitors have side-effects such as recognition disturbance, sleep disturbance, and excerbation of anxiety and agitation. Additionally, these inhibitors also have other side effects in the

digestive organs, such as nausea, vomiting and the like.

For the reason that the mood disorders such as depressive symptoms, depression and the like are diseases with severely strong psychalgalia, the manifestation of new symptoms on the basis of these side-effects are quite serious problems in the therapy of mood disorders (Shioe Kunihiko, Kariya Tetsuhiko, "SHINKEI SEISHIN YAKURI", Vol. 11, pp 37-48 (1989); Yamada Mitsuhiko, Ueshima Kunitoshi, "RINSHOU SEISHIN YAKURI", Vol. 1, pp 355-363 (1998)).

Although the mood disorders including depression and major depressive disorder are heterogeneous diseases, and the causes of these diseases are not been fully understood, it is likely that the abnormalities of monoaminergic central nervous system caused by serotonin, norepinephrine and dopamine and the like, and the abnormality of various hormones and peptides as well as various stressors are causes of depression and various mood disorders (Kubota Masaharu et al., "RINSHOU SEISHIN IGAKU", Vol. 29, pp 891-899 (2000)). For these reasons, even though antidepressant drugs, such as tricyclic antidepressants and serotonin reuptake inhibitors were used, these drugs are not always effective in treating all depressed patients. About 30% of the depressed patients do not respond to the primarily selected antidepressants (Nelson, J. C, et al., J. Clin. Psychiatry, 55, pp 12-19 (1994)).

Further, when a second or third antidepressant is administered to these patients, insufficient improvements of the symptoms occurs in about 10% of these patients (Inoeu Takeshi, Koyama Tsukasa, "RINSHOU SEISHIN IGAKU", Vol. 38, pp 868-870 (1996)). These patients are called as refractory depression patients.

In some cases, electric shock therapy is used to treat refractory depression, and the efficacy of this treatment has been reported. However, in fact, the condition of numerous patients is not improved (Inoue Takeshi, Koyama Tsukasa, "RINSHOU SEISHIN YAKURI", Vol. 2, pp 979-984 (1999)). Additionally, psychological anguish experienced by these patients and their families concerning the use of the electric shock therapy can be severe.

New therapeutic trials involve proposed combined therapies using an atypical antipsychotic drug, such as olanzapine, which is an agent for treating for schizophrenia (antipsychotic drug), together with an antidepressant drug such as serotonin reuptake inhibitor (EP 0 367 141, WO 98/11897, WO99/61027, WO99/62522, U.S. 2002/0123490A1 and the like). However, commercially available atypical anti-psychotic drugs have significant problems relating to their safety. For example, clozapine, olanzapine and quetiapine increase body weight and enhance the risk of diabetes mellitus (Newcomer, J. W. (Supervised Translated by Aoba Anri), "RINSHOU SEISHIN YAKURI",

Vol. 5, pp 911-925 (2002); Haupt, D. W. and Newcomer, J. W (Translated by Fuji Yasuo and Misawa Fuminari), "RINSHOU SEISHIN YAKURI", Vol. 5, pp 1063-1082 (2002)). In fact, urgent safety alerts have been issued in Japan relating to hyperglycemia, diabetic ketoacidosis and diabetic coma caused by olanzapine and quetiapine, indicating that these drugs were subjected to dosage contraindication to the patients with diabetes mellitus and patients having anamnesis of diabetes mellitus. Risperidone causes increases serum prolactin levels and produces extrapyramidal side effects at high dosages. Ziprasidone enhances the risk of severe arrhythmia on the basis of cardio-QTc prolongation action. Further, clozapine induces agranulocytosis, so that clinical use thereof is strictly restricted (van Kammen, D. P. (Compiled under Supervision by Murasaki Mitsuroh), "RINSHOU SEISHIN YAKURI", Vol. 4, pp 483-492 (2001)).

Accordingly what is needed are new compositions useful for treating mood disorders, particularly, depression and major depressive disorder, which are efficacious and do not cause the deleterious side effects associated with prior art compounds.

DISCLOSURE OF THE INVENTION

The present invention solves the problem described above by providing novel compositions and methods of using these compositions for treating mood disorders, particularly depression and major depressive

disorder.

The present invention provides solutions to the above-mentioned problems, and demonstrates that the mood disorders such as depression, major depressive and the like can be treated effectively by administering to a patient with such disorder a pharmaceutical composition comprising at least one carbostyril derivative that is a dopamine-serotonin system stabilizer in combination with at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier.

A preferred carbostyril derivative of the present invention that is a dopamine-serotonin system stabilizer is aripiprazole or a metabolite thereof. Another preferred carbostyril derivative of the present invention that is a dopamine-serotonin system stabilizer is a metabolite of aripiprazole called dehydroaripiprazole, also known as OPC-14857. Other such metabolites of aripiprazole included within the present invention are shown in Figure 8. Preferred metabolites are shown in Figure 8 indicated by the following designations: OPC-14857, DM-1458, DM-1451, DM-1452, DM-1454 and DCPP.

Aripiprazole, also called 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydro-2(1H)-quinolinone, is a carbostyril compound and is useful for treating schizophrenia (EP 0 367 141, U.S. Patent No. 5,006,528). Aripiprazole is also known as

7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril, Abilify, OPC-14597, OPC-31 and BMS-337039. Aripiprazole possesses 5-HT1A receptor agonist activity, and is known as useful compound for treating types of depression and refractory depressions, such as endogeneous depression, major depression, melancholia and the like (WO 02/060423, U. S. Patent Application 2002/0173513A1). Aripiprazole has activity as an agonist at the serotonin receptors and dopamine receptors, and acts as an agonist or partial agonist at the serotonin 5-HT1A receptor and as an agonist or partial agonist at the dopamine D_2 receptor. Aripiprazole is a dopamine-serotonin system stabilizer. Metabolites of aripiprazole are included within the scope of the present invention. One such metabolite of aripiprazole is called dehydroaripiprazole. Other such metabolites of aripiprazole included within the present invention are shown in Figure 8. Preferred metabolites are shown in Figure 8 indicated by the following designations: OPC-14857, DM-1458, DM-1451, DM-1452, DM-1454 and DCPP.

The at least one serotonin reuptake inhibitor used in the present invention includes but is not limited to the following: fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, escitalopram and salts thereof. In a preferred embodiment, the pharmaceutical composition comprises aripiprazole and citalopram in a

pharmaceutically acceptable carrier.

The novel compositions of present invention comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier may be combined in one dosage form, for example a pill. Alternatively the at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and the at least one serotonin reuptake inhibitor may be in separate dosage forms, each in a pharmaceutically acceptable carrier. These compositions are administered to a patient with a mood disorder, particularly depression or major depressive disorder, in an amount and dosage regimen effective to treat the mood disorder.

Accordingly, it is an object of the present invention to provide a pharmaceutical composition useful for treating a mood disorder.

It is an object of the present invention to provide a composition useful for treating a mood disorder, wherein the mood disorder is depression or major depressive disorder.

It is another object of the present invention to provide a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier.

Yet another object of the present invention is to provide a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier, wherein the carbostyril derivative is aripiprazole or a metabolite thereof.

Yet another object of the present invention is to provide a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier, wherein the carbostyril derivative is aripiprazole and the serotonin reuptake inhibitor is citalopram.

Yet another object of the present invention is to provide a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor, wherein the carbostyril derivative with activity as a dopamine-serotonin system stabilizer is a metabolite of aripiprazole and is dehydroaripiprazole (OPC-14857), DM-1458, DM-1451, DM-1452, DM-1454 or DCPP.

Yet another object of the present invention is to provide a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin

reuptake inhibitor, wherein the carbostyril derivative is dehydroaripiprazole.

It is an object of the present invention to provide a use of a composition useful for treating a mood disorder in the preparation of a medicament for treatment of a mood disorder, wherein the mood disorder is depression or major depressive disorder.

It is another object of the present invention to provide a use of a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier in the preparation of a medicament for treatment of a mood disorder.

Yet another object of the present invention is to provide a use of a composition comprising a carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier in the preparation of a medicament for treatment of mood disorders, wherein the carbostyril derivative is aripiprazole or a metabolite thereof.

Yet another object of the present invention is to provide a use of a composition comprising a carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier in the preparation of a medicament for

treatment of mood disorders, wherein at least one carbostyril derivative is aripiprazole and at least one serotonin reuptake inhibitor is citalopram.

Yet another object of the present invention is to provide a use of a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor pharmaceutically acceptable carrier in the preparation of a medicament for treatment of mood disorders, wherein the carbostyril derivative with activity as a dopamine-serotonin system stabilizer is a metabolite of aripiprazole and is dehydroaripiprazole (OPC-14857), DM-1458, DM-1451, DM-1452, DM-1454 or DCPP.

Yet another object of the present invention is to provide a use of a composition comprising a carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier in the preparation of a medicament for treatment of mood disorders, wherein the carbostyril derivative is dehydroaripiprazole.

It is an object of the present invention to provide a method for treating a mood disorder.

It is an object of the present invention to provide a method for treating a mood disorder wherein the mood disorder is depression or major depressive disorder.

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 at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor 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 at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor together in a pharmaceutically acceptable carrier, wherein the carbostyril derivative is aripiprazole or a metabolite thereof.

It is another object of the present invention to provide a method for treating major depressive disorder comprising administration to a patient with major depressive disorder of a composition comprising a carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor together with a pharmaceutically acceptable carrier, wherein the carbostyril derivative is aripiprazole and the serotonin reuptake inhibitor is citalopram.

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 at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier, wherein the carbostyril derivative is a metabolite of aripiprazole and is dehydroaripiprazole (OPC-14857), DM-1458, DM-1451, DM-1452, DM-1454 or DCPP.

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

It is another object of the present invention to provide a method for treating major depressive disorder comprising administration to a patient with major depressive disorder of a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier.

It is another object of the present invention

to provide a method for treating major depressive disorder comprising administration to a patient with major depressive disorder of a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor together with a pharmaceutically acceptable carrier, wherein the carbostyril derivative is aripiprazole or a metabolite thereof.

Still another object of the present invention is to provide a method for treating major depressive disorder comprising administration to a patient with major depressive disorder of a composition comprising at least one carbostyril derivative with activity as a dopamine-serotonin system stabilizer and at least one serotonin reuptake inhibitor in a pharmaceutically acceptable carrier, wherein the carbostyril derivative is a metabolite of aripiprazole and is dehydro-aripiprazole (OPC-14857), DM-1458, DM-1451, DM-1452, DM-1454 or DCPP.

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 DRAWINGS

Figure 1 is the thermogravimetric/

differential thermogram of the aripiprazole hydrate A obtained in Reference Example 4.

Figure 2 is the ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the aripiprazole hydrate A obtained in Reference 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 ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the aripiprazole anhydride crystals B obtained in Example 1.

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

Figure 6 is the thermogravimetric/differential thermogram of the aripiprazole hydrate A 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 schematric 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.

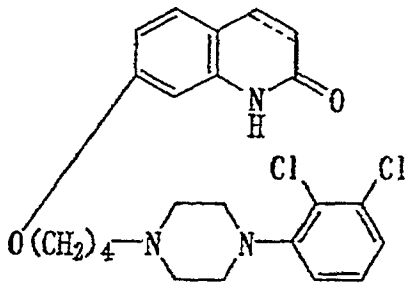
DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutical composition of the present

invention comprises a first ingredient comprising a carbostyril derivative active as a dopamine-serotonin system stabilizer and a second ingredient comprising a serotonin reuptake inhibitor, in a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention are useful in treating mood disorders, including depression and major depressive disorder.

The pharmaceutical composition: the first ingredient

The first ingredient comprises a carbostyril derivative active as a dopamine-serotonin system stabilizer. Such carbostyril 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 5-HT1A receptor and as an agonist or partial agonist at the dopamine D_2 receptor. Carbostyril 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 carbostyril derivatives represented by the following formula (1) are used:



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

In a preferred embodiment, this activity of the carbostyril derivative is as an agonist or partial agonist at the 5-HT1A receptor and an agonist or partial agonist at the dopamine D_2 receptor subtype. In another preferred embodiment, the carbostyril 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 DCPP. All of the aforementioned carbostyril 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-2(1H)-quinolinone, is a carbostyril 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-dihydrocarbostyril, Abilify, OPC-14597, OPC-31 and BMS-337039. Aripiprazole possesses 5-HT1A 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 (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 5-HT1A receptor and as an agonist or partial agonist at the dopamine D_2 receptor.

Aripiprazole is an antipsychotic drug having new mechanism of action which is different from that of other atypical antipsychotic drugs (Grunder, G. et al., Arch Gen Psychiatry, 60(10), pp 974-977, 2003). The available typical and atypical antipsychotic drugs act as antagonists at the dopamine-D_2 receptors. In contrast, aripiprazole acts as a partial agonist at the dopamine D_2 receptor (By 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-D_2 receptors, aripiprazole has activity as a partial agonist at the serotonin 5-HT1A receptors, as well as antagonist action at serotonin 5-HT2A receptors. Accordingly, aripiprazole is a drug belonging to new category defined as a dopamine-serotonin system stabilizer (dopamine-serotonin 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; Grunder, G. et al., Arch Gen Psychiatry, 60(10), pp 974-977, 2003).

Methods of Preparing Aripiprazole

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

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:

(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 appearance of a small peak at about 71°C and a gradual endothermic peak around 60°C to 120°C.

(2) It has an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 2. Specifically, it has

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).

(3) It has a powder x-ray diffraction spectrum which is substantially identical to the powder 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.

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 ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (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 2θ = 11.0°, 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°C/min).

(10) They exhibit an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate 5°C/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.

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 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 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 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. 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, 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 90-125°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 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 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. 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 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 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 are prepared by well-known methods, as described in

Example 1 of Japanese Unexamined Patent Publication No. 191256/1990.

7-(4-bromobutoxy)-3,4-dihydrocarbostyril, is reacted with 1-(2,3-dichlorophenyl)piperazine and the thus obtained crude aripiprazole crystals are recrystallized 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 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 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 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

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 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 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, succinic acid, etc. can be exemplified. Similar to aripiprazole of free forms, these acid addition salts can also be 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 further purified. As to the separation and purification means, for example, distillation method, solvent extraction method, dilution method, recrystallization method, column chromatography, ion-exchange chromatography, gel chromatography, affinity 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 serotonin reuptake inhibitor is used as the second ingredient. Compounds which function as serotonin reuptake inhibitors can be widely used as the serotonin reuptake inhibitors and are known to one of ordinary skill in the art.

Among the serotonin reuptake inhibitors, those having IC_{50} value (a concentration of the drug that inhibits serotonin reuptake by about 50%), measured by the method of Wong et al. (Neuropsychopharmacology, 8, pp 337-344 (1993)), the standard pharmacological assay method, is about 1000 nM or lower is preferable.

As to such serotonin reuptake inhibitors, for example, fluvoxamine (5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-O-(2-aminoethyl)oxime), fluoxetine (N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine), paroxetine (trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidine), sertraline (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylylamine hydrochloride), venlafaxine, milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxyamide), citalopram, escitalopram, duloxetine and the like may be used.

The serotonin reuptake inhibitor may be either in the form of a free base or a salt (an acid addition salt or the like). Further, the serotonin reuptake inhibitor may be either a racemic modifications or R and S enantiomers.

The serotonin reuptake inhibitors may be either a single use of one serotonin reuptake inhibitor, and in case of need, two or more of the serotonin reuptake inhibitors may be used in combination. Use of one serotonin reuptake inhibitor is preferred.

The serotonin reuptake inhibitor 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, succinic acid, etc. can be exemplified. Similar to the reuptake inhibitor of free forms, these acid addition salts can be also used as the active ingredient compounds in the present invention.

Among the serotonin reuptake inhibitors, a compound having 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 hydrogencabonate, potassium hydrogencarbonate and the like; a metal alcoholate, for example sodium methylate, potassium ethylate and the like can be exemplified.

The thus obtained salt form of serotonin reuptake inhibitor 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, 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 ingredient

As to combination of carbostyril derivatives with activity as dopamine-serotonin system stabilizers, non-limiting examples of aripiprazole and dehydroaripiprazole are described herein. When aripiprazole is combined with at least one serotonin reuptake inhibitor, the following are non-limiting examples of such combinations: aripiprazole/fluoxetine, aripiprazole/duloxetine, aripiprazole/venlafaxine,

aripiprazole/milnacipran, aripiprazole/citalopram, aripiprazole/fluvoxamine, aripiprazole/paroxetine, and aripiprazole/sertraline. A preferred embodiment comprises a combination of aripiprazole/citalopram.

In another embodiment of the present invention, aripiprazole, or a metabolite thereof may be combined with more than one serotonin reuptake inhibitor. 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 DCPP as shown in Figure 8. Any one of these metabolites may be used in the present invention. The following sentences describe a combination of dehydroaripiprazole with specific serotonin reuptake inhibitors, however it is to be understood that any one of DM-1458, DM-1451, DM-1452, DM-1454 or DCPP, 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 aripiprazole. As to combination of dehydroaripiprazole with serotonin reuptake inhibitor, the following are non-limiting examples of such combinations:

dehydroaripiprazole/fluoxetine,

dehydroaripiprazole/duloxetine,

dehydroaripiprazole/venlafaxine,

dehydroaripiprazole/milnacipran,

dehydroaripiprazole/citalopram,

dehydroaripiprazole/fluvoxamine, dehydroaripiprazole/paroxetine, and dehydroaripiprazole/sertraline. A preferred embodiment comprises a combination of dehydroaripiprazole and citalopram.

Method of Treating a Mood Disorder, Especially Major Depressive Disorder

Patients with mood disorders may be treated with the compositions of the present invention. A preferred disorder treated with the method and compositions of the present invention is depression or major depressive disorder. Treatment comprises administration of the compositions of the present invention to a patient with a mood disorder such as depression or major depressive disorder, in an amount and dose regimen effective to treat the mood disorder.

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 being after combination and symptoms of the patient (existence of other diseases beside mood disorders such as depression or major depressive disorder). General outlines of the dosage can be applied the following guidelines.

Aripiprazole or a metabolite, such as

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

The aripiprazole, or a metabolite thereof, may be combined with at least one of any of the following SRIs at the dosage ranges indicated:

Fluoxetine: generally about 1 to about 80 mg/once a day, preferably about 10 to about 40 mg/once a day;

Duloxetine: generally about 1 to 160 mg/once a day (or 80 mg/twice a day), preferably about 5 to about 20 mg/once a day;

Venlafaxine: generally about 10 to 150 mg/1 to 3 times a day, preferably about 25 to 125 mg/3 times a day;

Milnacipran: generally about 10 to 100 mg/1 to 2 times a day, preferably about 25 to about 50 mg/twice a day;

Citalopram: generally about 5 to about 50 mg/once a day, preferably about 10 to about 30 mg/once a day;

Escitalopram: generally about 5 to about 30 mg/once a day, preferably about 10 to about 20 mg/once a day;

Fluvoxamine: generally about 20 to 500 mg/once a day, preferably about 50 to 300 mg/once a

day;

Paroxetine: generally about 20 to about 50 mg/once a day, preferably about 20 to about 30 mg/once a day; or

Sertraline: generally, about 20 to about 500 mg/once a day, preferably about 50 to about 200 mg/once a day.

Generally, the weight ratio of the first ingredient to the second ingredient is selected in accordance with the above-mentioned guideline. As to 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 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, 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 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.

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, 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 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 carbostyril derivatives such as aripiprazole anhydride crystals as the first ingredient and serotonin reuptake inhibitor as the second ingredient, and the various carriers described above and packing them in hard gelatin capsules, soft capsules 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 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 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 in the total amount on the basis of the pharmaceutical composition.

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 forms, and the age, gender and other condition of the 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 by 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 intracutaneously, 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 carbostyril derivatives and serotonin reuptake inhibitors can be provide in vivo at the same time. In one embodiment, a carbostyril derivative together with a serotonin reuptake inhibitor are contained in one pharmaceutical

composition and this composition may be administered. On the other hand, each one of carbostyril derivative and a serotonin reuptake inhibitor are contained individually in a pharmaceutical preparation respectively, and each one of these preparations may be administered at the same time or in suitable intervals.

Dosage of the pharmaceutical composition of the present invention for treating and improving depression or major depressive disorder 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.

The pharmaceutical composition of the present invention is quite effective for treating or improving mood disorders such as depressive symptoms, depression, refractory depression, major depressive disorder and the like.

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 serotoninergic 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 being 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, major depressive disorder, all mood disorders, schizoaffective disorder, dementia with depressive symptoms and the like. A preferred disorder to be treated with the present invention is major depressive disorder.

The pharmaceutical composition of the present invention is useful for treating major depressive disorder, endogenous depression, melancholia, depression in combination with psychotic episodes, bipolar disorder with depressive phase, refractory depression, dementia of the Alzheimer's type with depressive symptoms, Parkinson's disease with depressive symptom, senile dementia, mood disorder associated with cerebral blood vessels and mood disorder following head injury and the like. In addition to the methods for treatment described herein, additional disclosure for designing clinical studies is provided in J. Clin. Psychiatry, 2002, 63:(12), pp 1164-1170; J. Clin. Psychiatry, 2002, 63:(8), pp 733-736; and J. Clin. Psychiatry, 2002, 63:(5), pp 391-395.

EXAMPLES

The present invention will be explained more in detail by illustrating Reference Examples, Example

and Formulation Sample Examples. First, analytical methods are explained.

Analytical Methods

(1) The ^{1}H-NMR spectrum was measured in DMSO-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 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 2θ-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

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 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 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 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.).

Reference Example 1

7-(4-Cholorobutoxy)-3,4-dihydrocarbostyril (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.

The crude product of aripiprazole (30 g) obtained above was recrystallized 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.

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 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-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 anhydride crystals. The melting point (mp) of these crystals was 139.5°C.

Further, the crystalline form of these crystals was colorless flake.

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

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, 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 diffraction spectrum of aripiprazole hydrate obtained by this method exhibited characteristic peaks at 2θ = 12.6°, 15.1°, 17.4°, 18.2°, 18.7°, 24.8° and 27.5°.

The powder x-ray diffraction spectrum of this

aripiprazole hydrate was identical to the powder x-ray 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) 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, and obtained 474.6 g (94.9%) of powder 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 ^{1}H-NMR (DMSO-d_6, TMS) spectrum which was substantially identical to the ^{1}H-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 2θ = 12.6°, 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 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.

Example 1

The aripiprazole hydrate A (powder) (44.29

kg) obtained in the Reference Example 4 was dried at 100°C for 18 hours by using a hot air dryer and further heated at 120°C for 3 hours, to obtain 42.46 kg (yield; 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 ^{1}H-NMR spectrum (DMSO-d_6, TMS) which was substantially identical to the ^{1}H-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 (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 2θ = 11.0°, 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

Receptor Binding at the 5-HT1A Receptor

1. Materials and Methods

1.1 Test Compound

7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril (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-HT1A receptor antagonist, manufactured by RBI (Natick, Mass.) were used as reference compounds.

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

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 water rather than DMSO.

1.5 Experimental Procedure for the [^{35}S]GTP$_\gamma$S Binding Assay

Test and reference compounds were studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 5, 10, 50, 100, 1000, 10000 and 50000 nM) for their effects upon basal [^{35}S]GTP$_\gamma$S binding to h5-HT1A 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 $MgCl_2$, 0.1 mM EGTA, pH = 7.4) containing GDP (1 µM), [^{35}S]GTP$_\gamma$S (0.1 nM) and h5-HT1A 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. ^{35}S 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 Test compound (aripiprazole) at the h5-HT1A 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 [^{3}H]8-OH-DPAT (1 nM; NEN Life Sciences; catalog # NET 929, lot # 3406035, Specific Activity = 124.9 Ci/mmol) binding to h5-HT1A 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 [^{3}H]8-OH-DPAT (396 μl), test compound or vehicle (8 μl) and buffer A (50 mM Tris.HCl, 10 mM $MgSO_4$, 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 4×1 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-HT1A receptor agonist which stimulates increases in basal [^{35}S]GTP$_\gamma$S binding to h5-HT1A receptors in recombinant CHO cell membranes. The test compound was studied at 10 concentrations to determine effects upon basal [^{35}S]GTP$_\gamma$S binding relative to that produced by 10 μM 5-HT. The relative potency (EC_{50}, 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-HT1A receptor was determined by its ability to prevent

[^{3}H]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 (IC_{50}, 95% confidence interval), which is the concentration of test compound that occupies half of the h5-HT1A sites specifically bound by [^{3}H]8-OH-DPAT. The affinity of h5-HT1A receptors for test compound (Ki, 95% confidence interval) was calculated by the equation, Ki = (IC_{50})/(1+([[^{3}H]8-OH-DPAT]/Kd), where the Kd for [^{3}H]8-OH-DPAT at h5-HT1A = 0.69 nM (NEN Life Sciences). All estimates of drug binding affinity, potency and intrinsic efficacy at the h5-HT1A 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]GTP$_\gamma$S binding. 1% DMSO tested alone had no effect upon basal or drug-induced [^{35}S]GTP$_\gamma$S binding.

The test compound (EC_{50} = 2.12 nM), 5-HT (EC_{50} = 3.67 nM), potently stimulated basal [^{35}S]GTP$_\gamma$S 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]GTP$_\gamma$S binding at all concentrations tested (Table 1). WAY-100635 did, however, completely inhibit the effects of 5-HT and test compound upon [^{35}S]GTP$_\gamma$S binding to h5-HT1A receptors in CHO cell membranes (Table 2). Tables 1 and 2 are shown below.

The test compound demonstrated high affinity binding to h5-HT1A receptors in CHO cell membranes (IC_{50} = 4.03 nM, 95% confidence interval = 2.67 to 6.08 nM; Ki = 1.65 nM, 95% confidence interval = 1.09 to 2.48 nM).

Table 1 Potency (EC_{50}) and Intrinsic Agonist Efficacy (E_{max}) of Test compound and Reference Drugs in a h5-HT1A [^{35}S]GTP$_\gamma$S CHO-cell Membrane Binding Assay.

Drug	EC_{50}, nM (95% Confidence Interval)	E_{max} (% ± SEM)	Goodness of Fit (r^2)
Test Compound	2.12 (0.87 to 5.16)	68.13 ± 3.16	0.986
5-HT	3.67 (1.56 to 8.63)	98.35 ± 4.47	0.986
WAY-100635	-	-	-

Table 2 Inhibitory Potency (IC_{50}) of WAY-100635 versus 1 μM Concentration of 5-HT and Test compound in a h5-HT1A [^{35}S]GTP$_\gamma$S 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

Pharmacological Test

The forced swimming test proposed by Porsolt et al. (Porsolt, R. D. et al.: Arch. Int. Pharmacodyn., 229, 327-336, 1977) is widely used as to an experimental animal model for predicting the antidepressant activity in clinical settings. In this experimental model, a test mouse is put in a cylinder in which a suitable amount of water is contained, and the antidepressant action of a test drug is detected by measuring the immobility time, as the indication, shown by the mouse. It was reported that the action of shortening the immobility time is correlated with clinically observed antidepressive action (Willner, P.: Psychopharmacology, 83: 1-16, 1984). The crisis of depression is closely concerned with lowering of serotonin 5-HT1A receptor neurotransmission action, and the present inventors have found the facts that

antidepressive action of antidepressants which affect to serotonin system can be detected more precisely using prolongation of the immobility time performed with WAY-100635, which is a selective serotonin 5-HT1A receptor antagonist. The prolongation of the immobility time performed by WAY-100635 is defined as the indication. In this manner, the antidepressive action of test antidepressants was determined by taking the prolongation of immobility time performed by WAY-100635 in the forced swimming test as the indication.

In a cylinder (diameter: 9 cm, height 20 cm), water was poured therein up to the height of 9.5 cm, from the bottom, then a mouse of ICR strain is placed in the cylinder. After placing the mouse in the cylinder, an immobility time of 6 minutes is measured. During the test, the water temperature is maintained at 23 to 24°C. A test drug is orally administered to the mouse at 1 or 2 hours before placing the mouse in the water. WAY-100635 is administered subcutaneously to the mouse 30 minutes before placing the mouse in the water.

During this test, aripiprazole is used in combination together with citalopram, escitalopram, fluoxetine, venlafaxine or milnacipran. Following such combination administration, a decrease in the immobility time (the antidepressant activity) is observed in comparison with the case of single use of each one of aripiprazole, citalopram, escitalopram,

fluoxetine, venlafaxine or milnacipran, respectively.

Further, when aripiprazole is used in combination with citalopram, escitalopram, fluoxetine, venlafaxine or milnacipran, a decrease in the immobility time (the antidepressant activity) is observed in comparison to administration of the available atypical antipsychotic drugs such as olanzapine, quetiapine, risperidone in combination with citalopram, fluoxetine, venlafaxine or milnacipran.

Example 4

Formulation Examples

Several non-limiting formulation examples of aripiprazole, dehydroaripiprazole and other metabolites with serotonin reuptake inhibitors are presented below.

Formulation Sample Example 1

Aripiprazole Anhydride Crystals B	5 mg
Fluoxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 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 was prepared.

Formulation Sample Example 2

Aripiprazole Anhydride Crystals B	5 mg
Duloxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

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

Formulation Sample Example 3

Aripiprazole Anhydride Crystals B	5 mg
Venlafaxine	75 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	275 mg

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

Formulation Sample Example 4

Aripiprazole Anhydride Crystals B	5 mg
Milnacipran	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

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

Formulation Sample Example 5

Aripiprazole Anhydride Crystals B	5 mg
Citalopram	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

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

Formulation Sample Example 6

Aripiprazole Anhydride Crystals B	5 mg
Fluvoxamine	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

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

Formulation Sample Example 7

Aripiprazole Anhydride Crystals B	5 mg
Paroxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

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

Formulation Sample Example 8

Aripiprazole Anhydride Crystals B	5 mg
Sertraline	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

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

Formulation Sample Example 9

Aripiprazole Anhydride Crystals B	5 mg
Escitalopram	10 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	210 mg

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

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

Formulation Sample Example 10

Dehydroaripiprazole	5 mg
Fluoxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 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 was prepared.

Formulation Sample Example 11

Dehydroaripiprazole	5 mg
Duloxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

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

Formulation Sample Example 12

Dehydroaripiprazole	5 mg
Venlafaxine	75 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	275 mg

According to a common method, the tablet containing the above mentioned fomuration was prepared.

Formulation Sample Example 13

Dehydroaripiprazole	5 mg
Milnacipran	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

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

Formulation Sample Example 14

Dehydroaripiprazole	5 mg
Citalopram	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

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

Formulation Sample Example 15

Dehydroaripiprazole	5 mg
Fluvoxamine	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

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

Formulation Sample Example 16

Dehydroaripiprazole	5 mg
Paroxetine	20 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	220 mg

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

Formulation Sample Example 17

Dehydroaripiprazole	5 mg
Sertraline	50 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	250 mg

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

Formulation Sample Example 18

Dehydroaripiprazole	5 mg
Escitalopram	10 mg
Starch	131 mg
Magnesium stearate	4 mg
Lactose	60 mg
Total	210 mg

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

Example 5

Method of Treatment of Patients Diagnosed with Major Depressive Disorder Who Were Previously Non-responsive or Partially Responsive to Anti-depressant Medication

Aripiprazole is evaluated as an augmentation therapy in depressed patients with major depressive

disorder who were previously non-responsive or partially responsive to anti-depressant medication comprising serotonin reuptake inhibitors. These patients currently receive therapy through administration of serotonin reuptake inhibitors.

Patients ranging in age from 18 to 65 years who have been diagnosed with major depressive disorder and are receiving therapy with a serotonin reuptake inhibitor are evaluated to ensure that they have a baseline Hamilton score for depression (item 17) of 14 or higher. Only patients with such Hamilton scores receive treatment. These patients are interviewed to obtain a complete medical and psychiatric history. Aripiprazole 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 is administered to these 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.

An improvement in alleviation of symptoms of depression is observed in these patients following administration of aripiprazole as shown by results of testing performed during and after the duration of aripiprazole administration. The Hamilton test for depression and other measures such as clinical global impression (CGI), abnormal involuntary movement scale (AIMS), Simpson Angus scale (SAS), and Barnes akathesia

scale (Barnes), commonly known to one of ordinary skill in the art, are administered to these patients.

Example 6

Method of Treatment of Patients with a New Diagnosis of Major Depressive Disorder

A combination of aripiprazole and at least one serotonin reuptake inhibitor is evaluated as a therapy for depression in patients newly diagnosed with major depressive disorder. Patients ranging in age from 18 to 65 years who are diagnosed with major depressive disorder are evaluated to ensure that they have a baseline Hamilton score for depression (item 17) of 14 or higher. Only patients with this Hamilton score receive treatment. These patients are interviewed to obtain a complete medical and psychiatric history. Aripiprazole 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 is administered to these 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 is administered together with at least one serotonin reuptake inhibitor, wherein the serotonin reuptake inhibitor is fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine or sertraline. The

dosages to be used for these serotonin reuptake inhibitors are provided elsewhere in this patent application.

The aripiprazole can be administered in one dosage form, for example a tablet, and the serotonin reuptake inhibitor may be administered in a separate one dosage form, for example a tablet. The administration may occur at about the same time or at different times during the day.

Alternatively, a dosage form containing aripiprazole in combination with at least one serotonin reuptake inhibitor may be administered. Such combinations include without limitation the following: aripiprazole/fluoxetine, aripiprazole/duloxetine, aripiprazole/venlafaxine, aripiprazole/milnacipran, aripiprazole/citalopram, aripiprazole/fluvoxamine, aripiprazole/paroxetine, and aripiprazole/sertraline. A preferred embodiment comprises a combination of aripiprazole and citalopram.

An improvement in alleviation of symptoms of depression is observed in these patients following administration of aripiprazole and the one or more serotonin reuptake inhibitors as shown by results of testing performed during and after the duration of aripiprazole and serotonin reuptake inhibitor administration. The Hamilton test for depression 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 an alleviation of the symptoms of depression.

Example 7

Method of Treatment of Patients Diagnosed with Major Depressive Disorder Who Were Previously Non-responsive or Partially Responsive to Anti-depressant Medication

Dehydroaripiprazole, an active metabolite of aripiprazole, is evaluated as an augmentation therapy in depressed patients with major depressive disorder who were previously non-responsive or partially responsive to anti-depressant medication comprising serotonin reuptake inhibitors. These patients currently receive therapy through administration of serotonin reuptake inhibitors.

Patients ranging in age from 18 to 65 years who have been diagnosed with major depressive disorder and are receiving therapy with a serotonin reuptake inhibitor are evaluated to ensure that they have a baseline Hamilton score for depression (item 17) of 14 or higher. Only patients with such Hamilton scores receive treatment. These patients are interviewed to obtain a complete medical and psychiatric history. Dehydroaripiprazole 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. Dehydroaripiprazole is administered to these 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.

An improvement in alleviation of symptoms of depression is observed in these patients following administration of aripiprazole as shown by results of testing performed during and after the duration of aripiprazole administration. The Hamilton test for depression and other measures such as clinical global impression (CGI), abnormal involuntary movement scale (AIMS), Simpson Angus scale (SAS), and Barnes akathesia rating scale (BARS), commonly known to one of ordinary skill in the art, are administered to these patients.

Example 8

Method of Treatment of Patients with a New Diagnosis of Major Depressive Disorder

A combination of dehydroaripiprazole and at least one serotonin reuptake inhibitor is evaluated as a therapy for depression in patients newly diagnosed with major depressive disorder. Patients ranging in age from 18 to 65 years who are diagnosed with major depressive disorder are evaluated to ensure that they have a baseline Hamilton score for depression (item 17) of 14 or higher. Only patients with this Hamilton score receive treatment. These patients are interviewed to obtain a complete medical and

psychiatric history. Dehydroaripiprazole 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. Dehydroaripiprazole is administered to these 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 dehydroaripiprazole is administered together with at least one serotonin reuptake inhibitor, wherein the serotonin reuptake inhibitor is fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine or sertraline.

The dehydroaripiprazole can be administered in one dosage form, for example a tablet, and the serotonin reuptake inhibitor may be administered in a separate one dosage form, for example a tablet. The administration may occur at about the same time or at different times during the day.

Alternatively, a dosage form containing dehydroaripiprazole in combination with at least one serotonin reuptake inhibitor may be administered. Such combinations include without limitation the following:

dehydroaripiprazole/fluoxetine,

dehydroaripiprazole/duloxetine,

dehydroaripiprazole/venlafaxine,

dehydroaripiprazole/milnacipran,

dehydroaripiprazole/citalopram,

dehydroaripiprazole/fluvoxamine, dehydroaripiprazole/paroxetine, and dehydroaripiprazole/sertraline. A preferred embodiment comprises a combination of dehydroaripiprazole and citalopram.

An improvement in alleviation of symptoms of depression is observed in these patients following administration of dehydroaripiprazole and the one or more serotonin reuptake inhibitors as shown by results of testing performed during and after the duration of dehydroaripiprazole and serotonin reuptake inhibitor administration. The Hamilton test for depression 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 an alleviation of the symptoms of depression.

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.

Example 9

Pharmacological test

The tail suspension test (TST) was originally described by Steru et al. (1985).[1] A mouse suspended by its tail shows periods of agitation and immobility. The antidepressant activity of a test drug can be detected as an index of shortening the immobility time. This test is widely used as to an experimental animal model for predicting the antidepressant activity of a test drug in clinical settings. An automated device for performing the TST was developed by the authors of the TST (1989).[2] We improved this device and developed our own device incorporating an electric balance, an A/D converter, a testing box (30×25×25 cm), and a personal computer. The mouse was suspended from a hook hanging from the ceiling in the testing box by adhesive tape applied 20 mm from the tip of the tail. The duration of immobility was measured by the computer for a period of 15 min following the start of suspension. The immobility time for a period of 10 min (5-15 min) was evaluated. The experiments were carried out in a sound-proof room.

Aripiprazole was suspended in 0.5% gum arabic-0.9% saline solution and citalopram was dissolved in 0.9% saline solution. Aripiprazole (3 mg/kg) and citalopram (3 mg/kg) were orally administered to mice 60 min before the start of suspension. In this test, the decrease in the

immobility time of the combination of aripiprazole with citalopram was statistically significant synergistic effect in comparison with the effects of aripiprazole- and citaroplam-treated groups (Table 3).

References

1) Steru L. et al.: The tail suspension test: A new method for screening antidepressants in mice. Psychopharmacology 85,367(1985).

2) Steru L. and Porsolt R.D.: The automated tail suspension test: A computerized device for evaluating psychotropic acitivity profiles. Jpn J Clin Pharmacol Ther 20,77(1989).

Table 3 Effects of aripiprazole and citalopram on duration of immobility in the tail suspension test in mice

Drug	Dose (mg/kg, p.o.)	Immobility time (sec, mean ± SE)	% of shortening for immobility time
Vehicle	-	499.2±13.6	-
Aripiprazole (Aripi.)	3	486.4±12.3	3
Citalopram (Citalo.)	3	468.7±24.2	6
Aripi.+Citalo.	3+3	380.6±19.2**##$	24

N=7-9, **p<0.01 vs. vehicle group (two-tailed t-test), ##p<0.01 vs. aripiprazole alone (two-tailed t-test), $$p$<0.05 vs. citalopram alone (two-tailed t-test).

The decrease in the immobility time of the combination of aripiprazole with citalopram was a statistically significant synergistic effect in comparison with the effects of aripiprazole- and citaroplam-treated groups (p<0.05, one-way ANOVA).

CLAIMS

1. A pharmaceutical composition comprising at least one carbostyril derivative in combination with at least one serotonin reuptake inhibitor.

2. The composition of claim 1 wherein the carbostyril derivative is a dopamine-serotonin system stabilizer.

3. The composition of claim 2 wherein the carbostyril derivative is aripiprazole.

4. The composition of claim 2 wherein the carbostyril derivative is a metabolite of aripiprazole.

5. The composition of claim 4 wherein the metabolite of aripiprazole is dehydroaripiprazole, DM-1458, DM-1451, DM-1452, DM-1454 or DCPP.

6. The composition of any one of claims 1 to 5, wherein at least one serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, escitalopram and salts thereof.

7. The composition of claim 6 wherein at least one serotonin reuptake inhibitor is citalopram.

8. The composition of claim 1, further comprising at least one pharmaceutically acceptable carrier.

9. The composition of any one of claims 1 to 7 being useful for treatment of mood disorders.

10. The composition of claim 9 wherein the mood

disorder is depression or major depressive disorder.

11. The composition of claim 9 wherein the mood disorder is major depressive disorder, all mood disorders, schizoaffective disorder or dementia with depressive symptoms.

12. The composition of any one of claims 1 to 7 being useful for treatment of major depressive disorder, endogenous depression, melancholia, depression in combination with psychotic episodes, bipolar disorder with depressive phase, refractory depression, dementia of the Alzheimer's type with depressive symptoms, Parkinson's disease with depressive symptom, senile dementia, mood disorder associated with cerebral blood vessels and mood disorder following head injury.

13. Use of a pharmaceutical composition comprising at least one carbostyril derivative in combination with at least one serotonin reuptake inhibitor, in the preparation of a medicament for treating disorders.

14. The use of claim 13 wherein the carbostyril derivative is a dopamine-serotonin system stabilizer.

15. The use of claim 14 wherein the carbostyril derivative is aripiprazole.

16. The use of claim 14 wherein the carbostyril derivative is a metabolite of aripiprazole.

17. The use of claim 16 wherein the metabolite of aripiprazole is dehydroaripiprazole, DM-1458, DM-1451,

DM-1452, DM-1454 or DCPP.

18. The use of any one of claims 13 to 17, wherein at least one serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, escitalopram and salts thereof.

19. The use of claim 18 wherein at least one serotonin reuptake inhibitor is citalopram.

20. The use of claim 13 wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier.

21. The use of any one of claims 13 to 19 wherein the medicament is useful for treatment of mood disorders.

22. The use of claim 21 wherein the mood disorder is depression or major depressive disorder.

23. The use of claim 21 wherein the mood disorder is major depressive disorder, all mood disorders, schizoaffective disorder or dementia with depressive symptoms.

24. The use of any one of claims 13 to 19, wherein the medicament is useful for treatment of major depressive disorder, endogenous depression, melancholia, depression in combination with psychotic episodes, bipolar disorder with depressive phase, refractory depression, dementia of the Alzheimer's type with depressive symptoms, Parkinson's disease with

depressive symptom, senile dementia, mood disorder associated with cerebral blood vessels and mood disorder following head injury.

25. A method of treating disorders in a patient comprising administration of an effective amount of a pharmaceutical composition comprising at least one carbostyril derivative in combination with at least one serotonin reuptake inhibitor.

26. The method of claim 25 wherein the carbostyril derivative is a dopamine-serotonin system stabilizer.

27. The method of claim 26 wherein the carbostyril derivative is aripiprazole.

28. The method of claim 26 wherein the carbostyril derivative is a metabolite of aripiprazole.

29. The method of claim 28 wherein the metabolite of aripiprazole is dehydroaripiprazole, DM-1458, DM-1451, DM-1452, DM-1454 or DCPP.

30. The method of any one of claims 25 to 29, wherein at least one serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline, escitalopram and salts thereof.

31. The method of claim 30 wherein at least one serotonin reuptake inhibitor is citalopram.

32. The method of claim 25, wherein the pharmaceutical composition further comprises at least

one pharmaceutically acceptable carrier.

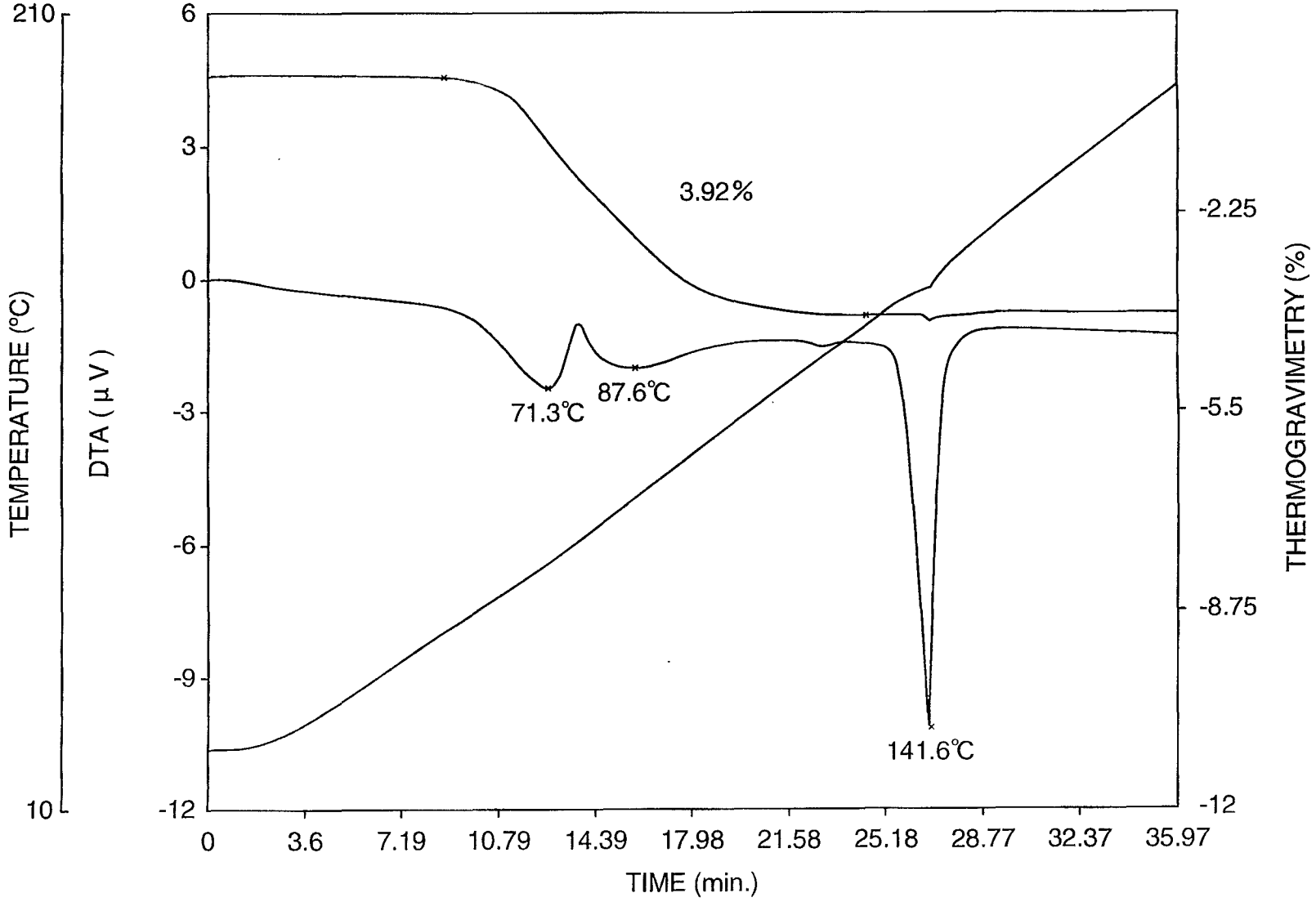
33. The method of any one of claims 25 to 31 wherein the disorders are mood disorders.

34. The method of claim 33 wherein the mood disorder is depression or major depressive disorder.

35. The method of claim 33 wherein the mood disorder is major depressive disorder, all mood disorders, schizoaffective disorder or dementia with depressive symptoms.

36. The method of any one of claims 25 to 31, wherein the disorders are major depressive disorder, endogenous depression, melancholia, depression in combination with psychotic episodes, bipolar disorder with depressive phase, refractory depression, dementia of the Alzheimer's type with depressive symptoms, Parkinson's disease with depressive symptom, senile dementia, mood disorder associated with cerebral blood vessels and mood disorder following head injury.

FIG.1


TEMPERATURE (°C)
210
10
DTA (μV)
6
3
0
-3
-6
-9
-12
THERMOGRAVIMETRY (%)
-2.25
-5.5
-8.75
-12
3.92%
71.3℃
87.6℃
141.6℃
0
3.6
7.19
10.79
14.39
17.98
21.58
25.18
28.77
32.37
35.97
TIME (min.)

2/8

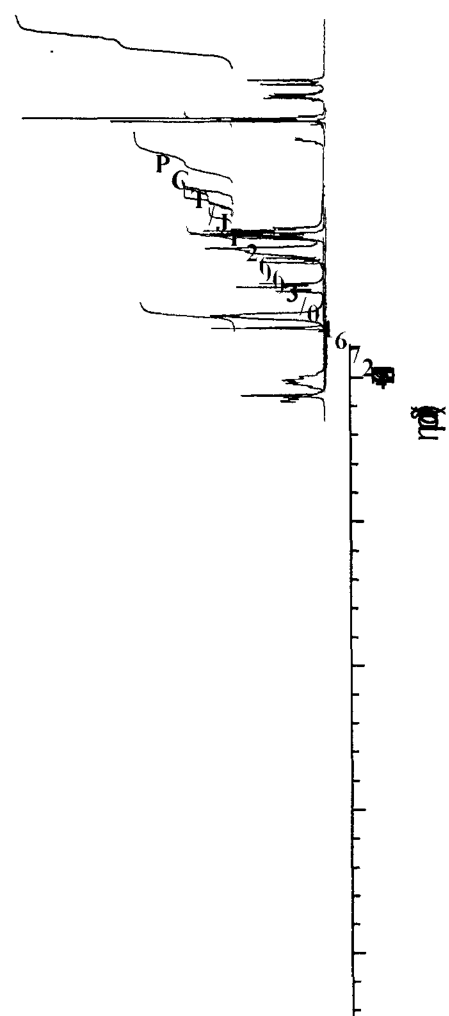
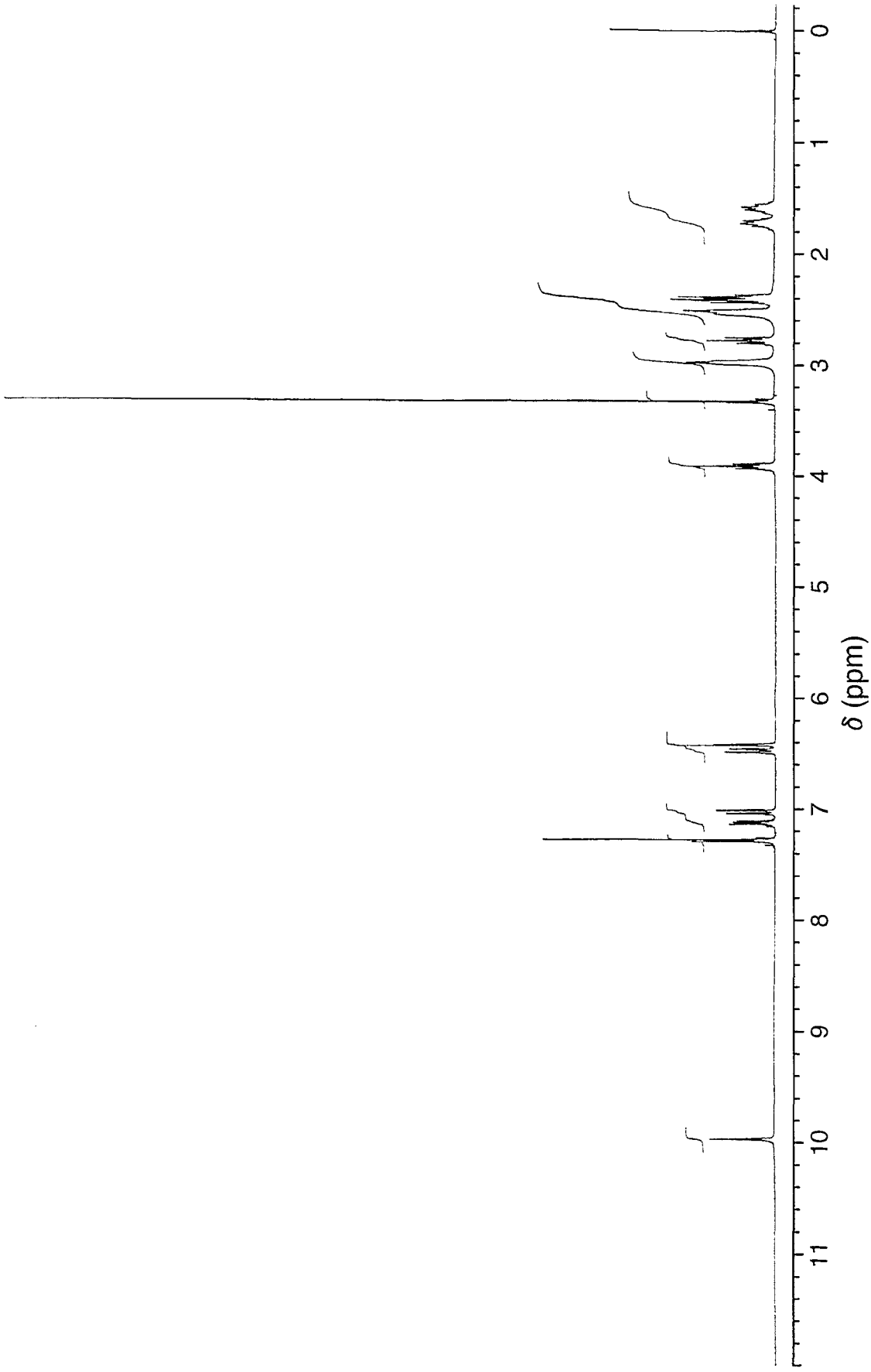


FIG.4



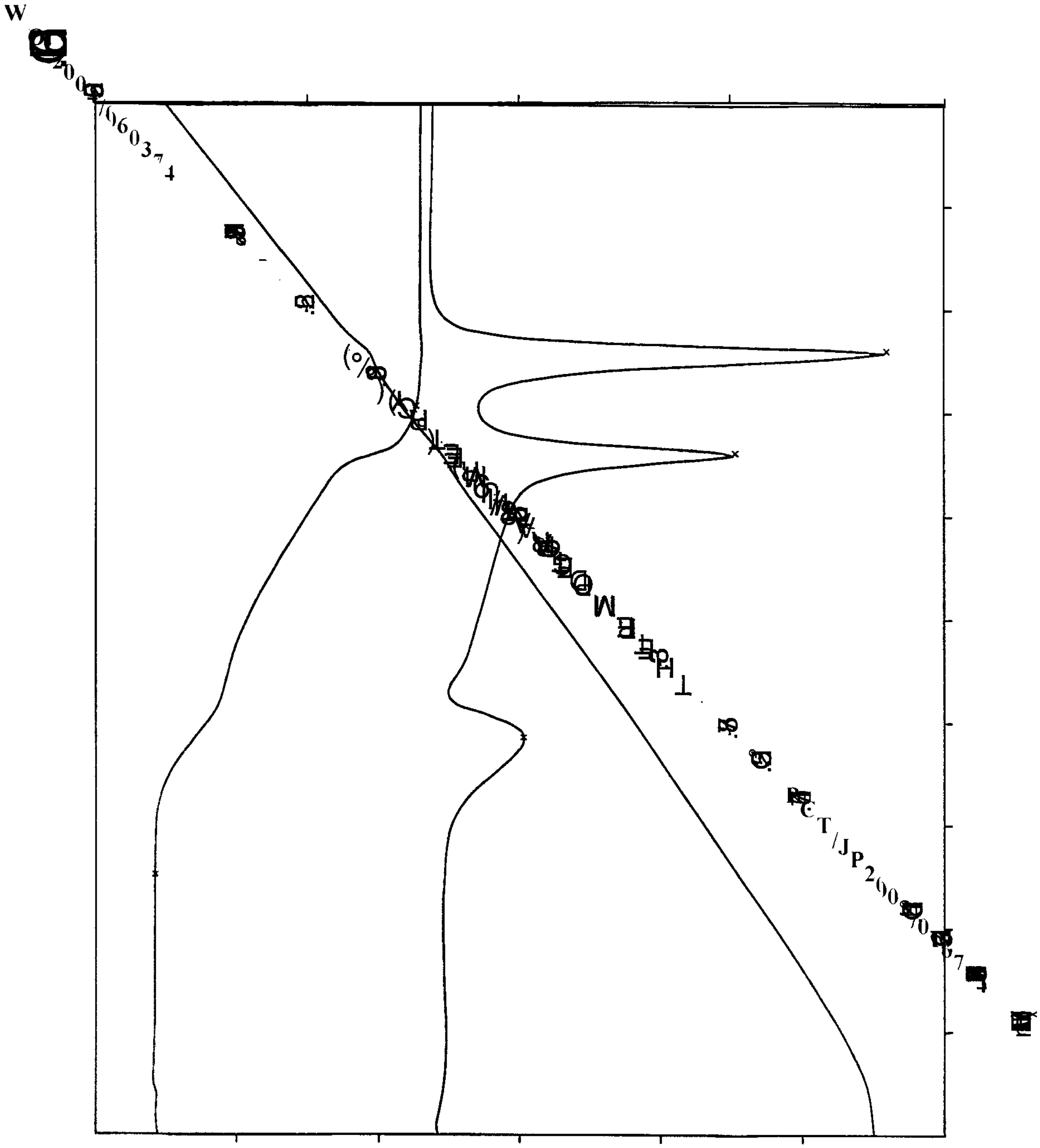


FIG.7

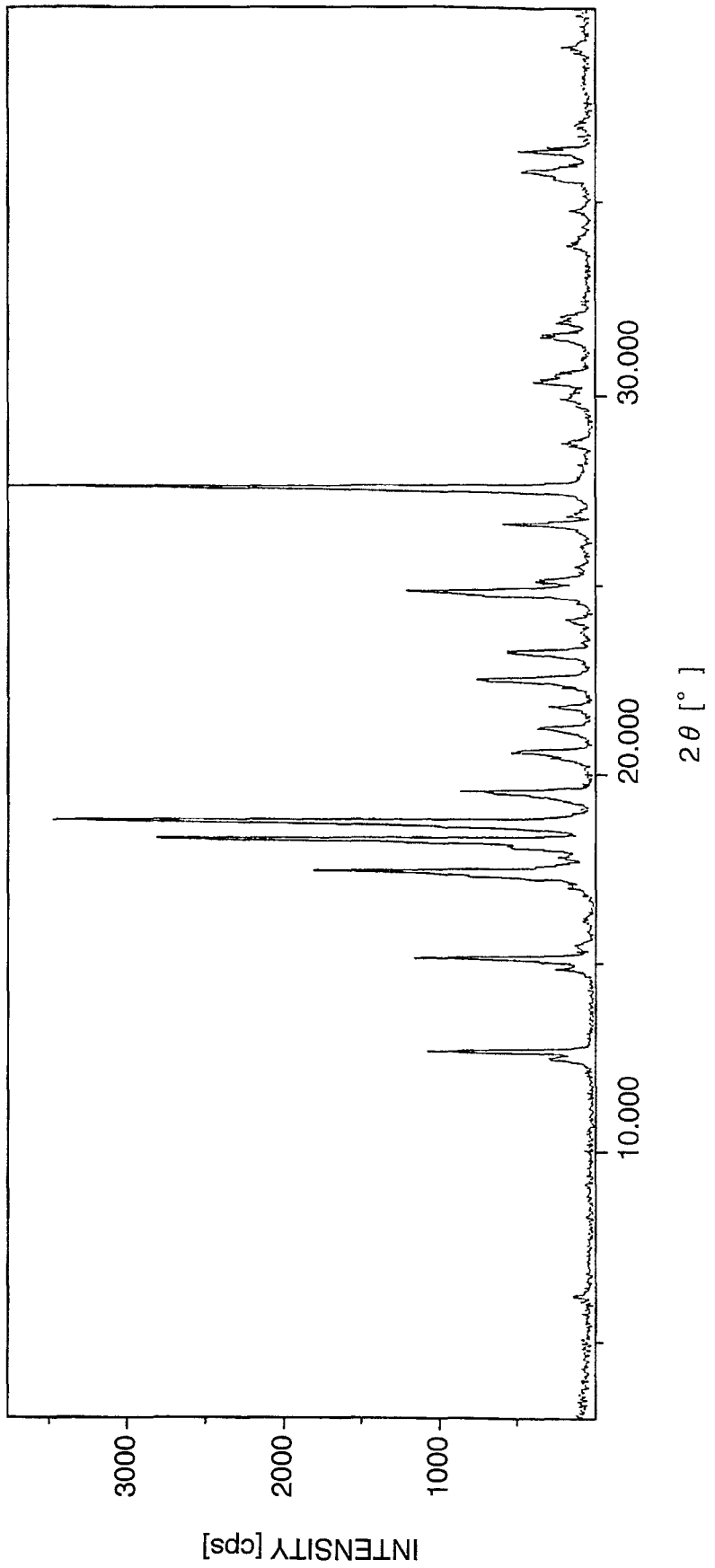
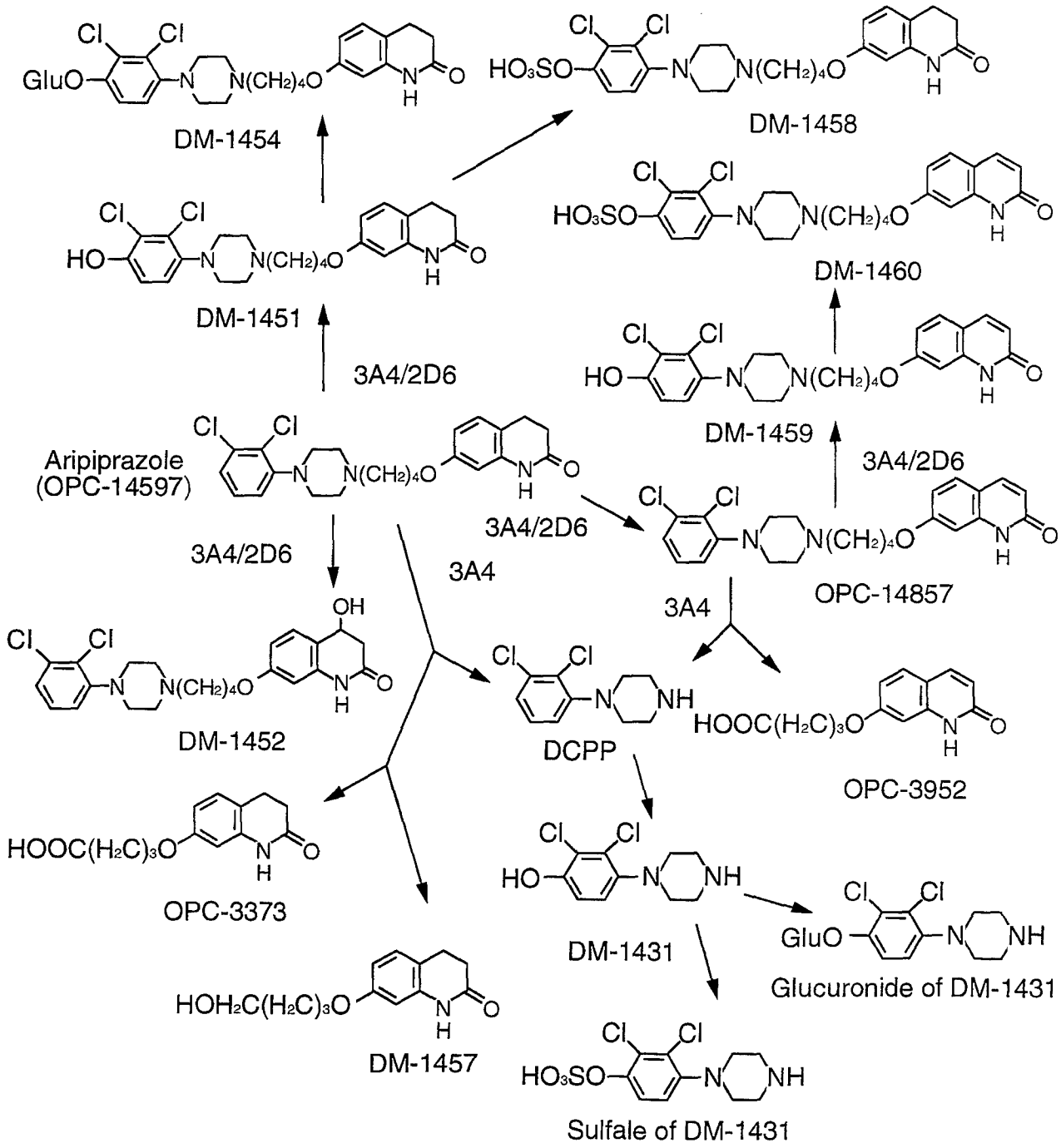


FIG.8


DM-1454
DM-1458
DM-1460
DM-1451
DM-1459
3A4/2D6
Aripiprazole
(OPC-14597)
3A4/2D6
3A4/2D6
3A4/2D6
3A4
OPC-14857
3A4
DM-1452
DCPP
OPC-3952
OPC-3373
DM-1431
Glucuronide of DM-1431
DM-1457
Sulfale of DM-1431

PCT/JP 03/16724

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/496 A61K31/381 A61K31/343 A61K31/15 A61K31/4525
A61K31/135 A61P25/24

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/156067 A1 (SVENSSON TORGNY ET AL) 24 October 2002 (2002-10-24) claims 1-10 ---	1-3,6, 8-15,18, 20-27, 30,32-36
Y	WO 02/060423 A (OTSUKA PHARMA CO LTD) 8 August 2002 (2002-08-08) cited in the application claims 1-5 --- -/--	1-36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2004	08/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LAWLER ET AL: "Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes" NEUROPSYCHOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHING, NEW YORK, NY, US, vol. 20, no. 6, June 1999 (1999-06), pages 612-627, XP002205416 ISSN: 0893-133X abstract ---	1-3, 6-15, 18-27, 30-36
Y	BURRIS K D ET AL: "ARIPIPRAZOLE, A NOVEL ANTIPSYCHOTIC, IS A HIGH-AFFINITY PARTIAL AGONIST AT HUMAN DOPAMINE D2 RECEPTORS" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 302, no. 1, July 2002 (2002-07), pages 381-389, XP001087706 ISSN: 0022-3565 abstract ---	1-3, 6-15, 18-27, 30-36
Y	GOODMAN ET AL: "THE PHARMACOLOGICAL BASIS OF THERAPEUTICS" , PHARMACOLOGICAL BASIS OF THERAPEUTICS, GOODMAN GILMAN'S PHARMACOLOGICAL BASIS OF THERAPEUTICS, NEW YORK, PERGAMON PRESS, US, VOL. ED. 10, PAGE(S) 451, 468 , 2001 XP002279121 page 451, column 2, paragraph 2 page 468, column 1, paragraph 4 ---	1-36
P,X	PRESKORN S H: "Relating clinical trials to psychiatric practice: Part I: The case of a 13-year old on aripiprazole and fluoxetine" JOURNAL OF PSYCHIATRIC PRACTICE 2003 UNITED STATES, vol. 9, no. 4, July 2003 (2003-07), pages 307-313, XP008029355 ISSN: 1527-4160 page 307, column 2, paragraph 2 page 308, column 2, paragraph 3 ---	1-3,6, 8-15,18, 20-27, 30,32-36
P,X	GREEN B: "FOCUS ON ARIPIPRAZOLE" CURRENT MEDICAL RESEARCH AND OPINION, HANTS, GB, vol. 20, no. 2, 12 December 2003 (2003-12-12), pages 207-213, XP008029340 page 211, column 2, paragraph 12 --- -/--	1-3,6, 8-15,18, 20-27, 30,32-36

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/010932 A (MIGALY PETER) 5 February 2004 (2004-02-05) claims 19,23,31	1-3,6, 8-15,18, 20-27, 30,32-36

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-36

The terms "carbostyril derivative" and "metabolite of aripiprazole" used in claims 1, 2, 4, 6-14, 16, 18-26, 28, 30-36 are vague and unclear and leave the reader in doubt as to the meaning of the technical features (i.e. the compounds) to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT)
Independent of the above, the Applicant has not provided any test to demonstrate whether a compound is a metabolite of apiprazole or not. There is therefore insufficient disclosure (Art. 5 PCT) to allow the skilled man to determine which compounds fall within the definition.

Claims 1-36 encompass a genus of compounds defined only by their function ("dopamine-serotonin system stabilizer" and "serotonin reuptake inhibitor"), wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

Present claims 9, 11, 13-21, 23, 25-33 and 35 relate to an extremely large number of disease states. The therapeutic application is defined as "mood disorders" or even "disorders" which does not allow any practical application in the form of a defined, real treatment of a pathological condition. It is noted that any disease may represent a disorder.
A lack of clarity (and/or conciseness) within the meaning of Art. 6 PCT therefore arises.
Independent of the above, the Applicant has not provided any test to demonstrate whether a disease is a mood disorder or not. There is therefore insufficient disclosure (Art. 5 PCT) to allow the skilled man to determine which diseases fall within the definition.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to compositions comprising aripiprazole, dehydroaripiprazole, DM-1458, DM-1451, DM-1452, DM-1454 or N-(2,3-Dichlorophenyl)piperazine in combination with fluoxetine, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, sertraline or escitalopram in relation to their use in the treatment of depression or major depressive disorder.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 03/16724

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-36
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:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 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.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002156067 A1	24-10-2002	CA 2431041 A1	11-07-2002
		EP 1353675 A2	22-10-2003
		WO 02053140 A2	11-07-2002
WO 02060423 A	08-08-2002	BR 0206237 A	23-12-2003
		CA 2429496 A1	08-08-2002
		CN 1484524 T	24-03-2004
		EP 1355639 A2	29-10-2003
		WO 02060423 A2	08-08-2002
WO 2004010932 A	05-02-2004	WO 2004010932 A2	05-02-2004

Electronic Acknowledgement Receipt

EFS ID:	1418111
Application Number:	10556600
International Application Number:	
Confirmation Number:	3822
Title of Invention:	Carbostyril derivatives and mood stabilizers for treating mood disorders
First Named Inventor/Applicant Name:	Tetsuro Kikuchi
Customer Number:	23373
Filer:	Kelly G. Hyndman/Lynette Mansfield
Filer Authorized By:	Kelly G. Hyndman
Attorney Docket Number:	Q81665
Receipt Date:	05-JAN-2007
Filing Date:	02-AUG-2006
Time Stamp:	07:48:03
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	Q81665IDS.pdf	98892	no	3
Warnings:					

Information:					
This is not an USPTO supplied IDS fillable form					
2	NPL Documents	Q81665RUOfficeAction.pdf	234903	no	6
Warnings:					
Information:					
3	Foreign Reference	Q81665WP2004060374.pdf	2542712	no	93
Warnings:					
Information:					
		Total Files Size (in bytes):	2876507		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/556,600	08/02/2006	Tetsuro Kikuchi	Q81665

CONFIRMATION NO. 3822

23373
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC20037

Title: Carbostyril derivatives and mood stabilizers for treating mood disorders

Publication No. US-2007-0031513-A1
Publication Date: 02/08/2007

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 703-305-3028.

Pre-Grant Publication Division, 703-605-4283

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
10/556,600	08/02/2006	1617	730	Q81665	16	2

CONFIRMATION NO. 3822

CORRECTED FILING RECEIPT

23373
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC20037

Date Mailed: 05/17/2007

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Tetsuro Kikuchi, Tokushima, JAPAN;
Taro Iwamoto, Princeton, NJ;
Tsuyoshi Hirose, Tokushima, JAPAN;

Assignment For Published Patent Application

OTSUKA PHARMACEUTICALS CO., LTD.

Power of Attorney: The patent practitioners associated with Customer Number 23373

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US04/13308 05/19/2004

Foreign Applications

UNITED STATES OF AMERICA 60473378 05/23/2003

If Required, Foreign Filing License Granted: 10/28/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US10/556,600**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Carbostyril derivatives and mood stabilizers for treating mood disorders

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under

37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, et al.

Docket No: Q81665

Appln. No.: 10/556,600

Group Art Unit: 1617

Confirmation No.: 3822

Examiner: Unknown

Filed: November 14, 2005

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

REQUEST FOR CORRECTED OFFICIAL FILING RECEIPT

ATTN: Office of Initial Patent Examination
Filing Receipt Correction
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We enclose a copy of the Official Filing Receipt for the above-identified application and request the following correction(s):

ASSIGNMENT FOR PUBLISHED PATENT APPLICATION:

DELETE:

~~**[OTSUKA PHARMACEUTICALS CO., LTD.]**~~

ASSIGNMENT FOR PUBLISHED PATENT APPLICATION:

OTSUKA PHARMACEUTICAL CO., LTD.

Verification for the requested correction(s) is indicated on the Executed Assignment

Document filed August 2, 2006.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: July 12, 2007

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPL NO.	FILING OR 371(c) DATE	ART UNIT	FIL FEE REC'D	ATTY.DOCKET NO	TOT CLMS	IND CLMS
10/556,600	08/02/2006	1617	730	Q81665	16	2

CONFIRMATION NO. 3822

CORRECTED FILING RECEIPT

23373
SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

OC000000023928261

Date Mailed: 05/17/2007

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Tetsuro Kikuchi, Tokushima, JAPAN;
Taro Iwamoto, Princeton, NJ;
Tsuyoshi Hirose, Tokushima, JAPAN;

Assignment For Published Patent Application

[OTSUKA PHARMACEUTICALS CO., LTD.]
OTSUKA PHARMACEUTICAL CO., LTD.

Power of Attorney: The patent practitioners associated with Customer Number **23373**.

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US04/13308 05/19/2004

Foreign Applications

UNITED STATES OF AMERICA 60473378 05/23/2003

If Required, Foreign Filing License Granted: 10/28/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is US10/556,600

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Carbostyril derivatives and mood stabilizers for treating mood disorders

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).