Supporting Information

Antipsychotic Benzamides Amisulpride and LB-102 Display Polypharmacy as Racemates, *S* enantiomers Engage Receptors D_2 and D_3 while *R* Enantiomers engage 5-HT_7.

Vince Grattan[†], Andrew R. Vaino[†], Zachary Prensky[†] and Mark S. Hixon[‡*]

[†] LB Pharmaceuticals Inc. 575 Madison Ave., New York, NY 10022

[‡] Mark S. Hixon Consulting LLC, 11273 Spitfire Road, San Diego, CA 92126

General Methods

Racemic amisulpride, along with *R* and *S* enantiomers were purchased. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker 400 Avance spectrometer or at 300 MHz on a Bruker Fourier 300. LCMS were measured on an Agilent 1100 HPLC eluting with water with 0.1% TFA (A) and acetonitrile with 0.07% TFA (B) from 95% A to 95% B over 5 min, holding for 1 min. Column temperature was 30^{o}C. UV detection was done at 210 and 254 nm.

***(R)*-amisulpride**

Triethylamine (7 mL, 50 mmol) was added to a suspension of 4 amino-5-ethylsulfonyl)-2-methoxybenzoic acid (10 g, 39 mmol) in dichloromethane (100 mL) and the mixture was stirred at room temperature under nitrogen until all the solid had dissolved. The mixture was cooled on an ice bath and ethyl chloroformate (4.1 mL, 42.4 mmol) was added. The mixture was stirred on an ice bath for 30 minutes and 1[(*2R*)-1-ethylpyrrolidin-2-yl]methanamine (5.4 g, 42.4 mmol) was added and the mixture on an ice bath was stirred for 1 hour. The reaction was quenched by addition of 1:1 water:saturated $NaHCO_3$ (100 mL), the organic phase removed and dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by chromatography using 10 % (0.5% NH_3) MeOH/CH_2Cl_2 on 150 g silica gel to afford the product (10g) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.1 (t, 3H, CH_3), 1.3 (t, 3H, CH_3), 1.7 (m, 3H), 1.9 (m, 1H), 2.2 (m, 2H), 2.7 (m, 1H), 2.8 (m, 1H), 3.1 (q, 2H, CH_2), 3.2 (m, 2H), 3.7 (m, 1H), 3.9 (s, 3H, OCH_3), 5.6 (s, 2H, NH_2), 6.3 (s, 1H_{ar}), 8.1 (br s, NH), 8.5 (s,

1H, NH). . Expected Mol. Wt. [$C_{17}H_{27}N_3O_4S$]: 369.2, Observed Mol. Wt. 370.1 [M + H^+]. HPLC Purity 98.9%.

***rac N*-methyl amisulpride (LB-102)**

To a solution of 4-amino-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-5-(ethylsulfonyl))-2-methoxybenzamide (2 g, 5.5 mmol) in 20 mL formic acid, acetic anhydride (0.68 g, 6.6 mmol) was added portionwise at 5-10°C. The reaction mixture was stirred overnight at room temperature, and carefully poured into aq. K_2CO_3 at 5-10°C. Solid NaCl was added and the mixture was extracted with $CHCl_3$. The combined organic extracts were dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 5-10% MeOH in $CHCl_3$ to afford 1.82 g (83%) of a yellowish gum, which was dissolved in in 80 mL THF. $BH_3{\cdot}Me_2S$ (1.09 mL, 11.5 mmol) was added portionwise at 5-10°C. The reaction mixture was stirred at 60 °C for 3 h, and carefully quenched with MeOH (40 mL). The reaction mixture was acidified with 10% HCl (15 mL) and the mixture was stirred at 60°C overnight. The solvents were evaporated under reduced pressure, the aqueous residue was diluted with H_2O and basified with aq NaOH to pH 10. The mixture was extracted with $CHCl_3$, the combined organic extracts were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel eluting with 5-10% MeOH in $CHCl_3$, following by purification by RP-HPLC eluting with a gradient MeCN-H_2O + 0.1% TFA. The fractions containing the target material were partially evaporated under reduced pressure, basified with aq NaOH to pH 10, and extracted with CH_2Cl_2. The combined extracts were dried with Na_2SO_4 and evaporated under reduced pressure to afford the product as a white solid after standing which solidified upon storage (0.93 g, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.1 (t, 3H, CH_3), 1.3 (t, 3H, CH_3), 1.6 (m, 3H), 1.9 (m, 1H), 2.2 (m, 2H), 2.5 (m, 1H), 2.7 (m, 1H), 2.9 (app d, 3H, NHC*H*$_3$), 3.1 (q, 2H, CH_2), 3.2 (m, 1H), 3.3 (m, 1H), 3.6 (m, 1H), 4.0 (s, 3H, OCH_3), 6.1 (s, 1H$_{ar}$), 6.8 (br s, 1H, H$_{ar}$), 8.1 (br s, NH), 8.5 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.2, 14.9, 21.2, 29.0, 29.9, 40.5, 47.8, 49.5, 53.7, 56.9, 61.0, 92.1, 110.2, 111.9, 136.1, 150.0, 162.2, 164.0. Expected Mol. Wt. [$C_{18}H_{29}N_3O_4S$]: 383.2, Observed Mol. Wt. 384.5 [M + H^+]. HPLC Purity 100%.

(*S*)-*N*-methyl amisulpride (LB-103)

A suspension of *(S)*-amisulpride (11.1 g, 20 mmol) was suspended in *N,N*-dimethylformamide dimethyl acetal (33 mL, 249 mmol) and stirred for 2 hours at 90^{o}C under nitrogen. The reaction mixture was cooled to room temperature and $NaBH_4$ (4 g, 106 mmol) was added portionwise (note, exothermic) and the reaction mixture stirred at room temperature for 1 hour. Saturated $NaHCO_3$ was added to quench the reaction, and the resulting suspension was extracted with dichloromethane (2 X 50 mL), the organic phase washed with brine, dried, filtered, and the solvent removed under reduced pressure. Purification was achieved by column chromatography eluting with CH_2Cl_2:MeOH:NH_3 (9.5:0.5:0.5 to 8.5:1.5:0.5) to obtain the product as a white solid (5.3 g).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.1 (2t, 2X 3H, CH_3), 1.5 (2, 1H) 1.6 (m, 2H), 1.8 (m, 1H), 2.1 (m, 1H), 2.3 (m, 2H), 2.5 (t, 1H), 2.6 (m, 1H), 2.7 (m, 1H), 2.9 (t, 3H), 3.1 (3, 2H), 3.2 (m, 2H), 3.3 (m, 3H), 3.5 (m, 1H), 4.0 (s, 3H, OCH_3), 6.3 (s, 1H$_{ar}$), 6.6 (m, 1H$_{ar}$), 8.1 (m, 1H, NH), 8.3 (s, 1H, NH). Expected Mol. Wt. [$C_{18}H_{27}N_3O_5S$] 383.2, Observed Mol. Wt. 384.4 [M + H^+]. HPLC purity was 96.5%.

(*R*)-*N*-methyl amisulpride (LB-104)

A suspension of 4-amino-*N*-{[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}-5-(ethylsulfonyl)-2-methoxybenzamide (11.2 g, 30.2 mmol) in *N,N*-dimethylformamide dimethyl acetal (34 mL, 254 mmol) was stirred at 90°C under nitrogen for two hours. The reaction temperature was lowered to 70°C and sodium tetrahydroborate (4 g, 106 mmol) was added in 4 portions of 1 g each at 20 minute intervals and the reaction mixture stirred for 1 hour at 90°C. The reaction mixture was cooled in an ice bath and the reaction was quenched by addition of 150 mL of saturated $NaHCO_3$. The resulting solution was extracted with dichloromethane (5 X 50 mL), the combined organic extracts dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. Purification was achieved by coloumn chromatography eluting with 9:1 CH_2Cl_2:MeOH to afford the product as a white solid (9.1 g).

^1H NMR (300 MHz, $CDCl_3$): δ 1.2 (t, 3H, CH_3), 1.3 (t, 3H, CH_3), 1.7 (m, 1H) 1.8 (m, 2H), 1.9 (m, 1H), 2.3 (m, 2H), 2.7 (m, 1H), 2.9 (m, 1H), 2.9 (d, 1H), 3.1 (q, 2H), 3.3 (m, 2H), 3.7 (m, 1H), 4.0 (s, 3H, OCH_3), 6.1 (s, $1H_{ar}$), 6.8 (m, $1H_{ar}$), 8.1 (m, 1H, NH), 8.6 (s, 1H, NH). Expected Mol. Wt. [$C_{18}H_{27}N_3O_4S$] 383.2, Observed Mol. Wt. 384.2 [$M + H^+$]. HPLC purity 97.7%.