Supporting Information

Tranylcypromine Substituted *cis*-Hydroxycyclobutylnaphthamides as Potent and Selective Dopamine D_3 Receptor Antagonists

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(±)-*Trans*-2-(4-Chlorophenyl)-*N*-propylcyclopropanamine ((±)-17). Propionaldehyde (35 mg, 0.60 mmol) was added to a solution of (±)-*trans*-2-(4-Chlorophenyl)-cyclopropanamine (100 mg, 0.60 mmol) in methanol (10 mL) and the reaction mixture was stirred at room temperature for 2 h. Sodium borohydride (34 mg, 0.90 mmol) was then added and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water (30 mL) and extracted with ethyl acetate (40 mL). Ethyl acetate was removed under vacuum and the residue was used directly without further purification.

(±)-*Trans*-2-(2-Chlorophenyl)-*N*-propylcyclopropanamine ((±)-18). Compound **(±)-18** was similarly prepared as compound **(±)-17** and was used directly without further purification.

(±)-*Trans*-2-(3-Chlorophenyl)-*N*-propylcyclopropanamine ((±)-19). Compound **(±)-19** was similarly prepared as compound **(±)-17** and was used directly without further purification.

(*E*)-3-(4-Chlorophenyl)-1-((*3aR,6S,7aS*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)prop-2-en-1-one (21). A solution of (*1R*)-(+)-2,10-camphorsultam (3.54 g, 16.49 mmol) in anhydrous THF (40 mL) was added to a stirred mixture of NaH (1.20 g, 30.00 mmol; 60% in mineral oil) in anhydrous THF (60 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. A solution of 4-chlorocinnamoyl chloride [prepared by stirring of 4-chlorocinnamic acid (2.50 g, 13.74 mmol) in $SOCl_2$ (15 mL) for 2 h at room temperature followed by concentration of the mixture under reduced pressure] in anhydrous THF (20 mL) was added slowly and the mixture was stirred at 0 °C for 2 h and then at room temperature overnight. The reaction was quenched by addition of water (40 mL) and the mixture was extracted with ethyl acetate (80 mLx3). The organic layer was washed successively with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed (Hexane:EtOAc = 4:1) to give compound **21** (4.5 g, 87% yield) as a colorless solid. 1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, *J* = 15.5 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 15.5 Hz, 1H), 3.99 (dd, *J* = 5.31, 7.32 Hz, 1H), 3.55 (d, *J* = 13.4 Hz, 1H), 3.47 (d, *J* = 13.4 Hz, 1H), 2.25-1.80 (m, 5H), 1.50-1.30 (m, 2H), 1.20 (s, 3H), 0.99 (s, 3H).

((*1S,2S*)-2-(4-Chlorophenyl)cyclopropyl)((*3aR,6S,7aS*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)methanone (22). A solution of *N*-methyl-*N*-nitrosotoluene-4-sulfonamide (Diazald) (25 g, 116.82 mmol) in diethyl ether (300 mL) was slowly added to a heated (70 °C, bath temperature) mixture of KOH (25.0 g, 446 mmol), diethyl ether (50 mL), water (150 mL), and 2-(2-ethoxyethoxy)ethanol (150 mL). The solution of diazomethane thus formed was continuously distilled into a stirred, cooled (ice-bath) solution of **21** (4.5 g, 11.9 mmol) and $Pd(OAc)_2$, (20 mg, 0.089 mmol) in CH_2Cl_2 (200 mL). The reaction was quenched by addition of a few drops of acetic acid after 10 h. The mixture was washed with aq. 5% $NaHCO_3$, dried over anhydrous Na_2SO_4. The organic solvents were concentrated under reduced pressure and the residue was recrystallized from EtOH to yield pure **22** (2.5 g, 52% yield). 1H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 3.91 (dd, *J* = 5.1, 7.5 Hz, 1H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.43 (d, *J* = 13.8 Hz, 1H), 2.65-2.50 (m, 2H), 2.25-1.70 (m, 6H), 1.50-1.25 (m, 3H), 1.20 (s, 3H), 0.98 (s, 3H).

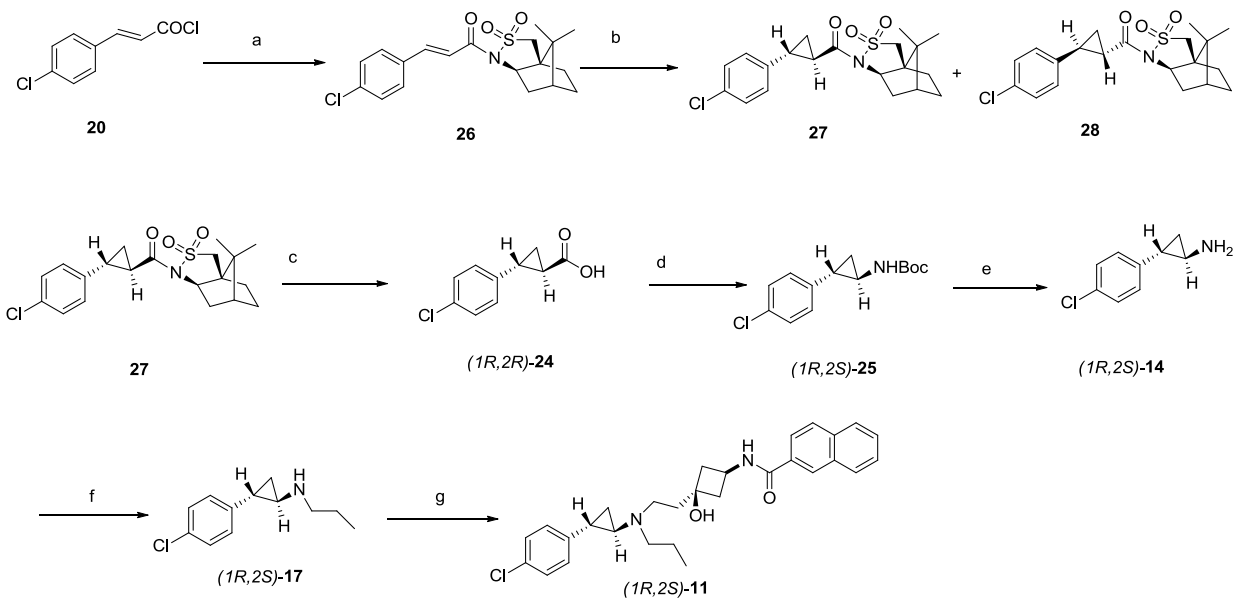
(*1S,2S*)-2-(4-Chlorophenyl)cyclopropanecarboxylic acid ((*1S,2S)*-24). Titanium (IV) isopropoxide (1.31 g, 4.60 mmol) was added to a solution of sultam **22** (1.8 g, 4.60 mmol) in benzyl alcohol (8 mL). The solution was heated at 150 °C for 30 min. The reaction was cooled to room temperature and quenched by addition of water (20 mL). The mixture was extracted with ethyl acetate (30 mL), dried over anhydrous Na_2SO_4, and filtered. Organic solvent was removed under reduced pressure and the residue was dissolved in MeOH (20 mL), and aq. 2 M LiOH (6 mL), and stirred at room temperature for 2 h. The mixture was concentrated and the remaining alkaline solution was washed with diethyl ether (3 x 15 mL), acidified with aq. 4 M HC1, extracted with CH_2Cl_2 (3 x 20 cm3), and the extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the pure acid **32** (420 mg, 47% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 2.65-2.50 (m, 1H), 1.90-1.80 (m, 1H), 1.75-1.60 (m, 1H), 1.40-1.30 (m, 1H).

***Tert*-Butyl ((*1S,2R*)-2-(4-chlorophenyl)cyclopropyl)carbamate ((*1S,2R*)-25).** Ethyl chloroformate (238 mg, 2.29 mmol) was added to a stirred, cooled 0 °C solution of the acid *(1S,2S)*-**24** (300 mg, 1.53 mmol) and triethylamine (200 mg, 2.00 mmol) in dry acetone (20 mL). After 2 h, NaN_3 (160 mg, 2.45 mmol) was added and the mixture was stirred for one additional hour. Water (30 mL) was added and the solution was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude azide thus obtained was dissolved in dry toluene (40 mL). The solution was heated to 90°C (bath temperature) for 3 h. The mixture was concentrated and the residue was dissolved in dry *tert*-butyl alcohol (50 mL) and heated to reflux for 16 h. The mixture was concentrated and the crude carbamate was purified by flash chromatography (Hexane:EtOAc=9:1) to give pure (*1S,2R*)-**25** (180 mg, 44% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 4.80 (s, 1H), 2.75-2.65 (m, 1H), 2.05-1.95 (m, 1H), 1.45 (s, 9H), 1.20-1.06 (m, 2H).

(*1S,2R*)-2-(4-Chlorophenyl)cyclopropanamine ((*1S,2R*)-14). Trifluoroacetic acid (1 mL) was added to a solution of (*1S,2R*)-**25** (180 mg, 0.674 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 12 h. The reaction was quenched by addition of aqueous Na_2CO_3 and the mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (*1S,2R*)-**14**. Compound (*1S,2R*)-**14** was used directly for the next step without further purification.

(*1S,2R*)-2-(4-Chlorophenyl)-*N*-propylcyclopropanamine ((*1S,2R*)-17). Compound (*1S,2R*)-**17** was similarly prepared as compound (±)-**17** and was used directly without further purification.

Scheme 1. Synthesis of compound *(1R,2S)*-**11.**



Reagents and conditions: (a) (*1S*)-(-)-2,10-camphorsultam, NaH, THF, 0 °C, 30 min; then RT overnight; (b) CH_2N_2, $Pd(OAc)_2$, DCM, RT, 10 h; (c)(i) $Ti(iOPr)_4$, BzOH, 150 °C, 30 min; (ii) 2M LiOH, MeOH, RT, 2 h; (iii) 4M HCl; (d) (i) Ethyl chloroformate, Et_3N, Acetone, 0 °C, 2 h; (ii) NaN_3, 1 h; (iii) 90 °C, Toluene, 3 h; (iv) Bu^tOH, reflux, 16 h. (e) TFA, DCM, RT, 12 h; (f) Propionaldehyde, $NaBH_4$, MeOH, RT; (g) N-(cis-3-hydroxy-3-(2-oxoethyl)cyclobutyl)-2-naphthamide, $NaBH(OAc)_3$, HOAc, DCM, RT, 4h.

(*E*)-3-(4-Chlorophenyl)-1-((*3aR,6R,7aR*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)prop-2-en-1-one (26). A solution of (*1S*)-(-)-2,10-camphorsultam (3.54 g, 16.49 mmol) in anhydrous THF (40 mL) was added to a stirred mixture of NaH (1.20 g, 30.00 mmol; 60% in mineral oil) in anhydrous THF (60 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. A solution of 4-chlorocinnamoyl chloride [prepared by stirring of 4-chlorocinnamic acid (2.50 g, 13.74 mmol) in $SOCl_2$ (15 mL) for 2 h at room temperature followed by concentration of the mixture under reduced pressure] in anhydrous THF (20 mL) was added slowly and the mixture was stirred at 0 °C for 2 h and then at room temperature overnight. The reaction was quenched by addition of water (40 mL) and the mixture was extracted with ethyl acetate (80 mLx3). The organic layer was washed successively with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed (Hexane:EtOAc = 4:1) to give compound **26** (5.0 g, 96% yield) as a colorless solid. 1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, *J* = 15.5 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 15.5 Hz, 1H), 3.99 (dd, *J* = 5.31, 7.32 Hz, 1H), 3.55 (d, *J* = 13.4 Hz, 1H), 3.47 (d, *J* = 13.4 Hz, 1H), 2.25-1.80 (m, 5H), 1.50-1.30 (m, 2H), 1.20 (s, 3H), 0.99 (s, 3H).

((*1R,2R*)-2-(4-Chlorophenyl)cyclopropyl)((*3aR,6R,7aR*)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)methanone (27). A solution of *N*-methyl-*N*-nitrosotoluene-4-sulfonamide (Diazald) (25 g, 116.82 mmol) in diethyl ether (300 mL) was slowly added to a heated (70 °C, bath temperature) mixture of KOH (25.0 g, 446 mmol), diethyl ether (50 mL), water (150 mL), and 2-(2-ethoxyethoxy)ethanol (150 mL). The solution of diazomethane thus formed was continuously distilled into a stirred, cooled (ice-bath)

solution of **26** (5.0 g, 13.2 mmol) and $Pd(OAc)_2$, (20 mg, 0.089 mmol) in CH_2Cl_2 (200 mL). The reaction was quenched by addition of a few drops of acetic acid after 10 h. The mixture was washed with aq. 5% $NaHCO_3$, dried over anhydrous Na_2SO_4. The organic solvents were concentrated under reduced pressure and the residue was recrystallized from EtOH to yield pure **27** (3.1 g, 60% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 3.91 (dd, *J* = 5.1, 7.5 Hz, 1H), 3.51 (d, *J* = 13.8 Hz, 1H), 3.43 (d, *J* = 13.8 Hz, 1H), 2.65-2.50 (m, 2H), 2.25-1.70 (m, 6H), 1.50-1.25 (m, 3H), 1.20 (s, 3H), 0.98 (s, 3H).

(*1R,2R*)-2-(4-Chlorophenyl)cyclopropanecarboxylic acid ((*1R,2R*)-24). Titanium (IV) isopropoxide (2.02 g, 7.12 mmol) was added to a solution of sultam **27** (2.8 g, 7.12 mmol) in benzyl alcohol (8 mL). The solution was heated at 150 °C for 30 min. The reaction was cooled to room temperature and quenched by addition of water (20 mL). The mixture was extracted with ethyl acetate (30 mL), dried over anhydrous Na_2SO_4, and filtered. Organic solvent was removed under reduced pressure and the residue was dissolved in MeOH (20 mL), and aq. 2 M LiOH (8 mL), and stirred at room temperature for 2 h. The mixture was concentrated and the remaining alkaline solution was washed with diethyl ether (3 x 15 mL), acidified with aq. 4 M HC1, extracted with CH_2Cl_2 (3 x 20 cm3), and the extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the pure acid *(1R,2R)*-**24** (620 mg, 44% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 2.65-2.50 (m, 1H), 1.90-1.80 (m, 1H), 1.75-1.60 (m, 1H), 1.40-1.30 (m, 1H).

***Tert*-Butyl ((*1R,2S*)-2-(4-chlorophenyl)cyclopropyl)carbamate ((*1R,2S*)-25).** Ethyl chloroformate (413 mg, 3.83 mmol) was added to a stirred, cooled 0 °C solution of the acid *(1R,2R)*-**24** (500 mg, 2.55 mmol) and triethylamine (335 mg, 3.32 mmol) in dry acetone (20 mL). After 2 h, NaN_3 (265 mg, 4.08 mmol) was added and the mixture was stirred for one additional hour. Water (30 mL) was added and the solution was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude azide thus obtained was dissolved in dry toluene (40 mL). The solution was heated to 90°C (bath temperature) for 3 h. The mixture was concentrated and the residue was dissolved in dry tert-butyl alcohol (50 mL) and heated to reflux for 16 h. The mixture was concentrated and the crude carbamate was purified by flash chromatography (Hexane:EtOAc=9:1) to give pure *(1R,2S)*-**25** (370 mg, 54% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.22 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 4.80 (s, 1H), 2.75-2.65 (m, 1H), 2.05-1.95 (m, 1H), 1.45 (s, 9H), 1.20-1.06 (m, 2H).

(*1R,2S*)-2-(4-Chlorophenyl)cyclopropanamine ((*1R,2S*)-14). Trifluoroacetic acid (1 mL) was added to a solution of *(1R,2S)*-**25** (180 mg, 0.674 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 12 h. The reaction was quenched by addition of aqueous Na_2CO_3 and the mixture was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give *(1R,2S)*-**14**. Compound *(1R,2S)*-**14** was used directly for the next step without further purification.

(*1R,2S*)-2-(4-Chlorophenyl)-*N*-propylcyclopropanamine ((*1R,2S*)-17). Compound *(1R,2S)*-**17** was similarly prepared as compound (±)-**17** and was used directly without further purification.