Chiral Resolution and Serendipitous Fluorination Reaction for the Selective Dopamine D3 Receptor Antagonist BAK2-66

Vivek Kumar,[†] Ashwini K. Banala,[†] Erick G. Garcia,[†] Jianjing Cao,[†] Thomas M. Keck,[†] Alessandro Bonifazi,[†] Jeffery R. Deschamps[§] and Amy Hauck Newman*[,†]

SUPPORTING DATA

EXPERIMENTAL METHODS

1. Chemistry

Reaction conditions and yields were not optimized and spectroscopic data and yields refer to the free base unless otherwise described for each compound. Flash column chromatography was performed using silica gel (EMD Chemicals, Inc.; 230-400 mesh, 60 Å). Eluting solvents are described for each compound. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were acquired using a Varian Mercury Plus 400 spectrometer. Chemical shifts are reported in parts-per-million (ppm) and referenced according to deuterated solvent for ^{1}H spectra ($CDCl_3$, 7.26), ^{13}C spectra ($CDCl_3$, 77.2). Combustion analysis was performed by Atlantic Microlab, Inc. (Norcross, GA) and reported values agree within 0.4% of calculated values. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. Anhydrous solvents were purchased from Aldrich and were used without further purification, except for tetrahydrofuran, which was freshly distilled from sodium-benzophenone ketyl. All other chemicals and reagents were purchased from Aldrich Chemical Co. On the basis of NMR, GC-MS, and combustion analysis data, all final compounds are >95% pure.

1.1.(*R*)-2-(2-(Oxiran-2-yl)ethyl)isoindoline-1,3-dione (3)[1]: To a solution of racemic 2-(2-(oxiran-2-yl)ethyl)isoindoline-1,3-dione (**2**, 10 g, 46 mmol) in THF (40 mL) was added (*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-buytlsalicylidene)-1,2-cyclohexanediaminocobalt (III)OAc (0.244 g, 0.37 mmol). The reaction mixture was stirred and cooled to 0 °C. Water (580 μL, 32.2 mmol, HPLC grade) was added drop wise to the reaction

mixture that was stirred at 0 °C for 30 min then at RT for 72h. The reaction mixture was diluted with ethyl acetate (100 mL), then washed with H_2O (50 mL) followed by brine (50 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated. The same procedure was repeated once more to improve the enantiomeric excess of the compound. Yield 3.0 g (30%, ee ≥99 %). Its absolute configuration was confirmed by X-ray crystallography (Fig 1). This compound was synthesized previously[1] in situ, from 2-(2-bromoethyl)oxirane, in 21% yield and chiral purity was checked only for the final molecule(*R*)-*N*-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-1*H*-indole-2-carboxamide (***R*-22/ (*R*)-PG648**) with >90% ee.

1.2.(*S*)-2-(2-(Oxiran-2-yl)ethyl)isoindoline-1,3-dione ((*S*)-3)[1]:The (*S*) enantiomer was prepared from commercially available (*S*)-2-(2-bromoethyl)oxirane (Aldrich) using the previously published procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87-7.85 (m, 2H),7.74-7.71 (m, 2H), 3.94-3.85 (m, 2H), 3.02-2.98 (m, 1H), 2.72 (t, *J* = 4.4 Hz, 1H), 2.46-2.44 (m, 1H), 2.02-1.96 (m, 1H), 1.90-1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.41, 134.11, 132.19, 123.41, 50.27, 46.51, 35.25, 31.73.

1.3.(*S*)-2-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)isoindoline-1,3-dione ((*S*)-4): The (*S*) enantiomer was prepared using the same procedure described for the racemic mixture.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.87-7.83 (m, 2H), 7.74-7.69 (m, 2H), 7.17-7.11 (m, 2H), 6.95-6.92 (m, 1H), 3.96-3.75 (m, 3H), 3.52 (bs, 1H), 3.04 (s, 4H), 2.84-2.80 (m, 2H), 2.60-2.59 (m, 2H), 2.47-2.36 (m, 2H), 1.82-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.67, 151.27, 134.19, 134.05, 132.34, 127.65, 124.79, 123.38, 118.73, 64.67, 63.94, 53.46, 51.53, 35.24, 33.77. $[\alpha]_D^{23}$ +23.4 (*c* 0.3, $CHCl_3$).

1.4.(S)-2-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-fluorobutyl)isoindoline-1,3-dione ((*S*)-5): The (*S*) enantiomer was prepared using the same procedure described for the racemic mixture.[2] ^{1}H NMR (400

MHz, $CDCl_3$) δ ppm 7.85 (dd, *J* = 12.4, 7.8 Hz, 2H), 7.74-7.70 (m, 2H), 7.16-7.11 (m, 2H), 6.95-6.92 (m, 1H), 4.87-4.83 (m, 0.5H), 4.74-4.70 (m, 0.5H), 3.90-3.84 (m, 2H), 3.06-3.03 (m, 4H), 2.79-2.69 (m, 5H), 2.63-2.53 (m, 1H), 2.14-1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.41, 151.38, 134.14, 132.25, 127.66, 127.57, 124.71, 123.43, 118.74, 90.71 (d, *J* = 169.1 Hz),62.09 (d, *J* = 21.3 Hz), 54.04, 54.03, 51.39, 34.65 (d, *J* = 5.3 Hz), 32.38 (d, *J* = 21.2 Hz). $[\alpha]_D^{23}$-2.7 (*c* 0.37, $CHCl_3$).

1.5.(*S*)-4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-fluorobutan-1-amine ((*S*)-6): The (*S*) enantiomer was prepared using the same procedure described for the racemic mixture[3] and was used in the next step without further purification.

1.6.(*S*)-*N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-fluorobutyl)benzofuran-2-carboxamide ((*S*)-BAK2-66): The (*S*) enantiomer was prepared using the same procedure described for the racemic mixture.[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69-7.67 (m, 1H),7.50-7.26 (m, 3H), 7.18-7.11(m, 2H),7.0 (brs,1H),6.94 (dd, J = 6.8, 2.4 Hz, 1H),5.0-4.82(m, 1H),3.71-3.65 (m, 2H),3.09 (brs, 4H),2.84-2.57 (m, 6H),2.14-1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.16, 154.83, 151.27, 148.78, 134.15, 127.72, 127.63, 127.58, 127.03, 124.75, 123.84, 122.87, 118.71, 111.83, 110.55, 91.35 (d, *J* = 167.8 Hz), 62.12 (d, *J* = 20.9 Hz),54.04, 51.34, 36.03 (d, *J* = 5.1 Hz),33.18 (d, *J* = 20.5 Hz), $[\alpha]_D^{25}$ -1.3 (*c* 1, $CHCl_3$).

1.7.(R)-*N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-fluorobutyl)benzofuran-2-carboxamide ((*R*)-BAK2-66): The (*R*) enantiomer was prepared using the same procedure described for the racemic mixture.[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.68-7.66 (m, 1H), 7.50-7.28 (m, 3H), 7.18-7.11(m, 2H), 7.0 (brs,1H), 6.94 (dd, J = 6.8, 2.4 Hz, 1H), 5.0-4.82(m, 1H), 3.71-3.65 (m, 2H),3.09 (brs, 4H), 2.84-2.57 (m, 6H), 2.14-1.99 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 159.15, 154.83, 151.27, 148.78, 134.15, 127.72, 127.63,

127.58, 127.02, 124.75, 123.85, 122.87, 118.70, 111.83, 110.55, 91.35 (d, *J* = 167.8 Hz), 62.12 (d, *J* = 20.9 Hz), 54.04, 51.35, 36.03 (d, *J* = 5.1 Hz), 33.18 (d, *J* = 20.5 Hz), $[\alpha]_D^{25}$+ 1.4 (*c* 1, $CHCl_3$).

1.8.2-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-4-fluorobutyl)isoindoline-1,3-dione (5b): Compound **5b** formed as a minor side product along with synthesis of **5a**. The product was purified using flash chromatography (30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (m, 2H), 7.71-7.67 (m, 2H), 7.09 (q, *J* = 15, 8 Hz, 2H), 6.78 (d, J = 5.2 Hz, 1H), 4.55 (dd, J = 48, 4.5 Hz, 2H), 3.94-3.80 (m, 2H), 2.94-2.81 (m, 7H), 2.69-2.67 (m, 2H), 2.04-1.95 (m, 1H), 1.79-1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.45, 151.38, 133.96, 132.35, 127.53, 127.38, 124.50, 123.23, 118.62, 82.83 (d, *J* = 172.1 Hz), 61.82 (d, *J* = 17.5 Hz), 51.83, 35.96, 25.67 (d, *J* = 6.8 Hz).

1.9.3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-4-fluorobutan-1-amine (7):The compound was prepared using the same procedure described for the (***S***)-**6** and used in the next step without further purification.

1.10.*N*-(3-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-4-fluorobutyl)benzofuran-2-carboxamide (8): The compound was prepared using the same procedure as described for **(*S*)-BAK2-66**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz, 1H), 7.54 (t, *J* = 8.8 Hz, 1H), 7.42-7.37 (m, 2H), 7.30-7.26 (m, 1H), 7.17-7.11 (m, 2H), 6.95 (dd, *J* = 7.2, 2.8 Hz, 1H), 4.29-4.20 (m, 1H), 4.07 (dd, *J* = 12.4, 7.2 Hz, 0.5H), 3.97-3.90 (m, 1H), 3.77 (t, *J* = 10 Hz, 0.5H), 3.68-3.60 (m, 0.5H), 3.54-3.49 (m, 0.5H), 3.1-2.88 (m, 5H), 2.76-2.71 (m, 4H), 2.31-2.17 (m, 1H), 2.04-1.83 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 158.70, 158.58, 154.88, 151.0, 149.42, 134.04, 127.51, 127.02, 126.61, 124.73, 123.58, 122.44, 118.58, 112.01, 63.46 (d, *J* = 248.6Hz), 51.98, 51.83, 51.11, 47.09 (d, *J* = 101.6 Hz), 30.53, 27.49. Yield 0.203 g (52%). The oxalate salt was precipitated from acetone; mp 218-220 °C. Anal. ($C_{23}H_{24}Cl_2FN_3O_2$. $C_2H_2O_4$.0.75H_2O) C, H, N.

1.11.(*R*)-4-Amino-1-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol ((*R*)-9): Hydrazine (1.05 g, 32.7 mmol) was added to a solution of **(*R*)-4** (4.9 g, 10.92 mmol) in EtOH (100 mL). The reaction mixture was stirred at reflux for 3h, concentrated and diluted with 30% K_2CO_3 solution. The crude product was extracted (3 x 20 mL) with $CHCl_3$, concentrated and used in next step without further purification.

1.12.(*R*)-*N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-1H-indole-2-carboxamide ((*R*)-PG648)[1]: CDI (1.12 g, 6.91 mmol) was added to a solution of indole-2-carboxylic acid (1.01 g, 6.28 mmol) in dry THF (20 mL) and stirred for 3h at RT. The reaction mixture was cooled to 0 °C and **(*R*)-9** (2.00 g, 6.28 mmol) was added dropwise after diluting with dry THF (20 mL). The reaction mixture was allowed to come to RT and stirred for 3h, concentrated, diluted with H_2O (50 mL) and extracted in $CHCl_3$ (3 x 20 mL). The organic layer was concentrated and the product was purified by flash column chromatography to provide 1.67 g (58 %) of pure product. The PTSA salt was precipitated in $CHCl_3$. Anal. ($C_{23}H_{26}Cl_2N_4O_2C_7H_8O_3S.0.75H_2O$) C, H, N. $[\alpha]_D^{23}$- 60.7 ($CHCl_3$, *c* 0.28), ee ≥99%.

1.13.(*S*)-4-Amino-1-(4-(2,3-dichlorophenyl)piperazin-1-yl)butan-2-ol (*S*)-9):The (*S*) enantiomer was prepared using the same procedure described for the **(*R*)-9**.

1.14.(*S*)-*N*-(4-(4-(2,3-Dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)-1H-indole-2-carboxamide ((*S*)-PG648)[1]: The (*S*) enantiomer was prepared using the same procedure described for **(*R*)-PG648**. The PTSA salt was precipitated in $CHCl_3$ and recrystallized in MeOH. Anal. ($C_{23}H_{26}Cl_2N_4O_2C_7H_8O_3S$) C, H, N. $[\alpha]_D^{23}$ + 61.3 ($CHCl_3$, *c* 0.315).

2. Chiral Chromatography Analysis

The chiral purity of compounds **(*R*)-3**, **(*R*)-5**, **(*R*)-BAK2-66** and **(*S*)-3**, **(*S*)-5**, **(*S*)-BAK2-66** were determined by HPLC analysis using Daicel CHIRALCEL OD-H 14325 semi-preparative column (I.D. x L = 10 x 250 mm). Elution was achieved using hexane/*i*-PrOH (85:15 v/v) for compound **3** and **BAK2-66** and hexane/*i*-PrOH (90:10 v/v) for compound **5** at a flow rate of 0.5 mL/min with ultraviolet absorption at 225 nm (Waters 2487 detector, Waters Corp.). Chromatographic data were acquired using the Empower 2 software. The retention times for compounds **(*R*)-3**, **(*R*)-5** and **(*R*)-BAK2-66** were 22.9, 41.5 and 64.9 min, respectively, and the opposite enantiomers **(*S*)-3**, **(*S*)-5** and **(*S*)-BAK2-66** had retention times of 19.5, 38.3 and 58.6 min, respectively.

Figure S.I. 1: HPLC chromatograms for intermediates 3, 5 and BAK2-66

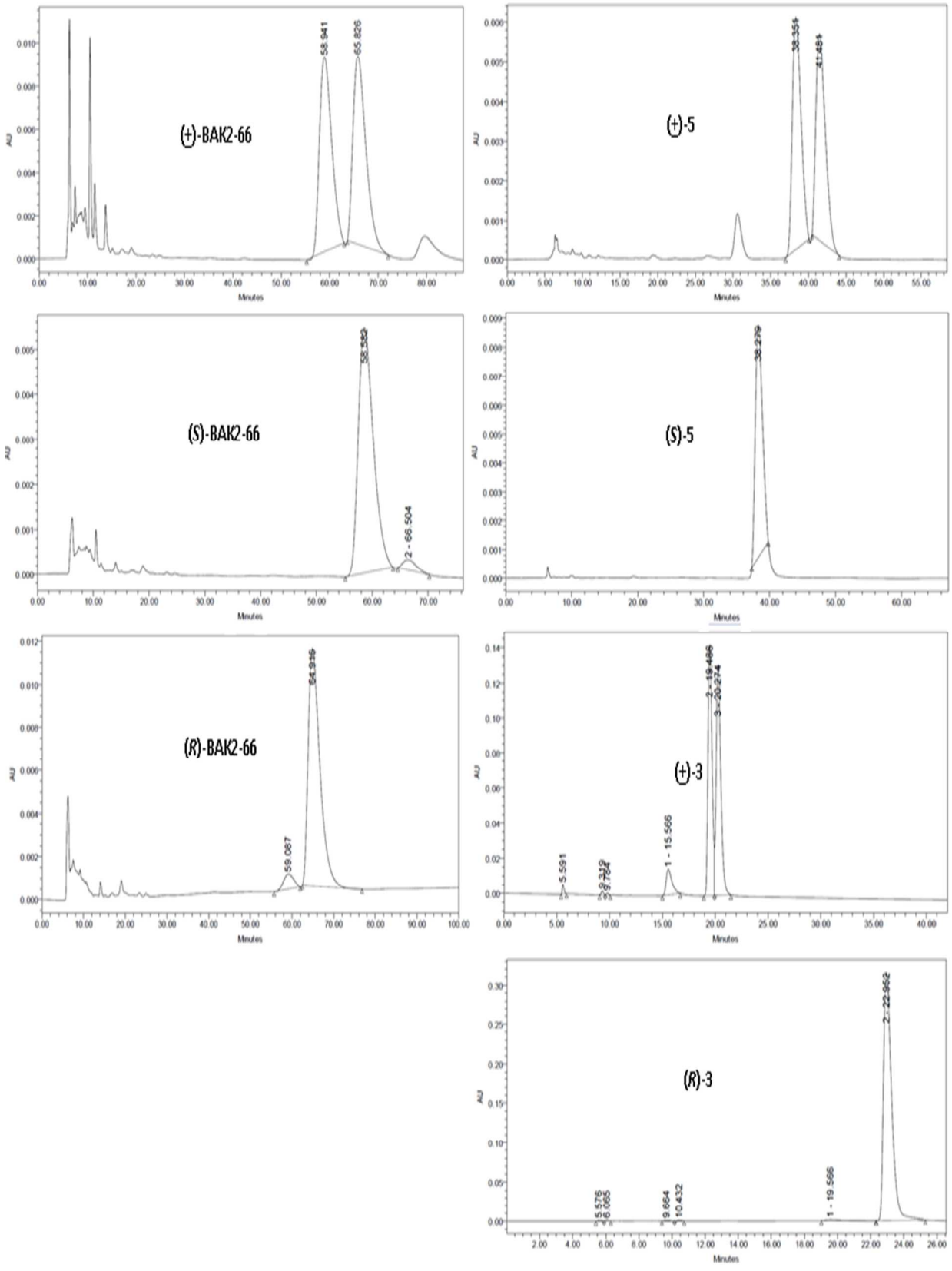
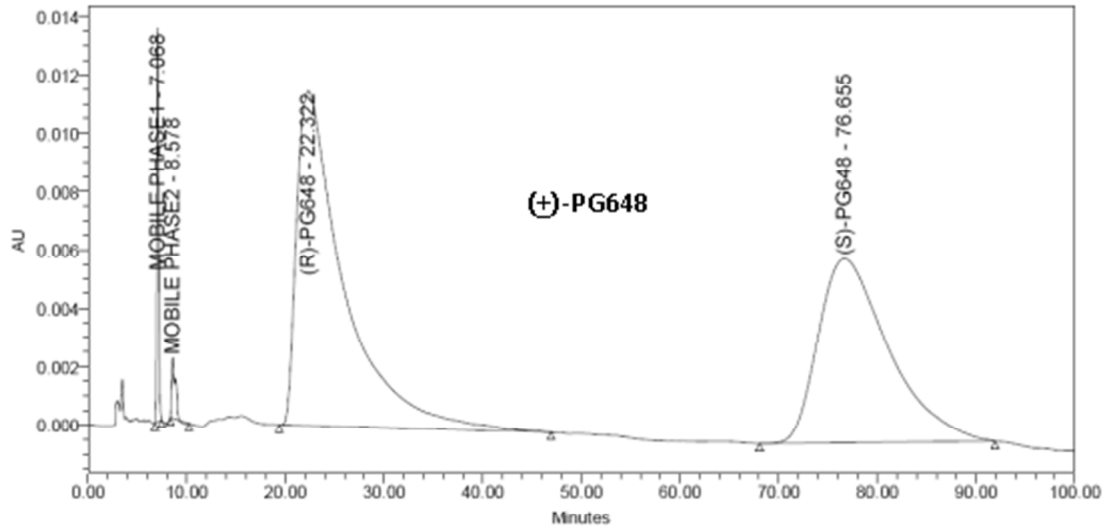
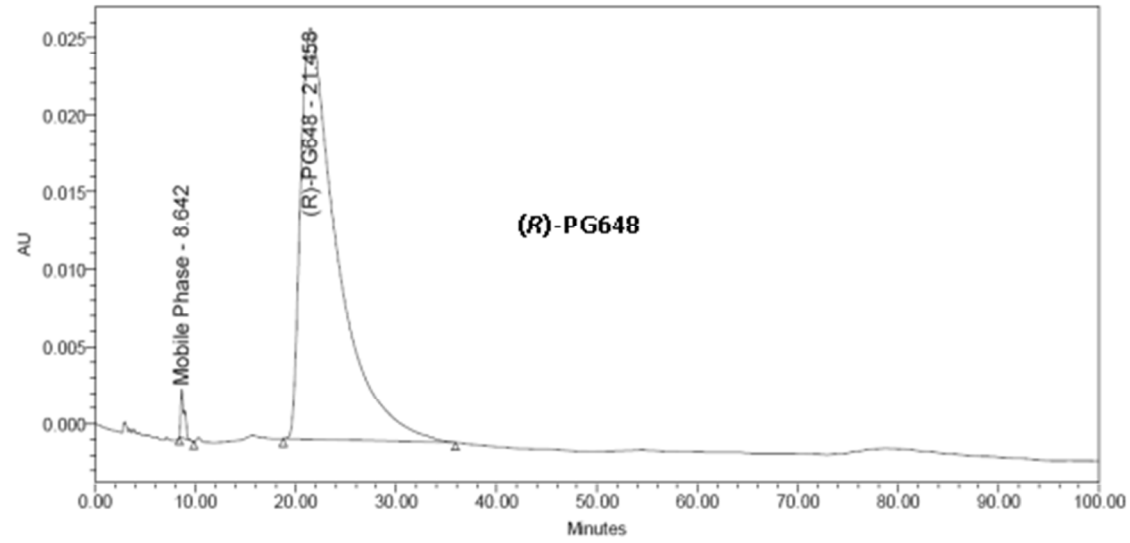


Figure S.I. 2: HPLC chromatogram for PG648





3. X-ray crystal data on compounds (*S*)-4, (*S*)-5, and (*S*)-BAK2-66

Single-crystal X-ray diffraction data on compounds **(*S*)-4** and **(*S*)-5** were collected using MoKα radiation and a Bruker APEX-2 CCD area detector. Single-crystal X-ray diffraction data on compound **(*S*)-BAK2-66** were collected using CuKα radiation and a Bruker Pt-135 CCD area detector. The crystals were prepared for data collection by coating with high viscosity microscope oil. The oil-coated crystal was mounted on a micro-mesh mount (Mitergen, Inc.), transferred to the diffractometer, and a data set collected at 150 K. The structures were solved by direct methods and refined by full-matrix least squares on F2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Corrections were applied for Lorentz, polarization, and absorption effects. Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å.

The absolute configuration was determined from the X-ray data using the methods of Hooft and Flack et al.[4,5]

3.1. For **(*S*)-4**, the 0.227 x 0.204 x 0.066 mm^3 crystal was orthorhombic in space group P $2_12_12_1$, with unit cell dimensions a = 4.7352(2), b = 9.8753(4), and c = 44.740(2) Å. Data was 95.3% complete to 29.15° θ (~ 0.73 Å) with an average redundancy of 2.98. The final anisotropic full matrix least-squares refinement on F^2 with 192 variables converged at R1 = 3.71%, for the observed data and wR2 = 9.37% for all data. The absolute structure was determined from the X-ray (Hooft(y) = -0.06(4)) based on the analysis of 2055 Bijvoet pairs.

3.2. For **(*S*)-5**, the 0.421 x 0.204 x 0.116 mm^3 crystal was orthorhombic in space group P $2_12_12_1$, with unit cell dimensions a = 4.5747(5), b = 9.6567(10), and c = 44.757(6) Å. Data was 99.0% complete to 28.53° θ (~ 0.75 Å) with an average redundancy of 5.07. The final anisotropic full matrix least-squares refinement

on F^2 with 192 variables converged at R1 = 3.97%, for the observed data and wR2 = 10.12% for all data. The absolute structure was determined unambiguously from the X-ray (Hooft(y) = 0.02(4)) based on the analysis of 1939 Bijvoet pairs.

3.3. For compound **(*S*)-BAK2-66** the 0.356 x 0.162 x 0.027 mm^3 crystal was triclinic in space group P 1, with unit cell dimensions a = 5.1054(4), b = 9.4632(7), c = 22.3841(15) Å, α = 99.542(3), β = 95.210(4), and γ = 91.296(4)°. Data was 87.5% complete to 68.18° θ (~ 0.83 Å) with an average redundancy of 1.98. The final anisotropic full matrix least-squares refinement on F^2 with 559 variables converged at R1 = 6.47%, for the observed data and wR2 = 15.780% for all data. The absolute structure was determined unambiguously from the X-ray (Flack parameter = 0.027(11).

Atomic coordinates for **(*S*)-4**, **(*S*)-5**, and **(*S*)-BAK2-66** have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 979271, 979272, and 979273 respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

4. hD2R, hD3R, hD4R [^{3}H]*N*-methylspiperone binding assays

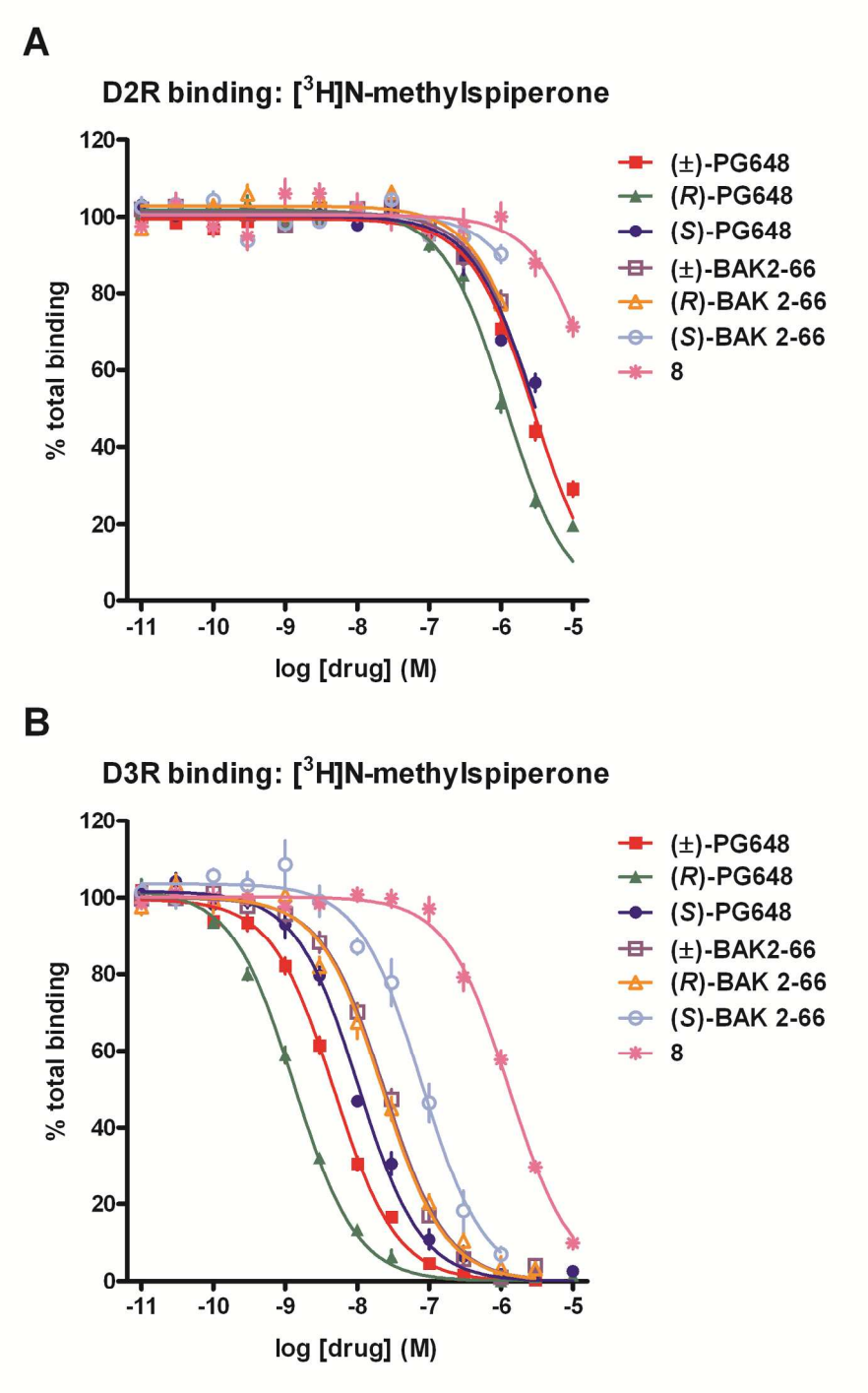
D2-like receptor binding was performed using procedures adapted from Bergman et al.[6] HEK293 cells stably expressing human D2R, D3R, or D4R were grown in a 50:50 mix of DMEM and Ham's F12 culture media, supplemented with 20 mM HEPES, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 1X antibiotic/antimycotic, 10% heat-inactivated fetal bovine serum, and 200 µg/ml hygromycin (Life Technologies, Grand Island, NY) and kept in an incubator at 37 °C and 5% CO_2. Upon reaching 80-90% confluence, cells were harvested using pre-mixed Earle's Balanced Salt Solution (EBSS) with 5 µM EDTA (Life Technologies) and centrifuged at 3000 rpm for 10 min at 21 °C. The supernatant was removed and the pellet was resuspended in 10 ml hypotonic lysis buffer (5 mM $MgCl_2 \cdot 6\ H_2O$, 5 mM Tris, pH 7.4 at 4 °C) and centrifuged at 30,000 g for 30 min at 4 °C. The pellet was then resuspended in fresh EBSS buffer

made from 8.7 g/L Earle's Balanced Salts without phenol red (US Biological, Salem, MA), 2.2 g/L sodium bicarbonate, pH to 7.4. A Bradford protein assay (Bio-Rad, Hercules, CA) was used to determine the protein concentration and membranes were diluted to 500 μg/ml and stored in a -80 °C freezer for later use.

On test day, all test compounds were freshly dissolved in 30% DMSO and 70% H_2O, typically to a stock concentration of 1 mM or 100 μM. If free-base compounds did not readily go into solution, 10 μl of glacial acetic acid was added. Each test compound was then diluted into 13 half-log serial dilutions using 30% DMSO vehicle; final test concentrations ranged from 100 μM to 10 pM. Frozen membranes were diluted in fresh EBSS to a 100 μg/ml stock for D2R or D3R binding, or 200 μg/ml for D4R binding. Radioligand competition experiments were conducted in glass tubes containing 300 μl fresh EBSS buffer with 0.2 mM sodium metabisulfite, 50 μl of diluted test compound, 100 μl of membranes (10 μg total protein for D2R & D3R binding, 20 μg for D4R binding), and 50 μl of [^{3}H]N-methylspiperone (0.4 nM final concentration; Perkin Elmer). Nonspecific binding was determined using 10 μM butaclamol (Sigma-Aldrich, St. Louis, MO) and total binding was determined with 30% DMSO vehicle. All compound dilutions were tested in triplicate and the reaction incubated for one hour at room temperature. The reaction was terminated by filtration through Whatman GF/B filters, presoaked for one hour in 0.5% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments, Gaithersburg, MD). The filters were washed 3 times with 3 ml of ice cold EBSS+ buffer and transferred to scintillation vials. 3 ml CytoScint liquid scintillation cocktail (MP Biomedicals, Solon, OH) was added and vials were counted using a Perkin Elmer Tri-Carb 2910 TR liquid scintillation counter (Waltham, MA). IC_{50} values for each compound were determined from dose-response curves (Figure S.I. 3) and K_i values were calculated using the Cheng-Prusoff equation.[7] Reported K_i ± SEM values were determined from at least three independent experiments. Compounds (R)-BAK2-66, (S)-BAK2-66, and 8 were tested at least once for

binding affinity in hD4R membranes; due to their low affinity for the receptor, a full complement of at least three repeated tests were not completed.

Figure S.I. 3: hD2R and hD3R radioligand competition binding curves



REFERENCES

1. Newman, A. H.; Grundt, P.; Cyriac, G.; Deschamps, J. R.; Taylor, M.; Kumar, R.; Ho, D.; Luedtke, R. R. *N*-(4-(4-(2,3-dichloro- or 2-methoxyphenyl)piperazin-1-yl)butyl)heterobiarylcarboxamides with functionalized linking chains as high affinity and enantioselective D3 receptor antagonists. *J. Med. Chem.***2009**, *52*, 2559-2570.
2. Banala, A. K.; Levy, B. A.; Khatri, S. S.; Furman, C. A.; Roof, R. A.; Mishra, Y.; Griffin, S. A.; Sibley, D. R.; Luedtke, R. R.; Newman, A. H. N-(3-Fluoro-4-(4-(2-methoxy or 2,3-dichlorophenyl)piperazine-1-yl)butyl)arylcarboxamides as selective dopamine D3 receptor ligands: critical role of the carboxamide linker for D3 receptor Selectivity. *J. Med. Chem.***2011**, *54*, 3581-3594.
3. Newman, A. H.; Beuming, T.; Banala, A. K.; Donthamsetti, P.; Pongetti, K.; LaBounty, A.; Levy, B.; Cao, J.; Michino, M.; Luedtke, R. R.; Javitch, J. A.; Shi, L. Molecular determinants of selectivity and efficacy at the dopamine D3 receptor. *J. Med. Chem.* **2012**, *55*, 6689-6699.
4. Hooft, R.W.W., Straver, L.H., Spek, A.L. Determination of absolute structure using Bayesian statistics on Bijvoet differences. *J. Appl. Cryst.*, **2008**, *41*, 96-103.
5. Flack, H.D. On enantiomorph-polarity estimation. *Acta Cryst.*, **1983**, *A39*, 876-881.
6. Bergman, J; Roof, R. A.; Furman, C. A.; Conroy, J. L.; Mello, N. K.; Sibley, D. R.; Skolnick, P. Modification of cocaine self-administration by buspirone (buspar®): potential involvement of D3 and D4 dopamine receptors*. Int. J. Neuropsychopharmacol.* **2013**, *16*, 445-458.
7. Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099-3108.