

Supporting Information

The Discovery of a Series of 5-Arylsulfonamido-3-(Pyrrolidin-2-ylmethyl)-1*H*-Indole Derivatives as Potent, Selective 5-HT₆ Receptor Agonists and Antagonists.

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Experimental Section

NMR spectra were recorded on Bruker AM-400 (400 MHz). NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. EI mass spectra were obtained on an Agilent SL MSD. LCMS were run on an Agilent 1100 LCMS system. RP Preparative HPLC was carried out on Gilson semi-prep HPLC system consisting of a 215 autosampler, 322 solvent pump, 307 make-up pump, and 155 UV/VIS detector. Chiral analyses were run on either an Agilent 1100 HPLC or a Berger SFC instrument. Optical rotations were run on a JASCO DIP-370 digital polarimeter. Melting Points were measured on a Büchi B-545. HRMS was carried out on a Bruker APEX II 9.4 T mass spectrometer.

Determination of 5-HT₆ Compound Intrinsic Activity using cAMP Accumulation.

Intracellular cAMP levels are measured using 24-well plates containing the human 5-HT₆ receptor stably transfected into HeLa cells. Upon initiation of the assay, the media from the cell maintenance is aspirated and the cells are preincubated at 37°C for 15 minutes in KREBS buffer. Following this primary incubation, the buffer is aspirated and an additional incubation is performed at 37°C for 5 minutes in KREBS buffer containing 500 μ M IBMS (3-isobutyl-1-methylxanthine). Subsequently, the cells are incubated with the test compound at concentrations ranging from 10⁻⁵ to 10⁻¹⁰ M for 10 minutes at 37°C (antagonist assay require a second incubation with the addition of 100 nM 5HT). The assay is terminated by the addition of 0.5 M perchloric acid. Intracellular cAMP levels were determined by radioimmunoassay through the cAMP SPA screening kit. Data were analyzed graphically with GraphPad Prism (GraphPad Software, San Diego, CA).

5-HT₆ Membrane Preparation. Cultured Hela cells expressing the Human cloned 5-hydroxytryptamine₆ (h5-HT₆) receptors are harvested and centrifuged at low speed (1,000 x g) for 5 min to remove the culture media. The harvested cells are suspended in 1 volume of fresh physiological phosphate buffered saline (PBS) solution and recentrifuged at the same speed. This operation is repeated once more. The collected cells are then homogenized in ten volumes of 50 mM Tris.HCl, pH 7.4 and 0.5 mM EDTA. The homogenate is centrifuged at 900 x g for 10 min and the supernatant collected. The supernatant is then centrifuged at 40,000g for 30 min. The pellet is resuspended in 10 volumes of Tris.HCl buffer and recentrifuged at the same speed. The final pellet is suspended in a small volume of Tris.HCl buffer and the tissue protein content is determined in aliquots of 10-25 μ L volumes. Bovine Serum Albumin is used as the standard in the protein determination by the method of Lowry et al., (*J. Biol. Chem.*, **193**, 265, 1951). The volume of the suspended cell membranes is adjusted to give a tissue protein concentration of 1.0 mg/ml of suspension. The prepared membrane suspension (10 times concentrated) is aliquoted in 1.0 ml volumes and stored at -70°C until used in subsequent binding experiments.

5-HT₆ Binding Assay. Total Bound well: Containing 80 μ L binding buffer, 20 μ L of 3 μ M [³H]-LSD, 100 μ L membrane protein (20-50 μ g protein). Total volume = 200 μ L.

Non Specific Well: Containing 60 μ L of buffer, 20 μ L of 1 μ M cold LSD, 20 μ L of 3 μ M [³H]-LSD, 100 μ L of membrane protein (20-50 μ g protein). Total volume = 200 μ L.

Compound Well: Containing 60 μ L of buffer, 20 μ L of test compound at different concentrations, 20 μ L of 3 μ M [³H]-LSD, 100 μ L of membrane protein (20-50 μ g protein). Total volume = 200 μ L.

Incubate at room temperature for 2 hours and harvest reaction mixture by using Packard 96 well harvest system followed by counting the plate in Top Count machine (Packard).

(*R*)-3-(1-Methyl-pyrrolidin-2-ylmethyl)-1H-indol-5-ylamine [(*R*)-12]. Prepared via literature procedure.²⁰ Enantiomeric purity 99.6% by chiral HPLC. Column: Chiralpak AD 250 x 4.6 mm; mobile phase: 90/10 heptane/ethanol; flow rate: 1 mL/min; injection: 1 μ L, 1 mg/mL in ethanol; temperature 40°C; detection: UV 215 nm. $[\alpha]^{25} = +57^\circ$ (MeOH, $c = 1.0$).

(*S*)-3-(1-Methyl-pyrrolidin-2-ylmethyl)-1H-indol-5-ylamine [(*S*)-12]. Prepared and purified as for the *R*-enantiomer. Enantiomeric purity 97.2% by chiral HPLC (conditions as (*R*)-12). $[\alpha]^{25} = -49^\circ$ (MeOH, $c = 0.9$).

(*R*)-N-[3-(1-Methyl-pyrrolidin-2-ylmethyl)-1H-indol-5-yl]-arylsulfonamide Array [(*R*)-13a-w]. A solution of (*R*)-12 in THF (20 M) was distributed to 8 mL vials (20 mmol, 1.0 mL per vial). To each vial was added triethylamine (40 mmol, 2.0 equiv) and a sulfonyl chloride (20 mmol). The resulting reactions were shaken on an orbital shaker for 4 – 8 h. When the sulfonylation reaction was judged to be complete by TLC or LCMS the solvent was removed under a N₂ stream. The residues were dissolved in a mixture of DMSO/methanol/water and purified by reverse phase HPLC.

(*S*)-N-[3-(1-Methyl-pyrrolidin-2-ylmethyl)-1H-indol-5-yl]-arylsulfonamide Array [(*S*)-13a-w]. The array was prepared as described for the *R*-enantiomers starting from (*S*)-12.

Compound	NH ₄ OH method ret. time (min)	NH ₄ OH method purity (%)	HCO ₂ H method ret. time (min)	HCO ₂ H method purity (%)	Formula	HRMS adduct	Calcd.	Found	Relative Intensity	Error (mAmu)
(R)-13-a	2.17	100	0.38	100	C.20.H.23.N.3.O.2.S.1	M+H	370.15828	370.15838	100	-0.1
(R)-13-b	2.06	100	0.38	98	C.20.H.22.F.1.N.3.O.2.S.1	M+H	388.14842	388.14896	100	-0.54
(R)-13-c	2.27	100	0.54	100	C.20.H.22.Cl.1.N.3.O.2.S.1	M+H	404.11912	404.11941	100	-0.29
(R)-13-f	2.33	100	1.37	100	C.20.H.22.Cl.1.N.3.O.2.S.1	M+H	404.11904	404.11941	100	-0.37
(R)-13-g	2.47	100	1.53	100	C.21.H.22.F.3.N.3.O.2.S.1	M+H	438.14594	438.14576	100	0.18
(R)-13-h	2.23	100	0.47	100	C.20.H.22.F.1.N.3.O.2.S.1	M+H	388.14892	388.14896	100	-0.04
(R)-13-k	2.51	100	1.49	100	C.20.H.22.1.N.3.O.2.S.1	M+H	496.05388	496.05502	100	-1.14
(R)-13-l	2.38	100	0.75	71.9	C.21.H.25.N.3.O.2.S.1	M+H	384.17358	384.17403	100	-0.45
(R)-13-m	2.25	100	0.46	100	C.21.H.25.N.3.O.3.S.1	M+H	400.16876	400.16894	100	-0.18
(R)-13-n	2.49	100	1.61	100	C.21.H.22.F.3.N.3.O.2.S.1	M+H	438.1459	438.14576	100	0.14
(R)-13-o	2.64	100	1.68	100	C.21.H.22.F.3.N.3.O.3.S.1	M+H	454.14105	454.14068	100	0.37
(R)-13-p	2.73	100	1.69	100	C.23.H.29.N.3.O.2.S.1	M+H	412.20582	412.20533	100	0.49
(R)-13-q	2.53	100	1.51	100	C.24.H.25.N.3.O.2.S.1	M+H	420.17349	420.17403	100	-0.54
(R)-13-u	2.49	100	1.66	100	C.20.H.21.Cl.2.N.3.O.2.S.1	M+H	438.0804	438.08043	100	-0.03
(R)-13-w	1.88	100	0.4	100	C.19.H.24.N.4.O.3.S.1	M+H	389.16376	389.16419	100	-0.43
(S)-13-a	2.27	100	0.37	100	C.20.H.23.N.3.O.2.S.1	M+H	370.15884	370.15838	100	0.46
(S)-13-c	2.27	100	0.61	100	C.20.H.22.Cl.1.N.3.O.2.S.1	M+H	404.11896	404.11941	100	-0.45
(S)-13-d	2.31	100	0.6	100	C.20.H.22.Br.1.N.3.O.2.S.1	M+H	448.06893	448.06889	93	0.04
(S)-13-f	2.32	100	1.38	100	C.20.H.22.Cl.1.N.3.O.2.S.1	M+H	404.11911	404.11941	100	-0.3
(S)-13-g	2.47	100	1.55	100	C.21.H.22.F.3.N.3.O.2.S.1	M+H	438.14535	438.14576	100	-0.41
(S)-13-j	2.43	100	1.33	100	C.20.H.22.Br.1.N.3.O.2.S.1	M+H	448.06777	448.06889	91	-1.12
(S)-13-m	2.25	100	0.47	100	C.21.H.25.N.3.O.3.S.1	M+H	400.16961	400.16894	100	0.67
(S)-13-n	2.64	100	1.6	100	C.21.H.22.F.3.N.3.O.2.S.1	M+H	438.14619	438.14576	100	0.43
(S)-13-o	2.64	100	1.69	100	C.21.H.22.F.3.N.3.O.3.S.1	M+H	454.14105	454.14068	100	0.37
(S)-13-p	2.72	101	1.69	100	C.23.H.29.N.3.O.2.S.1	M+H	412.20573	412.20533	100	0.4
(S)-13-q	2.51	100	1.52	100	C.24.H.25.N.3.O.2.S.1	M+H	420.17435	420.17403	100	0.32
(S)-13-r	2.8	100	1.74	97	C23.H24.Cl.1.N3.O2.S2	M+H	474.1073	474.10713	100	0.17
(S)-13-t	2.32	100	1.34	100	C.20.H.21.Cl.1.F.1.N.3.O.2.S.1	M+H	422.10948	422.10998	100	-0.5
(S)-13-u	2.49	100	1.68	100	C.20.H.21.Cl.2.N.3.O.2.S.1	M+H	438.08109	438.08043	100	0.66
(S)-13-v	2.48	100	1.38	100	C.21.H.24.Cl.1.N.3.O.3.S.1	M+H	434.13003	434.12997	100	0.06

NH₄OH method: solvent gradient = 95% A @ 0 min, 5% A @ 3.5 min, 5% A @ 5 min; solvent A = 0.05% NH₄OH in water; solvent B = 0.05% NH₄OH in ACN; flow rate 1 mL/min; column = Synergi MAX-RP 80A, 30 x 2 mm, 4 μM particle size; temperature 50°C. HCO₂H method: solvent gradient = 90% A @ 0 min, 5% A @ 3 min, 5% A @ 5 min; solvent A = 0.02% formic acid in water; solvent B = 0.02% formic acid in ACN; flow rate 1 mL/min; column = Xterra™ 30 x 2.1 mm MS C18, 3.5 μM particle size; temperature 50°C.

(*R*)-2-chloro-N-(3-((2*R*)-1-methyl-2-pyrrolidinyl)methyl)-1*H*-indol-5-yl)benzenesulfonamide [(*R*)-13c]. To a solution of (*R*)-12 (50 mg, 0.21 mmol) and diisopropylethyl amine (50 μ L) in THF (5 mL) was added 2-chlorobenzenesulfonyl chloride (50 mg, 0.23 mmol). The reaction was stirred at r.t. for 1-2 hours then concentrated. The residue was purified by flash chromatography on silica gel with 0-30% methanol (containing 1% ammonium hydroxide) in DCM to give (*R*)-13c as a tan solid (56 mg, 63 %): mp 204°C; ¹H NMR (DMSO-*d*₆) δ 10.73 (brs, 1H), 10.09 (brs, 1H), 7.85 (d, *J* = 8 Hz, 1H), 7.61-7.53 (m, 2H), 7.39 (d, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 7.14 (s, 1H), 7.07 (d, *J* = 4 Hz, 1H), 6.84 (dd, *J* = 8, 4 Hz, 1H), 2.95 (t, *J* = 7.2 Hz, 1H), 2.86 (dd, *J* = 13.8, 3.4 Hz, 1H), 2.35-2.31 (m, 1H), 2.30 (s, 3H), 2.13-2.06 (m, 2H), 1.62-1.42 (m, 2H); LRMS *m/z*: 404.2 (M+H)⁺; Anal. (C₂₀H₂₂ClN₃O₂S•0.5 H₂O) C, H, N; enantiomeric purity 100% by chiral SFC. Column: Chiralcel OF 250 x 4.6 mm; mobile phase: 40% methanol, 0.4% diethylamine in CO₂; flow rate: 5 mL/min; injection: 5 μ L, 1 mg/mL in ethanol; temperature 40°C; detection: UV 215 nm. $[\alpha]^{25} = +65^\circ$ (MeOH, *c* = 0.3).

(*R*)-3-chloro-N-(3-((2*R*)-1-methyl-2-pyrrolidinyl)methyl)-1*H*-indol-5-yl)benzenesulfonamide [(*R*)-13f]. Following the procedure for (*R*)-13c, (*R*)-13f was obtained as a tan solid (210 mg, 79 %): mp 74°C; ¹H NMR (CD₃OD) δ 7.71-7.22 (m 7H), 6.79 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.78-3.54 (m, 2 H), 3.47-3.29 (m, 1H), 3.27-3.16 (m 1H), 3.04 (dd, *J* = 18.9, 11.9 Hz, 1H), 2.33-1.96 (m, 4H); LRMS *m/z*: 404.2 (M+H)⁺; Anal. (C₂₀H₂₂ClN₃O₂S•2.3 H₂O) C, H, N; enantiomeric purity 100% by chiral HPLC. Column: Chiralcel OD-R 250 x 4.6 mm; mobile phase: 70% water/triethyl amine 30% ACN; flow rate: 1 mL/min; injection: 5 μ L, 1 mg/mL in ethanol; temperature 23°C; detection: UV 215 nm. $[\alpha]^{25} = +39^\circ$ (MeOH, *c* = 0.5).

(*R*)-2-(5-Amino-1*H*-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester [(*R*)-14]. 2-[5-(2,5-Dimethyl-pyrrol-1-yl)-1*H*-indole-3-carbonyl]-pyrrolidine-1-carboxylic acid benzyl ester (*R*)-11 (300 mg, 0.68 mmol) was dissolved in THF (0.125 M) and a solution of 2M lithium borohydride in THF (1.4 mL, 4 eq.) was added dropwise at room temperature. After the addition the reaction was heated at reflux for 4 h. The reaction was cooled in an ice bath and the resulting mixture was carefully quenched with methanol. After stirring overnight at room temperature, saturated aqueous sodium bicarbonate was added and the mixture extracted with ethyl acetate (3 x). The organic extracts were washed with brine, dried over sodium sulfate and filtered. The solvent was removed and the residue purified by flash chromatography on silica gel with 20 – 50% ethyl acetate in hexane to provide (*R*)-2-[5-(2,5-dimethyl-pyrrol-1-yl)-1*H*-indol-3-ylmethyl]-pyrrolidine-1-carboxylic acid benzyl ester (246 mg, 85%) as a white solid: mp 76°C; ¹H NMR (DMSO-*d*₆) δ 11.08 (br s, NH), 7.49-7.22 (m, 8H), 6.90-6.88 (m, 1H), 5.81 (s, 1H), 5.77 (s, 1H), 5.17-4.92 (m, 2H), 3.98 (m, 1H), 3.34-3.24 (m, 2H) 3.15-2.92 (m, 1H), 2.66 (dt, *J* = 13.7, 10.1 Hz, 1H), 1.94 (s, 6H), 1.84-1.66 (m, 4H); LRMS (*m/z*: 428.2 (M+H)⁺; Anal. (C₂₇H₂₉N₃O₂•0.2 H₂O) C, H, N; enantiomeric purity 100% by Chiral SFC. Column: Chiralcel OJ 250 x 4.6 mm; mobile phase: 15/0.4/84.6 methanol/diethylether/CO₂; flow rate: 5 mL/min; injection: 1 μ L, 1 mg/mL in methanol; temperature 40°C; detection: UV 215 nm. $[\alpha]^{25} = -20^\circ$ (MeOH, *c* = 0.3).

A solution of (*R*)-2-[5-(2,5-dimethyl-pyrrol-1-yl)-1*H*-indol-3-ylmethyl]-pyrrolidine-1-carboxylic acid benzyl ester (100 mg, 0.23 mmol) and di-*tert*-butyl dicarbonate (51 mg, 0.46 mmol) in ethyl acetate (0.6 M) was stirred for 48 h under hydrogen at atmospheric pressure in the presence of palladium hydroxide (0.05 wt equiv). The reaction mixture was filtered through Celite and the solvent evaporated. Column chromatography on silica gel, eluting with 20-50% ethyl acetate/hexanes afforded (*R*)-2-(5-amino-1*H*-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (67 mg, 74%) as a tan solid: mp 152°C; ¹H NMR (DMSO-*d*₆) δ 11.08 (br s, 1H), 7.46-7.34 (m, 2H), 7.24 (d, *J* = 4 Hz 1H), 6.88 (t, *J* = 8 Hz, 1H), 5.76 (s, 1H), 5.75 (s, 1H), 4.0-3.9 (m, 1H), 3.25-2.62 (m, 3H), 1.94 (s, 3H), 1.92 (m, 3H), 1.78-1.62 (m 4H), 1.36 (s, 9H); LRMS (*m/z*: 394.2 (M+H)⁺; Anal. (C₂₄H₃₁N₃O₂•0.1 H₂O) C, H, N; enantiomeric purity 100% by Chiral SFC. Column: Chiralcel OJ 250 x 4.6 mm; mobile phase: 15/0.4/84.6 isopropanol/diethylether/CO₂; flow rate: 5 mL/min; injection: 1 μ L, 1 mg/mL in methanol; temperature 40°C; detection: UV 215 nm; UV 215 nm. $[\alpha]^{25} = -1.7^\circ$ (MeOH, *c* = 0.5).

2-[5-(2,5-Dimethyl-pyrrol-1-yl)-1*H*-indole-3-carbonyl]-pyrrolidine-1-carboxylic acid tert-butyl ester was dissolved in 4:1 isopropanol/water (0.13 M) and treated with triethylamine (10 equiv)

and hydroxylamine hydrochloride (20 equiv). The mixture was heated at reflux for 6 h, cooled, and treated with solid sodium hydroxide (20 equiv) and stirred at room temperature overnight. The mixture was filtered through Celite, and extracted with ethyl acetate (3 x), dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by chromatography over silica gel, eluting with methanol/chloroform to afford **(R)-14** as an off-white solid (63% yield). mp 76°C; ¹H NMR (DMSO-d₆) δ 7.86 (br s, 1H), 7.15 (d, *J* = 12 Hz, 1H), 7.07-6.99 (m, 1H), 6.91 (s, 1H), 6.66 (d, *J* = 12 Hz, 1H), 4.12 (br s, 2H), 3.44-3.06 (m, 4 H), 2.62 (t, *J* = 16 Hz, 1H), 1.84-1.68 (m, 4H), 1.53 (s, 9H); LRMS *m/z*: 316.2 (M+H);. Anal. (C₁₈H₂₅N₃O₂ • 1.0 H₂O) C, H, N; enantiomeric purity 100% by chiral HPLC. Column: Chiralpak OD-R 250 x 4.6 mm; mobile phase: 55/45 0.1 N NaClO₄ buffer (pH= 6.91)/ACN; flow rate: 1 mL/min; injection: 5 uL, 1 mg/mL in ethanol; temperature 40°C; detection: UV 215 nm. [α]_D²⁵ = -9° (MeOH, *c* = 1.0).

(R)-N-(3-Pyrrolidin-2-ylmethyl-1H-indol-5-yl)-arylsulfonamide Array [(R)-15a-w]. A solution of **(R)-14** in THF (20 M) was distributed to 8 mL vials (20 mmol, 1 mL per vial). To each vial was added triethylamine (40 mmol, 2 equiv) and a sulfonyl chloride (20 mmol). The resulting reactions were shaken on an orbital shaker for 4 – 8 h. When the sulfonylation reaction was judged to be complete by TLC or LCMS 4N HCl in dioxane (1 mL) was added. The mixture was shaken overnight then the solvent was removed under N₂ stream. The residues were dissolved in a mixture of DMSO/methanol/water and purified by reverse phase HPLC.

(S)-2-[5-(2,5-Dimethyl-pyrrol-1-yl)-1H-indol-3-ylmethyl]-pyrrolidine-1-carboxylic acid benzyl ester Prepared and purified as for the *R*-enantiomer to give (390 mg, 67%) as a white solid: mp 75°C; ¹H NMR (DMSO-d₆) δ 11.08 (br s, NH), 7.50-7.17 (m, 8H), 6.90-6.84 (m, 1H), 5.81 (s, 1H), 5.77 (s, 1H), 5.19-4.92 (m, 2H), 4.03-3.98 (m, 1H), 3.37-3.24 (m, 2H) 3.14-2.92 (m, 1H), 2.77-2.61 (m, 1H), 1.94 (s, 6H), 1.85-1.68 (m, 4H); LRMS (*m/z*: 428.2 (M+H); Anal. (C₂₇H₂₉N₃O₂ • 0.3 H₂O) C, H, N; enantiomeric purity 99.4% by Chiral SFC. Column: Chiralcel OJ 250 x 4.6 mm; mobile phase: 15/0.4/84.6 methanol/diethylether/CO₂; flow rate: 5 mL/min; injection: 1 uL, 1 mg/mL in methanol; temperature 40°C; detection: UV 215 nm. [α]_D²⁵ = +22° (MeOH, *c*=0.4).

(S)-2-(5-Amino-1H-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester Prepared and purified as for the *R*-enantiomer to afford (223 mg, 81%) as a tan solid: mp 152°C; ¹H NMR (DMSO-d₆) δ 11.08 (br s, 1H), 7.45-7.34 (m, 2H), 7.27-7.19 (m, 1H), 6.88 (t, *J* = 8 Hz, 1H), 5.76 (s, 3H), 5.75 (s, 3H), 4.0-3.9 (m, 1H), 3.25-2.62 (m, 3H), 1.94 (s, 3H), 1.92 (m, 3H), 1.78-1.62 (m 4H), 1.36 (s, 9H); LRMS *m/z*: 394.2 (M+H);. Anal. (C₂₄H₃₁N₃O₂) C, H, N; enantiomeric purity 99.8% by Chiral SFC. Column: Chiralcel OJ 250 x 4.6 mm; mobile phase: 15/0.4/84.6 isopropanol/diethylether/CO₂; flow rate: 5 mL/min; injection: 1 uL, 1 mg/mL in methanol; temperature 40°C; detection: UV 215 nm. [α]_D²⁵ = +1.9° (MeOH, *c*=0.7).

(S)-2-(5-Amino-1H-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester [(S)-14]. Prepared and purified as for the *R*-enantiomer. mp 77°C; ¹H NMR (DMSO-d₆) δ 7.86 (br s, 1H), 7.15 (d, *J* = 12 Hz, 1H), 7.07-6.95 (m, 1H), 6.91 (s, 1H), 6.66 (d, *J* = 12 Hz, 1H), 4.11 (br s, 2H), 3.45-3.06 (m, 4 H), 2.62 (t, *J* = 16 Hz, 1H), 1.84-1.66 (m, 4H), 1.53 (s, 9H); LRMS *m/z*: 316.2 (M+H);. Anal. (C₁₈H₂₅N₃O₂ • 0.8 H₂O) C, H, N; enantiomeric purity 99.7% by chiral HPLC. Column: Chiralpak OD-R 250 x 4.6 mm; mobile phase: 55/45 0.1 N NaClO₄ buffer (pH= 6.91)/ACN; flow rate: 1 mL/min; injection: 5 uL, 1 mg/mL in ethanol; temperature 40°C; detection: UV 215 nm. [α]_D²⁵ = +14° (MeOH, *c* = 1.0).

(S)-N-(3-Pyrrolidin-2-ylmethyl-1H-indol-5-yl)-arylsulfonamide Array [(S)-15a-w]. This array was prepared essentially as for the *R*-enantiomers except starting with **(S)-14**

Compound	NH ₄ OH method ret. time (min)	NH ₄ OH method purity (%)	HCO ₂ H method ret. time (min)	HCO ₂ H method purity (%)	Formula	HRMS adduct	Calcd.	Found	Relative Intensity	Error (mAmu)
(R)-15-a	2.07	100	0.38	96	C.17.H.18.Br.1.N.3.O.2.S.2	M+H	440.00817	440.00966	89	-1.49
(R)-15-b	1.84	100	0.63	100	C.19.H.20.F.1.N.3.O.2.S.1	M+H	374.13261	374.13331	100	-0.7
(R)-15-c	2.19	100	0.74	100	C.19.H.20.F.1.N.3.O.2.S.1	M+H	374.13327	374.13331	94	-0.04
(R)-15-e	2.43	100	1.45	95	C.19.H.20.I.1.N.3.O.2.S.1	M+H	482.03929	482.03937	72	-0.08
(R)-15-f	2.21	95	1.08	100	C.19.H.20.Cl.1.N.3.O.2.S.1	M+H	390.10335	390.10376	100	-0.41
(R)-15-g	2.42	100	1.55	97	C.20.H.22.Cl.1.N.3.O.3.S.1	M+H	420.11286	420.11432	100	-1.46
(R)-15-h	2.14	97	0.596	100	C.20.H.23.N.3.O.2.S.1	M+H	370.15816	370.15838	100	-0.22
(R)-15-i	2.33	100	1.37	98	C.19.H.20.Cl.1.N.3.O.2.S.1	M+H	390.10345	390.10376	100	-0.31
(R)-15-j	2.43	98	1.455	97	C.19.H.19.Cl.2.N.3.O.2.S.1	M+H	424.06477	424.06478	100	-0.01
(R)-15-k	2.52	95	1.52	95	C.19.H.20.I.1.N.3.O.2.S.1	M+H	482.03879	482.03937	74	-0.58
(R)-15-l	2.42	100	0.69	100	C.19.H.21.N.3.O.2.S.1	M+H	356.14249	356.14273	100	-0.24
(R)-15-o	2.09	100	1.53	99	C.19.H.20.Br.1.N.3.O.2.S.1	M+H	434.05258	434.05324	78	-0.66
(R)-15-p	2.95	100	1.66	100	C.19.H.19.F.2.N.3.O.2.S.1	M+H	392.12386	392.12388	100	-0.02
(R)-15-s	1.84	100	0.69	100	C.19.H.20.Cl.1.N.3.O.2.S.1	M+H	390.10308	390.10376	100	-0.68
(R)-15-t	2.24	100	1.34	98	C.22.H.27.N.3.O.2.S.1	M+H	398.18975	398.18968	100	0.07
(R)-15-u	2.43	100	1.67	97	C.20.H.20.F.3.N.3.O.2.S.1	M+H	424.12945	424.13011	100	-0.66
(S)-15-f	2.18	100	1.37	100	C.19.H.20.Cl.1.N.3.O.2.S.1	M+H	390.10378	390.10376	100	0.02
(S)-15-h	2.11	95	0.46	100	C.19.H.20.F.1.N.3.O.2.S.1	M+H	374.13315	374.13331	100	-0.16
(S)-15-j	2.38	98	1.4	97	C.20.H.22.Cl.1.N.3.O.3.S.1	M+H	420.11372	420.11432	100	-0.6
(S)-15-m	2.28	95	0.46	100	C.20.H.23.N.3.O.3.S.1	M+H	386.15325	386.15329	100	-0.04
(S)-15-s	1.81	100	0.55	100	C.19.H.19.F.2.N.3.O.2.S.1	M+H	392.1235	392.12388	100	-0.38

NH₄OH method: solvent gradient = 95% A @ 0 min, 5% A @ 3.5 min, 5% A @ 5 min; solvent A = 0.05% NH₄OH in water; solvent B = 0.05% NH₄OH in ACN; flow rate 1 mL/min; column = Synergi MAX-RP 80A, 30 x 2 mm, 4 µM particle size; temperature 50°C. HCO₂H method: solvent gradient = 90% A @ 0 min, 5% A @ 3 min, 5% A @ 5 min; solvent A = 0.02% formic acid in water; solvent B = 0.02% formic acid in ACN; flow rate 1 mL/min; column = Xterra™ 30 x 2.1 mm MS C18, 3.5 µM particle size; temperature 50°C.

(*R*)-2-Chloro-N-(3-[[1-methyl-2-pyrrolidinyl]methyl]-1H-indol-5-yl)benzenesulfonamide [(*R*)-15c].

To a solution of (*R*)-14 (100 mg, 0.32 mmol) and triethylamine (88 μ L) in THF (2 mL) was added 2-chlorobenzenesulfonyl chloride (67 mg, 0.32 mmol). The reaction was stirred at r.t. for 1-2 hours then 4 N HCl (1 mL) was added and stirring at r.t. continued for 16 hours. The reaction was concentrated and the residue purified by flash chromatography on silica gel with 15% methanol (containing 10% ammonium hydroxide) in DCM to give (*R*)-15c as a tan solid (93 mg, 75 %): ^1H NMR (DMSO- d_6) δ 10.85 (s, 1H), 7.89 (dd, J = 8, 4 Hz, 1H), 7.64-7.50 (m, 2H), 7.39 (t, J = 4 Hz, 1H), 7.21-7.18 (m, 3H), 6.85 (dd, J = 8, 4 Hz, 1H), 5.32 (brs, 1H), 3.27-3.18 (m, 1H), 3.02-2.93 (m, 1H), 2.79 (dd, J = 14, 6 Hz, 2H), 2.64 (dd, J = 14, 8 Hz, 1H), 1.79-1.50 (m, 2H); LRMS m/z : 389.9 (M+H) $^+$; Anal. ($\text{C}_{19}\text{H}_{20}\text{ClN}_3\text{O}_2\text{S}\cdot 0.6 \text{ H}_2\text{O}$) C, H, N; enantiomeric purity 100% by chiral SFC. Column: Chiralpak AS-H 250 x 4.6 mm; mobile phase: 40% methanol, 0.4% diethylamine in CO_2 ; flow rate: 5 mL/min; injection: 5 μ L, 1 mg/mL in ethanol; temperature 40°C; detection: UV 215 nm. $[\alpha]^{25}_D = -19^\circ$ (MeOH, c = 0.5).

(*R*)-2-Iodo-N-(3-[[1-methyl-2-pyrrolidinyl]methyl]-1H-indol-5-yl)benzenesulfonamide [(*R*)-15e].

Following the procedure for (*R*)-15c, (*R*)-15e was obtained as a tan solid (90 mg, 58 %): ^1H NMR (CD_3OD) δ 10.75 (s, 1H), 8.07 (dd, J = 7.8, 2 Hz, 1H), 7.93 (dd, J = 7.8, 1.5 Hz, 1H), 7.45 (dt, J = 7.1, 2 Hz, 1H), 7.26 - 7.07 (m, 3H), 6.83 (dd, J = 8.5, 2 Hz, 1H), 3.18 - 3.01 (m, 1H), 2.96 - 2.89 (m, 1H), 2.78 - 2.66 (m, 3H), 2.62 - 2.52 (m, 1H), 1.76 - 1.52 (m, 3H), 1.28 - 1.13 (m, 1H); LRMS m/z : 482.1 (M+H) $^+$; Calcd for $\text{C}_{19}\text{H}_{20}\text{IN}_3\text{O}_2\text{S}\cdot 0.3 \text{ H}_2\text{O}$: C, 46.48; H, 4.23, N, 8.56. Found: C, 46.40; H, 4.06; N, 8.28; enantiomeric purity 100% by chiral SFC. Column: Chiralpak AS-H 250 x 4.6 mm; mobile phase: 40% methanol, 0.4% diethylamine in CO_2 ; flow rate: 5 mL/min; injection: 5 μ L, 1 mg/mL in ethanol; temperature 40°C; detection: UV 215 nm. $[\alpha]^{25}_D = -11^\circ$ (MeOH, c = 0.2).

Elemental Analyses for Target Compounds.

Compound	Name	Formula	Calcd.			Found		
			C	H	N	C	H	N
(R)-13c	(R)-2-chloro-N-(3-((2R)-1-methyl-2-pyrrolidinyl)methyl)-1H-indol-5-yl)benzenesulfonamide	C ₂₀ H ₂₂ ClN ₃ O ₂ S•0.5 H ₂ O	57.20	5.52	10.01	57.03	5.54	9.74
(R)-13f	(R)-3-chloro-N-(3-((2R)-1-methyl-2-pyrrolidinyl)methyl)-1H-indol-5-yl)benzenesulfonamide	C ₂₀ H ₂₂ ClN ₃ O ₂ S•2.3 H ₂ O	50.29	5.61	8.80	50.38	5.55	8.54
(R)-14	(R)-2-[5-(2,5-dimethyl-pyrrol-1-yl)-1H-indol-3-ylmethyl]-pyrrolidine-1-carboxylic acid benzyl ester	C ₂₇ H ₂₉ N ₃ O ₂ •0.2 H ₂ O	74.73	6.83	9.68	74.53	6.94	9.59
	(R)-2-(5-amino-1H-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester	C ₂₄ H ₃₁ N ₃ O ₂ •0.1 H ₂ O	72.66	7.93	10.59	72.56	8.22	10.46
	(R)-2-(5-Amino-1H-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester	C ₁₈ H ₂₃ N ₃ O ₂ •1.0 H ₂ O	62.22	7.83	12.09	62.85	7.51	12.14
	(S)-2-[5-(2,5-Dimethyl-pyrrol-1-yl)-1H-indol-3-ylmethyl]-pyrrolidine-1-carboxylic acid benzyl ester	C ₂₇ H ₂₉ N ₃ O ₂ •0.3 H ₂ O	74.18	6.83	9.61	74.28	6.84	9.31
	(S)-2-(5-Amino-1H-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester	C ₂₄ H ₃₁ N ₃ O ₂	73.25	7.94	10.68	73.13	8.34	10.46
(S)-14	(S)-2-(5-Amino-1H-indol-3-ylmethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester	C ₁₈ H ₂₃ N ₃ O ₂ •0.8 H ₂ O	63.39	7.86	12.32	63.56	7.53	12.24
(R)-15c	(R)-2-Chloro-N-(3-([1-methyl-2-pyrrolidinyl)methyl]-1H-indol-5-yl)benzenesulfonamide	C ₁₉ H ₂₀ ClN ₃ O ₂ S•0.6 H ₂ O	55.78	5.22	10.27	56.16	5.24	9.93
(R)-15e	(R)-2-Iodo-N-(3-([1-methyl-2-pyrrolidinyl)methyl]-1H-indol-5-yl)benzenesulfonamide	C ₁₉ H ₂₀ IN ₃ O ₂ S•0.3 H ₂ O	46.48	4.23	8.56	46.40	4.06	8.28

Binding Affinity for 5-HT₆ Receptor Antagonists against Serotonin and Dopamine Receptors Ki (nM)

Receptor	(S)-13d	(S)-13j	(S)-13r
5-HT ₆	5 ± 1	9 ± 1	2.0 ± 0.2
5-HT _{1B}	48% ^a	40 ± 3	41% ^a
5-HT _{1D}	37% ^a	7.3 ± 1	41% ^a
5-HT _{1F}	47% ^a	80% ^a	56% ^a
5-HT ₇	20% ^a	42% ^a	32% ^a

Receptors were all human clones stably expressed in CHO cells. Radioligands were as follows: 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1F}; [³H]-5-HT; 5-HT₆, 5-HT₇; [³H]LSD. Ki values were determined in triplicate except ^a % inhibition at 1000 nM.

