Synthesis and Biological Evaluation of Benzodioxanyl-Piperazine Derivatives as Potent Serotonin 5-HT_{1A} Antagonists: The Discovery of Lecozotan

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Supporting Information

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Experimental Section

Melting Points were determined on a Thomas-Hoover capillary or an Electrothermal melting point apparatus and are uncorrected. 1H-NMR spectra were recorded on a Varian Unity Plus 400 spectrometer using the residual DMSO signal at 2.49 parts per million (ppm) as an internal standard. The chemical shifts are reported in ppm downfield from zero, and coupling constants are reported in hertz (Hz). Solvate, hydrate and HCl protons are not included. Mass spectra were recorded on either a Hewlett-Packard 5995A, a Finnigan Trace MS or a Micromass LCT spectrometer. The infared spectra were recorded on a Perkin-Elmer 784 spectrometer. C,H,N combustion analyses were determined on either a Perkin-Elmer 2400 analyzer or were performed by Robertson Microlit (Madison, NJ). All analyzed compounds are within ±0.4% of the theoretical value unless otherwise indicated. Optical rotations were measured using a Perkin-Elmer 241-MC polarimeter. Acid chloride reagents, anhydrous potassium carbonate, anhydrous magnesium sulfate and 1N HCl/diethyl ether solution were purchased from Aldrich. Reaction solvents (acetonitrile, dichloromethane, ethyl acetate, hexane) were purchased from Aldrich packaged in Sure/Seal™ bottles. Solvents for extraction and chromatography (dichloromethane, ethyl acetate) were HPLC-grade OmniSolv® reagents purchased from EM Science. All reagents and solvents were used without further purification. Column chromatography was performed on Fisher basic alumina, activity I (60 – 325 mesh). Analytical high pressure liquid chromatography (HPLC) was performed on a Prodigy ODS 3 150, 4.6 mm i.d. column using a 0.2% trifluoroacetic acid/water/acetonitrile gradient with a flow rate of 1 mL/minute and UV detection at 215 nanometers. Chiral HPLC was performed on a Chiracel AD, 0.46 x 25 cm column using an isocratic solvent system consisting of 85:15 acetonitrile/water containing 0.1% diethylamine with a flow rate of 1 mL/minute and UV detection at 254 and 280 nanometers.

{(R)-2-[4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-pyridin-2-ylamine (9)

A solution of (S)-4,5-dihydro-5-methyl-3-(2-pyridyl)-3H-[1,2,3]-oxathiazole-2,2-dioxide[1] (**6**, 2.6 g, 12.1 mmol) and 1-(2,3-dihydro-1,4-benzodioxan-5-yl)piperazine[2] (**8**, 2.7 g, 12.1 mmol) in acetonitrile (100mL) was treated with anhydrous potassium carbonate (100 mg). The resulting suspension was stirred at 55-60^{o}C for 72 hours, during which time a precipitate formed. The resulting reaction mixture was cooled to room temperature and filtered to remove the precipitate (unreacted piperazine starting material). The filtrate was concentrated on a rotary evaporator and the residue was dissolved in 2N aqueous HCl (100 mL) and stirred at 50^{o}C for 6 hours. The reaction was then cooled to room temperature and neutralized with 2N aqueous sodium hydroxide. The aqueous mixture was extracted with dichloromethane (3 x 50 mL). The

combined organic layers were washed with water followed by brine and then dried over anhydrous magnesium sulfate. Concentration of the dried extracts yielded a brown oil (4.5 g) which was purified by column chromatography on basic alumina (eluted with ethyl acetate) to give the desired product **9** as a colorless oil which hardened under vacuum (3.3 g, 77%). The purity of **9** was determined to be 98.5% by analytical HPLC and was used in subsequent reactions without further purification.

Compound **9** was characterized as its hydrochloride salt, prepared by treating a portion of the material described above in ethyl acetate with an excess of 1N HCl in diethyl ether to give the dihydrochloride salt **9a**: mp 168-170 ^{o}C (softens at 135 ^{o}C); ^{1}H NMR (DMSO-*d6*) δ 7.88 (d, J = 5.5 Hz), 7.84 (m, 1H), 7.10 (m, 1H), 6.85 (m, 1H), 6.73 (t, J = 8.2 Hz, 1H), 6.54 (dd, J1 = 8.2 Hz, J2 = 1.2 Hz, 1H), 6.51 (dd, J1 = 12.5 Hz, J2 = 1.2 Hz, 1H), 4.20 (m, 4H), 3.92 (m, 1H), 3.65 (m, 2H), 3.50 – 3.10 (m, 8H), 1.37 (d, J = 6.2 Hz, 3H); MS (m/z) 355 ($M+1^{+}$); [α]D(25) = -20 (c=1, MeOH); Anal. ($C_{20}H_{26}N_4O_2$•2HCl•1.5H_2O) C, H, N.

{(S)-2-[4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-pyridin-2-ylamine (10)

Using an identical procedure described for the synthesis of compound **9**, (R)-4,5-dihydro-5-methyl-3-(2-pyridyl)-3H-[1,2,3]-oxathiazole-2,2-dioxide[1] (**7**, 1.33 g, 6.2 mmol) and 1-(2,3-dihydro-1,4-benzodioxan-5-yl)piperazine[2] (**8**, 1.36 g, 6.2 mmol) were converted to the desired {(S)-2-[4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-pyridin-2-ylamine **10** (1.54 g, 70% yield) which was determined to be 99% pure by analytical HPLC and was used in subsequent reactions without further purification. The compound was characterized as its dihydrochloride salt **10a**: mp 169-171 ^{o}C (softens at 135 ^{o}C); ^{1}H NMR (DMSO-*d6*) δ 7.86 (d, J = 5.6 Hz), 7.85 (m, 1H), 7.09 (m, 1H), 6.86 (m, 1H), 6.76 (t, J = 8.0 Hz, 1H), 6.54 (dd, J1 = 8.0 Hz, J2 = 1.1 Hz, 1H), 6.53 (dd, J1 = 12.4 Hz, J2 = 1.1 Hz, 1H), 4.17 (m, 4H), 3.93 (m, 1H), 3.64 (m, 2H), 3.55 – 3.09 (m, 8H), 1.35 (d, J = 6.0 Hz, 3H); MS (m/z) 355 ($M+1^{+}$); [α]D(25) = +20.4 (c=1, MeOH); Anal. ($C_{20}H_{26}N_4O_2$•2HCl•H_2O) C, H, N.

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[1]Brightwell, C.I.; Shepherd, R.G. Novel Processes and Intermediates for the Preparation of Piperazine Derivatives. PCT Application WO 9533725, published 12/14/95.

[2]Hartog, J.; Wouters, W.; vanWijngaarden, I. Blood Pressure-Lowering Piperazine Derivatives. EP 138280 B1, application published 4/24/85.

4-Chloro-N-{(2R)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (11a)

A solution of {(R)-2-[4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-pyridin-2-ylamine **9** (0.268 g, 0.76 mmol) in dichloromethane (1 mL) was treated at 0^{o}C with the dropwise addition of a dichloromethane solution of 4-chlorobenzoyl chloride (0.132 g, 0.268 mmol in 1 mL). The resulting mixture was allowed to come up to room temperature. After stirring for 16 hours the mixture was diluted with 3 mL of ethyl acetate followed by hexane. A white solid precipitated, which was collected by vacuum filtration, washed with hexane and dried under vacuum to yield the desired product **11a** as its monohydrochloride salt (0.33 g, 83%): mp 125-126^{o}C; ^{1}H NMR (DMSO-*d6*) δ 8.48 (d, J = 4.8 Hz, 1H), 7.70 (dt, J1 = 7.9 Hz, J2 = 1.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.26 (t, J1 = 6.8 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 8.1 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 4.44 (dd, J1 = 14.1 Hz, J2 = 5.1 Hz, 1H), 4.34 (dd, J1 = 14.8 Hz, J2 = 7.0 Hz, 1H), 4.24 (m, 4H), 3.76 (m, 1H), 3.69 (m, 1H), 3.58 (d, J = 12.1 Hz, 2H), 3.38 (m, 1H), 3.33 (q, J = 11.8 Hz, 2H), 3.10 (t, J = 11.9 Hz, 2H), 1.35 (d, J = 6.6 Hz, 3H); IR (KBr) 1655 cm-1 (C=O); MS 493 (*m/z*); [□]D(25) = +53.3 (c=1, methanol),), ee > 99.9% by chiral HPLC; Anal. ($C_{27}H_{29}ClN_4O_3$□HCl□1.25H_2O) C, H, N (N: calcd. 10.15, found 9.52).

4-(Trifluoromethyl)-N-{(2R)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (11b)

Using a procedure similar to that described for the synthesis of **11a**, a solution of intermediate **9** (0.14 g, 0.39 mmol) in dichloromethane (2.5 mL) was treated with 4-(trifluoromethyl)benzoyl chloride (0.082 g, 0.39 mmol in 1 mL) to yield the desired product **11b** as its white monohydrochloride salt (0.195 g, 89%): mp 150-153^{o}C; ^{1}H NMR (DMSO-*d6*) δ 8.43 (d, J = 4.0 Hz, 1H), 7.67 (dt, J = 7.6 Hz, J2 = 1.7 Hz, 1H), 7.62 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.23 (t, J1 = 7.1 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 6.74 (t, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H) 4.36 (m, 2H), 4.21 (m, 4H), 3.75 (m, 1H) 3.65 (m, 1H), 3.55 (d, J = 11.5 Hz, 2H), 3.35 (m, 1H), 3.29 (m, 2H), 3.06 (m, 2H), 1.33 (d, J = 6.3 Hz, 3H); IR

(ATR) 1655 cm-1 (C=O); MS 527 (*m/z*); [α]D(25) = +45.8 (c=1, methanol),), ee > 99.9% by chiral HPLC; Anal. ($C_{28}H_{29}F_3N_4O_3$•HCl•H_2O) C, H, N.

4-Cyano-N-{(2R)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (11c)

Using a procedure similar to that described for the synthesis of **11a**, a solution of intermediate **9** (0.846 g, 2.38 mmol) in dichloromethane (20 mL) was treated at 0°C with the dropwise addition of a dichloromethane solution of 4-cyanobenzoyl chloride (1.1 equivalents, 2.63 mmol in 5 mL). After stirring for 16 hours the mixture was poured into hexane (100 mL) to precipitate the desired product **11c** as its white monohydrochloride salt (1.2 g, 97% yield): mp 239-240°C; ^{1}H NMR (DMSO-*d6*) δ 8.42 (d, J = 4.9 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.70 (dt, J = 7.9 Hz, J2 = 2.0 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.25 (dt, J1 = 6.1 Hz, J2 = 2.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.76 (t, J = 8.1 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 4.46 (dd, J1 = 14.6 Hz, J2 = 4.9 Hz, 1H), 4.36 (dd, J1 = 14.2 Hz, J2 = 7.6 Hz, 1H), 4.23 (m, 4H), 3.72 (m, 1H), 3.55 (m, 1H), 3.55 (m, 2H), 3.38 (m, 1H), 3.31 (q, J = 11.4 Hz, 2H), 3.16 (t, J = 11.5, 2H), 1.36 (d, J = 6.6 Hz, 3H); IR (ATR) 2225 cm-1 (C≡N), 1655 cm-1 (C=O); MS 484 (*m/z*); [α]D(25) = +56.0 (c=0.6, methanol),), ee > 99.9% by chiral HPLC; Anal. ($C_{28}H_{29}N_5O_3$•HCl) C, H, N.

4-Nitro-N-{(2R)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (11d)

Using a procedure similar to that described for the synthesis of **11a**, a solution of intermediate **9** (0.16 g, 0.39 mmol) in dichloromethane (3 mL) was treated with 4-nitrobenzoyl chloride (0.084 g, 0.39 mmol in 1 mL) to yield the desired product **11d** as its yellow monohydrochloride salt (0.195 g, 89%): mp 157-159°C; ^{1}H NMR (DMSO-*d6*) δ 8.41 (d, J = 4.2 Hz, 1H), 8.08 (d, J = 8.8 Hz, 2H), 7.67 (dt, J = 7.6 Hz, J2 = 1.7 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.23 (dt, J1 = 6.0, Hz, J2 = 1.8 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.74 (t, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 4.37 (m, 2H), 4.20 (m, 4H), 3.73 (m, 1H), 3.64 (m, 1H), 3.55 (d, J = 11.1 Hz, 2H), 3.39 (m, 1H), 3.28 (m, 2H), 3.08 (m, 2H), 1.33 (d, J = 6.1 Hz, 3H); IR (ATR) 1655 cm-1 (C=O); MS (*m/z*) 504 ($M+1^+$); [α]D(25) = +59.0 (c=1, methanol),), ee > 99.9% by chiral HPLC; Anal. ($C_{27}H_{29}N_5O_5$•HCl•1.25 H_2O) C, H, N.

4-Chloro-N-{(2S)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (12a)

Using a procedure similar to that described for the synthesis of **11a**, a solution of intermediate **10** (0.10 g, 0.28 mmol) in dichloromethane (0.5 mL) was treated with the dropwise addition of a dichloromethane solution of 4-chlorobenzoyl chloride (0.054 g, 0.31 mmol in 0.5 mL) to yield the desired product **12a** as its white monohydrochloride salt (0.14 g, 93%): mp 127-128^{o}C; ^{1}H NMR (DMSO-*d6*) δ 8.49 (d, J = 4.9 Hz, 1H), 7.70 (dt, J1 = 7.8 Hz, J2 = 1.9 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.26 (t, J1 = 6.8 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 8.0 Hz, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.41 (dd, J1 = 13.9 Hz, J2 = 5.0 Hz, 1H), 4.34 (dd, J1 = 14.5 Hz, J2 = 7.1 Hz, 1H), 4.27 (m, 4H), 3.80 (m, 1H), 3.70 (m, 1H), 3.60 (d, J = 12.0 Hz, 2H), 3.40 (m, 1H), 3.31 (q, J = 12.0 Hz, 2H), 3.13 (t, J = 11.8 Hz, 2H), 1.38 (d, J = 6.4 Hz, 3H); IR (KBr) 1655 cm-1 (C=O); MS 493 (*m/z*); [α]D(25) = -54.4 (c=1, methanol), ee > 99.9% by chiral HPLC; Anal. ($C_{27}H_{29}ClN_4O_3$•HCl•H_2O) C, H, N.

4-(Trifluoromethyl)-N-{(2S)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (12b)

Using a procedure similar to that described for the synthesis of **11b**, a solution of intermediate **10** (0.10 g, 0.28 mmol) in dichloromethane (0.5 mL) was treated with the dropwise addition of a dichloromethane solution of 4-(trifluoromethyl)benzoyl chloride (0.065 g, 0.31 mmol in 0.5 mL) to yield the desired product **12b** as its white monohydrochloride salt (0.15 g, 95%): mp 152-154^{o}C; ^{1}H(DMSO-*d6*) δ 8.44 (d, J = 4.1 Hz, 1H), 7.68 (dt, J = 7.5 Hz, J2 = 1.7 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.25 (t, J1 = 7.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.80 (t, J = 8.0 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 6.59 (d, J = 8.1 Hz, 1H) 4.42 (m, 2H), 4.23 (m, 4H), 3.79 (m, 1H) 3.70 (m, 1H), 3.60 (d, J = 11.4 Hz, 2H), 3.37 (m, 1H), 3.30 (m, 2H), 3.08 (m, 2H), 1.40 (d, J = 6.4 Hz, 3H); IR (KBr) 1655 cm-1 (C=O); MS 527 (*m/z*); [α]D(25) = -45.3 (c=1, methanol), ee > 99.9% by chiral HPLC; Anal. ($C_{28}H_{29}F_3N_4O_3$•HCl•0.5H_2O) C, H, N (N: calc. 9.72, found 9.28).

4-Cyano-N-{(2S)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (12c)

Using a procedure similar to that described for the synthesis of **11c**, a solution of intermediate **10** (0.78 g, 2.20 mmol) in dichloromethane (5 mL) was treated at 0^{o}C with the dropwise addition of a dichloromethane solution of 4-cyanobenzoyl chloride (0.40 g, 2.42 mmol in 0.5 mL). The

desired product **12c** was obtained as its white monohydrochloride salt (0.95 g, 83% yield): mp 237-239°C; ^{1}H NMR (DMSO-*d6*) δ 8.41 (d, J = 5.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.69 (dt, J = 7.7 Hz, J2 = 1.9 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.23 (dt, J1 = 6.3 Hz, J2 = 1.9 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.77 (t, J = 8.0 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 4.40 (dd, J1 = 14.3 Hz, J2 = 4.8 Hz, 1H), 4.34 (dd, J1 = 14.0 Hz, J2 = 7.5 Hz, 1H), 4.21 (m, 4H), 3.75 (m, 1H), 3.62 (m, 1H), 3.53 (m, 2H), 3.38 (m, 1H), 3.30 (q, J = 11.6 Hz, 2H), 3.10 (t, J = 11.5, 2H), 1.32 (d, J = 6.6 Hz, 3H); IR (ATR) 2225 cm-1 (C≡N), 1655 cm-1 (C=O); MS 484 (*m/z*); [α]D(25) = -55.7 (c=0.6, methanol),), ee > 99.9% by chiral HPLC; Anal. ($C_{28}H_{29}N_5O_3$•HCl) C, H, N.

4-Nitro-N-{(2S)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride (12d)

Using a procedure similar to that described for the synthesis of **11d**, a solution of intermediate **10** (0.10 g, 0.28 mmol) in dichloromethane (0.5 mL) was treated with 4-nitrobenzoylchloride (0.056 g, 0.31 mmol in 0.5 mL) to yield the desired product **12d** as its yellow monohydrochloride salt (0.147 g, 97%): mp 156-158°C; ^{1}H NMR (DMSO-*d6*) δ 8.46 (d, J = 4.2 Hz, 1H), 8.13 (d, J = 8.9 Hz, 2H), 7.71 (dt, J = 7.5 Hz, J2 = 1.8 Hz, 1H), 7.55 (d, J = 8.9 Hz, 2H), 7.30 (dt, J1 = 6.1, Hz, J2 = 1.9 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 6.80 (t, J = 8.2 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 4.45 (m, 2H), 4.40 (m, 4H), 3.79 (m, 1H), 3.70 (m, 1H), 3.60 (d, J = 11.1 Hz, 2H), 3.341 (m, 1H), 3.31 (m, 2H), 3.15 (m, 2H), 1.39 (d, J = 6.0 Hz, 3H); IR (ATR) 1655 cm-1 (C=O); MS (*m/z*) 504 ($M+1^+$); [α]D(25) = -59.0 (c=1, methanol),), ee > 99.9% by chiral HPLC; Anal. ($C_{27}H_{29}N_5O_5$•HCl•1.5 H_2O) C, H, N.

Elemental Analyses for Compounds 9, 10, 11a – 11d and 12a – 12d

Compound	Formula	Calculated	Found
9a	$C_{20}H_{26}N_4O_2 \bullet 2HCl \bullet 1.5\ H_2O$	C 52.87 H 6.88 N 12.33	C 53.05 H 7.01 N 12.25
10a	$C_{20}H_{26}N_4O_2 \bullet 2HCl \bullet H_2O$	C 53.94 H 6.79 N 12.58	C 53.77 H 6.90 N 12.22
11a	$C_{27}H_{29}ClN_4O_3 \bullet HCl \bullet 1.25\ H_2O$	C 58.75 H 5.93 N 10.15	C 58.48 H 5.59 N 9.52
11b	$C_{28}H_{29}F_3N_4O_3 \bullet HCl \bullet H_2O$	C 57.90 H 5.55 N 9.64	C 58.30 H 5.53 N 9.52
11c	$C_{28}H_{29}N_5O_3 \bullet HCl$	C 64.67 H 5.81 N 13.47	C 64.69 H 5.93 N 13.52
11d	$C_{27}H_{29}N_5O_5 \bullet HCl \bullet 1.25\ H_2O$	C 57.65 H 5.82 N 12.45	C 57.53 H 5.70 N 12.05
12a	$C_{27}H_{29}ClN_4O_3 \bullet HCl \bullet H_2O$	C 59.23 H 5.89 N 10.23	C 59.35 H 5.58 N 9.91
12b	$C_{28}H_{29}F_3N_4O_3 \bullet HCl \bullet 0.5\ H_2O$	C 58.33 H 5.51 N 9.72	C 58.37 H 5.78 N 9.28
12c	$C_{28}H_{29}N_5O_3 \bullet HCl \bullet H_2O$	C 62.51 H 5.99 N 13.02	C 62.28 H 6.19 N 12.90
12d	$C_{27}H_{29}N_5O_5 \bullet HCl \bullet 1.5\ H_2O$	C 57.19 H 5.87 N 12.35	C 56.97 H 5.87 N 12.35

Effect of 5-HT_{1A} Agonist 8-OH-DPAT on Response Rate in Fixed Ratio Responding; Reversal of Agonist Effect by 5-HT_{1A} Antagonists – Raw Data for Figure 3

	Response Rate (responses/second)		
Test Compound	Control (Vehicle)	8-OH-DPAT[b]	8-OH-DPAT[b] + Test Compound[c]
WAY-100635 (0.3 mg/kg sc)	2.7 ± 0.3[a]	0.6 ± 0.2[a]	2.5 ± 0.6[a]
11c (1 mg/kg sc)	2.4 ± 0.5[a]	0.5 ± 0.2[a]	2.5 ± 0.2[a]

[a]Standard Error of the Mean. [g]0.3 mg/kg sc. [c]Given 30 minutes prior to administration of 8-OH-DPAT.

Selectivity Data for SRA-333 (compound 11c)*

	h5-HT_{1A}	Alpha-1	D2	D3	D4
Ki, nM	1.6	248	1,548	320	98

***Receptor Binding Assay Conditions**

Receptor	Radioligand	Blank (nonspecific)	Incubation Conditions
5-HT_{1A}	^{3}H-8-OH-DPAT	10 μM serotonin	25°C, 30 minutes
Alpha-1	^{3}H-prazosin	10 μM phentolamine	25°C, 30 minutes
D2	^{3}H-spiperone	10 μM d-butaclamol	25°C, 120 minutes
D3	^{3}H-spiperone	10 μM 7-OH-DPAT	25°C, 120 minutes
D4	^{3}H-spiperone	10 μM clozapine	25°C, 120 minutes

Other Receptors for which Compound 11c has > 100-fold selectivity (NovaScreen®)

Receptor	Radioligand
Adenosine Transporter	^{3}H-NBTI
Adenosine A1	^{3}H-CPX
Adenosine A2	^{3}H-CGS-21680
h-Adenosine A3*	^{125}I-ABMECA
Adrenergic Alpha 1B	^{3}H-7-OMe-prazosin
Adrenergic Alpha 2A	^{3}H-MK-912
Adrenergic Adrenergic 2B	^{3}H-MK-912
Adrenergic Alpha 2C	^{3}H-MK-912
Adrenergic Beta 1	^{125}I-Iodo-cyanopindolol
Adrenergic Beta 2	^{125}I-Iodo-cyanopindolol
Benzodiazepine, Peripheral	^{3}H-PK-11195
Dopamine Transporter	^{3}H-WIN-35428
Dopamine D1*	^{3}H-SCH23390
Dopamine D5*	^{3}H-SCH23390

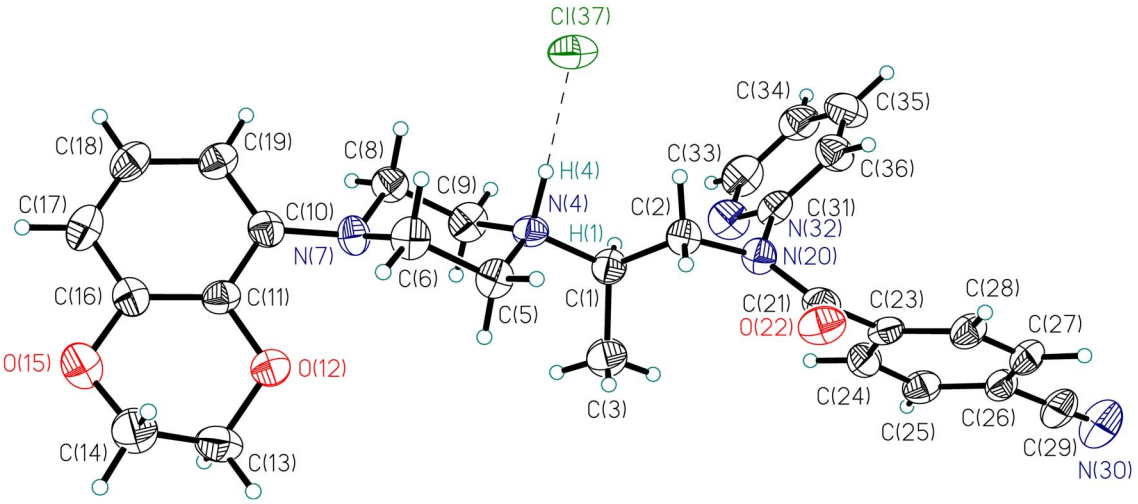
Receptor	Radioligand
Muscarinic, M2*	^{3}H-N-Me-Scopolamine
Muscarinic M3*	^{3}H-N-Me-Scopolamine
Muscarinic M4*	^{3}H-N-Me-Scopolamine
Muscarinic M5*	^{3}H-N-Me-Scopolamine
Nicotinic	^{3}H-Epibatidine
Norepinephrine Transporter	^{3}H-Nisoxetine
Opiate, Delta 1	^{3}H-DPDPE
Opiate, Delta 2*	^{3}H-Naltrindole
Opiate, Kappa*	^{3}H-Diprenorphine
Opiate,Mu*	^{3}H-Diprenorphine
Serotonin Transporter	^{3}H-N-Methylcitalopram
5-HT1B	^{125}I-(-)-Iodo-cyanpindol
5-HT1D	^{3}H-5-CT
h5-HT2A	^{3}H-Ketanserin

Receptor	Radioligand
GABA A, Agonist Site	^{3}H-GABA
GABA A, Bz, Central	^{3}H-Flunitrazepam
Glutamate, AMPA	^{3}H-AMPA
Glutamate, Kainate	^{3}H-Kainic Acid
Glutamate, NMDA	^{3}H-CGP-39653
Glutamate, Stry-insensitive glycine site on NMDA Receptor	^{3}H-MDL-105519
Glycine, Stry-sensitive	^{3}H-Strychnine
Histamine H1	^{3}H-Pyrilamine
Histamine H2	^{3}H-Tiotidine
Histamine H3	^{3}H-N-a-Methylhistamine
Imidazoline, I2, Central	^{3}H-2-BFI
Melatonin	^{125}I-2-Iodomelatonin
Muscarinic M1*	^{3}H-N-Me-Scopolamine

Receptor	RAdioligand
5-HT2C	^{3}H-Mesulergine
5-HT3	^{3}H-GR-65630
5-HT4	^{3}H-GR-113808
h5-HT5A*	^{3}H-LSD
h5-HT6*	^{3}H-LSD
h5-HT7*	^{3}H-LSD
Sigma 1	^{3}H-(+)-Pentazocine
Sigma 2	^{3}H-DTG
Glutamate, MK-801	^{3}H-MK-801
Glutamate, PCP	^{3}H-TCP
K-Channel, ATP-Sensitive	^{3}H-Glibenclamide
Na Channel, Site 2	^{3}H-20-a-Benzobatrachotoxin

***recombinant enzyme**

Crystal Data for Compound 11c (Monohydrochloride Salt)



CRYSTAL DATA: $C_{28}H_{30}ClN_5O_3$**.** Colorless needles from ethanol/hexanes.

EXPERIMENTAL: A colorless needle cut to 0.05 mm x 0.10 mm x 0.22 mm in size was mounted on a glass fiber with silicone grease and transferred to a Nonius KappaCCD diffractometer equipped with an MSC X-stream cryosystem and molybdenum Kalpha radiation (lambda = 0.71073 Angstroms). Six hundred frames of data were collected at 200(2) K with an omega oscillation range of 0.5 degree/frame, and an exposure time of 240 seconds/degree.[1] A total of 10,607 reflections (theta maximum = 22.50 degrees) were indexed, integrated and corrected for Lorentz an polarization effects using DENZO-SMN and SCALEPACK.[2] A Gaussian Face-Indexed absorption correction was then applied using SHELXTL[3] to give 3416 unique reflections (Rint = 0.0844) of which 2933 had I > 2sigma(I). The minimum and maximum transmission factors were 0.98135 and 0.99183, respectively. Postrefinement of the unit cell parameters gave a = 8.4682(4) Angstroms, b = 9.2948(3) Angstroms, c = 33.2986(15) Angstroms, alpha = beta = gamma = 90 degrees, and V = 2620.9(2) cubic Angstroms. Axial photographs and systematic absences were consistent with the compound having crystallized in the orthorhombic space group P2(1)2(1)2(1) (No. 19). The observed mean |E*E-1| value was 0.777 (versus the expectation values of 0.968 and 0.736 for centric and noncentric data, respectively).

The structure was solved by direct methods and refined by full-matrix least-squares on F^2^ using SHELXTL.[3] The coordinates and anisotropic displacement coefficients for the nonhydrogen atoms were free to vary. The coordinates for the piperazinium hydrogen H(4) were also refined, while those for the remaining hydrogens were allowed to ride on their respective carbons. The hydrogen atoms were assigned isotropic displacement coefficients U(H) = 1.2U(C), 1.5U(Cmethyl) or 1.5U(N), and the weighting scheme employed was w = 1/[\s^2^(Fo^2^) + (0.0209P)^2^ + 0.5003P] where P = (Fo^2^ + 2Fc^2^)/3. The refinement converged to R(F) = 0.0518, wR(F^2^) = 0.0944, and S = 1.118 for 2933 reflections with I >

2sigma(I), and R(F) = 0.0665, wR(F^2^) = 0.1027, and S = 1.118 for 3416 unique reflections and 338 parameters.[4] The maximum |delta/sigma| in the final cycle of least-squares was less than 0.001, and the residual peaks on the final difference-Fourier map ranged from -0.178 to 0.234 electrons/cubic Angstroms. Scattering factors were taken from the International Tables for Crystallography, Volume C.[5,6]

The Flack parameter refined to -0.11(10) [versus the expectation values of 0 for the correct hand and 1 for the wrong hand] indicating that the hand of the molecule can be unequivocally assigned as (1R).[7]

For comparison, a refinement of the inverted molecule having the wrong absolute structure, i.e., (1S), gave R(F) = 0.0526, wR(F^2^) = 0.0972, and S = 1.114 for 2933 reflections with I > 2sigma(I), and R(F) = 0.0673, wR(F^2^) = 0.1057, and S = 1.113 for 3416 unique reflections and 338 parameters. The Flack parameter based on the wrong absolute structure was 1.10(10).

Table 1. Crystal data and structure refinement for Compound **11c**

Name:	4-Cyano-N-{(2R)-2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide Hydrochloride
Empirical formula	C28 H30 Cl N5 O3
Formula weight	520.02
Temperature	200(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic,2(1)2(1)2(1) (No. 19)
Unit cell dimensions	a = 8.4682(4) A alpha = 90 deg. b = 9.2948(3) A beta = 90 deg. c = 33.2986(15) A gamma = 90 deg.
Volume	2620.9(2) A^3
Z, Calculated density	4, 1.318 Mg/m^3
Absorption coefficient	0.185 mm^-1
F(000)	1096

Crystal size	0.22 x 0.10 x 0.05 mm
Theta range for data collection	1.22 to 22.50 deg.
Limiting indices	-9<=h<=9, -9<=k<=10, -29<=l<=35
Reflections collected / unique	10607 / 3416 [R(int) = 0.0844]
Completeness to theta = 22.50	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	0.99183 and 0.98135
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3416 / 0 / 338
Goodness-of-fit on F^2	1.118
Final R indices [I>2sigma(I)]	R1 = 0.0518, wR2 = 0.0944
R indices (all data)	R1 = 0.0665, wR2 = 0.1027
Absolute structure parameter	-0.11(10)
Largest diff. peak and hole	0.234 and -0.178 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for Compound **11c**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	8258(4)	4692(4)	2633(1)	34(1)
C(2)	7791(4)	3693(4)	2975(1)	34(1)
C(3)	9883(5)	4351(5)	2465(1)	56(1)
N(4)	6971(3)	4691(3)	2316(1)	31(1)
C(5)	7069(5)	3446(4)	2027(1)	37(1)
C(6)	5757(5)	3552(4)	1716(1)	40(1)
N(7)	5860(3)	4934(3)	1507(1)	33(1)
C(8)	5610(5)	6114(4)	1789(1)	36(1)
C(9)	6918(5)	6098(4)	2094(1)	38(1)
C(10)	5156(4)	5038(4)	1126(1)	33(1)
C(11)	5794(4)	4247(4)	806(1)	32(1)
O(12)	7076(3)	3355(3)	893(1)	41(1)
C(13)	7949(5)	2988(4)	543(1)	46(1)
C(14)	6888(5)	2512(4)	214(1)	49(1)
O(15)	5830(3)	3646(3)	98(1)	48(1)
C(16)	5214(5)	4387(4)	420(1)	34(1)
C(17)	3987(5)	5351(4)	339(1)	42(1)
C(18)	3353(5)	6136(4)	653(1)	41(1)
C(19)	3893(4)	5976(4)	1040(1)	36(1)
N(20)	8844(4)	3913(3)	3323(1)	34(1)
C(21)	9699(5)	2764(5)	3474(1)	37(1)
O(22)	9484(3)	1522(3)	3353(1)	43(1)
C(23)	10938(4)	3101(4)	3778(1)	31(1)
C(24)	11977(5)	4239(4)	3719(1)	38(1)
C(25)	13174(5)	4475(4)	3994(1)	39(1)
C(26)	13314(4)	3602(4)	4330(1)	34(1)
C(27)	12275(5)	2448(4)	4387(1)	39(1)
C(28)	11121(5)	2203(4)	4105(1)	36(1)
C(29)	14509(6)	3911(4)	4631(2)	45(1)
N(30)	15418(5)	4219(4)	4866(1)	62(1)
C(31)	8599(4)	5177(4)	3559(1)	35(1)
N(32)	9042(4)	6432(4)	3398(1)	46(1)
C(33)	8771(5)	7622(4)	3617(2)	50(1)
C(34)	8102(5)	7605(5)	3993(1)	46(1)
C(35)	7661(5)	6290(5)	4148(1)	51(1)
C(36)	7901(4)	5054(4)	3928(1)	41(1)
Cl(37)	3931(1)	4848(1)	2790(1)	48(1)

Table 3. Bond lengths [A] and angles [deg] for Compound **11c**.

C(1)-N(4)	1.515(4)
C(1)-C(3)	1.519(5)
C(1)-C(2)	1.522(5)
C(2)-N(20)	1.477(5)
N(4)-C(9)	1.504(4)
N(4)-C(5)	1.509(4)
N(4)-H(4)	1.04(4)
C(5)-C(6)	1.521(5)
C(6)-N(7)	1.465(4)
N(7)-C(10)	1.403(5)
N(7)-C(8)	1.460(4)
C(8)-C(9)	1.504(5)
C(10)-C(11)	1.403(5)
C(10)-C(19)	1.410(5)
C(11)-C(16)	1.384(5)
C(11)-O(12)	1.397(4)
O(12)-C(13)	1.424(4)
C(13)-C(14)	1.484(6)
C(14)-O(15)	1.436(5)
O(15)-C(16)	1.377(4)
C(16)-C(17)	1.398(5)
C(17)-C(18)	1.383(5)
C(18)-C(19)	1.378(5)
N(20)-C(21)	1.385(5)
N(20)-C(31)	1.429(5)
C(21)-O(22)	1.236(4)
C(21)-C(23)	1.492(5)
C(23)-C(28)	1.380(5)
C(23)-C(24)	1.390(5)
C(24)-C(25)	1.384(5)
C(25)-C(26)	1.388(5)
C(26)-C(27)	1.400(5)
C(26)-C(29)	1.454(6)
C(27)-C(28)	1.376(5)
C(29)-N(30)	1.134(5)
C(31)-N(32)	1.338(5)
C(31)-C(36)	1.367(5)
N(32)-C(33)	1.344(5)
C(33)-C(34)	1.375(6)
C(34)-C(35)	1.377(6)
C(35)-C(36)	1.377(5)
N(4)-C(1)-C(3)	113.3(3)
N(4)-C(1)-C(2)	109.5(3)
C(3)-C(1)-C(2)	112.5(3)
N(20)-C(2)-C(1)	110.2(3)
C(9)-N(4)-C(5)	110.7(3)
C(9)-N(4)-C(1)	111.3(3)

C(5)-N(4)-C(1)	113.9(3)
N(4)-C(5)-C(6)	110.1(3)
N(7)-C(6)-C(5)	109.7(3)
C(10)-N(7)-C(8)	117.8(3)
C(10)-N(7)-C(6)	117.7(3)
C(8)-N(7)-C(6)	110.1(3)
N(7)-C(8)-C(9)	108.7(3)
N(4)-C(9)-C(8)	111.4(3)
N(7)-C(10)-C(11)	119.1(3)
N(7)-C(10)-C(19)	123.3(4)
C(11)-C(10)-C(19)	117.5(4)
C(16)-C(11)-O(12)	121.6(4)
C(16)-C(11)-C(10)	121.4(4)
O(12)-C(11)-C(10)	116.9(4)
C(11)-O(12)-C(13)	112.1(3)
O(12)-C(13)-C(14)	111.3(4)
O(15)-C(14)-C(13)	111.0(3)
C(16)-O(15)-C(14)	113.2(3)
O(15)-C(16)-C(11)	122.9(4)
O(15)-C(16)-C(17)	116.9(4)
C(11)-C(16)-C(17)	120.2(4)
C(18)-C(17)-C(16)	118.8(4)
C(19)-C(18)-C(17)	121.5(4)
C(18)-C(19)-C(10)	120.6(4)
C(21)-N(20)-C(31)	120.7(3)
C(21)-N(20)-C(2)	119.5(3)
C(31)-N(20)-C(2)	117.3(3)
O(22)-C(21)-N(20)	121.8(4)
O(22)-C(21)-C(23)	121.3(4)
N(20)-C(21)-C(23)	116.9(4)
C(28)-C(23)-C(24)	120.0(4)
C(28)-C(23)-C(21)	119.2(4)
C(24)-C(23)-C(21)	120.6(4)
C(25)-C(24)-C(23)	119.4(4)
C(24)-C(25)-C(26)	120.2(4)
C(25)-C(26)-C(27)	120.3(4)
C(25)-C(26)-C(29)	120.0(4)
C(27)-C(26)-C(29)	119.7(4)
C(28)-C(27)-C(26)	118.7(4)
C(27)-C(28)-C(23)	121.3(4)
N(30)-C(29)-C(26)	176.7(5)
N(32)-C(31)-C(36)	123.7(4)
N(32)-C(31)-N(20)	117.0(4)
C(36)-C(31)-N(20)	119.3(4)
C(31)-N(32)-C(33)	116.9(4)
N(32)-C(33)-C(34)	123.7(4)
C(33)-C(34)-C(35)	117.5(4)
C(36)-C(35)-C(34)	120.1(4)
C(31)-C(36)-C(35)	118.1(4)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for Compound **11c**. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	31(2)	35(2)	36(3)	4(2)	-2(2)	-5(2)
C(2)	36(2)	33(2)	34(3)	0(2)	-1(2)	-1(2)
C(3)	34(3)	84(3)	49(3)	9(3)	0(2)	0(2)
N(4)	25(2)	34(2)	35(2)	0(2)	2(2)	-2(2)
C(5)	40(3)	32(2)	39(3)	0(2)	-3(2)	-1(2)
C(6)	47(3)	32(2)	41(3)	-1(2)	-4(2)	-3(2)
N(7)	42(2)	29(2)	29(2)	2(2)	-3(2)	-3(2)
C(8)	39(3)	32(2)	37(3)	-1(2)	1(2)	1(2)
C(9)	44(3)	23(2)	48(3)	5(2)	-1(2)	-4(2)
C(10)	33(2)	33(2)	33(3)	4(2)	3(2)	-7(2)
C(11)	30(2)	27(2)	39(3)	4(2)	3(2)	2(2)
O(12)	41(2)	44(2)	40(2)	0(2)	0(2)	10(1)
C(13)	45(3)	43(3)	51(3)	-1(2)	13(3)	8(2)
C(14)	62(3)	37(2)	49(3)	-2(2)	0(3)	11(2)
O(15)	58(2)	46(2)	39(2)	-1(2)	2(2)	0(2)
C(16)	37(2)	33(3)	33(3)	0(2)	1(2)	-7(2)
C(17)	42(3)	37(2)	46(3)	6(2)	-14(2)	-5(2)
C(18)	36(3)	34(2)	53(3)	9(2)	-7(2)	2(2)
C(19)	33(2)	29(2)	46(3)	6(2)	-1(2)	1(2)
N(20)	39(2)	30(2)	32(2)	-5(2)	-2(2)	0(2)
C(21)	32(2)	41(3)	39(3)	3(2)	9(2)	0(2)
O(22)	39(2)	35(2)	55(2)	-11(2)	-1(2)	1(1)
C(23)	25(2)	32(2)	37(3)	-6(2)	-1(2)	7(2)
C(24)	35(3)	40(2)	39(3)	8(2)	3(2)	-2(2)
C(25)	30(2)	40(2)	48(3)	0(2)	0(2)	-1(2)
C(26)	35(3)	34(2)	33(3)	-3(2)	-4(2)	9(2)
C(27)	40(3)	32(2)	44(3)	5(2)	-3(2)	11(2)
C(28)	34(2)	30(2)	45(3)	5(2)	-2(2)	4(2)
C(29)	52(3)	27(2)	55(4)	3(2)	-7(3)	10(2)
N(30)	67(3)	46(2)	73(3)	-3(2)	-24(3)	4(2)
C(31)	32(2)	32(2)	41(3)	-3(2)	-9(2)	4(2)
N(32)	55(2)	31(2)	51(3)	-4(2)	3(2)	0(2)
C(33)	55(3)	32(3)	62(4)	0(3)	-5(3)	1(2)
C(34)	45(3)	44(3)	48(3)	-13(3)	-4(3)	8(2)
C(35)	46(3)	55(3)	50(3)	-1(3)	14(3)	2(2)
C(36)	47(3)	36(2)	39(3)	-1(2)	7(2)	0(2)
Cl(37)	34(1)	41(1)	67(1)	4(1)	12(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for Compound **11c**.

	x	y	z	U(eq)
H(1)	8308	5687	2746	41
H(2A)	6685	3886	3054	41
H(2B)	7861	2680	2884	41
H(3A)	10090	4962	2231	83
H(3B)	9924	3338	2385	83
H(3C)	10684	4534	2671	83
H(4)	5910(42)	4614(34)	2475(11)	47
H(5A)	6972	2528	2176	45
H(5B)	8108	3455	1890	45
H(6A)	5855	2755	1521	48
H(6B)	4718	3468	1851	48
H(8A)	4577	6000	1924	43
H(8B)	5607	7043	1643	43
H(9A)	7940	6259	1957	46
H(9B)	6756	6892	2288	46
H(13A)	8702	2206	607	56
H(13B)	8565	3834	452	56
H(14A)	7530	2218	-21	59
H(14B)	6270	1668	304	59
H(17)	3596	5465	73	50
H(18)	2527	6801	600	49
H(19)	3409	6503	1252	43
H(24)	11867	4848	3492	46
H(25)	13902	5238	3953	47
H(27)	12366	1846	4617	47
H(28)	10437	1401	4135	44
H(33)	9058	8525	3505	60
H(34)	7951	8468	4141	55
H(35)	7190	6236	4406	61
H(36)	7590	4142	4029	49

Table 6. Torsion angles [deg] for Compound **11c**.

N(4)-C(1)-C(2)-N(20)	-167.7(3)
C(3)-C(1)-C(2)-N(20)	65.3(4)
C(3)-C(1)-N(4)-C(9)	-82.2(4)
C(2)-C(1)-N(4)-C(9)	151.3(3)
C(3)-C(1)-N(4)-C(5)	43.9(4)
C(2)-C(1)-N(4)-C(5)	-82.6(4)
C(9)-N(4)-C(5)-C(6)	-52.4(4)
C(1)-N(4)-C(5)-C(6)	-178.8(3)
N(4)-C(5)-C(6)-N(7)	57.1(4)
C(5)-C(6)-N(7)-C(10)	157.8(3)
C(5)-C(6)-N(7)-C(8)	-63.2(4)
C(10)-N(7)-C(8)-C(9)	-157.6(3)
C(6)-N(7)-C(8)-C(9)	63.5(4)
C(5)-N(4)-C(9)-C(8)	53.9(4)
C(1)-N(4)-C(9)-C(8)	-178.3(3)
N(7)-C(8)-C(9)-N(4)	-58.7(4)
C(8)-N(7)-C(10)-C(11)	157.1(3)
C(6)-N(7)-C(10)-C(11)	-67.2(5)
C(8)-N(7)-C(10)-C(19)	-18.5(5)
C(6)-N(7)-C(10)-C(19)	117.3(4)
N(7)-C(10)-C(11)-C(16)	-175.4(3)
C(19)-C(10)-C(11)-C(16)	0.4(5)
N(7)-C(10)-C(11)-O(12)	2.2(5)
C(19)-C(10)-C(11)-O(12)	178.1(3)
C(16)-C(11)-O(12)-C(13)	17.2(5)
C(10)-C(11)-O(12)-C(13)	-160.5(3)
C(11)-O(12)-C(13)-C(14)	-47.5(4)
O(12)-C(13)-C(14)-O(15)	62.0(5)
C(13)-C(14)-O(15)-C(16)	-42.2(5)
C(14)-O(15)-C(16)-C(11)	12.1(5)
C(14)-O(15)-C(16)-C(17)	-170.1(3)
O(12)-C(11)-C(16)-O(15)	1.3(6)
C(10)-C(11)-C(16)-O(15)	178.9(3)
O(12)-C(11)-C(16)-C(17)	-176.3(3)
C(10)-C(11)-C(16)-C(17)	1.2(6)
O(15)-C(16)-C(17)-C(18)	-178.9(3)
C(11)-C(16)-C(17)-C(18)	-1.1(6)
C(16)-C(17)-C(18)-C(19)	-0.7(6)
C(17)-C(18)-C(19)-C(10)	2.3(6)
N(7)-C(10)-C(19)-C(18)	173.5(3)
C(11)-C(10)-C(19)-C(18)	-2.2(5)
C(1)-C(2)-N(20)-C(21)	-122.3(4)
C(1)-C(2)-N(20)-C(31)	75.4(4)
C(31)-N(20)-C(21)-O(22)	153.9(4)
C(2)-N(20)-C(21)-O(22)	-7.8(6)
C(31)-N(20)-C(21)-C(23)	-28.4(5)
C(2)-N(20)-C(21)-C(23)	169.9(3)

O(22)-C(21)-C(23)-C(28)	-42.9(5)
N(20)-C(21)-C(23)-C(28)	139.3(4)
O(22)-C(21)-C(23)-C(24)	132.2(4)
N(20)-C(21)-C(23)-C(24)	-45.6(5)
C(28)-C(23)-C(24)-C(25)	-1.1(6)
C(21)-C(23)-C(24)-C(25)	-176.2(4)
C(23)-C(24)-C(25)-C(26)	-1.3(6)
C(24)-C(25)-C(26)-C(27)	1.9(6)
C(24)-C(25)-C(26)-C(29)	-176.1(4)
C(25)-C(26)-C(27)-C(28)	0.0(6)
C(29)-C(26)-C(27)-C(28)	178.0(4)
C(26)-C(27)-C(28)-C(23)	-2.5(6)
C(24)-C(23)-C(28)-C(27)	3.1(6)
C(21)-C(23)-C(28)-C(27)	178.2(3)
C(21)-N(20)-C(31)-N(32)	125.0(4)
C(2)-N(20)-C(31)-N(32)	-72.9(4)
C(21)-N(20)-C(31)-C(36)	-56.6(5)
C(2)-N(20)-C(31)-C(36)	105.5(4)
C(36)-C(31)-N(32)-C(33)	0.0(6)
N(20)-C(31)-N(32)-C(33)	178.3(4)
C(31)-N(32)-C(33)-C(34)	1.2(6)
N(32)-C(33)-C(34)-C(35)	-1.4(7)
C(33)-C(34)-C(35)-C(36)	0.3(6)
N(32)-C(31)-C(36)-C(35)	-1.0(6)
N(20)-C(31)-C(36)-C(35)	-179.2(3)
C(34)-C(35)-C(36)-C(31)	0.8(6)

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[4] R(F) = R1 = SIGMA(||Fo|-|Fc||) / SIGMA|Fo|, wR(F^2^) = wR2 =[SIGMA(w(Fo^2^-Fc^2^)^2^) / SIGMA(w(Fo^2^)^2^)]^1/2^, and S = goodness-of-fit on F^2^ = [SIGMA(w(Fo^2^-Fc^2^)^2^) / (n-p)]^1/2^, where n is the number of reflections and p is the number of parameters refined.

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MISCELLANEOUS:

1. The piperazinium hydrogen H(4) is hydrogen bonded to a chloride anion with the following geometrical attributes (distances in Angstroms, angles in degrees): N(4)-H(4) = 1.04(4), H(4)...Cl(37) = 1.99(4), N(4)...CL(37) = 3.022(3), and N(4)-H(4)...Cl(37) = 170(3).

2. The environment of the amino nitrogen is nearly trigonal planar. The N(20) atom is 0.130(4) Angstroms off of the least-squares plane defined by the C(2), C(21) and C(31) atoms.

   (a) The C(2), N(20), C(21), O(22) and C(23) atoms are nearly coplanar suggesting that the N(20) lone pair of electrons is probably partially delocalized into the adjacent carbonyl group. The C(31) atom is 0.639(6) Angstroms off of the least-squares plane defined by C(2), N(20), C(21), O(22) and C(23).

Biological Assays

5-HT1A Binding Affinity Assay: The ability of the compounds described in this manuscript to displace the standard ligand [3H]-8-OH-DPAT from its binding site on human 5-HT_{1A} receptors stably cloned in CHO cells was assessed using a procedure identical to that described in the following reference – Dunlop, J.; Zhang, Y.; Smith, D.E.; Schechter, L.E. Characterization of the 5-HT1A Receptor Functional Coupling in Cells Expressing the Human 5-HT_{1A} Receptor as Assessed with the Cytosensor Microphysiometer. *J. Pharmacol. Tox. Methods* **1998**, *40*, 41-55.

Inhibition of Agonist-Induced Decreases in Forskolin-Stimulated cAMP Production: The ability of compounds described in this manuscript to inhibit 8-OH-DPAT-induced decreases in forskolin-stimulated cAMP production in CHO cells stably transfected with the human 5-HT_{1A} receptor was assessed using a procedure identical to that described in the following reference - Dunlop, J.; Zhang, Y.; Smith, D.E.; Schechter, L.E. Characterization of the 5-HT1A Receptor Functional Coupling in Cells Expressing the Human 5-HT_{1A} Receptor as Assessed with the Cytosensor Microphysiometer. *J. Pharmacol. Tox. Methods* **1998**, *40*, 41-55. Compounds were also assessed for any agonist activity using the same assay by examining the effect of the compounds on forskolin-stimulated cAMP production in the absence of the agonist 8-OH-DPAT. An Emax value of 0% indicates the absence of any agonist-like activity (as compared to 8-OH-DPAT, which demonstrated and Emax value of 100%).

Assessment of Agonism/Antagonism of the 5-HT1A Receptor using [^{35}S]-GPTγS Binding: The [^{35}S]-GTPγS binding assay was similar to that used by Lazareno and Birdsall (Lazareno, S.; Birdsall, N.J.M. Pharmacological Characterization of Acetylcholine-Stimulated [^{35}S]GTPγS Binding Mediated by Human Muscarinic m1 – m4 Receptors: Antagonist Studies. *Br. J. Pharmacol*. **1993**, *109*, 1120 – 1127). Briefly, membrane fragments from CHO cells stably transfected with the human 5-HT_{1A} receptor (prepared as described in Dunlop, J.; Zhang, Y.; Smith, D.E.; Schechter, L.E. Characterization of the 5-HT_{1A} Receptor Functional Coupling in Cells Expressing the Human 5-HT1A Receptor as Assessed with the Cytosensor Microphysiometer. *J. Pharmacol. Tox. Methods* **1998**, *40*, 41-55) were stored at –70 °C until needed. Membranes were rapidly thawed, centrifuged at 40,000 x g for 10 minutes and resuspended at 4 °C for 10 minutes in assay buffer (25 mM HEPES, 3 mM $MgCl_2$, 100 mM NaCl, 1 mM EDTA, 10 μM GDP, 500 mM DTT, pH 8.0). These membranes were then incubated for 30 minutes at 37 °C with [^{35}S]GTPγS (1nM) in the presence of vehicle, test compound (one to eight concentrations), or excess 8-OH-DPAT to define maximum agonist

response. All reactions were terminated by the addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech® filtration device to separate bound from free [^{35}S}GTPγS. Agonists produce an increase in the amount of [^{35}S]GTPγS bound whereas antagonists produce no increase in binding but rather block the increase produced by 8-OH-DPAT. Bound radioactivity was counted on a Packard TopCount. Results are expressed as a percent of control and analyzed using linear regression analysis (Prizm) to determine IC_{50}, EC_{50} and Emax values.

Antagonism of 8-OH-DPAT-Induced Decreases in Fixed Ratio Responding: The in vivo 5-HT_{1A} antagonist activity of the compounds described in this manuscript was assessed using a Fixed Ratio Responding Model (Blackman, D. in "Operant Conditioning: an Experimental Analysis of Behavior", part of *Methuen's Manuals of Physiology*, Butcher, J. ed., Methuen & Co, Ltd., 1974). In this model, rats (male, 300 – 350 gm) were trained to respond (lever press) under a fixed-ratio 30 schedule of fool presentation in order to receive a food pellet reinforcer. Under this schedule, completion of 30 responses resulted in the delivery of the food pellet. Experimental sessions consisted of a 10 minute agonist-pretreatment period, followed by a 10 minute response period. In the first component of the experiment, rats were divided into two groups and administered either vehicle (10% Tween 80/5% methylcellulose in sterile water) or the 5-HT_{1A} agonist 8-OH-DPAT (0.3 mg/kg sc) 10 minutes prior to testing. Administration of the agonist resulted in a significant decrease in the response rate (number of responses per second) relative to vehicle (see Table 2, manuscript). In the second component of the experiment, incremental doses of 8-OH-DPAT were examined to determine the ED_{50} value for the agonist response. In the third component of the experiment, test compounds were administered (sc) 30 minutes prior to testing and then a second 8-OH-DPAT dose-response study was performed to determine the ability of the test compound to antagonize the agonist response and induce a rightward shift in the 8-OH-DPAT dose response and resulting ED_{50} value. These results are presented in Table 3 of the manuscript. Rates of responding were calculated separately in each of the three components of the session by dividing the total number of responses by the total time the component was in effect for each animal. Mean control rates of responding in each component were determined by averaging data from all non-injection and vehicle control sessions that preceded drug test sessions. The effects of each dose or dose-combination were calculated as a percentage of the mean control rate in the corresponding component of the session for individual subjects and then averaged for the group of animals. ED_{50} values were defined as the dose of 5-OH-DPAT calculated to decrease response rates to 50% of mean control rates.