SUPPORTING INFORMATION

Synthesis and Structure Activity Relationship (SAR) of (5,7-disubstituted 3-phenylsulfonyl-pyrazolo[1,5-*a*]pyrimidin-2-yl)-methylamines as Potent Serotonin 5-HT_6 Receptor (5-HT_6R) Antagonists.

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1. Synthesis of substituted 5-methyl-2-methylamino-3-phenylsulfonyl-pyrazolo[1,5-*a*]pyrimidines 36 – 45 (Refer to Scheme 2 in the paper).

N^3-methyl-4-(phenylsulfonyl)-1*H*-pyrazole-3,5-diamines **33, 34**, and **46** (27.8 mmol each) were mixed with a corresponding 1,3-dicarbonyl compound, **48** – **52**, **53** (83.4 mmol each), and AcOH (20 mL). The mixtures were stirred overnight at ambient temperature. Then the samples were heated for 1–2 h at 80–100°C and cooled down. Precipitates were filtered, washed with AcOH, *i*-PrOH, and dried to produce 5-methyl-2-methylamino-3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines **36** – **45** as colorless solid compounds (yields: 63–75%) that were used in the follow up step without their further purification.

36 5-Methyl-2-(methylamino)-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-7-ol (yield: 84 %). ^{1}H NMR (DMSO-d_6) δ 11.50 (s, 1H), 8.12 (d, J = 7.6 Hz, 2H), 7.68 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 7.6 Hz, 2H), 5.94 (q, J = 5.2 Hz, 1H), 5.74 (s, 1H), 2.78 (d, J = 4.4 Hz, 3H), 2.36 (s, 3H). MS-ESI calculated for $C_{14}H_{14}N_4O_3S$ (M+H) 319, found m/z 319. LC-MS (UV-254), purity: 98%.

37: 6-Chloro-5-methyl-2-(methylamino)-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-7-ol (yield: 41 %). ^{1}H NMR (DMSO-d_6) δ 12.10–11.54 (brs, 1H), 8.11 (d, J = 7.2 Hz, 2H), 7.70 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 7.6 Hz, 2H), 6.11–5.93 (brs, 1H), 2.79 (s, 3H), 2.54 (s, 3H), 2.08 (s, 3H). MS-ESI calculated for $C_{14}H_{13}ClN_4O_3S$ (M+H) 353, found m/z 353. LC-MS (UV-254), purity: 98%.

38: 6-Chloro-3-(3-chlorophenylsulfonyl)-5-methyl-2-(methylamino)pyrazolo[1,5-*a*]pyrimidin-7-ol (yield: 63%). ^{1}H NMR (DMSO-d_6) δ 12.19-11.15 (brs, 1H), 8.24 (s, 1H), 8.08 (d, J = 8 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 6.09 (m, 1H), 2.80 (s, 3H), 2.54 (s, 3H). MS-ESI calculated for $C_{14}H_{12}Cl_2N_4O_3S$ (M+H) 388, found m/z 388. LC-MS (UV-254), purity: 98%.

39: 2-[3-(Phenylsulfonyl)-5-methyl-2-(methylamino)pyrazolo[1,5-*a*]pyrimidin-7-ylmethyl]isoindole-1,3-dione (yield: 9%). ^{1}H NMR ($CDCl_3$), δ: 7.97 (m, 2H), 7.93 (m, 2H), 7.80 (m, 2H), 7.44 (m, 1H), 7.34 (m, 2H), 6.64 (s, 1H), 6.04 (q, J = 4.8 Hz, 1H), 5.00 (s, 2H), 3.03 (d, J = 4.8 Hz, 3H), 2.62 (s, 3H). MS-ESI calculated for $C_{23}H_{19}N_5O_4S$ (M+H) 462, found m/z 462. LC-MS (UV-254), purity: 98%.

40: 2-[3-(Phenylsulfonyl)-7-methyl-2-(methylamino)pyrazolo[1,5-*a*]pyrimidin-5-ylmethyl]isoindole-1,3-dione (yield: 65%). ^{1}H NMR ($CDCl_3$), δ 8.15 (m, 2H), 7.93 (m, 2H), 7.81 (m, 2H), 7.53 (m, 1H), 7.47 (m, 2H), 6.44 (s, 1H), 6.05 (q, J = 5.2 Hz, 1H), 5.20 (s, 2H), 2.99 (d, J = 5.2 Hz, 3H), 2.54 (s, 3H). MS-ESI calculated for $C_{23}H_{19}N_5O_4S$ (M+H) 462, found m/z 462. LC-MS (UV-254), purity: 98%.

41: 3-[5-Methyl-2-(methylamino)-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl]propionic acid ethyl ester (yield: 20%). ^{1}H NMR ($CDCl_3$), δ 8.17 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 2H), 7.49 (m, 3H), 6.58 (s, 1H), 6.03 (q, J = 5.2 Hz, 1H), 4.14 (q, J = 7.6 Hz, 2H), 3.28 (t, J = 6.8 Hz, 2H), 3.03 (d, J = 5.6 Hz, 3H), 2.86 (t, J = 7.6 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 171.81, 160.03, 157.09, 145.20, 144.14, 143.95, 132.56, 128.95, 125.64,

118.48, 89.55, 60.02, 32.68, 28.90, 23.14, 22.75, 13.97, 13.37. MS-ESI calculated for $C_{19}H_{22}N_4O_4S$ (M+H) 403, found m/z 403. LC-MS (UV-254), purity: 98%.

42: 2-[5,7-Dimethyl-2-(methylamino)-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-6-yl]acetic acid ethyl ester (yield: 48%). ^{1}H NMR (400 MHz, DMSO-d_6), δ 8.03 (m, 2H), 7.53–7.62 (m, 3H), 6.36 (q, J = 4.8 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.82 (s, 2H), 2.92 (d, J = 4.8 Hz, 3H), 2.60 (s, 3H), 2,49 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H). MS-ESI calculated for $C_{18}H_{20}N_4O_4S$ (M+H) 389, found m/z 389. LC-MS (UV-254), purity: 98%.

43: 2-[5,7-Dimethyl-3-(3-fluorophenylsulfonyl)-2-(methylamino)pyrazolo[1,5-*a*]pyrimidin-6-yl]acetic acid ethyl ester (yield: 42 %). ^{1}H NMR (400 MHz, DMSO-d_6), δ 7.85 (t, J = 8 Hz, 2H), 7.62 (dt, J_1 = 8.8 Hz, J_2 = 6.4 Hz, 1H), 7.47 (dt, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 1H), 6.38 (q, J = 4.4 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.83 (s, 2H), 2.91 (d, J = 4.8 Hz, 3H), 2.60 (s. 3H), 1.18 (t, J = 6.8 Hz, 3H). MS-ESI calculated for $C_{19}H_{21}FN_4O_4S$ (M+H) 421, found m/z 421. LC-MS (UV-254), purity: 98%.

44*:* 2-[3-(3-Chlorophenylsulfonyl)-5,7-dimethyl-2-(methylamino)pyrazolo[1,5-*a*]pyrimidin-6-yl]acetic acid ethyl ester (yield: 84 %). ^{1}H NMR (400 MHz, DMSO-d_6), δ 8.10 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 6.39 (q, J = 5.1 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 3.83 (s, 2H), 2.91 (d, J = 5.2 Hz, 3H), 2.60 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H). MS-ESI calculated for $C_{19}H_{21}ClN_4O_4S$ (M+H) 437, found m/z 437. LC-MS (UV-254), purity: 98%.

45: 3-[5,7-Dimethyl-2-(methylamino)-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-6-yl]propionic acid ethyl ester (yield: 71 %). ^{1}H NMR (400 MHz, DMSO-d_6), δ 8.16 (m, 2H), 7.44–7.52 (m, 3H), 5.99 (q, J = 4.8 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.04 (d, J = 4.8 Hz, 3H), 2.98 (m, 2H), 2.67 (s, 3H), 2.61 (s, 3H), 2.46 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H). MS-ESI calculated for $C_{20}H_{24}N_4O_4S$ (M+H) 417, found m/z 417. LC-MS (UV-254), purity: 98%.

2. Synthesis of substituted (7-chloro-5-methyl-3-phenylsulfonyl-pyrazolo[1,5-*a*]pyrimidine-2-yl)-methylamines 54 – 56 (Refer to Schema 3 in the paper).

Compounds **36** – **38** (20 mmol each) were mixed with $POCl_3$ (6.12 g, 40 mmol) and sulfolane (25 mL) and stirred separately at 70 ^{o}C for 3 hr. The samples were cooled down and each mixture was poured into ice/water (200 mL). The formed precipitates were separated by filtration, washed with water, and dried to afford crude (7-chloro-5-methyl-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-2-yl)methylamines **54** – **56** (yields: 60–88%) that were used in the follow up step without further purification.

54*:* 7-Chloro-*N*,5-dimethyl-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-2-amine (yield: 91 %). ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 8.14 (s, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.48 (t, J = 7.6 Hz, 3H), 6.78 (s, 1H), 3.09 (s, 3H), 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 161.04, 158.22, 148.24, 143.09, 137.44, 132.26, 128.31, 126.18, 108.66, 92.32, 28.67, 24.34. MS-ESI calculated for $C_{14}H_{13}ClN_4O_2S$ (M+H) 337, found m/z 337. LC-MS (UV-254), purity: 98%.

55*:* 6,7-Dichloro-*N*,5-dimethyl-3-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidin-2-amine (yield: 31 %). ^{1}H NMR (DMSO-d_6) δ 8.03 (m, 2H), 7.63 (m, 1H), 7.56 (m, 2H), 6.67–6.53 (brs, 1H), 2.92 (s, 3H), 2.62 (s, 3H). MS-ESI calculated for $C_{14}H_{12}Cl_2N_4O_2S$ (M+H) 372, found m/z 372. LC-MS (UV-254), purity: 98%.

56*:* 6,7-Dichloro-3-(3-chlorophenylsulfonyl)-*N*,5-dimethylpyrazolo[1,5-*a*]pyrimidin-2-amine (yield: 57%). ^{1}H NMR (DMSO-d_6) δ 8.07 (s, 1H), 7.97 (d, J = 8 Hz, 1H), 7.71 (s, J = 8.4 Hz, 1H), 7.62 (t, J = 8 Hz, 1H), 6.63 (m, 1H), 2.92 (d, J = 4.4 Hz, 3H), 2.63 (s, 3H). MS-ESI calculated for $C_{14}H_{11}Cl_3N_4O_2S$ (M+H) 406, found m/z 406. LC-MS (UV-254), purity: 98%.