SUPPLEMENTARY MATERIAL TO

**Synthetic route towards potential bivalent ligands possessing opioid and D2/D3 pharmacophores**

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# **Isolated yields and spectroscopic data of synthesized compounds**

*8-(N-Phenylpropionamido)-5-azaspiro [4.5] decan-5-ium chloride (****8a****).* Yield: 0.27 g (64.5%); yellow oil. IR (ATR, cm-1): 2977.3 (C-H aliphatic), 1645.1 (C=O), 1272.8 (C-N amine). 1H NMR (500 MHz, CDCl3): δ = 7.53 – 7.40 (3H, m, Ar-H), 7.14 (2H, d, *J* = 7.1 Hz, Ar-H), 4.82 – 4.59 (1H, m, CH-H), 4.02 – 3.74 (6H, m, CH2-H), 3.66 – 3.51 (2H, m, CH2-H), 2.23 (br. s, 4H), 2.12 (2H, d, J = 13.5 Hz, CH2-2), 2.05 – 1.86 (4H, m, CH2-H), 0.98 (3H, t, *J* = 7.4 Hz, CH3-3) ppm. 13C NMR (126 MHz, CDCl3): δ = 174.1, 139.1, 130.3, 129.7, 129.2, 67.1, 59.3, 57.7, 51.0, 41.2, 28.7, 26.0, 21.8, 21.2, 9.6 ppm. HRMS-HESI-Orbitrap: calcd. for C18H27N2O+ [M] + 287.21179; found 287.21169.

*3-(N-Phenylpropionamido)-6-azaspiro [5.5] undecan-6-ium chloride (****8b****).* Yield: 0.29 g (66.2 %); yellow oil. IR (ATR, cm-1): 2943.0 (C-H aliphatic), 1647.4 (C=O), 1269.7 (C-N amine). 1H NMR (500 MHz, CDCl3): δ = 7.53 – 7.37 (3H, m, Ar-H,) 7.15 (2H, dd, *J* = 7.3, 1.9 Hz, Ar-H), 4.61 – 4.49 (1H, m, CH-H), 4.03 (2H, d, *J* = 12.6 Hz, CH2-H), 3.90 – 3.82 (2H, m, CH2-H), 3.78 (2H, t, *J* = 12.2 Hz, CH2-H), 3.59 (2H, br. s, CH2-H), 2.29 – 2.10 (2H, m, CH2-H), 2.07 (2H, d, *J* = 13.1 Hz, CH2-H), 1.98 – 1.87 (4H, m, CH2-H), 1.79 (4H, br. s, CH2-H), 0.98 (3H, t, *J* = 7.4 Hz, CH3-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 174.2, 139.8, 130.3, 129.3, 129.1, 64.2, 58.2, 53.7, 52.4, 28.8, 23.4, 21.3, 20.2, 19.7, 9.5 ppm. HRMS-HESI-Orbitrap: calcd. for C19H29N2O+ [M] + 301.22744; found 301.22694.

*N-phenylpiperidin-4-amine (****6****)* Obtained from **9** via three step procedure already known from literature.4,5 Overall yield: 8.00 g (84.5 %); pale yellow oil. 1H NMR (500 MHz, CDCl3): δ = 7.21 – 7.09 (2H, m, Ar-H), 6.67 (1H, t, J = 7.3 Hz, Ar-H), 6.60 (2H, d, *J* = 7.7 Hz, Ar-H), 3.52 (1H, br. s, NH-H), 3.36 (1H, br. s, CH-H), 3.11 (2H, dt, *J* = 12.8, 3.5 Hz, CH2-H), 2.71 (2H, td, *J* = 12.5, 2.5 Hz, CH2-H), 2.07 (2H, d, *J* = 12.5 Hz, CH2-H), 1.78 (1H, br. s, NH-H), 1.40 – 1.21 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 146.9, 129.2, 117.1, 113.2, 50.3, 45.5, 33.9 ppm.

*4-chloro-1-(4-phenylpiperazin-1-yl) butan-1-one (****7a****).* Yield: 0.90 g (97.3 %); pale yellow oil. IR (ATR, cm-1): 2916.3 (C-H aliphatic), 1644.4 (C=O), 869.9 (C-Cl).1H NMR (500 MHz, CDCl3): δ = 7.28 – 7.17 (2H, m, Ar-H), 6.97 – 6.77 (3H, m, Ar-H), 3.76 – 3.67 (2H, m, CH2-H), 3.64 – 3.54 (4H, m, CH2-H), 3.11 (4H, dt, *J* = 16.4, 5.2 Hz, CH2-H), 2.49 (2H, t, *J* = 7.1 Hz, CH2-H), 2.13 – 2.05 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 170.3, 151.0, 129.4, 120.7, 116.7, 49.8, 49.5, 45.5, 45.0, 41.7, 29.8, 28.0 ppm.

*4-chloro-1-(4-(3-methoxyphenyl) piperazin-1-yl) butan-1-one (****7b****).* Yield: 0.99 g (95.9 %); pale yellow oil. IR (ATR, cm-1): 2919.8 (C-H aliphatic), 1590.8 (C=O), 746.9 (C-Cl). 1H NMR (500 MHz, CDCl3): δ = 7.05 – 6.97 (1H, m, Ar-H), 6.94 – 6.82 (3H, m, Ar-H), 3.86 (3H, s, OCH3-H), 3.81 – 3.75 (2H, m, CH2-H), 3.69 – 3.60 (4H, m, CH2-H), 3.02 (4H, dt, *J* = 18.4, 5.1 Hz, CH2-H), 2.53 (2H, t, *J* = 7.1 Hz, CH2-H), 2.14 (2H, q, *J* = 6.5 Hz, CH2-H). ppm. 13C NMR (126 MHz, CDCl3): δ = 170.3, 152.4, 140.7, 123.7, 121.2, 118.5, 111.5, 55.5, 51.1, 50.7, 45.8, 45.0, 42.0, 29.9, 28.0 ppm.

*4-chloro-1-(4-(2,3-dichlorophenyl) piperazin-1-yl) butan-1-one (****7c****).* Yield: 1.14 g (97.9 %); pale yellow oil. IR (ATR, cm-1): 2921.7 (C-H aliphatic), 1644.6 (C=O), 784.2 (C-Cl), 715.0 (C-Cl).1H NMR (500 MHz, CDCl3): δ = 7.24 – 7.13 (2H, m, Ar-H), 6.93 (1H, dd, *J* = 7.7, 1.9 Hz, Ar-H), 3.84 – 3.77 (2H, m, CH2-H), 3.69 – 3.65 (4H, m, CH2-H), 3.07 – 2.98 (4H, m, CH2-H), 2.56 (2H, t, *J* = 7.1 Hz, CH2-H), 2.20 – 2.12 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 13C NMR (126 MHz, CDCl3) δ 170.4, 150.7, 134.2, 127.7, 125.3, 118.9, 51.7, 45.9, 45.8, 44.9, 41.9, 29.8, 28.0 ppm.

*4-(4-(phenylamino) piperidin-1-yl)-1-(4-phenylpiperazin-1-yl) butan-1-one (****13a****).* Yield: 0.34 g (49.2 %); pale yellow oil. IR (ATR, cm-1): 3340.7 (N-H amine), 3048.8 (C-H aromatic), 2939.2 (C-H aliphatic), 1637.7 (C=O), 1232.1 ( C-N amine).1H NMR (500 MHz, CDCl3): δ = 7.34 – 7.20 (2H, m, Ar-H), 7.22 – 7.07 (2H, m, Ar-H), 6.97 – 6.79 (3H, m, Ar-H), 6.76 – 6.63 (1H, m, Ar-H), 6.64 – 6.56 (2H, m, Ar-H), 3.86 – 3.73 (2H, m, CH2-H), 3.70 – 3.60 (2H, m, CH2-H), 3.51 (1H, br. s, NH-H), 3.37 – 3.24 (1H, m, CH-H), 3.21 – 3.11 (4H, m, CH2-H), 2.89 (2H, d, *J* = 11.4 Hz, CH2-H), 2.51 – 2.34 (4H m, CH2-H), 2.25 – 2.10 (2H, m, CH2-H), 2.06 (2H, d, *J* = 12.0 Hz, CH2-H), 1.95 – 1.81 (2H, m, CH2-H), 1.60 – 1.37 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 171.5, 151.1, 147.2, 129.4, 129.4, 120.7, 117.3, 116.7, 113.4, 58.0, 52.5, 50.0, 49.9, 49.5, 45.6, 41.6, 32.6, 31.1, 22.8 ppm.

*1-(4-(3-methoxyphenyl) piperazin-1-yl)-4-(4-(phenylamino) piperidin-1-yl) butan-1-one (****13b****).* Yield: 0.33 g (45.1%); pale yellow oil. IR (ATR, cm-1): 3340.4 (N-H amine), 3050.8 (C-H aromatic), 2936.6 (C-H aliphatic), 1636.4 (C=O), 1241.5 (C-N amine). 1H NMR (500 MHz, CDCl3): δ = 7.21 – 7.11 (2H, m, Ar-H), 7.11 – 6.99 (1H, m, Ar-H), 6.96 – 6.87 (3H, m, Ar-H), 6.73 – 6.63 (1H, m, Ar-H), 6.62 – 6.56 (2H, m, Ar-H), 3.87 (3H, s, OCH3-H), 3.83 – 3.77 (2H, m, CH2-H), 3.73 – 3.61 (2H, m, CH2-H), 3.52 (1H, br. s, NH-H), 3.34 – 3.24 (1H, m, CH-H), 3.01 – 2.96 (4H, m, CH2-H), 2.88 (2H, d, *J* = 11.0 Hz, 2H), 2.47 – 2.36 (4H, m, CH2-H), 2.14 (2H, t, *J* = 11.0 Hz, CH2-H), 2.05 (2H, d, *J* = 11.8 Hz, CH2-H), 1.94 – 1.78 (2H, m, CH2-H), 1.58 – 1.35 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 171.4, 152.3, 147.1, 140.7, 129.3, 123.6, 121.1, 118.4, 117.2, 113.3, 111.4, 57.9, 55.5, 52.4, 51.1, 50.6, 49.9, 45.9, 41.8, 32.5, 31.0, 22.7 ppm.

*1-(4-(2,3-dichlorophenyl) piperazin-1-yl)-4-(4-(phenylamino) piperidin-1-yl) butan-1-one (****13c****).* Yield: 0.45 g (55 %); pale yellow oil. IR (ATR, cm-1): 3341.4 (N-H amine), 3049.9 (C-H aromatic), 2940.6 (C-H aliphatic), 1638.1 (C=O), 1237.8 (C-N amine). 1H NMR (500 MHz, CDCl3): δ = 1H NMR (500 MHz, Chloroform-d) δ 7.21 – 7.11 (3H, m, Ar-H), 7.01 – 6.88 (2H, m, Ar-H), 6.71 – 6.64 (1H, m, Ar-H), 6.62 – 6.56 (2H, m, Ar-H), 3.84 – 3.77 (2H, m, CH2-H), 3.71 – 3.62 (2H, m, CH2-H), 3.52 (1H, br. s, NH-H), 3.36 – 3.28 (1H, m, CH-H), 3.05 – 2.97 (4H, m, CH2-H), 2.94 – 2.85 (2H, m, CH2-H), 2.46 – 2.36 (4H, m, CH2-H), 2.22 – 2.11 (2H, m, CH2-H), 2.10 – 2.02 (2H, m, CH2-H), 1.93 – 1.80 (2H, m, CH2-H), 1.60 – 1.41 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 171.5, 150.7, 147.2, 134.3, 129.4, 127.8, 127.7, 125.3, 118.8, 117.3, 113.3, 57.9, 52.5, 51.8, 51.2, 50.1, 45.9, 41.9, 32.6, 31.0, 22.7 ppm.

*N-phenyl-1-(4-(4-phenylpiperazin-1-yl) butyl) piperidin-4-amine (****5a****).* Yield: 0.33 g (84.8 %); pale yellow oil. IR (ATR, cm-1): 3397.6 (N-H amine), 3053.4(C-H aromatic), 2938.4 (C-H aliphatic), 1601.4(C=O), 1235.7 (C-N amine).1H NMR (500 MHz, CDCl3): δ = 7.32 – 7.24 (2H, m, Ar-H), 7.21 – 7.14 (2H, m, Ar-H), 6.98 – 6.91 (2H, m, Ar-H), 6.91 – 6.83 (1H, m, Ar-H), 6.73 – 6.65 (1H, m, Ar-H), 6.65 – 6.57 (2H, m, Ar-H), 3.46 (1H, br. s, NH-H), 3.39 – 3.28 (1H, m, CH-H), 3.27 – 3.18 (4H, m, CH2-H), 2.92 (2H d, *J* = 11.0 Hz, CH2-H), 2.65 – 2.57 (4H, m, CH2-H), 2.46 – 2.35 (4H, m, CH2-H), 2.15 (2H, t, *J* = 11.1 Hz, CH2-H), 2.08 (2H, d, *J* = 12.1 Hz, CH2-H), 1.62 – 1.44 (6H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 151.3, 147.0, 129.3, 129.1, 119.6, 117.2, 116.0, 113.2, 58.5, 58.4, 53.2, 52.4, 49.1, 32.4, 25.0, 24.9 ppm.

*1-(4-(4-(3-methoxyphenyl) piperazin-1-yl) butyl)-N-phenylpiperidin-4-amine (****5b****).* Yield: 0.42 g (84.2 %); pale yellow oil. IR (ATR, cm-1): 3307.5 (N-H amine), 3052.1(C-H aromatic), 2939.0 (C-H aliphatic), 1601.1(C=O), 1241.2 (C-N amine).1H NMR (500 MHz, CDCl3): δ = 7.19 – 7.12 (2H, m, Ar-H), 7.03 – 6.94 (1H, m, Ar-H), 6.97 – 6.89 (2H, m, Ar-H), 6.88 – 6.82 (1H, m, Ar-H), 6.72 – 6.64 (1H, m, Ar-H), 6.63 – 6.55 (2H, m, Ar-H), 3.85 (3H, s, OCH3-H), 3.53 (1H, br. s, NH-H), 3.40 – 3.24 (1H, m, CH-H), 3.10 (4H, br. s, CH2-H), 2.91 (2H, d, *J* = 11.2 Hz, CH2-H), 2.66 (4H, br. s, CH2-H), 2.47 – 2.35 (4H, m, CH2-H), 2.15 (2H, t, *J* = 11.0 Hz, CH2-H), 2.07 (2H, d, *J* = 11.8 Hz, CH2-H), 1.56 (4H, br. s, CH2-H), 1.55 – 1.44 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 153.8, 148.6, 142.9, 130.9, 124.5, 122.6, 119.8, 118.8, 114.8, 112.8, 60.1, 56.9, 55.0, 54.0, 52.2, 51.4, 33.9, 26.6 ppm.

*1-(4-(4-(2,3-dichlorophenyl) piperazin-1-yl) butyl)-N-phenylpiperidin-4-amine (****5c****).* Yield: 0.46 g (83.1 %); pale yellow oil. IR (ATR, cm-1): 3399.9 (N-H amine), 3051.9 (C-H aromatic), 2936.4 (C-H aliphatic), 1602.2 (C=O), 1242.3 (C-N amine), 781.3 (C-Cl). 1H NMR (500 MHz, CDCl3): δ = 7.19 – 7.05 (4H, m, Ar-H), 6.70 – 6.63 (1H, m, Ar-H), 6.62 – 6.56 (3H, m, Ar-H), 3.50 (1H, br. s, NH-H), 3.34 – 3.21 (1H, m, CH-H), 3.12 – 2.93 (4H, m, CH2-H), 2.86 (4H, d, *J* = 10.7 Hz, CH2-H), 2.39 – 2.29 (4H, m, CH2-H), 2.15 – 1.99 (6H, m, CH2-H), 1.55 – 1.47 (4H, m, CH2-H), 1.50 – 1.41 (2H, m, CH2-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 13C NMR (126 MHz, CDCl3) δ 151.8, 147.2, 134.1, 129.4, 127.5, 124.7, 124.6, 118.8, 117.3, 113.3, 58.7, 52.6, 51.4, 50.1, 46.4, 32.7, 25.4.ppm.

*N-Phenyl-N-(1-(4-(4-phenylpiperazin-1-yl) butyl) piperidin-4-yl) propionamide (****1a****).* Yield: 0.22 g (83 %); pale yellow oil. IR (ATR, cm-1): 3058.6 (C-H aromatic); 2939.1(C-H aliphatic); 1655.8 (C=O); 1238.4(C-N-amine). 1H NMR (500 MHz, CDCl3): δ = 7.49 – 7.32 (3H, m, Ar-H), 7.29 – 7.20 (2H, m, Ar-H), 7.11 – 7.00 (2H, m, Ar-H), 6.94 – 6.88 (2H, m, Ar-H), 6.89 – 6.81 (1H, m, Ar-H), 4.73 – 4.58 (1H, m, CH-H), 3.22 – 3.15 (4H, m, CH2-H), 2.94 (2H, d, *J* = 11.4 Hz, CH2-H), 2.62 – 2.53 (4H, m, CH2-H), 2.34 (4H, dt, *J* = 20.1, 6.2 Hz, CH2-H), 2.08 (2H, t, *J* = 11.5 Hz, CH2-H), 1.92 (2H, q, *J* = 7.3 Hz, CH2-H), 1.78 (2H, d, *J* = 11.6 Hz, CH2-H), 1.53 – 1.44 (4H, m, CH2-H, partially overlapped), 1.44 – 1.35 (2H, m, CH2-H, partially overlapped), 1.01 (3H, t, *J* = 7.4 Hz, CH3-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 173.6, 151.4, 138.9, 130.5, 129.4, 129.2, 129.2, 128.4, 119.7, 116.1, 58.5, 58.4, 53.3, 53.2, 52.2, 49.1, 30.5, 28.6, 25.1, 24.9, 9.7 ppm. HRMS-HESI-Orbitrap: calcd. for C28H40N4O [M+H] + 449.32749; found 449.32844.

*N-(1-(4-(4-(3-methoxyphenyl) piperazin-1-yl) butyl) piperidin-4-yl)-N-phenylpropionamide (****1b****).* Yield: 0.25 g (85.6 %); pale yellow oil. IR (ATR, cm-1): 3058.2 (C-H aromatic); 2939.1 (C-H alkane); 1655.5 (C=O); 1241.4 (C-N amine). 1H NMR (500 MHz, CDCl3): δ = 7.44 – 7.34 (3H, m, Ar-H), 7.11 – 7.04 (2H, m, Ar-H), 7.03 – 6.97 (1H, m, Ar-H), 6.96 – 6.90 (2H, m, Ar-H), 6.89 – 6.83 (1H, m, Ar-H), 4.78 – 4.54 (1H, m, CH-H), 3.86 (3H, s, OCH3-H), 3.09 (4H s, CH2-H), 2.95 (2H, d, *J* = 11.4 Hz, CH2-H), 2.64 (4H, s, CH2-H), 2.44 – 2.36 (2H, m, CH2-H), 2.37 – 2.28 (2H, m, CH2-H), 2.08 (2H, *t*, J = 11.3 Hz, CH2-H), 1.93 (2H, q, *J* = 7.3 Hz, CH2-H), 1.79 (2H, d, *J* = 11.5 Hz, CH2-H), 1.58 – 1.44 (4H, m, CH2-H, partially overlapped), 1.46 – 1.34 (2H, m, CH2-H, partially overlapped), 1.02 (3H, t, *J* = 7.4 Hz, CH3-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 173.6, 152.3, 141.4, 138.9, 130.5, 129.4, 128.3, 123.0, 121.1, 118.3, 111.3, 58.6, 58.5, 55.4, 53.5, 53.2, 52.3, 50.6, 30.5, 28.6, 25.2, 24.9, 9.7 ppm. HRMS-HESI-Orbitrap: calcd. for C29H42N4O2 [M+H] + 479.33805; found 479.33886.

*N-(1-(4-(4-(2,3-dichlorophenyl) piperazin-1-yl) butyl) piperidin-4-yl)-N-phenylpropionamide (****1c****).* Yield: 0.26 g (84.2 %); pale yellow oil. IR (ATR, cm-1): 3057.9 (C-H aromatic); 2940.2 (C-H aliphatic); 1653.8 (C=O); 1242.7 (C-N amine), 735.7(C-Cl). 1H NMR (500 MHz, CDCl3): δ = 7.45 – 7.33 (3H, m, Ar-H), 7.16 – 7.10 (2H, m, Ar-H), 7.10 – 7.02 (2H, m, Ar-H), 6.99 – 6.89 (1H, m, Ar-H), 4.71 – 4.60 (1H, m, CH-H), 3.05 (4H s, CH2-H), 2.96 (2H, d, *J* = 11.5 Hz, CH2-H), 2.62 (4H s, CH2-H), 2.47 – 2.37 (2H, m, CH2-H), 2.37 – 2.30 (2H, m, CH2-H), 2.10 (2H, t, *J* = 11.6 Hz, CH2-H), 1.97 – 1.88 (2H, m, CH2-H), 1.78 (2H, d, *J* = 12.6 Hz, CH2-H), 1.53 – 1.46 (4H, m, CH2-H, partially overlapped), 1.46 – 1.35 (2H, m, CH2-H, partially overlapped), 1.01 (3H, t, *J* = 7.4 Hz, CH3-H) ppm. 13C NMR (126 MHz, CDCl3): δ = 173.6, 151.3, 138.9, 134.1, 130.4, 129.4, 128.4, 127.5, 124.6, 118.7, 58.4, 58.3, 53.3, 53.1, 52.2, 51.2, 30.4, 28.6, 24.9, 24.8, 9.7 ppm. HRMS-Heated ESI-Orbitrap: calcd. for C28H38Cl2N4O [M+H] + 517.24954; found 517.25082.

# **Spectra of the final compounds**

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# **Spectra of the undesired products**

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