



SUPPLEMENTARY MATERIAL TO
**Synthesis of novel 2-(piperazino-1-yl-alkyl)-1H-benzimidazole
derivates and assessment of their interactions with the
D₂ dopamine receptor**

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ANALYTICAL AND SPECTRAL DATA FOR THE SYNTHESIZED COMPOUNDS

Methyl 2-[4-(2-methoxyphenyl)piperazin-1-yl]acetate (3a). Yield: 95.3 %; orange crystals; m.p.: 50 °C; IR (ATR, cm⁻¹): 2820.2, 1724.3, 1500.9, 1451.7, 1241.4, 1027.1, 751.3; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 2.75–2.80 (4H, *m*, piperazine), 3.12–3.17 (4H, *m*, piperazine), 3.29 (2H, *s*, CH₂), 3.74 (3H, *s*, COOCH₃), 3.85 (3H, *s*, OCH₃), 6.84–7.01 (4H, *m*, Ar-H); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 50.22, 51.56, 53.20, 55.16, 59.43, 111.01, 118.11, 120.86, 122.86, 141.03, 152.10, 170.64; MS (*m/z*, [M+H]⁺): Calcd. for C₁₄H₂₀N₂O₃: 265.15467. Found: 265.15493.

Ethyl 3-[4-(2-methoxyphenyl)piperazin-1-yl]propanoate (3b). Yield: 84.2 %; oil; IR (ATR, cm⁻¹): 2818.6, 1734.0, 1501.0, 1452.7, 1241.3, 1026.5, 749.6; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 1.28 (3H, *t*, *J* = 7.4 Hz, CH₃), 2.51–2.59 (2H, *m*, CH₂), 2.66–2.71 (*m*, 4H, piperazine), 2.75–2.83 (*m*, 2H, CH₂), 3.08–3.10 (*m*, 4H, piperazine), 3.86 (*s*, 3H, OCH₃), 4.16 (*q*, *J* = 7.4 Hz, *J* = 11.4 Hz, 2H, COOCH₂), 6.84–7.03 (*m*, 4H, Ar-H); ¹³C-NMR (50 MHz, CDCl₃), δ / ppm: 14.04, 32.13, 50.39, 52.94, 53.45, 55.13, 60.17, 110.99, 118.00, 120.80, 122.73, 141.12, 152.08, 172.35; MS (*m/z*, [M+H]⁺): Calcd. for C₁₆H₂₄N₂O₃: 293.18597. Found: 293.18584.

Ethyl 4-[4-(2-methoxyphenyl)piperazin-1-yl]butanoate (3c). Yield: 86.6 %; oil; IR (ATR, cm⁻¹): 2817.0, 1732.8, 1501.1, 1452.5, 1241.3, 1028.1, 750.6; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 1.26 (3H, *t*, *J* = 7.4 Hz, CH₃), 1.78–1.93 (2H, *m*, CH₂), 2.33–2.47 (4H, *m*, CH₂), 2.63–2.66 (4H, *m*, piperazine), 3.09 (4H, *s*,

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piperazine), 3.86 (3H, *s*, OCH₃), 4.13 (2H, *q*, *J* = 6.6 Hz & *J* = 7.4 Hz, COOCH₂), 6.83–7.04 (4H, *m*, Ar-H); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 14.11, 22.03, 32.19, 50.52, 53.23, 55.18, 57.64, 60.12, 111.01, 118.03, 120.84, 122.73, 141.25, 152.16, 173.49; MS (*m/z*, [M+H]⁺) Calcd. for C₁₇H₂₆N₂O₃: 307.20162. Found: 307.20152.

Methyl 5-[4-(2-methoxyphenyl)piperazin-1-yl]pentanoate (3d). Yield: 69.0 %; oil; IR (ATR, cm⁻¹): 2818.4, 1737.6, 1500.9, 1450.9, 1241.1, 1027.2, 751.1; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 1.67–1.71 (4H, *m*, CH₂), 2.35–2.38 (2H, *m*, CH₂), 2.51–2.54 (2H, *m*, CH₂), 2.76 (4H, *s*, piperazine), 3.17 (4H, *s*, piperazine), 3.67 (3H, *s*, COOCH₃), 3.86 (3H, *m*, OCH₃), 6.85–7.02 (4H, *m*, Ar-H); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 22.41, 25.80, 33.35, 50.10, 50.90, 52.93, 54.78, 57.70, 110.64, 117.63, 120.47, 122.33, 140.85, 151.75, 173.40; MS (*m/z*, [M+H]⁺) Calcd. for C₁₇H₂₆N₂O₃: 307.20162. Found: 307.20075.

Ethyl 6-[4-(2-methoxyphenyl)piperazin-1-yl]hexanoate (3e). Yield: 91.0 %; oil; IR (ATR, cm⁻¹): 2814.2, 1734.5, 1501.2, 1452.5, 1240.9, 1029.8, 748.0; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 1.22 (3H, *t*, *J* = 7.4 Hz, CH₃), 1.29–1.39 (2H, *m*, CH₂), 1.45–1.71 (4H, *m*, CH₂), 2.24–2.41 (4H, *m*, CH₂), 2.61 (4H, *s*, piperazine), 3.07 (4H, *s*, piperazine), 3.82 (3H, *s*, OCH₃), 4.09 (2H, *q*, *J* = 6 Hz & *J* = 8 Hz, COOCH₂), 6.80–7.00 (4H, *m*, Ar-H); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 14.07, 24.72, 26.42, 26.96, 34.08, 50.47, 53.33, 55.13, 58.42, 60.01, 110.95, 118.00, 120.80, 122.70, 141.23, 152.10, 173.59; MS (*m/z*, [M+H]⁺) Calcd. for C₁₉H₃₀N₂O₃: 335.23292. Found: 335.23342.

Ethyl 7-[4-(2-methoxyphenyl)piperazin-1-yl]heptanoate (3f). Yield: 92.2 %; oil; IR (ATR, cm⁻¹): 2818.4, 1734.5, 1501.4, 1450.3, 1240.1, 1028.6, 750.3; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 1.20 (3H, *t*, *J* = 7.4 Hz, CH₃), 1.28–1.34 (4H, *m*, CH₂), 1.46–1.63 (4H, *m*, CH₂), 2.21–2.35 (4H, *m*, CH₂), 2.60 (4H, *s*, piperazine), 3.06 (4H, *s*, piperazine), 3.80 (3H, *s*, OCH₃), 4.07 (2H, *q*, *J* = 7.2 Hz & *J* = 7.4 Hz, COOCH₂), 6.78–6.99 (4H, *m*, Ar-H); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 14.02, 24.65, 26.52, 27.03, 28.82, 34.03, 50.43, 53.29, 55.07, 58.53, 59.90, 110.90, 117.94, 120.75, 122.62, 141.19, 152.05, 173.55; MS (*m/z*, [M+H]⁺) Calcd. for C₂₀H₃₂N₂O₃: 349.24857. Found: 349.24825.

Methyl 8-[4-(2-methoxyphenyl)piperazin-1-yl]octanoate (3g). Yield: 82.8 %; oil; IR (ATR, cm⁻¹): 2828.2, 1754.6, 1521.4, 1448.8, 1236.3, 1025.6, 755.4; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 1.26–1.32 (6H, *m*, CH₂), 1.53–1.66 (4H, *m*, CH₂), 2.27–2.43 (4H, *m*, CH₂), 2.65–2.67 (4H, *m*, piperazine), 3.11 (4H, *s*, piperazine), 3.67 (3H, *s*, COOCH₃), 3.86 (3H, *s*, OCH₃), 6.84–7.04 (4H, *m*, Ar-H); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 24.79, 26.74, 27.34, 29.09, 33.97, 50.56, 51.33, 53.43, 55.25, 58.76, 111.06, 118.12, 120.91, 122.79, 141.33, 152.22, 174.24; MS (*m/z*, [M+H]⁺) Calcd. for C₂₀H₃₂N₂O₃: 349.24857. Found: 349.24849.

2-{[4-(2-Methoxyphenyl)piperazin-1-yl]methyl}-1H-benzimidazole (5a).

Yield: 16 %; oil; IR (ATR, cm^{-1}): 2817.2, 1502.0, 1455.7, 1240.3, 1026.5, 743.0; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 2.75–2.80 (4H, *m*, piperazine), 3.08–3.13 (4H, *m*, piperazine), 3.84 (3H, *s*, OCH_3), 3.91 (2H, *s*, CH_2), 6.84–7.06 (4H, *m*, Ar-H), 7.20–7.27 (2H, *m*, Ar-H), 7.57–7.60 (2H, *m*, Ar-H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 50.41, 53.64, 55.31, 56.46, 111.23, 118.14, 120.93, 122.02, 122.40, 123.11, 140.90, 151.90, 152.23; MS (m/z , $[\text{M}+\text{H}]^+$) Calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}$: 323.18664. Found: 323.18515.

2-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethyl}-1H-benzimidazole (5b).

Yield: 36.5 %; oil; IR (ATR, cm^{-1}): 2818.4, 1500.6, 1456.7, 1240.0, 1026.3, 745.2; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 2.77–2.92 (6H, *m*, 4H piperazine and 2H CH_2), 3.11–3.18 (6H, *m*, 4H piperazine and 2H CH_2), 3.87 (3H, *s*, OCH_3), 6.87–7.04 (4H, *m*, Ar-H), 7.17–7.25 (2H, *m*, Ar-H), 7.52–7.57 (2H, *m*, Ar-H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 25.03, 50.76, 52.94, 55.33, 58.06, 111.23, 114.67, 118.13, 120.95, 122.02, 123.24, 140.78, 152.21, 154.52; MS (m/z , $[\text{M}+\text{H}]^+$) Calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}$: 337.20229. Found: 337.20205.

2-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-1H-benzimidazole (5c).

Yield: 55.7 %; oil; IR (ATR, cm^{-1}): 2825.5, 1500.7, 1452.9, 1241.4, 1026.5, 746.5; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 1.96–2.08 (2H, *m*, CH_2), 2.64 (2H, *t*, $J = 5.6$ Hz, CH_2), 2.72 (4H, *s*, piperazine), 3.06–3.16 (6H, *m*, 4H piperazine and 2H CH_2), 3.85 (3H, *s*, OCH_3), 6.86–7.05 (4H, *m*, Ar-H), 7.16–7.18 (2H, *m*, Ar-H), 7.52–7.57 (2H, *m*, Ar-H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 23.61, 28.90, 50.49, 53.25, 55.24, 58.72, 111.18, 114.46, 118.03, 120.98, 121.66, 123.18, 140.77, 152.18, 155.58; MS (m/z , $[\text{M}+\text{H}]^+$) Calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}$: 351.21794. Found: 351.21682.

2-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1H-benzimidazole (5d).

Yield: 90.6 %; oil; IR (ATR, cm^{-1}): 2818.3, 1499.7, 1456.0, 1244.1, 1028.9, 793.3; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 1.55–1.70 (2H, *m*, CH_2), 1.83–1.94 (2H, *m*, CH_2), 2.43 (2H, *t*, $J = 6.8$ Hz, CH_2), 2.64 (4H, *s*, piperazine), 2.98 (2H, *t*, $J = 6.8$ Hz, CH_2), 3.12 (4H, *s*, piperazine), 3.84 (3H, *s*, OCH_3), 6.84–7.05 (4H, *m*, Ar-H), 7.14–7.21 (2H, *m*, Ar-H), 7.51–7.56 (2H, *m*, Ar-H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 25.38, 25.81, 28.45, 50.34, 53.18, 55.24, 57.24, 111.19, 114.52, 118.16, 120.98, 121.88, 123.08, 138.57, 140.94, 152.19, 155.38; MS (m/z , $[\text{M}+\text{H}]^+$) Calcd. for $\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}$: 365.23359. Found: 365.23263.

2-{5-[4-(2-Methoxyphenyl)piperazin-1-yl]pentyl}-1H-benzimidazole (5e).

Yield: 43.0 %; brown crystals, m.p.: 63 °C; IR (ATR, cm^{-1}): 2825.2, 1500.3, 1454.9, 1240.7, 1023.6, 752.8; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 1.33–1.48 (2H, *m*, CH_2), 1.60–1.75 (2H, *m*, CH_2), 1.80–1.93 (2H, *m*, CH_2), 2.54–2.62 (2H, *m*, CH_2), 2.84–2.95 (6H, *m*, 4H piperazine and 2H CH_2), 3.17–3.19 (4H, *m*, piperazine), 3.86 (3H, *s*, OCH_3), 6.85–7.06 (4H, *m*, Ar-H), 7.19–7.22 (2H, *m*, Ar-H), 7.54–7.58 (2H, *m*, Ar-H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 ,

δ / ppm): 25.54, 26.62, 27.82, 28.84, 49.94, 53.00, 55.20, 57.97, 111.15, 114.50, 118.18, 120.95, 121.88, 123.10, 138.52, 140.78, 152.12, 155.31; MS (m/z , $[M+H]^+$) Calcd. for $C_{23}H_{30}N_4O$: 379.24924. Found: 379.24889.

2-{6-[4-(2-Methoxyphenyl)piperazin-1-yl]hexyl}-1H-benzimidazole (5f). Yield: 69.0 %; brown crystals; m.p.: 134 °C; IR (ATR, cm^{-1}): 2828.5, 1503.0; 1454.6, 1240.6, 1019.5, 750; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.26–1.58 (6H, *m*, CH_2), 1.76–1.92 (2H, *m*, CH_2), 2.37 (2H, *t*, $J = 7.4$ Hz, CH_2), 2.61–2.65 (4H, *m*, piperazine), 2.90 (2H, *t*, $J = 8$ Hz, CH_2), 3.11 (4H, *s*, piperazine), 3.85 (3H, *s*, OCH_3), 6.84–7.04 (4H, *m*, Ar-H), 7.18–7.27 (2H, *m*, Ar-H), 7.51–7.58 (2H, *m*, Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 26.12, 26.94, 28.00, 28.96, 29.13, 50.29, 53.20, 55.22, 58.37, 111.13, 114.54, 118.18, 121.97, 121.89, 123.02, 138.55, 141.01, 152.17, 155.38; MS (m/z , $[M+H]^+$) Calcd. for $C_{24}H_{32}N_4O$: 393.26489. Found: 393.26320.

2-{7-[4-(2-Methoxyphenyl)piperazin-1-yl]heptyl}-1H-benzimidazole (5g). Yield: 72.0 %; oil; IR (ATR, cm^{-1}): 2962.9, 1497.9, 1449.6, 1261.7, 1026.4, 744.5; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.26–1.49 (8H, *m*, CH_2), 1.79–1.86 (2H, *m*, CH_2), 2.38 (2H, *t*, $J = 7.4$ Hz, CH_2), 2.68 (4H, *s*, piperazine), 2.89 (2H, *t*, $J = 8$ Hz, CH_2), 3.13 (4H, *s*, piperazine), 3.85 (3H, *s*, OCH_3), 6.84–6.94 (4H, *m*, Ar-H), 7.19–7.24 (2H, *m*, Ar-H), 7.52–7.56 (2H, *m*, Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 26.45, 27.21, 28.11, 29.05, 29.29, 50.40, 53.35, 55.28, 58.65, 111.13, 114.64, 118.22, 120.98, 121.99, 123.01, 138.47, 141.11, 152.22, 155.26; MS (m/z , $[M+H]^+$) Calcd. for $C_{25}H_{34}N_4O$: 407.28054. Found: 407.28007.

5-Methoxy-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-1H-benzimidazole (5h). Yield: 88.0%; oil; IR (ATR, cm^{-1}): 2817.0, 1498.4, 1458.2, 1237.6, 1027, 751.2; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.64–1.76 (2H, *m*, CH_2), 1.84–1.98 (2H, *m*, CH_2), 2.49 (2H, *t*, $J = 7.4$ Hz, CH_2), 2.70 (4H, *s*, piperazine), 2.96 (2H, *t*, $J = 7.2$ Hz, CH_2), 3.16 (4H, *s*, piperazine), 3.83 (3H, *s*, OCH_3), 3.87 (3H, *s*, OCH_3), 6.81–7.08 (7H, *m*, Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 25.09, 25.87, 28.40, 50.54, 53.31, 55.33, 55.82, 57.09, 111.17, 118.18, 121.02, 123.17, 141.03, 152.26, 155.98; MS (m/z , $[M+H]^+$) Calcd. for $C_{23}H_{30}N_4O_2$: 395.24415. Found: 395.24331.

5-Methoxy-2-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}-1H-benzimidazole (5i). Yield: 73.0 %; oil; IR (ATR, cm^{-1}): 2832.2, 1500.2, 1455.8, 1242.6, 1027.7, 752.9; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.38–1.45 (2H, *m*, CH_2), 1.71–1.90 (4H, *m*, CH_2), 2.77–2.94 (4H, *m*, CH_2), 3.09 (4H, *s*, piperazine), 3.28 (4H, *s*, piperazine), 3.83 (3H, *s*, OCH_3), 3.87 (3H, *s*, OCH_3), 6.82–6.92 (4H, *m*, Ar-H), 7.02–7.08 (1H, *m*, Ar-H), 7.46 (2H, *d*, $J = 8.0$ Hz, Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 22.59, 22.97, 25.21, 27.00, 48.25, 52.18, 55.38, 55.80, 56.82, 97.42, 111.26, 111.63, 115.19, 118.51, 121.09, 123.92, 138.19, 139.72,

152.10, 154.72, 156.18; MS (m/z , $[M+H]^+$) Calcd. for $C_{24}H_{32}N_4O_2$: 409.25980. Found: 409.26000.

5-Methoxy-2-{6-[4-(2-methoxyphenyl)piperazin-1-yl]hexyl}-1H-benzimidazole (5j). Yield: 67.1 %; oil; IR (ATR, cm^{-1}): 2856.0, 1501.3, 1457.2, 1247.5, 1026.2, 753.3; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.35–1.55 (4H, *m*, CH_2), 1.63–1.88 (2H, *m*, CH_2), 2.41 (2H, *t*, $J = 8.0$ Hz, CH_2), 2.67–2.72 (4H, *m*, piperazine), 2.85 (2H, *t*, $J = 7.4$ Hz, CH_2), 3.10–3.15 (4H, *m*, piperazine), 3.79 (3H, *s*, OCH_3), 3.85 (3H, *s*, OCH_3), 4.21–4.24 (2H, *m*, CH_2), 6.81–7.03 (4H, *m*, Ar-H), 7.38–7.43 (1H, *m*, Ar-H), 7.50–7.55 (1H, *m*, Ar-H), 7.67–7.74 (1H, *m*, Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 22.85, 23.59, 25.83, 26.78, 27.82, 50.05, 53.11, 55.24, 55.71, 58.22, 97.59, 111.12, 115.16, 118.18, 120.95, 123.10, 130.85, 140.87, 152.14, 154.98, 155.91; MS (m/z , $[M+H]^+$) Calcd. for $C_{25}H_{34}N_4O_2$: 423.27545. Found: 423.27570.

5-Methoxy-2-{7-[4-(2-methoxyphenyl)piperazin-1-yl]heptyl}-1H-benzimidazole (5k). Yield: 62.3 %; oil; IR (ATR, cm^{-1}): 2927.7, 1501.3, 1499.0, 1453.5, 1240.3, 1026.6, 748.2; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.58 (6H, *s*, CH_2), 2.16–2.23 (2H, *m*, CH_2), 2.53 (2H, *s*, CH_2), 2.85 (6H, *m*, 4H piperazine and 2H CH_2), 3.15 (6H, *m*, 4H piperazine and 2H CH_2), 3.81 (3H, *s*, OCH_3), 3.85 (3H, *s*, OCH_3), 6.84–7.01 (7H, *m* Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 25.57, 27.13, 29.13, 49.53, 52.60, 55.31, 55.77, 57.9, 97.67, 111.11, 118.29, 120.99, 123.20, 140.74, 152.14, 154.93, 155.96; MS (m/z , $[M+H]^+$) Calcd. for $C_{26}H_{36}N_4O_2$: 437.29110. Found: 437.29115.

5-Chloro-2-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-1H-benzimidazole (5l). Yield: 88.4 %; oil; IR (ATR, cm^{-1}): 2811.0, 1501.1, 1447.5, 1239.6, 1027.4, 751.2; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.59–1.69 (2H, *m*, CH_2), 1.82–1.96 (2H, *m*, CH_2), 2.39 (2H, *t*, $J = 7.2$ Hz, CH_2), 2.65 (4H, *s*, piperazine), 2.96 (2H, *t*, $J = 6.6$ Hz, CH_2), 3.12 (4H, *s*, piperazine), 3.84 (3H, *s*, OCH_3), 6.84–7.02 (4H, *m*, Ar-H), 7.12–7.17 (1H, *m*, Ar-H), 7.39–7.50 (2H, *m*, Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 25.18, 25.83, 28.45, 50.38, 53.18, 55.24, 57.11, 111.12, 114.48, 115.19, 118.16, 120.97, 122.39, 123.17, 127.43, 140.79, 152.16, 156.67; MS (m/z , $[M+H]^+$) Calcd. for $C_{22}H_{27}ClN_4O$: 399.19462. Found: 399.19367.

5-Chloro-2-{5-[4-(2-methoxyphenyl)piperazin-1-yl]pentyl}-1H-benzimidazole (5m). Yield: 65 %; oil; IR (ATR, cm^{-1}): 2824.8, 1500.7, 1450.7, 1241.2, 1027.0, 749.9; 1H -NMR (200 MHz, $CDCl_3$, δ / ppm): 1.35–1.62 (4H, *m*, CH_2), 1.77–1.91 (2H, *m*, CH_2), 2.39 (2H, *t*, $J = 8.0$ Hz, CH_2), 2.64 (4H, *s*, piperazine), 2.89 (2H, *t*, $J = 8.0$ Hz, CH_2), 3.11 (4H, *s*, piperazine), 3.85 (3H, *s*, OCH_3), 6.84–7.06 (4H, *m*, Ar-H), 7.13–7.18 (1H, *m*, Ar-H), 7.40–7.50 (2H, *m*, Ar-H); ^{13}C -NMR (50 MHz, $CDCl_3$, δ / ppm): 25.96, 26.63, 27.67, 28.98, 50.38, 53.33, 55.27, 58.22, 111.15, 118.20, 121.00, 122.50, 123.13, 127.58, 140.96, 152.19, 156.32; MS (m/z , $[M+H]^+$) Calcd. for $C_{23}H_{29}ClN_4O$: 413.21027. Found: 413.20891.

5-Chloro-2-{6-[4-(2-methoxyphenyl)piperazin-1-yl]hexyl}-1H-benzimidazole (5n). Yield: 74 %; oil; IR (ATR, cm^{-1}): 2825.8, 1500.6, 1451.2, 1241.8, 1027.6, 750.4; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 1.30–1.46 (6H, *m*, CH_2), 1.72–1.83 (2H, *m*, CH_2), 2.34 (2H, *t*, $J = 8.6$ Hz, CH_2), 2.63 (4H, *s*, piperazine), 2.86 (2H, *t*, $J = 7.4$ Hz, CH_2), 3.09 (4H, *s*, piperazine), 3.84 (3H, *s*, OCH_3), 6.84–7.06 (4H, *m*, Ar-H), 7.12–7.18 (1H, *m*, Ar-H), 7.38–7.48 (2H, *m*, Ar-H); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 26.27, 26.96, 27.91, 28.89, 29.09, 50.45, 53.27, 55.22, 58.42, 111.10, 118.16, 120.97, 122.46, 123.08, 127.52, 140.98, 152.14, 156.51; MS (m/z , $[\text{M}+\text{H}]^+$) Calcd. for $\text{C}_{24}\text{H}_{31}\text{ClN}_4\text{O}$: 427.22592. Found: 427.22408.

SUMMARY RESULTS OF MD SIMULATIONS

TABLE S-I. DRD2–ligand key interactions observed in 100 ns MD simulations

Ligand	Residue											
	Leu 94	Trp 100	Asp 114	Cys 118	Ile 184	Phe 382	Trp 386	Phe 389	Phe 390	Tyr 408	Thr 412	Tyr 416
5e		54	81	68	27		76	65	42	65	37	
5f	21	31	79	36	40		82	74	20	33	42	
5h		67	81	58			84	85	24	36		
5i	50	89	80	75			96	84	42	22	30	
5j	36	94	82	73	24	32	98	53	31	25		
5l		22	82	64	26		95	75	34	37		
5m		75	84	69			78	50	49	63	40	
5n	32	42	80	32			82	68	35	28		32

D2DR–ligand interactions presented in more than 20 % of the MS simulation time are shown. The numbers provided in the Table refer to the percentage of the total simulation time in which one interaction is observed to occur. Interacting residues in OBS are shaded in grey colour; residues found in EBP are white.