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SUPPLEMENTARY MATERIAL TO

Synthesis and biological evaluation of 5-substituted derivatives of benzimidazole

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ANALYTIC AND SPECTRAL DATA FOR COMPOUNDS **3** AND **20**–**27**

*Ethyl 4-[4-(2-chlorophenyl)piperazin-1-yl]butanoate (**3**).* ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 1.26 (3H, *t*, *J* = 6.6 Hz, CH_3), 1.85 (2H, *m*, CH_2), 2.33––2.48 (4H, *m*, CH_2COO and CH_2N), 2.63 (4H, *t*, *J* = 4.6 Hz, CH_2), 3.07 (4H, *t*, *J* = 5.0 Hz, CH_2), 4.16 (2H, *q*, *J* = 7.4 Hz, OCH_2), 6.91–7.37 (4H, *m*, 2-chlorophenyl group); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 14.15 (1C, CH_3), 22.09 (1C, CH_2), 32.19 (1C, **C**H_2COO), 51.13 (2C, CH_2), 53.18 (2C, CH_2), 57.57 (1C, CH_2N), 60.18 (1C, OCH_2), 120.26 (1C, CH–C_6, 2-chlorophenyl-group), 123.50 (1C, CH–C_4, 2-chlorophenyl-group), 127.49 (1C, CH–C_5, 2-chlorophenyl group), 128.67 (1C, C–C_2, 2-chlorophenyl group), 130.55 (1C, CH–C_3, 2-chlorophenyl group), 149.28 (1C, C–C_1, 2-chlorophenyl group), 173.50 (1C, CO).

*2-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}-1*H*-benzimidazole (**20**).* Yield: 579 mg (29 %); IR (ATR, cm^{-1}): 2957, 1617, 1588, 1480, 1234; ^{1}H--NMR: (200 MHz, $CDCl_3$, δ / ppm): 2.04 (2H, *m*, CH_2), 2.65 (2H, *t*, *J* = 5.6 Hz, CH_2N), 2.74 (4H, *t*, *J* = 5.2 Hz, CH_2), 3.08 (2H, *t*, *J* = 6.6 Hz, CH_2), 3.17 (4H, *t*, *J* = 4.4 Hz, CH_2), 6.97–7.59 (8H, *m*, 2-chlorophenyl group and benzimidazole), 9.64 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 23.52 (1C, CH_2), 29.08 (1C, CH_2), 51.13 (2C, CH_2), 53.29 (2C, CH_2), 58.79 (1C, CH_2N), 114.58 (2C, CH–C_4 and CH–C_7, benzimidazole), 120.19 (1C, CH–C_6, 2-chlorophenyl group), 121.79 (2C, CH–C_5 and C_6, benzimidazole), 124.01 (1C, CH–C_4, 2-chlorophenyl-group), 127.72 (1C, CH–C_5, 2-chlorophenyl-group), 128.80 (1C, C–C_2, 2-chlorophenyl-group), 130.75 (1C, CH–C_3, 2-chlorophenyl-group), 138.92 (2C, C–C_{3a} and C–C_{7a}, benzimidazole), 148.83 (1C, C–C_1, 2-chlorophenyl group), 155.51 (1C, C–C_2, benzimidazole); MS (*m*/*z*): 355.16927 ([M+H]$^+$, $C_{20}H_{23}ClN_4$).

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*2-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}-5-fluoro-1*H-*benzimidazole* ***(21)***. Yield: 1.38 g (96 %); IR (ATR, cm^{-1}): 2955, 1629, 1591, 1480, 1235; ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 2.04 (2H, *m*, CH_2), 2.70 (2H, *t*, *J* = 5.6 Hz, CH_2N), 2.80 (4H, *t*, *J* = 4.9 Hz, CH_2), 3.12 (2H, *t*, *J* = 6.2 Hz, CH_2), 3.21 (4H, *t*, *J* = 4 Hz, CH_2), 6.89–7.42 (7H, *m*, 2-chlorophenyl group and benzimidazole), 13.06 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 23.07 (1C, CH_2), 29.61 (1C, CH_2), 51.24 (2C, CH_2), 53.38 (2C, CH_2), 59.08 (1C, CH_2N), 109.57 (1C, CH–C_4, benzimidazole), 110.08 (1C, CH–C_6, benzimidazole), 120.07 (1C, CH–C_7, benzimidazole), 120.17 (1C, CH–C_6, 2-chlorophenyl group), 124.17 (1C, CH–C_4, 2-chlorophenyl-group), 127.82 (1C, CH–C_5, 2-chlorophenyl group), 128.85 (1C, C–C_2, 2-chlorophenyl group), 130.84 (1C, CH–C_3, 2-chlorophenyl group), 136.40 (1C, C–C_{7a}, benzimidazole), 138.80 (1C, C–C_{3a}, benzimidazole), 148.72 (1C, C–C_1, 2-chlorophenyl group), 156.78 (1C, C–C_2, benzimidazole), 161.48 (1C, C–C_5, benzimidazole); MS (*m*/*z*): 373.15986 ($[M+H]^+$, $C_{20}H_{22}ClFN_4$).

*5-Chloro-2-{3-[4-(2-chlorophenyl)piperazin-1-yl]propyl}-1*H-*benzimidazole* ***(22)***. Yield: 58 mg (11 %); IR (ATR, cm^{-1}): 2951, 1618, 1586, 1477, 1232; ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 2.05 (2H, *m*, CH_2), 2.70 (2H, *t*, *J* = 5 Hz, CH_2N), 2.80 (4H, *t*, *J* = 4.9 Hz, CH_2), 3.13 (2H, *t*, *J* = 6 Hz, CH_2), 3.21 (4H, *t*, *J* = 4.2 Hz, CH_2), 7.00–7.52 (7H, *m*, 2-chlorophenyl group and benzimidazole), 13.00 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 23.11 (1C, CH_2), 29.37 (1C, CH_2), 51.16 (2C, CH_2), 53.31 (2C, CH_2), 58.92 (1C, CH_2N), 114.47 (2C, CH–C_4 and CH–C_7, benzimidazole), 120.19 (1C, CH–C_6, 2-chlorophenyl group), 122.24 (1C, CH–C_6, benzimidazole), 124.16 (1C, CH–C_4, 2-chlorophenyl group), 127.27 (1C, CH–C_5, 2-chlorophenyl group), 127.80 (1C, C–C_5, benzimidazole), 128.82 (1C, C–C_2, 2-chlorophenyl group), 130.80 (1C, CH–C_3, 2-chlorophenyl group), 138.80 (2C, C–C_{3a} and C–C_{7a}, benzimidazole), 148.68 (1C, C–C_1, 2-chlorophenyl group), 156.77 (1C, C–C_2, benzimidazole); MS (*m*/*z*): 389.12990 ($[M+H]^+$, $C_{20}H_{22}Cl_2N_4$).

*5-Bromo-2-{3-[4-(2-chlorophenyl)piperazin-1-yl]propyl}-1*H-*benzimidazole* ***(23)***. Yield: 154 mg (27 %); IR (ATR, cm^{-1}): 2954, 1617, 1587, 1479, 1232; ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 2.04 (2H, *m*, CH_2), 2.68 (2H, *t*, *J* = 5.6 Hz, CH_2N), 2.79 (4H, *t*, *J* = 5.2 Hz, CH_2), 3.10 (2H, *t*, *J* = 4.6 Hz, CH_2), 3.16 (4H, *t*, *J* = 4.6 Hz, CH_2), 6.99–7.78 (7H, *m*, 2-chlorophenyl group and benzimidazole), 9.09 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 23.32 (1C, CH_2), 29.19 (1C, CH_2), 51.11 (2C, CH_2), 53.33 (2C, CH_2), 58.87 (1C, CH_2N), 114.60 (2C, CH–C_4 and CH–C_7, benzimidazole), 120.22 (1C, CH–C_6, 2-chlorophenyl group), 121.86 (1C, C–C_5, benzimidazole), 124.12 (1C, CH–C_4, 2-chlorophenyl group), 124.87 (1C, CH–C_6, benzimidazole), 127.78 (1C, CH–C_5, 2-chlorophenyl group), 128.85 (1C, C–C_2, 2-chlorophenyl-group), 130.80 (1C, CH–C_3, 2-chlorophenyl group), 138.92 (2C, C–C_{3a} and C–C_{7a}, benzimidazole), 148.77

(1C, C–C_1, 2-chlorophenyl group), 156.62 (1C, C–C_2, benzimidazole). MS (*m*/*z*): 433.07952 ($[M+H]^+$, $C_{20}H_{22}BrClN_4$).

*2-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}-5-iodo-1*H-*benzimidazole* ***(24)***. Yield: 333 mg (61 %); IR (ATR, cm^{-1}): 2956, 1618, 1590, 1480, 1233; ^{1}H--NMR (200 MHz, $CDCl_3$, δ / ppm): 2.04 (2H, *m*, CH_2), 2.66 (2H, *t*, *J* = 5.6 Hz, CH_2N), 2.75 (4H, *t*, *J* = 5.2 Hz, CH_2), 3.12 (2H, *t*, *J* = 6.2 Hz, CH_2), 3.20 (4H, *t*, *J* = 6.2 Hz, CH_2), 6.94–7.59 (6H, *m*, 2-chlorophenyl group and benzimidazole), 7.87 (1H, *s*, C_4 benzimidazole), 9.08 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 23.47 (1C, CH_2), 29.08 (1C, CH_2), 51.13 (2C, CH_2), 53.29 (2C, CH_2), 58.81 (1C, CH_2N), 95.01 (1C, C–C_5, benzimidazole), 114.58 (1C, CH–C_7, benzimidazole), 120.21 (1C, CH–C_6, 2-chlorophenyl group), 121.84 (1C, CH–C_4, benzimidazole), 124.05 (1C, CH–C_4, 2-chlorophenyl-group), 127.74 (1C, CH–C_5, 2-chlorophenyl group), 128.82 (1C, C–C_2, 2-chlorophenyl group), 130.78 (2C, CH–C_3, 2-chlorophenyl group and CH–C_6 benzimidazole), 138.90 (2C, C–C_{3a} and C–C_{7a}, benzimidazole), 148.81 (1C, C–C_1, 2-chlorophenyl group), 155.51 (1C, C–C_2, benzimidazole); MS (*m*/*z*): 481.06633 ($[M+H]^+$, $C_{20}H_{22}ClIN_4$).

*2-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}-5-methyl-1*H-*benzimidazole* ***(25)***. Yield: 559 mg (29 %); IR (ATR, cm^{-1}): 2948, 1629, 1538, 1479, 1230; ^{1}H--NMR (200 MHz, $CDCl_3$, δ / ppm): 2.03 (2H, *m*, CH_2), 2.45 (3H, *s*, CH_3), 2.66 (2H, *t*, *J* = 5.6 Hz, CH_2N), 2.77 (4H, *t*, *J* = 5.2 Hz, CH_2), 3.10 (2H, *t*, *J* = 6.2 Hz, CH_2), 3.20 (4H, *t*, *J* = 4.8 Hz, CH_2), 7.00–7.45 (7H, *m*, 2-chlorophenyl group and benzimidazole), 9.22 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 21.59 (1C, CH_3), 23.43 (1C, CH_2), 29.15 (1C, CH_2), 51.18 (2C, CH_2), 53.35 (2C, CH_2), 58.85 (1C, CH_2N), 114.45 (2C, CH–C_4 and CH–C_7, benzimidazole), 120.24 (1C, CH–C_6, 2-chlorophenyl group), 123.25 (1C, CH–C_6, benzimidazole), 124.07 (1C, CH–C_4, 2-chlorophenyl group), 127.74 (1C, CH–C_5, 2-chlorophenyl group), 128.87 (1C, C–C_2, 2-chlorophenyl group), 130.82 (1C, CH–C_3, 2-chlorophenyl group), 131.55 (1C, C–C_5, benzimidazole), 138.80 (2C, C–C_{3a} and C–C_{7a}, benzimidazole), 148.86 (1C, C–C_1, 2-chlorophenyl group), 155.09 (1C, C–C_2, benzimidazole); MS (*m*/*z*): 369.18450 ($[M+H]^+$, $C_{21}H_{25}ClN_4$).

*2-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}-5-(trifluoromethyl)-1*H-*-benzimidazole* ***(26)***. Yield: 640 mg (78 %); IR (ATR, cm^{-1}): 2944, 1632, 1590, 1481, 1234; ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 2.06 (2H, *m*, CH_2), 2.74 (2H, *t*, *J* = 5 Hz, CH_2N), 2.84 (4H, *t*, *J* = 5 Hz, CH_2), 3.15 (2H, *t*, *J* = 6.2 Hz, CH_2), 3.22 (4H, *t*, *J* = 5 Hz, CH_2), 7.01–7.69 (6H, *m*, 2-chlorophenyl group and benzimidazole), 7.83 (1H, *s*, C_4 benzimidazole), 9.05 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / ppm): 22.89 (1C, CH_2), 29.51 (1C, CH_2), 51.15 (2C, CH_2), 53.33 (2C, CH_2), 58.92 (1C, CH_2N), 112.65 (1C, CH–C_4, benzimidazole), 114.38 (1C, CH–C_7, benzimidazole), 118.89 (1C, CH–C_6, 2-chlorophenyl group), 120.19 (1C, CH–C_6, benzimidazole), 122.24 (1C, CF_3), 123.83 (1C, C–C_5, benzimidazole), 124.30 (1C, CH–C_4, 2-chlorophenyl group), 127.85 (1C,

CH–C_5, 2-chlorophenyl group), 128.89 (1C, C–C_2, 2-chlorophenyl group), 130.86 (1C, CH–C_3, 2-chlorophenyl group), 138.20 (2C, C–C_{3a} and C–C_{7a}, benzimidazole), 148.61 (1C, C–C_1, 2-chlorophenyl group), 157.99 (1C, C–C_2, benzimidazole). MS (*m*/*z*): 423.15682 ($[M+H]^+$, $C_{21}H_{22}ClF_3N_4$).

*2-{3-[4-(2-Chlorophenyl)piperazin-1-yl]propyl}-5-methoxy-1*H-*benzimidazole (**27**)*. Yield: 178 mg (71 %); IR (ATR, cm^{-1}): 2948, 1631, 1590, 1483, 1232; ^{1}H-NMR (200 MHz, $CDCl_3$, δ / ppm): 2.04 (2H, *m*, CH_2), 2.67 (2H, *t*, *J* = 5.6 Hz, CH_2N), 2.80 (4H, t, *J* = 5.4 Hz, CH_2), 3.09 (2H, *t*, *J* = 6.2 Hz, CH_2), 3.19 (4H, *t*, *J* = 4.6 Hz, CH_2), 3.82 (3H, *s*, OCH_3), 6.82–7.45 (7H, *m*, 2-chlorophenyl group and benzimidazole), 9.01 (1H, *bs*, NH); ^{13}C-NMR (50 MHz, $CDCl_3$, δ / / ppm): 23.34 (1C, CH_2), 28.71 (1C, CH_2), 50.93 (2C, CH_2), 53.20 (2C, CH_2), 55.81 (1C, OCH_3), 58.56 (1C, CH_2N), 97.83 (1C, CH–C_4, benzimidazole), 111.03 (1C, CH–C_6, benzimidazole), 115.05 (1C, CH–C_7, benzimidazole), 120.21 (1C, CH–C_6, 2-chlorophenyl group), 124.14 (1C, CH–C_4, 2-chlorophenyl group), 127.74 (1C, CH–C_5, 2-chlorophenyl group), 128.82 (1C, C–C_2, 2-chlorophenyl group), 130.78 (1C, CH–C_3, 2-chlorophenyl group), 133.41 (1C, C–C_{7a}, benzimidazole), 139.16 (1C, C–C_{3a}, benzimidazole), 148.70 (1C, C–C_1, 2-chlorophenyl group), 155.00 (1C, C–C_2, benzimidazole), 155.96 (1C, C–C_5, benzimidazole); MS (*m*/*z*): 385.17957 ($[M+H]^+$, $C_{21}H_{25}ClN_4O$).