

Chemical Modifications on 4-Arylpiperazine-Ethyl Carboxamide Derivatives Differentially Modulate Affinity for 5-HT_{1A}, D4.2, and α_{2A} Receptors: Synthesis and In Vitro Radioligand Binding Studies

Amaury Graulich,^A Marc Léonard,^A MéliSSa Résimont,^A Xi-Ping Huang,^B Bryan L. Roth,^B and Jean-François Liégeois^{A,C}

^ADrug Research Center, Laboratory of Medicinal Chemistry, University of Liège, Avenue de l'Hôpital 1 (B36), B-4000 Liège 1, Belgium.

^BDepartment of Pharmacology, School of Medicine and Division of Medicinal Chemistry and Natural Products, School of Pharmacy, University of North Carolina Chapel Hill Medical School, 4072 Genetic Medicine Building, CB 7365, Chapel Hill, NC 27599, USA.

^CCorresponding author. Email: JF.liegeois@ulg.ac.be

Chemical and physical characteristics of phthalimide derivatives

N-{2-[4-phenyl-piperazin-1-yl]ethyl}phthalimide: Melting point 154-155 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.69 (m, 6H), 3.13 (t, *J* = 4.7, 4H), 3.87 (t, *J* = 6.6, 2H), 6.83 (t, *J* = 7.2, 1H), 6.89 (d, *J* = 8.2, 2H), 7.24 (m, 2H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₀H₂₁N₃O₂ (335.407). Calculated C 71.62, H 6.31, N 12.53. Found C 71.32, H 5.99, N 12.56.

N-{2-[4-(2-fluorophenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 106-108 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.71 (brs, 6H), 3.05 (brs, 4H), 3.86 (t, *J* = 6.5, 2H), 6.92 (m, 2H), 6.98 (m, 2H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.85 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₀H₂₀FN₃O₂ (353.390). Calculated C 67.97, H 5.70, N 11.89. Found C 67.60, H 5.88, N 11.98.

N-{2-[4-(3-fluorophenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 177-178 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.67 (brt, *J* = 4.7, 4H), 2.70 (masked t, *J* = 6.4, 2H), 3.13 (brt, *J* = 4.8, 4H), 3.86 (t, *J* = 6.7, 2H), 6.49 (m, 1H), 6.55 (d, *J* = 13.5, 1H), 6.64 (dd, *J* = 1.8, *J* = 8.3, 1H), 7.16 (q, *J* = 8.0, 1H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₀H₂₀FN₃O₂ (353.390). Calculated C 67.97, H 5.70, N 11.89. Found C 67.89, H 5.98, N 12.15.

N-{2-[4-(4-fluorophenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 147-148 °C. ¹H NMR (500MHz, CDCl₃) δ : 2.69 (m, 6H), 3.05 (brt, *J* = 4.6, 4H), 3.86 (t, *J* = 6.6, 2H), 6.84 (m, 2H), 6.93 (m, 2H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₀H₂₀FN₃O₂ (353.390). Calculated C 67.97, H 5.70, N 11.89. Found C 67.84, H 5.82, N 12.04.

N-{2-[4-(2-chlorophenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 121-122 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.72 (m, 6H), 3.02 (brs, 4H), 3.87 (t, *J* = 6.6, 2H), 6.94 (d, *J* = 7.6, 1H), 7.00 (d, *J* = 8.0, 1H), 7.19 (t, *J* = 7.7, 1H), 7.33 (d, *J* = 6.9, 1H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.85 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₀H₂₀ClN₃O₂ (369.849). Calculated C 64.95, H 5.45, N 11.36. Found C 64.65, H 5.61, N 11.51.

N-{2-[4-(3-chlorophenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 161-162 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.67 (brt, *J* = 4.6, 4H), 2.70 (masked t, *J* = 6.4, 2H), 3.12 (brt, *J* = 4.6, 4H), 3.86 (t, *J* = 6.5, 2H), 6.75 (m, 2H), 6.84 (s, 1H), 7.13 (t, *J* = 8.1, 1H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₀H₂₀ClN₃O₂ (369.849). Calculated C 64.95, H 5.45, N 11.36. Found C 65.05, H 5.22, N 11.41.

N-{2-[4-(4-chlorophenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 170-171 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.67 (brt, *J* = 4.4, 4H), 2.70 (masked t, *J* = 6.4, 2H), 3.09 (brt, *J* = 4.8, 4H), 3.86 (t, *J* = 6.4, 2H), 6.80 (d, *J* = 8.8, 2H), 7.17 (d, *J* = 8.8, 2H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₀H₂₀ClN₃O₂ (369.849). Calculated C 64.95, H 5.45, N 11.36. Found C 64.84, H 5.46, N 11.40.

N-{2-[4-(3-trifluoromethylphenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 125-126 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.70 (m, 6H), 3.16 (t, *J* = 4.3, 4H), 3.87 (t, *J* = 6.4, 2H), 7.04 (t, *J* = 8.5, 2H), 7.07 (s, 1H), 7.31 (t, *J* = 8.0, 1H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₁H₂₀F₃N₃O₂ (403.398). Calculated C 62.53, H 5.00, N 10.42. Found C 62.37, H 5.34, N 10.60.

N-{2-[4-(2-methylphenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 139.140 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.29 (s, 3H), 2.71 (m, 6H), 2.87 (brm, 4H), 3.87 (t, *J* = 6.6, 2H), 6.97 (m, 2H), 7.13 (m, 2H), 7.72 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.86 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₁H₂₃N₃O₂ (349.434). Calculated C 72.18, H 6.63, N 12.03. Found C 72.32, H 6.95, N 12.16.

N-{2-[4-(3-methylphenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 136-138 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.30 (s, 3H), 2.69 (m, 6H), 3.12 (brt, 4H), 3.86 (t, *J* = 6.7, 2H), 6.65 (d, 1H), 6.71 (m, 2H), 7.12 (t, 1H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₁H₂₃N₃O₂ (349.434). Calculated C 72.18, H 6.63, N 12.03. Found C 72.41, H 7.01, N 12.17.

N-{2-[4-(4-methylphenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 152-154 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.25 (s, 3H), 2.68 (m, 6H), 3.08 (brt, *J* = 4.8, 4H), 3.86 (t, *J* = 6.6, 2H), 6.81 (d, *J* = 8.5, 2H), 7.04 (d, *J* = 8.4, 2H), 7.70 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.84 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₁H₂₃N₃O₂ (349.434). Calculated C 72.18, H 6.63, N 12.03. Found C 72.37, H 6.77, N 12.24.

N-{2-[4-(2-methoxyphenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 111-112 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.71 (m, 6H), 3.03 (brs, 4H), 3.85 (s, 3H), 3.87 (masked t, 2H), 6.83 (d, *J* = 8.4, 1H), 6.88 (m, 2H), 6.97 (m, 1H), 7.71 (dd, *J* = 3.1, *J* = 5.4, 2H), 7.85 (dd, *J* = 3.1, *J* = 5.4, 2H). Anal. C₂₁H₂₃N₃O₃ (365.433). Calculated C 69.02, H 6.34, N 11.50. Found C 69.03, H 6.49, N 11.50.

N-{2-[4-(3-methoxyphenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 116-117 °C. ¹H NMR (500 MHz, CDCl₃) δ : 2.68 (m, 6H), 3.13 (brt, *J* = 4.7, 4H), 3.77 (s, 3H), 3.86 (t, *J* =

6.5, 2H), 6.38 (dd, $J = 2.0, J = 8.1$, 1H), 6.43 (m, $J = 2.2$, 1H), 6.51 (dd, $J = 2.0, J = 8.1$, 1H), 7.14 (t, $J = 8.1$, 1H), 7.71 (dd, $J = 3.1, J = 5.4$, 2H), 7.84 (dd, $J = 3.1, J = 5.4$, 2H). Anal. $C_{21}H_{23}N_3O_3$ (365.433). Calculated C 69.02, H 6.34, N 11.50. Found C 68.91, H 6.57, N 11.55.

N-{2-[4-(4-methoxyphenyl)-piperazin-1-yl]ethyl}phthalimide: Melting point 156-158 °C. 1H NMR (500 MHz, $CDCl_3$) δ : 2.69 (m, 6H), 3.03 (brt, $J = 4.8$, 4H), 3.75 (s, 3H), 3.86 (t, $J = 6.7$, 2H), 6.82 (m, 2H), 6.86 (m, 2H), 7.70 (dd, $J = 3.1, J = 5.4$, 2H), 7.84 (dd, $J = 3.1, J = 5.4$, 2H). Anal. $C_{21}H_{23}N_3O_3$ (365.433). Calculated C 69.02, H 6.34, N 11.50. Found C 69.12, H 6.71, N 11.60.

N-{2-[4-phenyl-1,2,3,6-tetrahydropyridin-1-yl]ethyl}phthalimide: Melting point 149-151 °C. 1H NMR (500 MHz, $CDCl_3$) δ : 2.54 (m, 2H), 2.80 (m, 4H), 3.25 (d, $J = 3.0$, 2H), 3.91 (t, $J = 6.8$, 2H), 6.04 (m, 1H), 7.26 (m, 3H), 7.37 (m, 2H), 7.70 (dd, $J = 3.1, J = 5.4$, 2H), 7.84 (dd, $J = 3.1, J = 5.4$, 2H). Anal. $C_{21}H_{20}N_2O_2$ (332.403). Calculated C 75.88, H 6.06, N 8.43. Found C 75.81, H 6.44, N 8.62.