Supporting Information

Synthesis and Biological Evaluation of *N*-Substituted Quinolinimides, as Potential Ligands for in Vivo Imaging studies of δ-Opioid Receptors

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Contents

General. All reagents were purchased from Acros Organics, Fluka or Sigma-Aldrich and were used without further purification. Anhydrous THF was distilled over sodium/benzophenone. Triethylamine, pyridine, toluene, dioxane, DMF, ether and acetonitrile were distilled from calcium hydride at atmospheric pressure under nitrogen.

All melting points were determined on a Koffler Bank and are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were measured on a Brucker DPX 250, at 250 MHz (^{1}H), 62.5 MHz (^{13}C) and 235 MHz (^{19}F). Samples were dissolved in an appropriate deuterated solvent ($CDCl_3$). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane (TMS, 0.00 ppm), which was used as an internal standard. Coupling constants are given in Hz and coupling patterns are abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), sextet (sextuplet), m (mutiplet), dd (doublet of doublet) and dt (doublet of triplet). Mass spectra (MS) were obtained on a Nermag R10 or Jeol Gcmate spectrometer at 70 eV. Relative intensities are given in brackets. Infrared spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrophotometer in KBr or NaCl and peaks are given in cm^{-1}. Microanalyses were measured on a ThermoQuest CHNS-O and were within ± 0.4% of the calculated values. TLCs were run on pre-coated aluminium plates of silica gel $60F_{254}$ (Merck) and Rf were established using an UV-lamp at 254 nm. Liquid chromatographies were achieved on Merck 60 silica gel (40-63 µm) columns. Extractions were performed with cartridges Chromabond® PTS phase separation (Macherey Nagel).

[^{11}C]Carbon dioxide was produced by IBA Cyclone 18/9 cyclotron through the $^{14}N(p,\alpha)^{11}C$ nuclear reaction of a gas target filled with nitrogen containing 0.5% oxygen at pressure of 20 bars irradiated with 16 MeV protons. [^{11}C]Methyl ioidide was synthesized from [^{11}C]carbon dioxide using the previously described procedure (*50*). Radioactivity was measured with a Capintec R15C.

Semi-preparative HPLC were performed on system equipped of a Waters 501 pump, a Merck L-4250 UV detector in series with Novelec β^{+}-flow detector, a Valco Vici injector. Analytical HPLC were performed with a Merck L-6200 pump, a Merck L-4250 UV detector in series with Novelec β^{+}-flow detector, a Valco Vici injector. The identity of the labeled compound was determined by the co-injection with the unlabeled reference.

4-Butyl-benzenesulfonyl chloride (***11***)**.** To a solution of butylbenzene (10.0 g, 74.0 mmol) in chloroform (140 mL) was added dropwise chlorosulfonic acid (30 mL, 0.44 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 24 h, then poured on ice (approx. 400 g). The aqueous phase was thoroughly extracted with dichloromethane (3 x 240 mL) and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (500 mL) and with water (500 mL), then dried over $MgSO_4$, and the solvents evaporated. The crude residue was purified by chromatography on silica gel (7:3 heptanes/dichloromethane) to afford **11** (15.75 g, 91%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 1.65 (qu, *J* = 7.6 Hz, 2H), 1.37 (sextet, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 152.1, 142.1, 130.0, 127.4, 36.1, 33.4, 22.6, 14.2; IR (NaCl): 1594, 1490, 1370, and 1180 cm^{-1}; MS (EI) m/z (%): 234 ($M^{+\cdot}$ ($C_{10}H_{13}O_2{}^{37}Cl$), 3), 232 ($M^{+\cdot}$ ($C_{10}H_{13}O_2{}^{35}Cl$), 9), 197 (100), 133 (31), 91 (53); Anal. ($C_{10}H_{13}ClO_2S$) C, H.

*4-(4-Fluorobutyl)-benzenesulfonyl chloride (**12**). Step A.* Preparation of (4-fluorobutyl)benzene: tetra-*n*-butylammonium fluoride in THF (1 M, 23.3 mL, 23.3 mmol) was added to a solution of 4-phenylbutyl-*p*-toluene sulfonate (4.73 g, 15.55 mmol) in THF (50 mL) under nitrogen. The reaction mixture was heated to 55°C and stirred for 2 h. The reaction mixture was concentrated by rotary evaporation. The crude residue was purified by chromatography on silica gel (1:1 pentanes/dichloromethane) to give (4-fluorobutyl)benzene (1.97 g, 83%) as a colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.35-7.10 (m, 5H), 4.44 (dt, *J* = 47.0 Hz, *J* = 5.5 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 1.85-1.60 (m, 4H); ^{19}F NMR ($CDCl_3$) δ -218.74; ^{13}C NMR ($CDCl_3$) δ 142.0, 128.4, 128.3, 125.9, 84.0 (d, *J* = 165.0 Hz), 35.4, 30.0 (d, *J* = 19.5 Hz), 27.0 (d, *J* = 5.1 Hz); IR (NaCl): 1603, 1560, 1496, 1430, 1040 cm^{-1}; MS (EI) m/z (%): 152 ($M^{+\cdot}$, 70), 91 (100), 65 (14). *Step B.* Compound **12** was synthesized as described for **11** from (4-fluorobutyl)benzene (1.10 g, 7.23 mmol). The crude residue was purified by

chromatography on silica gel (3:2 heptanes/dichloromethane) to afford **12** (779 mg, 43%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 4.48 (dt, *J* = 47.0 Hz, *J* = 5.5 Hz, 2H), 2.80 (t, *J* = 7.4 Hz, 2H), 1.95-1.50 (m, 4H); ^{19}F NMR ($CDCl_3$) δ -219.25; ^{13}C NMR ($CDCl_3$) δ 150.8, 142.2, 129.7, 127.3, 83.7 (d, *J* = 165.0Hz), 35.60, 30.0 (d, *J* = 19.8 Hz), 26.8 (d, *J* = 4.7 Hz); IR (NaCl): 1593, 1490, 1376, and 1175 cm^{-1}; MS (EI) m/z (%): 252 ($M^{+\cdot}$ ($C_{10}H_{12}O_2SF^{37}Cl$), 1), 250 ($M^{+\cdot}$ ($C_{10}H_{12}O_2SF^{35}Cl$), 3), 215 (100), 199 (12), 167 (15), 91 (12); Anal. ($C_{10}H_{12}ClFO_2S$) C, H.

4-Butyl-N-(2-phenylethyl)-benzenesulfonamide ***(13)****.* To a solution of 2-phenylethylamine (1.21 g, 9.9 mmol) in pyridine (9.6 mL) stirred under nitrogen in a cooling bath at –20°C was added **11** (3.0 g, 12.89 mmol). The resultant yellow solution was stirred for 18 h at room temperature. The reaction mixture was quenched with water (30 mL). The aqueous phase was thoroughly extracted with dichloromethane (3 x 30 mL) and the combined organic layers were washed with hydrochloric acid solution 2.0 N and brine (50 mL), and dried over $MgSO_4$. The solvents were evaporated to obtain **13** (3.04 g, 97%) as a viscous brown oil. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.30-7.15 (m, 5H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.60 (t, *J* = 6.2 Hz, 1H), 3.19 (q, *J* = 7.0 Hz, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 1.60 (qu, *J* = 7.5 Hz, 2H), 1.35 (sextet, *J* = 7.5 Hz, 2H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 148.3, 137.9, 137.1, 129.1, 128.8, 128.7, 127.1, 126.1, 44.3, 35.9, 35.5, 33.2, 22.3, 13.9; IR (NaCl): 3244, 1317 and 1154 cm^{-1}; MS (EI) m/z (%): (226 (60), 197 (100), 133 (31), 91 (32); Anal. ($C_{18}H_{23}NO_2S$) C, H, N.

4-(4-Fluorobutyl)-N-(2-phenylethyl)-benzenesulfonamide ***(14).*** Prepared as described above from **12** (630 mg, 2.51 mmol). Yield 635 mg, 98%; viscous brown oil. ^{1}H NMR ($CDCl_3$) δ 7.12 (d, *J* = 8.3 Hz, 2H), 7.35-7.20 (m, 5H), 7.07 (d, *J* = 7.9 Hz, 2H), 4.47 (t, *J* = 6.2 Hz, 1H), 4.46 (dt, *J* = 47.0 Hz, *J* = 5.5 Hz, 2H), 3.22 (q, *J* = 6.8 Hz, 2H), 2.77 (t, *J* = 7.0

Hz, 2H), 2.73 (t, *J* = 8.1 Hz, 2H), 1.85-1.60 (m, 4H); ^{19}F NMR ($CDCl_3$) δ -219.08; ^{13}C NMR ($CDCl_3$) δ 147.4, 137.7, 137.5, 129.1, 128.7, 127.2, 126.8, 83.7 (d, *J* = 165.0 Hz), 44.2, 35.8, 35.3, 29.9 (d, *J* = 19.8 Hz), 26.7 (d, *J* = 4.7 Hz); IR (NaCl): 3280, 1327 and 1159 cm^{-1}; MS (EI) m/z (%): 234 (45), 186 (41), 173 (100), 131 (55), 106 (44), 91 (59), 78 (41); Anal. ($C_{18}H_{22}FNO_2S$) C, H, N.

*2-Chloro-6-(3-hydroxy-propyl)-pyrrolo[3,4-b]pyridine-5,7-dione (**18**). Step A*: a mixture of diacid **15** (2.41 g, 11.96 mmol) and thionyl chloride (20 mL) was refluxed for 3.5 h under nitrogen. After evaporation, the resulting solid was triturated with hot chloroform (35 mL) and filtered off. The filtrate was concentrated and the resulting crude anhydride (1.89 g, 86%) was used directly in the next step. *Step B*: anhydride (1.89 g, 10.29 mmol), 3-aminopropan-1-ol (796 mg, 10.39 mmol), toluene (40 mL) and triethylamine (550 µL) were placed in three-necked flask under nitrogen equipped with a Dean Stark and a reflux condenser. The reaction mixture was heated at reflux for 18 h. The reaction mixture was quenched with water (30 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with 10% aqueous solution of $NaHCO_3$ (50 mL) and water (2 x 50mL), and dried over $MgSO_4$, filtered and concentrated under vacuum to afford a yellow solid. The crude residue was purified by chromatography on silica gel (7:3 ethyl acetate/heptanes) to afford **18** (1.36 g, 55%) as a white solid. mp 114°C; ^{1}H NMR ($CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 3.91 (t, *J* = 6.0 Hz, 2H), 3.67 (dt, *J* = 5.8 Hz, *J* = 5.8 Hz, 2H), 2.10 (t, *J* = 6.0 Hz, 1H), 1.92 (qu, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 165.7, 165.4, 158.3, 152.1, 133.4, 128.5, 125.9, 59.4, 35.2, 31.1; IR (KBr): 3425, 1776, 1712, and 1040 cm^{-1}; MS (EI) m/z (%): 242 ($M^{+\cdot}$ ($C_{10}H_9N_2O_3{}^{37}Cl$), 7), 240 ($M^{+\cdot}$ ($C_{10}H_9N_2O_3{}^{35}Cl$), 15), 224 (16), 222 (45), 212 (18), 210 (46), 197 (39), 194 (67), 195 (100), 184 (38), 182 (36), 168 (23), 167 (28), 140 (54), 139 (36), 113 (61), 112 (44), 76 (45); Anal. ($C_{10}H_9ClN_2O_3$) C, H, N.

*2-Bromo-6-(3-hydroxy-propyl)-pyrrolo[3,4-b]pyridine-5,7-dione (**19**). Step A*: a mixture of diacid **16** (2.50 g, 10.16 mmol) and acetic anhydride (5.5 mL) was refluxed for 3 h under nitrogen. After cooling to room temperature, chloroform (13 mL) was added and the reaction mixture was concentrated under vacuum to afford the anhydride (1.99 g, 86%) which was used directly in the next step. *Step B*: as described above starting from anhydride (1.99 g, 8.73 mmol), the reaction led to a crude residue which was purified by chromatography on silica gel (7:3 ethyl acetate/heptanes) to afford **19** (1.22 g, 49%) as a yellow solid. mp 131°C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 3.92 (t, *J* = 6.5 Hz, 2H), 3.65 (dt, *J* = 5.7 Hz, *J* = 5.7 Hz, 2H), 2.07 (t, *J* = 5.8 Hz, 1H), 1.92 (qu, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 165.8, 165.3, 152.4, 149.3, 132.9, 132.3, 126.2, 59.4, 35.2, 31.1; IR (KBr): 3446, 1774, 1704, and 1040 cm^{-1}; MS (EI) m/z (%): 287 ($[M+1]^+$ ($C_{10}H_{10}N_2O_3{}^{81}Br$), 14), 286 ($M^{+\cdot}$ ($C_{10}H_9N_2O_3{}^{81}Br$), 30), 285 ($[M+1]^+$ ($C_{10}H_{10}N_2O_3{}^{79}Br$), 16), 284 ($M^{+\cdot}$ ($C_{10}H_9N_2O_3{}^{79}Br$), 30), 268 (77), 266 (71), 256 (73), 254 (69), 241 (100), 239 (91), 228 (68), 226 (37), 213 (29), 211 (38), 185 (48), 183 (42), 159 (59), 157 (88), 104 (39), 76 (77); Anal. ($C_{10}H_9BrN_2O_3$) C, H, N.

*2-Methyl-6-(3-hydroxypropyl)-pyrrolo[3,4-b]pyridine-5,7-dione (**20**). Step A*: the intermediate anhydride was synthesized from **17** (2.50 g, 13.8 mmol) as described above and used directly in the next step. *Step B*: from anhydride (2.20 g, 13.5 mmol), the reaction led to a crude residue which was purified by chromatography on silica gel (ethyl acetate) to afford **20** (1.37 mg, 46%) as a yellow solid. mp 130°C; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 3.93 (t, *J* = 6.4 Hz, 2H), 3.64 (dt, *J* = 5.8 Hz, *J* = 5.8 Hz, 2H), 2.78 (s, 3H), 2.29 (t, *J* = 6.3 Hz, 1H), 1.91 (qu, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 167.3, 167.1, 166.4, 151.8, 131.3, 127.2, 124.9, 59.3, 34.7, 31.4, 25.1; IR (KBr): 3396, 1778, 1712, and 1044 cm^{-1}; MS (EI) m/z (%): 220 (M^+, 27), 202 (51), 190 (44), 176 (69), 175 (100), 164 (30),

163 (31), 148 (28), 147 (26), 120 (71), 119 (41), 93 (75), 92 (46), 65 (35); Anal. ($C_{11}H_{12}N_2O_3$) C, H, N.

General procedure for the synthesis of compounds 21-23. Alcohol **18-20** (6.6 mmol) was dissolved in ethyl acetate (48 mL), and IBX (20 mmol) was added. The resulting suspension was heated to 80°C for 4 h under vigorous stirring. The reaction mixture was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with ethyl acetate (3 x 12 mL) and the filtrate concentrated to afford aldehyde.

*2-Chloro-6-(3-oxopropyl)-pyrrolo[3,4-b]pyridine-5,7-dione (**21**).* Yield 100%; white solid; mp 118°C; ^{1}H NMR ($CDCl_3$) δ 9.81 (t, *J* = 1.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 4.10 (t, *J* = 7.0 Hz, 2H), 2.93 (dt, *J* = 7.0 Hz, *J* = 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 198.9, 164.9, 164.8, 158.5, 152.0, 133.6, 128.7, 125.9, 42.0, 32.2; IR (KBr): 2844, 2732, 1782, 1723, and 1706 cm^{-1}; MS (EI) m/z (%): 240 ($M^{+\cdot}$ ($C_{10}H_7N_2O_3{}^{37}Cl$), 12), 239 ($[M+1]^+$ ($C_{10}H_8N_2O_3{}^{35}Cl$), 37), 238 ($M^{+\cdot}$ ($C_{10}H_7N_2O_3{}^{35}Cl$), 19), 212 (31), 211 (23), 210 (95), 197 (28), 195 (83), 184 (38), 183 (34), 182 (100), 140 (58), 139 (58), 113 (39), 112 (37), 111 (37), 76 (48); Anal. ($C_{10}H_7ClN_2O_3$) C, H, N.

*2-Bromo-6-(3-oxopropyl)-pyrrolo[3,4-b]pyridine-5,7-dione (**22**).* Yield 95%; white solid; mp 151°C; ^{1}H NMR ($CDCl_3$) δ 9.80 (t, *J* = 1.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 4.08 (t, *J* = 7.0 Hz, 2H), 2.92 (dt, *J* = 7.0 Hz, *J* = 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 199.2, 165.5, 165.0, 152.5, 149.8, 133.3, 132.8, 126.5, 42.3, 32.5; IR (KBr): 2844, 2734, 1780, 1720, 1709 cm^{-1}; MS (EI) m/z (%): 285 ($[M+1]^+$ ($C_{10}H_8N_2O_3{}^{81}Br$), 10), 284 ($M^{+\cdot}$ ($C_{10}H_7N_2O_3{}^{81}Br$), 17), 283 ($[M+1]^+$ ($C_{10}H_8N_2O_3{}^{79}Br$), 12), 282 ($M^{+\cdot}$ ($C_{10}H_7N_2O_3{}^{79}Br$), 13), 256 (83), 254 (80), 241 (56), 239 (58), 228 (100), 226 (99), 211 (20), 185 (47), 183 (45), 157 (43), 104 (27), 76 (62); Anal. ($C_{10}H_7BrN_2O_3$) C, H, N.

*2-Methyl-6-(3-oxopropyl)-pyrrolo[3,4-b]pyridine-5,7-dione (**23**).* Yield 100%; white solid; mp 90°C; ^{1}H NMR ($CDCl_3$) δ 9.81 (t, *J* = 1.0 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.47 (t,

J = 7.8 Hz, 1H), 4.05 (t, *J* = 7.1 Hz, 2H), 2.90 (dt, *J* = 7.0 Hz, *J* = 1.0Hz, 2H), 2.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 199.3, 166.5, 166.4, 166.2, 151.6, 131.4, 127.3, 124.8, 42.2, 31.9, 25.0; IR (KBr): 2850 and 2734, 1780, 1720, 1712 cm^{-1}; MS (EI) m/z (%): 218 ($M^{+\cdot}$, 8), 190 (100), 189 (47), 175 (60), 162 (93), 161 (37), 120 (64), 119 (70), 93 (30), 92 (39), 91 (42), 64 (24); Anal. ($C_{11}H_{10}N_2O_3$) C, H, N.