Supporting Information

The Synthesis of Two Fluoro Analogues of the Nicotinic Acetylcholine Receptor Agonist UB-165

Andrew Sutherland,[1] Timothy Gallagher,[1*] Christopher G.V. Sharples,[2] and Susan Wonnacott[2]

[1]*School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom*

[2]*Department of Biology and Biochemistry, University of Bath, Bath BA2 7AY, United Kingdom*

t.gallagher@bristol.ac.uk

General experimental details

All solvents were purified and dried, as required, according to standard literature procedures. 5-bromo-2-fluoropyridine (**7**) and 2-fluoropyridine (**12**) were commercially available and used without further purification. BuLi refers to *n*-BuLi. Chemical shift values are given in parts per million and *J* values are reported in Hz, and proton and carbon assignments are based on two-dimensional and DEPT experiments. For *N*-vinyloxycarbonyl (Voc) protected compounds, carbamate resonance resulted in broadened ^{1}H, ^{13}C and ^{19}F spectra, which resulted in significant, though not universal doubling of lines. Where doubling of signals was apparent, this has been indicated.

2-(5-Bromo-2-fluoro-3-pyridyl)-9-vinyloxycarbonyl-9-azabicyclo[4.2.1]non-2-ene (9). IR (film) ν (cm^{-1}): 2960, 1701, 1646, 1420, 1332, 1161, 729. ^{1}H NMR (400 MHz, $CDCl_3$): 8.15 (0.5 H, m, ArH), 8.11 (0.5 H, m, ArH), 8.08 (0.5 H, dd, *J* = 8.2, 2.7 Hz, ArH), 7.80 (0.5 H, dd, *J* = 8.2, 2.7 Hz, ArH), 7.22 (0.5 H, dd, *J* = 13.9, 6.3 Hz, Voc), 7.18 (0.5 H, dd, *J* = 13.9, 6.6 Hz, Voc), 5.89 (1 H, m, 3-H), 4.80 (0.5 H, dd, *J* = 13.9, 1.7 Hz, Voc), 4.69 (1 H, m, 1-H), 4.57 (1 H, m, 6-H), 4.46 (0.5 H, dd, *J* = 6.2, 1.7 Hz, Voc), 4.43-4.34 (2 x 0.5 H, m, Voc), 2.64-1.62 (8 H, m, 4-H_2, 5-H_2, 7-H_2 and 8-H_2). ^{13}C NMR (67.9 MHz, $CDCl_3$): 161.3 (d, *J* = 241.2 Hz, C), 150.7 (C), 146.5 (CH), 146.3 (C), 142.6 (CH), 142.5 (C), 142.3 (C), 142.0 (CH), 133.9 (CH), 95.5/95.2 (CH_2), 59.1/59.0 (CH), 57.2/56.9 (CH), 31.9/31/8 (CH_2), 30.0/29.1 (CH_2), 28.2 (CH_2), 24.3/24.2 (CH_2). ^{19}F NMR (283 MHz, $CDCl_3$): -70.8 and -72.0 (2 x br d, *J* ca. 8 Hz). HRMS: calcd for $C_{16}H_{17}{}^{81}BrFN_2O_2(MH^+)$, 369.04370; found, 369.04488.

2-(2-Fluoro-3-pyridyl)-9-vinyloxycarbonyl-9-azabicyclo[4.2.1]non-2-ene (15) by Reike zinc reduction of 9. Freshly cut lithium (7.2 mg, 1.02 mmol) and naphthalene (0.13 g, 1.02 mmol) in THF (3 mL) under a nitrogen atmosphere were stirred at room temperature for 2 h. Part of this solution (0.2 mL) was transferred to a second flask and to this was added a solution of anhydrous zinc chloride (0.12 M in THF, 1.09 mL, 0.13 mmol). After 10 minutes, bromide **9** (25 mg, 0.068 mmol) in THF (5 mL) was added, and the suspension was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and quenched with water (5 mL). The reaction mixture was extracted with dichloromethane (2 x 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with 30% ethyl acetate in light petroleum gave the title compound **15** (0.013 g, 65%) as a colorless oil. Spectroscopic data were identical to those described above.

2-(2-Hydroxy-5-pyridyl)-9-azabicyclo[4.2.1]non-2-ene hydrochloride salt (16). 2-(2-Fluoro-5-pyridyl)-9-vinyloxycarbonyl-9-azabicyclo[4.2.1]non-2-ene (**8**) (38 mg, 0.13 mmol) was dissolved in

1,4-dioxane (6 mL) and water (2 mL). Concentrated hydrochloric acid (0.5 mL) was added and the reaction mixture was heated under reflux for 24 h. The reaction mixture was cooled to room temperature and the solvent removed under high vacuum. The resulting residue was dissolved in water (10 mL) and washed with chloroform (2 x 10 mL). The aqueous layer was then concentrated *in vacuo* to give the title compound **16** (32 mg, 97%) as a colorless solid. IR (film) ν (cm^{-1}): 3385, 1651, 1601, 1422, 838. ^{1}H NMR (400 MHz, CD_3OD): 8.31 (1 H, dd, *J* = 9.3, 2.4 Hz, ArH), 8.17 (1 H, d, *J* = 2.4 Hz, ArH), 7.19 (1 H, d, *J* = 9.3 Hz, ArH), 6.41 (1 H, m, 3-H), 4.65 (1 H, d, *J* = 9.3 Hz, 1-H), 4.33 (1 H, m, 6-H), 2.72-2.52, 2.39-2.24 and 2.09-1.91 (8 H, m, 4-H_2, 5-H_2, 7-H_2 and 8-H_2). ^{13}C NMR (100.5 MHz, CD_3OD): 145.5 (CH), 137.2 (CH), 136.6 (C), 134.0 (CH), 129.8 (C), 114.4 (C), 63.0 (CH), 59.7 (CH), 58.9 (CH), 30.5 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 23.0 (CH_2). HRMS: calcd for $C_{13}H_{17}N_2O$ (MH^+), 217.1341; found, 217.1332.

2-(2-Fluoro-3-pyridyl)-9-azabicyclo[4.2.1]non-2-ene fumaric acid salt (5). The reaction was carried out as described for the synthesis of **4**. Using **15**, this gave the title compound **5** (17 mg, 57%) as a colorless solid. IR (film) ν (cm^{-1}): 3332, 2926, 1702, 1567, 1426, 1235, 1189. ^{1}H NMR (270 MHz, CD_3OD): 8.05 (1 H, ddd, *J* = 4.9, 3.0, 2.0 Hz, ArH), 7.74 (1 H, ddd, *J* = 9.4, 7.4, 2.0 Hz, ArH), 7.24 (1 H, ddd, *J* = 7.4, 4.9, 2.0 Hz, ArH), 6.67 (2 H, s, fumarate), 6.22 (1 H, ddd, *J* = 8.7, 5.0, 1.5 Hz, 3-H), 4.44 (1 H, m, 1-H), 4.23 (1 H, m, 6-H), 2.66-2.38, 2.33-2.08 and 1.98-1.79 (8 H, m, 4-H_2, 5-H_2, 7-H_2 and 8-H_2). ^{13}C NMR (100.5 MHz, CD_3OD): 168.7 (C), 159.8 (d, *J* = 244.3 Hz, C), 146.6 (CH), 146.4 (CH), 145.5 (C), 140.6 (CH), 138.0 (C), 134.4 (CH), 122.2 (CH), 59.7 (CH), 59.3 (CH), 30.5 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 23.1 (CH_2). ^{19}F NMR (283 MHz, CD_3OD): -69.7 (br d, *J* ca. 10 Hz). HRMS: calcd for $C_{13}H_{16}FN_2$ (MH^+), 219.1298; found, 219.1230.