Supporting Information

Synthesis and small-animal positron emission tomography evaluation of [^{11}C]-elacridar as a radiotracer to assess the distribution of P-glycoprotein at the blood-brain barrier

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Contents:

Non-key intermediates

2-(2-Carboxyphenylamino)-3-methoxybenzoic acid (2)

A suspension of 2-amino-3-methoxybenzoic acid (3.34 g, 20 mmol), 2-bromobenzoic acid (4.42 g, 22 mmol, 1.1 eq.), K_2CO_3 (5.53 g, 40 mmol, 2 eq.) and copper powder (0.25 g, 4 mmol, 0.2 eq.) was stirred in EtOH (40 mL) and heated to reflux for 1.5 h. The suspension was cooled to rt and H_2O (40 mL) was added. The mixture was filtered with cellite as a filtering aid to remove the copper. The filter bed was washed with H_2O and the resulting solution was acidified with concentrated HCl to a pH of 2-3. The resulting suspension was stirred for 1 h at 10°C, and then the solid was filtered, washed with H_2O and dried under vacuum to yield compound **2** as a white solid (5.07 g, 92.8% theoretical yield).

^{1}H-NMR (d_6-DMSO): δ 3.73 (s, 3H, OCH_3), 6.25-6.42 (m, 1H), 6.60-6.81 (m, 1H), 7.16-7.51 (m, 4H), 7.74-7.91 (m, 1H), 10.16 (bs, 1H), 12.82 (bs, 2H); ^{13}C-NMR (d_6-DMSO): δ 55.6 (OCH_3), 112.8 (Cq), 114.5 (CH), 115.5 (CH), 116.9 (CH), 122.2 (CH), 124.4 (CH), 126.5 (Cq), 129.2 (Cq), 131.0 (CH), 133.1 (CH), 147.0 (Cq), 153.7 (Cq), 168.0 (COOH), 169.3 (COOH)

5-Methoxyacridone-4-carboxylic acid (3)

Compound **2** (2.87 g, 10 mmol) was dissolved in CH_3CN (25 mL) and heated to reflux. Phosphorus oxychloride (2 mL, 22 mmol, 2.2 eq.) was added over 1 h. The solution was refluxed for further 2 h and then cooled to 10-15°C. H_2O (17 mL) was added and the mixture heated to reflux for 2.5 h. The suspension was cooled to 10°C and filtered. The solid was washed with H_2O and CH_3CN and then dried under vacuum to give the title compound (2.54 g, 94.2% theoretical yield).

^{1}H-NMR (d_6-DMSO): δ 4.06 (s, 3H, OCH_3), 7.17-7.45 (m, 3H), 7.72-7.6 (m, 1H), 8.38-8.57 (m, 2H), 12.24 (s, 1H), 13.84 (bs, 1H); ^{13}C-NMR (d_6-DMSO): δ 56.5 (OCH_3), 112.9 (CH), 115.0 (Cq), 117.0 (CH), 120.4 (CH), 121.0 (Cq), 121.6 (Cq), 121.8 (CH), 130.8 (Cq), 132.4 (CH), 136.8 (CH), 140.4 (Cq), 147.5 (Cq), 169.1 (COOH), 176.3 (CO)

6,7-Dimethoxy-2-(4-nitrophenethyl)-1,2,3,4-tetrahydroisochinoline (7)

A mixture of 4-nitrophenethylbromide (1.159 g, 5 mmol), 6,7-dimethoxy-1,2,3,4-tetrahydroisochinoline hydrochloride (1.148 g, 5 mmol, 1 eq.), K_2CO_3 (0.776 g, 5.5 mmol, 1.1 eq.) and KI (166 mg, 1 mmol, 0.2 eq.) was stirred in DMF (7.5 mL) at 70°C for 24 h. The mixture was cooled to 50°C and MeOH (2.5 mL) was added. After cooling to 30°C H_2O (15 mL) was added. The suspension was stirred at 10°C for 1 h and filtered. The solid was washed twice with H_2O and dried under vacuum to afford the title compound (1.127 g, 67% theoretical yield).

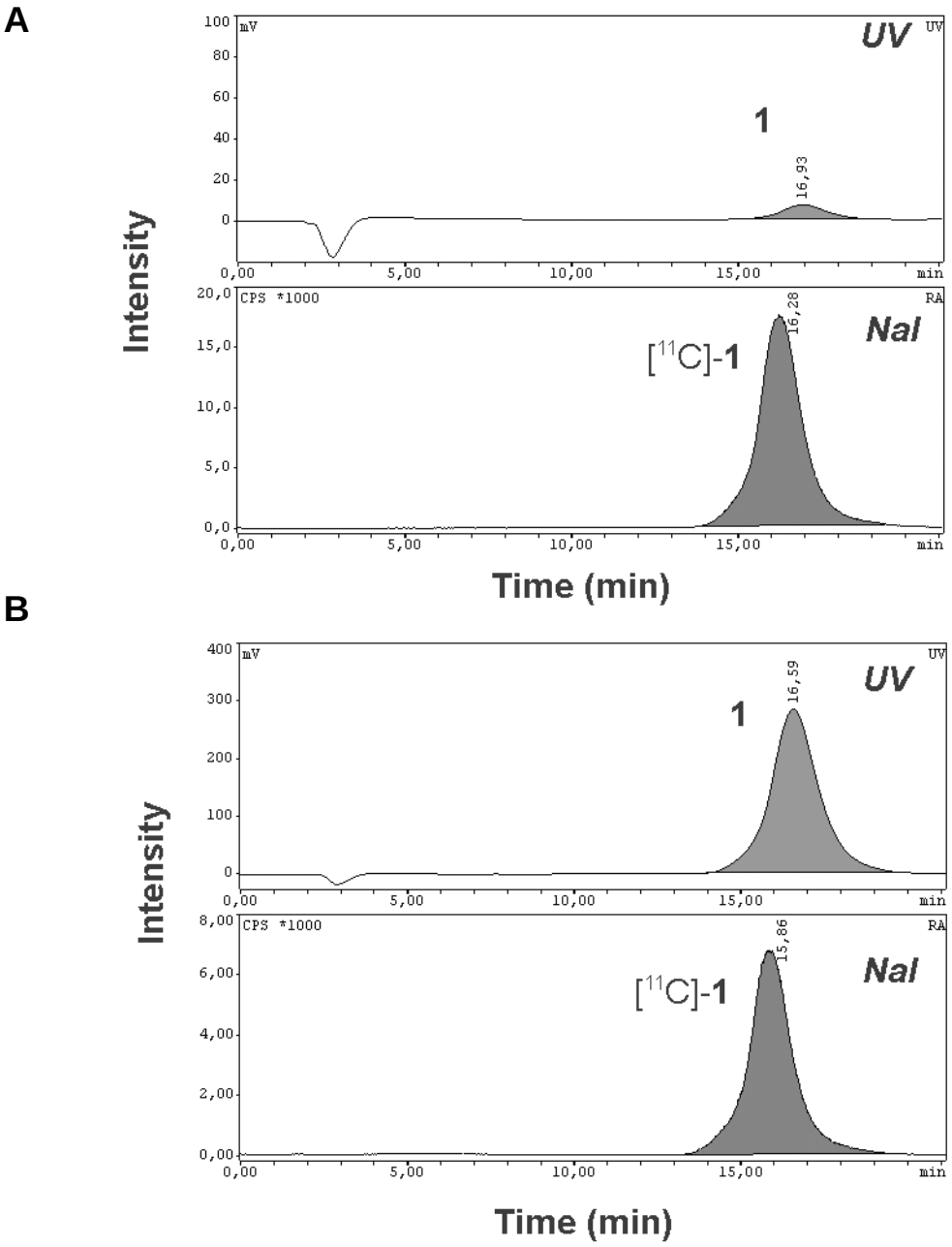
^{1}H-NMR ($CDCl_3$): δ 2.80-3,22 (m, 8H, 4×CH_2), 3.73 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, 2×OCH_3), 6.54 (s, 1H), 6.61 (s, 1H), 7.35-7.48 (d, 2H, *J*= 8.7 Hz), 8.08-8.21 (d, 2H, *J*= 8.7 Hz); ^{13}C-NMR ($CDCl_3$): δ 28.0 (CH_2), 33.4 (CH_2), 50.7 (CH_2), 55.1 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 58.6 (CH_2), 109.3 (CH), 111.2 (CH), 123.6 (2×CH), 125.0 (Cq), 125.5 (Cq), 129.5 (2×CH), 146.5 (Cq), 147.4 (Cq), 147.7 (Cq), CNO_2 not detected

6,7-Dimethoxy-2-(4-aminophenethyl)-1,2,3,4-tetrahydroisochinoline (8)

Compound **7** (1.711 g, 5 mmol) was stirred in EtOH (50 mL) under argon for 30 min. Then Pd/C catalyst (10% w/w, 0.171 g) was added and hydrogen gas introduced into the reaction mixture. The reaction mixture was stirred under normal pressure until hydrogen uptake was complete (10-20 h). The mixture was filtered and evaporated to give the title compound (1.37 g, 88% theoretical yield).

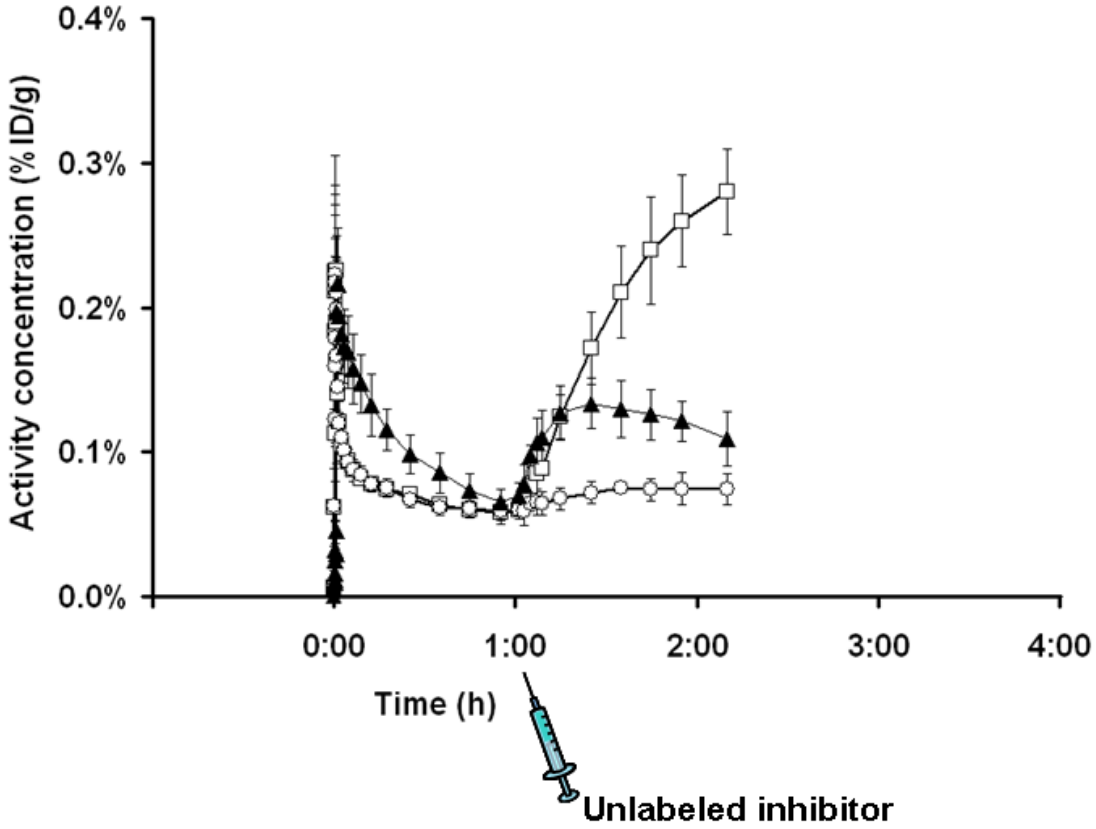
^{1}H-NMR ($CDCl_3$): δ 2.60-2.92 (m, 8H, 4×CH_2), 3.65 (s, 2H, CH_2), 3.84 (2s, 6H, 2×OCH_3), 6.49-6.71 (m, 4H), 6.97-7.08 (d, 2H, *J*= 8.4 Hz); ^{13}C-NMR ($CDCl_3$): δ 28.6 (CH_2), 33.1 (CH_2), 51.0 (CH_2), 55.6 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 60.5 (CH_2), 109.4 (CH), 111.3 (CH), 115.3 (2×CH), 126.0 (Cq), 126.3 (Cq), 129.5 (2×CH), 130.2 (Cq), 144.5 (Cq), 147.2 (Cq), 147.5 (Cq)

HPLC chromatogram of [^{11}C]-1



A: Analytical HPLC chromatogram of purified [^{11}C]-**1** formulated for i.v. injection demonstrating a radiochemical purity >98%. **B**: Analytical HPLC chromatogram of [^{11}C]-**1** co-injected with unlabeled **1** (10 µL of a 1 mg/mL solution in CH_3CN) demonstrating co-elution of [^{11}C]-**1** with **1**. In the upper channel UV absorption (wavelength: 227 nm) and in the lower channel radioactivity is measured. For HPLC conditions see experimental section.

TACs for [^{11}C]-1 PET scans during which 1 or tariquidar was administered



Whole-brain TACs (mean %ID/g±SD, *n*=3) for 150-min [^{11}C]-**1** PET scans in rats, during which unlabeled **1** (5 mg/kg, open squares) or tariquidar (3 mg/kg, open circles) was administered as an i.v. bolus at 60 min after start of the scan. For comparison, TACs for (*R*)-[^{11}C]-verapamil PET scans (*n*=5, solid triangles), during which tariquidar (3 mg/kg) was injected, are shown.