Supporting Information

Chemical delivery system of metaiodobenzylguanidine (MIBG) to the central nervous system.

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S1 Title page

S2 Synthesis of *N*-(3-iodobenzyl)-guanidine (**4**) and *N*-(3-iodobenzyl)-*N'*-(3-carbonyl-quinoline)-guanidine (**1**).

***N*-(3-iodobenzyl)-guanidine (4).** Guanidine hydrochloride **4,HCl** (311 mg, 1 mmol) was prepared from a solution of *m*-iodobenzylguanidine dihydrogenocarbonate[1] (607 mg, 1.8 mmol) and 37% HCl (1.8 mmol). Under nitrogen, *N*-(3-iodobenzyl)-guanidine **4** was obtained by consecutive addition of guanidine hydrochloride **4,HCl** (311 mg, 1 mmol) and potassium *tert*-butyl oxide (134 mg, 1.2 mmol) in dimethylformamide (5 mL). After heating at 50 °C for 30 min, the freshly prepared guanidine base **4** was obtained.

***N*-(3-iodobenzyl)-*N'*-(3-carbonyl-quinoline)-guanidine (1). (a) *via* 3-quinoline carboxylic acid methyl ester.** Sulfuric acid (200 mL) was added to a solution of 3-quinoline carboxylic acid (173 mg, 1 mmol) in methanol (30 mL). The mixture was stirred at 100 °C for 12 h. Then, the solution was evaporated and the residue was dissolved in water (20 mL). The aqueous solution was extracted with chloroform (3 x 10 mL). The combined organic phases were dried and evaporated under reduced pressure. The intermediate ester (150 mg, 0.8 mmol) was obtained in 80% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 9.38 (s, 1H), 8.78 (s, 1H), 8.10 (d, 1H, *J*= 8.5 Hz), 7.87 (d, 1H, *J* = 8.1 Hz), 7.79 (dt, 1H, *J* = 1.1 Hz, *J* = 8.1 Hz), 7.57 (dt, 1H, *J* = 1.1 Hz, *J* = 8.1 Hz), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.28, 150.3,150.1, 139.3, 132.3, 129.7, 129.5, 127.9, 127.24, 123.4, 52.89. A solution of 3-quinoline carboxylic acid methyl ester (90 mg, 0.46 mmol) in dimethylformamide (3 mL) was added to a freshly prepared guanidine base **4** obtained from guanidine hydrochloride **4,HCl** (169 mg, 0.5 mmol) and the mixture was heated at 100 °C for 3 h. The solvent was evaporated and water (20 mL) was added to the residue. The resulting mixture was kept at 4 °C for 5 days, and the precipitate was filtered, washed with water and dried. Compound **1** was obtained in 44% yield as a beige powder. **(b) *via* 2-[3-*N*-(tert-butyl)carbamoyl-prop-2-enyl]-quinoline-3-carboxylate.** Under nitrogen, NBI (240 mg, 1 mmol) was added to a mixture of 3-quinoline carboxylic acid (173 mg, 1 mmol) and triethylamine (140 μL, 1 mmol) in dimethylformamide (2 mL). The mixture was stirred at room temperature for 4 h and then poured on iced water (50 mL). The precipitate was collected, washed with water and dried. The intermediate ester (131 mg, 0.44 mmol) was isolated in 44% yield as a yellow powder. ^{1}H NMR (DMSO-*d6*): δ 9.35 (d, 1H, *J* = 1.7 Hz), 9.09 (d, 1H, *J* = 1.7 Hz), 8.26 (d, 1H, *J* = 7.8 Hz), 8.14 (d, 1H, *J* = 8.2 Hz), 7.96 (dt, 1H, *J* = 1.1 Hz, *J* = 8.0 Hz), 7.76 (dt, 1H, *J* = 1.1 Hz, *J* = 8.0 Hz), 7.51 (s, 1H), 5.80 (s, 1H), 2.06 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (DMSO-*d6*): δ 162.2, 162.1, 153.1, 149.6, 149.2, 139.1, 132.3, 129.6, 128.8, 127.7, 126.5, 122.5, 112.1, 49.9, 28.3, 20.9. Anal. ($C_{18}H_{20}N_2O_3$) C, H, N. Then the product (110 mg, 0.36 mmol) in dimethylformamide (3 mL) was added to a freshly prepared guanidine base **4** obtained from guanidine hydrochloride **4,HCl** (123 mg, 0.39 mmol) and the mixture was stirred at 140 °C for 2 h. The solvent was evaporated under reduced pressure. Water (10 mL) was added to the residue, and after 12 h at 4 °C, the precipitate formed was filtered, washed with water, and dried. Compound **1** was isolated in 85% yield.

Reference

(1) Wieland, D. M.; Wu, J.; Brown, L. E.; Mangner, T. J.; Swanson, D. P.; Beierwaltes, W. H. Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with [^{131}I]iodobenzylguanidine. *J. Nucl. Med.* **1980**, *21*, 349-353.