Neuropharmacology 143 (2018) 349–350

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Corrigendum

Corrigendum to “Bumepamine, a brain-permeant benzylamine derivative of bumetanide, does not inhibit NKCC1 but is more potent to enhance phenobarbital's antiseizure efficacy” [Neuropharmacology 143 (2018) 186–204]

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The authors regret that the description of the synthesis of bumepamine in the above-mentioned article lacked an important aspect and is therefore incorrect.

The correct synthesis of bumepamine is given below.

The authors would like to apologise for any inconvenience caused.

2.2 Synthesis of bumepamine

Bumetanide (**1**) (500 mg, 1.37 mmol) was dissolved in 9 mL dry *N*,*N*-dimethylformamide and *N*,*N*-diisopropylethylamine (765 µL, 4.39 mmol), followed by addition of aniline (250 µL, 2.74 mmol). The mixture was cooled on an ice-bath. COMU (707 mg, 1.65 mmol) was added in one portion and the mixture was gradually warmed to room temperature and stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted twice with ethyl acetate (EtOAc). The combined organic layers were washed with water, brine and dried over Na_2SO_4. The crude product was purified by column chromatography (toluene:EtOAc:Et_3N, 3:2:0.01). The desired product (**2**; the phenylamide of bumetanide) (540 mg, 1.22 mmol) was obtained in 89% yield as a slightly yellow solid. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.79 (d, J = 2.1 Hz, 1H), 7.68–7.71 (m, 2H), 7.50 (d, J = 2.1 Hz, 1H), 7.36–7.40 (m, 2H), 7.28–7.32 (m, 2H), 7.14–7.19 (m, 1H), 7.05–7.09 (m, 1H), 6.93–6.96 (m, 2H), 3.17 (t, J = 6.7 Hz, 2H), 1.40–1.48 (m, 2H), 1.13–1.21 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz) d_4-MeOH δ 167.83, 157.87, 144.02, 140.63, 139.74, 138.38, 133.97, 130.61, 129.82, 125.77, 124.01, 122.45, 116.66, 115.22, 114.88, 43.71, 32.03, 20.87, 14.03. HRMS (ESI) calculated for $C_{23}H_{26}N_3O_4S$ $[M+H]^+$ 440.1644, found 440.1646.

Next, the phenylamide of bumetanide (**2**) (250 mg, 0.57 mmol) was dissolved in 12 mL tetrahydrofuran and borane dimethylsulfide complex (90 µL, 0.95 mmol) was added at room temperature. The reaction mixture was stirred for 16 h at 70 °C and cooled to room temperature. Since some starting material was still present, an additional amount of the borane dimethylsulfide complex (90 µL, 0.95 mmol) was added and the reaction was stirred for 5 h at 70 °C. The reaction mixture was cooled to room temperature and then quenched with half-saturated aqueous $NaHCO_3$ solution. The mixture was extracted three times with EtOAc and the combined organic layers were dried over Na_2SO_4. The crude product was purified by column chromatography (CH_2Cl_2:MeOH, 50:1). The obtained oily substance was dried under vacuum for 4 hours and then dissolved in 10 mL dry diethyl ether (Et_2O). 2M HCl in Et_2O (135 µL, 0.27 mmol) was added and the flask left to stand for 10 minutes. The salt that was formed was filtered, washed three times with Et_2O and the desired product (**3**; bumepamine) (90 mg, 0.21 mmol) was obtained as a slightly beige solid in 37% yield. ^{1}H NMR (400 MHz, d_4-MeOH) δ 7.52–7.60 (m, 3H), 7.44–7.46 (m, 2H), 7.33 (d, J = 2.0 Hz, 1H), 7.68–7.30 (m, 2H), 7.04–7.08 (m, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.86–6.89 (m, 2H), 4.64 (s, 2H), 3.00 (t, J = 6.8 Hz, 2H), 1.29–1.37 (m, 2H), 1.06–1.15 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz) d_4-MeOH δ 157.9, 144.2, 139.1, 138.9, 136.1, 131.5, 131.1, 130.6, 129.8, 124.3, 124.0, 118.1, 116.8, 116.6, 56.5, 43.6, 31.8, 20.8, 14.0. HRMS (ESI) calcd for $C_{23}H_{28}N_3O_3S$ $[M+H]^+$ 426.1851, found 426.1852.

DOI of original article: https://doi.org/10.1016/j.neuropharm.2018.09.025
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https://doi.org/10.1016/j.neuropharm.2018.10.012

Available online 19 October 2018
0028-3908/

All reactions were carried out under positive pressure of argon, with oven-dried glassware using standard Schlenk techniques. Dry solvents were obtained from Acros Organics (Thermo Fisher, Karlsruhe, Germany) in Acroseal bottles and used without further purification. Aniline was distilled over CaH_2 and used directly after distillation. Bumetanide was purchased from Alfa Aesar (Thermo Fisher) and used without further purification. Reactions were monitored by thin-layer chromatography (0.2 mm, silica gel 60, F_{254}, aluminium-backed, Macherey-Nagel; Düren, Germany), with detection by UV light (254 nm). Flash chromatography was performed on Merck silica (60M). NMR spectra were recorded on an AMX-400 instrument (Bruker) at 400 MHz or at 100 MHz for ^{1}H and ^{13}C, respectively. Deuterated methanol was used as solvent and spectra were calibrated against the residual solvent peak (3.31 ppm and 49.00 ppm for ^{1}H and ^{13}C, respectively). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet), coupling constant (reported in Hertz (Hz)), integration. Electrospray (ESI-HRMS) mass spectra were obtained using an Applied Biosystems API 150EX LC/MS system.