Supporting information for

Pharmacological and electrophysiological characterization of novel NMDA receptor antagonists

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Chemical Synthesis. **General Methods**.

Melting points were determined in open capillary tubes with a MFB 595010M Gallenkamp. 400 MHz ^{1}H/100.6 MHz ^{13}C NMR spectra, and 500 MHz ^{1}H NMR spectra were recorded on Varian Mercury 400, and Varian Inova 500 spectrometers, respectively. The chemical shifts are reported in ppm (δ scale) relative to internal tetramethylsilane, and coupling constants are reported in Hertz (Hz). Assignments given for the NMR spectra of the new compounds have been carried out on the basis of DEPT, COSY ^{1}H/^{1}H (standard procedures), and COSY ^{1}H/^{13}C (gHSQC and gHMBC sequences) experiments. IR spectra were run on Perkin-Elmer Spectrum RX I spectrophotometer. Absorption values are expressed as wave-numbers (cm^{-1}); only significant absorption bands are given. Column chromatography was performed either on silica gel 60 Å (35−70 mesh) or on aluminium oxide, neutral, 60 Å (50-200 μm, Brockmann I). Thin-layer chromatography was performed with aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref 1.05554), and spots were visualized with UV light, iodine or 1% aqueous solution of $KMnO_4$. The analytical samples of all of the new compounds which were subjected to pharmacological evaluation possessed purity ≥95% as evidenced by their elemental analyses.

6-(Methoxycarbonyl)-3,4,8,9-tetramethyltetracyclo[4.4.0.0^{3,9}.0^{4,8}]decane-1-carboxylic acid (**13**). A suspension of anhydride **12**[1] (1.575 g, 6.05 mmol) in methanol (50 mL) was heated to reflux for 24 h. The reaction mixture was allowed to cool down to room temperature and the methanol was removed under reduced pressure to afford hemiester **13** as a yellowish solid (1.714 g,

[1] Avila, W. B., Silva, R. A. (1970) 3,4,8,9-Tetramethyltetracyclo[4.4.0.0^{3,9}.0^{4,8}]decane-1,6-dioic anhydride. *J. Chem. Soc. D,* 94-95.

quantitative yield). The analytical sample was obtained by crystallization from hot ethyl acetate, mp 168-169 °C. IR (ATR) ν: 708, 721, 729, 767, 806, 871, 922, 990, 1036, 1062, 1103, 1116, 1173, 1196, 1217, 1269, 1289, 1369, 1416, 1431, 1449, 1700, 1736, 2583, 2718, 2925, 2950 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.965 [s, 6H, 3(9)-C<u>H</u>$_3$ or 4(8)-C<u>H</u>$_3$], 0.969 [s, 6H, 4(8)-C<u>H</u>$_3$ or 3(9)-C<u>H</u>$_3$], 1.12-1.18 [c. s., 4H, 2(10)-H_a and 5(7)-H_a], 2.09-2.17 [c. s., 4H, 2(10)-H_b and 5(7)-H_b], 3.65 (s, 3H, OCH_3). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ: 15.31 [CH_3, C3(9)-CH_3 or C4(8)-CH_3], 15.32 [CH_3, C4(8)-<u>C</u>H_3 or C3(9)-<u>C</u>H_3], 42.0 (C, C6), 42.1 [CH_2, C5(7) and C2(10)], 45.2 [C, C3(9) or C4(8)], 45.3 [C, C4(8) or C3(9)], 51.5 (CH_3, OCH_3), 52.21 (C, C1 or C6), 52.27 (C, C6 or C1, C), 175.3 (C, <u>C</u>O_2CH_3), 181.4 (C, CO_2H). HRMS-ESI+ m/z $[M+H]^+$ calcd for $[C_{17}H_{24}O_4+H]^+$: 293.1747, found: 293.1759.

Methyl 3,4,8,9-tetramethyltetracyclo[4.4.0.0^{3,9}.0^{4,8}]decane-1-carboxylate (**14**). In a three-neck round-bottom flask equipped with a thermometer, magnetic stirring and argon atmosphere, a solution of hemiester **13** (1.134 g, 4.1 mmol) and 2,2'-dithiobis(pyridine)-1,1'-dioxide (1.325 g, 5.25 mmol) in anhydrous THF (40 mL) was prepared. The round-bottom flask was wrapped with aluminium foil and the reaction was cooled to 0 °C with an ice bath. *n*-tributylphosphine (1.4 mL, 5.74 mmol) was added and the reaction was stirred at room temperature for 2 h. Then, *t*-butylthiol (2.3 mL, 20.5 mmol) was added, the aluminium foil removed and the reaction was irradiated with two 100 W bulbs for 2 h. Et_2O (35 mL) was added to the resulting solution and the organic layer was washed with a saturated $NaHCO_3$ solution (3 x 20 mL), aqueous 5 N HCl solution (3 x 20 mL), water (2 x 20 mL) and brine (2 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to obtain a mixture of ester and *n*-tributylphosphine (1.012 g). Column chromatography (Hexane/Ethyl acetate mixture) gave the ester **14** as a white solid (507 mg, 50% yield), mp 145-146 °C. IR (ATR) ν: 758, 782, 796,

810, 1033, 1099, 1199, 1260, 1305, 1426, 1446, 1720, 2867, 2924, 2947 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.73 [dd, *J* = 11.6 Hz, *J'* = 2.4 Hz, 2H, 5(7)-H_a], 0.95 [s, 12H, 3(9)-C<u>H</u>$_3$ and 4(8)-C<u>H</u>$_3$], 1.00 [d, *J* = 11.2 Hz, 2H, 2(10)-H_a], 1.79 (dd, 11.6 Hz, *J'* = 1.6 Hz, 2H, 5(7)-H_b), 1.90 [d, *J* = 11.2 Hz, 2H, 2(10)-H_b], 2.66 (m, 1H, 6-H), 3.68 (s, 3H, OCH_3). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ: 15.5 [CH_3, C3(9)-CH_3 and C4(8)-CH_3], 36.6 (CH, C6), 38.1 [CH_2, C5(7)], 41.6 [CH_2, C2(10)], 44.9 [C, C3(9) or C4(8)], 45.5 [C, C4(8) or C3(9)], 48.2 (C, C1), 51.6 (CH_3, OCH_3), 177.7 (C, CO). HRMS-ESI+ m/z [*M*+H]$^+$ calcd for [$C_{16}H_{24}O_2$+H]$^+$: 249.1849, found: 249.1855.

3,4,8,9-Tetramethyltetracyclo[4.4.0.0^{3,9}.0^{4,8}]decane-1-carboxylic acid (**15**). A mixture of **14** (485 mg, 1.95 mmol) in a 40% methanol solution of KOH (10 mL) was heated to reflux for 2 h. Water (10 mL) was added and the reaction was refluxed for 3 h. The reaction mixture was allowed to cool down to room temperature and the methanol was removed *in vacuo*. Water (20 mL) was added to the residue and the solution acidified with concentrated HCl until pH=1. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **15** as a white solid (462 mg, quantitative yield), mp 160 °C (sublimation). IR (ATR) ν: 675, 746, 796, 880, 900, 933, 955, 988, 1105, 1155, 1216, 1282, 1309, 1370, 1383, 1408, 1458, 1479, 1580, 1678, 2860, 2916, 2951 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.75 [dd, *J* = 11.2 Hz, *J'* = 2.6 Hz, 2H, 5(7)-H_a], 0.95 [s, 6H, 3(9)-C<u>H</u>$_3$ or 4(8)-C<u>H</u>$_3$], 0.96 [s, 6H, 4(8)-C<u>H</u>$_3$ or 3(9)-C<u>H</u>$_3$], 1.06 [d, *J* = 11.2 Hz, 2H, 2(10)-H_a], 1.80 [dd, *J* = 11.2 Hz, *J'* = 1.6 Hz, 2H, 5(7)-H_b], 1.94 [d, *J* = 11.2 Hz, 2H, 2(10)-H_b], 2.73 (m, 1H, 6-H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ: 15.5 [CH_3, C3(9)-CH_3 and C4(8)-CH_3], 36.4 (CH, C6), 38.1 [CH_2, C5(7)], 41.7 [CH_2, C2(10)], 44.9 [C, C3(9) or C4(8)], 45.7 [C, C4(8) or C3(9)], 48.2 (C, C1), 183.8 (C, CO). HRMS-ESI+ m/z [*M*+H]$^+$ calcd for [$C_{15}H_{22}O_2$+H]$^+$: 235.1693, found: 235.1698.

3,4,8,9-Tetramethyltetracyclo[4.4.0.0^{3,9}.0^{4,8}]decane-1-carboxamide (**16**). In a round-bottom flask equipped with a condenser, magnetic stirring and a $CaCl_2$ tube, a solution of **15** (175 mg, 0.75 mmol) in $SOCl_2$ (3 mL, 41.07 mmol) was heated to reflux for 2 h. Then, the excess of $SOCl_2$ was removed *in vacuo* and the residue was dissolved in toluene to azeotropically remove the remaining $SOCl_2$ (3 x 5 mL). The oil was dissolved in DCM (3 mL), cooled to 0 °C and aq. 50% NH_4OH solution (6 mL) was added dropwise. The reaction was stirred vigorously at room temperature for 24 h. The resulting suspension was extracted with DCM (4 x 10 mL). The combined organics were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure yielding a yellowish solid (163 mg). Column chromatography (Hexane/Ethyl acetate mixture) gave the amide **16** as a white solid (109 mg, 63% yield), mp 152-153 °C. IR (ATR) ν: 677, 708, 816, 900, 1001, 1024, 1082, 1107, 1122, 1226, 1292, 1330, 1370, 1383, 1398, 1451, 1476, 1608, 1676, 2860, 2919, 2946, 3397 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.77 [dd, *J* = 11.6 Hz, *J'* = 2.4 Hz, 2H, 5(7)-H$_a$], 0.91 (d, J = 10.8 Hz, 2H, 2(10)-H$_a$], 0.95 [s, 12H, 3(9)-C<u>H</u>$_3$ and 4(8)-C<u>H</u>$_3$], 1.82 [dd, *J* = 11.6 Hz, *J'* = 1.6 Hz, 2H, 5(7)-H$_b$], 1.92 [d, *J* = 10.8 Hz, 2H, 2(10)-H$_b$], 2.57 (m, 1H, 6-H). ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ: 15.5 [CH_3, C3(9)-<u>C</u>H$_3$ or C4(8)-<u>C</u>H$_3$], 15.6 [CH_3, C4(8)-<u>C</u>H$_3$ or C3(9)-<u>C</u>H$_3$], 37.6 (CH, C6), 38.3 [CH_2, C5(7)], 41.6 [CH_2, C2(10)], 44.9 [C, C3(9) or C4(8)], 45.6 [C, C3(9) or C4(8)], 49.1 (C, C1), 180.1 (C, CO). HRMS-ESI+ m/z [*M*+H]$^+$ calcd for [$C_{15}H_{23}NO$+H]$^+$: 234.1852, found: 234.1849.