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# Tricyclic derivatives of bispidine as AMPA receptor allosteric modulators

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NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer using $CDCl_3$ for calibration. High resolution mass spectra were recorded using a Thermo Scientific Orbitrap Elite spectrometer. Column chromatography was performed using ultrapure grade silica gel 60–200 μm. TLC monitoring was carried out using Merck Silica gel 60 $F_{254}$ plates, compounds were visualized by $I_2$ and UV 254 nm. Melting points were measured in the block using an open capillary on a REACH Devices RD-MP apparatus.

*Compounds* **2a**, **2c** *and* **2d** *(general procedure).* To a suspension of the corresponding amine $RNH_2$ and $K_2CO_3$ in anhydrous $CH_3CN$, a solution of 3,7-di(chloroacetyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one **1** in anhydrous $CH_3CN$ was added in a ratio $RNH_2$–compound **1**–$K_2CO_3$ 1 : 1 : 8. The mixture was stirred until the complete consumption of starting material as monitored by TLC. Then $K_2CO_3$ was filtered and washed several times with anhydrous $CH_3CN$. The solvent from combined organic filtrates was evaporated *in vacuo* affording a crude product, which was further purified by column chromatography on silica gel with $CHCl_3$→$CHCl_3$–EtOH 80 : 1, 50 : 1 and finally 20 : 1.

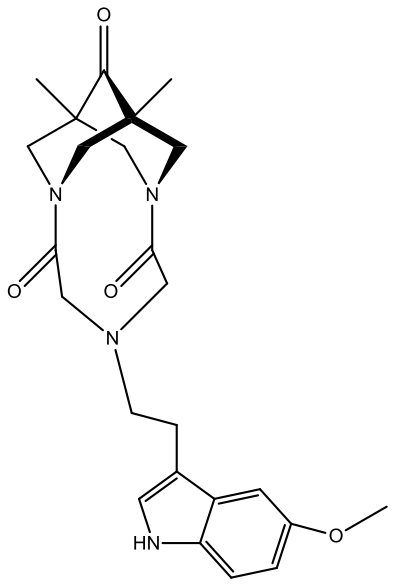
*6-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]-1,11-dimethyl-3,6,9-triazatricyclo[7.3.1.1$^{3,11}$]tetradecane-4,8,12-trione* **2a**. Yield 70 %, white solid, mp 136–138 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.61 (s, 3H, Me–C$^{1,11}$<), 0.95 (s, 3H, Me–C$^{1,11}$<), 2.72, 2.91 and 3.32 (d, 6H, bispidine), 2.97 (m, 4H, 2$CH_2$), 3.83–3.86 (m, 5H, MeO and bispidine), 4.73 and 4.89 (d, 4H, CO–$CH_2$–N<, *J* 13 Hz), 6.85, 6.99, 7.06, 7.30 (4H, arom), 8.54 (s, 1H, NH). $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$: 14.7, 15.7, 22.1, 44.5, 45.3, 53.9, 55.6, 57.2, 59.9, 100.2, 111.5, 112, 122.4, 127, 131.4, 153.5, 168, 210.8. HRMS (ESI), *m*/*z*: 439.2333 (calc. for $C_{24}H_{30}N_4O_4$ $[M+H]^+$, *m*/*z*: 439.2340).

*6-(1,3-Benzodioxol-5-ylmethyl)-1,11-dimethyl-3,6,9-triazatricyclo[7.3.1.1$^{3,11}$]tetradecane-4,8,12-trione* **2c**. Yield 80 %, white solid, mp 109–110 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 0.94 (s, 3H, Me–C$^{1,11}$<), 1.04 (s, 3H, Me–C$^{1,11}$<), 2.70, 2.98, 3.13 and 3.73 (d, 8H, bispidine), 3.47 (s, 2H, $CH_2$), 4.88 (d, 4H, CO–$CH_2$–N<, *J* 13.5 Hz), 5.96 (s, 2H, O–$CH_2$–O), 6.71–6.78 (3H, arom). $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$: 15.3, 15.8, 44.9, 45.3, 53.8, 54.9, 59.8, 61.8, 100.9, 107.9, 109.5, 123, 129.1, 147.2, 147.6, 167.7, 210.6. HRMS (ESI), *m*/*z*: 400.1861 (calc. for $C_{21}H_{25}N_3O_5$ $[M+H]^+$, *m*/*z*: 400.1867).

*6-[2-(1*H*-Indol-3-yl)ethyl]-1,11-dimethyl-3,6,9-triazatricyclo[7.3.1.1$^{3,11}$]tetradecane-4,8,12-trione* **2d**. Yield 65 %, white solid, mp 177–179 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.52 (s, 3H, Me–C$^{1,11}$<), 0.85 (s, 3H, Me–C$^{1,11}$<), 2.75 and 4.04 (d, 4H, bispidine), 2.90–2.99 (m, 8H, $CH_2CH_2$N and bispidine), 4.57 and 4.71 (d, 4H, CO–$CH_2$–N<, *J* 13 Hz), 6.98, 7.06, 7.23, 7.33, 7.61 and 10.83 (6H, arom). $^{13}$C NMR (100.4 MHz, DMSO-$d_6$) $\delta$: 15.0, 16.0, 21.8, 44.5, 45.2, 53.6, 54.6, 57.1, 60.2, 79.2, 111.4, 111.9, 118.5, 121, 122.8, 127.1, 136.4, 168.1, 211.2. HRMS (ESI), *m*/*z*: 409.2225 (calc. for $C_{23}H_{28}N_4O_3$ $[M+H]^+$, *m*/*z*: 409.2234 ).

PV-314-2019-3_001001r

# $^1$H NMR compound 2a



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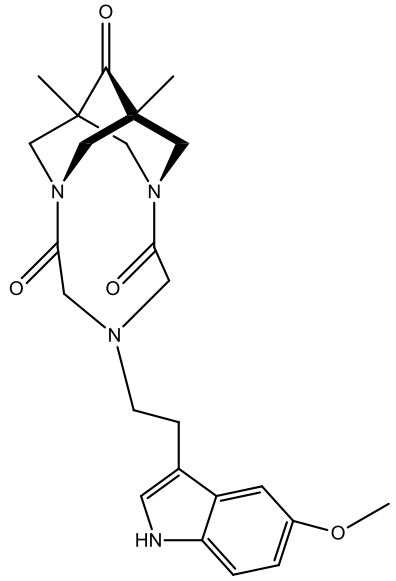

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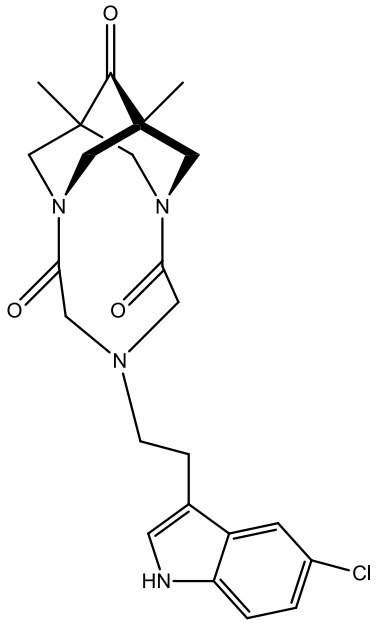

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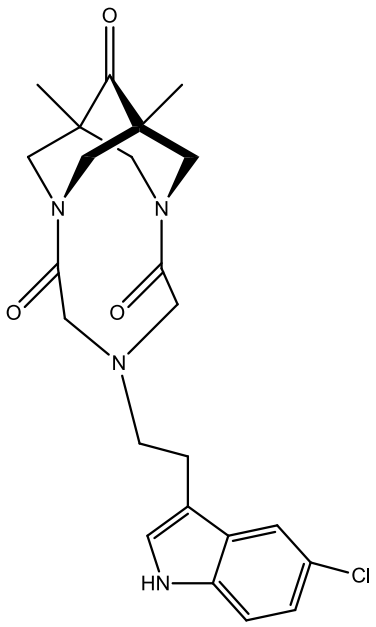
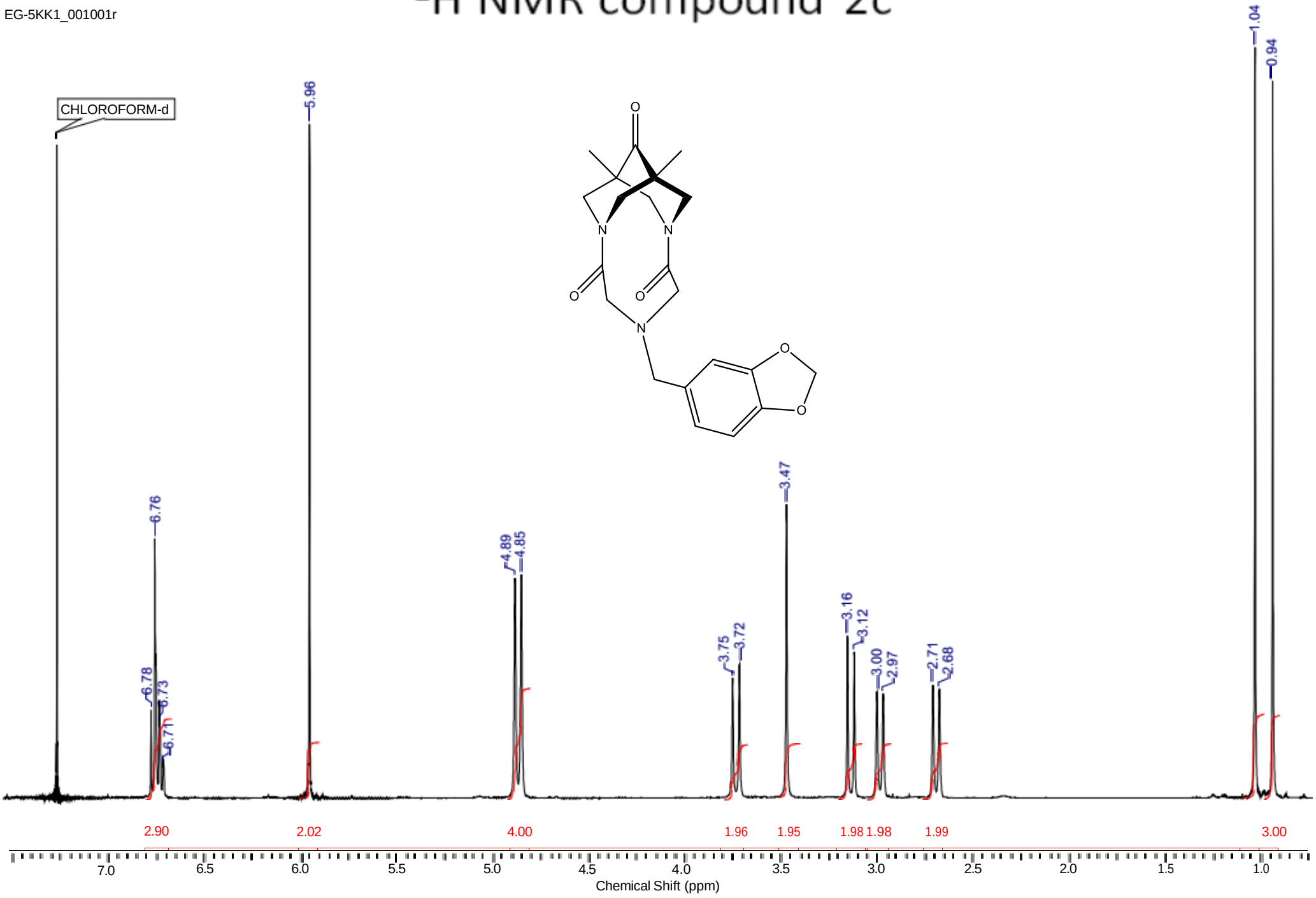


# $^{1}$H NMR compound 2c

EG-5KK1_001001r



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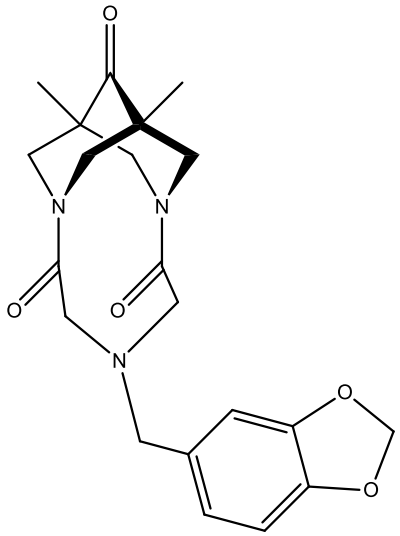
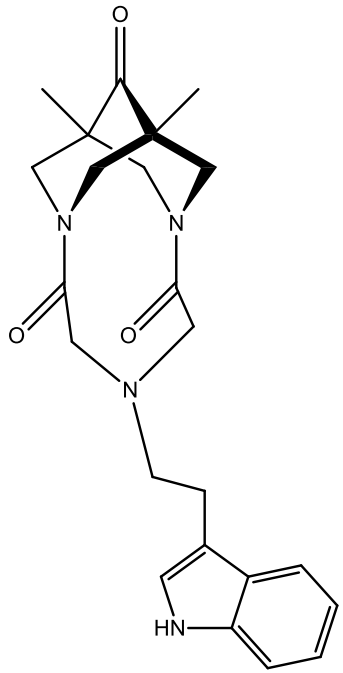


PV-138E_001001r

# $^1$H NMR compound 2d



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