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7-Benzyl-1,5-dimethyl-3-piperonyloyl-3,7-diazabicyclo[3.3.1]nonan-9-one as an allosteric modulator of glutamatergic system

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1. General information

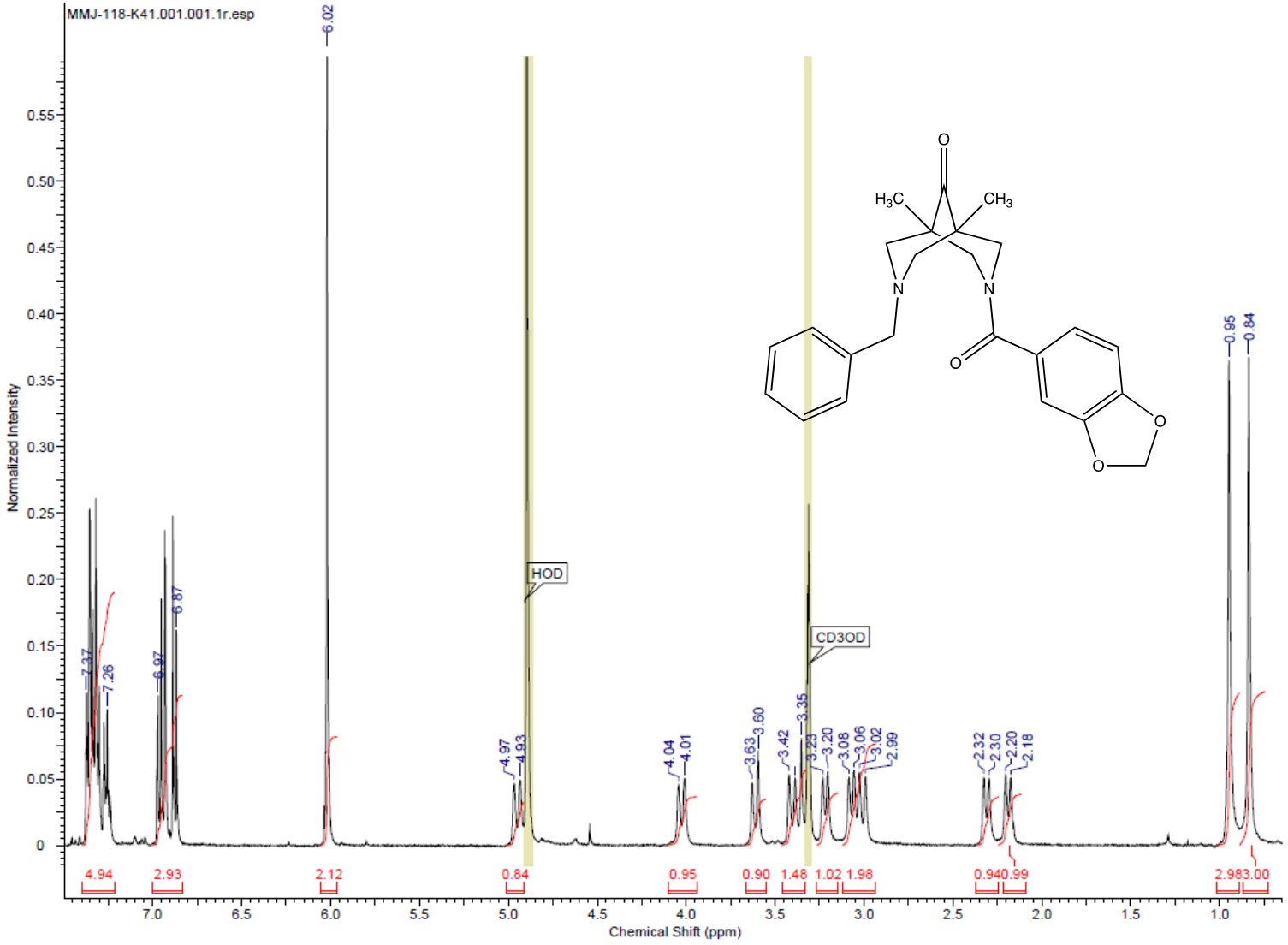
NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 100.4 MHz for ^{13}C) at room temperature. Chemical shifts (δ) were measured with reference to the solvent (CD_3OD) and are given in ppm. HRMS were recorded on a Bruker micrOTOF II instrument using electrospray ionization (ESI). TLC were carried out on Silufol silica gel coated plates; the spots were visualized with UV light (254 nm). Column chromatography was performed on silica gel (230–400 mesh, Merck). Melting points were measured in the block using an open capillary on a REACH Devices RD-MP apparatus.

2. Data for compound 5

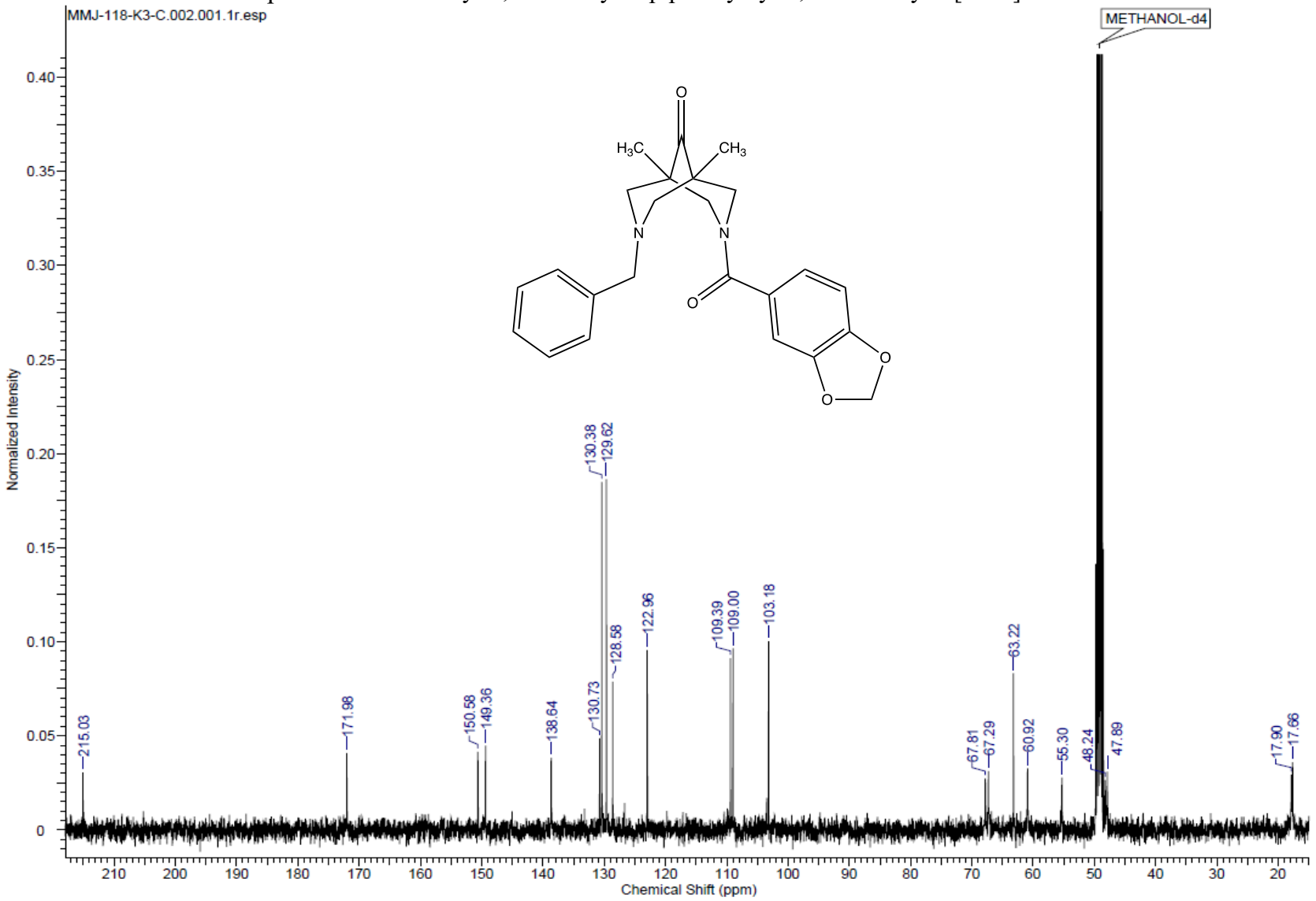
7-Benzyl-1,5-dimethyl-3-piperanyloyl-3,7-diazabicyclo[3.3.1]nonan-9-one **5**. Yield 82 %, white crystalline solid, mp 70–72 °C, R_f 0.45 ($CHCl_3$/EtOH 20:1). ^{1}H NMR (400 MHz, CD_3OD) δ: 0.83 (s, 3H), 0.95 (s, 3H), 2.19 (d, 1H, J = 11 Hz), 2.31 (d, 1H, J = 11.2 Hz), 2.99–3.08 (m, 2H), 3.22 (d, 1H, J = 10.9 Hz), 3.31–3.42 (m, 2H), 3.61 (d, 1H, J = 13.1 Hz), 4.02 (d, 1H, J = 13.6 Hz), 4.95 (d, 1H, J = 13.4 Hz), 6.02 (s, 2H), 6.86–6.97 (m, 3H), 7.24–7.37 (m, 5H). ^{13}C NMR (100.4 MHz, CD_3OD) δ: 15.70, 15.94, 45.93, 46.28, 53.34, 58.96, 61.26, 65.34, 65.85, 101.22, 107.04, 107.44, 121.00, 128.62, 127.67, 128.42, 128.77, 136.68, 147.40, 148.63, 170.02, 213.07. HRMS (ESI), m/z 407.1951 (calc. for $C_{24}H_{27}N_2O_4$ [M + H]$^+$, m/z: 407.1965).

3. NMR spectra of compound 5

^{1}H NMR spectrum of 7-benzyl-1,5-dimethyl-3-piperonyloyl-3,7-diazabicyclo[3.3.1]nonan-9-one **5**



^{13}C NMR spectrum of 7-benzyl-1,5-dimethyl-3-piperonyloyl-3,7-diazabicyclo[3.3.1]nonan-9-one **5**



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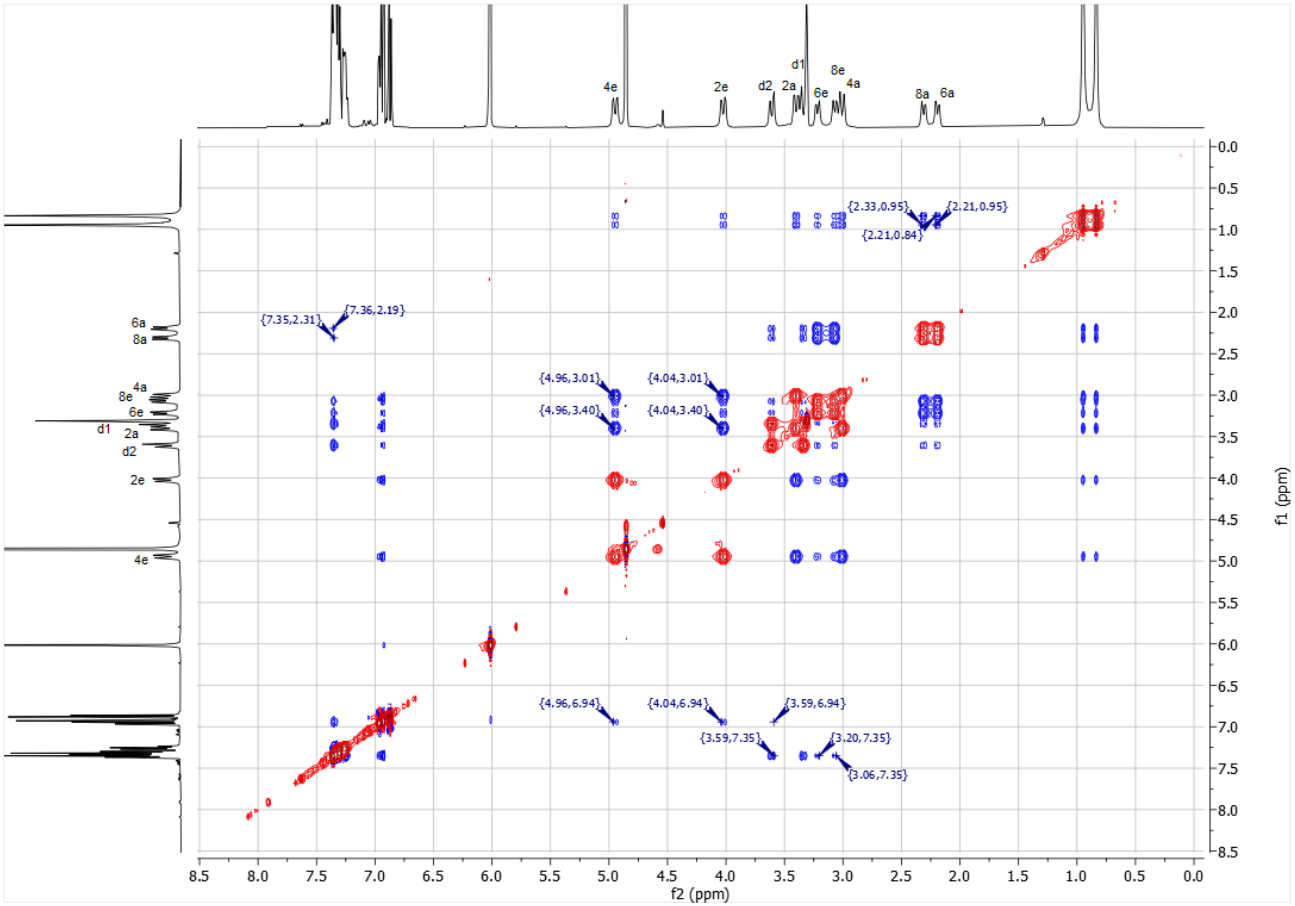
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d2
2a
d1
6e
8e
4a
8a
6a
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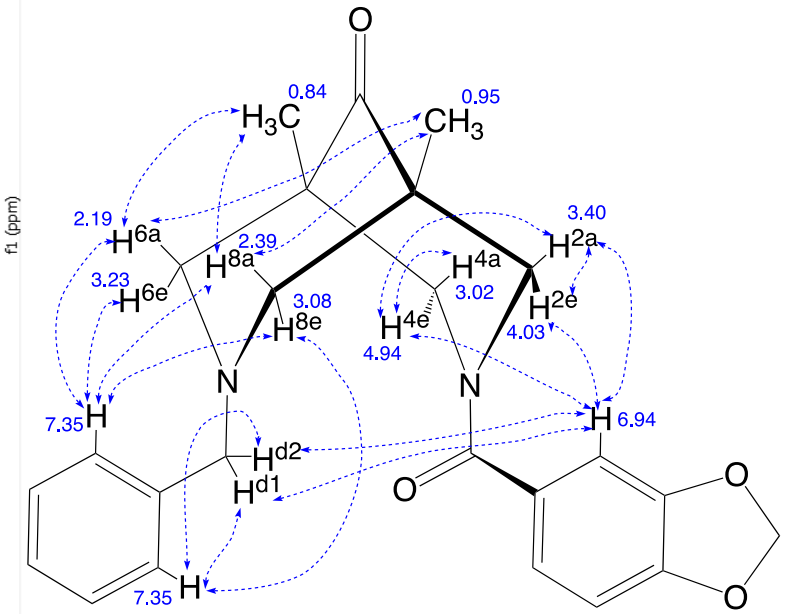
{3.06,7.35}
f2 (ppm)
f1 (ppm)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H4e
3.40
H2a
H2e
4.03
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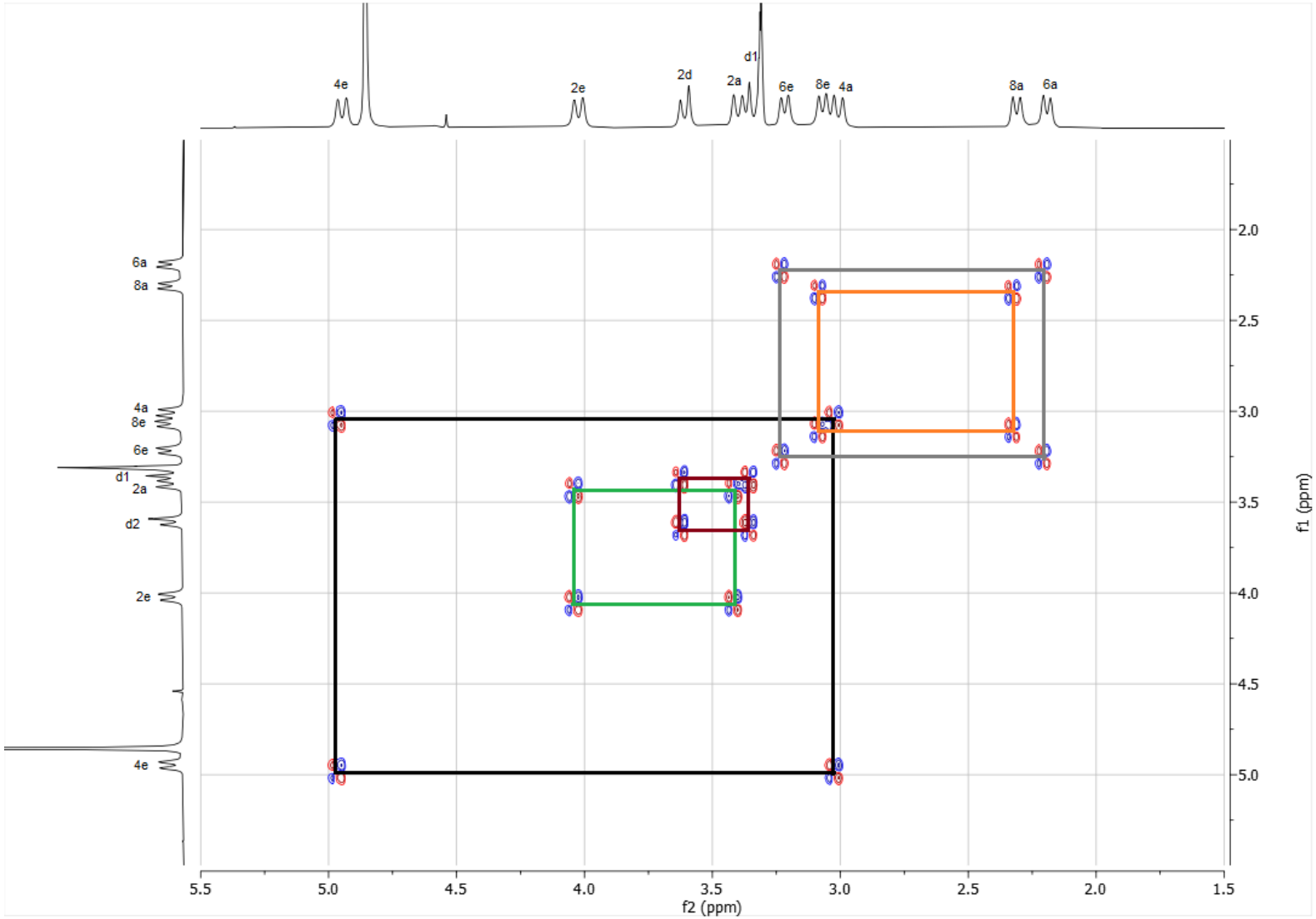
H
Hd2
Hd1
H
7.35
H
6.94
O
O
O

COSY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2d
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d1
6e
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8a
6a
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8e
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3.0
2.5
2.0
1.5
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3.0
3.5
4.0
4.5
5.0
f1 (ppm)

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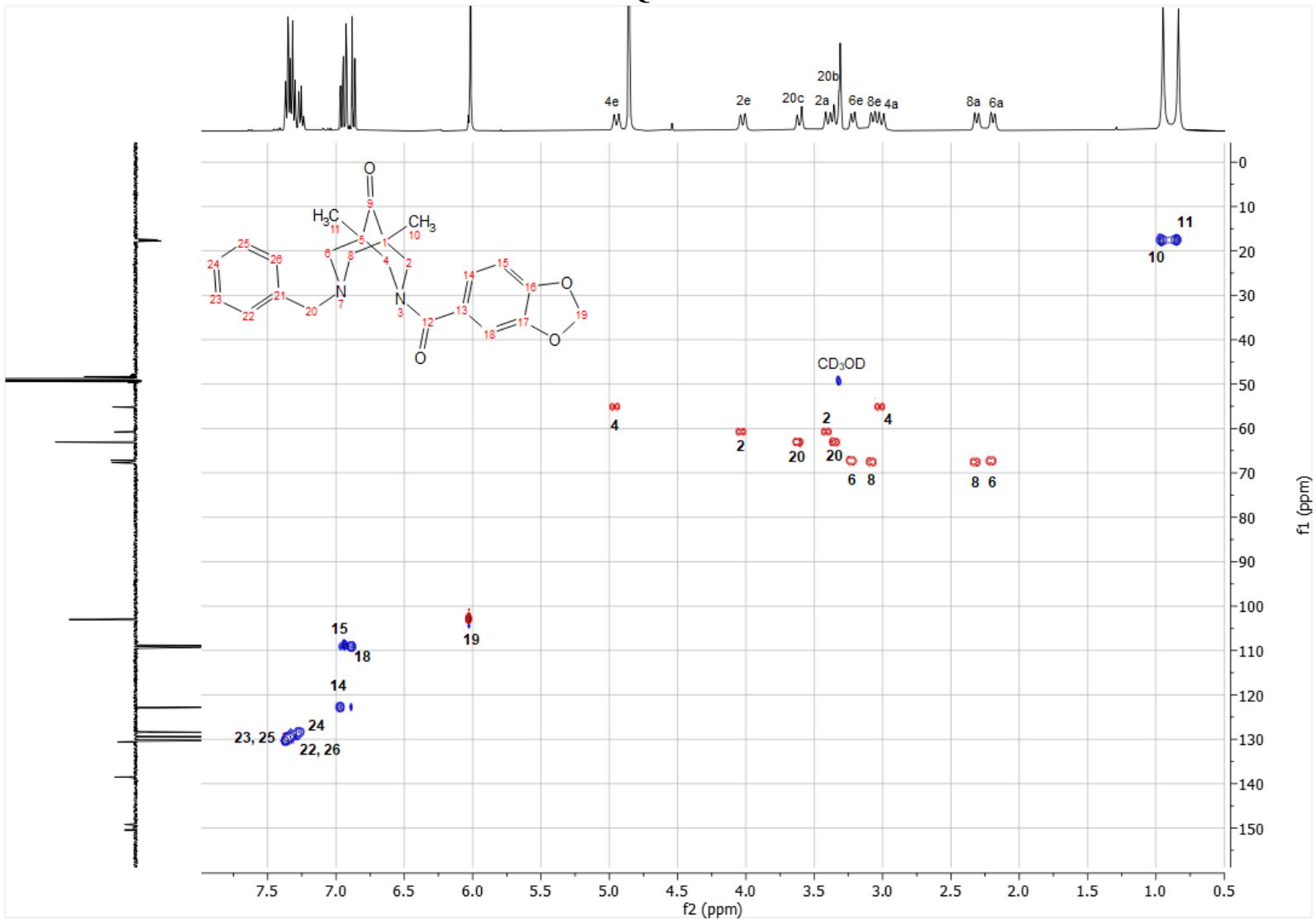

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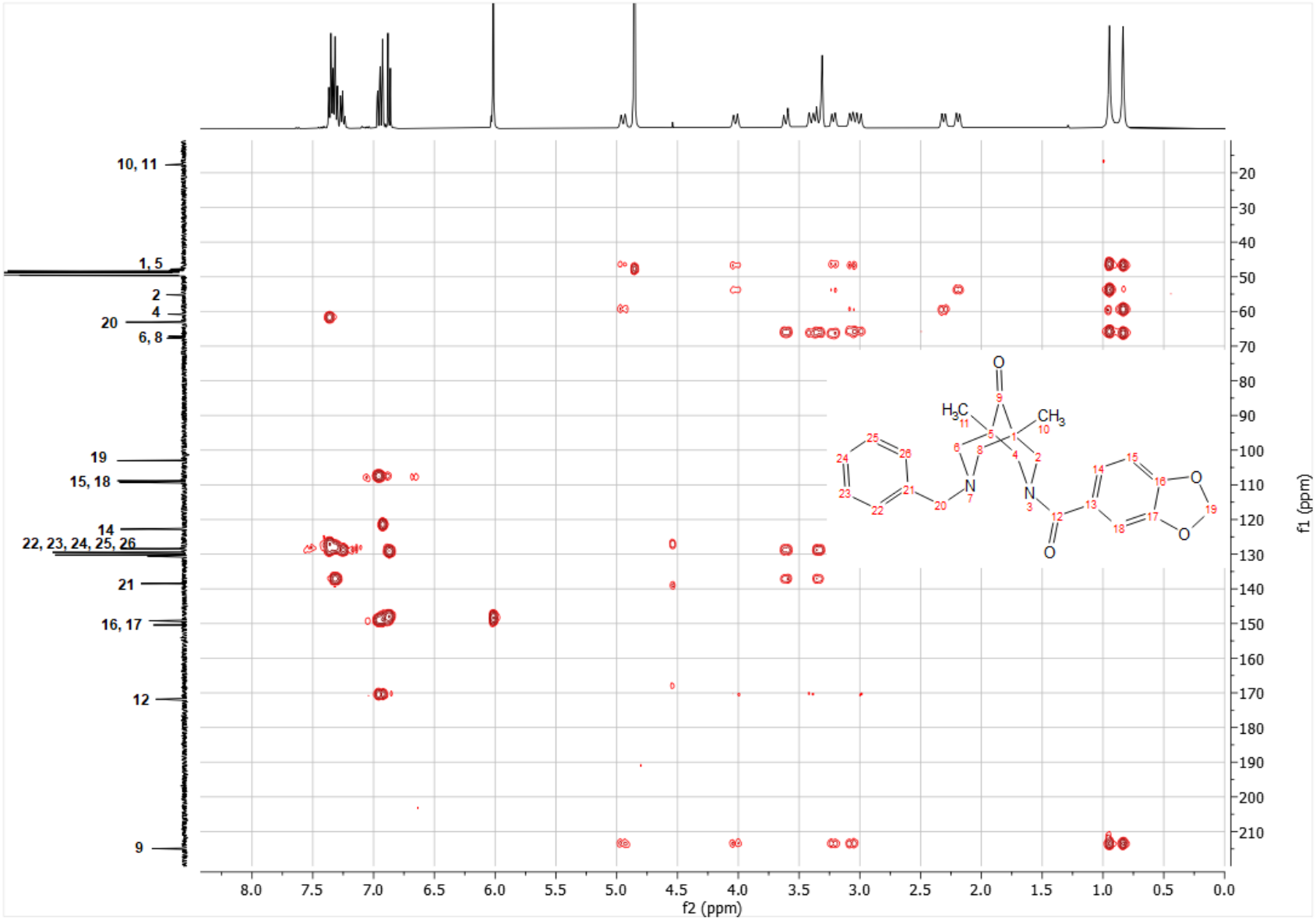

4. Molecular docking and molecular dynamics simulation

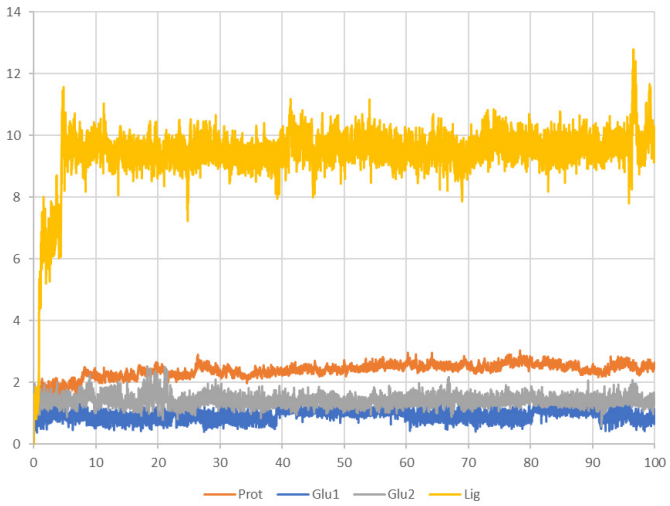

Figure S1. RMSD plots of the protein, glutamate, and ligand heavy atoms for compound **5** during molecular dynamics simulations of the modulator complex with the dimeric ligand binding domain of the GluA2 AMPA receptor (RMSD, Å; Time, ns).