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Novel AMPA receptor allosteric modulators of bis(pyrimidine) series: synthesis and SAR evaluation

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Table of contents

1. Experimental section S2
2. Literature S4
3. Copies of NMR spectra S5
4. Figure S1 S21
5. Figure S2 S22

1. Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer Agilent 400-MR (400.0, 100.6 and 376.3 MHz for ^{1}H, ^{13}C and ^{19}F, respectively) at room temperature; chemical shifts δ were measured with reference to the solvent for ^{1}H ($CDCl_3$, δ = 7.26 ppm) and ^{13}C ($CDCl_3$, δ = 77.16 ppm). When necessary, assignments of signals in NMR spectra were made using 2D techniques. Accurate mass measurements (HRMS) were obtained on Bruker micrOTOF II mass spectrometer with electrospray ionization (ESI). Analytical thin layer chromatography was carried out with silica gel plates (supported on aluminum); the detection was done by UV lamp (254 nm). Column chromatography was performed on silica gel (Macherey-Nagel, Silica 60, 0.015-0.04 mm). Compounds **3a**,[S1] **3b**,[S2] **3c**,[S3] **4a-c**,[S3] **5**,[S4] **6**[S3] and **7**[S5] were obtained as described. All other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified according to literature procedures prior to use.

Synthesis of bis(pyrimidines) ***2a–d*** *(general procedure).* A mixture of the corresponding 4-(pyrimidin-4-yloxy)phenol **4a**–**c** or **6** (1.0 mmol) and Cs_2CO_3 (652 mg, 2.0 mmol) in absolute DMF (10 mL) was stirred for 10 min at r.t., under argon. 4-Halogenopyrimidine **5** or **7** (2.0 mmol) was added. The reaction mixture was stirred at 85 °C for 6 h, allowed to cool down to r.t., quenched with an equal volume of water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried over $MgSO_4$; the solvent was evaporated under reduced pressure. The products were isolated via preparative column chromatography (SiO_2).

4-{4-[(2-Methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)oxy]phenoxy}-5,6,7,8-tetrahydroquinazoline (2a).

Yield 88% (329 mg). White solid, m.p. 163-165 °C, Rf=0.2 (EtOAc).

^{1}H NMR ($CDCl_3$, δ, ppm): 1.76-1.91 (m, 4H, C(6)H_2, C(7)H_2, THQ), 2.03-2.17 (m, 2H, C$^{6}H_2$, cy-pent-Pyr), 2.46 (s, 3H, CH_3), 2.71-2.76 (m, 2H, C(5)H_2, THQ), 2.78-2.83 (m, 2H, C(8)H_2, THQ), 2.84-2.89 (m, 2H, C(5)H_2, cy-pent-Pyr), 2.90-2.95 (m, 2H, C(7)H_2, cy-pent-Pyr), 7.08-7.17 (m, 4H, 4CH, Ar), 8.42 (s, 1H, CH, THQ);

^{13}C NMR ($CDCl_3$, δ, ppm): 21.79 (CH_2), 21.86 (CH_2), 21.92 (CH_2), 22.05 (CH_2), 25.4 (CH_3), 26.7 (C(5)H_2, cy-pent-Pyr), 31.8 (C(8)H_2, THQ), 34.2 (C(7)H_2, cy-pent-Pyr), 117.2 (C(4a), cy-pent-Pyr), 117.4 (C(4a), THQ), 122.67 (2CH, Ar), 122.71 (2CH, Ar), 149.5 (C, Ar), 149.8 (C, Ar), 154.6 (CH, THQ), 165.1 (C), 166.7 (C), 166.9 (C), 167.1 (C), 176.8 (C(7a), cy-pent-Pyr).

HRMS (ESI^+, m/z): calcd. for $C_{22}H_{22}N_4O_2$ $[M+H]^+$ 375.1816, found 375.1814.

2-Methyl-4-{4-[(5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenoxy}-5,6,7,8-tetrahydroquinazoline (2b).

Yield 64% (248 mg). White solid, m.p. 156-158 °C, R_f = 0.2 (EtOAc).

^{1}H NMR ($CDCl_3$, δ, ppm): 1.74-1.96 (m, 8H, 4CH_2), 2.43 (s, 3H, CH_3), 2.66-2.71 (m, 2H, CH_2), 2.73-2.80 (m, 4H, 2CH_2), 2.81-2.86 (m, 2H, CH_2), 7.05-7.24 (m, 4H, 4CH, Ar), 8.46 (s, 1H, CH, THQ);

^{13}C NMR ($CDCl_3$, δ, ppm): 21.7 (CH_2), 21.9 (CH_2), 22.0 (CH_2), 22.1 (CH_2), 22.2 (CH_2), 22.3 (CH_2), 25.5 (CH_3), 31.9 (2CH_2), 114.0 (C, THQ), 117.5 (C, THQ), 122.6 (2CH, Ar), 122.7 (2CH, Ar), 149.4 (C, Ar), 150.1 (C, Ar), 154.8 (CH, THQ), 164.1 (C, THQ), 166.7 (C, THQ), 166.83 (C, THQ), 166.88 (C, THQ), 167.2 (C, THQ).

HRMS (ESI$^+$, m/z): calcd. for $C_{23}H_{24}N_4O_2$ $[M+H]^+$ 389.1972, found 389.1974.

2-Methyl-4-{4-[(5,6,7,8-tetrahydroquinazolin-4-yl)oxy]phenoxy}-6,7,8,9-tetrahydro-5*H*-cyclohepta[*d*]pyrimidine (2c)

Yield 46% (185 mg). White solid, m.p. 206-207 °C, R_f = 0.1 (petroleum ether – EtOAc 1:2).

^{1}H NMR ($CDCl_3$, δ, ppm): 1.59-1.76 (m, 4H, 2CH_2, cy-hept-Pyr), 1.81-1.96 (m, 6H, 2CH_2, THQ + CH_2, cy-hept-Pyr), 2.45 (s, 3H, CH_3), 2.71-2.81 (m, 2H, CH_2, THQ), 2.82-2.87 (m, 2H, CH_2, THQ), 2.87-2.92 (m, 2H, CH_2, cy-hept-Pyr), 2.93-2.98 (m, 2H, CH_2, cy-hept-Pyr), 7.08-7.22 (m, 4H, 4CH, Ar), 8.48 (s, 1H, CH, THQ);

^{13}C NMR ($CDCl_3$, δ, ppm): 21.95 (CH_2, THQ), 22.02 (CH_2, THQ), 22.2 (CH_2, THQ), 24.5 (CH_2, cy-hept-Pyr), 25.6 (CH_3), 25.9 (CH_2, cy-hept-Pyr), 27.1 (CH_2, cy-hept-Pyr), 32.0 (CH_2, THQ), 32.5 (CH_2, cy-hept-Pyr), 38.7 (CH_2, cy-hept-Pyr), 117.5 (C(4a), THQ), 119.0 (C(4a), cy-hept-Pyr), 122.5 (2CH, Ar), 122.7 (2CH, Ar), 149.3 (C, Ar), 150.7 (C, Ar), 154.4 (CH, THQ), 164.4 (C(2), cy-hept-Pyr), 166.1 (C(4), cy-hept-Pyr), 166.9 (C, THQ), 167.2 (C, THQ), 173.1 (C(9a), cy-hept-Pyr).

HRMS (ESI$^+$, m/z): calcd. for $C_{24}H_{26}N_4O_2$ $[M+H]^+$ 403.2129, found 403.2127.

4-{4-[(6-*tert*-Butyl-2-methylpyrimidin-4-yl)oxy]phenoxy}-5,6,7,8-tetrahydroquinazoline (2d).

Yield 84% (327 mg). White solid, m.p. 141-144 °C, R_f = 0.5 (petroleum ether – EtOAc 1:1).

^{1}H NMR ($CDCl_3$, δ, ppm): 1.30 (s, 9H, 3CH_3, *t*-Bu), 1.85-1.95 (m, 4H, C(6)H_2, C(7)H_2), 2.55 (s, 3H, CH_3, Pyr), 2.77-2.82 (m, 2H, C(5)H_2), 2.84-2.90 (m, 2H, C(8)H_2), 6.63 (s, 1H, CH, Pyr), 7.16-7.21 (m, 4H, 4CH, Ar), 8.49 (s, 1H, CH, THQ).

^{13}C NMR ($CDCl_3$, δ, ppm): 21.96 (CH_2), 22.04 (CH_2), 22.2 (CH_2), 26.2 (CH_3, Pyr), 29.4 (3CH_3, *t*-Bu), 32.0 (C(8)H_2), 37.6 (C, *t*-Bu), 99.6 (CH, Pyr), 117.6 (C(4a), THQ), 122.7 (2CH, Ar), 122.9 (2CH, Ar), 149.7 (C, Ar), 150.0 (C, Ar), 154.9 (CH, THQ), 167.06 (C, THQ), 167.14 (C, THQ), 167.7 (C(2), Pyr), 170.0 (C(4), Pyr), 180.3 (C(6), Pyr).

HRMS (ESI$^+$, m/z): calcd. for $C_{23}H_{26}N_4O_2$ $[M+H]^+$ 391.2129, found 391.2132.

2. Literature

S1. A. Gangjee, Y. Zhao, S. Raghavan, C. C. Rohena, S. L. Mooberry and E. Hamel, *J. Med. Chem.*, 2013, **56**, 6829.

S2. G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 1963, 5642.

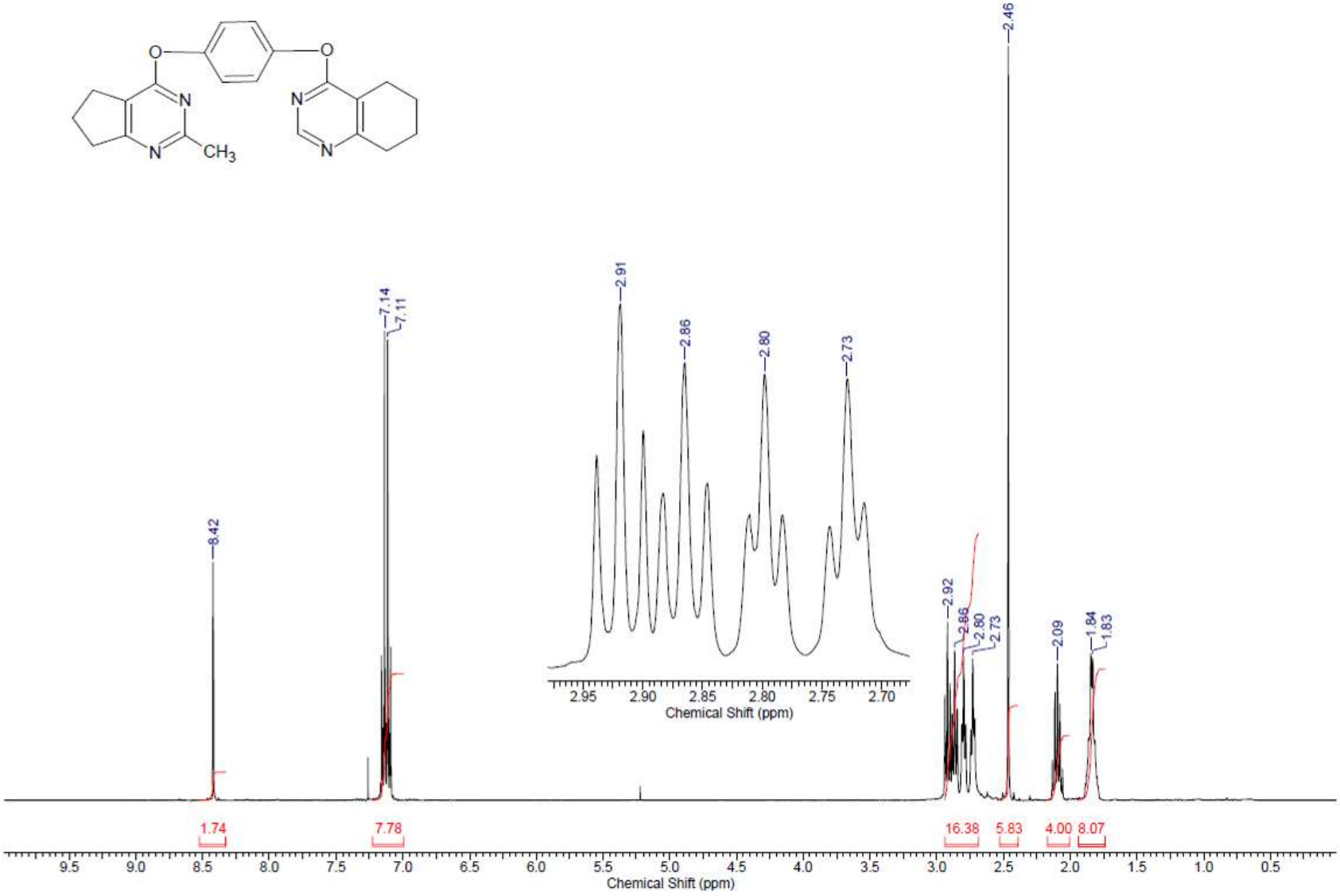
S3. K. N. Sedenkova, D. V. Zverev, A. A. Nazarova, M. I. Lavrov, E. V. Radchenko, Y. K. Grishin, A. V. Gabrel'yan, V. L. Zamoyski, V. V. Grigoriev, E. B. Averina and V. A. Palyulin, *Molecules*, 2022, **27**, 8252.

S4. A. T. Tran, D. Wen, N. P. West, E. N. Baker, W. J. Brittonc and R. J. Payne, *Org. Biomol. Chem.*, 2013, **11**, 8113.

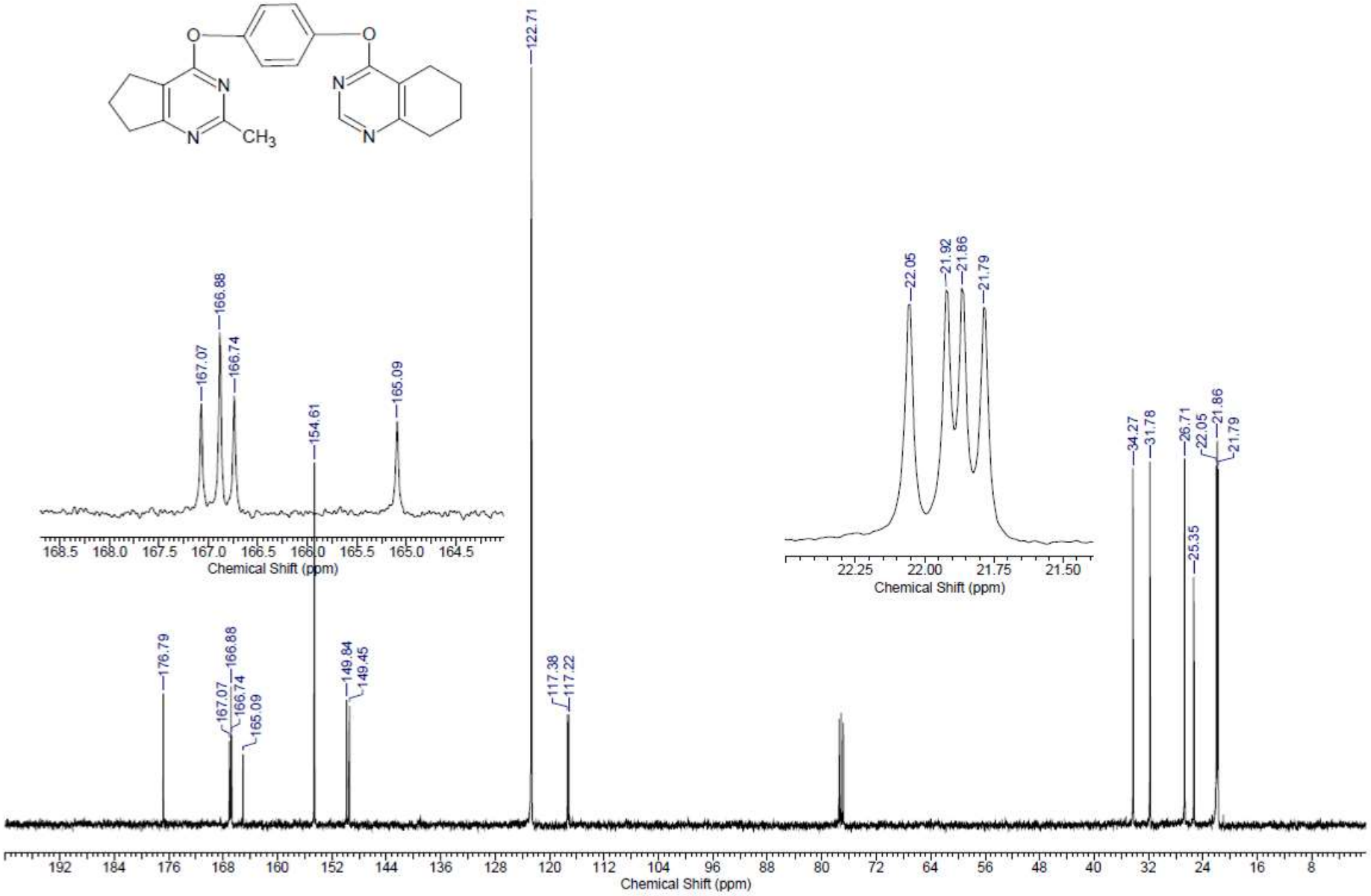
S5. J. Y. Kim, D. Kim, S. Y. Kang, W.-K. Park, H. J. Kim, M. E. Jung, E.-J. Son, A. N. Pae, J. Kim and J. Lee, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6439.

3. Copies of NMR spectra

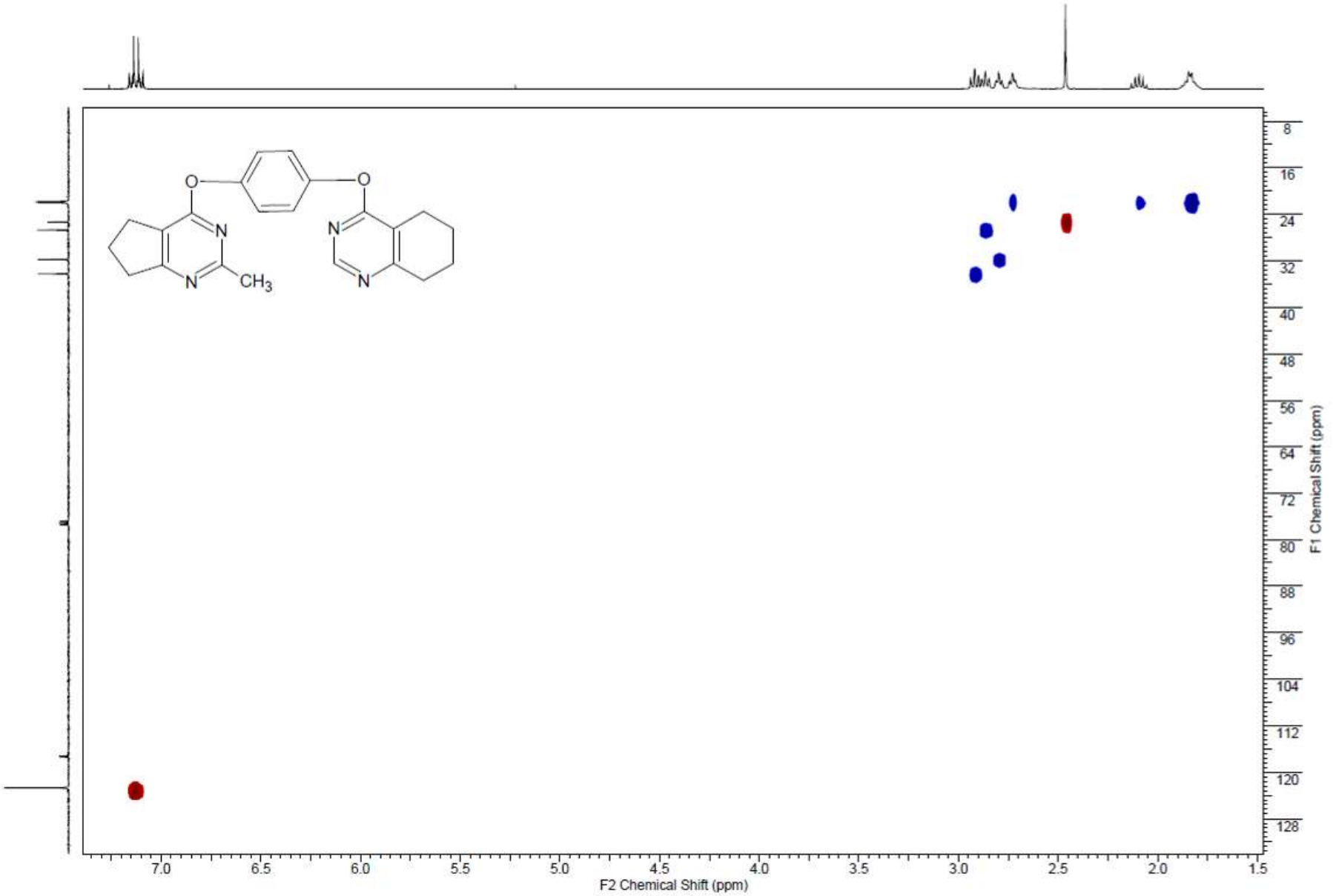
^{1}H NMR spectrum ($CDCl_3$) of compound 2a



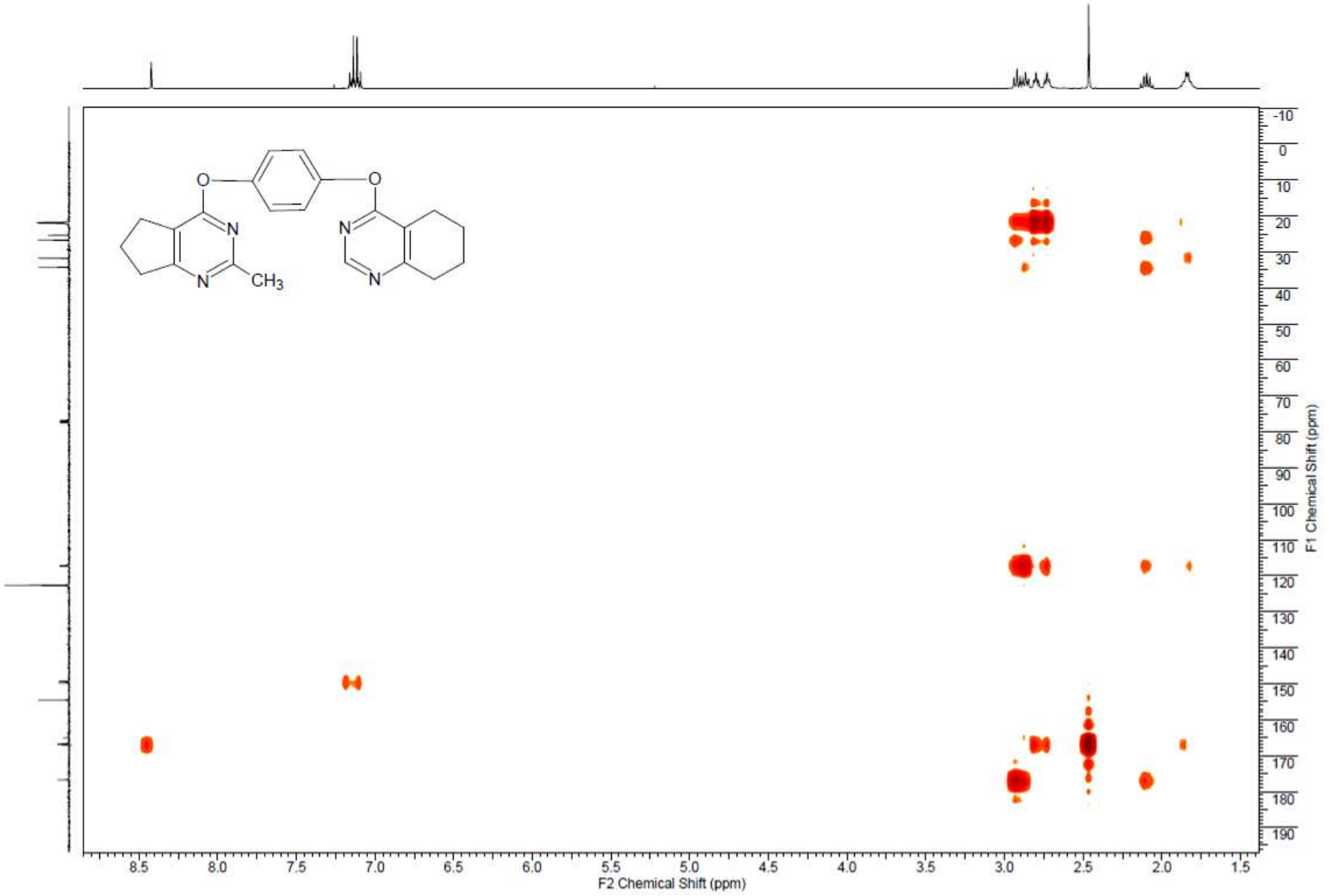
^{13}C NMR spectrum ($CDCl_3$) of compound 2a



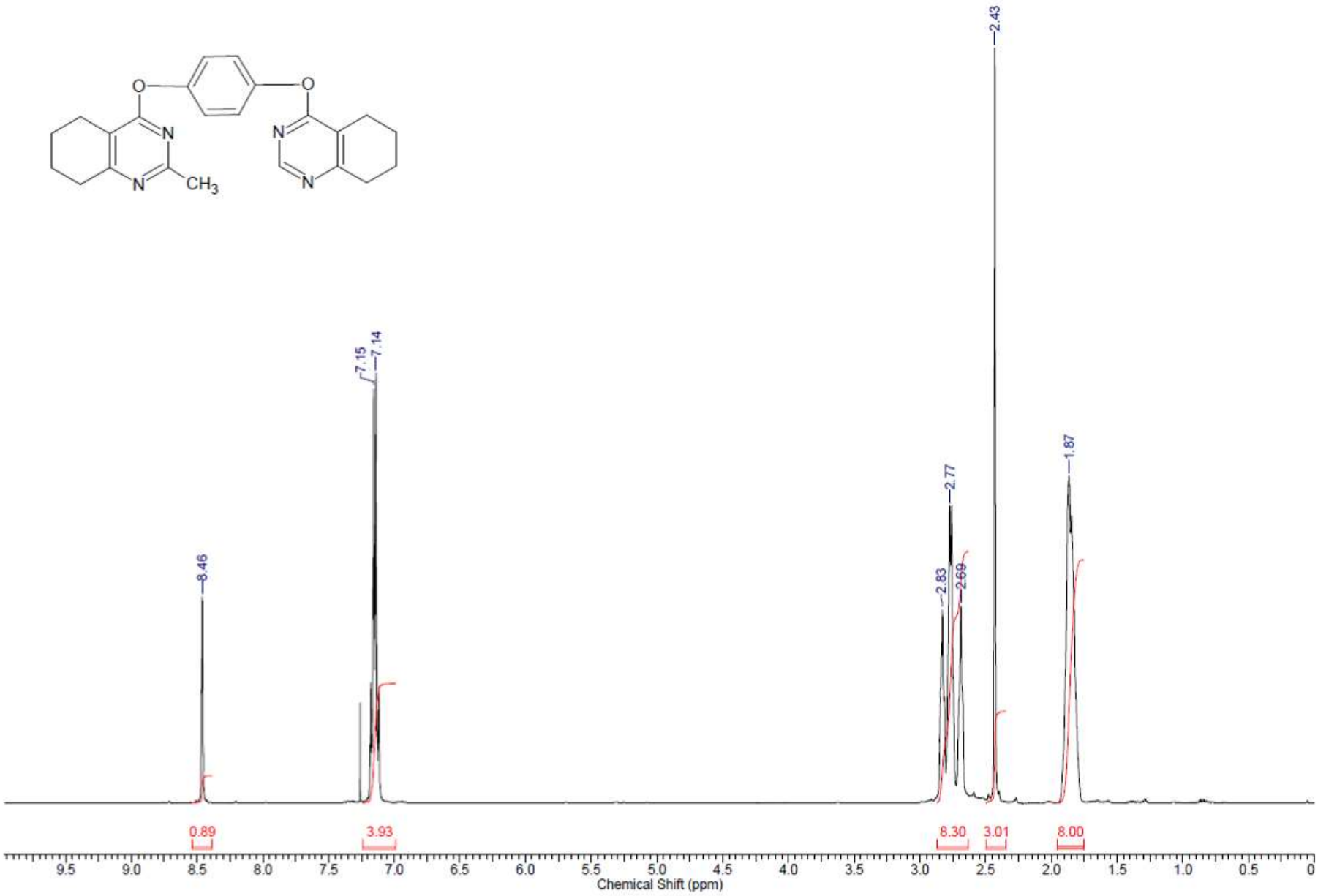
HSQC NMR spectrum ($CDCl_3$) of compound 2a



HMBC NMR spectrum ($CDCl_3$) of compound 2a



^{1}H NMR spectrum ($CDCl_3$) of compound 2b



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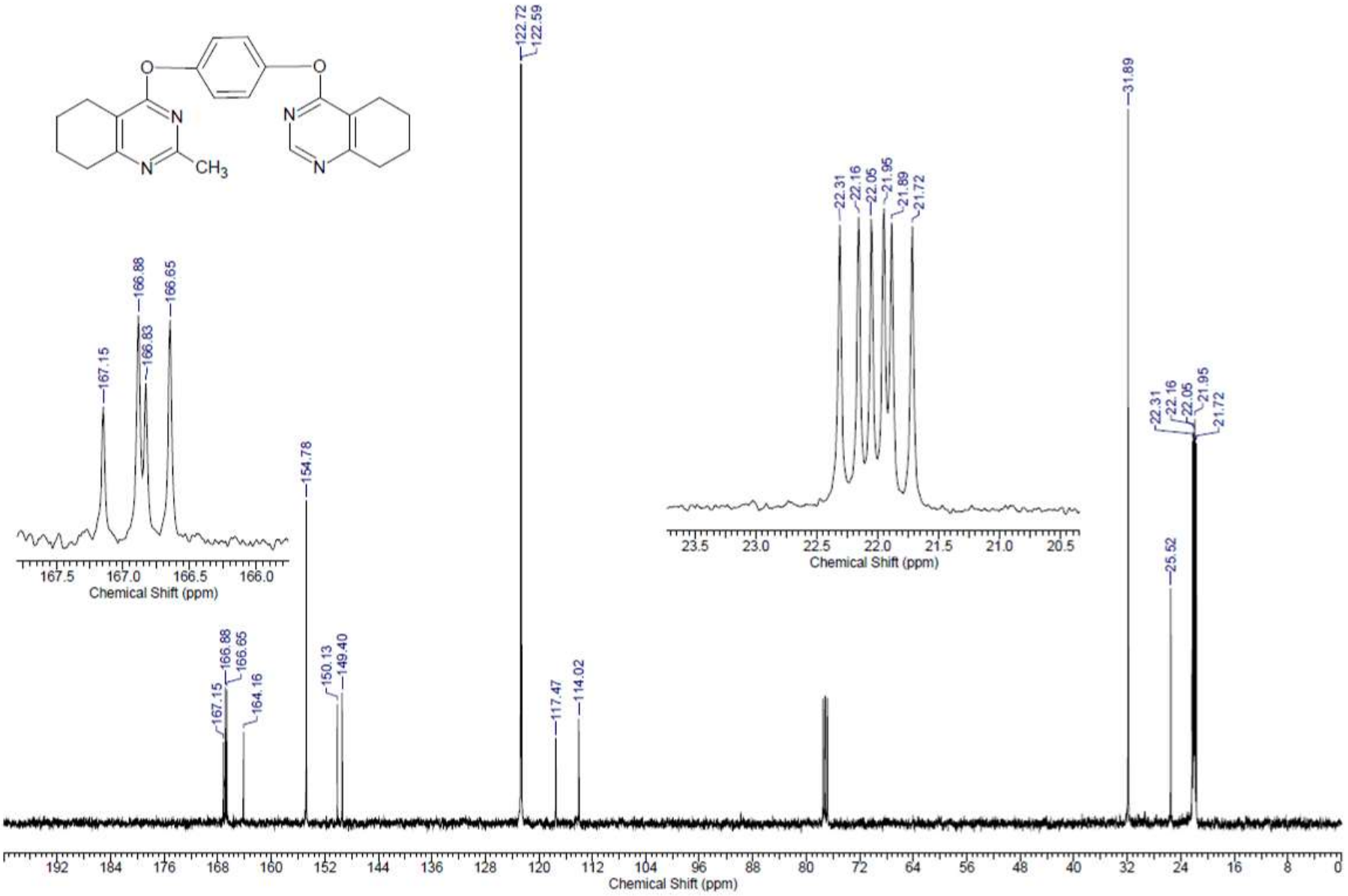

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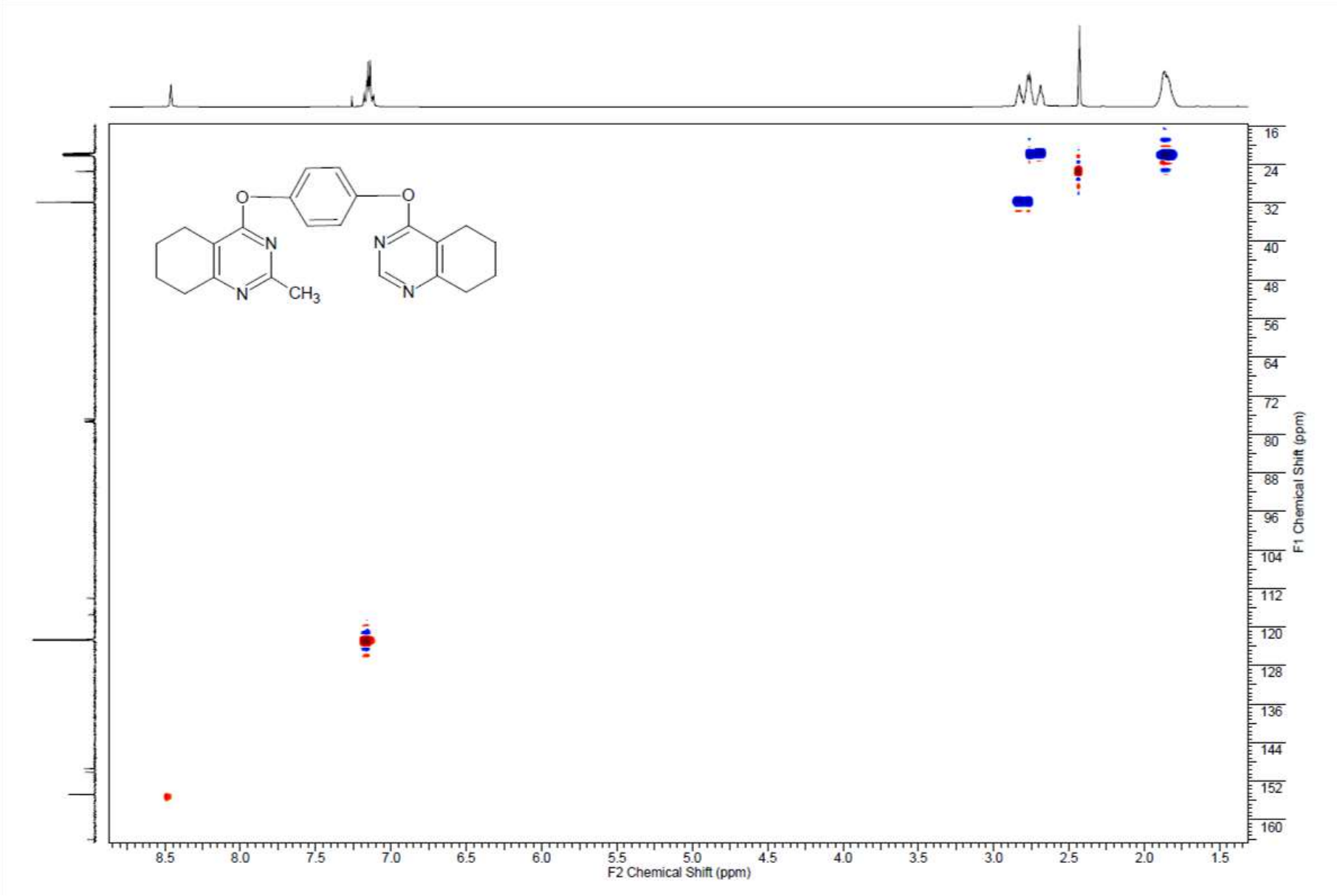
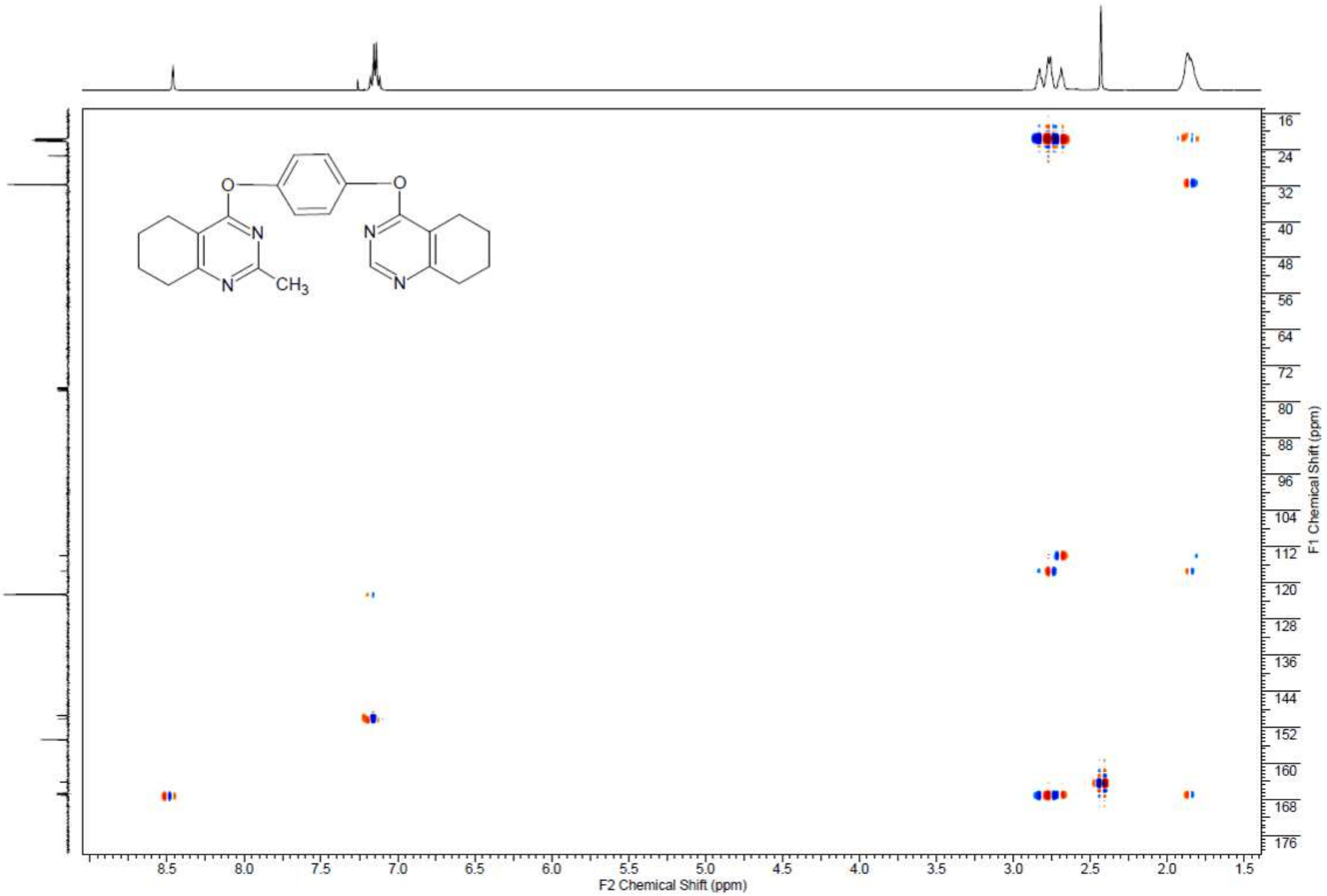
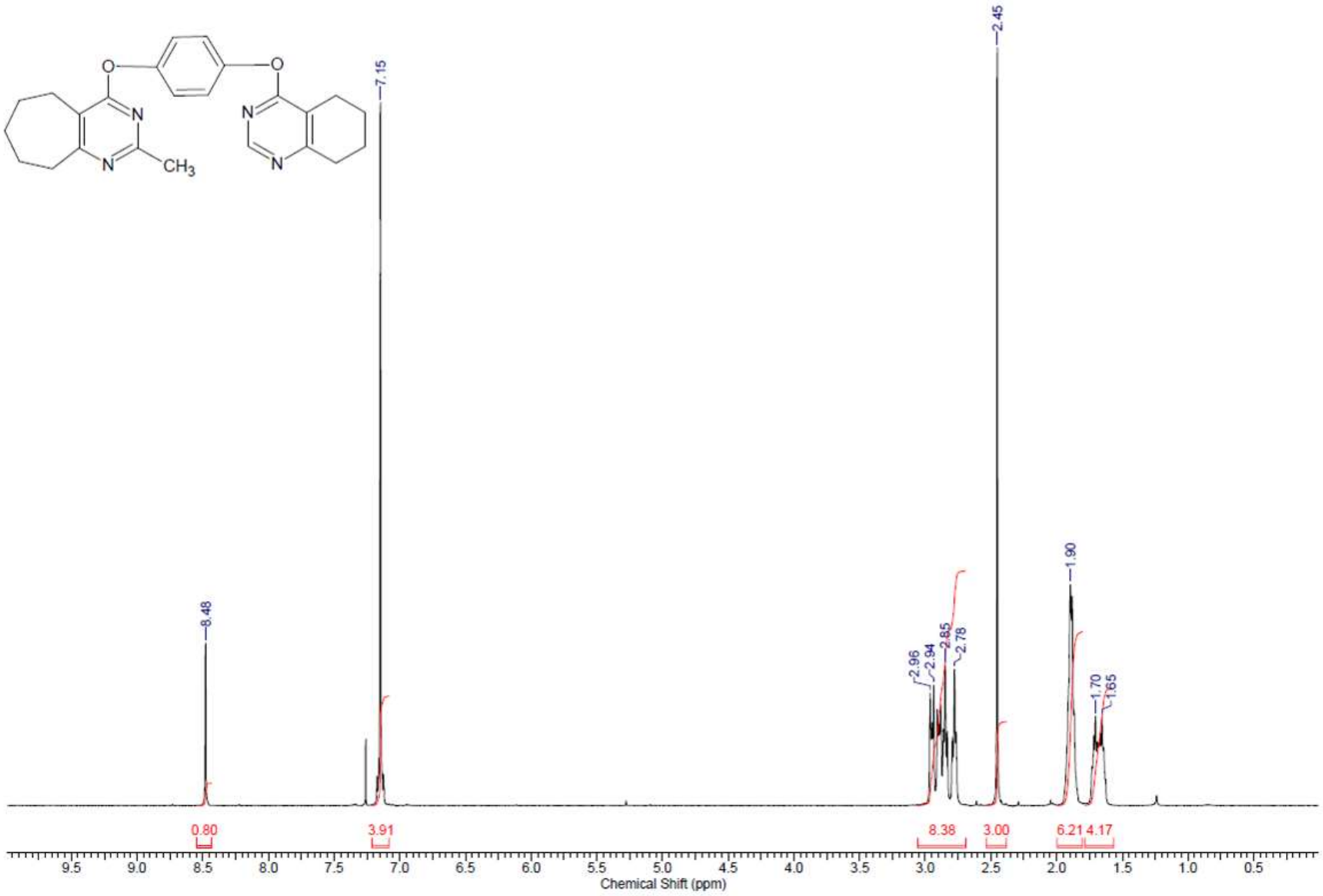


HMBC NMR spectrum ($CDCl_3$) of compound 2b



^{1}H NMR spectrum ($CDCl_3$) of compound 2c



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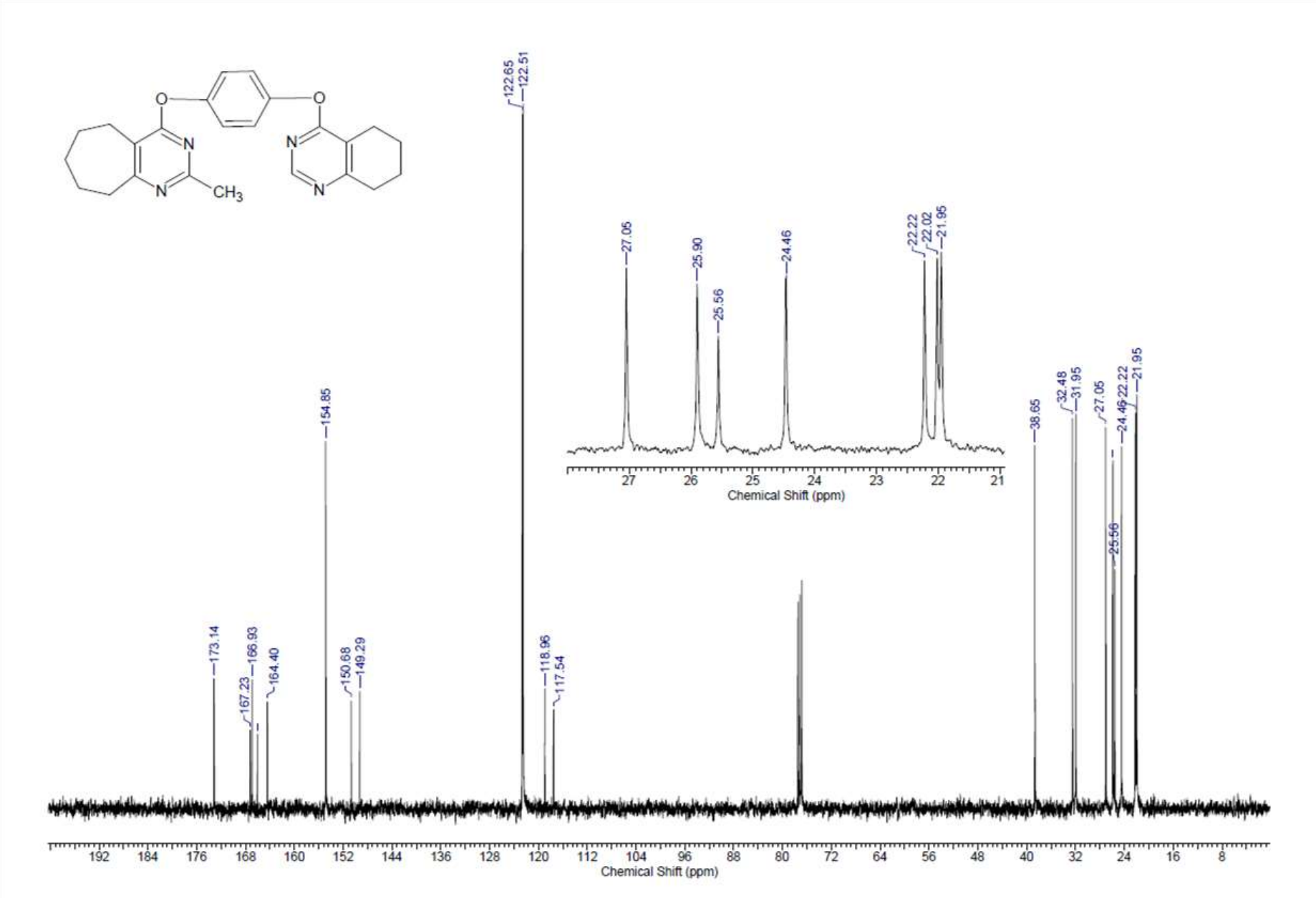
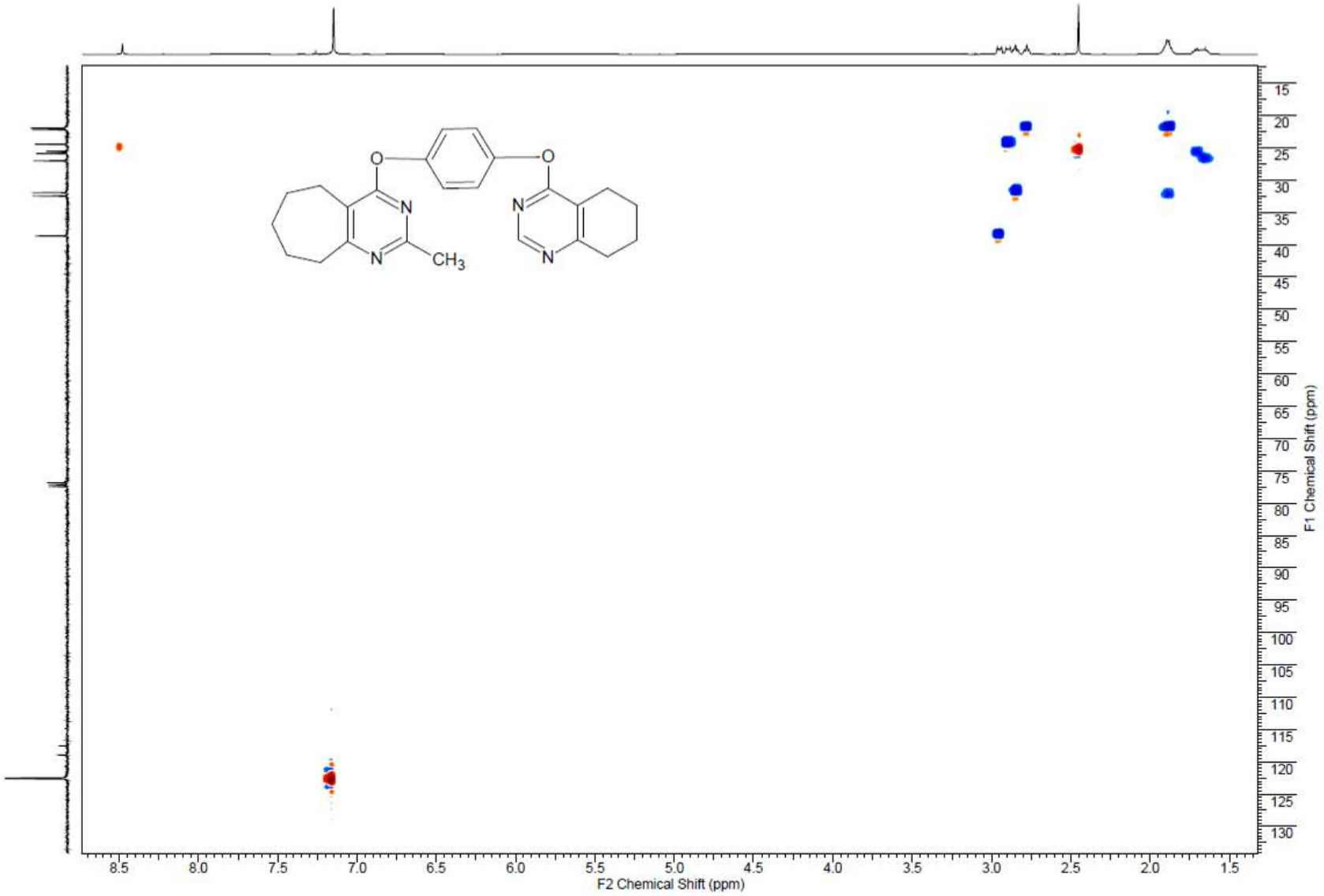
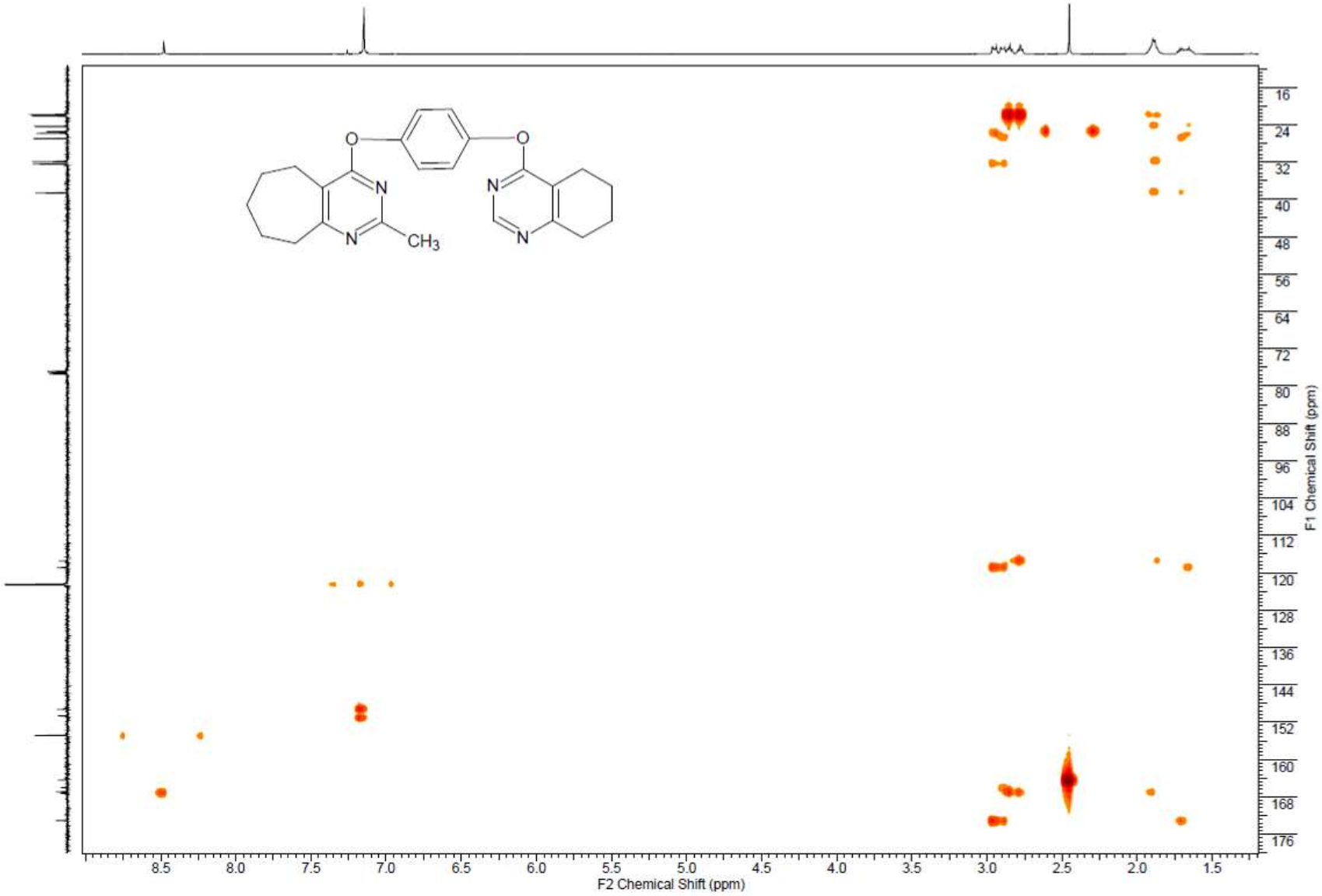


HSQC NMR spectrum ($CDCl_3$) of compound 2c



HMBC NMR spectrum ($CDCl_3$) of compound 2c



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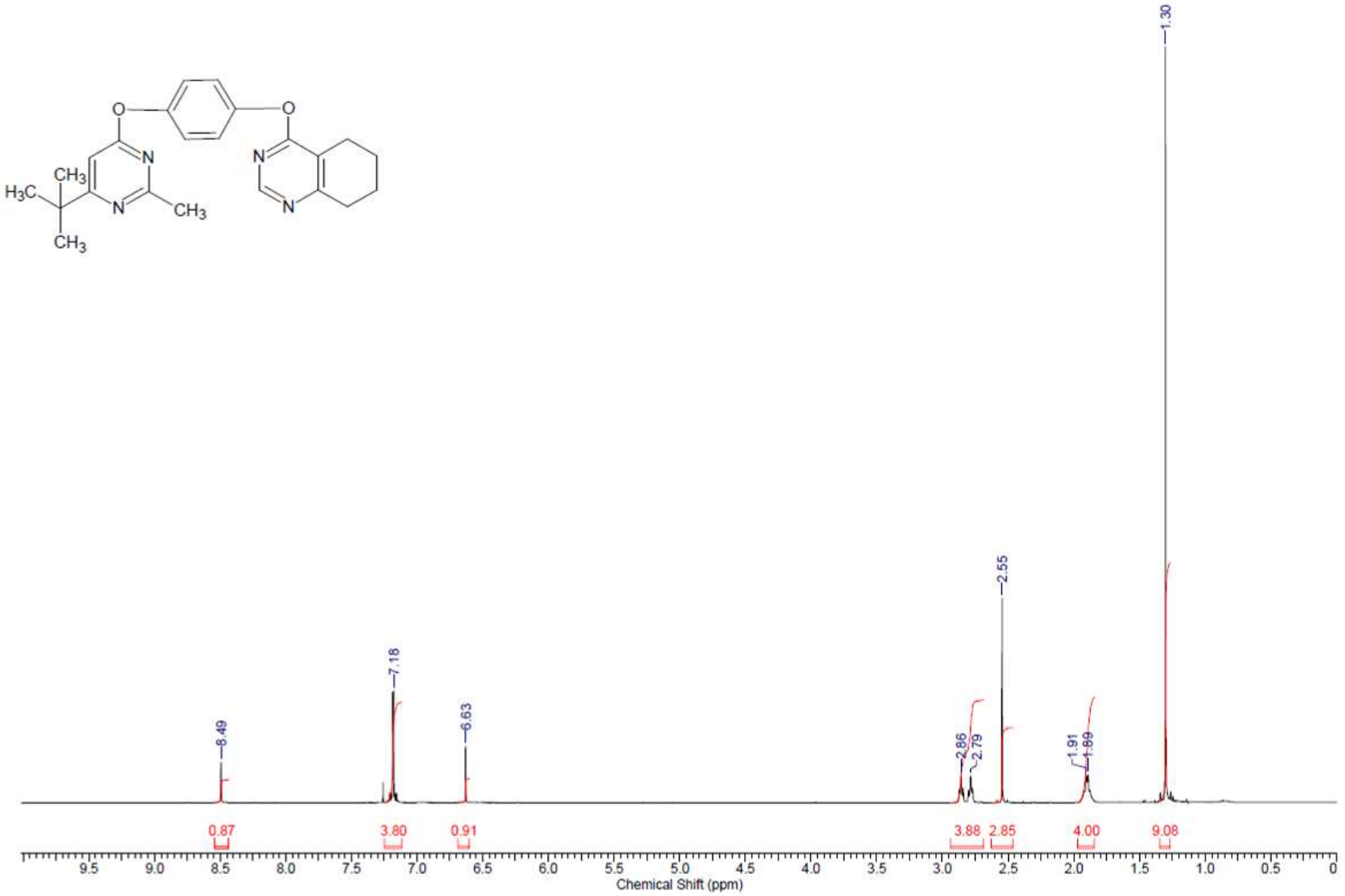

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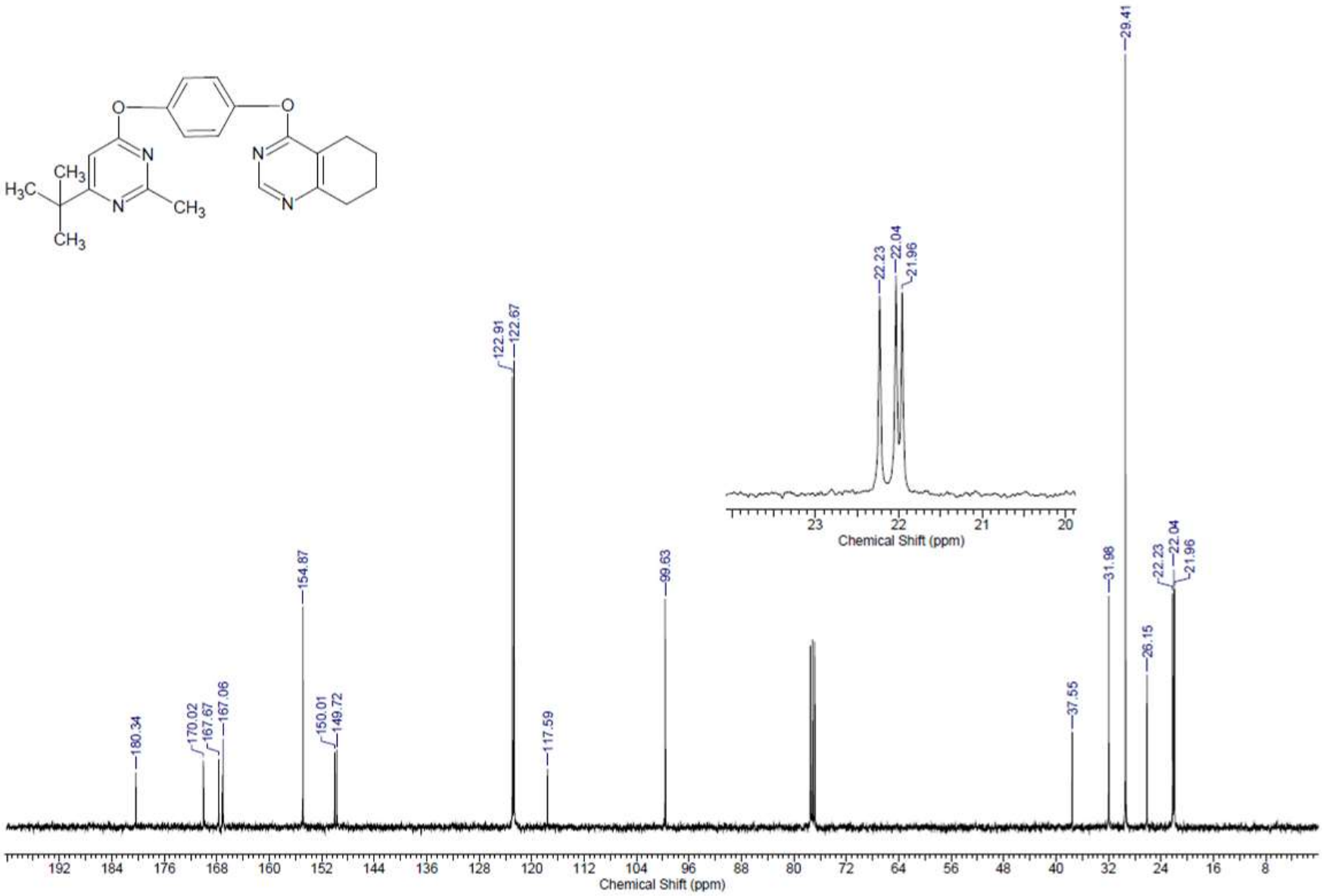

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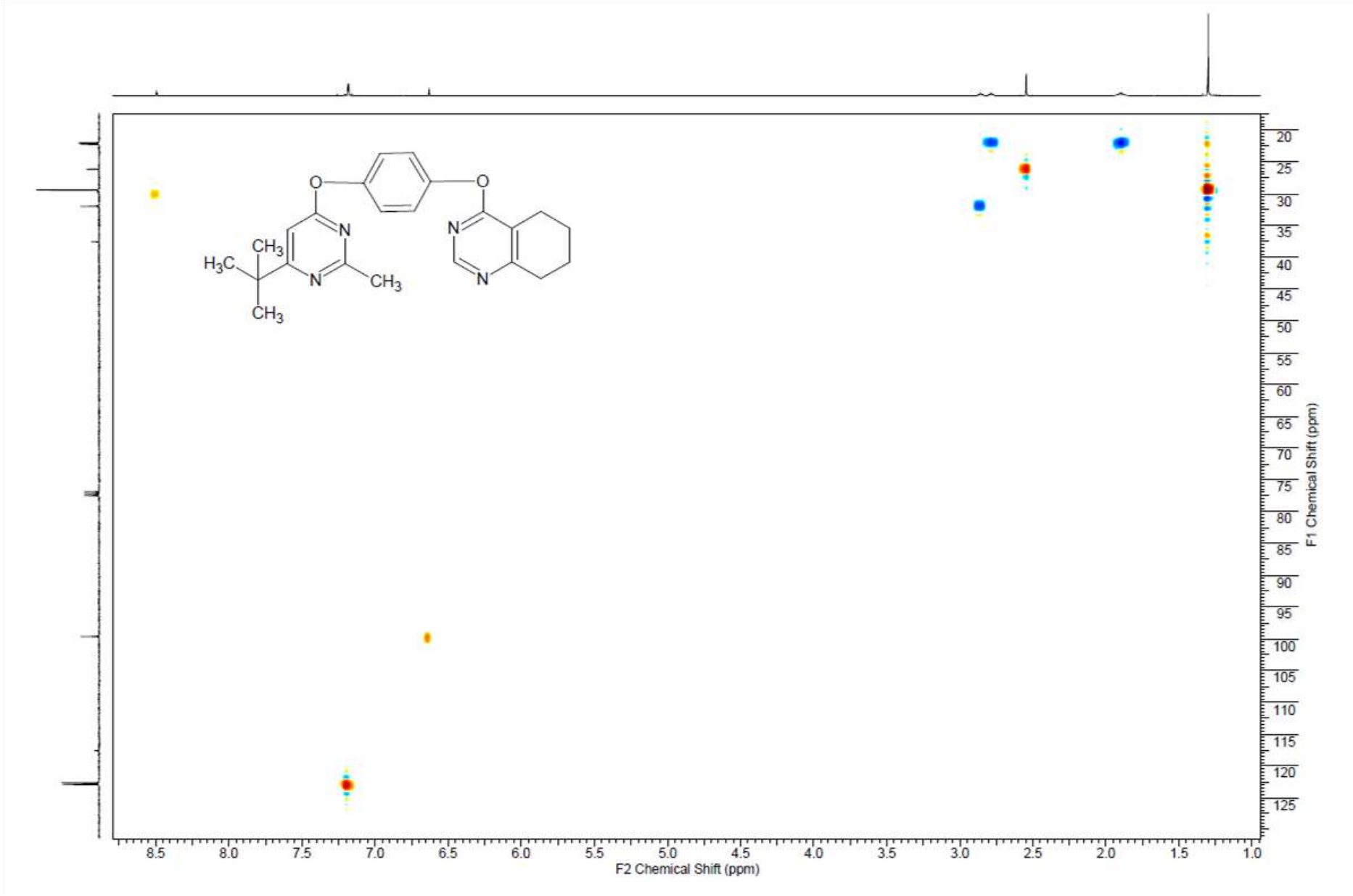

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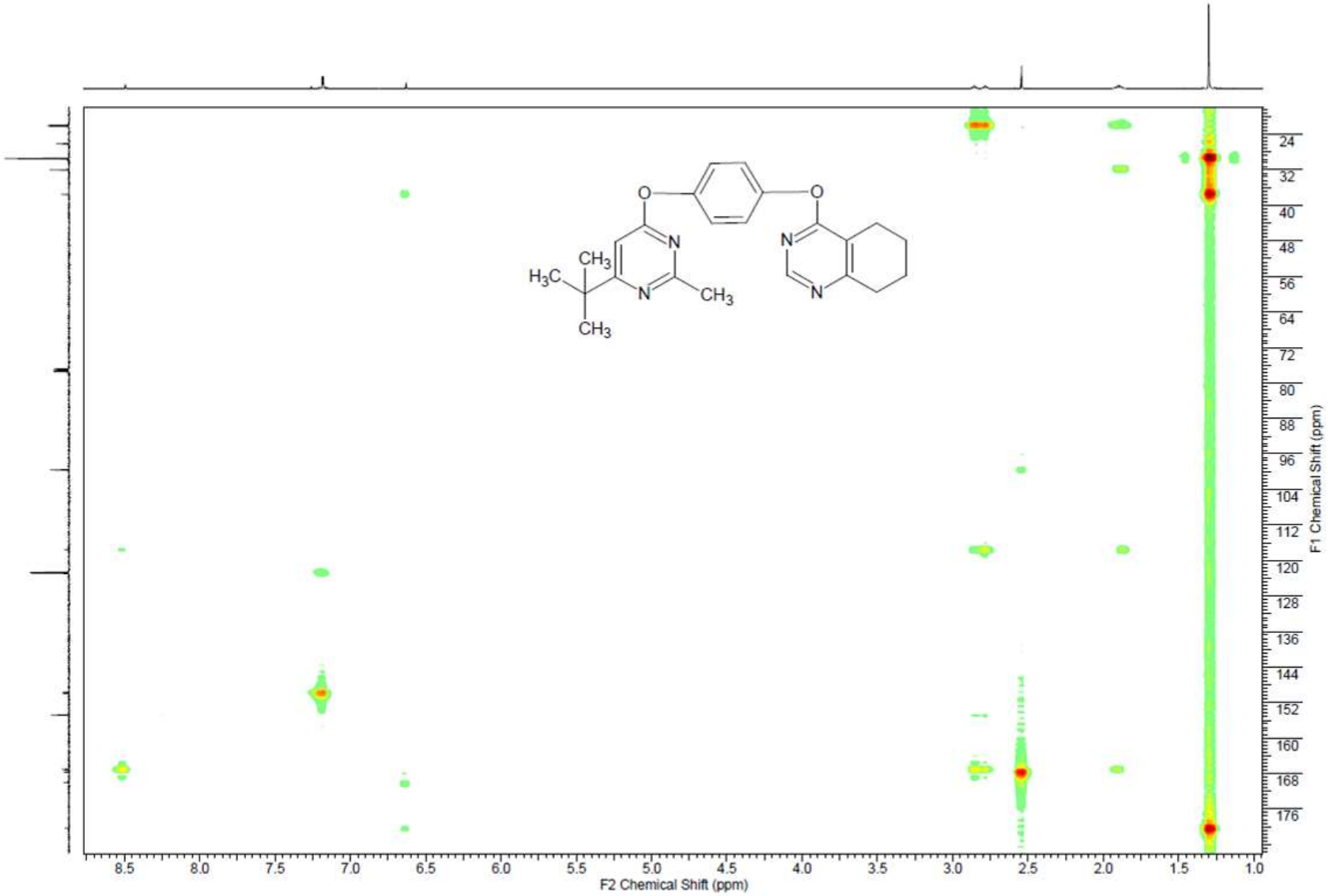

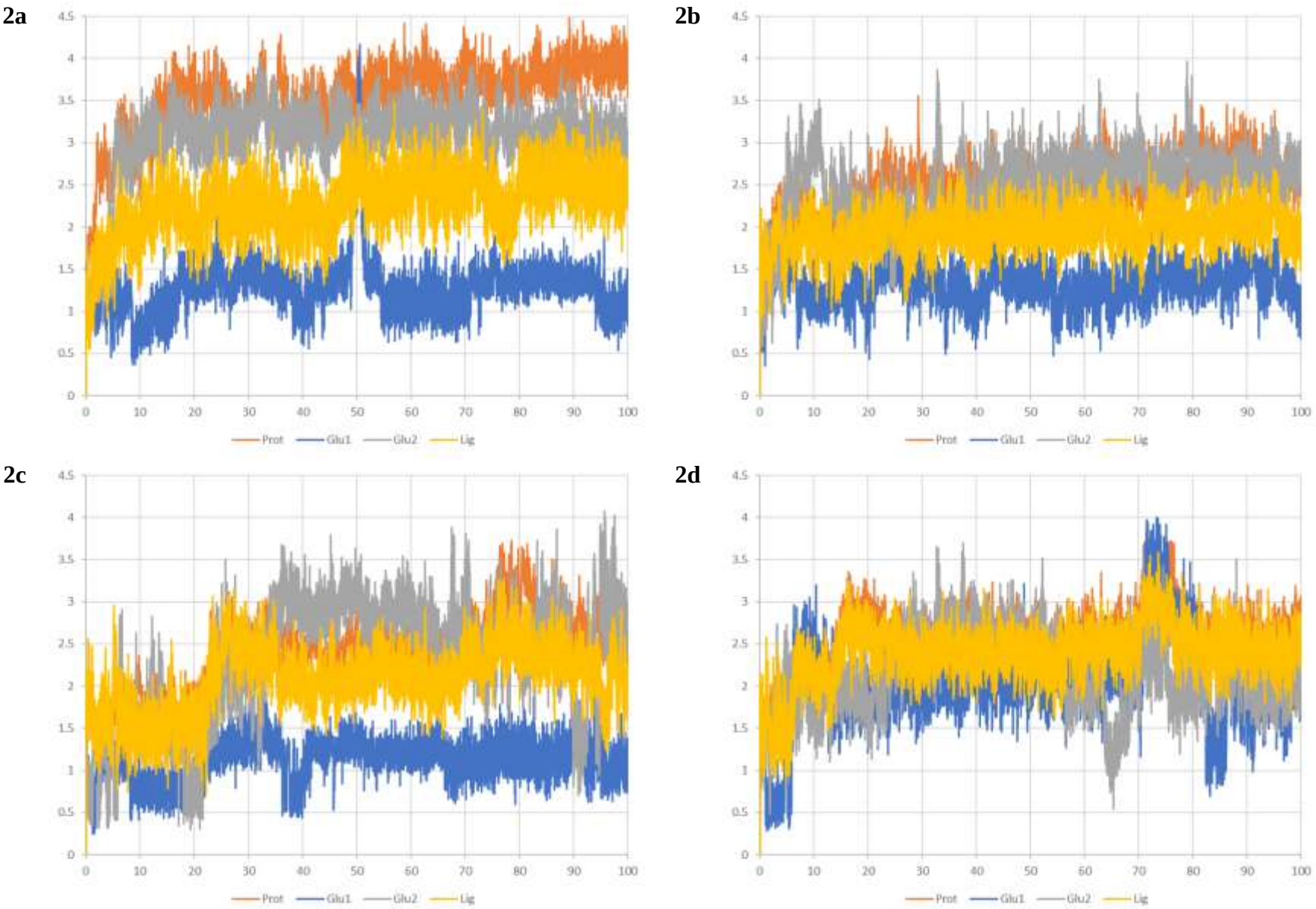

Figure S1. RMSD plots of the protein, glutamate, and ligand heavy atoms for compounds **2a–d** during molecular dynamics simulations of the modulator complex with the dimeric ligand binding domain of the GluA2 AMPA receptor (RMSD, Å; Time, ns).

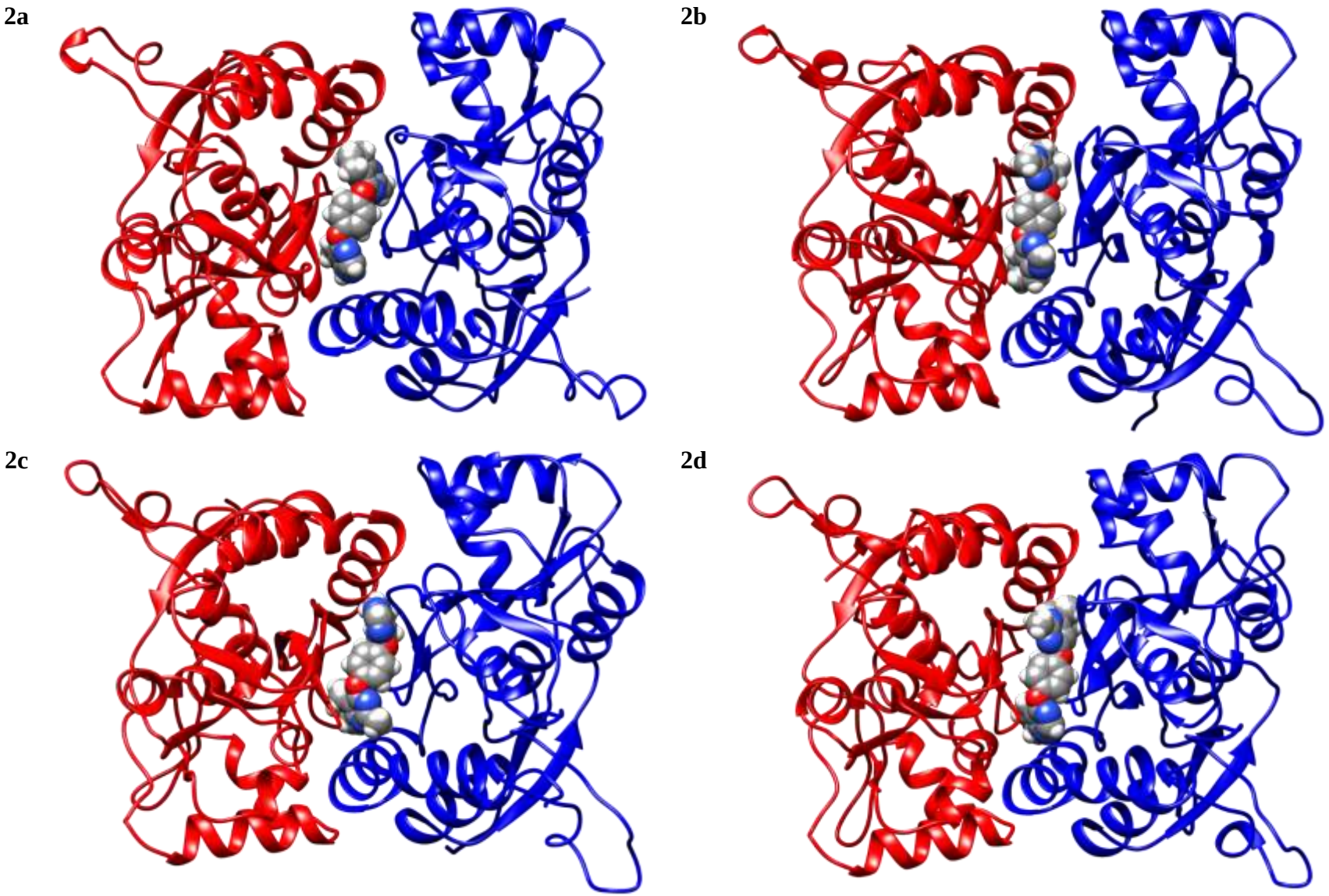

Figure S2. Binding modes of compounds **2a–d** in the PAM binding site refined using molecular dynamics simulations (100 ns). For each compound, a general view of the dimeric ligand binding domain of AMPA receptor (GluA2) and the ligand position are shown.