# Supporting information

# Chemical Investigation of the Calcareous Marine Sponge *Pericharax heteroraphis*, Clathridine-A Related Derivatives Isolation, Synthesis and Osteogenic Activity

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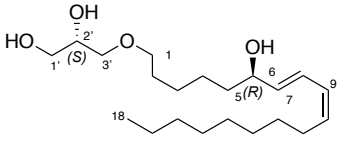
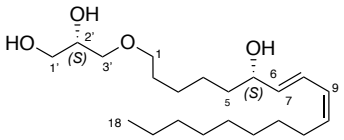
**Table 1.** Queensland Museum (QM) accession numbers, species and corresponding OTUs.

| Reference | QM Registration | Genus species | OTU |
|---|---|---|---|
| P559 | G339004 | Petrosia sp. | QM2721 |
| P560 | G339005 | Cinachyrella sp. | QM4680 |
| P561 | G339006 | Echinodictyum asperum | QM0133 |
| P562 | G339007 | Suberea laboutei | QM1511 |
| P563 | G339008 | Stylissa cf. carteri | QM0336 |
| P564 | G339009 | Myrmekioderma sp. | QM4997 |
| P571 | G339016 | Dendrilla sp. | QM2575 |
| P572 | G339017 | Dysidea lizardensis sp. | QM1519 |
| P573 | G339018 | Aplysilla sp. | QM2034 |
| P574 | G339019 | Haliclona (Haliclona) sp. | QM4999 |
| P575 | G339020 | Haliclona (Haliclona) sp. | QM4499 |
| P579 | G339024 | Stylissa massa | QM0925 |
| P581 | G339026 | Hyrtios cf. erectus | QM0796 |
| P582 | G339027 | Pericharax heteroraphis | QM0668 |
| P586 | G339031 | Acanthodendrilla cf. 1948 | QM1948 |
| P587 | G339032 | Hyrtios erectus | QM0796 |
| P588 | G339033 | Axinyssa sp. | QM3251 |
| P589 | G339034 | Oscarella sp. | |
| P590 | G339035 | Fascaplysinopsis sp. | QM1549 |
| P593 | G339038 | Leiosella sp. | QM6001 |
| P594 | G339039 | Hyrtios erectus | QM0796 |
| P595 | G339040 | Hyrtios erectus | QM0796 |
| P596 | G339041 | Psammocina sp. | QM1944 |
| P597 | G339042 | Rhaphoxya pallida | QM0465 |
| P600 | G339045 | Jaspis sp. | QM4187 |
| P601 | G339046 | Stylissa cf. carteri | QM0922 |
| P602 | G339047 | Haliclona (Haliclona) sp. | QM1971 |
| P603 | G339048 | Pseudoceratina sp. | QM1947 |
| P605 | G339050 | Leucetta chagosensis | QM1402 |
| P607 | G339052 | Halichondrida (Halichondrida) sp. | QM1429 |
| P608 | G339053 | Ircinia sp. | QM1244 |
| P609 | G339054 | Pericharax sp. | QM1361 or QM2065 |
| P616 | G339061 | Astrosclera willeyana | QM0656 |
| P618 | G339063 | Pericharax sp. | QM2116 |
| P620 | G339065 | Petrosia sp. | QM4179 |
| P621 | G339066 | Petrosia sp. | QM2035 |
| P622 | G339067 | Lissodendoryx (Ectydoryx) sp. | QM1281 |
| P625 | G339070 | Fascaplysinopsis sp. | QM6004 |
| P628 | G339073 | Stylissa cf. carteri | QM0922 |
| P633 | G339078 | Dysidea cf. pallescens sp. | QM0630 |
| P634 | G339079 | Halichondrida (Halichondrida) sp. | QM1984 |
| P636 | G339081 | Suberea sp. | QM2121 |
| P640 | G339085 | Ircinia sp. | QM2707 |
| P642 | G339087 | Cacospongia sp. | QM6009 |
| P646 | G339091 | Fascaplysinopsis sp. | |
| P658 | G339103 | Chelonaplysilla delicata | QM1829 |
| P660 | G339105 | Petrosia sp. | QM1895 |

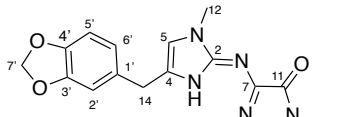
**Figure S0**: Isolated natural products.



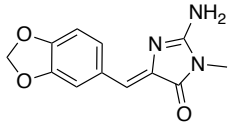
(2'*S*, 6*R*) pericharaxin A (**1**)



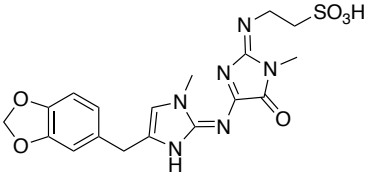
(2'*S*, 6*S*) pericharaxin B (**2**)



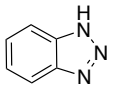
X = O: clathridine A (**3**)
X = NH: clathridimine (**4**)



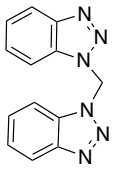
leucettamine B (**5**)



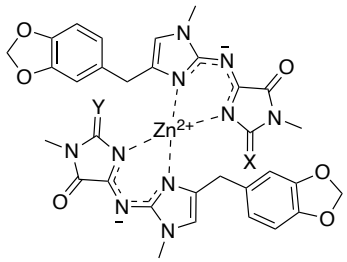
(9*E*)-clathridine-9-N-(2-sulfoethyl)imine (**6**)



benzotriazole, (BTZ , **7**)



bis-BTZ-methane (**8**)



X = Y = O: homodimeric (clathridine A)$_2$Zn$^{2+}$ (**9**)
X = O, Y = NH: heterodimeric (clathridine A-clathridimine)Zn$^{2+}$ (**10**)

**Figure S1.** $^{1}H$ NMR spectrum of natural clathridine A (**3**) in $CDCl_3$ (500 MHz).

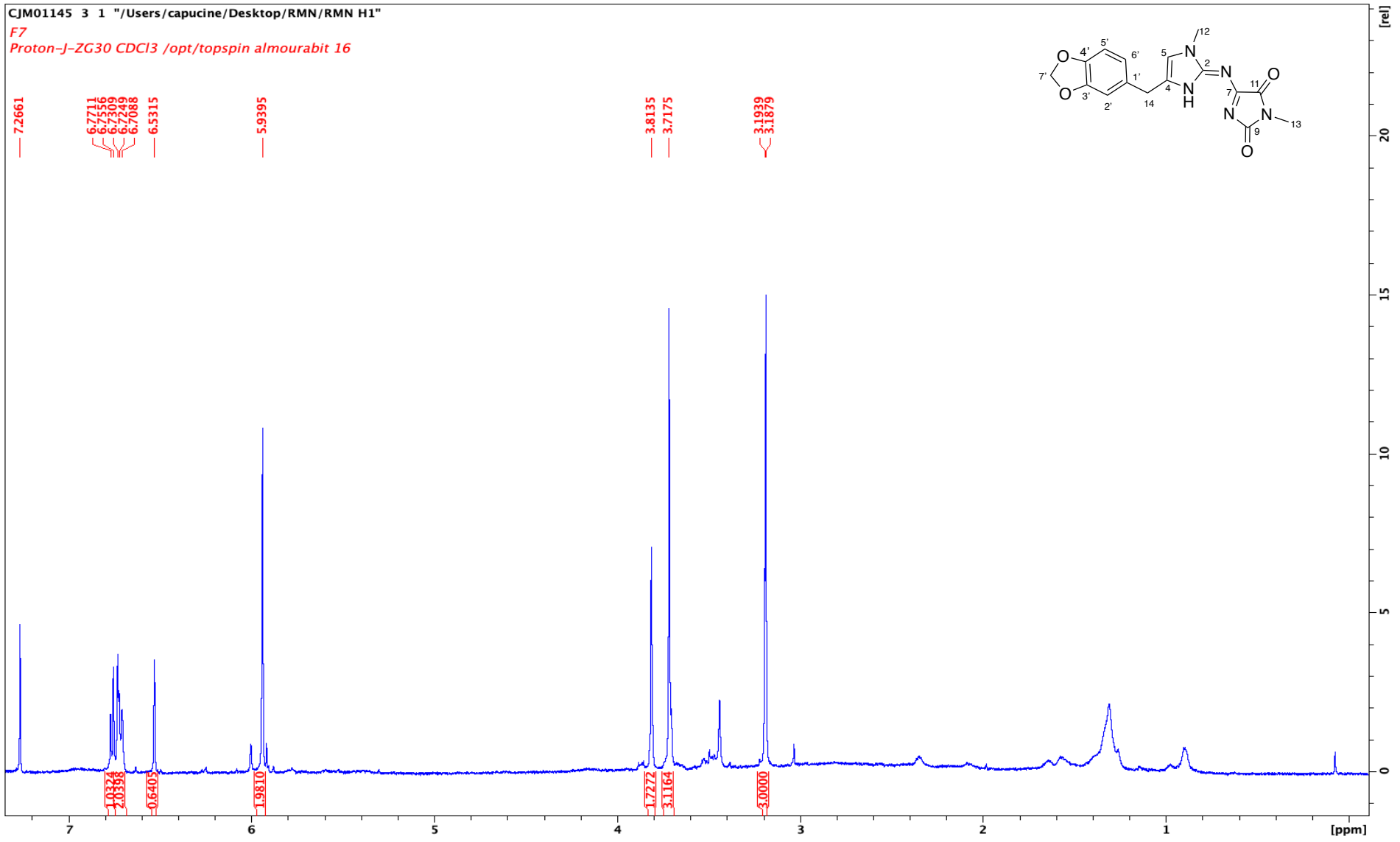


**Figure S2.** $^{1}$H NMR spectrum of synthetic preclathridine A (**15**) in $CDCl_3$ (300 MHz).

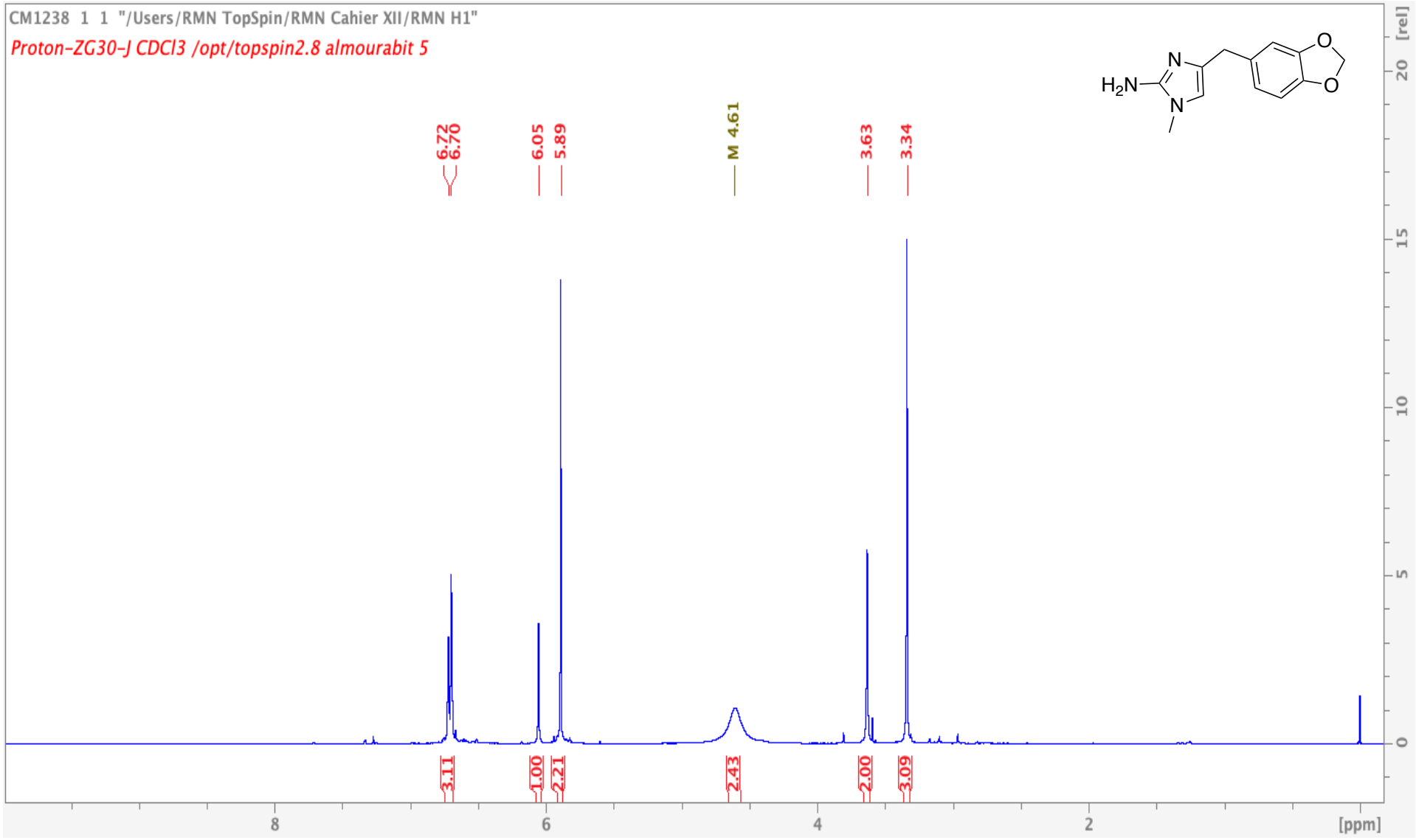


**Figure S3.** $^{13}C$ NMR spectrum of synthetic preclathridine A (**15**) in $CDCl_3$ (75 MHz).

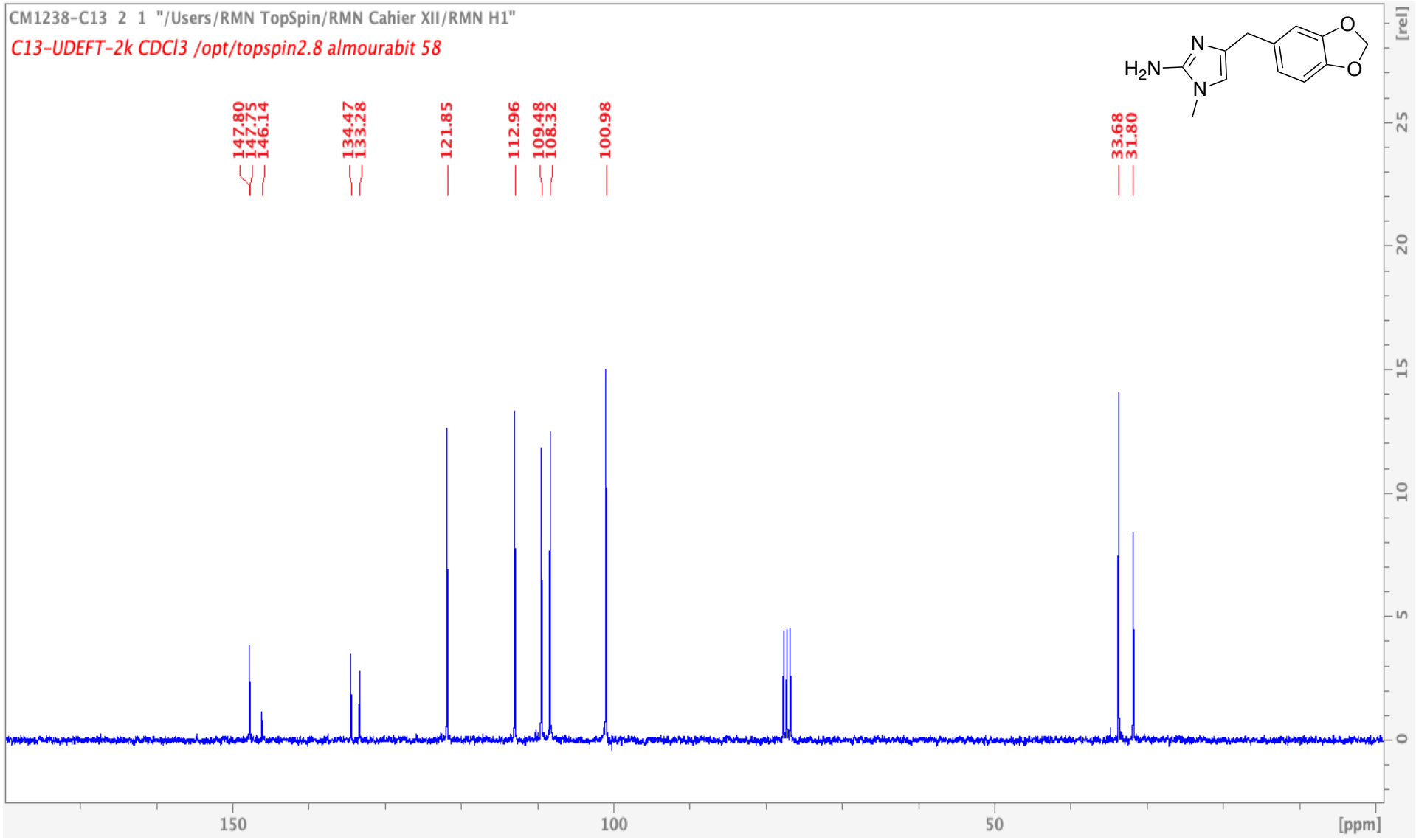


**Figure S4.** $^{1}H$ NMR spectrum of synthetic clathridine A (**3**) in $CDCl_3$ (300 MHz).

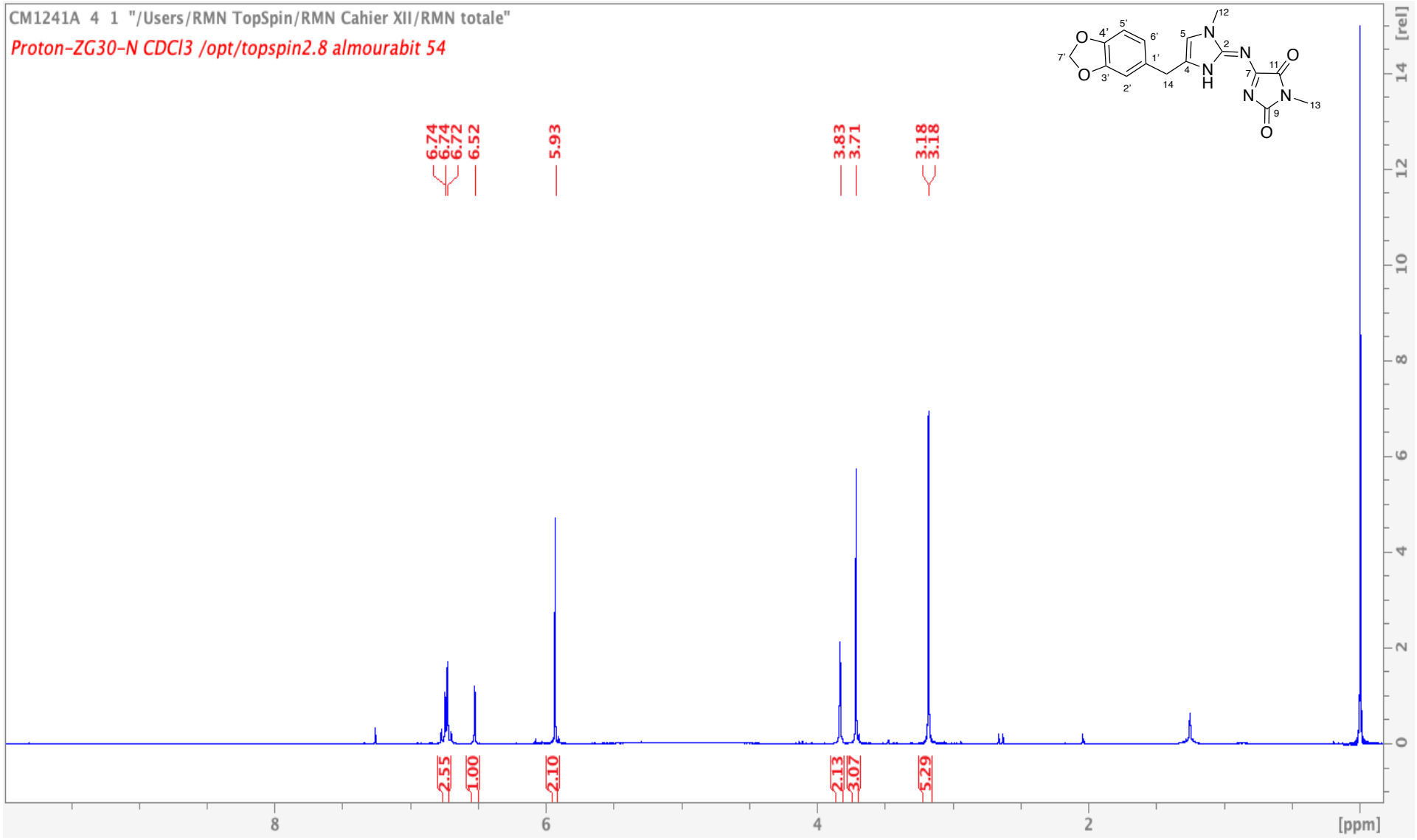


**Figure S5.** $^{13}C$ NMR spectrum of synthetic clathridine A (**3**) in $CDCl_3$ (75 MHz).

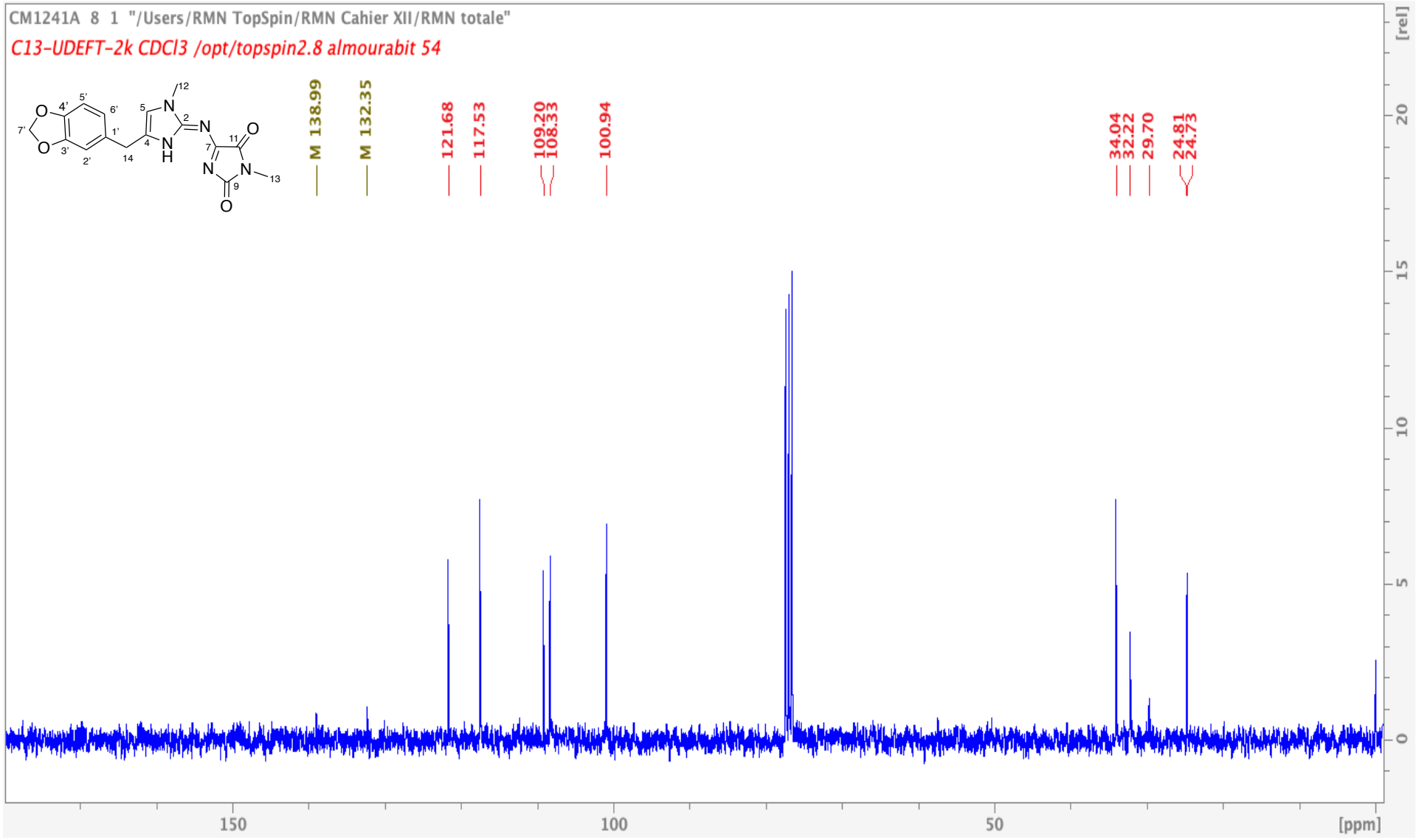


**Figure S6.** $^{1}H$-$^{13}C$ HMBC NMR spectrum of synthetic clathridine A (**3**) in $CDCl_3$ (300 MHz).

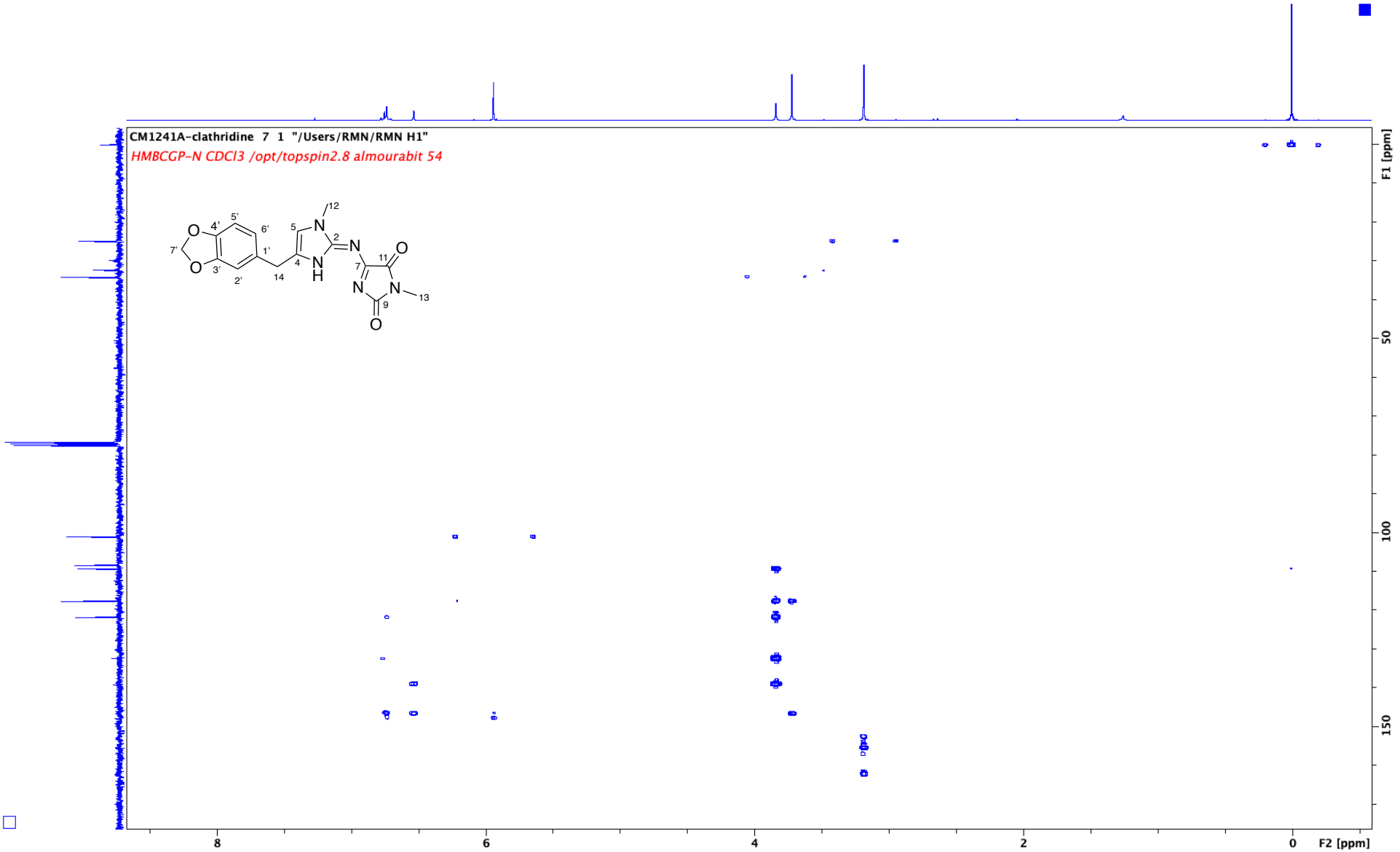


**Figure S7.** $^{1}H$ NMR spectrum of compound **18** in $CDCl_3$ (300 MHz).

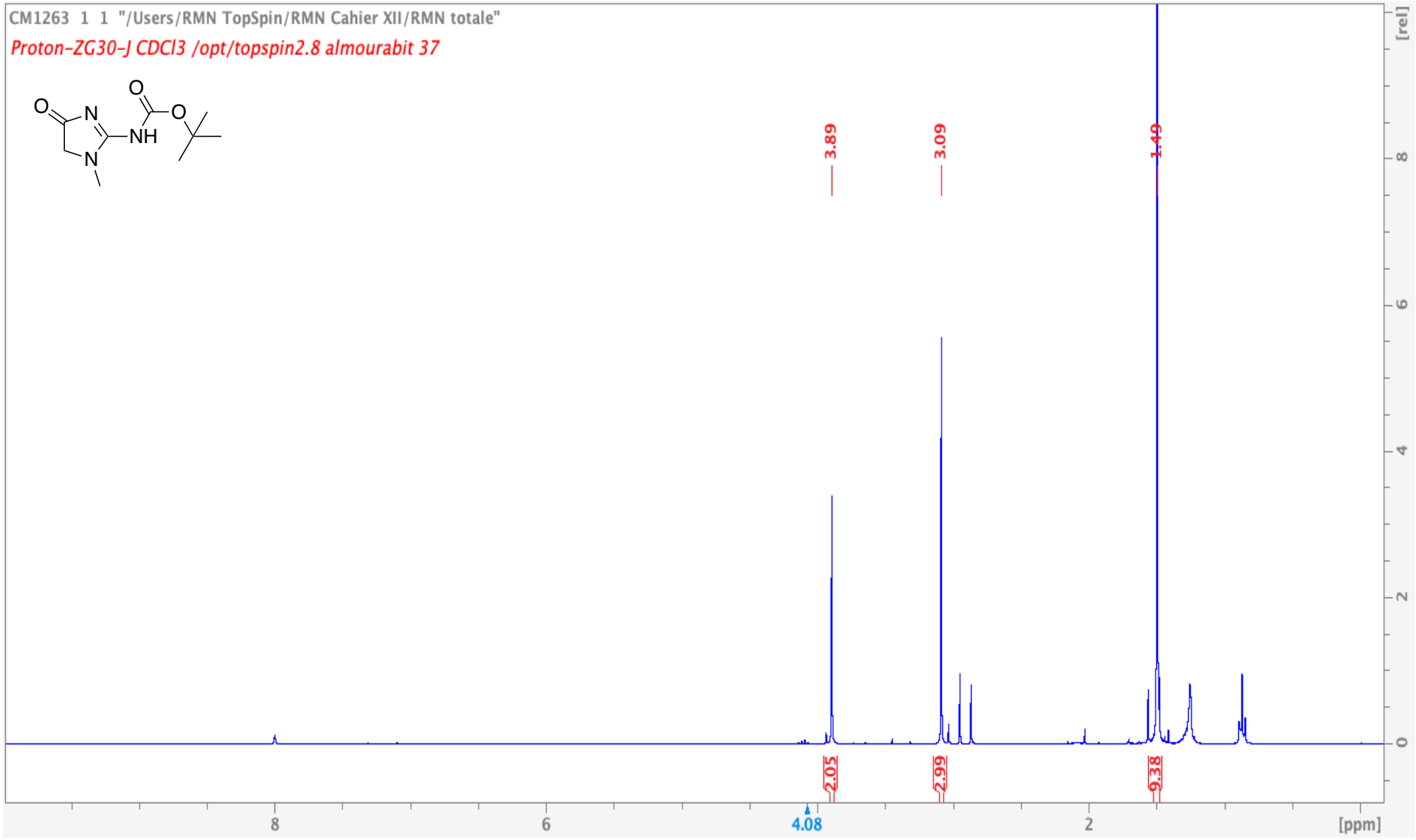


**Figure S8.** $^{13}C$ NMR spectrum of compound **18** in $CDCl_3$ (75 MHz).

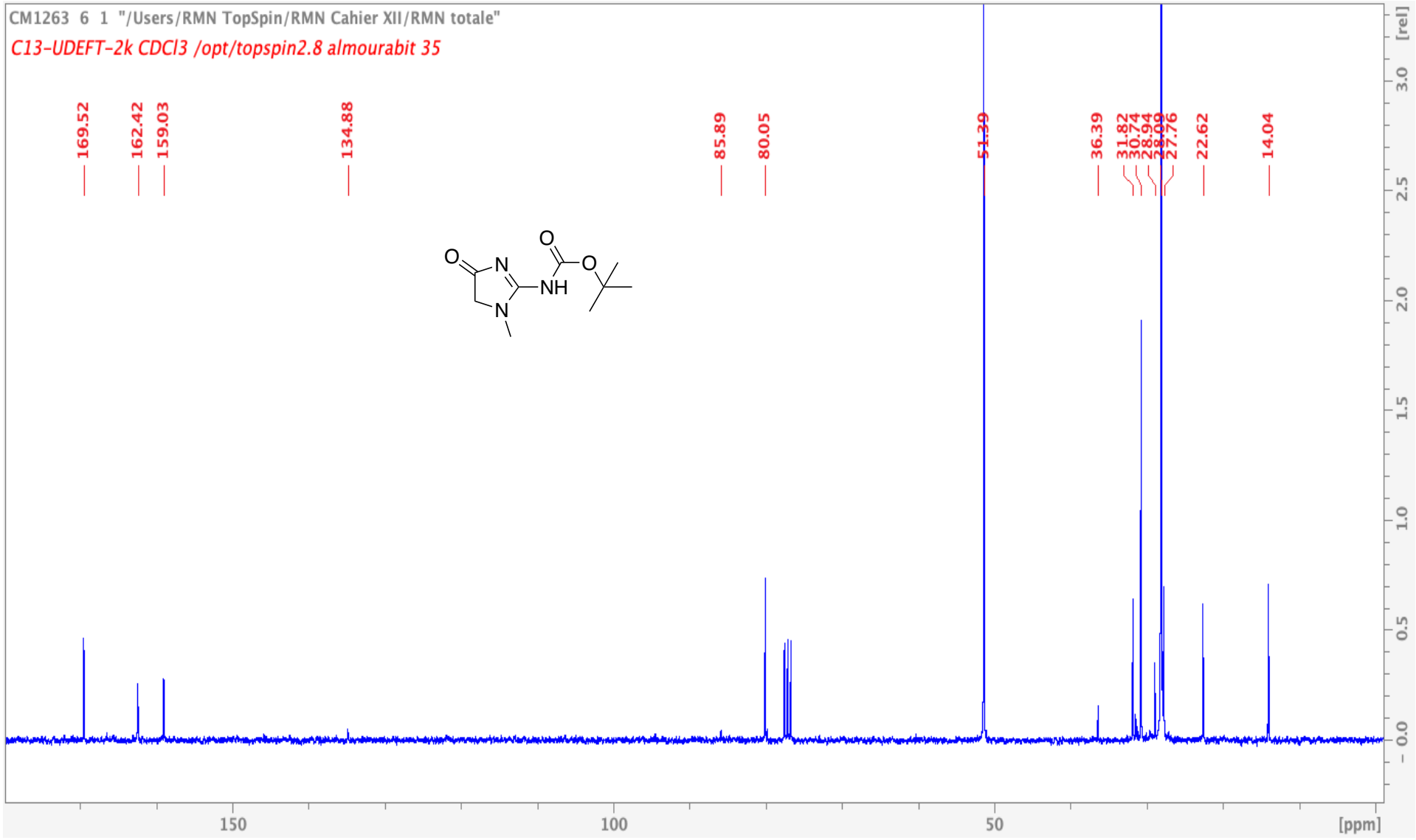


**Figure S9.** $^{1}H$ NMR spectrum of compound **19** in $CDCl_3$ (500 MHz).

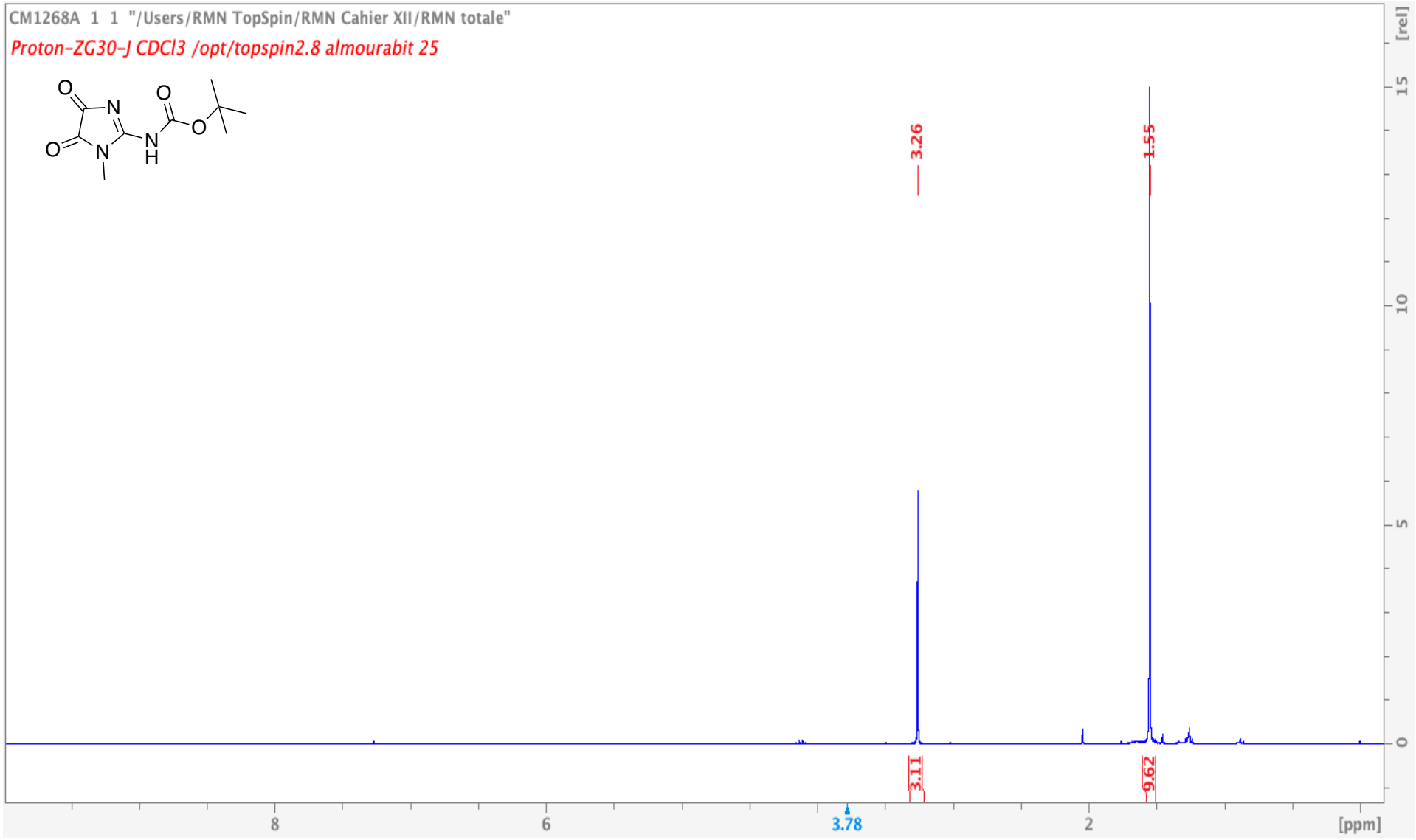


**Figure S10.** $^{13}C$ NMR spectrum of compound **19** in $CDCl_3$ (75 MHz).

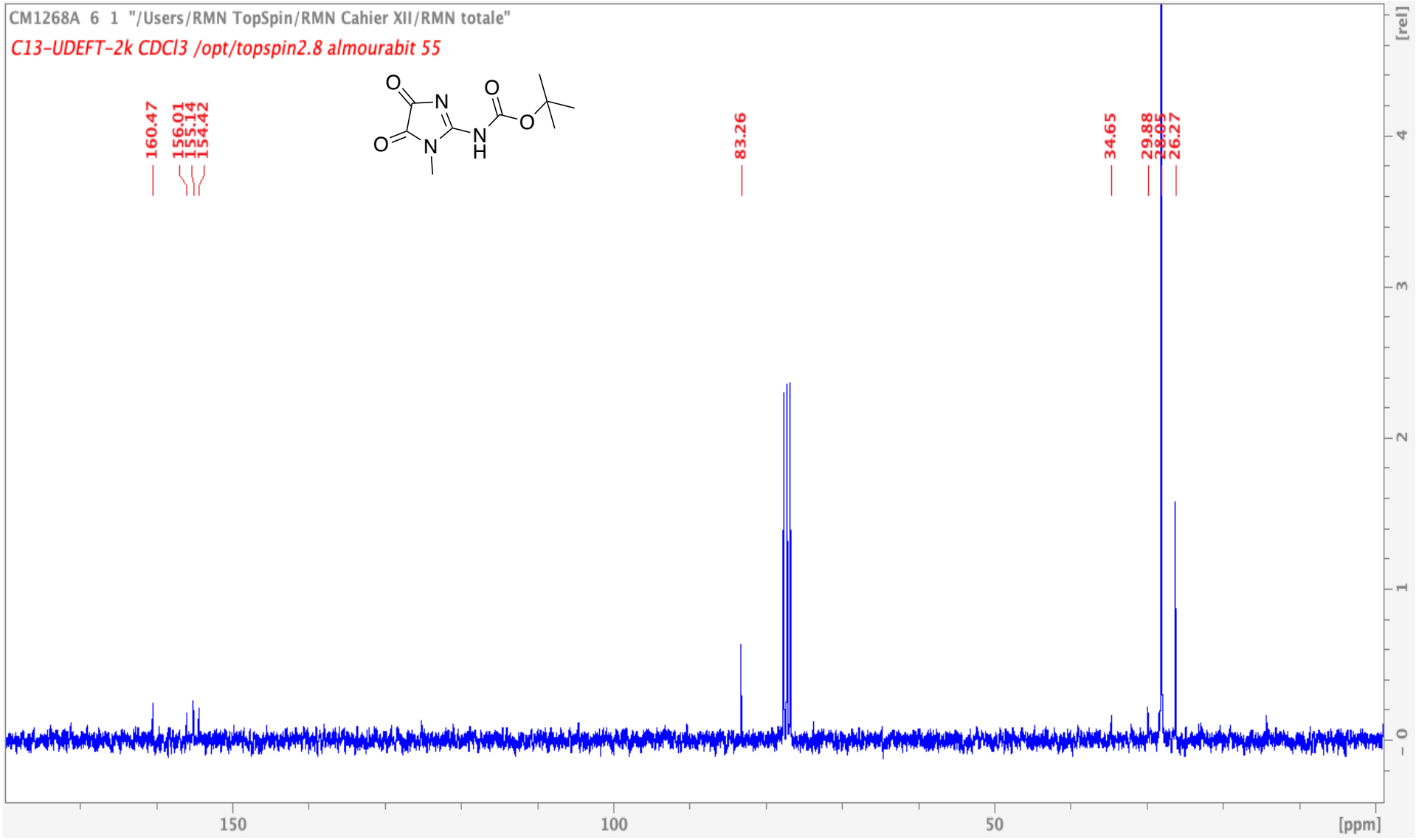


**Figure S11.** $^{1}H$ NMR spectrum of compound **20** in $CDCl_3$ (500 MHz).

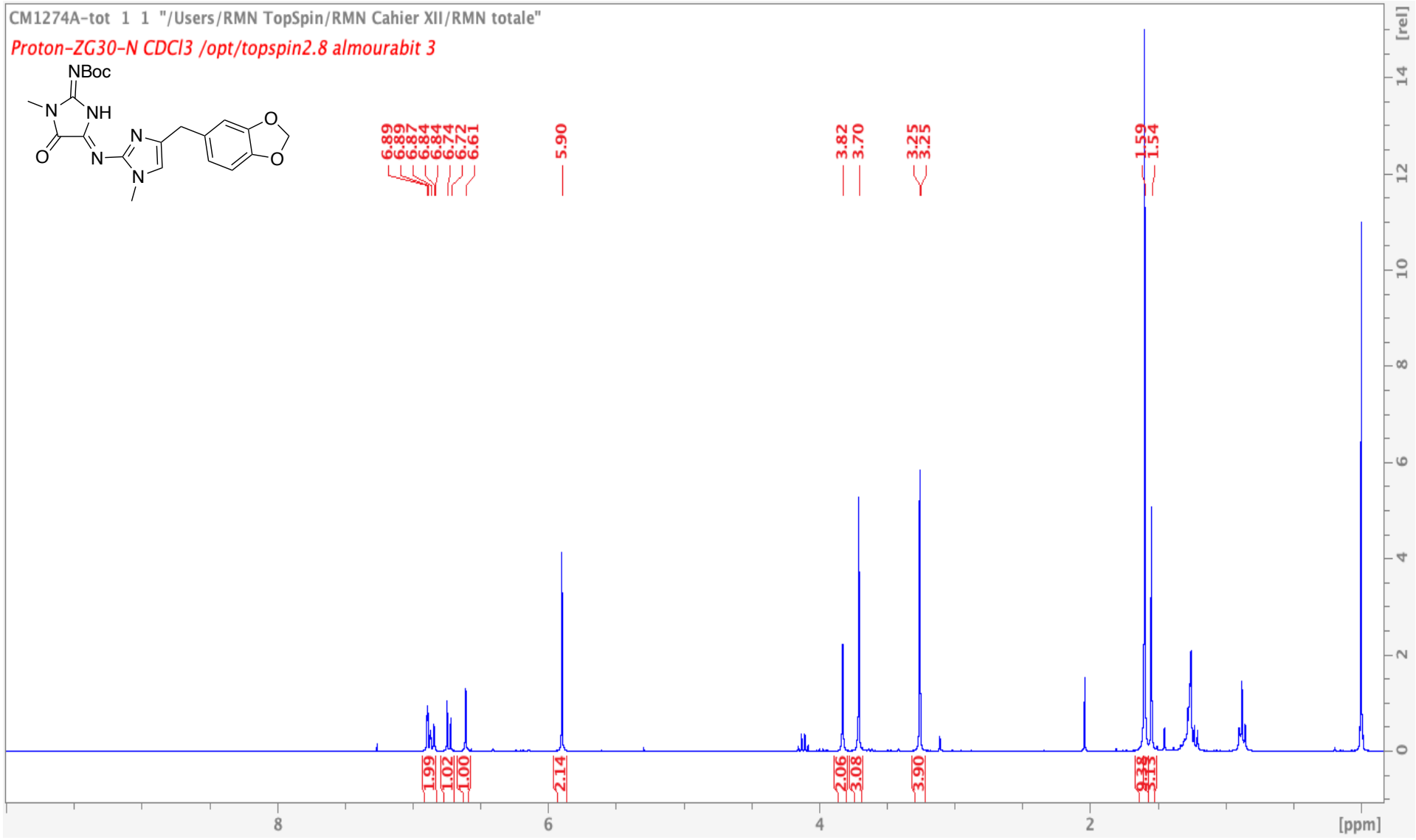


**Figure S12.** $^{13}C$ NMR spectrum of compound **20** in $CDCl_3$ (75 MHz).

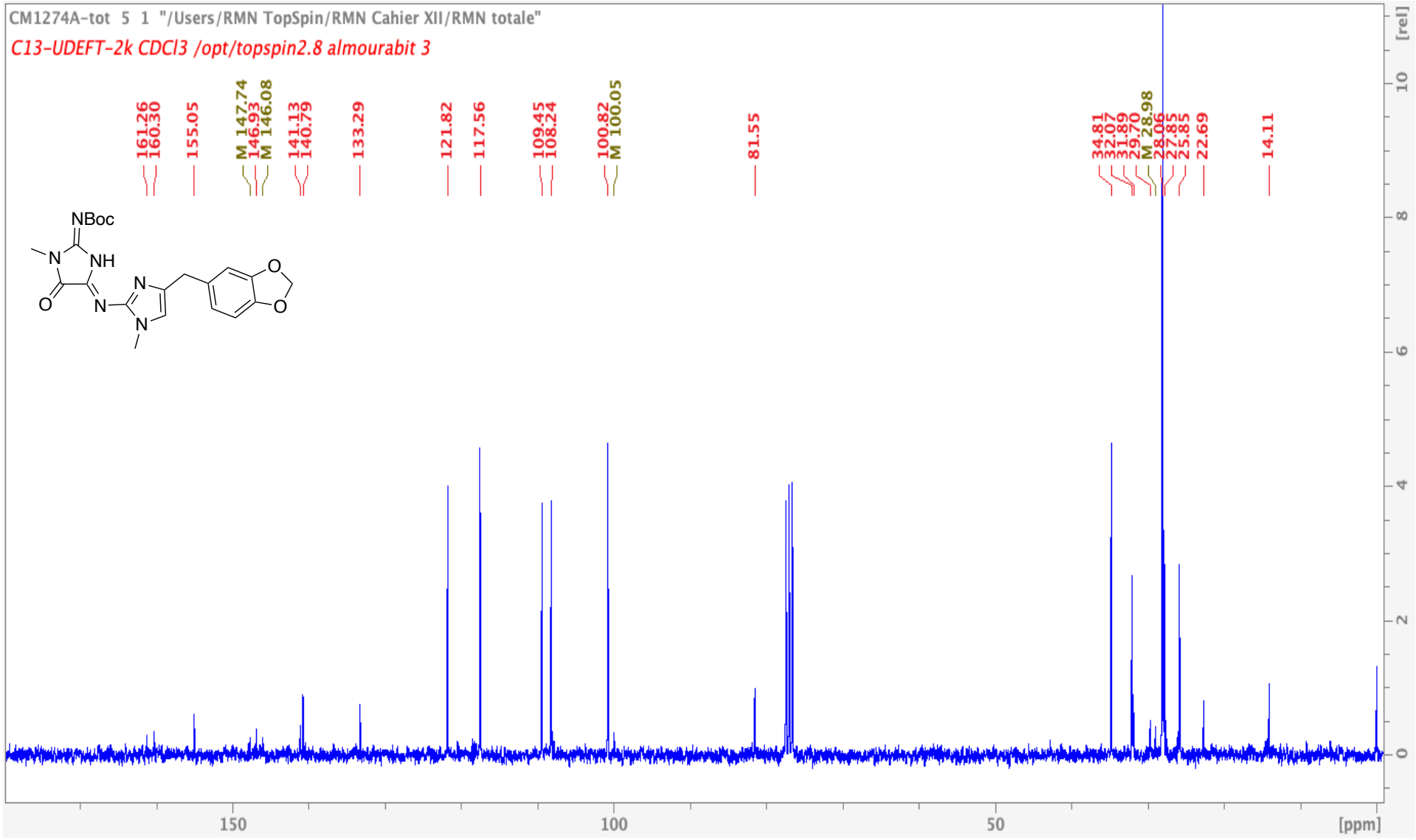


**Figure S13.** $^{1}H$ NMR spectrum of synthetic clathridimine (**4**) in $CDCl_3$ (300 MHz).

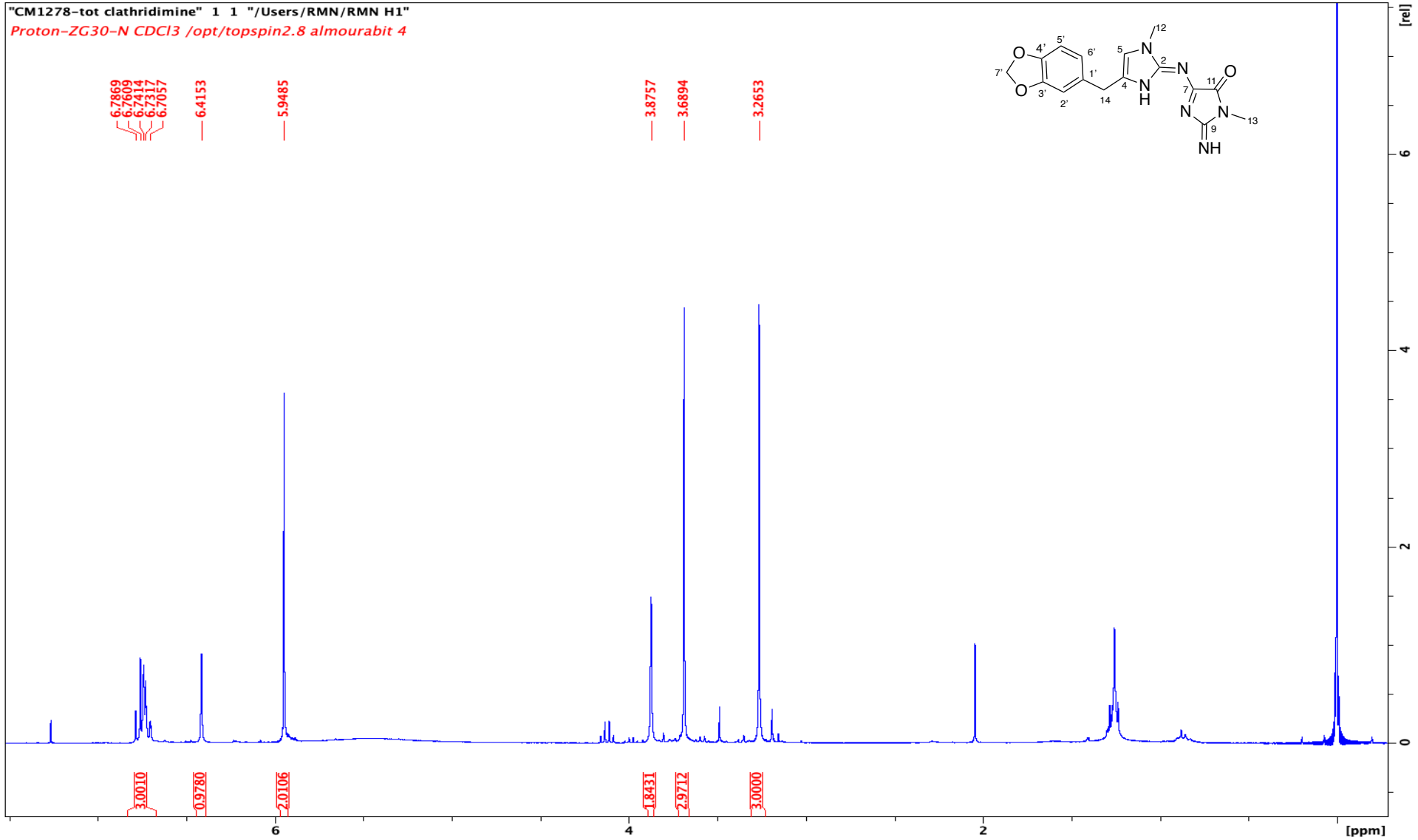


**Figure S14.** $^{13}C$ NMR spectrum of synthetic clathridimine (**4**) in $CDCl_3$ (75 MHz).

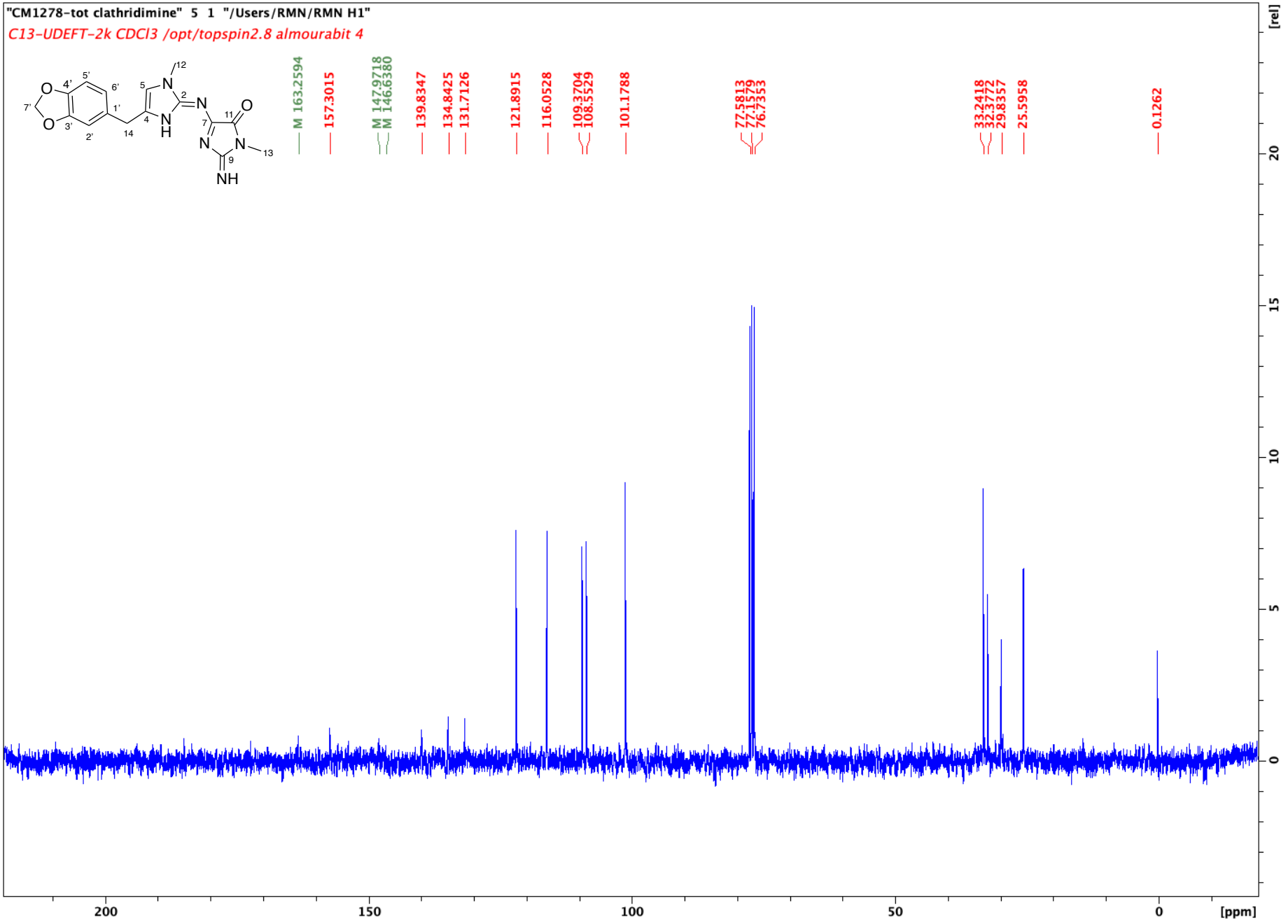


**Figure S15.** $^{1}H$-$^{13}C$ HMBC NMR spectrum of synthetic clathridimine (**4**) in $CDCl_3$ (300 MHz).

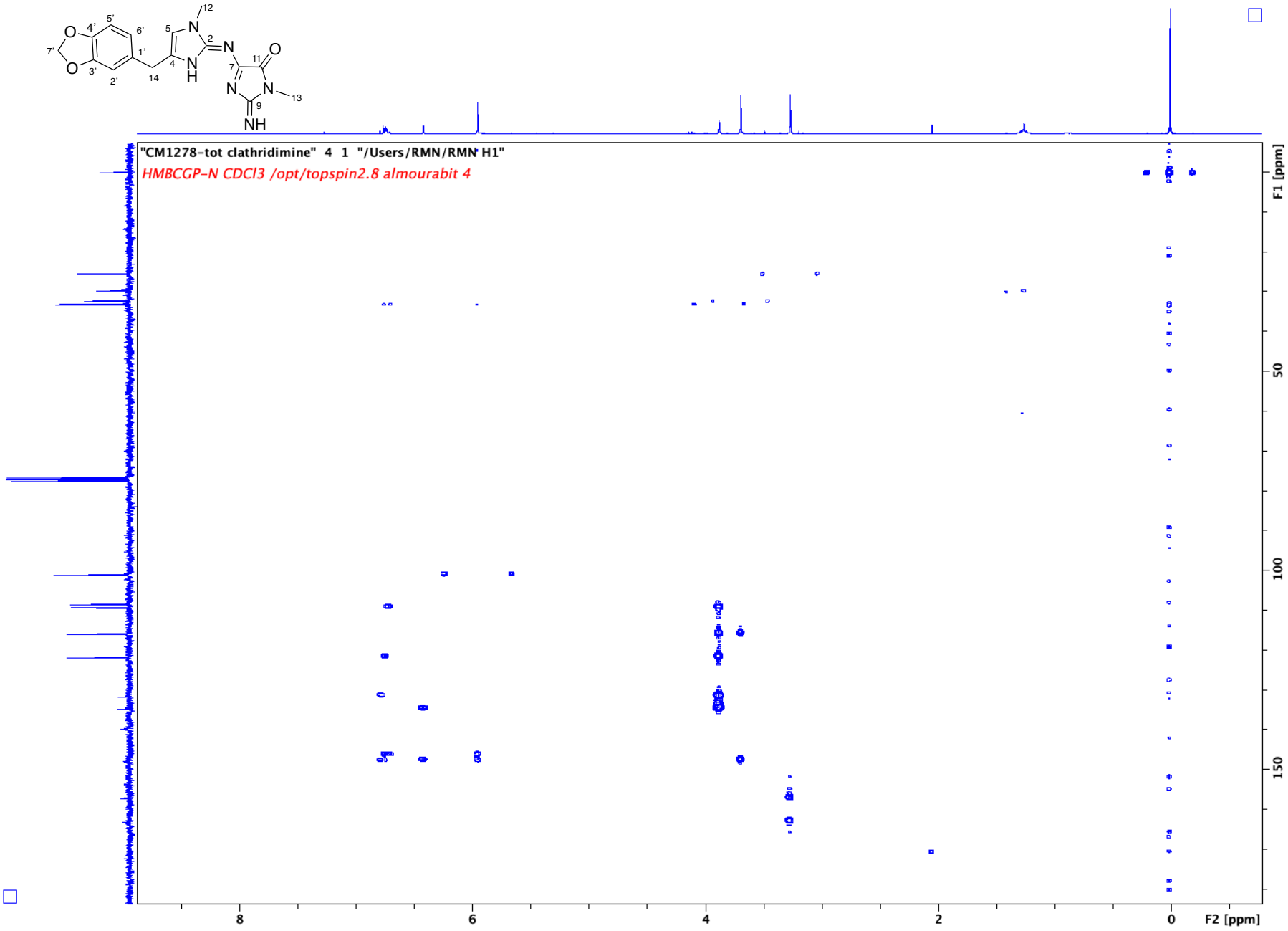


**Figure S16.** $^{1}H$ NMR spectrum of compound **20** in $CD_3OD$ (300 MHz).

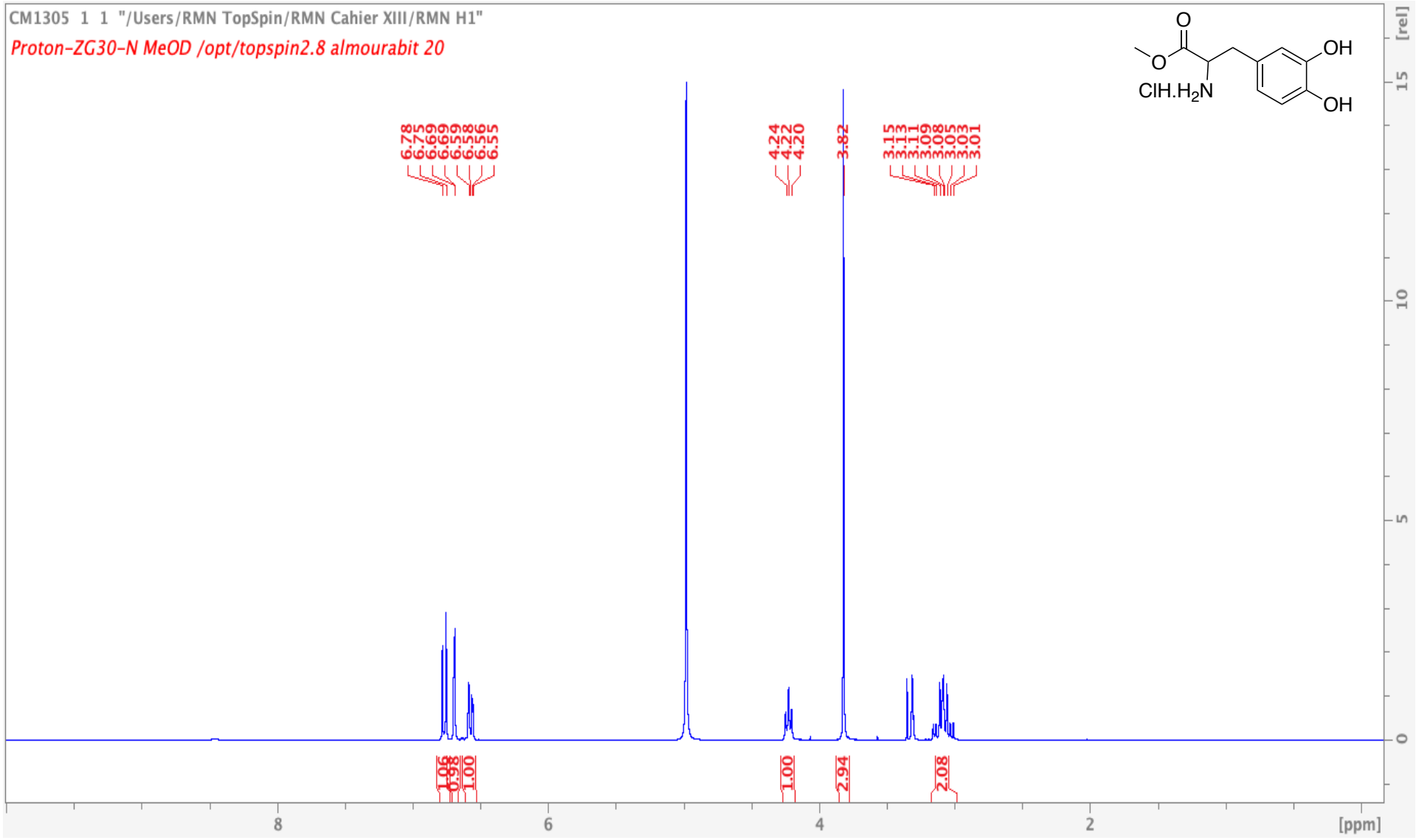


**Figure S17.** $^{13}C$ NMR spectrum of compound **20** in $CD_3OD$ (75 MHz).

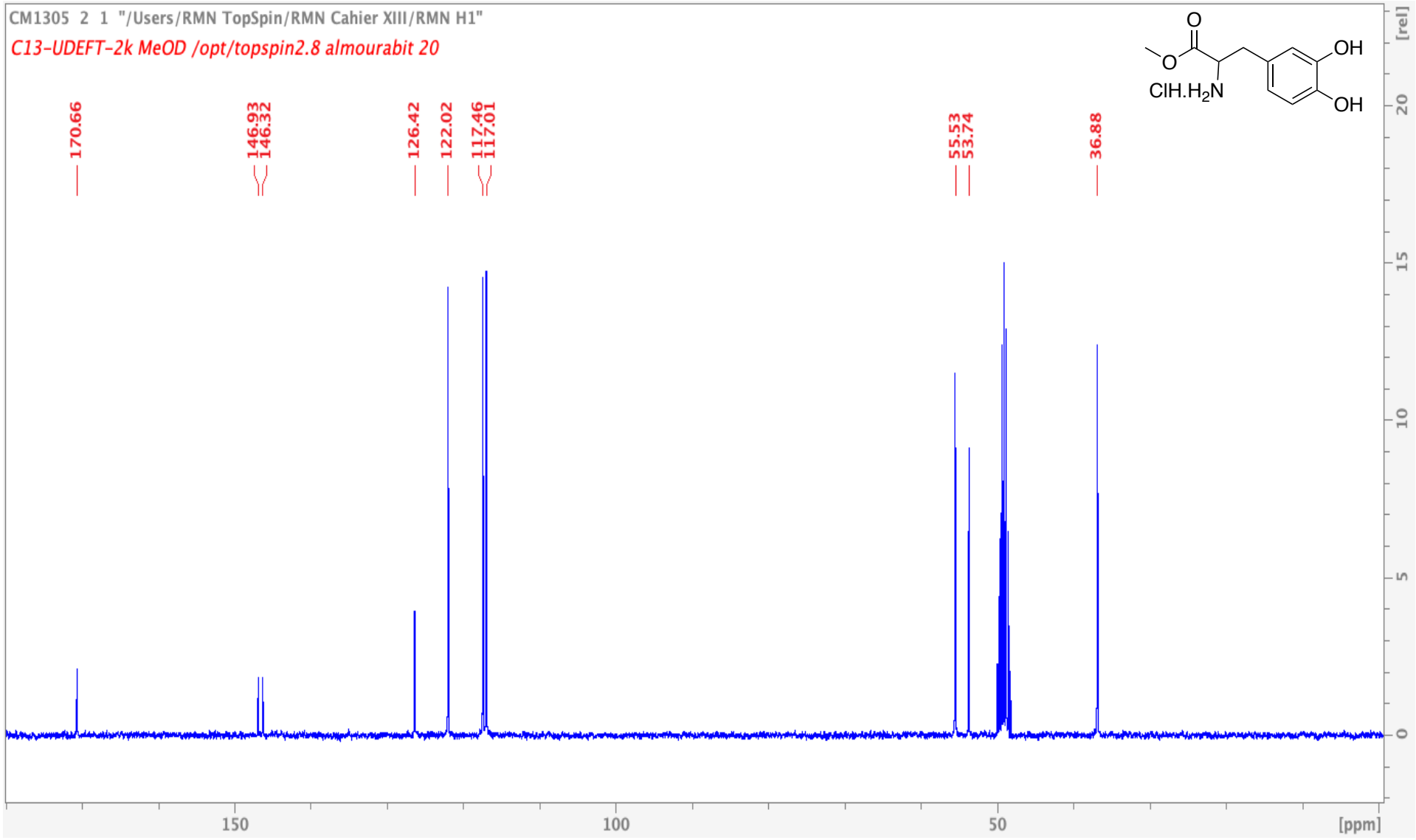


**Figure S18.** $^{1}H$ NMR spectrum of compound **21** in $CD_3OD$ (300 MHz).

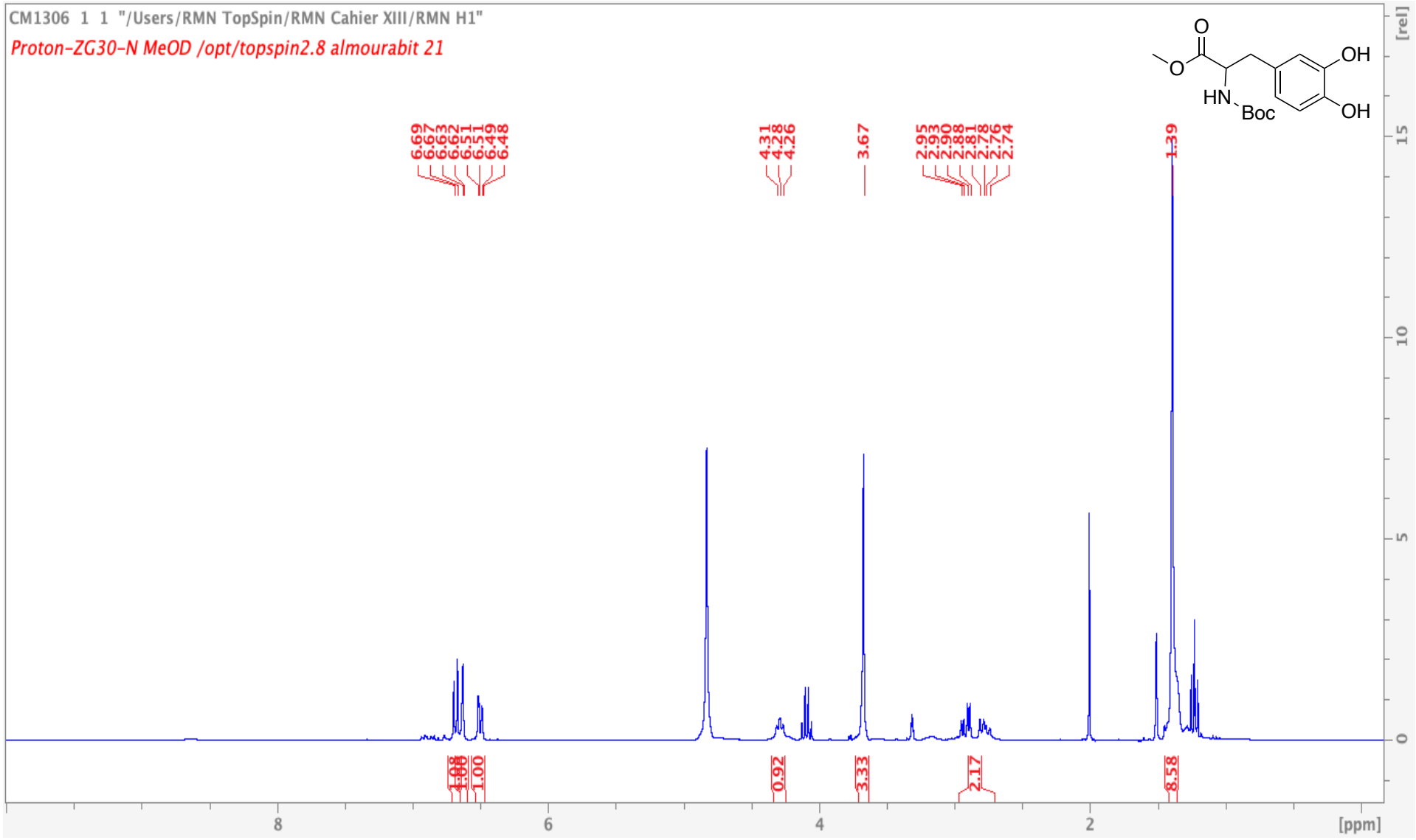


**Figure S19.** $^{13}C$ NMR spectrum of compound **21** in $CD_3OD$ (75 MHz).

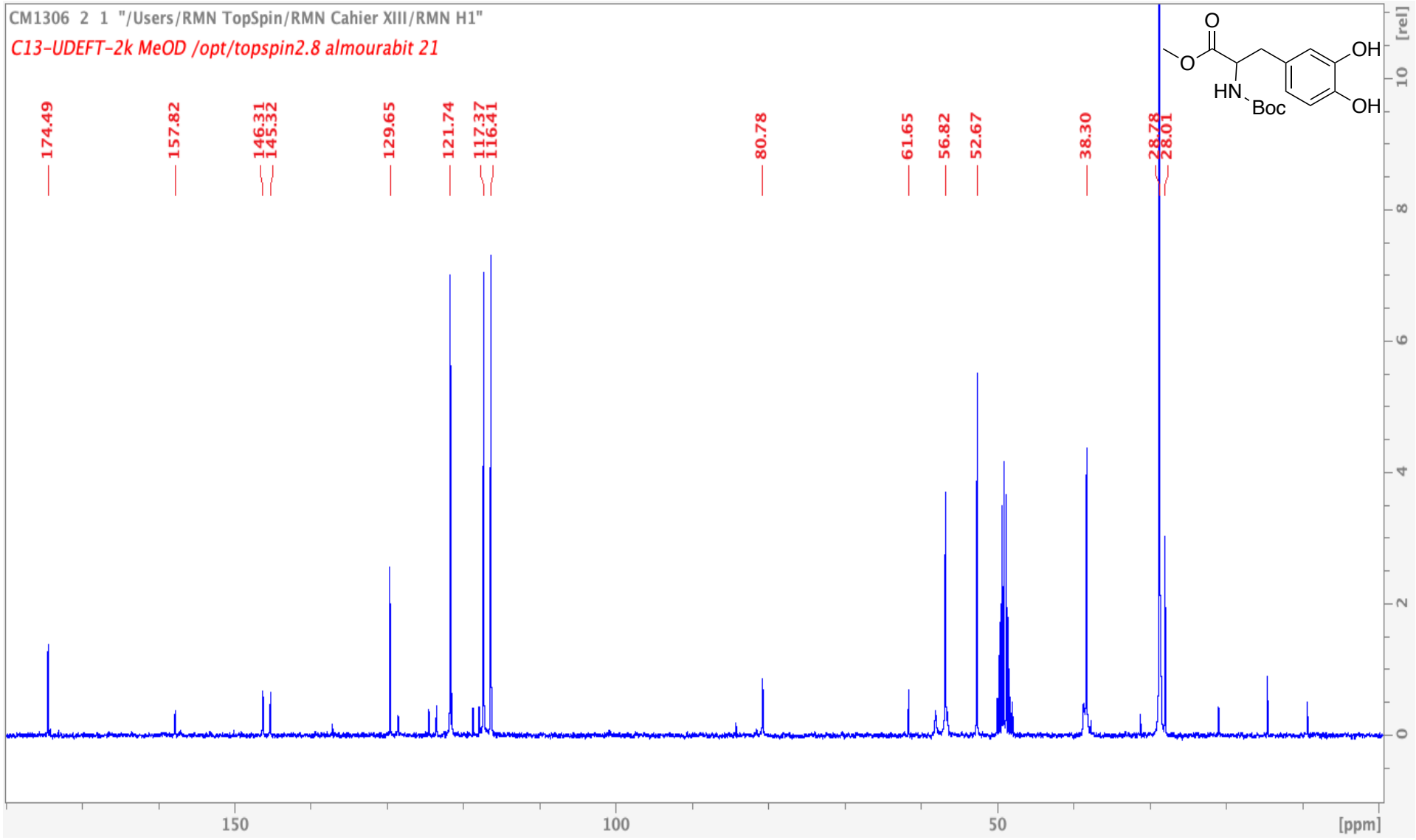


**Figure S20.** $^{1}H$ NMR spectrum of compound **22** in $CDCl_3$ (300 MHz).

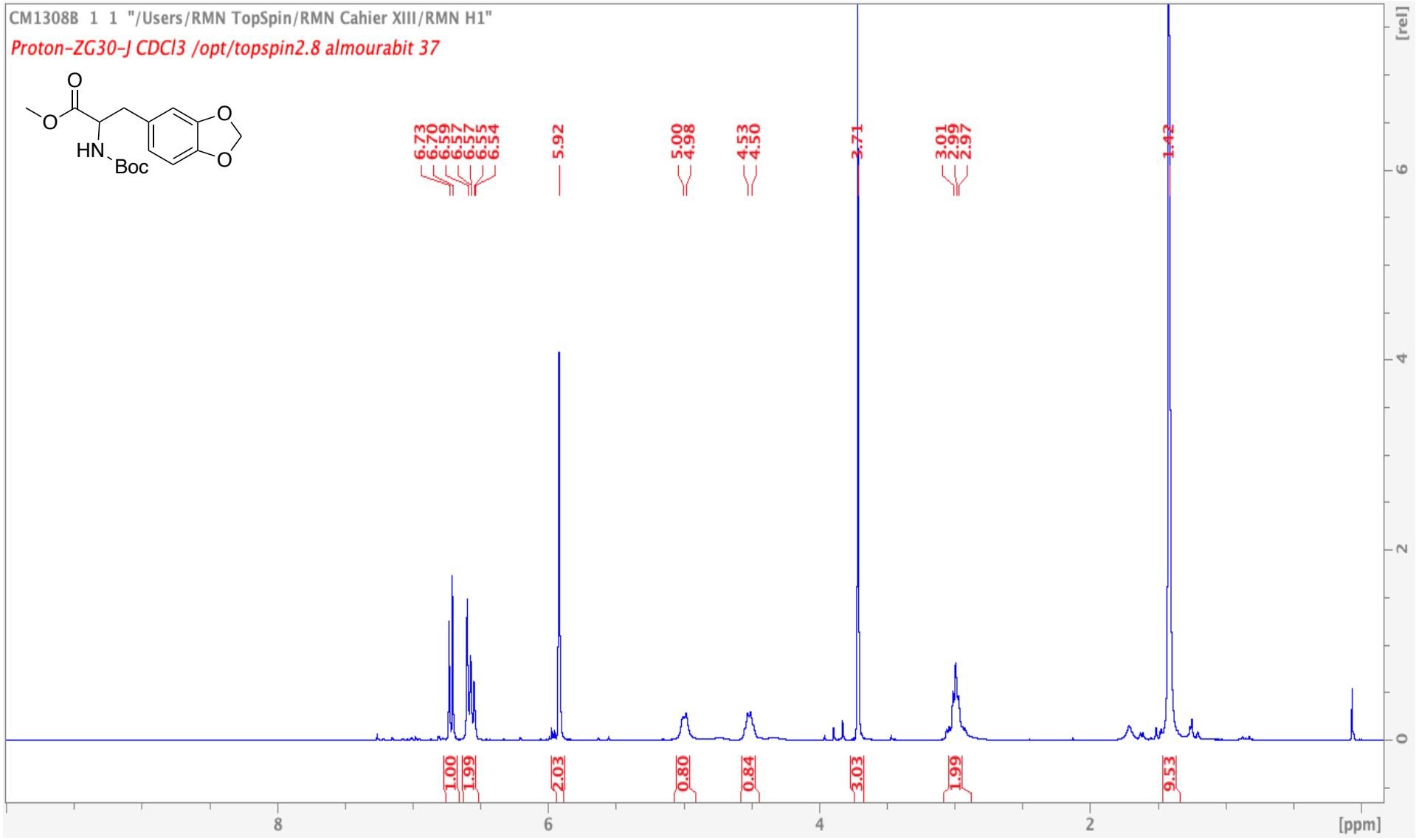


**Figure S21.** $^{13}C$ NMR spectrum of compound **22** in $CDCl_3$ (75 MHz).

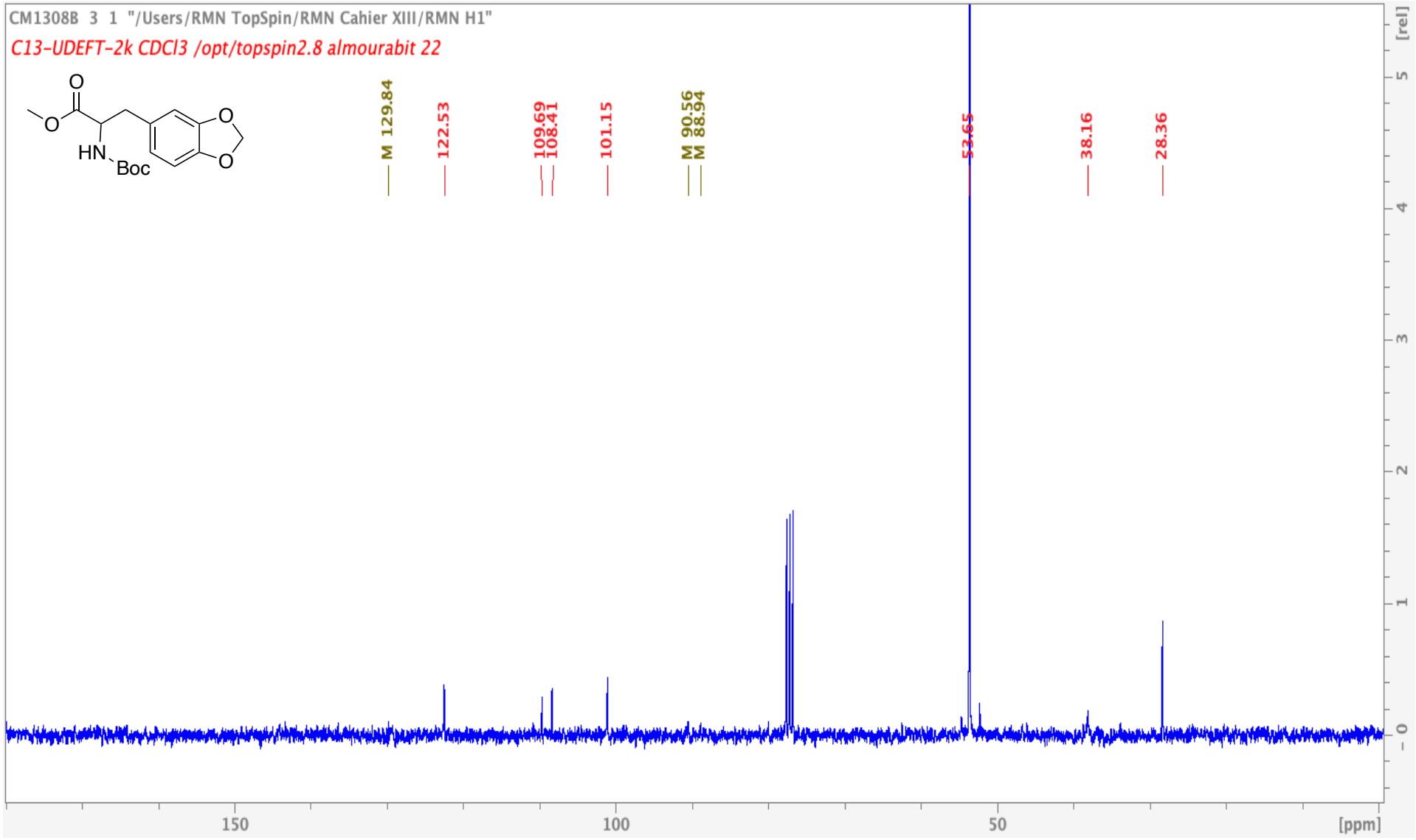


**Figure S22.** $^{1}H$ NMR spectrum of compound **23** in $CD_3OD$ (300 MHz).

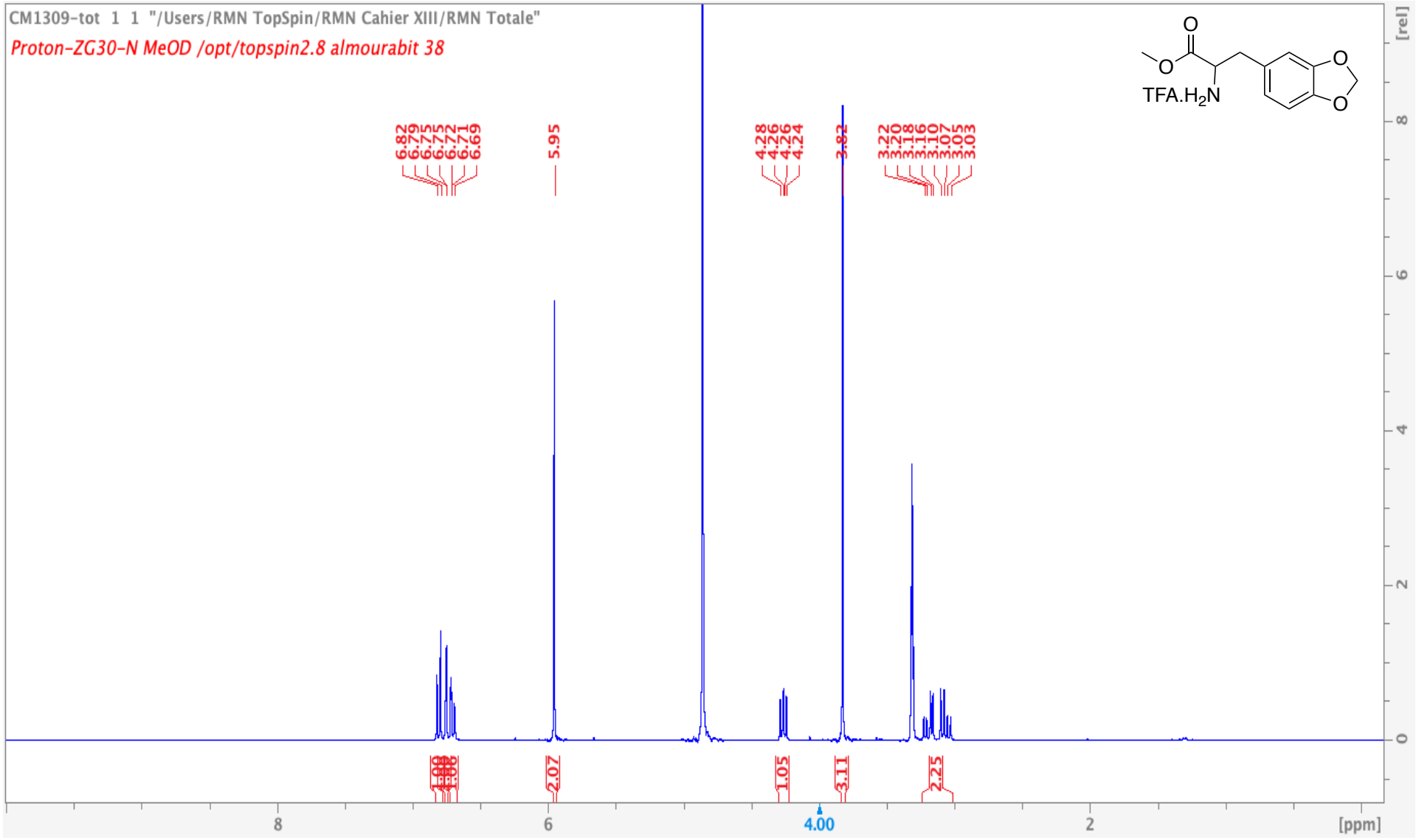


**Figure S23.** $^{13}C$ NMR spectrum of compound **23** in $CD_3OD$ (75 MHz).

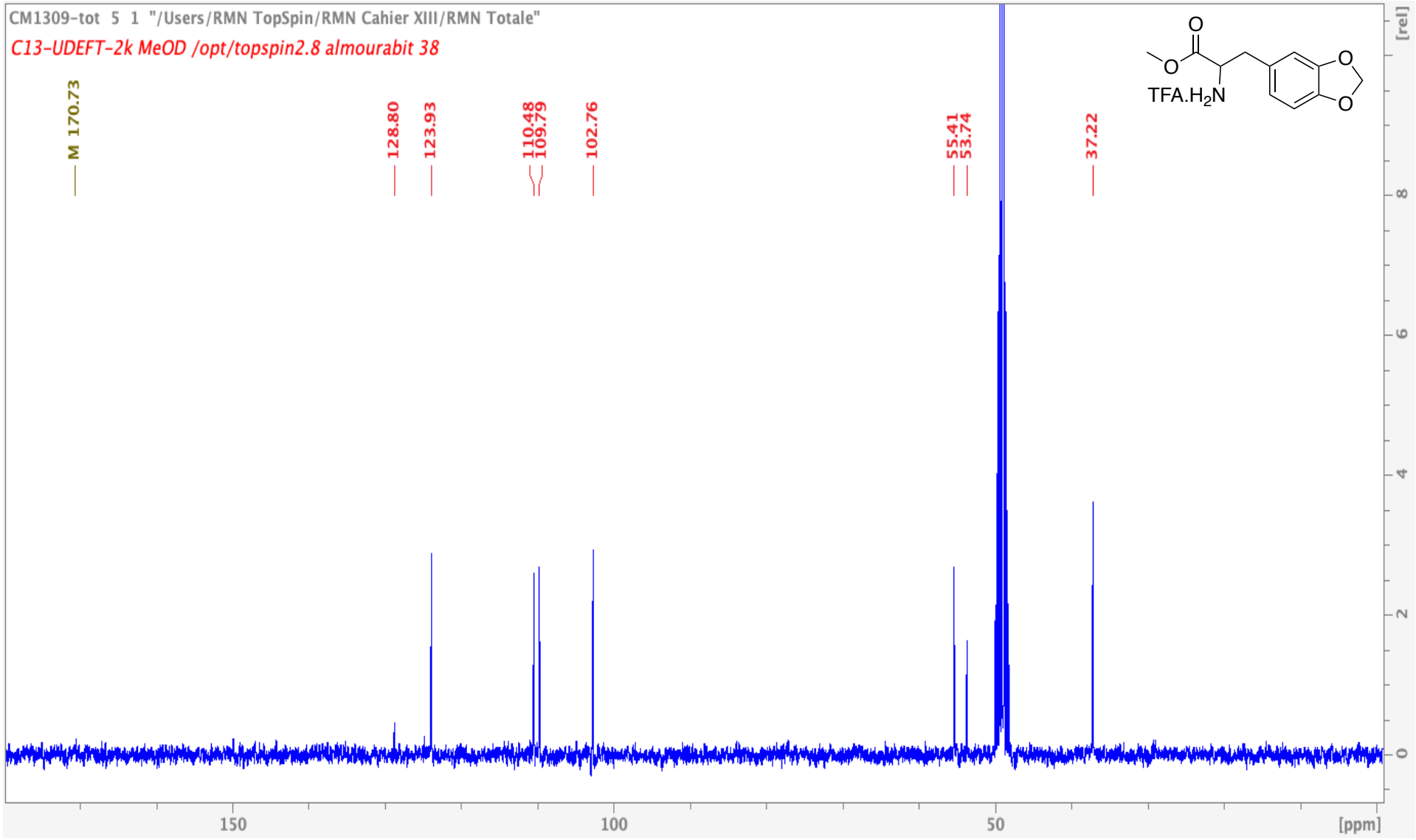


**Figure S24.** $^{1}H$ NMR spectrum of compound **24** in $CDCl_3$ (300 MHz).

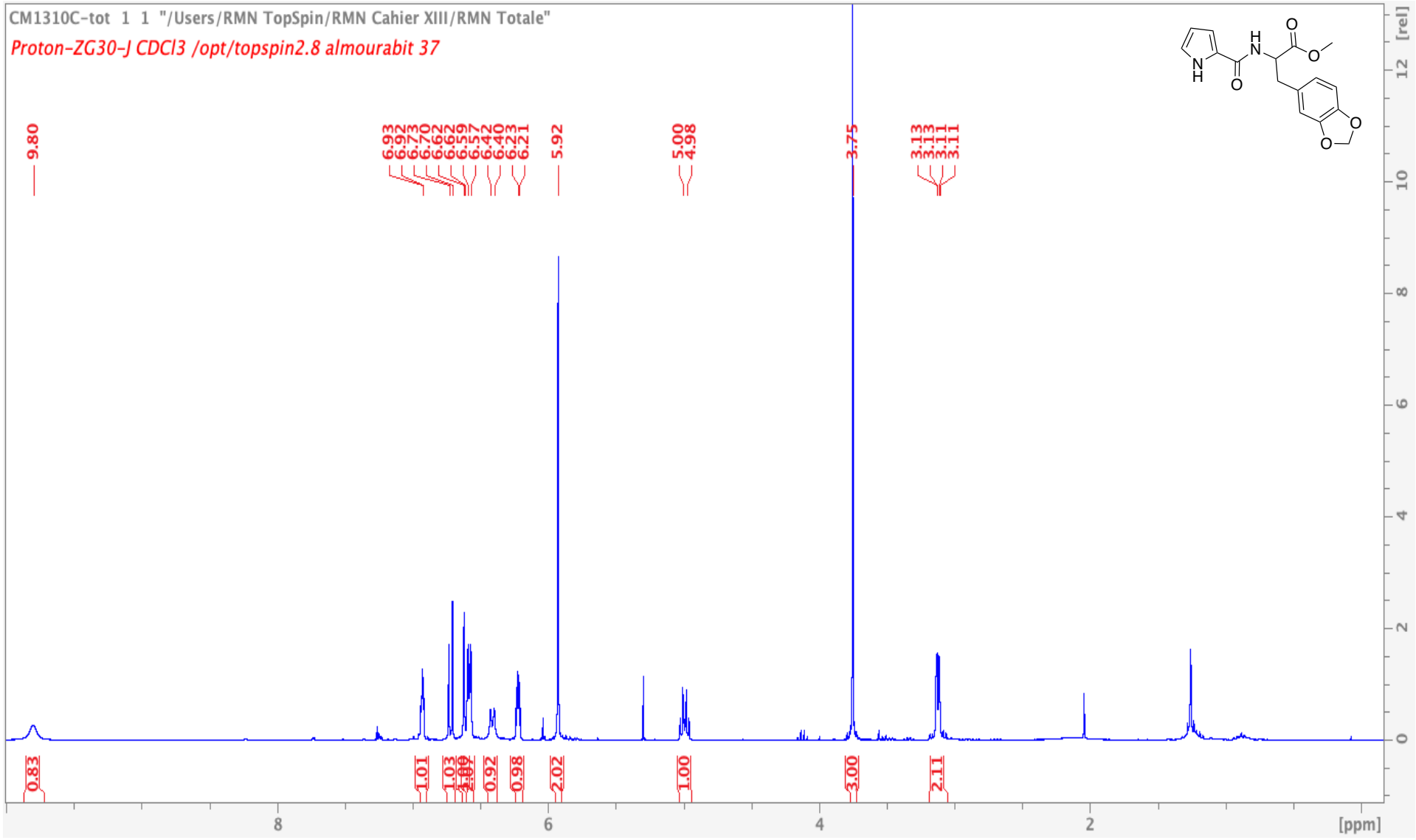


**Figure S25.** $^{13}C$ NMR spectrum of compound **24** in $CDCl_3$ (75 MHz).

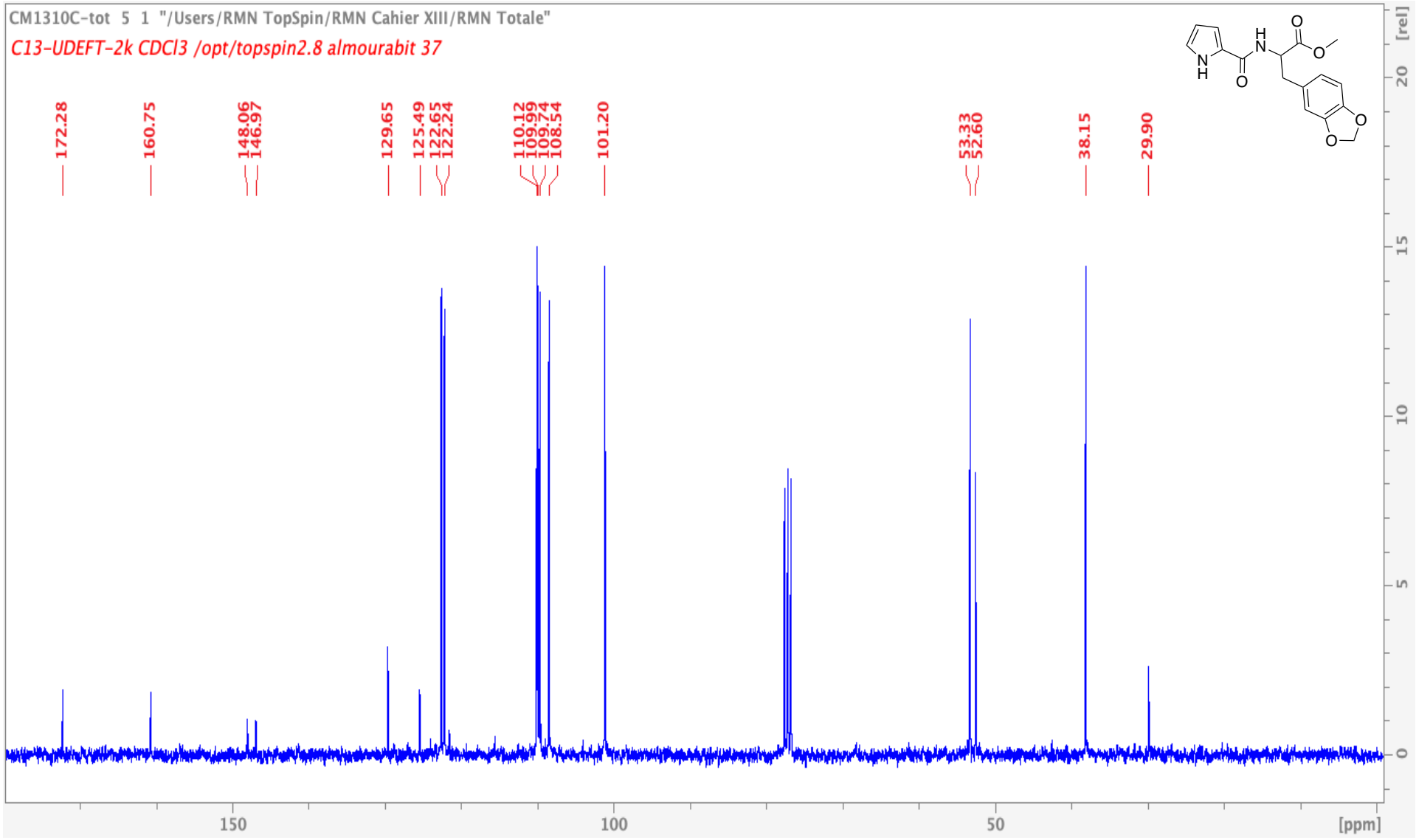


**Figure S26.** $^{1}H$ NMR spectrum of compound **25** in $CDCl_3$ (300 MHz).

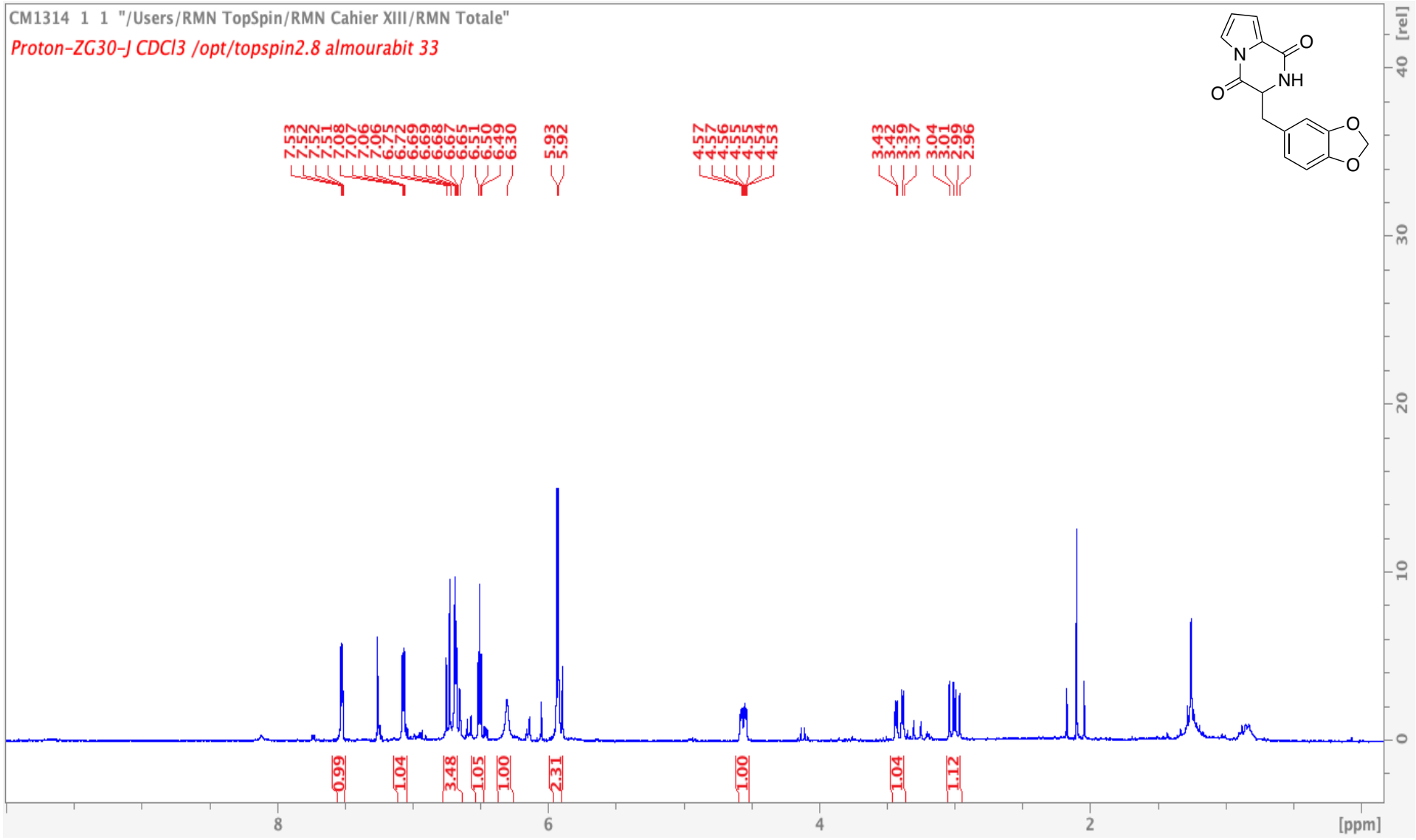


**Figure S27.** $^{13}C$ NMR spectrum of compound **25** in $CDCl_3$ (75 MHz).

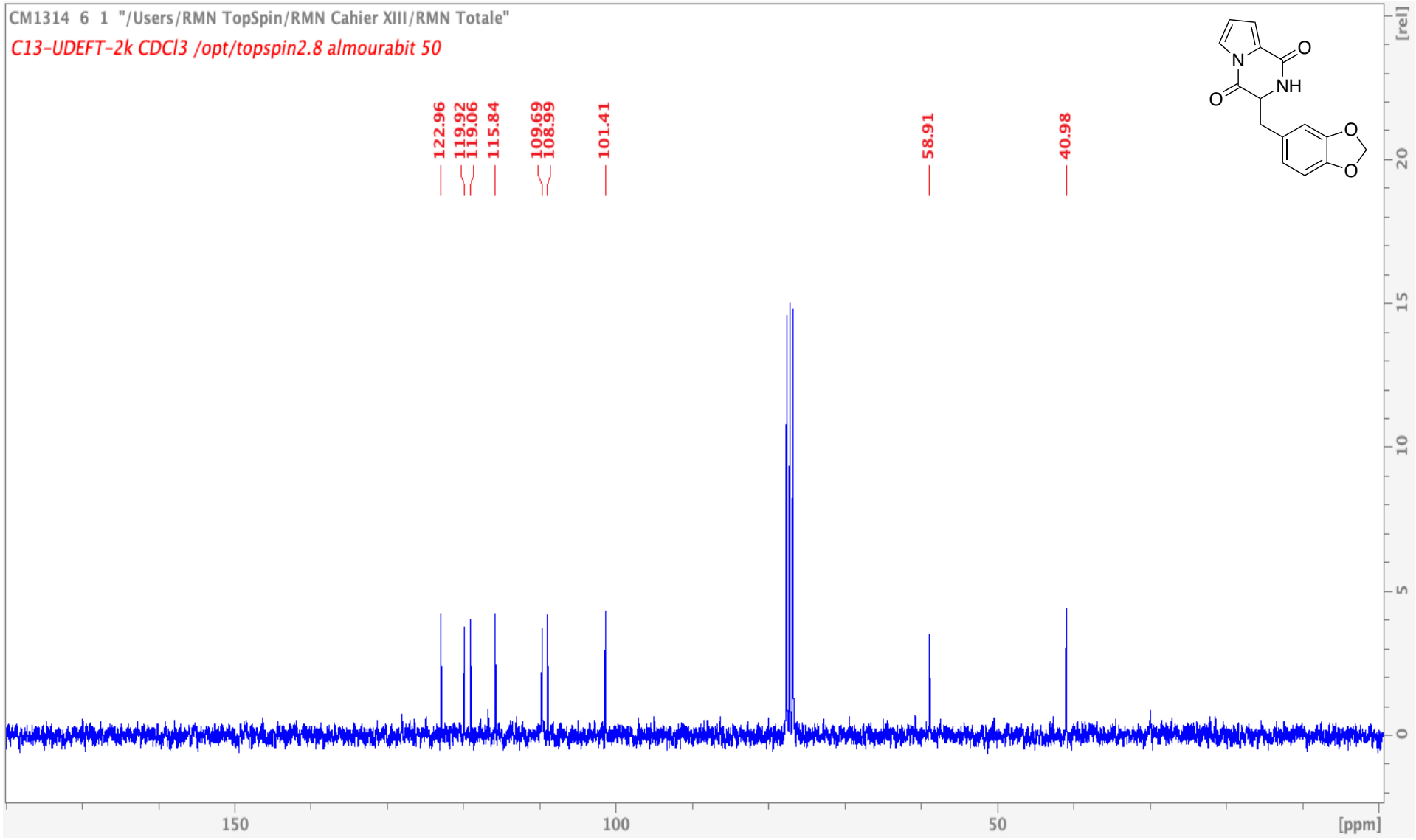


**Figure S28.** $^{1}H$ NMR spectrum of compound **26** in Acetone-$d_6$ (300 MHz).

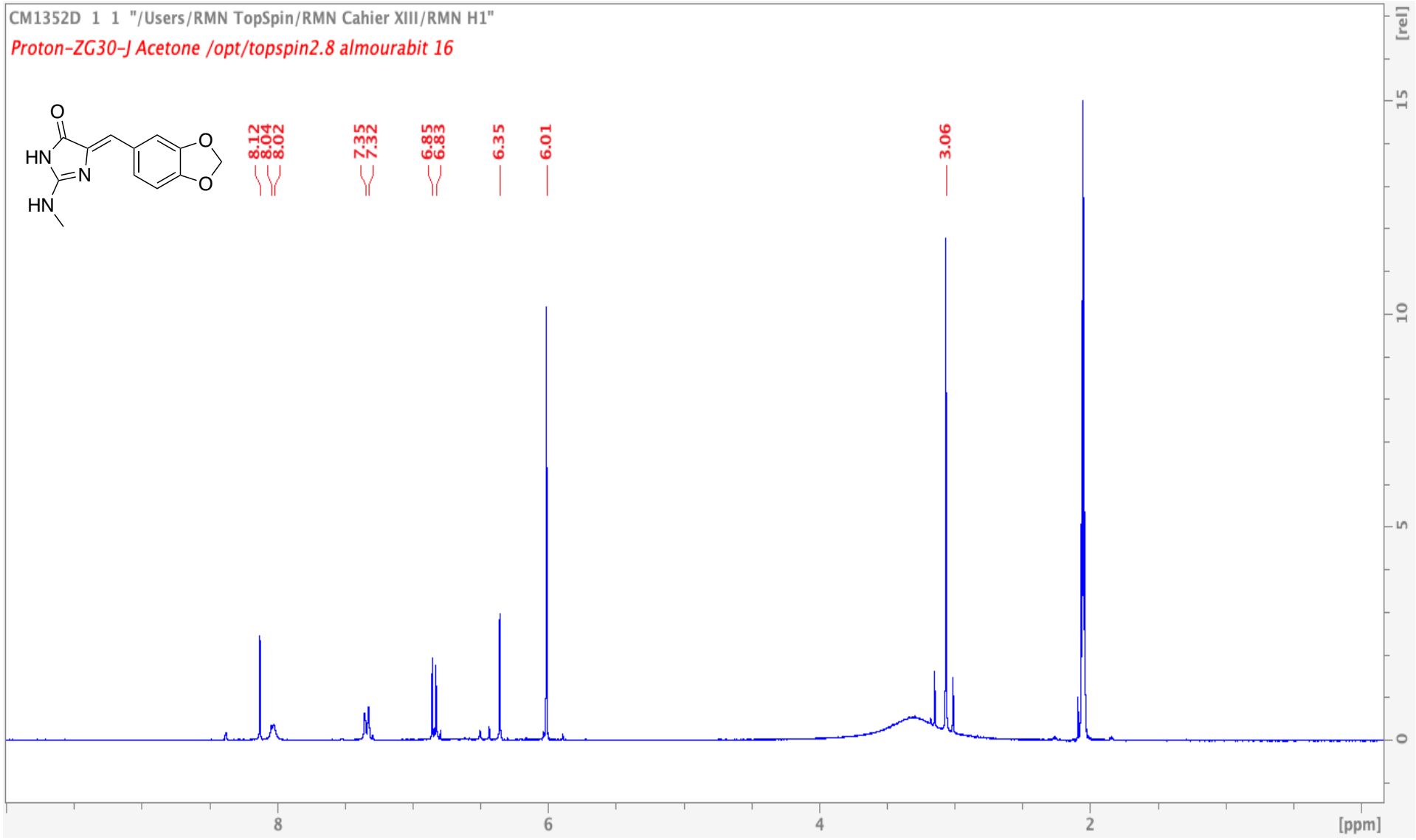


**Figure S29.** $^{1}$H NMR spectrum of leucettamine B (**5**) in Acetone-$d_6$ (300 MHz).

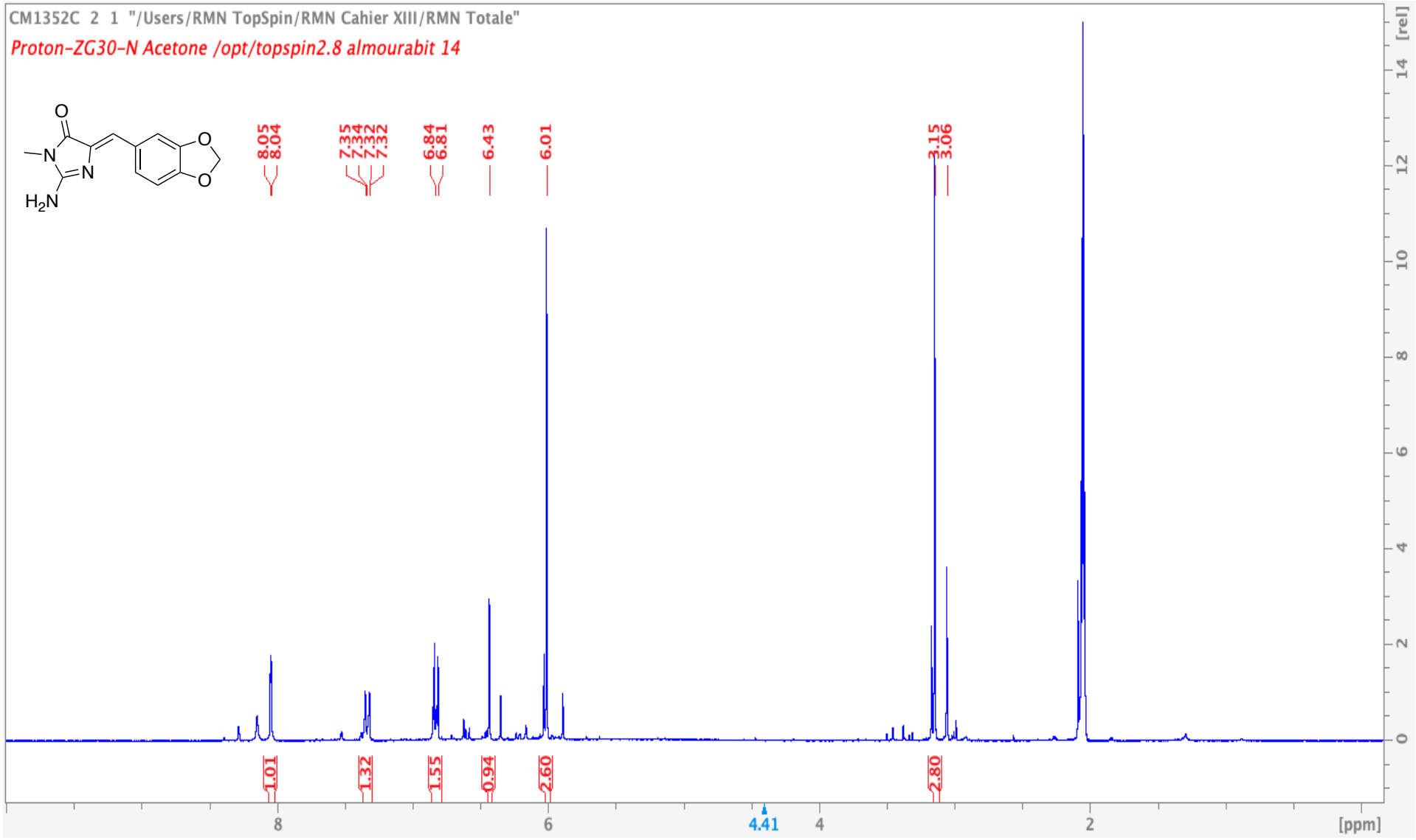


**Figure S30.** $^{13}C$ NMR spectrum of leucettamine B (**5**) in Acetone-$d_6$ (75 MHz).

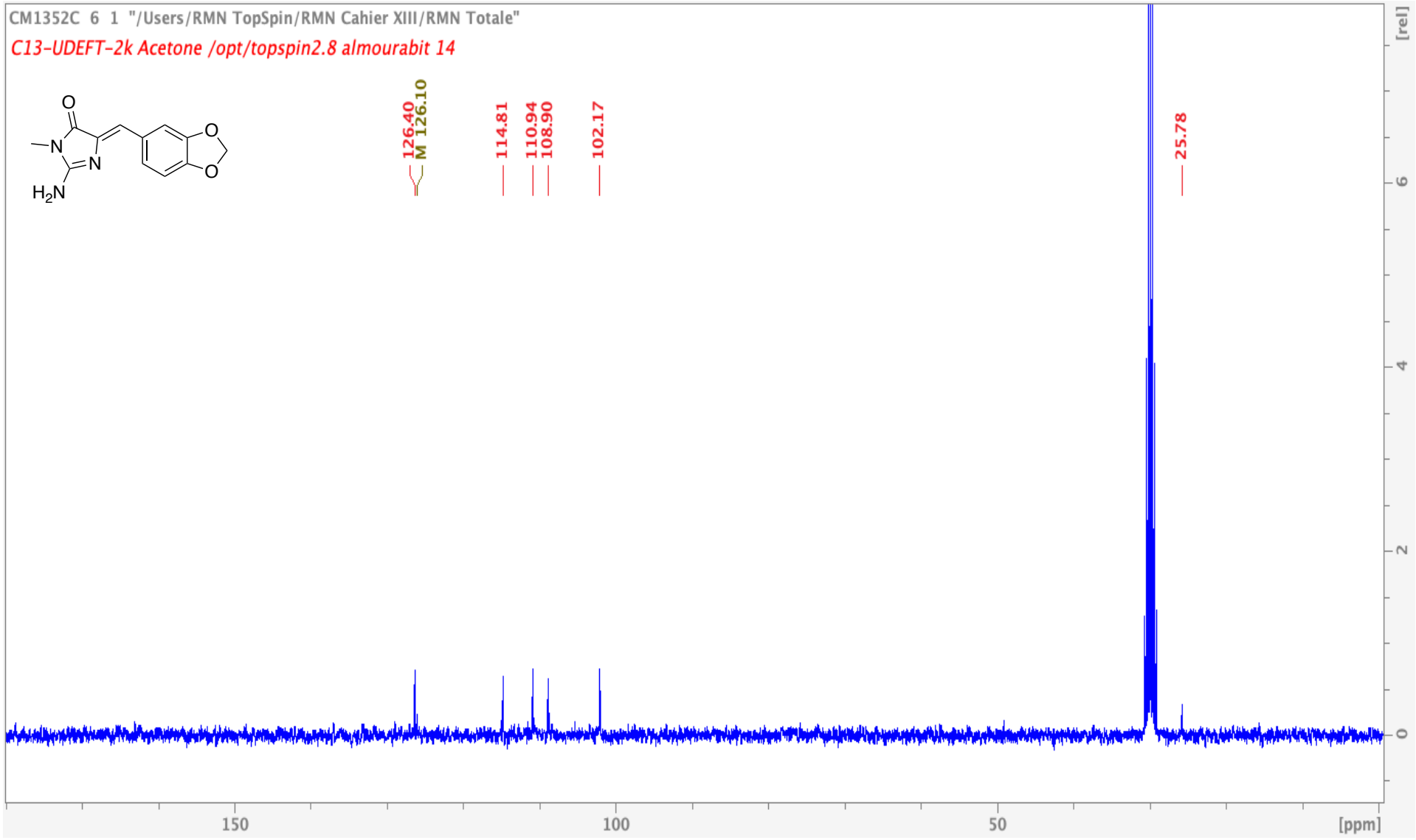


**Figure S31.** $^{1}H$-$^{13}C$ HMBC NMR spectrum of leucettamine B (**5**) in Acetone-$d_6$ (75 MHz).

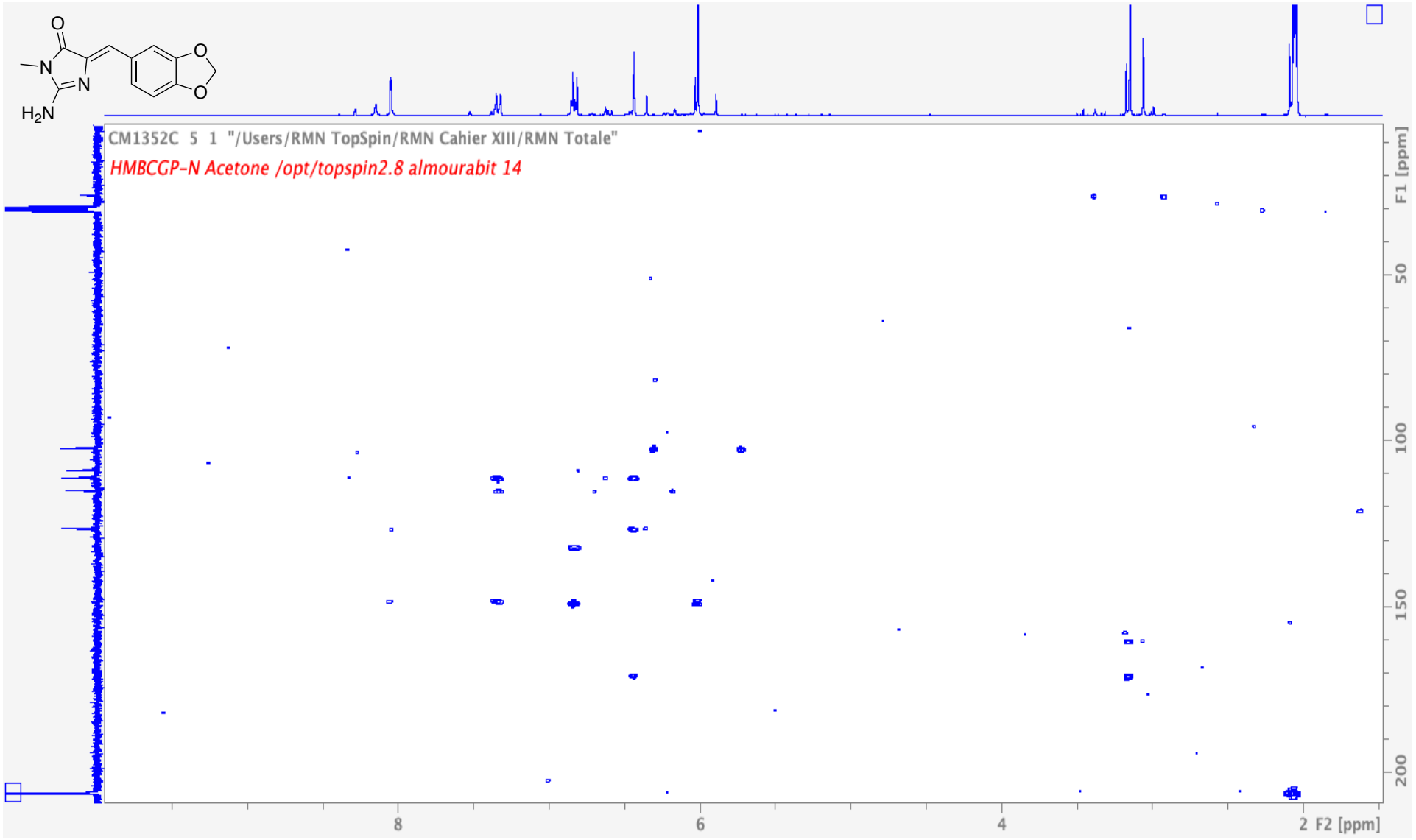


**Figure S32.** $^{1}H$ NMR spectrum of natural homodimeric (clathridine A)$_2$ $Zn^{2+}$ (**9**) in $CDCl_3$ (500 MHz).

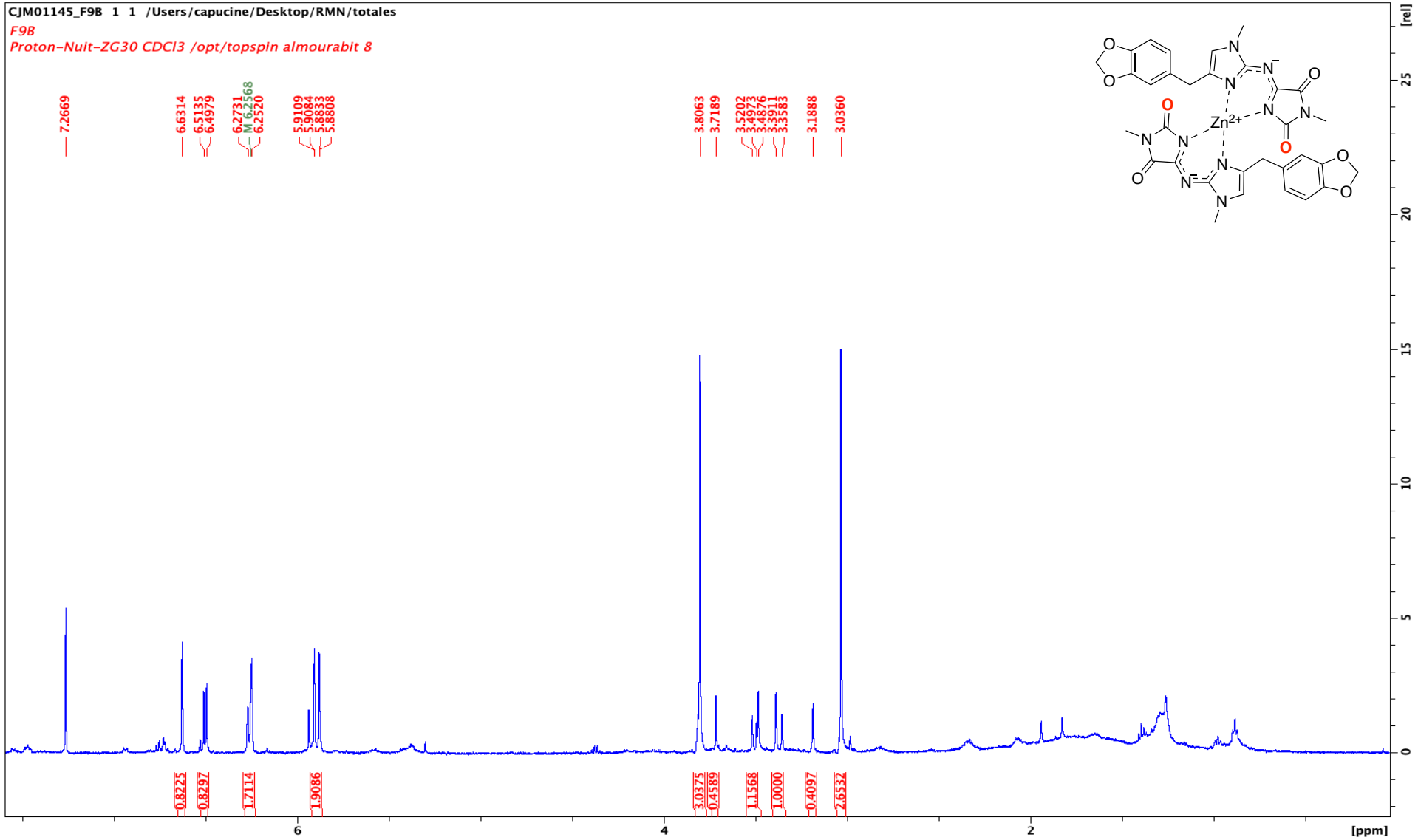


**Figure S33.** $^{1}H$-$^{13}C$ HSQC NMR spectrum of natural homodimeric (clathridine A)$_2$ $Zn^{2+}$ (**9**) in $CDCl_3$ (500 MHz).

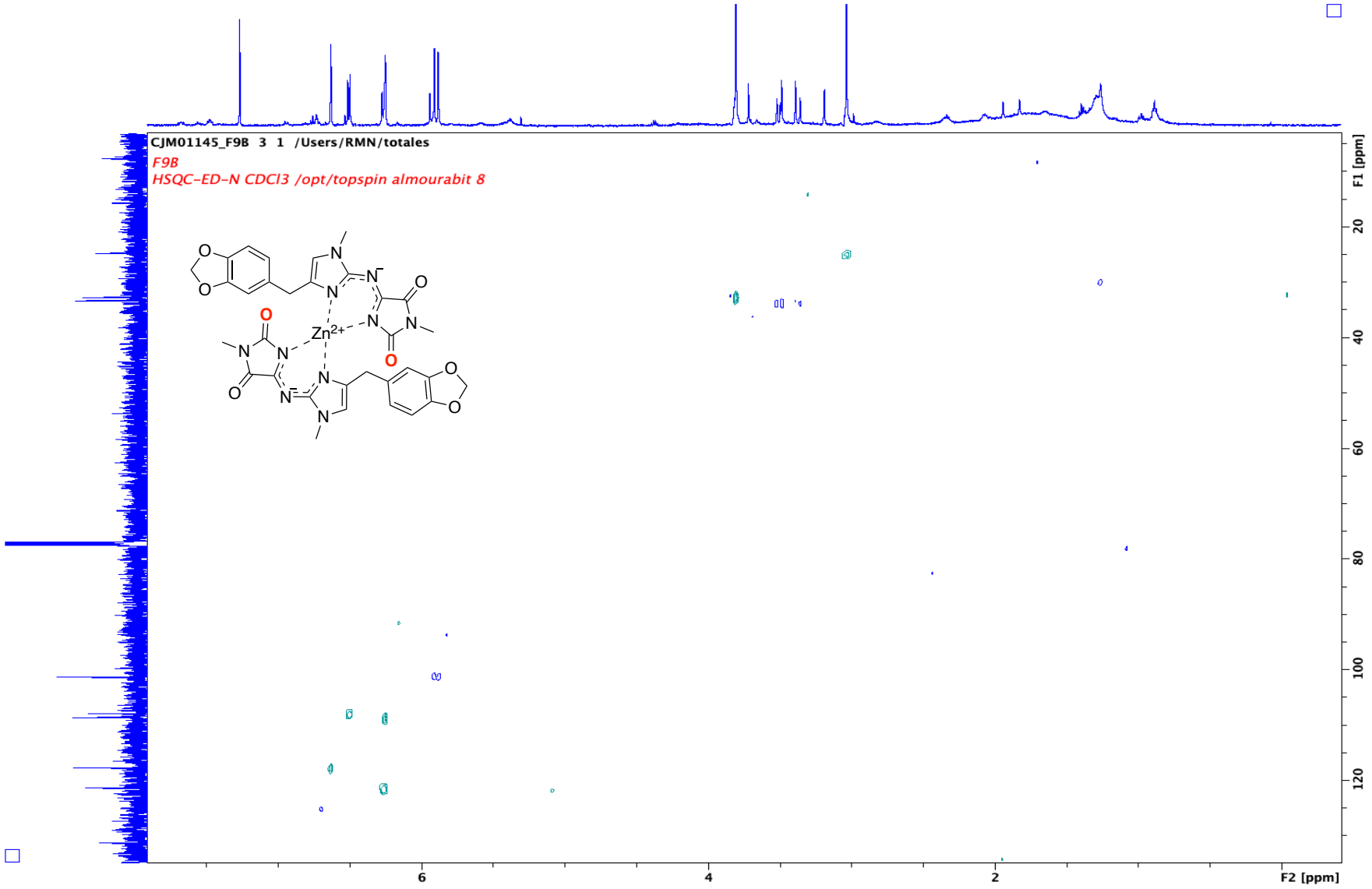


**Figure S34.** $^{1}H$-$^{13}C$ HMBC NMR spectrum of natural homodimeric (clathridine A)$_2$ $Zn^{2+}$ (**9**) in $CDCl_3$ (500 MHz).

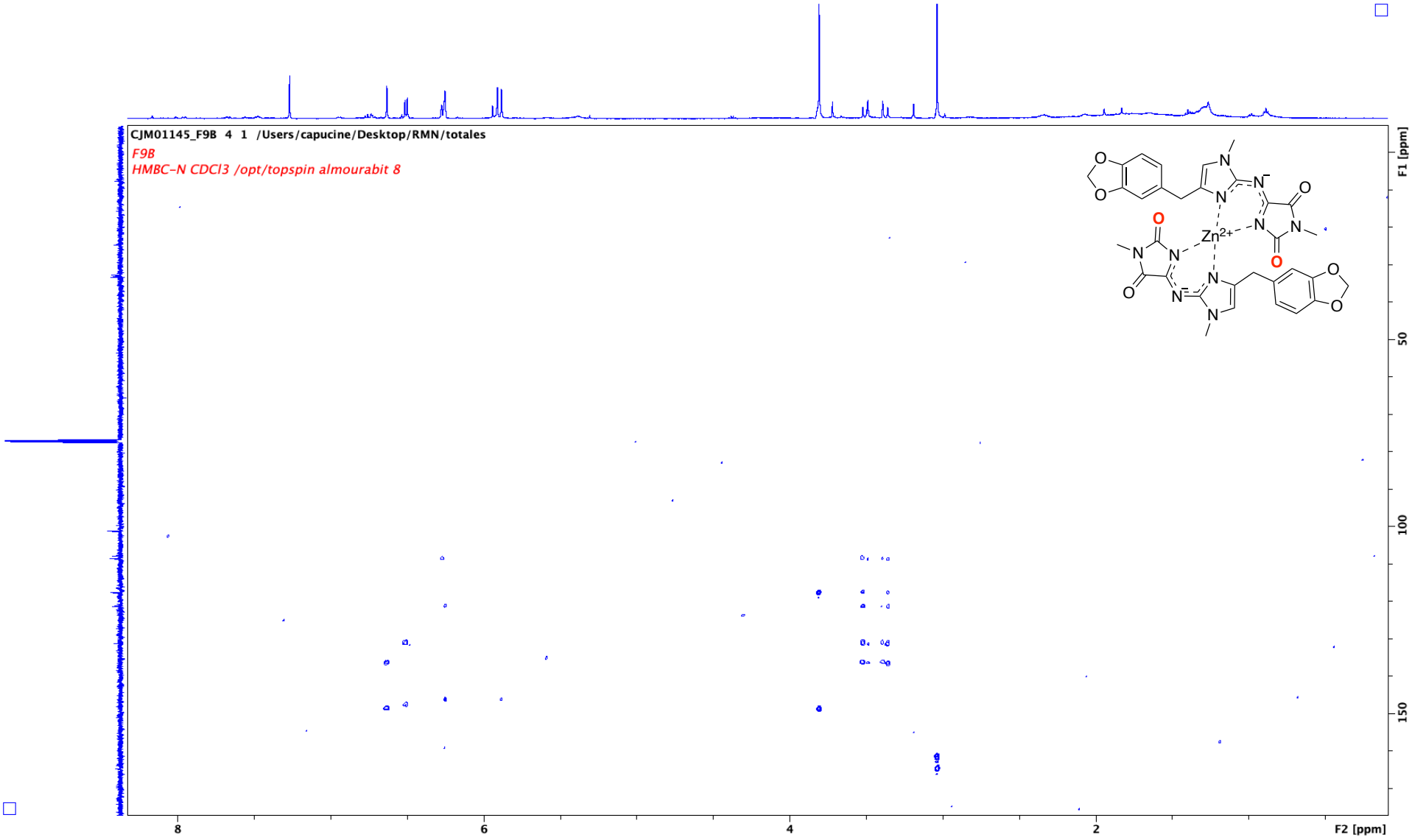


**Figure S35.** $^{1}H$ NMR spectrum of synthetic homodimeric (clathridine A)$_2$ $Zn^{2+}$ (**9**) in $CDCl_3$ (500 MHz).

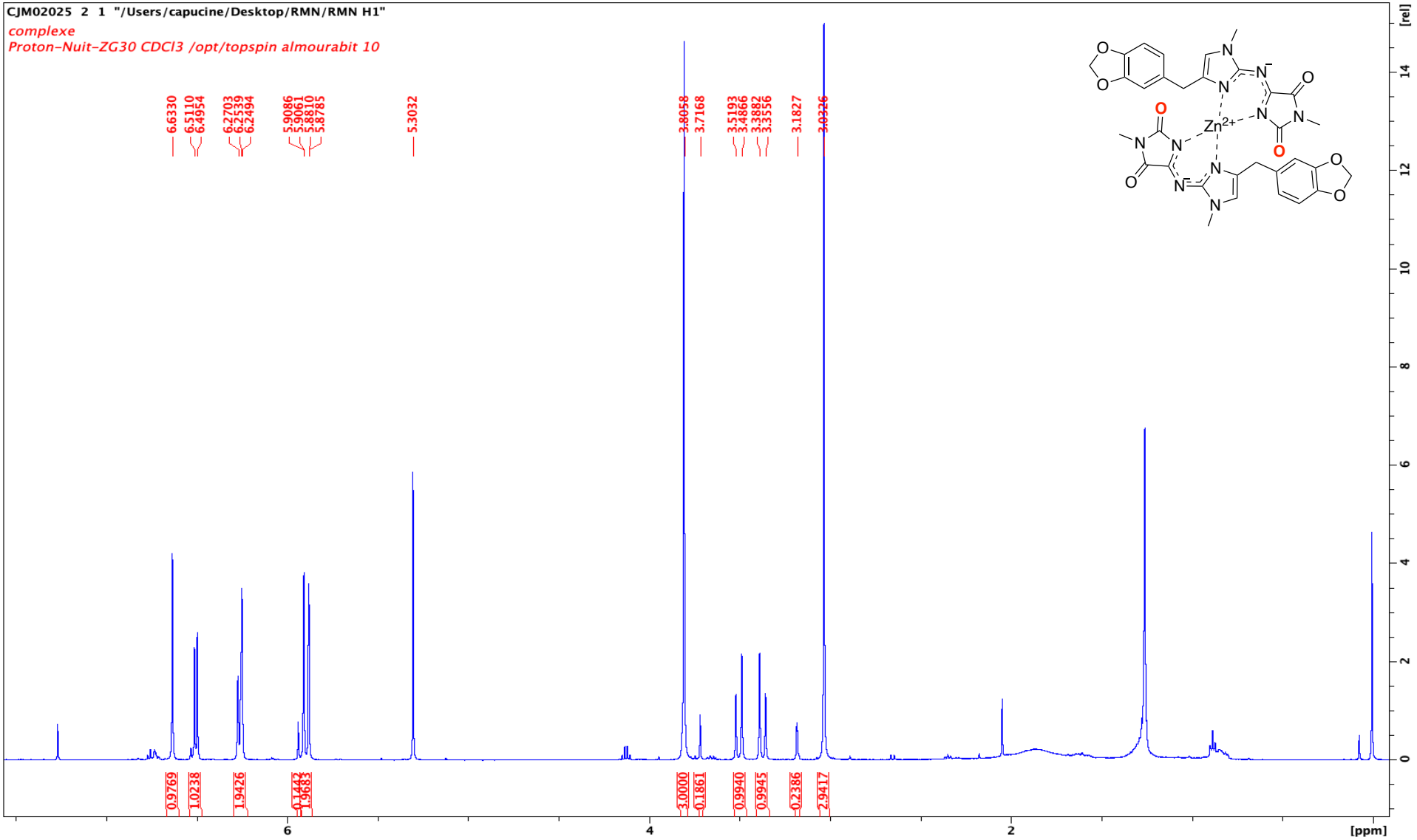


**Figure S36.** $^{13}C$ NMR spectrum of synthetic homodimeric (clathridine A)$_2$ $Zn^{2+}$ (**9**) in $CDCl_3$ (125 MHz).

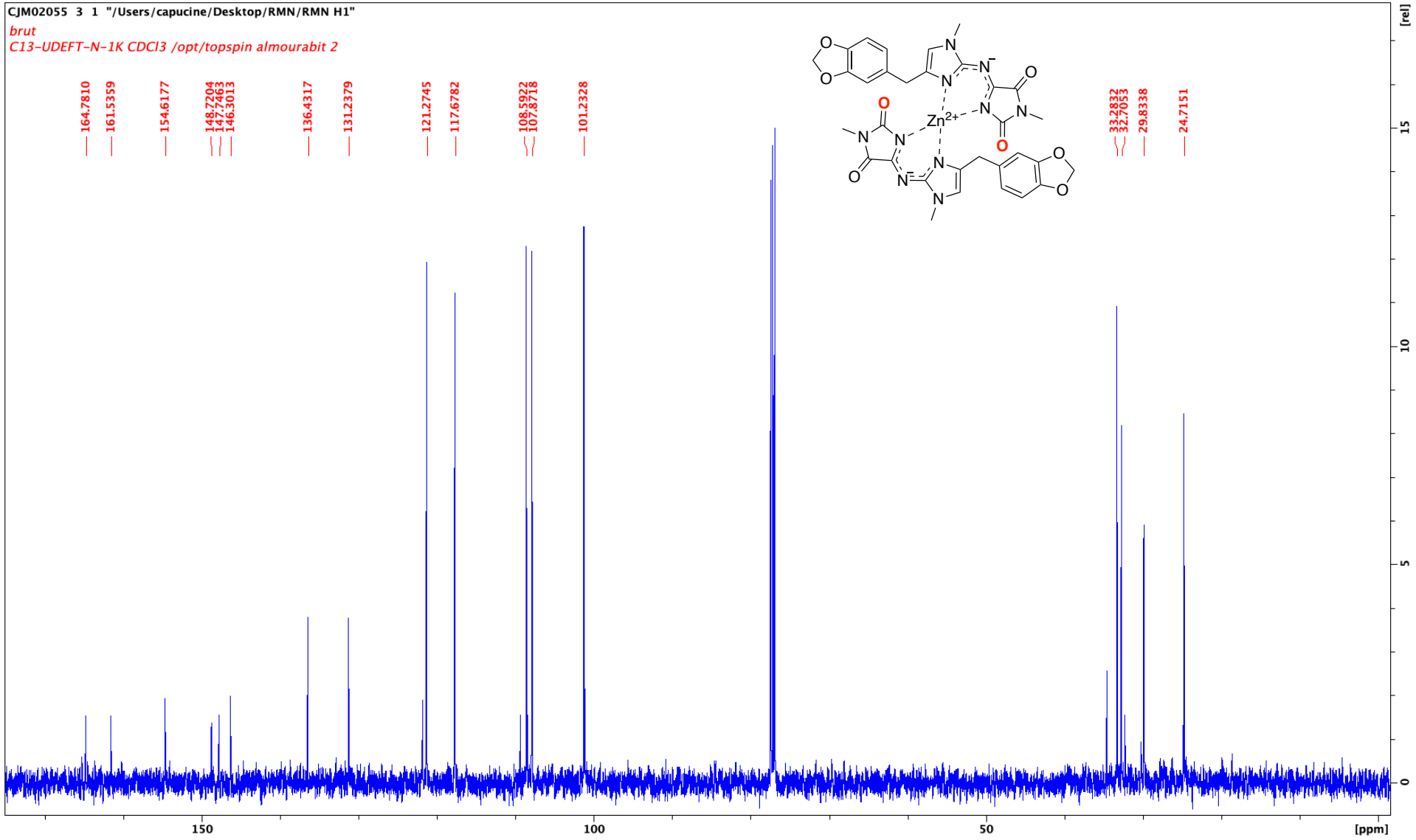
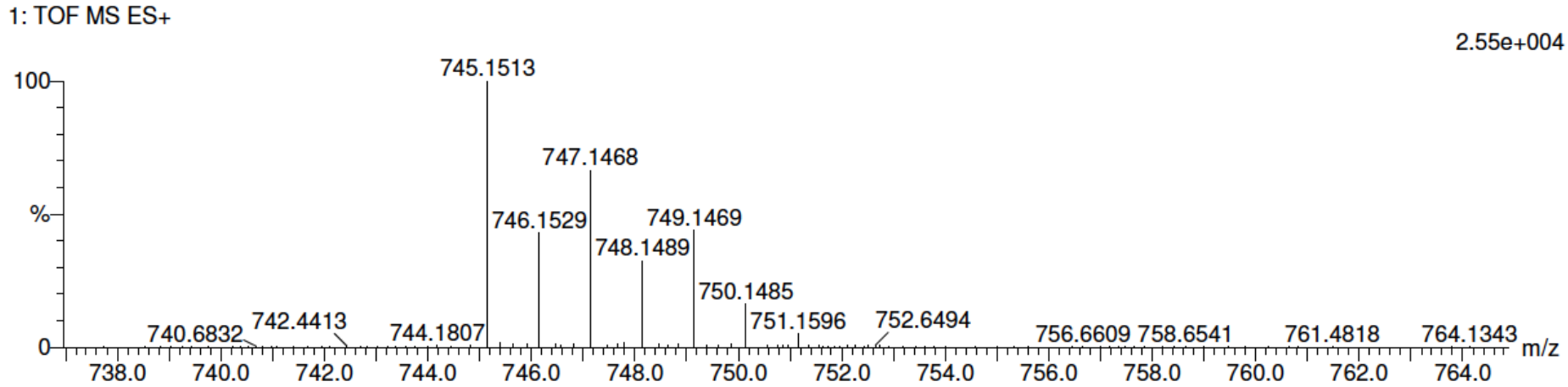


**Figure S37.** HR-ESI mass spectrum of the synthetic homodimeric (clathridine A)$_2$ $Zn^{2+}$ (**9**).




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 10.0 | 50.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 745.1513 | 745.1528 | -1.5 | -2.0 | 26.5 | 112.1 | 0.8 | C41 H33 N2 O8 64Zn |
| | 745.1461 | 5.2 | 7.0 | 23.5 | 111.9 | 0.6 | C32 H29 N10 O8 64Zn |

**Figure S38.** $^{1}H$ NMR spectrum of synthetic heterodimeric (clathridine A-clathridimine) $Zn^{2+}$ (**10**) in $CDCl_3$ (500 MHz).

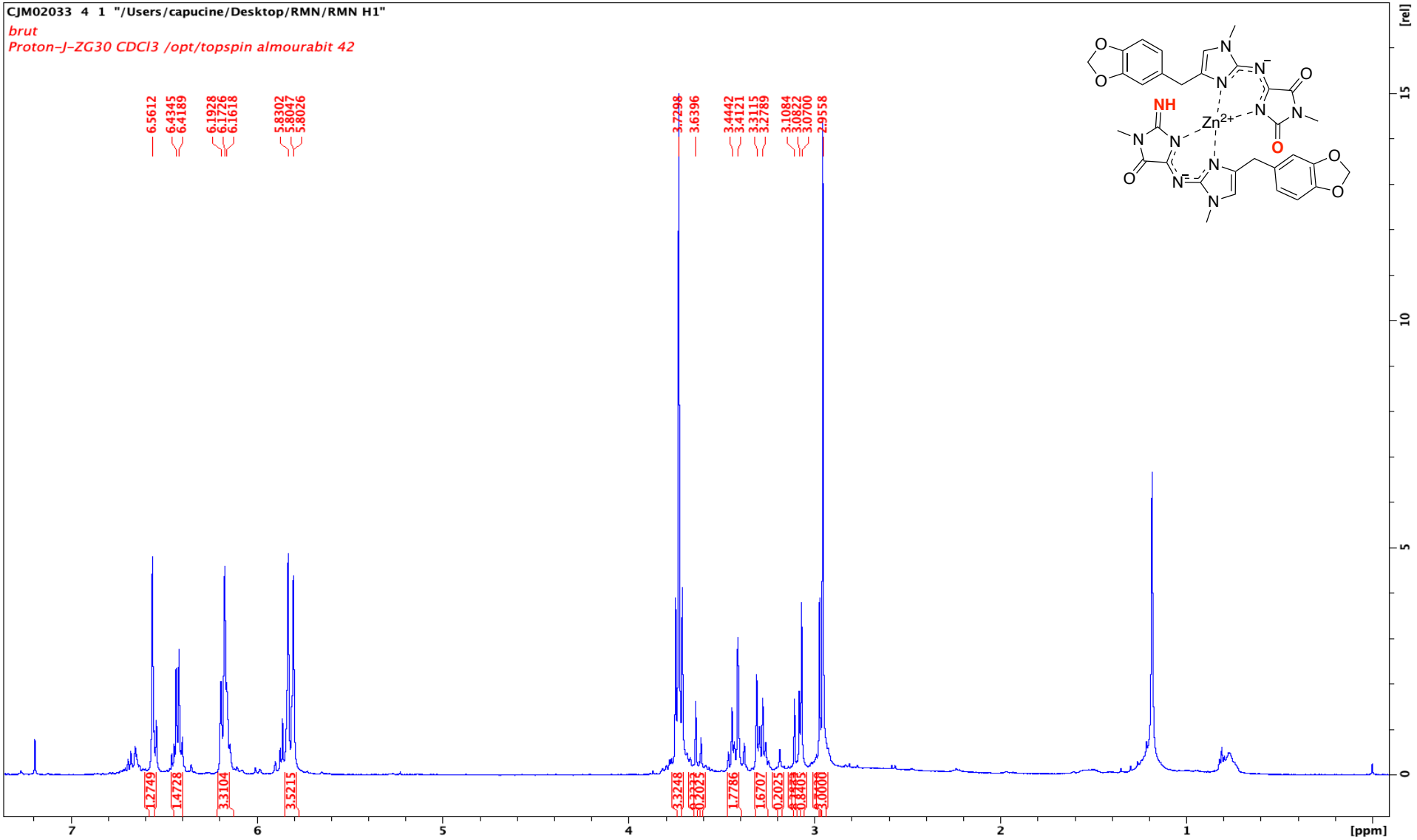


**Figure S39.** $^{13}C$ NMR spectrum of synthetic heterodimeric (clathridine A-clathridimine) $Zn^{2+}$ (**10**) in $CDCl_3$ (125 MHz).

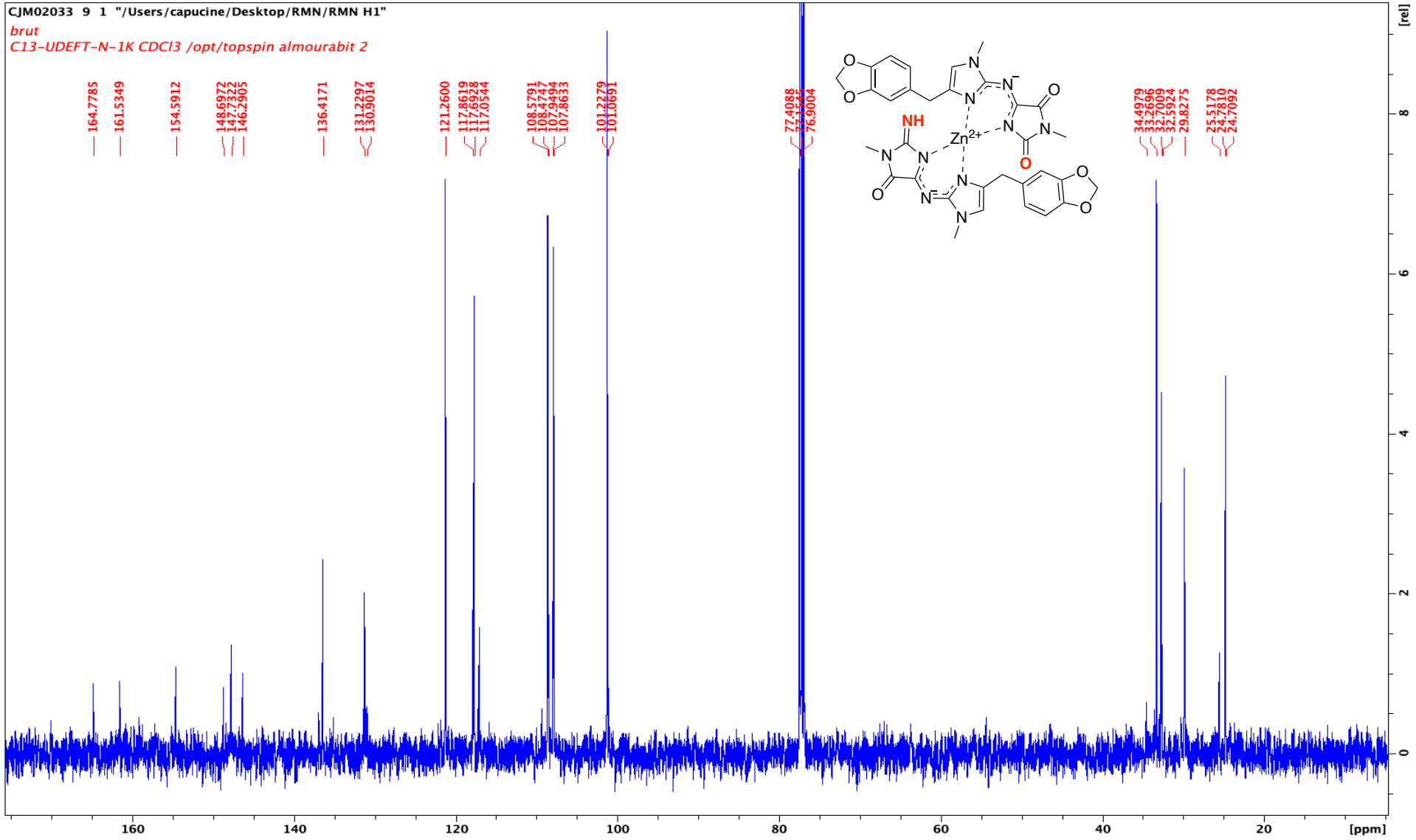
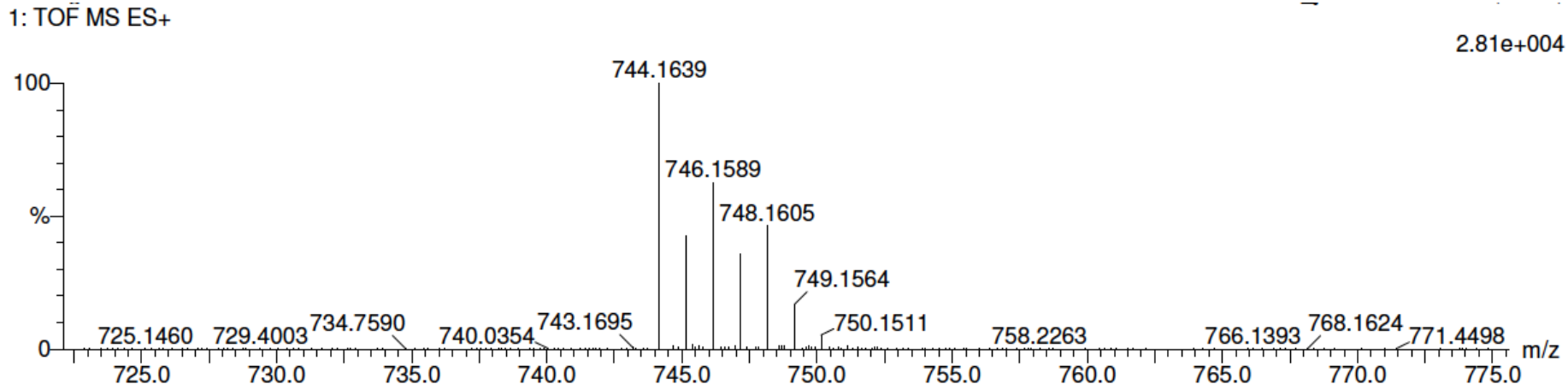


**Figure S40.** HR-ESI mass spectrum of the synthetic heterodimeric (clathridine A-clathridimine) $Zn^{2+}$ (**10**).




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 10.0 | 50.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 744.1639 | 744.1621 | 1.8 | 2.4 | 23.5 | 119.9 | 1.2 | C32 H30 N11 O7 64Zn |
| | 744.1576 | 6.3 | 8.5 | 26.5 | 120.0 | 1.3 | C42 H34 N O8 64Zn |
| | 744.1693 | -5.4 | -7.3 | 19.5 | 120.1 | 1.4 | C26 H30 N15 O8 64Zn |
| | 744.1688 | -4.9 | -6.6 | 26.5 | 120.2 | 1.5 | C41 H34 N3 O7 64Zn |

**Figure S41.** $^{1}H$ NMR spectrum of synthetic homodimeric (clathridimine)$_2$ $Zn^{2+}$ (**27**) in $CDCl_3$ (500 MHz).

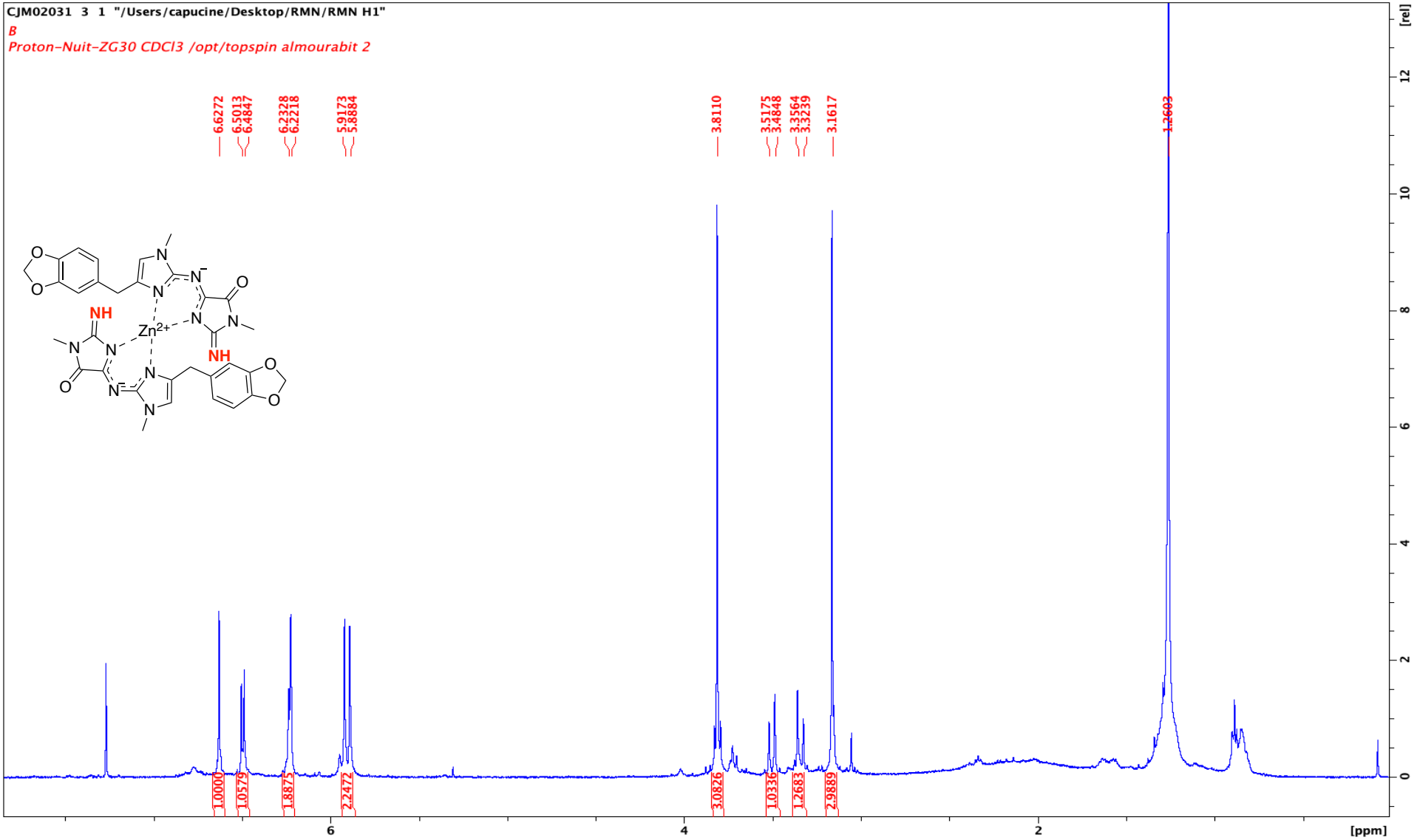


**Figure S42.** $^{13}C$ NMR spectrum of synthetic homodimeric (clathridimine)$_2$ $Zn^{2+}$ (**27**) in $CDCl_3$ (125 MHz).

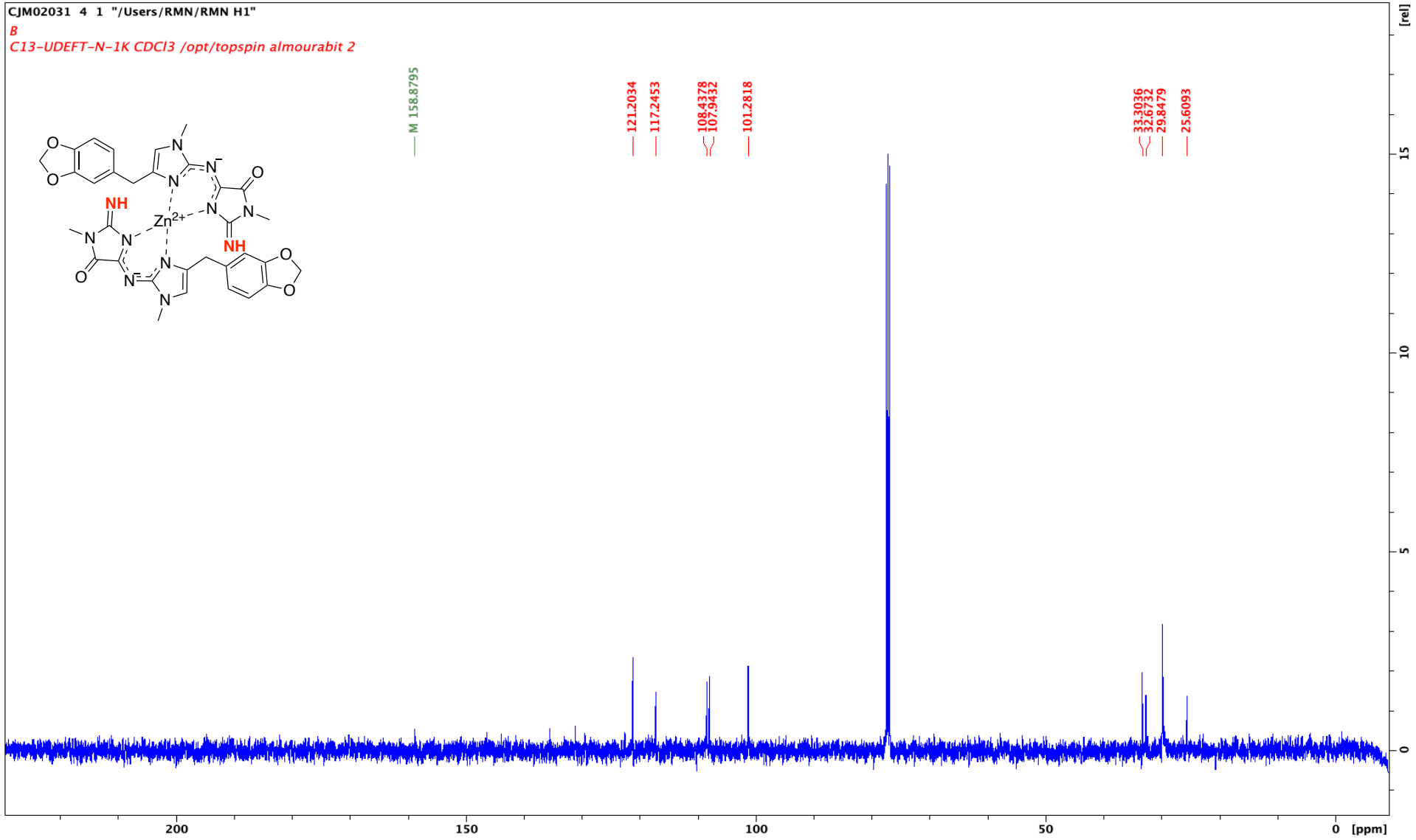


**Figure S43.** $^{1}H$-$^{13}C$ HMBC NMR spectrum of synthetic homodimeric (clathridimine)$_2$ $Zn^{2+}$ (**27**) in $CDCl_3$ (125 MHz).

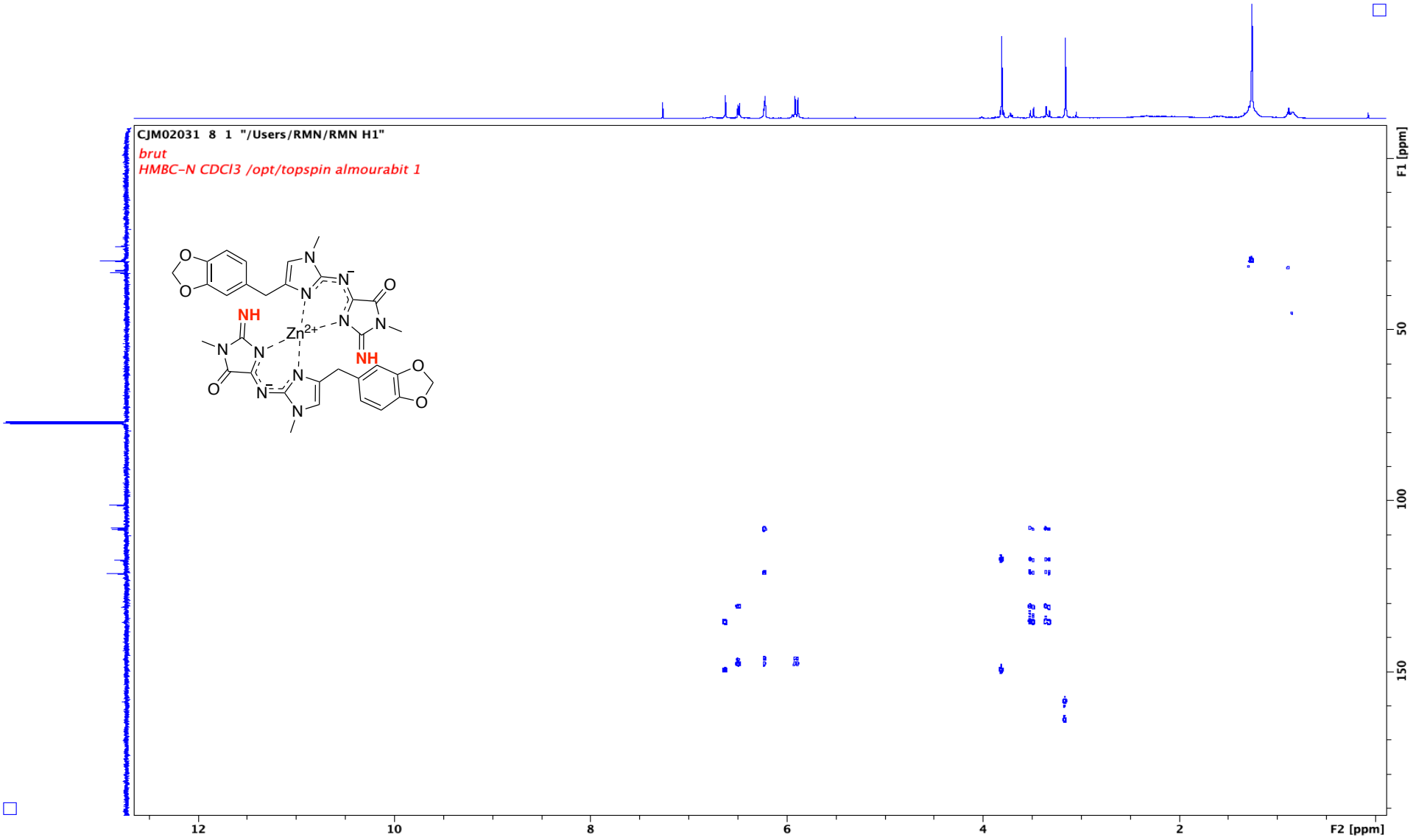
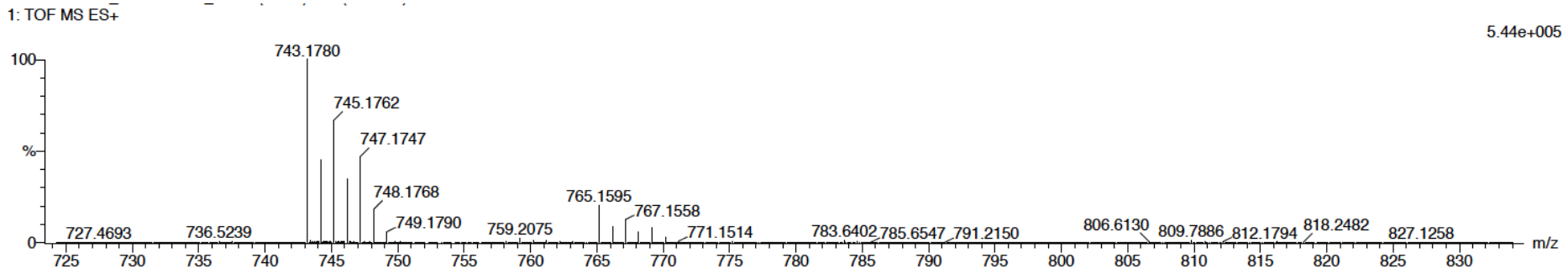


**Figure S44.** HR-ESI mass spectrum of the synthetic homodimeric (clathridimine)$_2$ $Zn^{2+}$ (**27**).




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Minimum: | | | | -1.5 | | | |
| Maximum: | | 5.0 | 5.0 | 100.0 | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | i-FIT (Norm) | Formula |
| 743.1780 | 743.1781 | -0.1 | -0.1 | 23.5 | 2112.7 | 0.4 | C32 H31 N12 O6 Zn |
| | 743.1768 | 1.2 | 1.6 | 18.5 | 2114.3 | 1.9 | C31 H35 N8 O10 Zn |
| | 743.1808 | -2.8 | -3.8 | 22.5 | 2114.4 | 2.0 | C36 H35 N6 O8 Zn |
| | 743.1749 | 3.1 | 4.2 | 31.5 | 2116.4 | 4.0 | C43 H31 N6 O3 Zn |
| | 743.1776 | 0.4 | 0.5 | 30.5 | 2118.5 | 6.2 | C47 H35 O5 Zn |
| | 743.1789 | -0.9 | -1.2 | 35.5 | 2118.5 | 6.2 | C48 H31 N4 O Zn |

**Figure S45:** LC-MS profiles of the synthetic mixture of complexes (blue) and the sponge crude extract (red), indicating the detection of the dimeric complexes including the minor heterodimeric complex **10**.

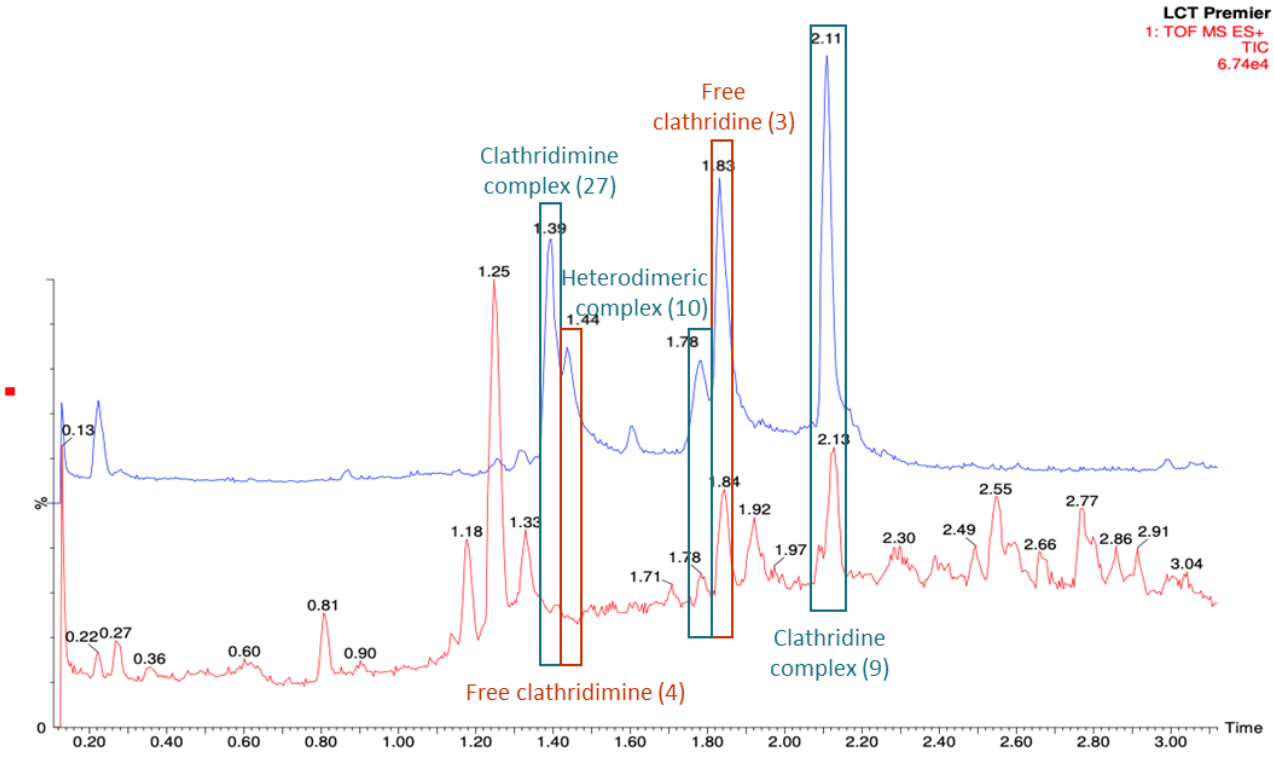



**Figure S46**: Superposition of the 1H NMR spectra of homodimeric (clathridine A)2Zn2+ (**9**) (green), homodimeric (clathridimine)2 Zn2+ (**27**) (red) and heterodimeric (clathridine A-clathridimine) Zn2+ (**10**) (blue).

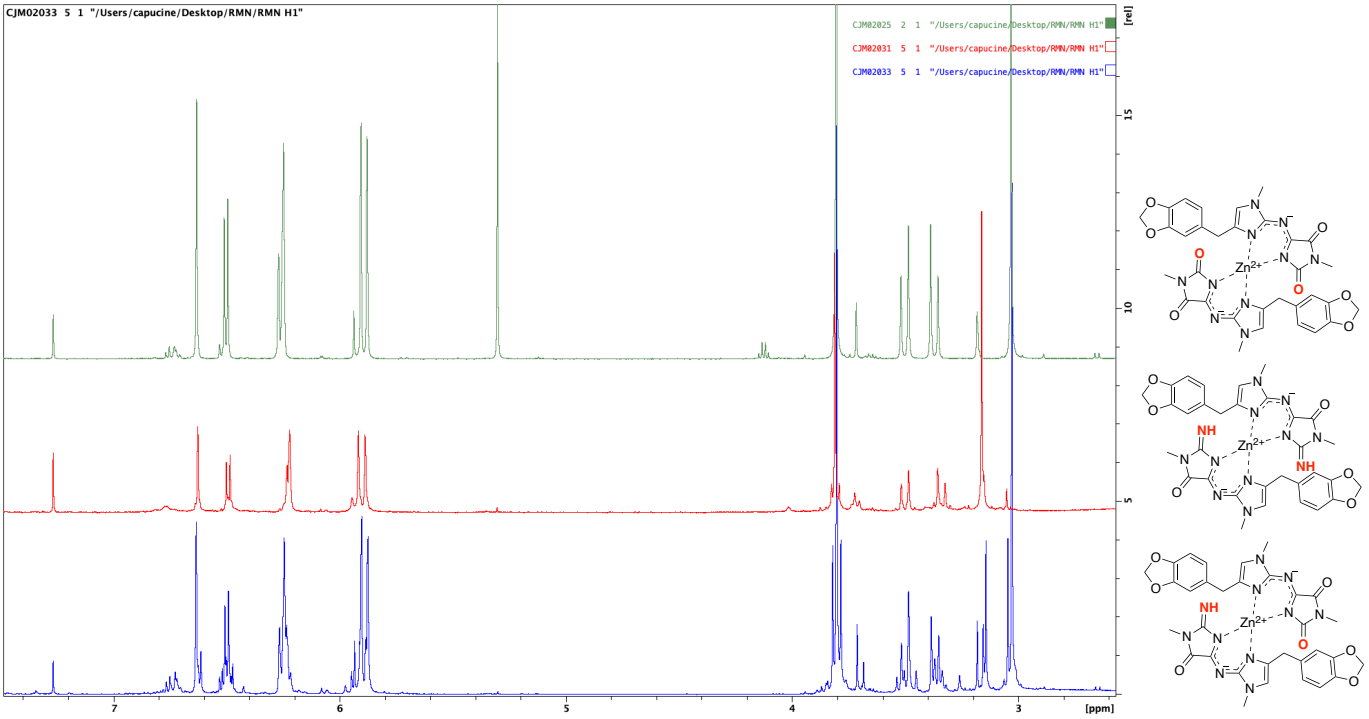
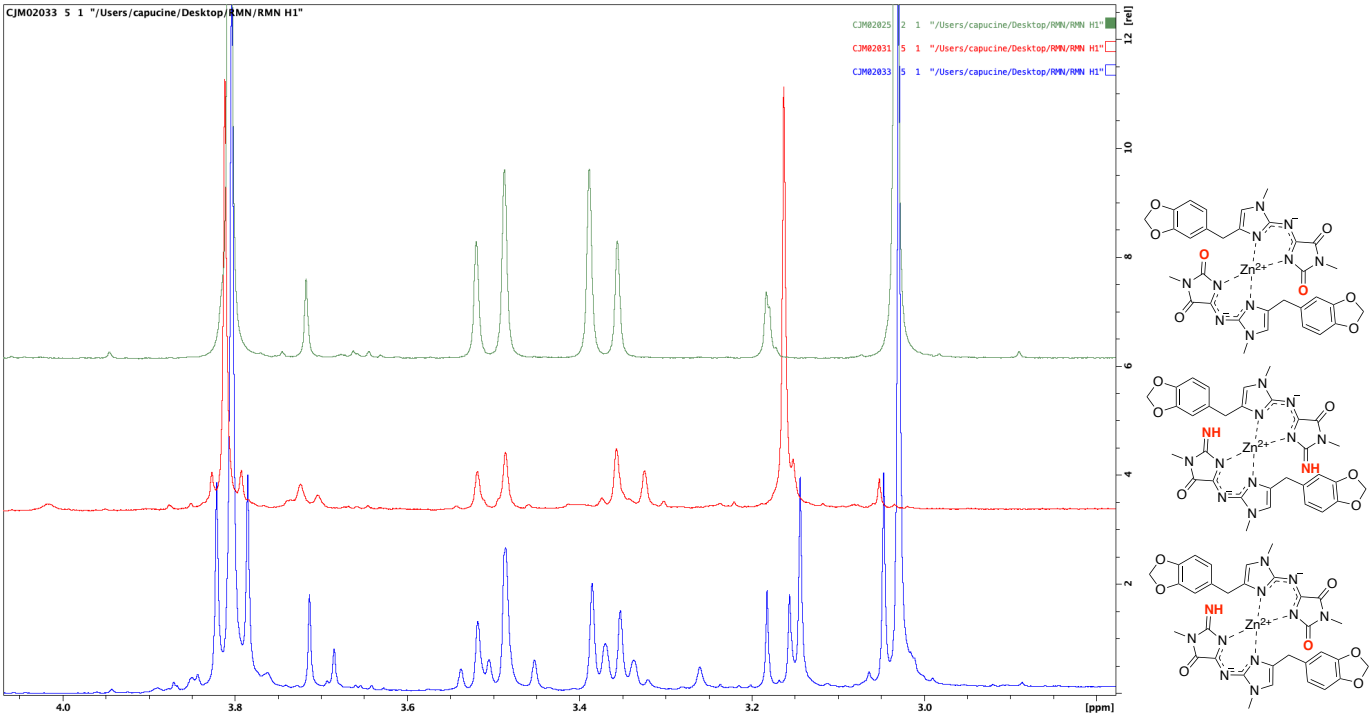


**Figure S47**: Zoom on the superposition of the 1H NMR spectra between 3 and 4 ppm, of homodimeric (clathridine A)2Zn2+ (**9**) (green), homodimeric (clathridimine)2 Zn2+ (**27**) (red) and heterodimeric (clathridine A-clathridimine) Zn2+ (**10**) (blue).



## Single Crystal X-ray Crystallography (SC-XRD)

**Crystal structure determination of homodimeric (clathridine A)$_2$ Zn$^{2+}$ (9).**

***Crystal data for homodimeric (clathridine A)$_2$ Zn$^{2+}$ (9)*:** $C_{32}H_{28}N_{10}O_8Zn[+1H_2O]$ (M =764.03 g/mol): triclinic, space group P-1 (no. 2), a = 9.4098(3) Å, b = 9.7775(3) Å, c = 21.1162(8) Å, $\alpha$ = 78.633(3)°, $\beta$ = 87.210(3)°, $\gamma$ = 63.813(3)°, V = 1707.55 (11) Å$^3$, Z = 2, T = 293.00 K, $\mu$ (Mo K$\alpha$) = 0.789 mm$^{-1}$, Dcalc = 1.486 g/cm$^3$, 32850 reflections measured (5.058° ≤ 2$\Theta$ ≤ 52.744°), 6964 unique ($R_{int}$ = 0.0385, $R_{sigma}$ = 0.0304) which were used in all calculations. The final $R_1$ was 0.0337 (I > 2$\sigma$(I)) and $wR_2$ was 0.0885 (all data).

**Experimental**

Crystals of compound **9** were obtained by slow evaporation of saturated DCM.

Single crystals suitable to X-ray diffraction structural analyses were transferred upon a microscope slide and one of them selected under a binocular, mounted on a nylon loop and fixed with Paratone® oil. Then, X-ray diffraction and crystallographic data were collected at room temperature using redundant ω scans on a Rigaku XtaLabPro single-crystal diffractometer using microfocus Mo K$\alpha$ radiation and a HPAD PILATUS3 R 200K detector. CrysAlisPro 1.171.43.56a [1] was employed for the data processing, with SCALE3 ABSPACK scaling algorithm implemented for the empirical absorption correction using spherical harmonics and numerical absorption correction based on gaussian integration over a multifaceted crystal model.

Using Olex2 [2], the structures was readily solved by intrinsic phasing methods (SHELXT [3]), and by full-matrix least-squares methods on F$^2$ using SHELXL [4]. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms, most of them were identified in difference maps and were treated as riding on their parent atoms.

Examination of this refined structure using the SQUEEZE procedure in PLATON [5] highlighted a void of volume of 177 Å$^3$ around the position 0 0 0.5 corresponding to crystallographic inversion centre. This void was filled by particularly disordered solvent whose contribution (calculated electron count of 17 electrons per void, *i.e. ca* one water molecule that could not be modelled properly) to the structure amplitudes was removed. Therefore, the likely half water molecule present in the asymmetric unit of the crystal was not included in the given chemical formula and other crystal data.

The molecular graphics presented here were computed with Mercury 2023.2.0 [6].

Crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (the deposition number is 2299450). Copies of the data can be obtained free of charge from the CCDC at www.ccdc.cam.ac.uk.

**Citations**


[1] Rigaku OD (2018). CrysAlis PRO. Rigaku Oxford Diffraction, Yarnton, Oxfordshire, England.

[2] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.

[3] Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.

[4] Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

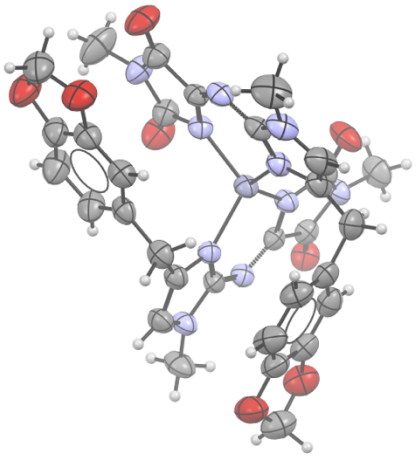
[5] Spek, A. L. (2015). Acta Cryst. C71, 9-18.

[6] Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E., Shields, G. P., Taylor, R., Towler, M. & van de Streek, J. (2006). J. Appl. Cryst.39, 453-457.

**Table 2:** Crystal data and structure refinement

| **Identification code** | | **Compound 9** |
|---|---|---|
| **Empirical Formula** | | $C_{32}H_{28}N_{10}O_8Zn$, 1[$H_2O$] |
| **Formula Weight** | | 764.03 |
| **Crystal Color, Habit** | | [light yellow, Prism] |
| **Crystal Dimensions (mm³)** | | 0.24 × 0.2 × 0.05 |
| **Crystal System** | | triclinic |
| **Space Group** | | *P-1* |
| **Unit cell dimensions** | *a* (Å) | 9.4098(3) |
| | *b* (Å) | 9.7775(3) |
| | *c* (Å) | 21.1162(8) |
| | $\alpha$ (°) | 78.633(3) |
| | $\beta$ (°) | 87.210(3) |
| | $\gamma$ (°) | 63.813(3) |
| **Volume (Å³)** | | 1707.55(11) |
| **Z value** | | 2 |
| **Calculated density $D_{calc.}$ (g.cm$^{-3}$)** | | 1.486 |
| **Absorption coefficient μ (mm$^{-1}$)** | | 0.789 |
| **F (000)** | | 788.0 |
| **Diffractometer** | | Rigaku XtaLAB PRO |
| **Radiation type** | | Mo $K_{\sim}$ |
| **Wavelength (Å)** | | 0.71073 |
| **Voltage, Current (kV, mA)** | | (50, 0.6) |
| ***T* (K)** | | 293.00 |
| **2θ range for data collection (°)** | | 5.058 to 52.744 |
| **Limiting indices** | | -11 ≤ h ≤ 11,<br>-11 ≤ k ≤ 12,<br>-26 ≤ l ≤ 26 |
| **Reflections collected/unique** | | 32850/6964 |
| **Completeness to θ full (%)** | | 99.8 |
| **$R_{int}$** | | 0.0385 |
| **Absorption correction** | | Gaussian |
| **Refinement method** | | Full-matrix least-squares on $F^2$ |
| **Data/restraints/parameters** | | 6964/0/472 |
| **Goodness-of-fit on $F^2$** | | 1.047 |
| **Final R indices [*I*>2σ(*I*)]** | $R_1$<br>$wR_2$ | 0.0337<br>0.0846 |
| **R indices (all data)** | $R_1$<br>$wR_2$ | 0.0424<br>0.0885 |
| **Largest Δ peak and hole (e.Å$^{-3}$)** | | 0.26/-0.23 |
| **CCDC Deposit Number** | | 2299450 |

**Figure S48**: (left) ORTEP drawing of homodimeric (clathridine A)$_2$ $Zn^{2+}$ (**9**) with thermal ellipsoids drawn at the 50% probability level; (right) Labelling scheme of the structure.



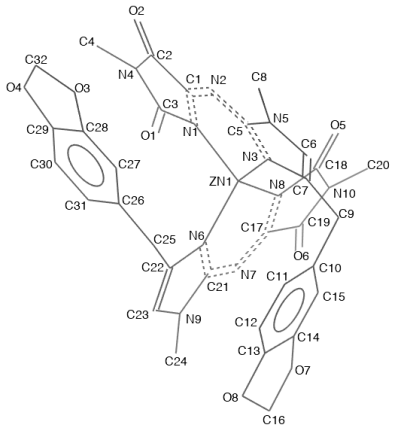


**Figure S49**: Energy diagram of intermediates involved in the hydrolysis reaction with one water molecule.

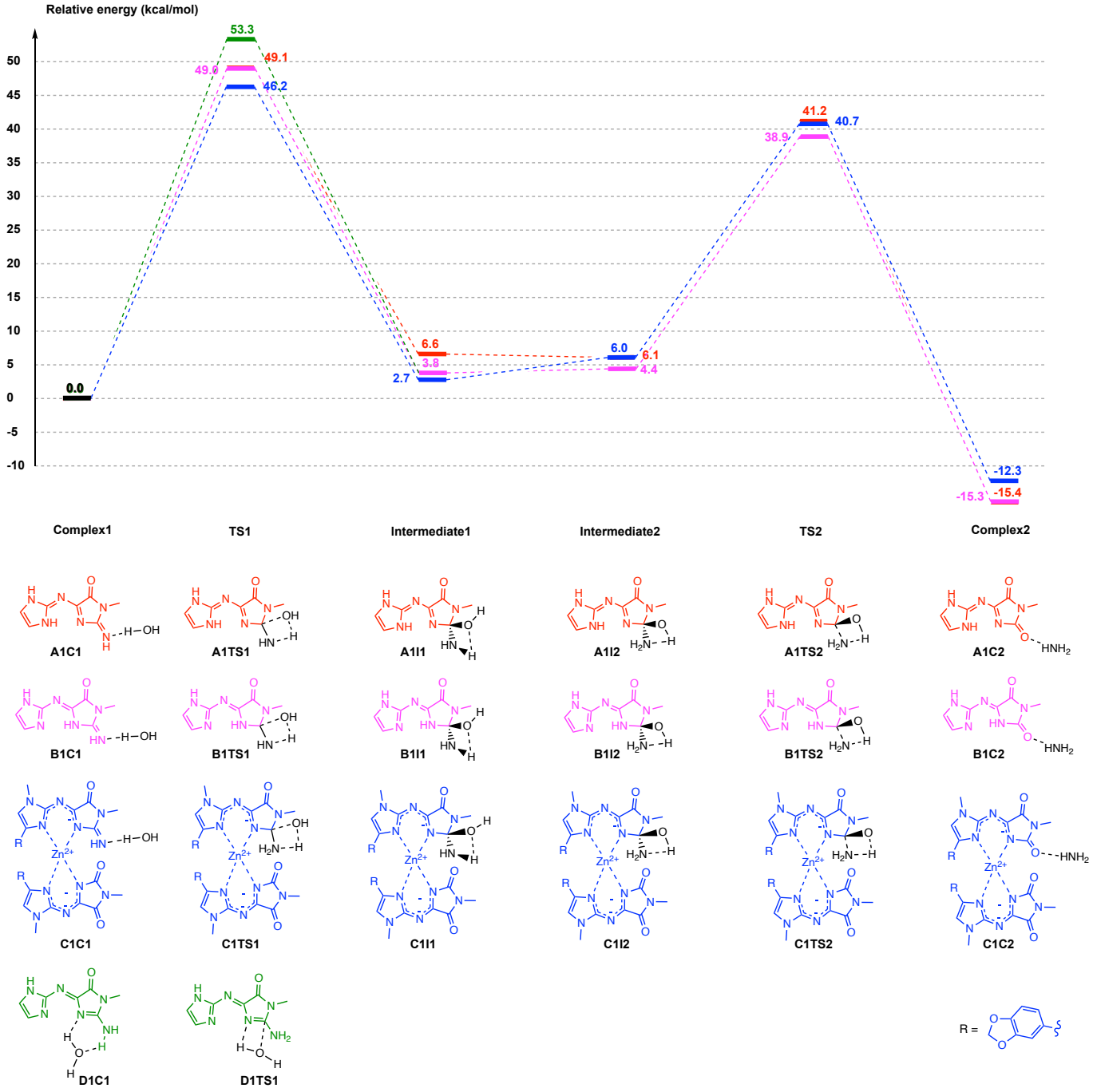


**Figure S50**: Energy diagram of intermediates involved in the hydrolysis reaction considering two water molecules.

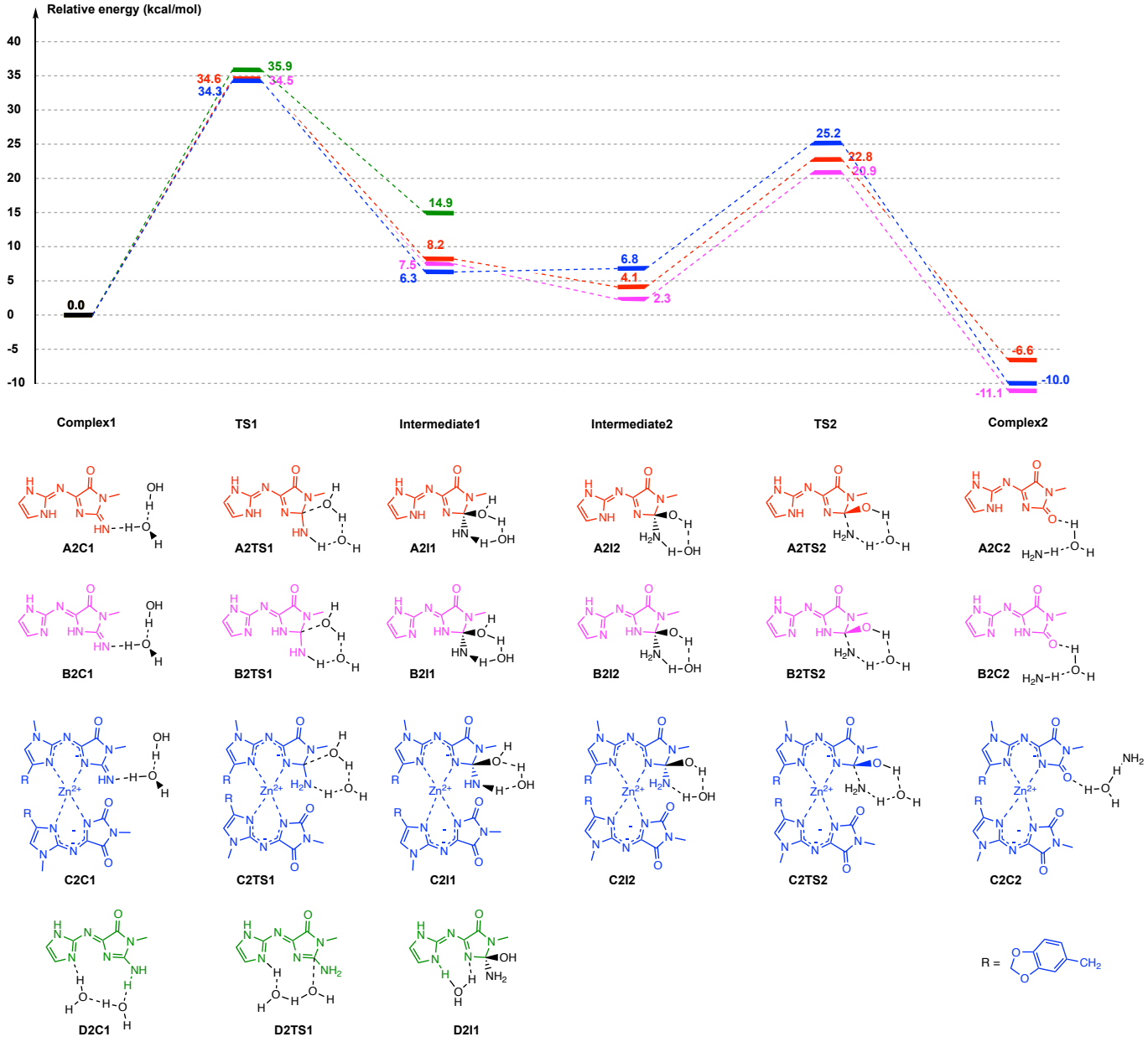



**Figure S50**: mineralization in comparison to Leucettamine B. Alizarin red nodules quantification of the ATDC5 cells micromass at Day 7, Day14 and Day21