Supplementary data

A pair of new enantiomeric hybrid phthalide–adenines with a rare 5-oxa-1-azaspiro[3,4]octane moiety and two pairs of new enantiomeric hybrid paraethyl phenol–adenines from *Ligusticum chuanxiong*

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[1] Both authors contributed equally to this work.

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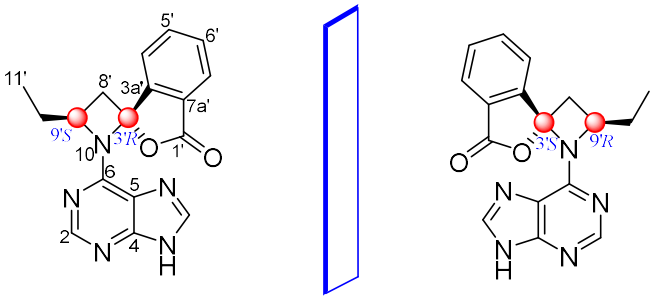
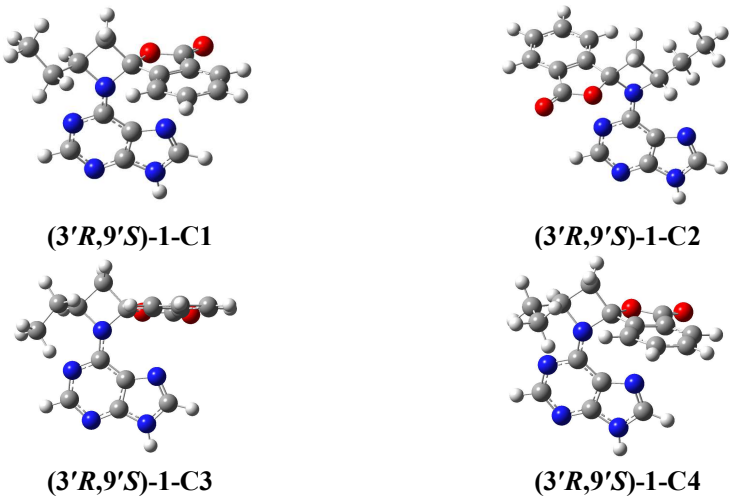
ECD calculation of compound 1.



(3′*R*,9′*S*)-**1** (3′*S*,9′*R*)-**1**

Conformation searches based on molecular mechanics with MMFF94s force field were performed for (3′*R*,9′*S*)-**1** and gave four conformers (Boltzmann distribution ≥ 1%) [1]. The selected conformers were optimized using DFT at the B3LYP/6-31G (d) level in vacuum with the Gaussian 16 program (Table S1) [2]. The B3LYP/6-31G (d)-optimized conformers (Boltzmann distribution ≥ 1%) were then reoptimized at the *ω*B97XD/DGDZVP level in acetonitrile. ECD computations for the *ω*B97XD/DGDZVP-optimized conformers (Fig. S1) were carried out at the CAM-B3LYP/DGDZVP level in acetonitrile [3]. Finally, according to the Boltzmann distribution theory and their relative Gibbs free energy (ΔG), the ECD spectrum for (3′*R*,9′*S*)-**1** was generated using SpecDis 1.71 with σ = 0.26 eV and a UV shift of −3 nm [4]. The corresponding theoretical ECD spectrum of (3′*S*,9′*R*)-**1** was depicted by inverting that of (3′*R*,9′*S*)-**1**.



(3′*R*,9′*S*)-1-C1 **(3′*R*,9′*S*)-1-C2**

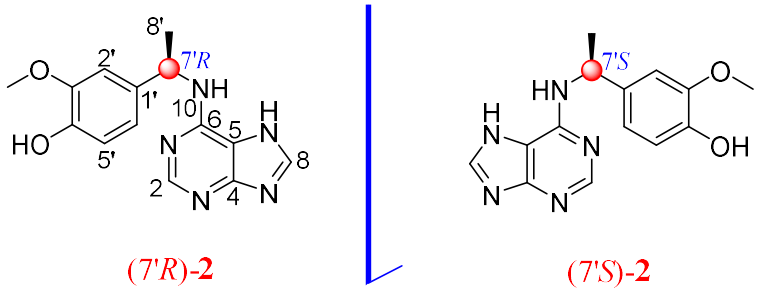
(3′*R*,9′*S*)-1-C3 **(3′*R*,9′*S*)-1-C4**

Fig. S1. *ω*B97XD/DGDZVP optimized four conformers of (3′*R*,9′*S*)-**1** (Boltzmann distribution ≥ 1%).

Table S1. Energy analysis for the conformers of (3′*R*,9′*S*)-**1**.

Conf.	MMFF energy	B3LYP/6-31G(d) Gibbs free energy (298.15 K)			ωB97XD/DGDZVP Gibbs free energy (298.15 K)		
	ΔE (Kcal/mol)	G (Hartree)	ΔG (Kcal/mol)	Boltzmann distribution	G (Hartree)	ΔG (Kcal/mol)	Boltzmann distribution
(3′*R*,9′*S*)-1-C1	0.00	-1080.809793	0.0000	0.379	-1080.581001	0.0000	0.805
(3′*R*,9′*S*)-1-C2	1.08	-1080.810152	-0.2250	0.554	-1080.579437	0.9810	0.154
(3′*R*,9′*S*)-1-C3	1.51	-1080.807376	1.5170	0.029	-1080.576618	2.7500	0.008
(3′*R*,9′*S*)-1-C4	1.73	-1080.807617	1.3650	0.038	-1080.577995	1.8860	0.033

ECD calculation of compound 2.



Conformation searches based on molecular mechanics with MMFF94s force field were performed for (7′*S*)-**2** and gave four conformers (Boltzmann distribution ≥ 1%) [1]. The selected conformers were optimized using the DFT at B3LYP/6-31G (d) level in vacuum with the Gaussian 16 program (Table S2) [2]. The B3LYP/6-31G (d)-optimized conformers were then reoptimized at the ωB97XD/DGDZVP level in acetonitrile. ECD computations for the ωB97XD/DGDZVP-optimized conformers (Boltzmann distribution ≥ 1%; Fig. S2) were carried out at the CAM-B3LYP/DGDZVP level in acetonitrile [3]. Finally, according to the Boltzmann distribution theory and their relative Gibbs free energy (ΔG), the ECD spectrum for (7′*S*)-**2** was generated using SpecDis 1.71 with σ = 0.25 eV and a UV shift of +15 nm [4]. The corresponding theoretical ECD spectrum of (7′*R*)-**2** was depicted by inverting that of (7′*S*)-**2**.

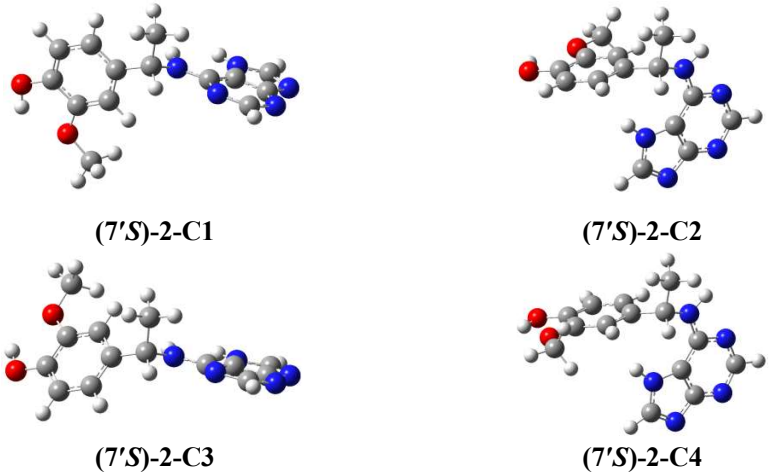
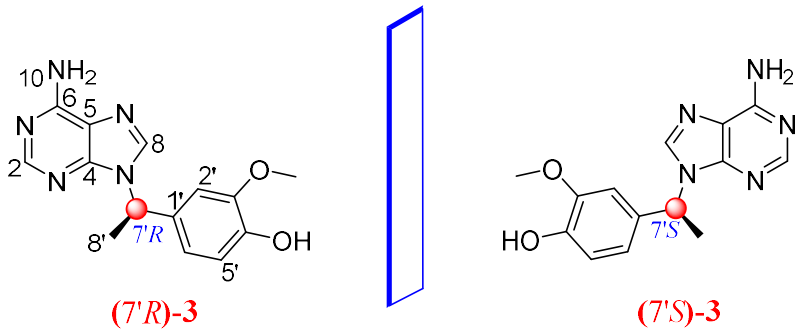


Fig. S2. *ω*B97XD/DGDZVP optimized four conformers of (7′*S*)-**2** (Boltzmann distribution ≥ 1%).

Table S2. Energy analysis for the conformers of (7′*S*)-**2**.

Conf.	MMFF energy	B3LYP/6-31G(d) Gibbs free energy (298.15 K)			*ω*B97XD/DGDZVP Gibbs free energy (298.15 K)		
	ΔE (Kcal/mol)	G (Hartree)	ΔG (Kcal/mol)	Boltzmann distribution	G (Hartree)	ΔG (Kcal/mol)	Boltzmann distribution
(7′*S*)-2-C1	0.00	-966.482995	0.0000	0.057	-966.283448	0.0000	0.021
(7′*S*)-2-C2	0.43	-966.485460	-1.5470	0.777	-966.286636	-2.0010	0.609
(7′*S*)-2-C3	0.67	-966.482153	0.5280	0.023	-966.283946	-0.3120	0.035
(7′*S*)-2-C4	2.02	-966.483856	-0.5400	0.142	-966.286072	-1.6470	0.335

ECD calculation of compound 3.



Conformation searches based on molecular mechanics with MMFF94s force field were performed for (7′*R*)-**3** and gave four conformers (Boltzmann distribution ≥ 1%) [1]. The selected conformers were optimized using DFT at the B3LYP/6-31G (d) level in vacuum with the Gaussian 16 program (Table S3)

[2]. The B3LYP/6-31G (d)-optimized conformers (Boltzmann distribution ≥ 1%) were then reoptimized at the ωB97XD/DGDZVP level in acetonitrile. ECD computations for the ωB97XD/DGDZVP-optimized conformers (Boltzmann distribution ≥1%; Fig. S3) were carried out at the CAM-B3LYP/DGDZVP level in acetonitrile [3]. Finally, according to the Boltzmann distribution theory and their relative Gibbs free energy (ΔG), the ECD spectrum for (7′*R*)-**3** was generated using SpecDis 1.71 with σ = 0.45 eV and a UV shift of +11 nm [4]. The corresponding theoretical ECD spectrum of (7′*S*)-**3** was depicted by inverting that of (7′*R*)-**3**.

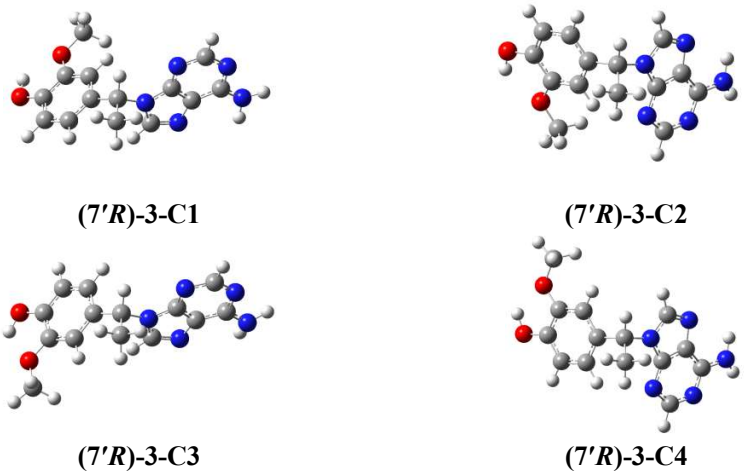


Fig. S3. ωB97XD/DGDZVP optimized four conformers of (7′*R*)-**3** (Boltzmann distribution ≥ 1%).

Table S3. Energy analysis for the conformers of (7′*R*)-**3**.

Conf.	MMFF energy	B3LYP/6-31G(d) Gibbs free energy (298.15 K)			ωB97XD/DGDZVP Gibbs free energy (298.15 K)		
	ΔE (Kcal/mol)	G (Hartree)	ΔG (Kcal/mol)	Boltzmann distribution	G (Hartree)	ΔG (Kcal/mol)	Boltzmann distribution
(7′*R*)-3-C1	0.00	-966.499845	0.0000	0.611	-966.293503	0.0000	0.370
(7′*R*)-3-C2	0.81	-966.498775	0.6710	0.197	-966.292853	0.4080	0.186
(7′*R*)-3-C3	0.82	-966.498629	0.7630	0.168	-966.293566	-0.0400	0.395
(7′*R*)-3-C4	1.98	-966.496804	1.9080	0.024	-966.291597	1.1960	0.049

References

[1] (a) Goto, H.; Osawa, E. Corner flapping: a simple and fast algorithm for exhaustive generation of ring

conformations. *J. Am. Chem. Soc.* 1989, 111, 8950−8951. (b) Goto, H.; Osawa, E. An efficient algorithm for searching low-energy conformers of cyclic and acyclic molecules. *J. Chem. Soc., Perkin Trans. 2* 1993, 2, 187−198.

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[3] Lodewyk, M.W.; Siebert, M.R.; Tantillo, D. J. Computational prediction of ^{1}H and ^{13}C chemical shifts: a useful tool for natural product, mechanistic, and synthetic organic chemistry. *Chem. Rev.* 2012, 112, 1839-1862..

[4] Grimblat, N.; Zanardi, M.M.; Sarotti, A.M. Beyond DP4: an improved probability for the stereochemical assignment of isomeric compounds using quantum chemical calculations of NMR shifts. *J. Org. Chem.* 2015, 80, 12526-12534.

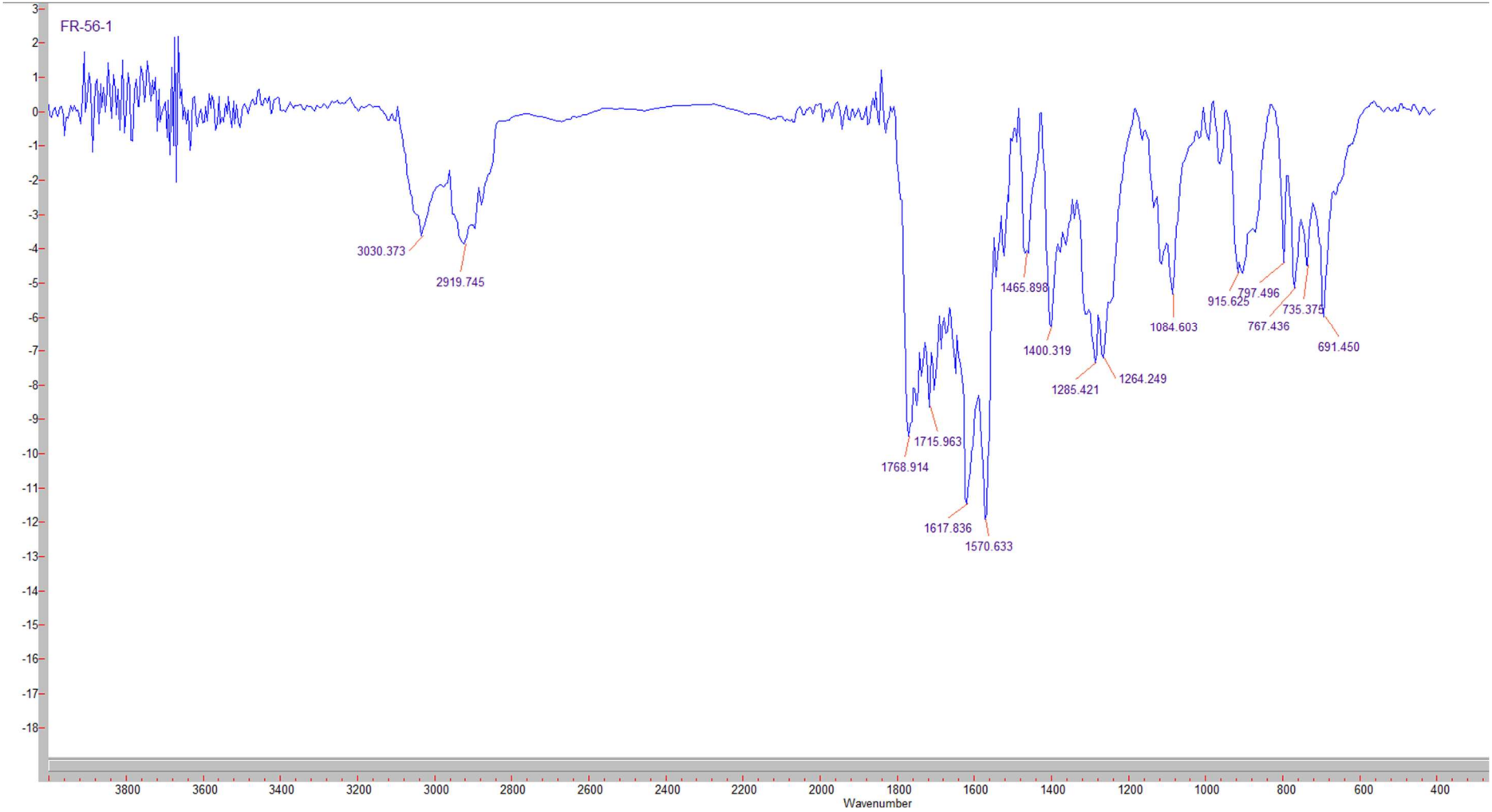

Fig. S4. The IR spectrum of compound **1**.

Single Mass Analysis
Tolerance = 0.5 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
585 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O	Na
344.1126	344.1123	0.3	0.9	12.5	C17 H15 N5 O2 Na	260.3	n/a	n/a	17	15	5	2	1

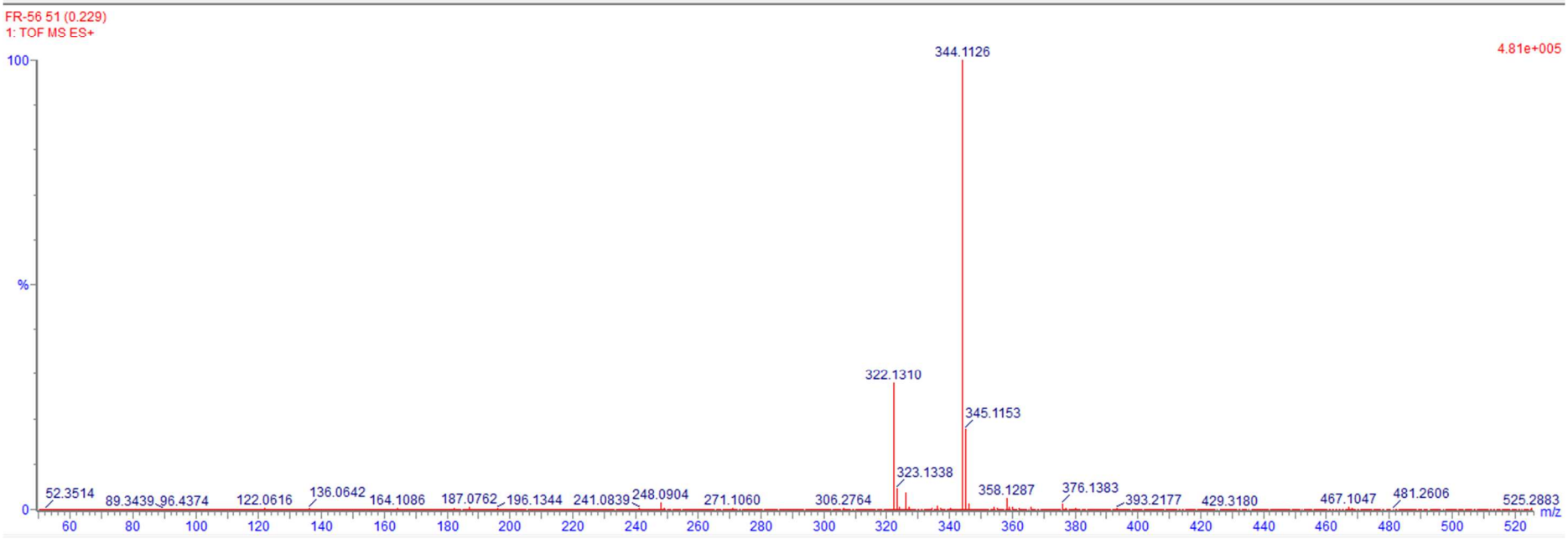

Fig. S5. The (+)-HR-ESI-MS spectroscopic data of compound **1**.

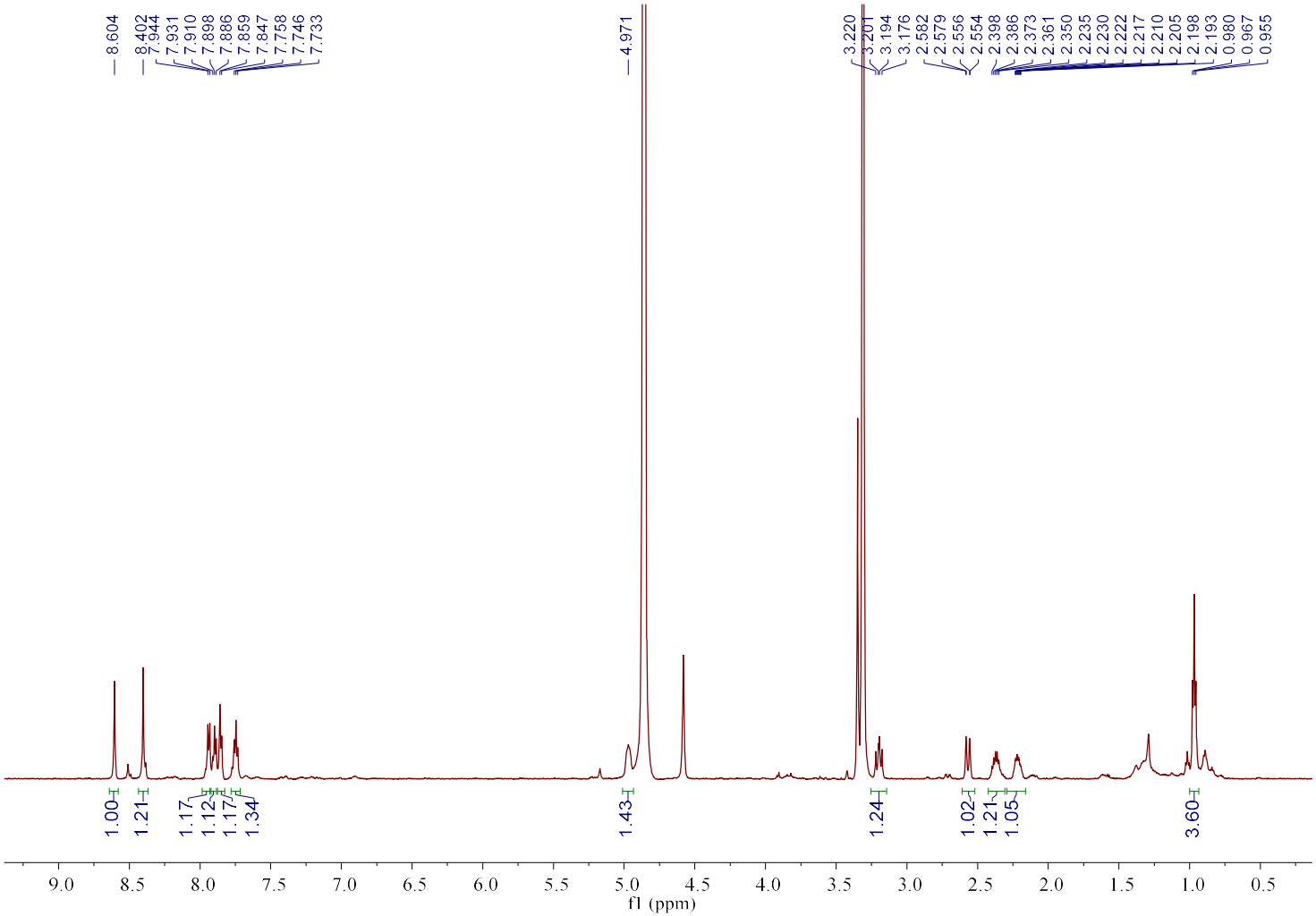

Fig. S6. The ^{1}H NMR spectrum of compound **1** in CD_3OD.

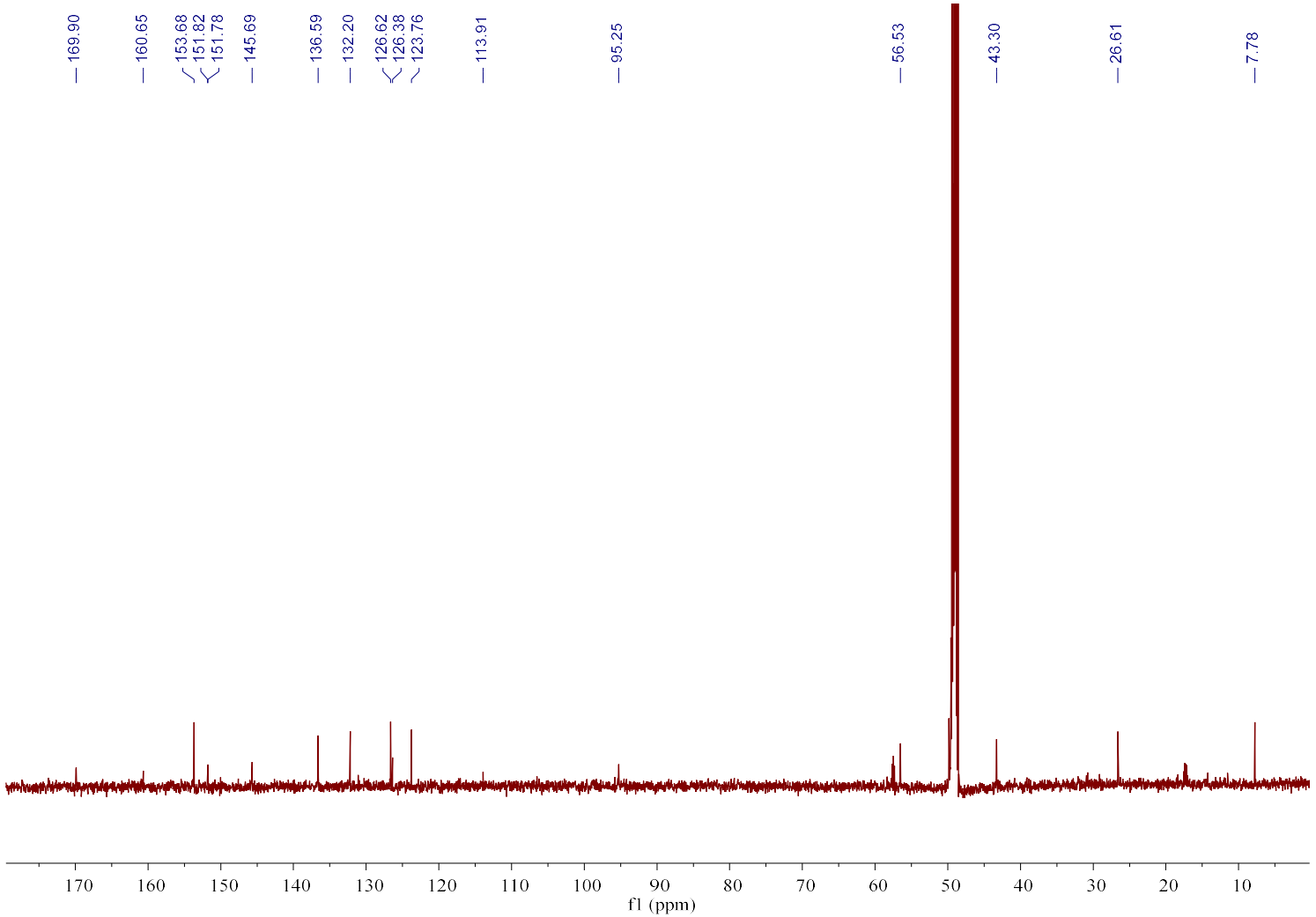

Fig. S7. The ^{13}C NMR spectrum of compound **1** in CD_3OD.

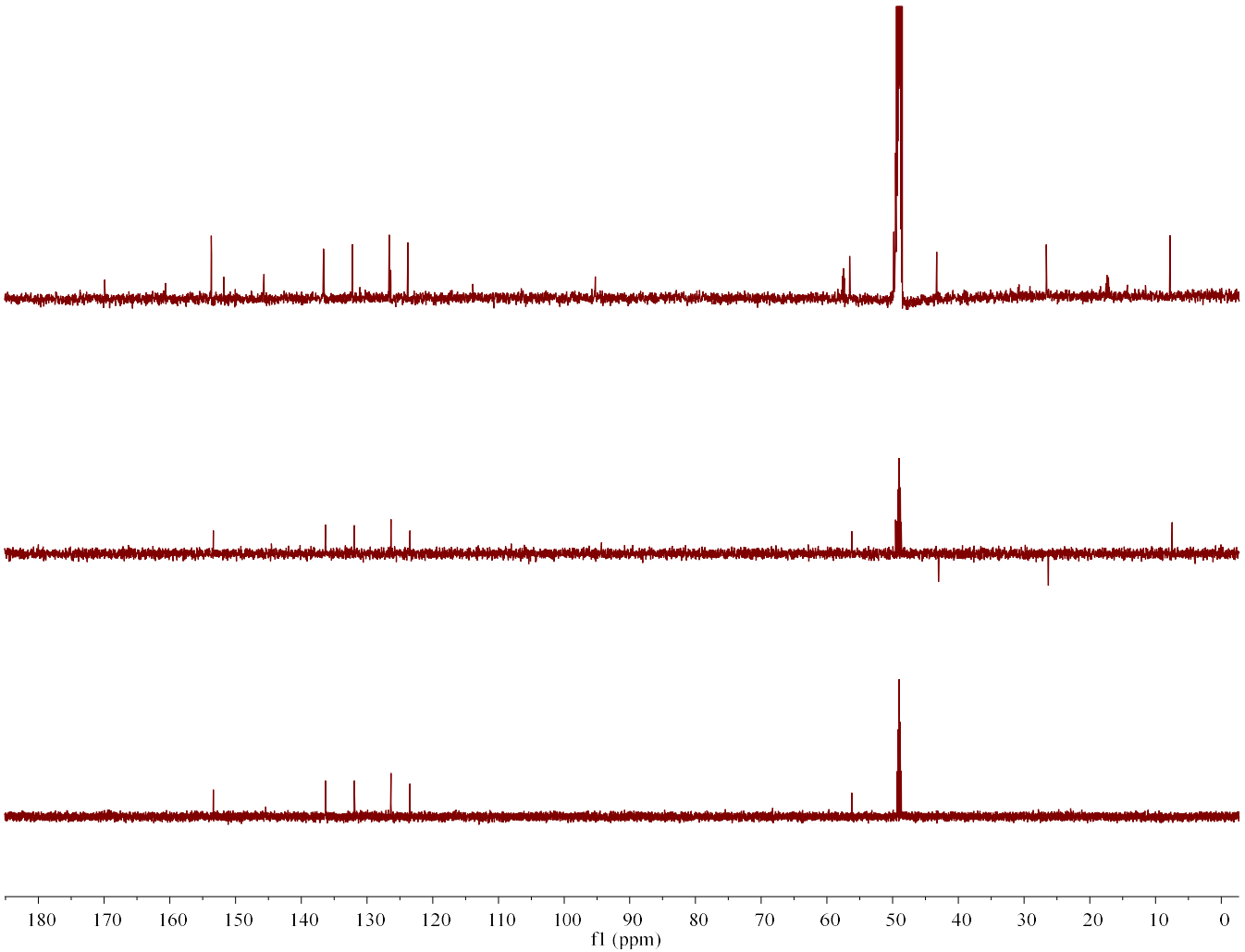

Fig. S8. The DEPT spectrum of compound **1** in CD_3OD.

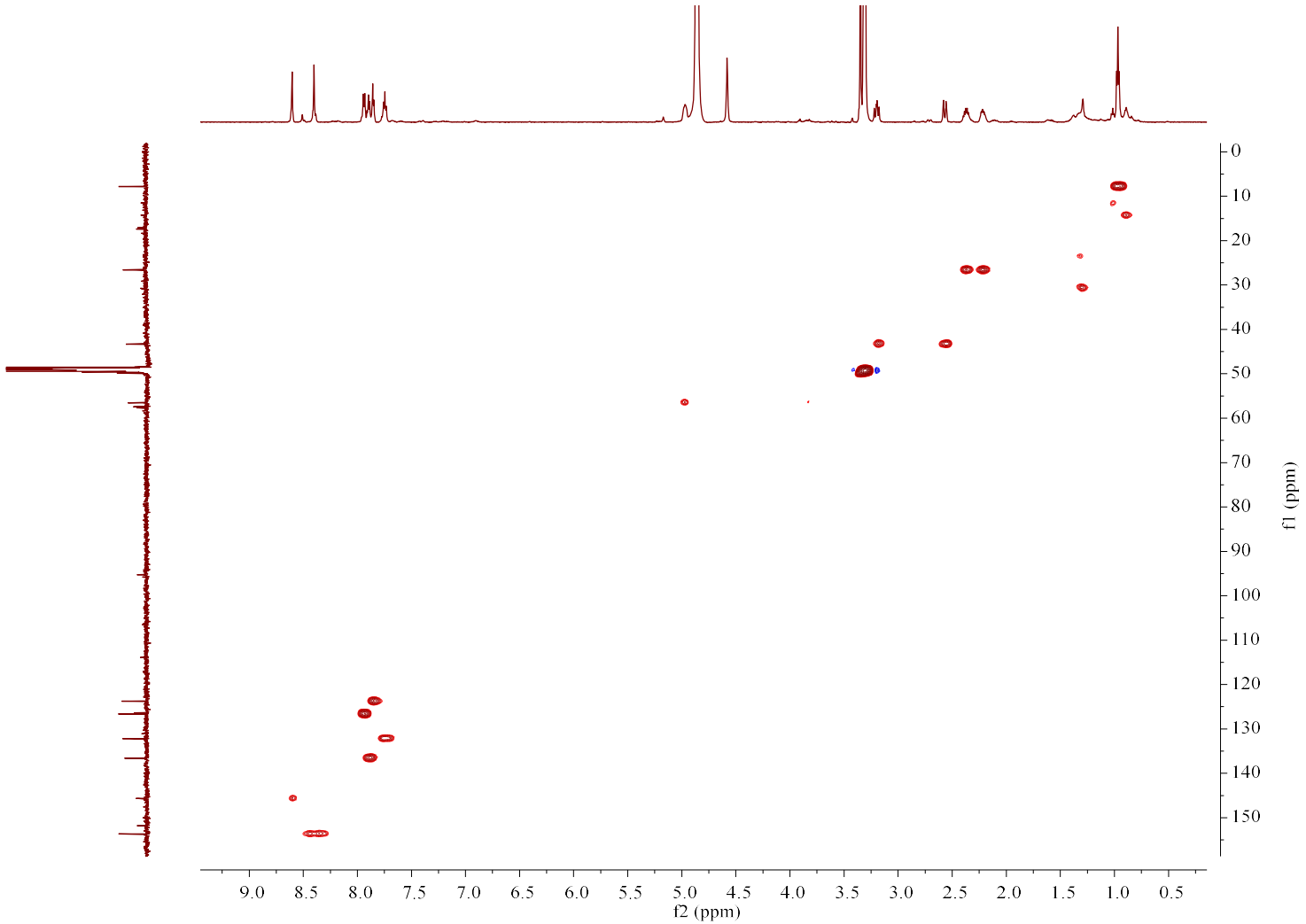

Fig. S9. The HSQC spectrum of compound **1** in CD_3OD.

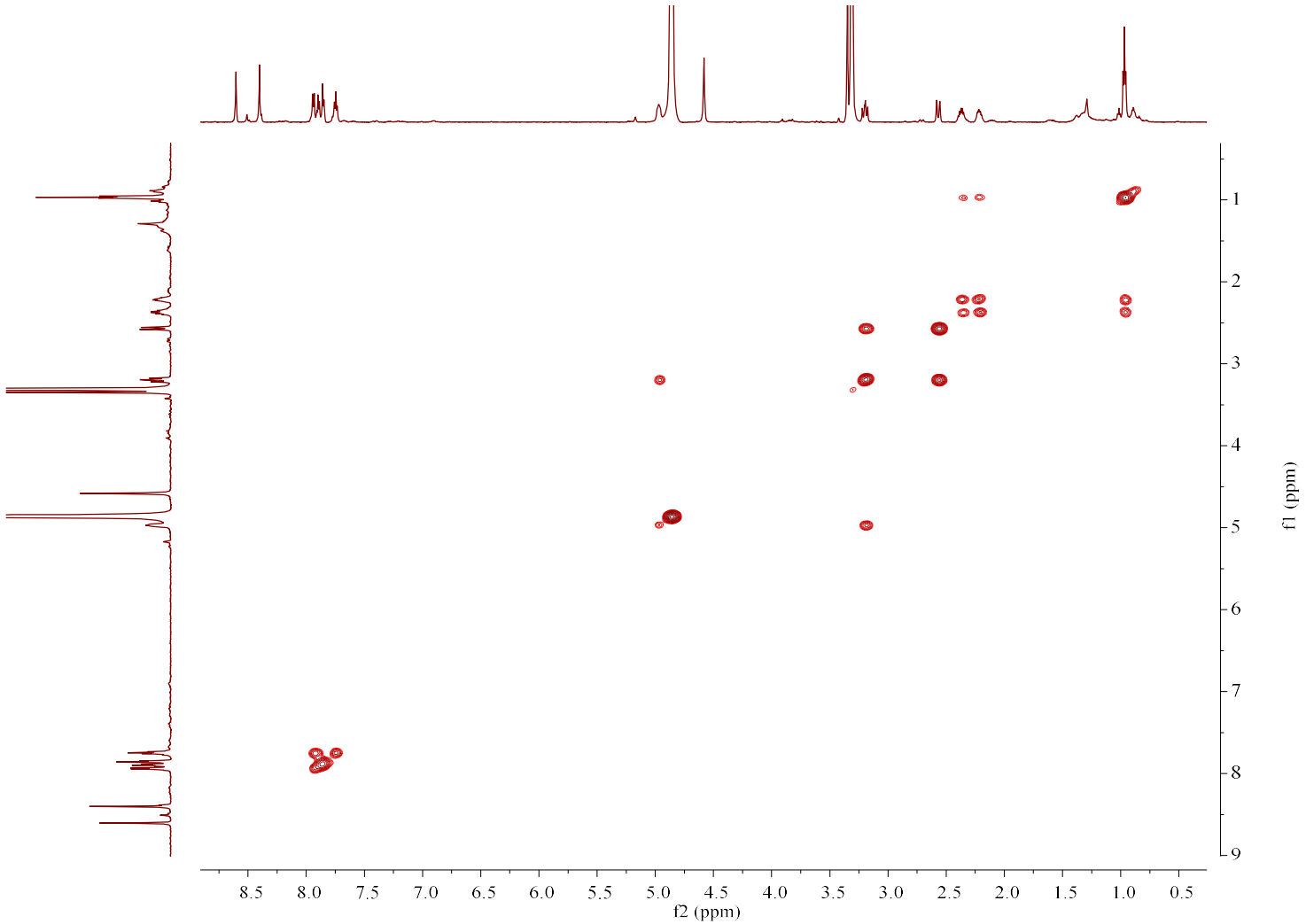

Fig. S10. The ^{1}H-^{1}H COSY spectrum of compound **1** in CD_3OD.

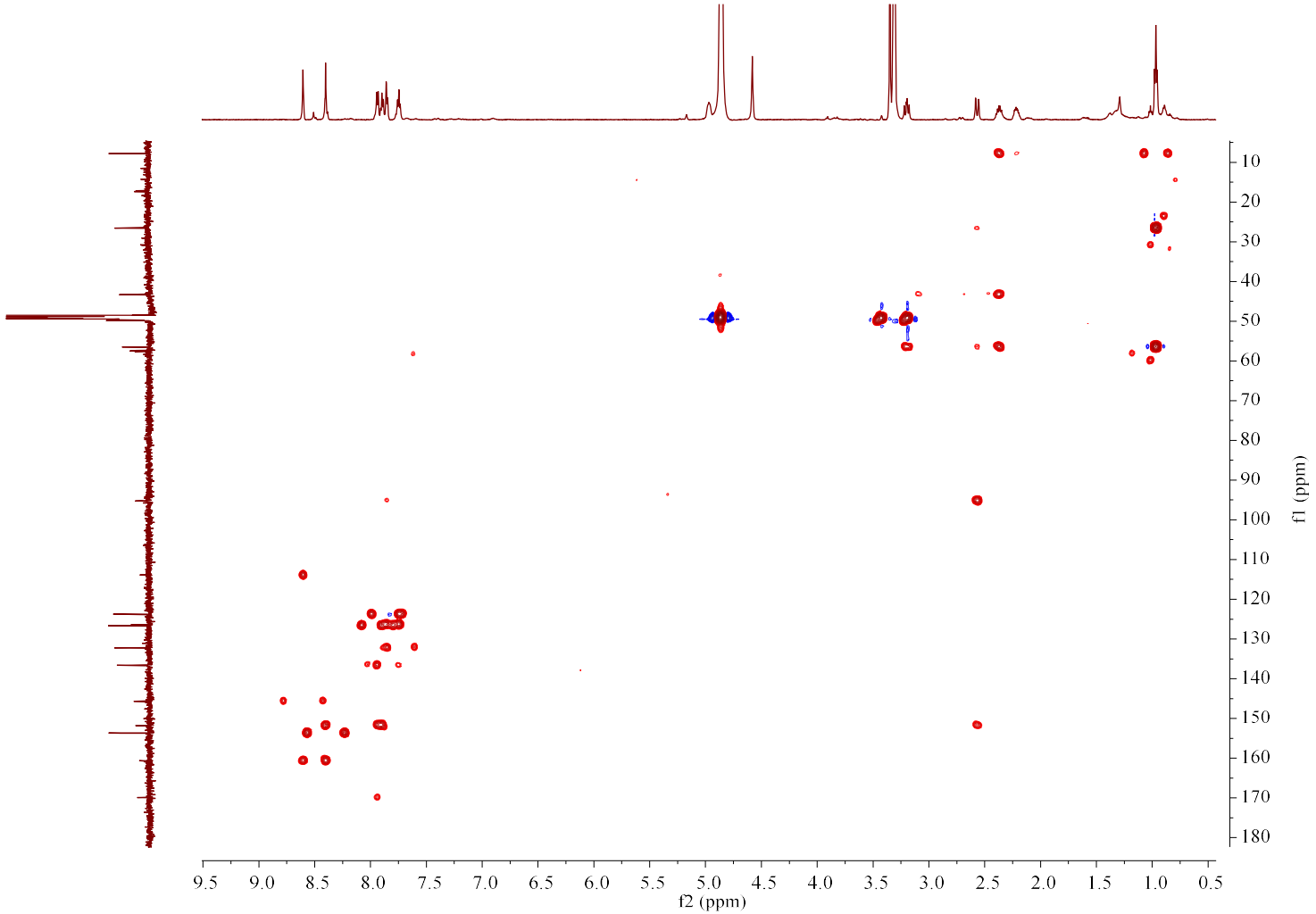

Fig. S11. The HMBC spectrum of compound **1** in CD_3OD.

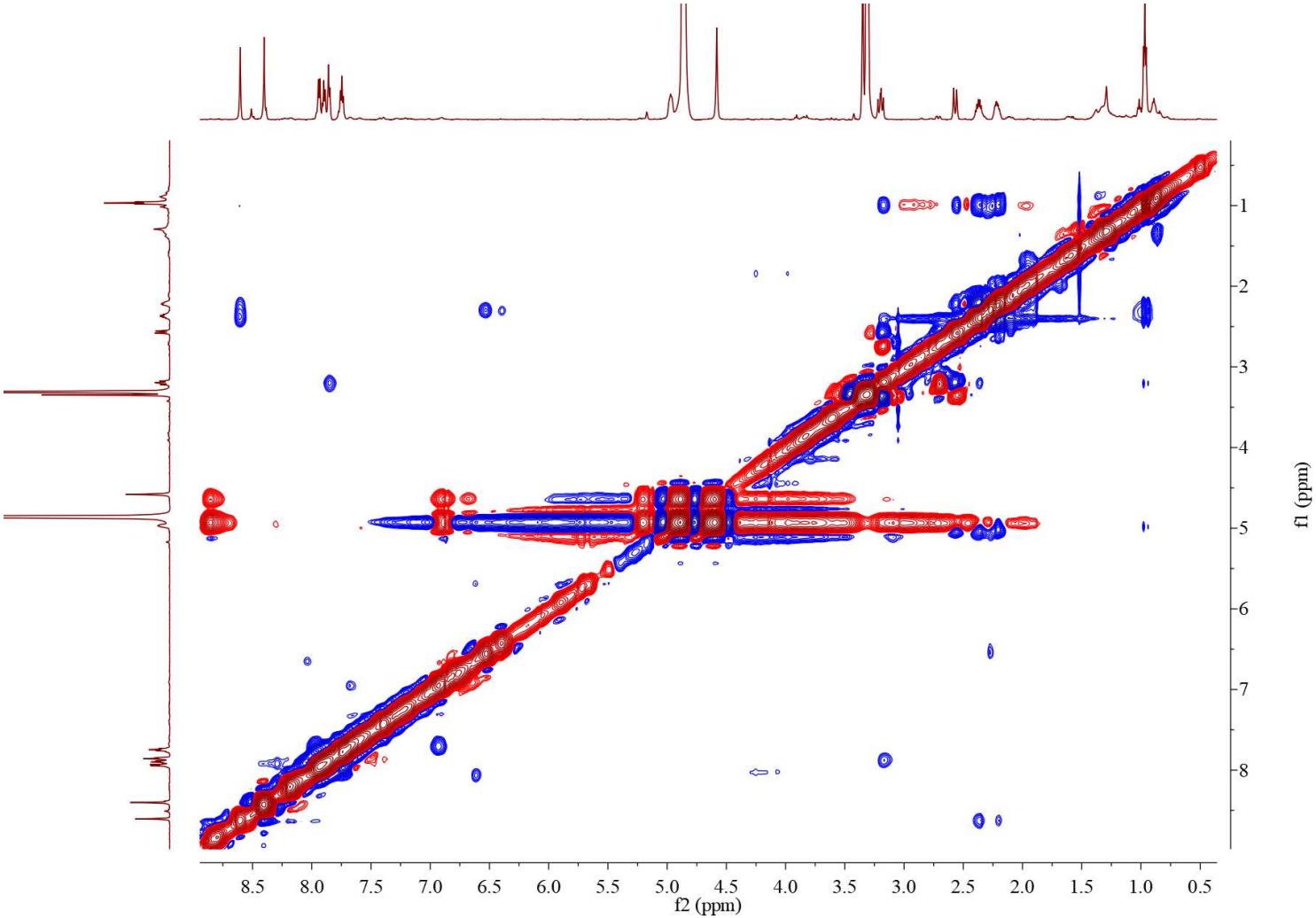

Fig. S12. The NOESY spectrum of compound **1** in CD_3OD.

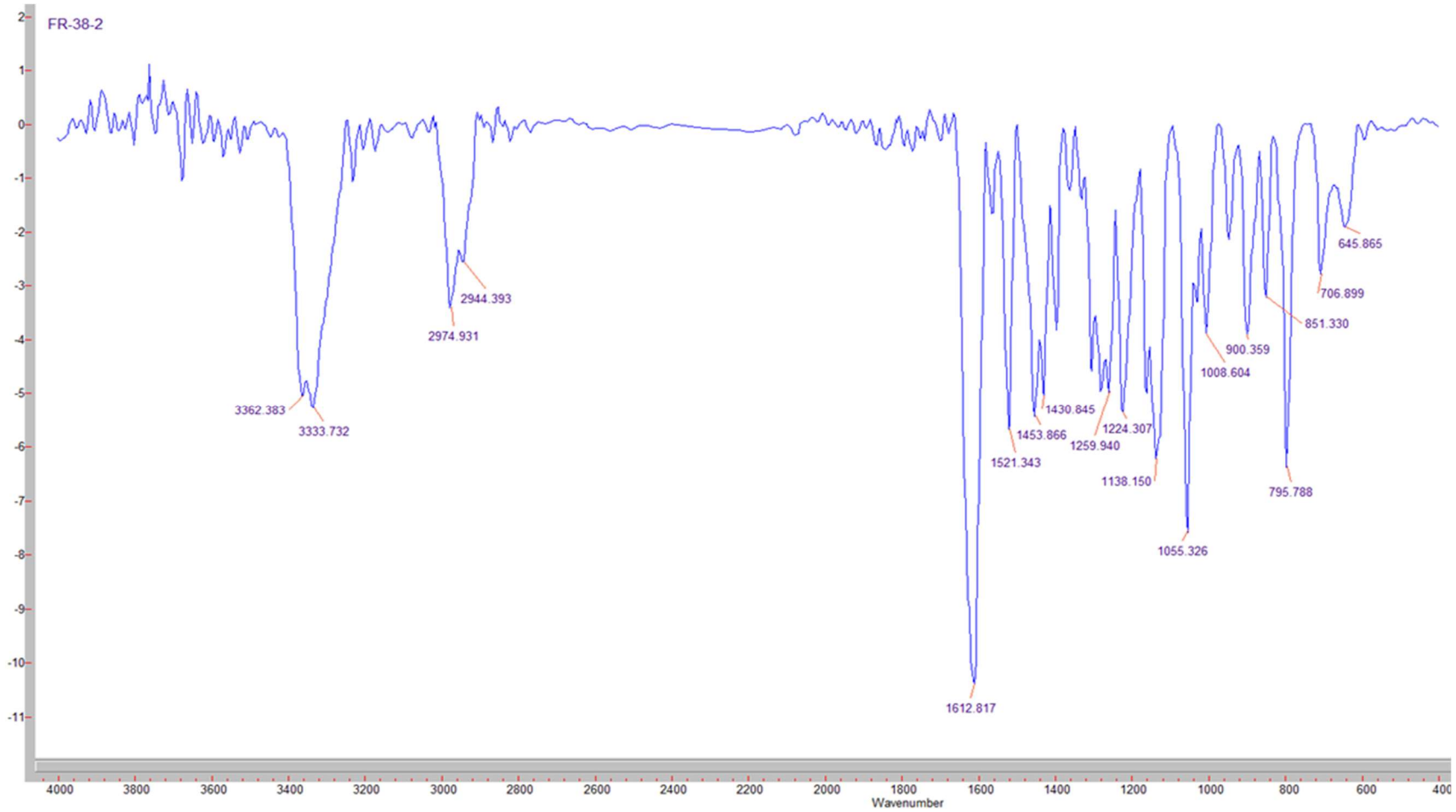

Fig. S13. The IR spectrum of compound **2**.

Single Mass Analysis
Tolerance = 0.5 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
369 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O	Na
308.1127	308.1123	0.4	1.3	9.5	C14 H15 N5 O2 Na	26.8	n/a	n/a	14	15	5	2	1

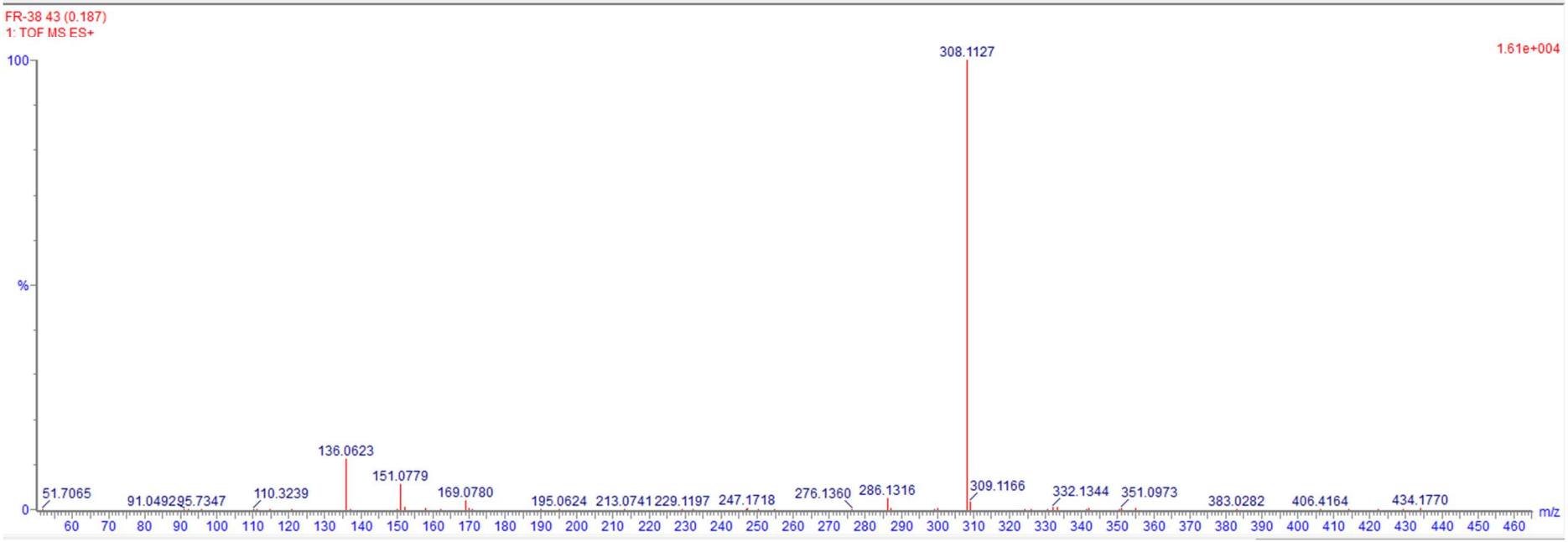

Fig. S14. The (+)-HR-ESI-MS spectroscopic data of compound **2**.

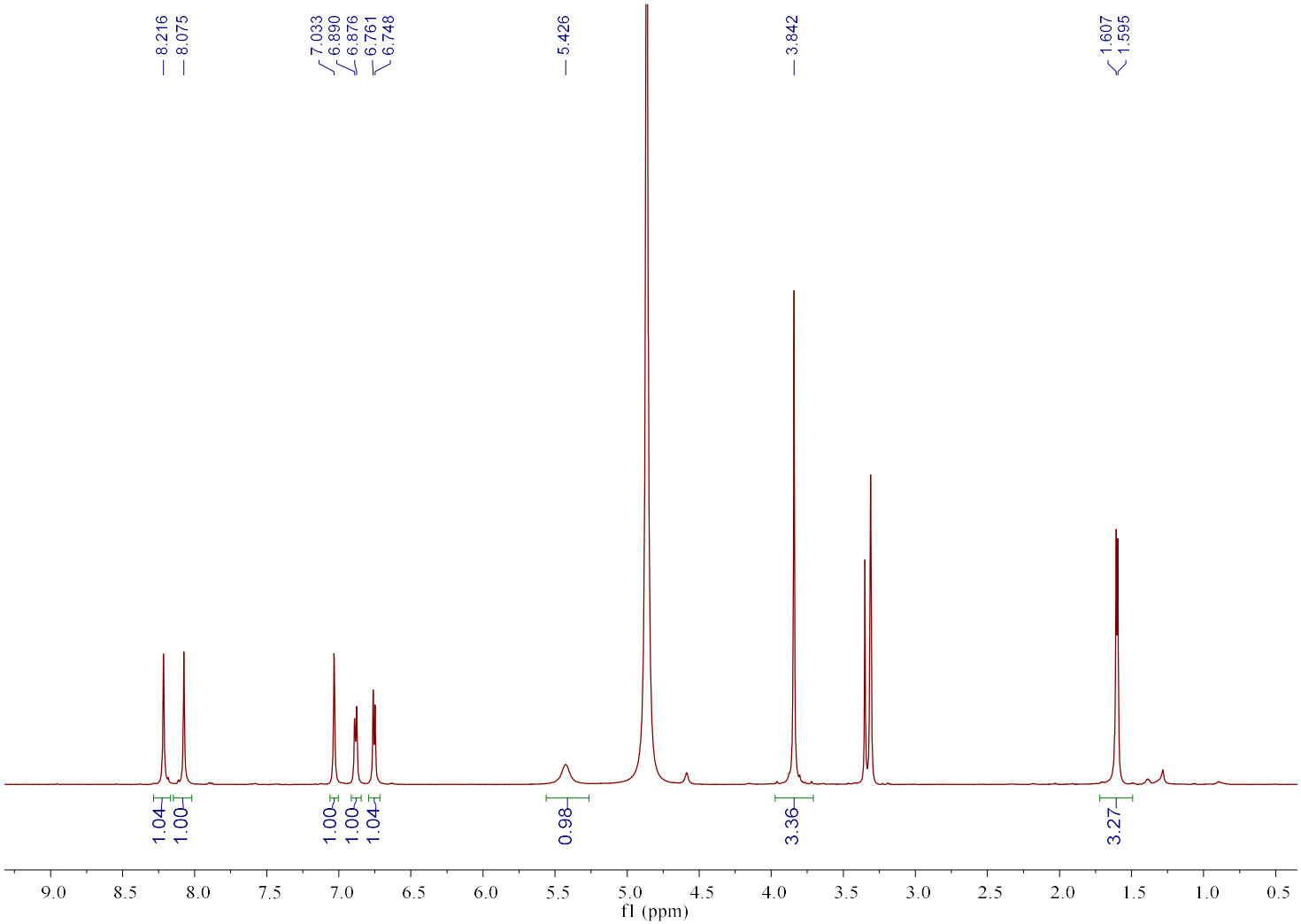

Fig. S15. The ^{1}H NMR spectrum of compound **2** in CD_3OD.

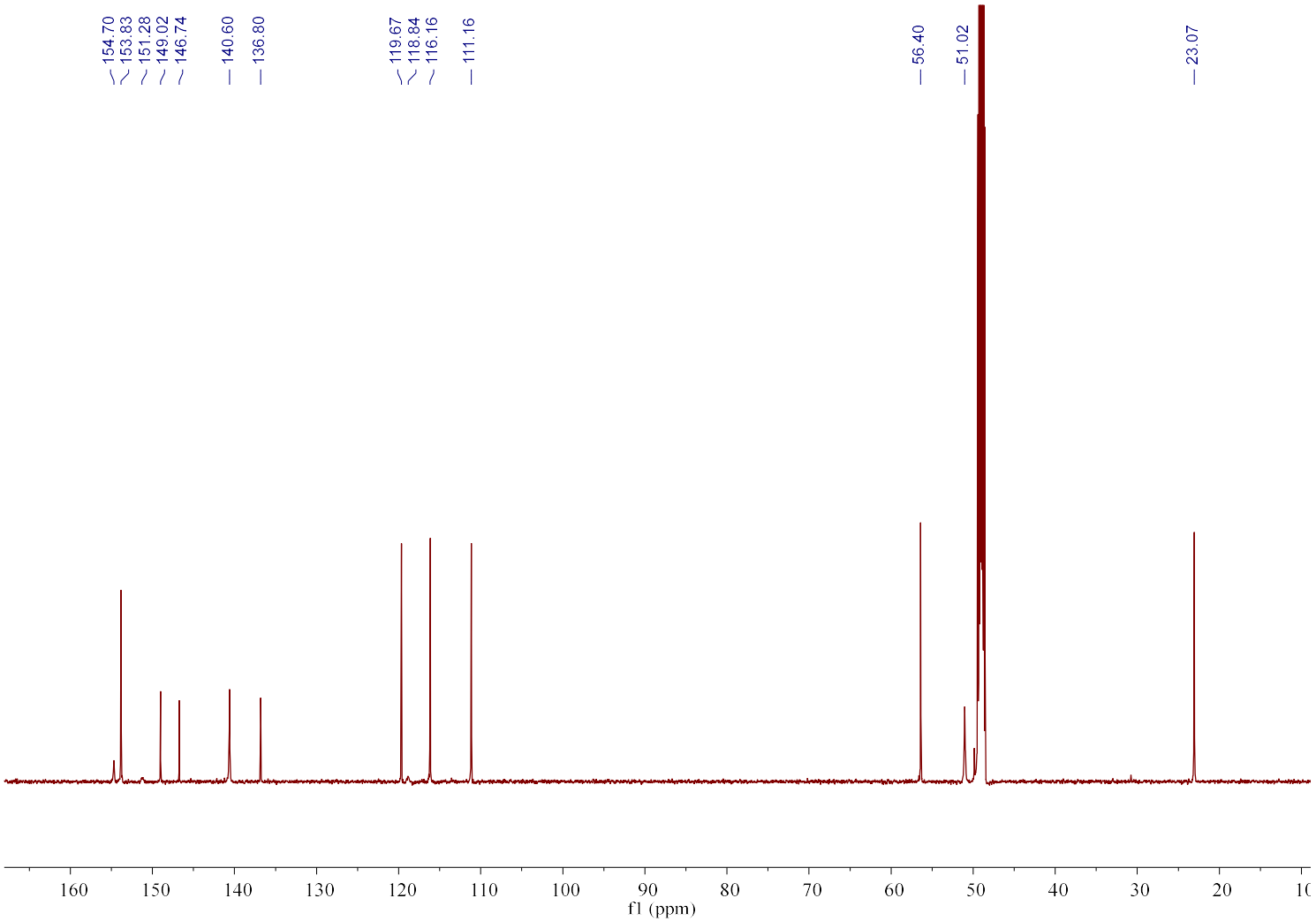

Fig. S16. The ^{13}C NMR spectrum of compound **2** in CD_3OD.

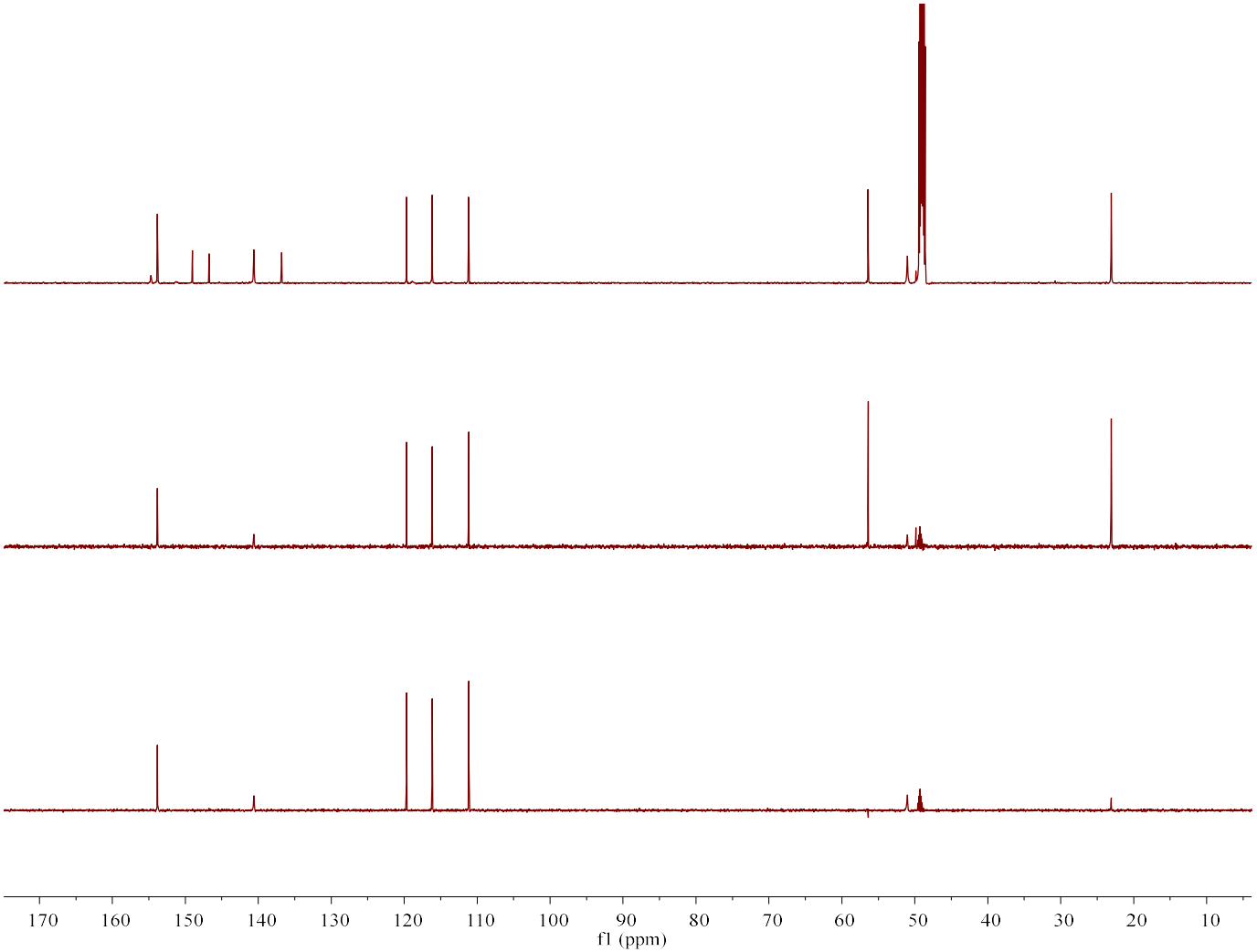

Fig. S17. The DEPT spectrum of compound **2** in CD_3OD.

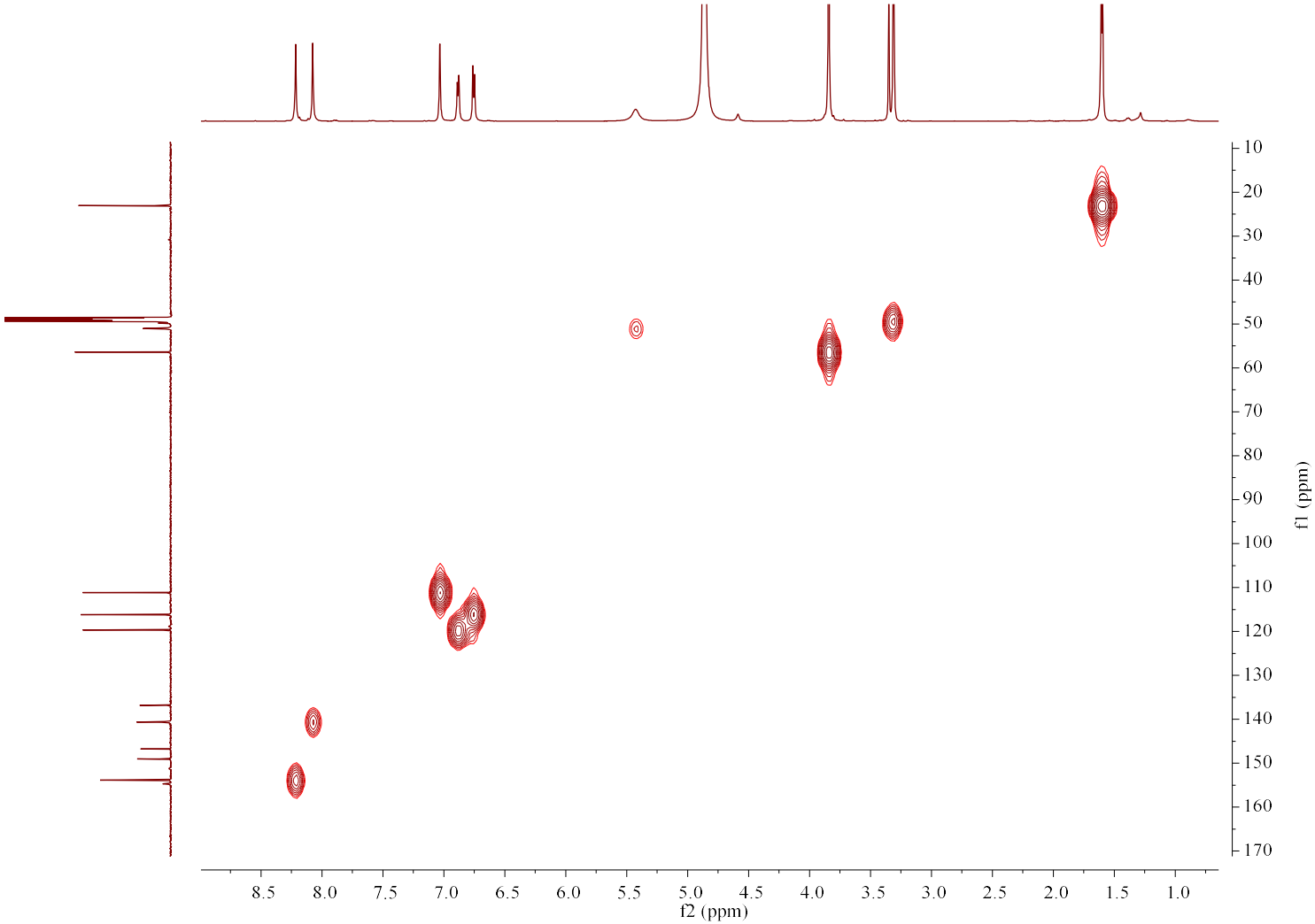

Fig. S18. The HSQC spectrum of compound **2** in CD_3OD.

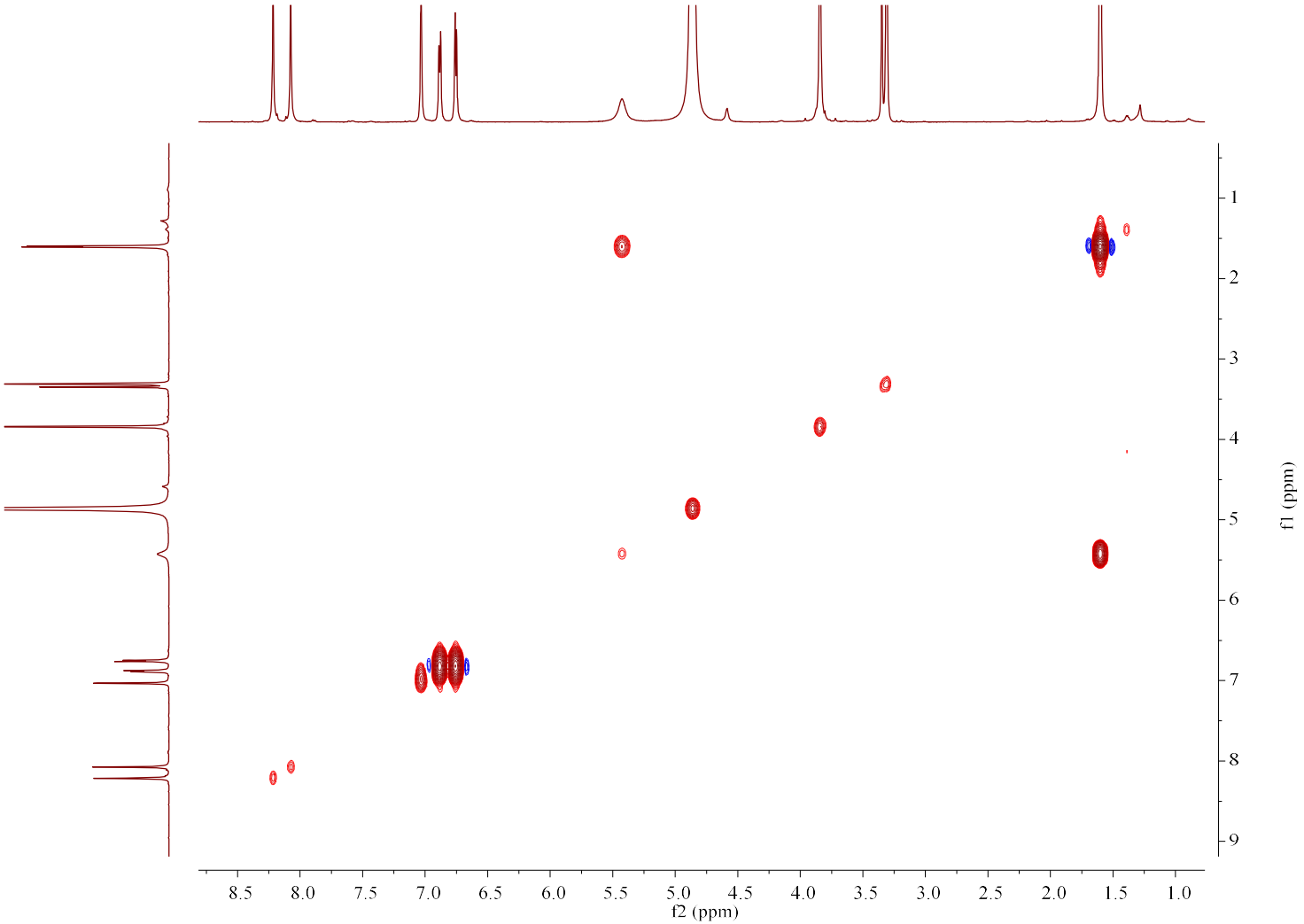

Fig. S19. The ^{1}H-^{1}H COSY spectrum of compound **2** in CD_3OD.

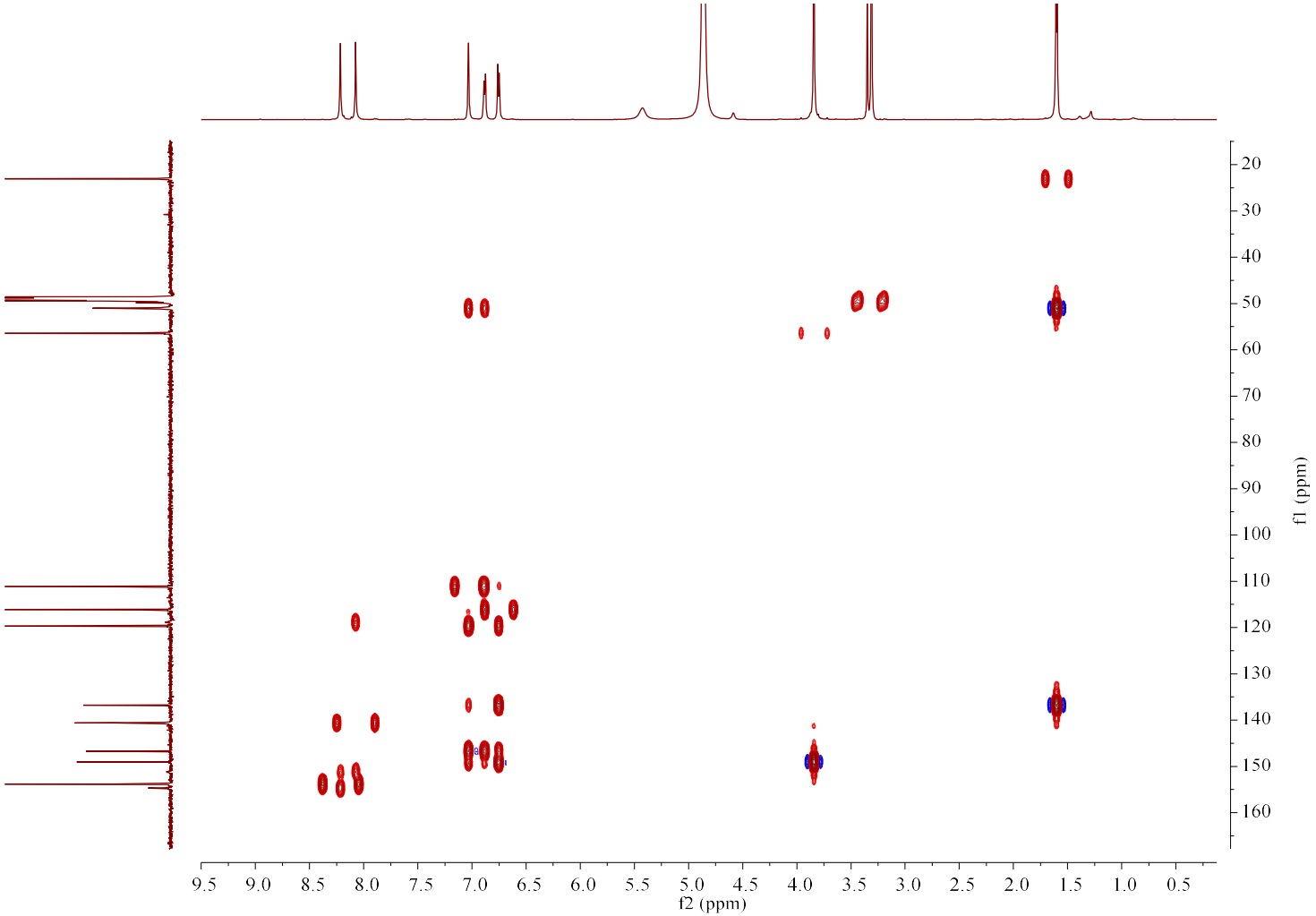

Fig. S20. The HMBC spectrum of compound **2** in CD_3OD.

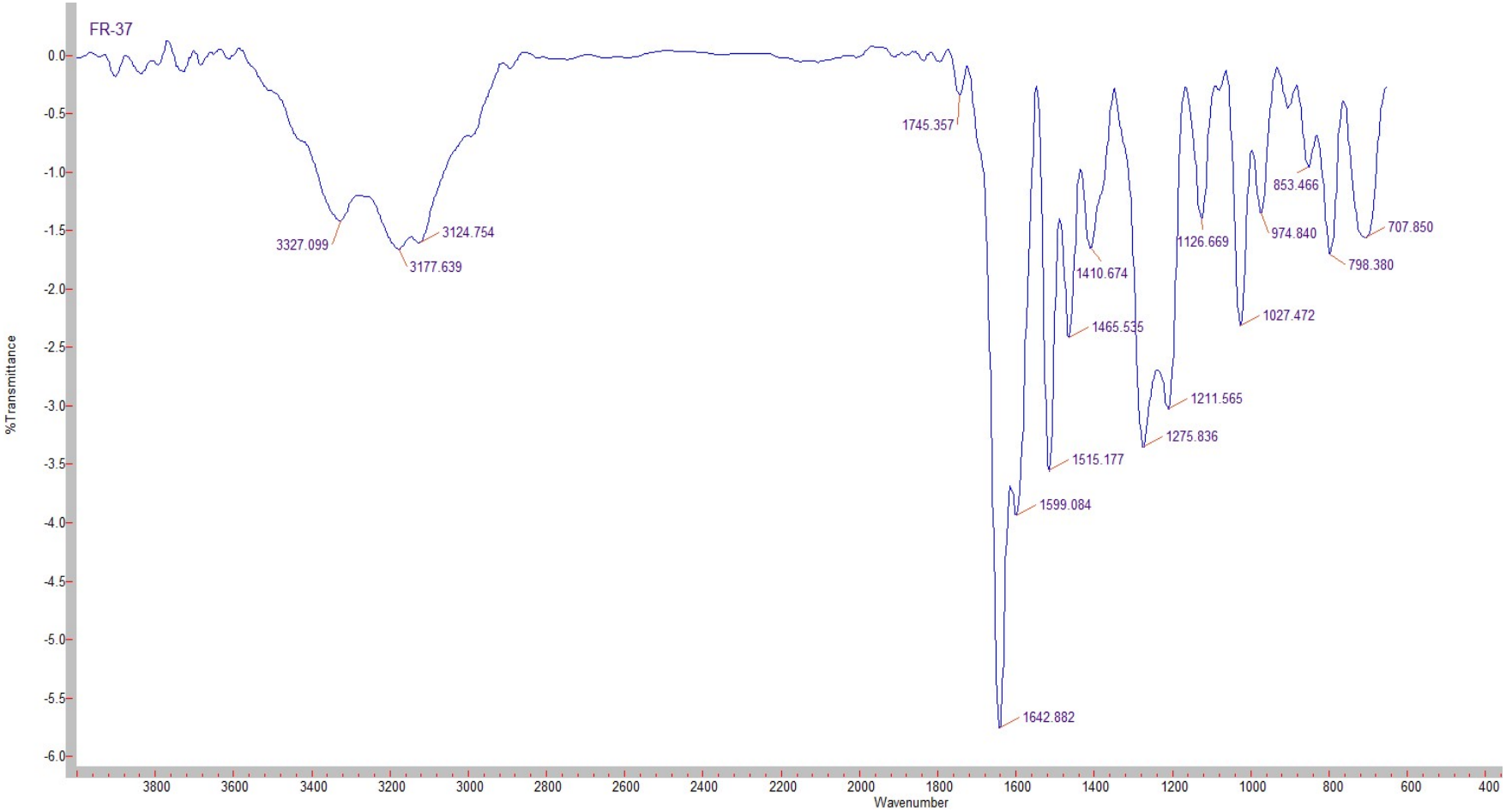

Fig. S21. The IR spectrum of compound **3**.

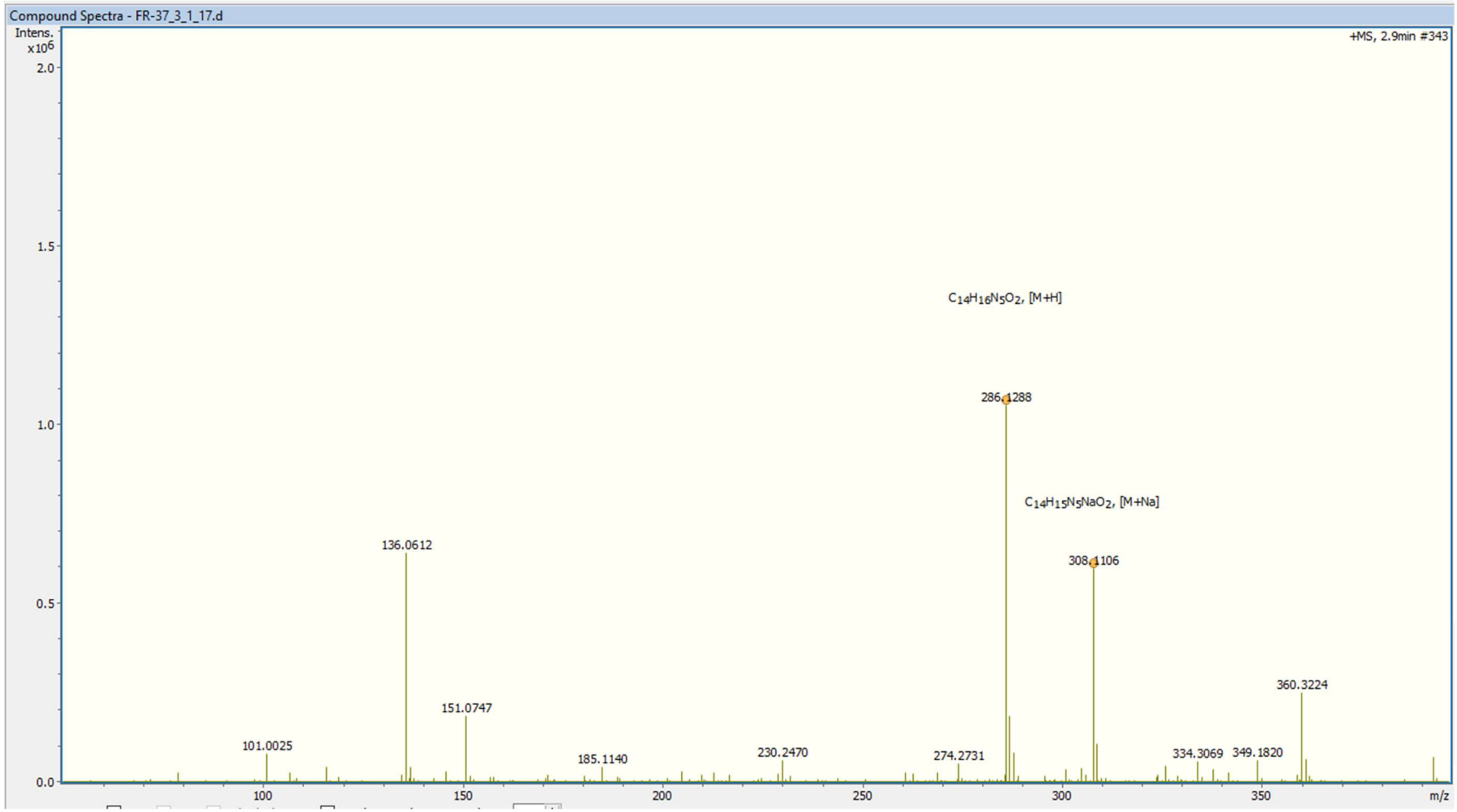

Fig. S22. The (+)-HR-ESI-MS spectroscopic data of compound **3**.

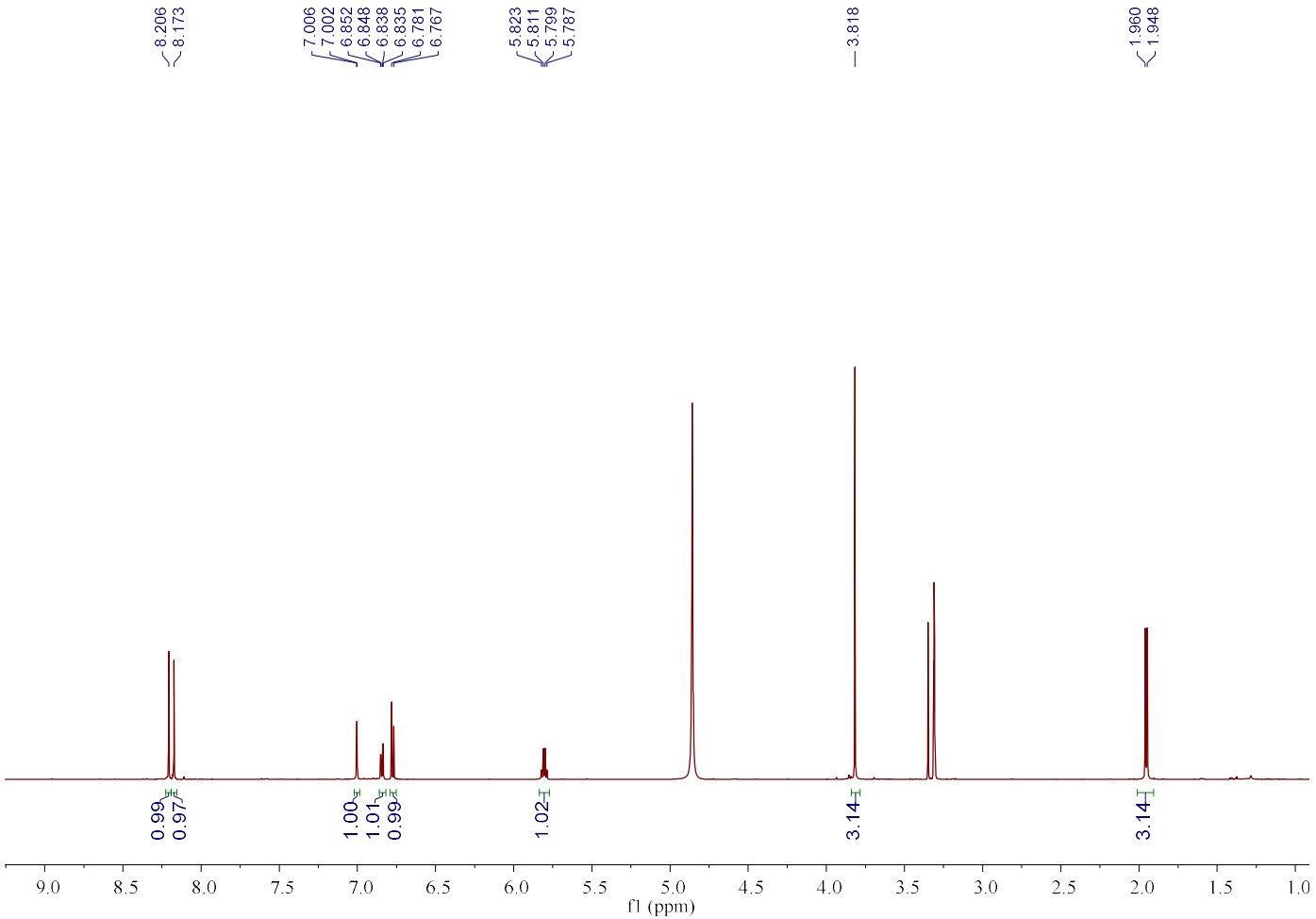

Fig. S23. The ^{1}H NMR spectrum of compound **3** in CD_3OD.

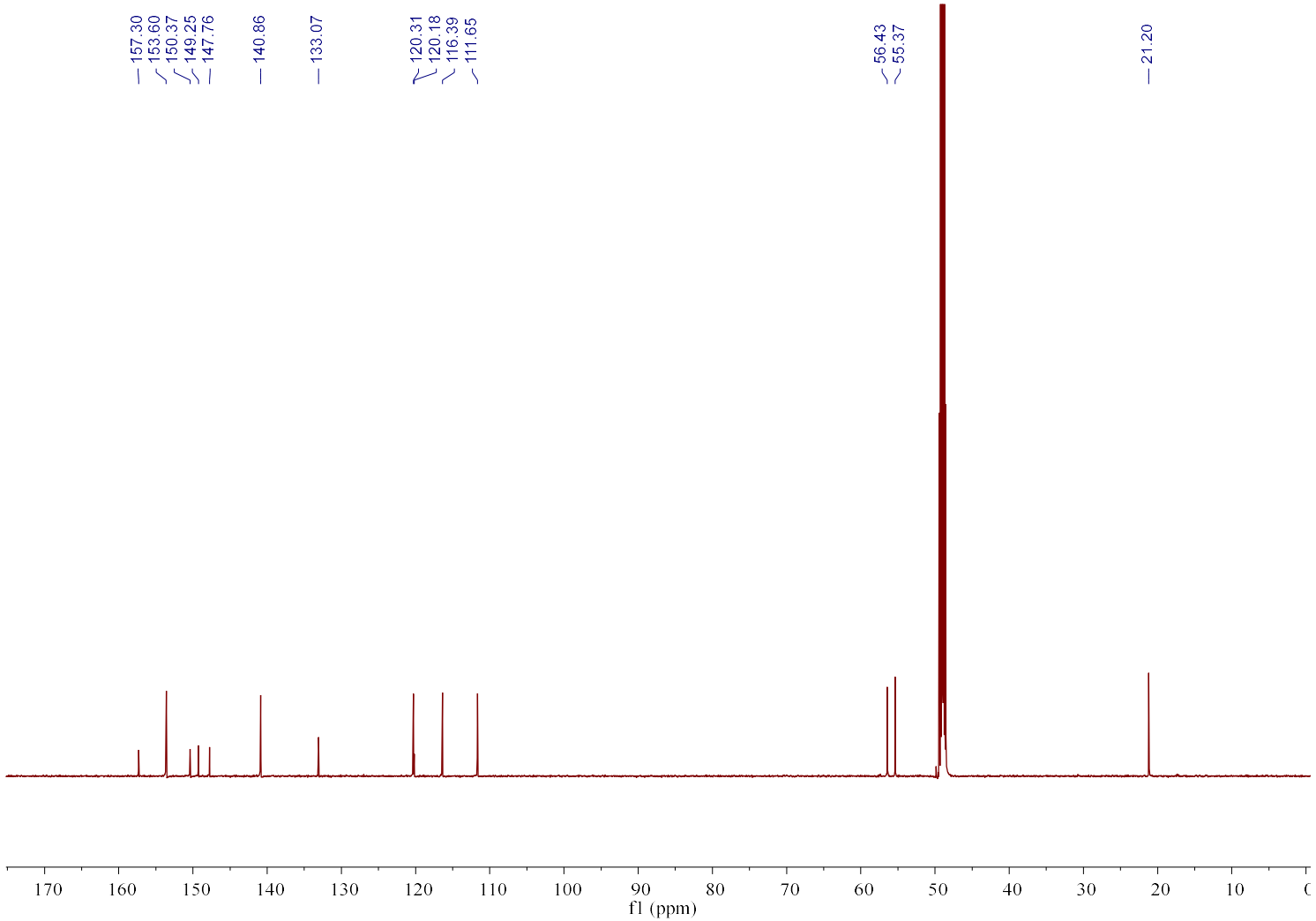

Fig. S24. The ^{13}C NMR spectrum of compound **3** in CD_3OD.

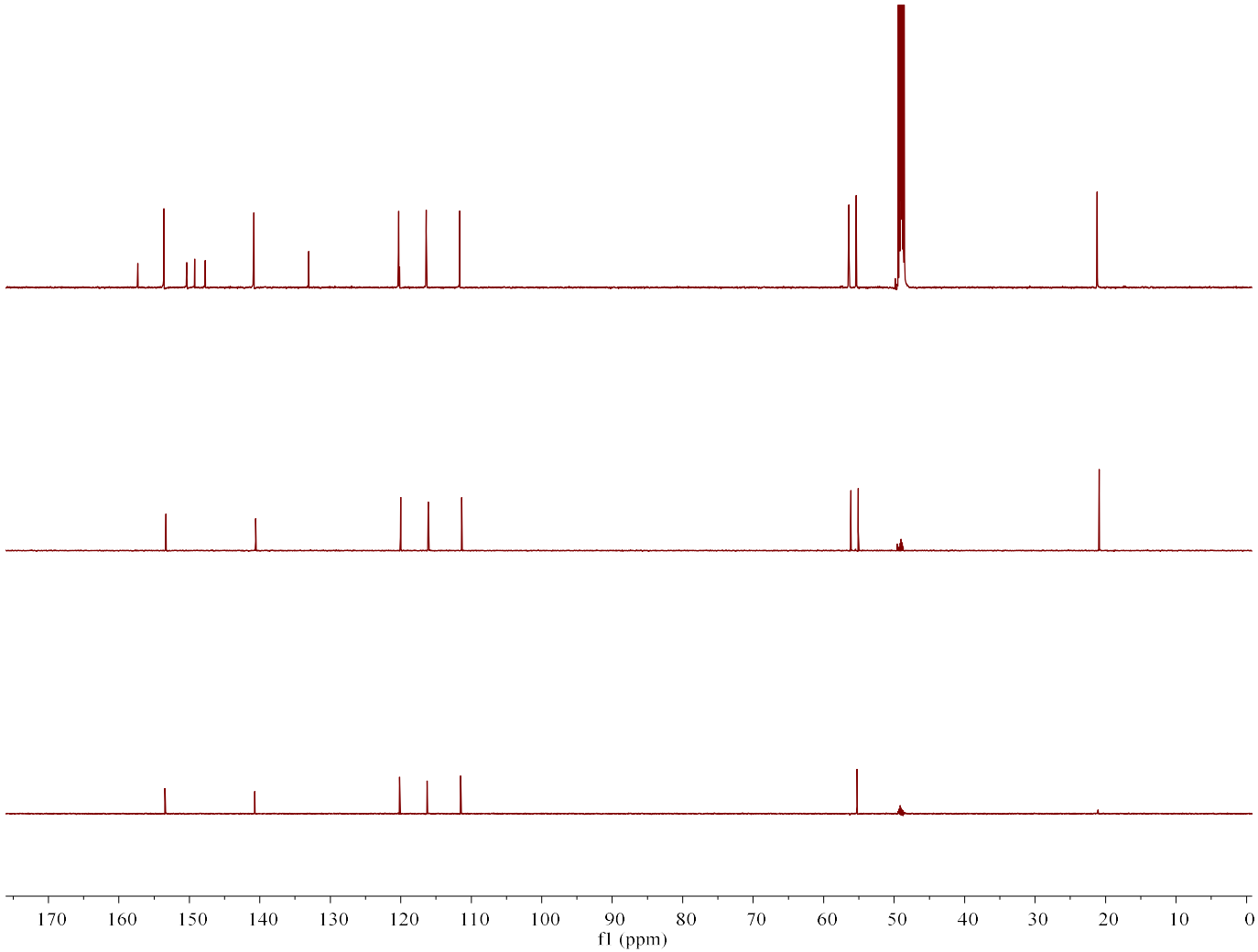

Fig. S25. The DEPT spectrum of compound **3** in CD_3OD.

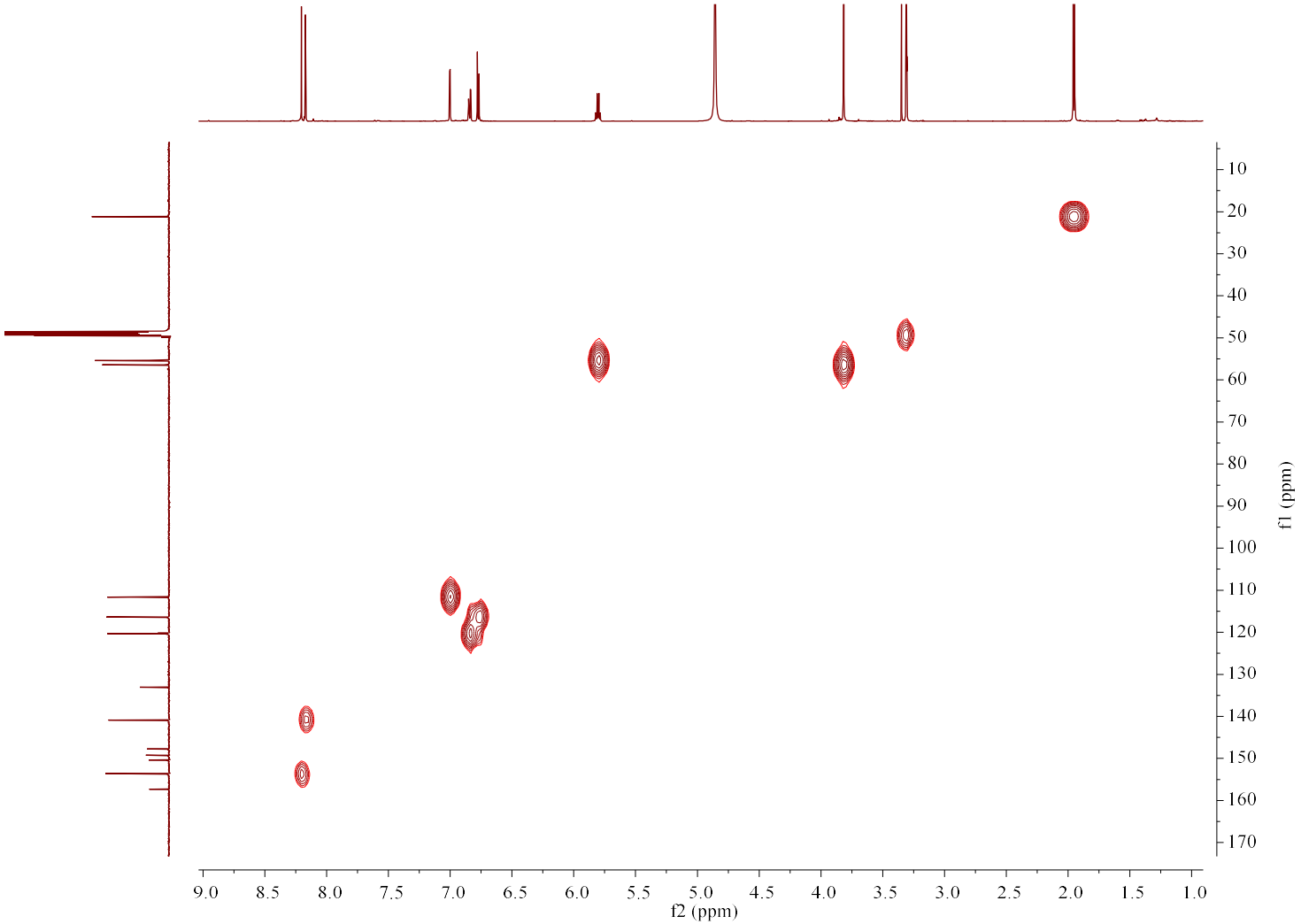

Fig. S26. The HSQC spectrum of compound **3** in CD_3OD.

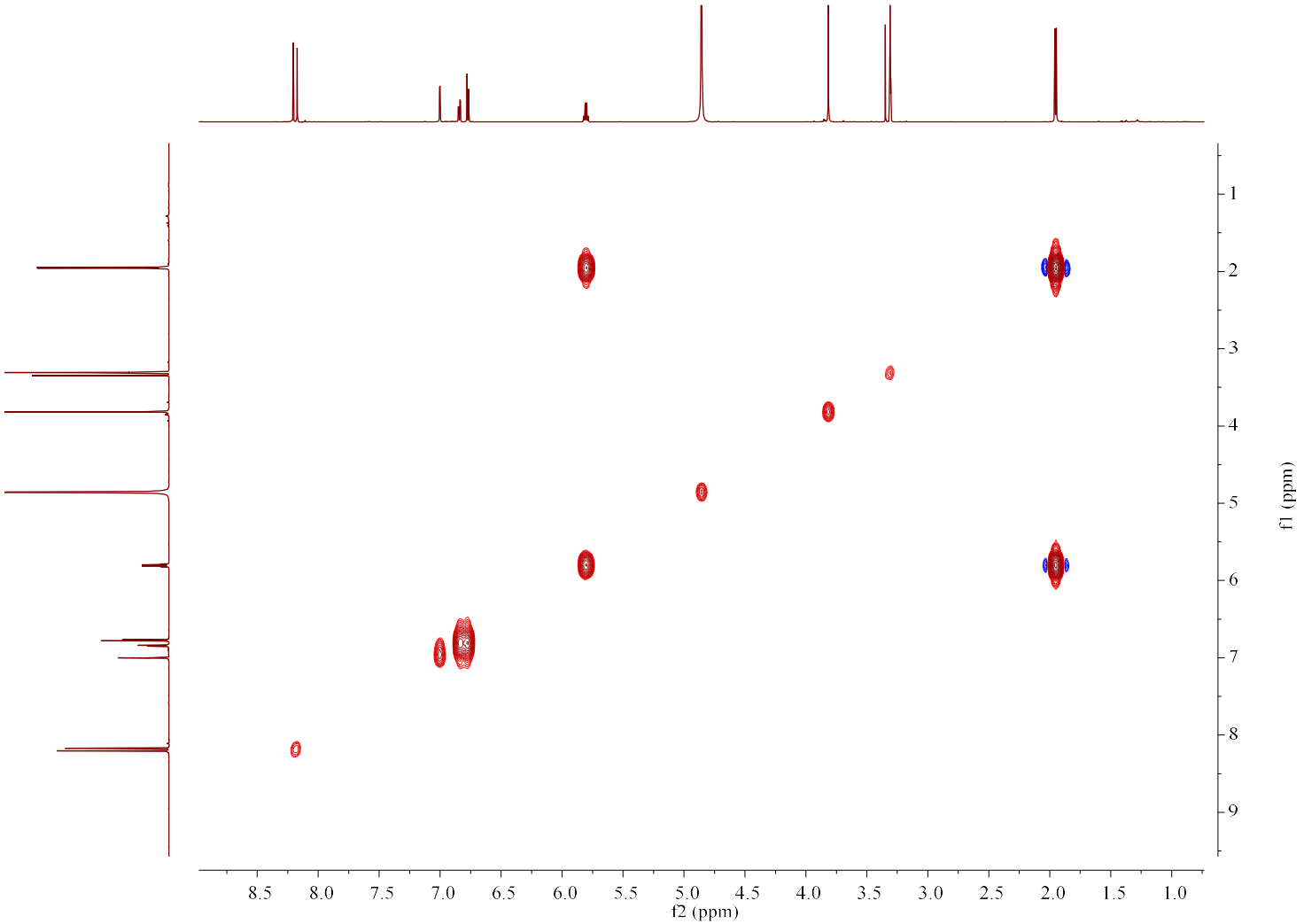

Fig. S27. The ^{1}H-^{1}H COSY spectrum of compound **3** in CD_3OD.

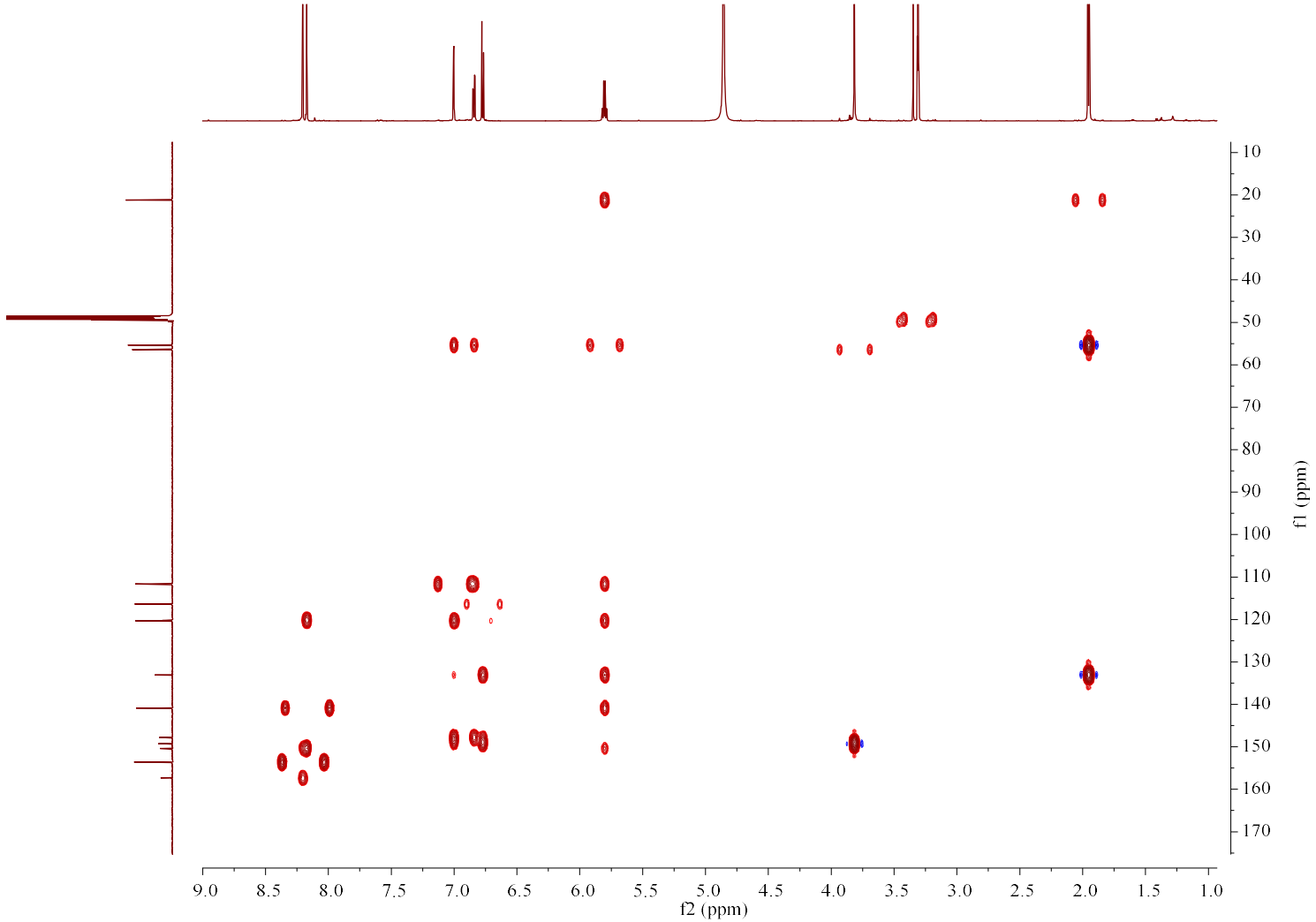

Fig. S28. The HMBC spectrum of compound **3** in CD_3OD.