

SUPPLEMENTARY MATERIAL

Unusual Tetrahydropyridoindole-Containing Tetrapeptides with Human Nicotinic Acetylcholine Receptors targeting Activity Discovered from Antarctica-Derived Psychrophilic *Pseudogymnoascus* sp. HDN17-933

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ABSTRACT

Chemical investigation of the psychrophilic fungus *Pseudogymnoascus* sp. HDN17-933 derived from Antarctica led to the discovery of six new tetrapeptides psegynamides A-F (**1-6**), whose planar structures were elucidated by extensive NMR and MS spectrometric analyses. Structurally, psegynamides D-F (**4-6**) possess unique backbones bearing a tetrahydropyridoindoles unit, which make them the first examples discovered in naturally occurring peptides. The absolute configurations of structures were unambiguously determined using solid-phase total synthesis assisted by Marfey's method, and all compounds were evaluated for their inhibition of human (h) nicotinic acetylcholine receptor subtypes. Compound **2** showed significant inhibitory activity. Preliminary structure-activity relationship investigation revealed that the tryptophan residue and the C-terminal with methoxy group were important to the inhibitory activity. Further, the high binding affinity of compound **2** to $\alpha 4\beta 2$ was explained by molecular docking studies.

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Table S1. Table of compounds (**1-6**) (100 μ M) inhibition of ACh-evoked peak current amplitude mediated by human (h) $\alpha 1\beta 1\epsilon\delta$, $\alpha 1\beta 1\gamma\delta$, $\alpha 3\beta 2$, $\alpha 3\beta 4$, $\alpha 4\beta 2$, $\alpha 7$ and $\alpha 9\alpha 10$ nAChRs.

Table S2. Free binding energy estimation and molecular interactions of compounds **1-6**

GGGCAACGTGTCGACGGGTTGCCGCAGGCCTCCCGGGTAACCT
ACCACCCTTTGTTTATTATACTTTGTTGCTTTGGCAGGCCTGCCC
TCGGGCTGCTGGCTCCGGCCGGCGAGCGCTTGCCAGAGGACCT
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CAGCGAAATGCGATAAGTAATGTGAATTGCAGAATTCAGTGAAT
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CCCGGTCGTGTGCTCGCCAGCAACCCCCAATTTTTTTCAGGTTG
ACCTCGGATCAGGTAGGGATACCCGCTGAACTTAAGCATATCAA
TAAGCGGAGGAAATTACAG

Figure S1. 18S rRNA sequences data of *Pseudogymnoascus* sp. HDN17-933

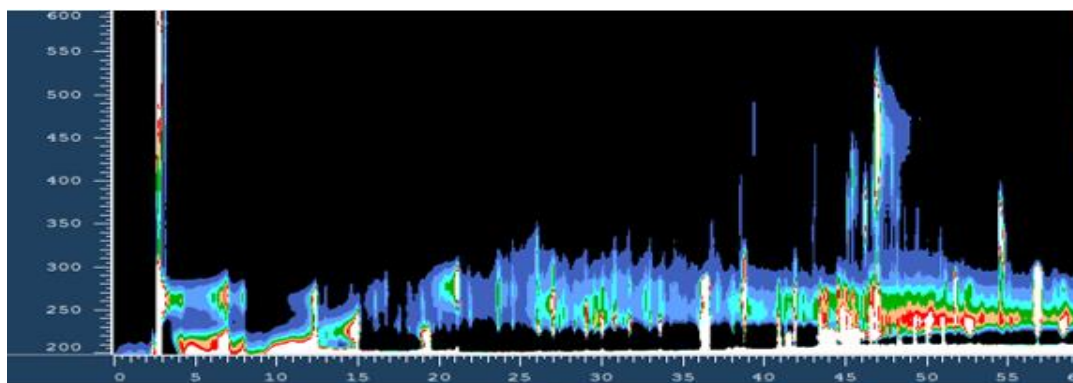


Figure S2. HPLC analysis of the crude extract of HDN17-933.

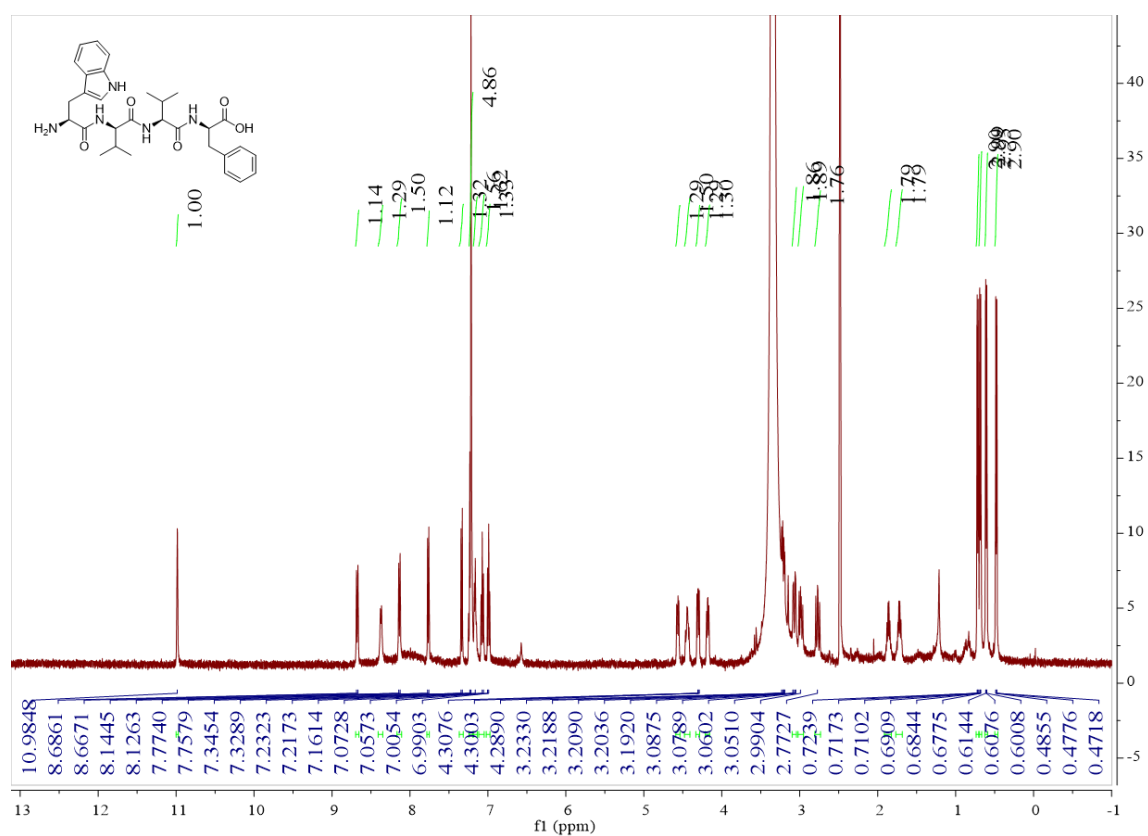


Figure S3. ¹H-NMR spectrum (600 MHz, DMSO-*d*₆) of compound 1

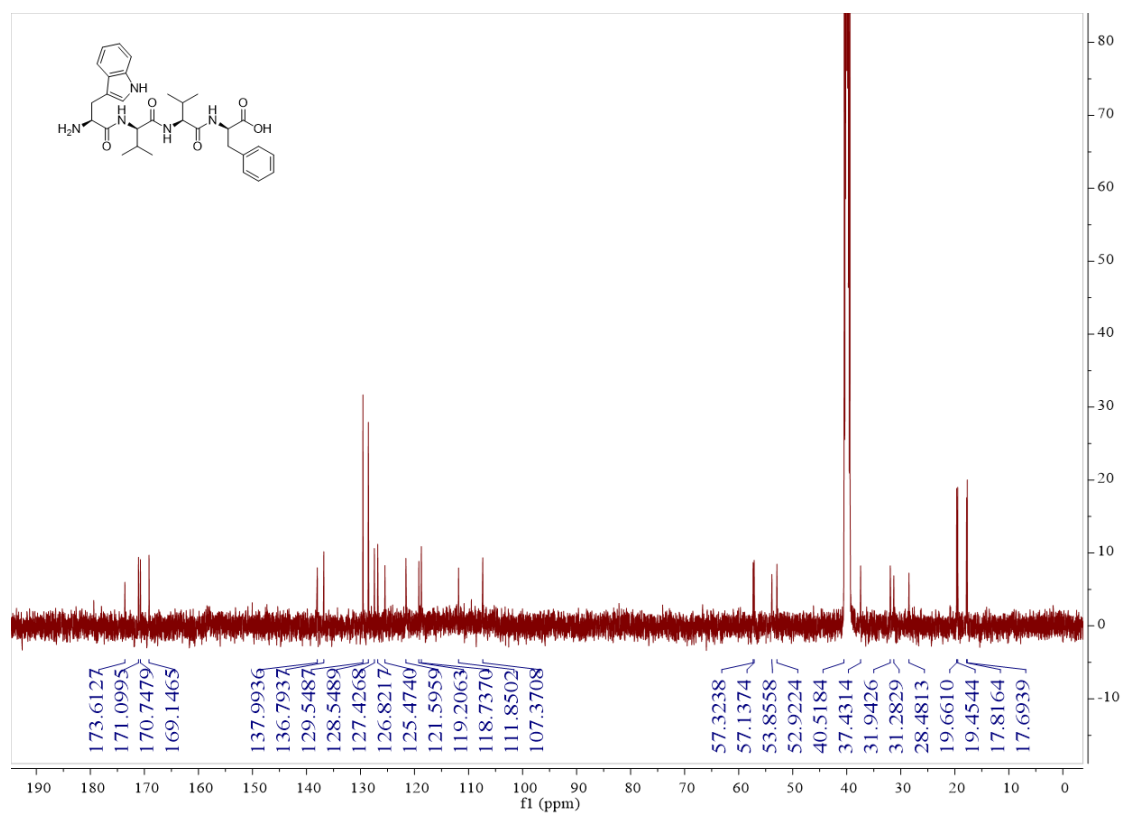


Figure S4. ¹³C-NMR spectrum (150 MHz, DMSO-*d*₆) of compound **1**

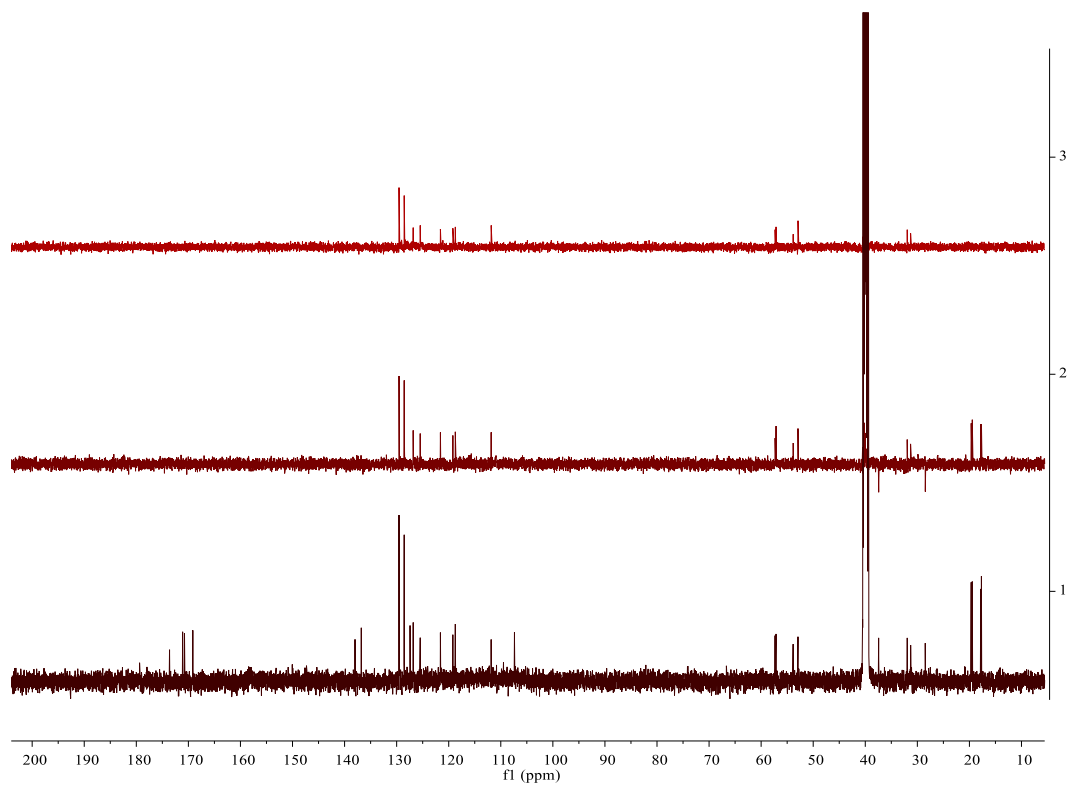


Figure S5. DEPT (150 MHz, DMSO-*d*₆) spectrum of compound **1**.

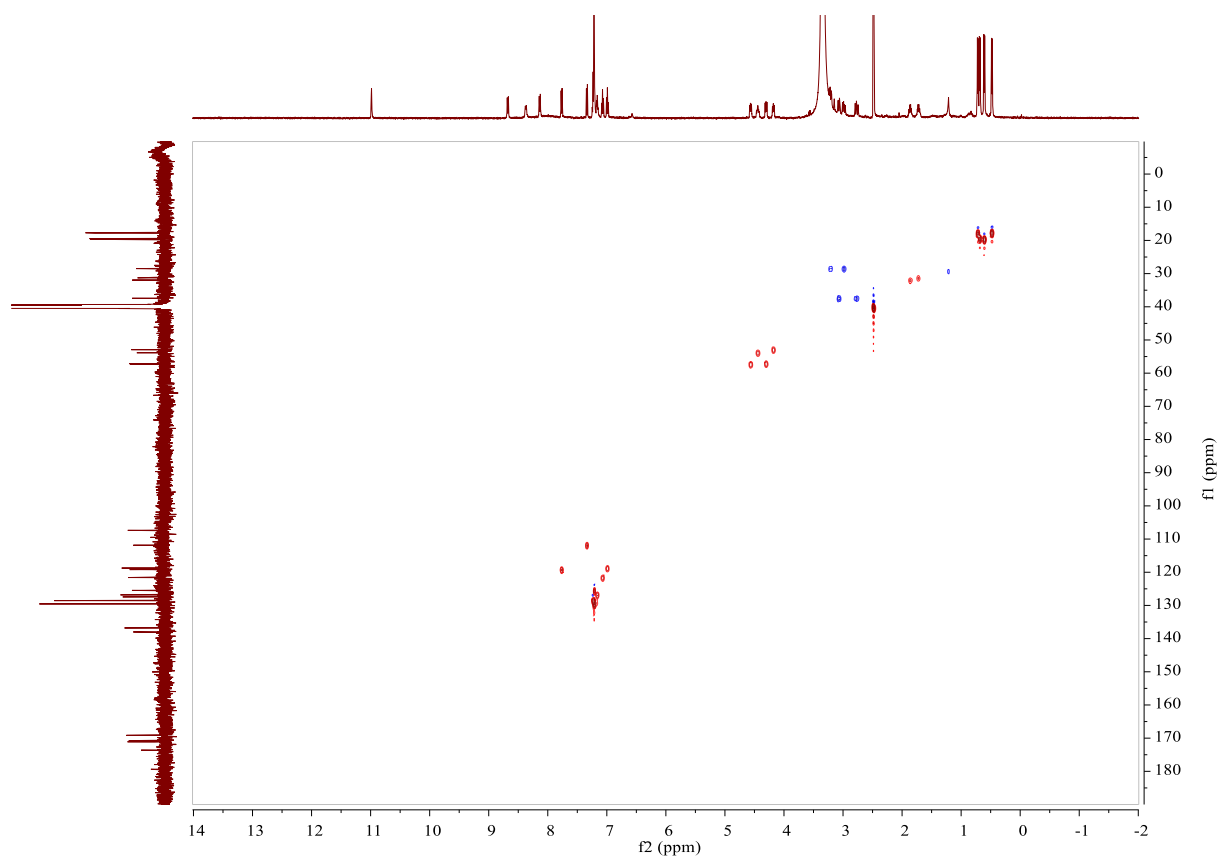


Figure S6. HSQC spectrum (600 MHz, $\text{DMSO}-d_6$) of compound **1**.

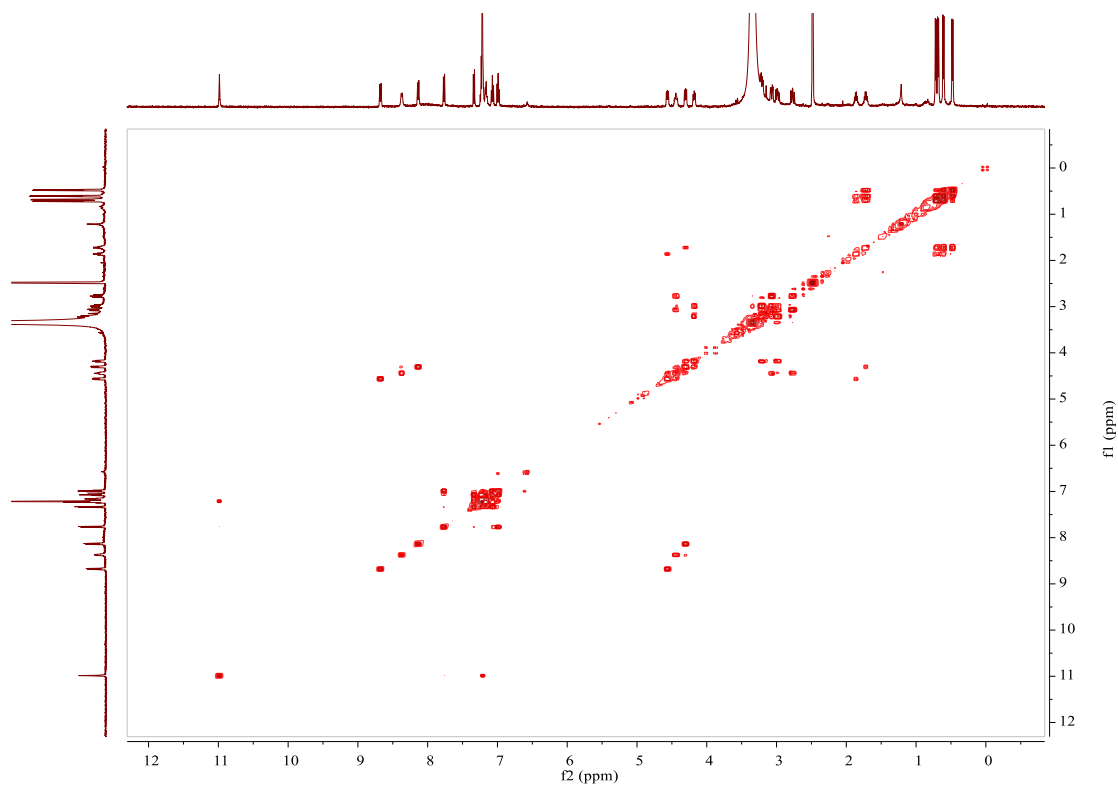


Figure S7. ^1H - ^1H COSY spectrum (600 MHz, $\text{DMSO}-d_6$) of compound **1**

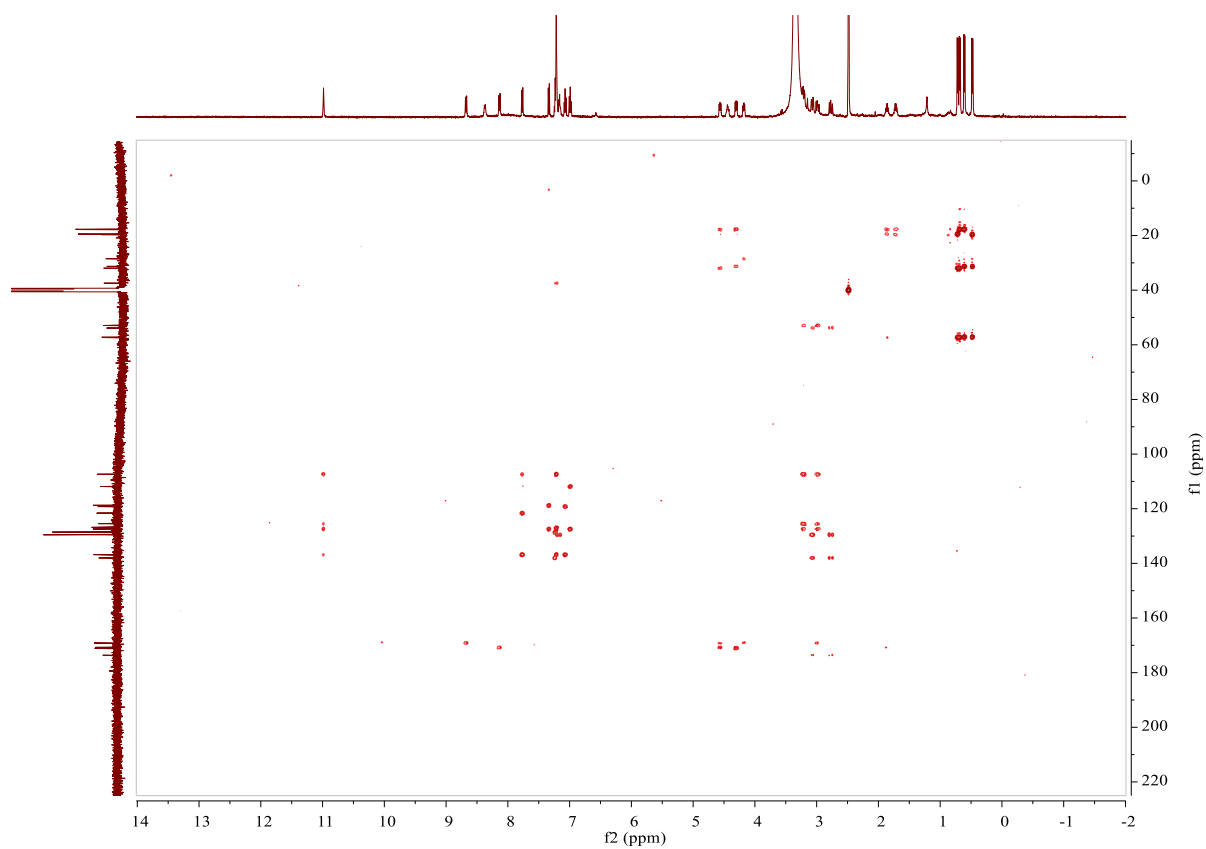


Figure S8. HMBC spectrum (600 MHz, $\text{DMSO}-d_6$) of compound **1**

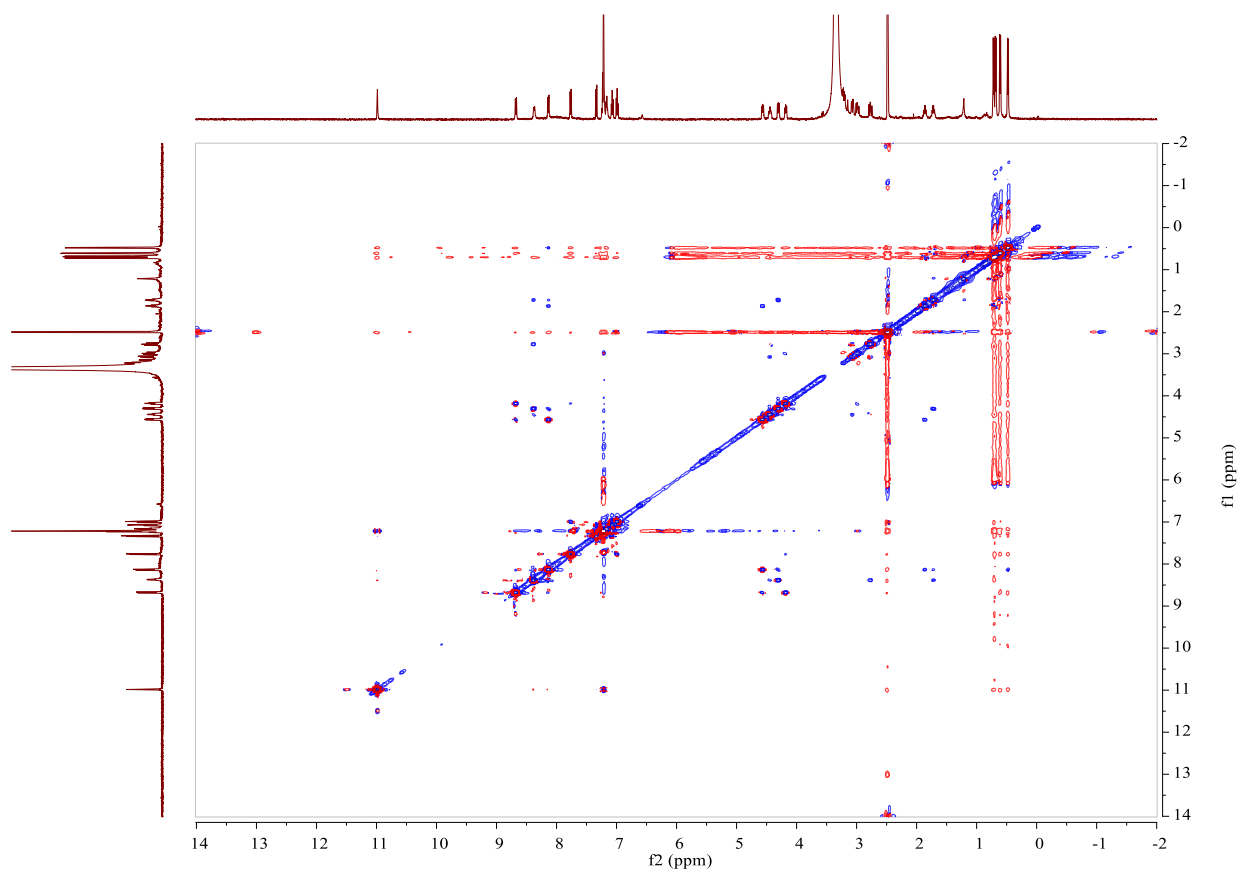


Figure S9. NOESY spectrum (600 MHz, DMSO-*d*₆) of compound **1**

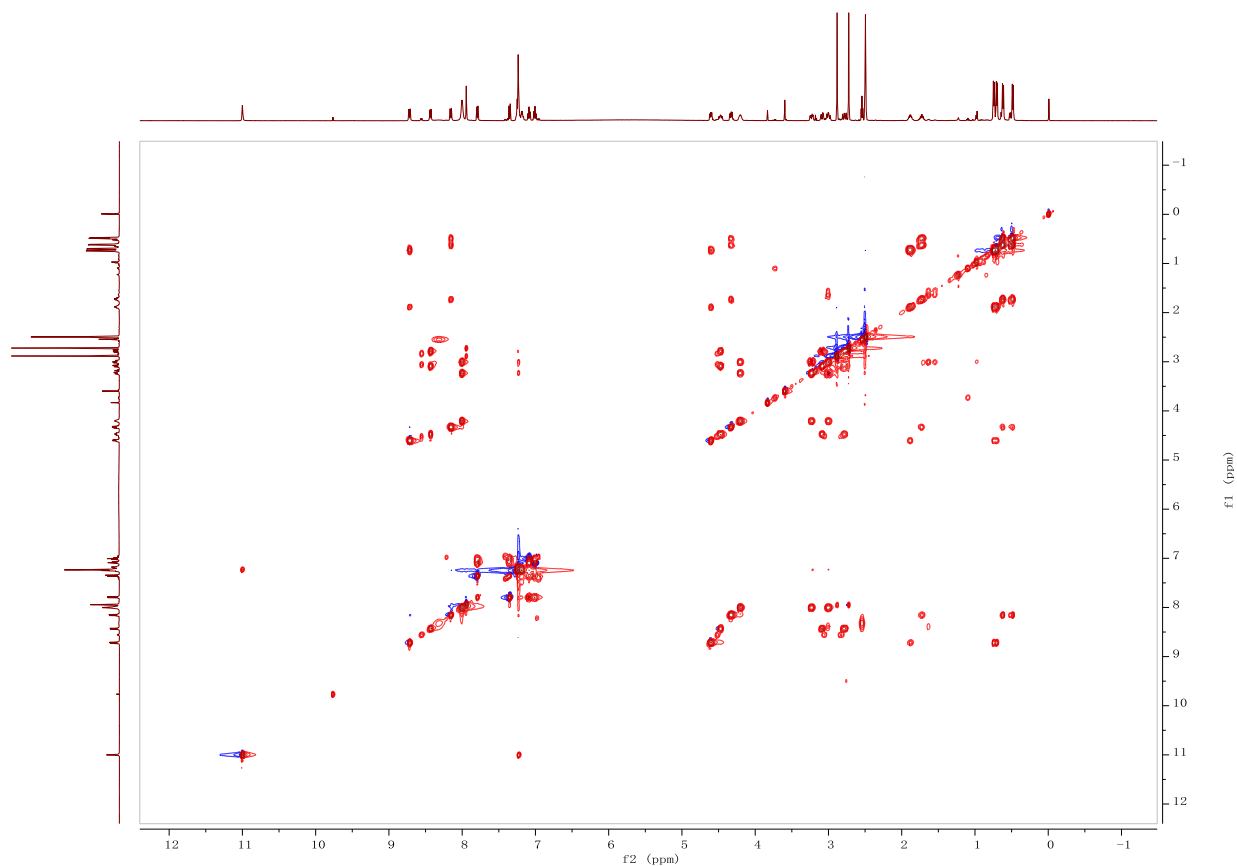


Figure S10. TOCSY spectrum (600 MHz, DMSO-*d*₆) of compound **1**

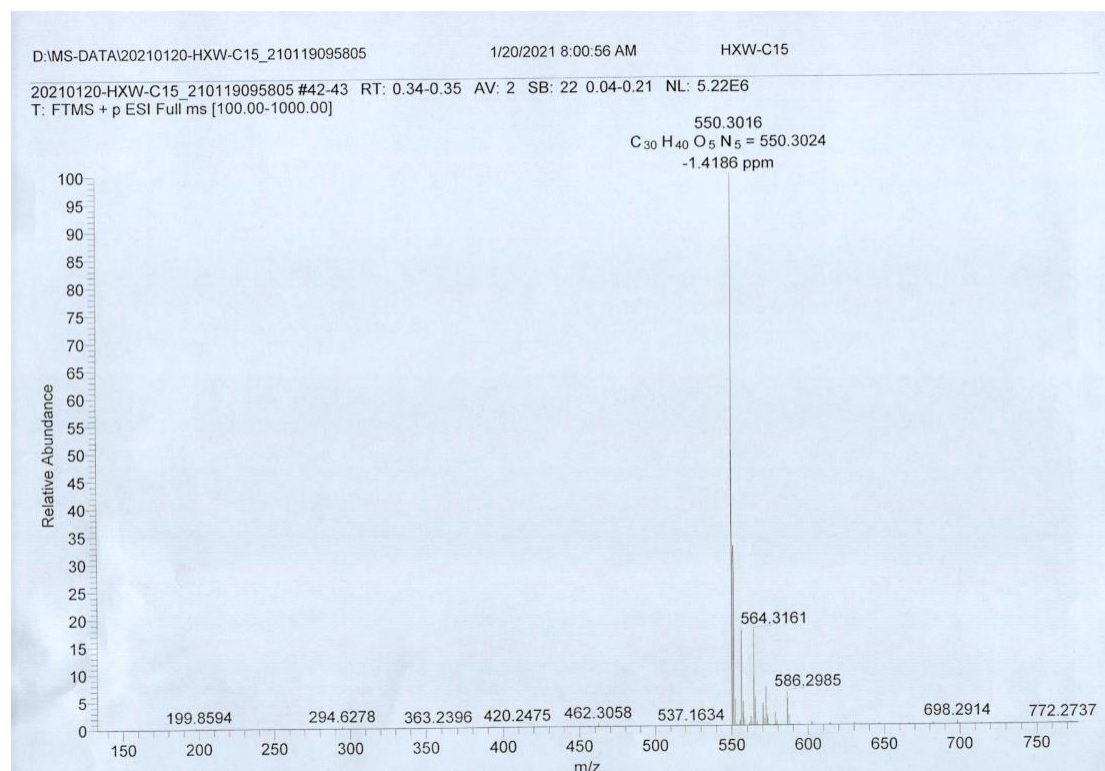


Figure S11. HRESIMS spectrum of compound **1**.

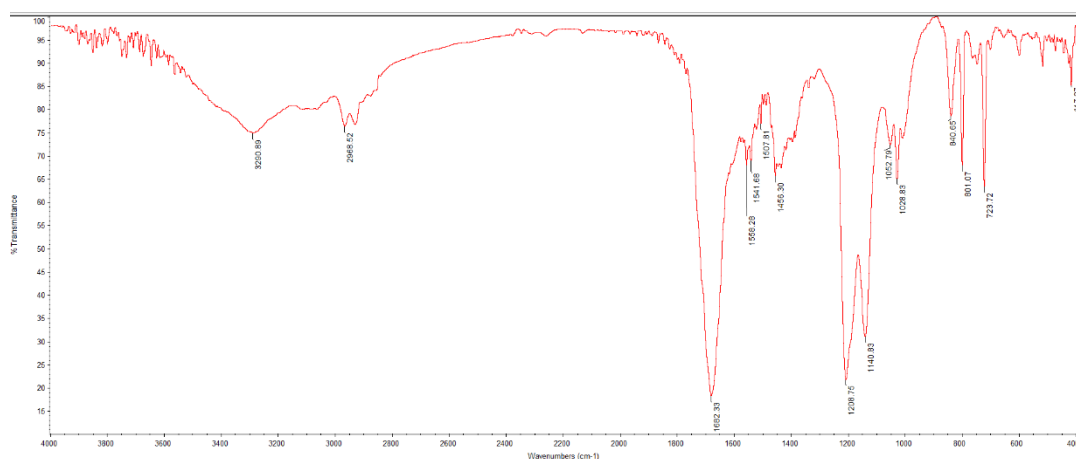


Figure S12. IR spectrum of compound **1**.

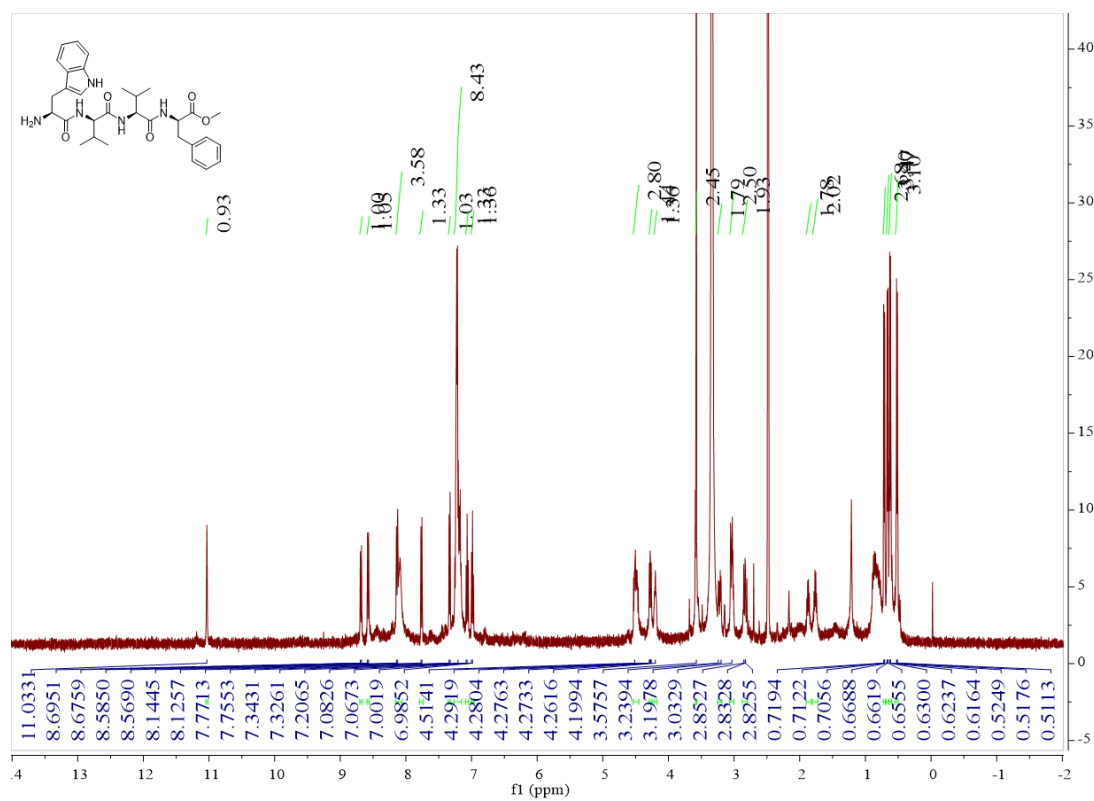


Figure S13. ¹H-NMR spectrum (600 MHz, DMSO-*d*₆) of compound **2**

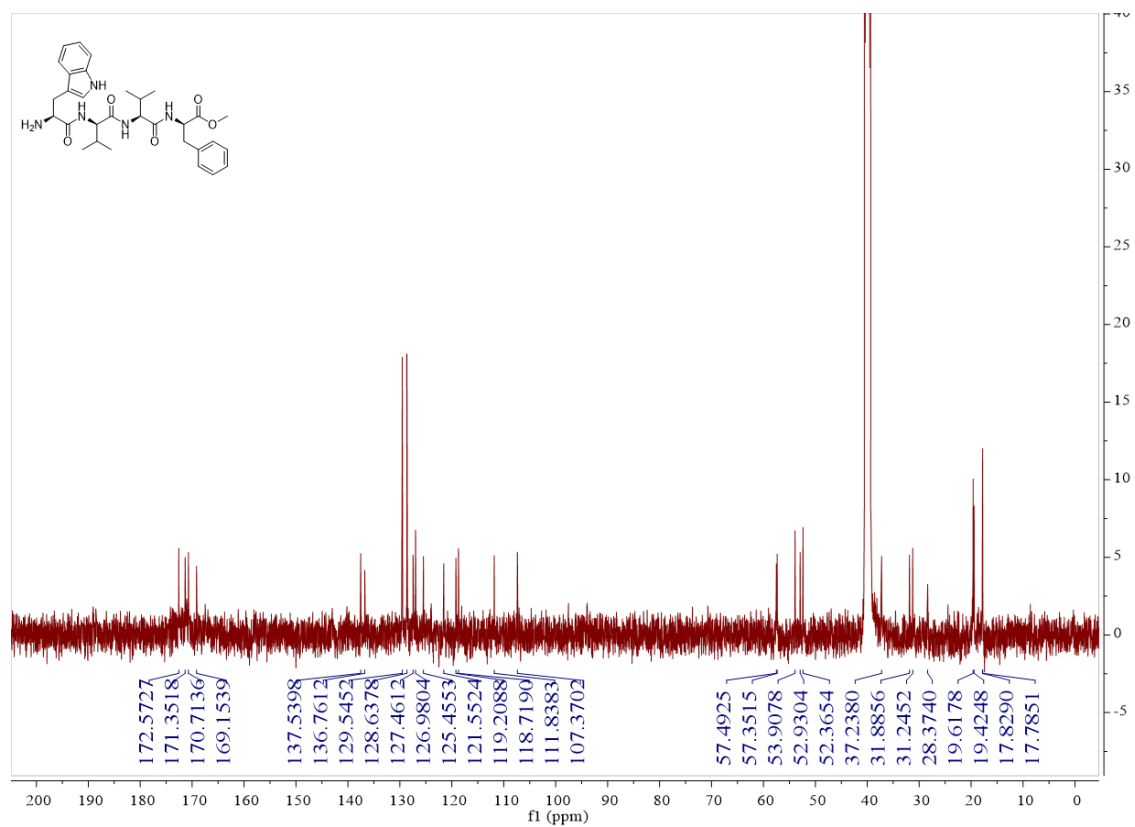


Figure S14. ¹³C-NMR spectrum (150 MHz, DMSO-*d*₆) of compound **2**

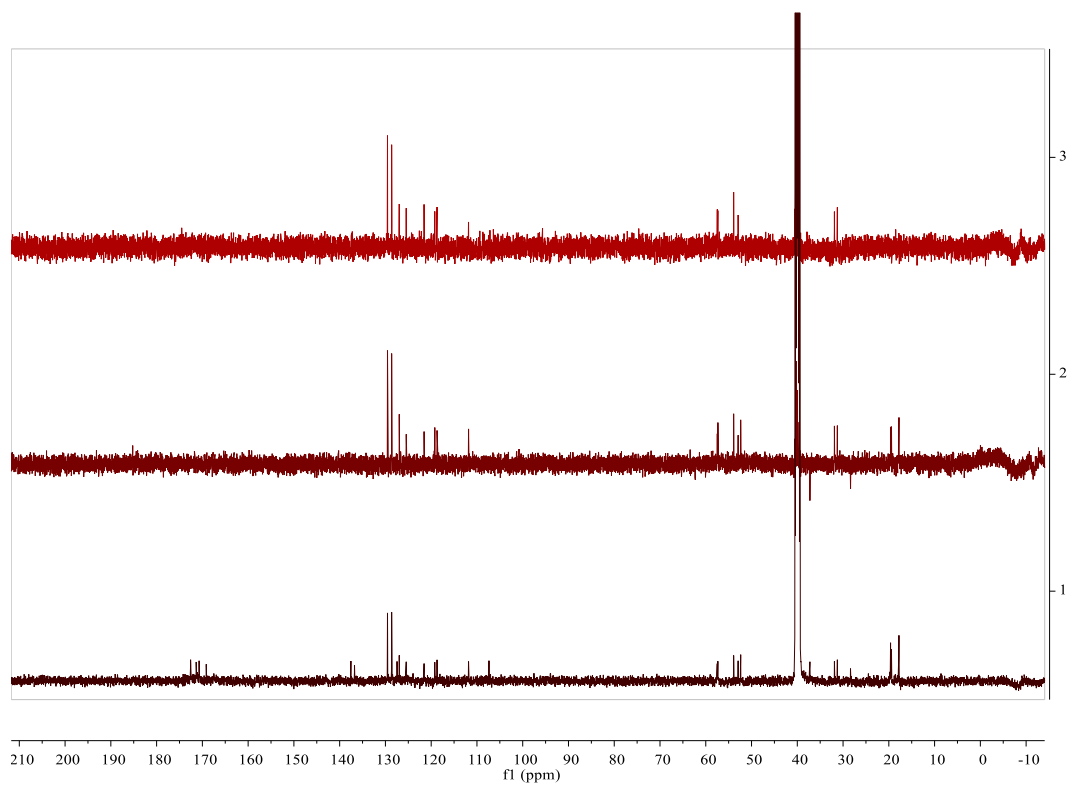


Figure S15. DEPT (150 MHz, DMSO-*d*₆) spectrum of compound **2**

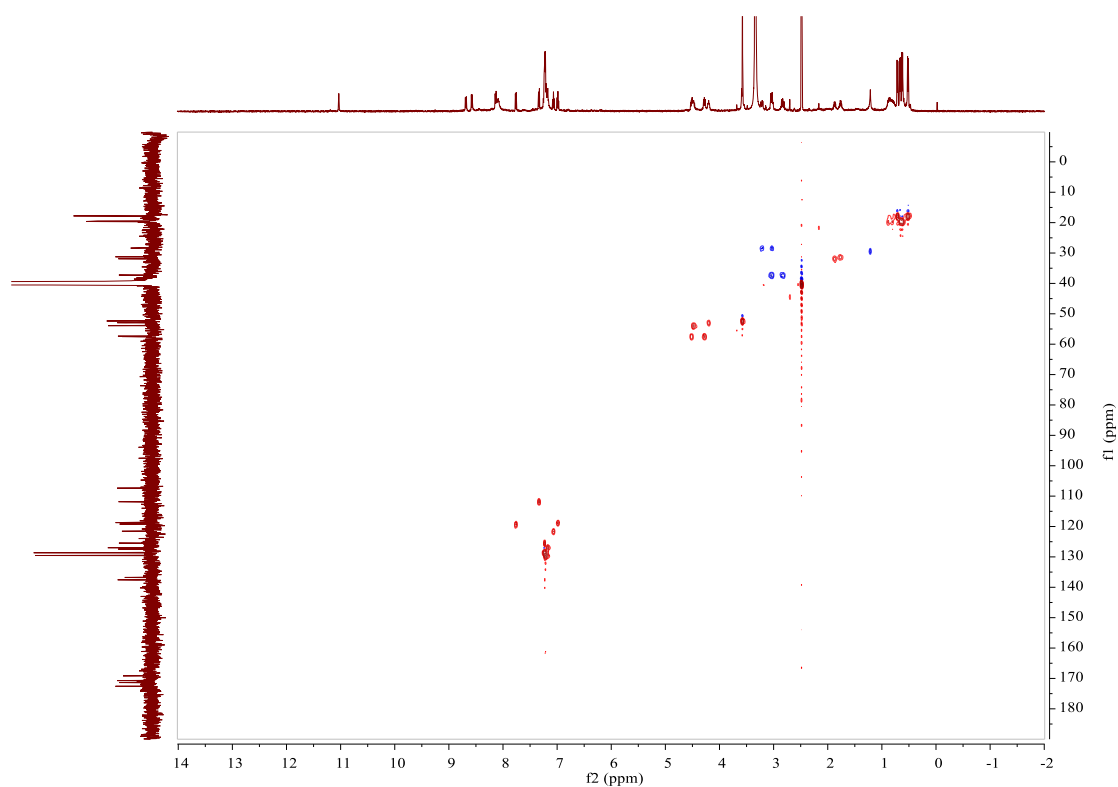


Figure S16. HSQC spectrum (600 MHz, DMSO- d_6) of compound **2**

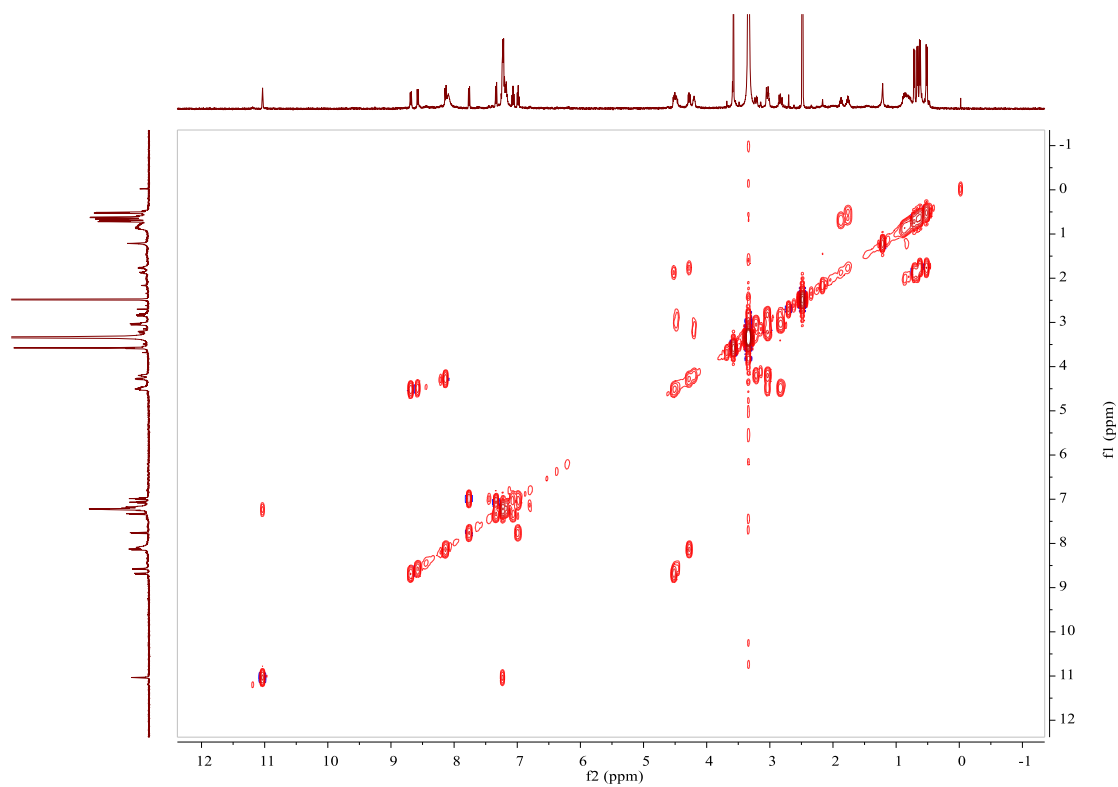


Figure S17. ^1H - ^1H COSY spectrum (600 MHz, DMSO- d_6) of compound **2**

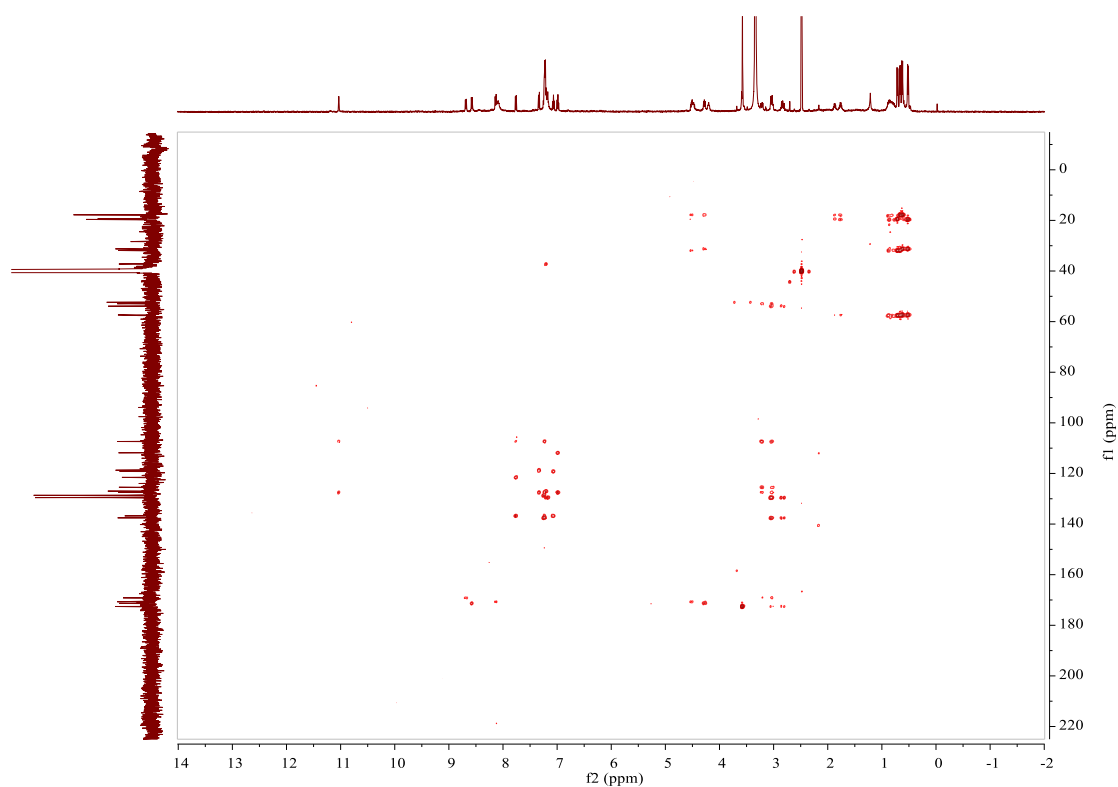


Figure S18. HMBC spectrum (600 MHz, DMSO-*d*₆) of compound **2**

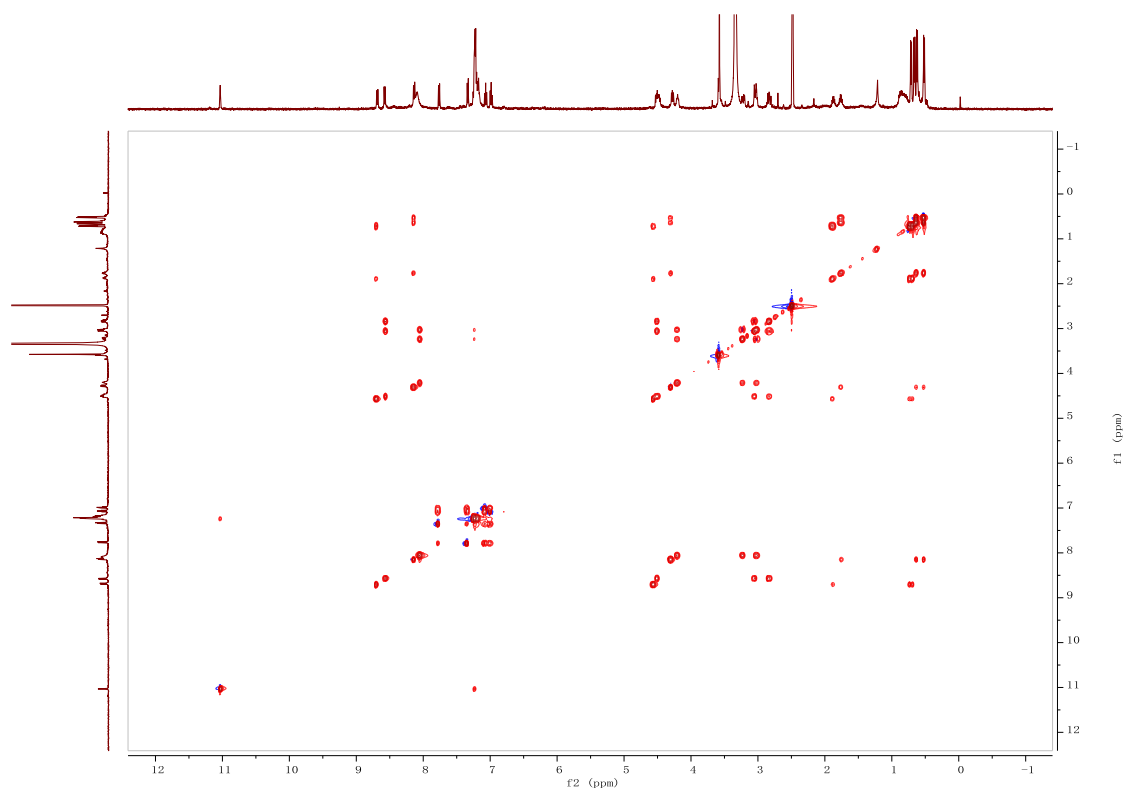


Figure S19. TOCSY spectrum (600 MHz, DMSO-*d*₆) of compound **2**

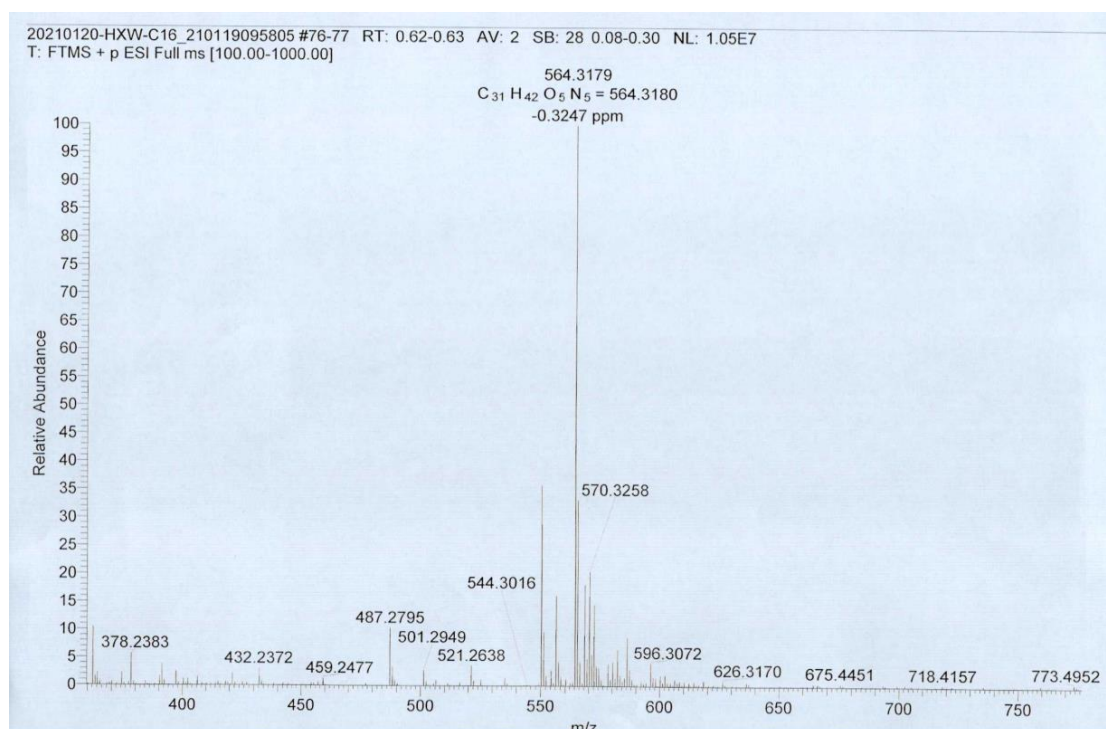


Figure S20. HRESIMS spectrum of compound **2**

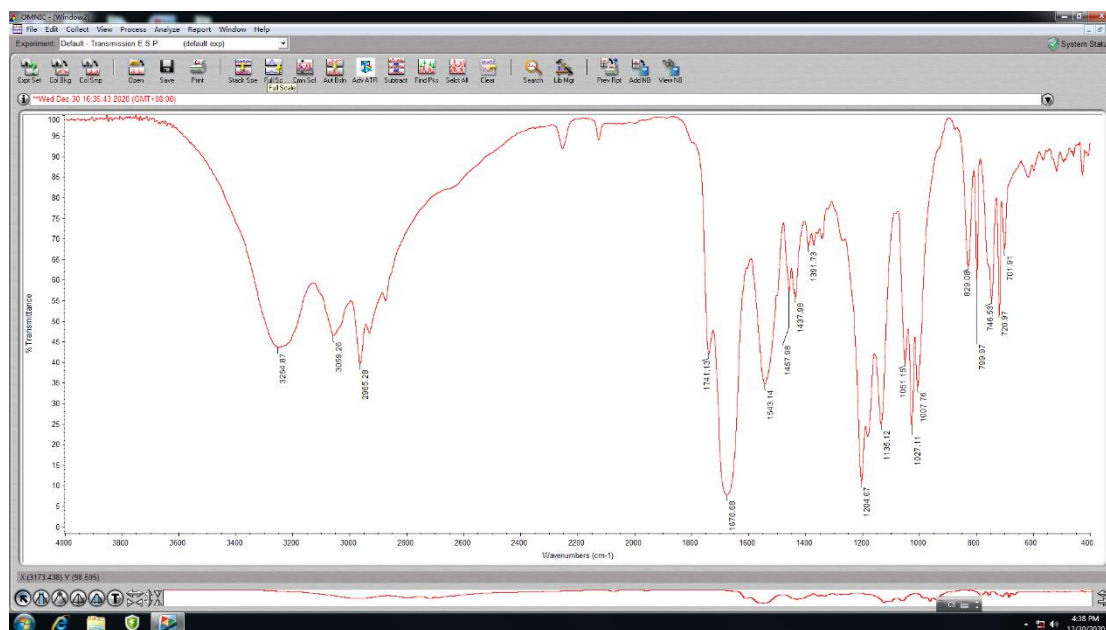


Figure S21. IR spectrum of compound **2**

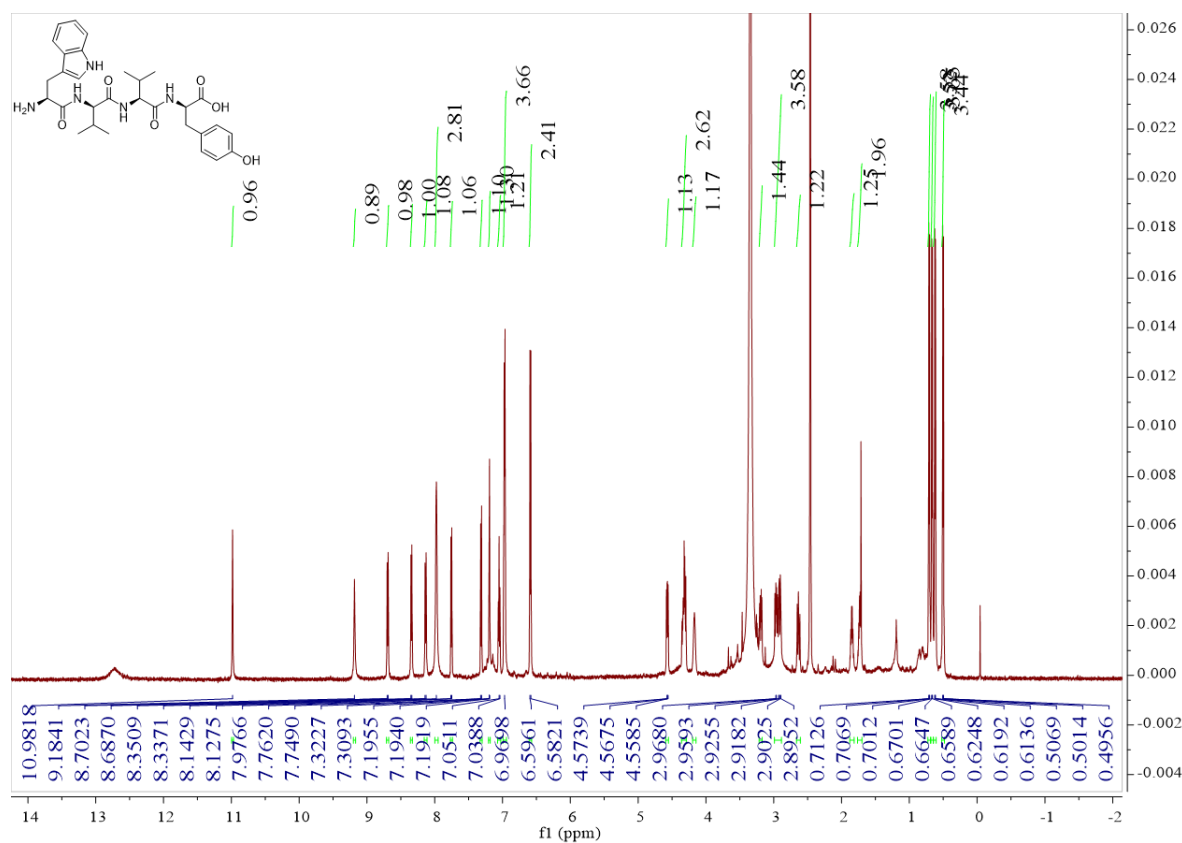


Figure S22. ¹H-NMR spectrum (600 MHz, DMSO-*d*₆) of compound **3**

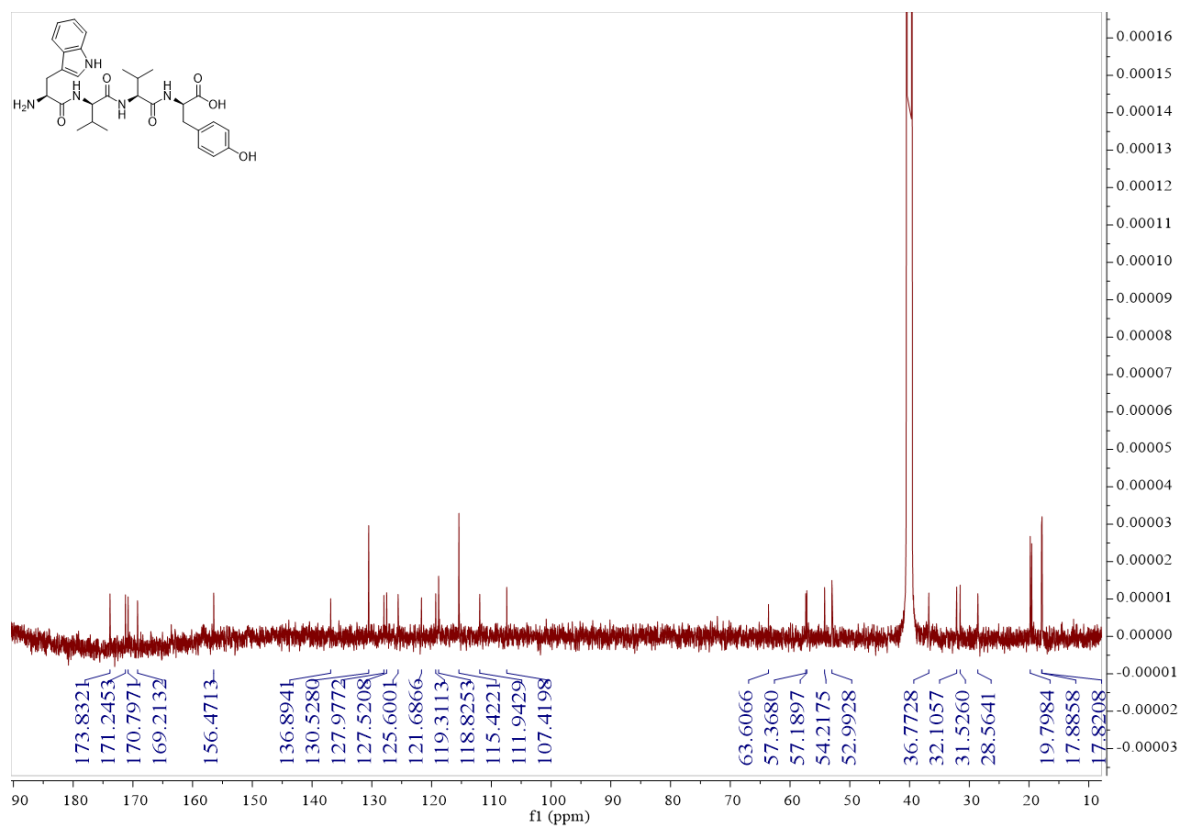


Figure S23. ¹³C-NMR spectrum (150 MHz, DMSO-*d*₆) of compound **3**

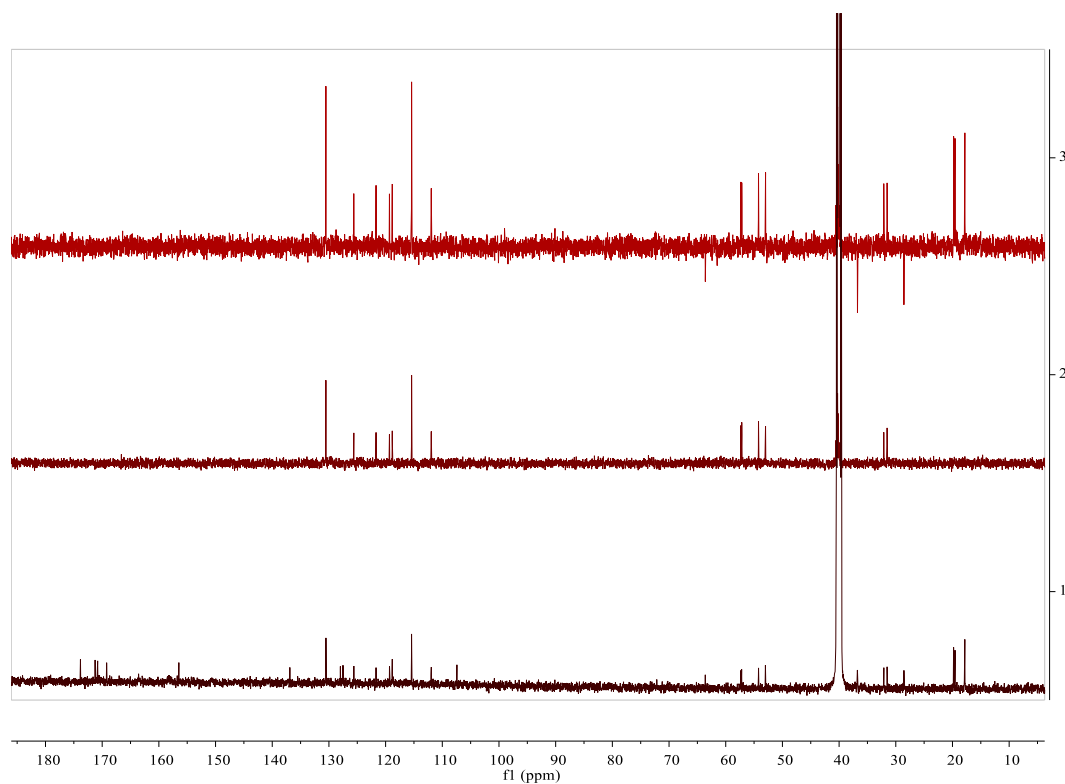


Figure S24. DEPT (150 MHz, DMSO- d_6) spectrum of compound **3**

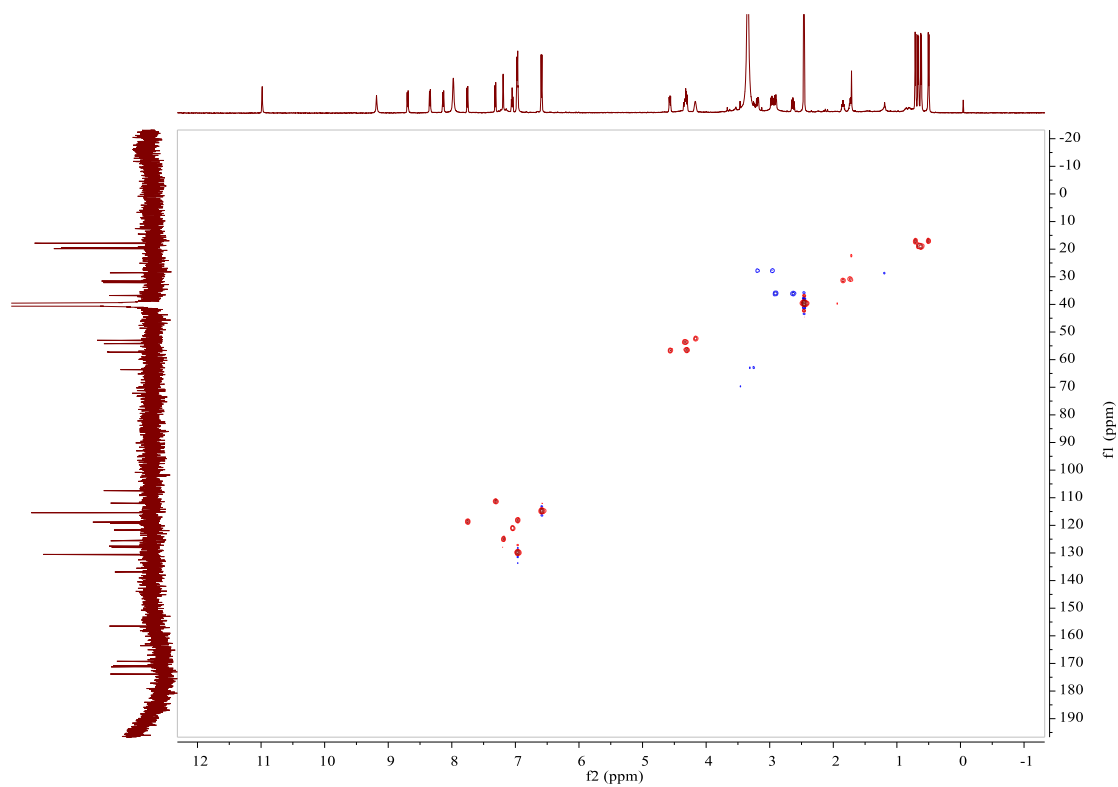


Figure S25. HSQC spectrum (600 MHz, DMSO- d_6) of compound **3**

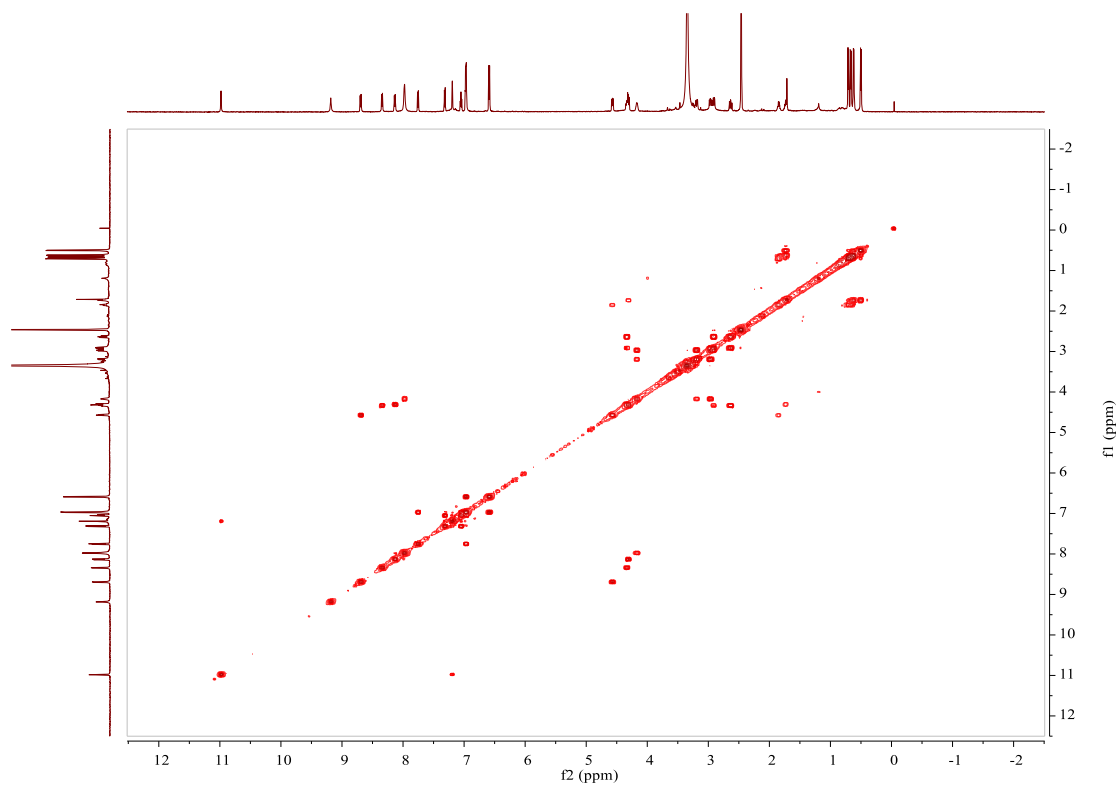


Figure S26. ^1H - ^1H COSY spectrum (600 MHz, $\text{DMSO-}d_6$) of compound **3**

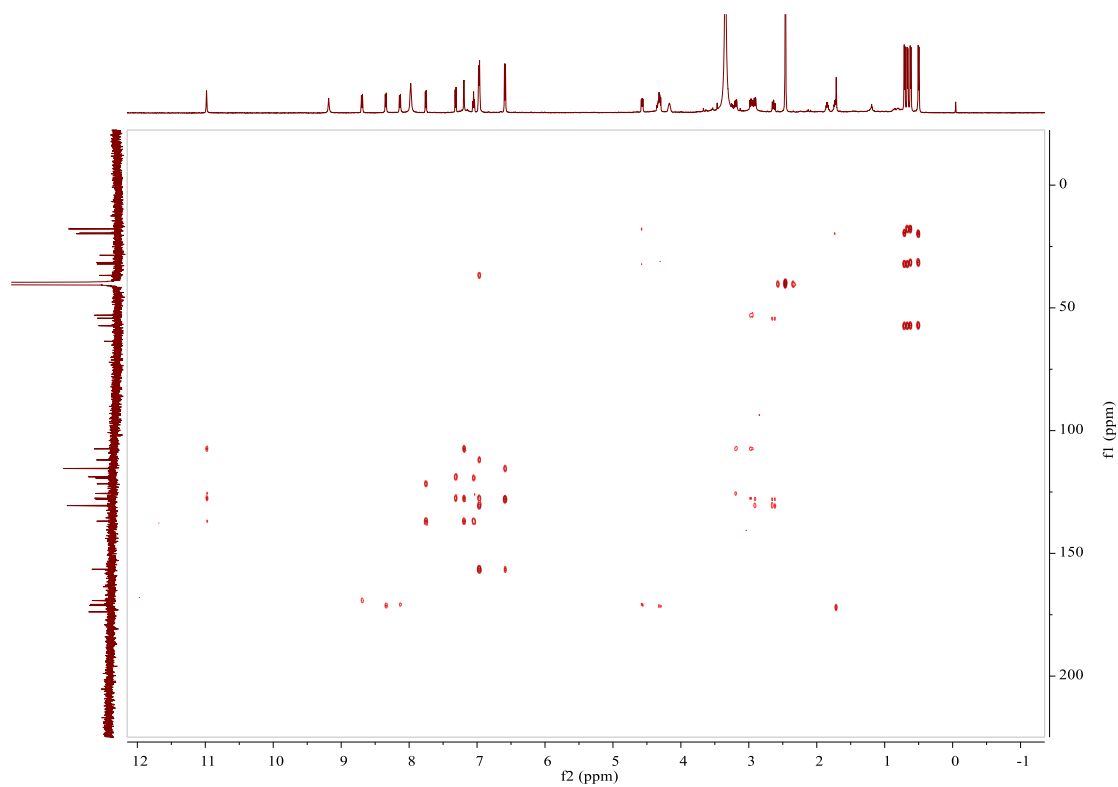


Figure S27. HMBC spectrum (600 MHz, $\text{DMSO-}d_6$) of compound **3**

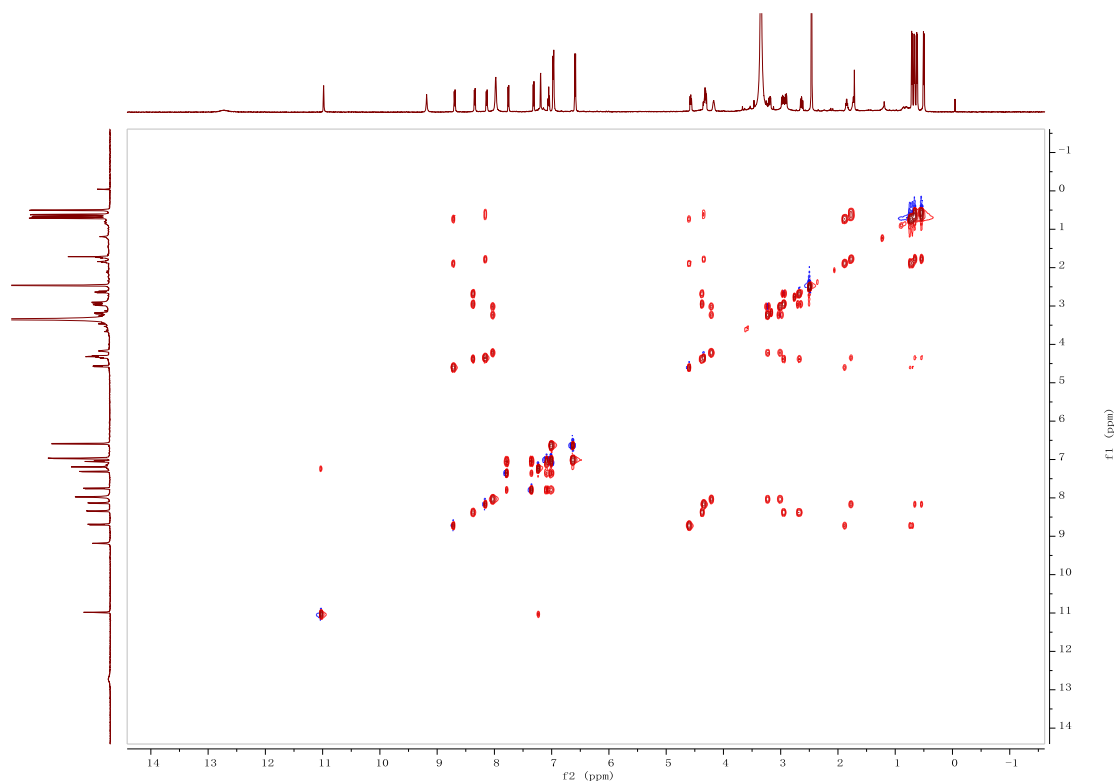


Figure S28. TOCSY spectrum (600 MHz, DMSO- d_6) of compound **3**

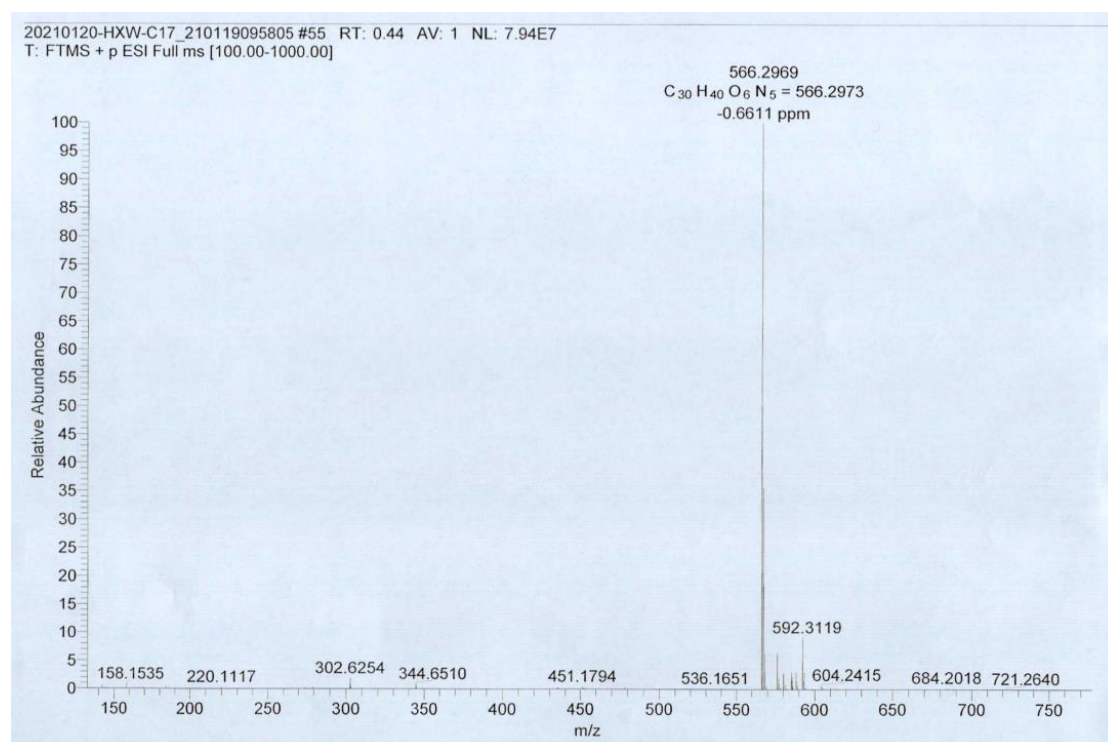


Figure S29. HRESIMS spectrum of compound **3**

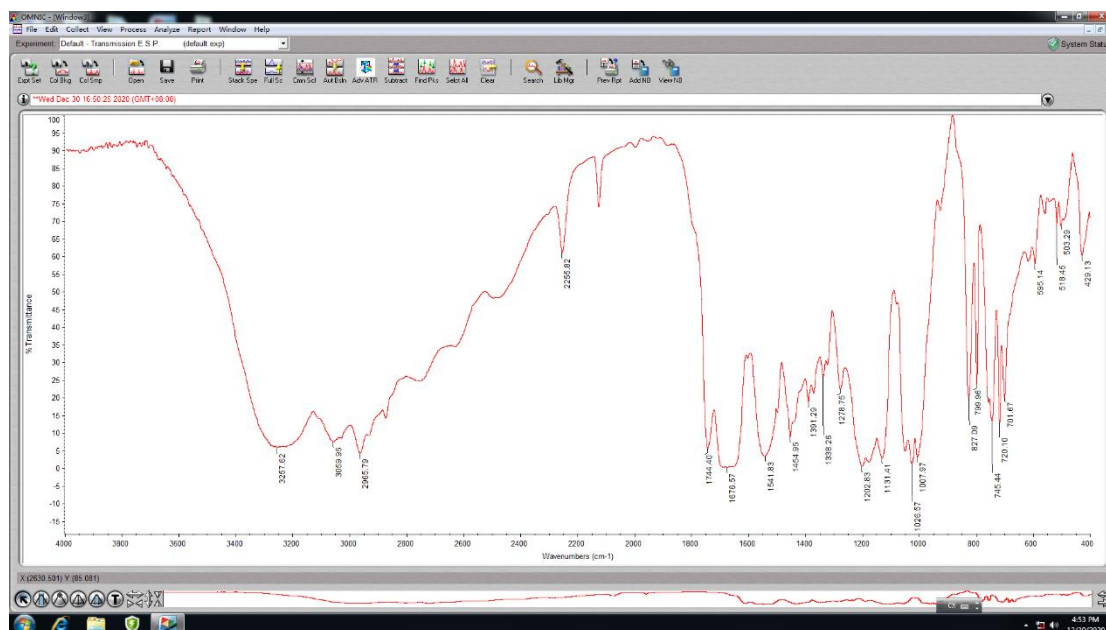


Figure S30. IR spectrum of compound **3**

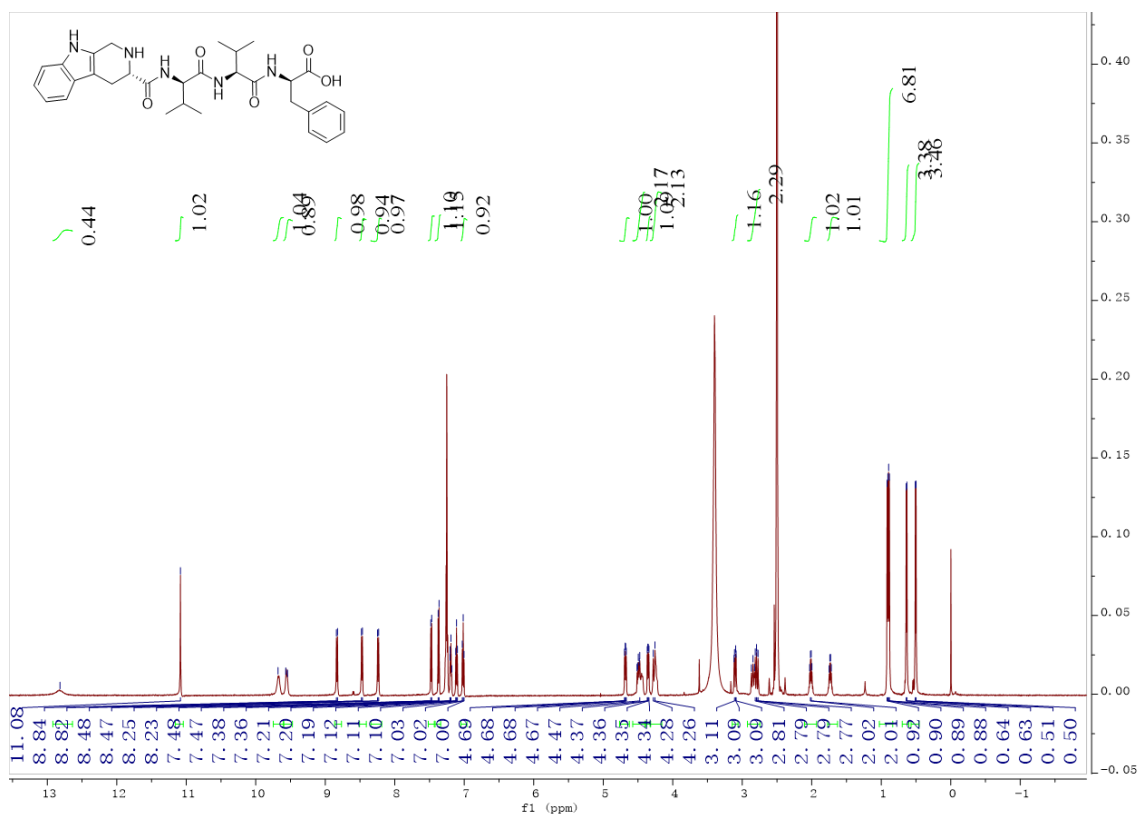


Figure S31. ¹H-NMR spectrum (600 MHz, DMSO-*d*₆) of compound **4**

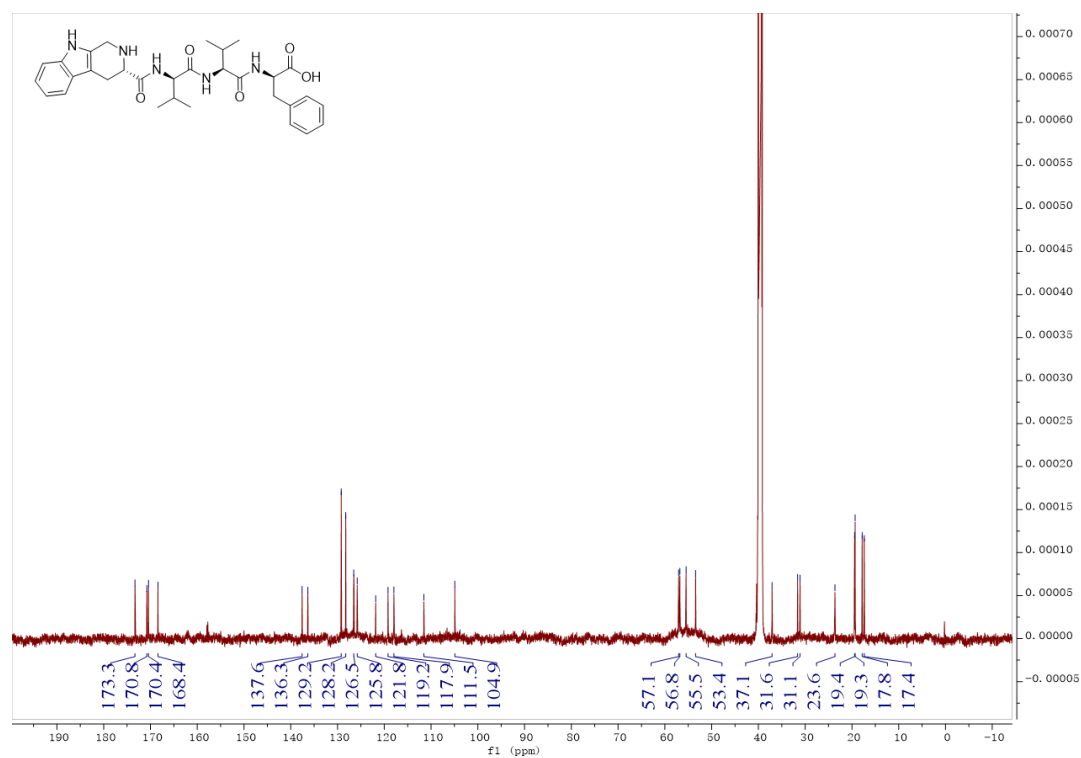


Figure S32. ¹³C-NMR spectrum (150 MHz, DMSO-*d*₆) of compound **4**

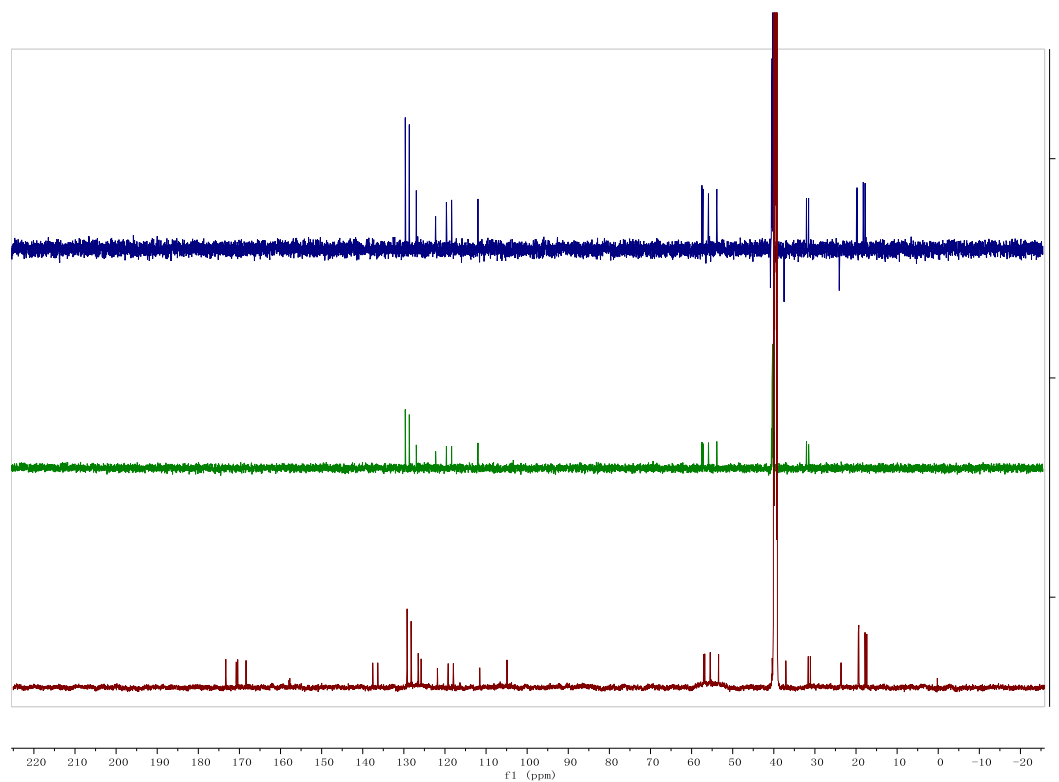


Figure S33. DEPT (150 MHz, DMSO-*d*₆) spectrum of compound **4**

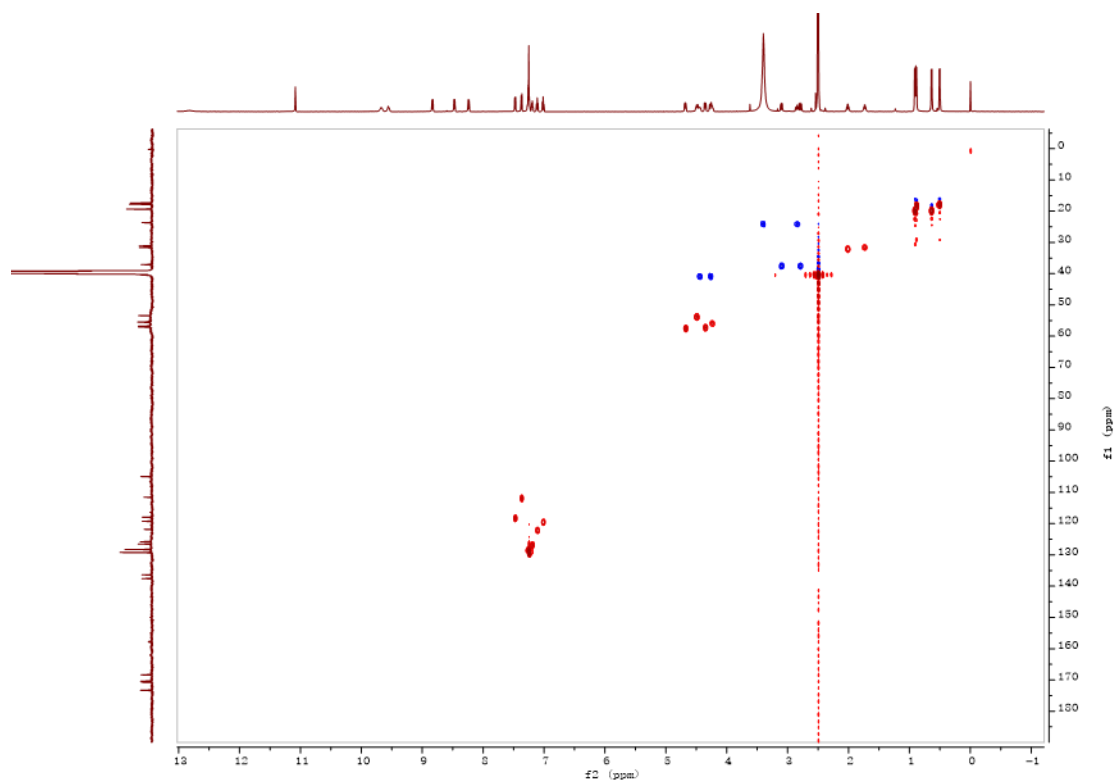


Figure S34. HSQC spectrum (600 MHz, DMSO-*d*₆) of compound **4**

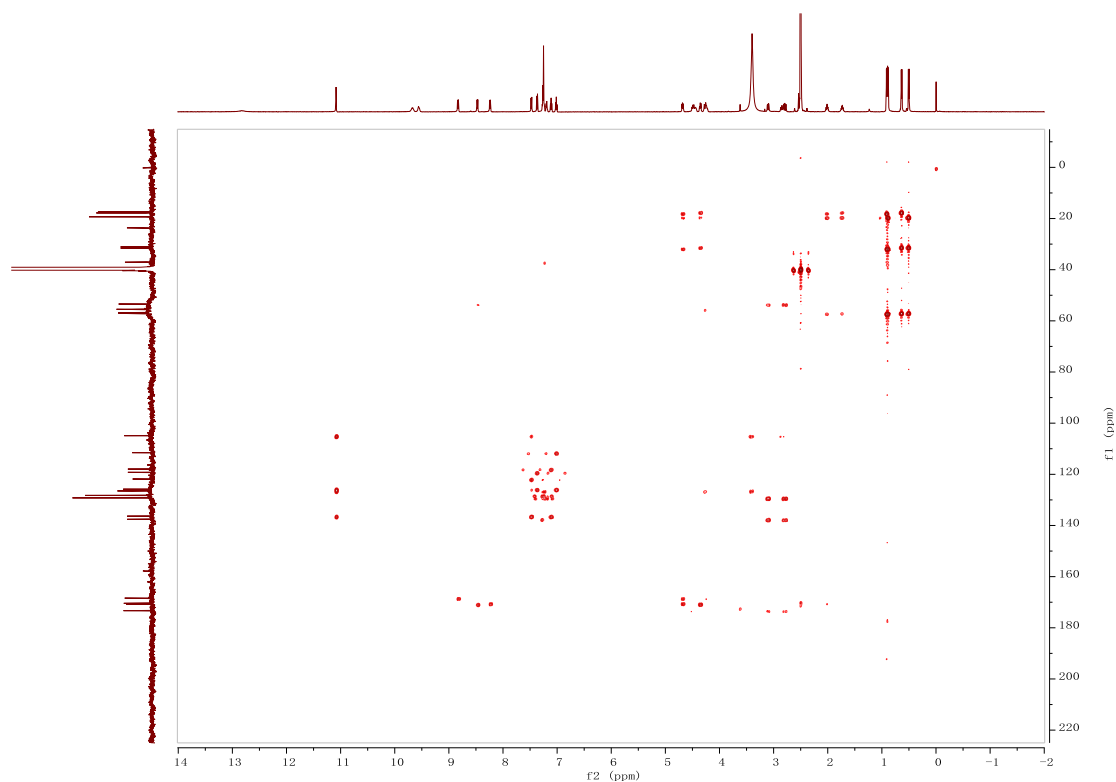


Figure S35. HMBC spectrum (600 MHz, DMSO-*d*₆) of compound **4**

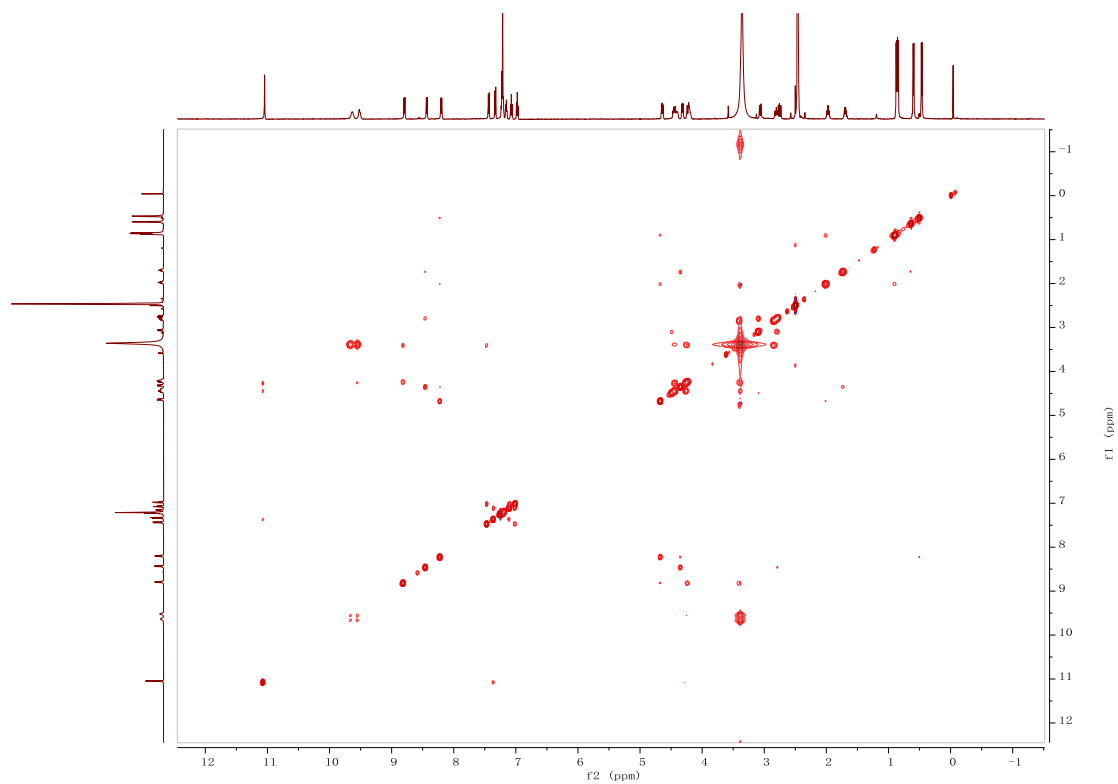


Figure S36. NOESY spectrum (600 MHz, DMSO-*d*₆) of compound **4**

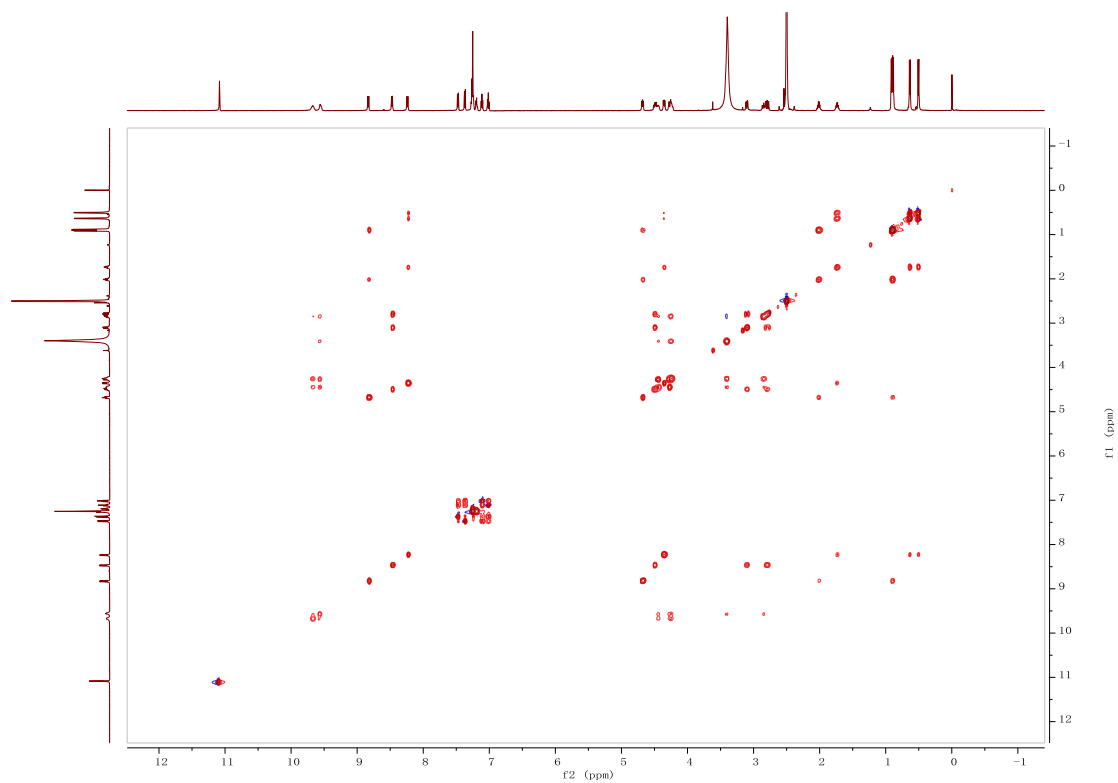


Figure S37. TOCSY spectrum (600 MHz, DMSO-*d*₆) of compound **4**

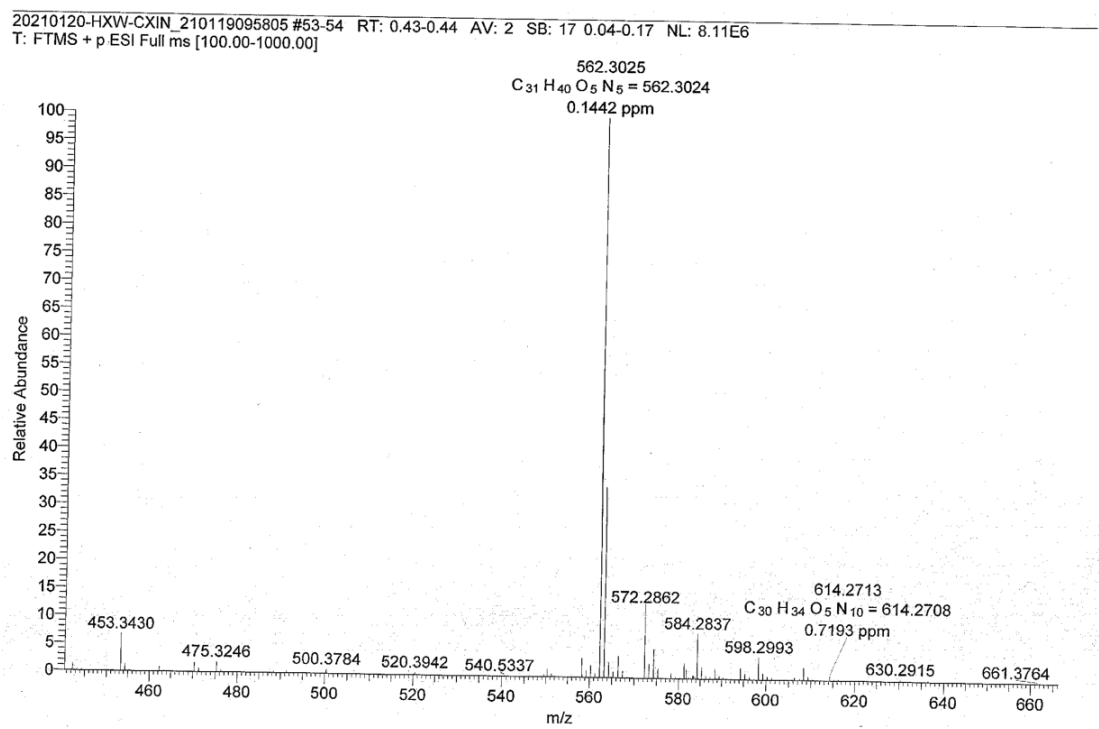


Figure S38. HRESIMS spectrum of compound **4**

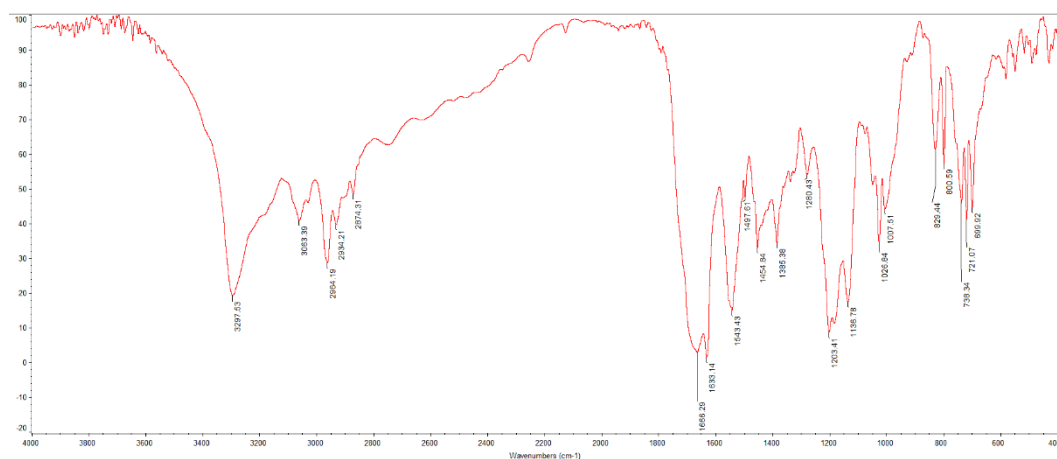


Figure S39. IR spectrum of compound **4**

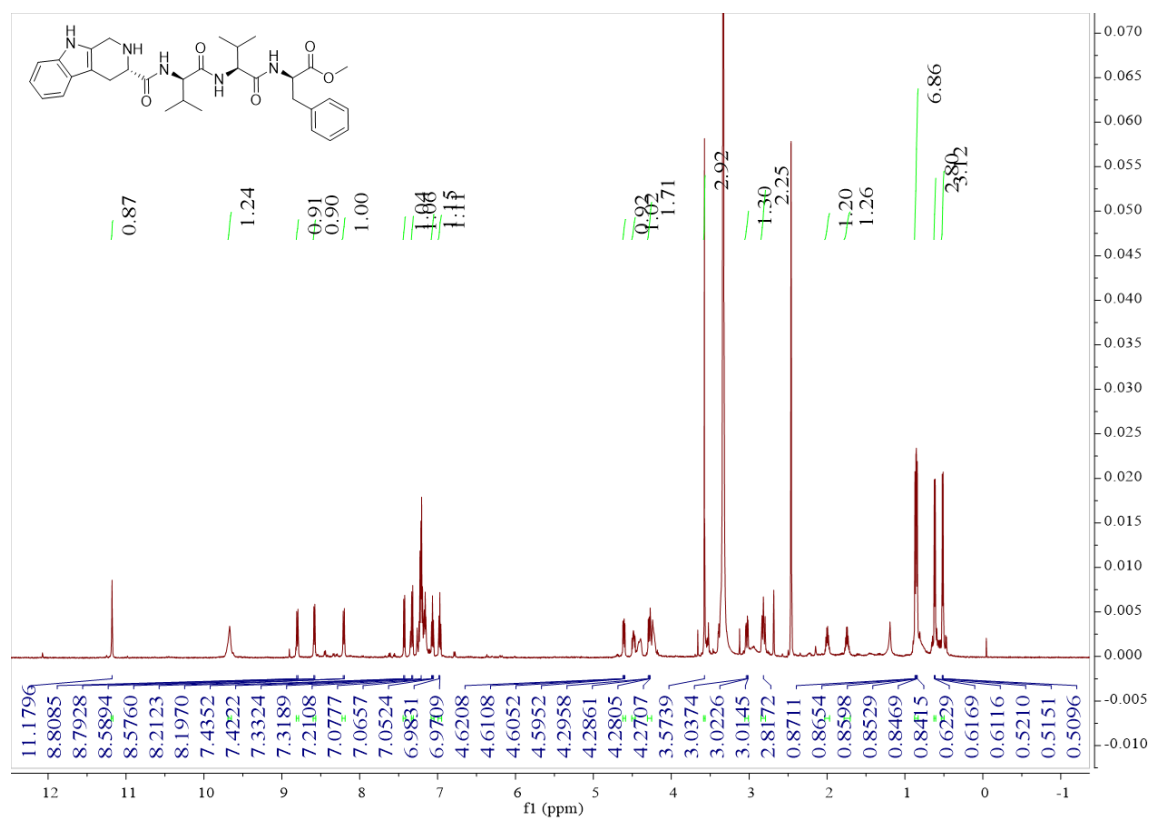


Figure S40. ¹H-NMR spectrum (600 MHz, DMSO-*d*₆) of compound **5**

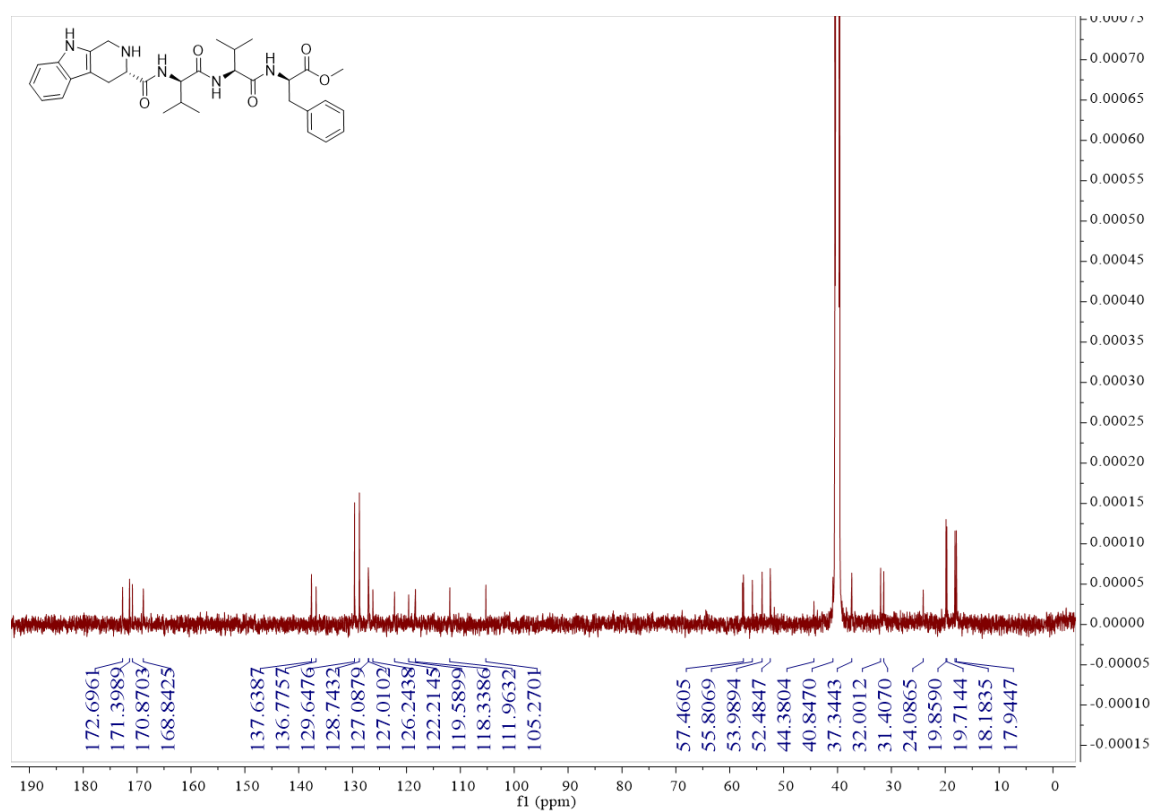


Figure S41. ¹³C-NMR spectrum (150 MHz, DMSO-*d*₆) of compound **5**

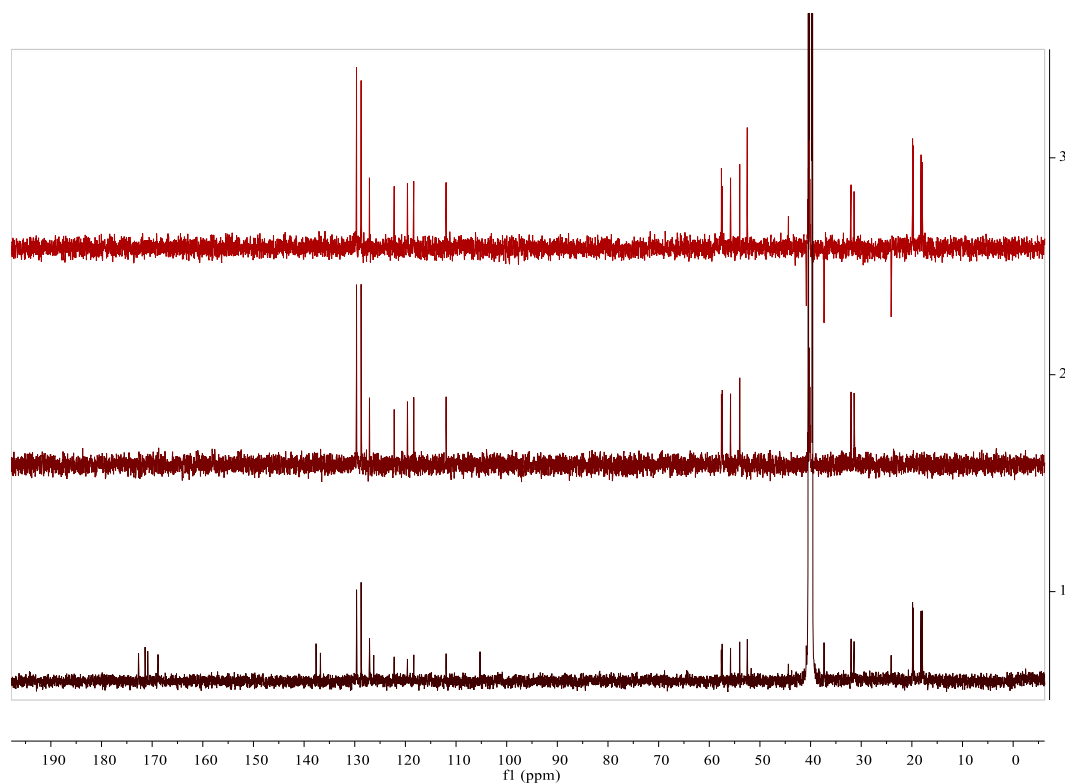


Figure S42. DEPT (150 MHz, DMSO- d_6) spectrum of compound **5**

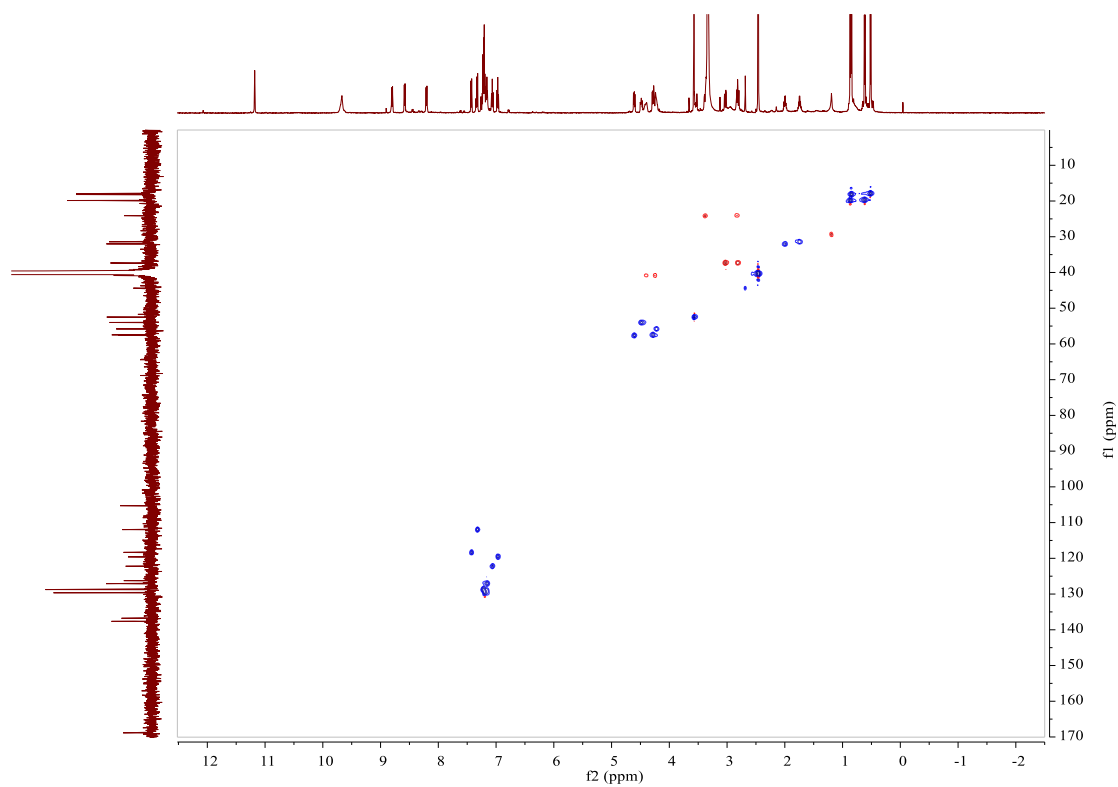


Figure S43. HSQC spectrum (600 MHz, DMSO- d_6) of compound **5**

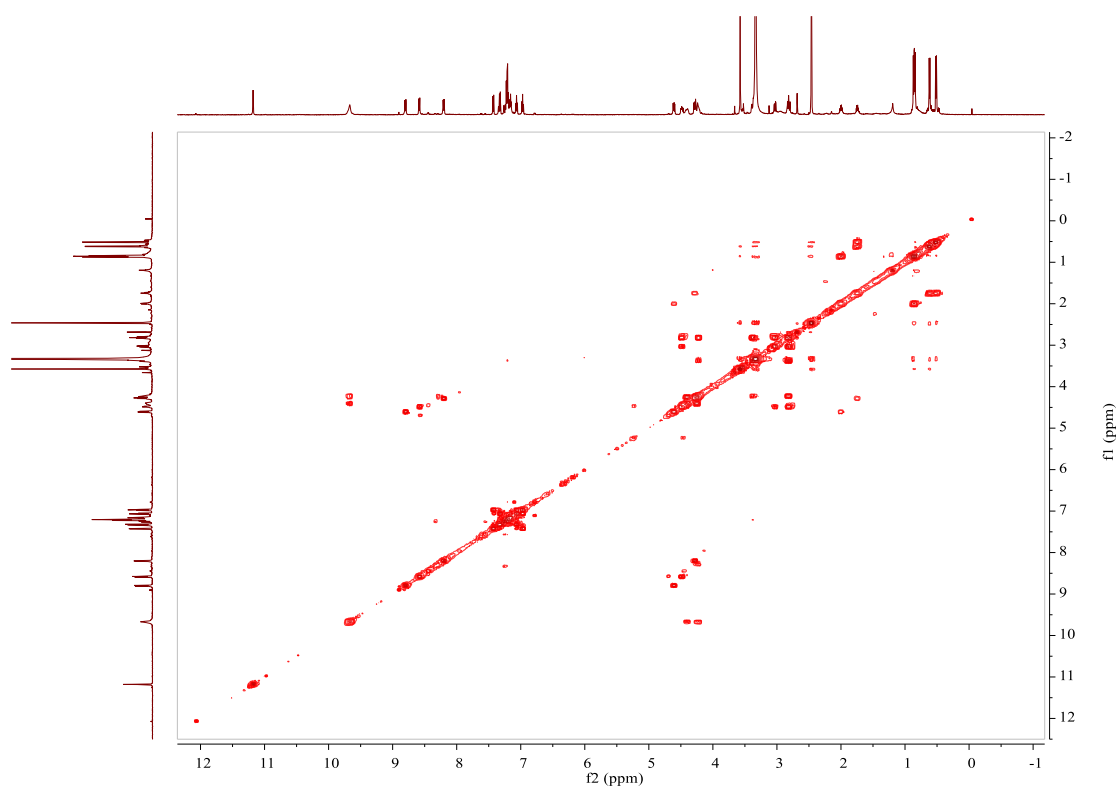


Figure S44. ^1H - ^1H COSY spectrum (600 MHz, $\text{DMSO}-d_6$) of compound **5**

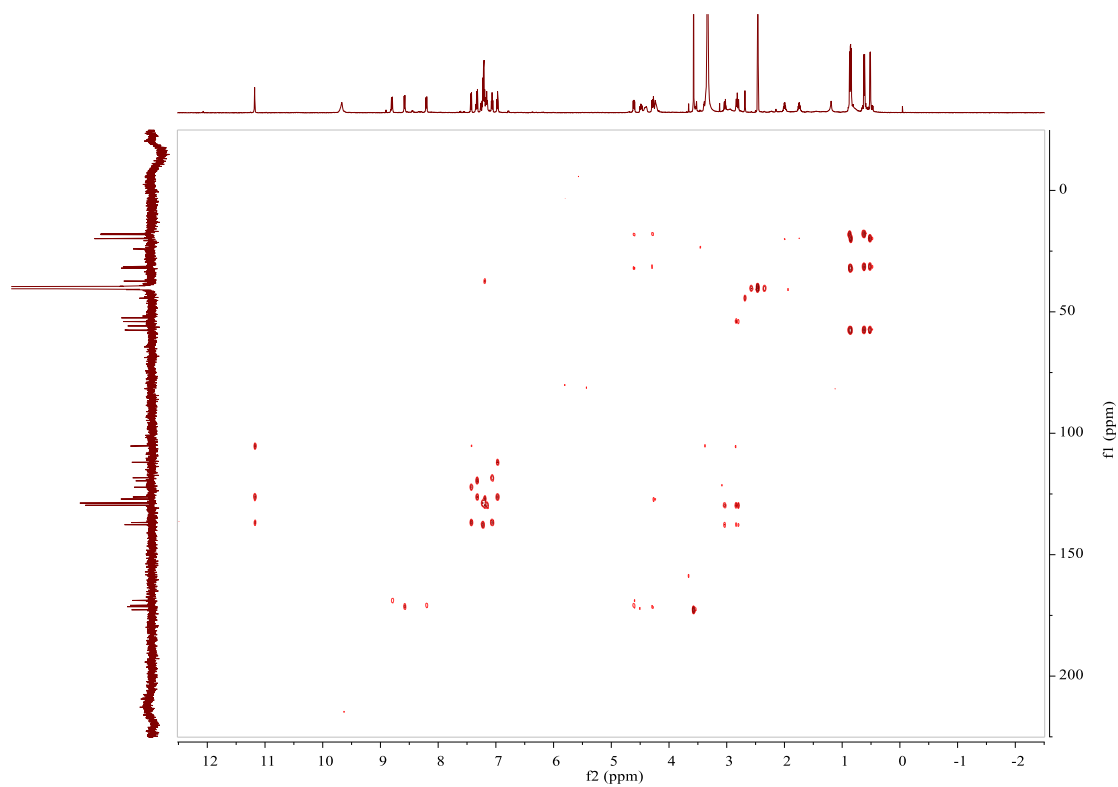


Figure S45. HMBC spectrum (600 MHz, $\text{DMSO}-d_6$) of compound **5**

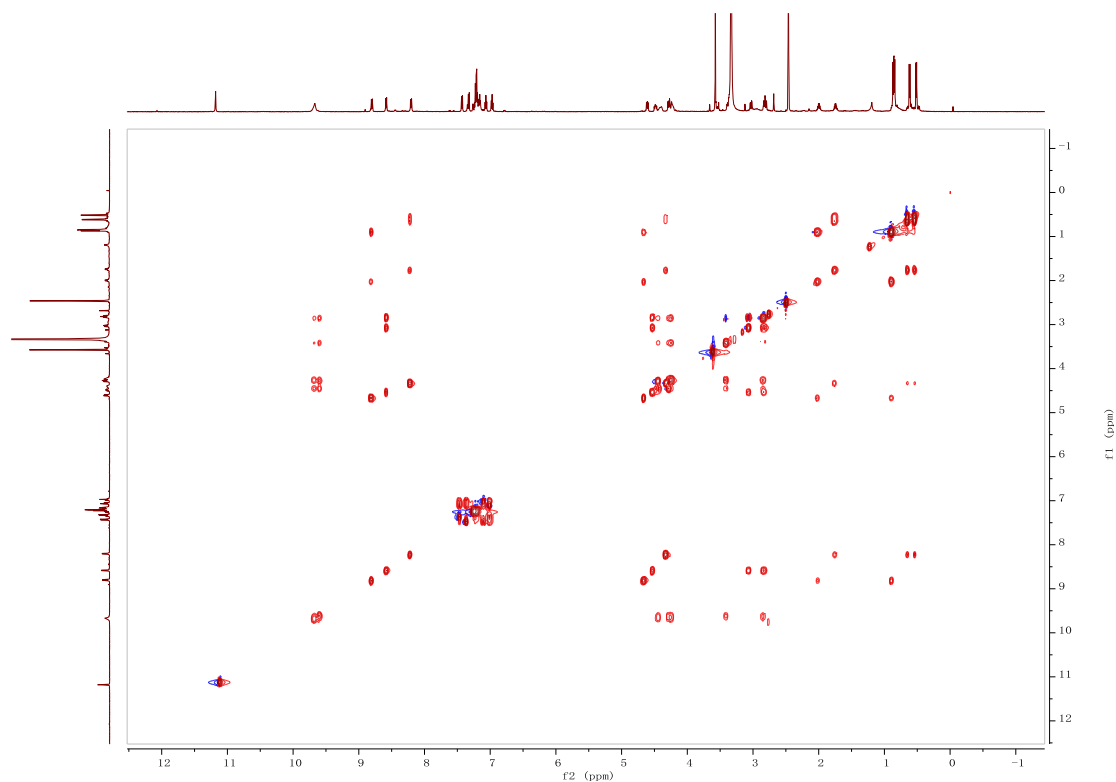


Figure S46. TOCSY spectrum (600 MHz, DMSO- d_6) of compound **5**

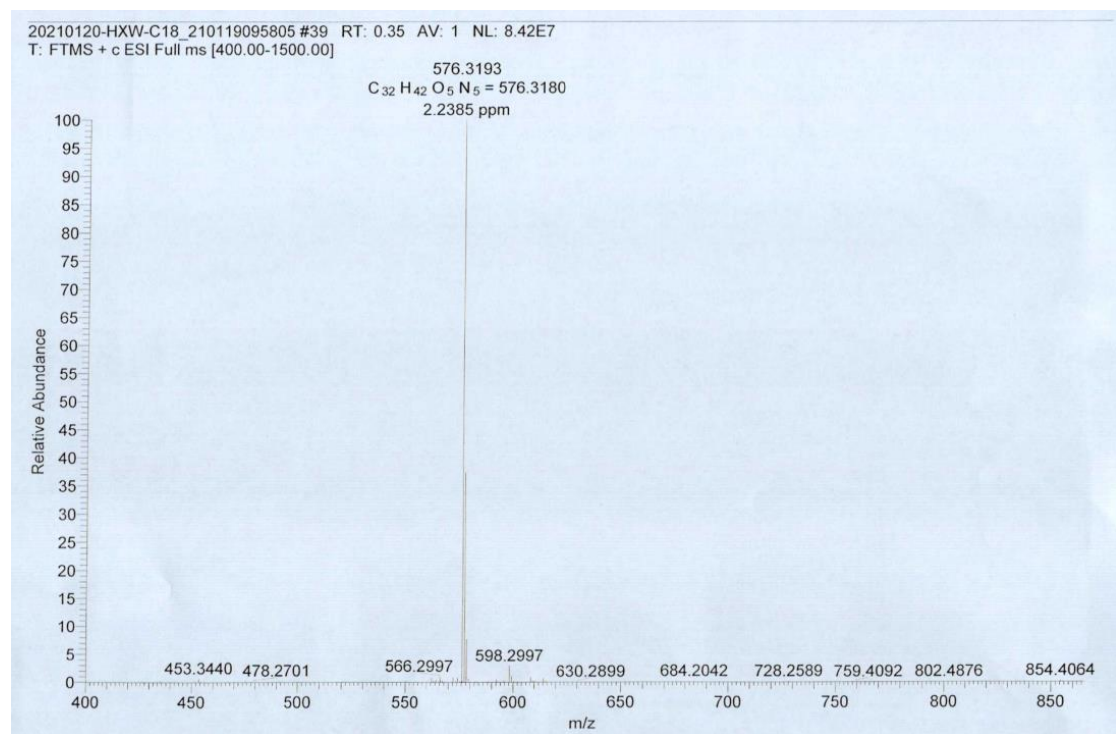


Figure S47. HRESIMS spectrum of compound **5**

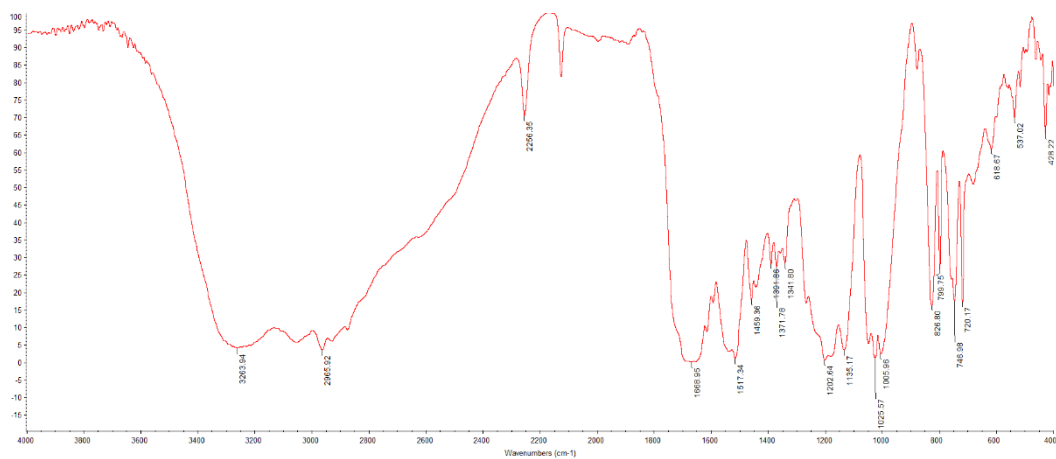


Figure S48. IR spectrum of compound **5**

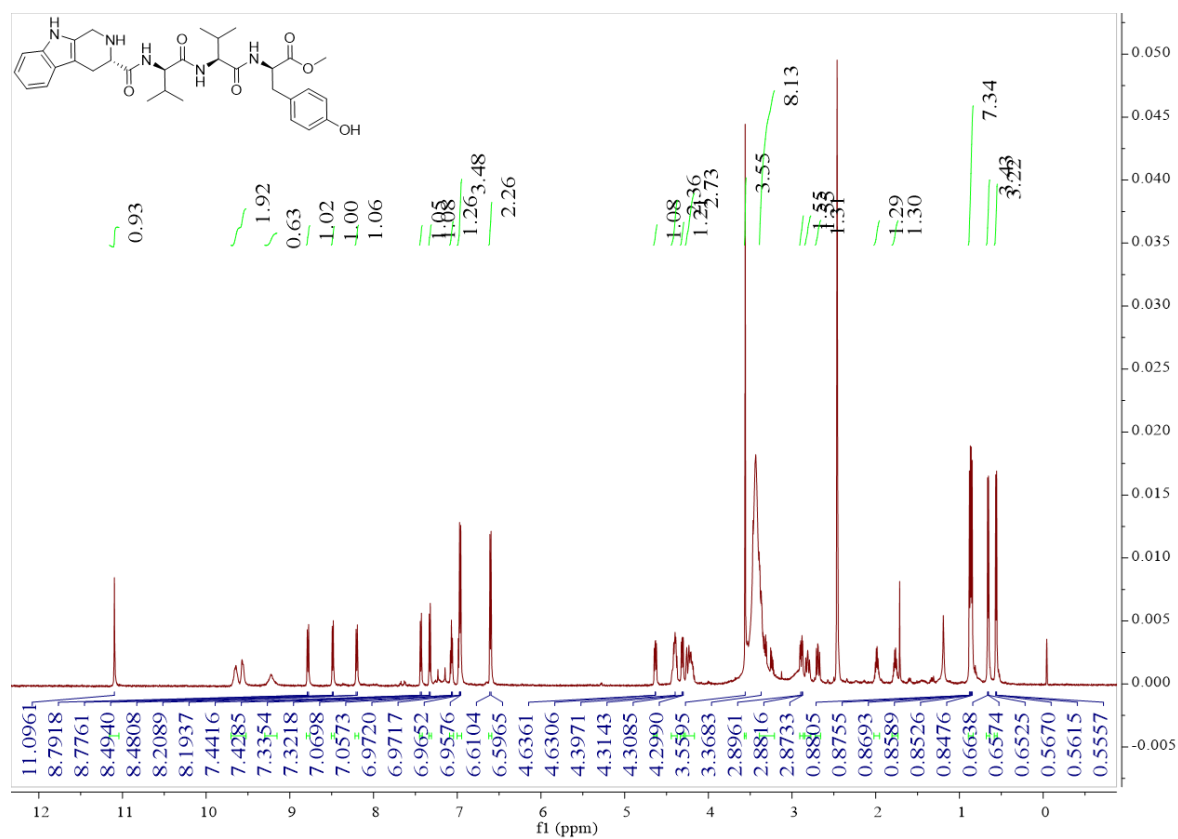


Figure S49. ^1H -NMR spectrum (600 MHz, $\text{DMSO}-d_6$) of compound **6**

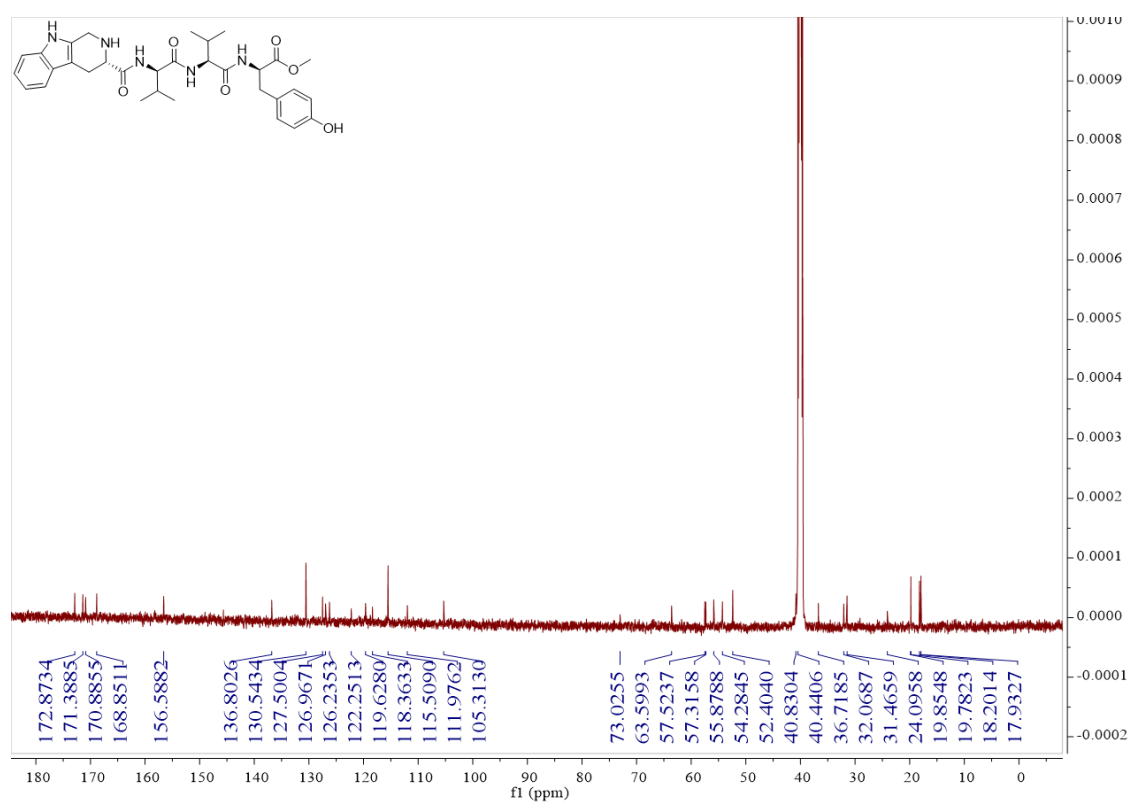


Figure S50. ¹³C-NMR spectrum (150 MHz, DMSO-*d*₆) of compound **6**

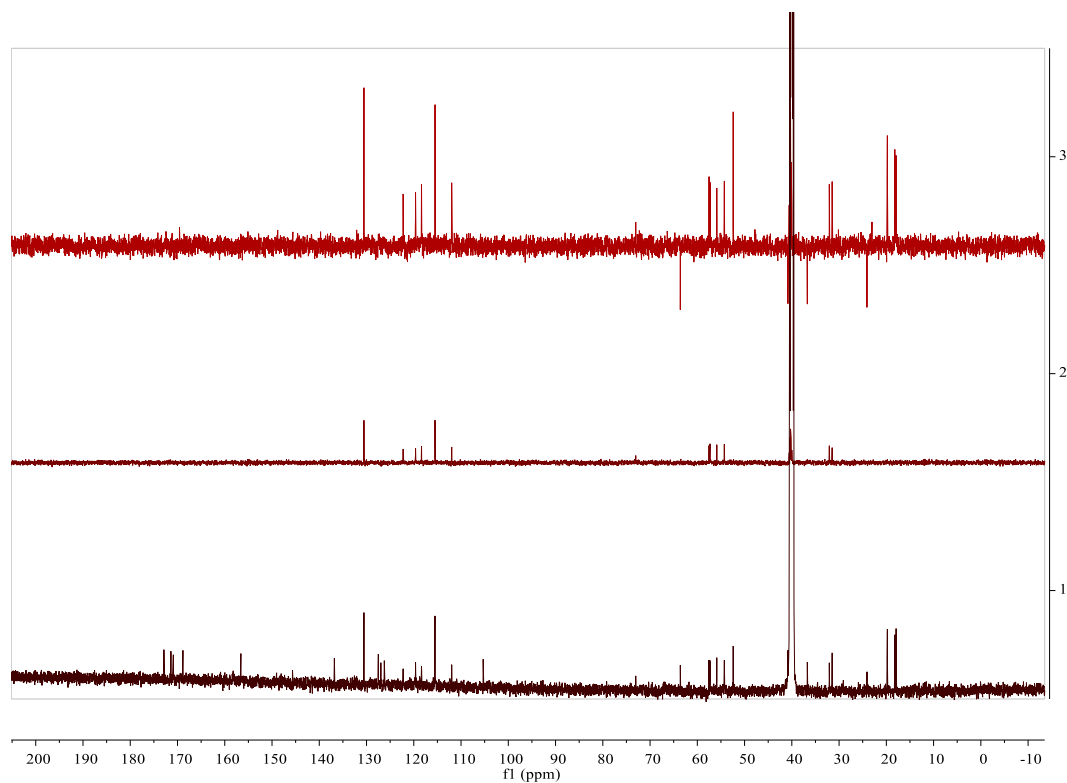


Figure S51. DEPT (150 MHz, DMSO-*d*₆) spectrum of compound **6**

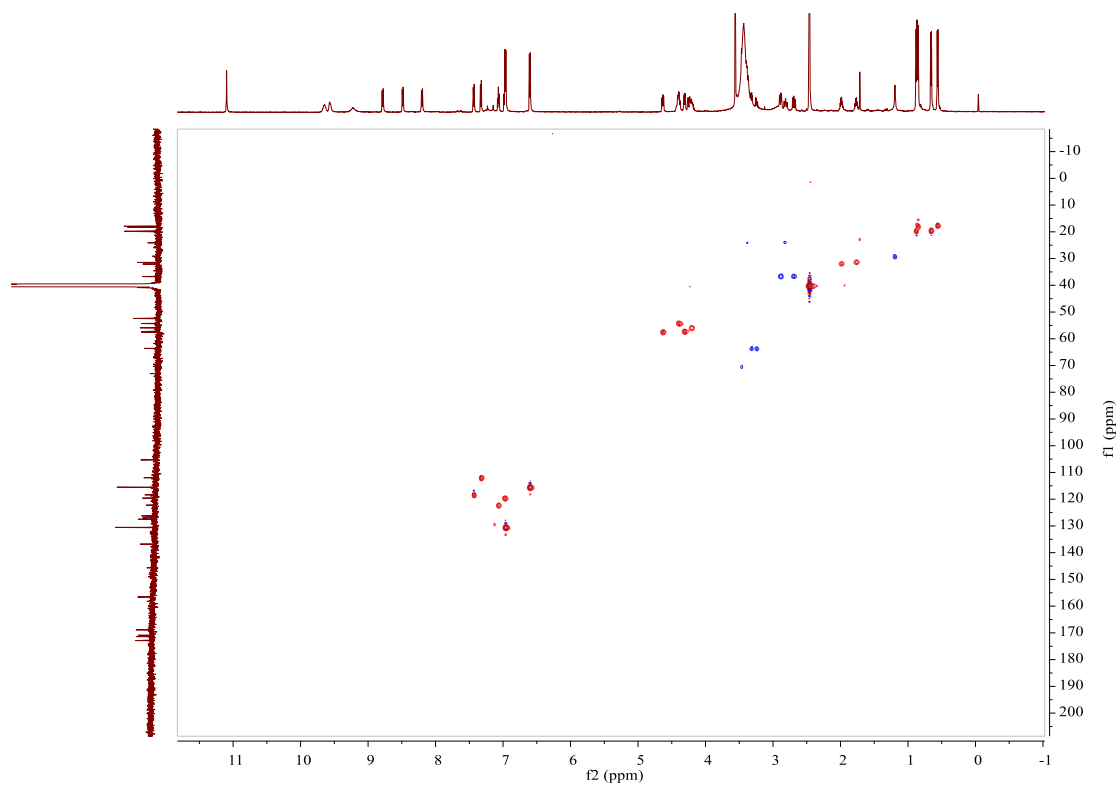


Figure S52. HSQC spectrum (600 MHz, $\text{DMSO-}d_6$) of compound **6**

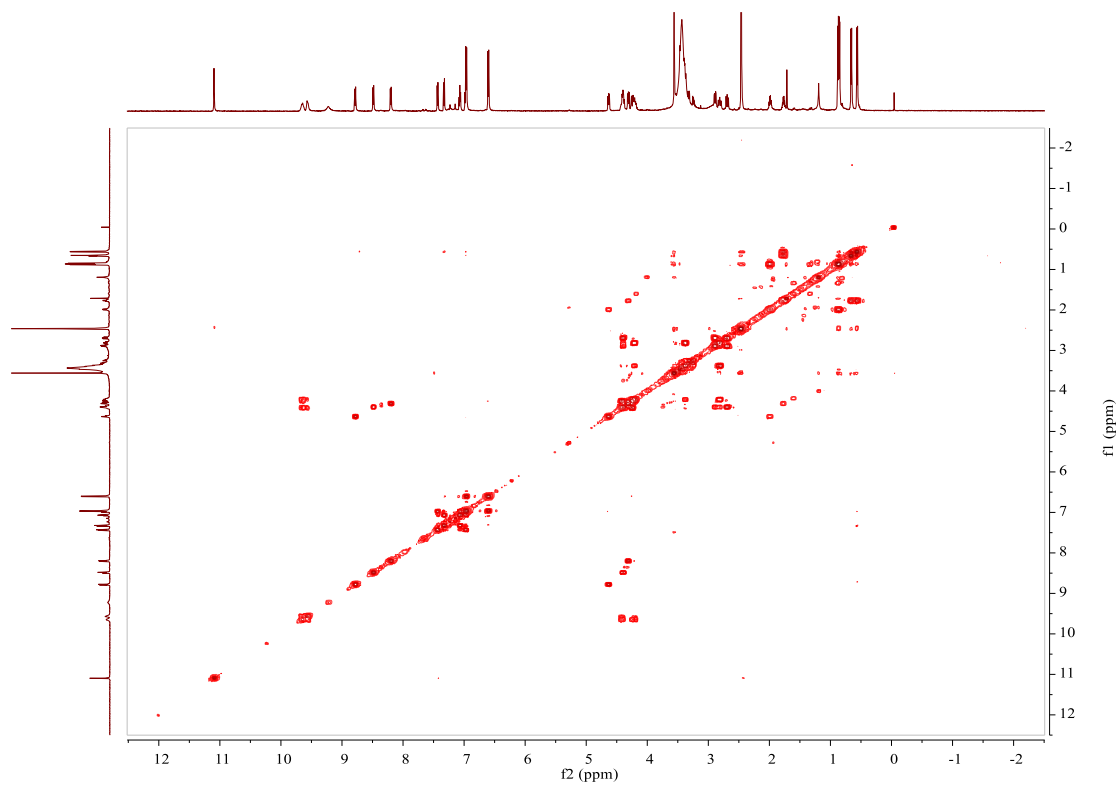


Figure S53. ^1H - ^1H COSY spectrum (600 MHz, $\text{DMSO-}d_6$) of compound **6**

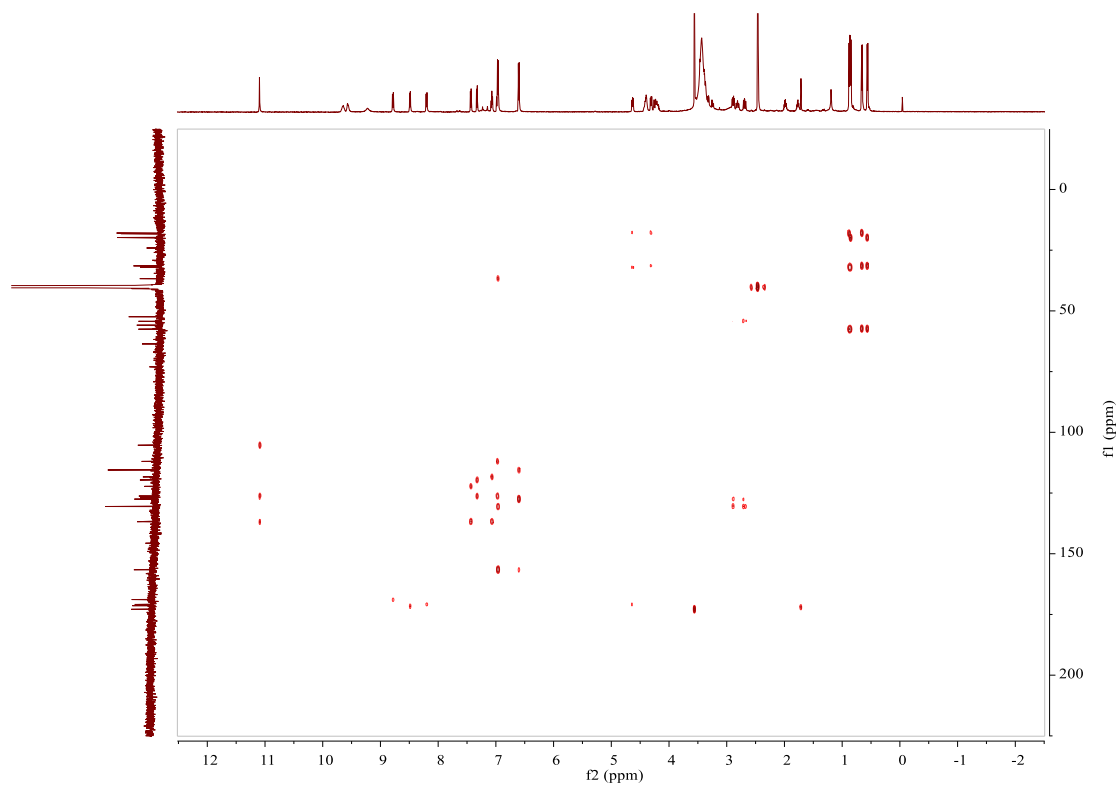


Figure S54. HMBC spectrum (600 MHz, DMSO- d_6) of compound **6**

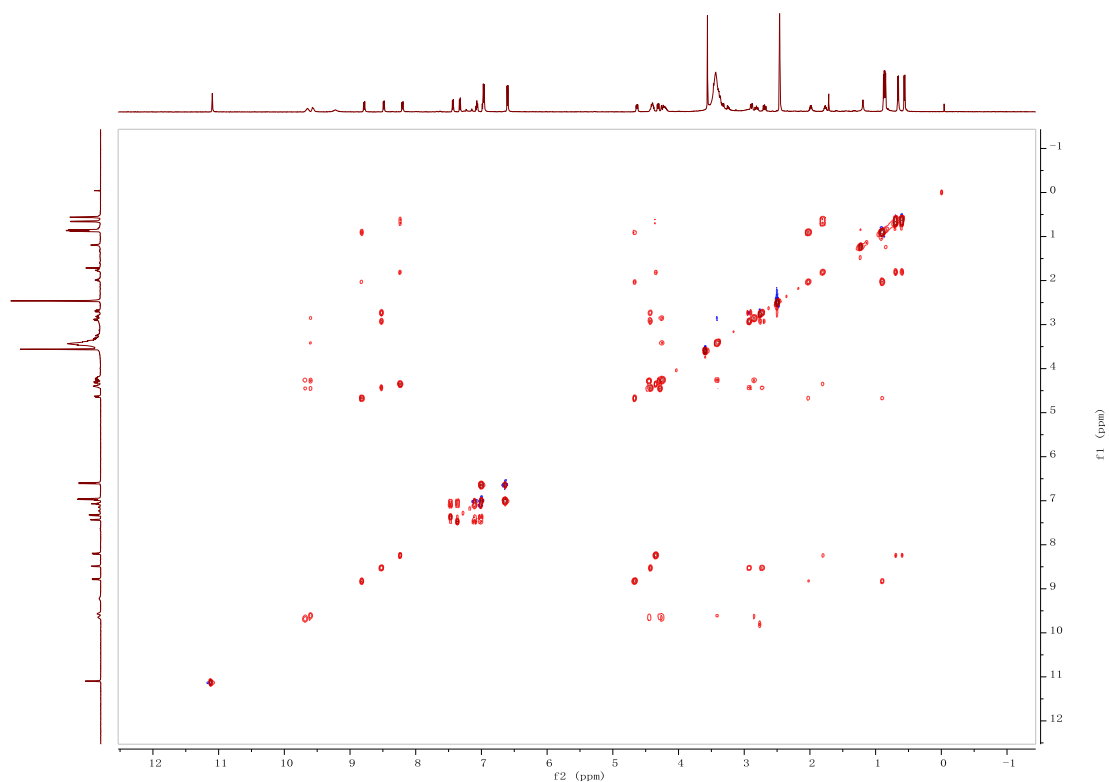


Figure S55. TOCSY spectrum (600 MHz, DMSO- d_6) of compound **6**

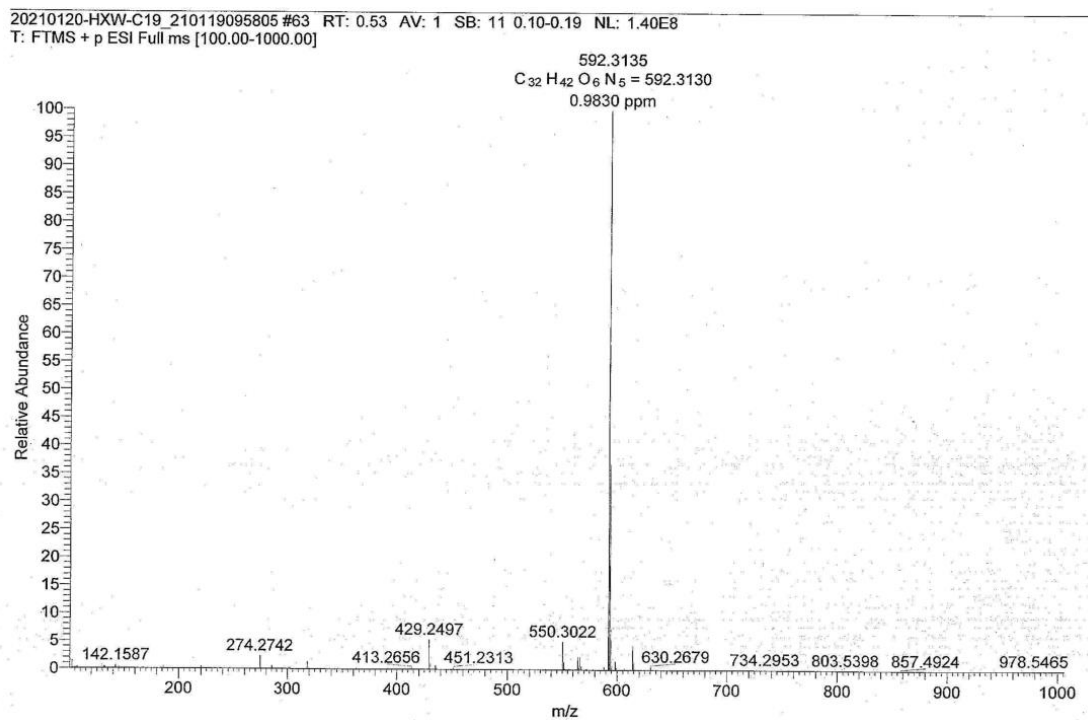


Figure S56. HRESIMS spectrum of compound **6**

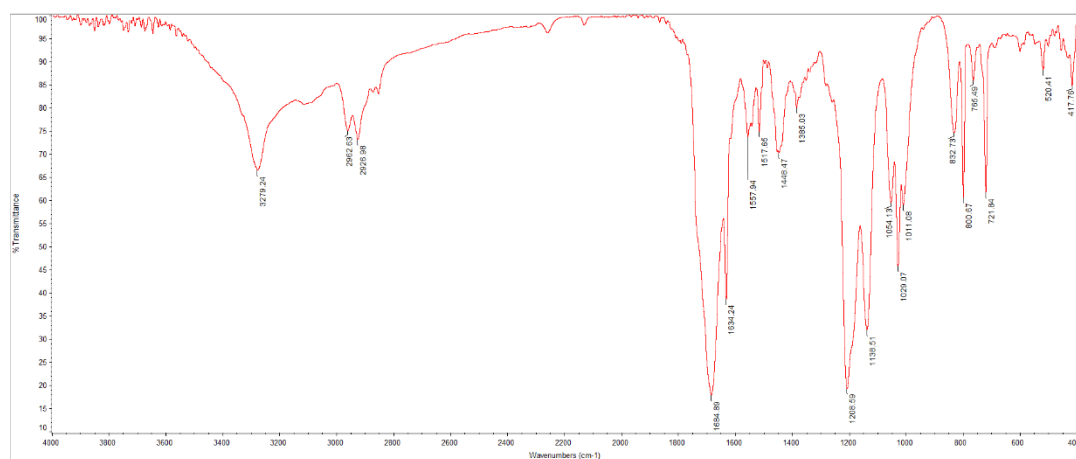


Figure S57. IR spectrum of compound **6**

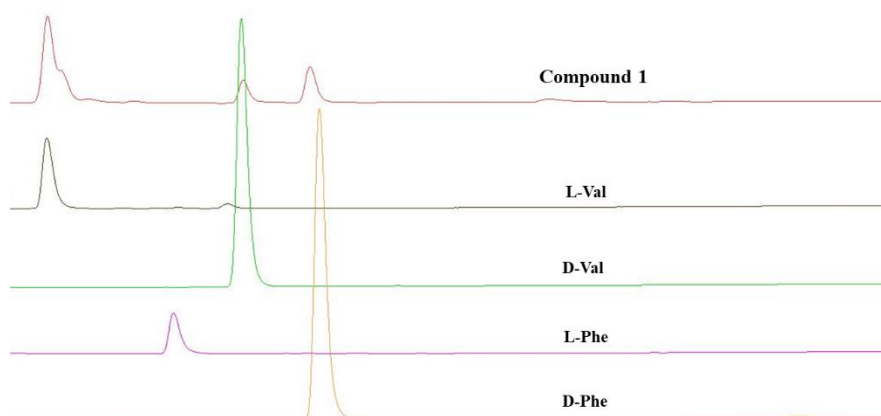


Figure S58. Advanced Marfey's acid hydrolytic analysis of compound **1**

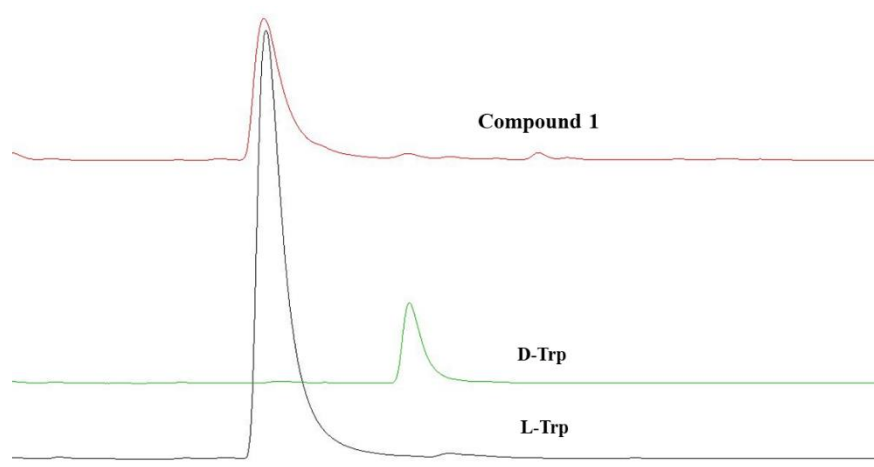


Figure S59. Advanced Marfey's alkaline hydrolytic analysis of compound **1**

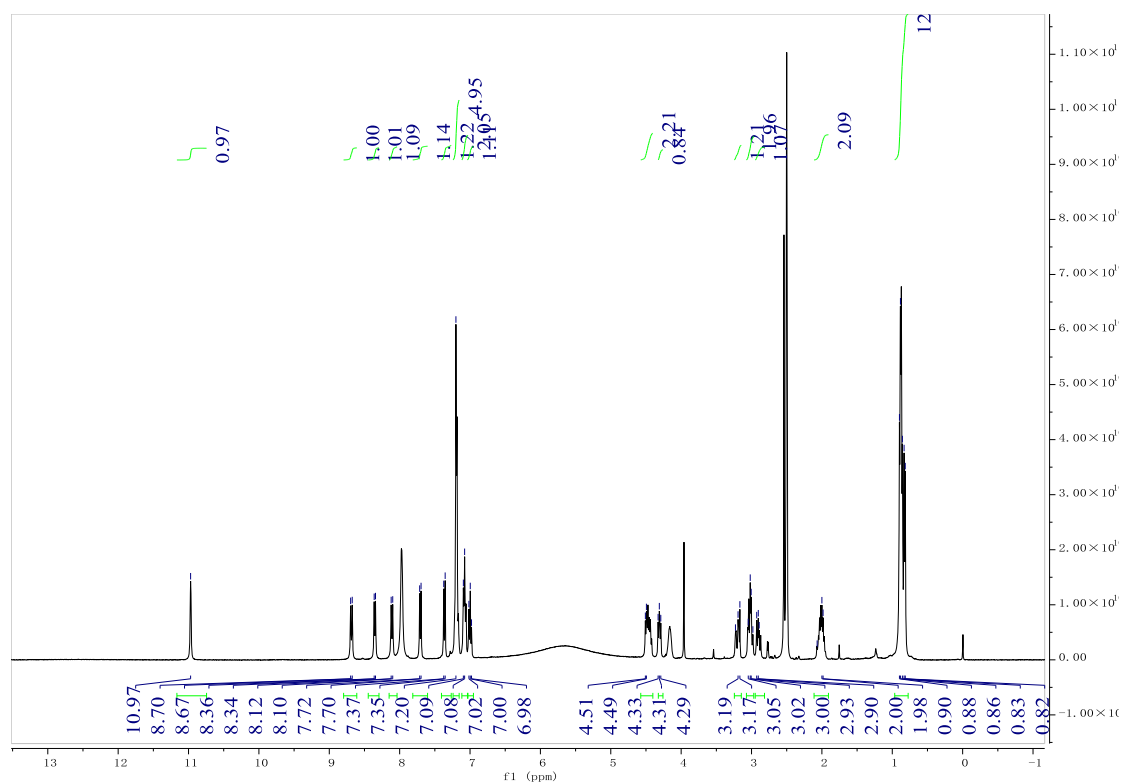
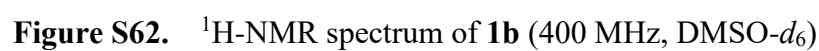
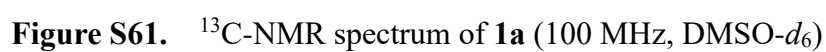


Figure S60. ^1H -NMR spectrum of **1a** (400 MHz, $\text{DMSO}-d_6$)



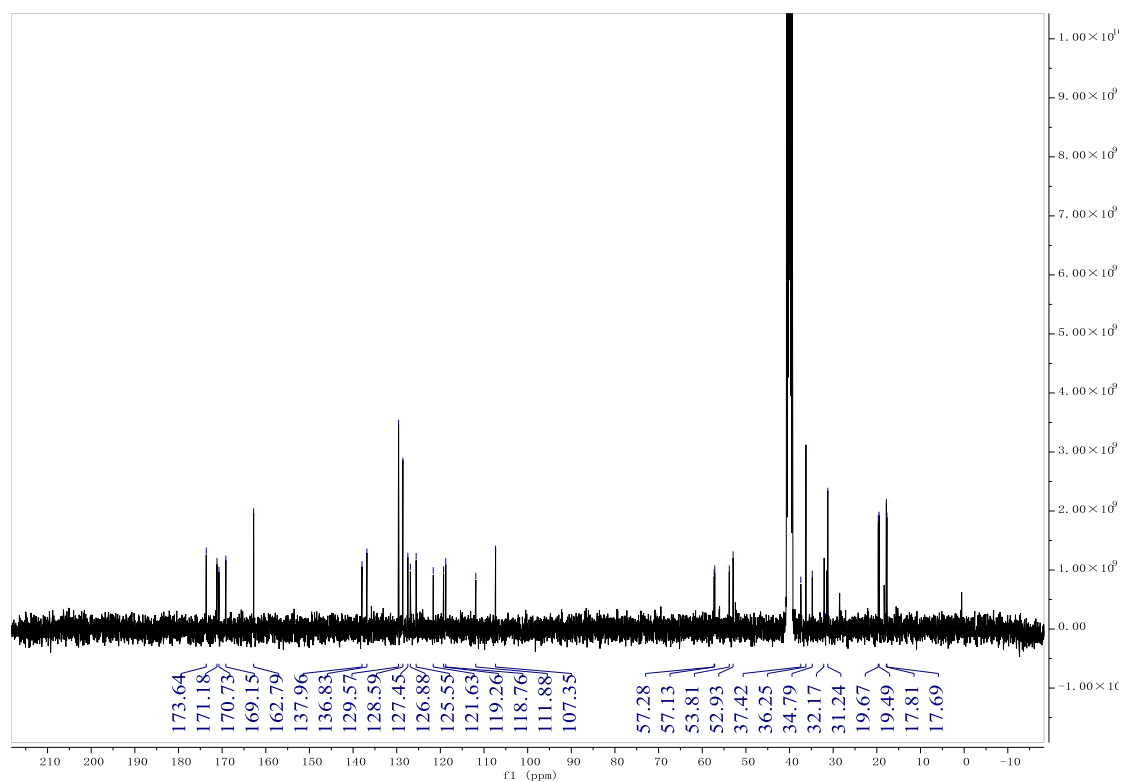


Figure S63. ^{13}C -NMR spectrum of **1b** (100 MHz, DMSO- d_6)

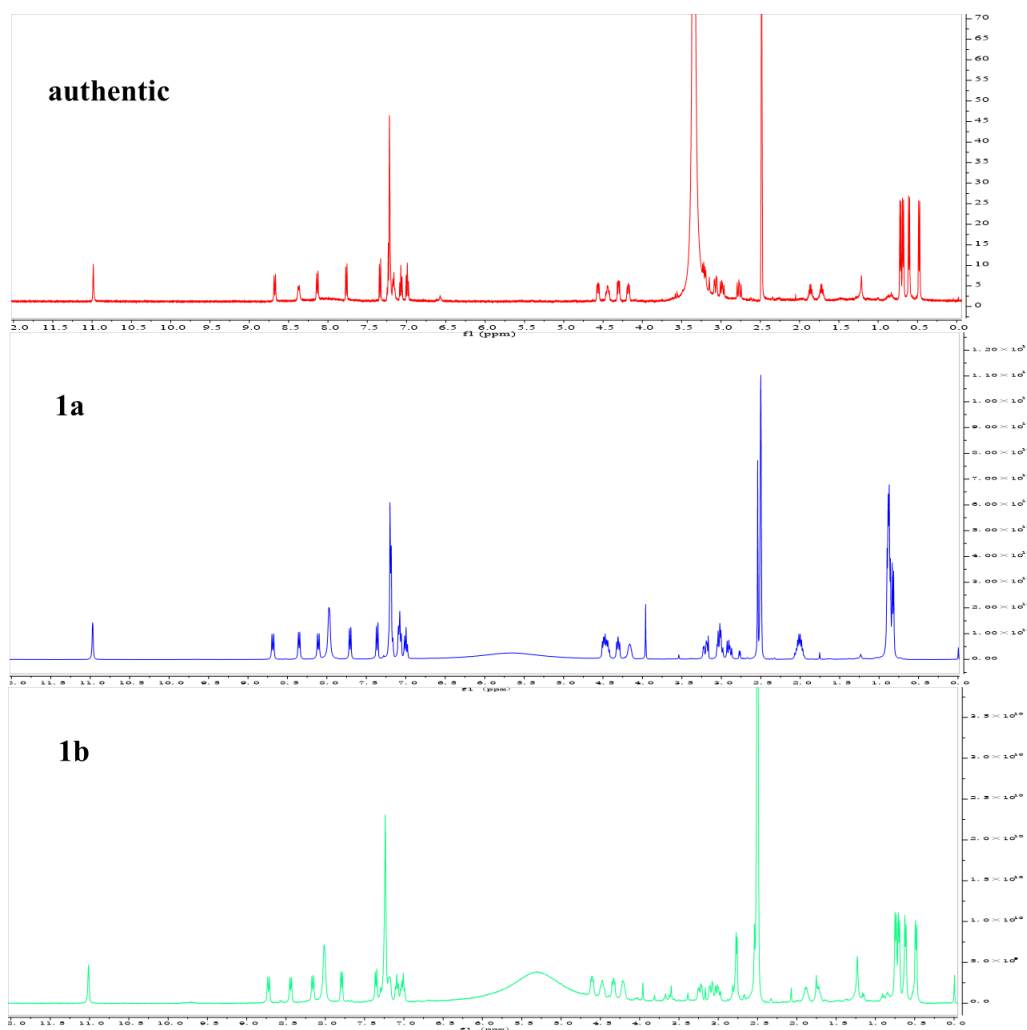


Figure S64. Comparison of ^1H -NMR spectra of authentic **1**, **1a**, and **1b**

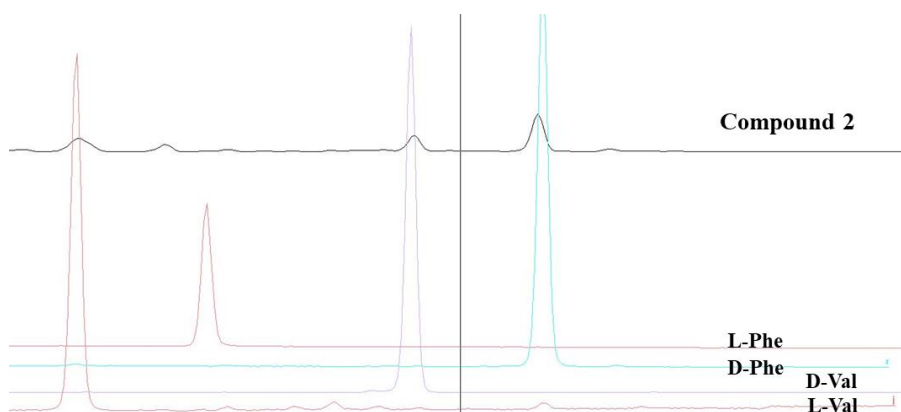


Figure S65. Advanced Marfey's acid hydrolytic analysis of compound **2**

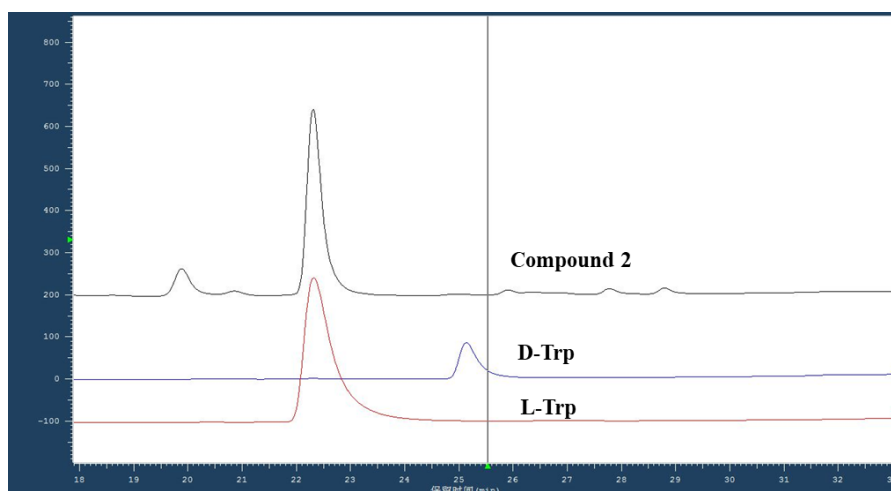


Figure S66. Advanced Marfey's alkaline hydrolytic analysis of compound **2**

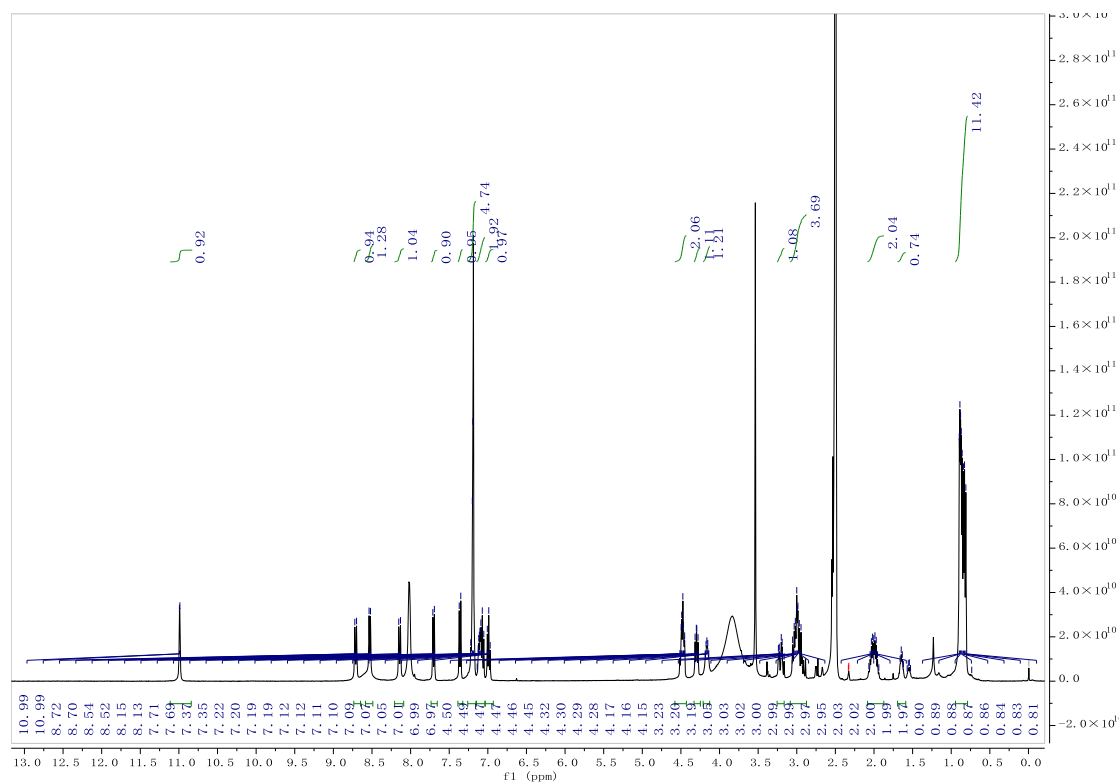
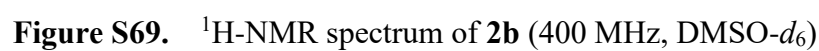
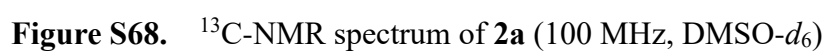


Figure S67. ^1H -NMR spectrum of **2a** (400 MHz, $\text{DMSO}-d_6$)



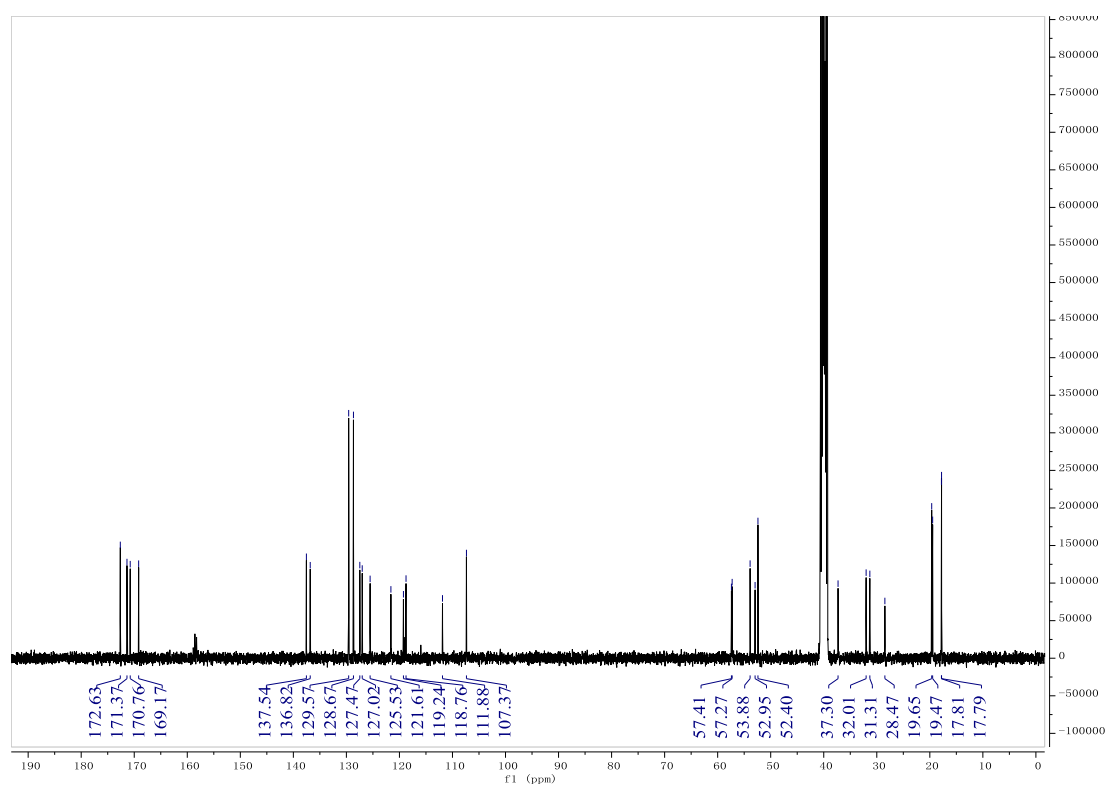


Figure S70. ^{13}C -NMR spectrum of **2b** (100 MHz, DMSO- d_6)

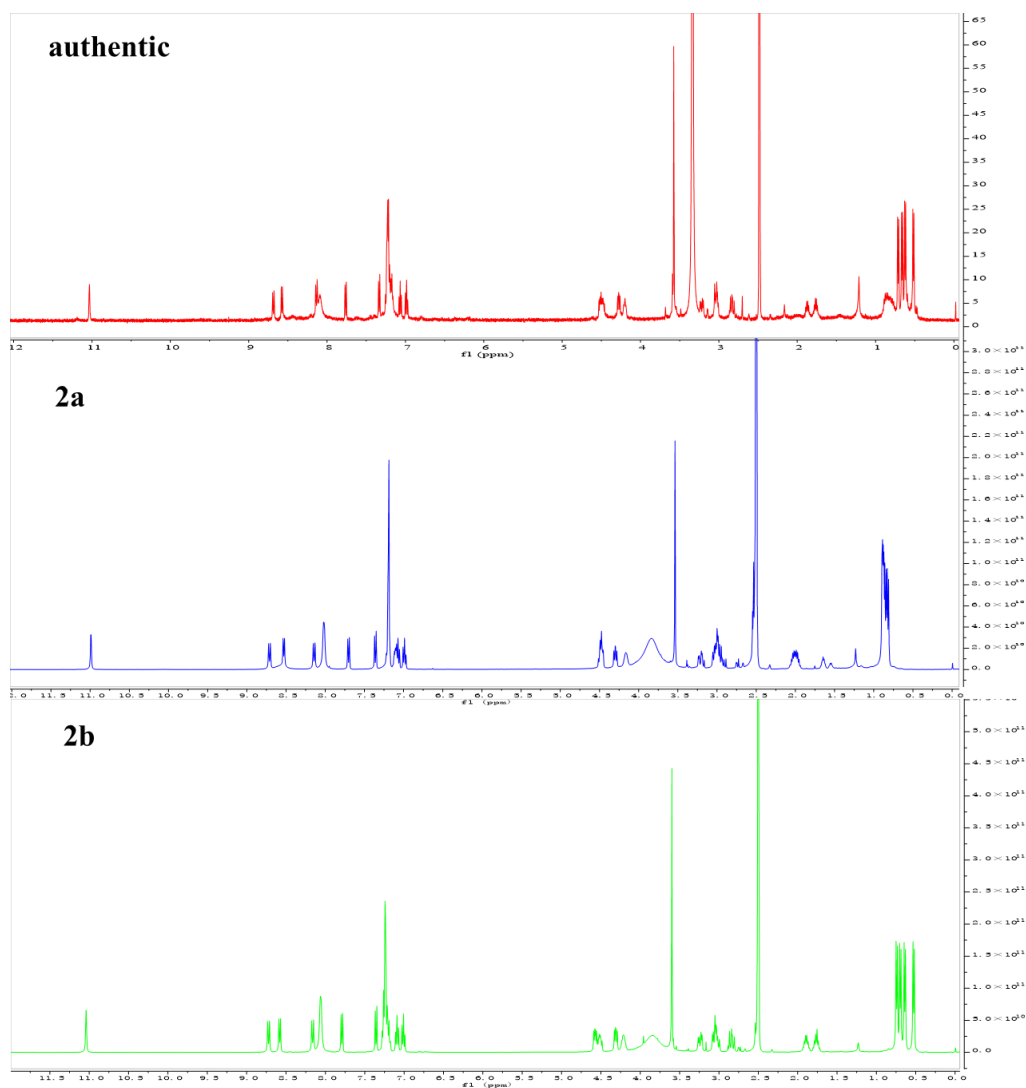


Figure S71. Comparison of ^1H -NMR spectra of authentic **2**, **2a**, and **2b**

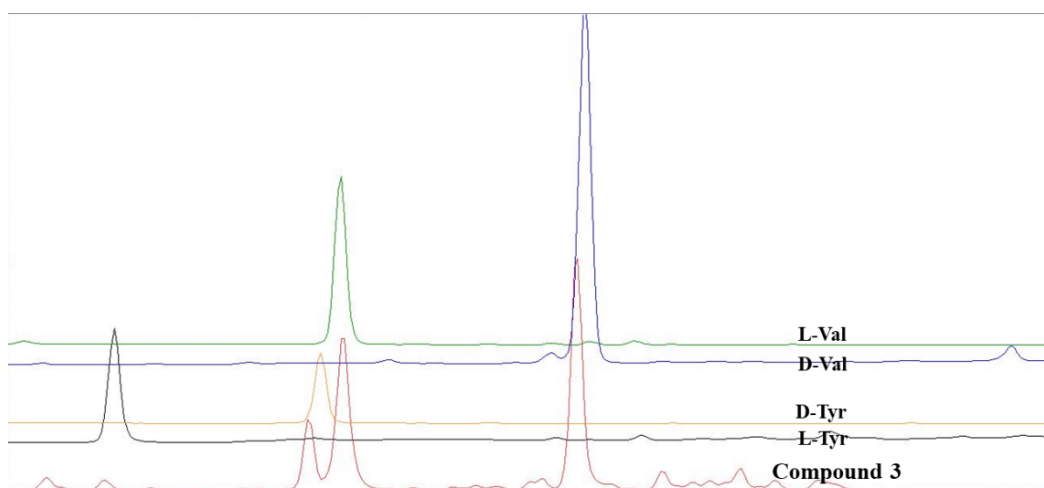


Figure S72. Advanced Marfey's acid hydrolytic analysis of compound **3**

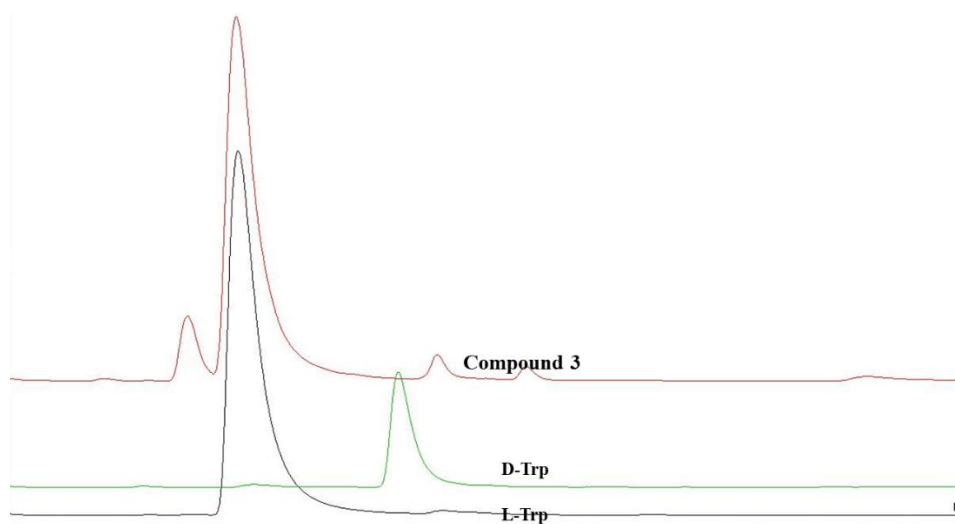


Figure S73. Advanced Marfey's alkaline hydrolytic analysis of compound **3**

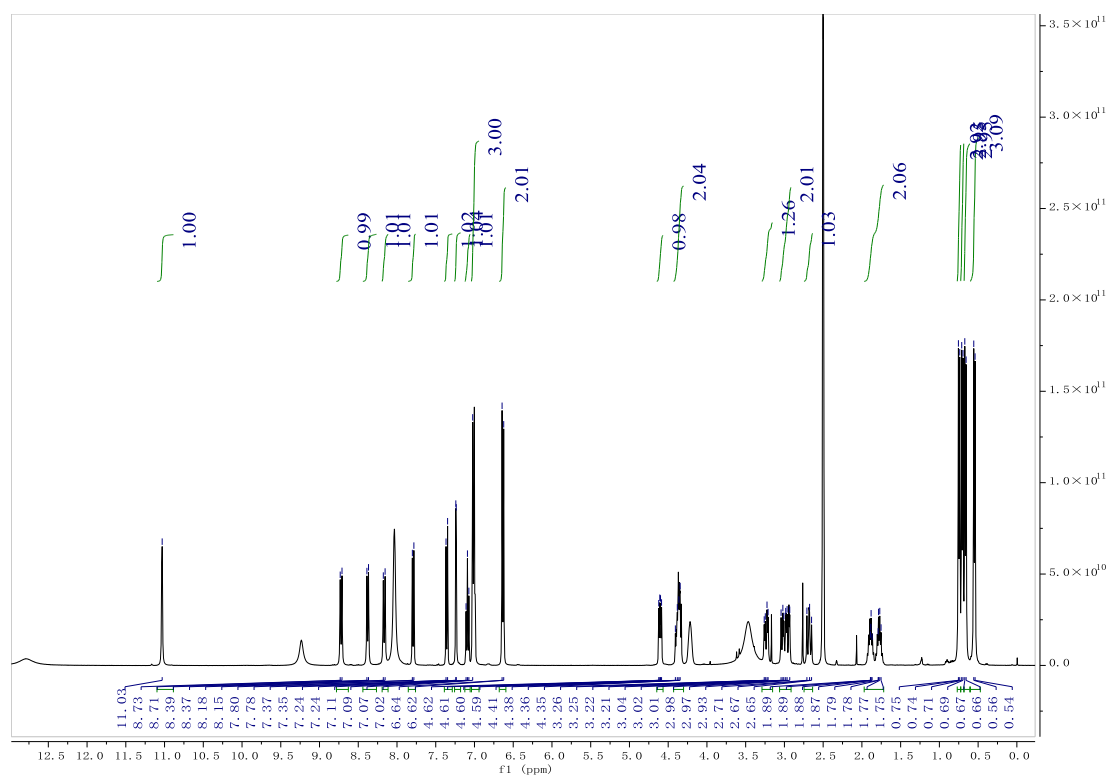


Figure S74. ^1H -NMR spectrum of synthetic **3** (400 MHz, $\text{DMSO-}d_6$)

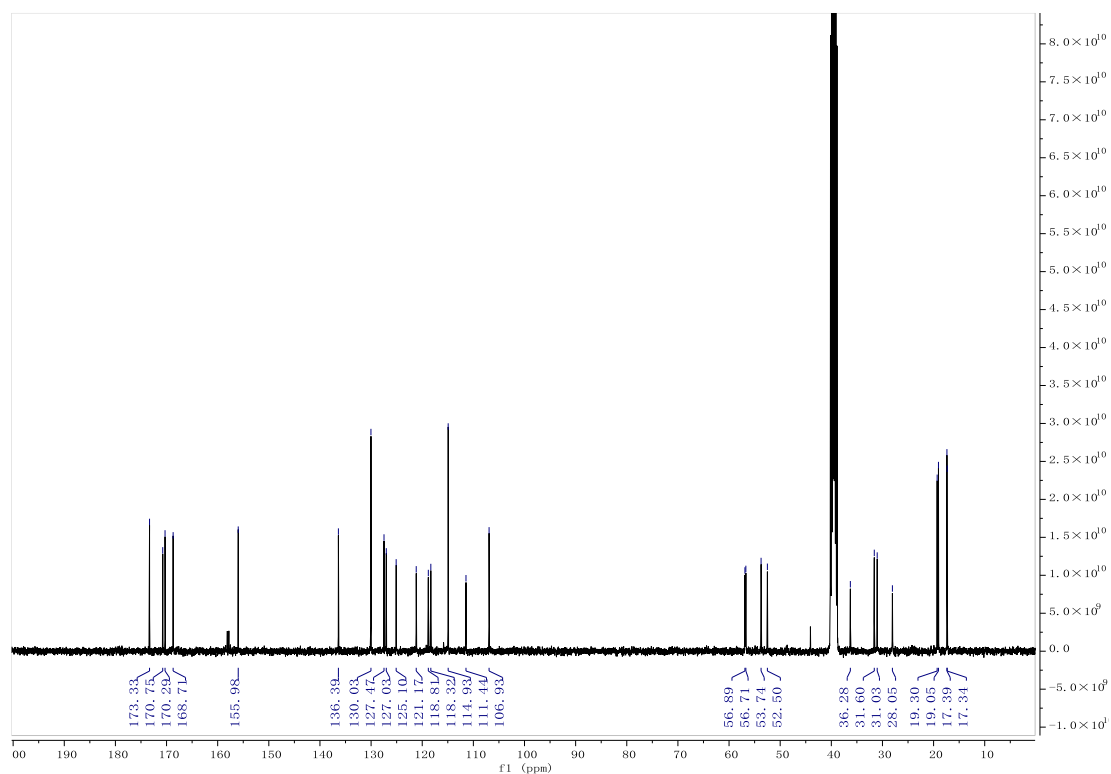


Figure S75. ¹³C-NMR spectrum of synthetic **3** (100 MHz, DMSO-*d*₆)

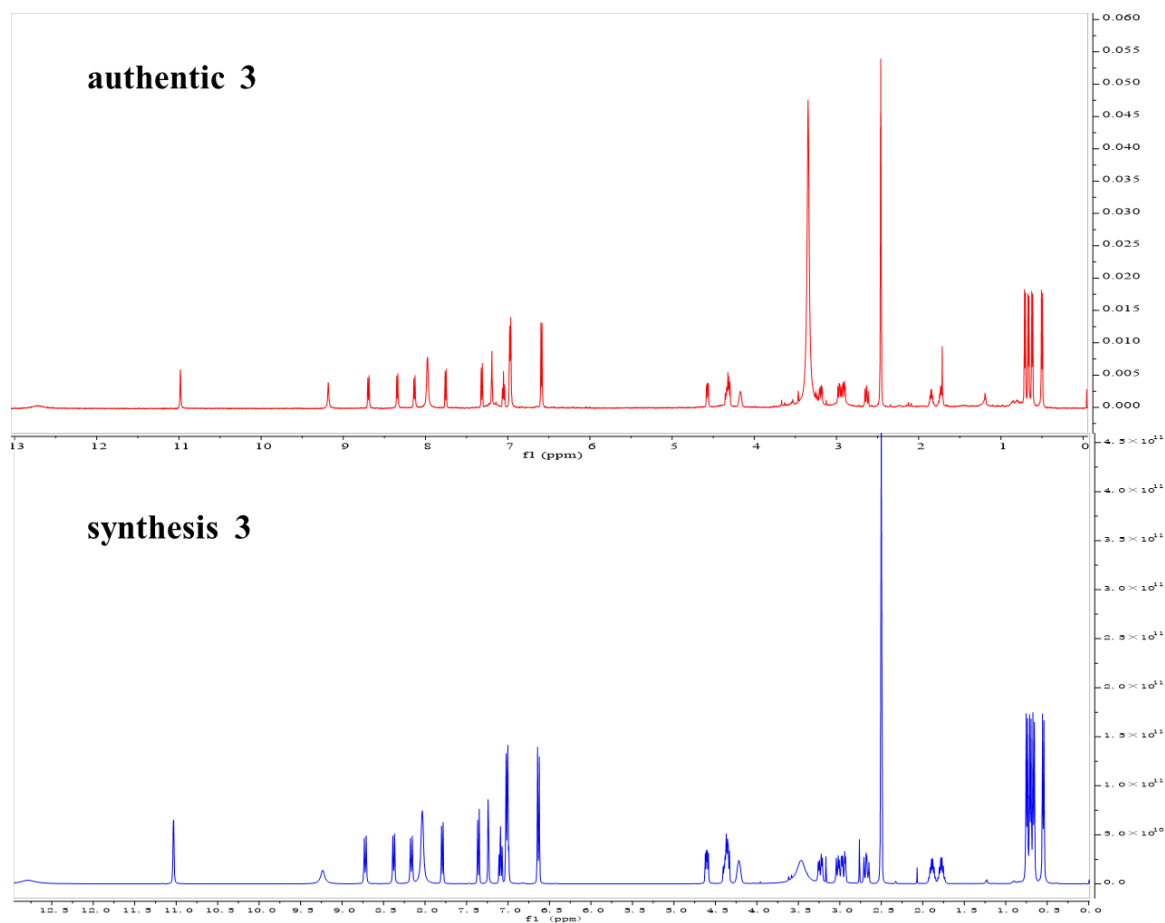


Figure S76. Comparison of ¹H-NMR spectra of **3** with synthetic **3**

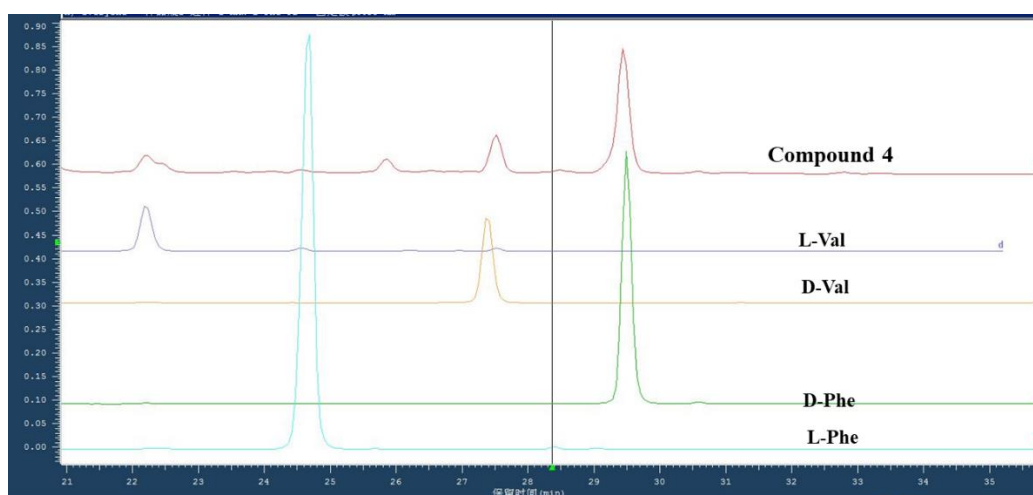


Figure S77. Advanced Marfey's acid hydrolytic analysis of compound **4**

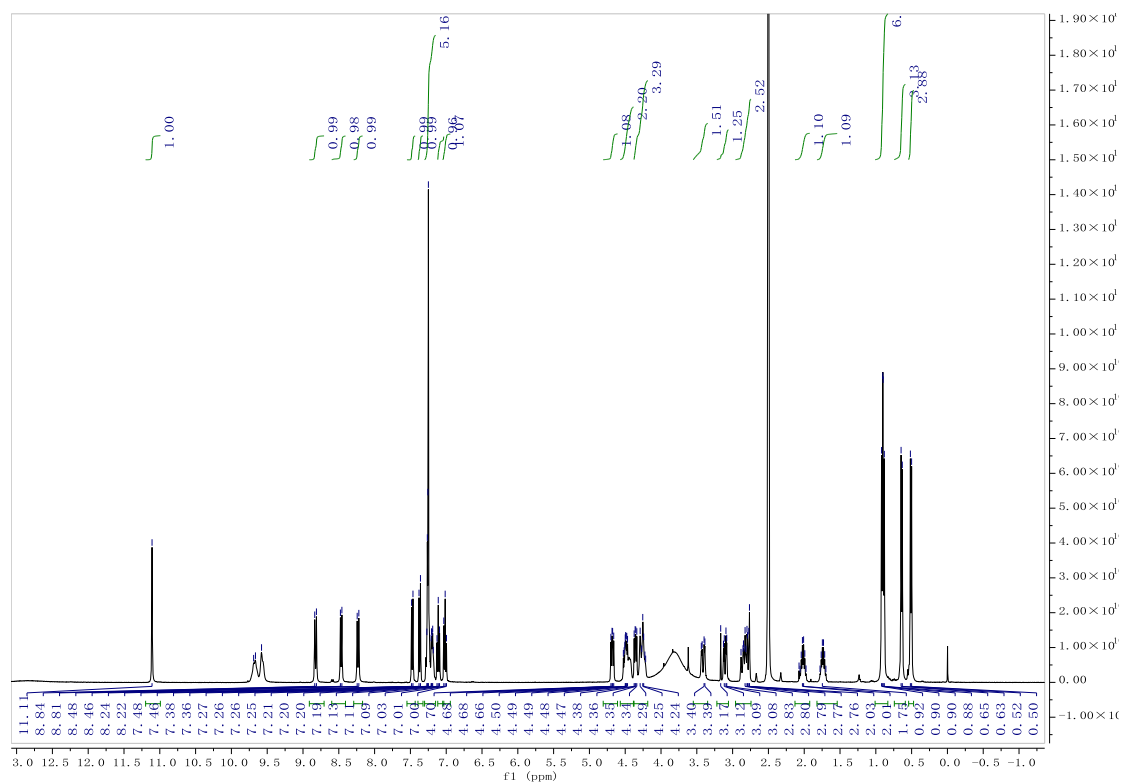


Figure S78. ^1H -NMR spectrum of synthetic **4** (400 MHz, $\text{DMSO}-d_6$)

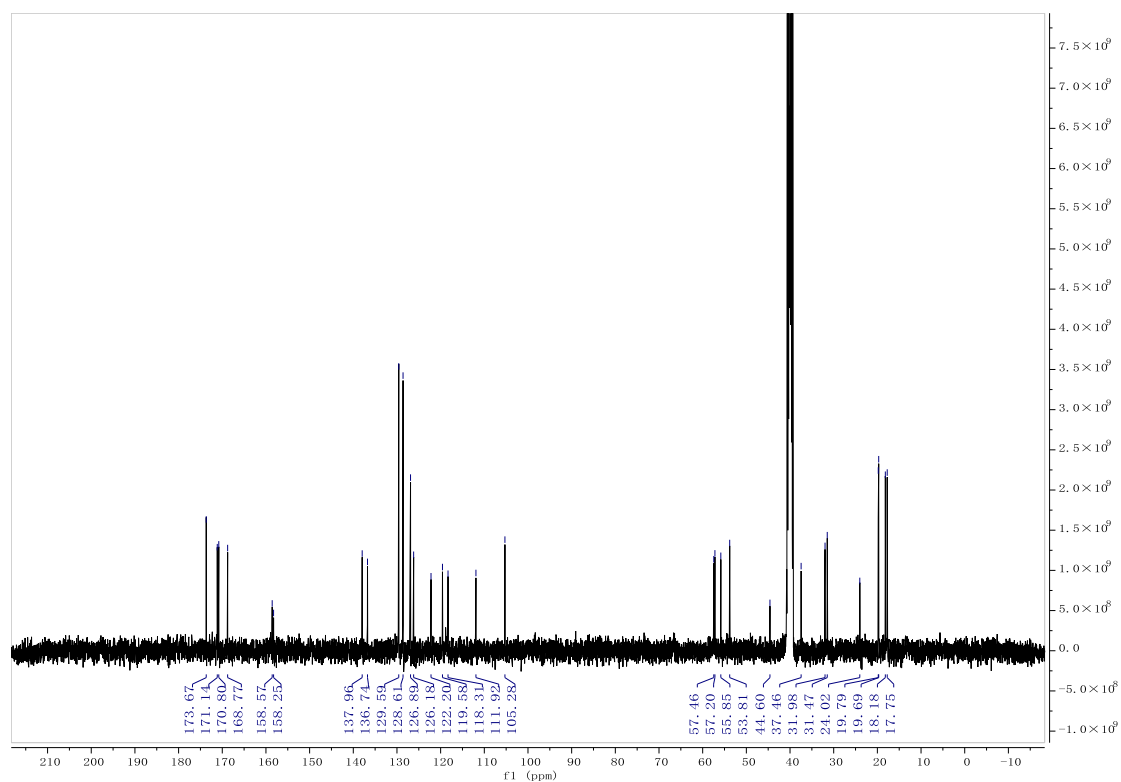


Figure S79. ^{13}C -NMR spectrum of synthetic **4** (100 MHz, $\text{DMSO}-d_6$)

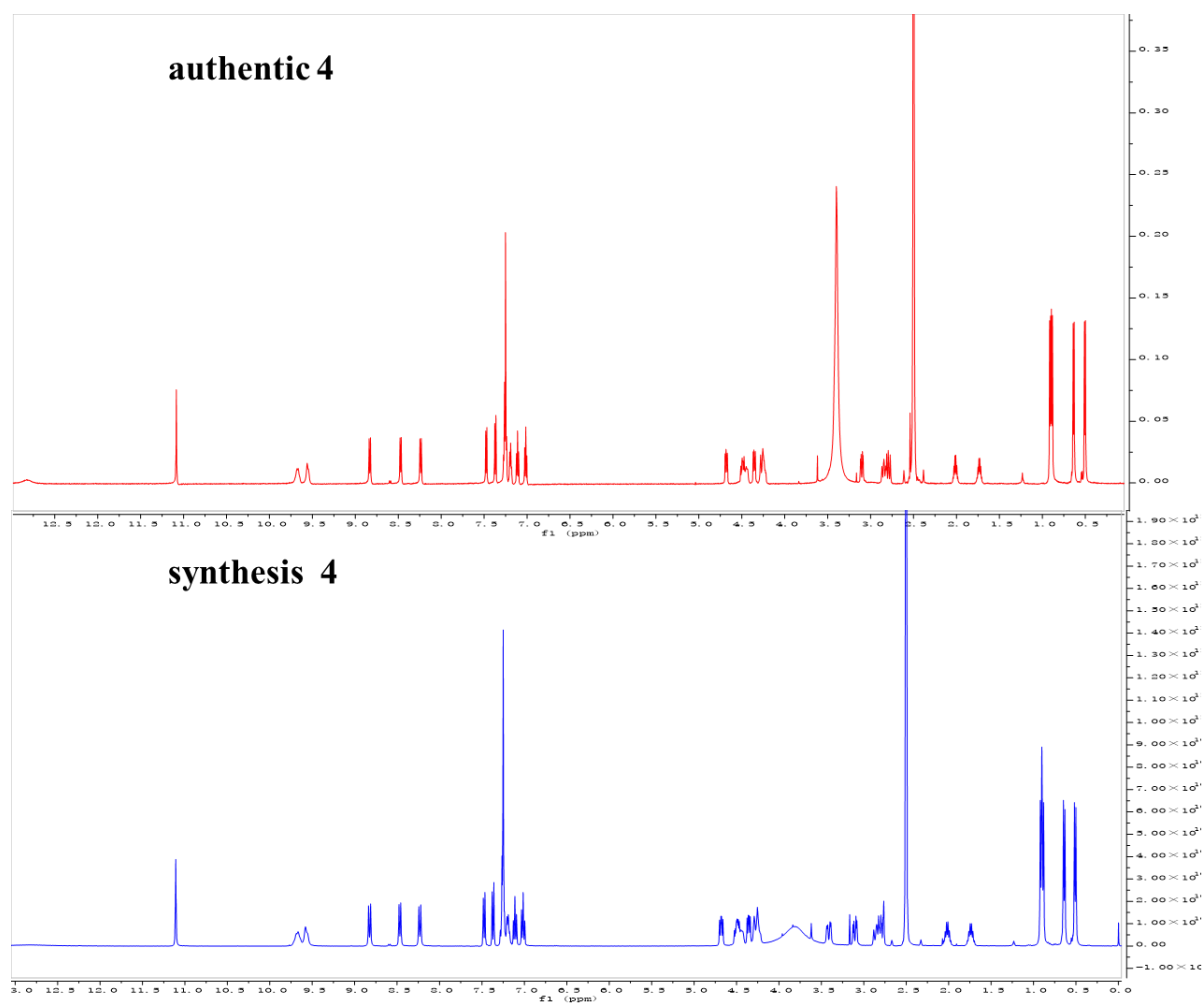


Figure S80. Comparison of ¹H-NMR spectra of **4**, with synthetic **4**

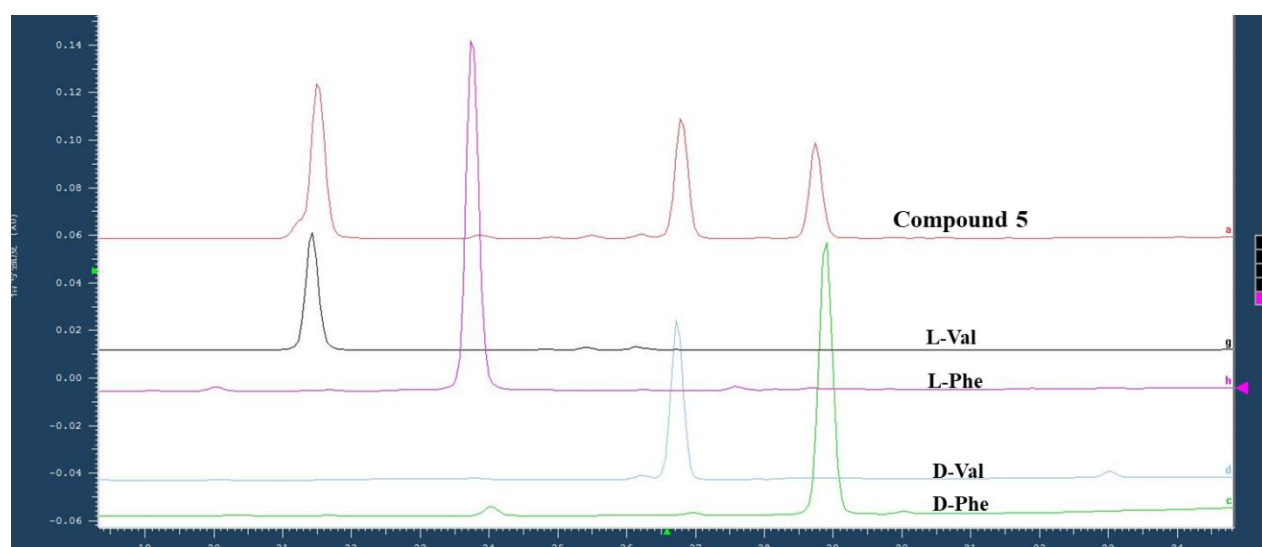


Figure S81. Advanced Marfey's acid hydrolytic analysis of compound **5**

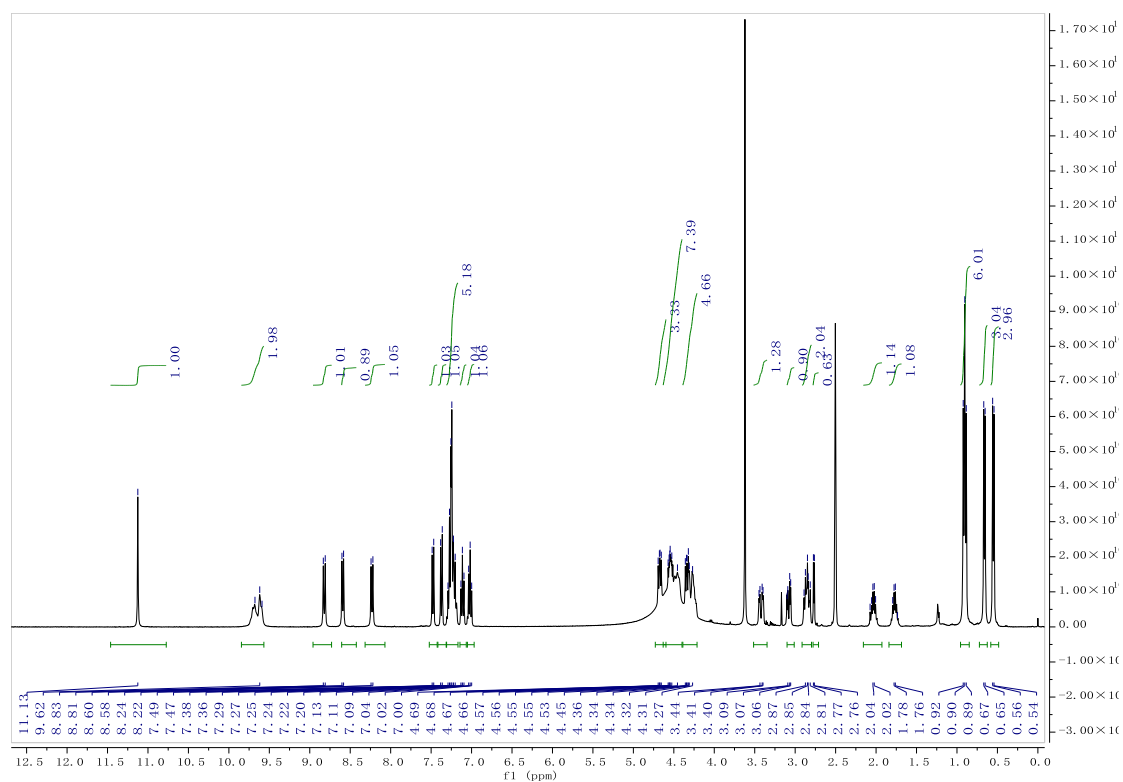


Figure S82. ¹H-NMR spectrum of synthetic **5** (400 MHz, DMSO-*d*₆)

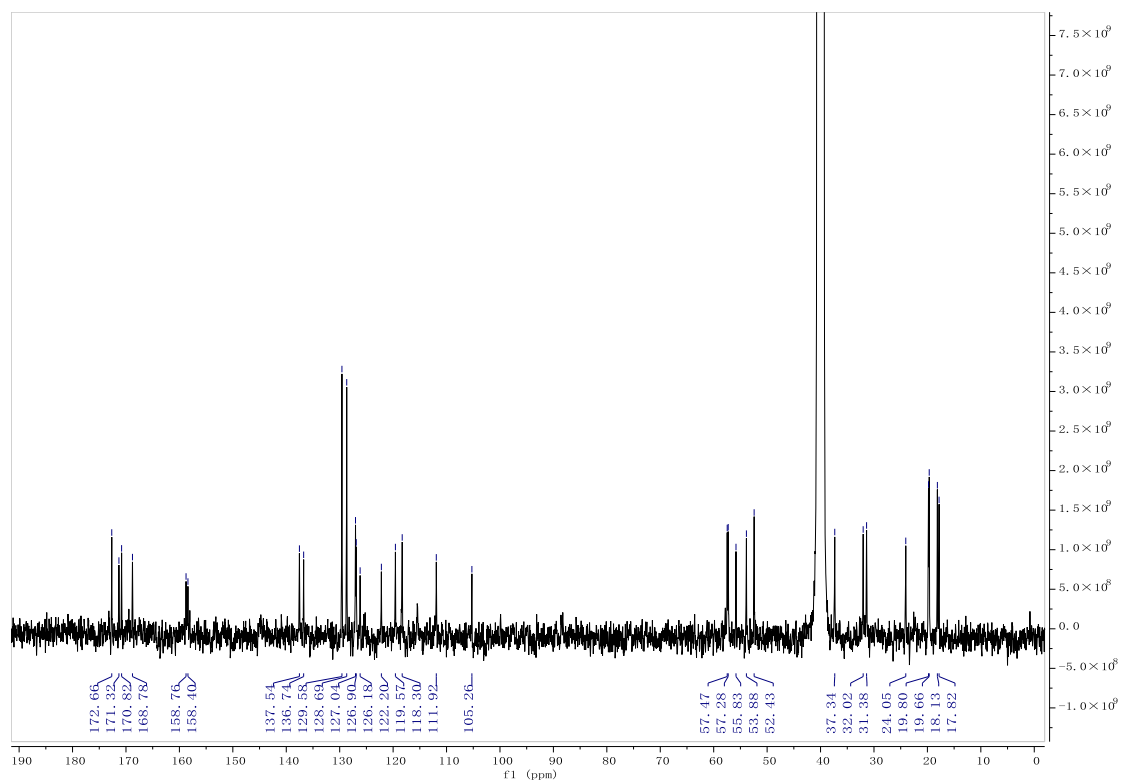


Figure S83. ¹³C-NMR spectrum of synthetic **5** (100 MHz, DMSO-*d*₆)

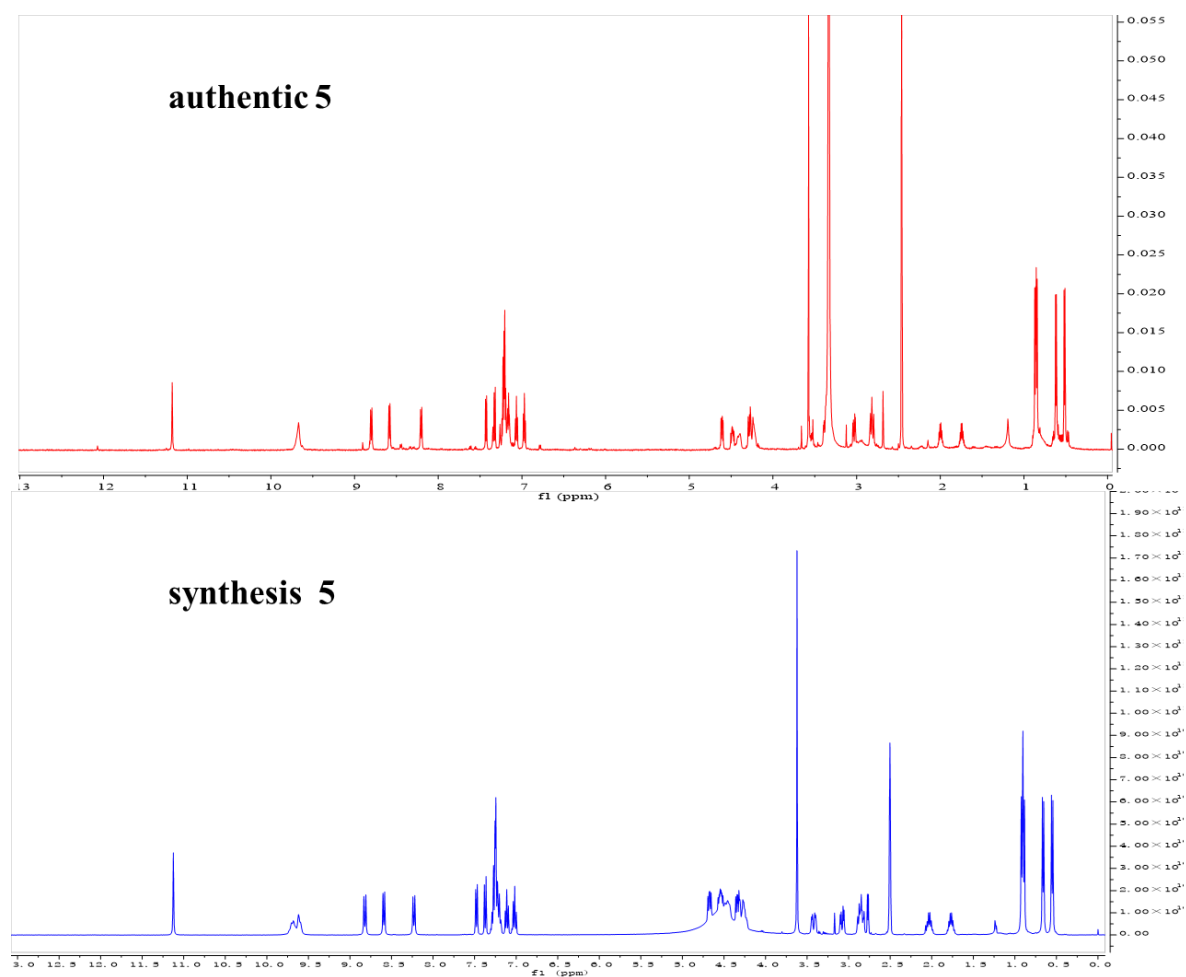


Figure S84. Comparison of ¹H-NMR spectra of **5** with synthetic **5**

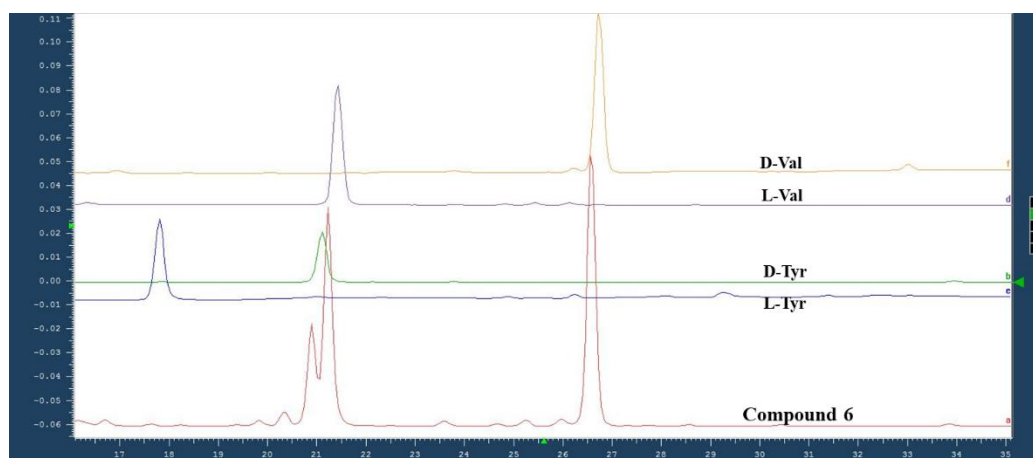


Figure S85. Advanced Marfey's acid hydrolytic analysis of compound **6**

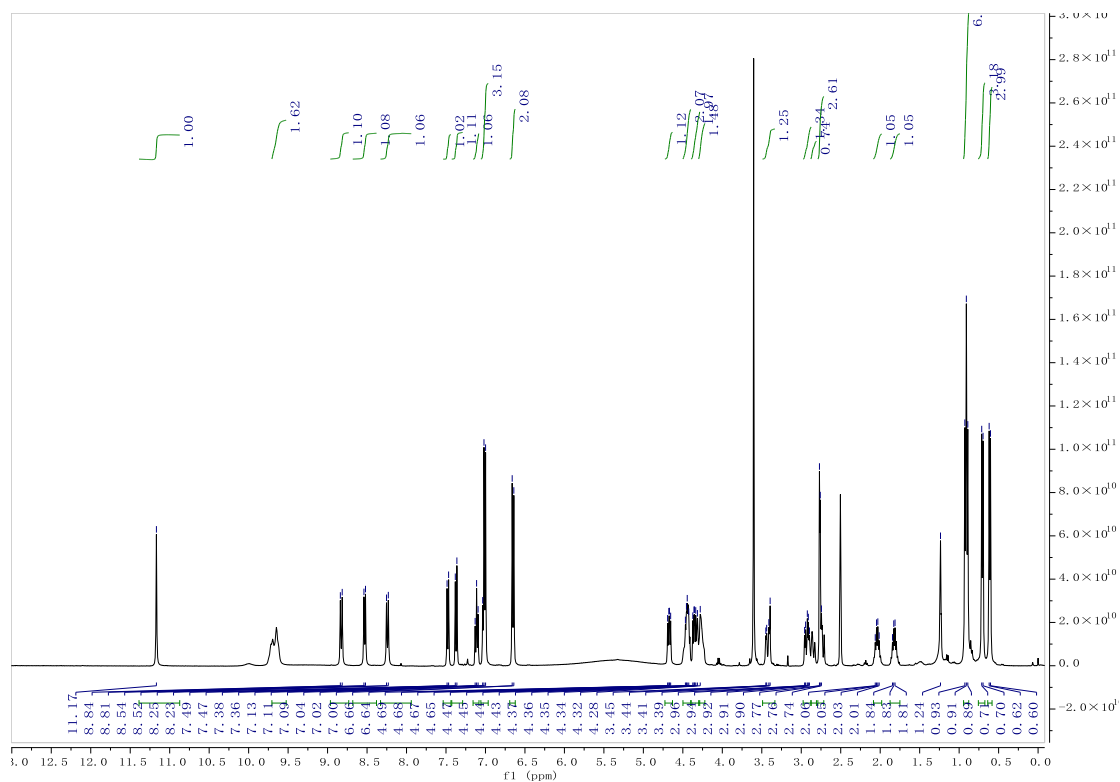


Figure S86. ^1H -NMR spectrum of synthetic **6** (400 MHz, $\text{DMSO}-d_6$)

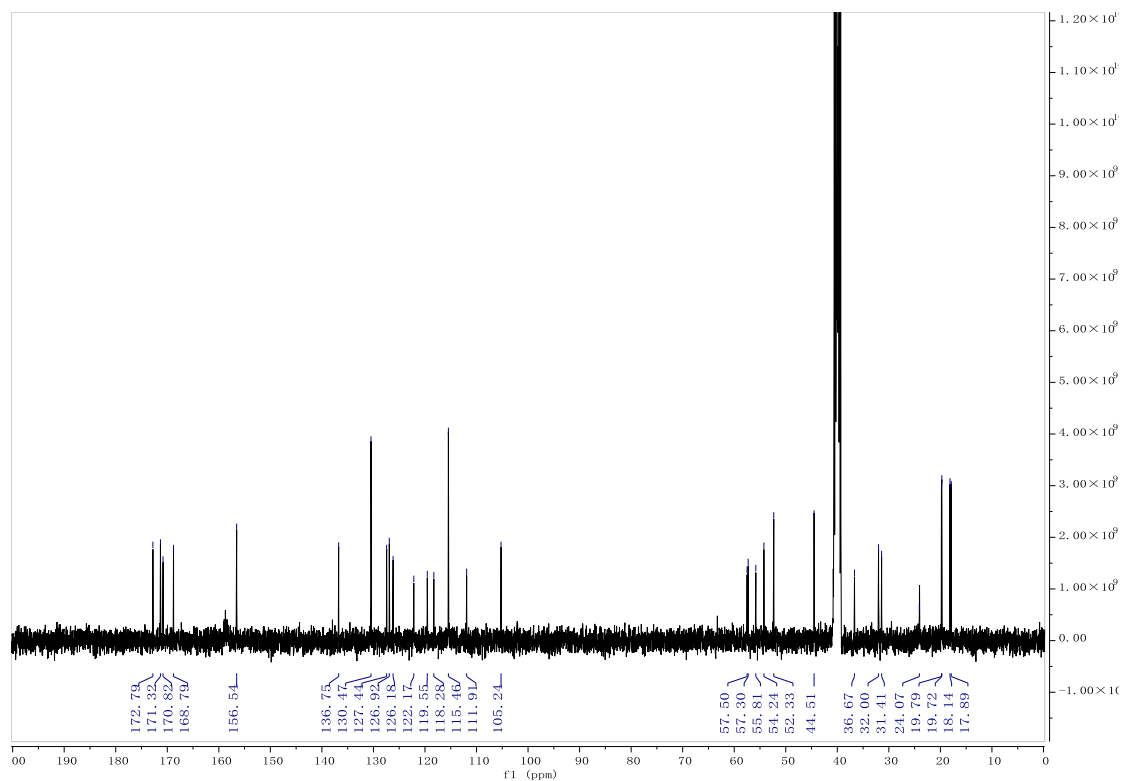


Figure S87. ^{13}C -NMR spectrum of synthetic **6** (100 MHz, $\text{DMSO}-d_6$)

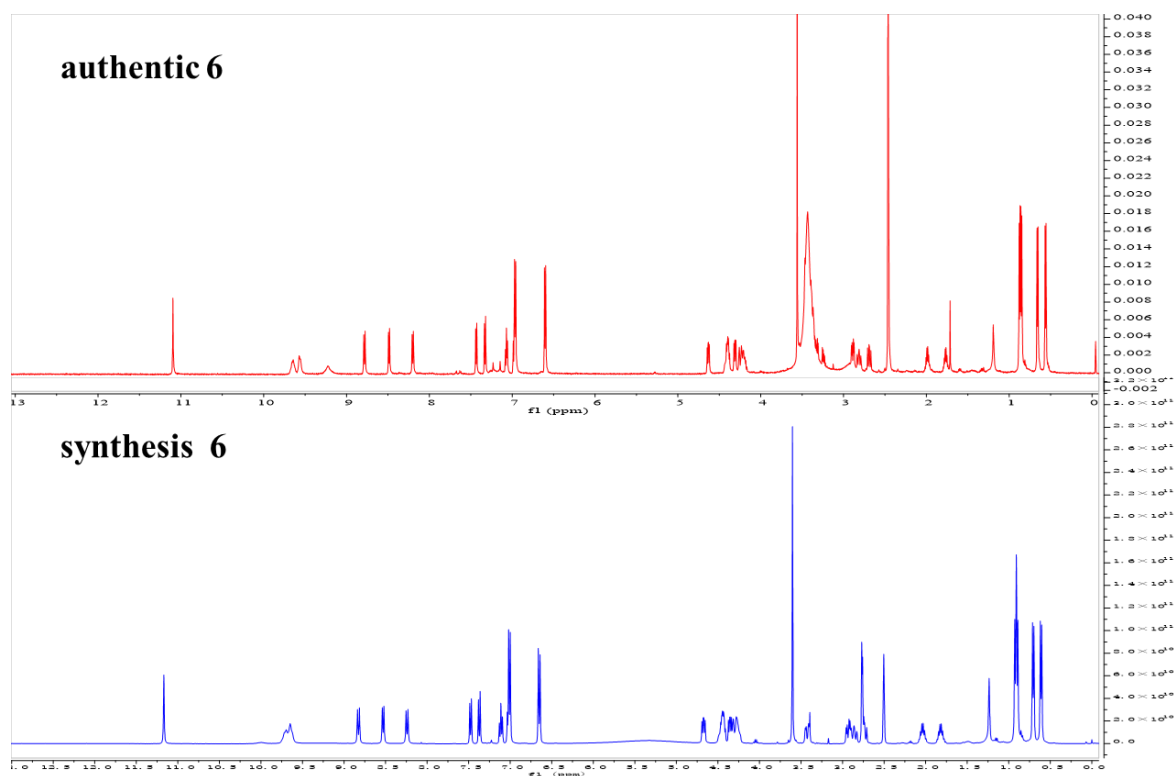


Figure S88. Comparison of ^1H -NMR spectra of **6** with synthetic **6**

Table S1. Table of compounds (**1-6**) ($100\ \mu\text{M}$) inhibition of ACh-evoked peak current amplitude mediated by human (h) $\alpha 1\beta 1\epsilon\delta$, $\alpha 1\beta 1\gamma\delta$, $\alpha 3\beta 2$, $\alpha 3\beta 4$, $\alpha 4\beta 2$, $\alpha 7$ and $\alpha 9\alpha 10$ nAChRs. Whole-cell currents at h $\alpha 1\beta 1\epsilon\delta$ and h $\alpha 1\beta 1\gamma\delta$ were activated by $5\ \mu\text{M}$ ACh, h $\alpha 3\beta 2$ and h $\alpha 9\alpha 10$ were activated by $6\ \mu\text{M}$ ACh, and h $\alpha 3\beta 4$, h $\alpha 4\beta 2$, and h $\alpha 7$ were activated by 300, 3, and $100\ \mu\text{M}$ ACh, respectively (mean \pm SD, $n = 6 - 11$).

Compounds	Relative current amplitude						
	(h) $\alpha 1\beta 1\epsilon\delta$	(h) $\alpha 1\beta 1\gamma\delta$	(h) $\alpha 3\beta 2$	(h) $\alpha 3\beta 4$	(h) $\alpha 4\beta 2$	(h) $\alpha 7$	(h) $\alpha 9\alpha 10$
1	0.190 ± 0.056	0.664 ± 0.062	0.435 ± 0.071	0.462 ± 0.069	0.637 ± 0.053	0.293 ± 0.074	0.103 ± 0.027
2	0.024 ± 0.011	0.017 ± 0.014	0.236 ± 0.069	0.071 ± 0.028	0.301 ± 0.039	0.566 ± 0.072	0.075 ± 0.036
3	0.648 ± 0.067	0.861 ± 0.084	0.451 ± 0.056	0.675 ± 0.040	0.793 ± 0.078	0.368 ± 0.088	0.509 ± 0.041
4	0.757 ± 0.065	0.985 ± 0.019	0.924 ± 0.069	0.670 ± 0.049	0.972 ± 0.057	0.228 ± 0.049	0.824 ± 0.064
5	0.392 ± 0.069	0.799 ± 0.063	0.656 ± 0.074	0.656 ± 0.051	0.837 ± 0.061	0.399 ± 0.061	0.374 ± 0.073
6	0.618 ± 0.047	0.802 ± 0.096	0.579 ± 0.077	0.777 ± 0.053	0.938 ± 0.076	0.838 ± 0.066	0.760 ± 0.062

Table S2. Free binding energy estimation and molecular interactions of compounds

1-6		
ligand	free bindingenergy (kcal/mol)	molecular interaction
compound 1	-4.0	Trp ¹ : H-donor with PHE106(B) Phe ⁴ : H-acceptor with SER84(B)
compound 2	-4.2	Trp ¹ : H-donor with SER180(A) and ARG48(B); pi-H with GLN50(B) Val ³ : H-donor with ASP49(A) Phe ⁴ -OCH ₃ :H-acceptor with ARG48(B)
compound 3	-3.9	Trp ¹ : H-donor with ALA108(B) Val ² : H-acceptor with LYS85(B)
compound 4	-2.8	Val ³ : H-acceptor with ASN109(B) Phe ⁴ : pi-H with ASP96(A)
compound 5	-3.1	Val ³ :H-pi with PHE144(A) Phe ⁴ -OCH ₃ : pi-H with ARG214(A)
compound 6	-3.4	Val ³ : H-pi with PHE144(A)