Supporting Information

Linear Peptides Containing $_{D}$-Leucine with Neuroprotective Activities from the Leech *Whitmania pigra* Whitman

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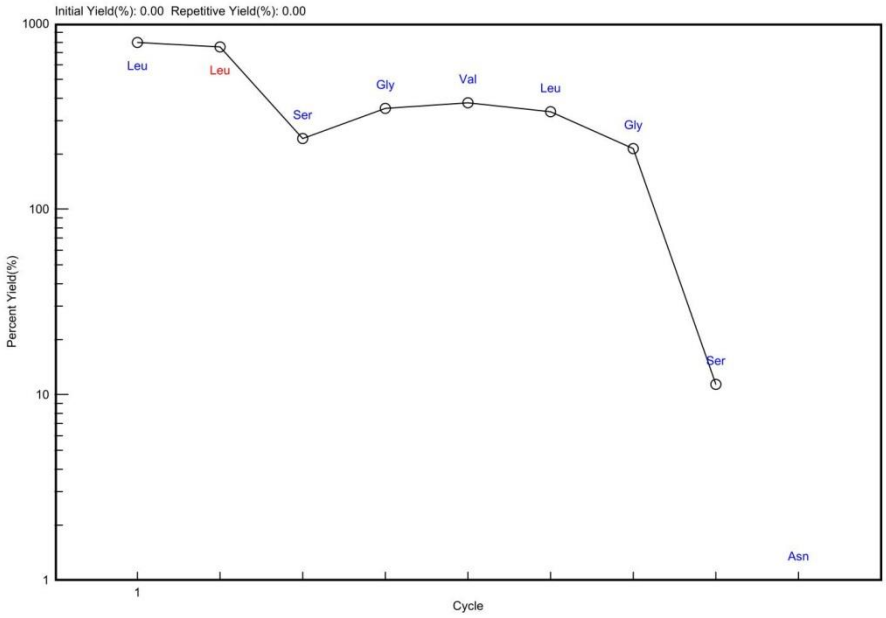
7. UV and IR spectra of synthetic 1-3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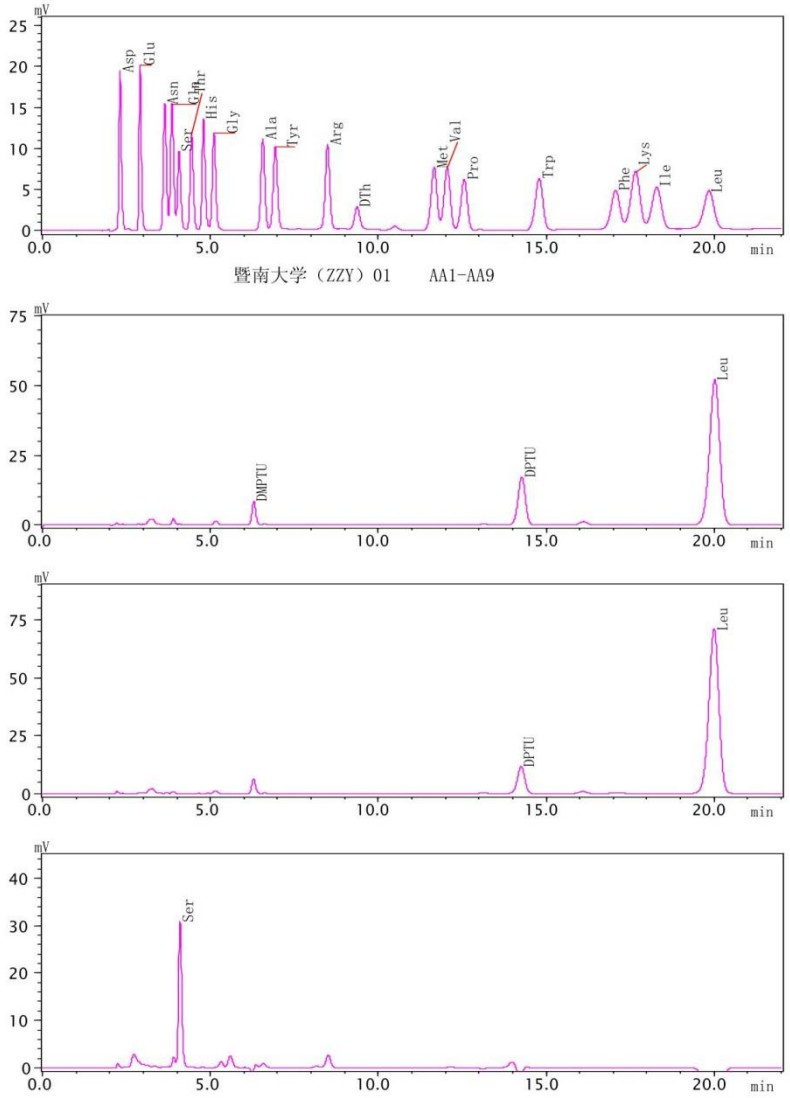
Cycle

标准氨基酸图谱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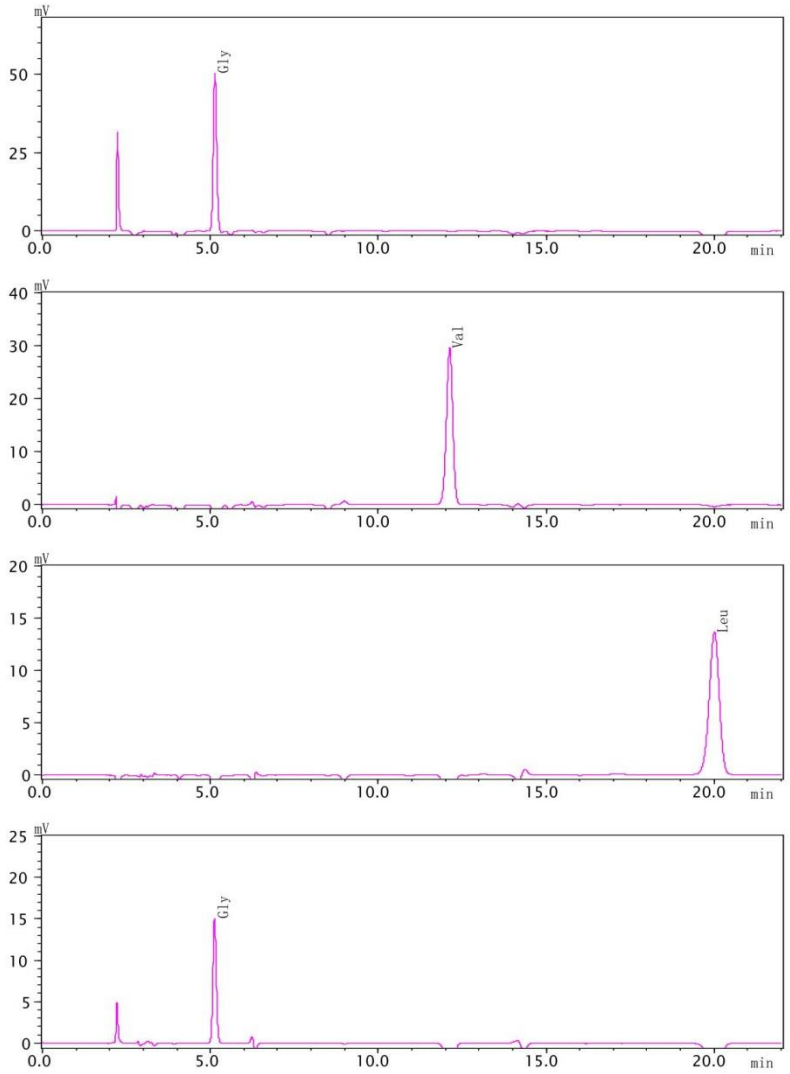
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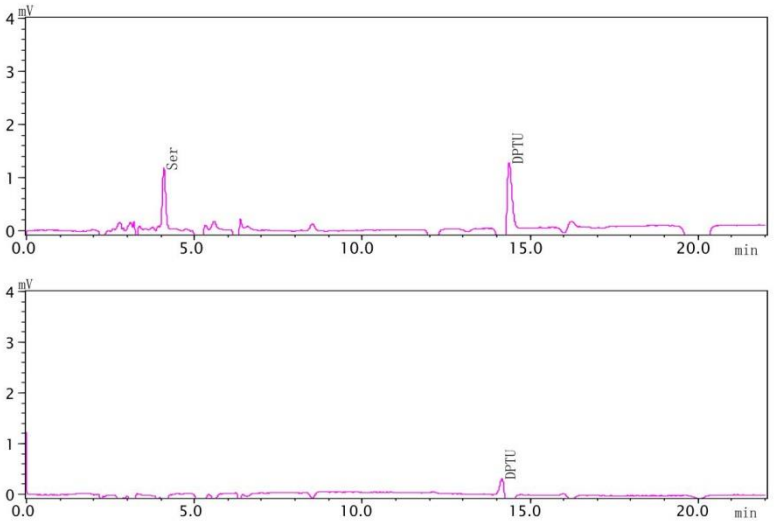
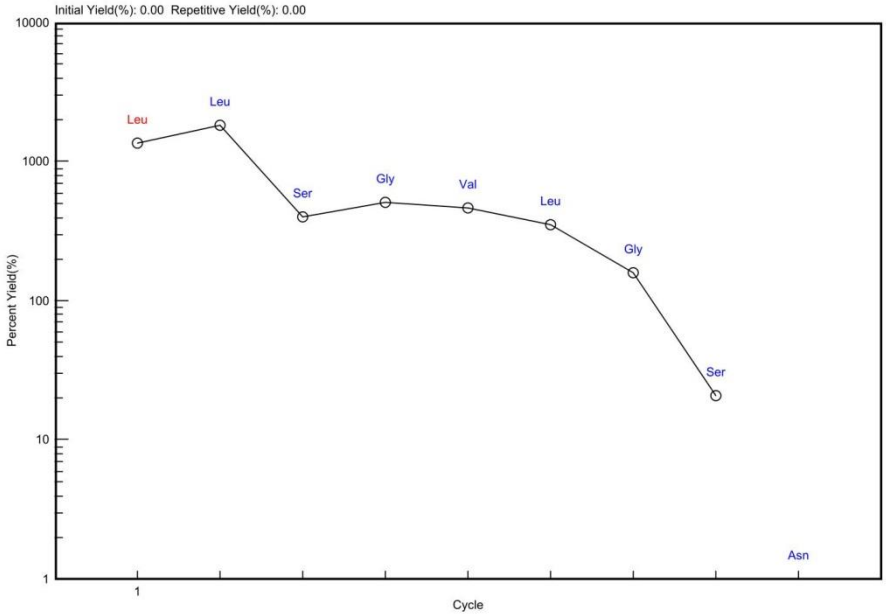


Figure S1. The result of amino acid sequence of **1.**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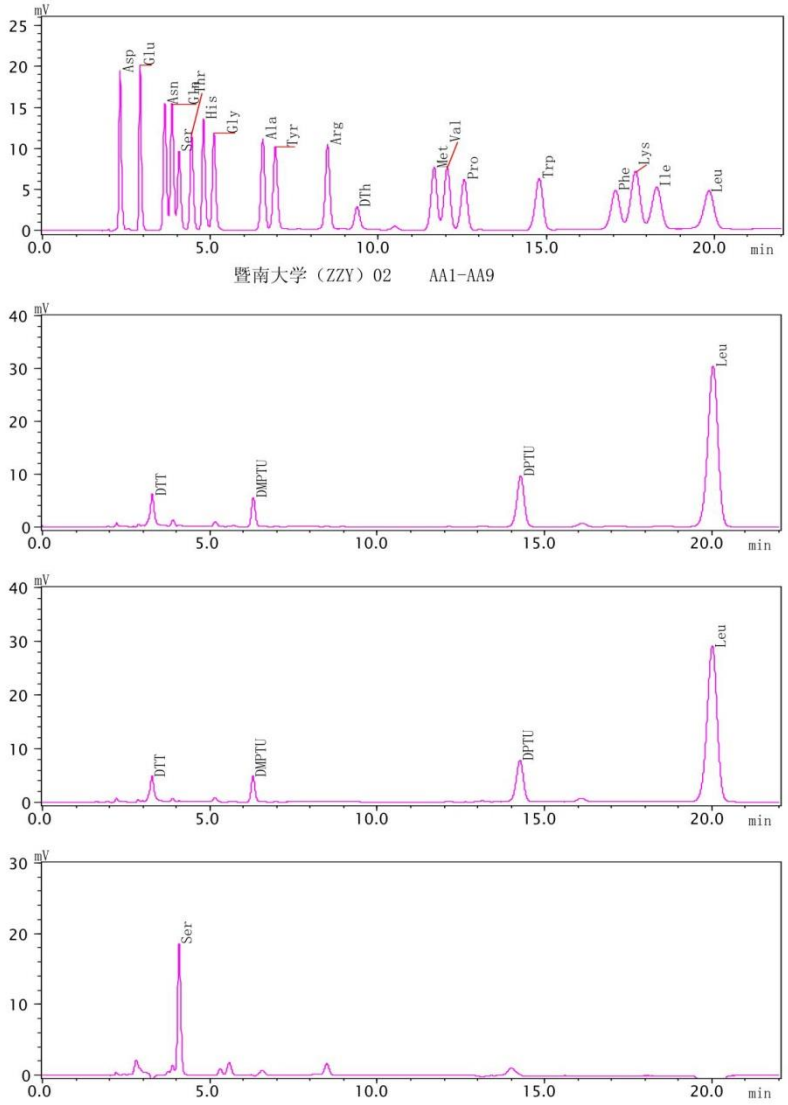
Cycle

标准氨基酸图谱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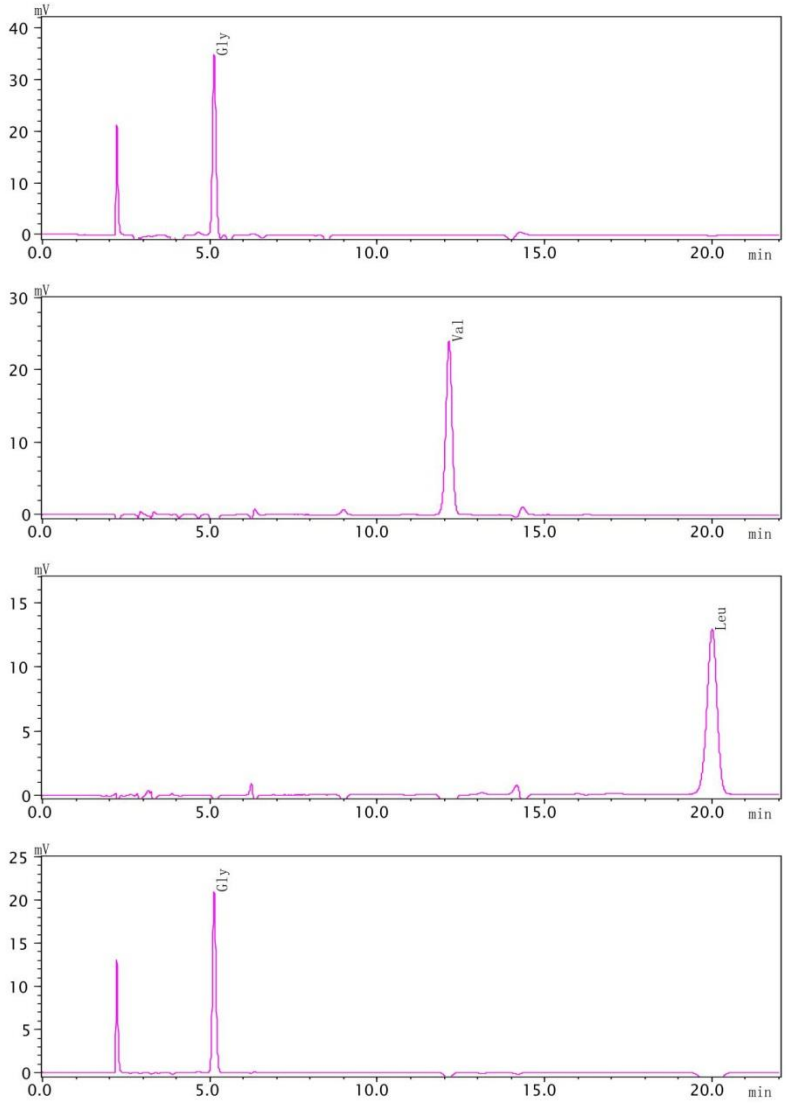
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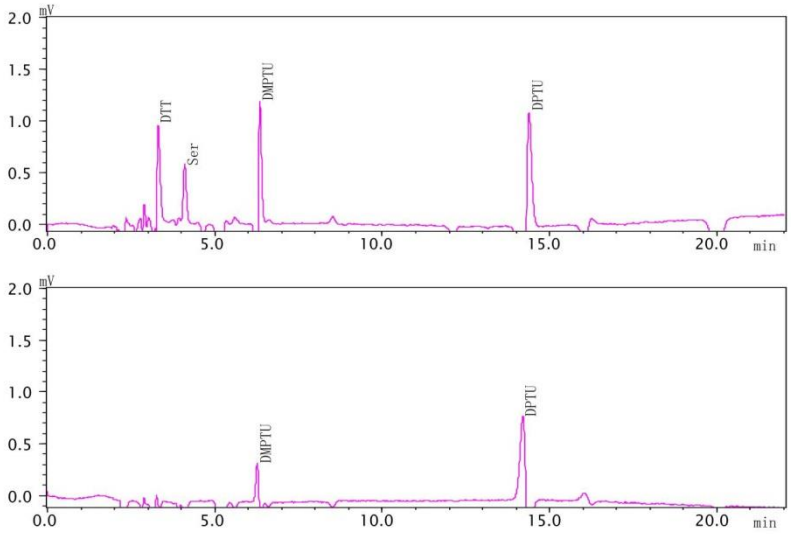
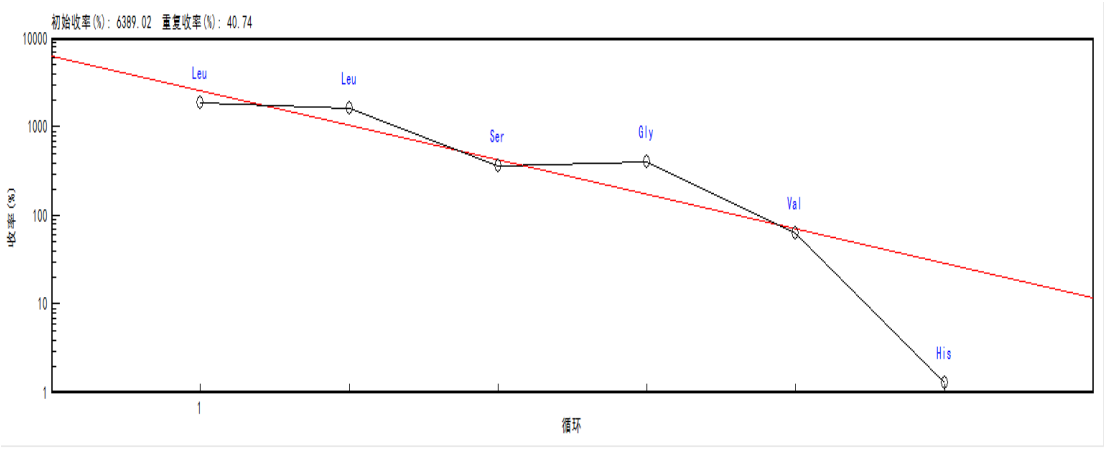


Figure S2. The result of amino acid sequence of **2.**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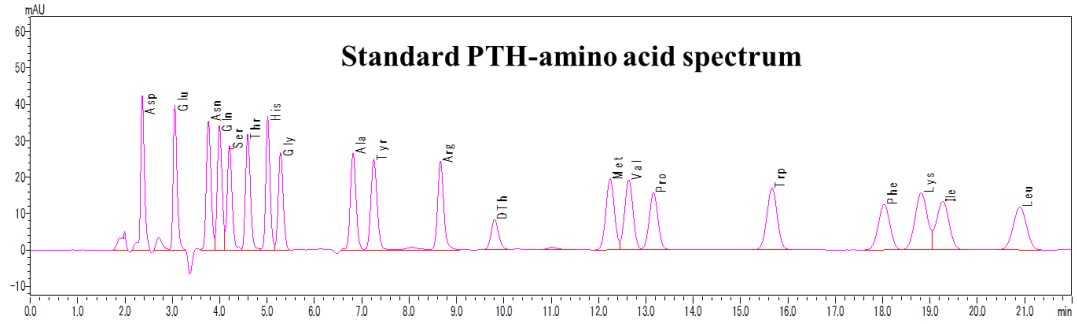
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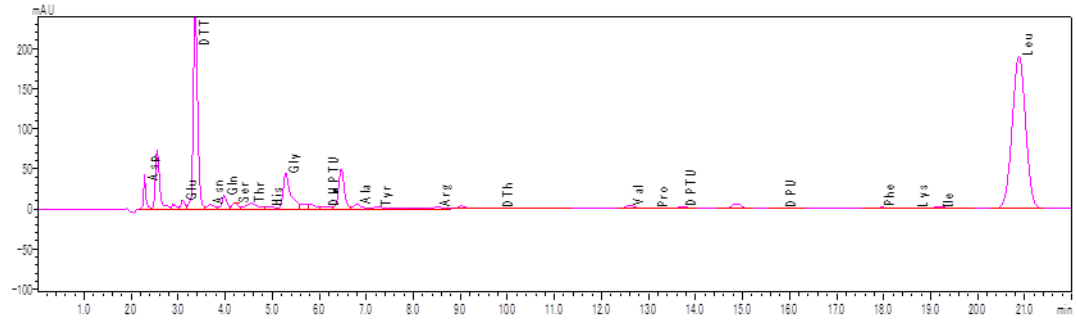
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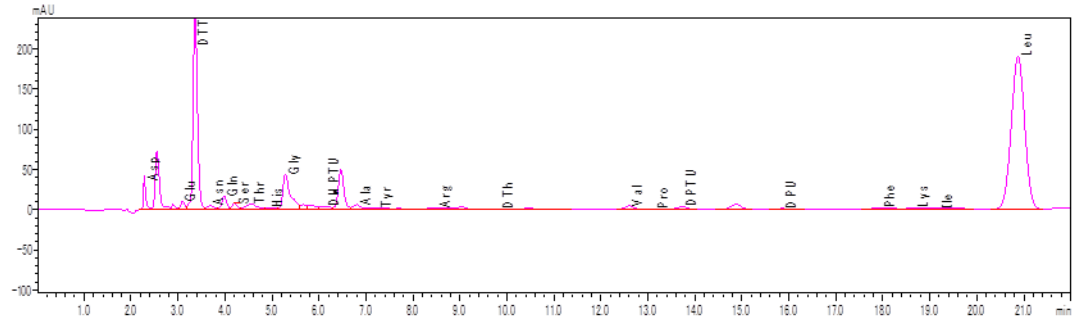
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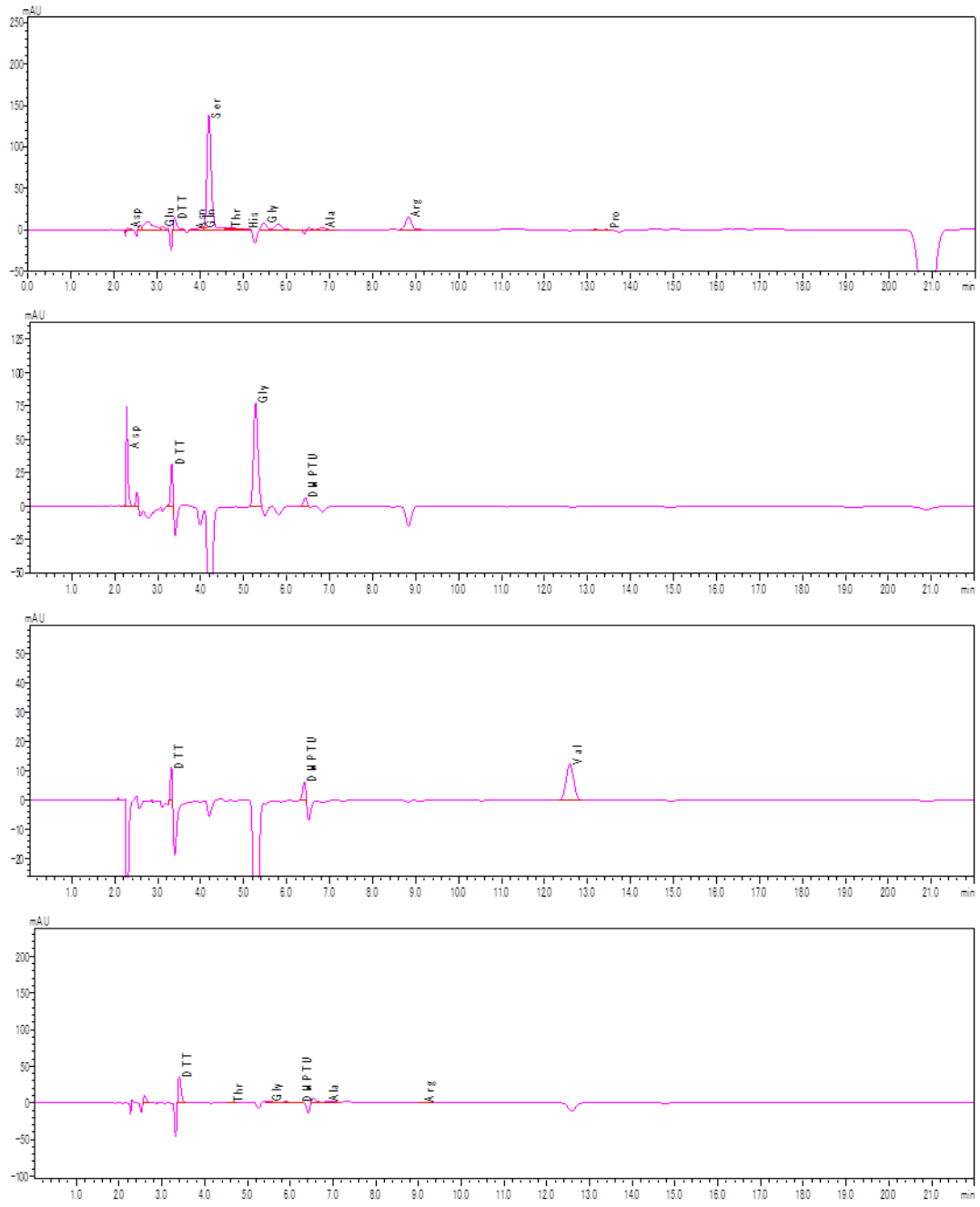


Figure S3. The result of amino acid sequence of **3.**

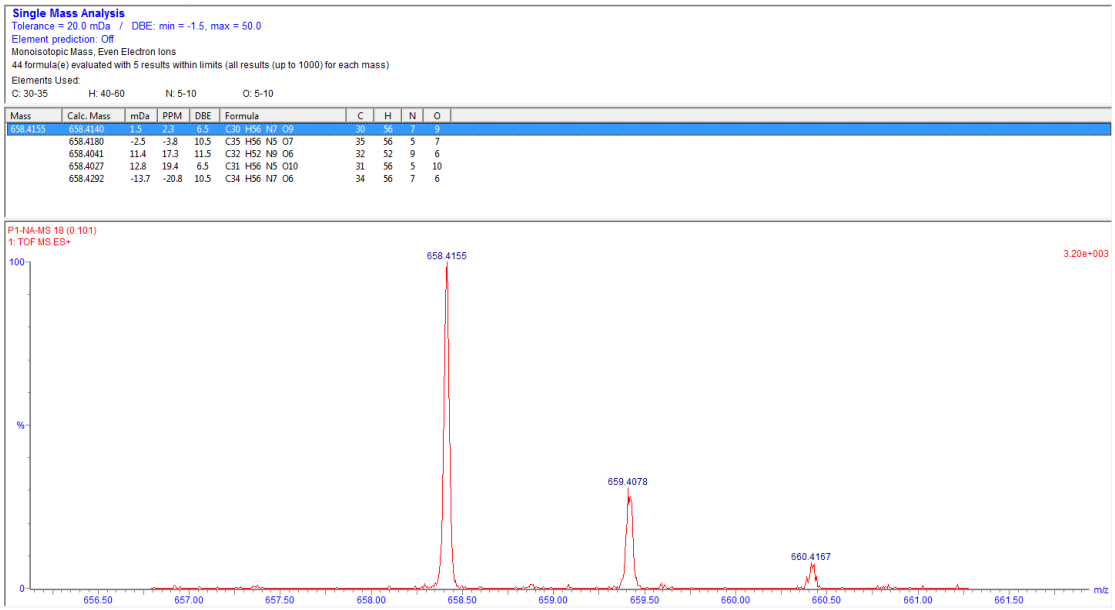


Figure S4. HRESIMS spectrum of **1**.

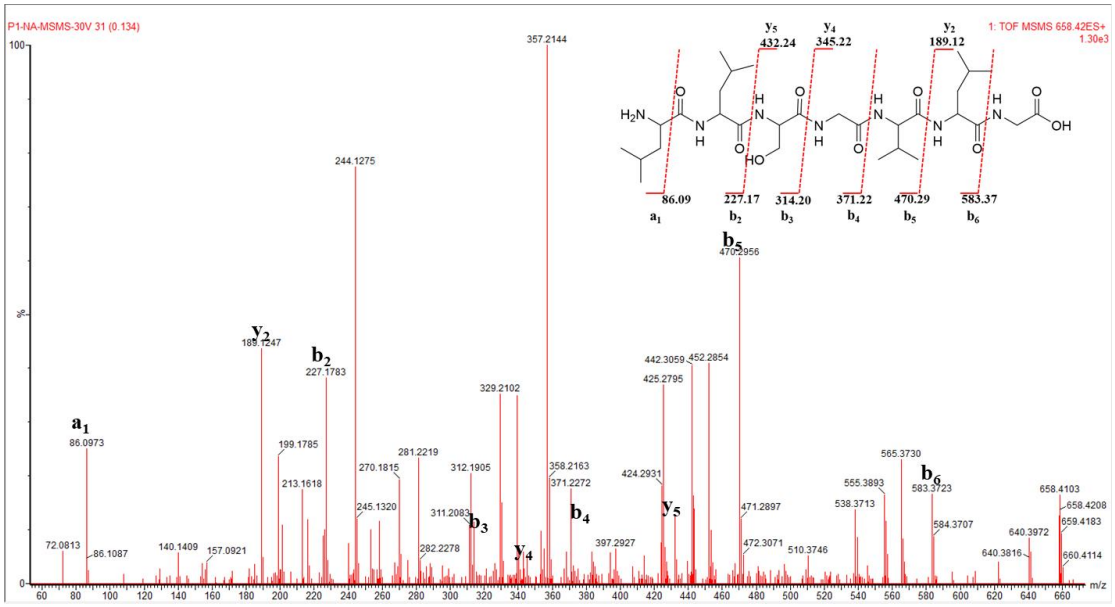


Figure S5. ESIMS/MS spectrum of **1**.

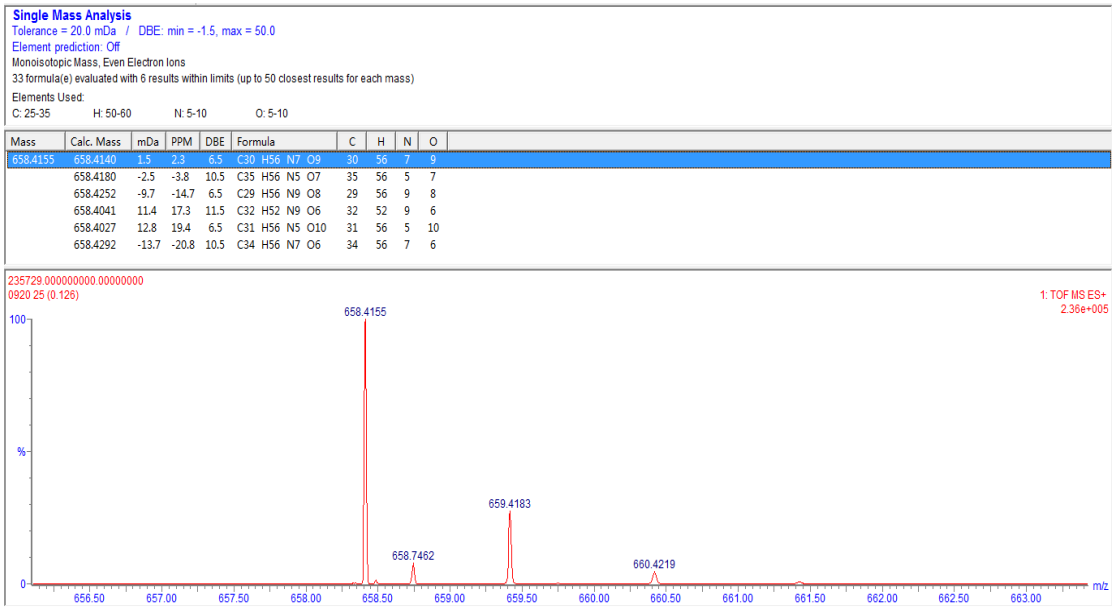


Figure S6. HRESIMS spectrum of **1a**.

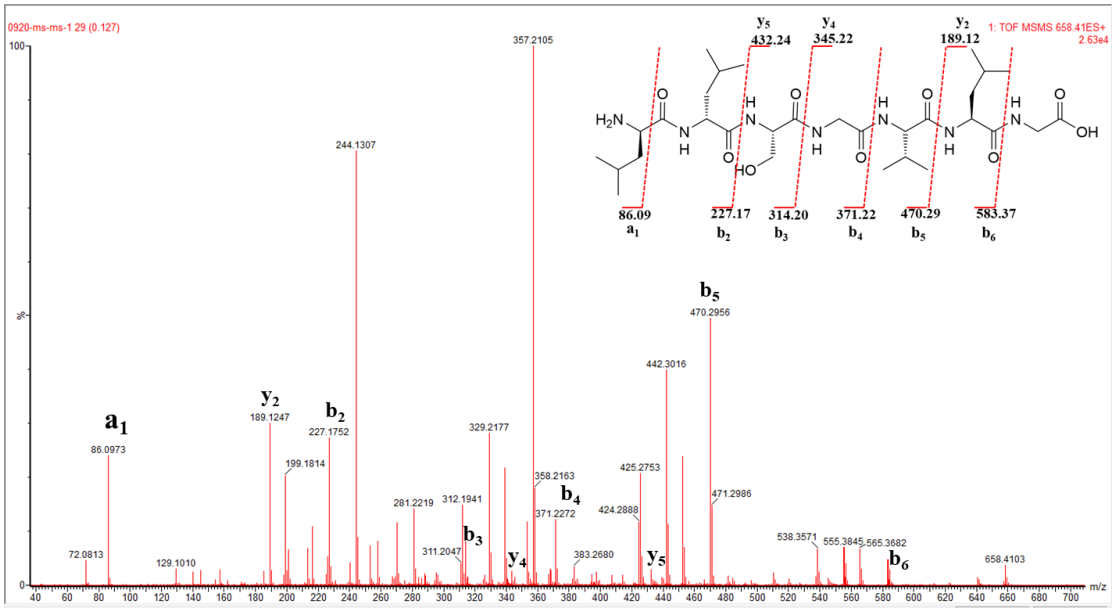


Figure S7. ESIMS/MS spectrum of **1a**.

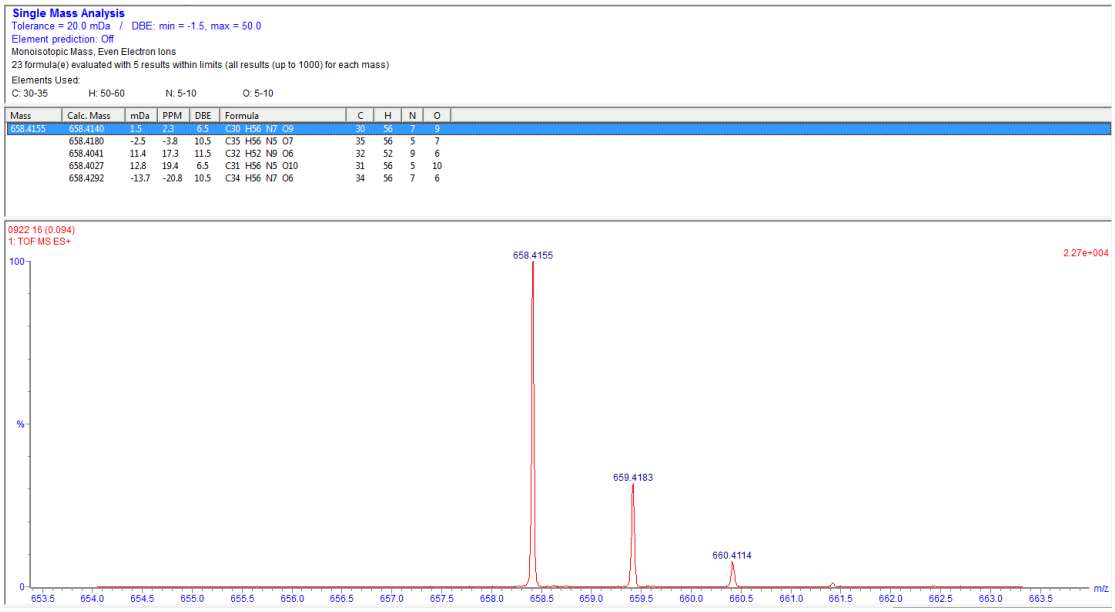


Figure S8. HRESIMS spectrum of **1b**.

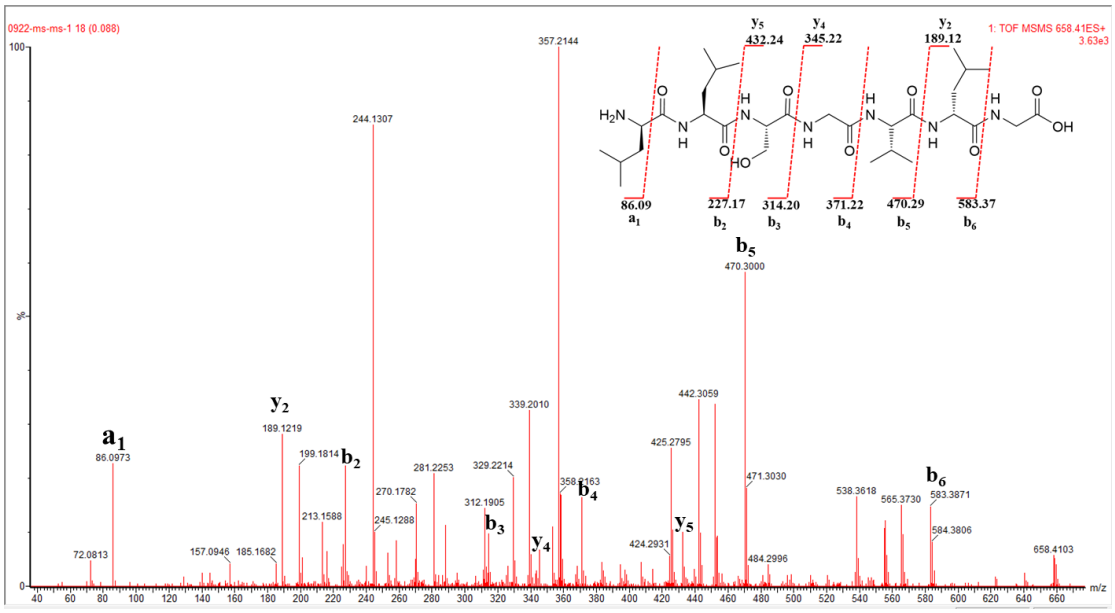
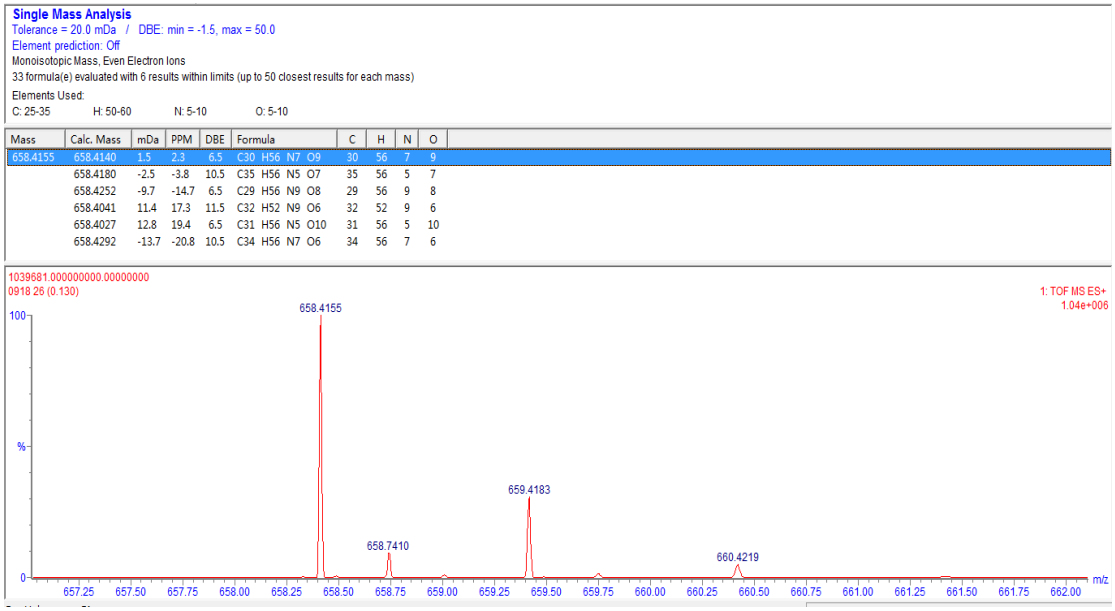


Figure S9. ESIMS/MS spectrum of **1b**.



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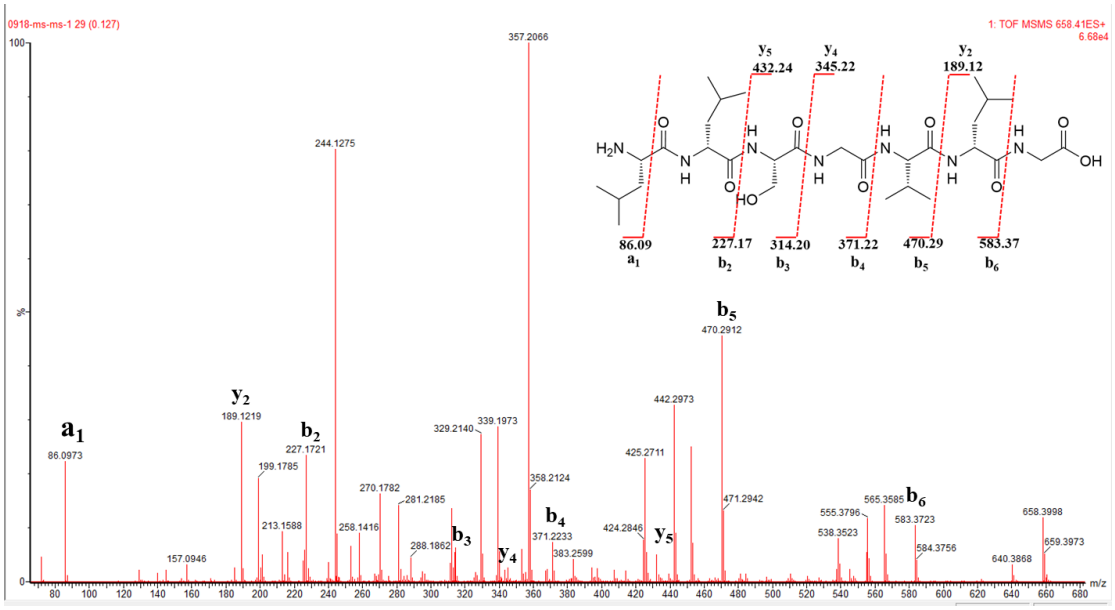

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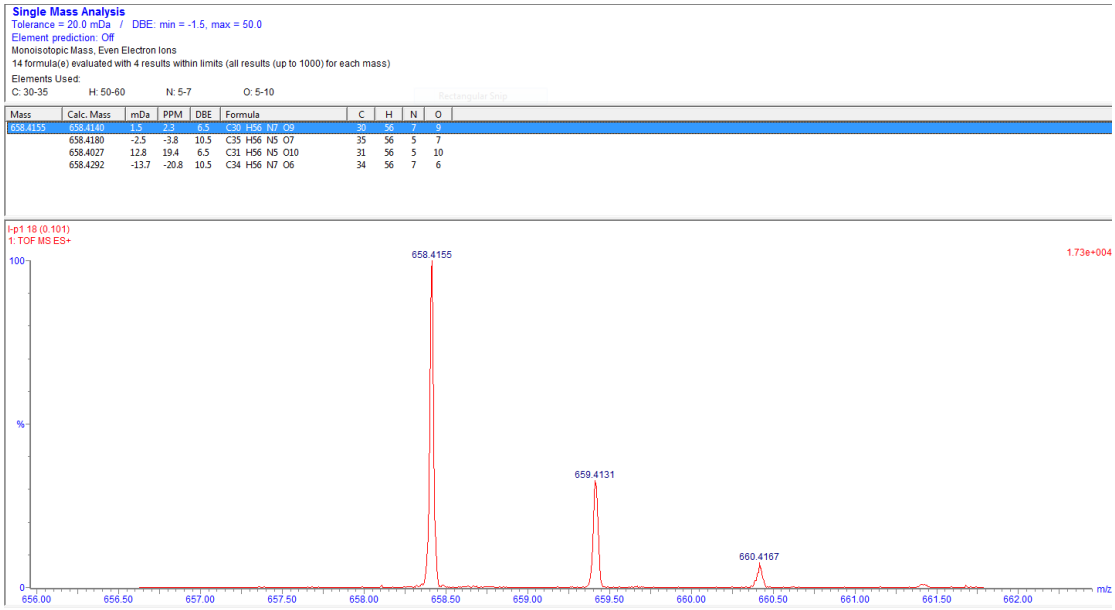


Figure S12. HRESIMS spectrum of **L-1**.

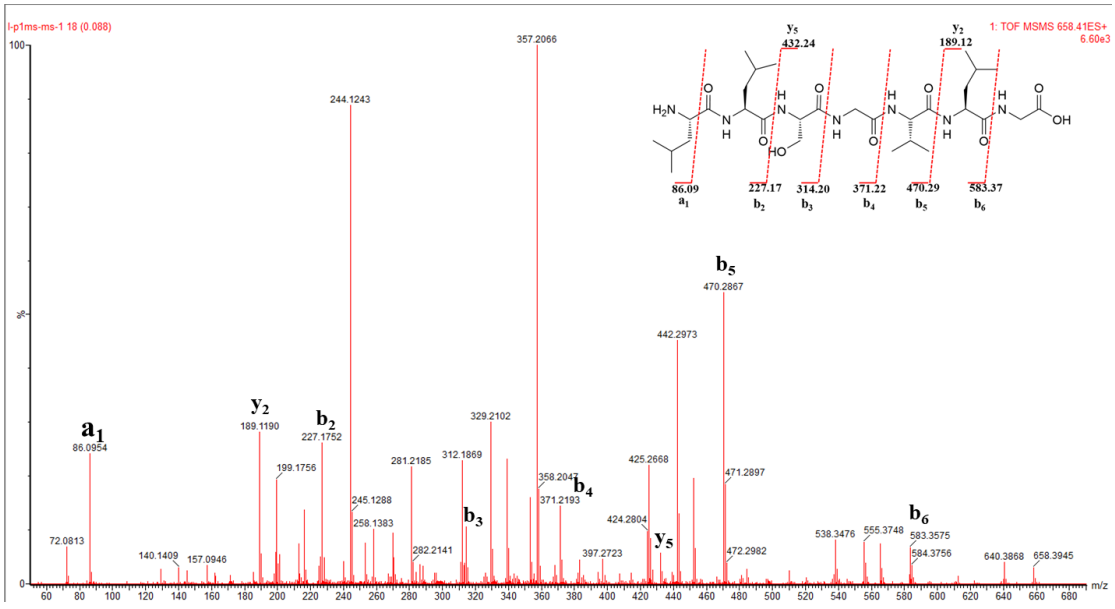


Figure S13. ESIMS/MS spectrum of **L-1**.

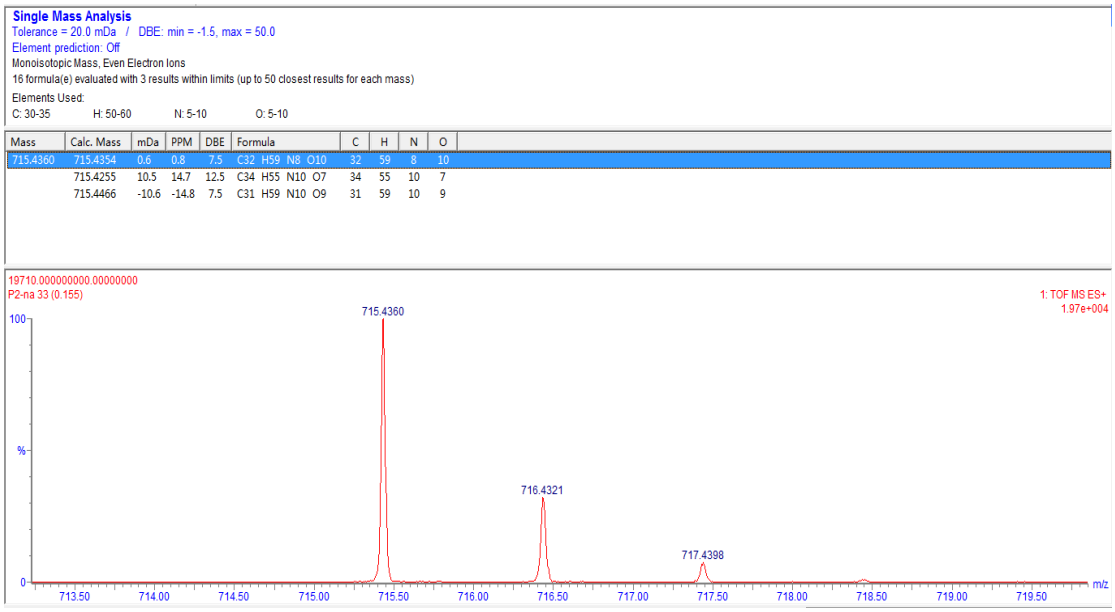


Figure S14. HRESIMS spectrum of **2**.

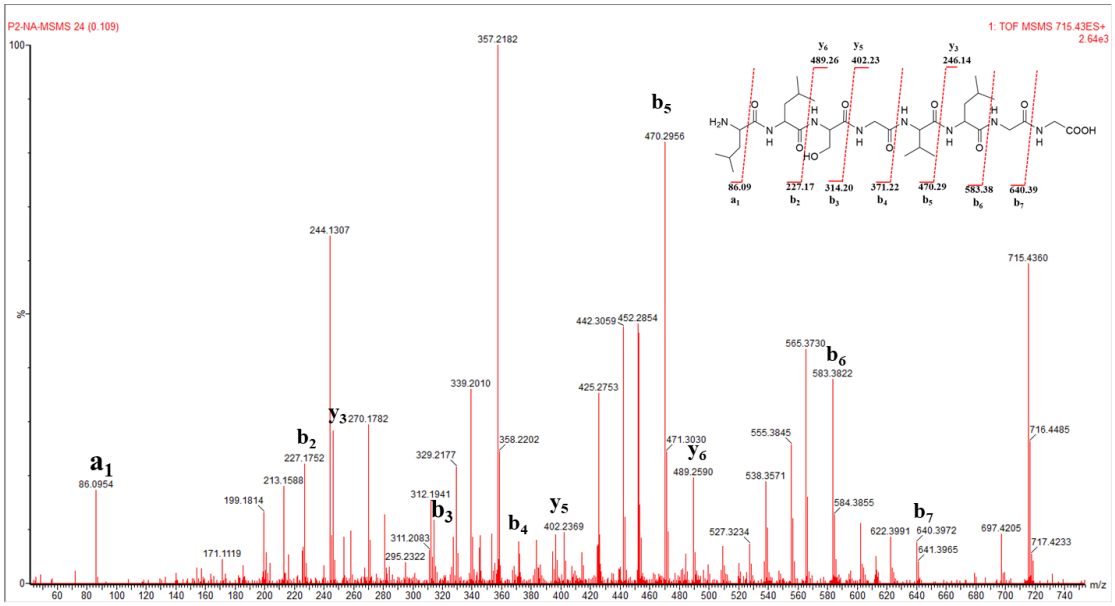


Figure S15. ESIMS/MS spectrum of **2**.

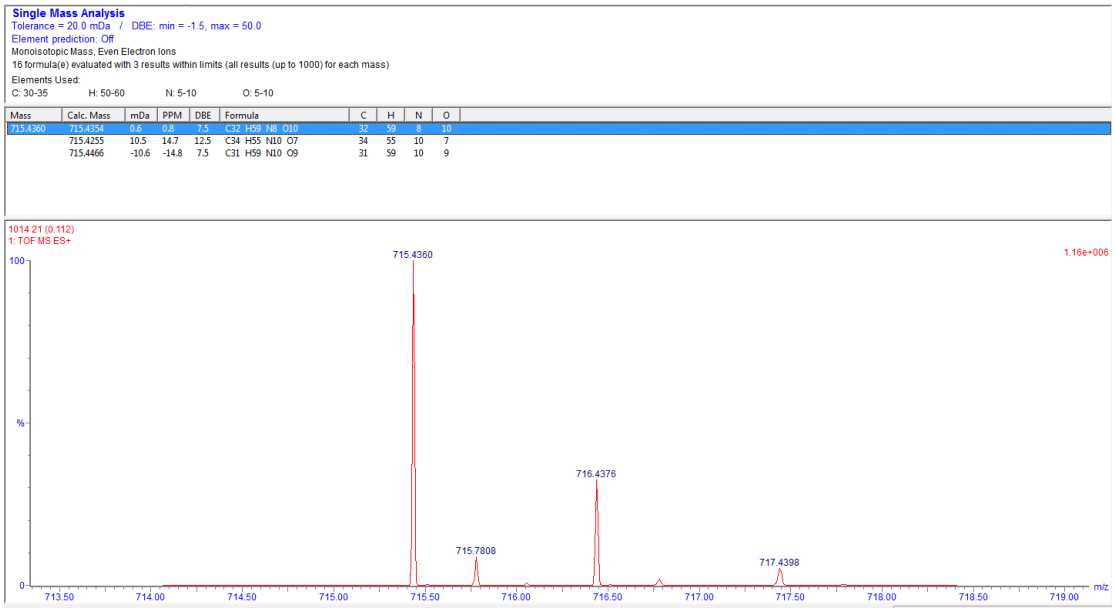
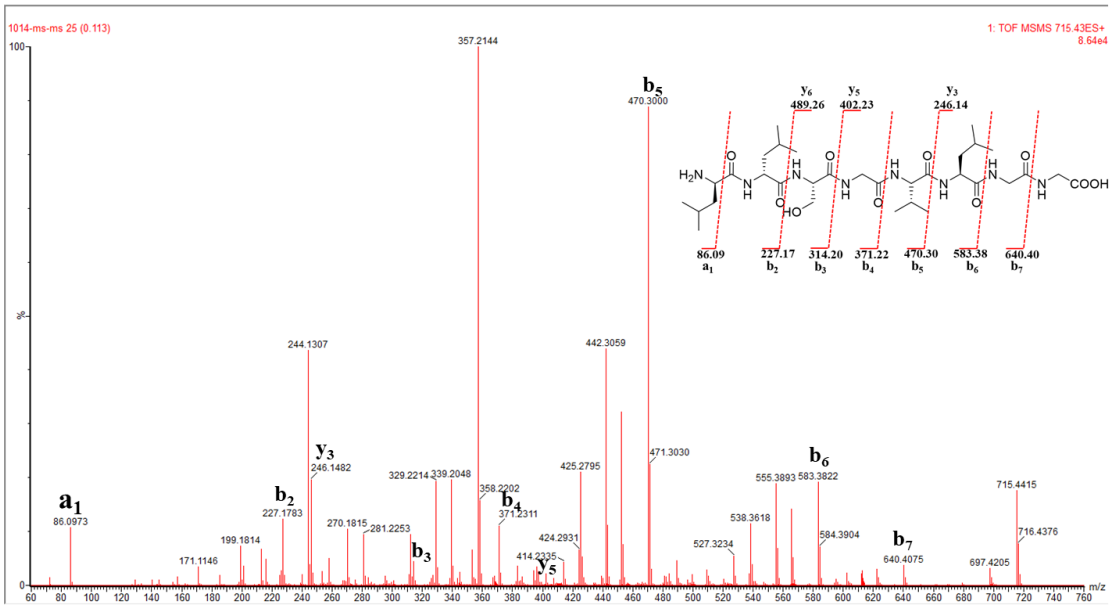


Figure S16. HRESIMS spectrum of **2a**



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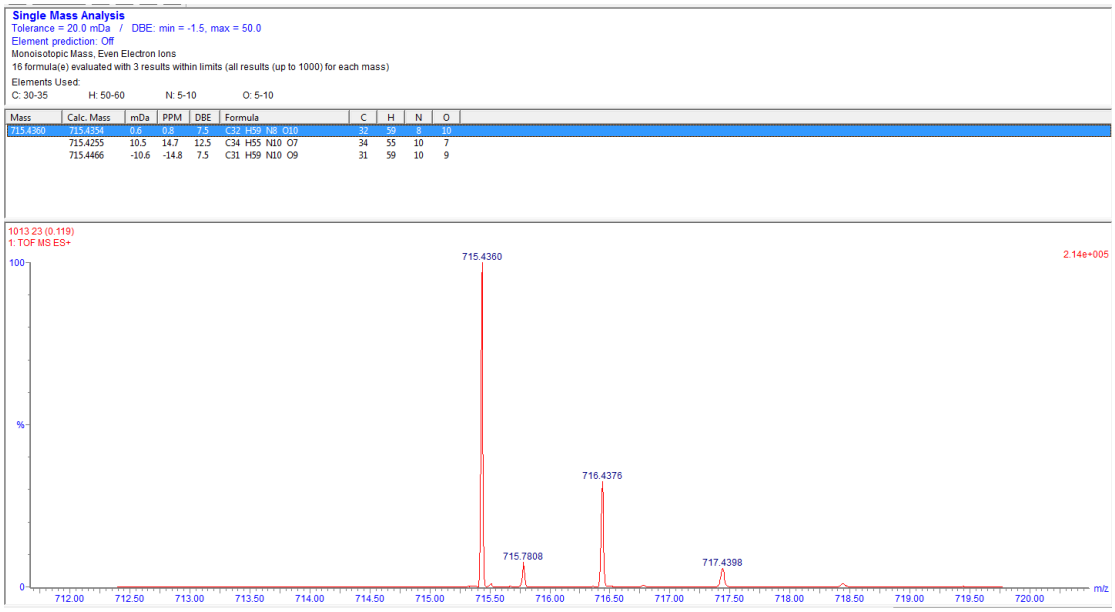


Figure S18. HRESIMS spectrum of **2b**

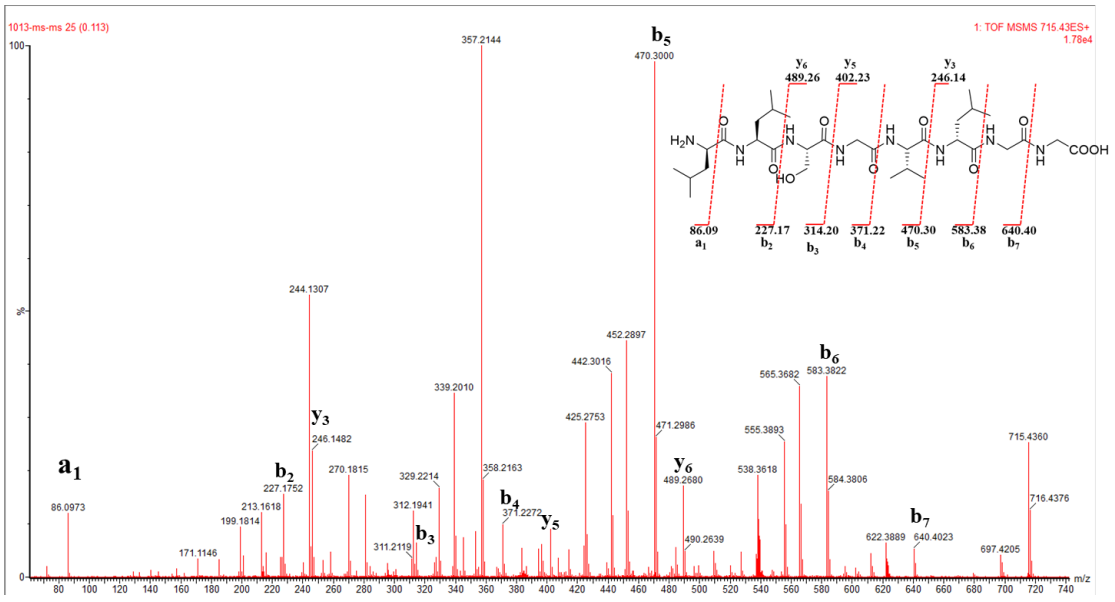
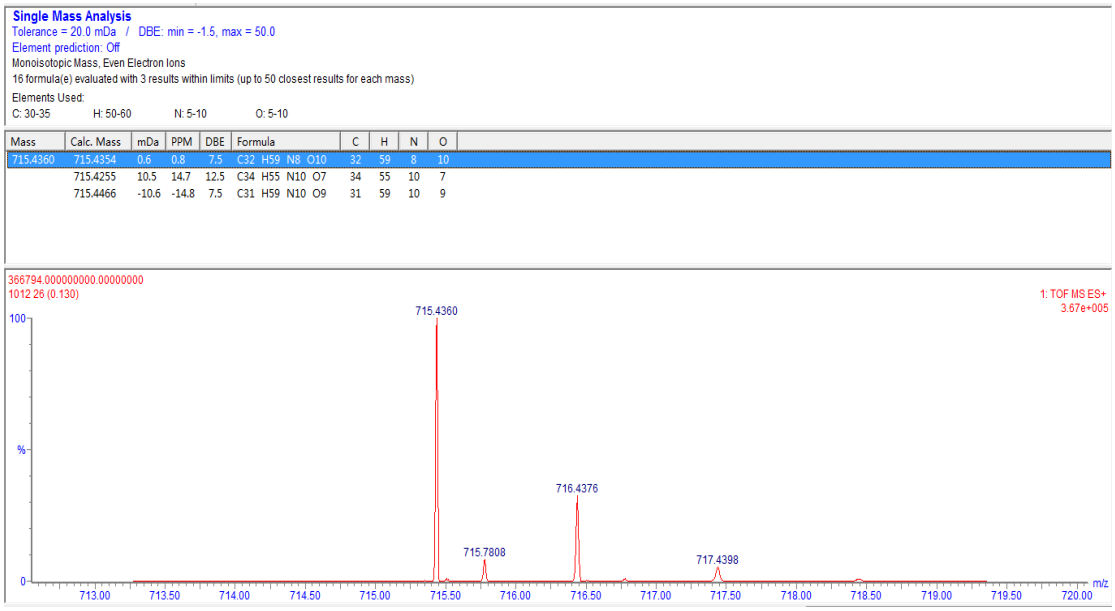


Figure S19 ESIMS/MS spectrum of **2b**



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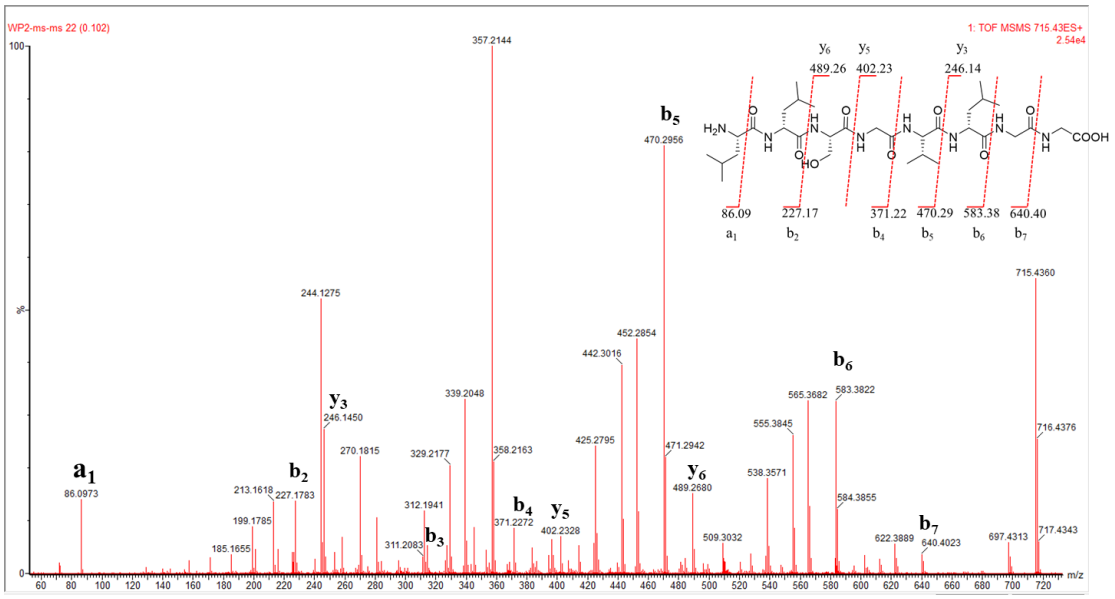

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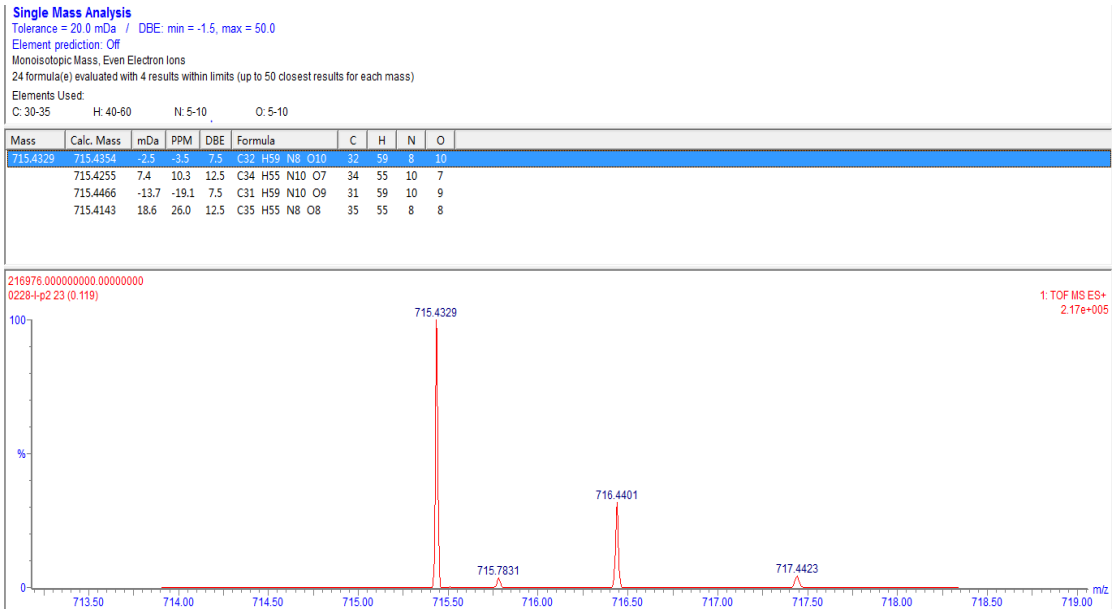
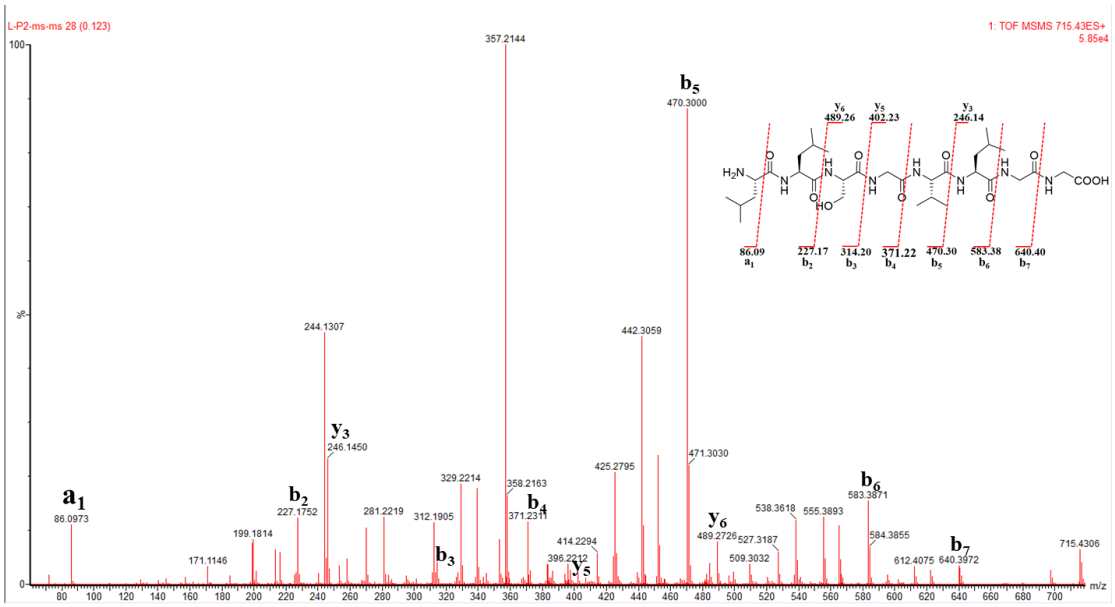


Figure S22. HRESIMS spectrum of **L-2**.



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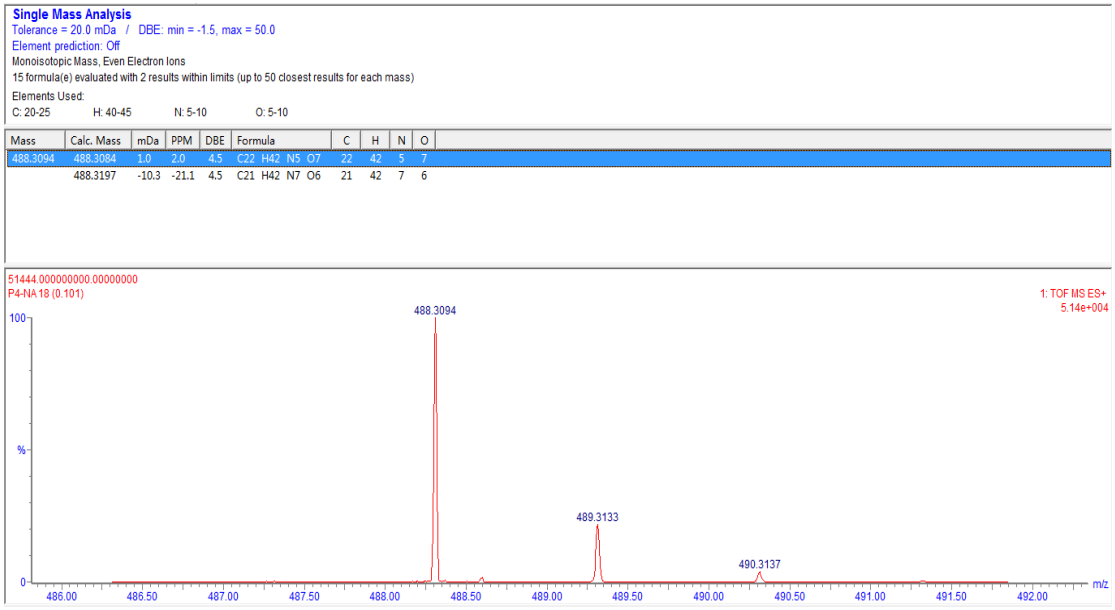

Figure S24. HRESIMS spectrum of **3**.

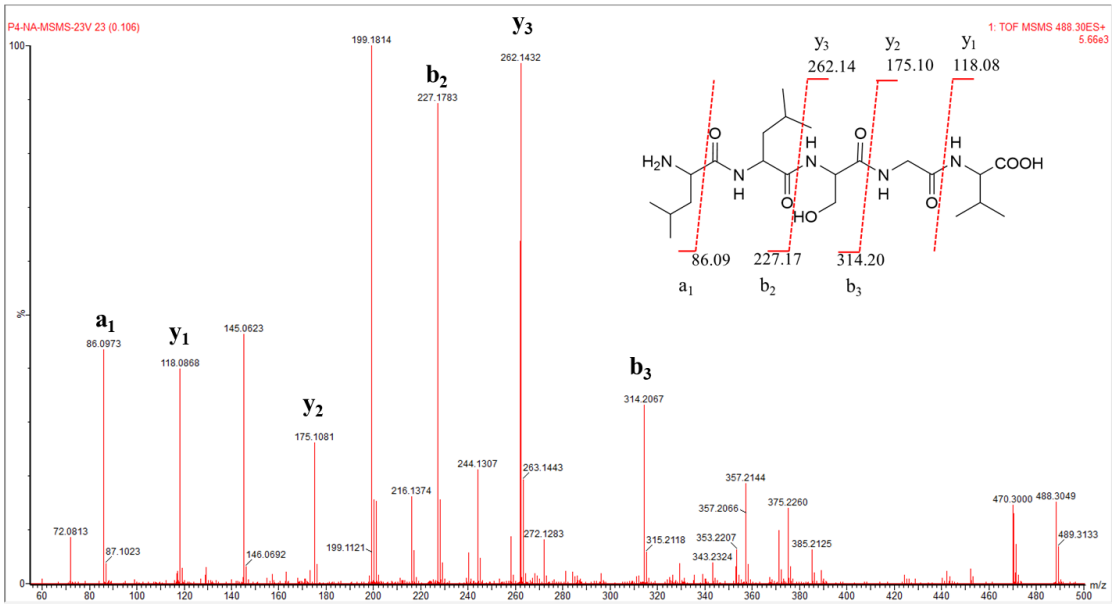

Figure S25. ESIMS/MS spectrum of **3**.

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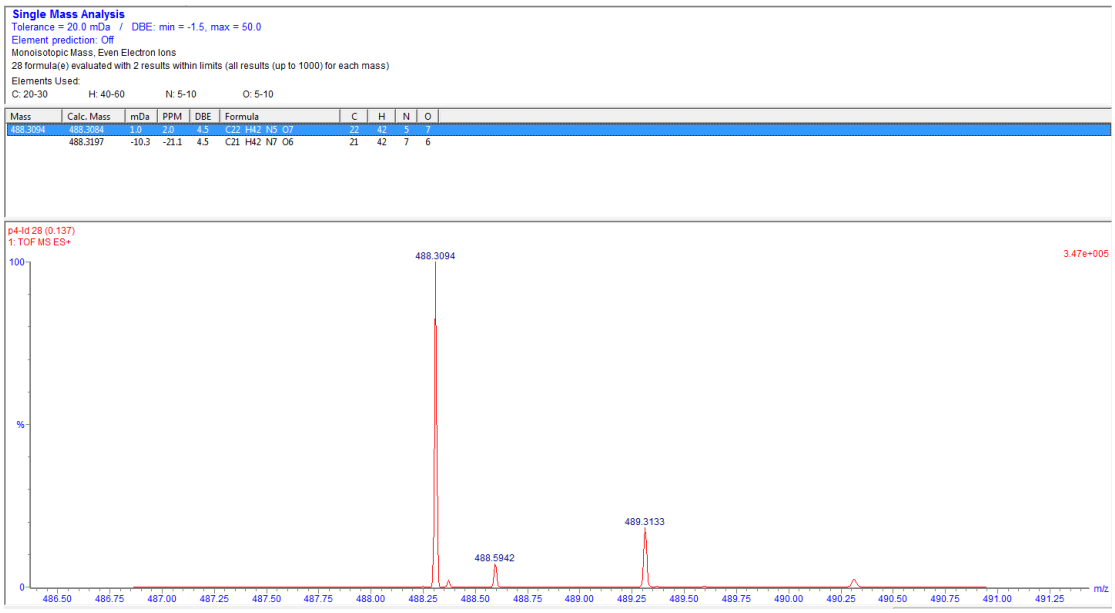

Figure S26. HRESIMS spectrum of **3a**.

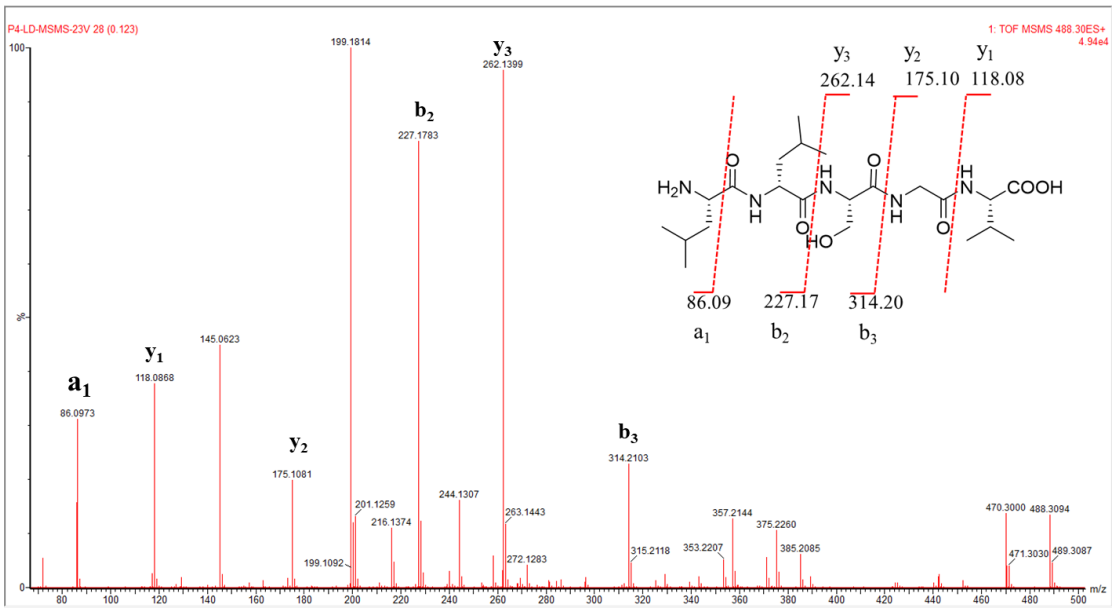

Figure S27. ESIMS/MS spectrum of **3a**.

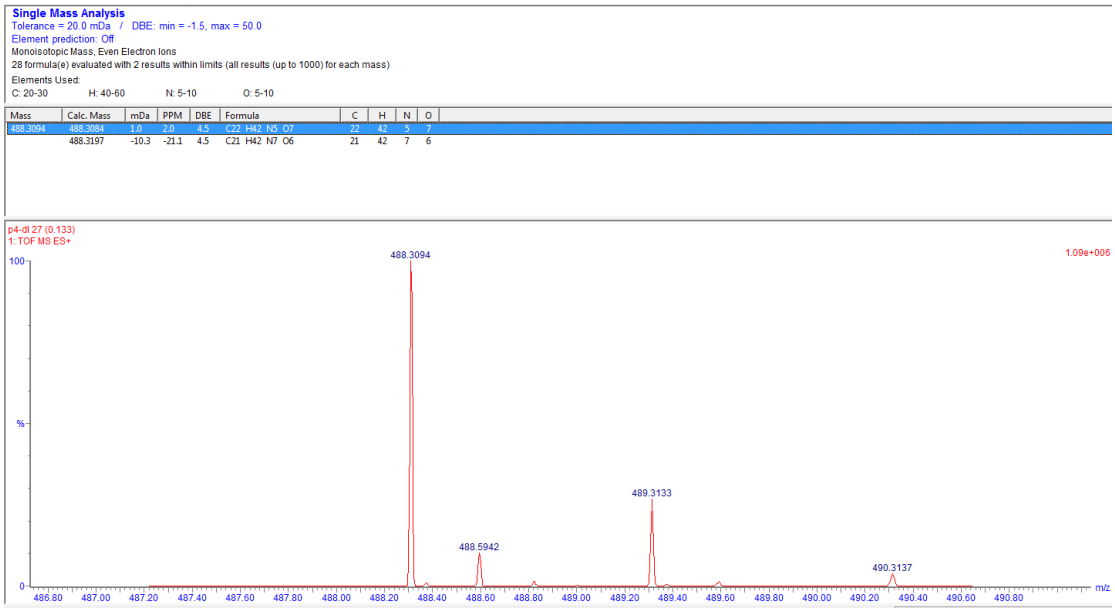

Figure S28. HRESIMS spectrum of **3b**.

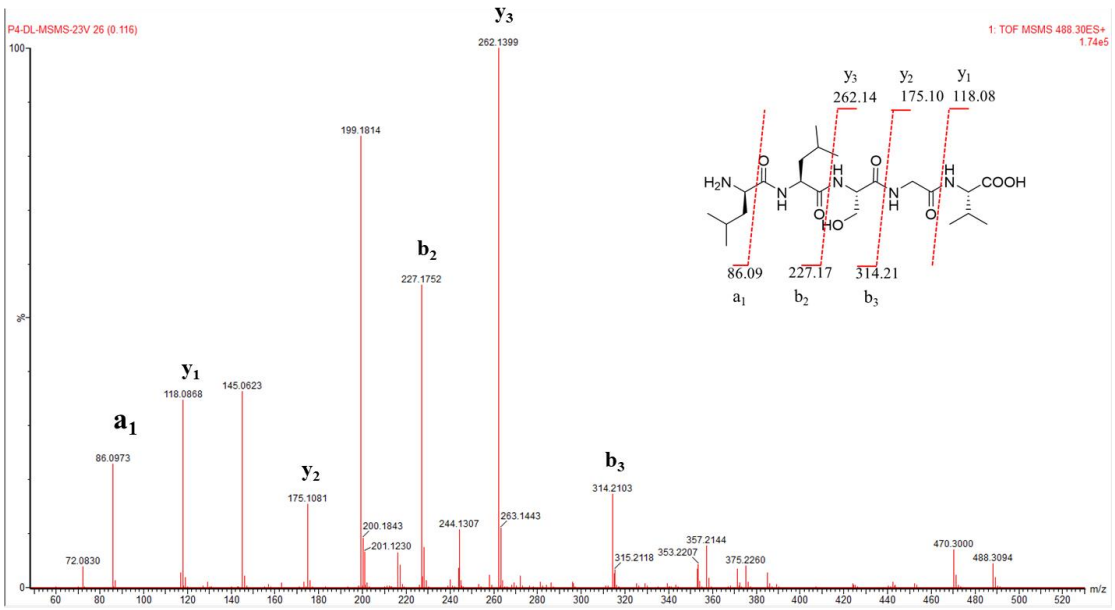

Figure S29. ESIMS/MS spectrum of **3b**.

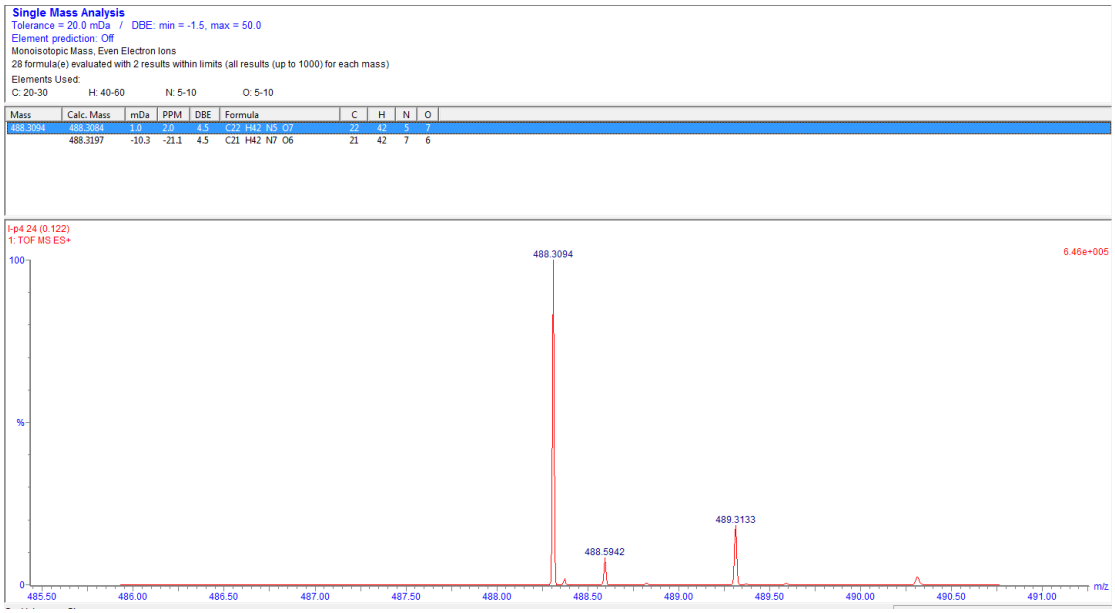

Figure S30. HRESIMS spectrum of **L-3**.

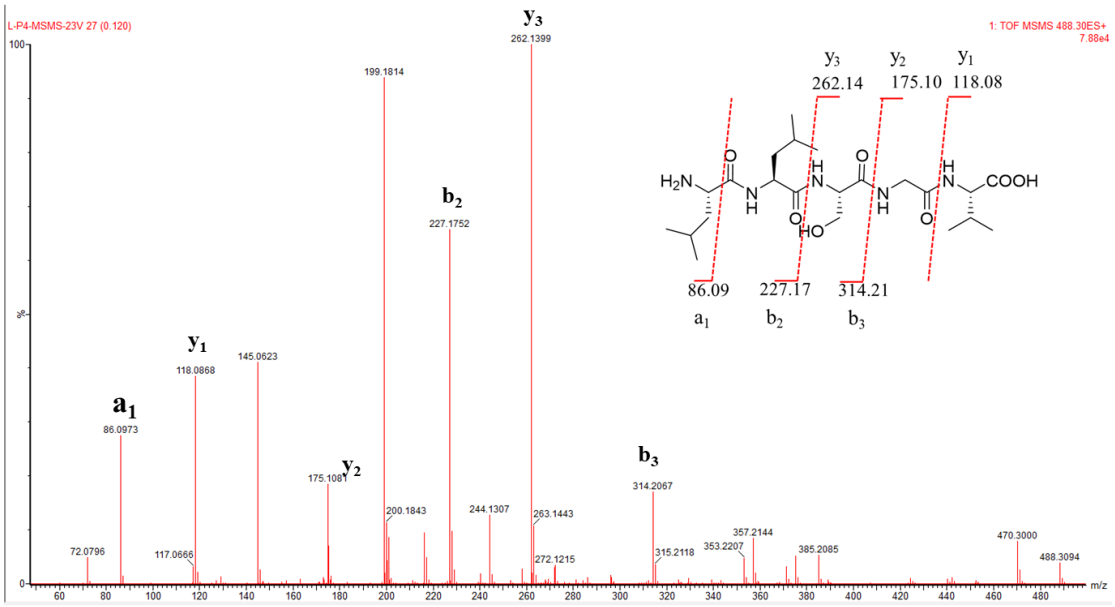

Figure S31. ESIMS/MS spectrum of **L-3**.

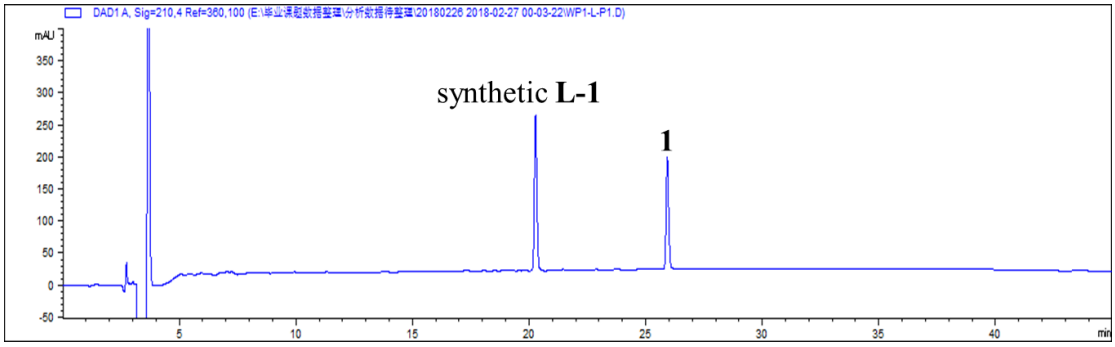

Figure S32. HPLC analysis of a mixture of natural **1** and synthetic **L-1**.

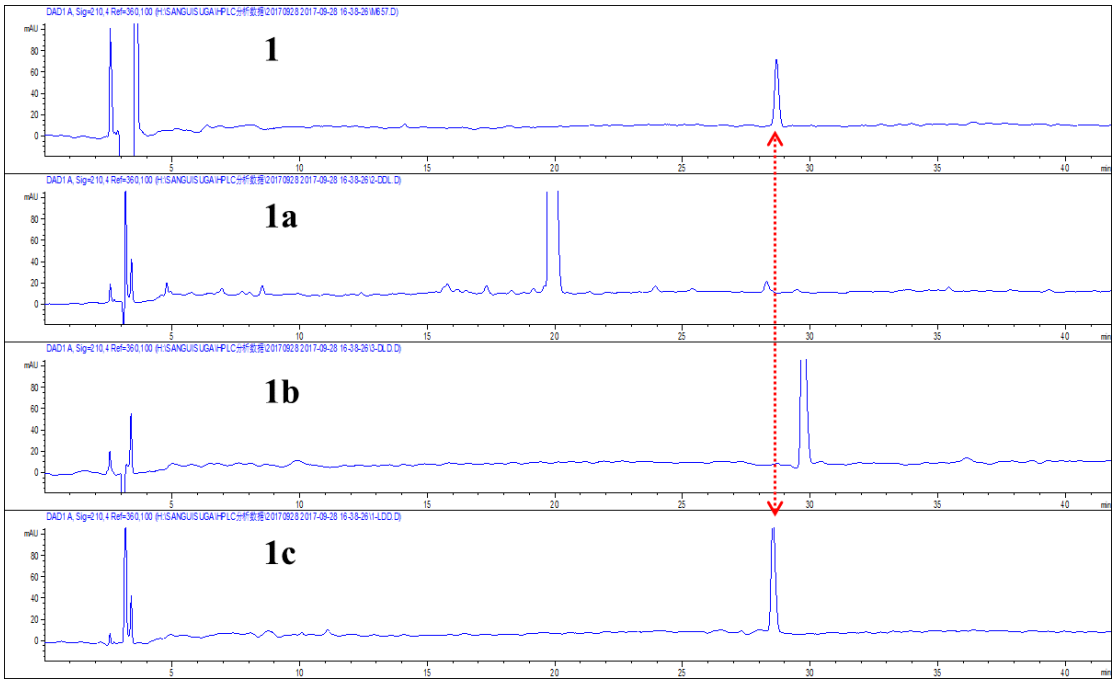

Figure S33. HPLC chromatograms for **1, 1a, 1b,** and **1c.**

The retention time of synthetic **1c** was identical to that of natural **1**

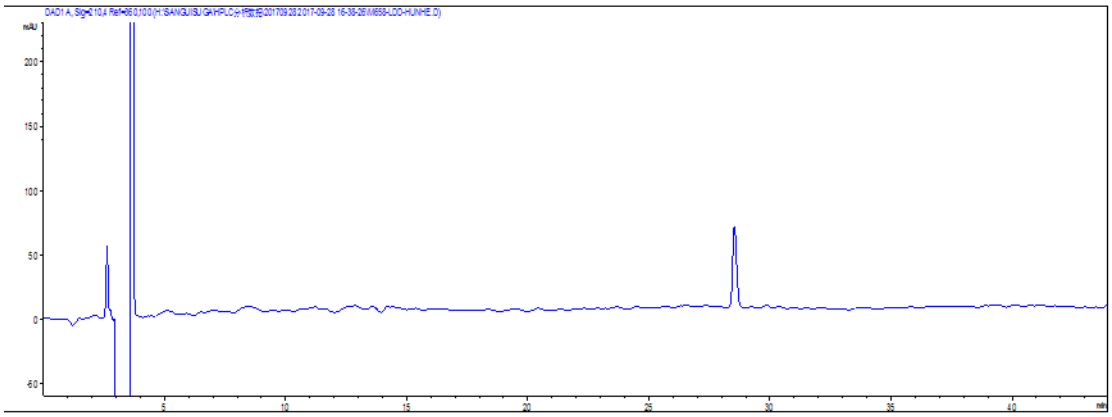

Figure S34. Co-elution of natural **1** and synthetic **1c** in equal amount.

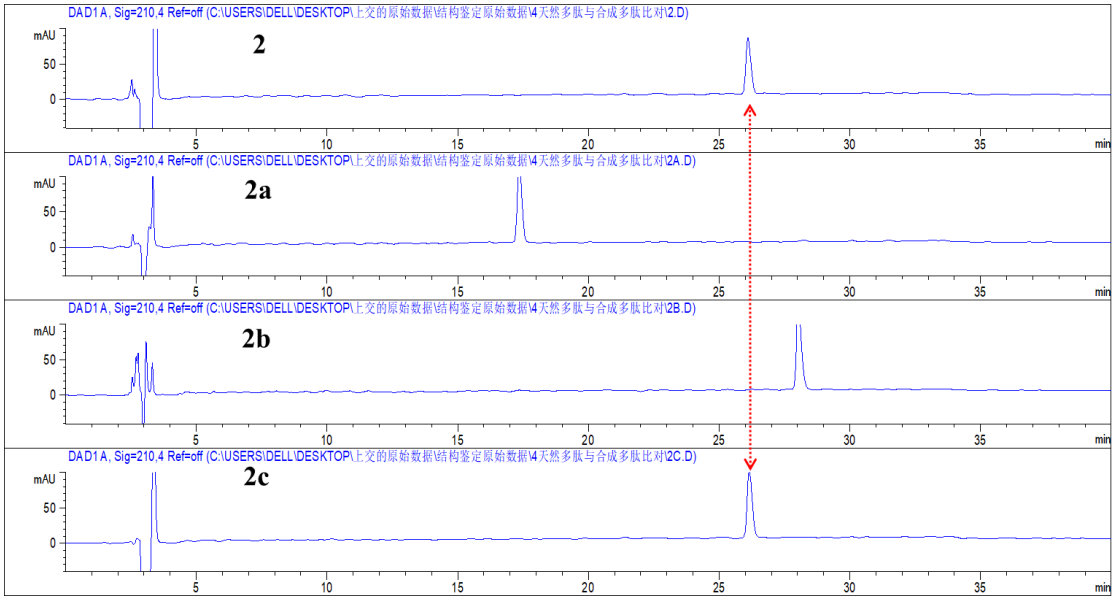

Figure S35. HPLC chromatograms for **2**, **2a, 2b,** and **2c**.

The retention time of synthetic **2c** was identical to that of natural **2**

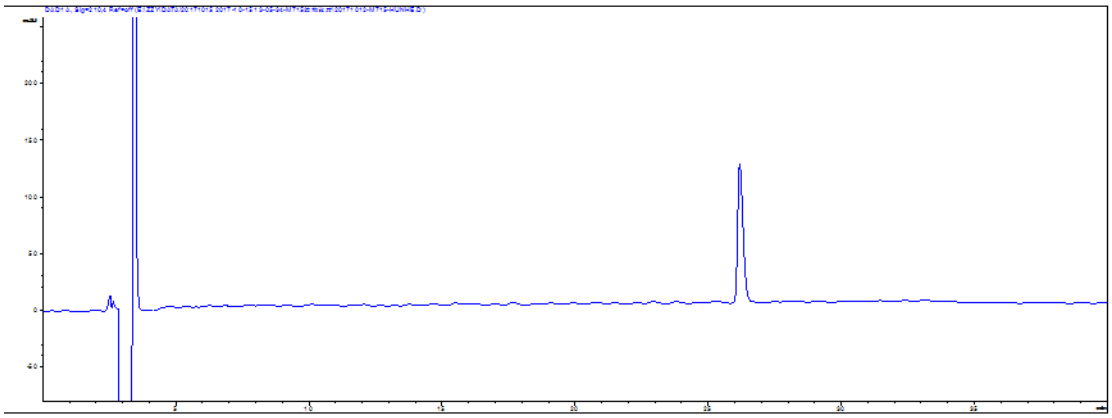

Figure S36. Co-elution of natural **2** and **2c** in equal amount.

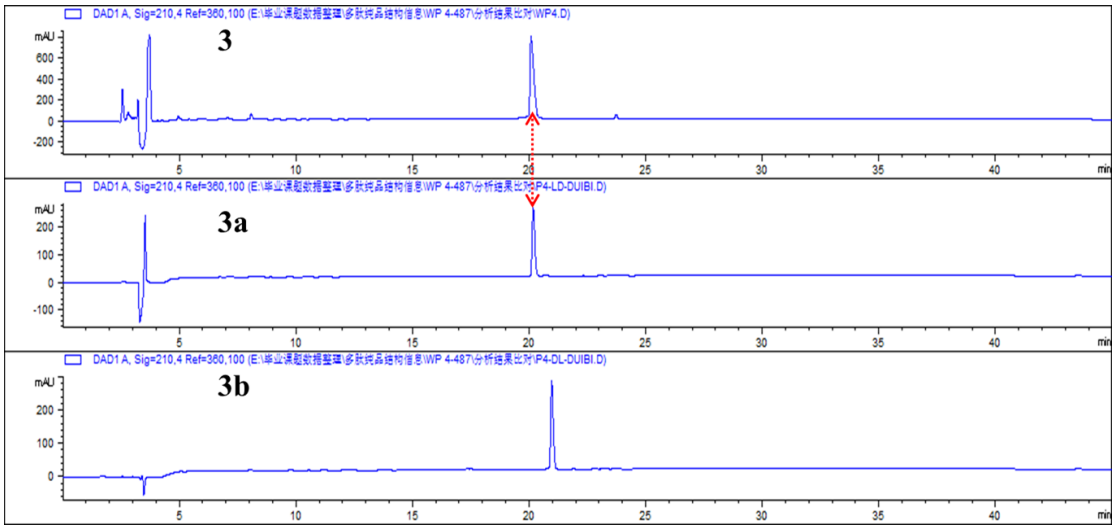

Figure S37. HPLC chromatograms for **3**, **3a,** and **3b**.

The retention time of synthetic **3a** was identical to that of natural **3.**

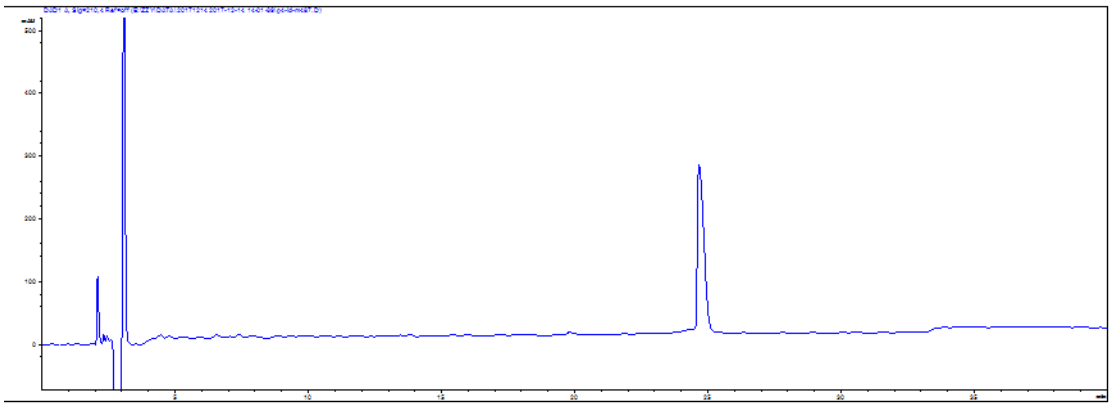

Figure S38. Co-elution of natural **3** and **3a** in equal amount.

Figures S39-S48. Marfey's analysis of 1 and 2

Amino acids	Retention time (min)[α] L	D	Measured	Assignment
Ser	20.9	21.1		
Val	32.0	36.2		
Leu	36.6	40.6		
Gly	24.2			
1			20.9; 24.2; 32.0; 36.6; 40.6	$_{L}$-Ser; Gly; $_{L}$-Val; $_{L}$-Leu; $_{D}$-Leu
2			20.9; 24.2; 32.0; 36.6; 40.6	$_{L}$-Ser; Gly; $_{L}$-Val; $_{L}$-Leu; $_{D}$-Leu

[α]Chromatographic separation was achieved on a C_{18} column (Cosmosil 5C_{18}-MS-Ⅱ, 4.6 mm × 250 mm, 5 μm, 1.0 mL/min).

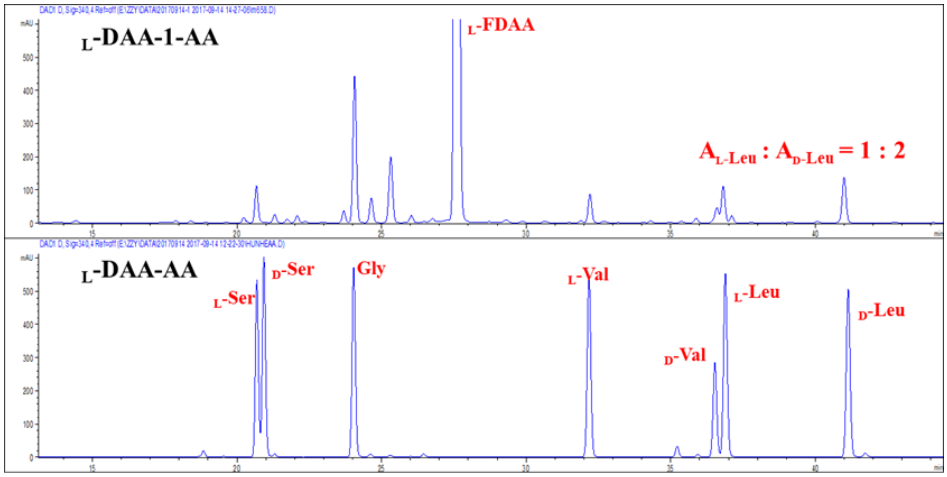

Figure S39. Marfey's analysis result of **1**.

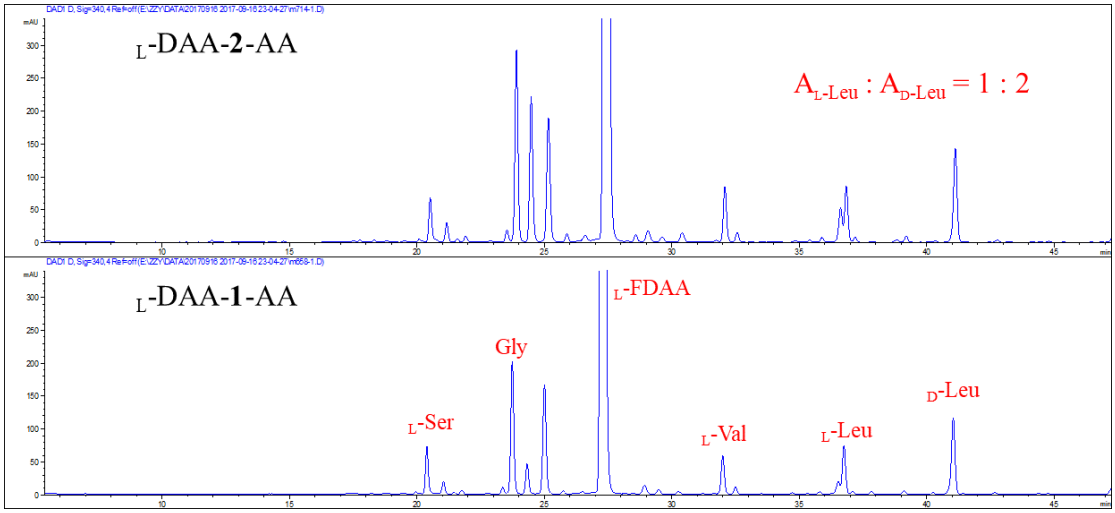

Figure S40. Marfey's analysis result of **2**.

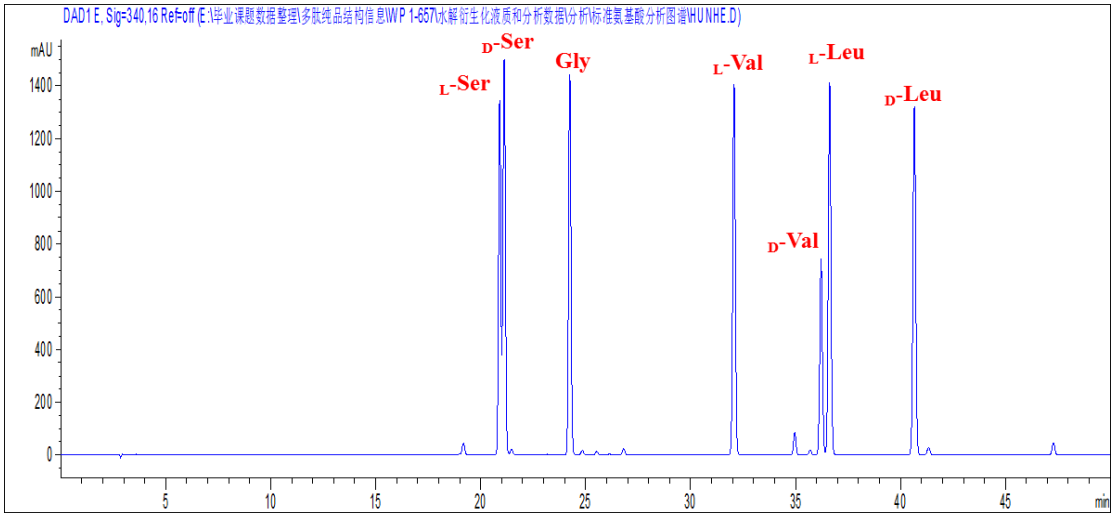

Figure S41. HPLC chromatogram for the mixture of L-DAA-standard amino acids applied for **1** and **2**

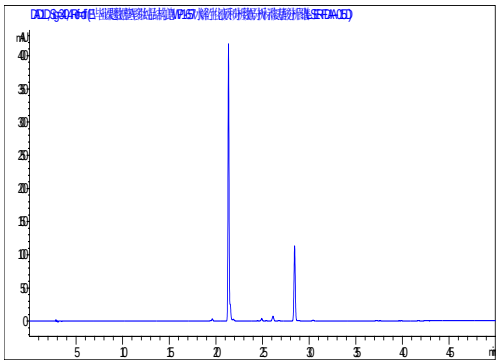

Figure S42. HPLC chromatogram for L-DAA-L-Ser.

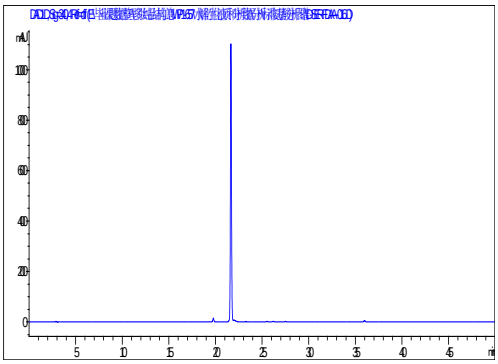

Figure S43. HPLC chromatogram for L-DAA-D-Ser.

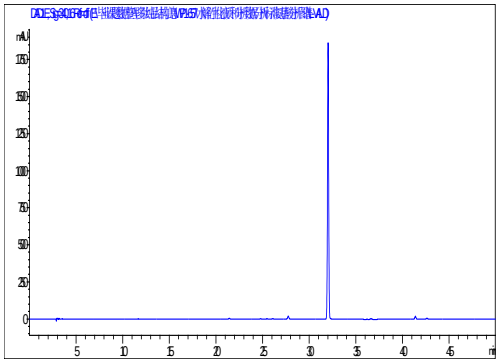

Figure S44. HPLC chromatogram for $_{L}$-DAA-$_{L}$-Val.

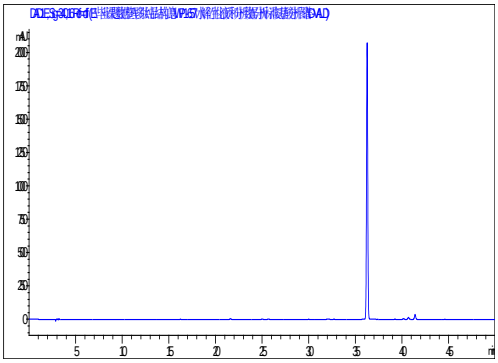

Figure S45. HPLC chromatogram for $_{L}$-DAA-$_{D}$-Val.

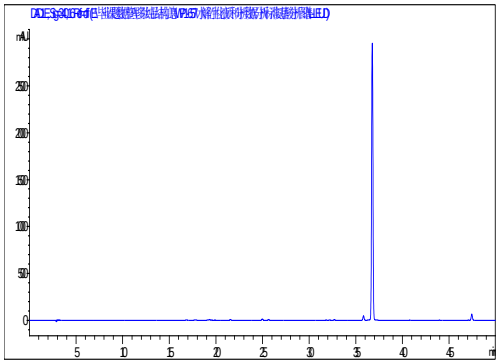

Figure S46. HPLC chromatogram for $_{L}$-DAA-$_{L}$-Leu.

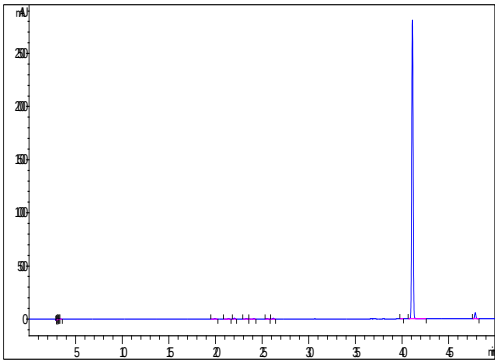

Figure S47. HPLC chromatogram for $_{L}$-DAA-$_{D}$-Leu.

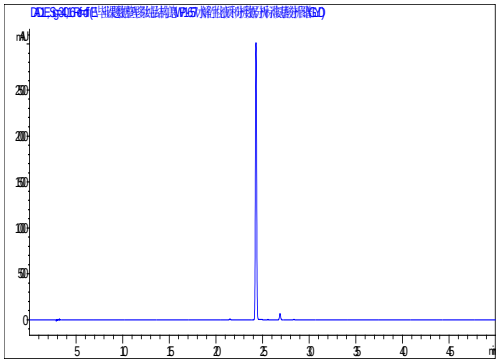

Figure S48. HPLC chromatogram for $_{L}$-DAA-Gly.

Figures S49-S57. Marfey's analysis of 3

Amino acids	Retention time (min)[α] L	D	Measured	Assignment
Ser	21.9	22.1		
Val	33.4	37.6		
Leu	38.0	42.1		
Gly	25.4			
3			21.9; 25.4; 33.4; 38.0; 42.1	$_{L}$-Ser; Gly; $_{L}$-Val; $_{L}$-Leu; $_{D}$-Leu

[α]Chromatographic separation was achieved on a C_{18} column (YMC-Pack ODS-A, 4.6 mm × 250 mm, 5 μm, 1.0 mL/min).

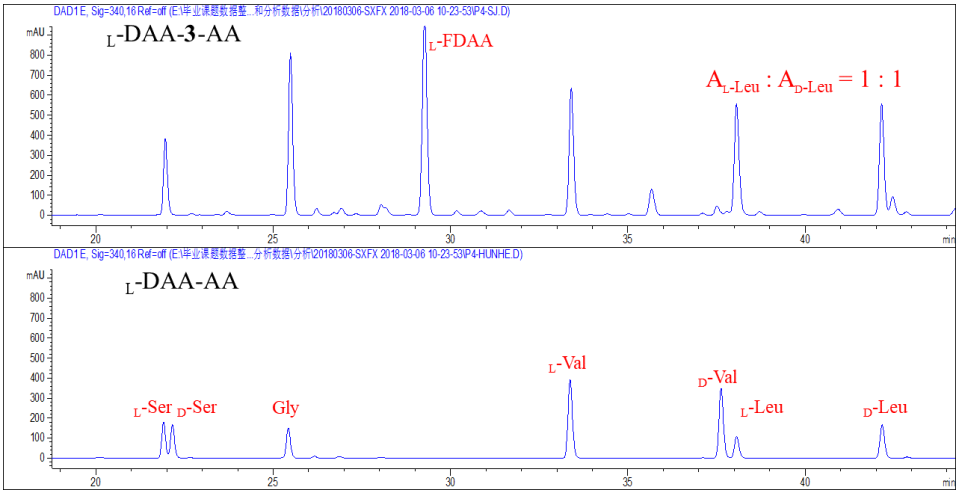

Figure S49. Marfey's analysis result of **3**.

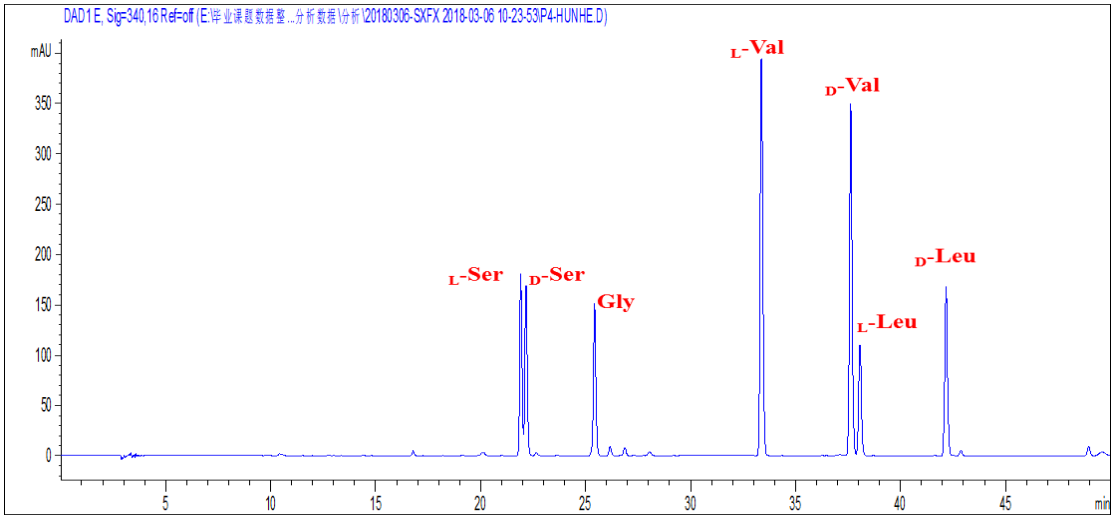

Figure S50. HPLC chromatogram for the mixture of $_{L}$-DAA-standard amino acids applied for **3.**

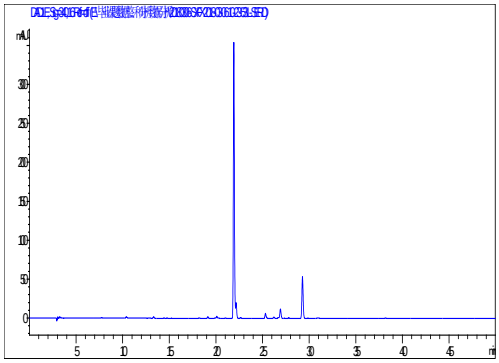

Figure S51. HPLC chromatogram for $_{L}$-DAA-$_{L}$-Ser.

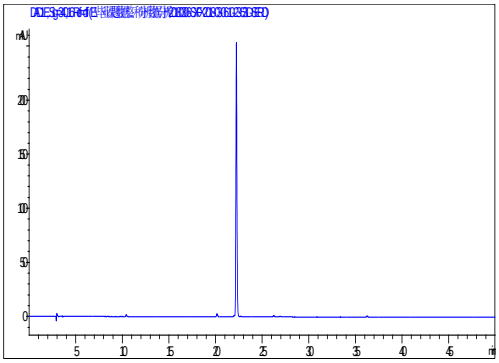

Figure S52. HPLC chromatogram for $_{L}$-DAA-$_{D}$-Ser.

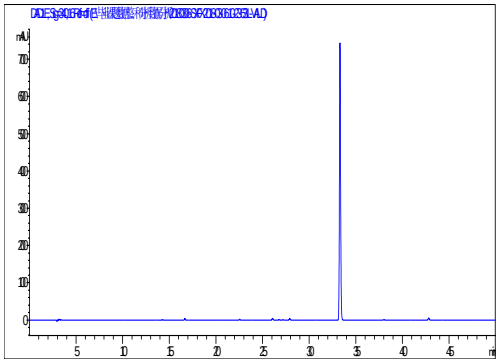

Figure S53. HPLC chromatogram for $_{L}$-DAA-$_{L}$-Val.

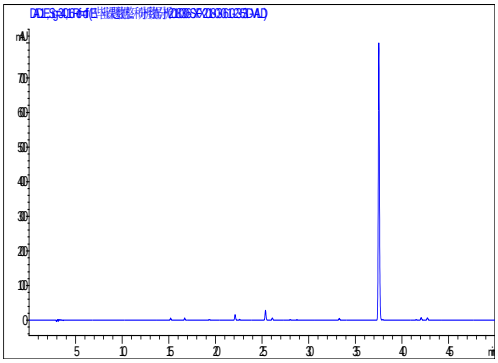

Figure S54. HPLC chromatogram for $_{L}$-DAA-$_{D}$-Val.

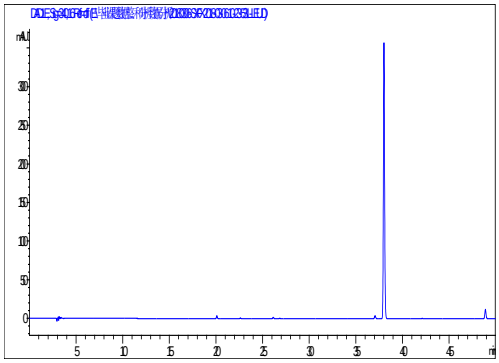

Figure S55. HPLC chromatogram for $_{L}$-DAA-$_{L}$-Leu.

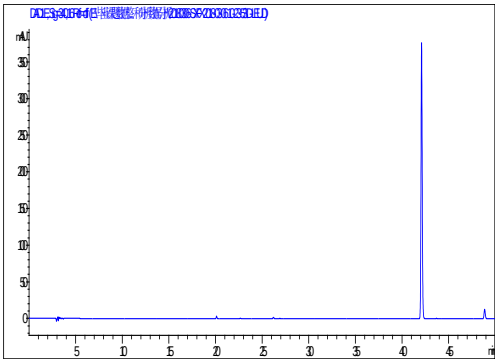

Figure S56. HPLC chromatogram for $_{L}$-DAA-$_{D}$-Leu.

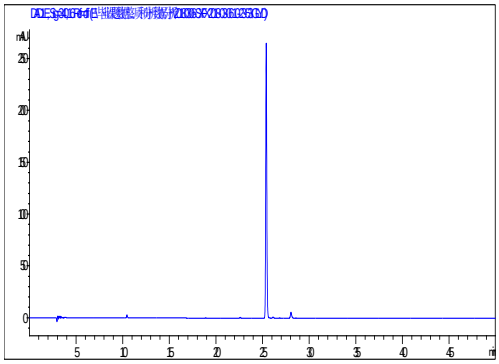

Figure S57. HPLC chromatogram for $_{L}$-DAA-Gly.

Figures S58-S69. Purity assay of synthetic 1-3 and their isomers.

HPLC condition: HPLC analysis was performed on an Agilent 1200 system equipped with a binary solvent system, an automatic sample manger and a diode array detector. Chromatographic separation was achieved on a Cosmosil $5C_{18}$-MS-Ⅱ reversed-phase column (4.6 mm × 250 mm, 5 μm) with a gradient elution using TFA (0.1%) in H_2O (mobile phase A) and TFA (0.1%) in CH_3CN (mobile phase B). The gradient elution program was 10-40% B from 0 to 30 min, 40-50% B from 30 to 40 min and 40-10% B from 40 to 50 min (1.0 mL/min). The elution profile was monitored at 210 nm.

Peptides	Purity (%)	Figure
1a	95.54	**Figure S58**
1b	95.13	**Figure S59**
1c	99.25	**Figure S60**
L-1	95.07	**Figure S61**
2a	95.8	**Figure S62**
2b	99.5	**Figure S63**
2c	97.0	**Figure S64**
L-2	95.0	**Figure S65**
3a	98.41	**Figure S66**
3b	95.30	**Figure S67**
L-3	95.59	**Figure S68**

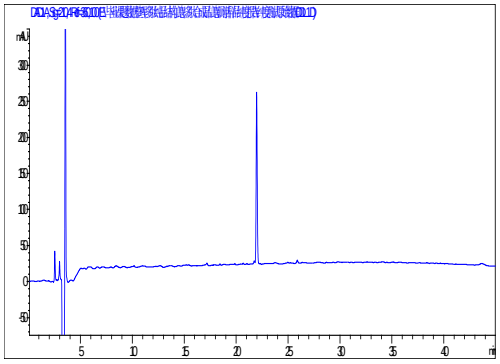

Figure S58. Purity assay for **1a** (99.25%).

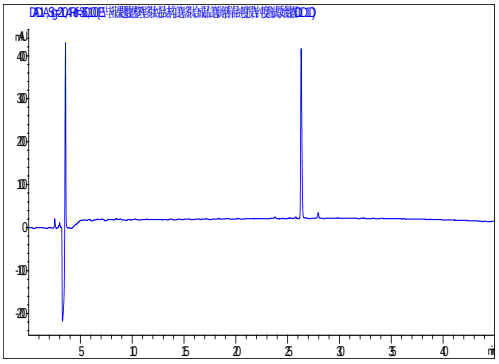

Figure S59. Purity assay for **1b** (95.13%).

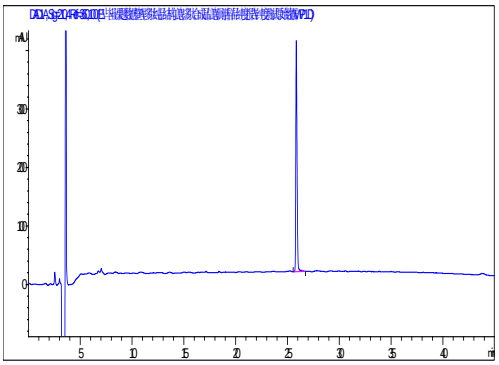

Figure S60. Purity assay for **1c** (95.54%).

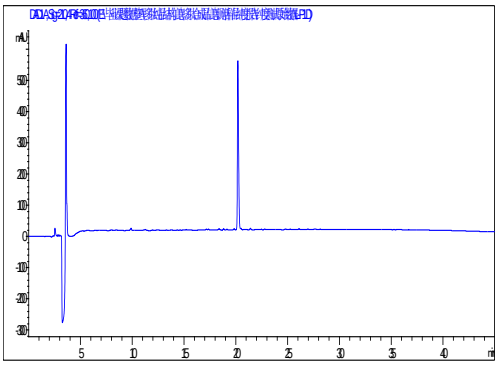

Figure S61. Purity assay for **L-1** (95.07%).

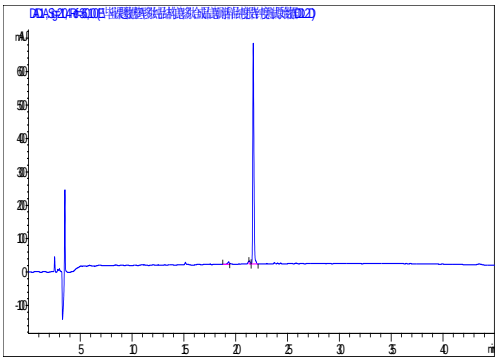

Figure S62. Purity assay for **2a**-(97.0%).

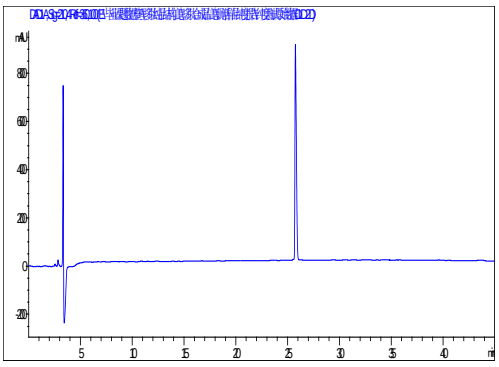

Figure S63. Purity assay for **2b** (99.50%).

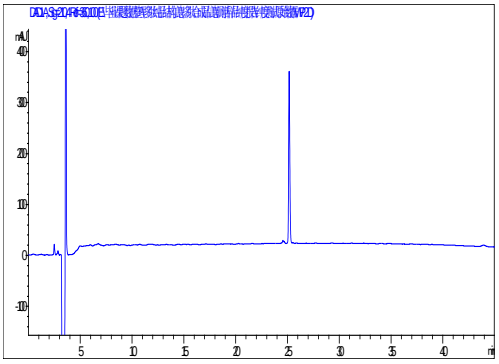

Figure S64. Purity assay for **2c** (95.8%).

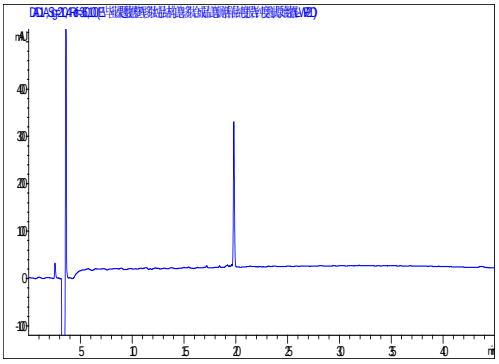

Figure S65. Purity assay for **L-2** (95.0%).

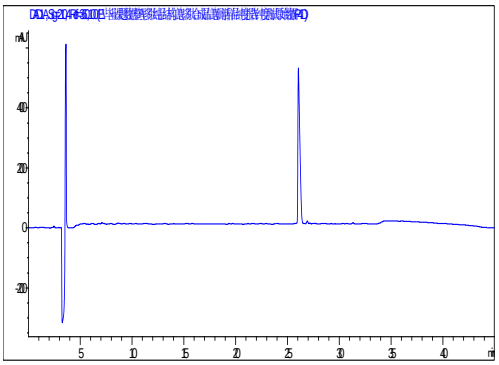

Figure S66. Purity assay for **3a** (98.41%).

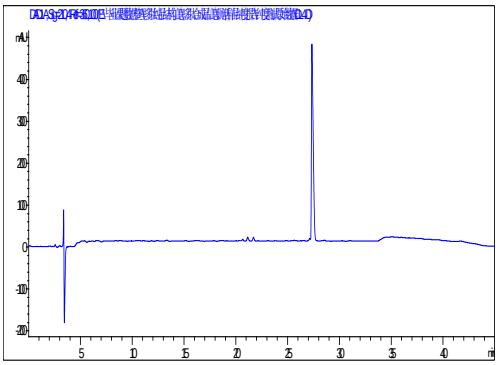

Figure S67. Purity assay for **3b** (95.30%).

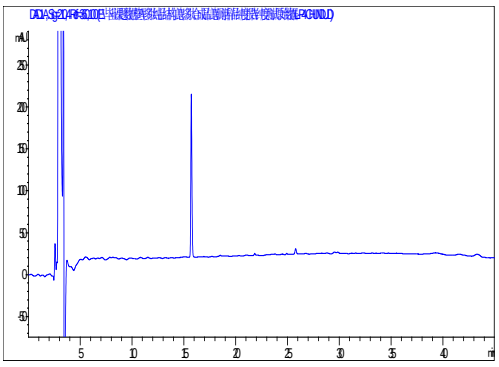

Figure S68. Purity assay for **L-3** (95.59%).

UPLC-HRESIMS analysis of normal saline extract of the fresh bodies of *Whitmania pigra* Whitman

Whitmantides A-C (**1-3**) are three new linear peptides containing $_D$-leucine. It's the first time to discover DAACPs from leeches. In order to confirm that the whitmantides A-C are naturally occurring in the leech, the identification of those compounds in the normal saline extract of the fresh bodies of *Whitmania pigra* Whitman was carried out using UPLC-HRESIMS. Three chromatographic peaks with the exact mass data and identical retention times of whitmantides A-C were presented in the extracted ion current (EIC) chromatogram for the normal saline extract of fresh bodies, which was shown in **Figures S69-S75**. The results indicated that whitmantides A-C are presented in the animal itself.

Preparation of sample solution: The fresh whole bodies of *W. pigra* (75 g) were anaesthetized with EtOH and frozen at -80 ℃ for 12 h. Then the ice-cold leeches were homogenated with a homogenizer. The homogenates were soaked in normal saline at -20 ℃ for 24 h and then melted at 4 ℃, which was repeated for three times. After centrifugation at 3600 *g* for 20 min, the supernatant was dealt with centrifugal ultrafiltration using Amicon Ultra-15 (50 and 10 kDa nominal molecular mass cutoffs) at a speed of 4000 *g* for 40 min. The permeate with molecular mass < 10 kDa was desalted by SPE column and filtered through a 0.22 μm membrane prior to further UPLC-HRESIMS analysis.

UPLC conditions: UPLC analysis was performed on a Waters Acquity UPLC system consisting of an automatic sample manger, a binary solvent system and a PDA detector. All the separations were achieved on an ACQUITY UPLC ® CSH ™ C_{18} column (1.7 μm, 2.1 mm ×100 mm) with a gradient elution using formic acid (0.1%) in H_2O (mobile phase A) and CH_3CN (mobile phase B). The gradient elution program was 5-15% B from 0 to 10 min, 15–50% B from 10 to 15 min, 50–95% B from 15 to 17 min and 95–5% B from 17 to 18 min (0.3 mL/min).

MS conditions: HRESIMS analysis was carried on a Waters Xevo-G2 Q-TOF mass spectrometer equipped with an ESI source. The mass range was set at *m/z* 20 to 1000 Da. Mass spectra were acquired in positive mode and the operating parameters were set as follow: extraction cone voltage of 4 V; sample cone voltage of 30 V; capillary voltage, 2.5 kV; source temperature, 110 ℃ ; desolvation temperature, 350 ℃; cone gas flow, 30 L/h; desolvation gas flow, 800 L/h.

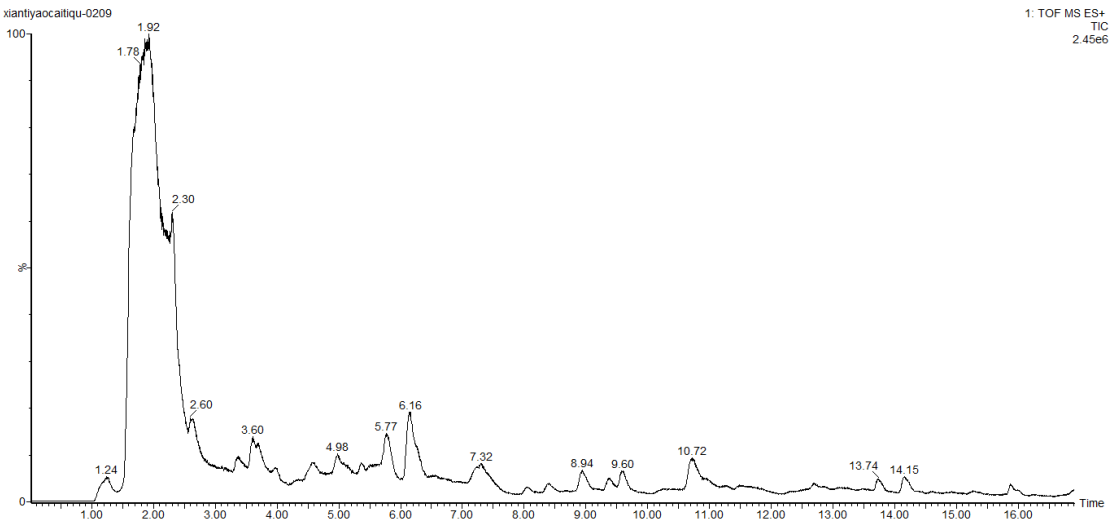

Figure S69. The total ion current (TIC) chromatogram for the normal saline extract of the fresh whole bodies of *W. pigra*.

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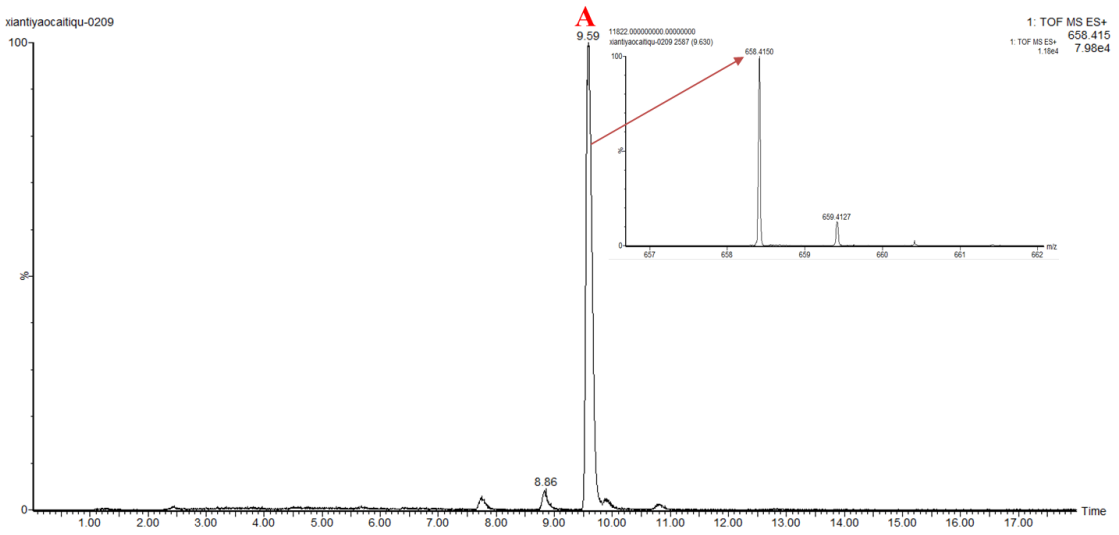

Figure S70. The extract ion current (EIC) chromatogram for *m/z* 658.415 $[M + H]^+$ from the normal saline extract of the fresh whole bodies of *W. pigra*; Peak A: retention time: 9.59 min; *m/z* 658.4150 $[M + H]^+$.

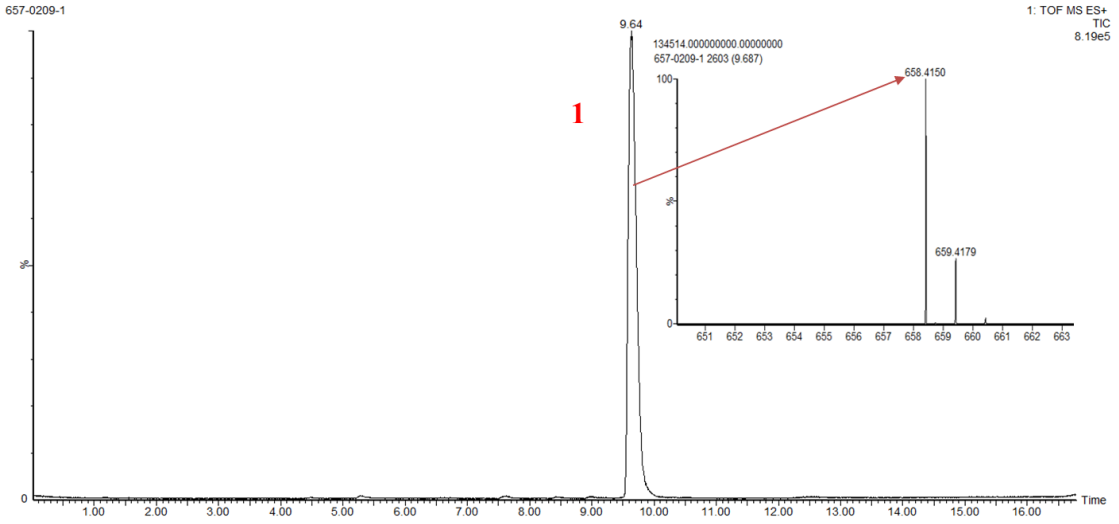

Figure S71. The total ion current (TIC) chromatogram for **1**; retention time: 9.64 min; *m/z* 658.4150 $[M + H]^+$.

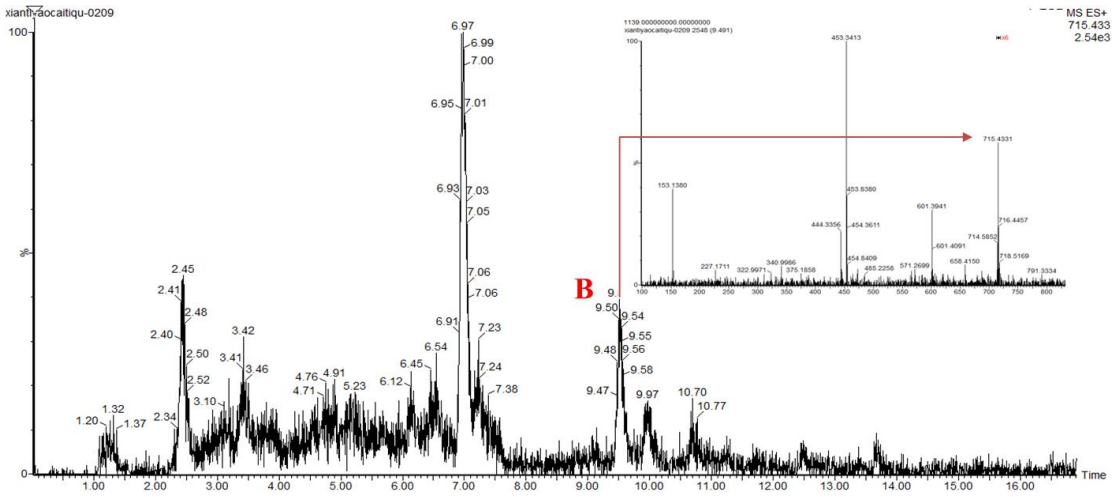

Figure S72. The extract ion current (EIC) chromatogram for *m/z* 715.433 $[M + H]^+$ from the normal saline extract of the fresh whole bodies of *W. pigra*; Peak B: retention time: 9.52 min; *m/z* 715.4331 $[M + H]^+$.

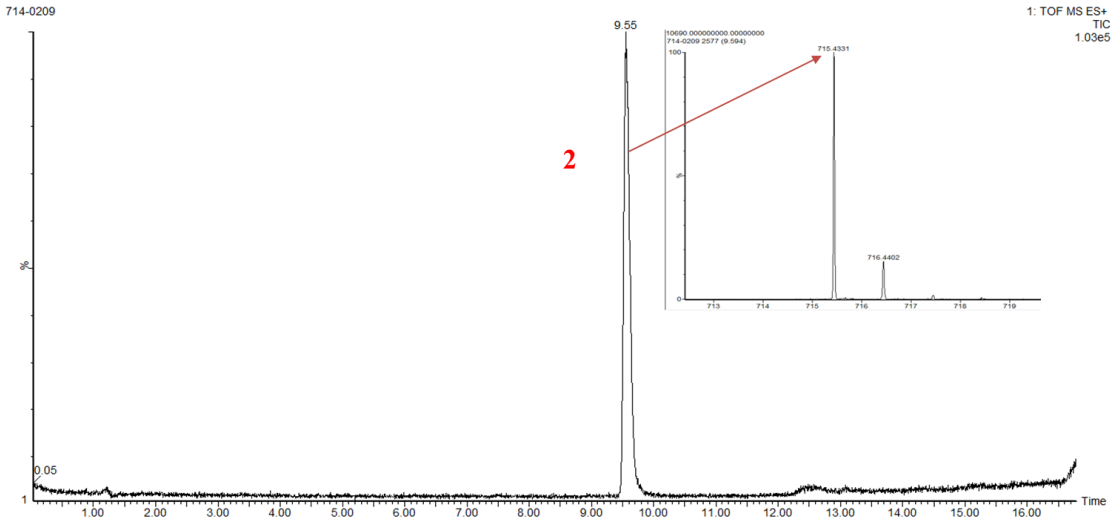

Figure S73. The total ion current (TIC) chromatogram for **2**; retention time: 9.55 min; *m/z* 715.4331 $[M + H]^+$.

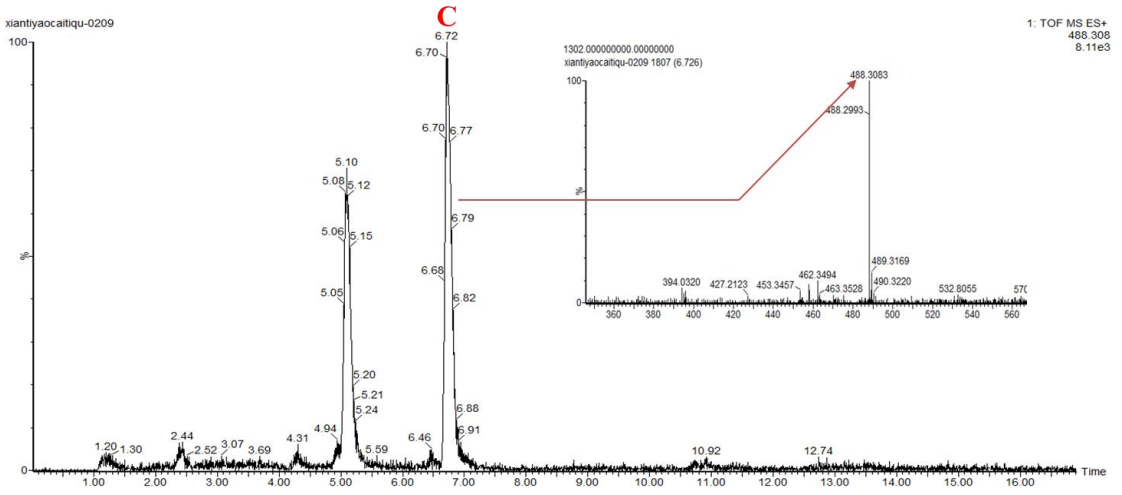

Figure S74. The extract ion current (EIC) chromatogram for *m/z* 488.308 $[M + H]^+$ from the normal saline extract of the fresh whole bodies of *W. pigra*; Peak C: retention time: 6.72 min; *m/z* 488.3083 $[M + H]^+$.

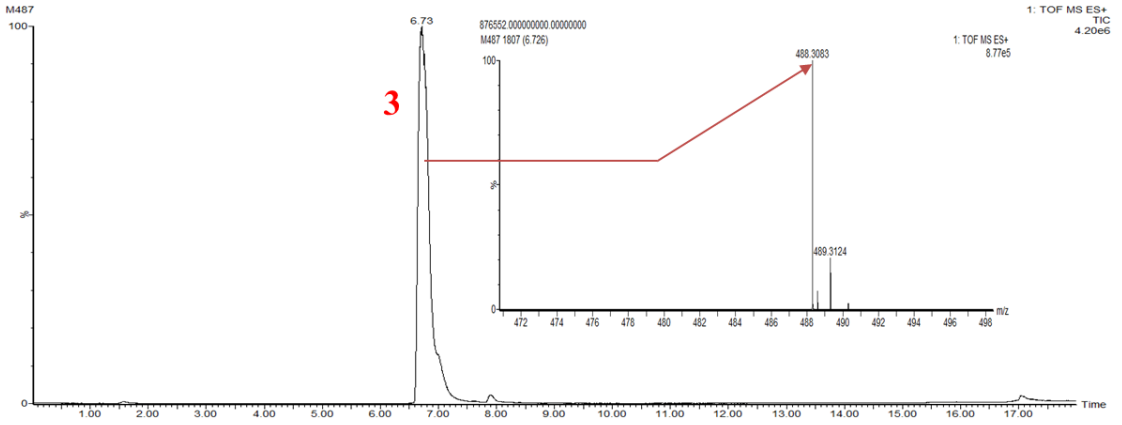

Figure S75. The total ion current (TIC) chromatogram for **3**; retention time: 6.73 min; *m/z* 488.3083 $[M + H]^+$.

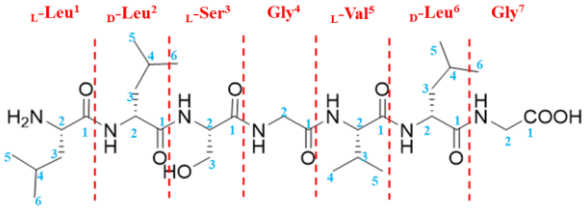

Table S1. NMR Spectroscopic Data (400M, CD_3CN: D_2O: TFA-*d*=3: 2: 0.1) for synthetic **1**[a]

position	δ_C type	δ_H [mult, *J* (Hz)]
$_L$-Leu^1		
1	171.2 C	
2	52.7, CH	4.60 [b]
3	40.7, CH_2	2.28 [b]
4	25.0, CH	2.29 [b]
5	21.2, CH_3	1.52 [b]
6	21.4, CH_3	1.54 [b]
$_D$-Leu^2		
1	173.2, C	
2	52.8, CH	4.92 [b]
3	40.3, CH_2	2.24 [b]
4	25.3, CH	2.25 [b]
5	22.3, CH_3	1.51 [b]
6	22.4, CH_3	1.52 [b]
$_L$-Ser^3		
1	172.7, C	
2	56.5, CH	4.96 [b]
3	62.1, CH_2	4.45 [b]; 4.43 [b]
Gly^4		
1	171.7, C	
2	41.8, CH_2	4.49 [b]
$_L$-Val^5		
1	173.8, C	
2	60.3, CH	4.68 [b]
3	31.0, CH	2.67 [b]
4	18.7, CH_3	1.52 [b]
5	19.4, CH_3	1.54 [b]
$_D$-Leu^6		
1	174.9, C	
2	53.5, CH	4.97 [b]
3	40.7, CH_2	2.26 [b]
4	25.4, CH	2.23 [b]
5	23.2, CH_3	1.57 [b]
6	23.3, CH_3	1.57 [b]
Gly^7		
1	175.0, C	
2	43.3, CH_2	4.52 [b]

[a]Signals assigned using 2D NMR data. [b]Overlapping signal.

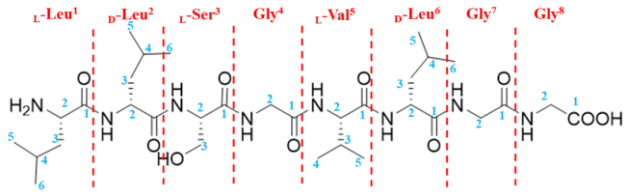

Table S2. NMR Spectroscopic Data (400M, CD_3CN: D_2O: TFA-*d*=3: 2: 0.1) for synthetic **2**[a]

position	δ_C type	δ_H [mult, *J* (Hz)]
$_L$-Leu^1		
1	171.2, C	
2	52.7, CH	4.53 [b]
3	40.7, CH_2	2.24 [b]
4	25.0, CH	2.20 [b]
5	21.2, CH_3	1.45 [b]
6	21.4, CH_3	1.51 [b]
$_D$-Leu^2		
1	173.2, C	
2	53.4, CH	4.86 [b]
3	40.3, CH_2	2.24 [b]
4	25.3, CH	2.20 [b]
5	22.3, CH_3	1.52 [b]
6	22.4, CH_3	1.52 [b]
$_L$-Ser^3		
1	172.7, C	
2	56.4, CH	4.95 [b]
3	62.1, CH_2	4.36 [b]
Gly^4		
1	171.8, C	
2	42.0, CH_2	4.48 [b]
$_L$-Val^5		
1	174.2, C	
2	60.3, CH	4.67
3	31.0, CH	2.59, [b]
4	18.7, CH_3	1.52 [b]
5	19.3, CH_3	1.44 [b]
$_D$-Leu^6		
1	175.0, C	
2	53.5, CH	4.94 [b]
3	40.3, CH_2	2.24 [b]
4	25.4, CH	2.20 [b]
5	23.2, CH_3	1.52 [b]
6	23.3, CH_3	1.52 [b]
Gly^7		
1	172.0, C	
2	43.2, CH_2	4.48 [b]
Gly^8		
1	175.3, C	
2	43.3, CH_2	4.48 [b]

[a]Signals assigned using 2D NMR data. [b]Overlapping signal.

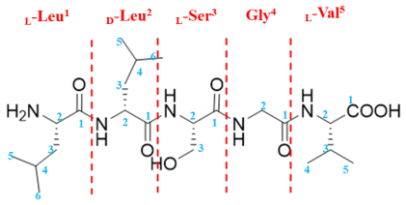

Table S3. NMR Spectroscopic Data (400M, D_2O) for synthetic **3**[a]

position	δ_C type	δ_H [mult, *J* (Hz)]
$_L$-Leu^1		
1	170.4, C	
2	51.8, CH	4.07, [b] m
3	39.8, CH_2	1.74, [b] m; 1.74, [b] m
4	23.9, CH	1.73, [b] m
5	21.1, CH_3	0.90, [b] m
6	20.3, CH_3	0.90, [b] m
$_D$-Leu^2		
1	174.8, C	
2	52.6, CH	4.46, [b] m
3	39.4, CH_2	1.62, [b] m; 1.72, [b] m
4	24.3, CH	1.63, [b] m
5	22.1, CH_3	0.97, [b] m
6	21.4, CH_3	0.97, [b] m
$_L$-Ser^3		
1	172.1, C	
2	55.6, CH	4.49, [b] m
3	60.9, CH_2	3.87, dd (11.1, 4.5); 3.93, dd (12.0. 5.0)
Gly^4		
1	170.7, C	
2	42.5, CH_2	3.99, [b] m; 4.00, [b] m
$_L$-Val^5		
1	178.4, C	
2	60.7, CH	4.07, m
3	30.3, CH	2.11, m
4	17.1, CH_3	0.87, d (6.8)
5	18.8, CH_3	0.91, d (6.7)

[a]Signals assigned using 2D NMR data. [b]Overlapping signal.

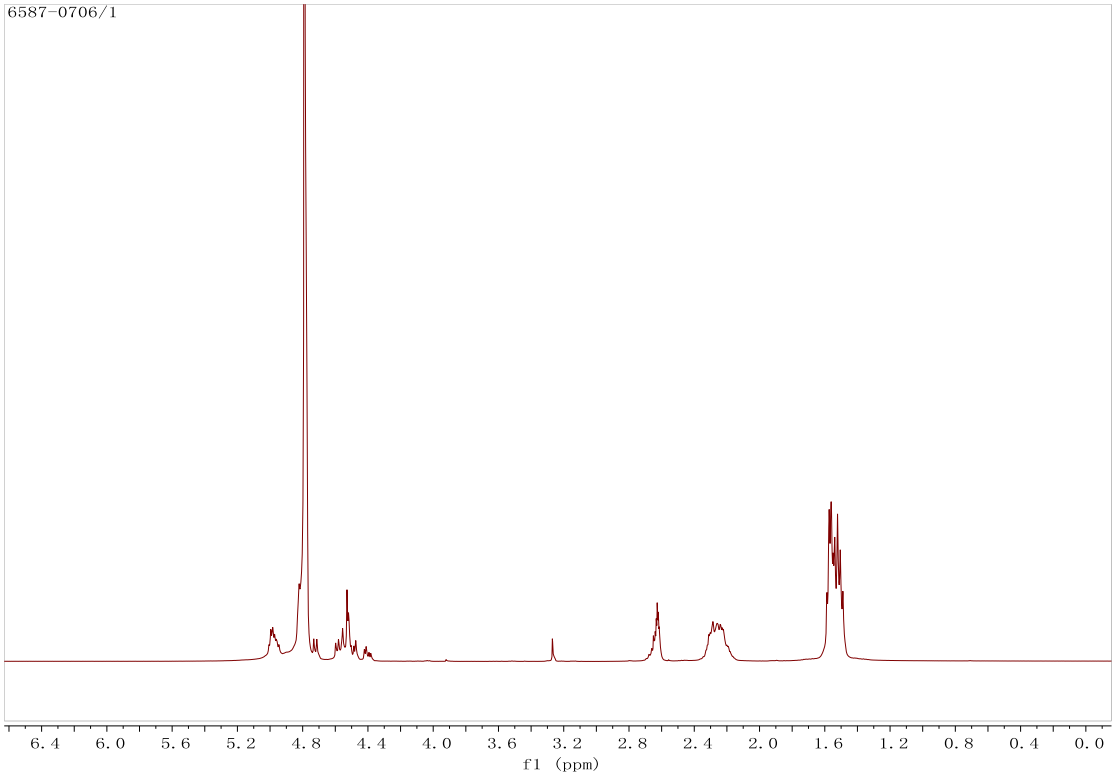

Figure S76 ^{1}H NMR spectrum (400 MHz) of synthetic **1** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

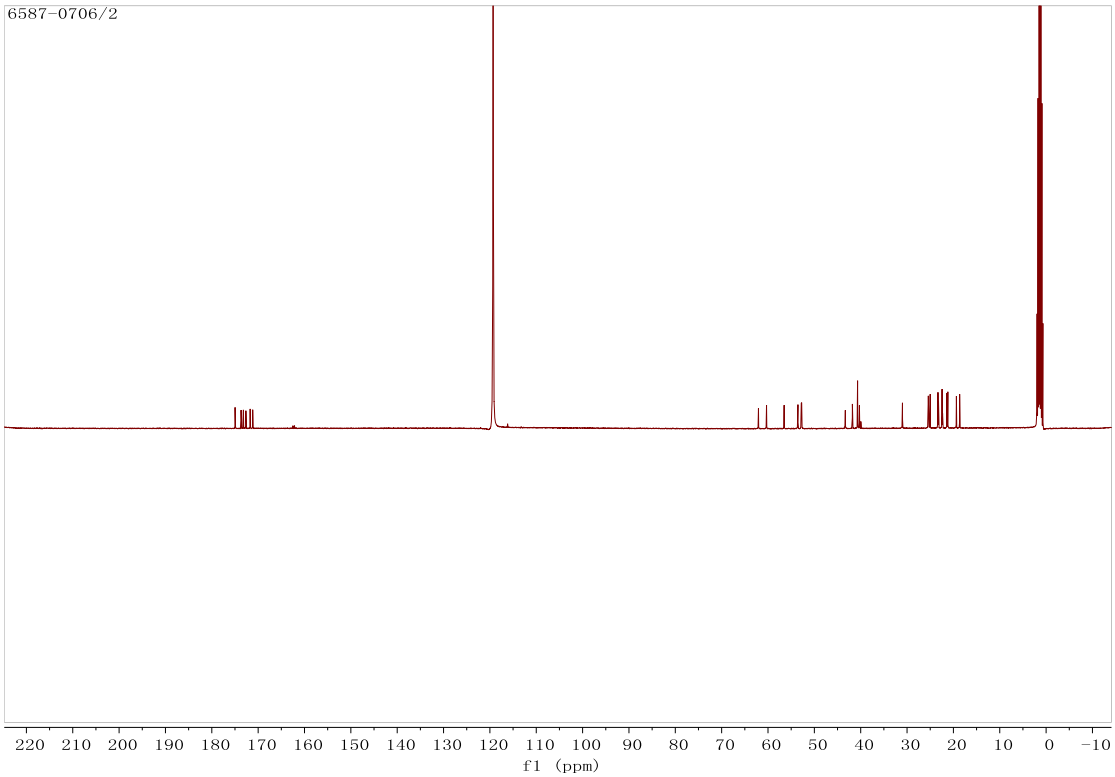

Figure S77 ^{13}C NMR spectrum (100 MHz) of synthetic **1** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

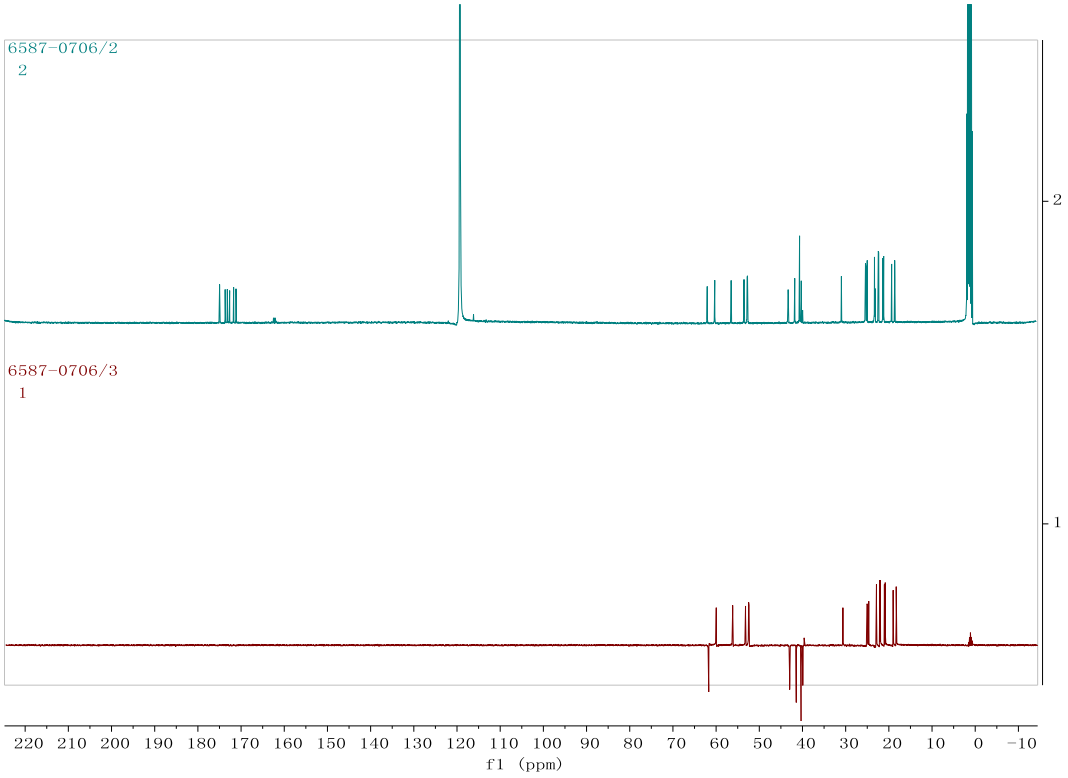

Figure S78 DEPT-135 spectrum (100 MHz) of synthetic **1** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

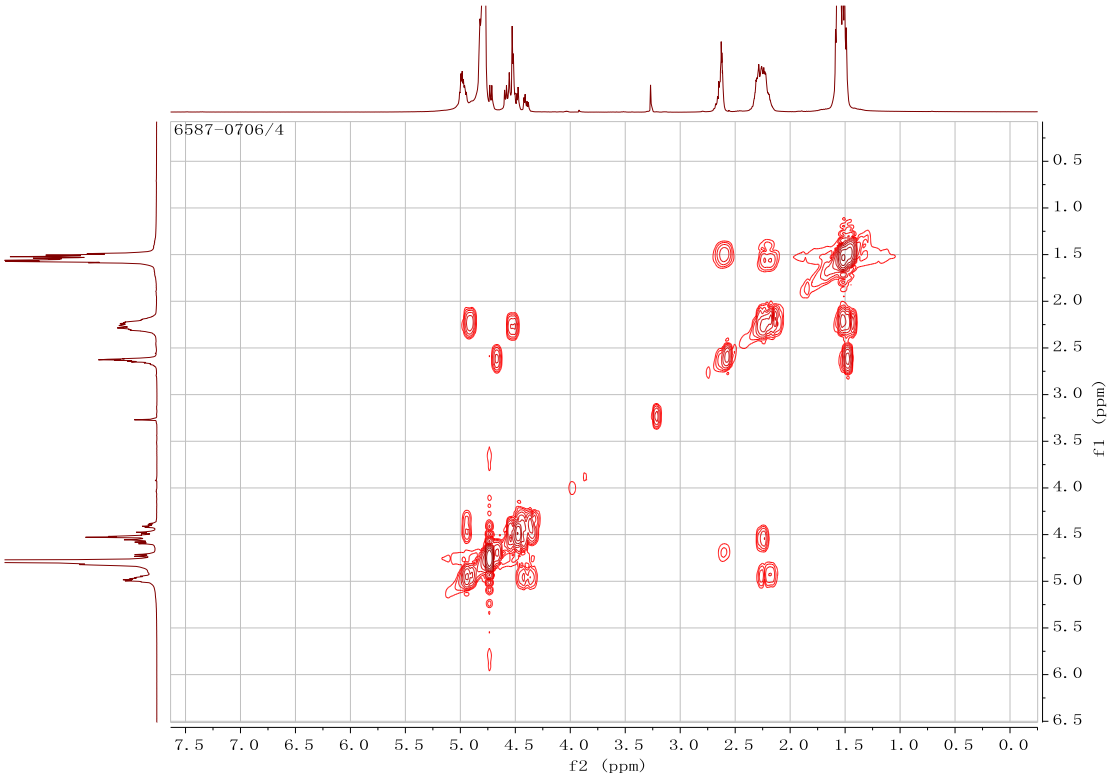

Figure S79 ^{1}H-^{1}H COSY spectrum of synthetic **1** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

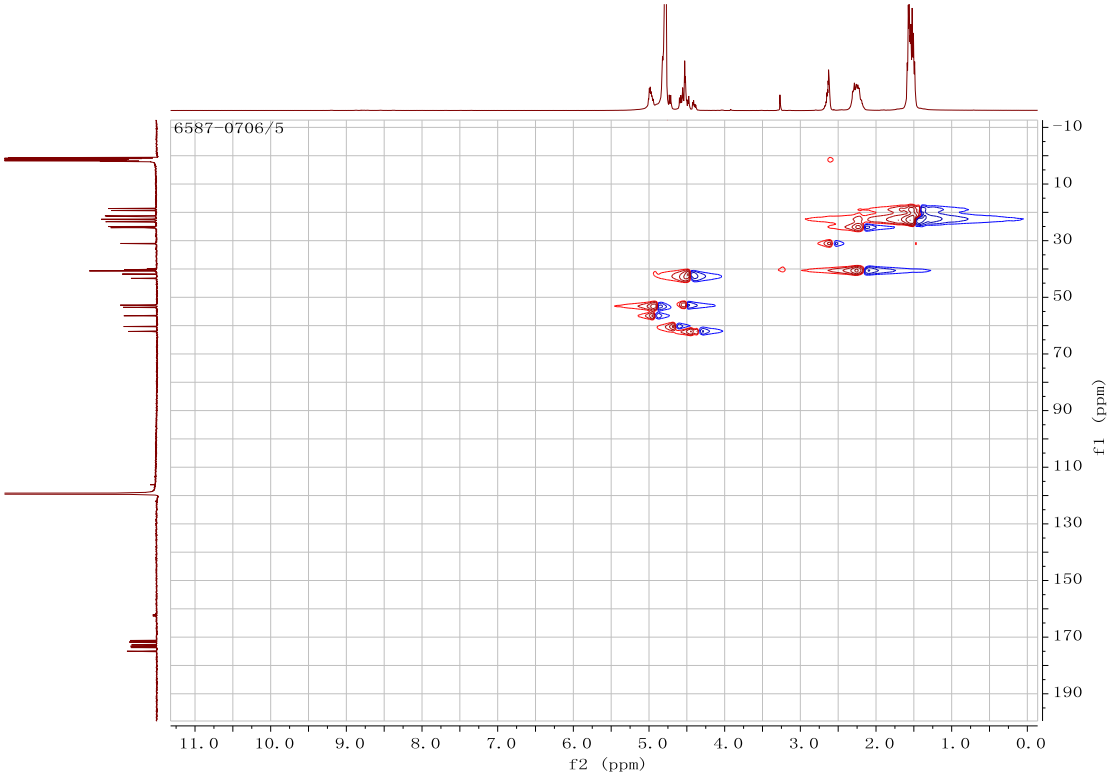

Figure S80 HSQC spectrum of synthetic **1** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

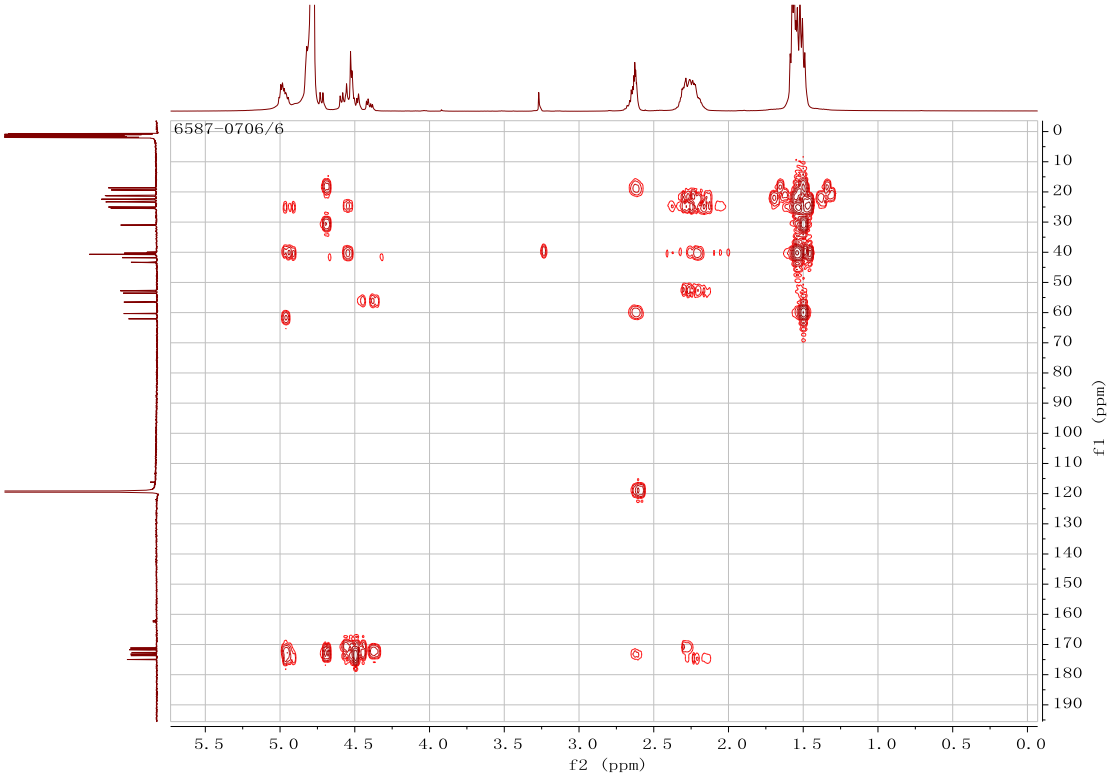

Figure S81 HMBC spectrum of synthetic **1** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

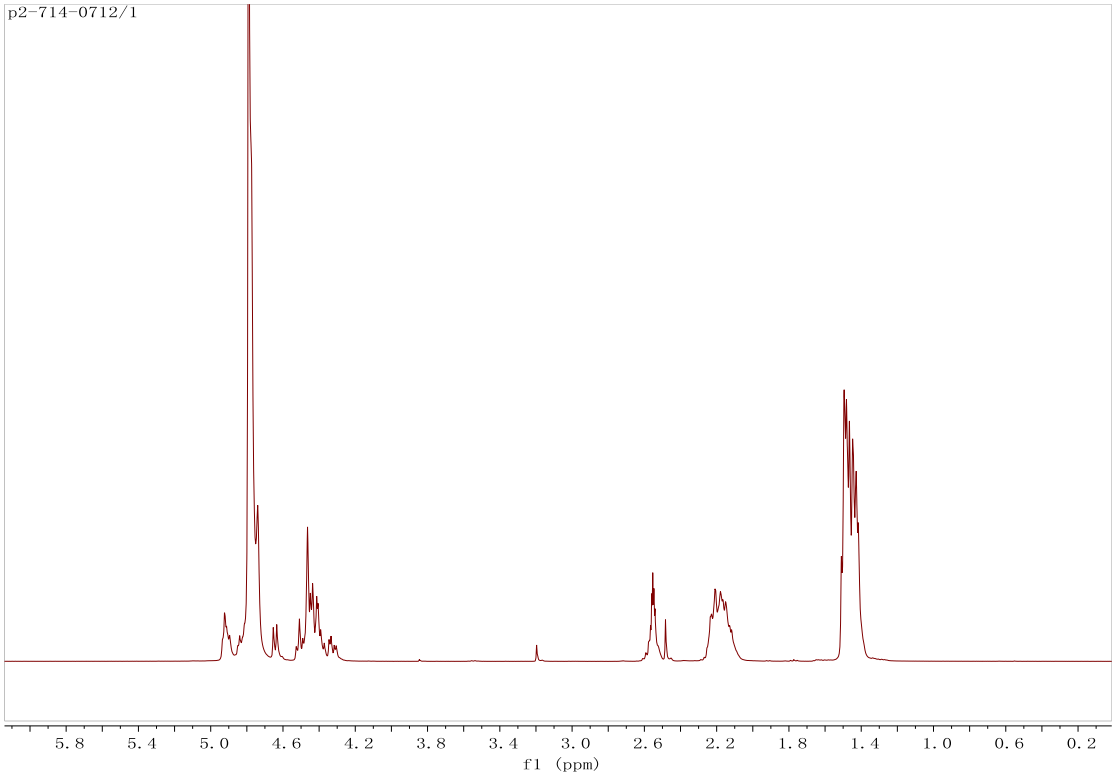

Figure S82 ^{1}H NMR spectrum (400 MHz) of synthetic **2** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

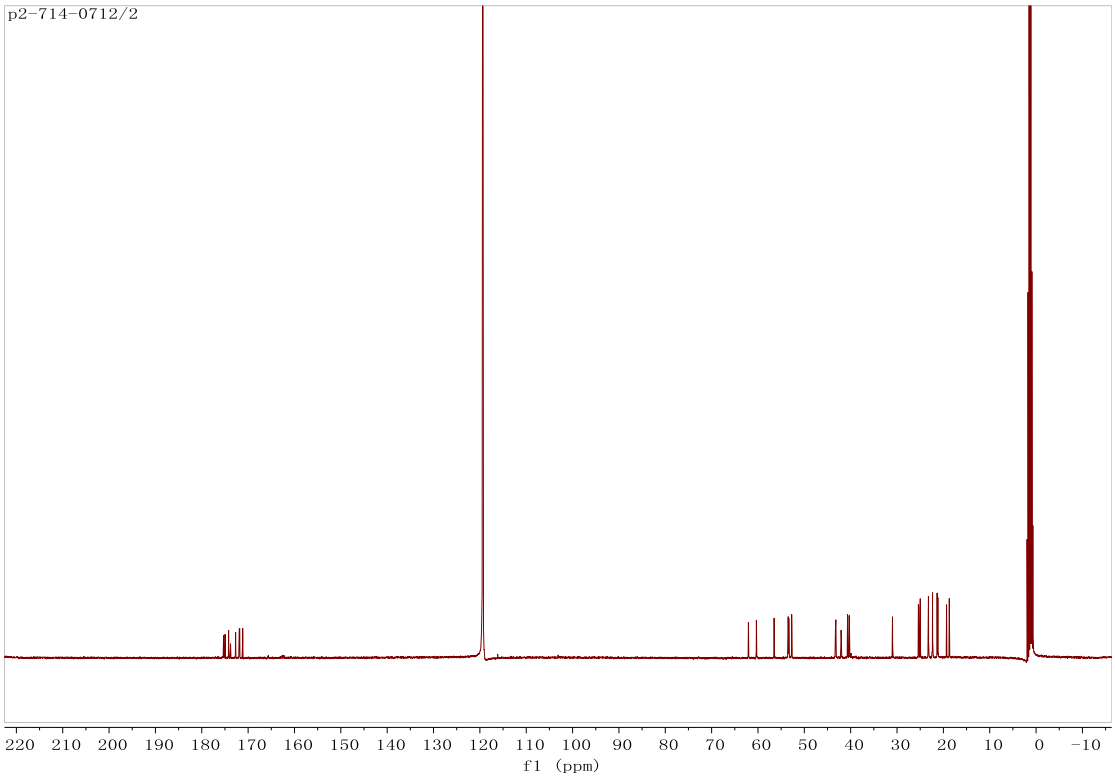

Figure S83 ^{13}C NMR spectrum (100 MHz) of synthetic **2** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

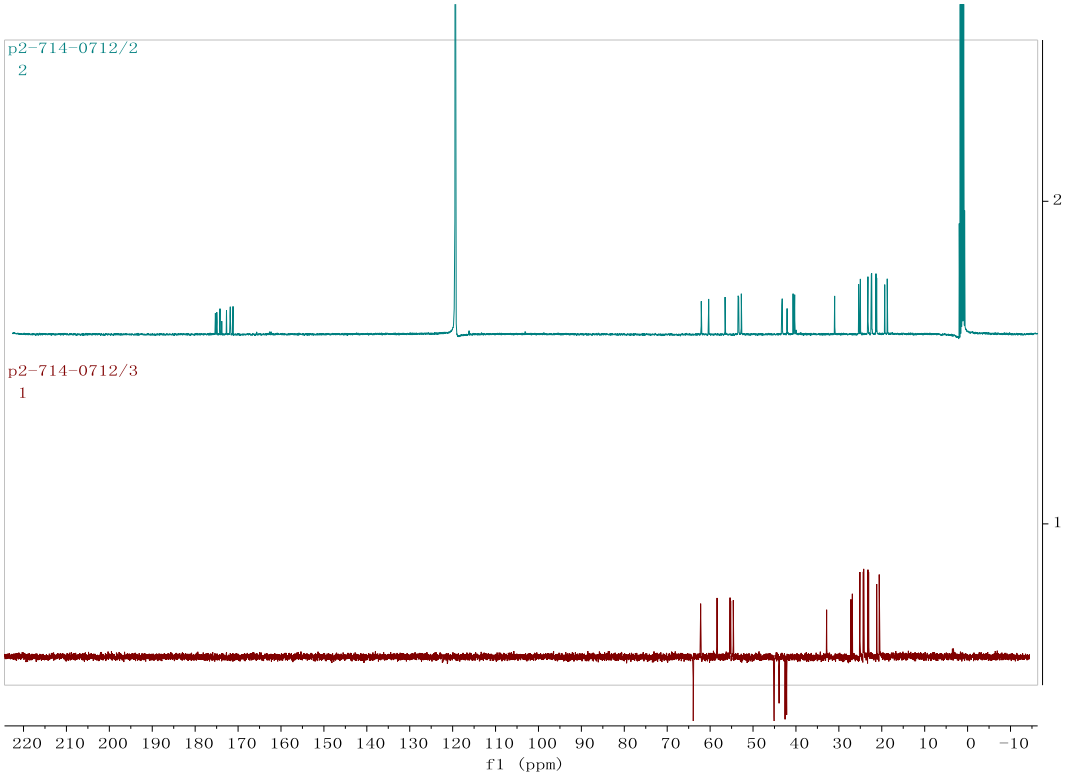

Figure S84 DEPT-135 spectrum (100 MHz) of synthetic **2** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

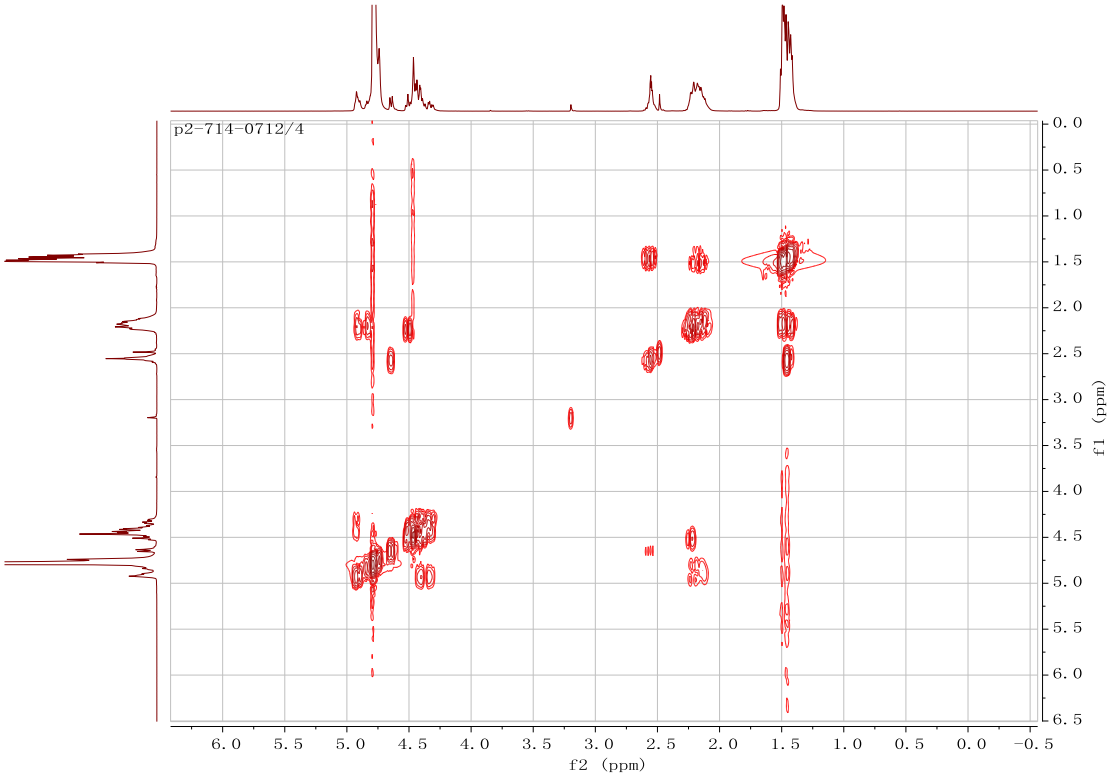

Figure S85 ^1H-^1H COSY spectrum of synthetic **2** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

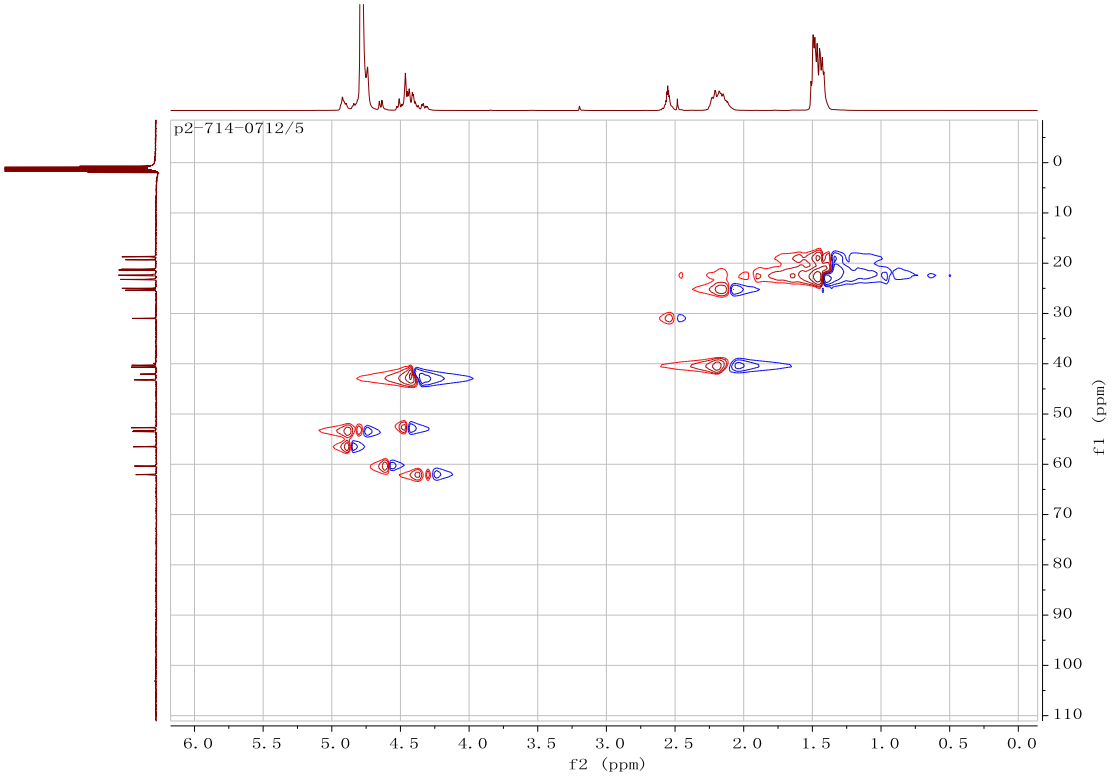

Figure S86 HSQC spectrum of synthetic **2** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

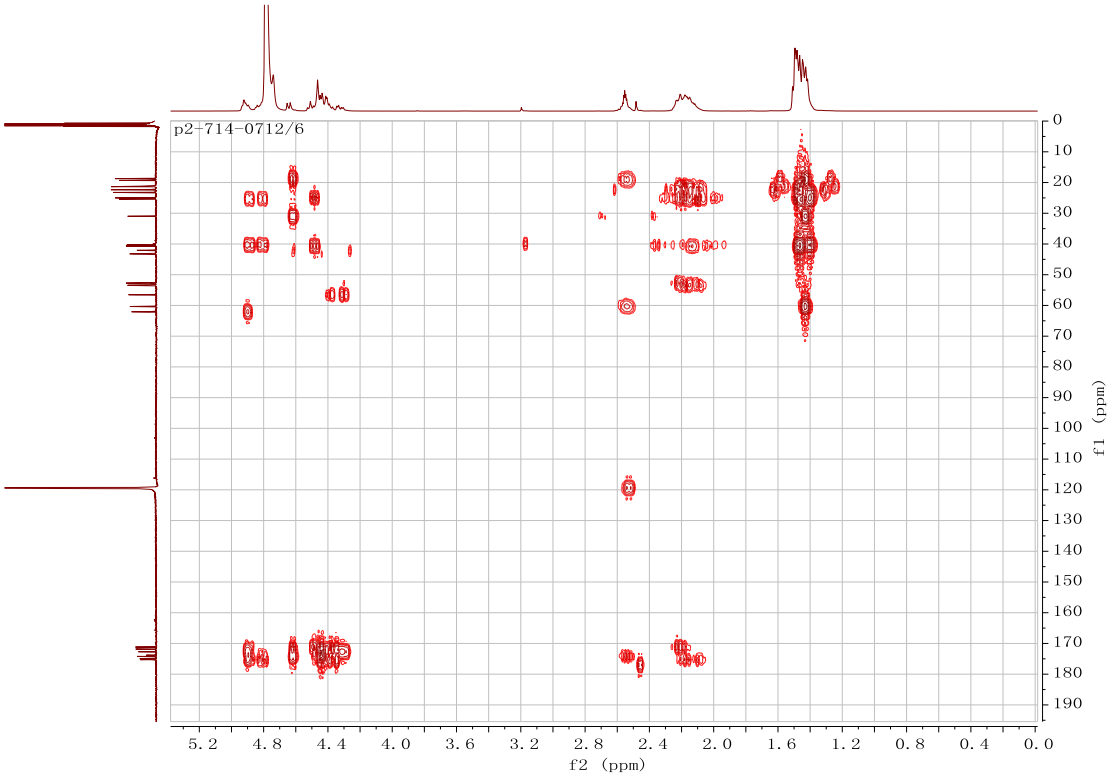

Figure S87 HMBC spectrum of synthetic **2** in mixture solvent (CD_3CN: D_2O: TFA-*d*=3: 2: 0.1)

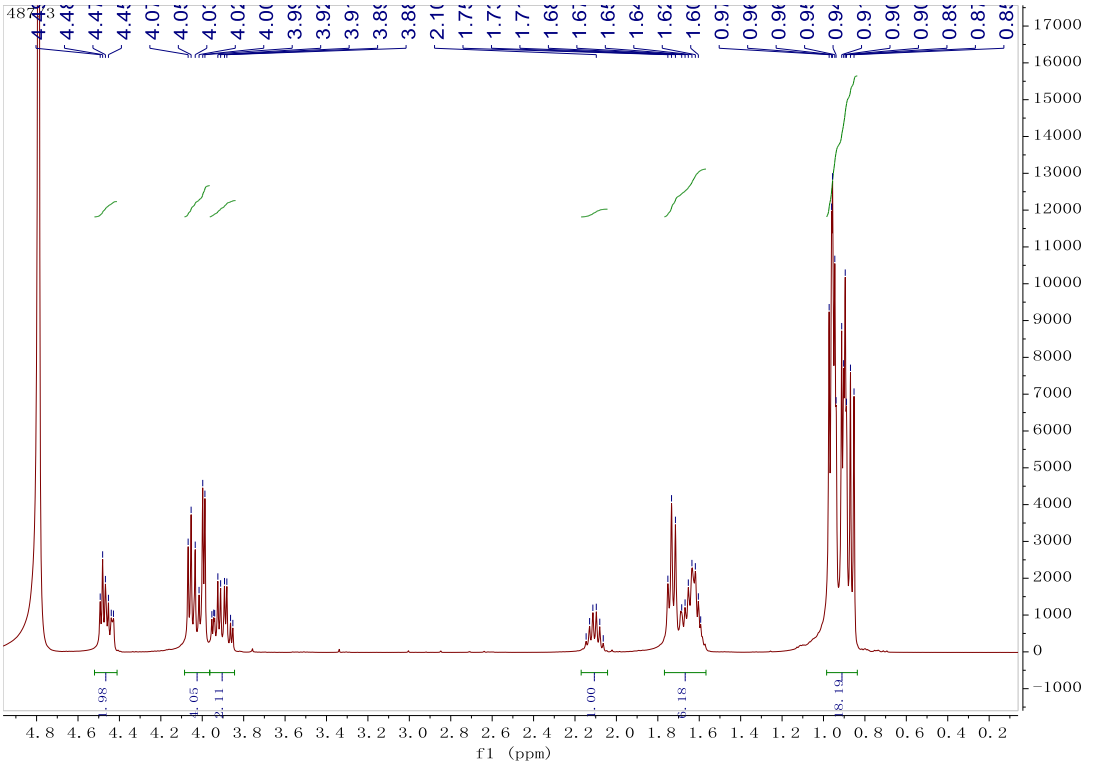

Figure S88 ^{1}H NMR spectrum (400 MHz) of synthetic **3** in D_2O

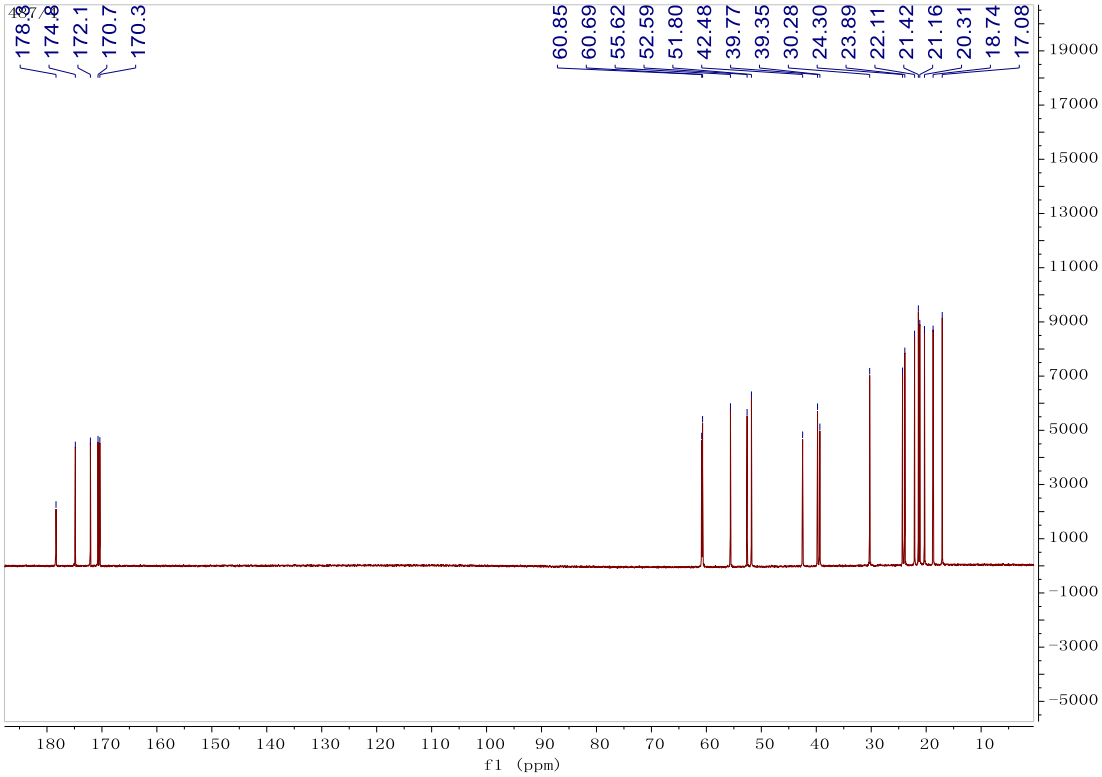

Figure S89 ^{13}C NMR spectrum (100 MHz) of synthetic **3** in D_2O

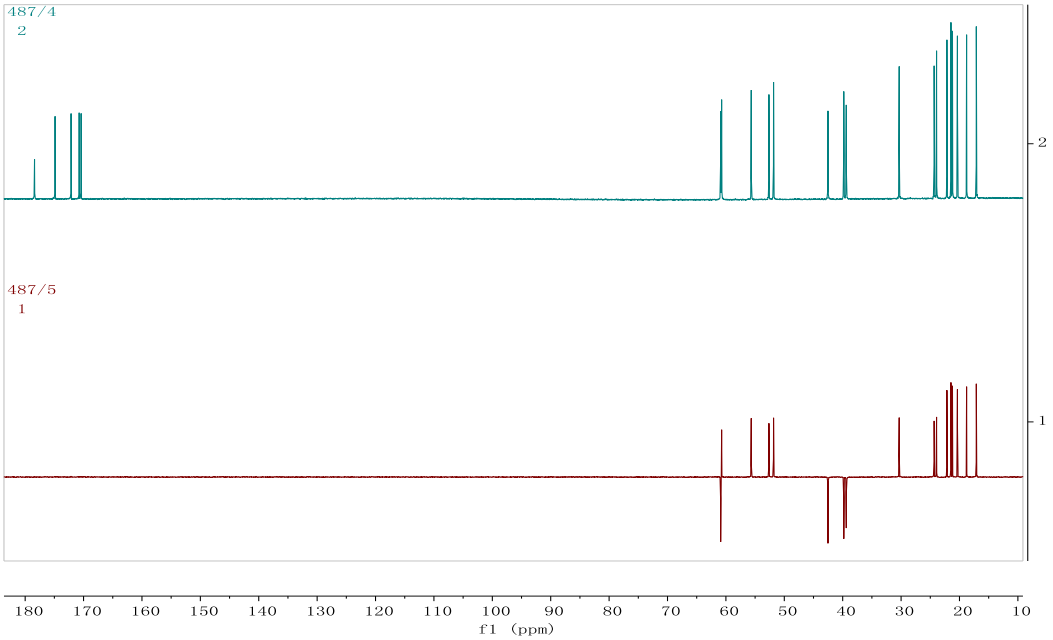

Figure S90 DEPT-135 spectrum (100 MHz) of synthetic **3** in D_2O

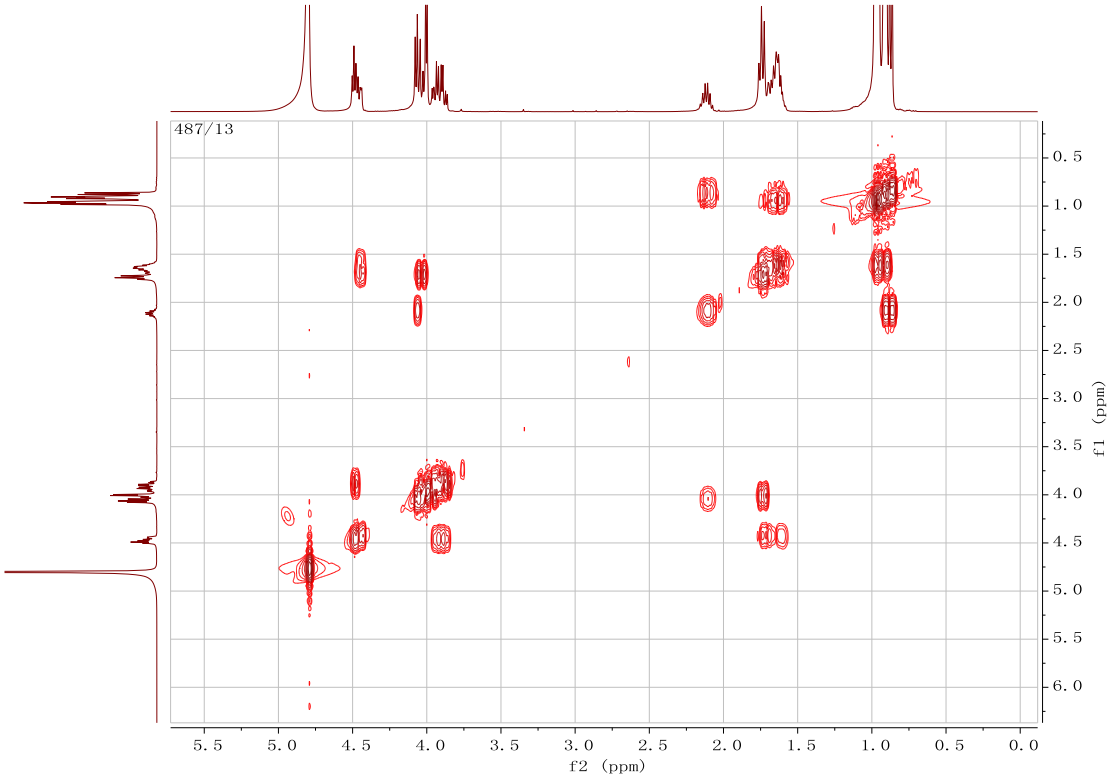

Figure S91 ^{1}H-^{1}H COSY spectrum of synthetic **3** in D_2O

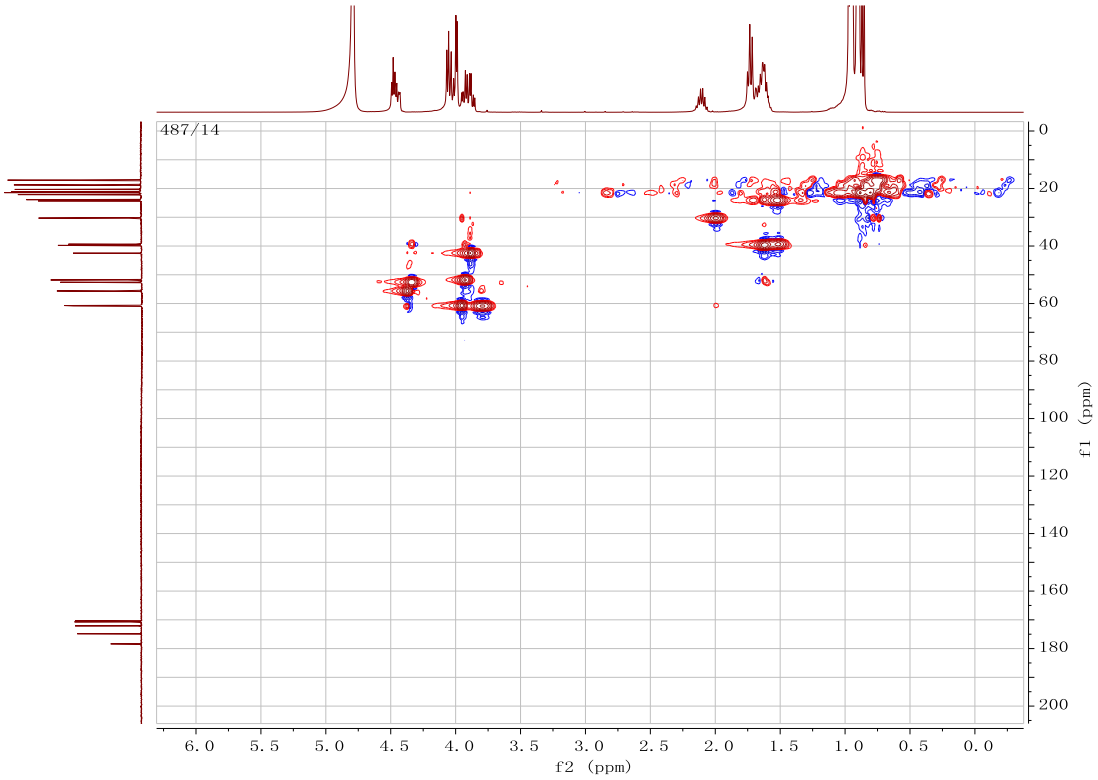

Figure S92 HSQC spectrum of synthetic **3** in D_2O

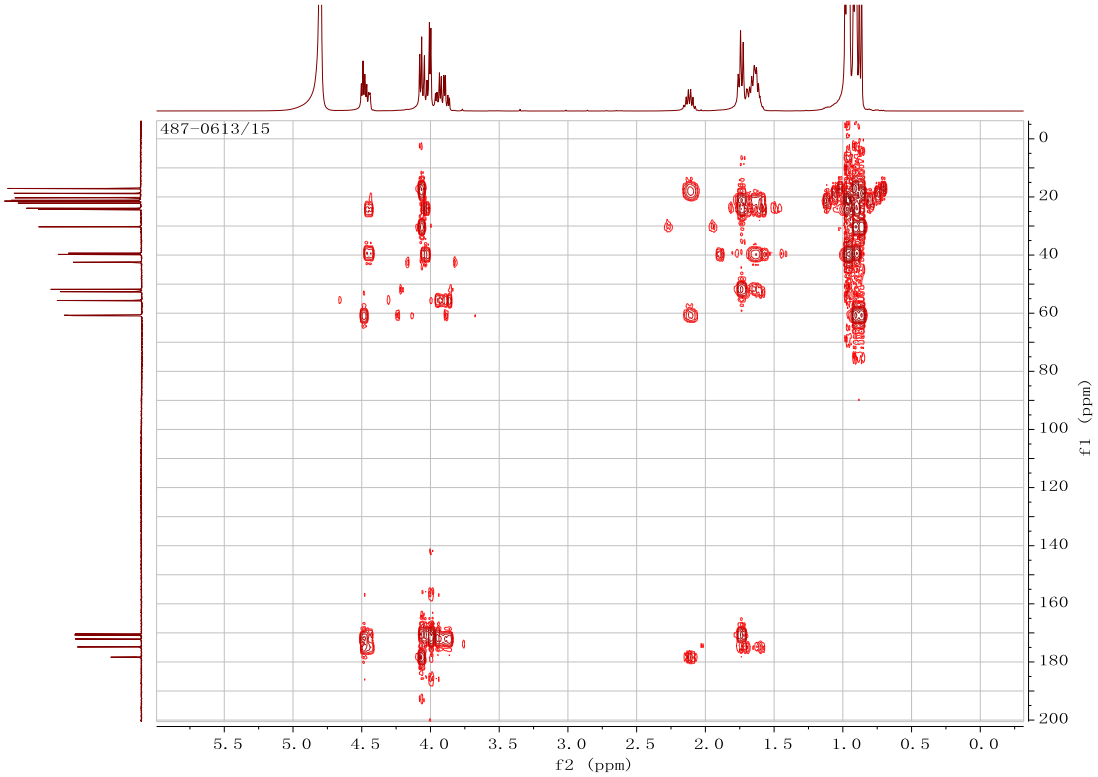

Figure S93 HMBC spectrum of synthetic **3** in D_2O

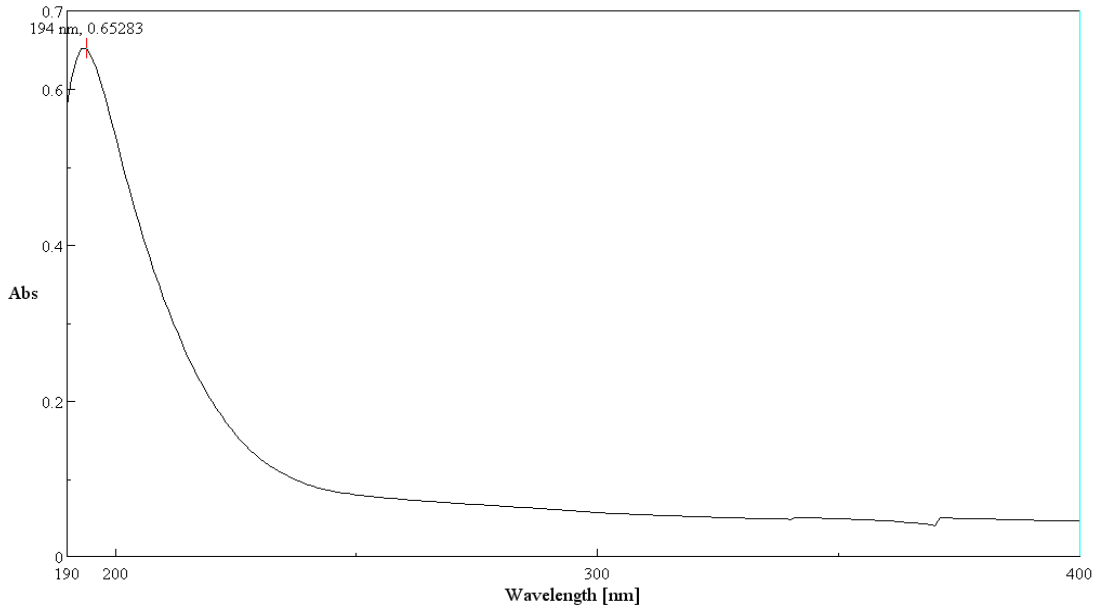

Figure S94. UV spectrum (H_2O) of synthetic **1**

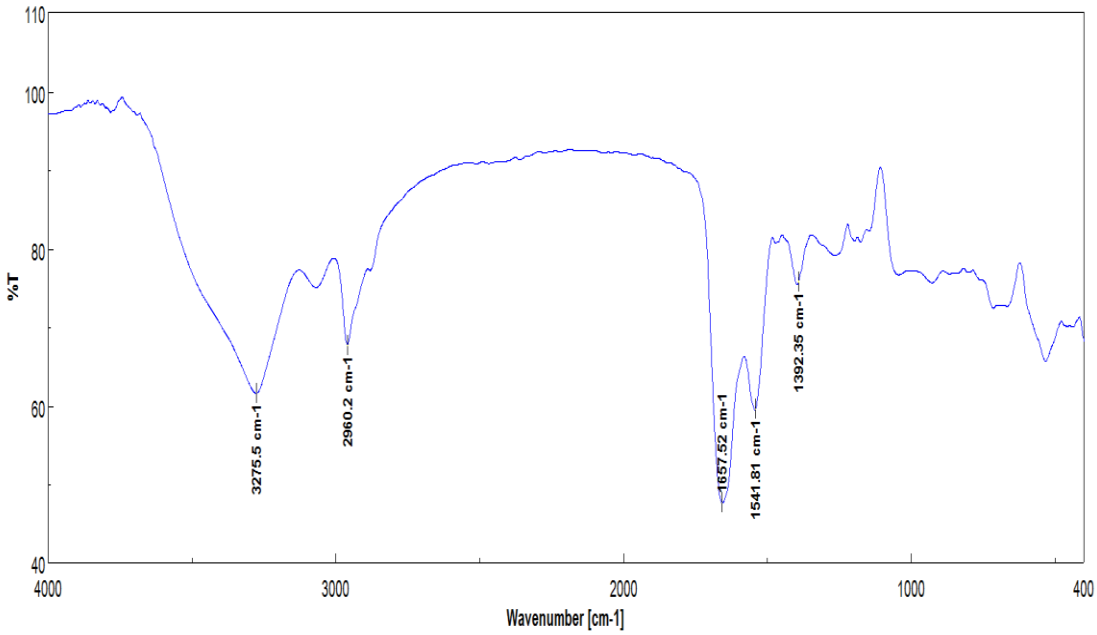

Figure S95. IR spectrum (KBr) of synthetic **1**

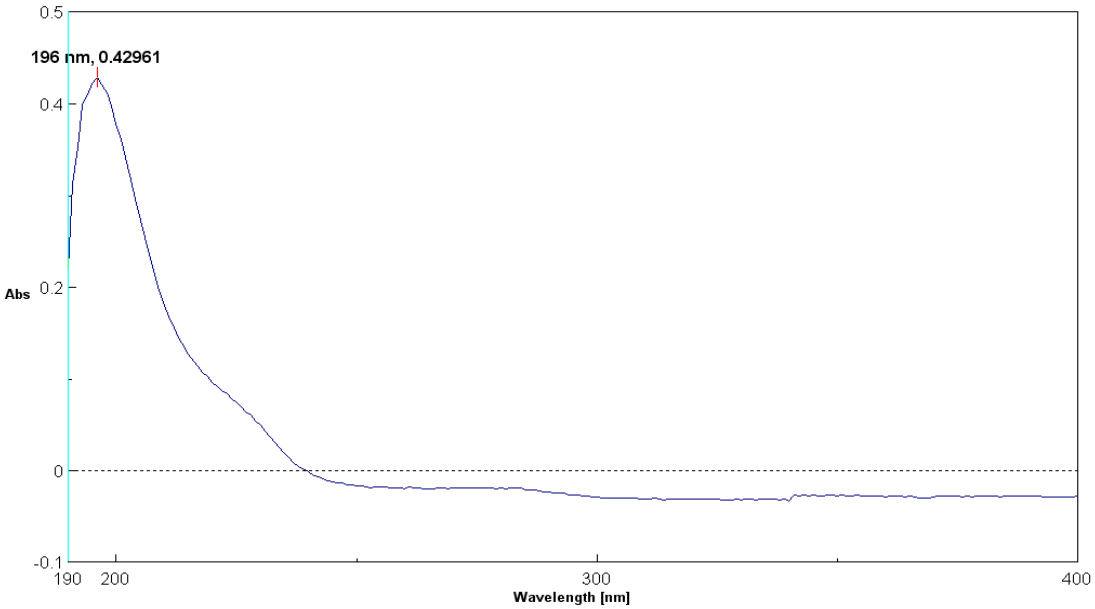

Figure S96. UV spectrum (H_2O) of synthetic **2**

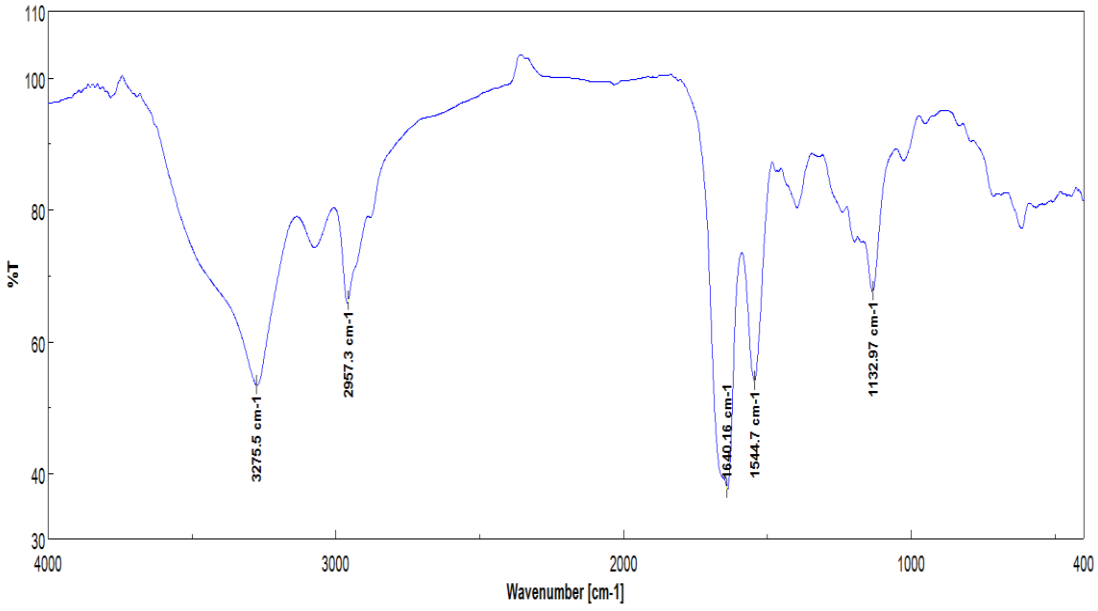

Figure S97. IR spectrum (KBr) of synthetic **2**

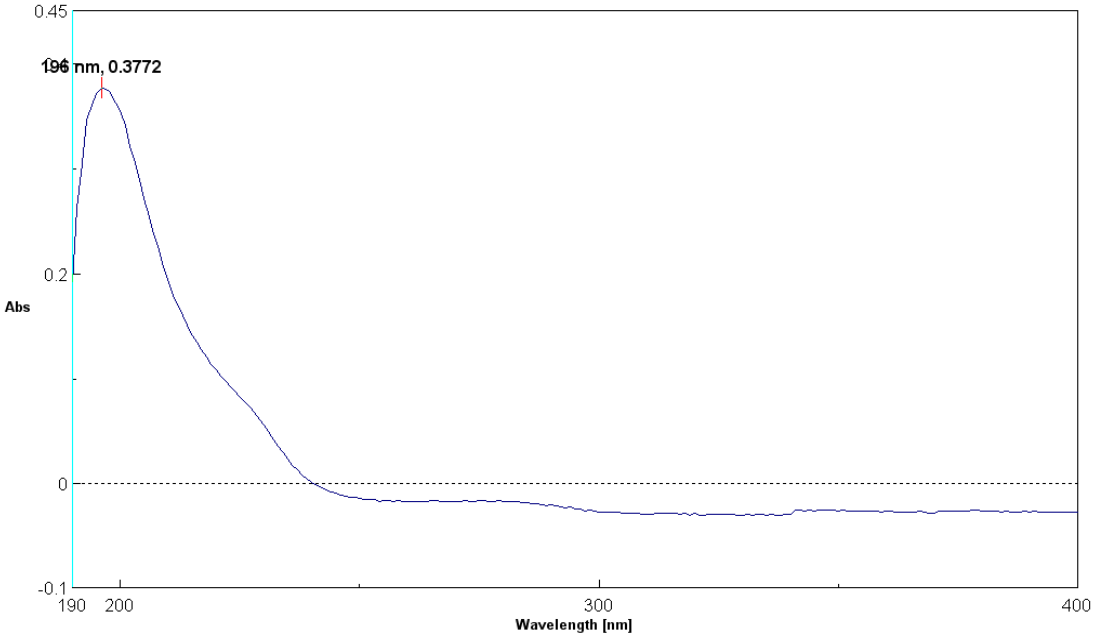

Figure S98. UV spectrum (H_2O) of synthetic **3**

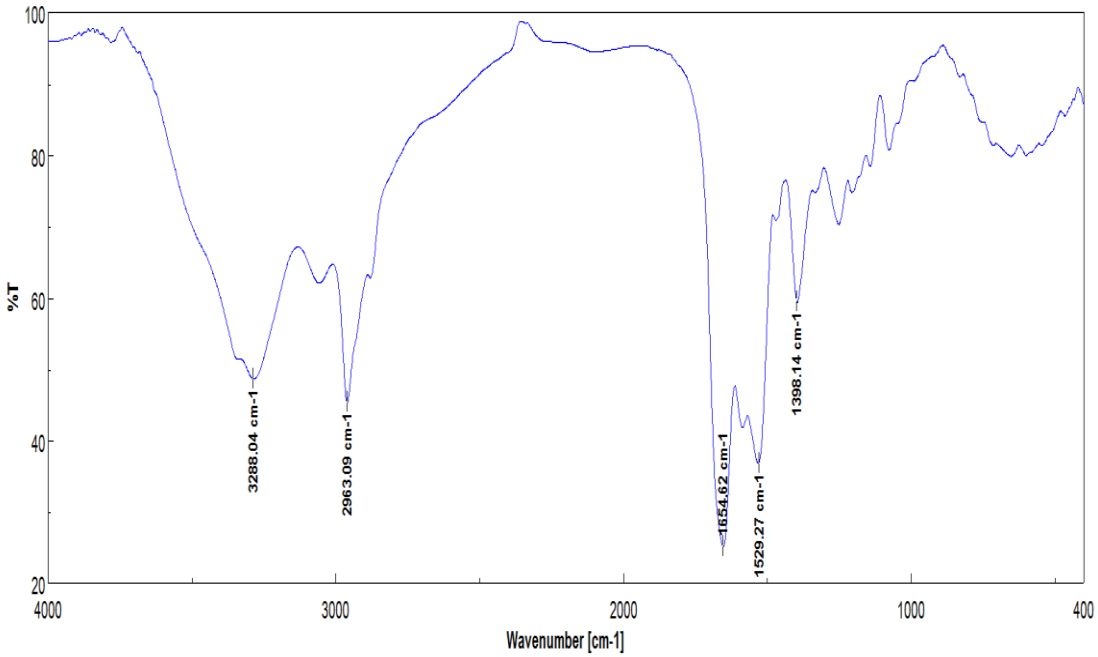

Figure S99. IR spectrum (KBr) of synthetic **3**