Electronic Supplementary Information

Angiotensin II analogs comprised of Pro-Amb (γ-turn scaffold) as angiotensin II type 2 (AT_2) receptor agonists

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General Methods:-

2-chlorotritylchloride resin and Fmoc protected amino acid derivatives were obtained from Novabiochem, Switzerland. DMF (lab reagent grade) was obtained from Merck and distilled twice over pthalic anhydride under reduced pressure. DCM (lab reagent grade) was obtained from Merck and distilled after overnight suspension over anhydrous K_2CO_3 (Merck). 3-Amino-2-methoxy-benzoic acid, DIC and DCC were obtained from Sigma-Aldrich. 1-hydroxybenzotriazole (HOBt) was purchased from Anaspec. All other reagents were obtained from commercial sources and used as received. The purity of synthesized peptides were analyzed using analytical RP-HPLC as described in SPPS section. The characterization of synthesized peptides were done using CD, FTIR, NMR, HRMS etc. The NMR studies were done on 700 MHz Bruker instrument using H_2O:D_2O (9:1) as a solvent. In the ^1H NMR spectra, it was not possible to integrate the peaks due to water suppression, hence number of protons in the NMR peak were assigned using HSQC and HMBC.

Synthetic procedures:

Solid-phase peptide synthesis (SPPS):

Designed peptides were synthesized using solid phase peptide synthesis (SPPS) on semi-automatic peptide synthesizer act-90 from Advanced Chemtec using Fmoc/tert-butyl protection. The starting polymer was 2-chlorotritylchloride resin (1.6 mmol/g), and for the Fmoc amino acids, the side chain protecting groups were Asp(OtBu), Arg(Pbf) and His(Trt). Removal of the Fmoc group was achieved by reaction with 20% piperidine in DMF for 10 min thrice. Coupling of the amino acids (4 equiv.) were performed in DCM: DMF (1:1) (10 ml) using DIC:HOBt (1:1) (4 equiv.) for 90 min. Completion of coupling was confirmed by positive and negative Kaiser test. For proline (Pro) and 3-amino-2methoxy-benzoic acid (Amb), isatin and chloranil tests were used, respectively. After the introduction of each amino acid, excess amino acids were washed by DMF, 4 times. The final peptide resins were cleaved by a cleavage cocktail: TFA/H_2O/TIS/EDT/phenol (250:2.5:1:1:1), for 4 h. The filtrate was concentrated on rota-vapour at reduced pressure and later co-evaporated with distilled diethyl ether, twice. The residue obtained was dissolved in minimum volume of methanol and desalted by eluting through sephadex LH-20 chromatography using methanol as mobile phase. The desired fractions were confirmed by LCMS and lyophilized to obtain peptide as white amorphous powder. The purity of peptides was examined by analytical RP-HPLC using LiChrosolv C-18 column with a flow-rate of 0.8 ml/min and the pressure was 1400 psi. The mobile phases for HPLC were 0.001 % TFA in ACN (solvent A) and 0.001% TFA in H_2O (solvent B). The gradient of solvent A to solvent B were varied as follows: 0 to 5 min (10 %), 5 to 40 min (10 % to 90 %), 40 to 45 min (90% to 10 %) and 45 to 50 min (10 %).

3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-methoxybenzoicacid: 3-amino-2-methoxybenzoic acid (1eq) was dissolved in dioxane (2:1) and an aqueous solution of sodium bicarbonate (2 eq) was added with stirring. The resulting solution was cooled to 5° and Fmoc-Cl (1.05 eq) was added slowly as a solution in dioxane (cooled). The resulting mixture was stirred at

0° for 1 h and allowed to warm to room temperature overnight. Dioxane was evaporated on rota vapour. The concentrate was precipitated using 2N HCl. Then, it was filtered and the residue was washed several times with water. The off-white powder obtained from residue was air dried for two days and used further on SPPS without any further purification.

2-(3-{[1-(2-Amino-5-guanidino-pentanoyl)-pyrrolidine-2-carbonyl]-amino}-2-methoxy-benzoylamino)-3-methyl-pentanoic acid 1: The peptide was prepared as mentioned in section A of SPPS. $[\alpha]^{25.3}{}_{D}$: 4.1 (*c* 0.002, CH_3OH). IR (nujol) ν (cm^{-1}): 3376.96, 3087.66, 3062.93, 3027.69, 2925, 2856.17, 2729.31, 1854.86, 1700.76, 1652.98, 1605.34, 1496.08, 1489.41, 1461.52, 1377.61, 1312.3, 1209.32, 1155.41, 1081.56, 1030.54, 893.73, 843.5, 727.8, 694.26. ^{1}H NMR[1] (700 MHz, H_2O:D_2O (9:1)) δ : 9.84 (s, 1H), 8.70 (d, *J* = 7.9 Hz, 1H), 8.07 (broad, 1H), 7.61 (dd, *J* = 8.11, 1.5 Hz, 1H), 7.44 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 5.9 Hz, 1H), 6.55 (broad, 1H), 4.65 (m, 1H), 4.41 (m, 1H), 4.36 (t, *J* = 6.1 x (2)Hz, 1H), 3.75 - 3.69 (m, 5H), 3.60 - 3.57 (m, 2H), 3.15- 3.12 (m, 2H), 2.41 - 2.37 (m, 1H), 2.08 - 1.88 (m, 5H), 1.68 - 1.57 (m, 2H), 1.48 - 1.43 (m, 1H), 1.24 - 1.19 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (176 MHz, H_2O:D_2O (9:1)) δ: 176.9, 174.2, 170.0, 169.4, 158.2, 158.1, 152.2, 130.9, 130.3, 129.2, 128.7, 126.0, 63.5, 62.2, 59.7, 59.6, 52.7, 49.3, 41.7, 41.6, 37.7, 30.6, 28.2, 26.0, 26.0, 24.2, 16.3, 11.8. HRMS $C_{25}H_{40}O_3N_7$ $[M+H]^+$ calculated mass 534.3035, observed mass 534.3026.

1-[2-{2-[3-({1-[2-(2-Amino-3-carboxy-propionylamino)-5-guanidino-pentanoyl]-pyrrolidine-2-carbonyl}-amino)-2-methoxy-benzoylamino]-3-methyl-pentanoylamino}-3-(1H-imidazol-4-yl)-propionyl]-pyrrolidine-2-carboxylic acid 2: The peptide was prepared as mentioned in section A of SPPS. $[\alpha]^{25.42}{}_{D}$: -32.9067 (*c* 0.003, CH_3OH). IR (nujol) ν (cm^{-1}) : 3554.11, 3365.11, 3171.62, 3087.11, 2919.62, 2727.52, 2670.93, 2036.48, 1937.58, 1855.22, 1702.99, 1605.47, 1496.2, 1461.21, 1377.55, 1307.96, 1204.93, 1170.55, 1154.55, 1081.3, 1042.46, 1030.52, 973.78, 893.1, 842.74, 800.69, 727.72, 694.26, 666.04, 594.63.^{1}H NMR[1] (700 MHz, H_2O:D_2O (9:1)) δ: 9.79 (s, 1H), 8.65 - 8.61 (m, 5H), 8.50 (d, *J* = 1.3 Hz, 1 H), 7.6 (dd, *J* = 8.1, 1.4 Hz,

1H), 7.37 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.26 (s, 1H), 7.2 (t, *J* = 7.9x(2) Hz, 2H), 7.08 (t, *J* = 5.5x(2) Hz, 2H), 5.98 (m, 1H), 4.64 (m, 1H), 4.57 (m, 1H), 4.31 (m, 1H), 4.27 (m, 2H), 3.8 (m, 2H), 3.71 (m, 2H), 3.65 (s, 3H), 3.62 (m, 2H), 3.53 (m, 2H), 3.19 (m, 1H), 3.1 (m, 3H), 2.93 (dd, *J* = 17.9, 4.7 Hz, 1H), 2.83 (dd, *J* = 17.9, 8.1 Hz, 1H), 2.35 (m, 1H), 2.21 (m, 1H), 2.02 (m, 3H), 1.91 (m, 3H), 1.78 (m, 2H), 1.68 (m, 1H), 1.61 (m, 2H), 1.4 (m, 1H), 1.15 (m, 1H), 0.82(m, 3H), 0.79(m, 3H). ^{13}C NMR (176MHz ,H_2O+D_2O) δ = 177.7, 174.7, 174.6, 174.6, 174.4, 172.5, 170.6, 169.9, 169.9, 158.1, 158.1, 152.1, 134.8, 134.8, 131.0, 130.5, 129.4, 129.0, 128.6, 126.1, 118.9, 63.4, 62.2, 61.4, 60.0, 52.8, 52.7, 51.5, 51.0, 49.3, 49.0, 48.2, 41.9, 37.4, 36.7, 32.2, 30.7, 30.2, 28.7, 27.1, 26.0, 25.8, 25.7, 25.2, 16.0, 11.2. HRMS $C_{40}H_{59}O_{11}N_{12}$ $[M+H]^+$ calculated mass 883.4421, observed mass 883.4428; $C_{40}H_{58}O_{11}N_{12}Na$ $[M+Na]^+$ calculated mass 905.4240, observed mass 905.4240.

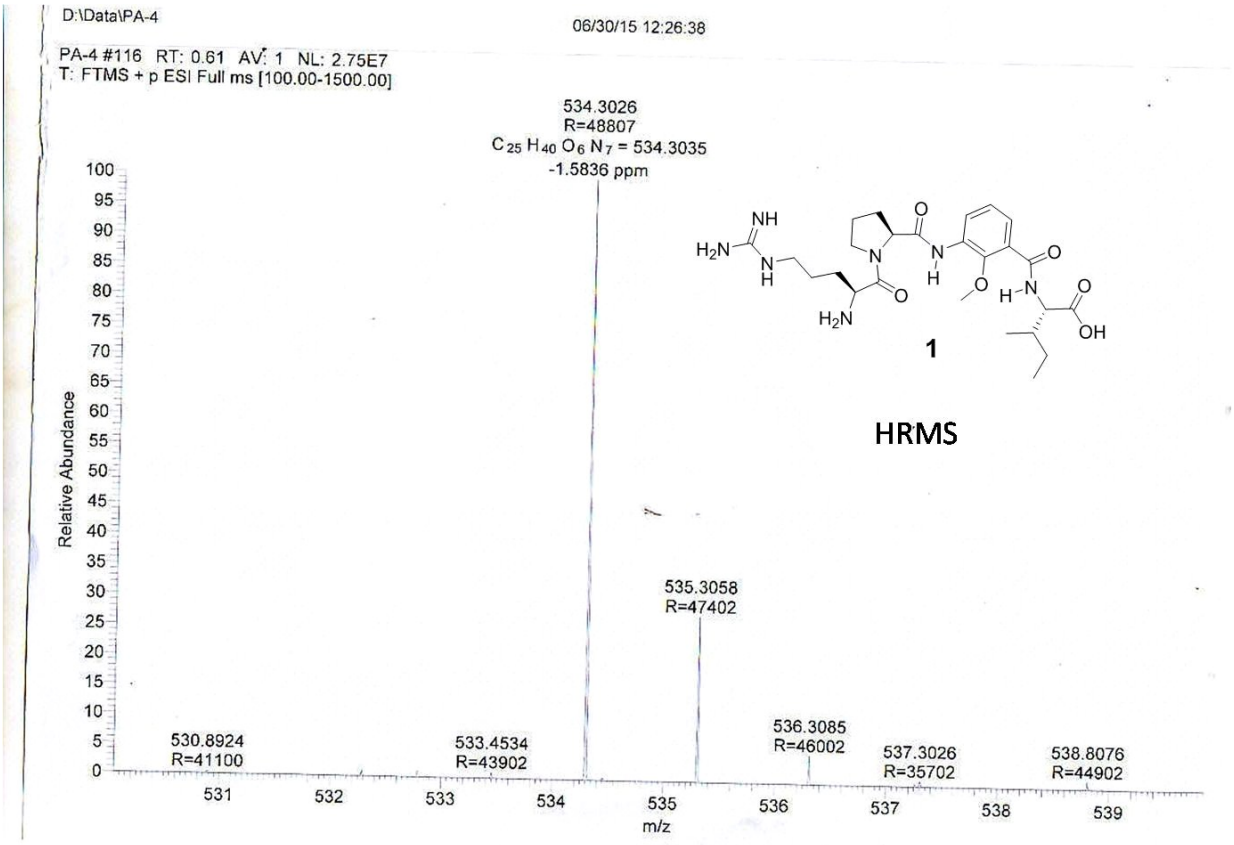
3-Amino-N-{1-[2-(3-{1-[2-[2-(1-carboxy-2-phenyl-ethylcarbamoyl)-pyrrolidin-1-yl]-1-(1H-imidazol-4-ylmethyl)-2-oxo-ethylcarbamoyl]-2-methyl-butylcarbamoyl}-2-methoxy-phenylcarbamoyl)-pyrrolidine-1-carbonyl]-4-guanidino-butyl}-succinamic acid 3: The peptide was prepared as mentioned in section A of SPPS. $[\alpha]^{25.3}{}_D$: -21.2 (*c* 0.002, CH_3OH). IR (nujol) ν (cm^{-1}): 3365.62, 3177.77, 2922.83, 2854.97, 2725.92, 2363.75, 2041.28, 1700.75, 1653.17, 1461.22, 1377.47, 1310.21, 1204.97, 1155.51, 1080.39, 973.4, 892.96, 847.48, 801.42, 727.55, 694.17, 667.8, 552.2, 540.09. ^{1}H NMR[1] (700MHz, H_2O:D_2O (9:1)) δ : 9.79 (s, 1H), 8.64 (d, *J* = 7.52 Hz, 1H), 8.59 (d, *J* = 7.5 Hz, 1H), 8.54 (d, *J* = 8.11 Hz, 1H), 8.47 (m, 1H), 8.18 (d, *J* = 7.52 Hz, 1H), 7.61 (m, 1H), 7.37(m, 1H), 7.27 (m, 2H), 7.2 (m, 4H), 7.08 (t, *J* = 5.88 Hz, 1H), 6.57 (broad, 1H), 4.98 (m, 1H), 4.63 (m, 1H), 4.56 (m, 1H), 4.54 (m, 1H), 3.8 (m, 2H), 3.65 (m, 3H), 3.52 (m, 1H), 3.11 (m, 4H), 3.02 (m, 2H), 2.94 (m, 1H), 2.83 (m, 1H), 2.35(m, 1H), 2.12 (m, 1H), 2.0 (m, 3H), 1.86 (m, 2H), 1.78 (m, 3H), 1.68 (m, 1H), 1.6 (m, 2H), 1.38 (m, 1H), 1.14 (m, 1H), 0.79 (m, 6H). ^{13}C NMR (176MHz, H_2O:D_2O(9:1)) δ : 176.4, 174.9, 174.7, 174.6, 174.4, 172.5, 170.8, 170.0, 169.9,158.2, 158.1, 152.2, 137.8, 134.8, 131.0, 130.5, 129.9, 129.5, 129.0, 128.6, 128.3, 126.1, 118.9, 63.4, 62.2, 61.7, 60.1, 55.8, 52.8, 52.7, 51.5, 51.1, 49.3, 49.2, 41.9,

37.8, 37.4, 36.8, 30.7, 30.5, 28.7, 27.2, 26.0, 25.8, 25.7, 25.2, 16.0, 11.2. HRMS $C_{49}H_{68}O_{12}N_{13}$ $[M+H]^+$ calculated mass 1030.5105, observed mass 1030.5105; $C_{49}H_{67}O_{12}N_{13}Na$ $[M+Na]^+$ calculated mass 1052.4924, observed mass 1052.4916.

Cell Culture. To study *in vitro* morphological effects: NG108-15 [108CC15] (ATCC® HB12317™) cells were cultured in Dulbecco's modified Eagle's medium with 10% fetal bovine serum, HAT supplement (hypoxanthine, aminopterin and thymidine), and 50 mg/L gentamycin at 37 °C in 75 cm^2 Nunclon Δ flasks in a humidified atmosphere of 95% air and 5% CO_2, as previously described.[2,3] Subcultures were performed at subconfluency. Under these conditions, cells express only the AT_2 receptor subtype.[2,3] Cells were stimulated during 3 days (once daily) - (first stimulation 24 h after plating). Cells were cultured for 3 subsequent days under these conditions. For all experiments, cells were plated at the same initial density of 3.6×10^4 cells/35 mm Petri dish and test concentrations for compounds used were 1 μM and 0.1 μM. Cells were then treated in the absence or presence of Ang II (100 nM), PD 123,319 (10 μM) AT_2 receptor antagonist. After 3 days of treatment, cells were examined under a phase contrast microscope and micrographs were taken. For determination of cells with Neurites, cells were examined under a phase contrast microscope, and micrographs were taken after 3 days under various experimental conditions. Cells with at least one neurite longer than a cell body were counted as positive for neurite outgrowth. The number of cells with neurites represents the percentage of the total amount of cells in the micrographs. At least two different experiments were conducted for each condition, each in duplicate. At least five images were taken per petri dish; hence, a total of 250−400 cells from each of the duplicate dishes were examined.

References:

1. The proton signals were unable to be integrateed due to water suppression. The number of protons *i.e*, CH, CH_2 and CH_3 were determined using HMBC and HSQC.
2. B. Buisson, S. P. Bottari, M. de Gasparo, N. Gallo-Payet and M. D. Payet, *FEBS Lett.,* 1992, **309**, 161.
3. L. Laflamme, M. de Gasparo, J-M Gallo, M. D. Payet and N. Gallo-Payet, *J. Biol. Chem,* 1996, **271**, 22729.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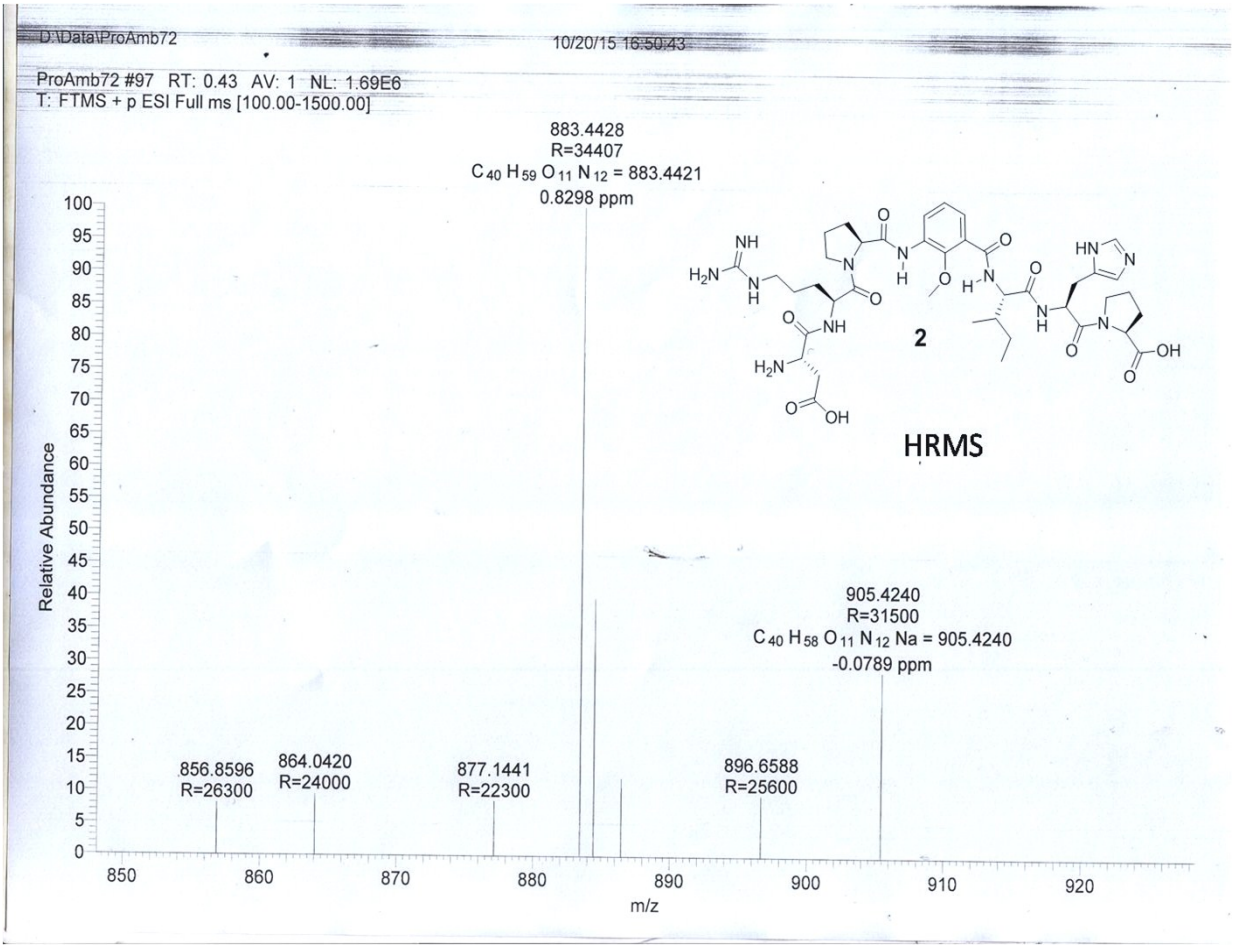
R=48807
C25 H40 O6 N7 = 534.3035
-1.5836 ppm
535.3058
R=47402
530.8924
R=41100
533.4534
R=43902
536.3085
R=46002
537.3026
R=35702
538.8076
R=44902
Relative Abundance
m/z

1

HRMS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ProAmb72 #97 RT: 0.43 AV: 1 NL: 1.69E6
T: FTMS + p ESI Full ms [100.00-1500.00]
883.4428
R=34407
C40 H59 O11 N12 = 883.4421
0.8298 ppm
905.4240
R=31500
C40 H58 O11 N12 Na = 905.4240
-0.0789 ppm
856.8596
R=26300
864.0420
R=24000
877.1441
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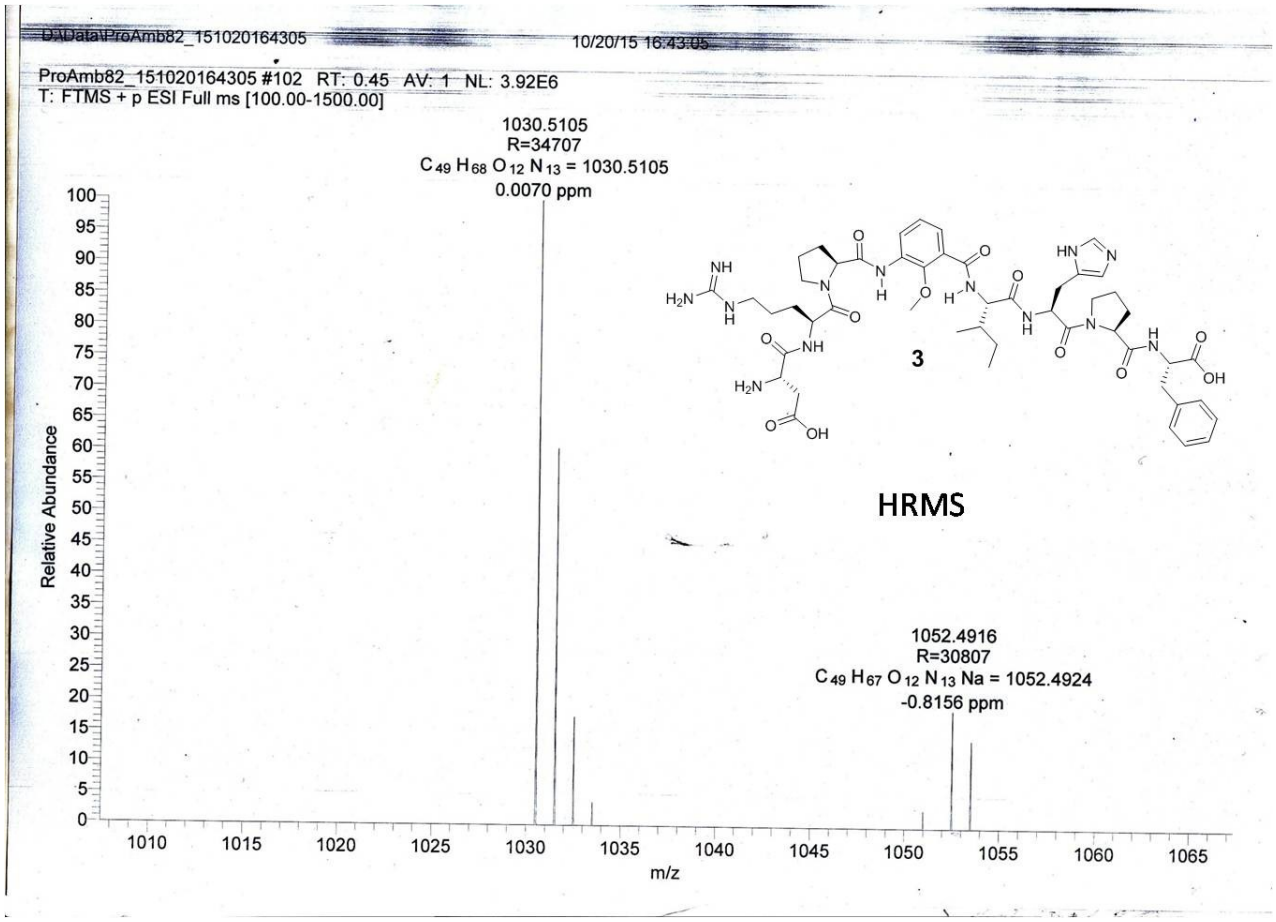
896.6588
R=25600
Relative Abundance
m/z

2

HRMS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T: FTMS + p ESI Full ms [100.00-1500.00]
1030.5105
R=34707
C49 H68 O12 N13 = 1030.5105
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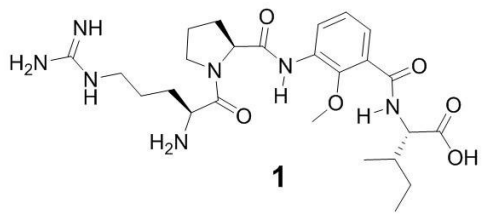
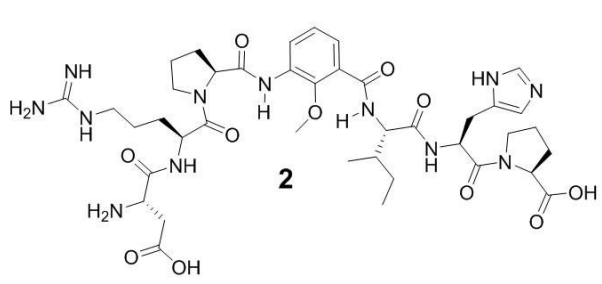
Relative Abundance
m/z
3
HRMS



1

^{1}H NMR (700 MHz ,H_2O:D_2O(9:1))



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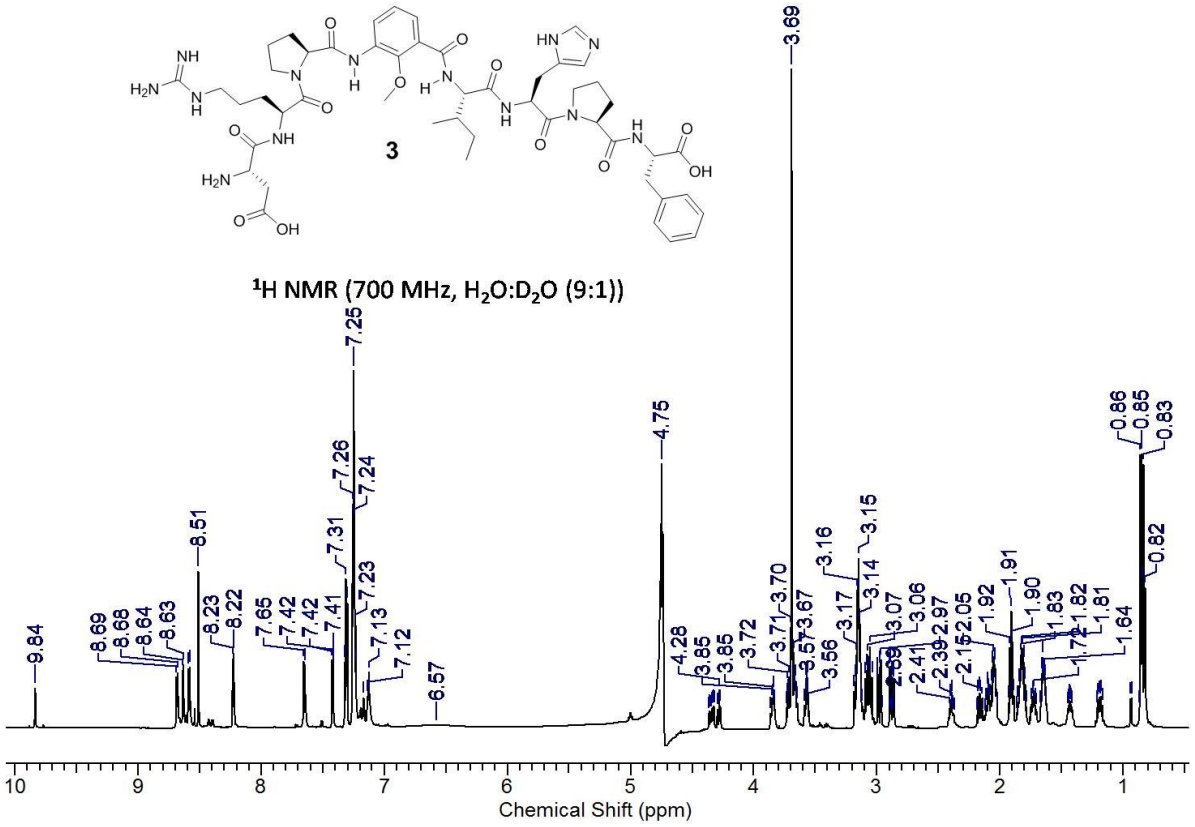
^{1}H NMR (700 MHz ,H_2O:D_2O(9:1))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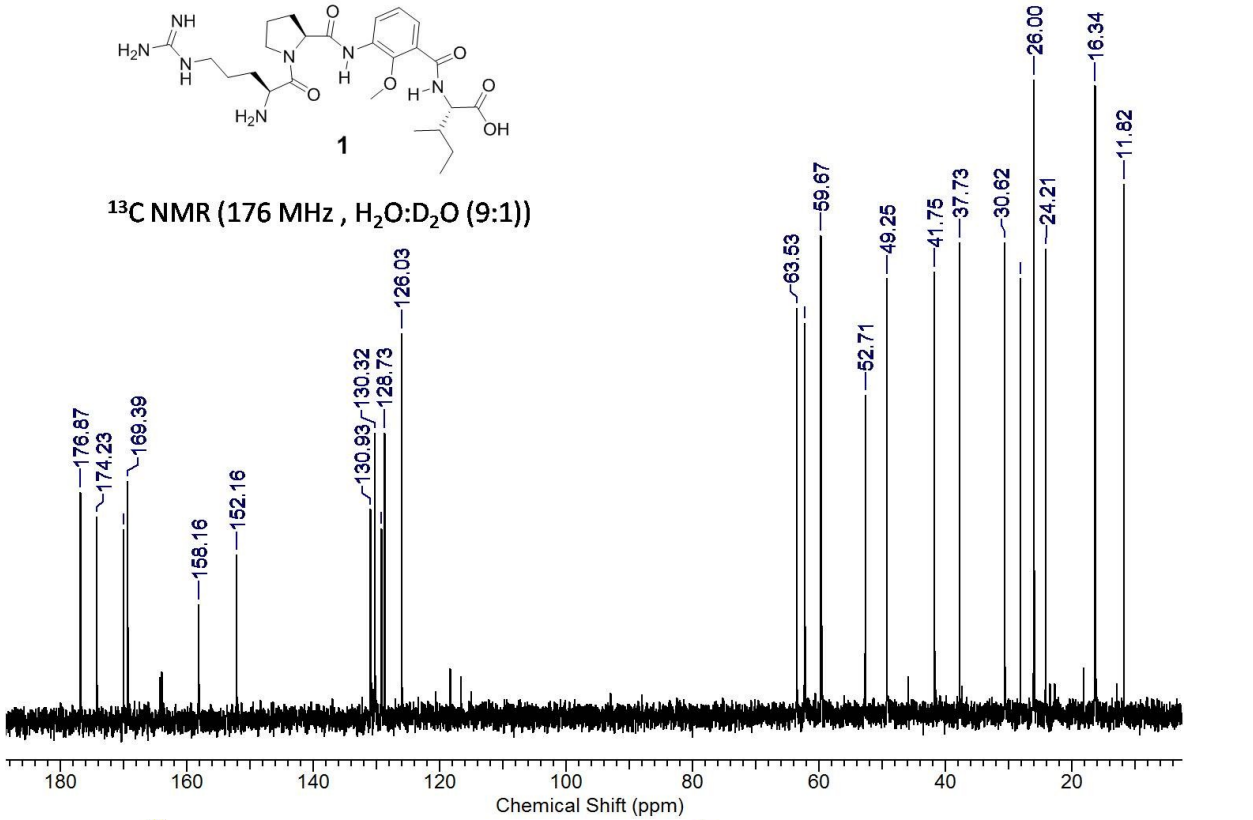
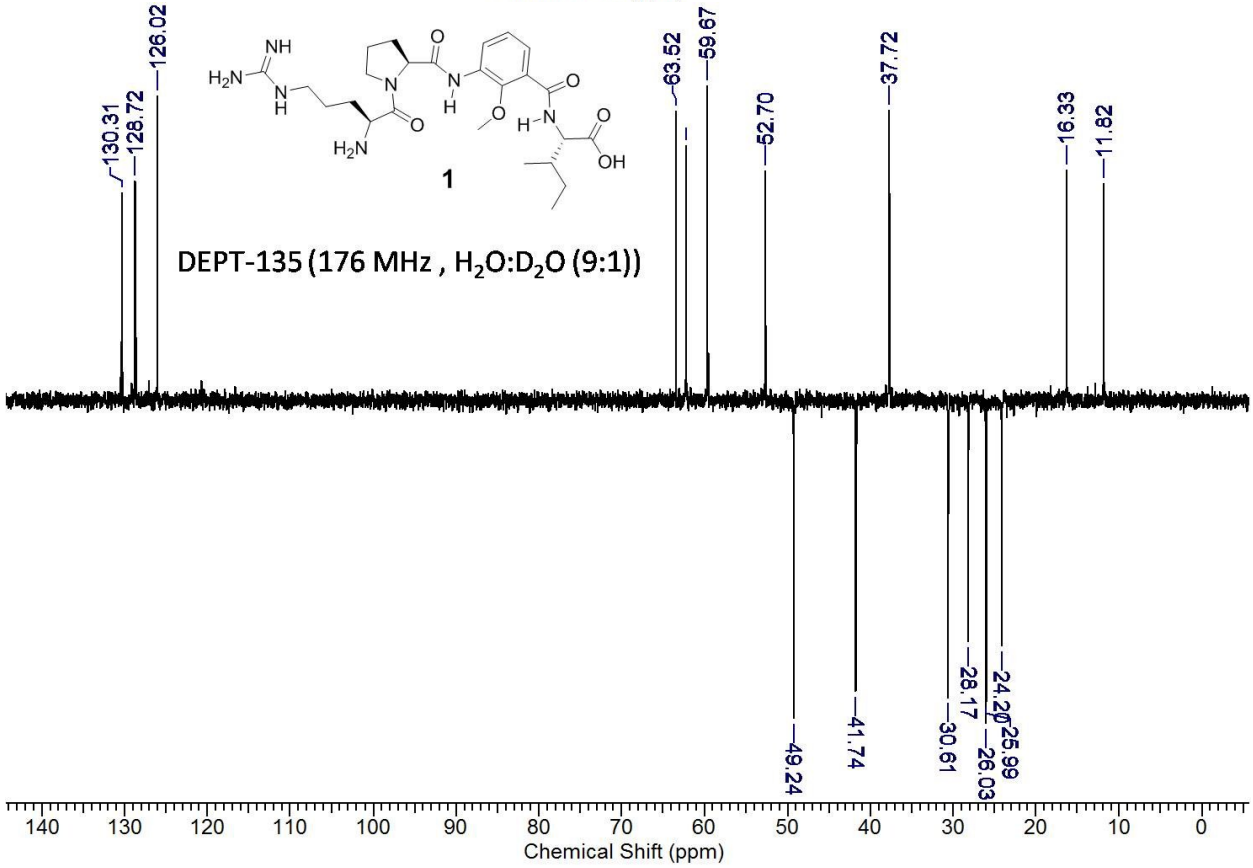
^{1}H NMR (700 MHz, H_2O:D_2O (9:1))
Chemical Shift (ppm)


1
^{13}C NMR (176 MHz , H_2O:D_2O (9:1))
176.87
174.23
169.39
158.16
152.16
130.93
130.32
128.73
126.03
63.53
59.67
52.71
49.25
41.75
37.73
30.62
26.00
24.21
16.34
11.82
Chemical Shift (ppm)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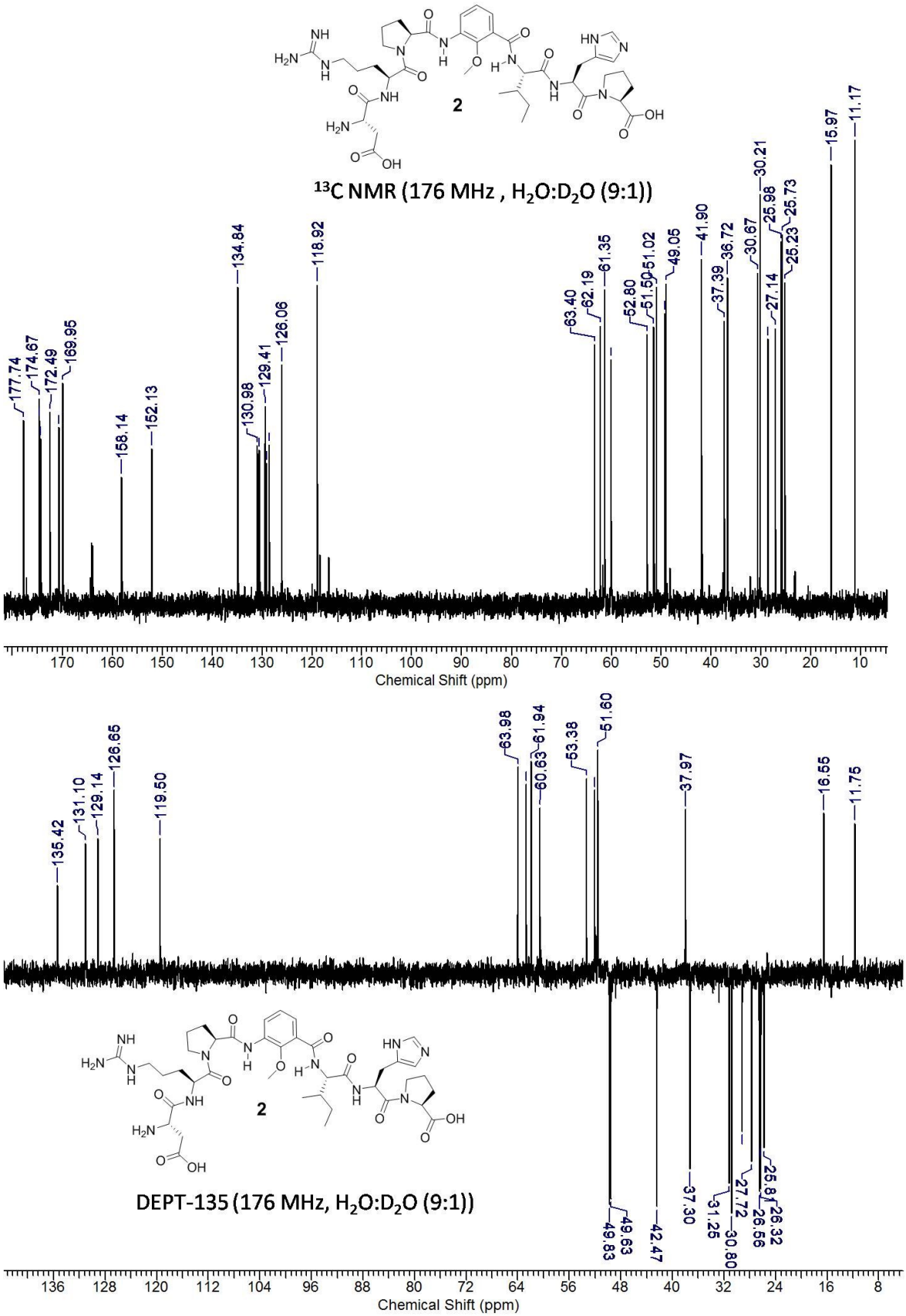
DEPT-135 (176 MHz , H_2O:D_2O (9:1))
130.31
128.72
126.02
63.52
59.67
52.70
37.72
16.33
11.82
49.24
41.74
30.61
28.17
26.03
25.99
24.20
Chemical Shift (ppm)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177.74
174.67
172.49
169.95
158.14
152.13
134.84
130.98
129.41
126.06
118.92
63.40
62.19
61.35
52.80
51.50
51.02
49.05
41.90
37.39
36.72
30.67
30.21
25.98
25.73
25.23
27.14
15.97
11.17
Chemical Shift (ppm)
135.42
131.10
129.14
126.65
119.50
63.98
61.94
60.63
53.38
51.60
37.97
16.55
11.75
2
DEPT-135 (176 MHz, H_2O:D_2O (9:1))
49.83
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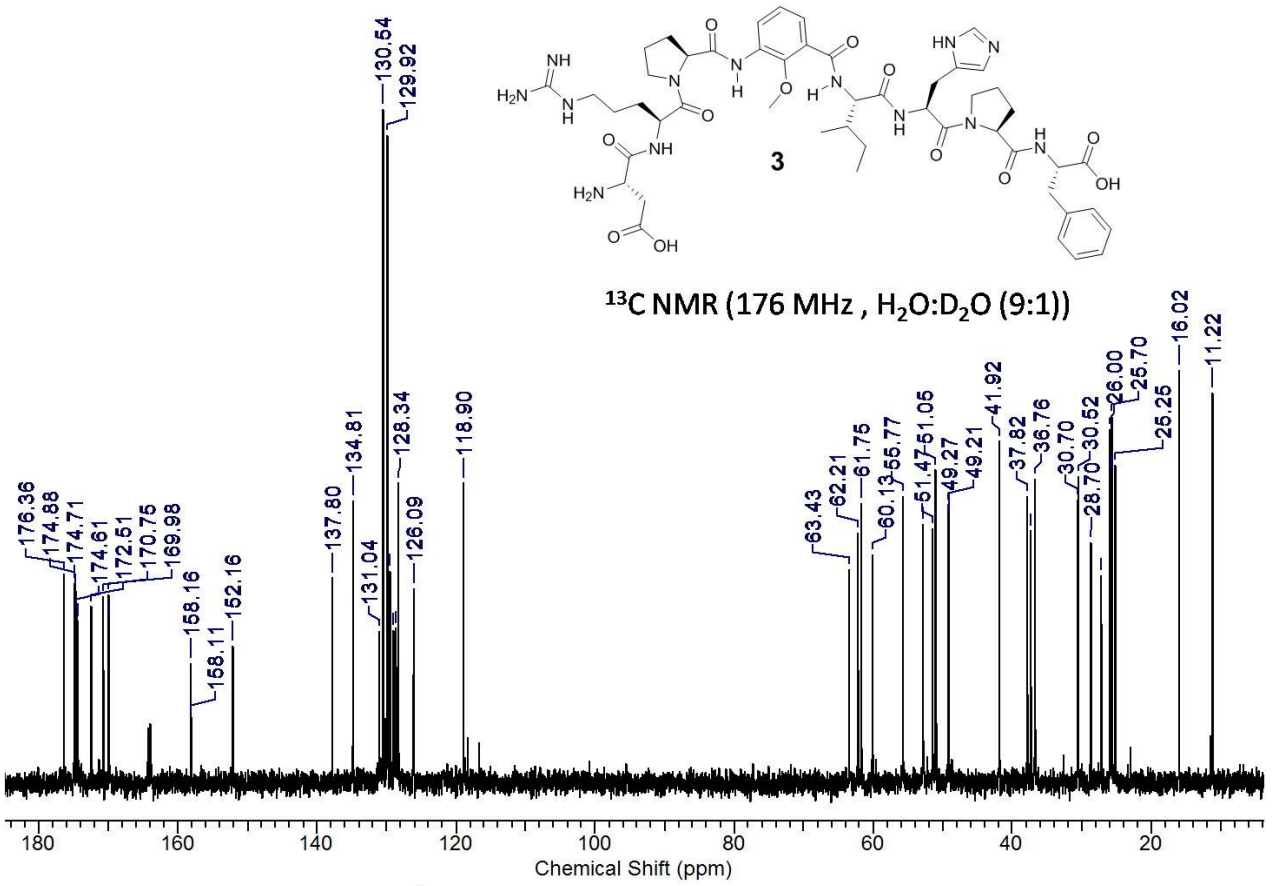
42.47
37.30
31.25
30.80
27.72
26.32
Chemical Shift (ppm)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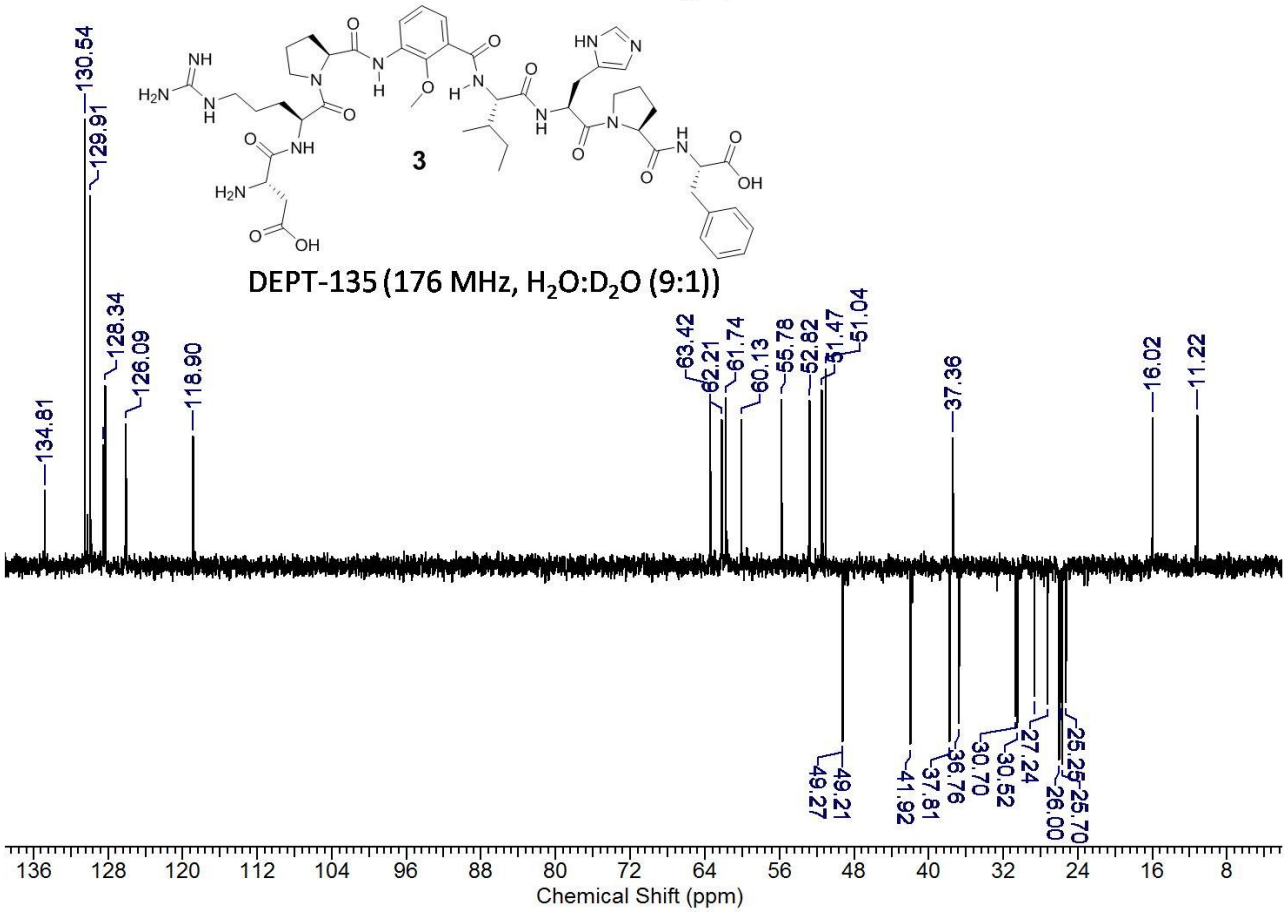
^{13}C NMR (176 MHz , H_2O:D_2O (9:1))
Chemical Shift (ppm)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DEPT-135 (176 MHz, H_2O:D_2O (9:1))
Chemical Shift (ppm)

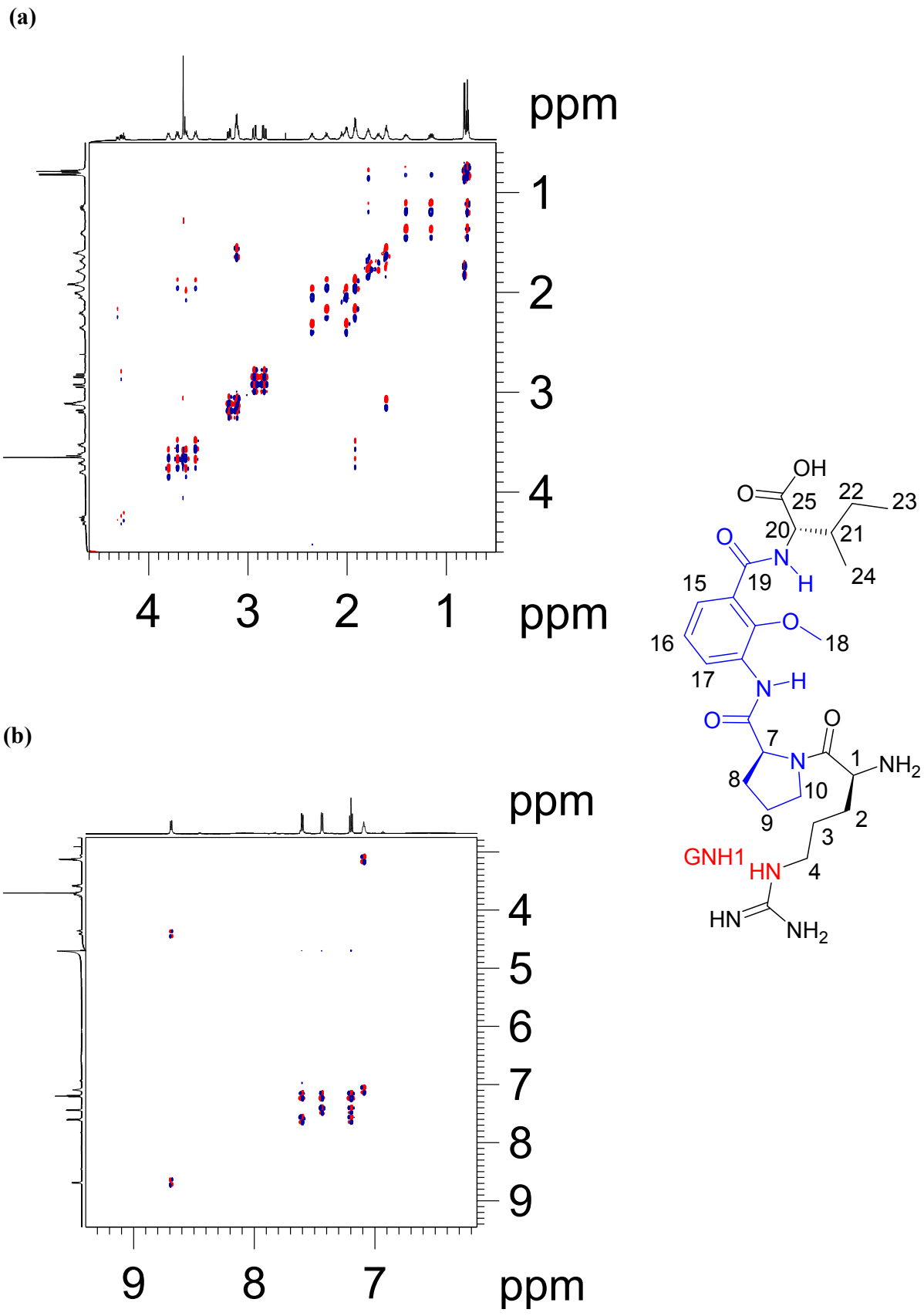
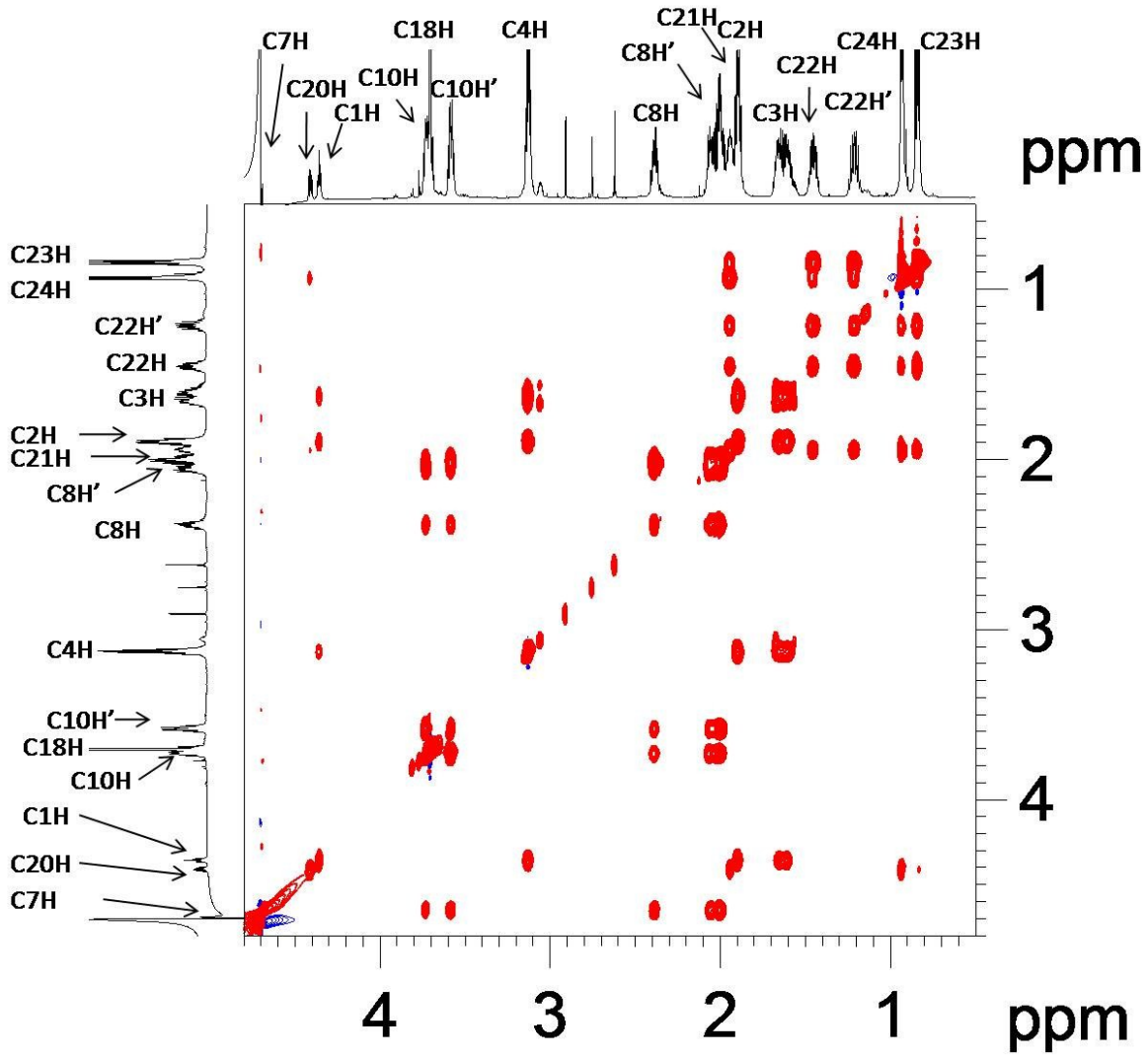


Figure : Partial COSY spectra of **1** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.



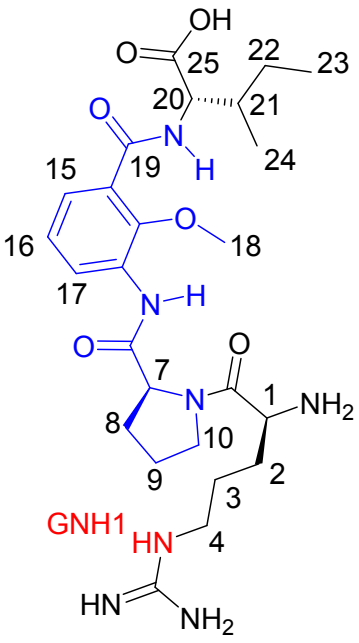


Figure: Partial TOCSY spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with significant assignments.

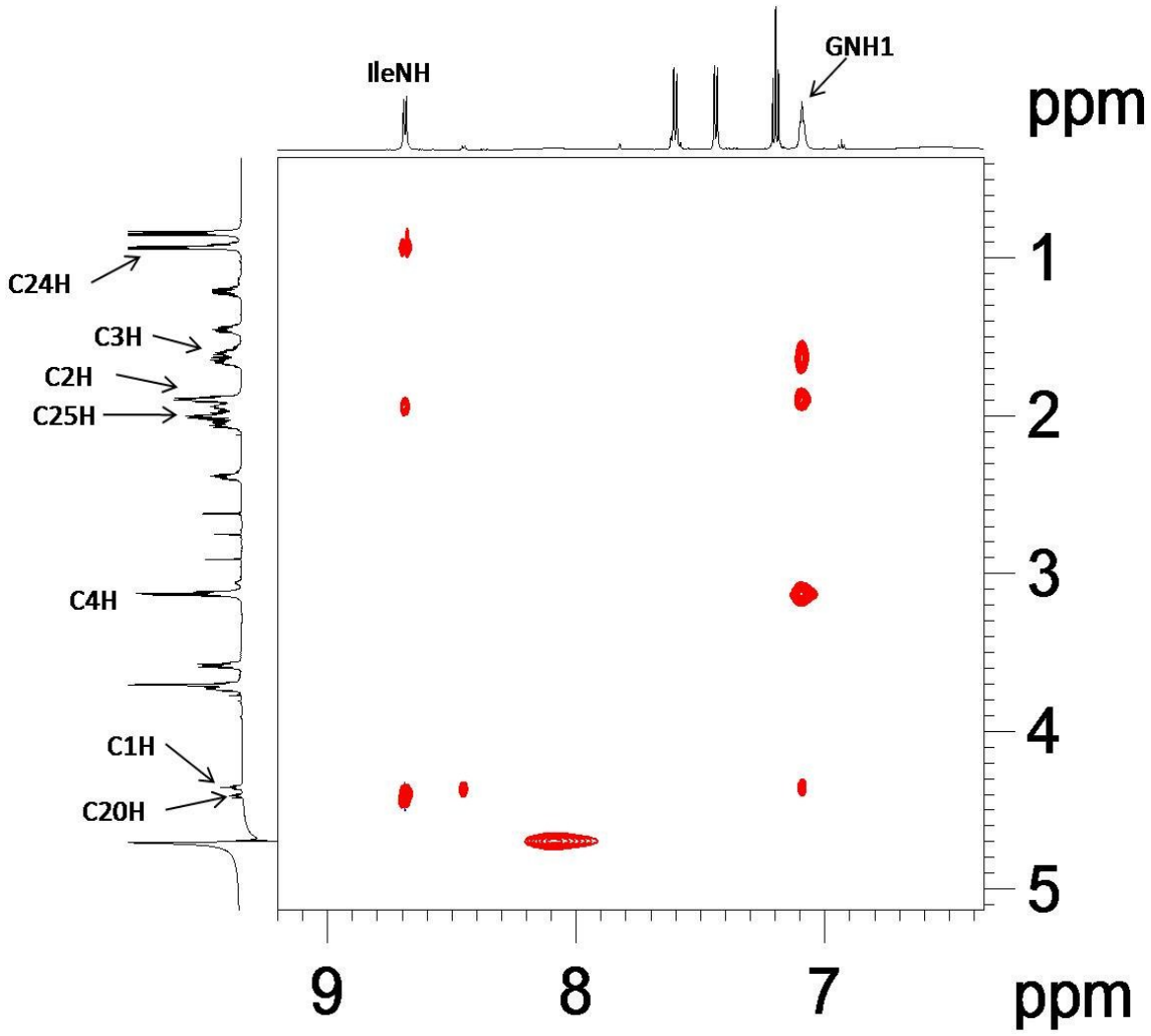
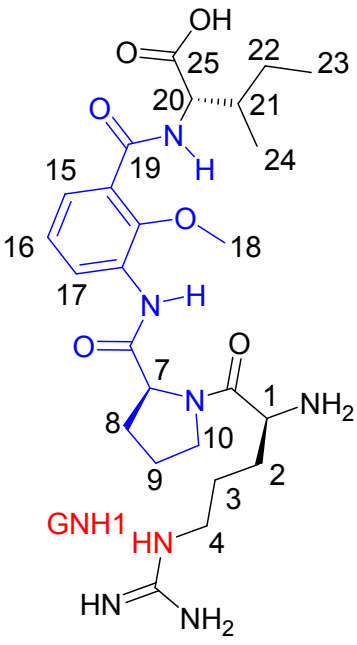
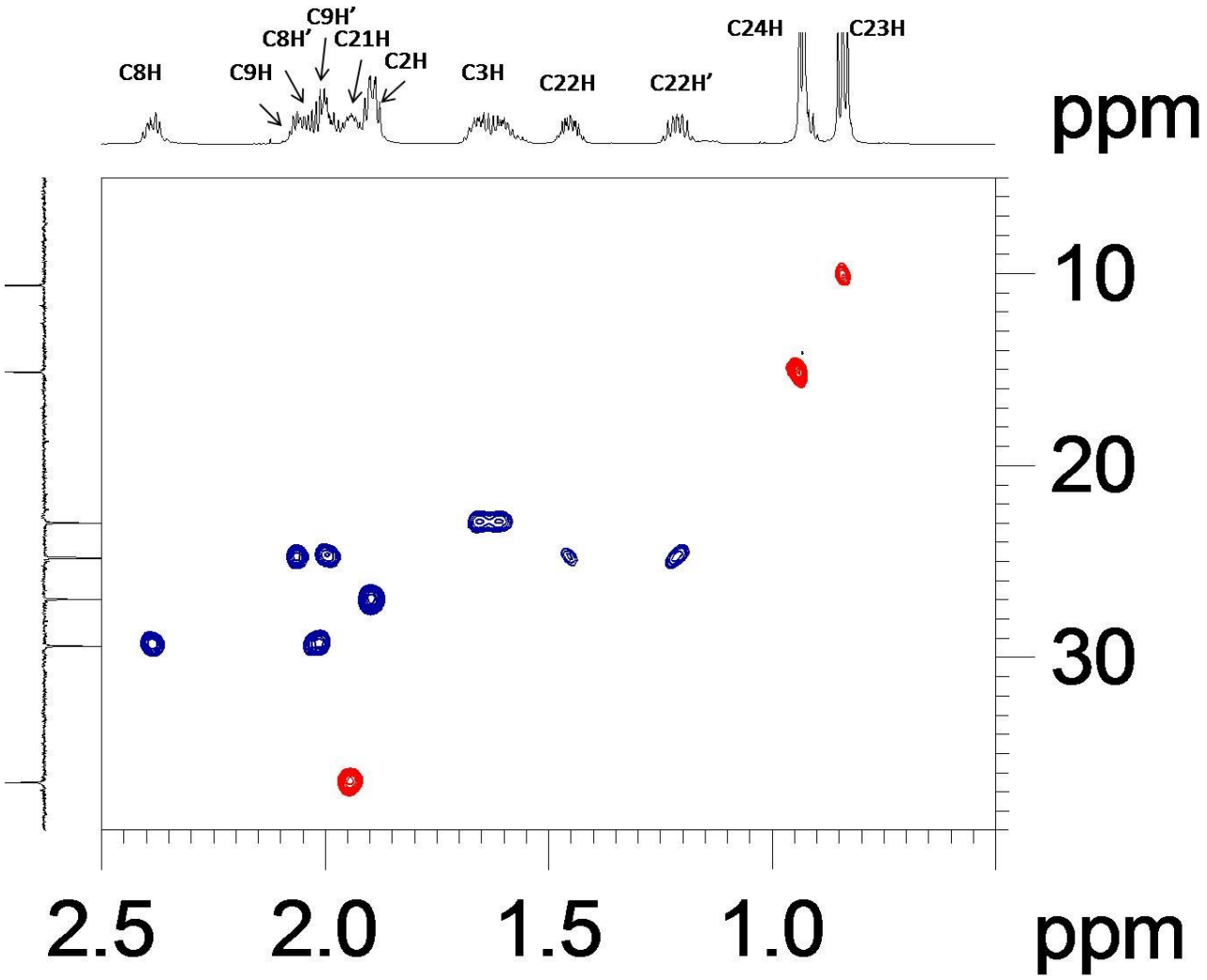


Figure: Partial TOCSY spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying aromatic region with significant assignments.





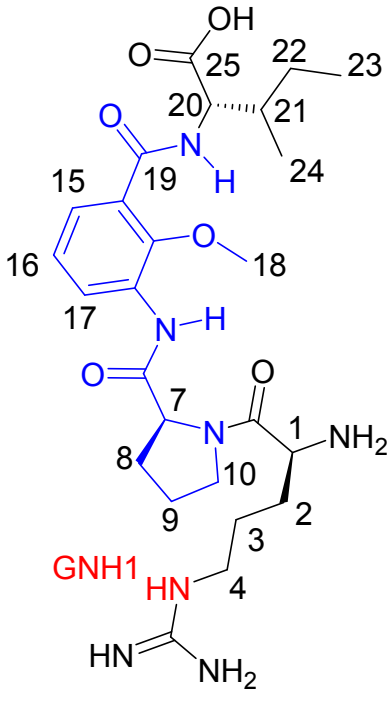


Figure: Partial HSQC spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with significant assignments.

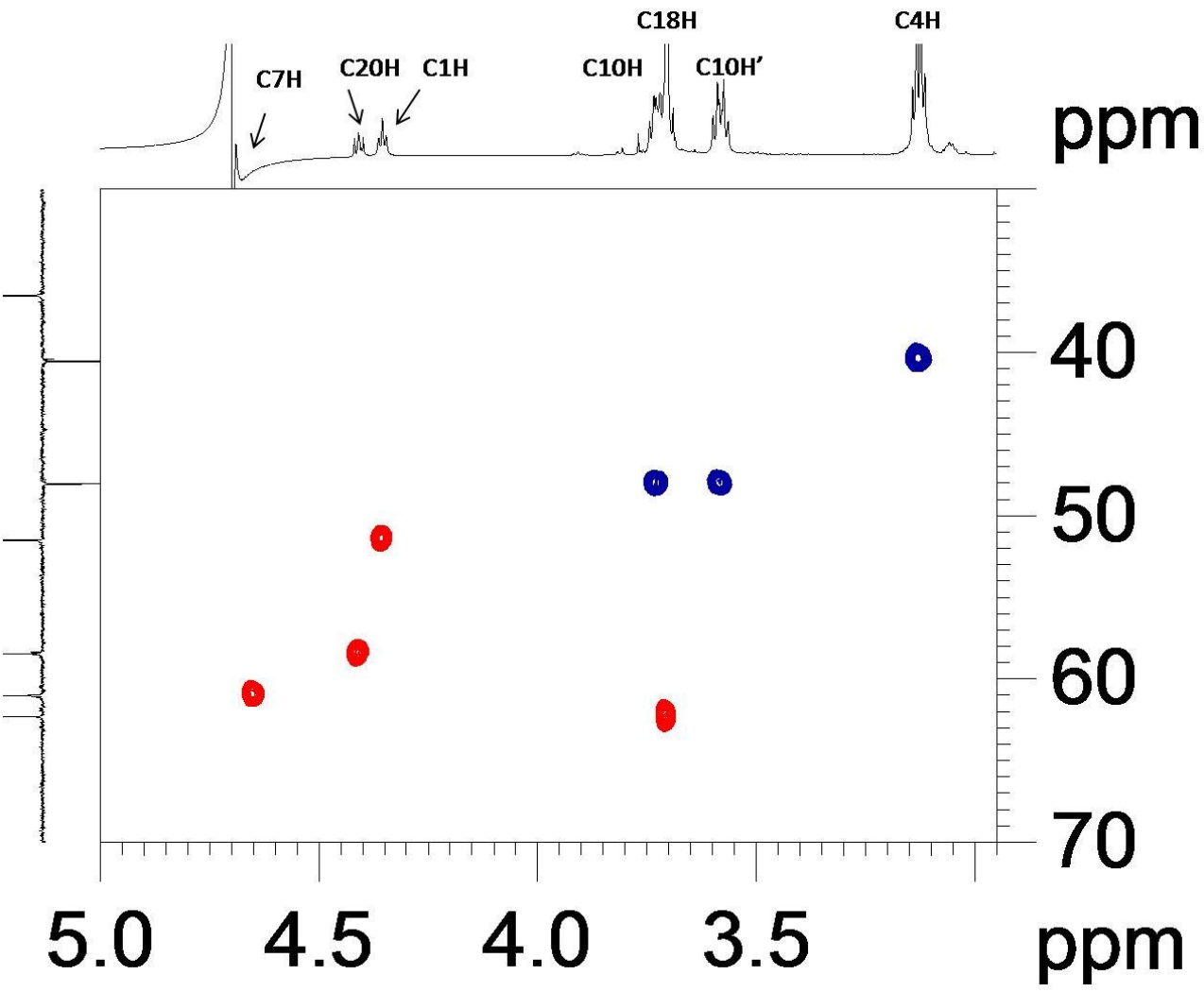
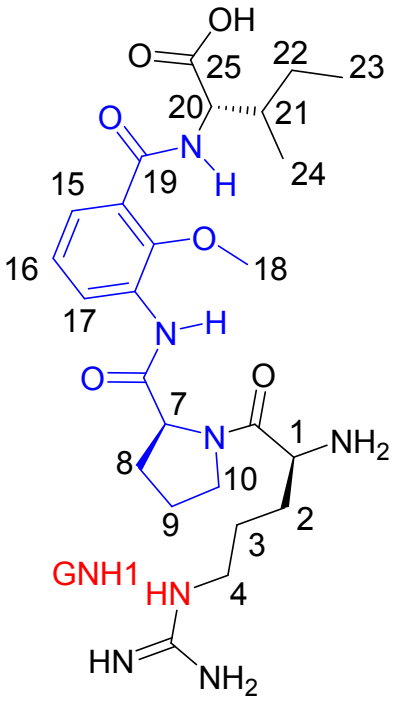


Figure: Partial HSQC spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with significant assignments.



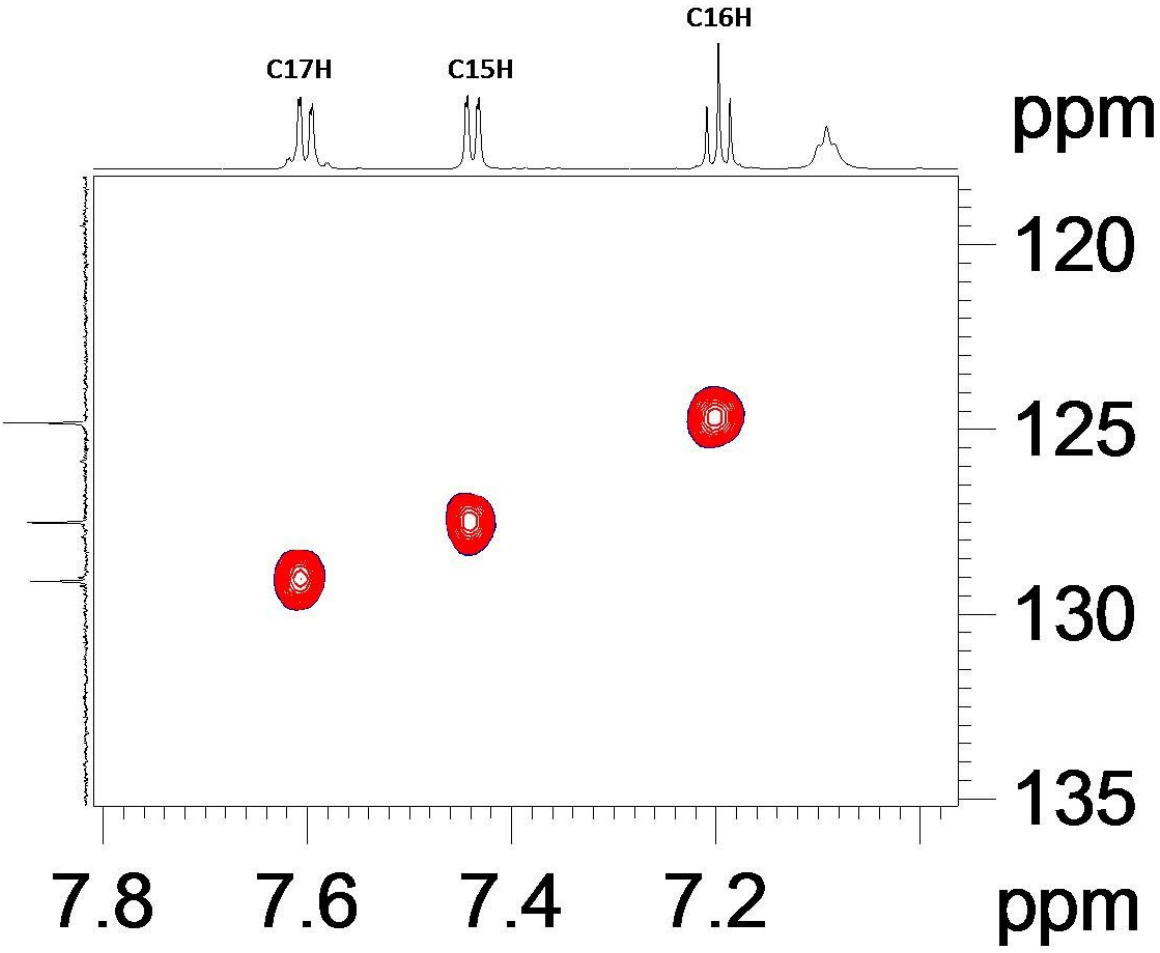
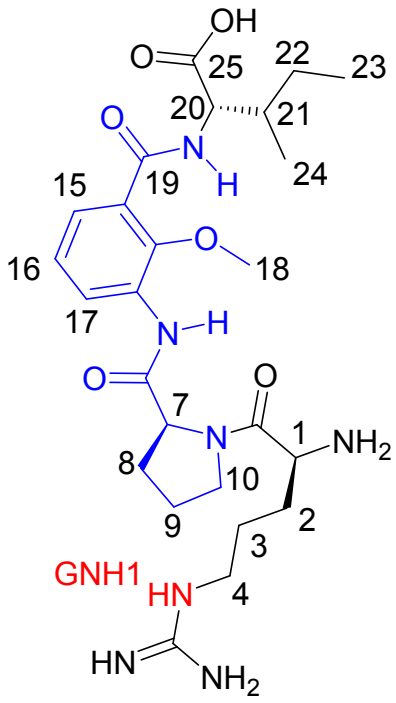


Figure: Partial HSQC spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying aromatic region with significant assignments.



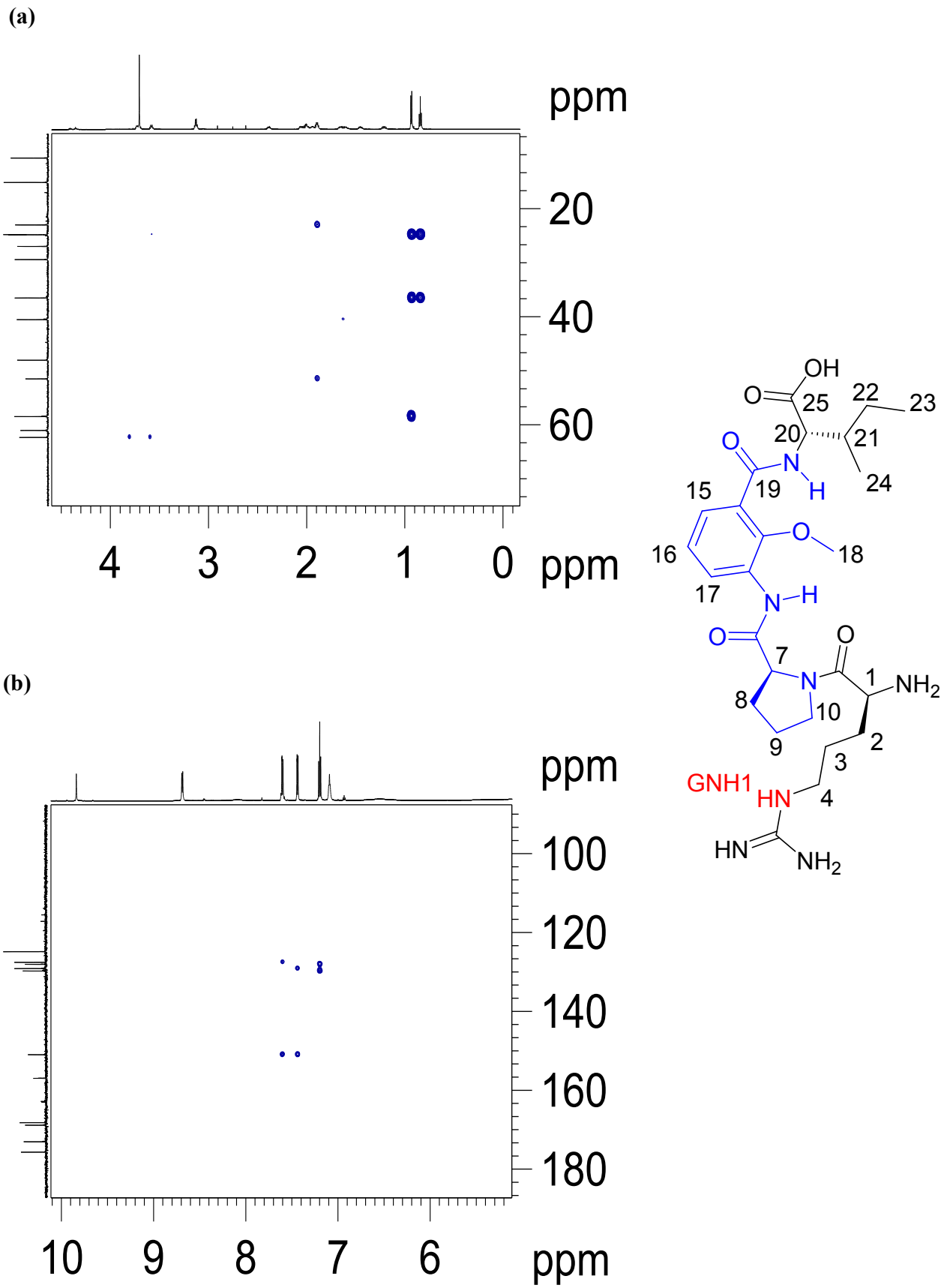


Figure : Partial HMBC spectra of **1** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.

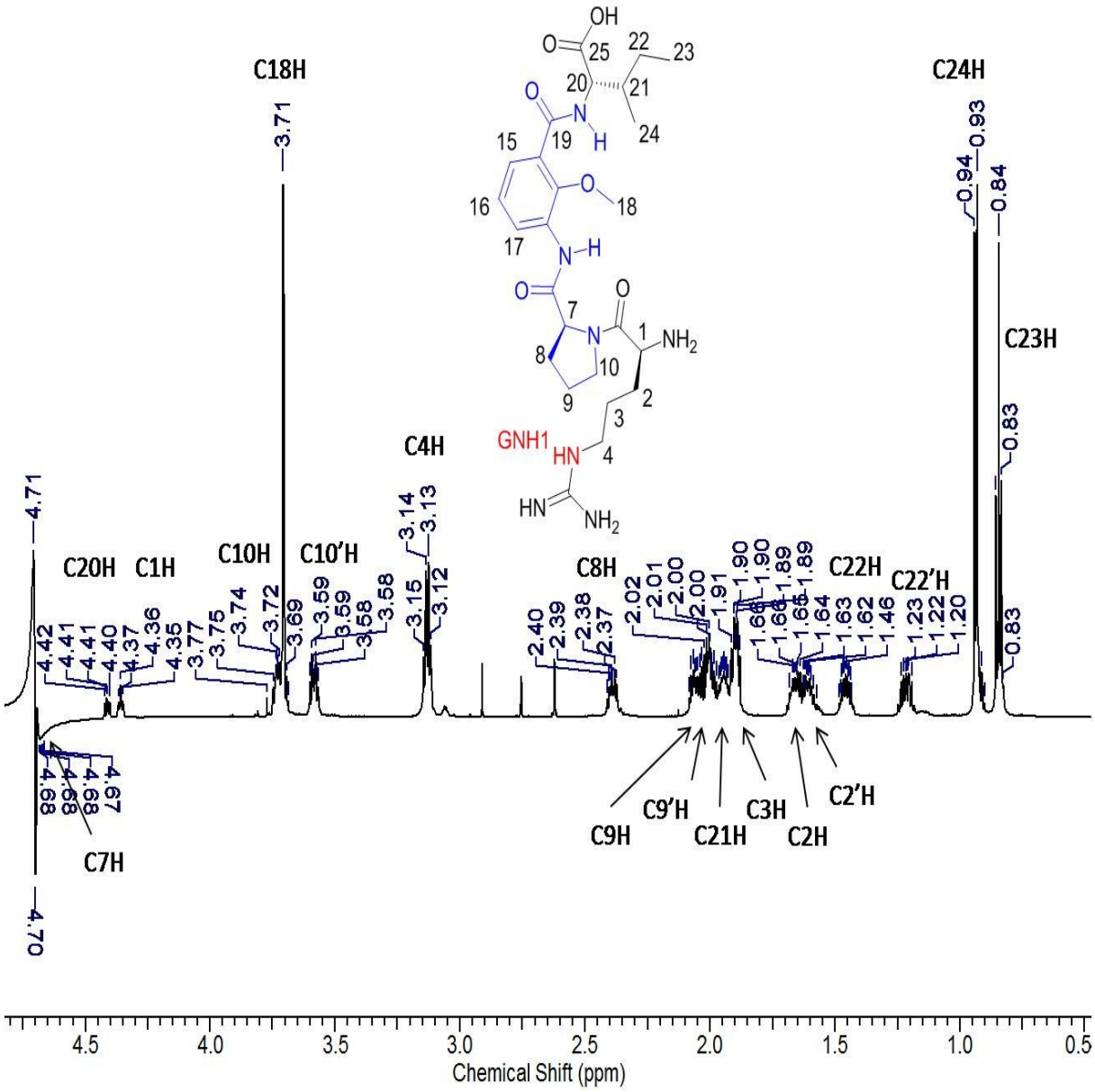


Figure: 1H NMR spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with complete assignments.

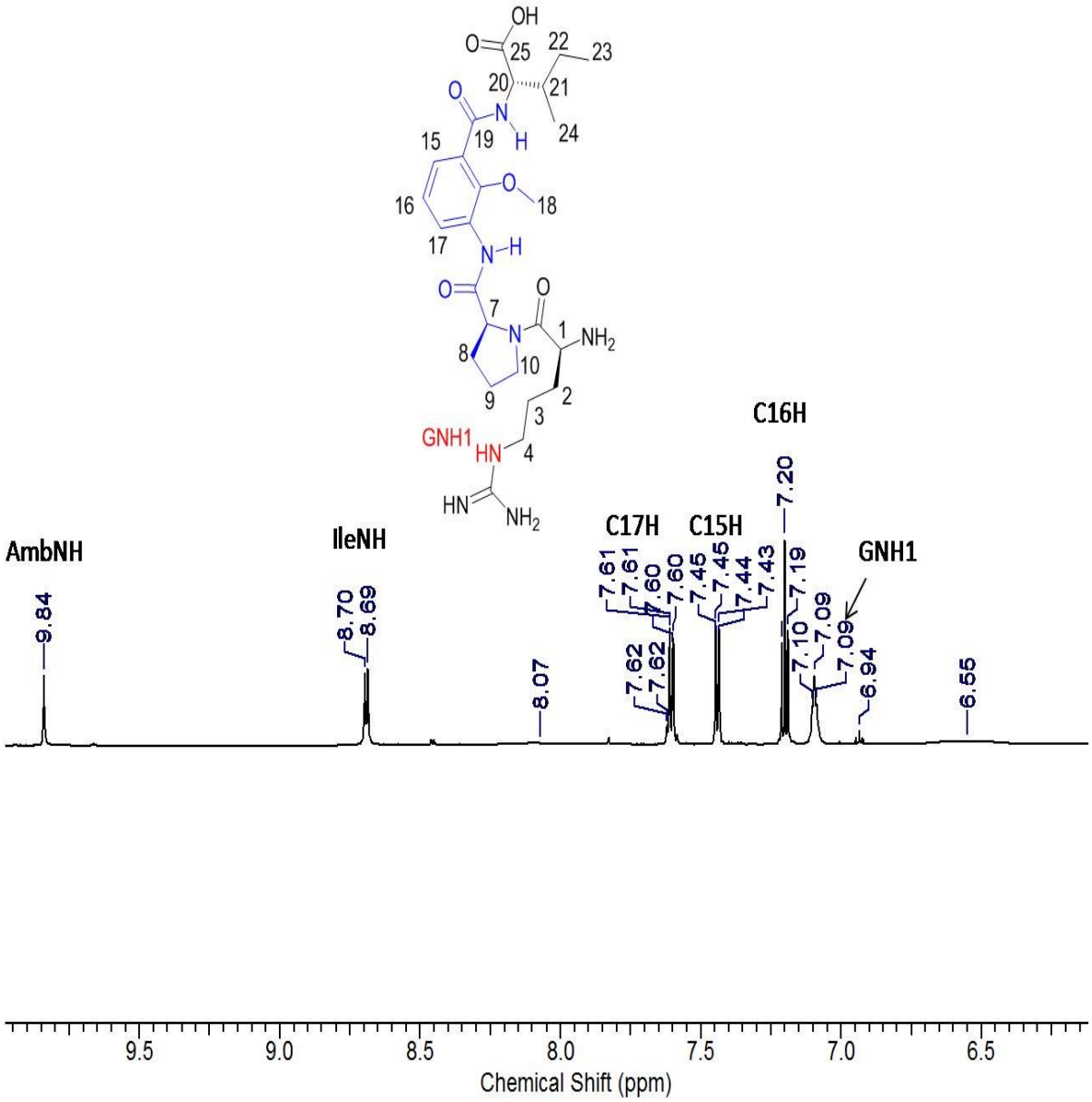


Figure: 1H NMR spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying aromatic region with complete assignments.

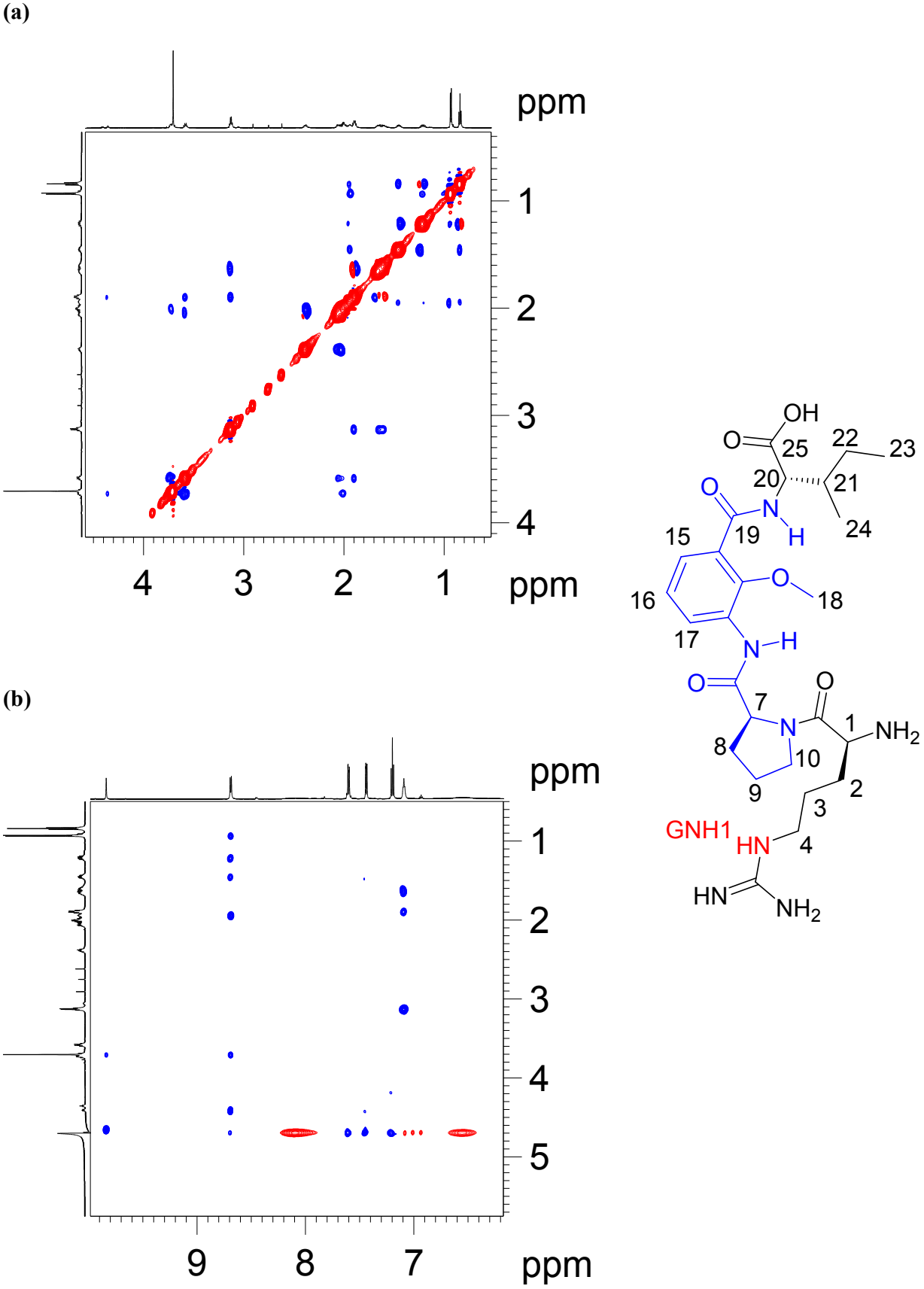
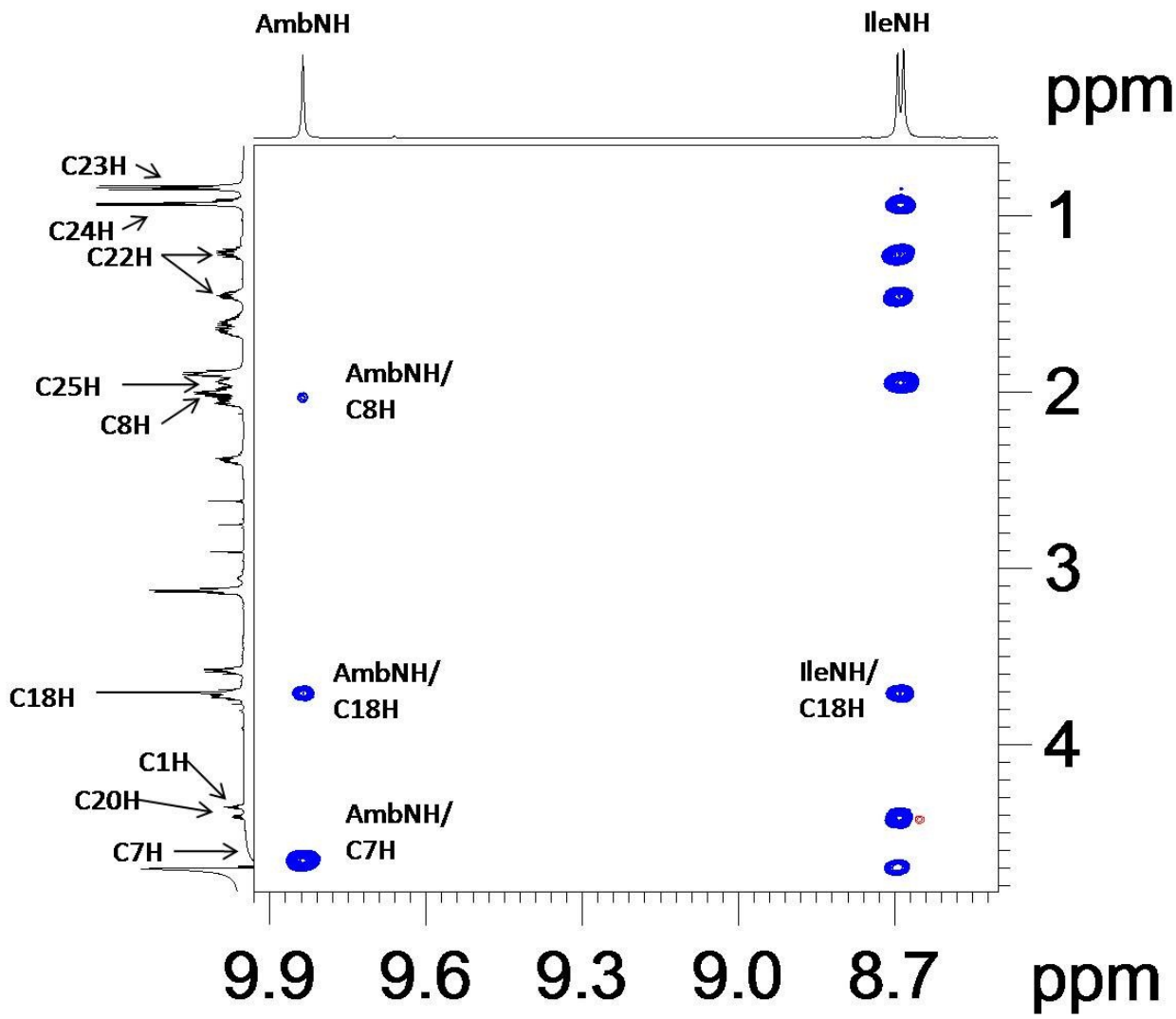


Figure : Partial ROESY spectra of **1** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.



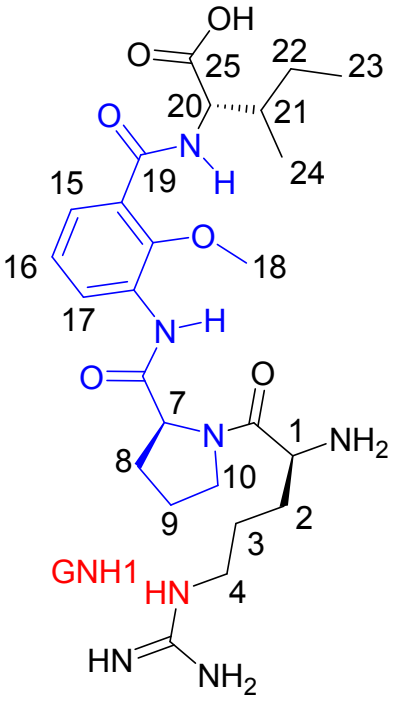


Figure: Partial ROESY spectra of **1** (700 MHz, H_2O:D_2O (9:1)) displaying significant nOe interactions essential for γ-turn conformation.

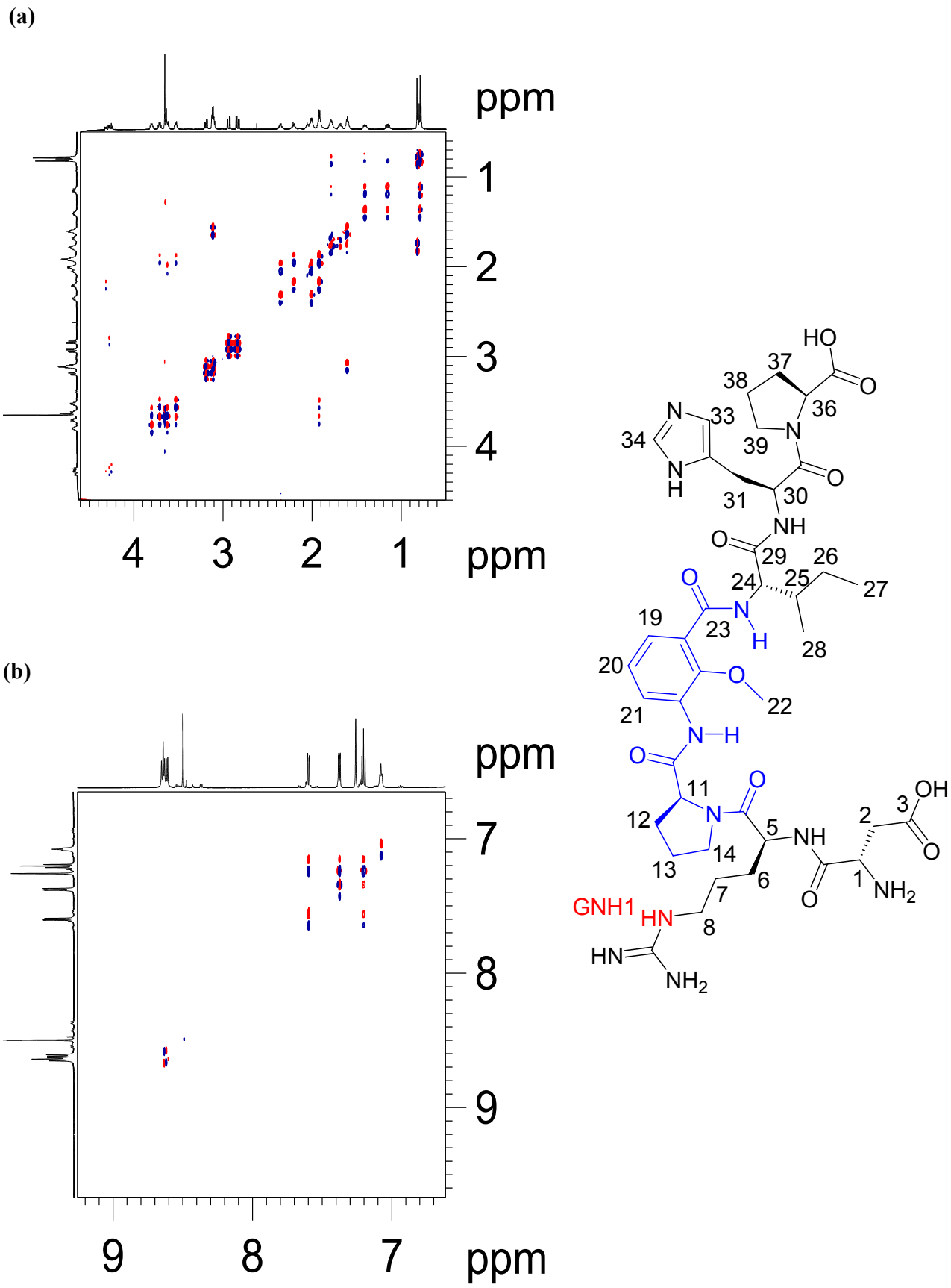
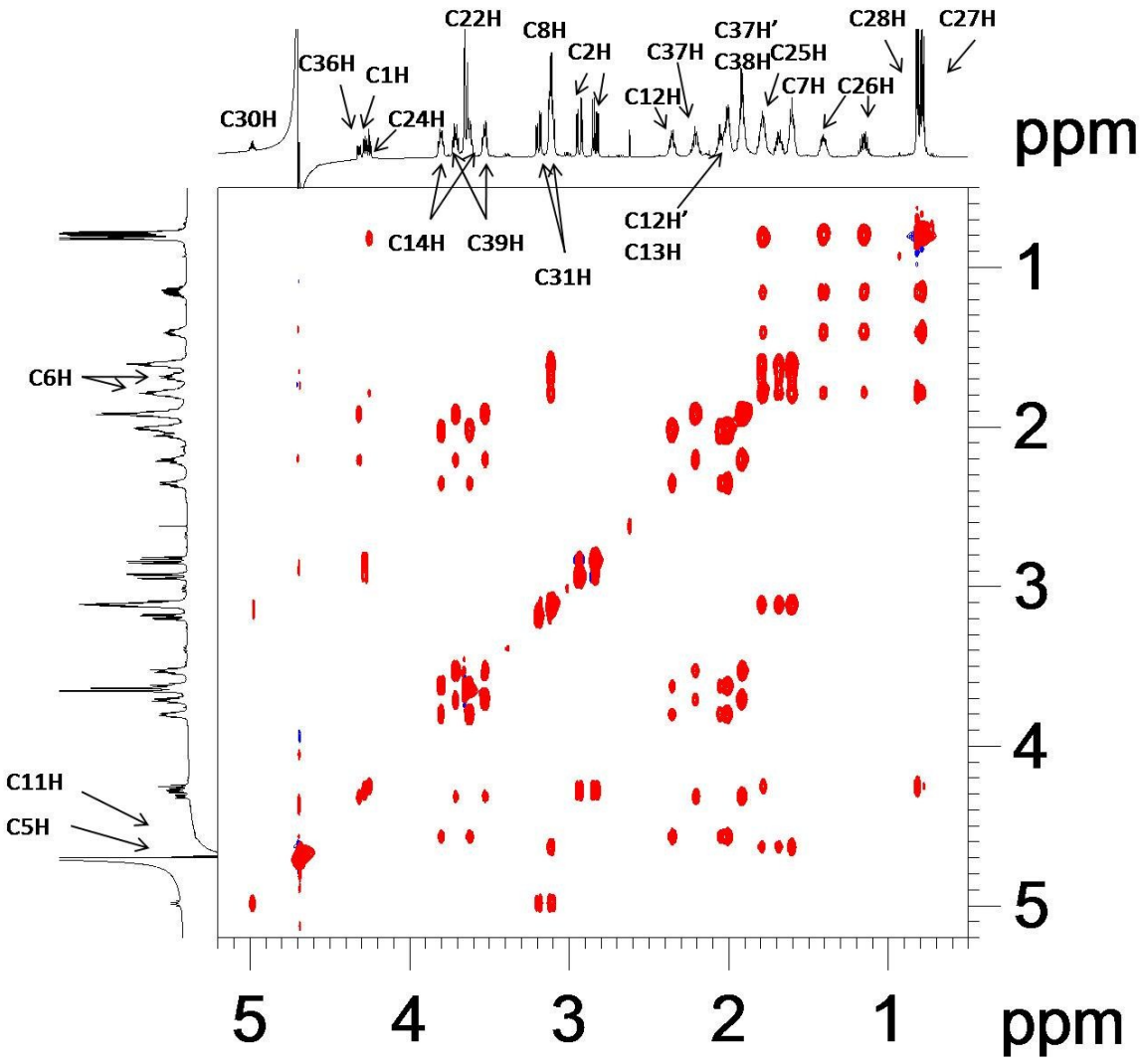


Figure : Partial COSY spectra of **2** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.



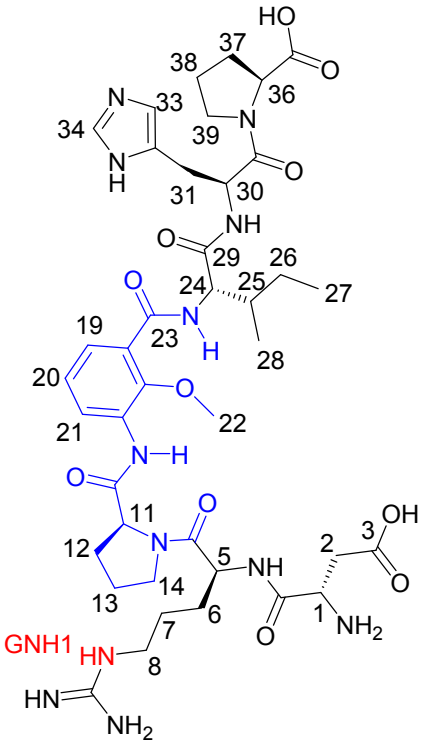
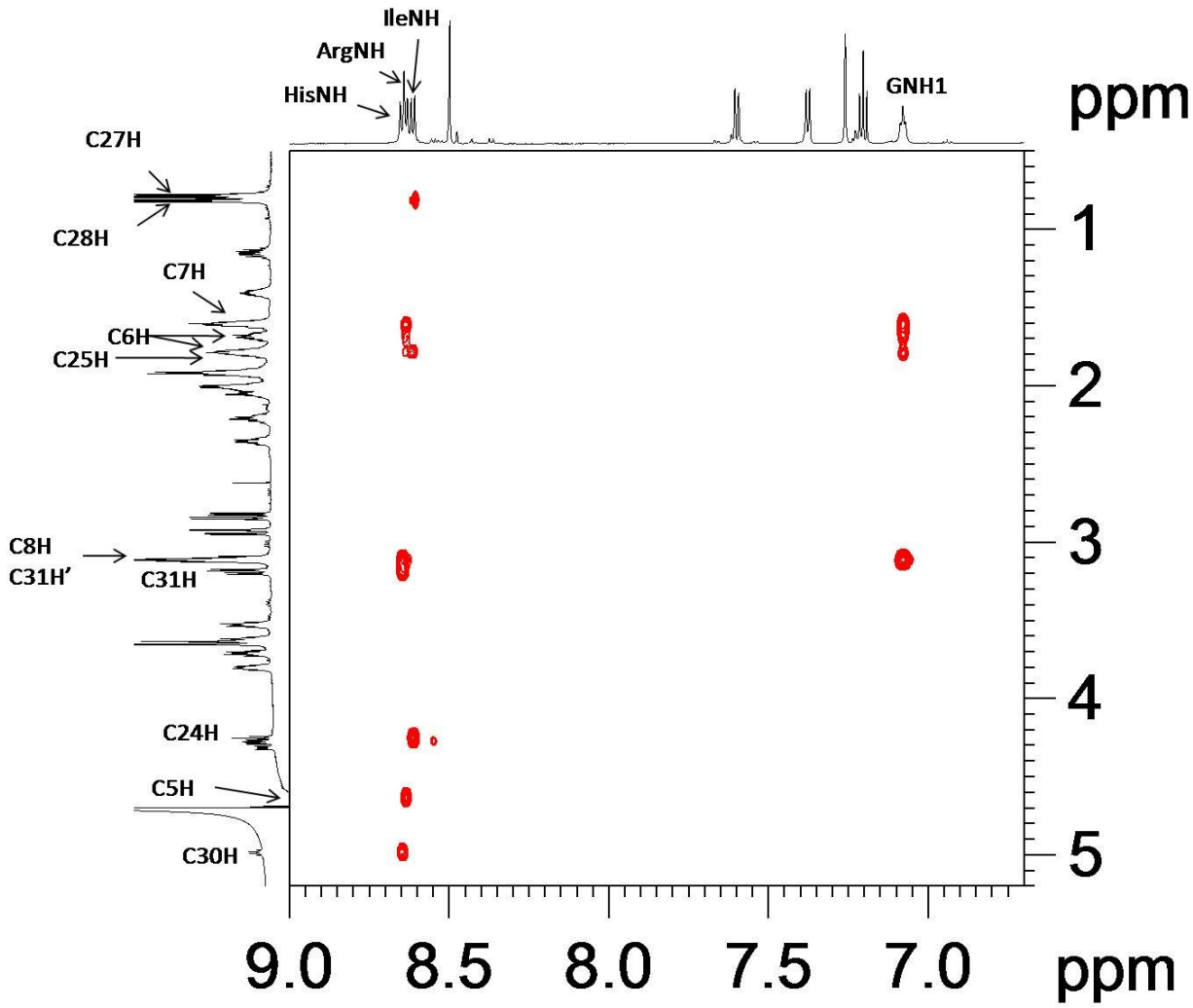


Figure: Partial TOCSY spectra of **2** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with significant assignments.



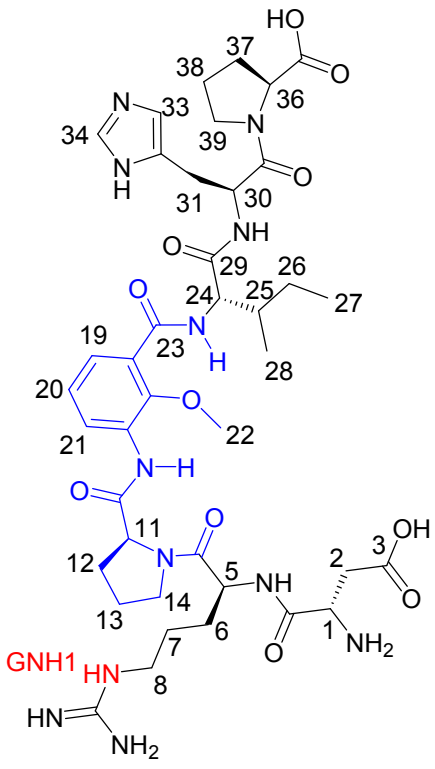
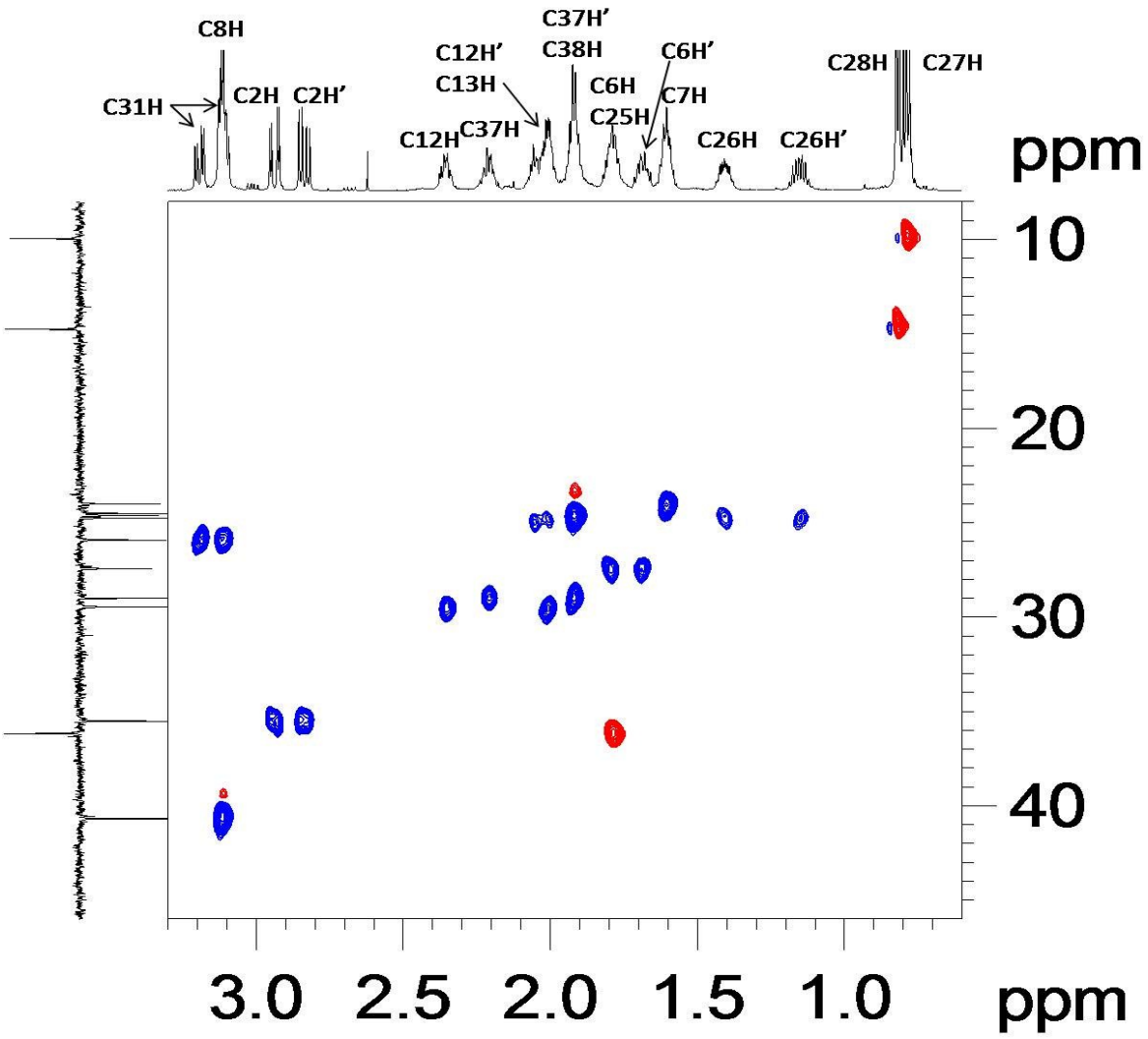


Figure: Partial TOCSY spectra of **2** (700 MHz, H_2O:D_2O (9:1)) displaying aromatic region with significant assignments.



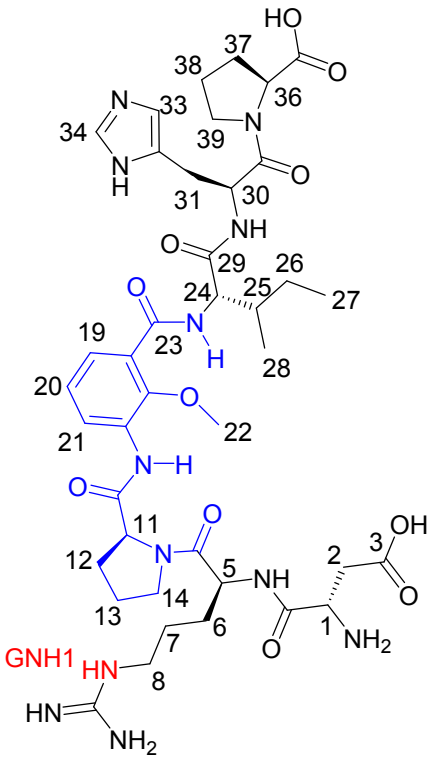
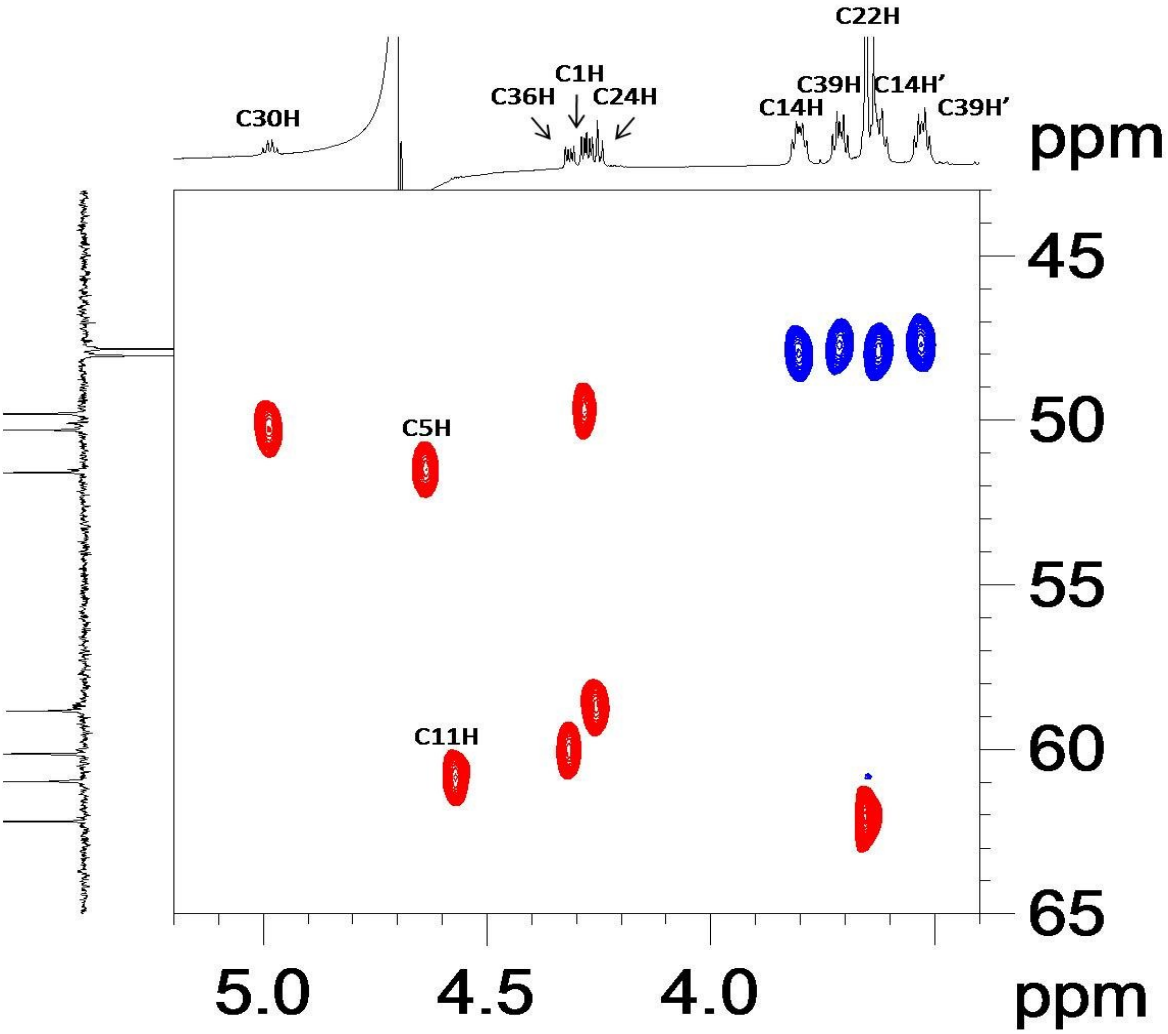
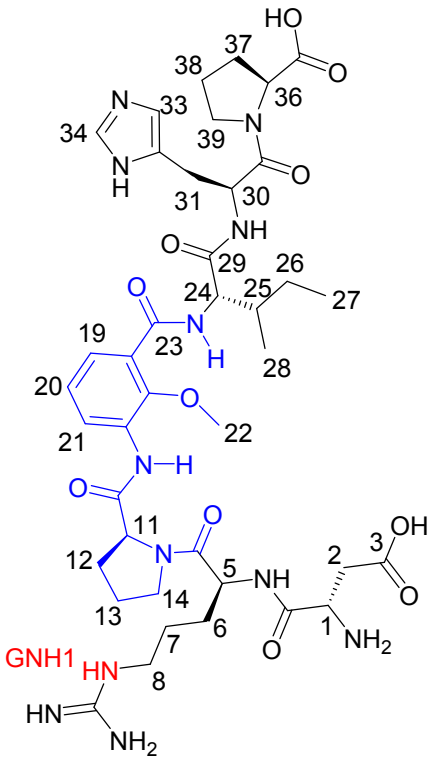


Figure: Partial HSQC spectra of **2** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with significant assignments.





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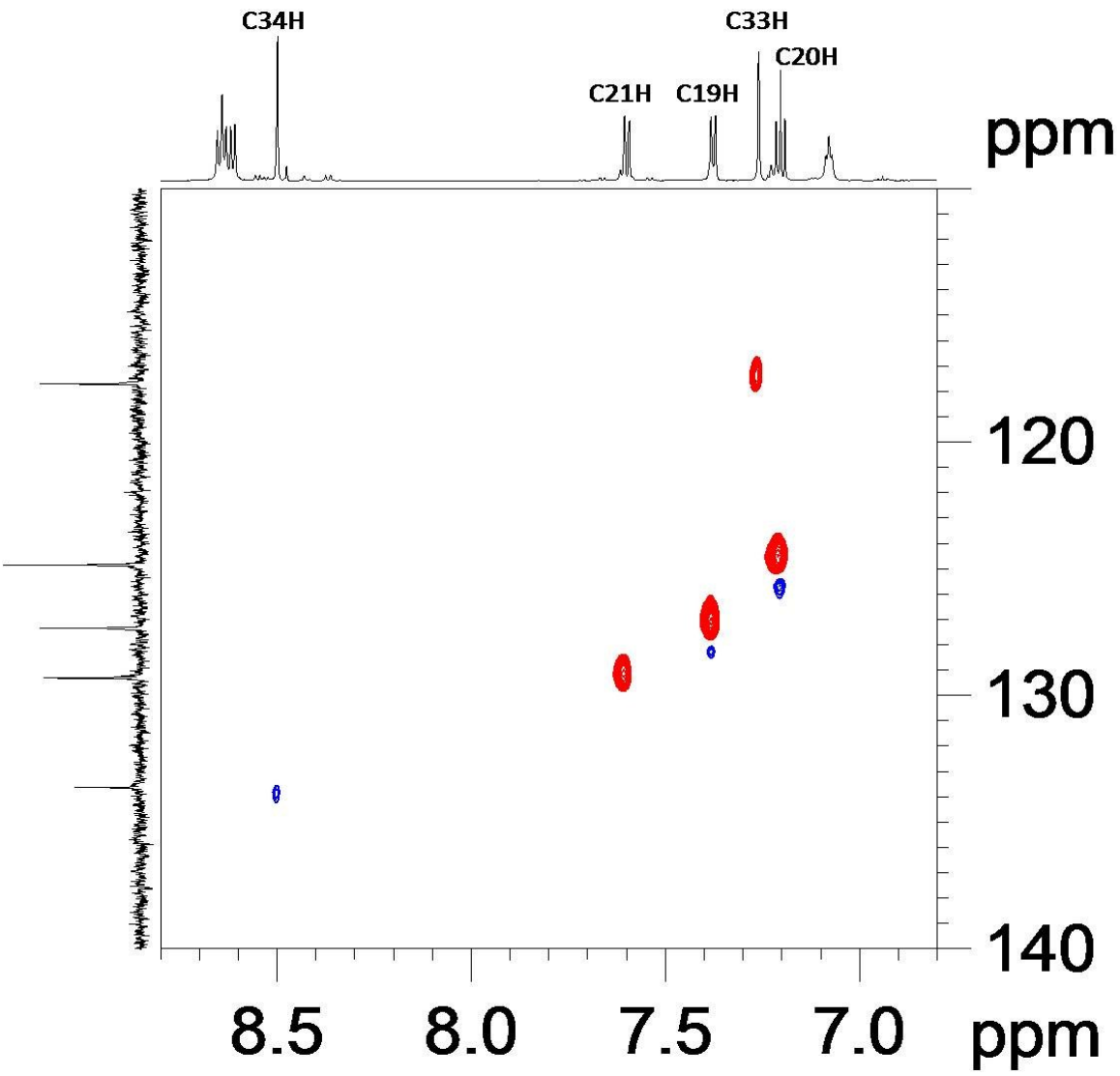

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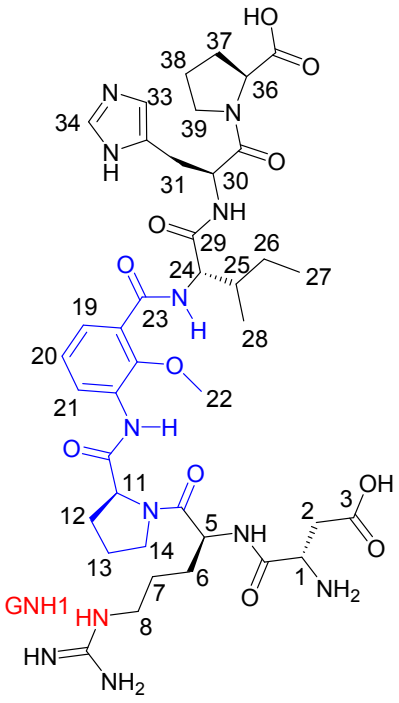


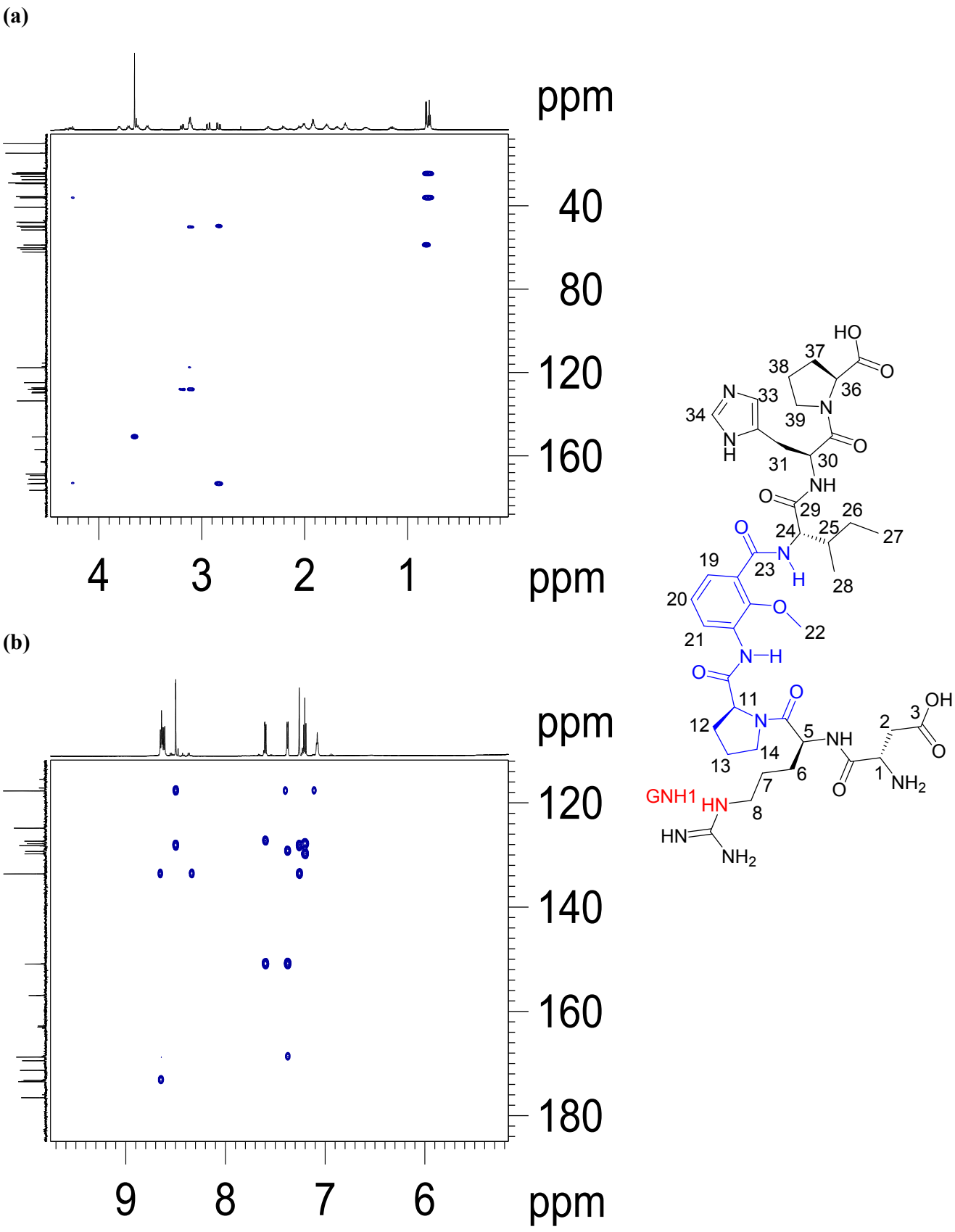


Figure : Partial HMBC spectra of **2** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.

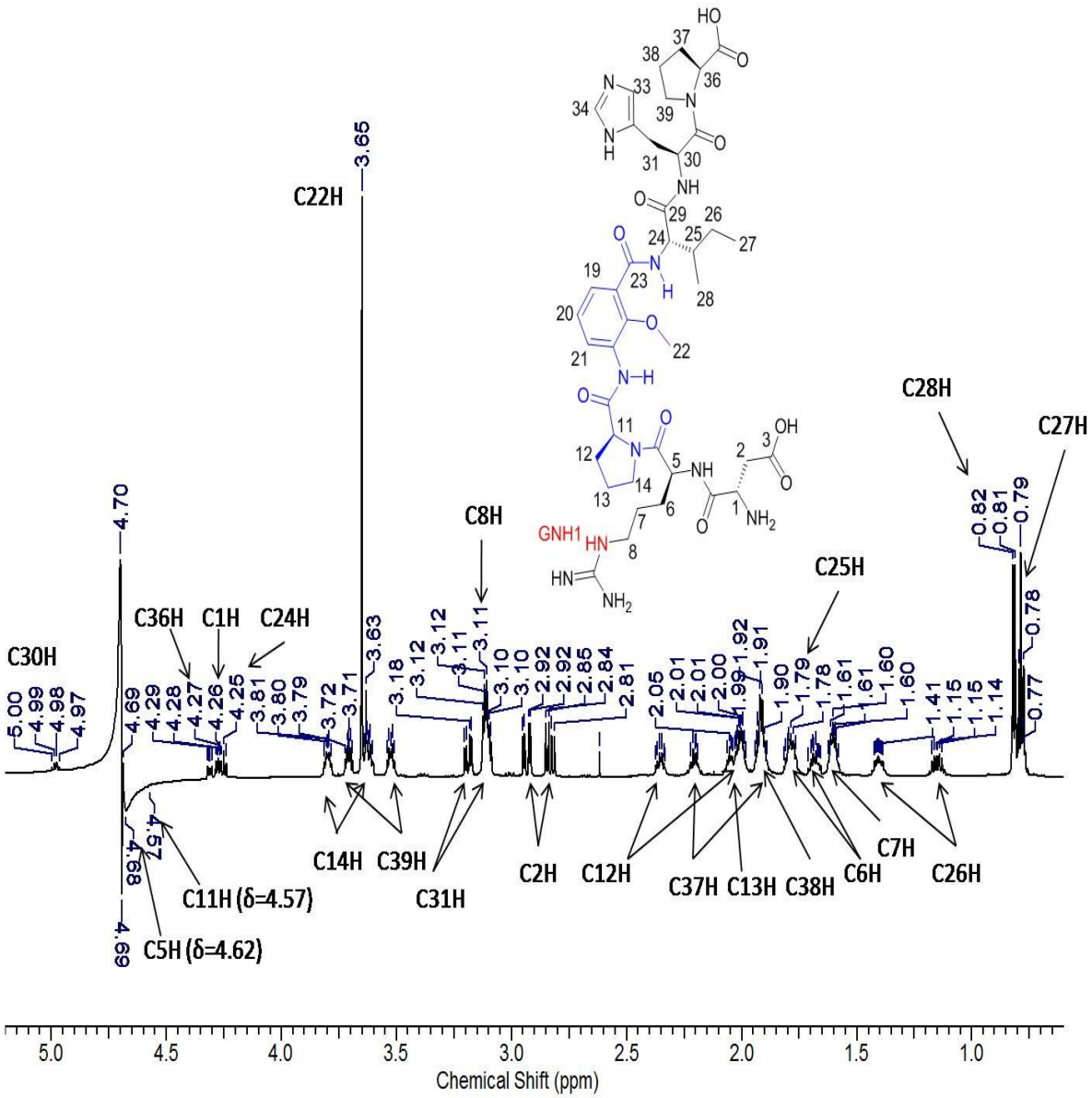


Figure: 1H NMR spectra of **2** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with complete assignments.

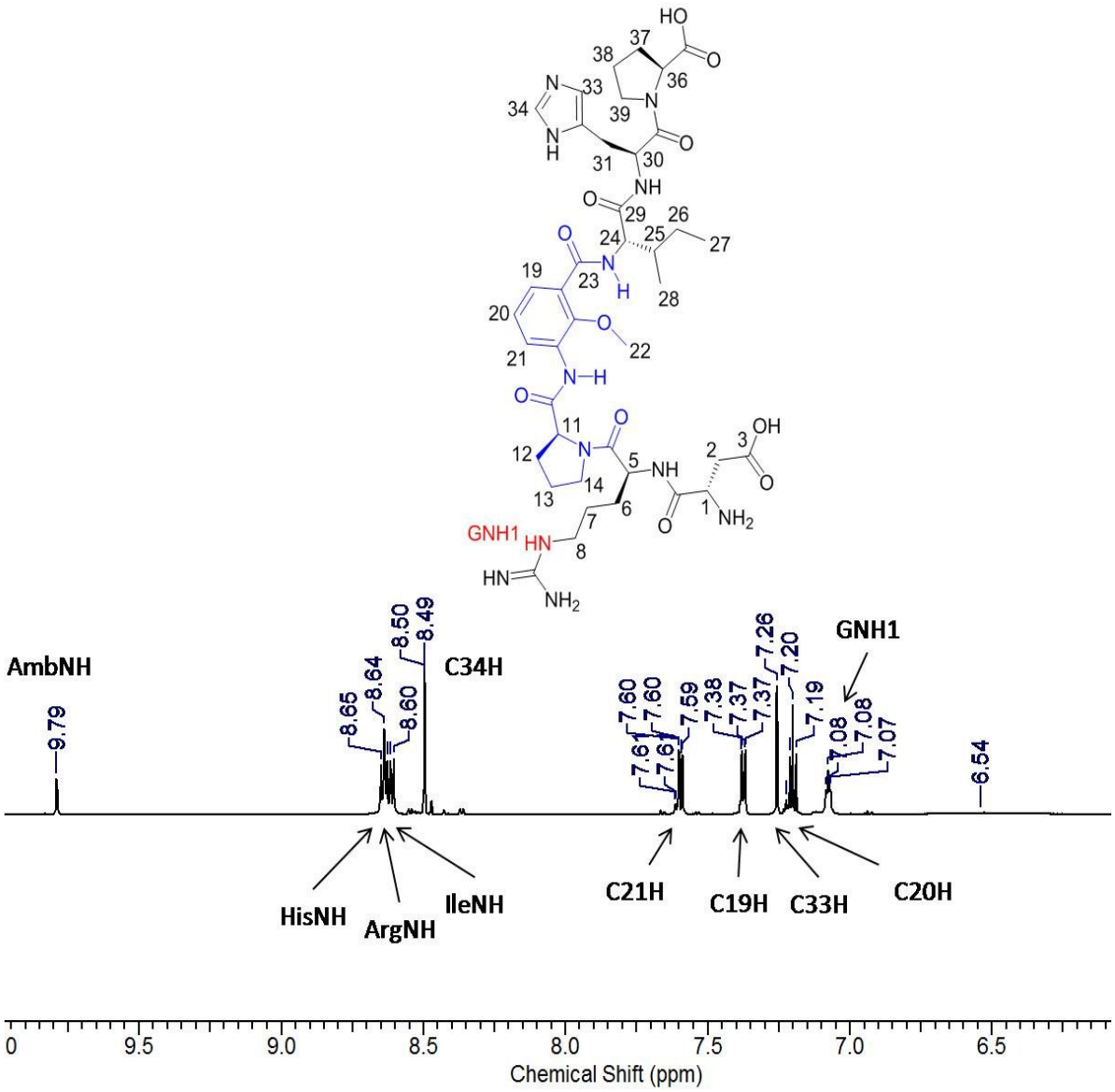


Figure: 1H NMR spectra of **2** (700 MHz, H_2O:D_2O (9:1)) displaying aromatic region with complete assignments.

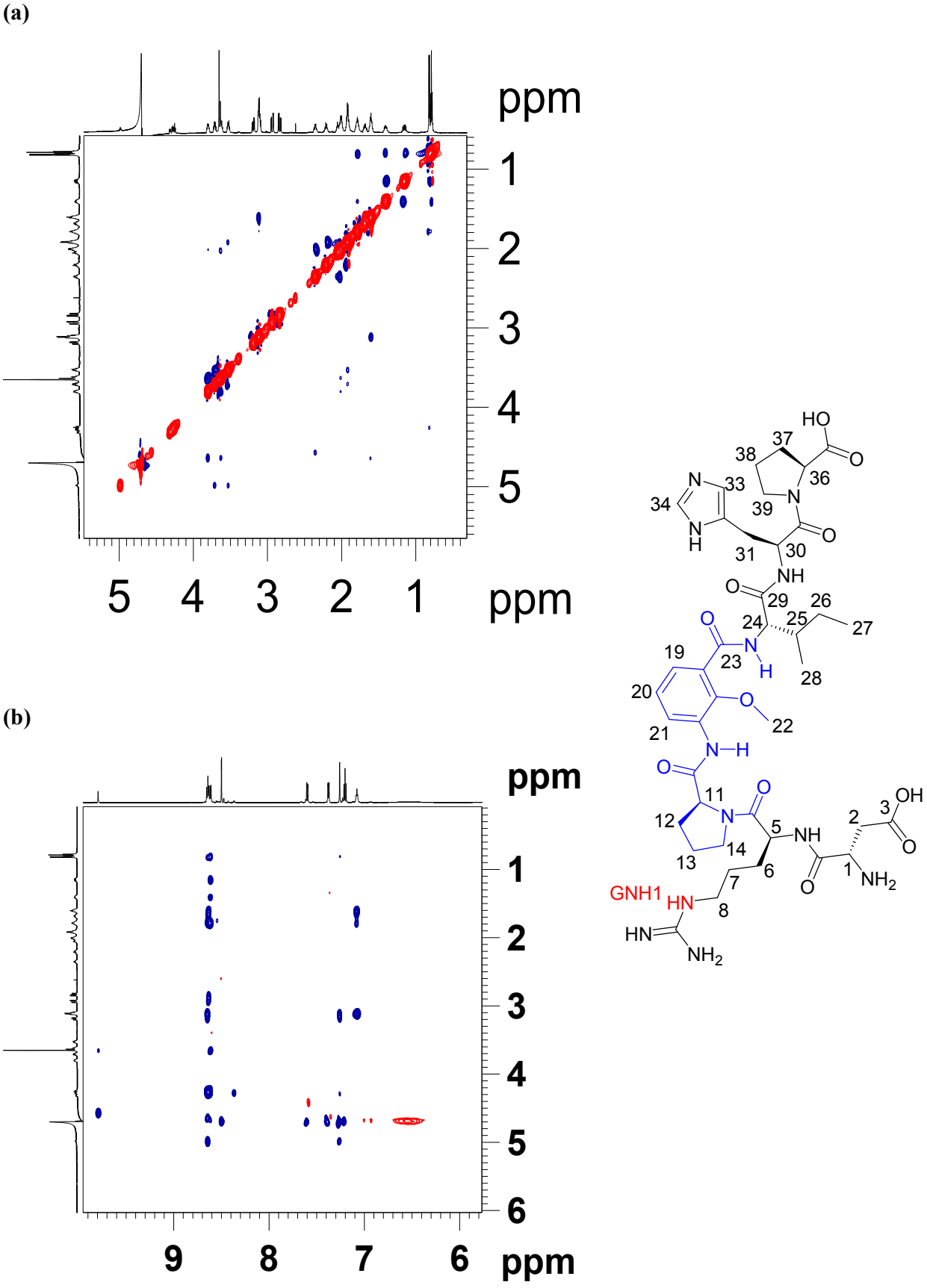
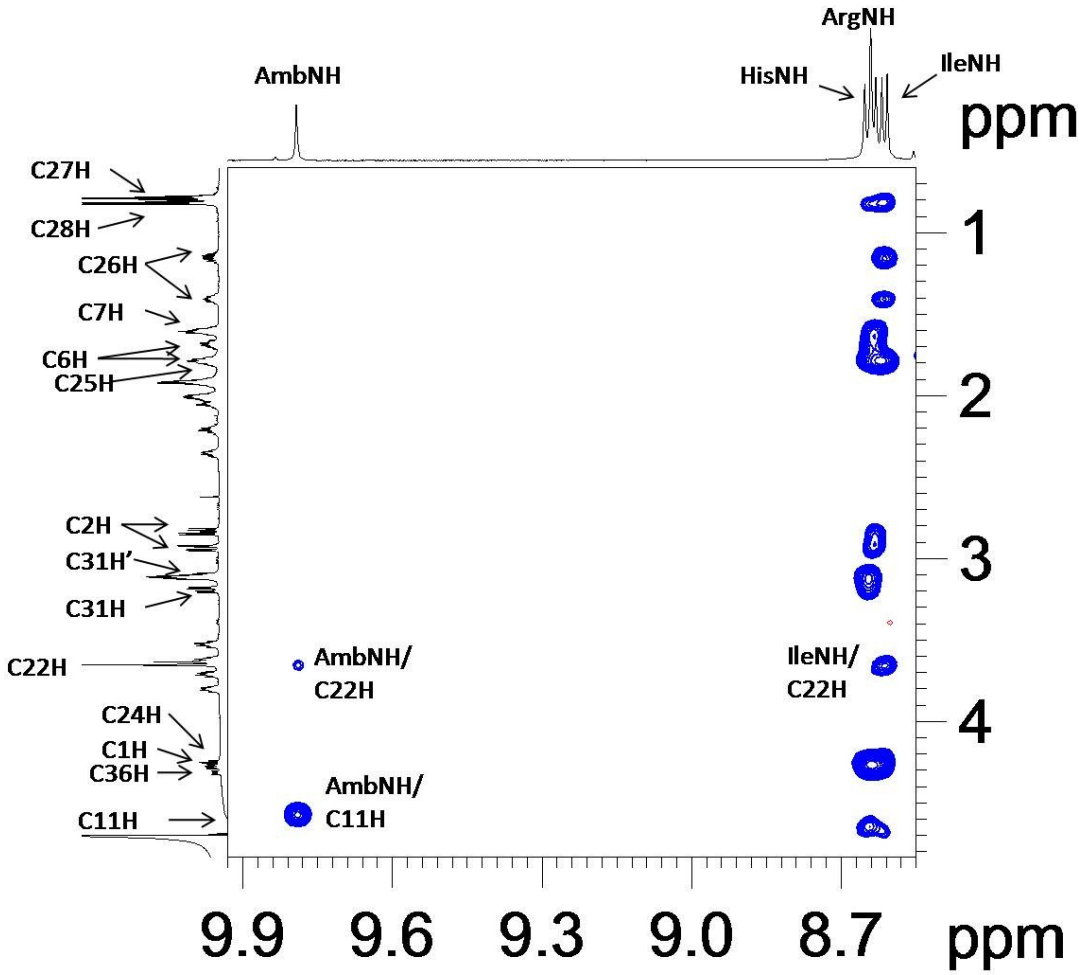


Figure : Partial ROESY spectra of **2** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.



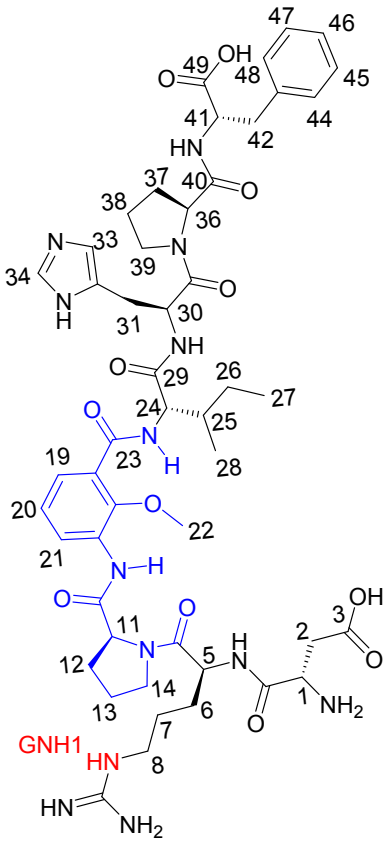


Figure: Partial ROESY spectra of **2** (700 MHz, H_2O:D_2O (9:1)) displaying significant nOe interactions essential for γ-turn conformation.

(a)

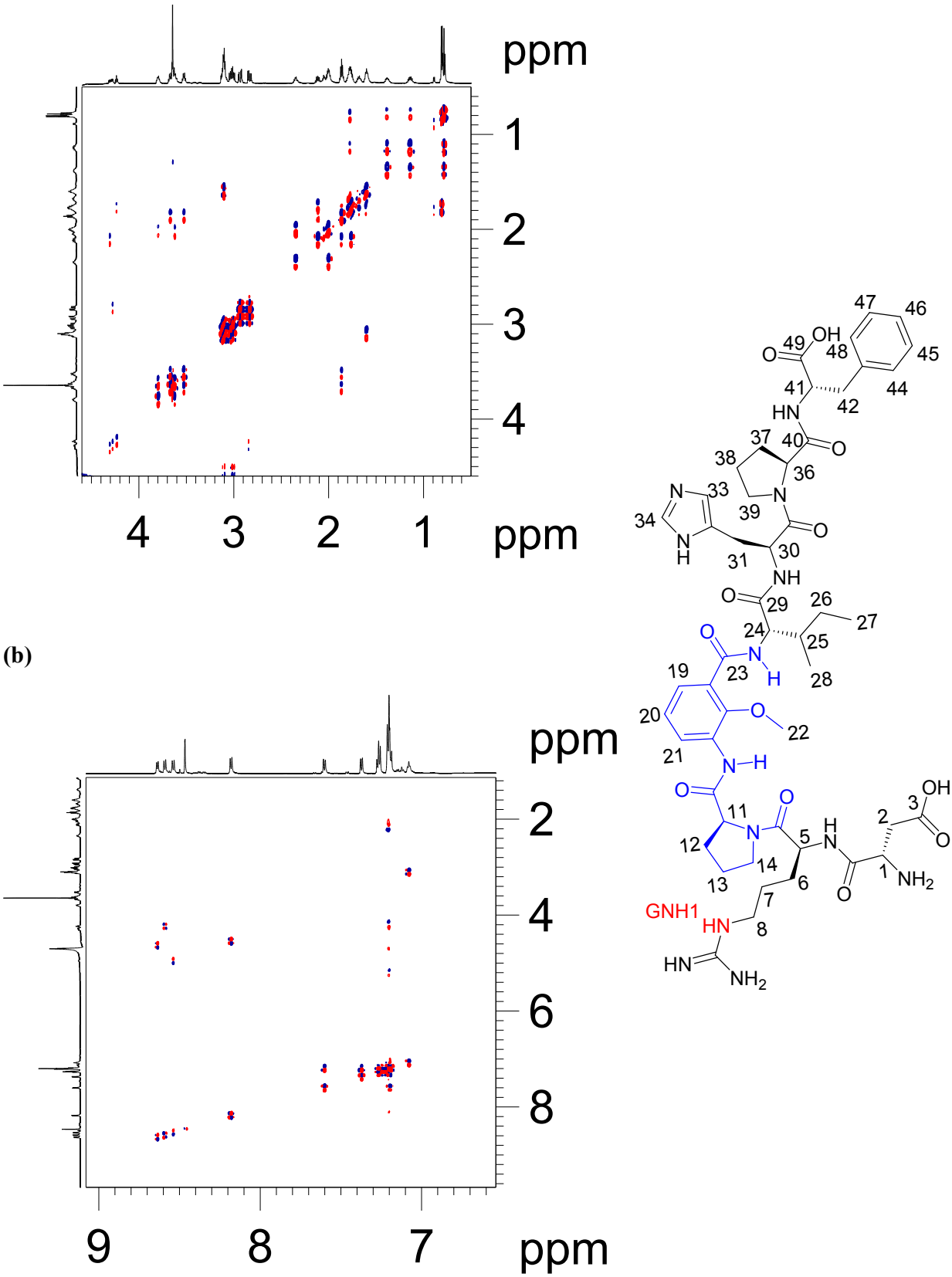
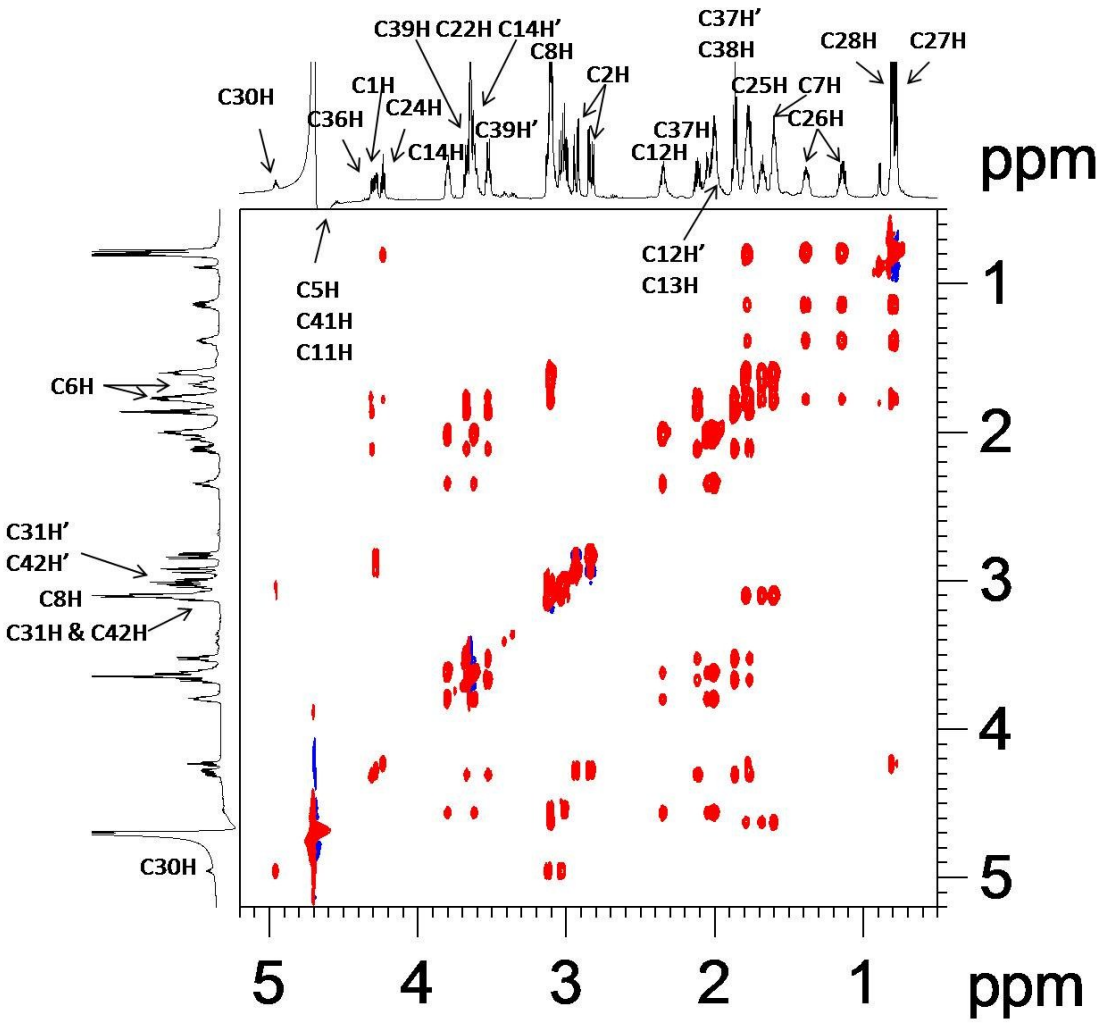


Figure : Partial COSY spectra of **3** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.



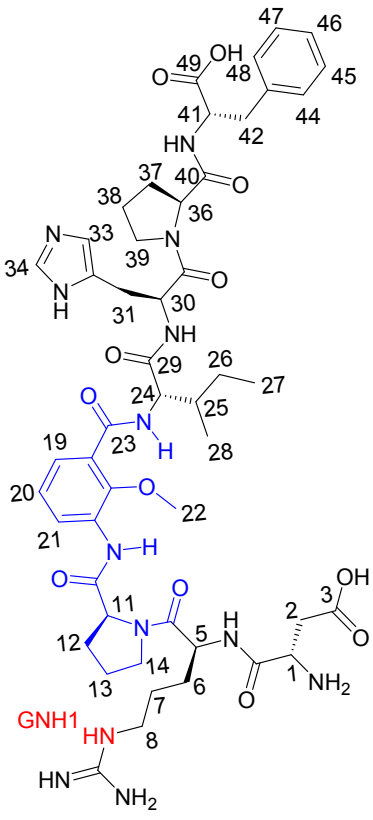
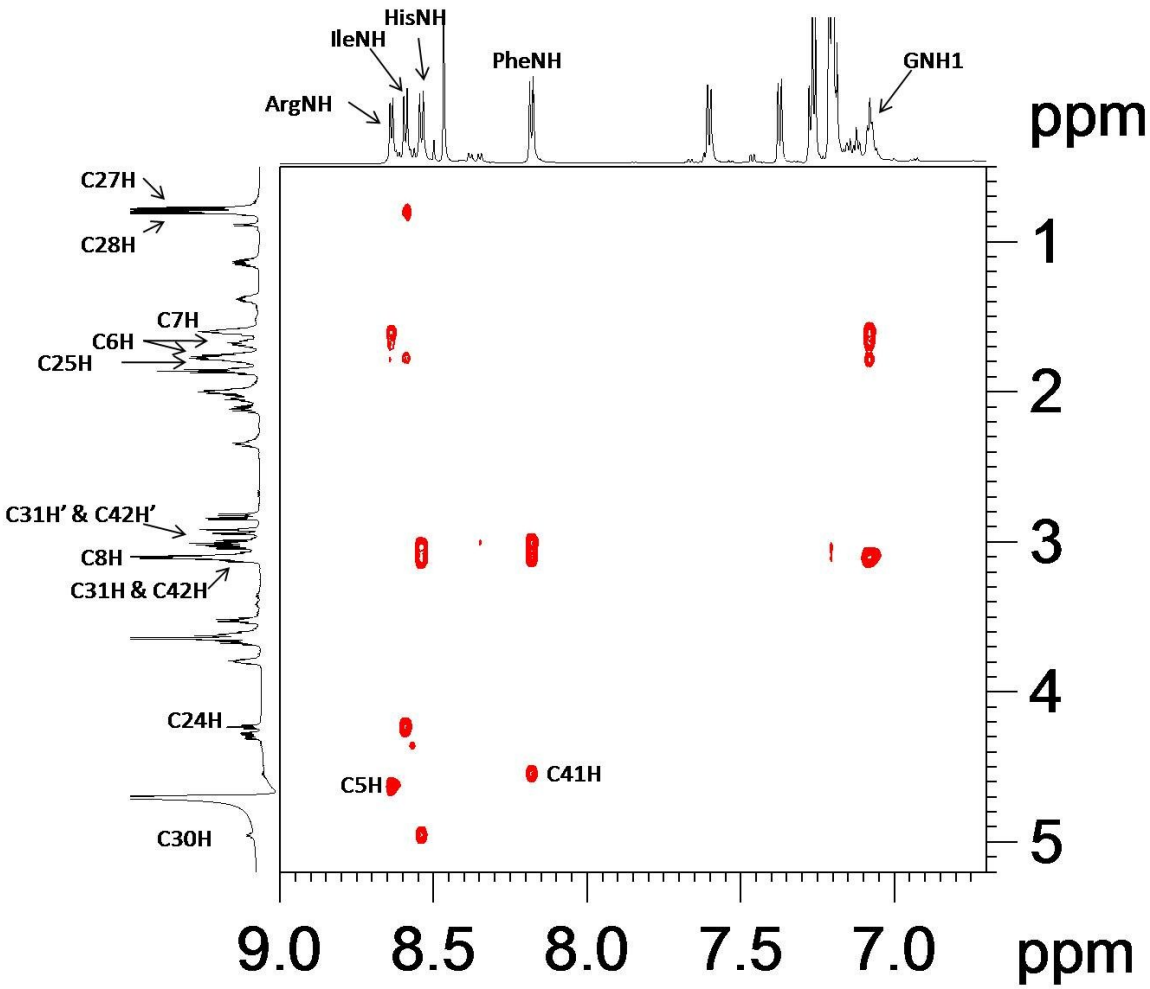


Figure: Partial TOCSY spectra of **3** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with significant assignments.



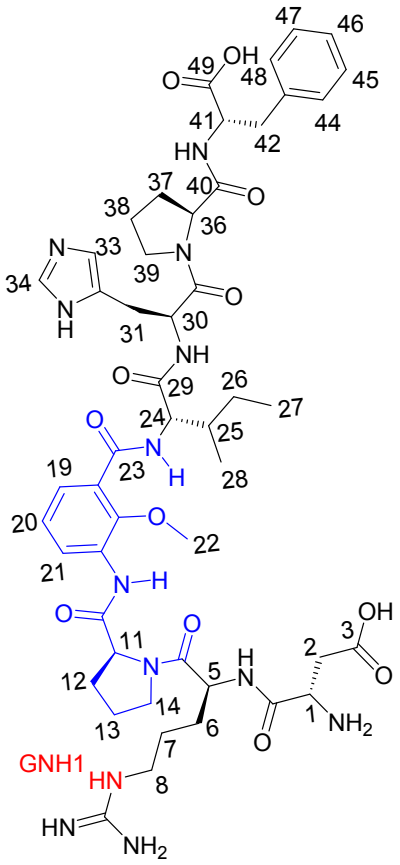
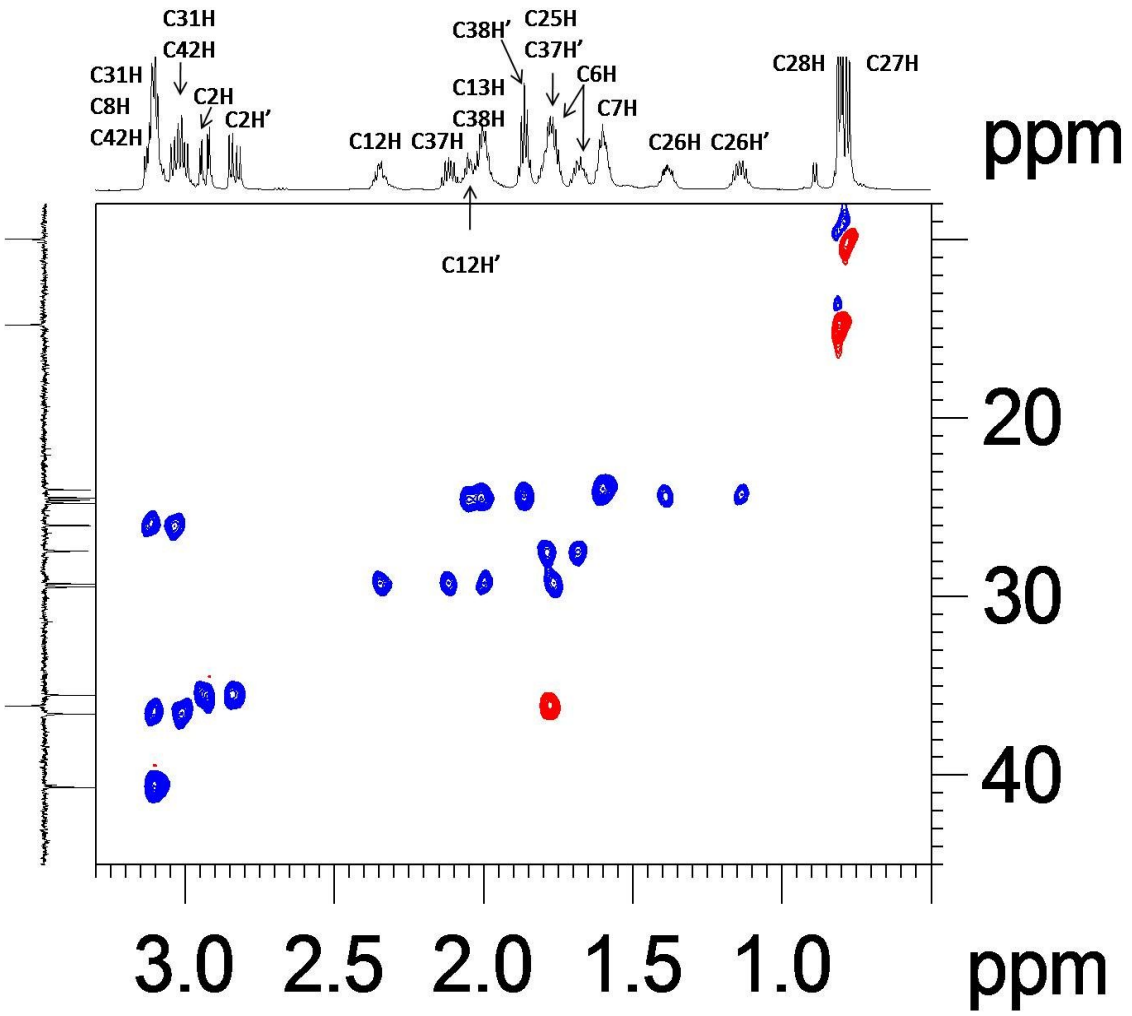


Figure: Partial TOCSY spectra of **3** (700 MHz, H_2O:D_2O (9:1)) displaying aromatic region with significant assignments.



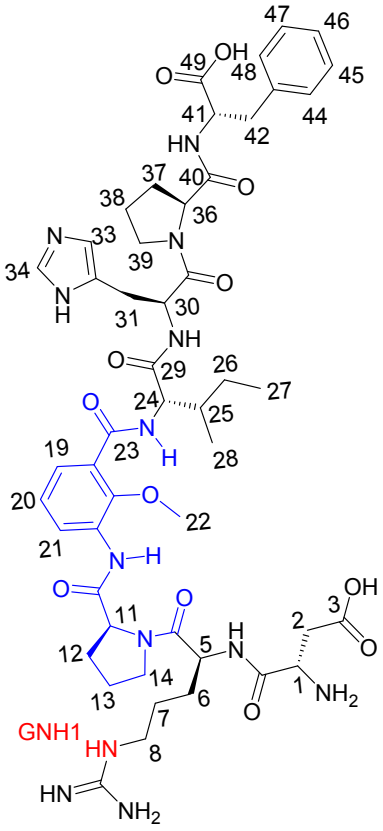
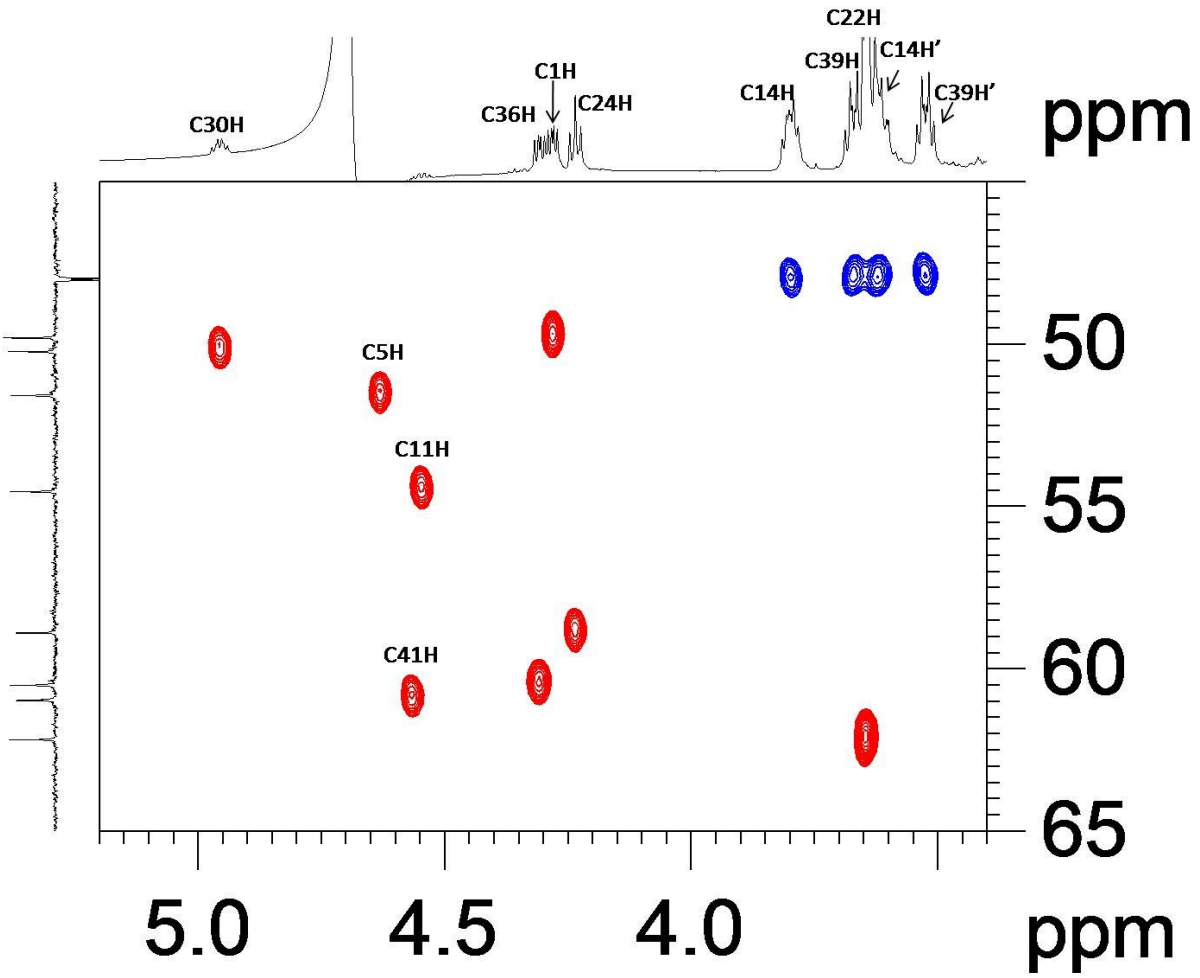
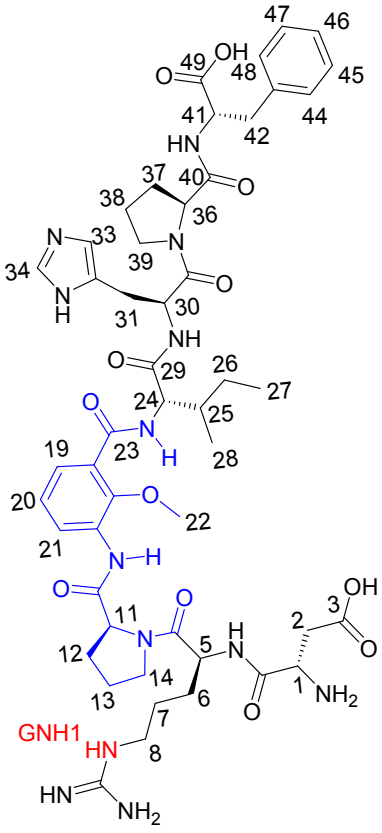


Figure: Partial HSQC spectra of **3** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with significant assignments.





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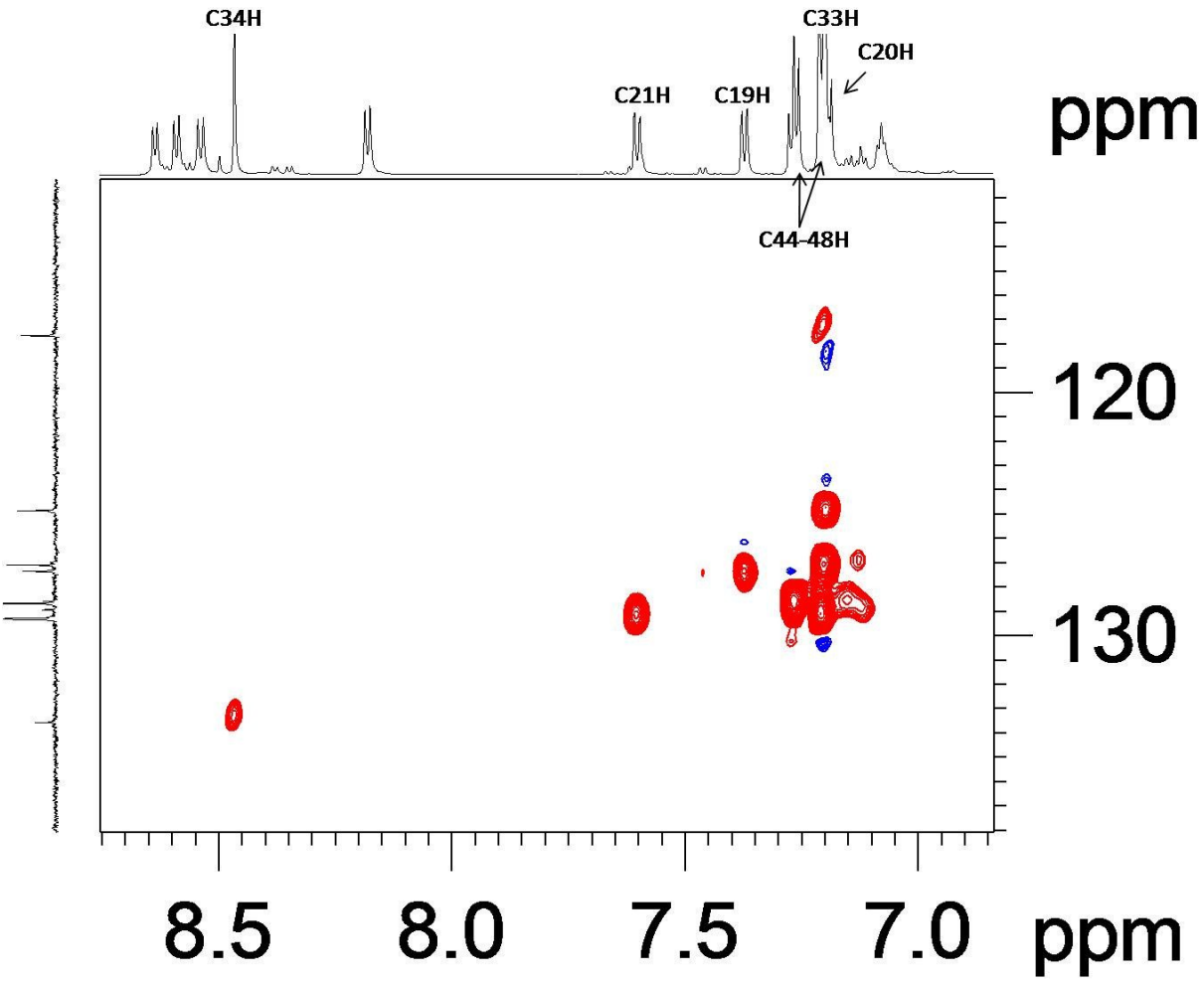

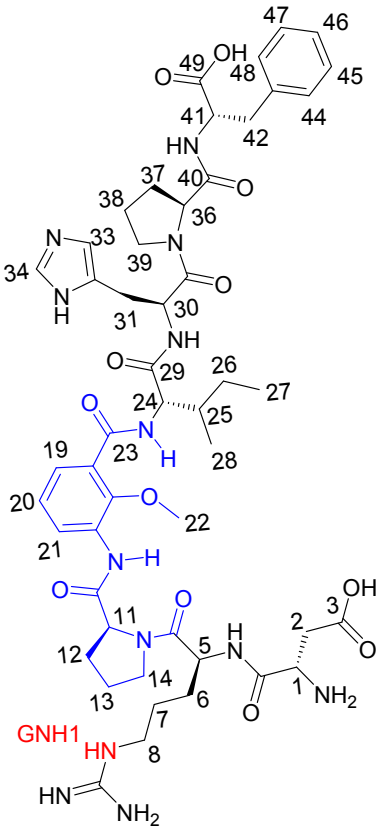

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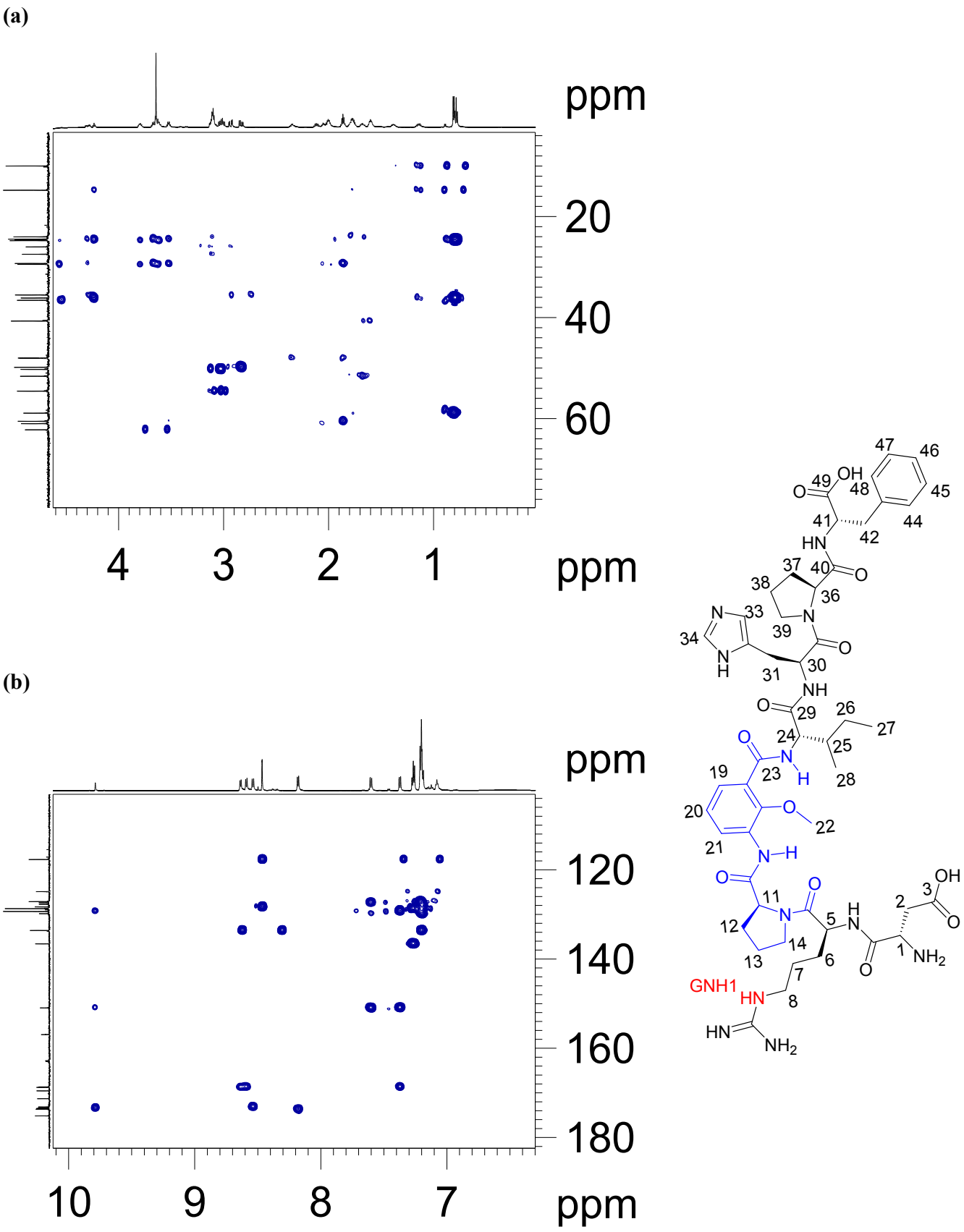


Figure : Partial HMBC spectra of **3** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.

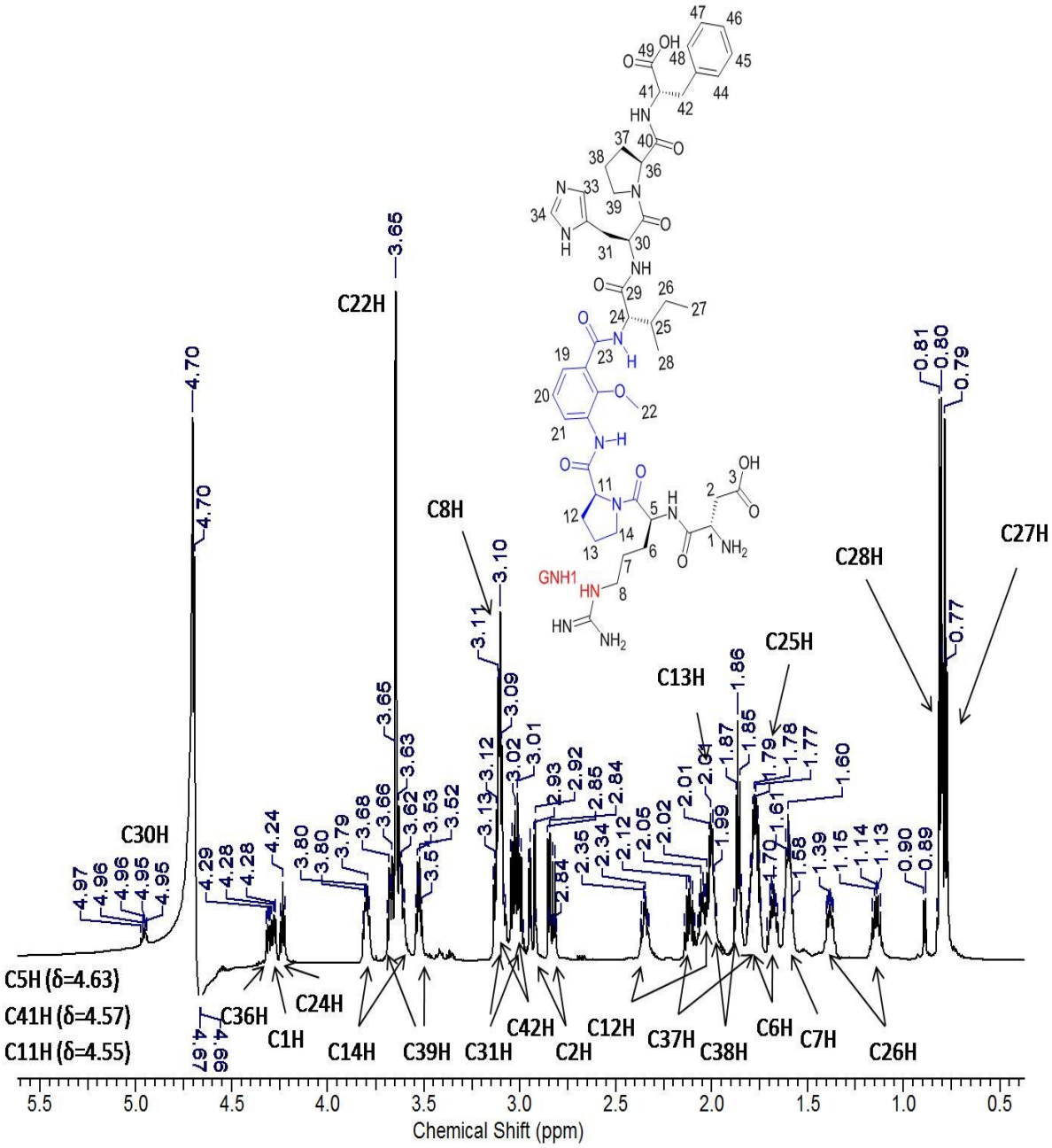


Figure: 1H NMR spectra of **3** (700 MHz, H_2O:D_2O (9:1)) displaying aliphatic region with complete assignments.

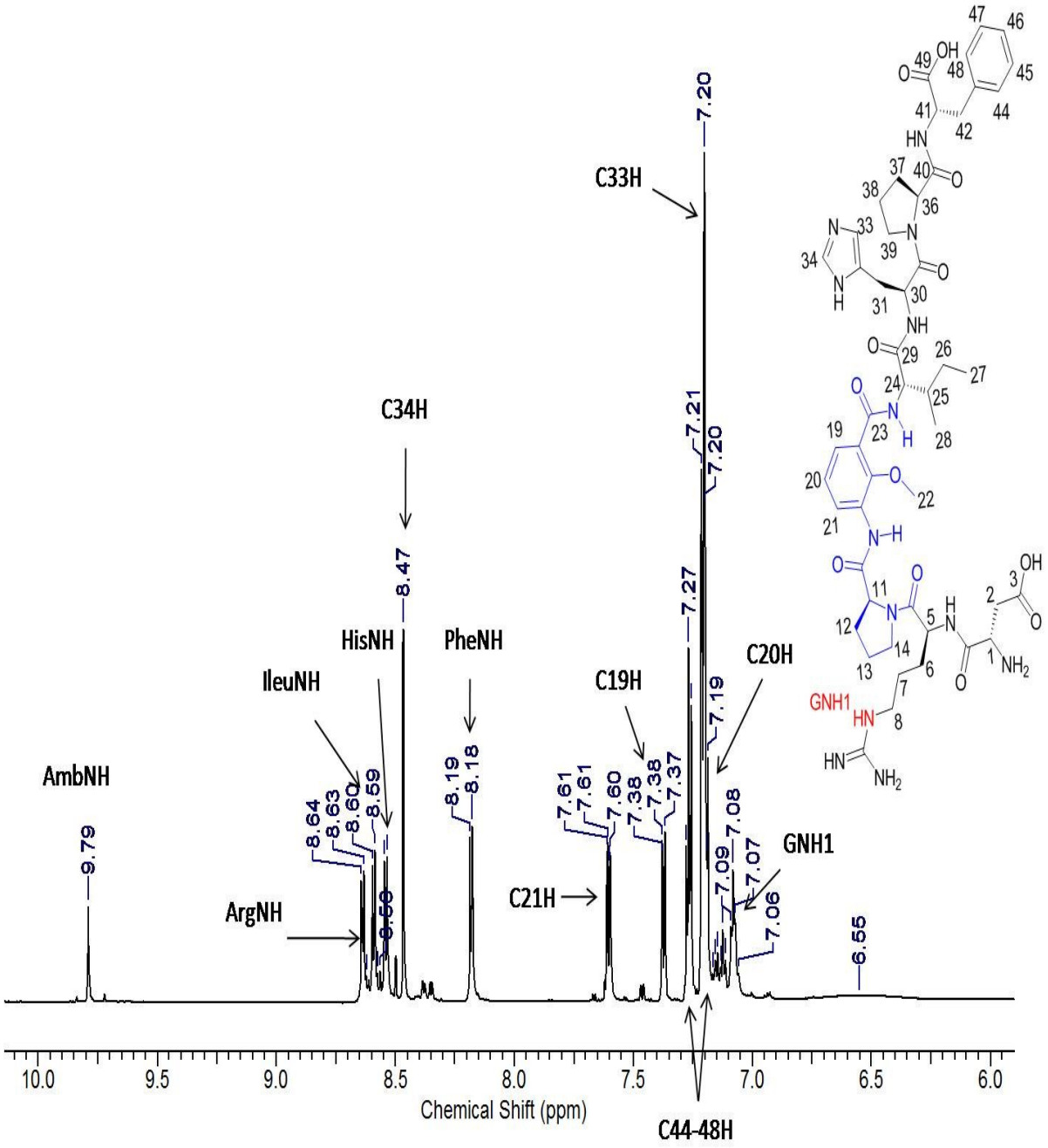
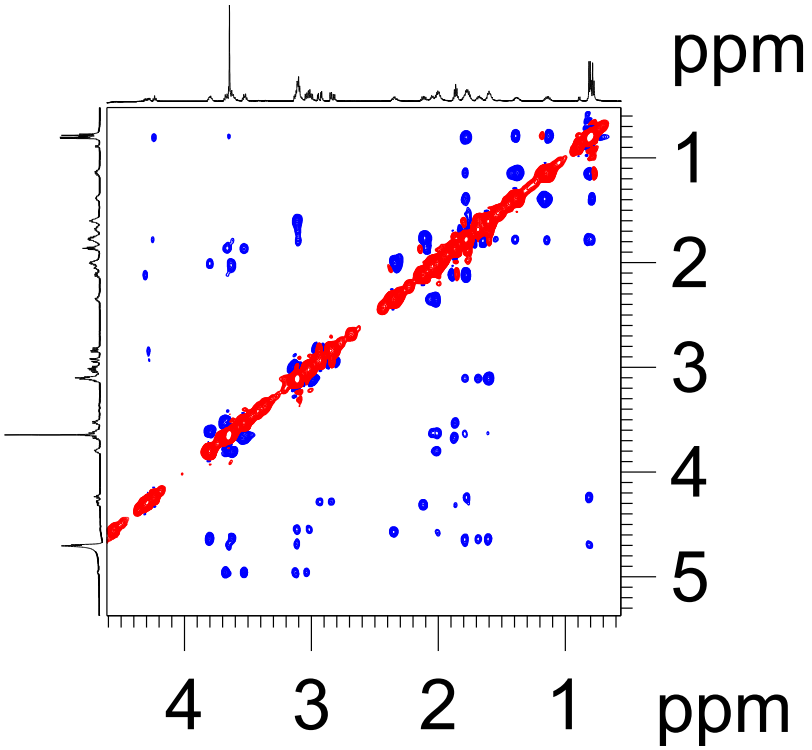
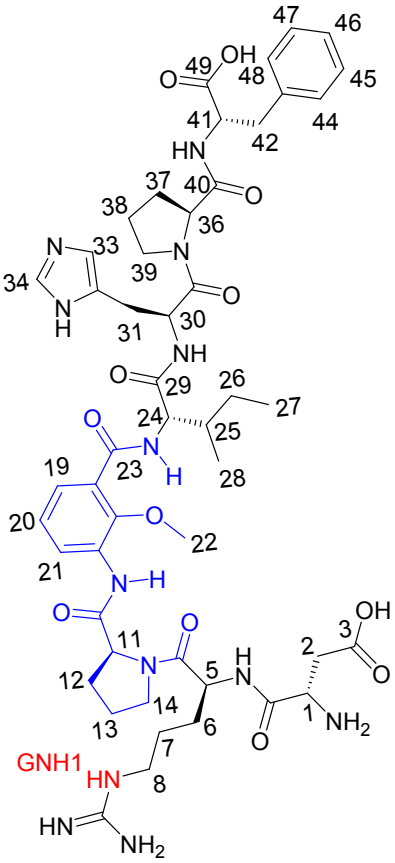


Figure: 1H NMR spectra of **3** (700 MHz, H_2O:D_2O (9:1)) displaying aromatic region with complete assignments.

(a)





(b)

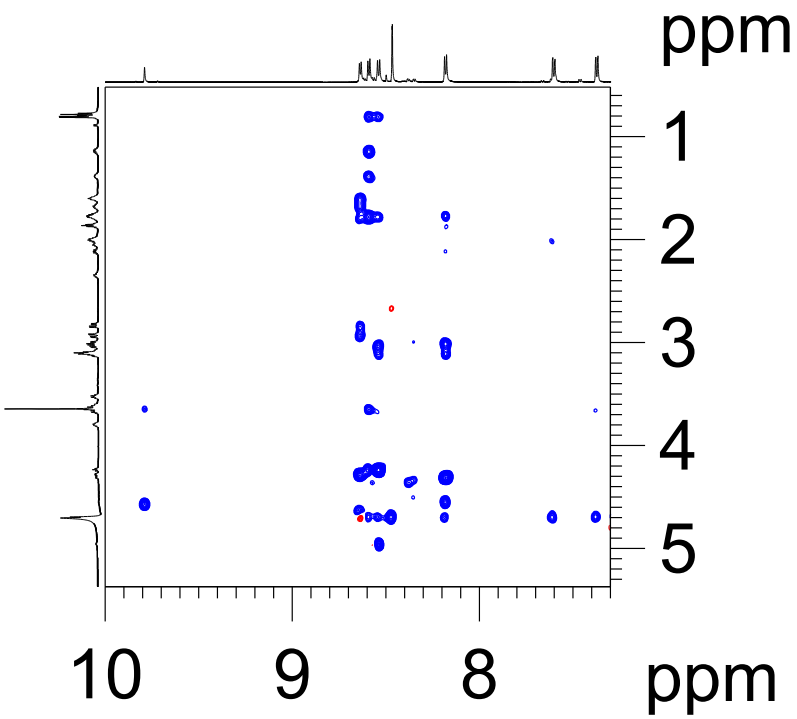
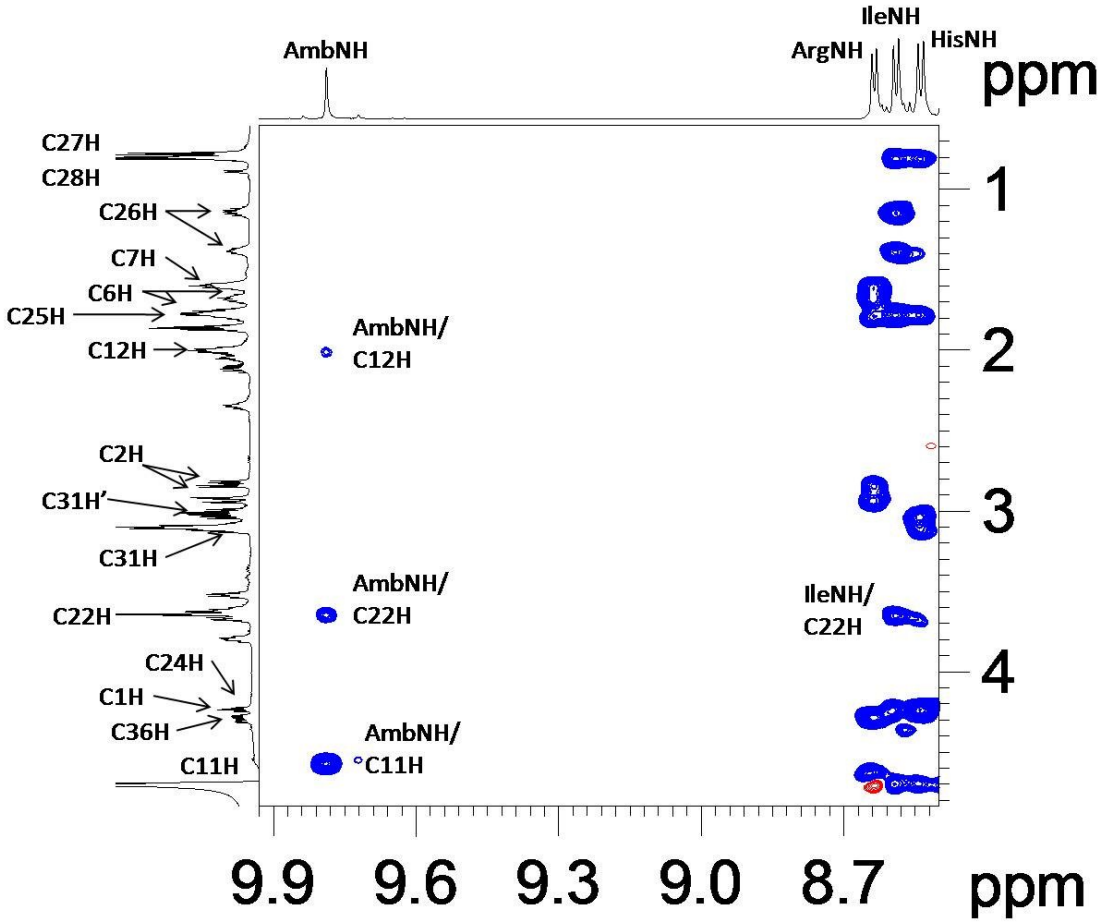
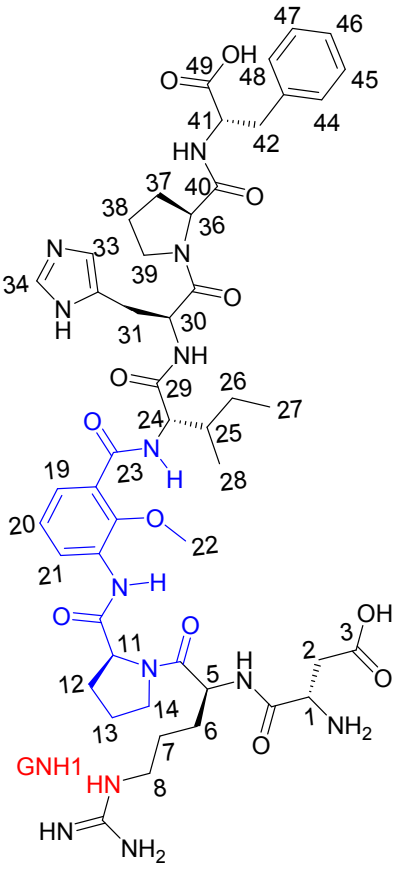


Figure : Partial ROESY spectra of **3** (700 MHz, H_2O:D_2O (9:1)): aliphatic (a) and aromatic (b) regions.





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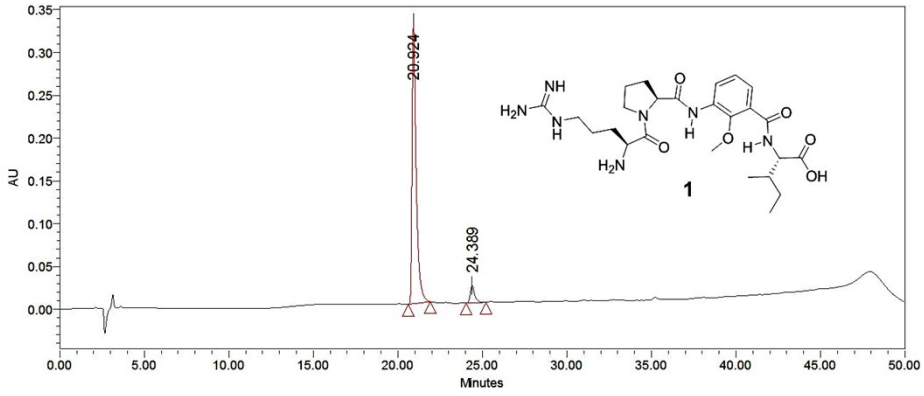

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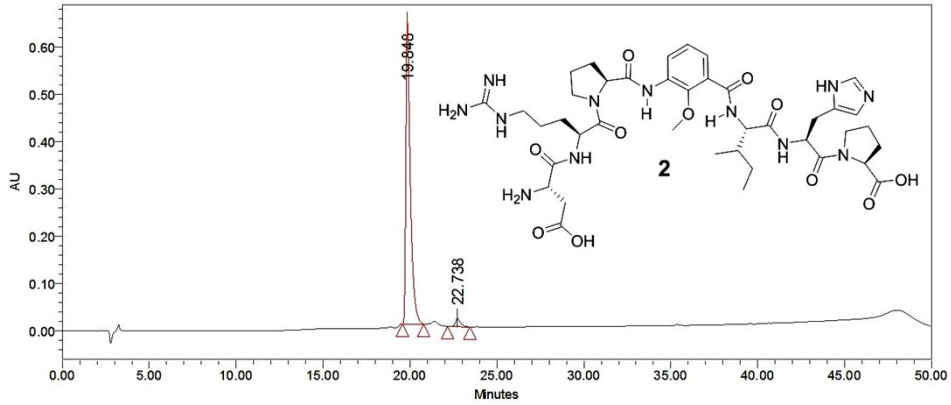

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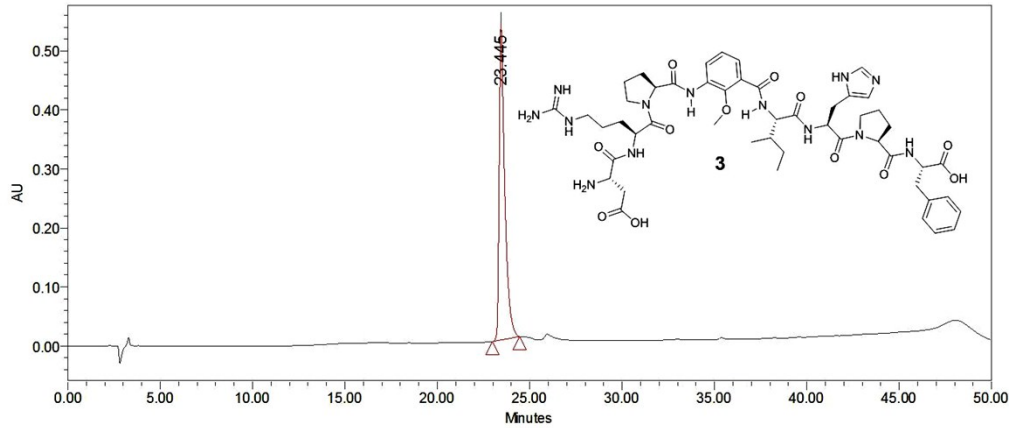
2	22.738	375067	3.20	18406



Sr.No	Retention Time	Area	% Area	Height
1	23.445	11155882	100.00	538684