Triazolo-β-Aza-ε-Amino Acid and Its Aromatic Analogue as Novel Scaffolds for β-turn Peptidomimetics

Subhendu Sekhar Bag,* Subhashis Jana, Afsana Yashmeen and Suranjan De

Bio-organic Chemistry Laboratory, Department of Chemistry, Indian Institute of Technology Guwahati-781039, India. Tel.: +91-258-2324; Fax: +91-258-2349; Email: ssbag75@iitg.ernet.in

1. Experimental Section

1.1. General (Materials and Methods)

All reactions were carried out under nitrogen atmosphere using flame-dried glassware. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60- 120 mesh) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25). ^{1}H NMR spectra were recorded either at 400MHz or at 600 MHz and ^{13}C NMR spectra were recorded either at 100 MHz or at 125 MHz (mentioned accordingly). Coupling constants (*J* value) were reported in hertz (Hz). The chemical shifts were shown in ppm downfield form tetramethylsilane, using residual chloroform (δ = 7.26 in ^{1}H NMR, δ = 77.23 in ^{13}C NMR), DMSO (δ = 2.5 in ^{1}H NMR, δ = 39.5 in ^{13}C NMR), as an internal standard. Mass spectra were recorded with a HR mass spectrometer and data analysed by using built-in software. IR spectra were recorded in KBr on a FT-IR spectrometer.

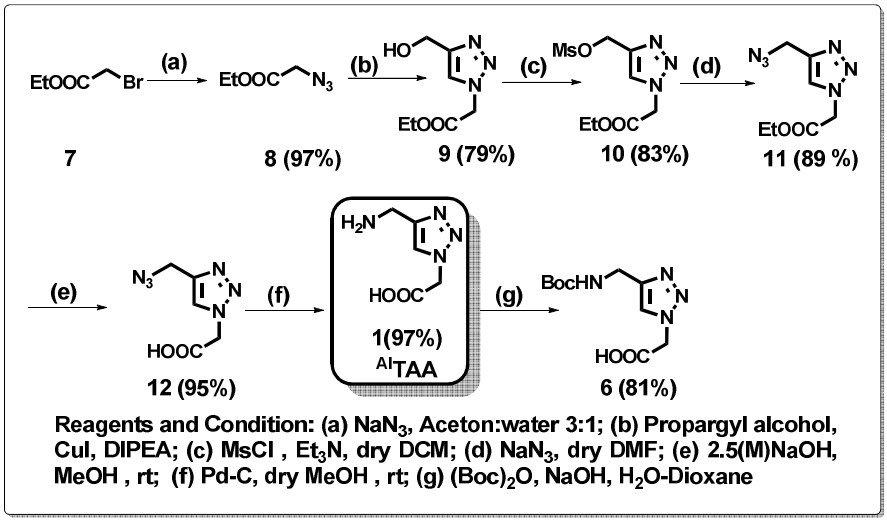
All 2D NMR Experiments were carried out on 600 MHz spectrometer at room temperature using 7 - 10 mM concentration in d_6-DMSO solvent. Spectra were acquired with 2048 x 256 in both dimension (F2 and F1) and other parameter are given below.

TOCSY : Free induction decay (FID) with NS = 16 and DS =32, relaxation delay (D1) 2s, mixing time (D9) 0.08s, acquisition time (AQ) 0.085s, spectral width 12019 Hz.

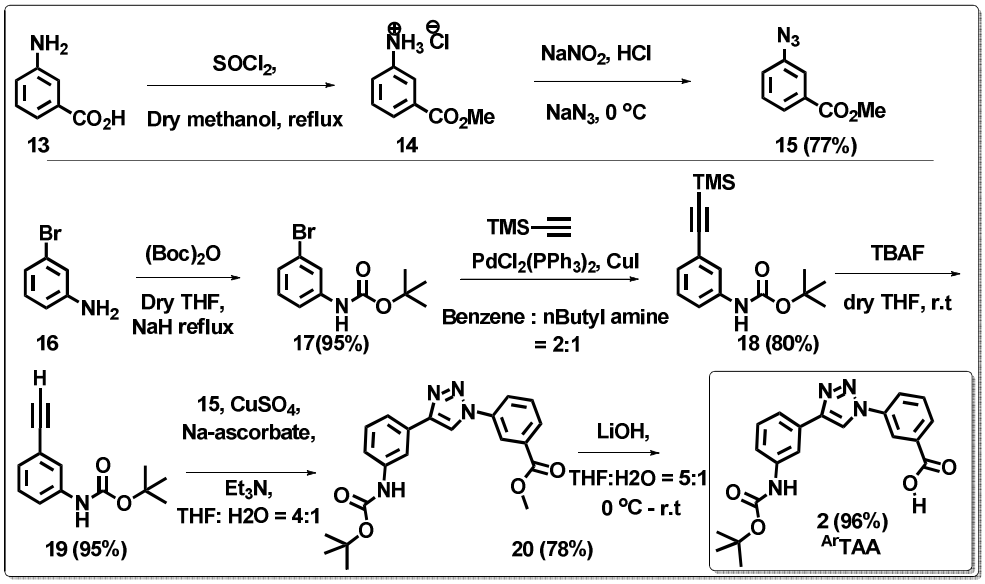
ROESY : Free induction decay (FID) with NS = 16 and DS =16, relaxation delay (D1) 2s, mixing time (P15) 0.02s, acquisition time (AQ) 0.085s, spectral width (SWH) 12019 Hz.

NOESY : Free induction decay (FID) with NS = 8 and DS =16, relaxation delay (D1) 2s, mixing time (D8) 0.6s, acquisition time (AQ) 0.085s, spectral width (SWH) 12019 Hz.

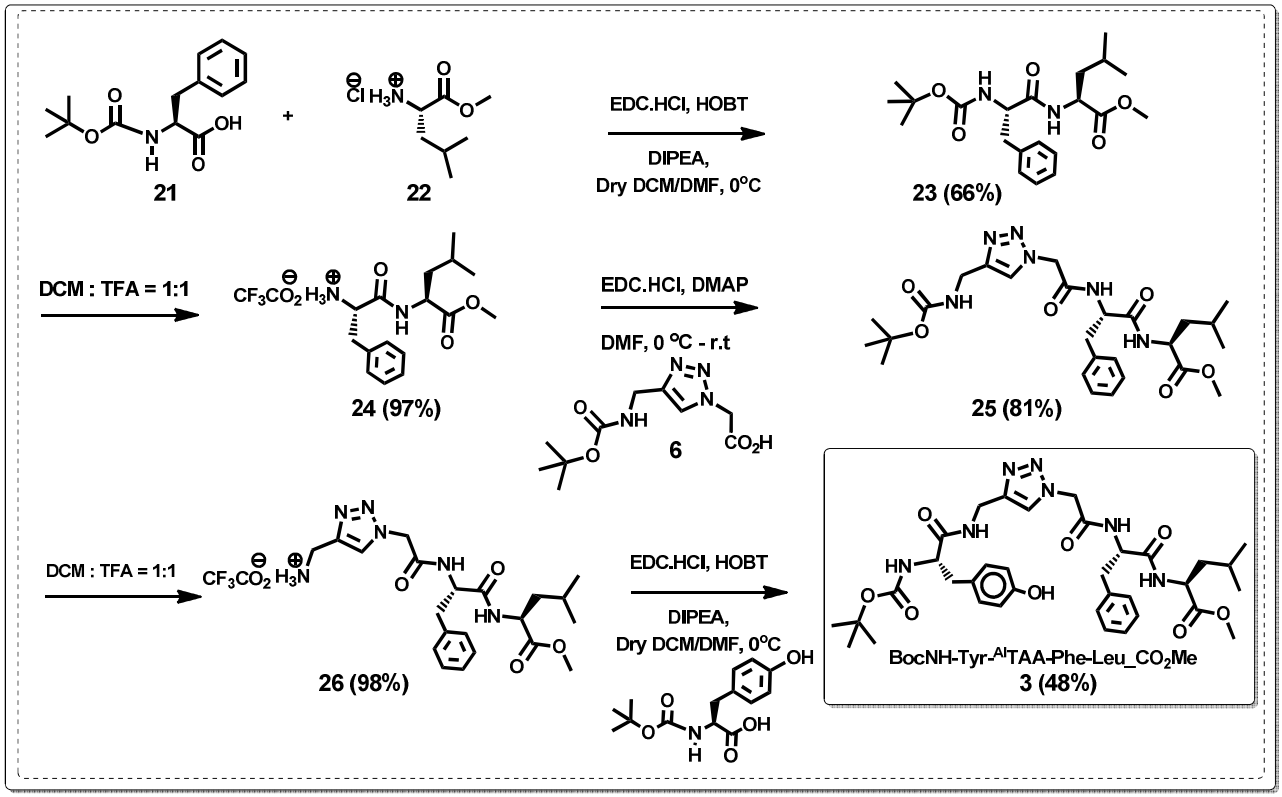
2. Synthetic Schemes



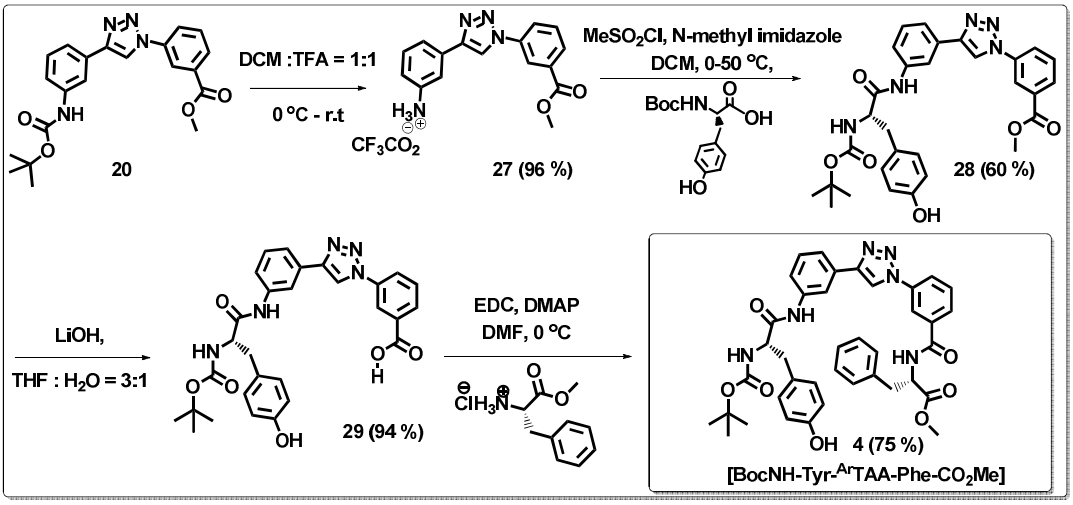
Scheme S1. Synthetic scheme for the triazolo aliphatic amino acid scaffold (**1**, **^{Al}TAA**).



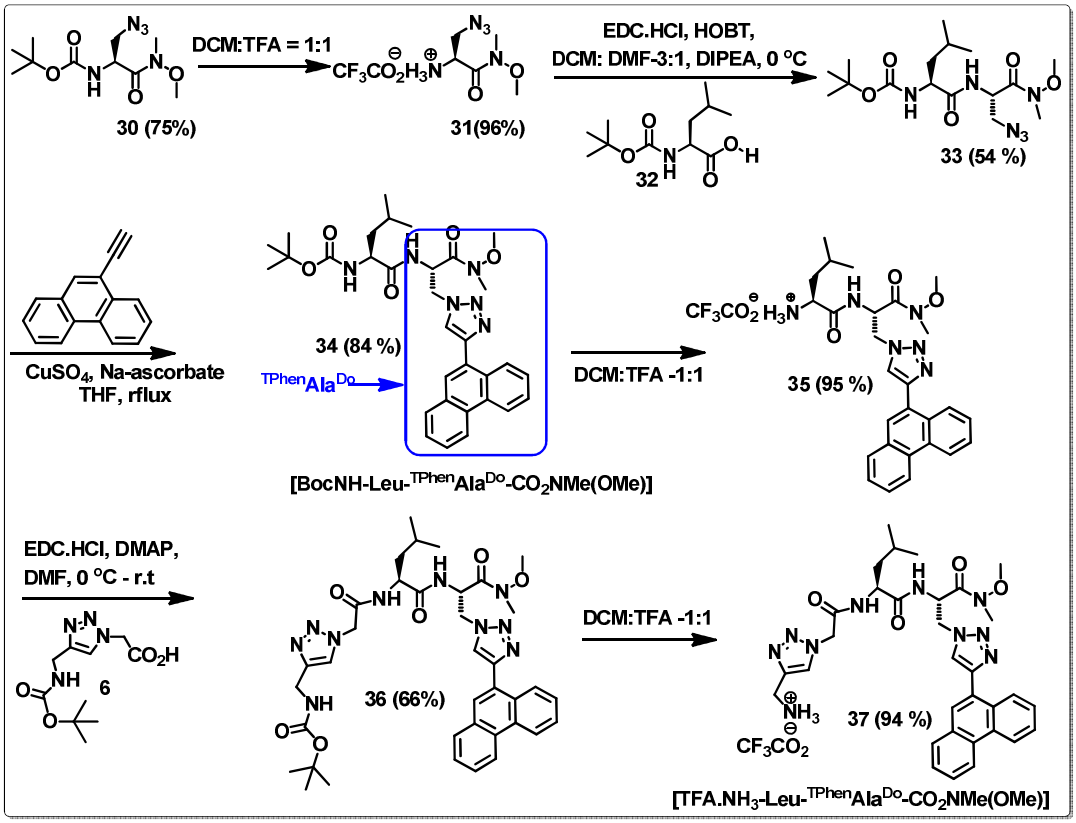
Scheme S2. Synthetic scheme for the triazolo aromatic amino acid scaffold (**2**, ^{Ar}**TAA**).



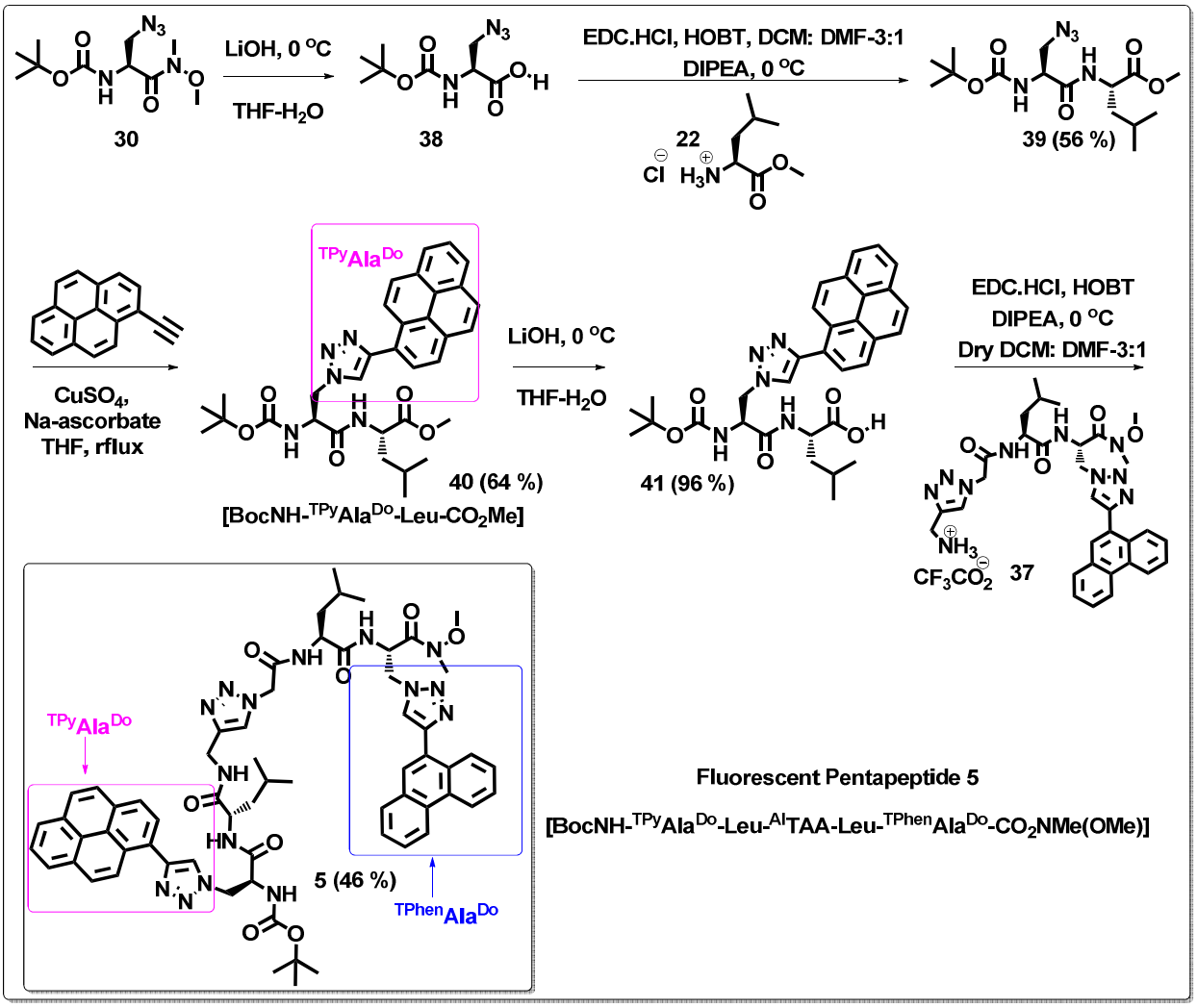
Scheme S3. Synthetic scheme for the Leu-enkephalin analogue **tetrapeptide 3** (**BocNH-Tyr-^{Al}TAA-Phe-Leu-CO$_2$Me**) containing triazolo aliphatic amino acid scaffold **1** in the backbone.



Scheme S4. Synthetic scheme for the model **tripeptide 4** (**BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me**) containing triazolo aromatic amino acid scaffold **2** in the backbone.



Scheme S5. Synthetic scheme for the intermediate fluorescent **Dipeptide 34** containing triazolyl unnatural amino acid (triazolyl phenanthrene (**^{TPhen}Ala^{Do}**) and the corresponding **tripeptide salt 37** containing triazolo aliphatic amino acid scaffold **1** in the backbone [**TFA.NH_3Leu-^{TPhen}Ala^{Do}-CONMe(OMe)**]. **Dipeptide 34 was used as a fluorescent Donor monomer in the FRET Study.**



Scheme S6. Synthetic scheme for the intermediate fluorescent **Dipeptide 40** containing triazolyl unnatural amino acid (triazolyl pyrene (**^{TPy}Ala^{Do}**) and the **Target Fluorescent Pentapeptide 5** containing triazolo aliphatic amino acid scaffold **1** in the backbone [BocNH-**^{TPy}Ala^{Do}**-Leu-**^{Al}TAA**-Leu-**^{TPhen}Ala^{Do}**-CO_2NMe(OMe)]. **Dipeptide 40 was used as a fluorescent Acceptor monomer in the FRET study.**

3. General Synthetic Procedures Adopted for the Synthesis of Target amino acids Scaffolds and Peptides

3.1. ***General procedure for the peptide coupling*:** To a solution N-protected amino acids (1.0 equivalent) in 3:1 mixture of dry DCM and DMF, 1-[3-dimethyl amino propyl]-3-ehtylcarbo-diimide hydrochloride (EDC.HCl) (1.2 equivalent) and HOBT (1.2 equivalent) were added and the reaction mixture was stirred for 1h at 0 ^{o}C under inert N_2 atmosphere. Then the amine salt of Wienreb amide or methyl ester protected corresponding amino acids or dipeptides (1.1 equivalent) were added followed by diisopropylethylamine (DIPEA) (2.4 equivalent). The reaction mixture was stirred for another 10 h at 0 ^{o}C to room temperature. Then solvent was dried by rotary evaporator, after which it was partitioned between EtOAc and aqueous $NaHCO_3$ solution (50 ml each). The organic layer was washed with brine solution. Pure product was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 1:1).

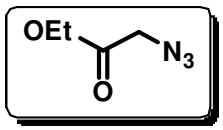
3.2. ***General procedure for [3+2] cyclo-addition reaction*:** The azido derivative of dipeptide was taken in 5:1 dry THF and water and degassed for 5 min with nitrogen gas. After adding alkyne (1.1 equivalent) degassing was continued for the next 5 min. Then, 6 mol % sodium ascorbate and 1 mol% powdered $CuSO_4$ were added. Then 1.2 equivalent Et_3N was added and reaction mixture was degassed and allowed to proceed for 18-20 h at about 65 to 70 ^{o}C. After total consumption of the starting azide, the reaction mixture was evaporated completely and work up was done by EtOAc and NH_4Cl solution. The organic layer was washed with brine, dried over Na_2SO_4.The title trizolyl unnatural dipeptides were separated by column chromatography and characterized.

3.3. ***General procedure for the deprotection of the methyl ester*:** To a solution of the respective methyl ester protected peptide in THF : H_2O = 5 : 1, lithium hydroxide (1.5 equivalent) was added at 0 ^{o}C. The reaction mixture was stirred for about 3-4 hour until starting material was fully consumed. Reaction was monitored by TLC. After completion of the reaction, solvent was dried by rotary evaporator. Then water (4-5 ml) was added to the reaction mixture and cooled to 0 ^{o}C. The dilute acetic acid was added to the reaction mixture to adjust pH- 3 to 4. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. The hydrolysed compound was isolated by column chromatography (Si-gel, $CHCl_3$:MeOH = 10:1). Yield was 90-96%.

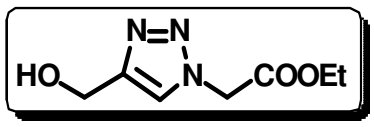
3.4. ***General procedure for the deprotection of the Boc-protecting group:*** The respective NH-Boc protected amino acids or peptides were dissolved in CH_2Cl_2 and cooled to 0 °C. TFA (equal amount as the solvent) was added and the solution was allowed to warm to room temperature. After stirring at room temperature until starting material was consumed (TLC monitoring), the reaction mixture was evaporated *in vacuo.* The residual TFA was evaporated by triturating the mixture with dry toluene thrice, evaporated thrice and dried to afford the product in quantitative yield. But in some cases to get free amine, water (4-5 ml) was added to the reaction mixture after evaporation and cooled to 0 ^{o}C. Then diluted aqueous Et_3N was added to the reaction mixture to adjust pH- 8. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo* to yield the crude product in quantitative yield to use for the next step.

4. Synthesis of Aliphatic Triazolo Amino Acid Scaffold (1,^{Al}TAA)

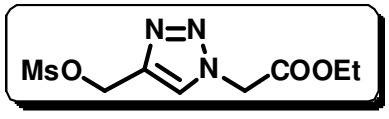
4.1. ***Synthesis of ethyl azido acetate*** **(8):**[1] To a solution of ethyl bromoacetate **7** (1510 mg, 9.04 mmol) in water/acetone (1:3, 0.25 M) was added NaN_3 (881.6 mg, 13.56 mmol) and the mixture was heated at 60 ^oC for 4 hours. Then the reaction mixture was diluted with DCM and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in *vacuo*. The crude material was obtained in quantitative yield. The product **8** is oily liquid. Yield 97%. IR (KBr) 2955, 2103, 1741, 1441, 1372, 1175, 1064 cm^{-1}. The azide was used for the next step without further purification and characterisation.



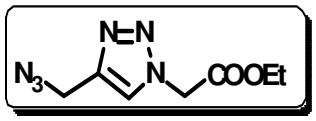
4.2. ***Synthesis of ethyl 2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl) acetate*** **(9):** The prepared ethyl azido acetate **8** (500 mg, 3.876 mmol) was taken in dry THF and water (3:1) and degassed for 5 min with N_2. Then propargyl alcohol (0.246 ml, 5.8 mmol) was added and both the stirring and degassing were continued for the next 5 min. Consequently 0.06 equivalent of sodium ascorbate and 0.01 equivalent of powder $CuSO_4$ were added to the reaction mixture. Then the reaction mixture was degassed and allowed to proceed for next 12 hours at room temperature. After total consumption of the starting azide, the reaction mixture was evaporated, diluted with EtOAc. The organic layer was washed with NH_4Cl solution, brine, and dried over Na_2SO_4. The title compound **9** was isolated by column chromatography (Si-gel, PE:EA = 1:1) in pure form as white solid (560 mg, Yield 79%). %). ^1H NMR ($CDCl_3$; 600 MHz) δ 1.26 (3H, t, J = 3.0 Hz); 4.21 (2H, q, J = 5.4 Hz); 4.74 (2H, d, J = 7.8 Hz); 5.10 (2H, s); 7.63 (1H, s). ^{13}C NMR ($CDCl_3$; 125 MHz) δ 13.9, 50.7, 55.7, 62.3, 123.8, 148.2, 166.6. HRMS calcd. for $C_7H_{12}N_3O_3$ $[M + H]^+$ 186.0808, found 186.0887.



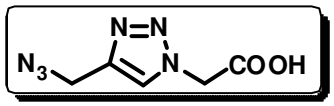
4.3. ***Synthesis of ethyl 2-(4-(((methylsulfonyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)acetate(10)*****:** Compound **9** (100 mg, 0.54 mmol) was taken in a dry CH_2Cl_2. Mesyl chloride (0.06 ml, 0.81 mmol) and triethyl amine (0.113 ml, 0.81 mmol) were added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at 0 ^oC till the starting material was consumed. After that the reaction mixture was diluted with DCM and washed with water and dried over Na_2SO_4 and then evaporated in *vacuo*. The pure compound **10** was then isolated by column chromatography (si-gel, PE:EA = 2:1) as a colourless oil (129 mg, Yield 83%) and utilised immediately for the next step without further characterisation.



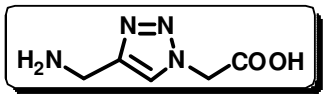
4.4. ***Synthesis of ethyl 2-(4-(azidomethyl)-1H-1,2,3-triazol-1-yl)acetate*** **(11):** To a solution of the mesyl derivative **10** (129 mg, 0.523mmol) in dry DMF (5 ml), NaN_3 (40.7 mg, 0.627 mmol) was added and stirrer for 18 h at 50 ^oC. The reaction mixture was partitioned between EtOAc and water (20 ml each). The organic layer was washed with brine solution, dried with Na_2SO_4, filtered and then evaporated. The title compound **11** was isolated by column chromatography (si-gel, PE:EA = 5:1) in pure form as white solid (98 mg, Yield 89%). mp 43-44 ^oC; IR (KBr) 3447, 3138, 3006, 2108, 1739, 1634, 1464, 1407, 1259, 1021, 771 cm^{-1}. ^1H NMR ($CDCl_3$; 600 MHz) δ 1.29 (3H, t, J = 6.6 Hz); 4.27 (2H, q, J = 7.2 Hz); 4.51 (2H, s); 5.17 (2H, s); 7.17 (1H, s). ^{13}C NMR ($CDCl_3$; 125 MHz) δ 14.0, 45.5, 50.9, 62.5, 124.0, 142.9, 166.2. HRMS calcd. for $C_7H_{10}N_6O_2$ $[M + H]^+$ 211.0899, found 211.0950.



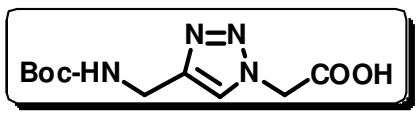
4.5. ***Synthesis of 2-(4-(azidomethyl)-1H-1,2,3-triazol-1-yl)acetic acid*** **(12):** To a solution of compound **11** in methanol, 1.5 equivalent of lithium hydroxide was added and stirred for about 2-3 hours at room temperature until starting material was vanished. After that in the reaction mixture, dilute HCl was added until the pH became 4. Then it was partitioned between EtOAc and water (20 ml each). The organic layer was washed with brine solution, dried with Na_2SO_4, filtered and then evaporated. The prepared title compound **12** was used for next step without further purification (Yield 95%). IR (KBr) 3153, 2101, 1725, 1557, 1447, 1414, 1362, 1333, 1231, 1068, 822 cm^{-1}. ^1H NMR (CD_3OD; 400 MHz) δ 4.49 (2H, s); 5.30 (2H, s); 8.06 (1H, s). ^{13}C NMR (CD_3OD; 100 MHz) δ 46.1, 51.8, 126.6, 144.0, 169.9. HRMS calcd. for $C_5H_5N_6O_2$ $[M - H]^-$ 181.1321, found 181.1583.



4.6. ***Synthesis of 2-(4-(aminomethyl)-1H-1,2,3-triazol-1-yl)acetic acid*** **(1):** To a solution of the compound **12** in methanol (200 mg, 1.1 mmol) Pd/C is added and to it hydrogen gas balloon was set and stir the reaction mixture for 3-4 hours. The solvent methanol was then evaporated and the crude mass was dissolved in water and then filtered, filtrate is evaporated to afford the title compound **1** with quantitative yield. mp 285-286 ^oC; IR (KBr) 3418, 3153, 1614, 1393, 1308, 1233 cm^{-1}. ^1H NMR (D_2O; 600 MHz) δ 4.34 (2H, s); 5.06 (2H, s); 8.07 (1H, s). ^{13}C NMR (D_2O; 125 MHz) δ 34.0, 53.2, 126.3, 139.6, 173.1. HRMS calcd. for $C_5H_9N_4O_2$ $[M + H]^+$ 157.0727, found 157.0713.



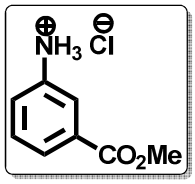
4.7. ***Synthesis of N-t-butyloxycarbonyl-2-(4-(azidomethyl)-1H-1,2,3-triazol-1-yl)acetic acid*** **(6):** In a solution of 2-(4-(azidomethyl)-1H-1,2,3-triazol-1-yl)acetic acid **1** (200 mg, 1.28 mmol) in 1:1 mixture of 1,4 dioxane and water (3 ml each) was added NaOH (102.6 mg, 2.56 mmol) followed by di-t-butyl dicarbonate (0.44 ml, 1.92 mmol) maintaining the pH between 7.5-8.5. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture was washed with ethyl acetate (2 x 10 ml) and the aqueous phase was treated with dil. HCl to bring pH 4 in cold condition. Immediately the solution was extracted with ethyl acetate and the organic layer was washed with water, brine, dried and evaporated under *vacuo* to furnish the Boc-



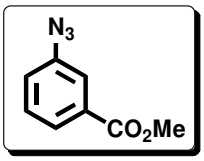
protected 2-(4-(azidomethyl)-1H-1,2,3-triazol-1-yl) acetic acid **6** as white solid in pure form (265.4 mg, Yield 81%). mp 105-106 ^{o}C; ^{1}H NMR (CD_3OD; 400 MHz) δ 1.43 (9H, s); 4.31 (2H, s); 5.25 (2H, s); 7.87 (1H, s). ^{13}C NMR (CD_3OD; 100 MHz) δ 28.9, 36.8, 51.8, 80.6, 125.6, 147.4, 158.4, 170.0. HRMS calcd. for $C_{10}H_{15}N_4O_4$ [M - H]$^-$ 255.254, found 255.2255.

5. Synthesis of Aromatic Triazolo Amino Acid Scaffold (2,^{Ar}TAA)

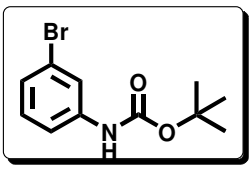
5.1. ***Synthesis of methyl 3-azidobenzoate*** **(14):** To a solution of *m*-amino benzoic acid (**13**) (1200 mg) in methanol 1.5 equivalent of $SOCl_2$ was added at 0 ^{o}C and the reaction mixture was refluxed for 3-4 hours under N_2 atmosphere. After completion of the reaction, solvent was dried in rotary evaporator and washed the reaction mixture with toluene 3 times. The title compound **14** thus isolated in quantitative yield was utilized for the next step without further purification or characterization.



5.2. ***Synthesis of methyl 3-azidobenzoate*** **(15):** Starting material **14** (1500 mg) was dissolved in water and acidify with dil. HCl under cool condition (0 ^{o}C). Next, 2.5 equivalent of $NaNO_2$ in water was added drop wise to this solution. After ten minute the reaction mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine solution and dried over Na_2SO_4. The title compound **15** was isolated by column chromatography (si-gel, PE) in pure form as colourless oil (1093 mg, Yield 77%). The formation of azide was confirmed by IR spectra [IR (KBr) 2953, 2844, **2115**, 1727, 1585, 1484, 1443, 1300, 1140, 752 cm^{-1}] and was used for the next step without further purification and characterisation.

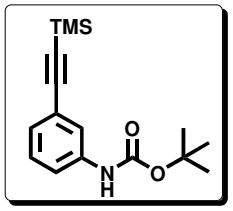


5.3. ***Synthesis of tert-butyl (3-bromophenyl) carbamate*** **(17):** To a suspension of washed (by hexane) NaH (1.1 equivalent) in THF was added 3-bromo aniline **16** (0.62 ml, 5.8 mmol). The mixture was heated to reflux for 1h and then cooled to room temperature. Boc-anhydride (1.5 ml, 1.2 equivalent) was added to this reaction mixture and stirred for 30 minute. A second portion of sodium hydride was next added and the reaction mixture was brought back to reflux overnight. The reaction was cooled to room temperature and carefully quenched by water. The reaction mixture was extracted with EtOAc thrice. The combined organic layers were dried over Na_2SO_4. The pure product **17** was isolated by column chromatography (Si-gel, PE : EtOAc = 10:1) (1490 mg, 5.4 mmol, Yield 95%) and was utilized for the next step without further purification or characterization.

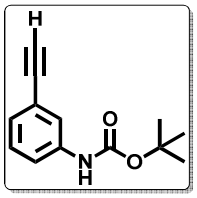


5.4. ***Synthesis of tert-butyl (3-((trimethylsilyl)ethynyl)phenyl)carbamate*** **(18):** To a solution of **17** (300 mg, 1.1 mmol) in a mixture of dry benzene : n-butyl amine = 2:1 was added $PdCl_2(PPh_3)_2$ (38.6 mg, 0.05 mmol) and was degassed by bubbling with N_2 gas for 10 minutes. After that trimethylsilyl acetylene (230 µl, 1.5 equivalent) and CuI (4.2 mg, 0.02 equivalent) were added and heated to 80 ^{o}C for 12 hour. Then the reaction mixture was

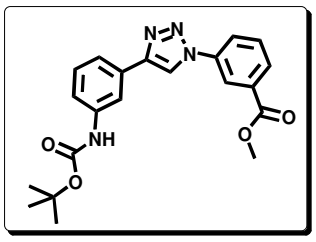
dried by rotary evaporator, after which it was partitioned between EtOAc and aqueous NH_4Cl solution (20 ml each). The organic layer was washed with brine. Pure product **18** (256 mg, 0.88 mmol) was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 10:1). Yield 80%. ^{1}H NMR ($CDCl_3$; 400 MHz) δ 0.15 (9H, s); 1.42 (9H, s); 6.52 (1H, bs); 7.04 (1H, d, J = 6.8 Hz); 7.1 (1H, t, J = 8.2 Hz); 7.17 (1H, d, J = 8.4 Hz); 7.48 (1H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 0.1, 28.4, 80.8, 94.3, 104.9, 121.8, 123.9, 126.1, 126.7, 128.9, 138.4, 152.7.



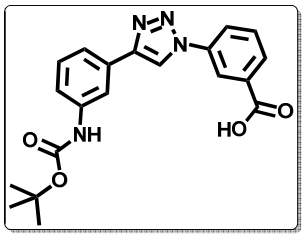
5.5. ***Synthesis of tert-butyl (3-ethynylphenyl)carbamate*** **(19):** Compound **18,** 800 mg (2.76 mmol) was dissolved in 8 ml dry THF, 1080 mg (1.5 equv) tetrabutyl ammonium fluoride was added to the solution at room temperature and stirrer overnight. Then solvent was dried by rotary evaporator, then it was partitioned between EtOAc and water. The organic layer was washed with brine solution. Pure product **19** (570 mg, 2.62 mmol) was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 10:1). Yield 95%. ^{1}H NMR ($CDCl_3$; 400 MHz) δ 1.5 (9H, s); 3.04 (1H, s); 6.63 (1H, s); 7.14 (1H, d, J = 7.6 Hz); 7.19 (1H, t, J = 8 Hz); 7.43 (1H, d, J = 8 Hz); 7.53 (1H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 28.4, 77.3, 80.9, 83.5, 119.2, 122.1, 122.8, 126.8, 129.1, 138.5, 152.7.



5.6. ***Synthesis of methyl 3-(4-(3-((tert-butoxycarbonyl)amino)phenyl)-1H-1,2,3-triazol-1-yl)benzoate*** **(20) :** To a solution of ethynyl derivative **19**, (600 mg, 2.76 mmol) in 5:1 dry THF: water mixture the azide **15**, (586 mg, 3.3 mmol) was added under N_2 atmosphere. Then, 6 mol % sodium ascorbate and 1 mol% powdered $CuSO_4$ were added. Then 1.2 equivalent Et_3N was added and reaction mixture was degassed and stirred for 18-20 h at 65 to 70 ^{o}C. After total consumption of the starting alkyne, the reaction mixture was evaporated completely and diluted with EtOAc. The organic layer was washed NH_4Cl solution, brine, and dried over Na_2SO_4. Pure product **20** (850 mg, 2.15 mmol) was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 2:1). Yield 78%. mp 168 ^{o}C; IR (KBr) 3328, 3137, 2965, 2919, 1718, 1593, 1448, 1289, 1151, 762 cm^{-1}. ^{1}H NMR ($CDCl_3$; 400 MHz) δ 1.54 (9H, s); 3.99 (1H, s); 6.69 (1H, s); 7.32 (1H, d, J = 7.2 Hz); 7.38 (1H, t, J = 8.0 Hz); 7.64 (1H, t, J = 7.6 Hz); 8.01 (1H, s), 8.1 (2H, q, J = 7.4, 5.6 Hz); 8.31 (1H, s); 8.39 (1H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 28.4, 77.3, 80.9, 83.5, 119.2, 122.1, 122.8, 126.8, 129.1, 138.5, 152.7. ^{13}C NMR ($CDCl_3$; 100 MHz) δ 28.5, 52.8, 80.1, 115.8, 117.9, 118.6, 120.6, 121.1, 124.9, 129.8, 130.2, 130.9, 132.1, 137.3, 139.2, 148.6, 152.9, 166.1. HRMS calcd. for $C_{21}H_{23}N_4O_4$ $[M + H]^+$ 395.1712, found 395.1757.



1.2.3 ***Synthesis of 3-(4-(3-((tert-butoxycarbonyl)amino)phenyl)-1H-1,2,3-triazol-1-yl)benzoic acid*** **(2):** Using the general procedure of methyl ester hydrolysis, starting from 850 mg (2.15 mmol) of **20**, 784.3 mg (2.064 mmol) of the title compound **2** was isolated as a white solid material and used for the next step. Yield 96%. mp 235 ^{o}C; ^{1}H NMR (d_6-DMSO; 400 MHz) δ 1.47 (9H, s); 7.36 (2H, s); 7.51 (1H, s); 7.75 (1H, t, J = 7.6 Hz); 8.04



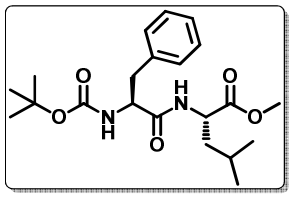
(1H, d, J = 6.8 Hz), 8.16 (1H, s); 8.08 (1H, d, J = 8.0 Hz); 8.46 (1H, s); 9.33 (1H, s); 9.47 (1H, s); ^{13}C NMR (d_6-DMSO; 100 MHz) δ 28.4, 79.6, 115.3, 118.5, 119.9, 120.1, 120.6, 120.7, 124.4, 129.5, 130.8, 132.9, 137.1, 140.4, 147.9, 153.2, 166.7. HRMS calcd for $C_{20}H_{19}N_4O_4$ [M - H]$^-$ 379.3892, found 379.3237.

6. Synthesis of Tetrapeptide 3[with Aliphatic Scaffold 1; Leu-Enkephalin Analogue], Model Tripeptide 4 (with aromatic Scaffold 2) and the Fluorescent Pentapeptide 5 [with Aliphatic Scaffold 1] Containing Triazolyl Donor/Acceptor Unnatural Fluorescent Amino Acids:

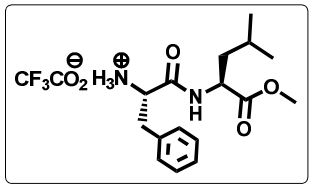
The targeted peptides were synthesized following the general procedure of peptide coupling protocol as was discussed earlier. The pure final products were isolated by column chromatography and characterised.

6.1. Synthesis of Tetrapeptide 3[with Aliphatic Scaffold 1; Leu-Enkephalin Analogue; BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me]

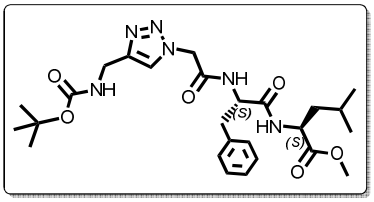
6.1.1. ***Synthesis of ((S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-4-methylpentanoate*** **(23):** Using general procedure of peptide coupling protocol starting from N-protected L-phenylalanine **21**, (1500 mg, 5.66 mmol), and the amine salt of methyl ester-L-leucine **22** (991 mg, 6.79 mmol)**,** the title compound **23** (1464.3 mg, 3.73 mmol) was isolated as white solid after purification by si-gel column chromatography. Yield 66%. mp 101 ^{o}C; IR (KBr) 3391, 3067, 2966, 2937, 1751, 1683, 1648, 1545, 1390, 1200, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$; 400 MHz) δ 0.90 (6H, t, J = 6.0 Hz); 1.26 (1H, s); 1.432 (9H, s); 1.66-1.58 (2H, m); 3.10 (2H, ddd, J = 6.0, 9.2 Hz); 3.69 (3H, s); 4.12 (1H, m); 4.84 (1H, d, J = 6.8 Hz); 4.98 (1H, d, J = 7.6); 6.66 (1H, d, J = 7.2 Hz); 7.10 (2H, d, J = 7.6 Hz); 7.29-7.20 (3H, m); ^{13}C NMR ($CDCl_3$; 100 MHz); δ 22.1, 22.7, 24.7, 28.4, 31.7, 38.1, 41.3, 52.4, 53.2, 80.1, 127.2, 128.6, 129.4, 135.9, 155.6, 171.8, 172.4. HRMS calcd. for $C_{21}H_{32}N_2O_5Na$ [M + Na]$^+$ 415.2201, found 415.2222.



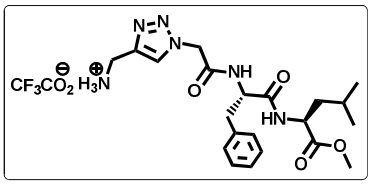
6.1.2. ***Synthesis of Boc-deprotected ((S)-methyl 2-((S)-2-(tert-butoxycarbonyl)amino)-3-phenylpropanamido)-4-methylpentanoate*** **(24):** Using the general procedure of Boc deprotection, starting from compound **23** (212 mg, 0.54 mmol) the product **24** was obtained in quantitative yield and was used for the next step without further purification and characterization.



6.1.3. ***Synthesis of (S)-methyl 2-((S)-2-(2-(4-(((tert-butoxycarbonyl)amino)methyl)-1H-1,2,3-triazol-1-yl)acetamido)-3-phenylpropanamido)-4-methylpentanoate*** **(25):** To a solution of N-protected aliphatic scaffold amino acid ^{Al}**TAA** (**6**, 140 mg, 0.54 mmol) in dry DMF, 1-[3-dimethyl amino propyl]-3-ehtylcarbo-diimide hydrochloride (EDC.HCl) (156 mg, 0.817 mmol), DMAP (200 mg, 1.64 mmol) were added successively at 0 ^{o}C and stirred for 20 minutes. The amine salt of methyl ester protected dipeptide **24** was then added and the reaction mixture was stirred for another 18h at 0 ^{o}C to room temperature. After completion of the reaction, the solvent was dried by rotary evaporator, after which it was partitioned between EtOAc and water (50 ml each). The organic layer was washed with brine solution. Pure product **25** (262 mg, 0.494 mmol) was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 1:1) as solid compound. Yield 81%. mp 73-74 ^{o}C. IR (KBr) 3438, 3314, 3066, 2957, 2100, 1746, 1690, 1657, 1533, 1454, 1367, 1252, 1169, 1052, 746, 702 cm^{-1}. ^{1}HNMR ($CDCl_3$; 400 MHz) δ 0.84 (6H, d, J = 5.2 Hz); 1.43 (9H, s); 1.58-1.48 (3H, m); 3.09-2.93 (2H, ddd, J = 6.4 Hz, 20 Hz), 3.69 (3H, s); 4.36 (2H, d, J = 5.2 Hz); 4.49 (1H, q, J = 7.6 Hz); 4.76 (1H, q, J = 6.8 Hz); 4.96 (2H, bs); 5.48 (1H, bs); 6.77 (1H, d, J = 6.8 Hz); 7.19 (2H, d, J = 6.4 Hz); 7.23 (3H, d, J = 6.8 Hz); 7.58 (1H, s); 7.61 (1H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 21.8, 22.5,24.6, 28.3, 35.9, 38.5, 40.5, 51.1, 51.9, 52.2, 54.6, 79.3, 123.6, 126.8, 128.4, 129.3, 136.2, 145.5, 155.9, 165.6, 171.3, 172.8. HRMS calcd. for $C_{26}H_{39}N_6O_6$ $[M + H]^+$ 531.2930, found 531.2856.

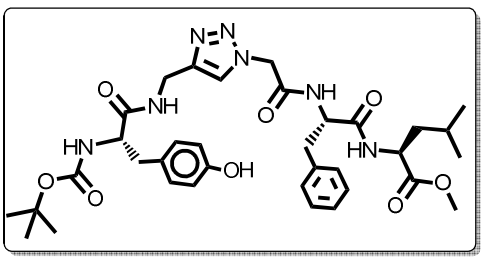


6.1.4. ***Synthesis of Boc deprotected (S)-methyl 2-((S)-2-(2-(4-(((tert-butoxy carbonyl) amino)methyl)-1H-1,2,3-triazol-1-yl)acetamido)-3-phenylpropanamido)-4-methylpentanoate*** **(26):** Using the general procedure of Boc deprotection, starting from compound **25** (262.8 mg, 0.496 mmol) the product **26** was obtained in quantitative yield and was used for the next step without further purification and characterization.



6.1.5. Synthesis of Leu-Enkephalin Analogue Tetrapeptide 3 [BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me]:

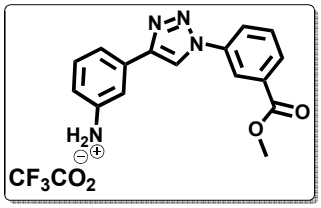
Methyl2-((S)-2-(2-(4-(((S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl) propanamido) methyl)-1H-1,2,3-triazol-1-yl)acetamido)-3-phenylpropanamido)-4-methylpentanoate **(3) :** Using general procedure of peptide coupling protocol starting from 140 mg (0.496 mmol) of Boc-protected L-tyrosine and 214 mg (0.496 mmol) of compound **26**, 165 mg (0.238 mmol) of the target tetrapeptide **3** was isolated pure by column chromatography (Si-gel, EtOAc) as a white solid. Yield 48%. mp 158 ^{o}C; IR (KBr) 3439, 3371, 2958, 2931, 2871, 1751, 1690, 1658, 1516, 1367, 1252, 1166, 1052, 749 cm^{-1}. ^{1}H NMR (d_6-



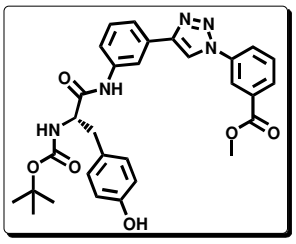
DMSO; 600 MHz) δ 0.83 (3H, d, J = 4.2 Hz); 0.88 (3H, d, J = 4.2 Hz); 1.36 (9H, s); 1.58-1.50 (3H, m); 2.81-2.72 (2H, m); 3.03 (2H, bs); 3.61 (3H, s); 4.06-4.01 (1H, m); 4.3 (2H, bs); 4.38 (1H, bs); 4.59 (1H, bs); 5.03 (2H, dd, J = 15.6, 54.6 Hz); 6.61 (1H, d, J = 6.6 Hz); 6.84 (1H, d, J = 7.2 Hz); 6.69 (1H, d, J = 4.8); 6.92 (1H, bs); 7.01 (1H, d, J = 6.6 Hz); 7.09 (1H, s); 7.25 (4H, s); 7.33 (1H, s); 8.40 (1H, d, J = 40.8 Hz); 8.52 (1H, d, J = 4.8 Hz); 8.6 (1H, d, J = 7.2 Hz); ^{13}C NMR (d_6-DMSO; 125 MHz) δ 21.3, 22.7, 24.2, 28.1, 34.3, 35.6, 36.8, 50.4, 51.4, 51.9, 53.7, 59.8, 78.6, 114.8, 115.1, 120.9, 121.3, 124.1, 126.4, 129.2, 130.1, 130.2, 130.3, 137.3, 144.6, 155.6, 165.1, 170.4, 171.0, 171.8, 172.6. HRMS calcd. for $C_{35}H_{48}N_7O_8$ $[M + H]^+$ 694.3550, found 694.3540.

6.2. Synthesis of Model Tripeptide 4 (with aromatic Scaffold 2)[BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me]

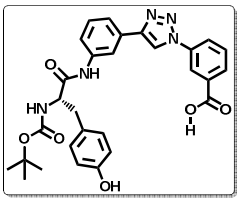
6.2.1. ***Synthesis of Boc-deprotected methyl 3-(4-(3-((tert-butoxycarbonyl)amino)phenyl)-1H-1, 2,3-triazol-1-yl)benzoate*** **(27):** Using the general procedure of Boc-deprotection, starting from compound **20** (163.5 mg, 0.415 mmol) the product **27** was obtained in quantitative yield and was used without further purification and characterization.



6.2.2. ***Synthesis of (S)-methyl 3-(4-(3-(2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)phenyl)-1H-1,2,3-triazol-1-yl)benzoate*** **(28) :** In a dry R.B, Boc-protected tyrosine (130 mg, 0.462 mmol) in dry DCM was cooled to 0 ^{o}C in an ice bath. To this solution N-methyl imidazole (110 µl, 1.38 mmol), followed by methanesulphonyl chloride (35 µl, 0.462 mmol) were added under nitrogen atmosphere. After 15 minutes of stirring, the ice bath was removed to attain the solution to room temperature. The free amine of **27** (122 mg, 0.415 mmol) dissolved in dry DCM, was then added to the reaction mixture which was then heated with stirring at 50 ^{o}C overnight. Then the solvent was dried by rotary evaporator, and diluted with EtOAc. The organic layer was washed with $NaHCO_3$ solution, brine solution and dried over Na_2SO_4 and evaporated. Pure product **28** (155 mg, 0.276 mmol) was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 1:1). Yield 60%. IR (KBr) 3425, 3316, 2917, 1693, 1519, 1294, 1165, 1049, 753 cm^{-1}. ^{1}H NMR (d_6-DMSO; 600 MHz) δ 1.38 (9H, s); 2.72-2.77 (1H, m); 2.85-2.92 (1H, m); 3.91 (3H, s); 4.29 (1H, m); 6.66 (2H, d, J = 7.2 Hz); 6.7 (1H, d, J = 7.8 Hz); 7.16 (2H, d, J = 7.8 Hz); 7.43 (1H, t, J = 6.8 Hz); 7.59 (2H, d, J = 7.2 Hz); 7.98 (1H, d, J = 7.8 Hz); 8.06 (1H, s); 8.25 (1H, s); 8.48 (1H, s), 9.28 (1H, s); 9.36 (1H, s); 10.5 (1H, s); ^{13}C NMR (d_6-DMSO; 125 MHz) δ 28.3, 36.8, 52.7, 57.2, 78.4, 115.1, 116.3, 119.5, 119.9, 120.3, 120.9, 124.6, 128.1, 129.3, 129.6, 130.4, 130.7, 130.8, 131.5, 137.0, 139.7, 147.6, 155.6, 155.9, 165.5, 171.3. HRMS calcd. for $C_{30}H_{32}N_5O_6$ $[M + H]^+$ 558.2352, found 558.2346.

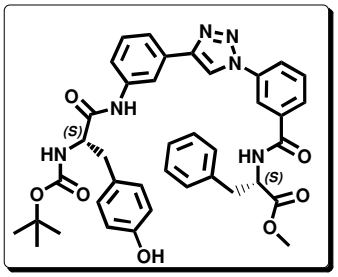


6.2.3. ***Synthesis of (S)-3-(4-(3-(2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy phenyl) propan amido)phenyl)-1H-1,2,3-triazol-1-yl)benzoic acid*** **(29):** Using the general procedure of methyl ester hydrolysis , starting from 115 mg (0.206 mmol) of compound **28**, 106.5 mg (0.196 mmol) of the title compound **29** was isolated as a white solid material and used for the next step without further purification and characterization. Yield 94%. Mp 192-193 ^{o}C. ^{1}H NMR (d_6-DMSO; 400 MHz) δ 1.14 (9H, s); 2.57 (1H, m); 2.74 (1H, m); 4.09 (1H, dd, J = 5.2, 7.6 Hz); 6.48 (2H, d, J = 7.6 Hz); 6.84 (1H, t, J = 7.2 Hz); 6.94 (2H, d, J = 7.6 Hz); 7.25 (2H, t, J = 8.0 Hz); 7.43 (2H, d, J = 7.6 Hz); 7.54 (1H, t, J = 8.0 Hz); 7.75 (1H, s); 7.87 (1H, d, J = 8.0 Hz); 7.97 (1H, d, J = 8.4 Hz); 8.07 (1H, s), 9.17 (1H, s); 10.01 (1H, s). HRMS calcd. for $C_{29}H_{28}N_5O_6$ [M - H]$^-$ 542.5625, found 542.4428.



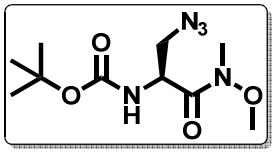
6.3. Synthesis of Model Tripeptide 4 (with Aromatic Scaffold 2) [BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me]

Synthesis of (S)-methyl 2-(3-(4-(3-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)propanamido)phenyl)-1H-1,2,3-triazol-1-yl)benzamido)-3 phenylpropanoate **(4) :** Acid group free dipeptide **29** (100 mg, 0.184 mmol)**,** and methyl ester of N-deprotected phenylalanine (27 mg, 0.22 mmol) were taken in dry DMF solvent under nitrogen atmosphere and cooled to 0 ^{o}C. The resulting suspension was treated with dimethyl amino pyridine (DMAP) (67 mg, 0.552 mmol) and then with EDC.HCl (52 mg, 0.276 mmol). After stirring at 0 °C to r.t for 16 h, the reaction mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution before being dried (Na_2SO_4). The target tripeptide **4** (97 mg, 0.137 mmol) was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 0.5:1). Yield 75%. mp 196 ^{o}C; IR (KBr) 3409, 3311, 2925, 1715, 1662, 1528, 1237, 1165, 1033, 686 cm^{-1}. ^{1}H NMR (d_6-DMSO; 600 MHz) δ 1.32 (9H, s); 2.79 (1H, m); 2.91 (1H, dd, J = 4.8, 9.0 Hz); 3.11 (1H, dd, J = 10.2, 3.6 Hz); 3.19 (1H, dd, J = 5.4, 8.4 Hz); 3.64 (3H, s); 4.26 (1H, m); 4.73 (1H, m); 6.65 (2H, d, J = 7.8 Hz); 6.96 (1H, d, J = 7.8 Hz); 7.11 (1H, d, J = 8.4 Hz); 7.19 (1H, t, J = 7.2 Hz); 7.28 (4H, m); 7.43 (1H, d, J =7.8 Hz); 7.59 (2H, d, J = 7.8 Hz); 7.72 (1H, t, J = 8.1 Hz); 7.91 (1H, d, J = 7.8 Hz); 8.11 (1H, dd, J = 1.8, 6.6 Hz), 8.25 (1H, s); 8.38 (1H, s); 9.27 (1H, s); 9.28 (1H, s); 10.15 (1H, s); ^{13}C NMR (d_6-DMSO; 125 MHz) δ 28.3, 36.4, 36.8, 52.2, 54.9, 57.1, 78.4, 115.1, 116.3, 119.1, 119.5, 119.9, 120.8, 123.1, 126.7, 127.7, 128.1, 128.4, 129.2, 129.6, 130.3, 130.6, 135.4, 136.8, 137.6, 139.6, 147.5, 15564, 155.9, 165.5, 171.3, 172.2. HRMS calcd. for $C_{39}H_{41}N_6O_7$ [M + H]$^+$ 705.3031, found 705.3057.

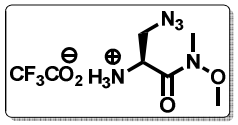


6.4. Synthesis of the Target Fluorescent Pentapeptide 5 [with Aliphatic Scaffold 1] Containing Triazolyl Donor/Acceptor Unnatural Fluorescent Amino Acids [BocNH-^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CO_2NMe(OMe)]:

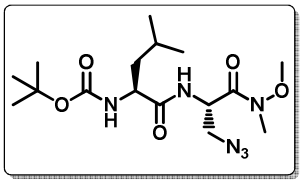
6.4.1. ***Synthesis of (S)-tert-butyl (3-azido-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate*** **(30):**[2] Using our previous method from 1000 mg (5 mmol) of NBoc-protected L-serine, 540 mg (1.97 mmol) of the title compound **30** was preapred. Overall Yield 75 %.



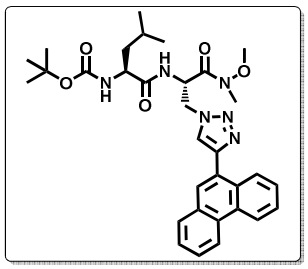
6.4.2. ***Synthesis of Boc deprotected (S)-tert-butyl (3-azido-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)carbamate*** **(31):** Using the general procedure of Boc-deprotection, starting from compound **30** (500 mg, 1.832 mmol) the product **31** was obtained in quantitative yield and was used for the next step without further purification and characterization.



6.4.3. **Synthesis of *tert-butyl ((S)-1-(((S)-3-azido-1-(methoxy(methyl)amino)-1-oxopropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate*** **(33) :** Using general procedure of peptide coupling protocol, starting from 1000 mg (4.32 mmol) of N-Boc-protected leucine **32** and 752 mg (4.32 mmol) of N-deprodected serine azide **31**, 900 mg (2.33 mmol) of the title compound **33** was isolated. The product was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 2:1) as colourless oil. Yield 54%. IR (KBr) 3335, 3244, 2966, 2105, 1685, 1643, 1523, 1272, 1170, 928 cm^{-1}. ^1H NMR ($CDCl_3$; 400 MHz) δ 0.89 (6H, d, J = 3.2 Hz); 1.4 (9H, s); 1.47-1.43 (1H, m); 1.63 (2H, m); 3.19 (3H, s); 3.55-3.51 (1H, m); 3.63-3.60 (1H, m); 3.72 (3H, s); 4.15 (1H, bs); 5.03 (1H, bs); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 21.8, 23.1, 24.8, 28.3, 32.3, 41.4, 49.6, 51.9, 53.6, 61.8, 80.1, 155.6, 169.1, 172.8. HRMS calcd. for $C_{16}H_{31}N_6O_5$ $[M + H]^+$ 387.2277, found 387.2165.

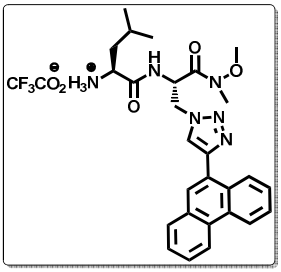


6.4.4. ***Synthesis of tert-butyl ((S)-1-(((S)-1-(methoxy(methyl)amino)-1-oxo-3-(4-(phenanthren-9-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate*** **(34) :** Using general procedure of [3+2] cyclo-addition reaction, starting from 250 mg (0.647 mmol) of azide derivative of dipeptide **33** and 157 mg (0.78 mmol) of 9-ethynyl phenanthrene, 320 mg (0.54 mmol) of the title compound **34** was isolated as a light brown gummy material (Si-gel, PE : EtOAc = 1:1). Yield 84%. mp 94-95 ^oC. IR (KBr) 3331, 2958, 2929, 2136, 1657, 1518, 1366, 1165, 1048, 729 cm^{-1}. ^1H NMR ($CDCl_3$; 400 MHz); δ 0.86 (6H, d, J = 5.2 Hz); 1.32 (9H, s); 1.47-1.41 (1H, m); 1.63-1.54 (2H, m); 3.25 (3H, s); 3.8 (3H, s); 4.06 (1H, bs); 4.82 (2H, dd, J = 4.4, 9.6 Hz); 4.99 (1H, d, J = 13.6 Hz);

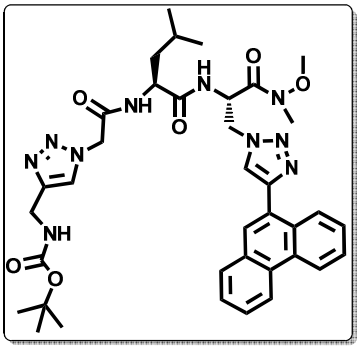


5.29 (1H, bs); 7.11 (1H, d, *J* = 6.4 Hz); 7.66-7.54 (4H, m); 7.87 (1H, d, *J* = 7.6 Hz); 8.01 (1H, s); 8.17 (1H, s); 8.14 (1H, d, *J* = 8 Hz); 8.69 (2H, dd, *J* = 8.0, 15.6 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz); δ 21.5, 22.8, 24.5, 28.1, 32.3, 41.1, 50.1, 50.2, 53.4, 61.7, 79.6, 122.3, 122.7, 124.4, 126.2, 126.5, 126.6, 126.7,126.8, 128.1, 128.7, 129.9, 130.1, 130.5, 131.1, 146.5, 155.6, 162.4, 168.2, 173.1. HRMS calcd for $C_{32}H_{41}N_6O_5$ $[M + H]^+$ 589.3137, found 589.3039.

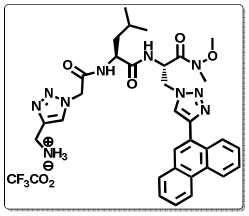
6.4.5. ***Synthesis of Boc deprotected tert-butyl ((S)-1-(((S)-1-(methoxy(methyl)amino)-1-oxo-3-(4-(phenanthren-9-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)amino)-4-methyl-1-oxopentan- 2-yl)carbamate*** **(35):** Using the general procedure of Boc-deprotection, starting from compound **34** (319.5 mg, 0.543 mmol) the product **35** was obtained in quantitative yield and was used for the next step without further purification and characterization.



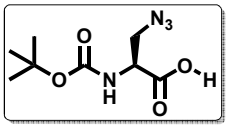
6.4.6. ***Synthesis of tert-butyl ((1-((5S,8S)-8-isobutyl-3-methyl-4,7,10-trioxo-5-((4-(phenanthren-9-yl)-1H-1,2,3-triazol-1-yl)methyl)-2-oxa-3,6,9-triazaundecan-11-yl)-1H-1,2,3-triazol-4-yl)methyl)carbamate*** **(36) :** To a solution of N-protected aliphatic amino acid scaffold ^{Al}**TzAA** (**6**, 160 mg, 0.625 mmol) in dry DMF, 1-[3-dimethyl amino propyl]-3-ehtylcarbo-diimide hydrochloride (EDC.HCl) (178 mg, 0.937 mmol), followed by DMAP (288 mg, 1.87 mmol) were added at 0 ^{o}C. Next, the amine salt of Weinreb amide, the dipeptide **35**, was added and the reaction mixture was stirred for 18h at 0 ^{o}C to room temperature. After completion of the reaction, the solvent was dried by rotary evaporator, and partitioned between EtOAc and water (50 ml each). The organic layer was washed with brine solution. The product tripeptide **36** (300 mg, 0.414 mmol) was isolated in pure form by column chromatography (Si-gel, EtOAc) as light brown solid compound. Yield 66%. mp 106-107 ^{o}C. IR (KBr) 3449, 3422, 3314, 2958, 2869, 2100, 1680, 1660, 1524, 1366, 1250, 1168, 1054, 729 cm^{-1}. ^{1}HNMR ($CDCl_3$; 400 MHz) δ 0.84 (6H, t, *J* = 6.0 Hz); 1.39 (9H, s); 1.63-1.46 (3H, m); 3.29 (3H, s); 3.85 (3H, s); 4.24 (2H, d, *J* = 4.4 Hz); 4.46-4.41 (1H, m); 4.87-4.82 (2H, m); 4.96 (2H, d, *J* = 7.2 Hz); 5.13 (1H, bs); 5.35 (1H, q, *J* = 5.2 Hz, 7.2 Hz); 6.69 (1H, bs); 7.55 (1H, s); 7.62 (2H, t, *J* = 7.2 Hz); 7.69 (2H, q, *J* = 6.8, 4.8 Hz); 7.91 (1H, d, *J* = 7.2 Hz); 7.97 (2H, d, *J* = 6.0 Hz); 8.33 (1H, d, *J* = 8.0 Hz); 8.7 (1H, d, *J* = 8.0 Hz); 8.76 (1H, d, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$; 100 MHz) δ 21.8, 22.8, 24.7, 28.4, 32.5, 36.1, 40.4, 50.2, 50.4, 52.3, 52.4, 62.0, 79.5, 122.5, 123.1, 123.8, 124.6, 126.3, 126.5, 126.8, 127.1, 127.3, 128.4, 128.9, 130.1, 130.3, 130.6, 131.2, 145.6, 146.6, 155.9, 165.9, 168.2, 172.1. HRMS calcd. for $C_{37}H_{47}N_{10}O_6$ $[M + H]^+$ 727.3679, found 727.3658.



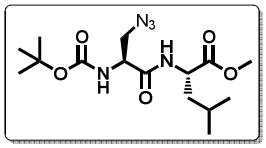
6.4.7. ***Synthesis of Boc deprotected tert-butyl ((1-((5S,8S)-8-isobutyl-3-methyl-4,7,10-trioxo-5-((4-(phenanthren-9-yl)-1H-1,2,3-triazol-1-yl)methyl)-2-oxa-3,6,9-triazaundecan-11-yl)-1H-1,2,3-triazol-4-yl)methyl)carbamate*** **(37):** Using the general procedure for Boc-deprotection, starting from compound **36** (300.0 mg, 0.414 mmol) the product **37** was obtained in quantitative yield and were used for the next step without further purification and characterization.



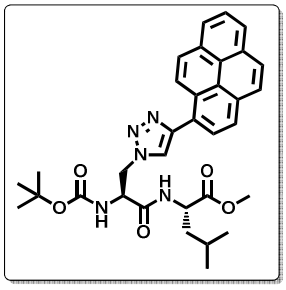
6.4.8. ***Synthesis of (S)-3-azido-2-((tert-butoxycarbonyl)amino)propanoic acid*** **(38):** Using the general procedure of methyl ester hydrolysis, starting from 500 mg (1.83 mmol) of **30** , 390 mg (1.69 mmol) of the title compound **38** was isolated as a yellowish brown solid material and used for the next step without further purification and characterization. Yield 92%.



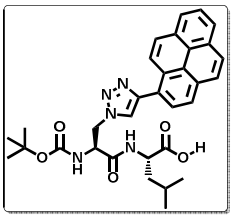
6.4.9. **Synthesis of** ***(S)-methyl 2-((S)-3-azido-2-((tert-butoxycarbonyl)amino)propanamido)-4-methylpentanoate*** **(39):** Using the general procedure for peptide coupling protocol, starting from 1000 mg (4.34 mmol) of N-protected serine azide **38** and 570 mg (4.34 mmol) of N-deprodected amine salt of methyl ester-L-leucine **22**, 870 mg (2.43 mmol) of the title compound **39** was isolated in pure form by column chromatography (Si-gel, PE : EtOAc = 2:1) as light yellow oil. Yield 56%. IR (KBr) 3326, 2960, 2873, 2105, 1745, 1666, 1524, 1368, 1250, 1023, 858, 780 cm^{-1}. ^1H NMR ($CDCl_3$; 400 MHz) δ 0.88 (6H, d, J = 5.6 Hz); 1.41 (9H, s); 1.63-1.51 (3H, m); 3.51 (1H, dd, J = 4.8, 6.8 Hz); 3.68 (3H, s); 3.74-3.70 (1H, m); 4.30 (1H, bs); 4.56 (1H, bs); 5.51 (1H, d, J = 6.4 Hz); 6.97 (1H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 21.9, 22.8, 24.8, 28.3, 41.3, 51.0, 52.2, 52.4, 53.7, 80.8, 155.5, 169.5, 173.1. HRMS calcd for $C_{15}H_{27}N_5O_5Na$ $[M + Na]^+$ 380.1908, found 380.1909.



6.4.10. ***Synthesis of (S)-methyl 2-((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyren-1-yl)-1H-1,2,3-triazol-1-yl)propanamido)-4-methylpentanoate*** **(40) :** Using the general procedure of [3+2] cyclo-addition reaction, starting from 200 mg (0.56 mmol) of azide derivative of dipeptide **39** and 152 mg (0.78 mmol) of 1-ethynyl pyrene, 210 mg (0.36 mmol) of the title compound **40** was isolated as a light yellow gummy material (Si-gel, PE : EtOAc = 1:1). Yield 64%; IR (KBr) 3336, 2961, 1669, 1515, 1258, 1165, 847, 724 cm^{-1}. ^1H NMR ($CDCl_3$; 400 MHz); δ 0.69 (6H, d, J = 6.4 Hz); 0.88-0.086 (2H, m); 1.46 (9H, s); 1.54-1.49 (2H, m); 3.67 (3H, s); 4.57 (1H, m); 4.87 (2H, bs); 5.05 (1H, m); 6.05 (1H, d, J = 8.4 Hz); 7.19 (1H, d, J = 6.8 Hz); 8.02-7.97 (1H, m); 8.09-8.05 (3H, m); 8.11 (1H, s); 8.16-8.13 (3H, m); 8.22-8.19 (1H, m); 8.66 (1H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz); δ 21.7, 22.8, 24.9, 28.4, 41.3, 43.5, 51.1, 52.5, 54.6, 81.3, 124.6, 124.8, 124.9, 125.1, 125.2, 125.3, 125.5, 126.2, 127.2, 127.4, 128.0, 128.3, 128.6, 131.0, 131.3, 131.5, 147.5, 155.7, 169.0, 172.8. HRMS calcd for $C_{33}H_{38}N_5O_5$ $[M + H]^+$ 584.2867, found 584.2874.

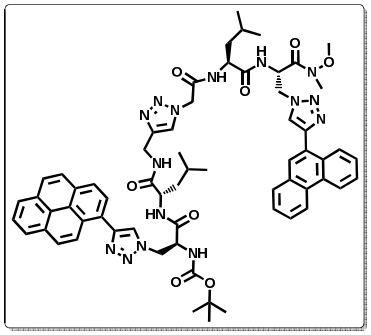


6.4.11. ***Synthesis of (S)-3-(4-(3-(2-((tert-butoxycarbonyl)amino)-3-(4-hydroxy phenyl) propan amido)phenyl)-1H-1,2,3-triazol-1-yl)benzoic acid*** **(41):** Using the general procedure of methyl ester hydrolysis, starting from 209 mg (0.358 mmol) of **40**, 195.6 mg (0.344 mmol) of the title compound **41** was isolated (Si-gel, PE : EtOAc = 2:1) as a yellowish brown solid material and used for the next step without further characterization. Yield 96%. ^{1}H NMR ($CDCl_3$,d_6-DMSO mix.; 400 MHz); δ 0.76-0.88 (6H, m); 1.30 (9H, s); 1.37-1.31 (1H, m); 1.65-1.57 (2H, m); 4.36 (1H, q, J = 5.6 Hz, 8.0 Hz); 4.73 (2H, d, J = 8.4 Hz); 4.93 (1H, q, J = 2.0 Hz, 7.6 Hz); 6.57 (1H, d, J = 7.6 Hz); 7.89 (1H, s); 8.03-7.96 (1H, m); 8.03 (2H, bs); 8.06 (1H, bs); 8.14 (2H, q, J = 4.0 Hz, 3.2 Hz); 8.17 (2H, d, J = 6.8 Hz); 8.34 (1H, s); 8.64 (1H, d, J = 9.2 Hz).^{13}C NMR ($CDCl_3$ + d_6-DMSO; 100 MHz) δ 21.3, 22.8, 24.3, 28.0, 29.1, 30.9, 35.9, 50.9, 54.2, 61.0, 79.0, 97.6, 124.0, 124.4, 124.7, 124.8, 124.9, 125.2, 126.0, 126.8, 127.1, 127.2, 127.4, 127.7, 128.2, 130.4, 130.5, 130.9, 146.0, 155.0, 162.2, 168.7, 174.4. HRMS calcd for $C_{32}H_{34}N_5O_5$ $[M - H]^-$ 568.6428, found 568.5032.



6.4.12. Synthesis of the Target Fluorescent Pentapeptide 5 [with Aliphatic Scaffold 1] [BocNH-^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CO_2NMe(OMe)]

Snthesis of tert-butyl ((S)-1-(((S)-1-(((1-((5S,8S)-8-isobutyl-3-methyl-4,7,10-trioxo-5-((4-(phenanthren-9-yl)-1H-1,2,3-triazol-1-yl)methyl)-2-oxa-3,6,9-triazaundecan-11-yl)-1H-1,2,3-triazol-4-yl)methyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-1-oxo-3-(4-(pyren-1-yl)-1H-1,2,3-triazol-1-yl)propan-2-yl)carbamate **(5) :** Using the general procedure of peptide coupling protocol, starting from 180 mg (0.316 mmol) of **41** and 198 mg (0.316 mmol) of **37**, 170 mg (0.15 mmol) of the target fluorescent pentapeptide **5** was isolated pure by Si-gel (60-120 mesh) column chromatography (CH_3Cl:MeOH = 20:1) as a gummy material which after washing with ether afforded light yellow solid. Yield 46%. mp 185 ^{o}C; IR (KBr) 3472, 3421, 3281, 3076, 2955, 2103, 1674, 1649, 1636, 1543, 1367, 1248, 1166, 1050, 847, 729 cm^{-1}. ^{1}H NMR (d_6-DMSO; 600 MHz) δ 0.77 (3H, d, J = 6.0 Hz); 0.82 (3H, d, J = 6.6 Hz); 1.28 (9H, s); 1.44-1.41 (4H, m); 1.56-1.53 (2H, m); 3.16 (3H, s); 3.72 (3H, s); 4.26 (2H, bs); 4.36 (2H, bs); 4.72-4.69 (2H, m); 4.8 (2H, dd, J = 4.8, 8.4 Hz); 4.91 (1H, d, J = 8.4 Hz); 5.06 (2H, dd, J = 15.6 Hz, 51.0 Hz); 5.34 (1H, bs); 7.27 (1H, d, J = 7.2 Hz); 7.66-7.65 (2H, m); 7.76-7.69 (3H, m); 7.98 (1H, d, J = 7.8 Hz); 8.02 (1H, s); 8.09 (1H, t, J = 7.8 Hz); 8.22-8.19 (3H, m); 8.23 (1H, s); 8.33-8.28 (3H, m); 8.36-8.35 (1H, m); 8.41 (1H, d, J = 10.2 Hz); 8.5 (3H, bs); 8.62 (1H, s); 8.65 (1H, s); 8.86-8.81 (2H, m); 8.89 (1H, t, J = 7.2 Hz); ^{13}C NMR (d_6-DMSO; 125 MHz) δ 21.4, 22.9, 23.1, 24.0, 24.1, 28.0, 30.8, 34.3, 35.8,40.9, 49.4, 49.7, 50.6, 51.2, 51.3, 51.4, 54.4, 78.8, 122.8, 123.3, 123.9, 124.1, 124.3, 124.8, 125.1, 125.2, 125.3, 125.5, 126.2, 126.5, 126.7, 126.9, 127.0, 127.1, 127.2, 127.3, 127.5, 127.7, 127.9, 128.7, 129.5, 129.7, 130.2, 130.4, 130.5, 130.8, 130.9, 144.4, 145.2, 145.7, 155.1, 162.4, 165.3, 168.7, 171.8, 171.9. HRMS calcd for $C_{64}H_{72}N_{15}O_8$ $[M + H]^+$ 1178.5767, found 1178.5771.



7. ORTEP Diagram and Crystallographic Description of Aromatic Amino Acid Scaffold 2 [BocNH-^{Ar}TAA-CO_2Me)]

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART [3] software and refined with SAINT[4] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS[4]. The structure was solved by direct methods implemented in SHELX-97[5] program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Crystals were isolated in from acetonitrile/chloroform mixture at room temperature.

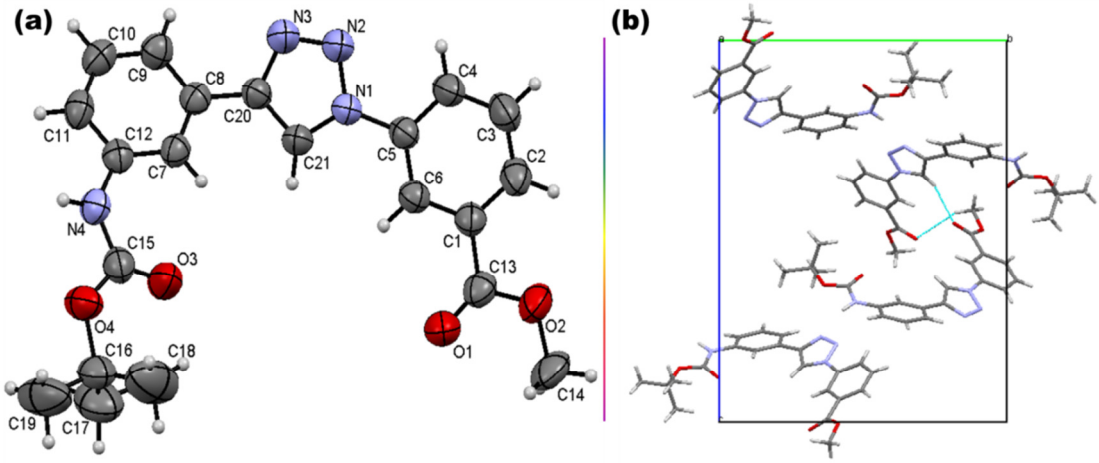


Figure S1a. (a) ORTEP diagram with 50% thermal ellipsoid and (b) crystal packing (unit cell) of aromatic triazolo amino acid scaffold **2** (^{Ar}**TAA**).

The crystal structure analysis of scaffold **2** revealed an interesting observation. Recrystalisation of **2** from acetonitrile yielded beautiful brown needle-shaped crystal (mp 168 ^{o}C). Single crystal X-ray diffraction analysis showed that the crystals were orthorhombic and classified into the chiral space group $P2_12_12_1$. This interesting observation knocked us to examine the possible origin of the solid state chirality as well as to examine whether the same chirality is maintained in solution. The packing diagram showed that the scaffold had a 2-fold screw axis of symmetry, unit cell contained four molecules and the aminophenyl unit was 25.1 ^{o} out of plane with respect to triazole unit. The other phenyl unit remained almost in the plane of triazole. Overall the scaffold adopted a hairpin shape wherein the two hairpins packed face-to-face via weak H-bonding interaction leading to "S"-shaped structure (Fig. S1a (a-b)). The molecular arrangement revealed that each "S"-shaped units were linked each other via ArCH….$N_{Triazole}$, ArCH-π bonding (side way) and hydrophobic interaction through ^{t}Butyl-units to link "S"- units linearly leading to a helical like construct (Fig. S1b (a-c)).

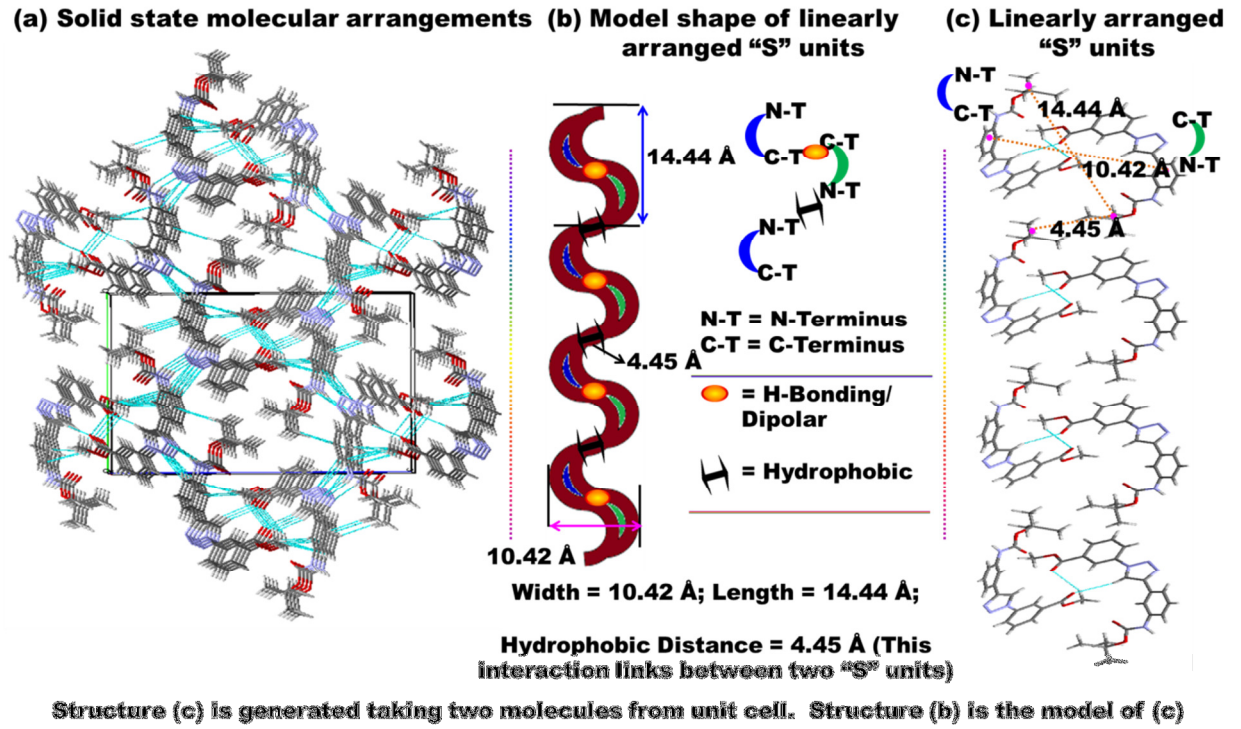


Figure S1b. (a) ORTEP diagram with 50% thermal ellipsoid; (b) crystal packing (unit cell); and (c) Solid state molecular arrangement of aromatic triazolo amino acid scaffold **2** (**^{Ar}TAA**).

Table S1. Summary table of crystal parameter of scaffold **2** (**^{Ar}TAA**).

Empirical formula	$C_{21}H_{22}N_4O_4$
CCDC Number	CCDC 981750
Formula weight	394.43
Crystal habit, colour	needle, brown
Crystal size, mm^3	0.40 x 0.24 x 0.22
Temperature, T	296(2) K
Wavelength, λ	0.71073 Å
Crystal system	orthorhombic
Space group	$P2_12_12_1$, No.19
Unit cell dimensions	a = 5.9906(6) Å
	b = 15.7335(18) Å
	c = 21.9353(19) Å
	$\alpha = \beta = \gamma = 90°$
Volume, V	2067.5(4) Å^3
Z	4
Calculated density	1.267 Mg/m^3
Absorption coefficient, μ	0.090 mm^{-1}
F(000)	832
θ range for data collection	1.59° to 24.99°

Limiting indices	$-7 \leq h \leq 7$, $-18 \leq k \leq 12$, $-24 \leq l \leq 25$
Reflection collected / unique	10672 / 3576 [R(int) = 0.0668]
Completeness to θ	99.2 %
Max. and min. transmission	0.974 and 0.980
Refinement method	Full−matrix least−squares on F^2
Data / restraints / parameters	3576 / 0 / 266
Goodness−of−fit on F^2	0.973
Final R indices [I>2sigma(I)]	$R1$ = 0.0501, $wR2$ = 0.1086
R indices (all data)	$R1$ = 0.0877, $wR2$ = 0.1248
Largest diff. peak and hole	0.161 and −0.164 e.Å^{-3}

Table S2. Summary table of symmetry axis of scaffold **2** (**^{Ar}TAA**).

No.	Symm. Op.	Description	Detail description	Order	Type
1	x,y,z	Identity	Identity	1	1
2	1/2-x,-y,1/2+z	Screw axis (2-fold)	2-fold screw axis with direction [0, 0, 1] at 1/4, 0, z with screw component [0, 0, 1/2]	2	2
3	-x,1/2+y,1/2-z	Screw axis (2-fold)	2-fold screw axis with direction [0, 1, 0] at 0, y, 1/4 with screw component [0, 1/2, 0]	2	2
4	1/2+x,1/2-y,-z	Screw axis (2-fold)	2-fold screw axis with direction [1, 0, 0] at x, 1/4, 0 with screw component [1/2, 0, 0]	2	2

Table S3. Summary table of some bond distances and torsion angles of scaffold **2** (**^{Ar}TAA**).

No. of atoms	Bond distances(Å)	No. of atoms	Bond angles (^{o})	No. of atoms	torsion angles (^{o})
N4 – C12	1.411	C15 – N4 - C12	126.6	C15 – N4 – C12 – C7	-23.04
C12 – C7	1.377	N4 - C12 – C7	123.2	N4 – C12 – C7 – C8	-179.6
C7 – C8	1.401	C12 – C7 – C8	120.5	C7 – C8 – C20 – C21	25.1
C8 – C20	1.469	C7 – C8 – C20	119.7	C21 – N1 – C5 – C6	6.6
C20 – C21	1.367	C8 – C20 – C21	130.4	C5 – C6 – C1 – C13	179.7
C21 – N1	1.339	C20 – C21 – N1	105.6	C6 – C1 – C13 – O1	9.7
N1 – C5	1.434	C21 – N1 – C5	130.8	C6 – C1 – C13 – O2	11.6
C5 – C6	1.376	N1 – C5 – C6	119.9		
C6 – C1	1.391	C5 – C6 – C1	119.5		
C1 – C13	1.492	C6 – C1 – C13	118.1		

8. Spectroscopic Evidences of Various Interactions and β-Turn Structures in the Peptides 3, 4 and 5

8.1. Study of Circular Dichroism Spectroscopy

Circular dichroism spectra were recorded using a CD spectropolarimeter with a cell path length of 10 nm at 25 ^{o}C. All the samples were prepared in spectroscopic grade methanol solvent with 60 μM concentration.

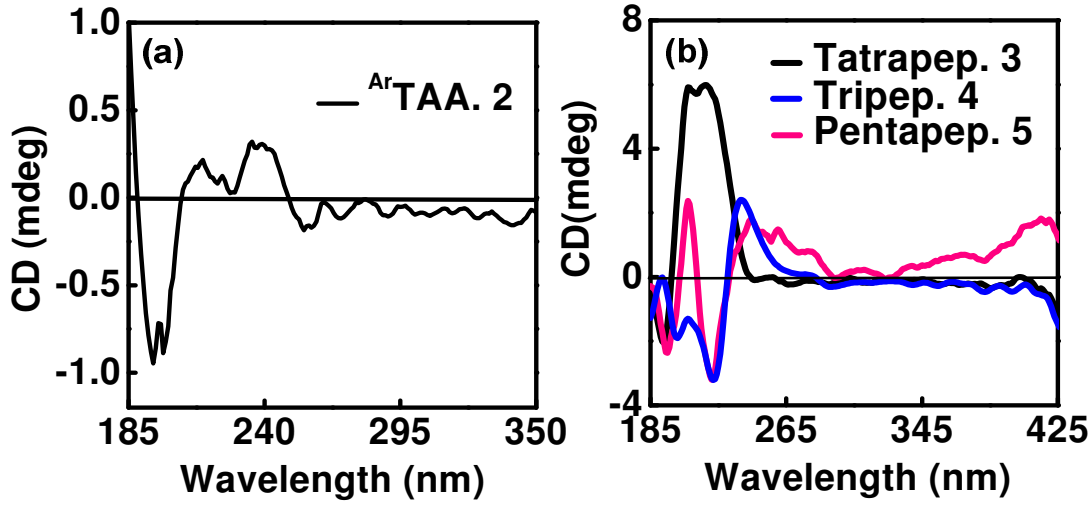


Figure S2. CD spectra of synthesized amino acids scaffolds **1-2** and peptides **3-5** in methanol solvent (60 μM concentration).

Tetrapeptide **3** showed a strong positive band at around 206 nm and a negative band at around 191 nm indicating a type II β-turn conformation. Moreover, the signature of aromatic π-π stacking interaction between Phe and Tyr in peptide **3** was also evident from the appearance of a positive band at around 217 nm.

The fluorescent pentapeptide **5** also exhibited a strong positive band at 207 nm and a negative band at 193 nm indicating a predominantly type II β-turn conformation. The positive bands at 308 and 350 nm indicated the absorption due to the fluorescent triazolyl phenanthrene and pyrene, respectively, amino acids.

The tripeptide **4** containing the aromatic scaffold in the backbone showed a negative and a positive band at 202 and 211 nm, respectively. Moreover, the presence of a positive band at 238 nm followed by a negative band at 221 nm signified the absorption of chiral aromatic triazolyl amino acid scaffold as well of the tyrosine in the tripeptide **4**. Overall, the tripeptide **4** showed a β-sheet like structure with 20% turn conformation (Fig. S2).

8.2. Infrared Spectroscopy

IR spectra were recorded using dry KBr with solid and dry compound.

Table S4. Summary table of IR spectra

Peptides	Free N-H (cm^{-1})	H bonded N-H (cm^{-1})
Tetrapeptide_3	3415	3314
Tripeptide_4	3409	3311
Pentapeptde_5	3421	3281

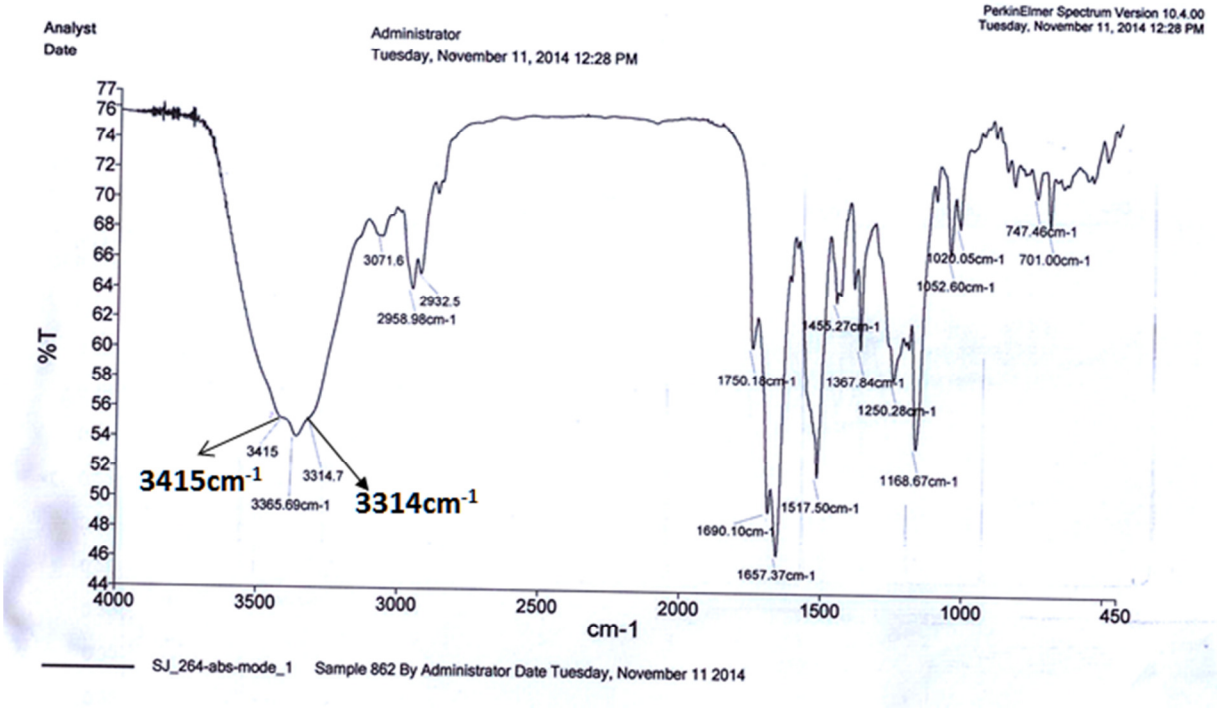


Figure S3. IR spectra of **Tetrapeptide 3** (**BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me**).

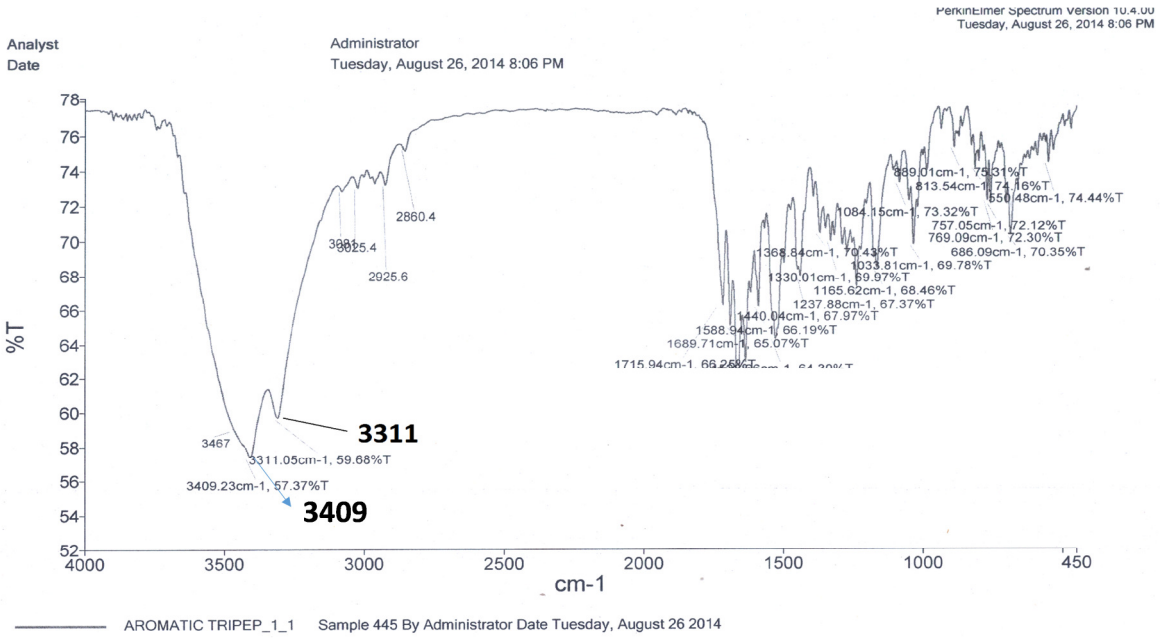


Figure S4. IR spectra of **Tripeptide 4** (**BocNH-Tyr-^{Ar}TAA-Phe- CO_2Me**).

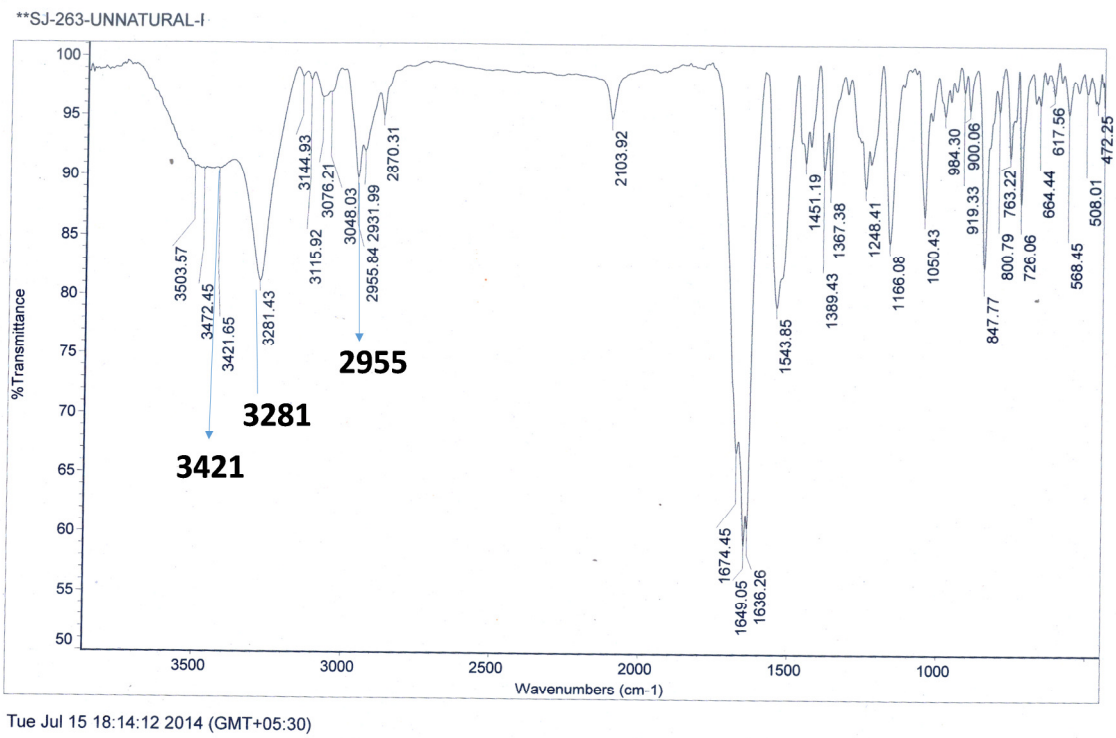


Figure S5. IR spectra of **Pentapeptide 5** (**BocNH-^{TPy}Ala^{Ac}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CONMe(OMe)**).

8.3. Variable Temperature ^{1}H NMR Data of Scaffolds 1-2 and Peptide 3-5

The presence of intramolecular H-bonds was assessed by determining the variation of chemical shifts of the various NHs with temperature (Figure S6, S9, S11 and S13), in d6-DMSO in which all NHs exhibited different chemical shifts. The Triazole C-H of N-terminal amino acid (**Pentapeptide 5**) also exhibited temperature effect. All the amide NH's, and triazole C-H exhibited ($\Delta\delta/\Delta T$) values that are moderate to close to Kessler limit of -3 to **-**6 ppb/K indicating presence of strong to moderate intramolecular H-bonding and supported the predominant turn or turn like structure of the peptides (Table S5, S6 and S7).

Table S5. Values of temperature coefficients of chemical shifts of amide NHs or triazole-CH in Aliphatic and Aromatic amino acids scaffolds **^{Al}TAA (1)** and **^{Ar}TAA (2)**, respectively.

Amide-NH or Triazole-CH	($\Delta\delta/\Delta T$) ppb/k
^{Al}TAA.1_Amide-NH	-7.7
^{Al}TAA.1_ Triazole-CH	-0.5
^{Ar}TAA.2_Amide-NH	-6.1
^{Ar}TAA.2_ Triazole-CH	-3.3

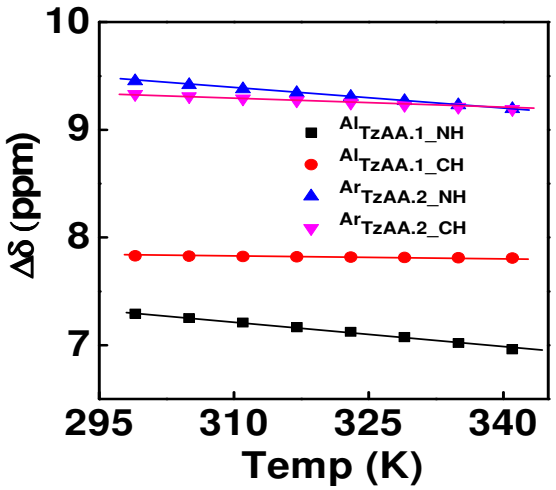


Figure S6. Temperature dependence of amide-NH/triazole-CH chemical shift of **1, ^{Al}TzAA and 2, ^{Ar}TAA.**

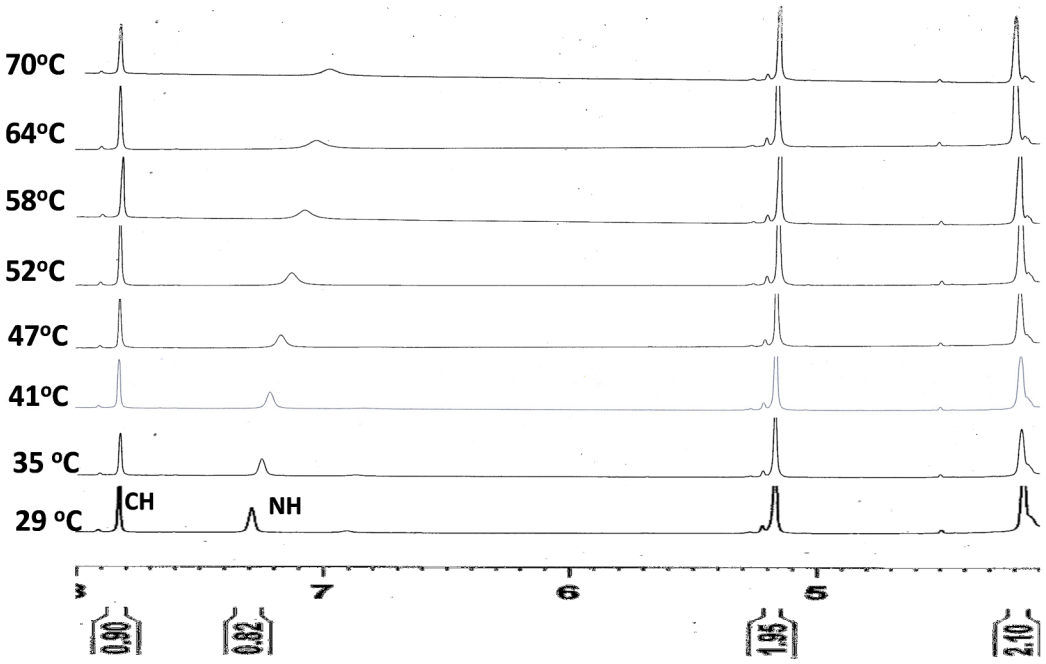


Figure S7. Variable temperature ^{1}H NMR spectra **of 1, ^{Al}TAA** in d_6-DMSO showing temperature dependence of amide-NH/triazole-CH chemical shift.

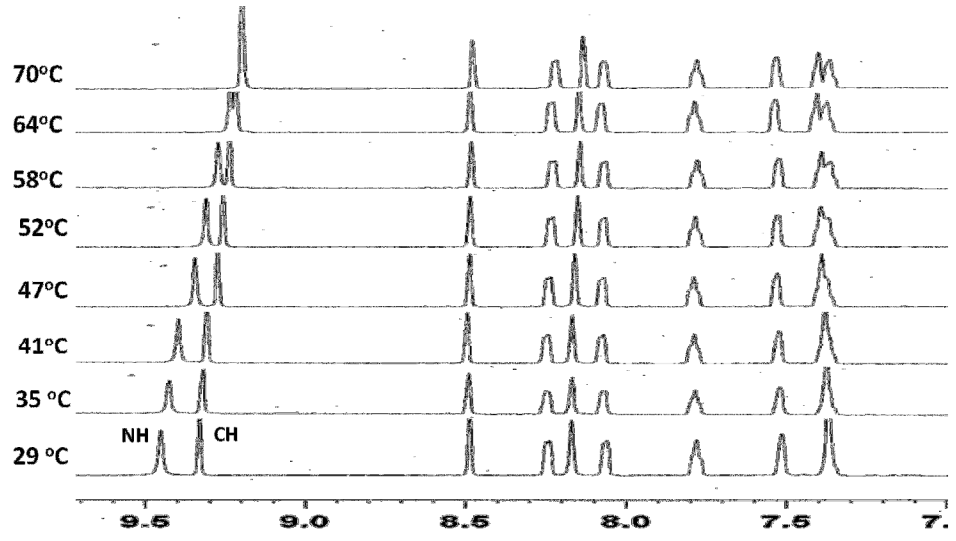
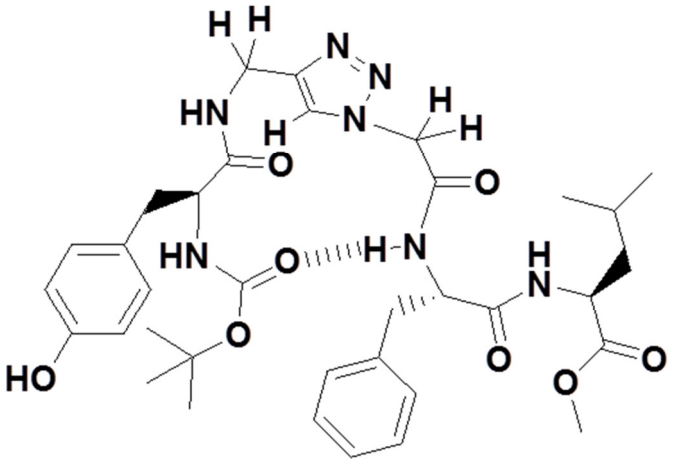


Figure S8. Variable Temperature ^{1}H NMR spectra **of 2, ^{Ar}TAA** in d_6-DMSO showing temperature dependence of amide-NH/triazole-CH chemical shift.

Table S6. Values of temperature co-efficient of amide-NH/triazole-CH chemical shifts of **TetraPeptide 3** (**BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me**)

Amide-NH or Triazole-CH	($\Delta\delta/\Delta T$) ppb/k
Carbamate_NH 1	-9.1
^{Al}**TAA**- scaffold_NH 2	-5.5
C-terminal Leucine_NH 3	-7.03
C-terminal Phe_NH 4	-6.43
^{Al}**TAA**_triazole CH 1	0.0005



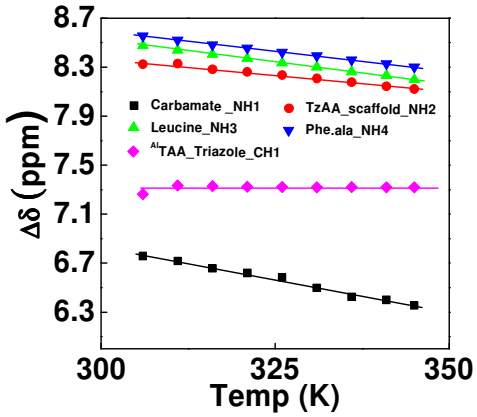


Figure S9. Temperature dependence of amide-NH/triazole-CH chemical shift in **Tetrapeptide 3**

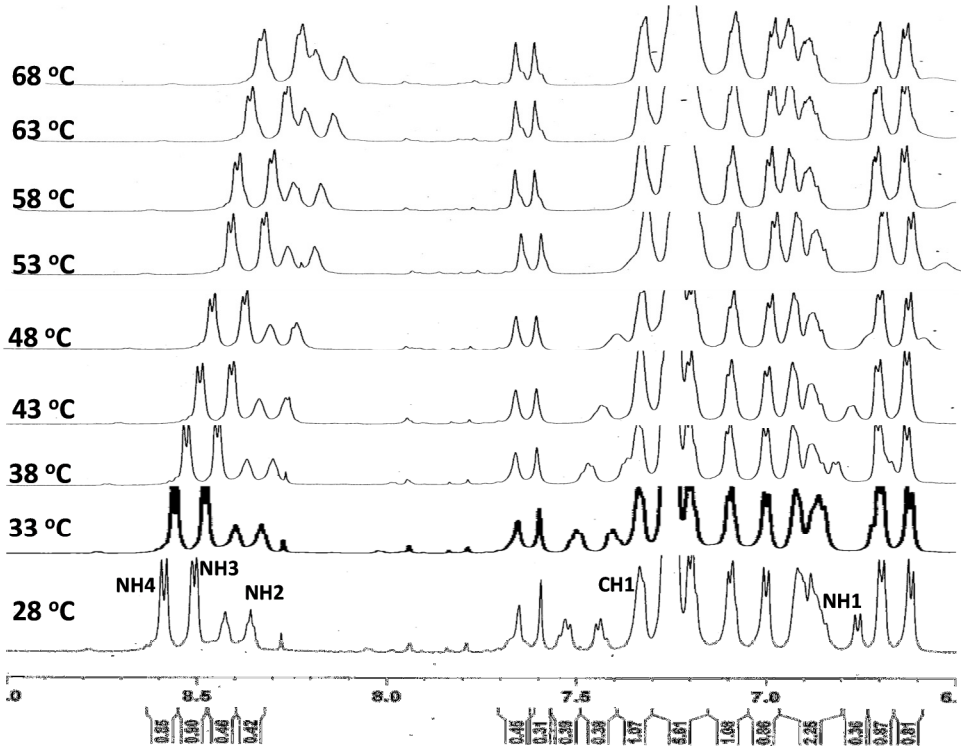
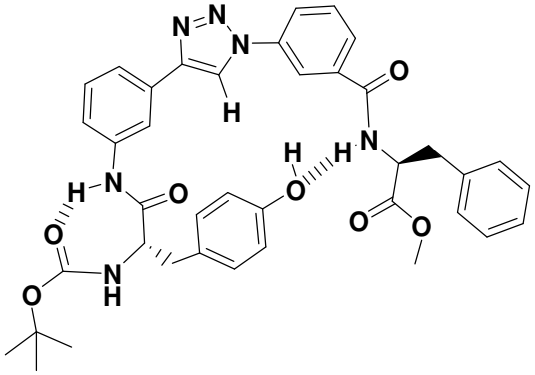


Figure S10. Variable temperature ^{1}H NMR spectra of **tetrapeptide 4** in d_6-DMSO showing temperature dependence of amide-NH/triazole-CH chemical shift.

Table S7. Values of amide-NH/triazole-CH chemical shifts of **Tripeptide 4** (**BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me**).

Amide-NH or Triazole-CH	**($\Delta\delta/\Delta$T) ppb/k**
Carbamate_NH 1	-9.42
^{Ar}**TAA** scaffold_NH 2	-6.32
C-terminal Phe_NH 3	-5.64
^{Ar}**TAA**_triazole-CH 1	-3.36
Tyrosine_OH	-6.48



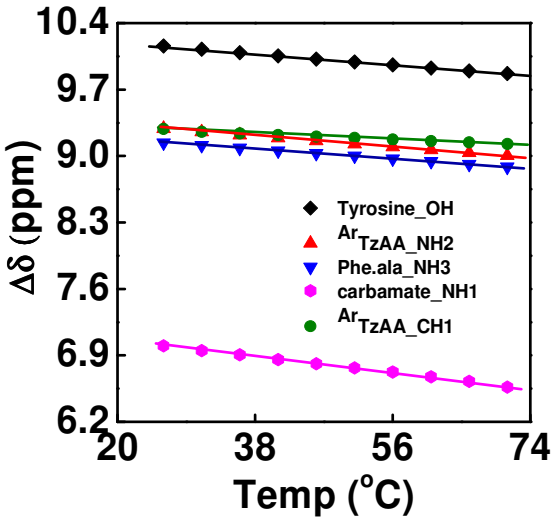


Figure S11. Temperature dependence of amide-NH/triazole-CH chemical shift in **Tripeptide 4.**

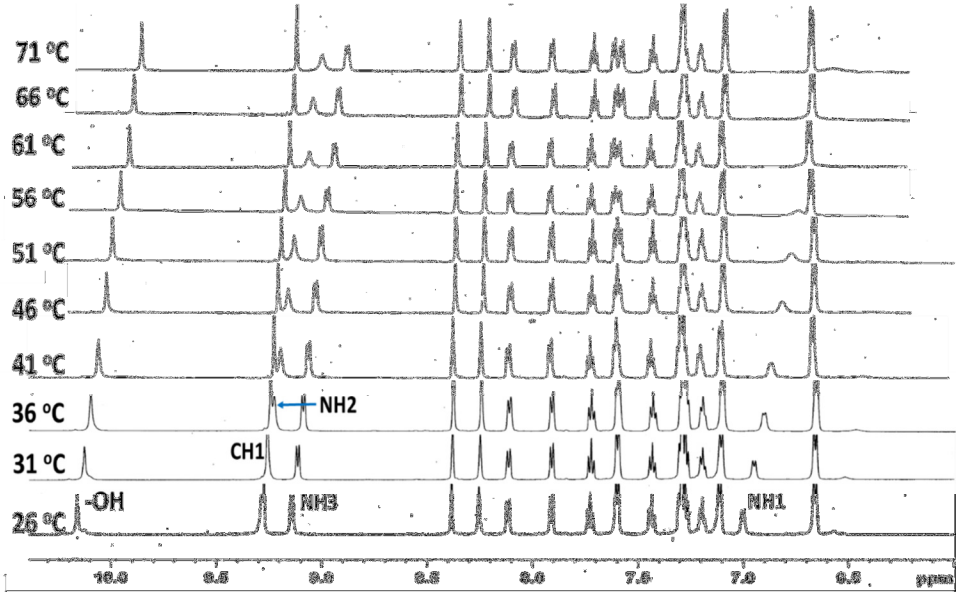


Figure S12. Variable temperature ^{1}H NMR spectra of **Tripeptide 4** in d_6-DMSO showing temperature dependence of amide-NH/triazole-CH chemical shift.

Table S8. Values of NH/CH chemical shifts with temperature of **Pentapeptide 5** (**BocNH-^{TPy}Ala^{Ac}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CONMe(OMe)**).

Amide-NH or Triazole-CH	(Δδ/ΔT) ppb/k
Carbamate_NH 1	- 7.2
N-terminal_Leucine_NH 2	- 4.3
^{Al}**TAA**_scaffold_NH 3	- 0.36
C-terminal_Leucine_NH 4	-3.4
C-terminal_Serine_NH 5	-6.4
^{TPy}**Ala**_triazole_CH 1	-1.5
^{Al}**TAA**_scaffold_triazole-CH 2	0.3
^{TPhen}**Ala**_triazole_CH 3	-0.51

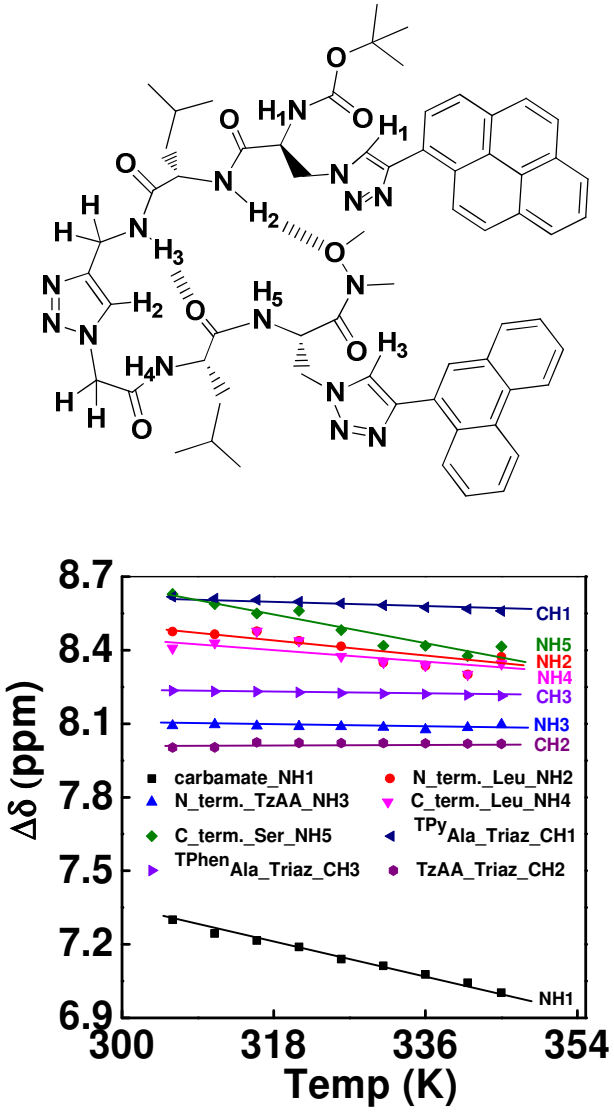


Figure S13. Temperature dependence of amide-NH/triazole-CH chemical shift in **Pentapeptide 5.**

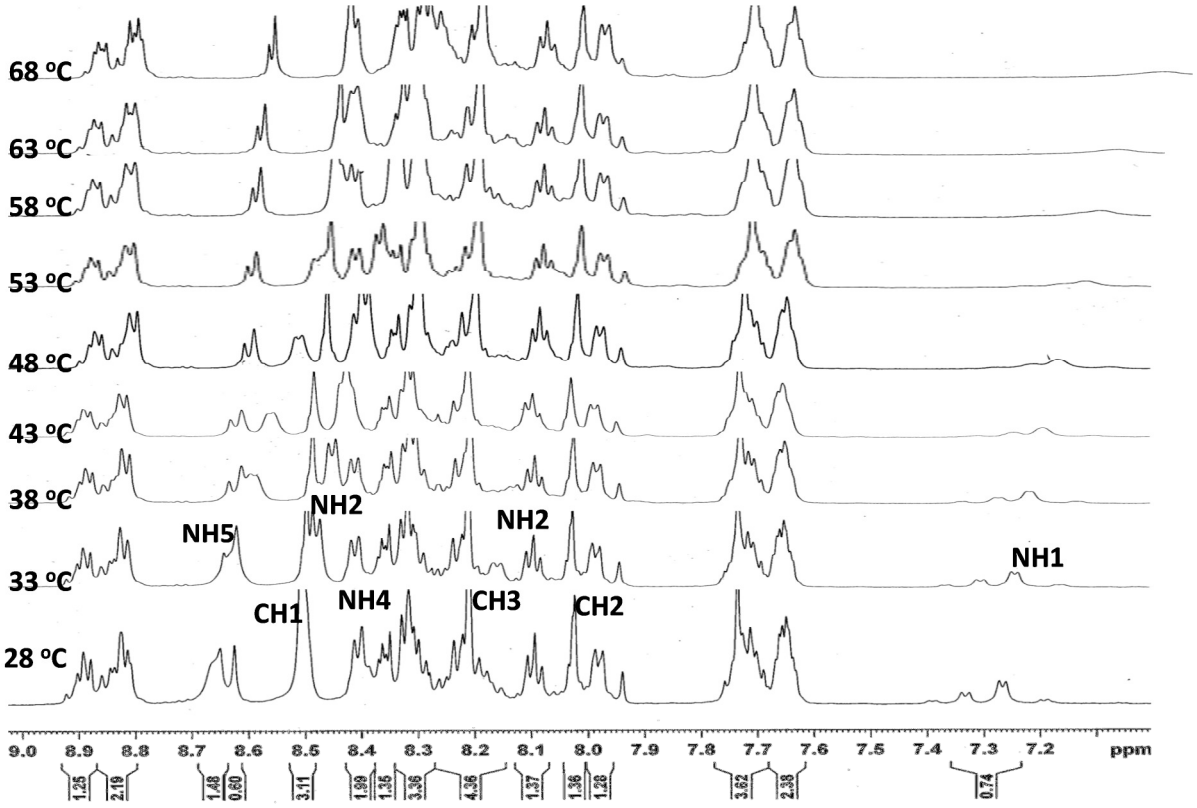


Figure S14. Variable temperature ^{1}H NMR spectra of **Pentapeptide 5** in d_6-DMSO showing temperature dependence of amide-NH/triazole-CH chemical shift.

9. Conformational Analysis of Peptides 3, 4 and 5 by 2D NMR Spectroscopy

9.1. Conformational Analysis of Tetrapeptide 3

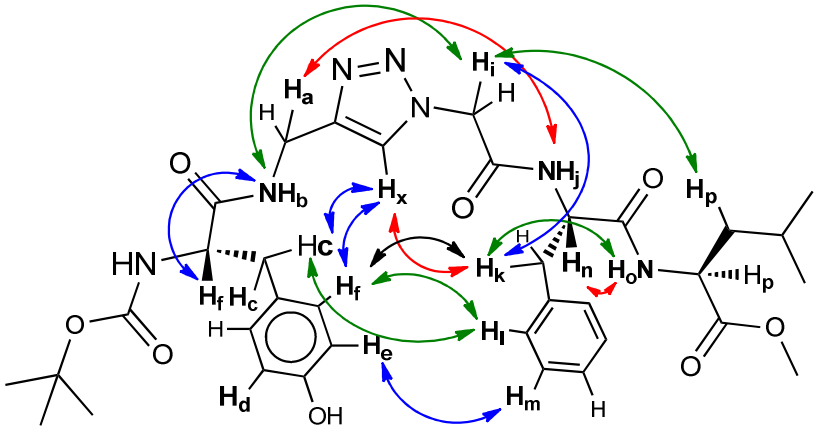


Figure S15. Various possible interactions revealed from various 2D NMR study in **Tetrapeptide 3 (BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me).**

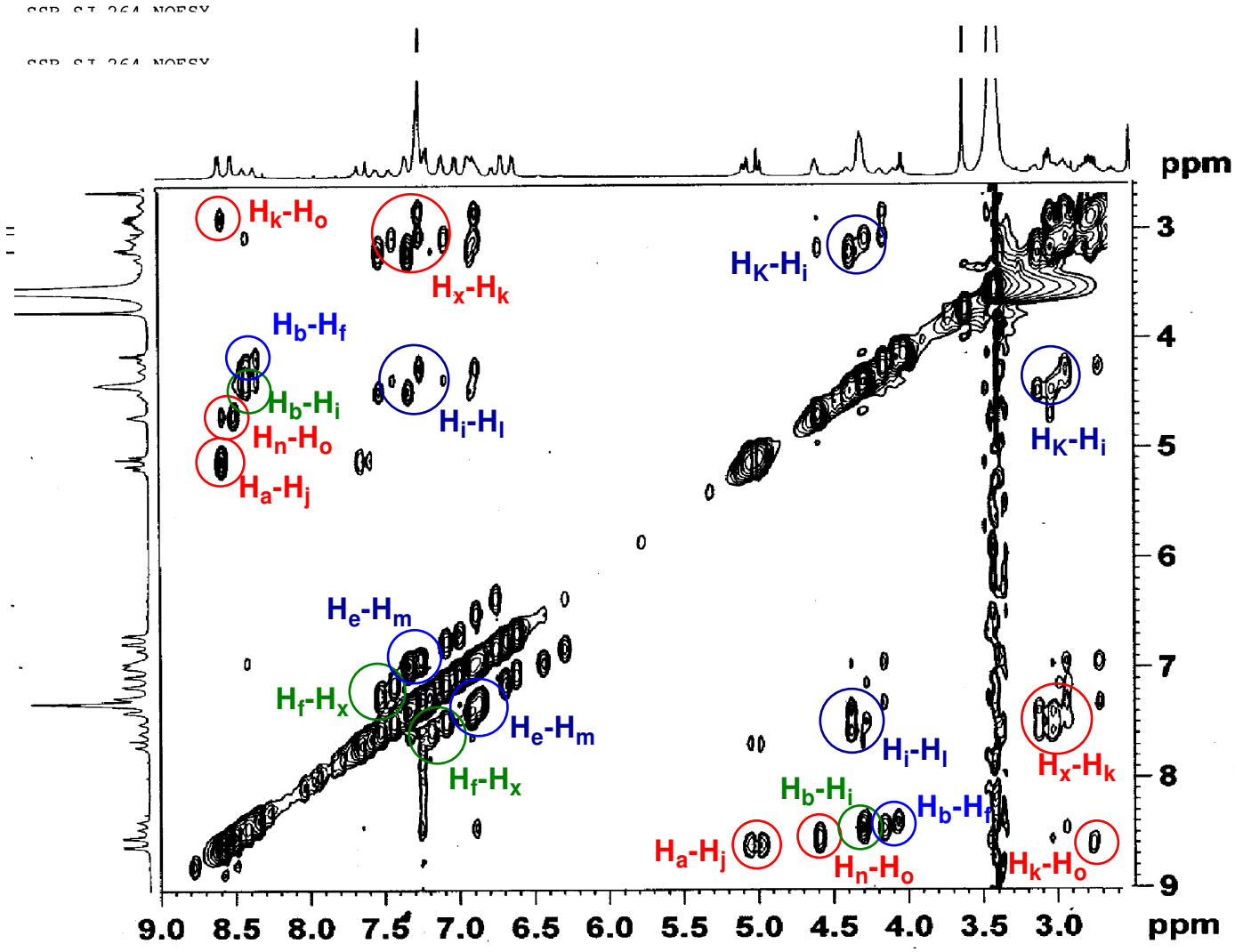


Figure S16. Expanded NOESY spectra of **Tetrapeptide 3** (**BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me**).

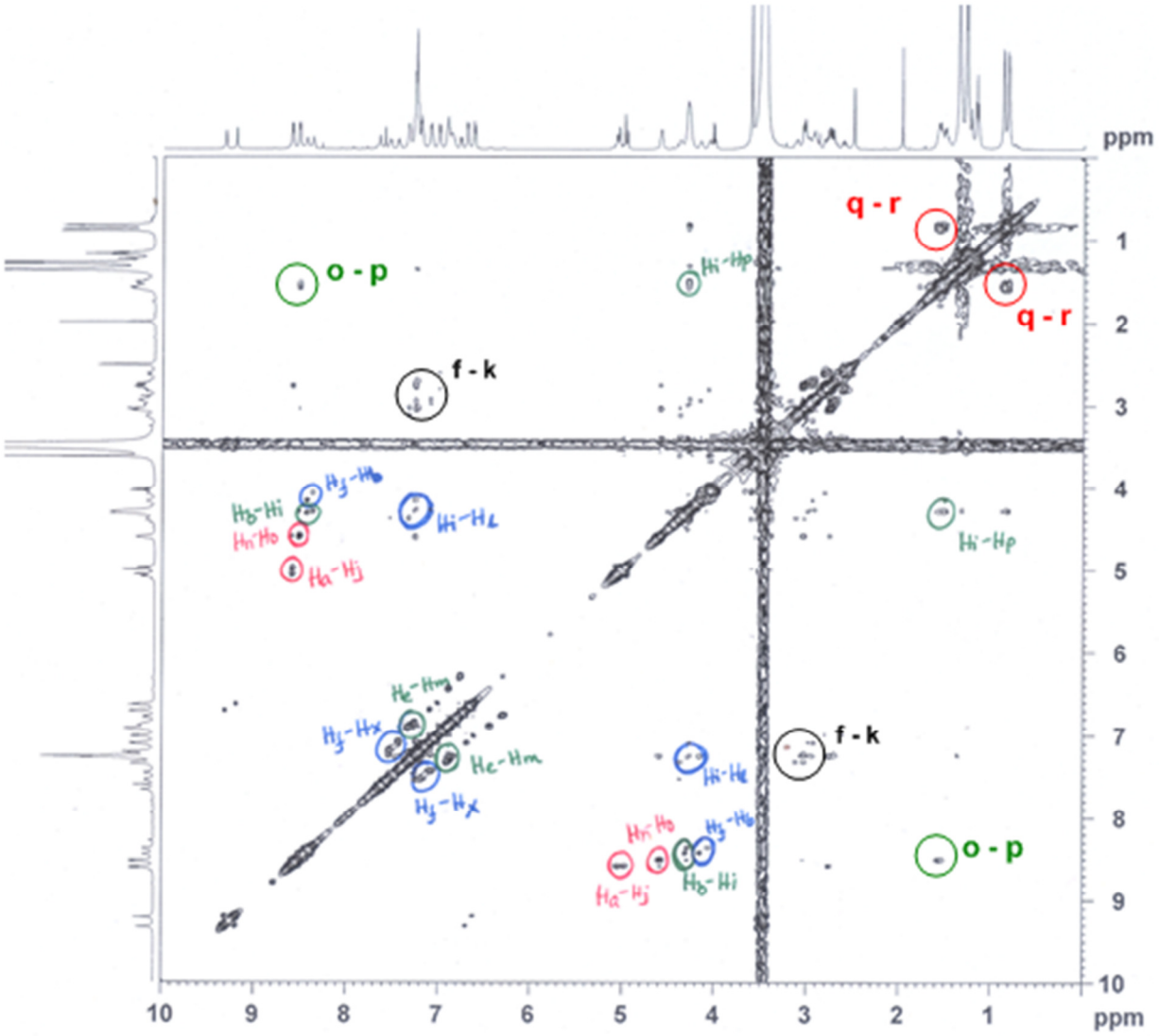


Figure S17. ROESY spectra of **Tetrapeptide 3** (**BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me**).

9.2. Conformational Analysis of Tripeptide 4

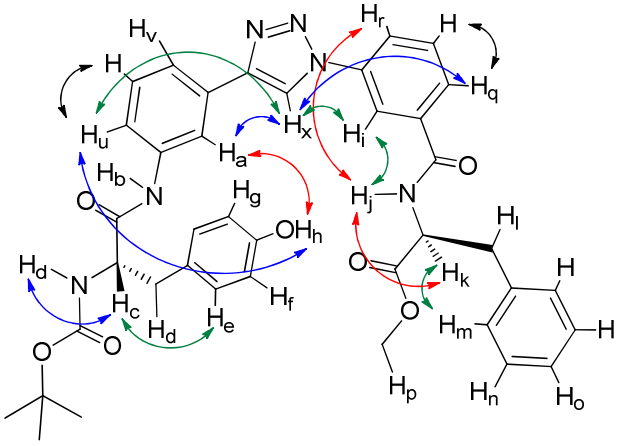


Figure S18. Various possible interactions revealed from various 2D NMR study in **Tripeptide 4 (BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me)**

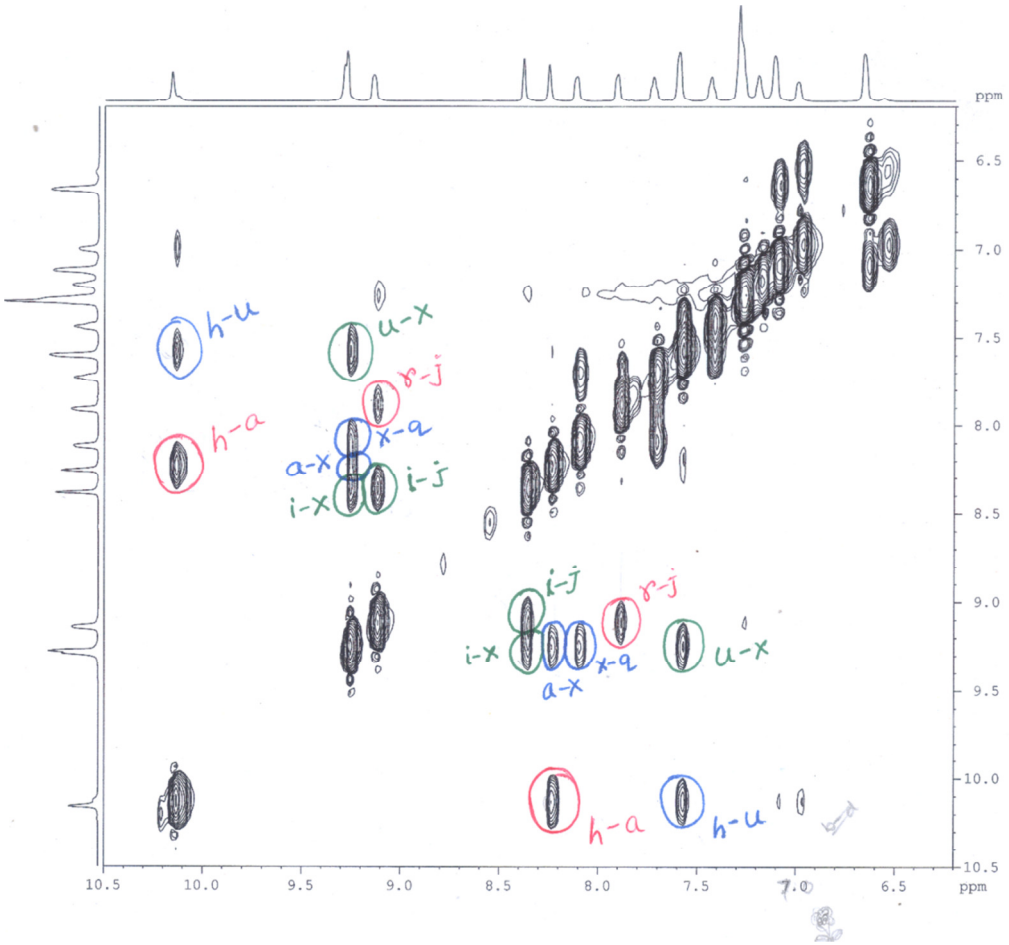


Figure S19. Expanded NOESY spectra of **Tripeptide 4 (BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me)**.

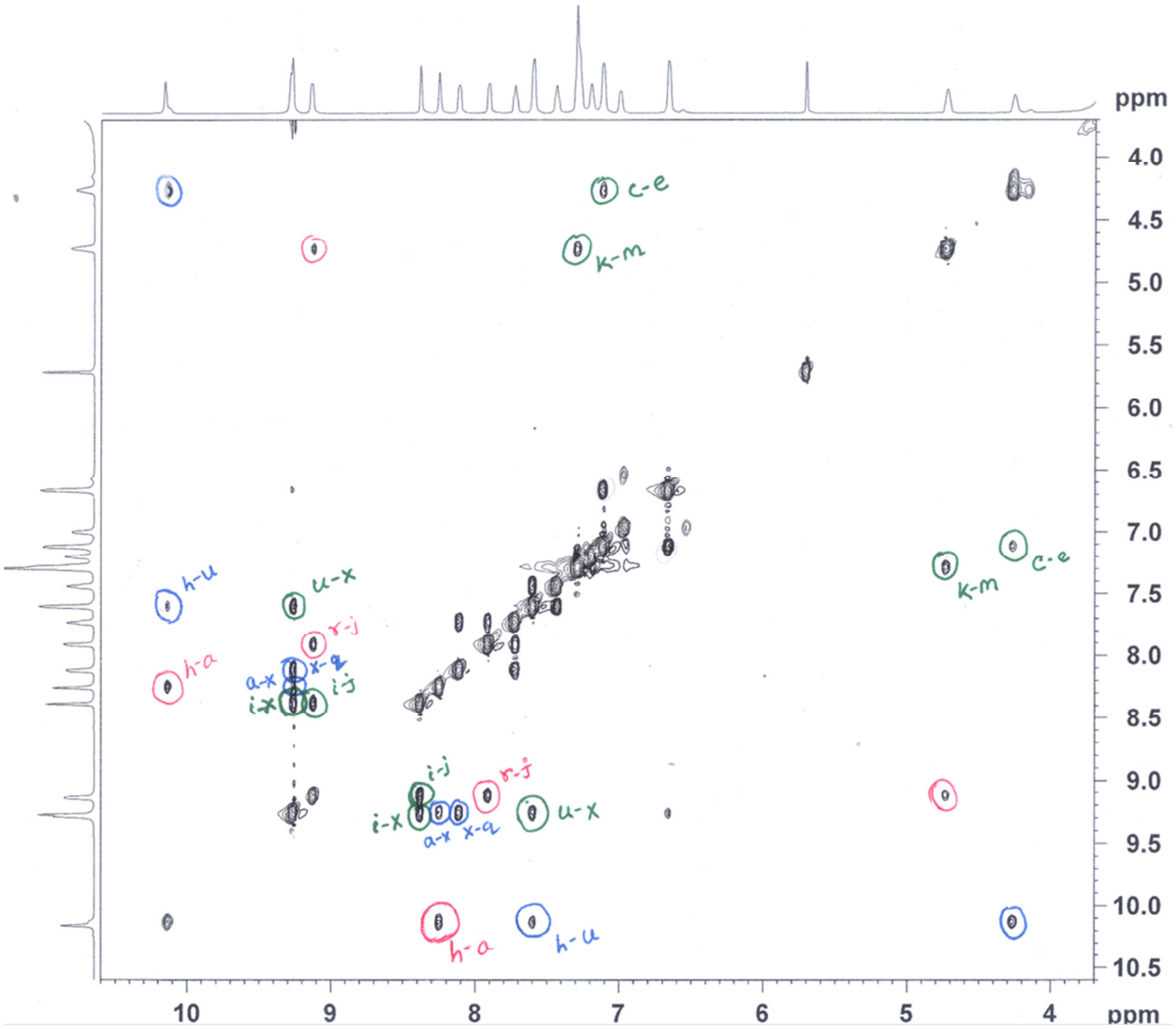


Figure S20. Expanded ROESY spectra of **Tripeptide 4 (BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me)**.

9.3. Conformational Analysis of Fluorescent Pentapeptide 5

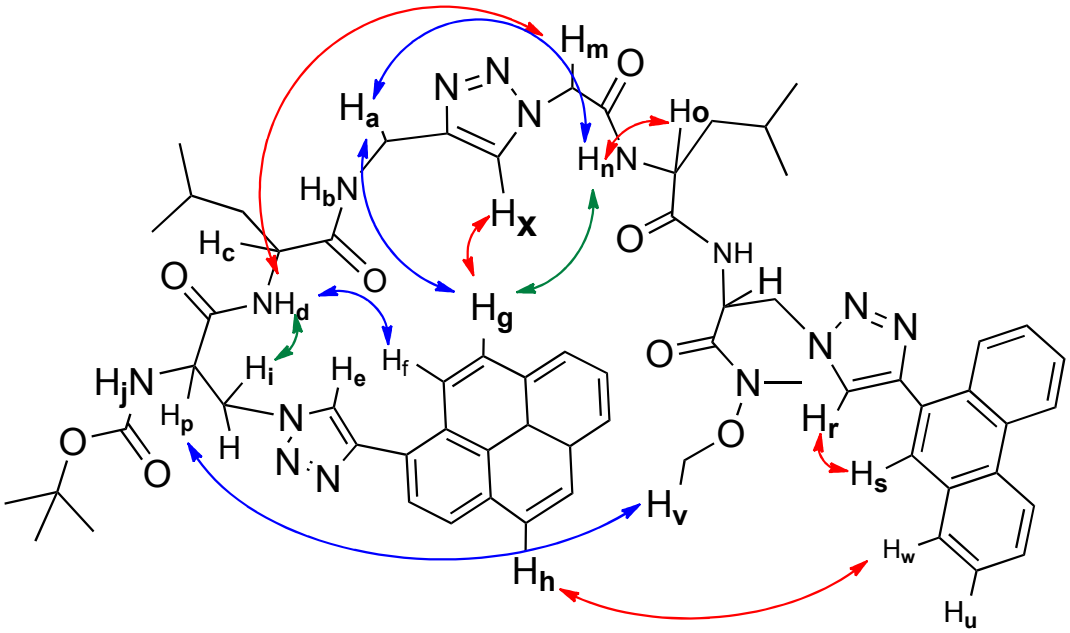


Figure S21. Various possible interactions revealed from various 2D NMR study in **Pentapeptide 5 (BocNH-^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CONMe(OMe)).**

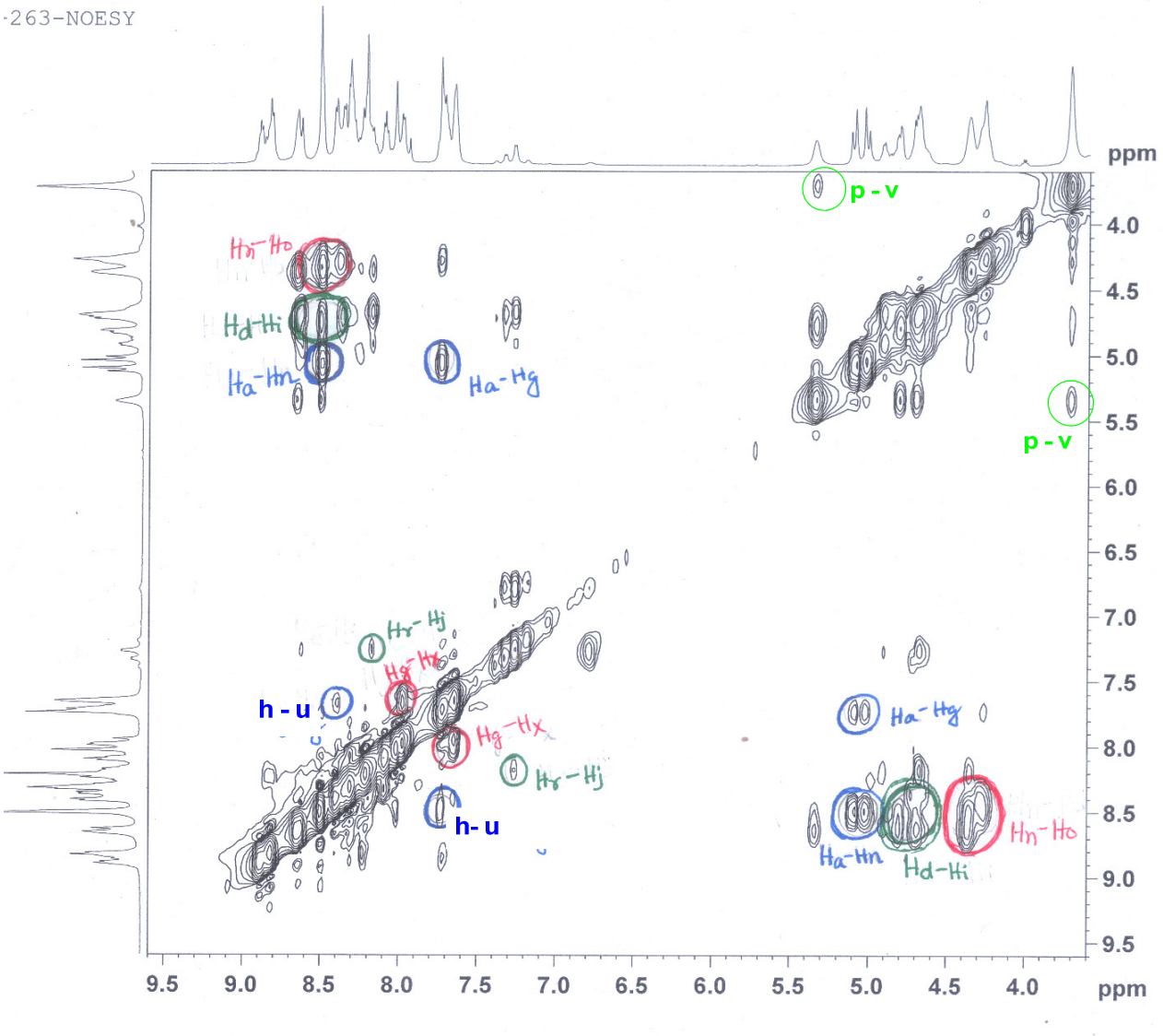


Figure S22. Expanded NOESY spectra of **Pentapeptide 5 (BocNH-^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CONMe(OMe))**.

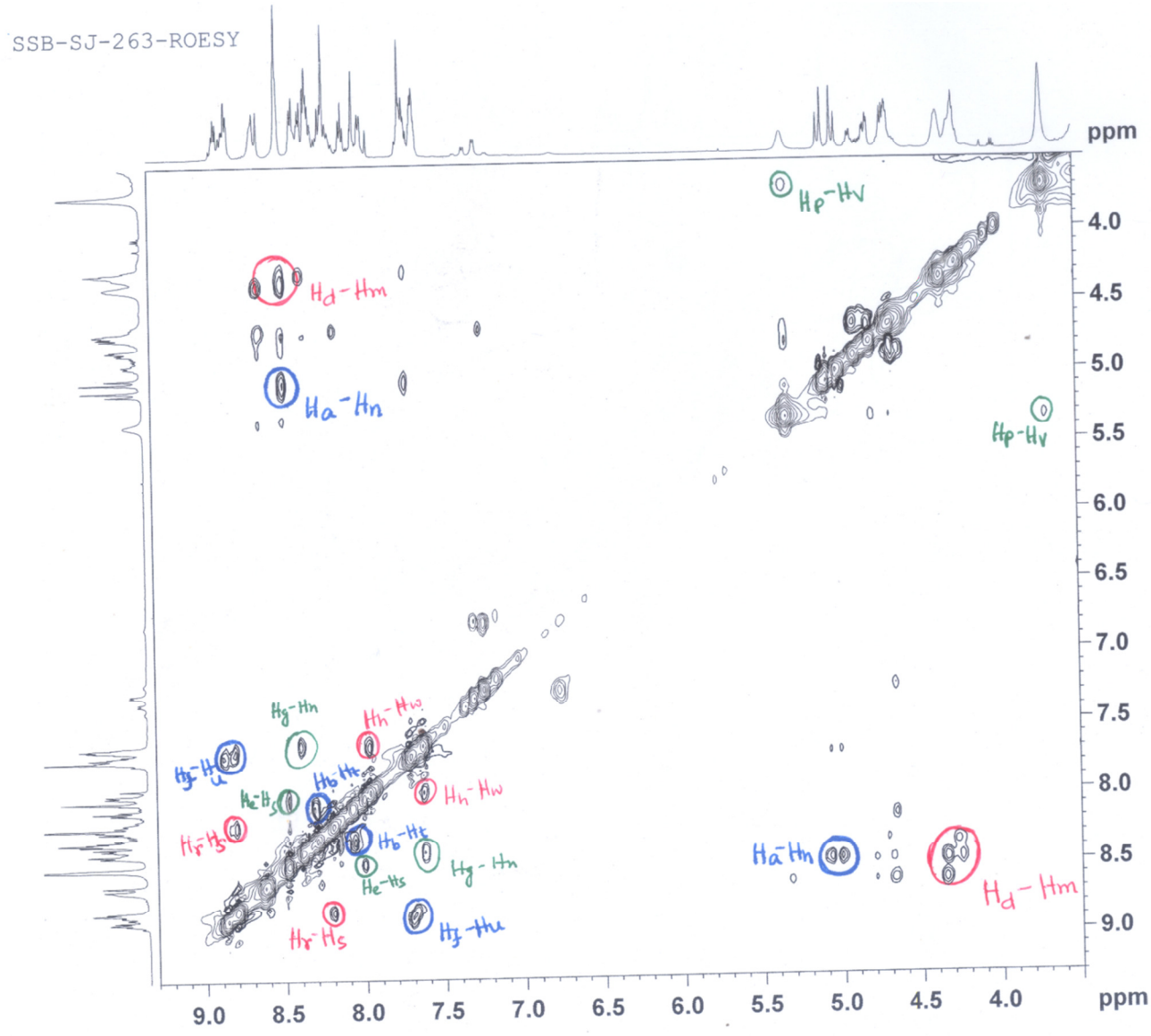


Figure S23. Expanded ROESY spectra of **Pentapeptide 5 (BocNH-^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CONMe(OMe))**.

10. MacroModel Study and Molecular Dynamics Simulation for Peptides 3-5[6-9]

10.1. Optimization of the Peptides and Conformational Search of Optimized Structures

Molecular modeling study of the peptides was carried out using Schrodinger MacroModel (Maestro vs. 9.0) software with OPLS 2005 force field in water. A conjugate gradient minimization scheme [PRCG (Polak-Ribiere Conjugate Gradient)] that uses the Polak-Ribiere first derivative method with restarts every 3N iterations was employed for the minimization of the peptides.

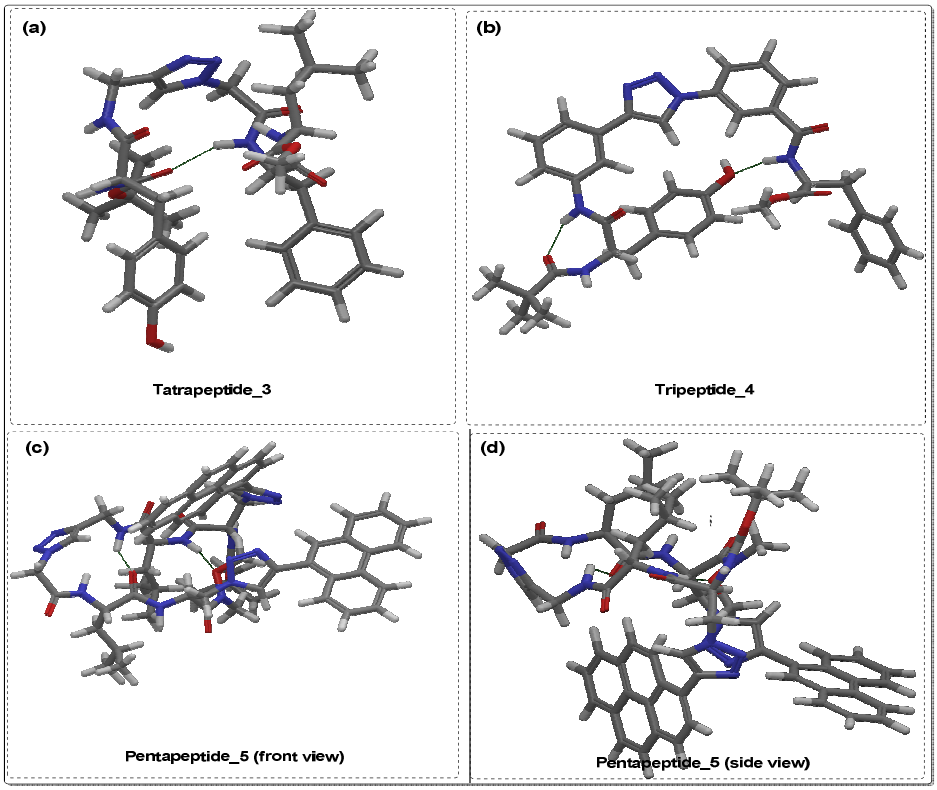


Figure S24A. OPLS 2005 force field energy minimized conformations in water of the peptides (a) **Tetrapeptide 3** (**BocNH-Tyr-^{Al}TAA-Phe-Leu-CO_2Me**), (b) **Tripeptide 4** (**BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me**), and (c-d) **Pentapeptide 5** (**BocNH-^{TPy}Ala^{Ac}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do} CONMe(OMe)**).

Next, we carried out conformational search using OPLS 2005 force field at constant dielectric in water with "large scale low-frequency-mode conformational search" (Mixed torsional/Large scale low-mode sampling = MCMM/LMCS) method using Schrodinger Macromodel (Maestro vs. 9.0) software package. It is a hybrid functional method wherein Low-Mode Conformational Search Methods is hybridized with Monte Carlo Multiple Minimum (MCMM) global searching. This method uses a combination of the random changes in torsion angles and/or molecular position from the MCMM method, together with the low-mode steps from the LLMOD method used in Large scale low-mode.

A total of 500 structures were processed with 500 maximum no. of steps iteration. A global search analysis eliminates redundant conformers using RMS deviation for all compared atoms exceed the threshold Cutoff of 0.5 Å. An optimal minimization method was chosen for minimizing the generating conformers.

A total of 84 (for Tetrapeptide **3**), 221 (for Tripeptide **4**) and 91 (for Pentapeptide **5**) minimized and well converged conformers were generate out of which the one conformer appeared 4 times (for Tetrapeptide **3**), 4 times (for Tripeptide **4**) and 6 times (for Pentapeptide **5**) which remained within 1.00 k.cal/mole (4.18 kJ/mole) global minimum with a convergence threshold of 0.031 to 0.015 to 0.007 RMSD (threshold cutoff = 0.05). These conformers were taken as the starting structures for MD simulation studies.

10.2. Molecular Dynamics Simulation of Optimized Structure of the Peptides

We carried out MD simulations for the peptides using an OPLS 2005 force field. The starting structures for the duplexes were the global minimum conformers. The MD simulations were performed using Schrodinger Macromodel (Maestro vs. 9.0) software package with OPLS 2005 force field in which the systems were subjected to 100 ps simulations time (with time step of 1.5 fs and equilibrium time 1.0 ps) at constant temperature (300 K) and pressure (1 atm) with shaking bonds to hydrogens. An optimal minimization method was chosen for minimizing the generated structures (with maximum iteration of 1000) with gradiant convergence threshold of 0.05.

The phenanthrene unit of C-terminal amino acid (^{TPhen}**Ala**^{Do}) and the Pyrene moiety of N-terminal amino acid (^{TPy}**Ala**^{Do}) in pentapeptide **5**, were chosen as freely moving moieties during the simulation. The aromatic units of the aromatic amino acids in peptides **3-4** were also chosen as freely moving moieties during the simulation.

Figure 33 showed the final structures of the peptides **3-5** obtained after the MD simulations. As shown in Figure 33, none of the peptide was distorted and retained their global minimum conformation.

The optimized geometry, conformational search and the MD simulation of the tetrapeptide **3** and pentapeptide **5** containing aliphatic triazolo amino acid scaffold (^{Al}**TAA**) in the backbone fully supported the type II β-turn conformation with H-bond involving >CO at i and NH at i+3. The short chain tripeptide **4** containing aromatic triazolo amino acid scaffold (^{Ar}**TAA**) in the backbone showed some turn structure having backbone H-bond between carbamate >C=O at i and amide-NH (Scaffold) at i + 2 which is also possible as was revealed from a VT-NMR study reflecting a γ-turn structure. Moreover, it was stabilized by a second side chain H-bonding involving –OH of Tyr at N-terminus and amide NH of Phe at C-terminus. The existence of 20% turn structure revealed from the CD spectroscopic study thus was supported by this observation from Macromodel study in tripeptide **4**. The observed H-bonding possibility revealed from the Modeling study was also supported from the VT-NMR study in all cases. The close proximity of Tyr and Phe and the strong aromatic interactions in peptide **3** as was revealed from NMR studies was also supported by the MD simulation. All the observations from MD simulation studies are consistent with the other spectroscopic studies.

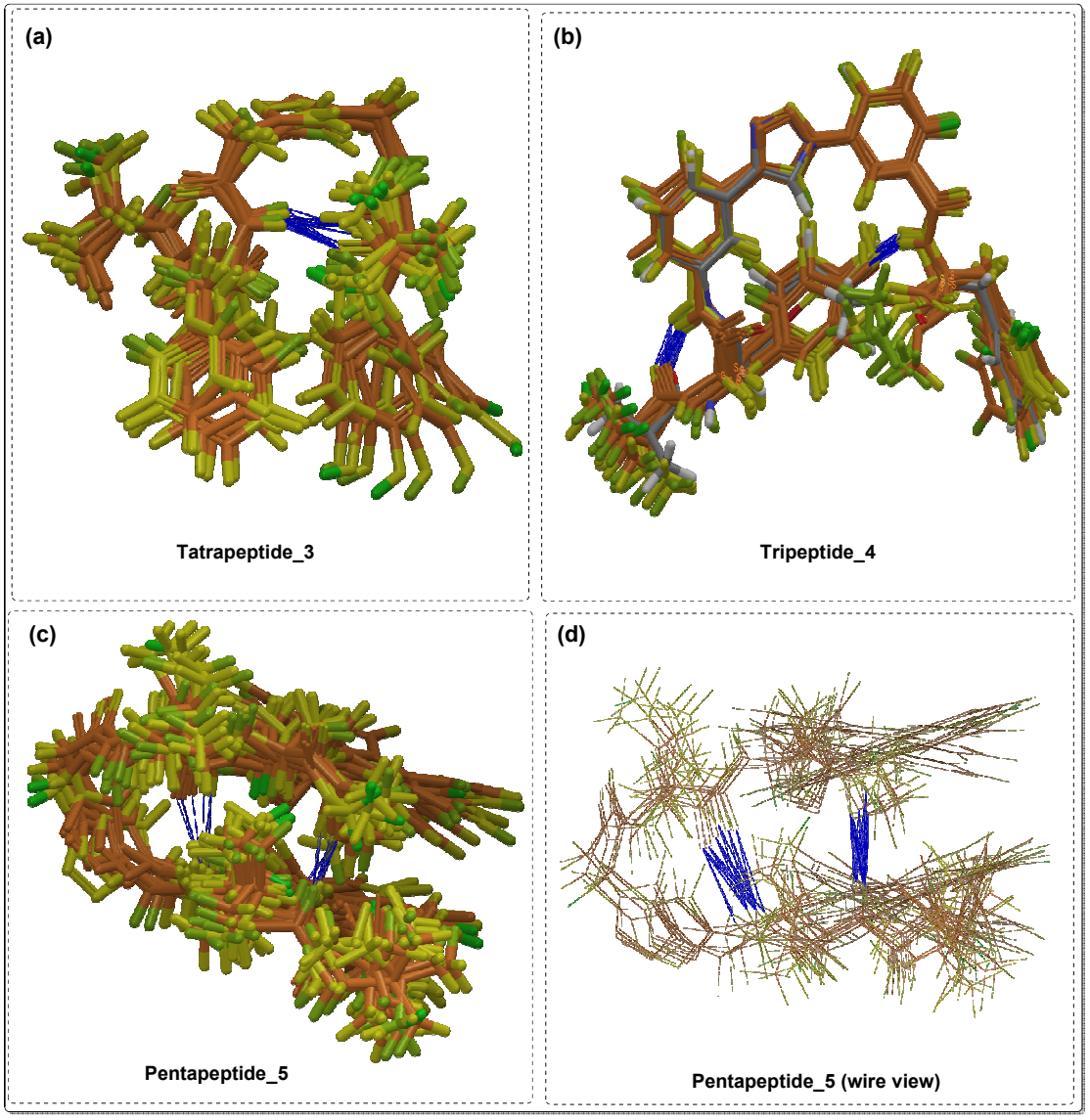


Figure 24B. Clustering of structures (within 21 kJ/mole global minima) obtained from molecular dynamics simulation for the peptides (a) **Tetrapeptide 3** (BocNH-Tyr-^{Al}**TAA**-Phe-Leu-CO_2Me), (b) **Tripeptide 4** (BocNH-Tyr-^{Ar}**TAA**-Phe-CO_2Me), (c) and (d) **Pentapeptide 5** (BocNH-^{TPy}**Ala**^{Do}-Leu-^{Al}**TAA**-Leu-^{TPhen}**Ala**^{Do}-CONMe(OMe)), one is wire view.

The parameters for simulation were so choosen as they fit well with peptides (evidenced from related other literatures) which ultimately supported our experimental observations. The potential function, Optimized Potential for Liquid Simulations (OPLS), developed by Jorgensen et al. have a simple form and they have been parametrized directly to reproduce experimental thermodynamic and structural data in solution phase or in fluid state. Consequently, they are computationally efficient and their description of proteins in solution should be superior to many alterantives that have been developed with limited condensed-phase data. [7]

The OPLS_2005 force field, as implemented in the Schrödinger suite 2009, follows all the functional form of the OPLS-AA family of force fields with additional stretch, bend, and torsional parameters for better coverage of ligand functional groups.[8] Therefore, the calculations presented in this work were performed using the OPLS_2005 all-atom force field with water as explicit solvent and were run with the parameters in the Maestro v 9.0 interface to Schrödinger suite 2009.[9]

Though the simulation considers the physiological conditions such as water, temperature etc., however this has been applied to study the dynamics of a single peptide. The simulation did not take care for other factors such as interaction with other small or large cell bio-molecules and the steric factors imposed in such cell environment. Therefore, the simulation is unable to mimic the dynamics of a cellular protein in presence of other cell bio-molecules.

11. Study of Photophysical Property

11.1. *UV-visible and steady state fluorescence measurements method*

UV-visible: All the UV –visible spectra of the compounds (10 µm) were measured in different solvents using a UV-Visible spectrophotometer with a cell of 1 cm path length at 25 ^{o}C. All the samples solutions were prepared with spectroscopic grade solvents. The measurements were carried out in absorbance mode. The absorbance values of the sample solutions were measured in the wavelength regime of 200–550 nm. All the sample solutions were prepared just before doing the experiment.

Steady state fluorescence: All the sample solutions with same concentration, as described in UV measurement experiments, prepared with spectroscopic grade solvent were used for measuring *steady state fluorescence*. Fluorescence spectra were obtained using a fluorescence spectrophotometer at 25 °C using 1 cm path length cell. The excitation wavelengths for the monomers were set at λ^{abs}_{max}, emission spectra were measured in the wavelength regime of 300–700 nm with an integration time of 0.2 sec. All the sample solutions were prepared just before doing the experiment. Fluorescence emissions were collected exciting the peptide solutions at the wave length corresponding to their absorption maxima. Steady-state fluorescence emission spectra were recorded at room temperature as an average of five scans using an excitation slit of 3.0 nm, emission slit 3.0 nm, and scan speed of 120 nm/min.The fluorescence quantum yields (Φ_f) were determined using quinine sulphate as a reference with the known Φ_f $(0.54)^3$ in 0.1 molar solution in sulphuric acid. The following equation was used to calculate the quantum yield,

$$\Phi_S = \Phi_R \frac{Fl_S^{Area}}{Fl_R^{Area}} \frac{Abs_R}{Abs_S} \frac{n_S^2}{n_R^2}$$

where, Φ_R is the quantum yield of standard reference, Fl_S^{Area} (sample) and Fl_R^{Area} (reference) are the integrated emission peak areas, Abs_S (sample) and Abs_R (reference) are the absorbances at the excitation wavelength, and n_S (sample) and n_R (reference) are the refractive indices of the solutions.

11.2. UV-visible and Fluorescence Spectra

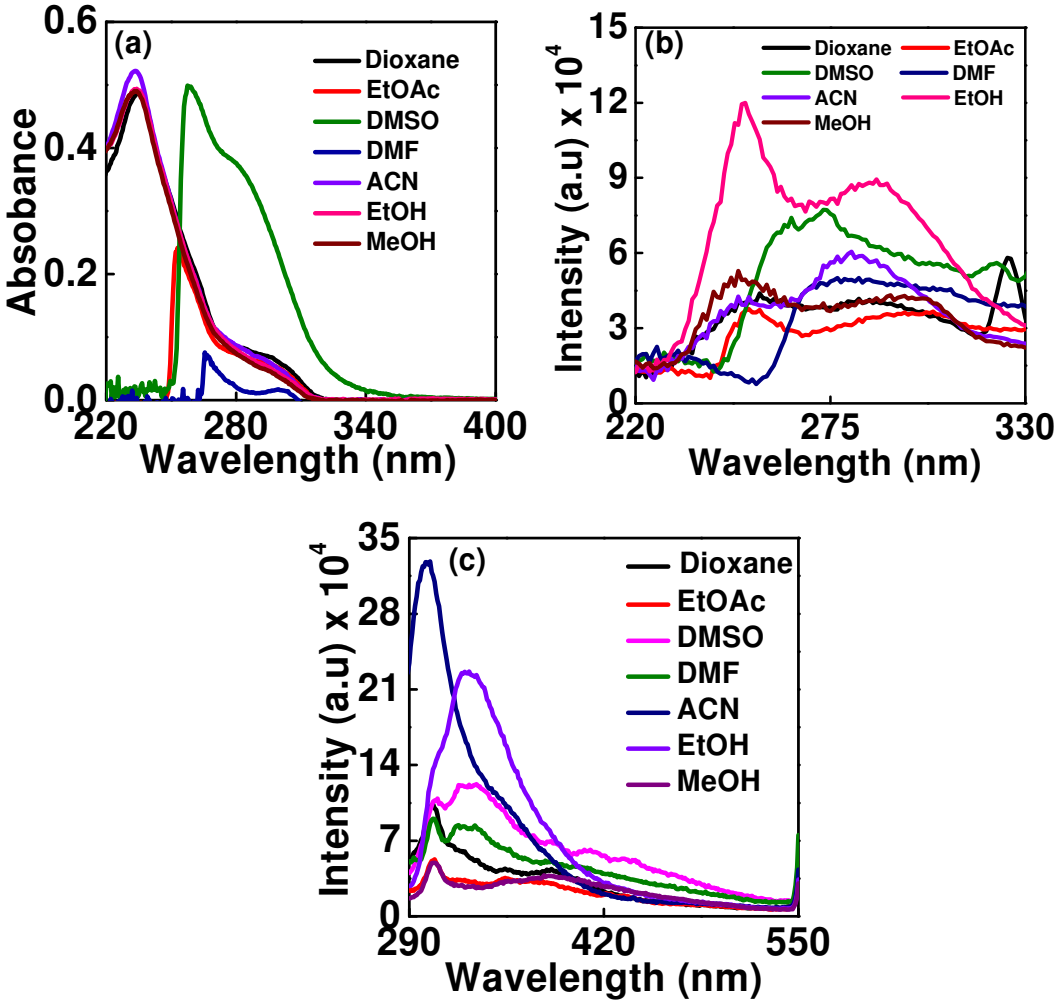


Figure S25. UV-Visible (a), excitation (b), and fluorescence emission spectra (c) of the **Aromatic Amino Acid Scaffold 2 [BocNH-^{Ar}TAA-CO_2H]** in different solvents [10 μM, r.t.; $\lambda_{ex} = \lambda_{max} \approx 280$ nm in each solvent].

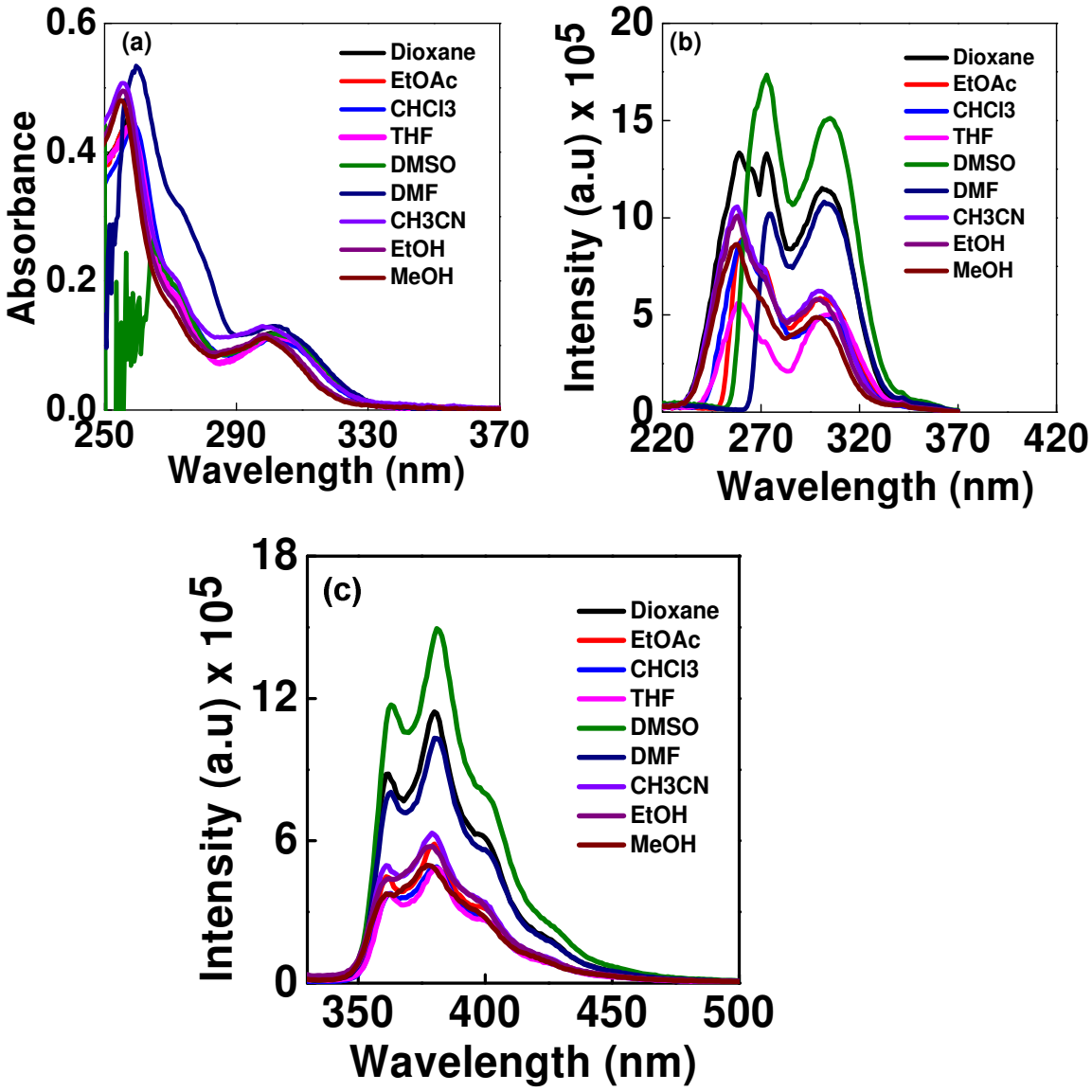


Figure S26. UV-Visible (a), excitation (b), and fluorescence emission spectra (c) of **Dipeptide 34 [BocLeU-^{TPhen}Ala-CO(NMe)OMe; Considered as the only Donor Chromophore in FRET study]** in different solvents [10 μM, r.t.; $\lambda_{ex} = \lambda_{max} \approx 300$ nm in each solvent].

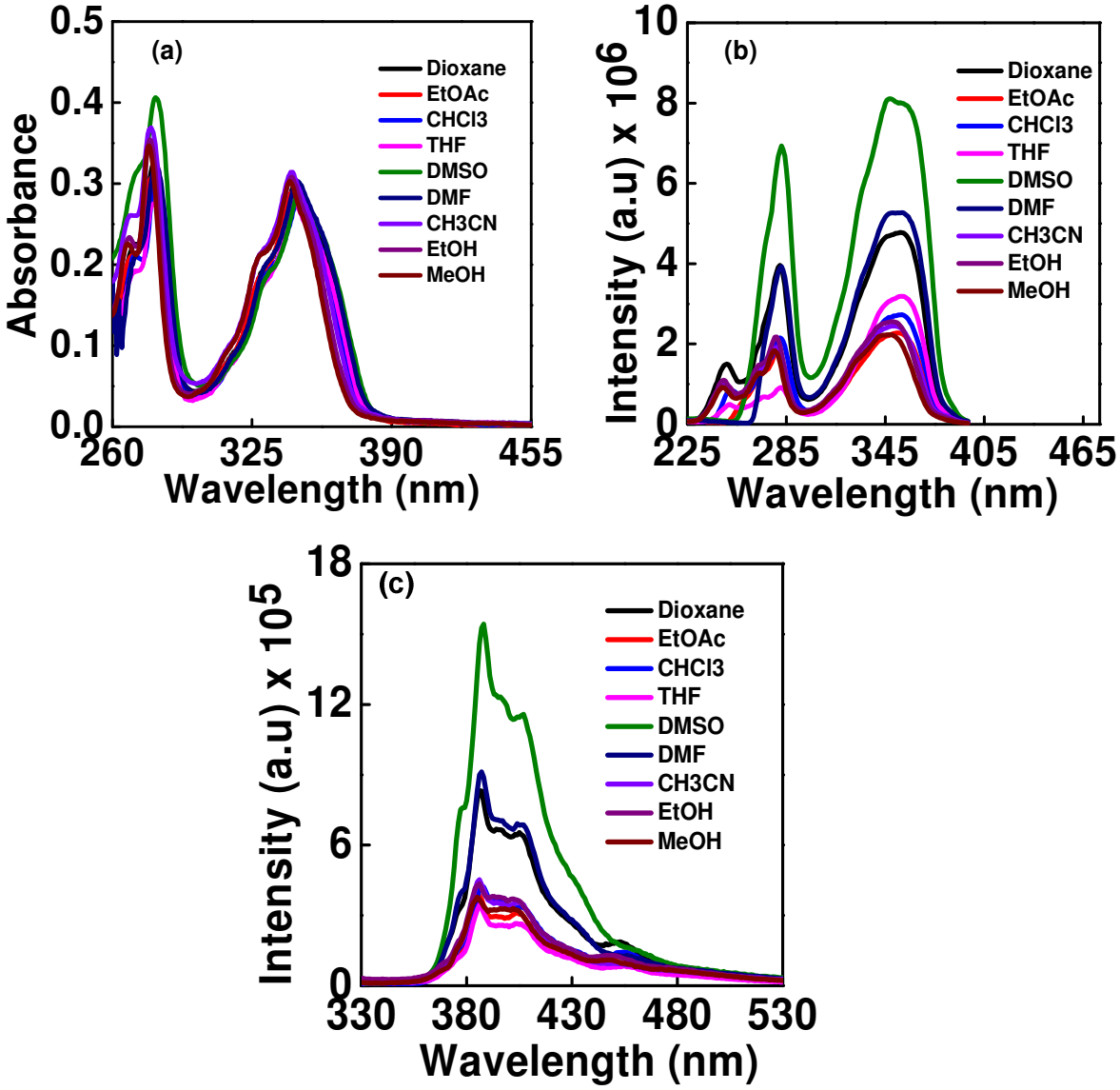


Figure S27. UV-Visible (a), excitation (b), and fluorescence emission spectra (c) of **Dipeptide 40 [Boc^{TPy}Ala^{Do}-Leu-CO$_2$Me; Considered as the only Acceptor Chromophore in FRET study]** in different solvents [10 μM, r.t.; $\lambda_{ex} = \lambda_{max} \approx 345$ nm in each solvent].

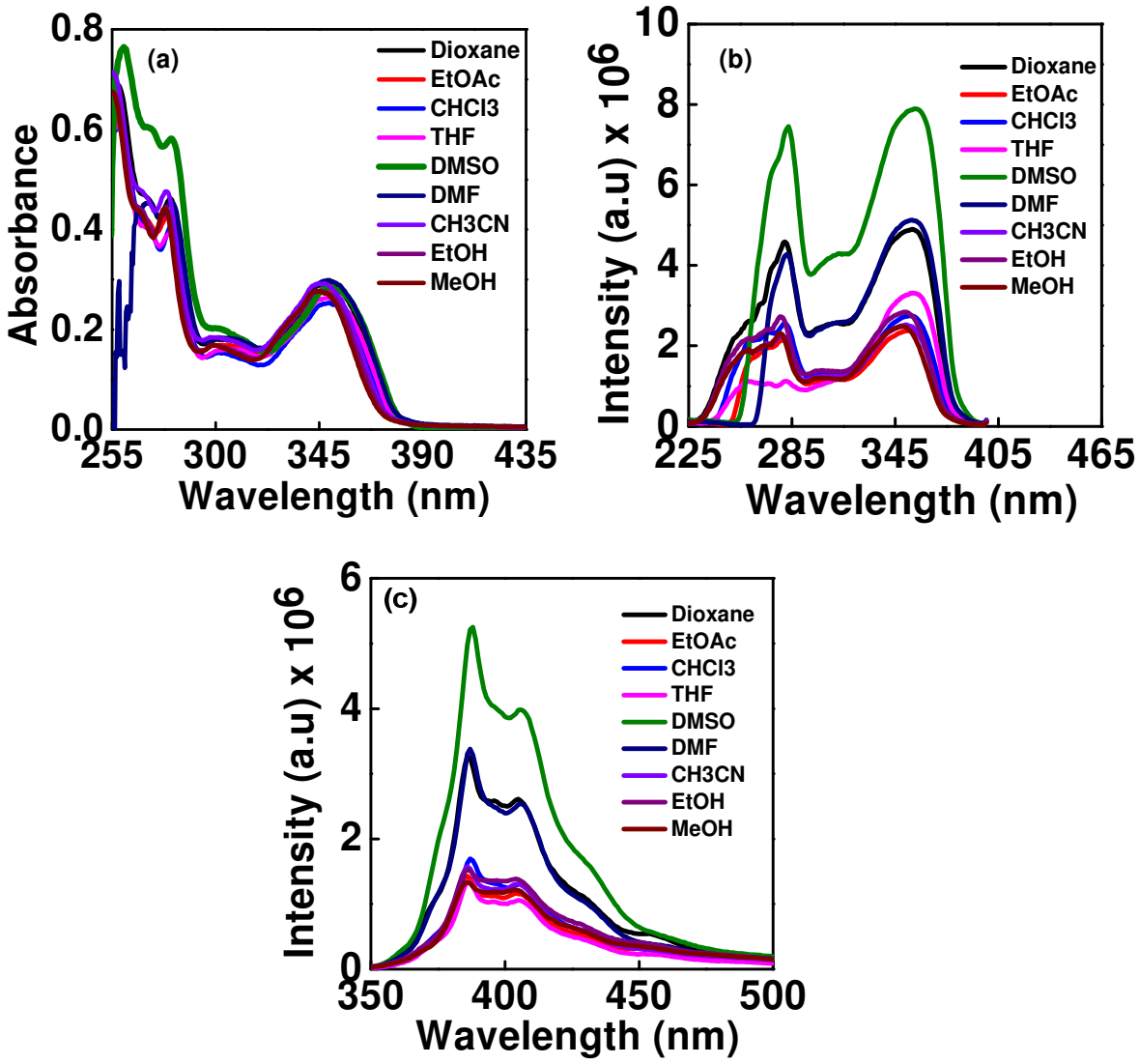


Figure S28. UV-Visible (a), excitation (b), and fluorescence emission spectra (c) of Fluorescent **Pentapeptide 5 [Boc^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CO_2Me]** in different solvents [10 μM, r.t.; $\lambda_{ex} = \lambda_{max} \approx 300$ and 345 nm in each solvent].

11.3. Photophysical Summary of Synthesized Dipeptide 34 [The Donor Chromophore; BocLeU-^{TPhen}Ala-CO(NMe)OMe], Dipeptide 40 [The Acceptor Chromophore; Boc^{TPy}Ala-LeuCO$_2$Me] and Pentapeptide 5 [The Donor-Acceptor chromophore labeled FRET peptide; Boc^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CO$_2$Me]

Table S9. Summary table of photophysical properties of the **Dipeptide 34**

Entry	Solvents	Δf	UV-Vis & Fluorescence		
			λ_{max}^{abs} (nm)	λ_{max}^{fl} (nm)	Φ_f
Dipeptide 34 [The Donor Chromophore Only]	Dioxane	0.021	258, 269, 301	362, 380, 399	0.12
	$CHCl_3$	0.148	259, 270, 301	361, 380, 395	0.05
	EtOAc	0.201	257, 269, 300	361, 381, 398	0.06
	THF	0.210	258, 271, 302	361, 380, 397	0.05
	DMSO	0.265	265, 271, 301	362, 381, 399	0.14
	DMF	0.275	259, 270, 302	362, 380, 397	0.10
	EtOH	0.290	254, 269, 298	361, 378, 396	0.07
	ACN	0.307	255, 269, 299	360, 379, 395	0.06
	MeOH	0.309	255, 270, 298	361, 377, 395	0.06
	Buffer (pH=7.0)	0.318	256, 300	362, 376, 395	0.09

Table S10. Summary table of photophysical properties of the **Dipeptide 40**

Entry	Solvents	Δf	UV-Vis & Fluorescence		
			λ_{max}^{abs} (nm)	λ_{max}^{fl} (nm)	Φ_f
Dipeptide 40 [The Acceptor Chromophore Only]	Dioxane	0.021	279, 331, 345	386, 405, 423	0.22
	$CHCl_3$	0.148	280, 334, 346	386, 406, 426	0.13
	EtOAc	0.201	278, 330, 343	387, 406, 426	0.10
	THF	0.210	279, 332, 344	386, 405, 425	0.15
	DMSO	0.265	280, 334, 344	387, 406, 428	0.40
	DMF	0.275	280, 333, 346	387, 406, 426	0.23
	EtOH	0.290	277, 330, 343	385, 403, 422	0.11
	ACN	0.307	278, 331, 343	386, 404, 424	0.10
	MeOH	0.309	276, 329, 342	385, 403, 422	0.10
	Buffer (pH=7.0)	0.318	283,330, 344, 355	383, 396, 466	0.05

Table S11. Summary table of photophysical properties of the **Pentapeptide 5**

Entry	Solvents	Δf	UV-Vis & Fluorescence		
			λ_{max}^{abs} (nm)	λ_{max}^{fl} (nm)	Φ_f
Pentapeptide 5 [The FRET Peptide]	Dioxane	0.021	280, 305, 348	386, 405, 424	0.33
	$CHCl_3$	0.148	280, 301, 349	386, 405, 425	0.19
	EtOAc	0.201	279, 304, 346	386, 404, 426	0.16
	THF	0.210	280, 305, 348	386, 405, 424	0.15
	DMSO	0.265	280, 301, 350	387, 406, 427	0.46
	DMF	0.275	281, 305, 349	387, 406, 426	0.32
	EtOH	0.290	278, 299, 345	386, 404, 423	0.19
	ACN	0.307	278, 299, 346	385, 404, 423	0.16
	MeOH	0.309	277, 299, 344	385, 403, 423	0.18
	Buffer (pH=7.0)	0.318	284, 308, 357	385, 398, 466	0.02

12. Study of Fluorescence Resonance Energy Transfer (FRET) in Pentapeptide 5

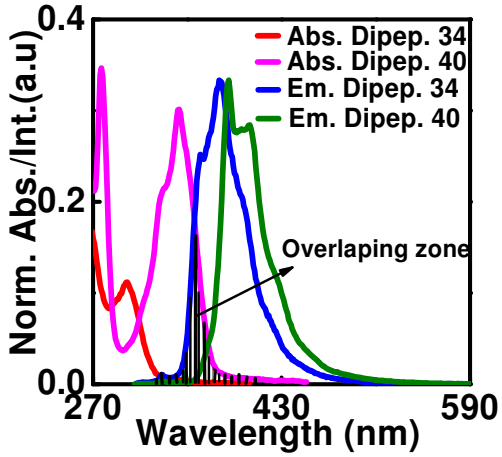


Figure S29. (a) Overlaping of emission spectra of **Dipeptide containing fluorescent amino acid ^{TPhen}Ala^{Do}** (**34**) (act as a FRET donor) and the absorption spectra of **Dipeptide containing fluorescent amino acid ^{TPy}Ala^{Do}** (**40**) (act as a FRET acceptor) (10 μM each, r.t.; λ_{ex} = 300 nm in CH_3OH).

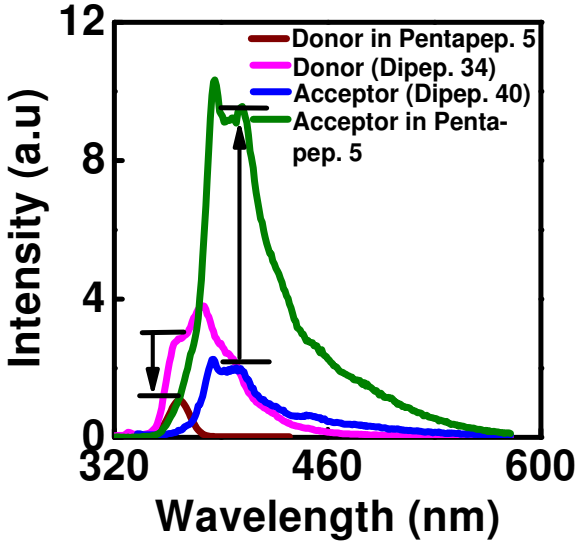


Figure S30. Fluorescence spectra of individual donor (**dipeptide 34**) and acceptor amino acid (**dipeptide 40**) and the **Pentapeptide 5** which contain these two dipeptides. In **Pentapeptide 5**, acceptor emission increased by almost five times in presence of donor, whereas the donor emission decreases almost three times of the individual donor emission. This change in fluorescence intensity is visual evidence of FRET (The mole fraction of donor/acceptor in **dipeptide 34** and **40** and **pentapeptide 5** were kept fixed in methanol solvent).

Calculation of the Forster distance and FRET efficiency: The fluorescence resonance energy transfer (FRET) and the Förster distance for the FRET were calculated using the following three equations. The efficiency of energy transfer, *E*, was calcula-ted using the equation (1)

$$E=\frac{R_0^6}{R_0^6+r^6}=1-\frac{F}{F_0} \quad \textbf{.....(1)}$$

where F and F_0 are the fluorescence intensity of donor in the presence and absence of acceptor, r is the distance between donor and the acceptor and R_0 is the critical distance when the energy*v* transfer efficiency is 50% . The Förster distance R_0 (Å) was calculated by the following equation (2)

$$R_0=[8.79\times10^{-5}\kappa^2 n^{-4}\Phi_D J(\lambda)]^{1/6} \textbf{.....(2)}$$

where κ^2 is the orientation, n is the refractive index of the medium, Φ_D is the quantum yield of the donor in the absence of acceptor $J(\lambda)$ is the overlap integral of the fluorescence emission spectrum of the donor and the absorption spectrum of the acceptor given by the following equation (3)

$$J=\frac{\int_0^\infty F_D(\lambda)\varepsilon_A(\lambda)\lambda^4 d\lambda}{\int_0^\infty F_D(\lambda)d\lambda} \quad \textbf{.....(3)}$$

where $F_D(\lambda)$ is the fluorescence intensity of the donor in the wavelength range λ to $\lambda + \Delta\lambda$ with the total intensity normalized to unity. $\varepsilon_A(\lambda)$ is the molar extinction coefficient of the acceptor as a function of wavelength (λ).

Using the values of κ^2= 2/3, n = 1.329, Φ_D = 0.06, and the obtained overlap integral, $J(\lambda)$ =1.1085 x 10^{15}, the R_0 and r values were calculated which were found to be R_0 = 31 Å and r = 23 Å. R_0 is the critical distance when the energy transfer efficiency is 50 % and r is the distance between the donor and acceptor.

Energy Transfer efficiency (E) = 1- τ/τ_0 = 85 %. τ and τ_0 are the fluorescence life time of donor in the presence and absence of acceptor.

13. Time Resolved Fluorescence Study and Spectra of Peptides

The fluorescence lifetime experiment was carried out using a time resolved fluorescence spectrophotometer at 25 °C using 1 cm path length cell with the same samples as described for steady state spectroscopic study. A 290 nm and 340 nm laser were used as excitation light source. The lifetime data were calculated by software with fixed fitting range. The time correlated single photon counting (TCSPC) method was used to calculate the lifetime data. The life time data (Global Analysis) were calculated by the FAST software package with fitting range 205 – 4000 channels.

Table S12. Summary table of fluorescence lifetimes of the peptides **34, 40** and **5**

	Compound	λ_{ex}	λ_{em} [nm]	τ_1 [ns]	τ_2 [ns]	$\langle\tau\rangle$ [ns]	k_f [$10^8 s^{-1}$]	k_{nr} [$10^8 s^{-1}$]	χ^2
ACN	**Dipeptide 34 [The Donor Chromophore Only]**	293	370	2.58 (11%)	13.17 (89%)	12.9	0.04	0.73	0.96
	Dipeptide 40 [The Acceptor Chromophore Only]	293	400	3.55 (39%)	15.6 (61%)	14.1	0.07	0.64	1.06
		343	400	3.25 (27%)	15.52 (73%)	14.7	0.06	0.61	1.07
	Pentapeptide 5 [The FRET Peptide]	293	370	1.94 (60%)	15.4 (40%)	13.2	0.12	0.63	1.04
		293	400	5.36 (18%)	16.45 (82%)	15.7	0.10	0.53	1.03
		343	400	1.71 (28%)	16.2 (73%)	15.5	0.10	0.54	1.1
MeOH	**Dipeptide 34 [The Donor Chromophore Only]**	293	370	1.99 (49%)	13.78 (51%)	12.2	0.04	0.77	1.1
	Dipeptide 40 [The Acceptor Chromophore Only]	293	400	5.55 (41%)	18.2 (59%)	15.9	0.06	0.56	1.08
		343	400	3.93 (42%)	17.64(58 %)	15.7	0.06	0.57	1.1
	Pentapeptide 5 [The FRET	293	370	1.95 (73%)	16.5 (26%)	12.8	0.14	0.64	1.1
		293	400	2.95 (42%)	19.01 (58%)	17.4	0.10	0.47	1.1

	Peptide]	343	400	3.3 (35%)	18.4 (65%)	17.1	0.10	0.48	1.1
For lifetimes of the fluorescent amino acids λex = 293 and 343 nm; Concentration of each fluorescent amino acid = 10 μM; <τ>, k_f, and k_{nr} are weighted means from the biexponential fits: $<\tau> = 1/(\alpha_1/\tau_1 + \alpha_2/\tau_2)$, $k_f = \Phi_f/<\tau>$, and $k_{nr} = (1- \Phi_f)/<\tau>$.									

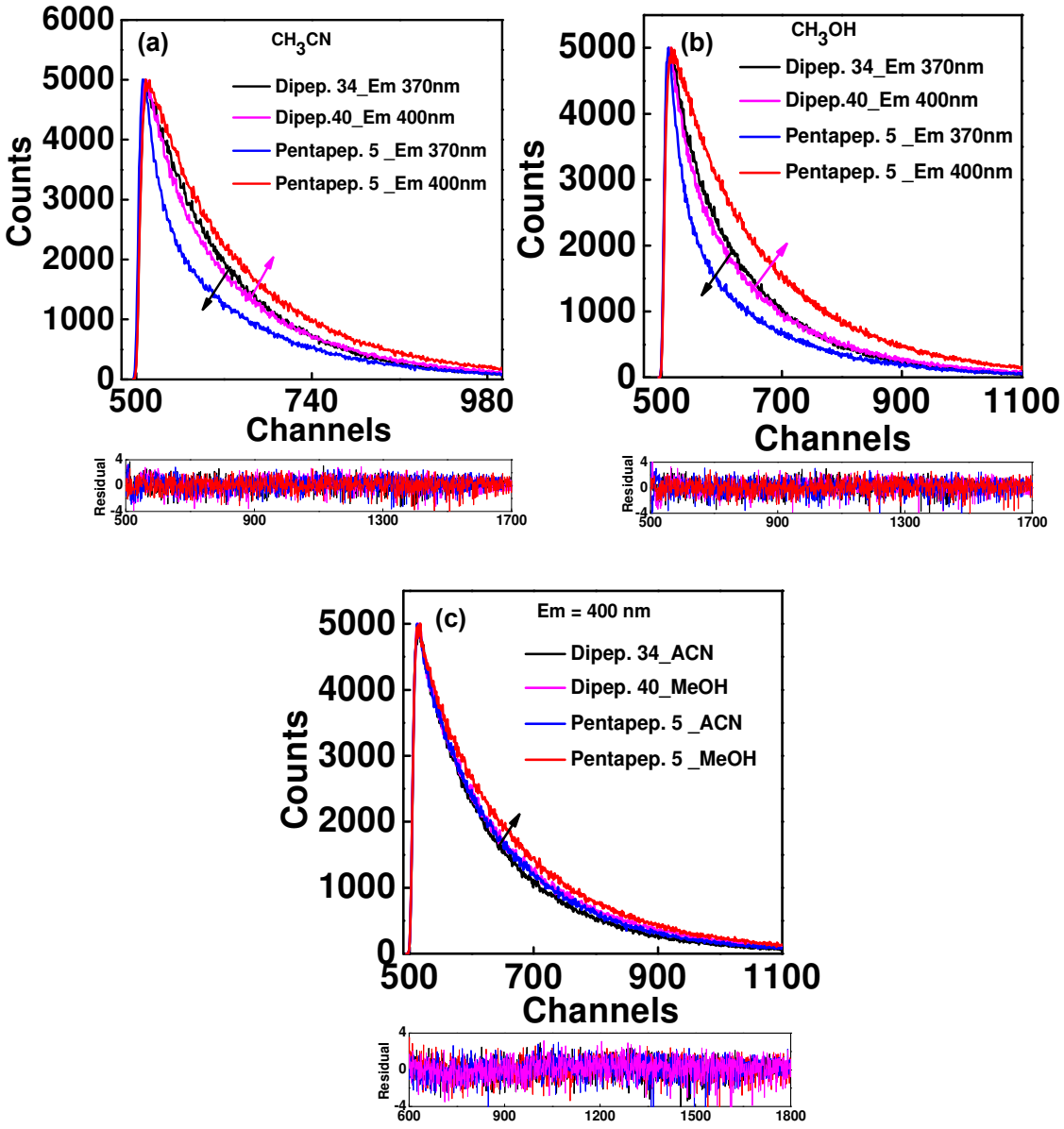


Figure S31. Time resolved fluorescence and corresponding residual spectra of **Dipeptide 34, 40** and **pentapeptide 5** using (a) 293 LED in acetonitrile (b) 293 LED in methanol and (c) 343 LED in both the solvent (1ns = 10 chan.).

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14. ^{1}H and ^{13}C NMR Spectra of Some Synthesized Compounds

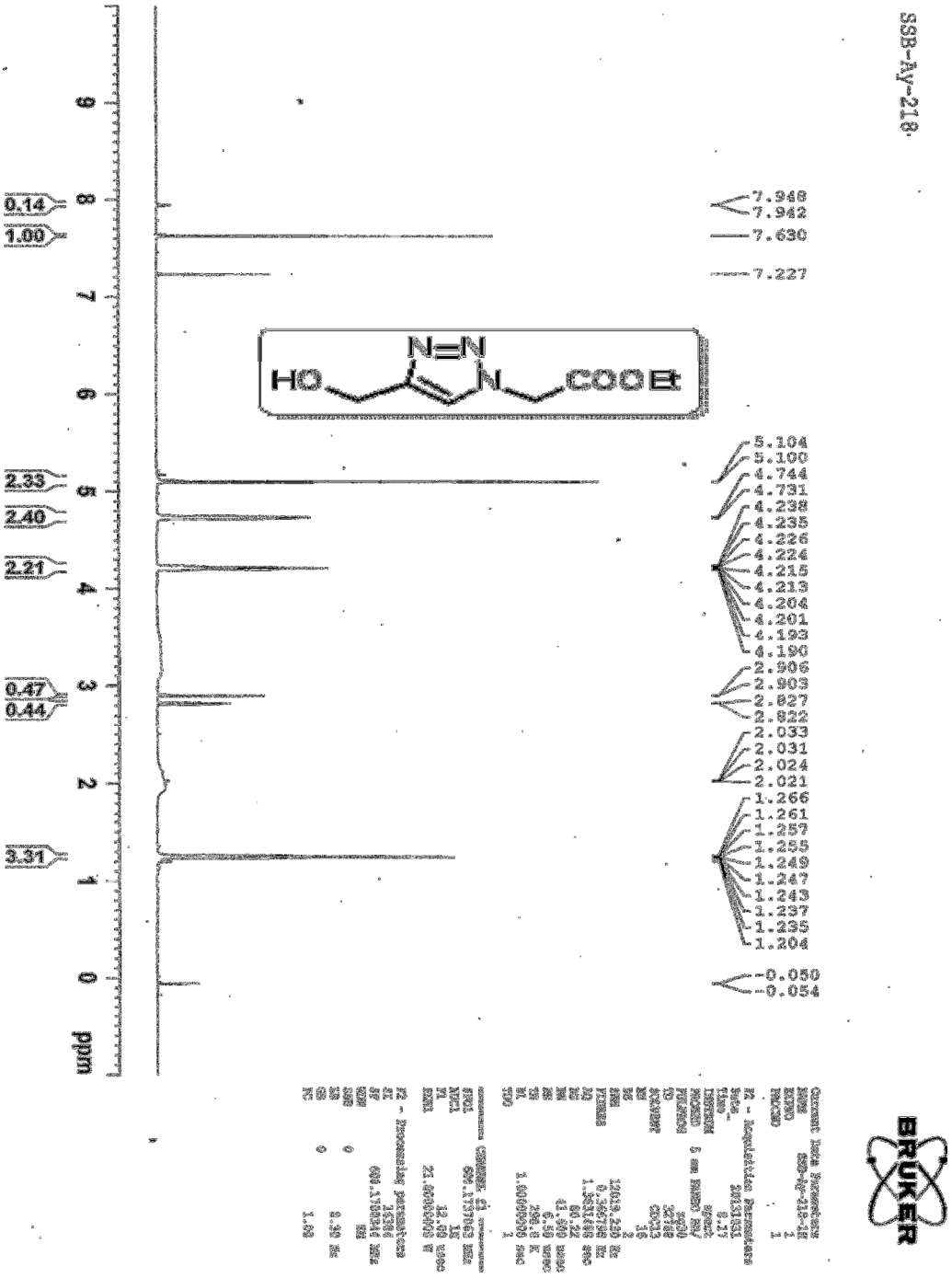

Figure S32. ^{1}H Spectra of synthesized compound **9.**

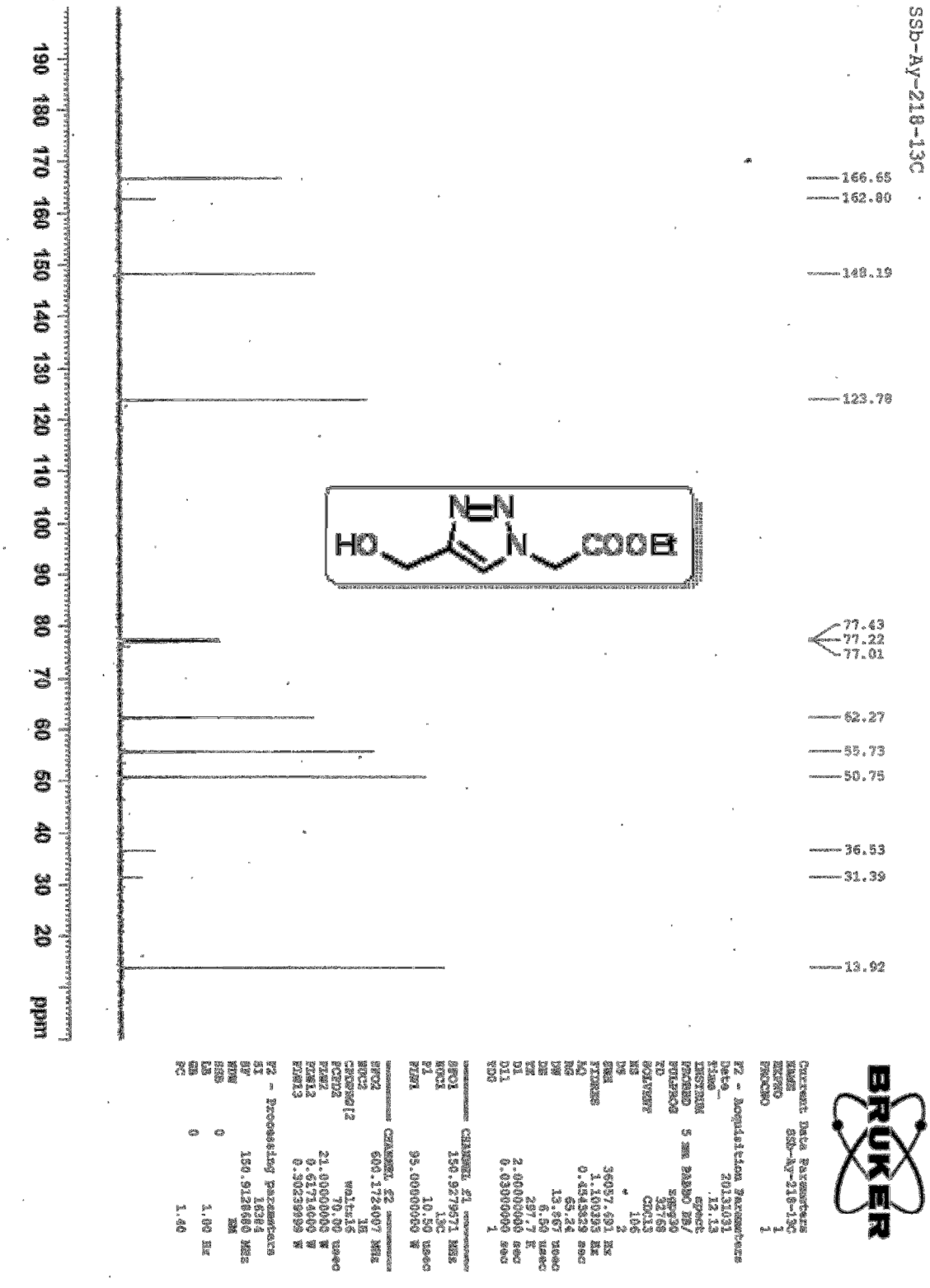

Figure S33. ^{13}C Spectra of synthesized compound **9.**

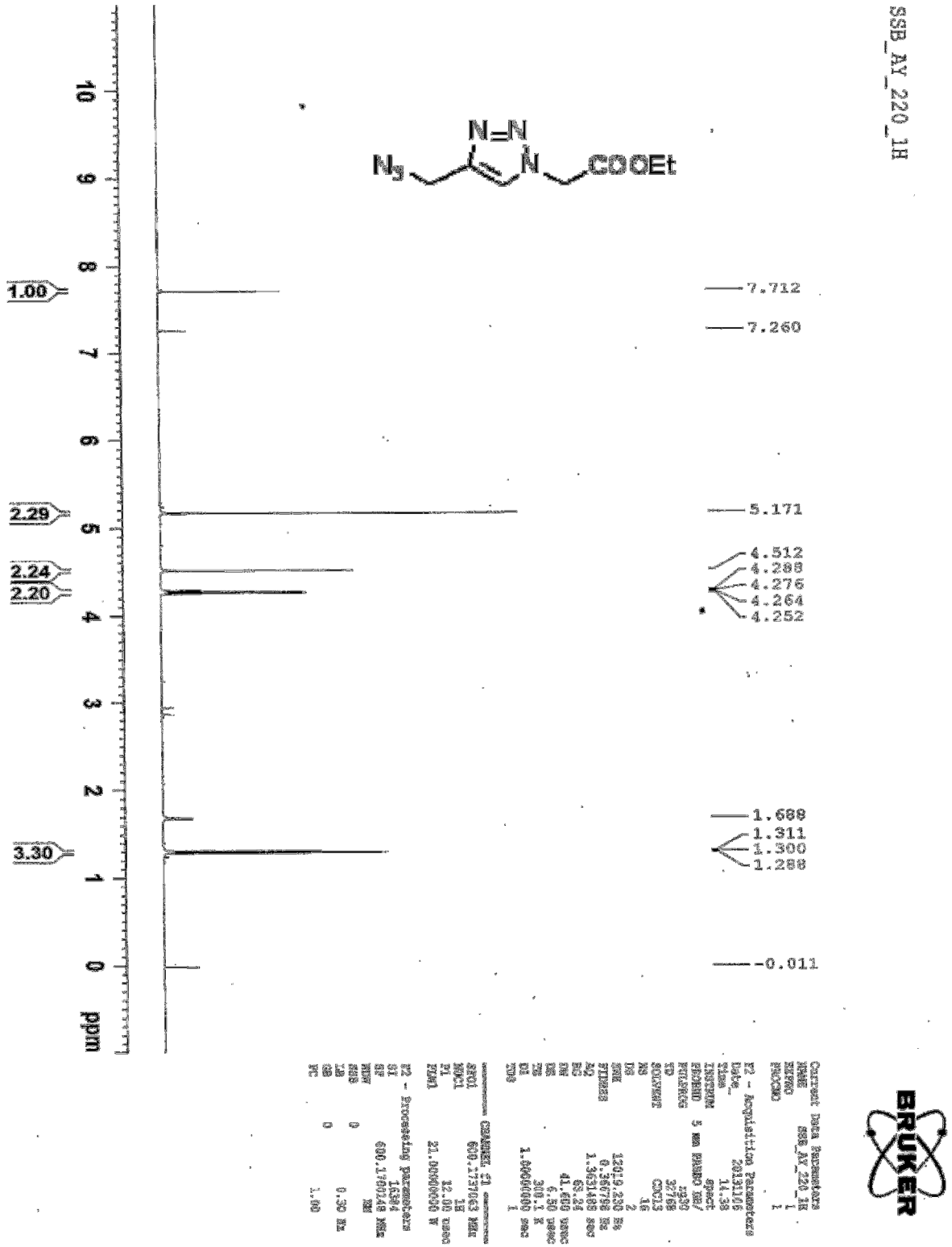

Figure S34. [1]H Spectra of synthesized compound **9.**

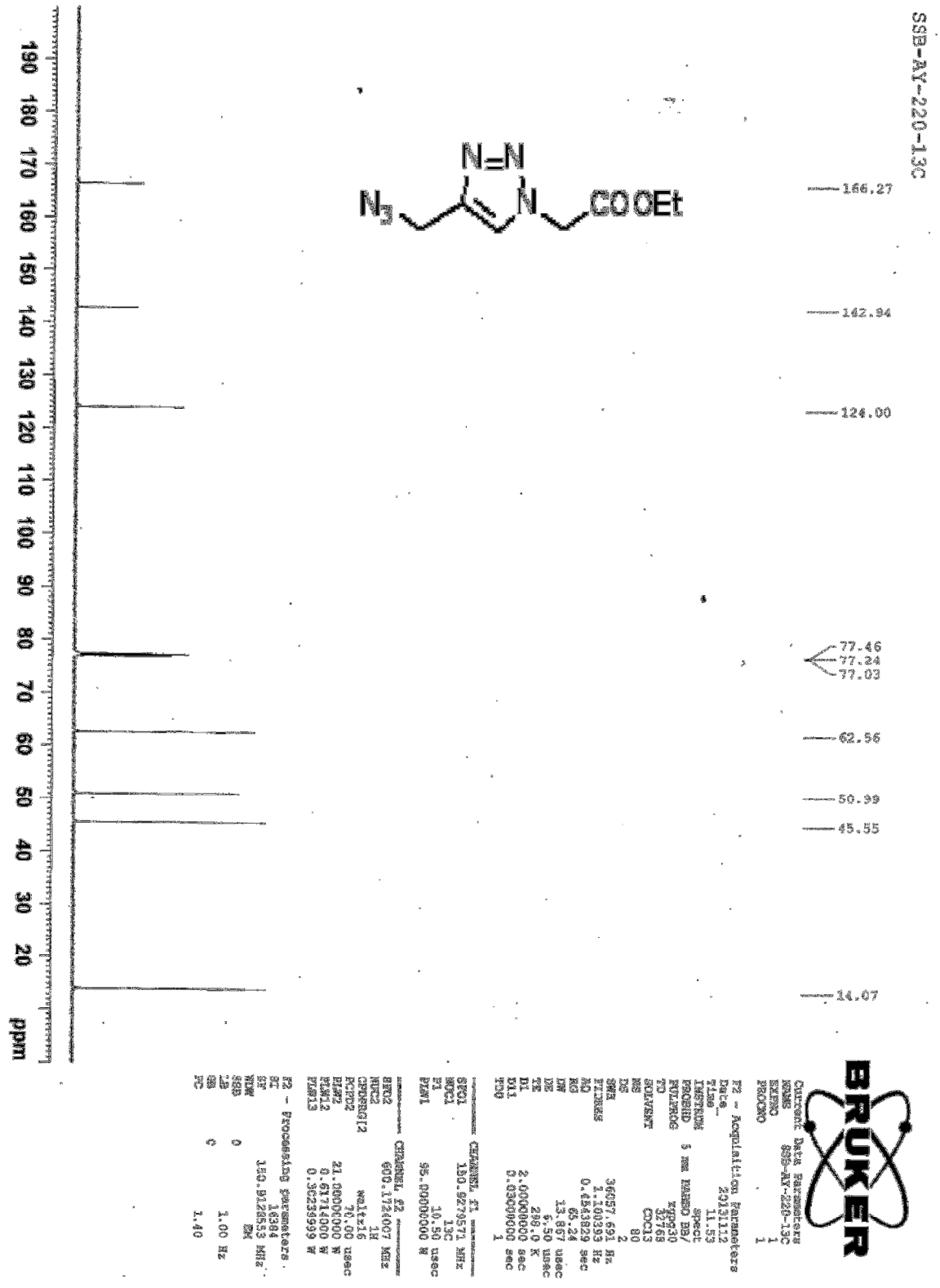

Figure S35. ^{13}C Spectra of synthesized compound **9.**

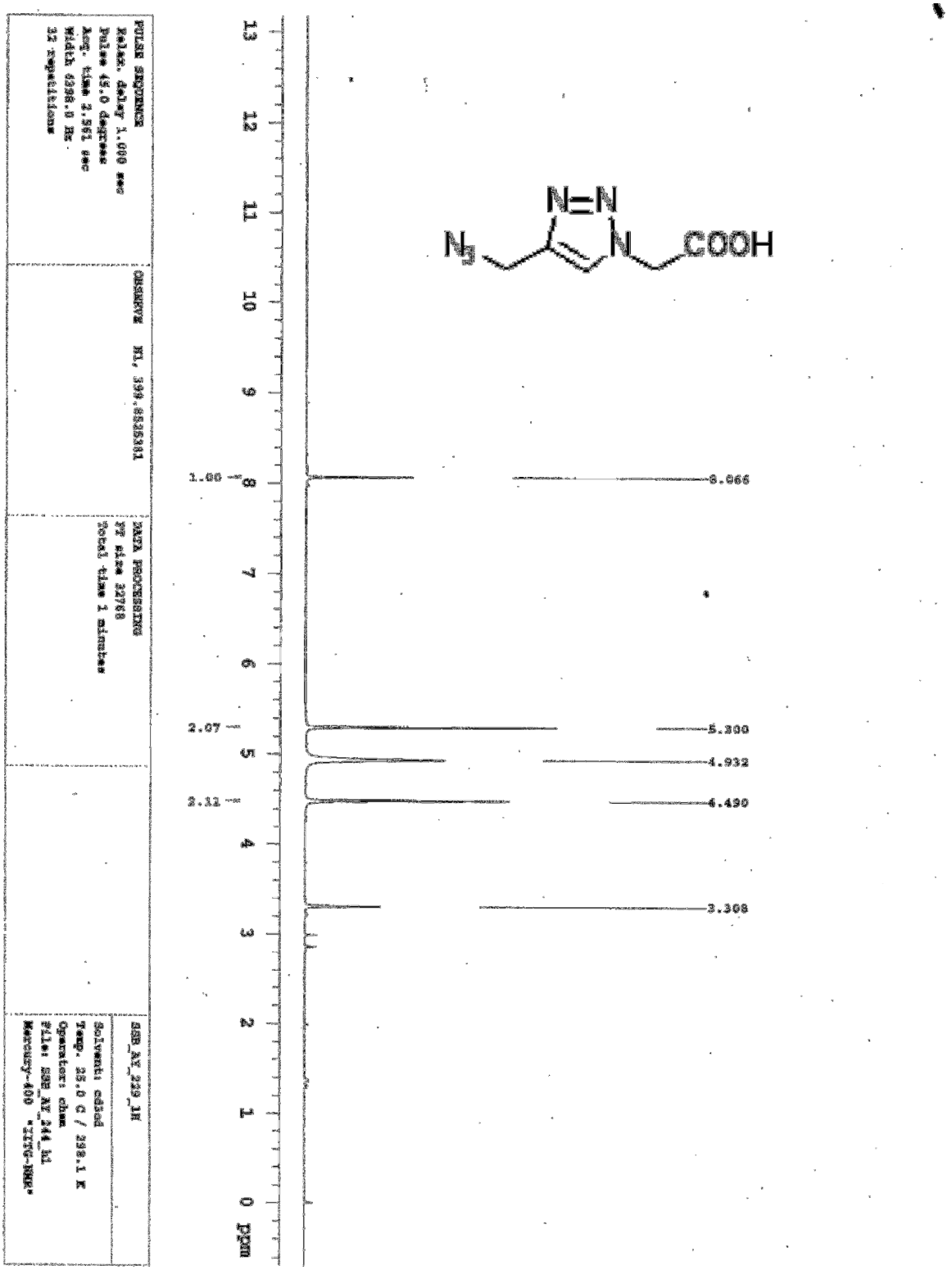

Figure S36. [1]H Spectra of synthesized compound **12.**

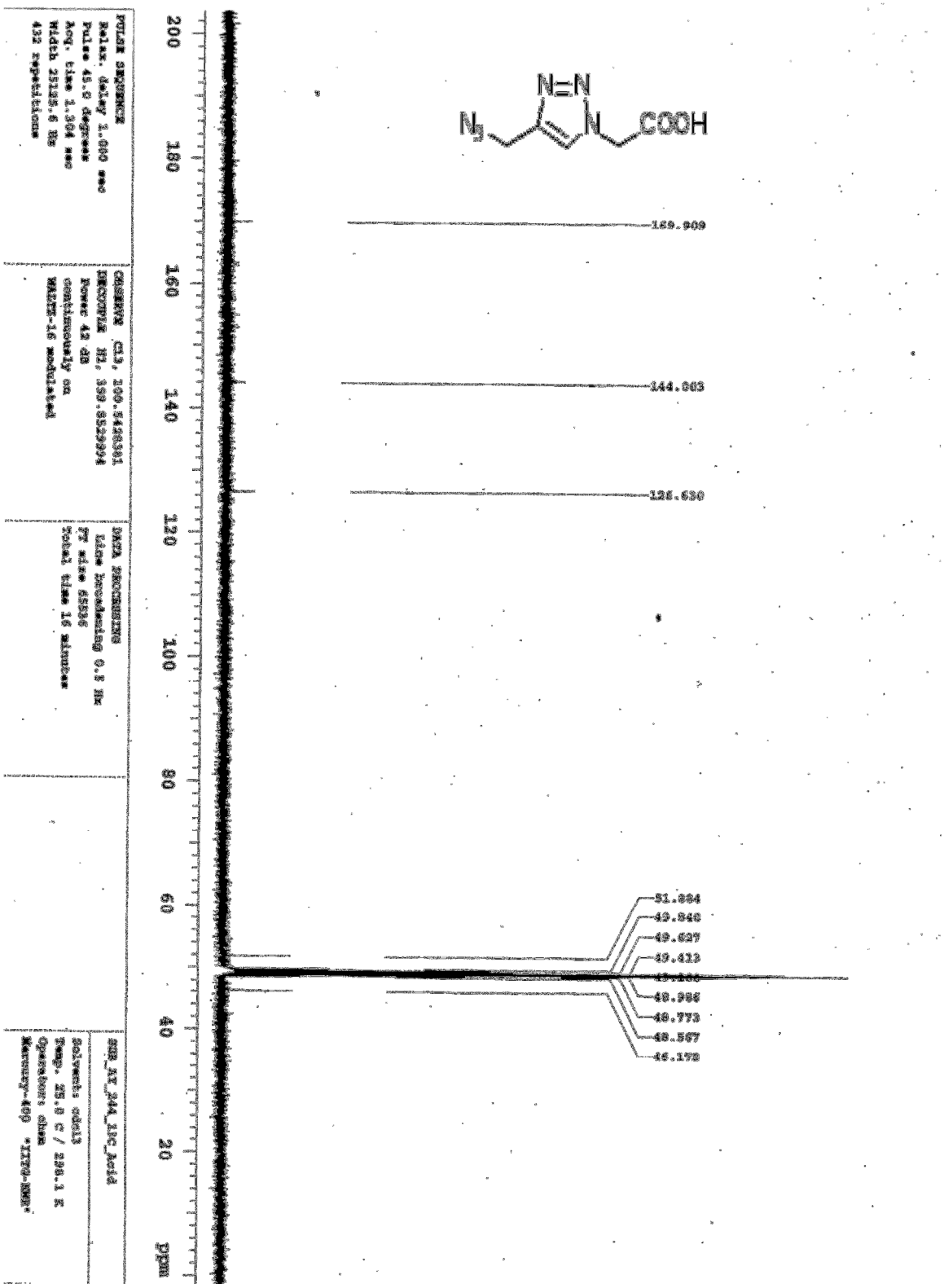

Figure S37. ^{13}C Spectra of synthesized compound **12.**

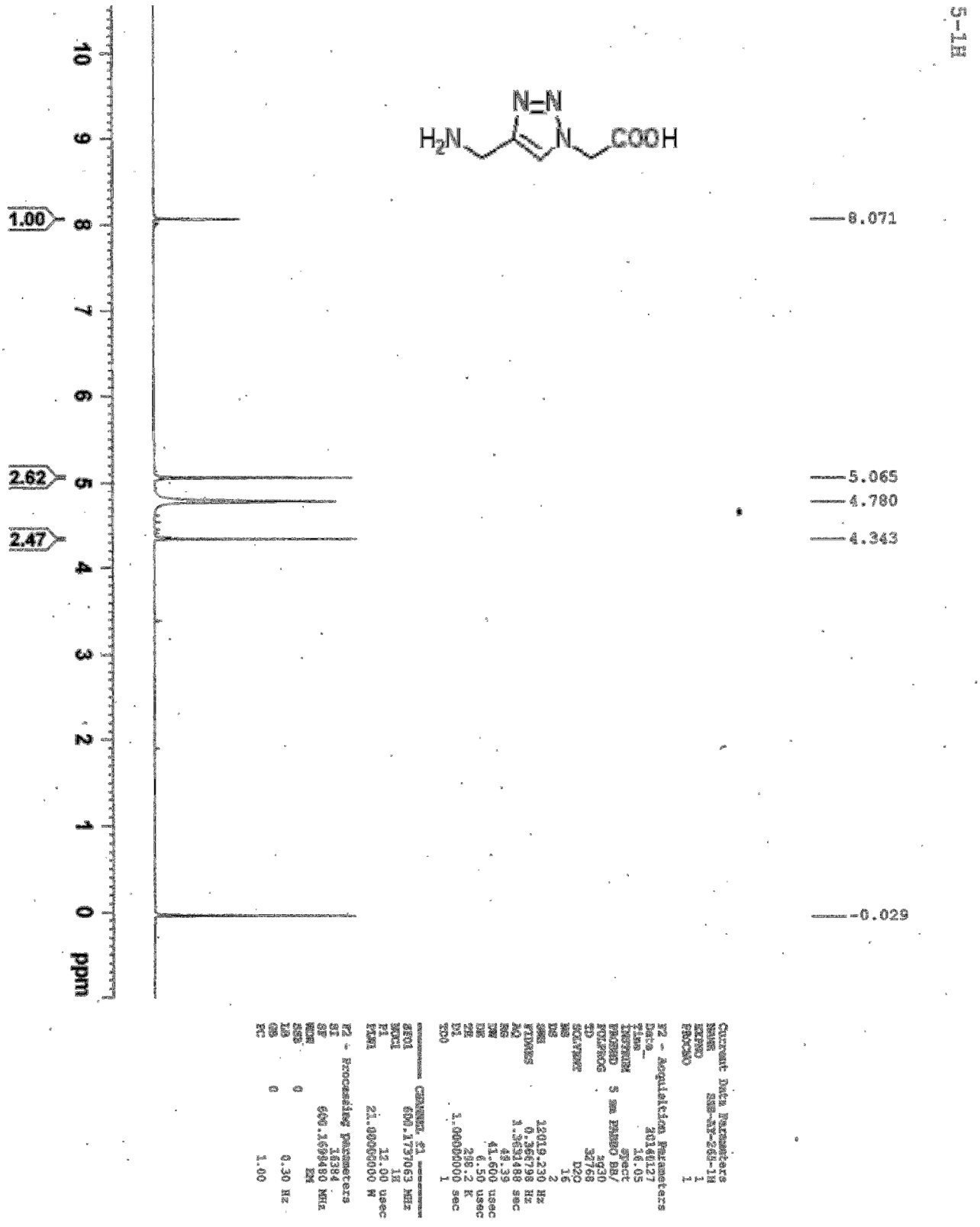

Figure S38. ^{1}H Spectra of synthesized compound **1.**

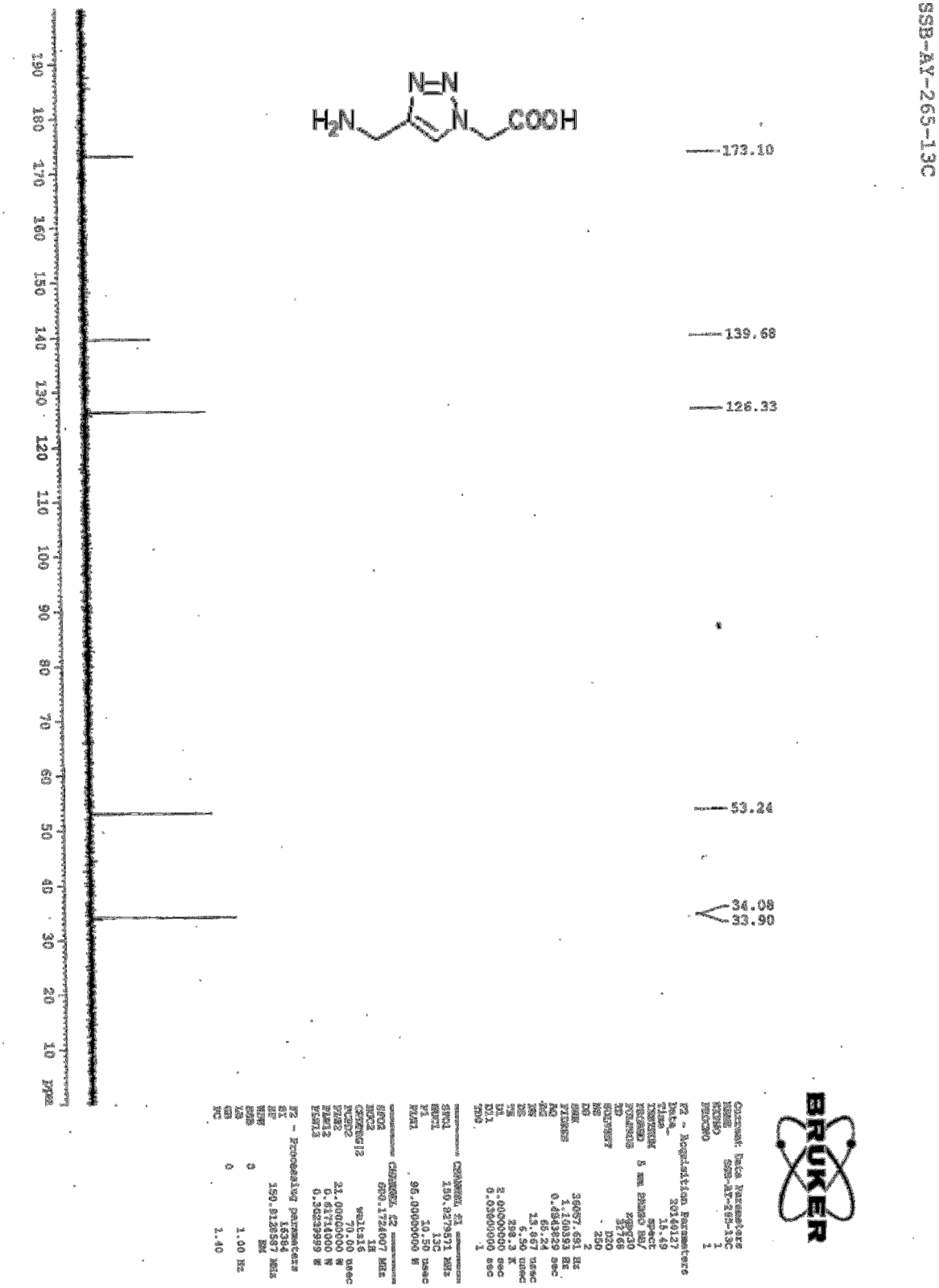

Figure S39. ^{13}C Spectra of synthesized compound **1.**

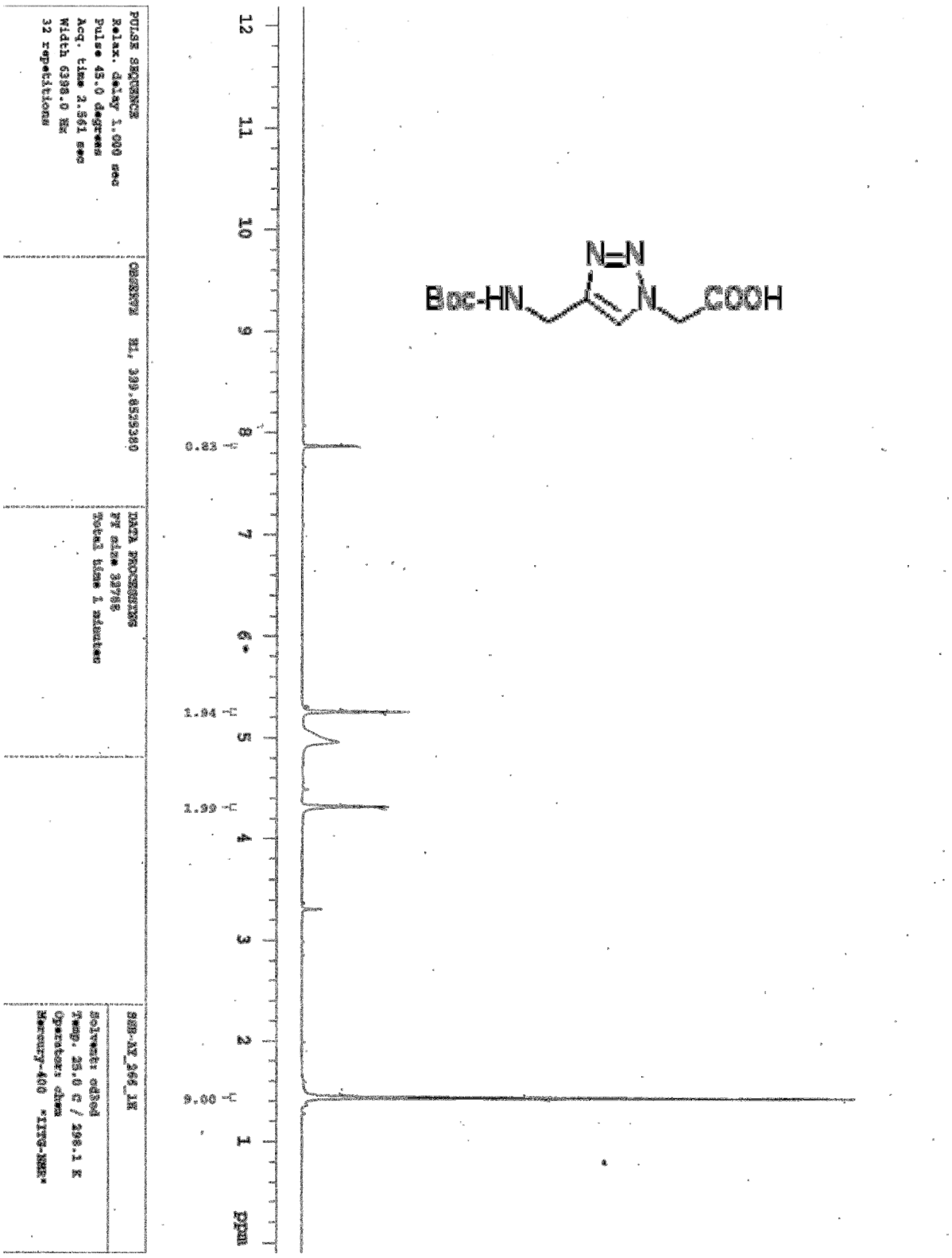

Figure S40. ^{1}H Spectra of synthesized compound **6.**

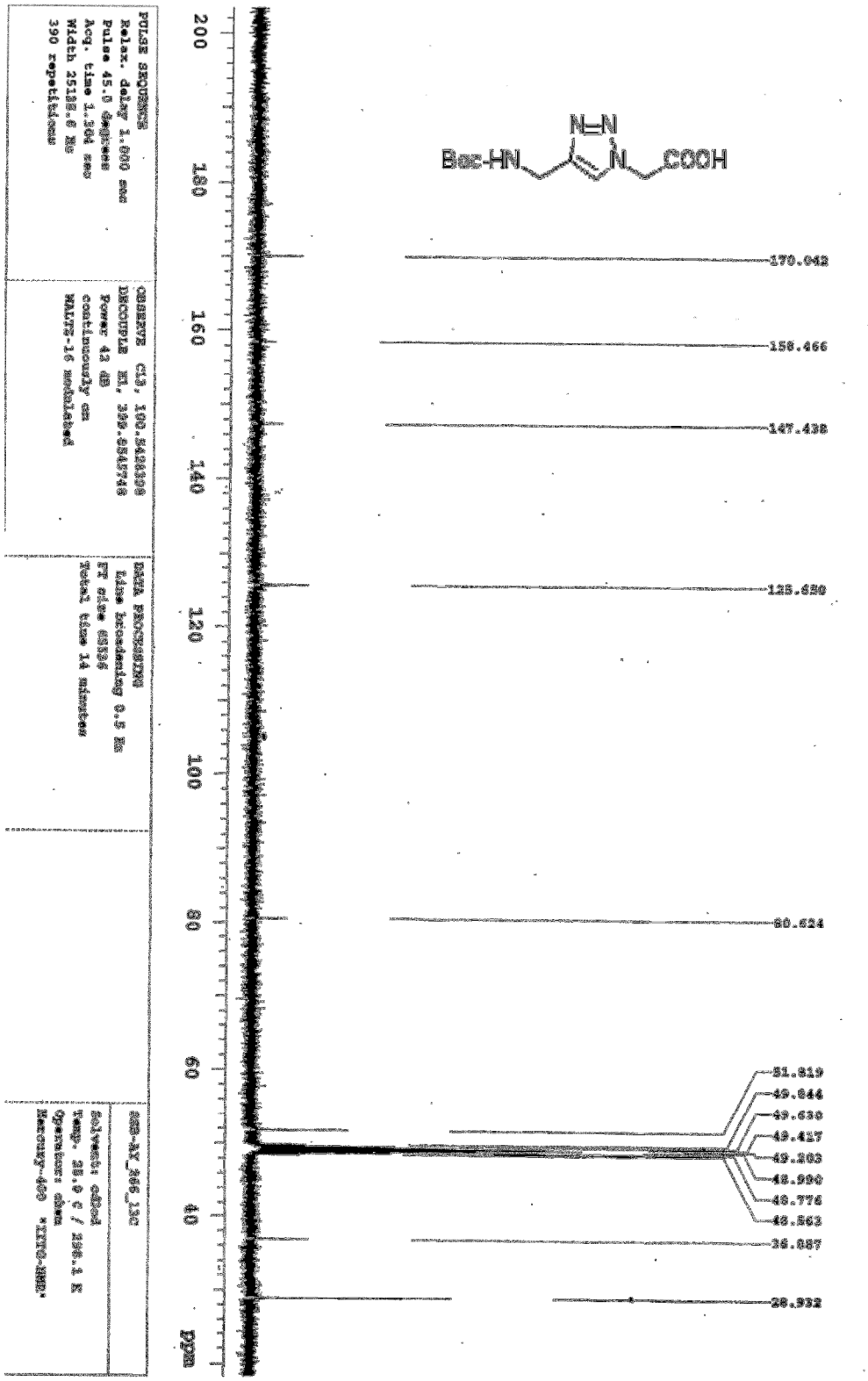

Figure S41. ^{13}C Spectra of synthesized compound **6.**

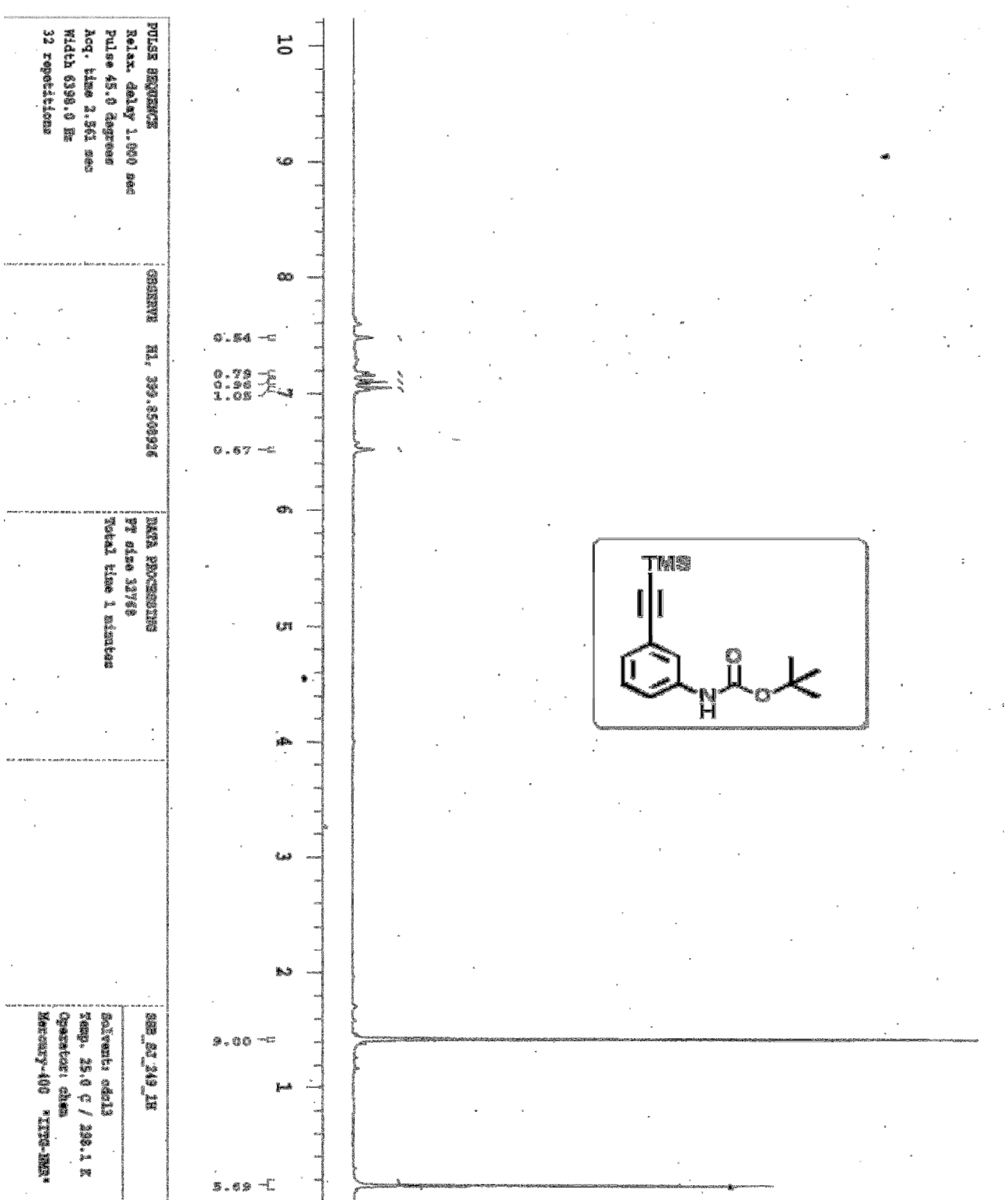

Figure S42. [1]H Spectra of synthesized compound **18.**

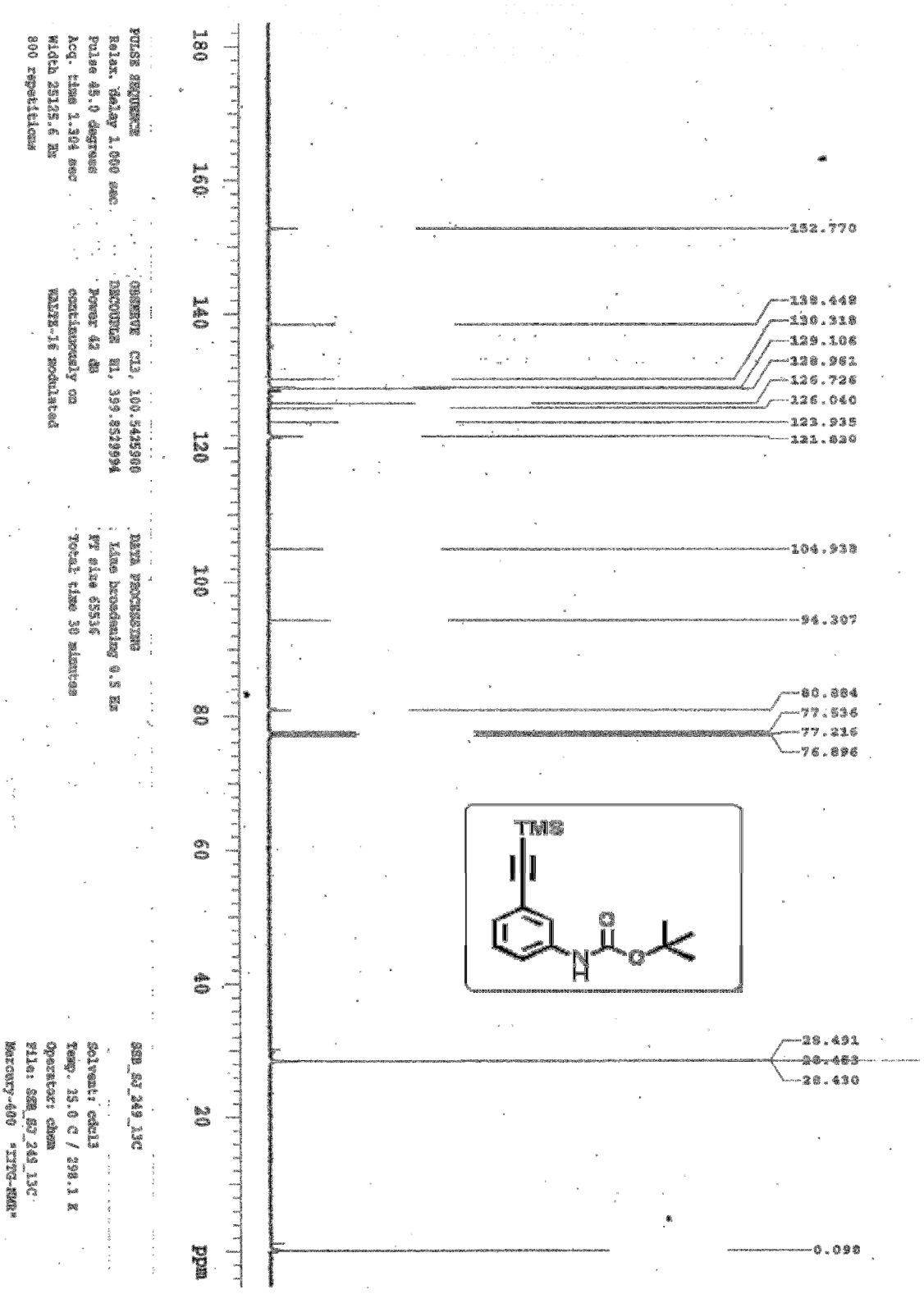

Figure S43. ^{13}C Spectra of synthesized compound **18.**

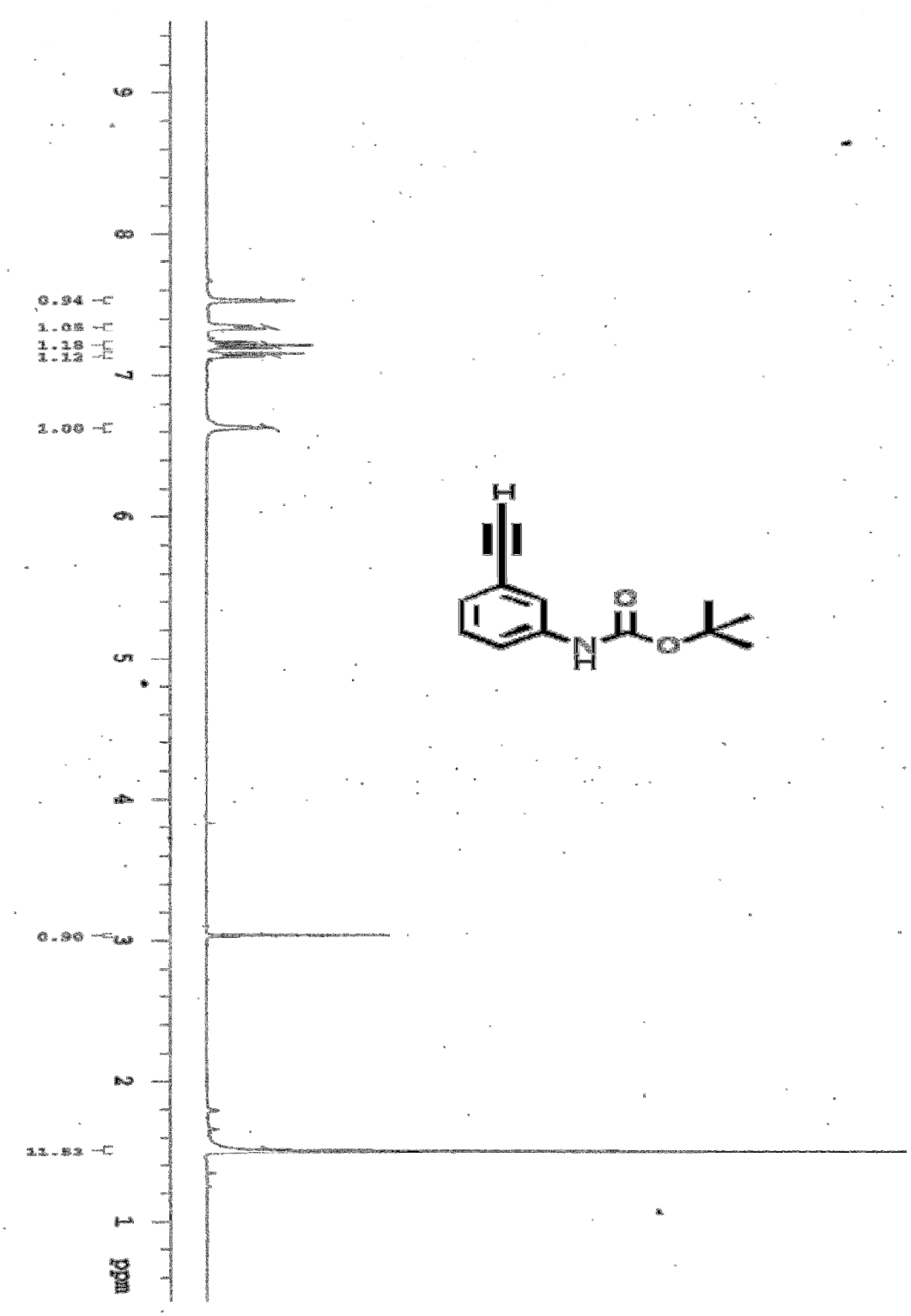

Figure S44. ^{1}H Spectra of synthesized compound **19.**

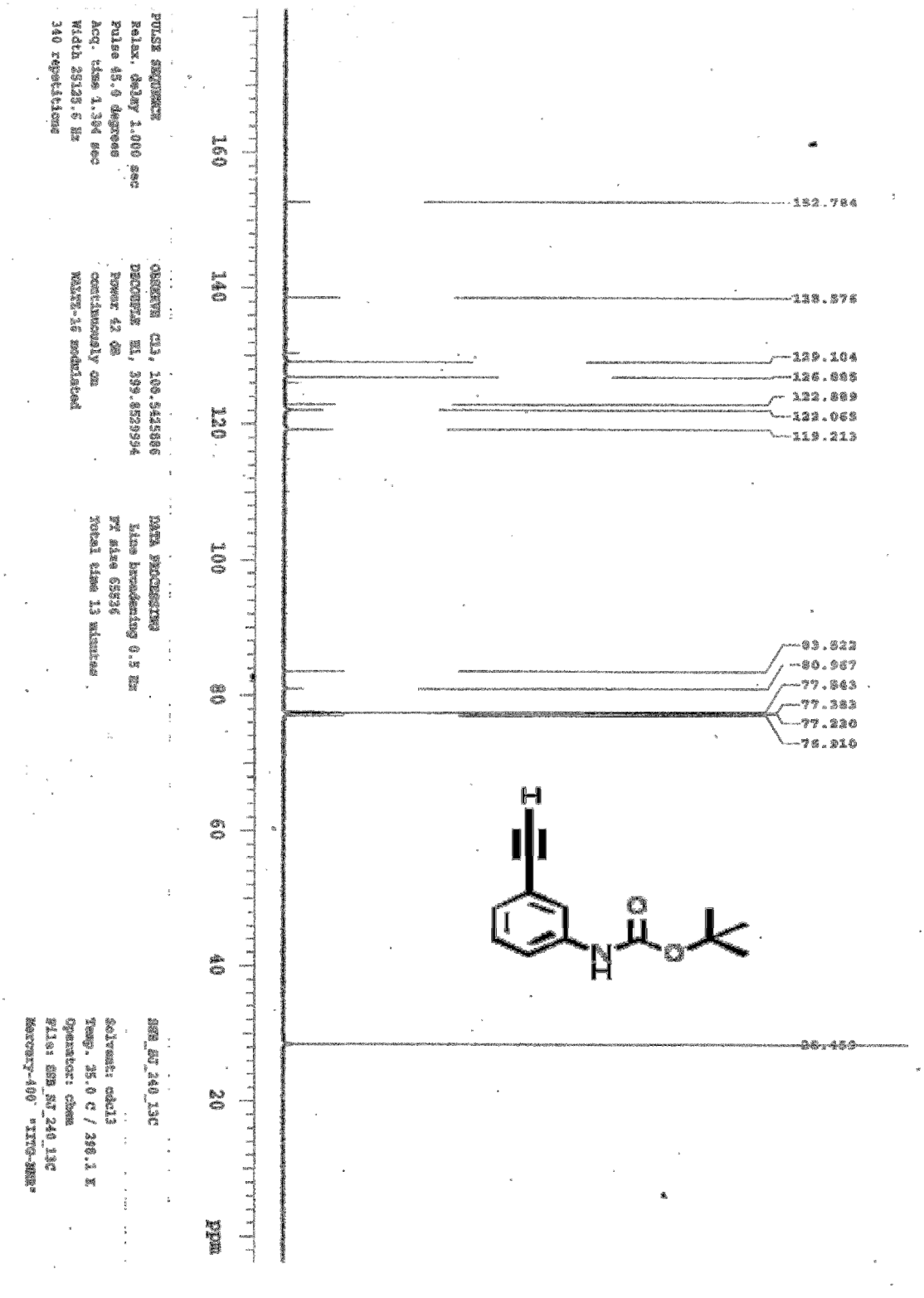

Figure S45. ^{13}C Spectra of synthesized compound **19.**

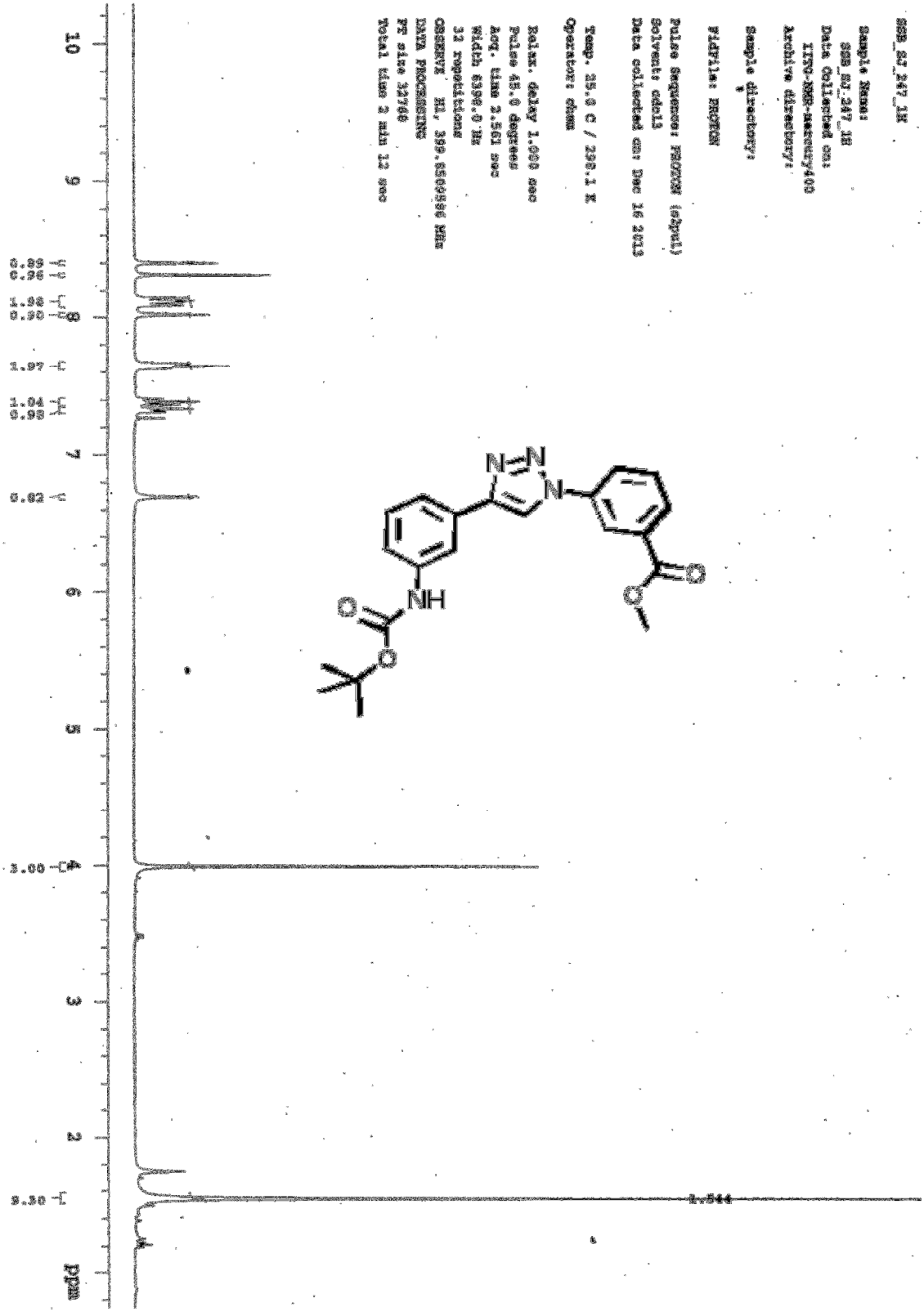

Figure S46. [1]H Spectra of synthesized compound **20.**

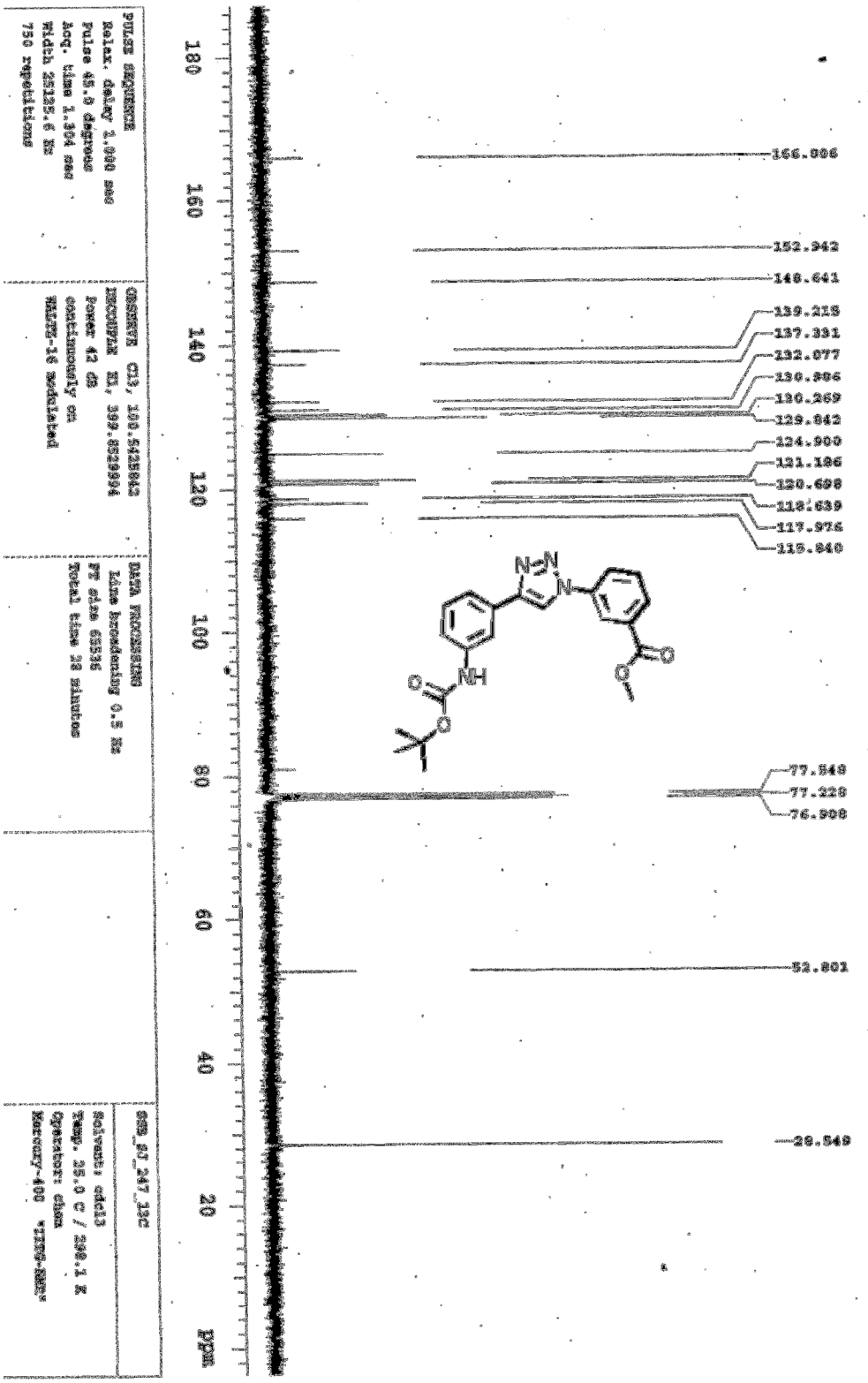

Figure S47. ^{13}C Spectra of synthesized compound **20.**

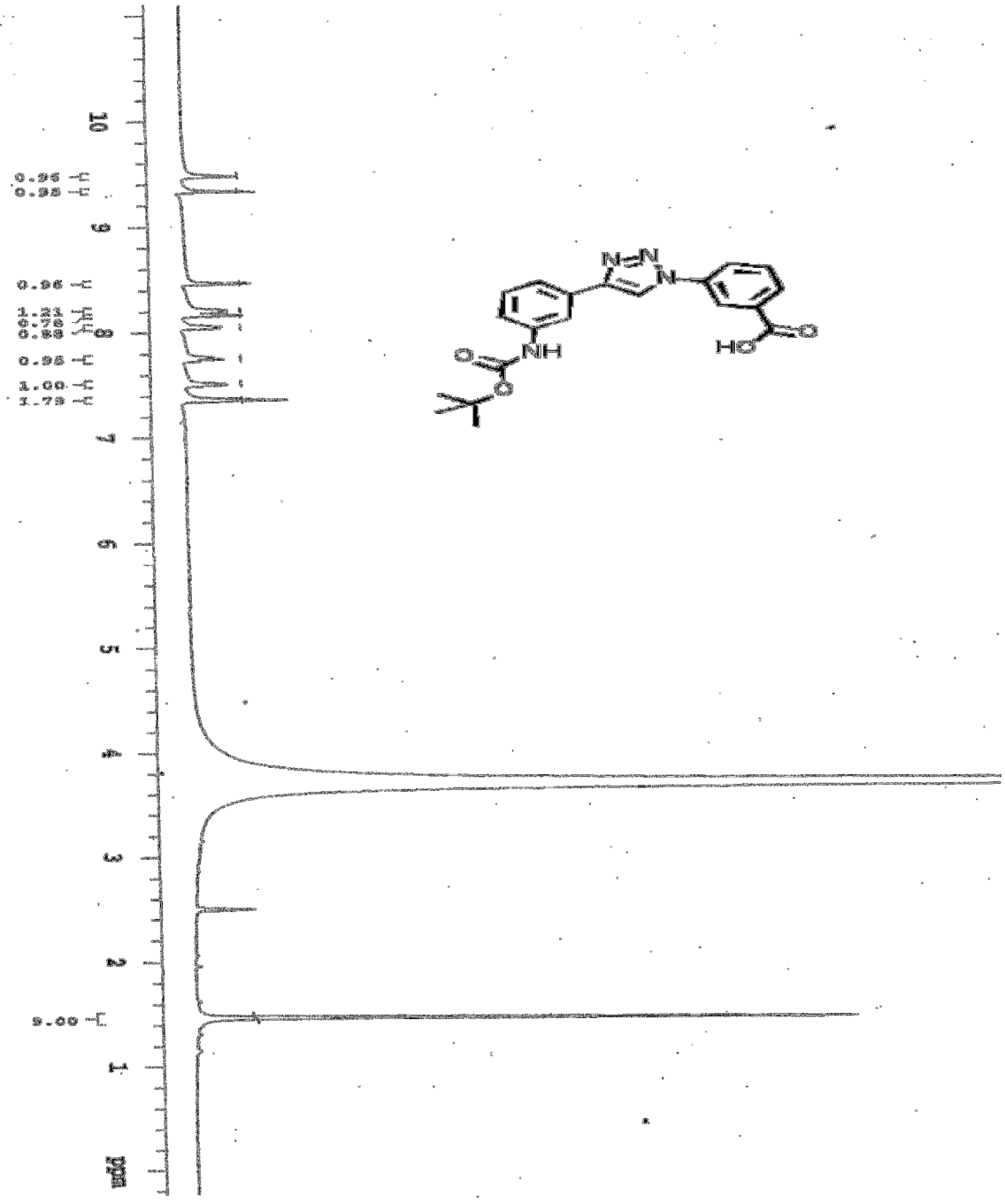

Figure S48. ^{1}H Spectra of synthesized compound **2.**

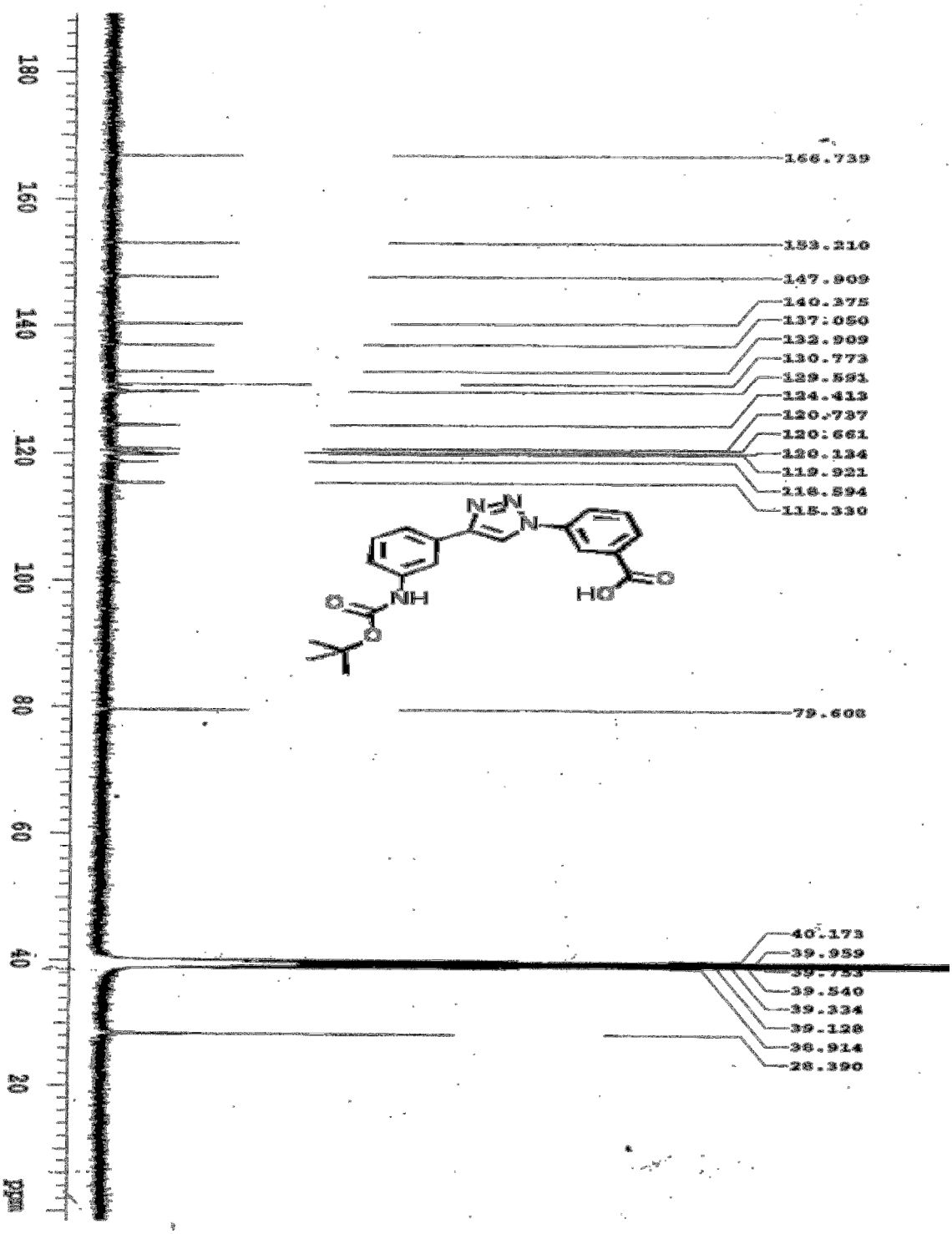

Figure S49. ^{13}C Spectra of synthesized compound **2.**

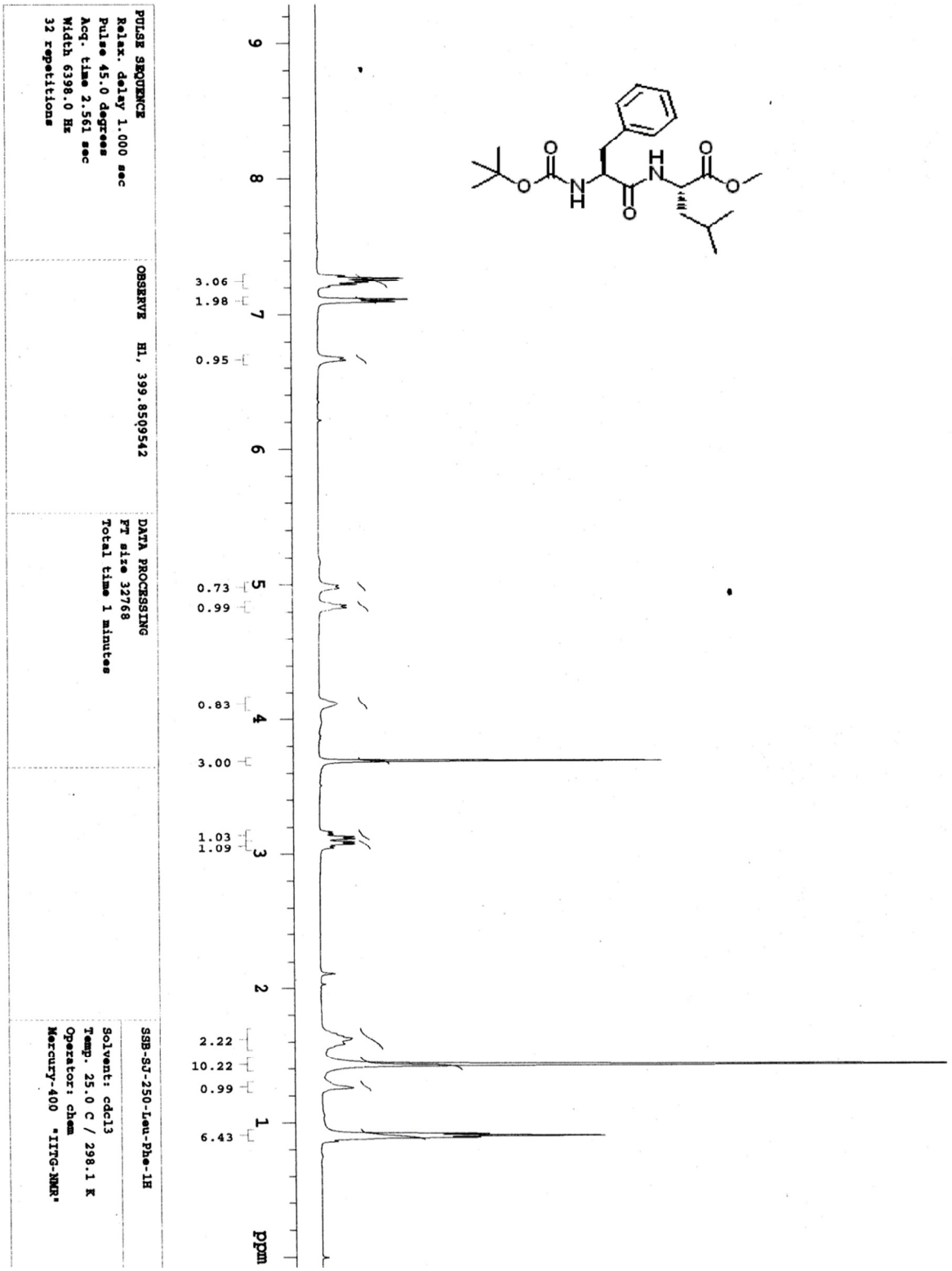

Figure S50. ^{1}H Spectra of synthesized compound **23.**

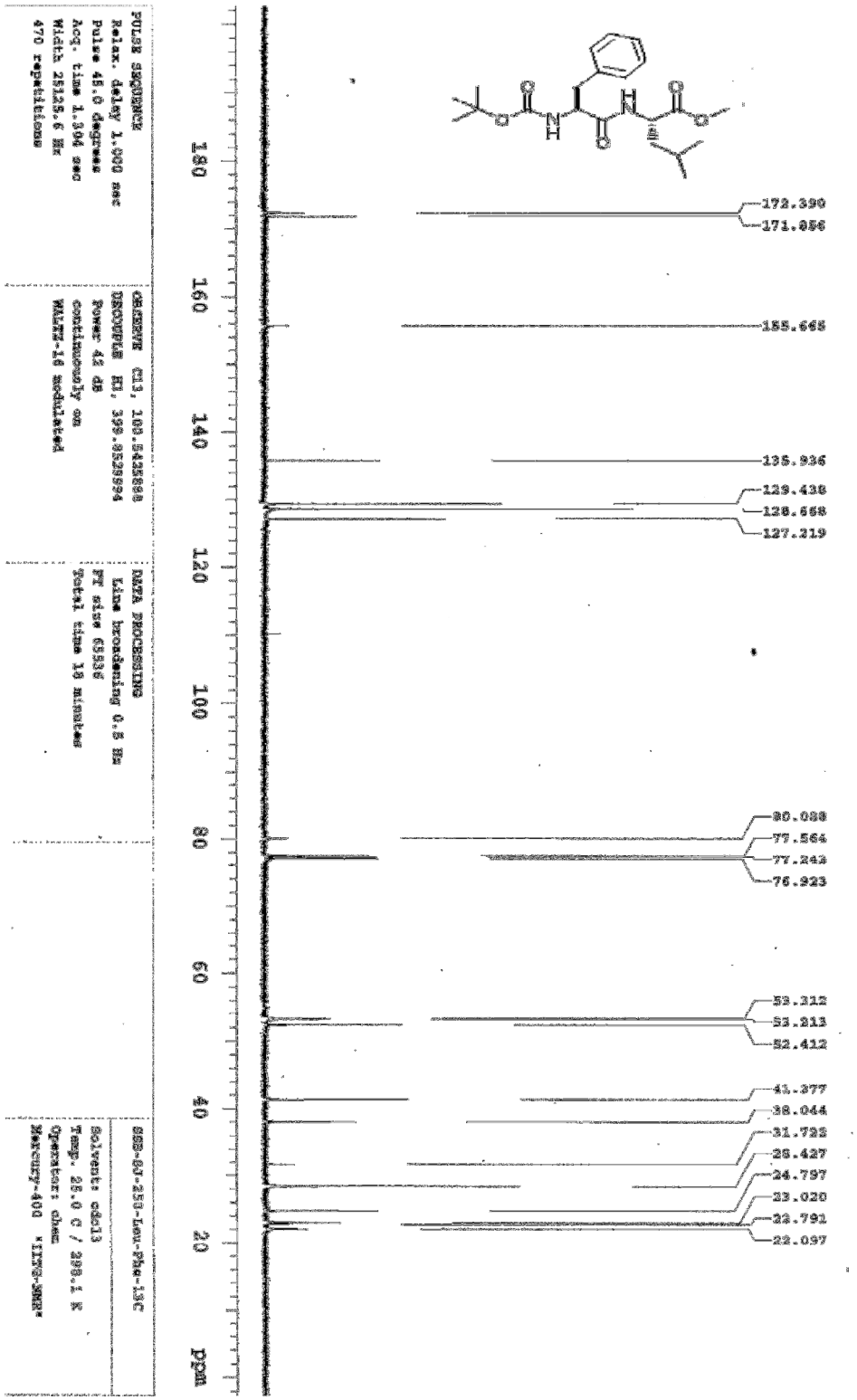

Figure S51. ^{13}C Spectra of synthesized compound **23.**

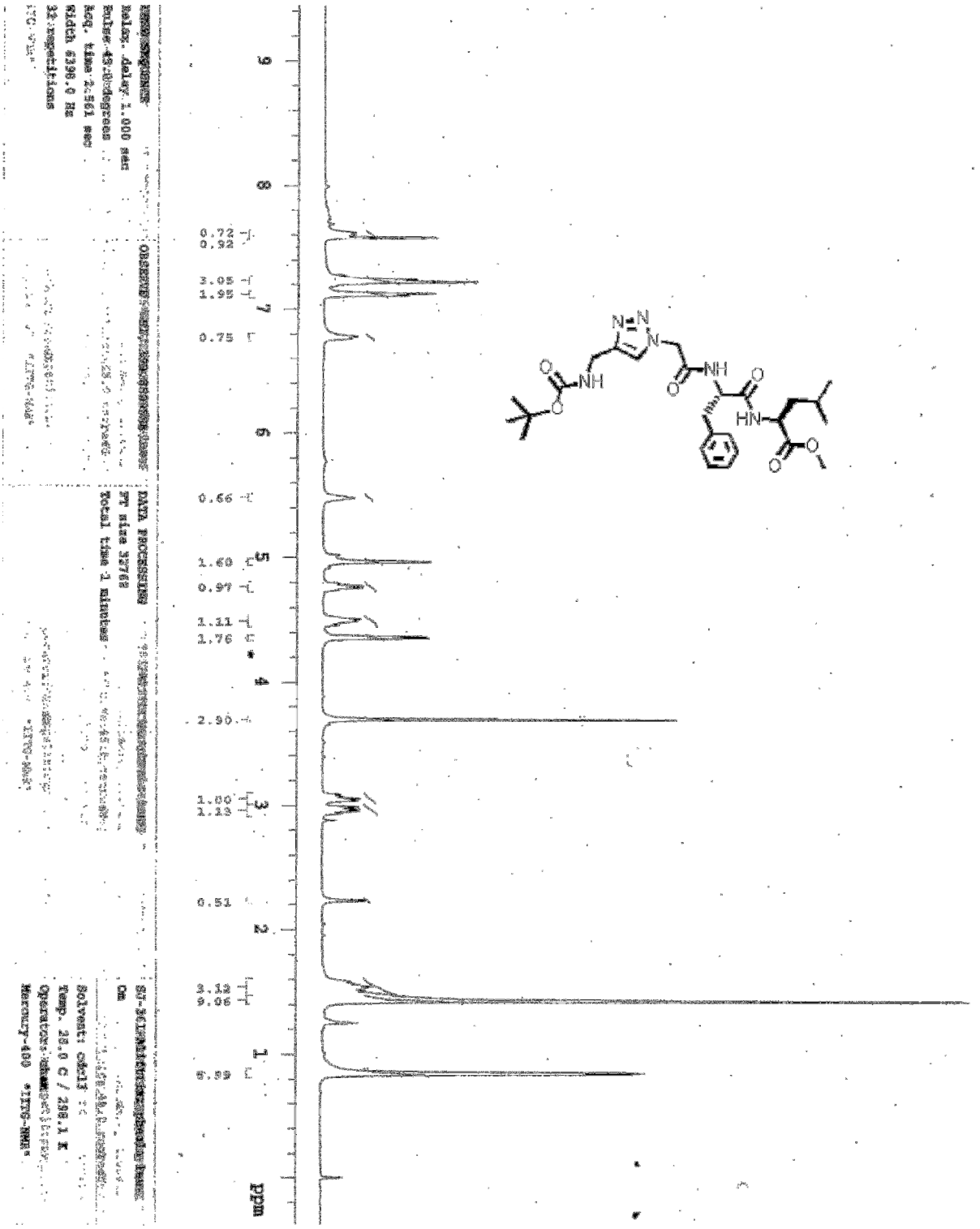

Figure S52. ^{1}H Spectra of synthesized compound **25.**

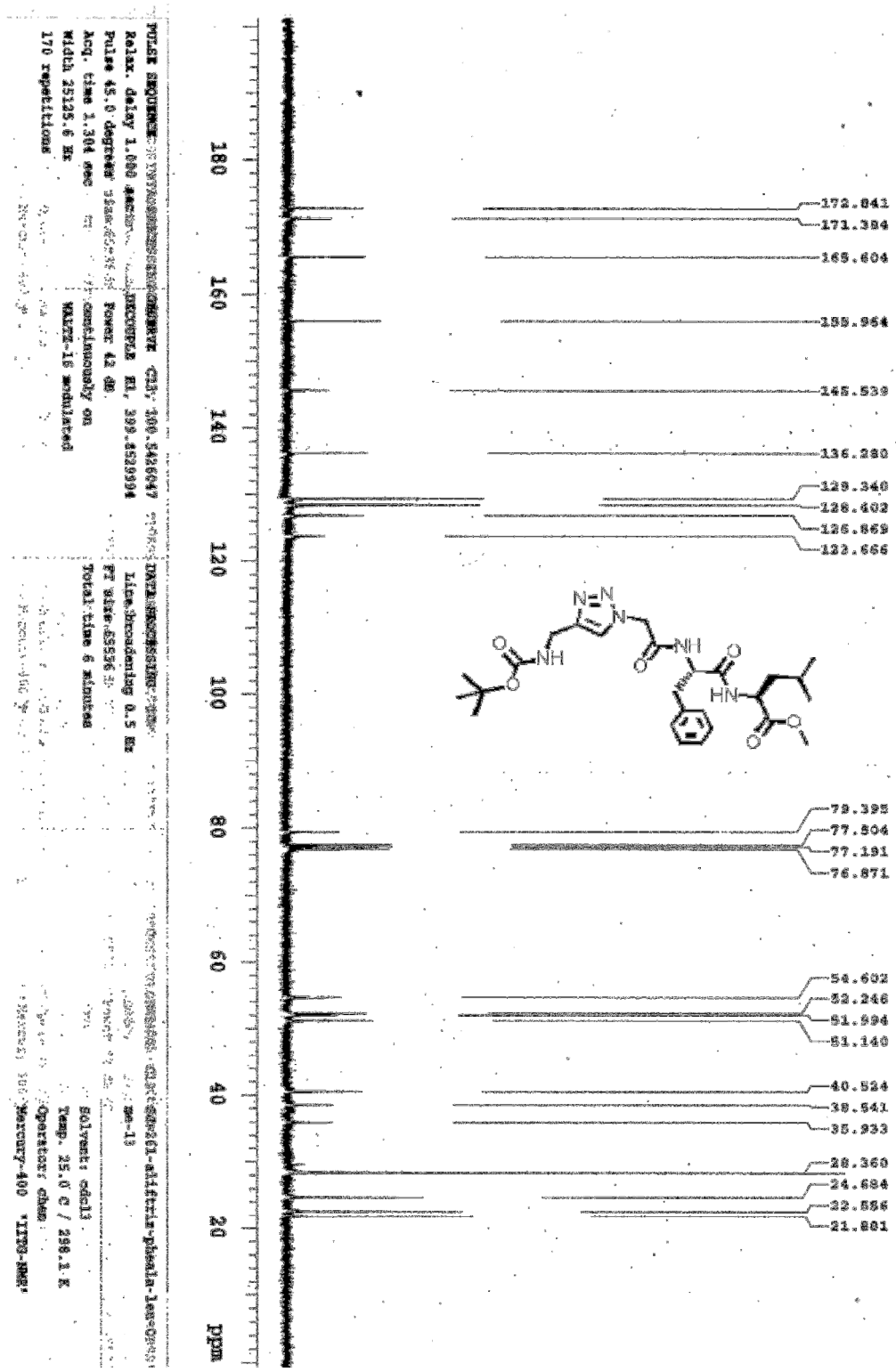

Figure S53. ^{13}C Spectra of synthesized compound **25.**

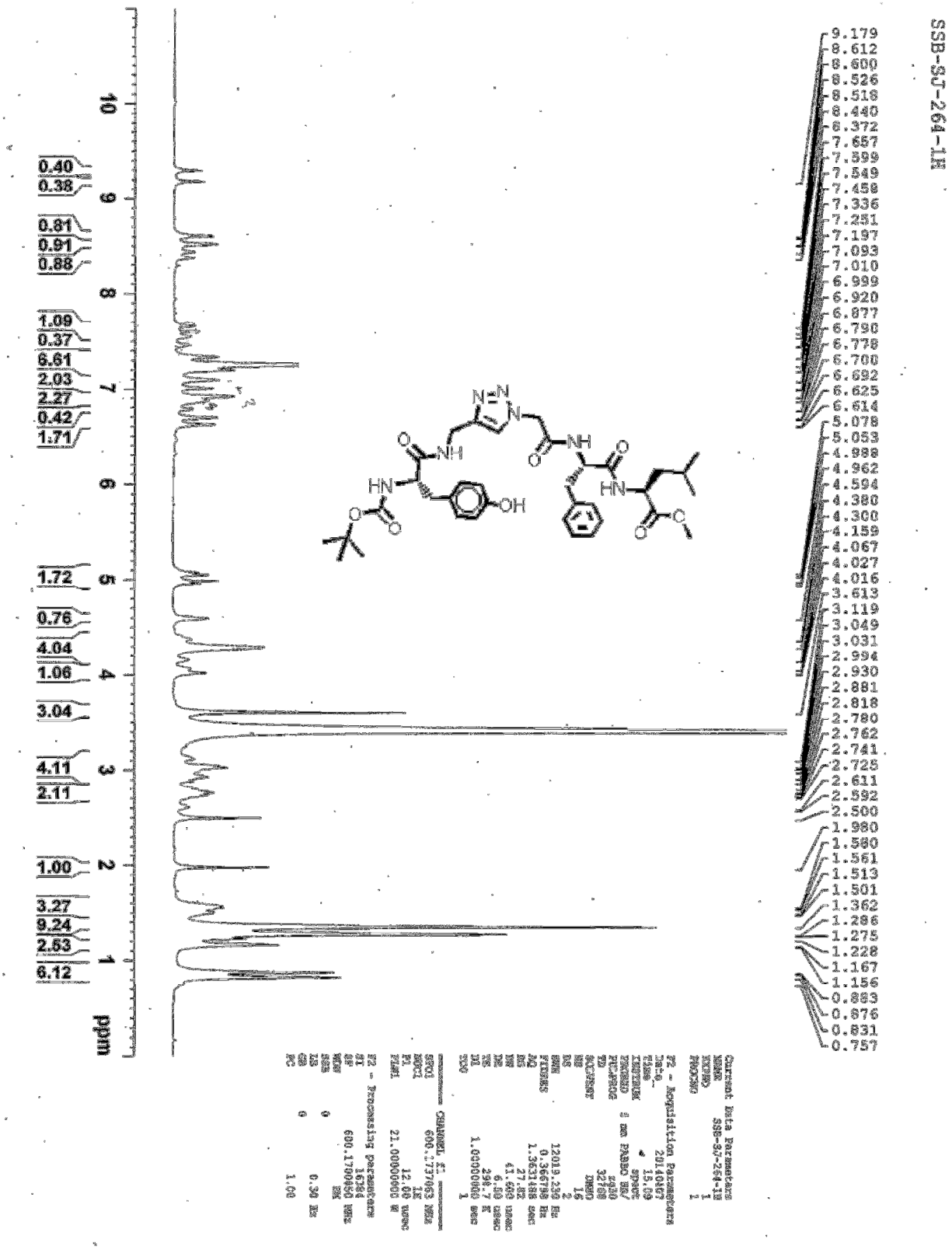

Figure S54. ^{1}H Spectra of synthesized compound **3.**

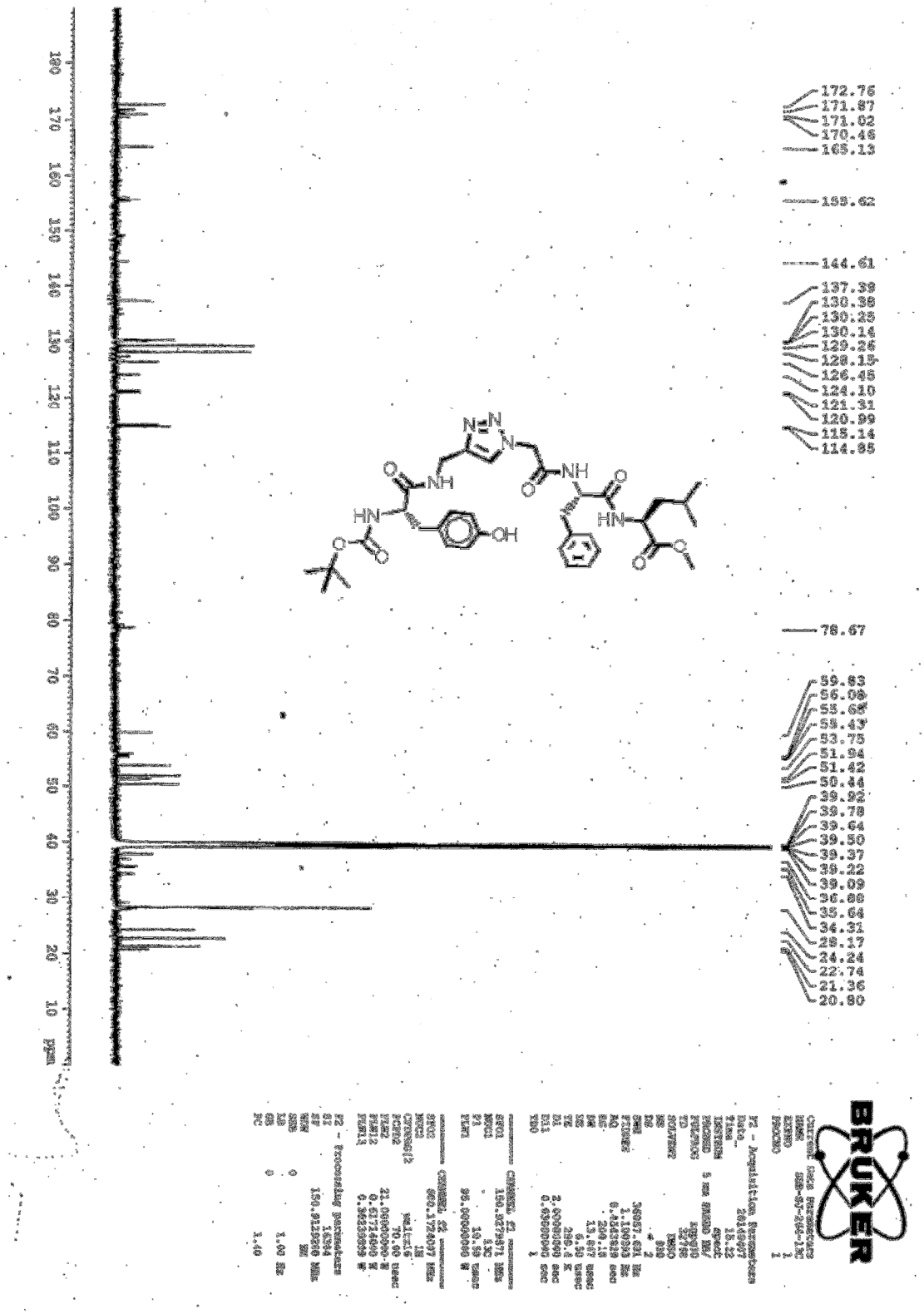

Figure S55. ^{13}C Spectra of synthesized compound **3.**

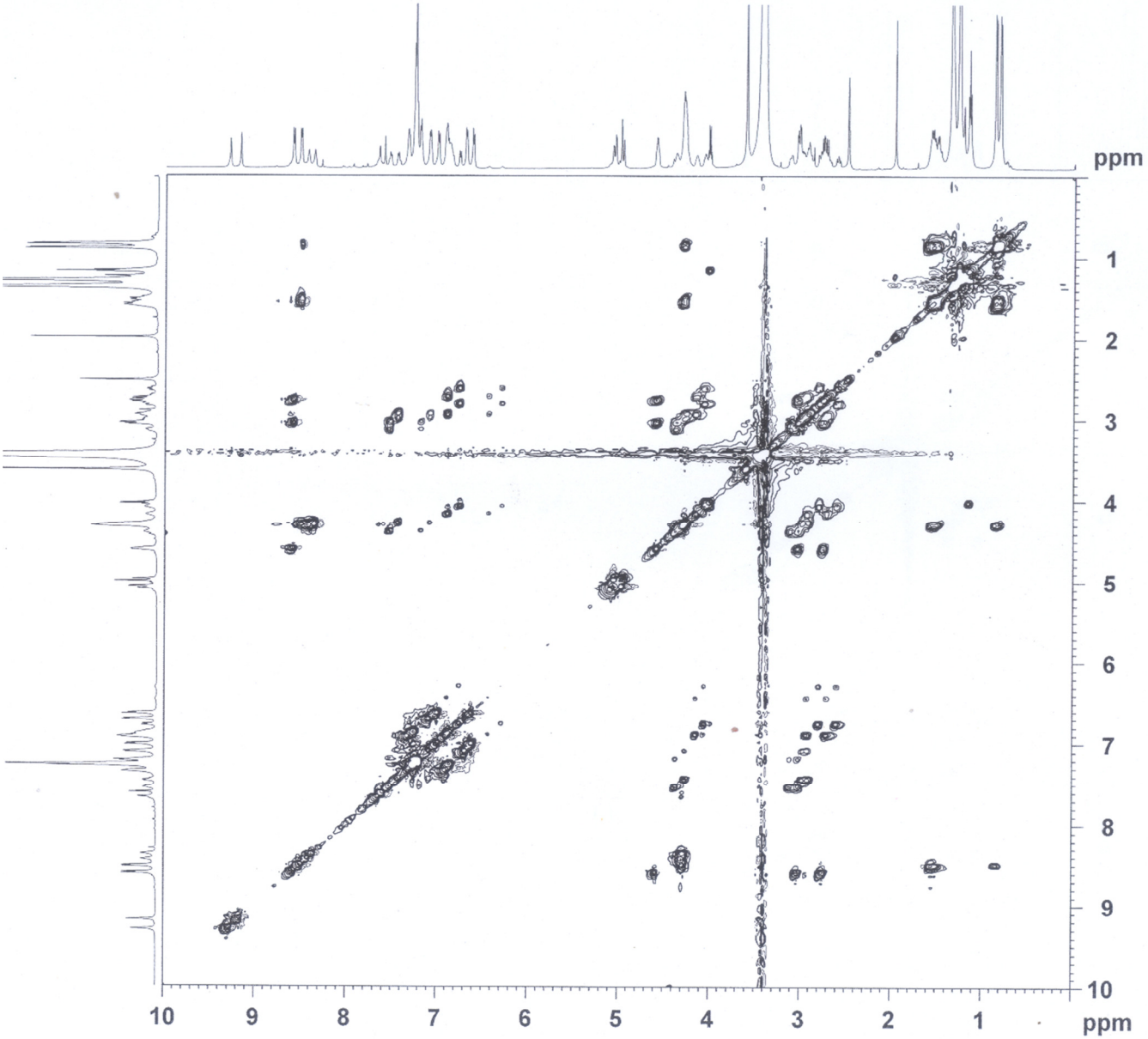

Figure S56. TOCSY spectra of **Tetrapeptide 3** (**BocNH-Tyr-^{Al}TAA Phe-Leu-CO_2Me**).

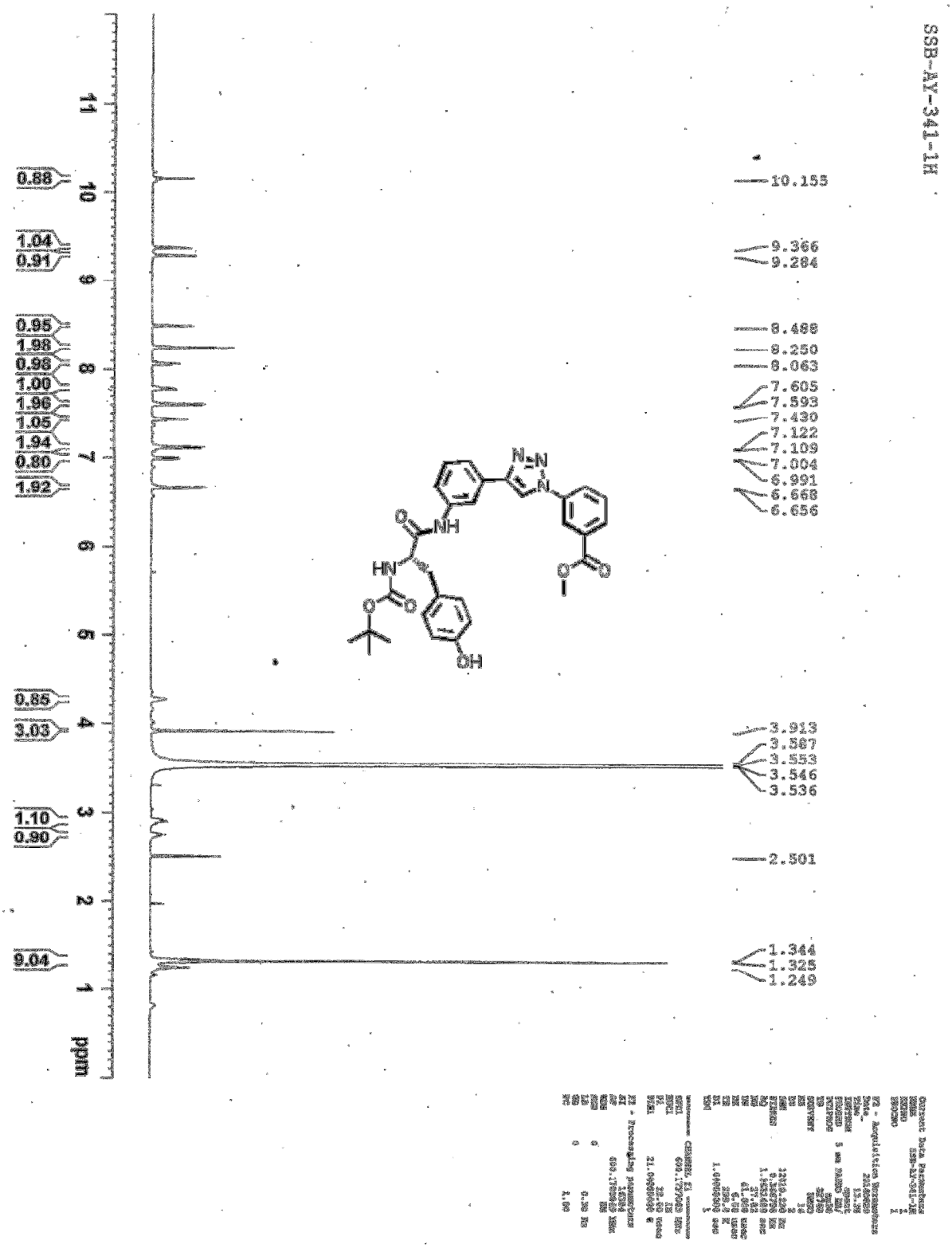

Figure S57. ^{1}H Spectra of synthesized compound **28.**

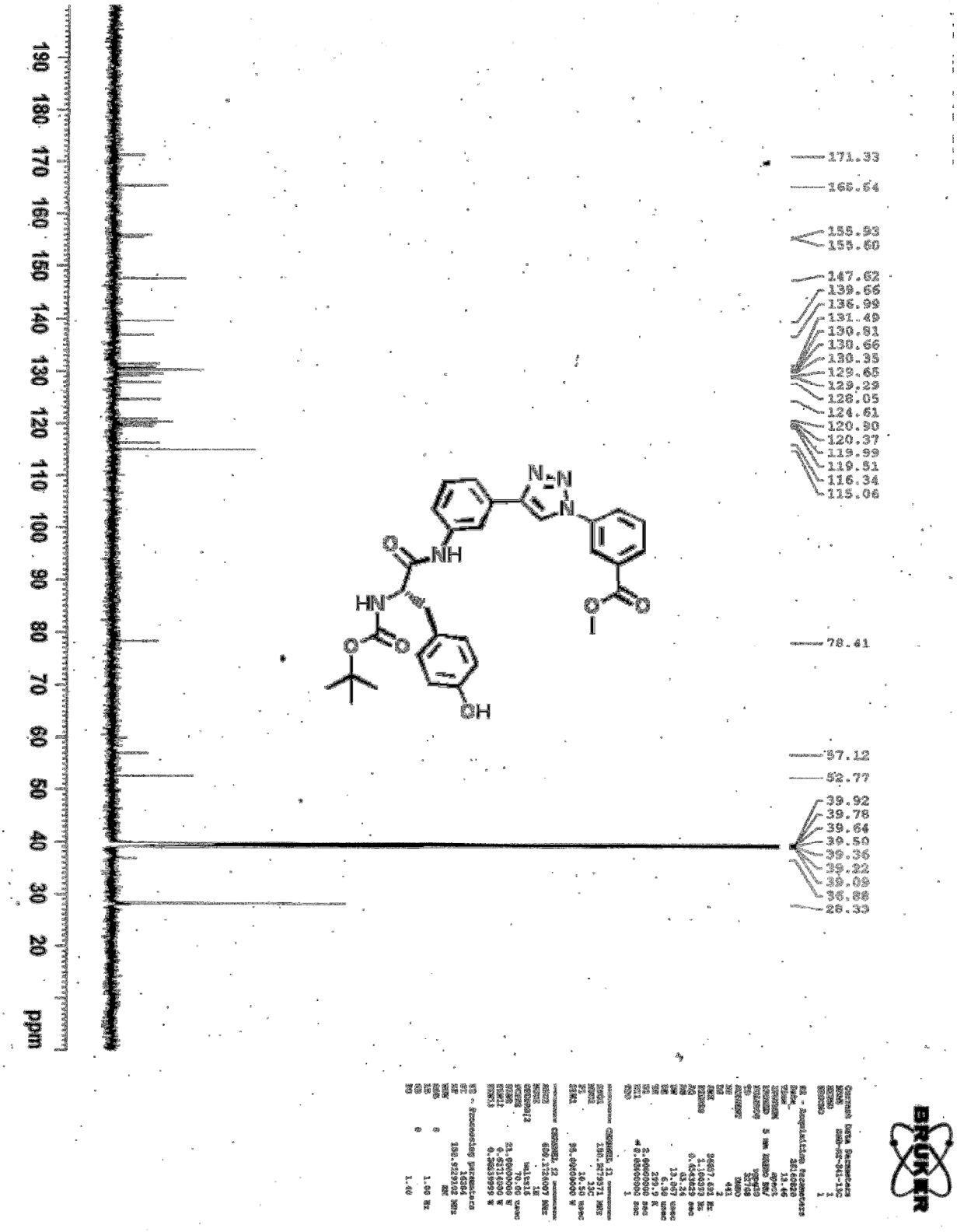

Figure S58. ^{13}C Spectra of synthesized compound **28.**

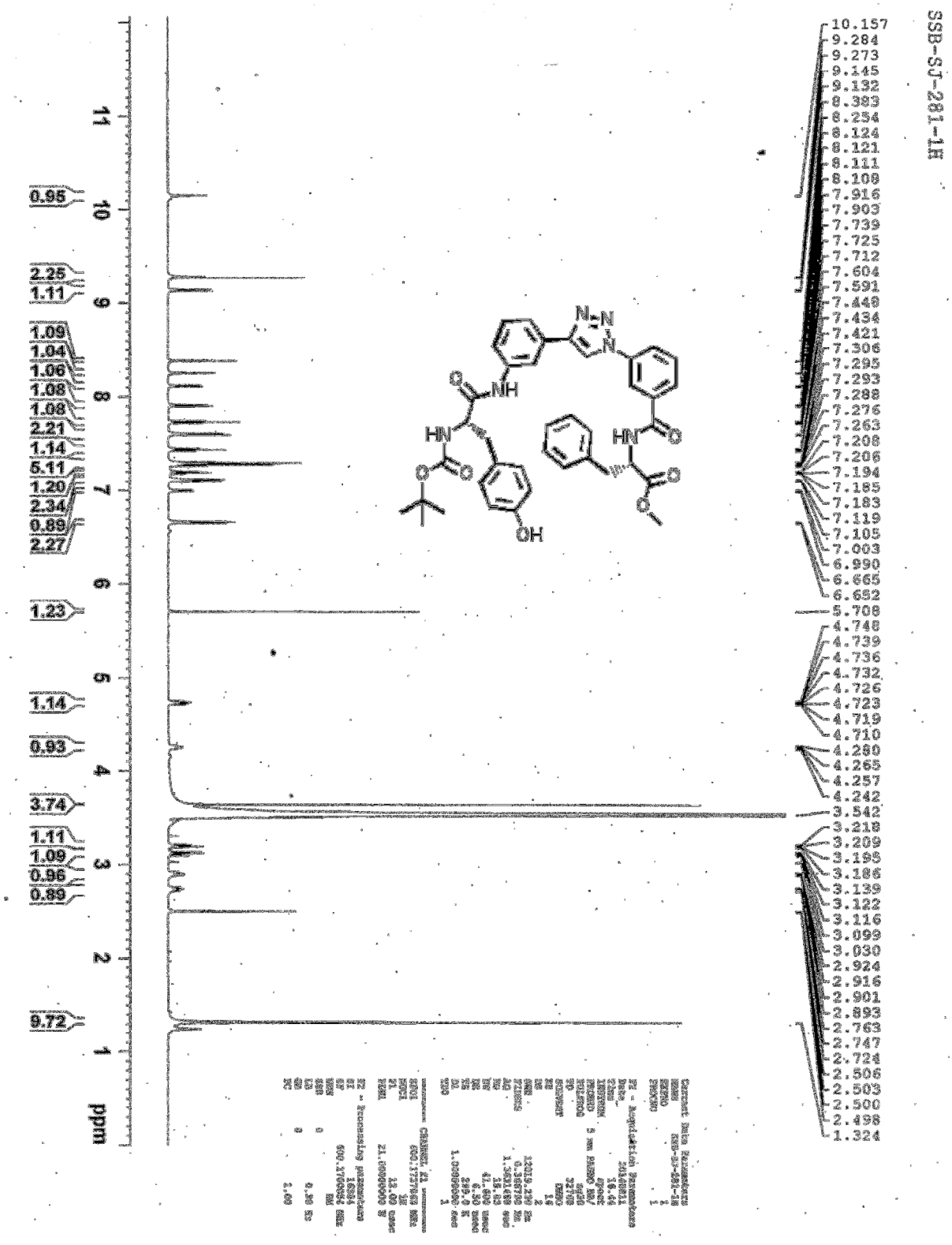

Figure S59. ^{1}H Spectra of synthesized compound **4.**

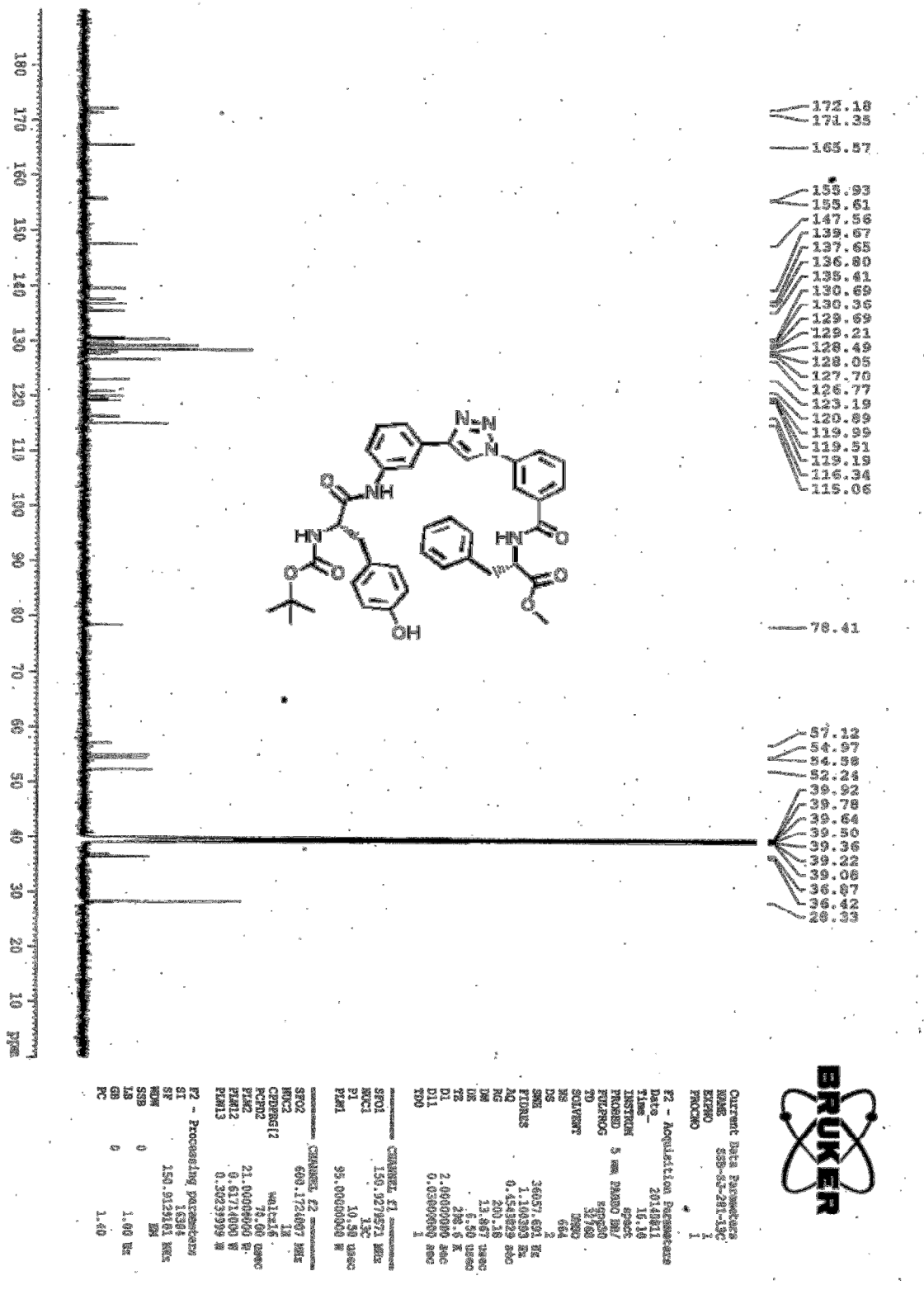

Figure S60. ^{13}C Spectra of synthesized compound **4.**

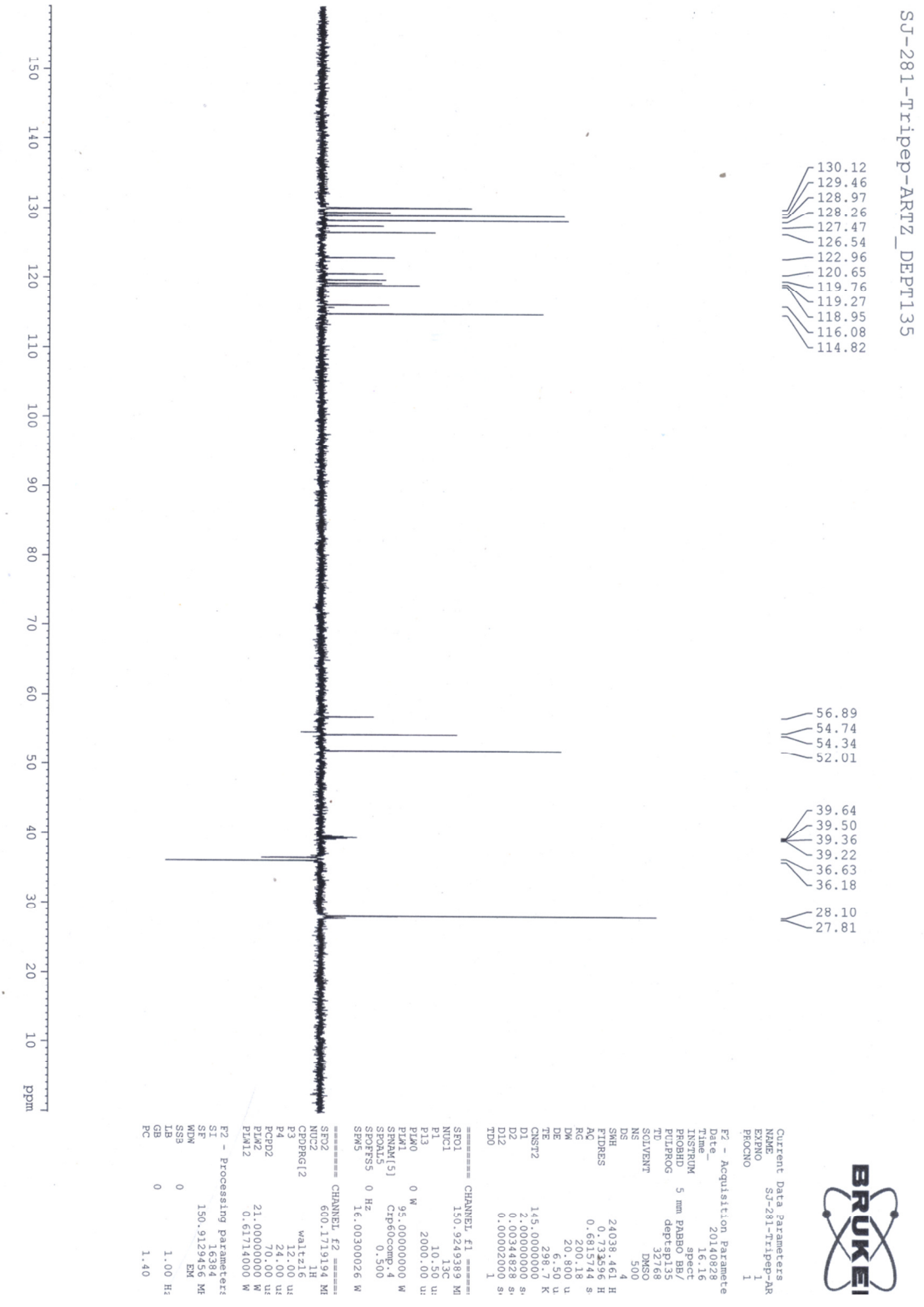

Figure S61. DEPT135 spectra of synthesized compound **4.**

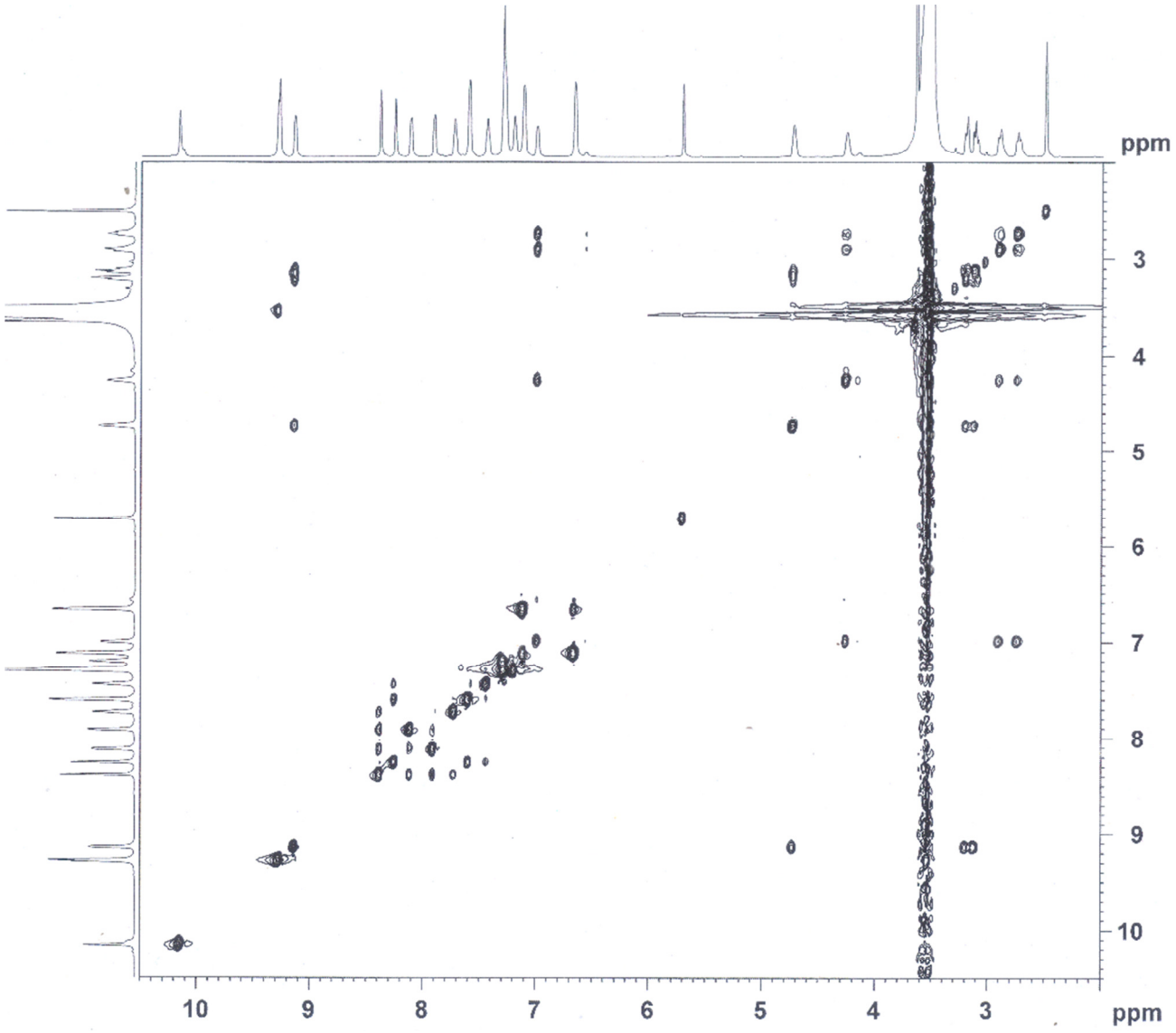

Figure S62. TOCSY spectra of **Tripeptide 4 (BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me)**.

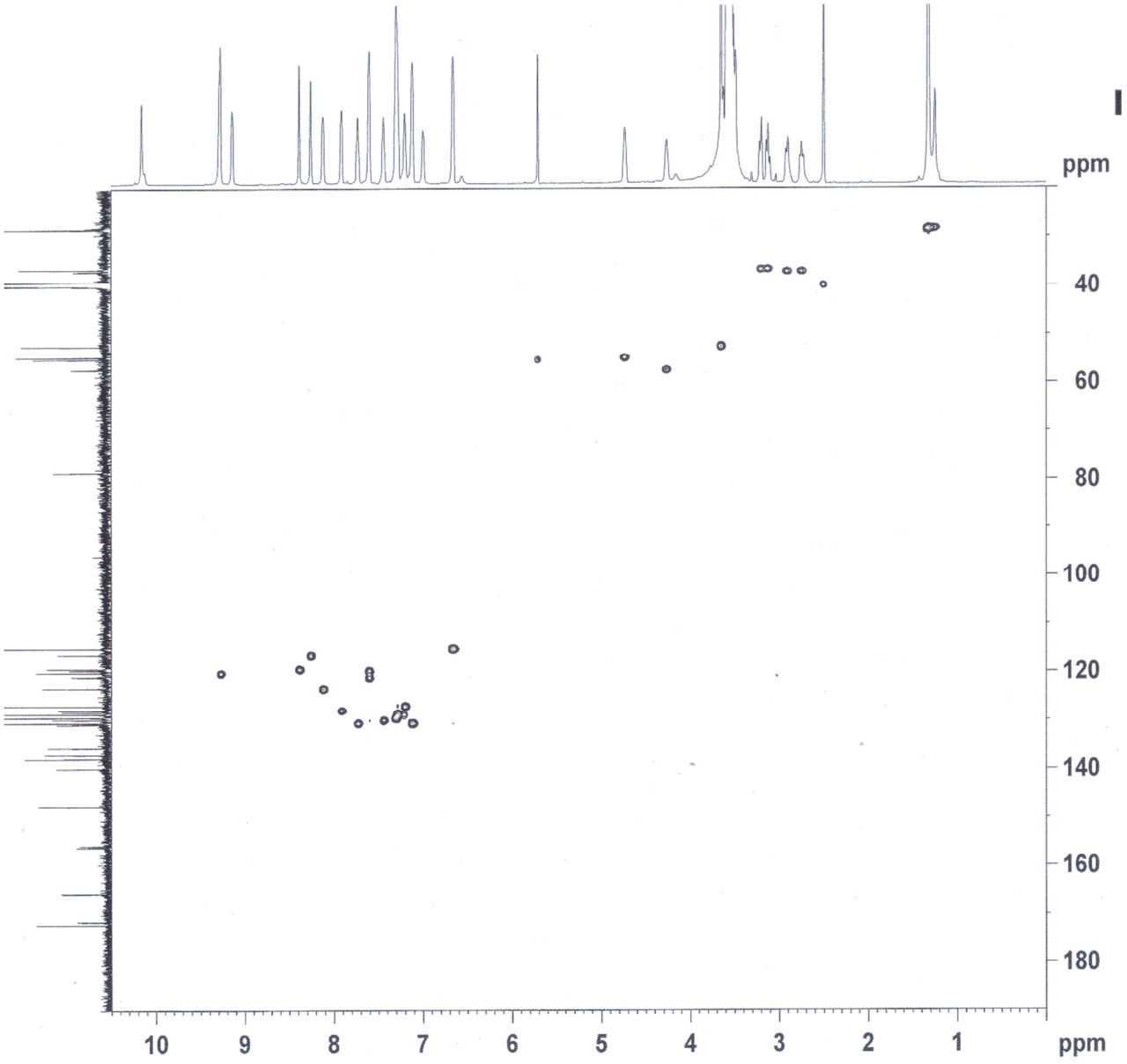

Figure S63. HSQC spectra of **Tripeptide 4 (BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me)**.

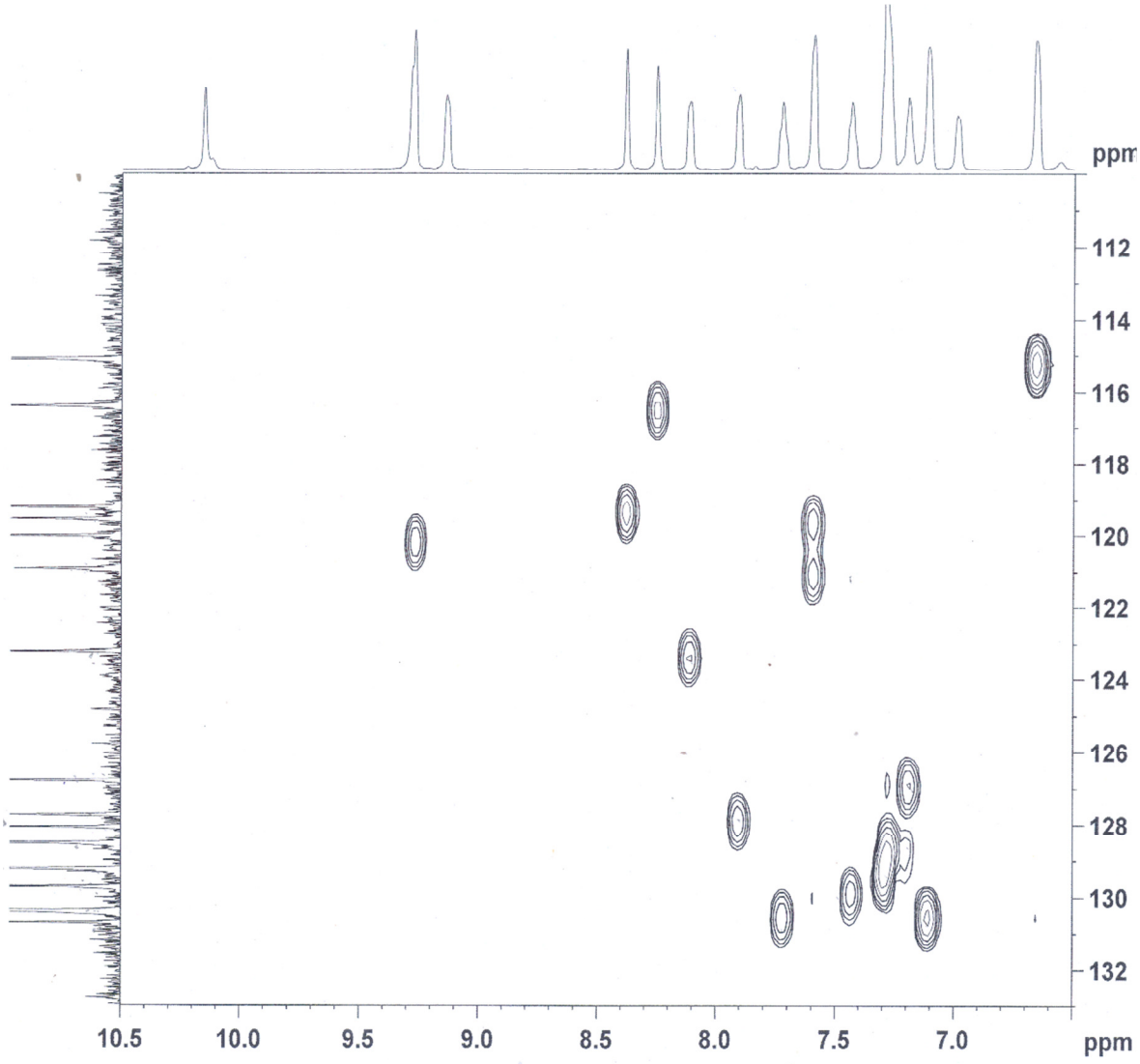

Figure S64. Expanded HSQC spectra of **Tripeptide 4 (BocNH-Tyr-^{Ar}TAA-Phe-CO_2Me)**.

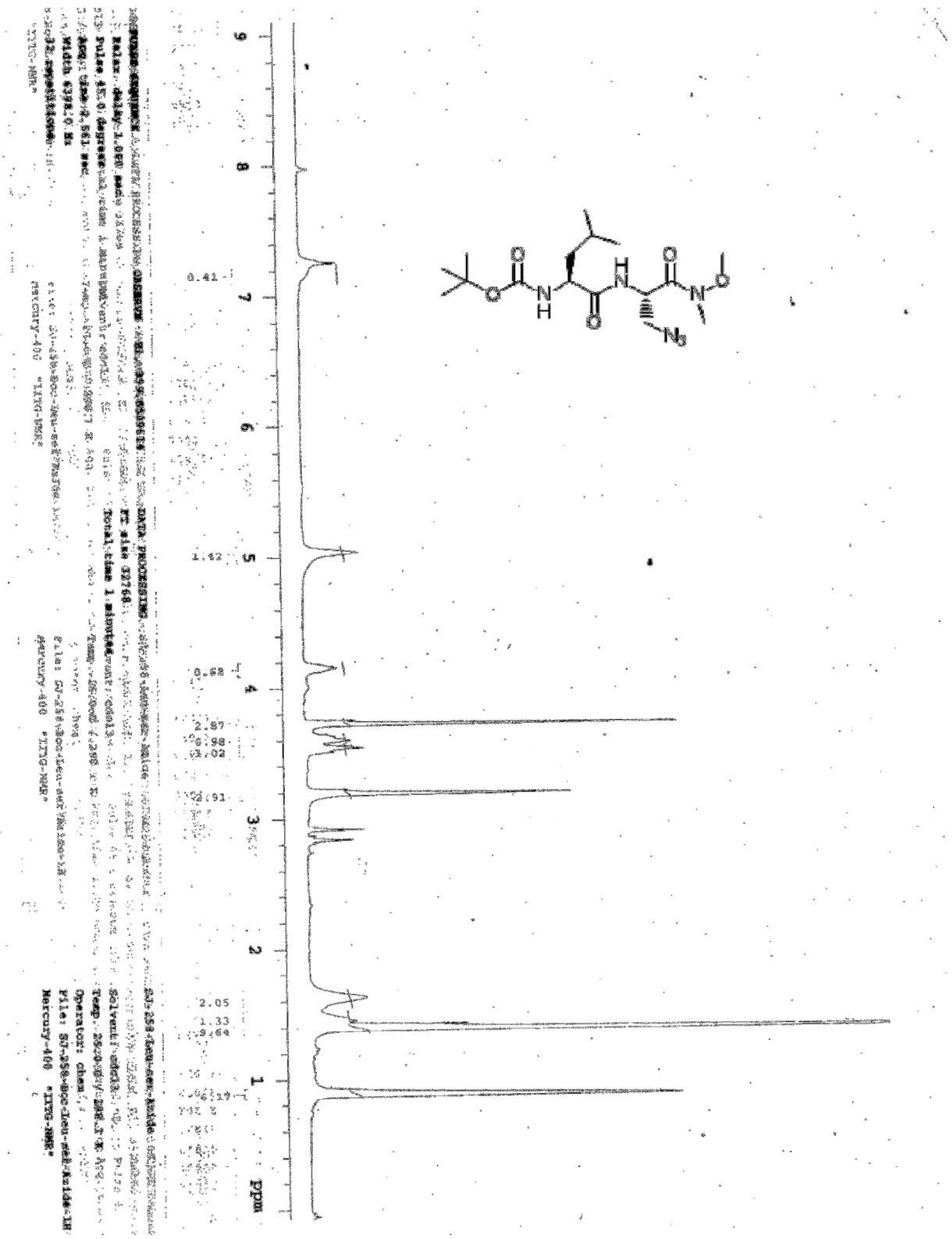

Figure S65. ^{1}H Spectra of synthesized compound **33.**

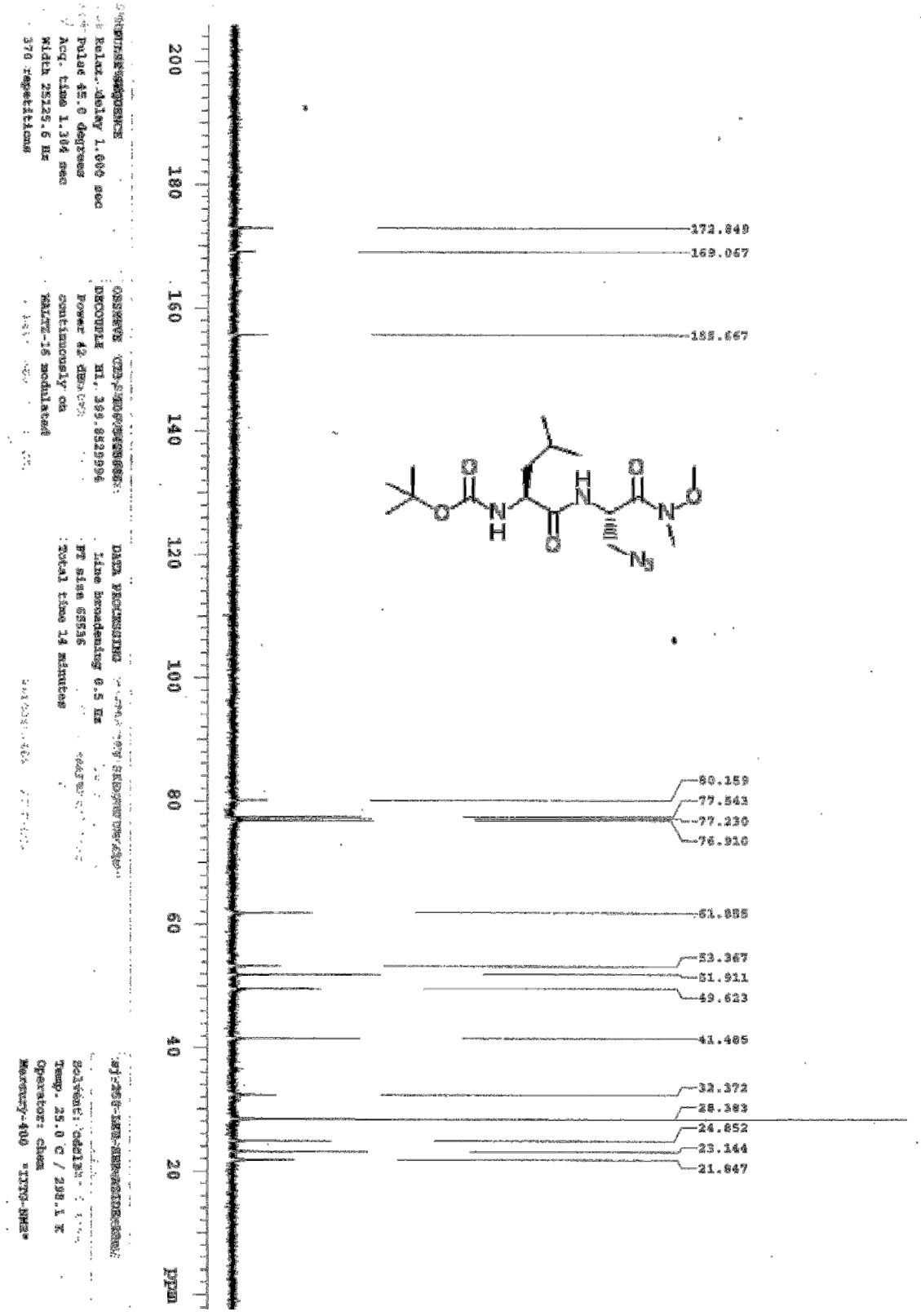

Figure S66. ^{13}C Spectra of synthesized compound **33.**

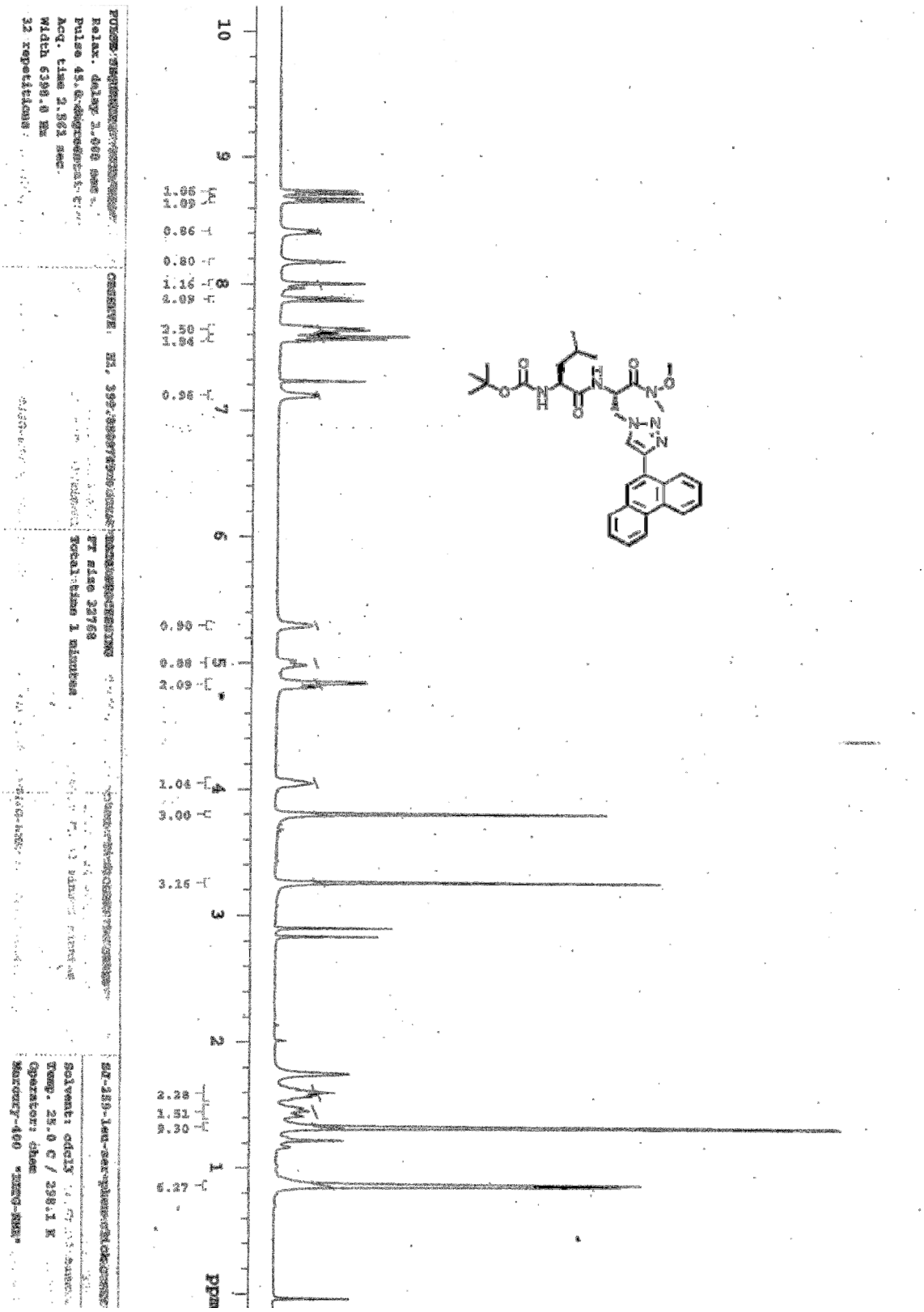

Figure S67. ^{1}H Spectra of synthesized compound **34.**

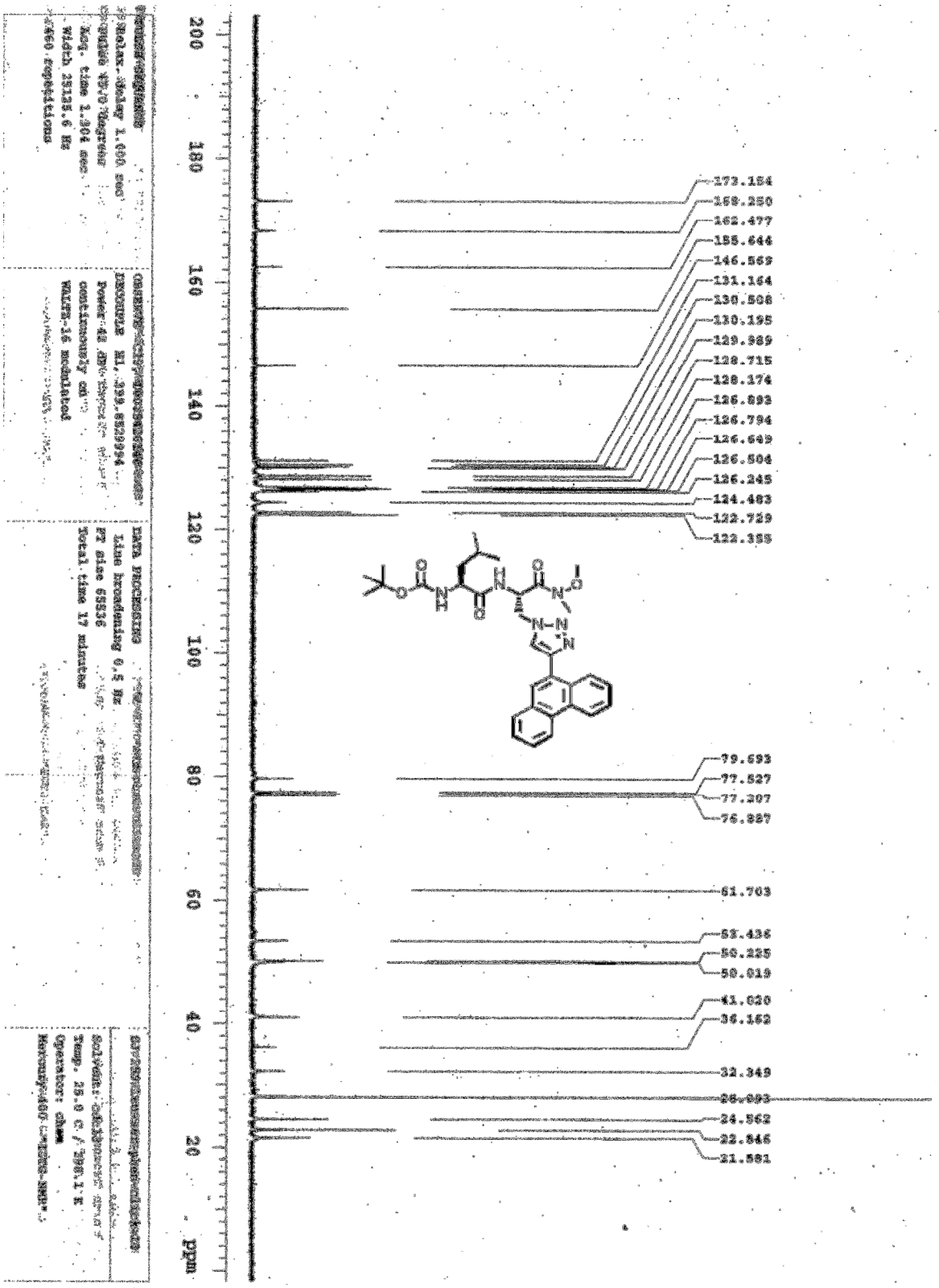

Figure S68. ^{13}C Spectra of synthesized compound **34.**

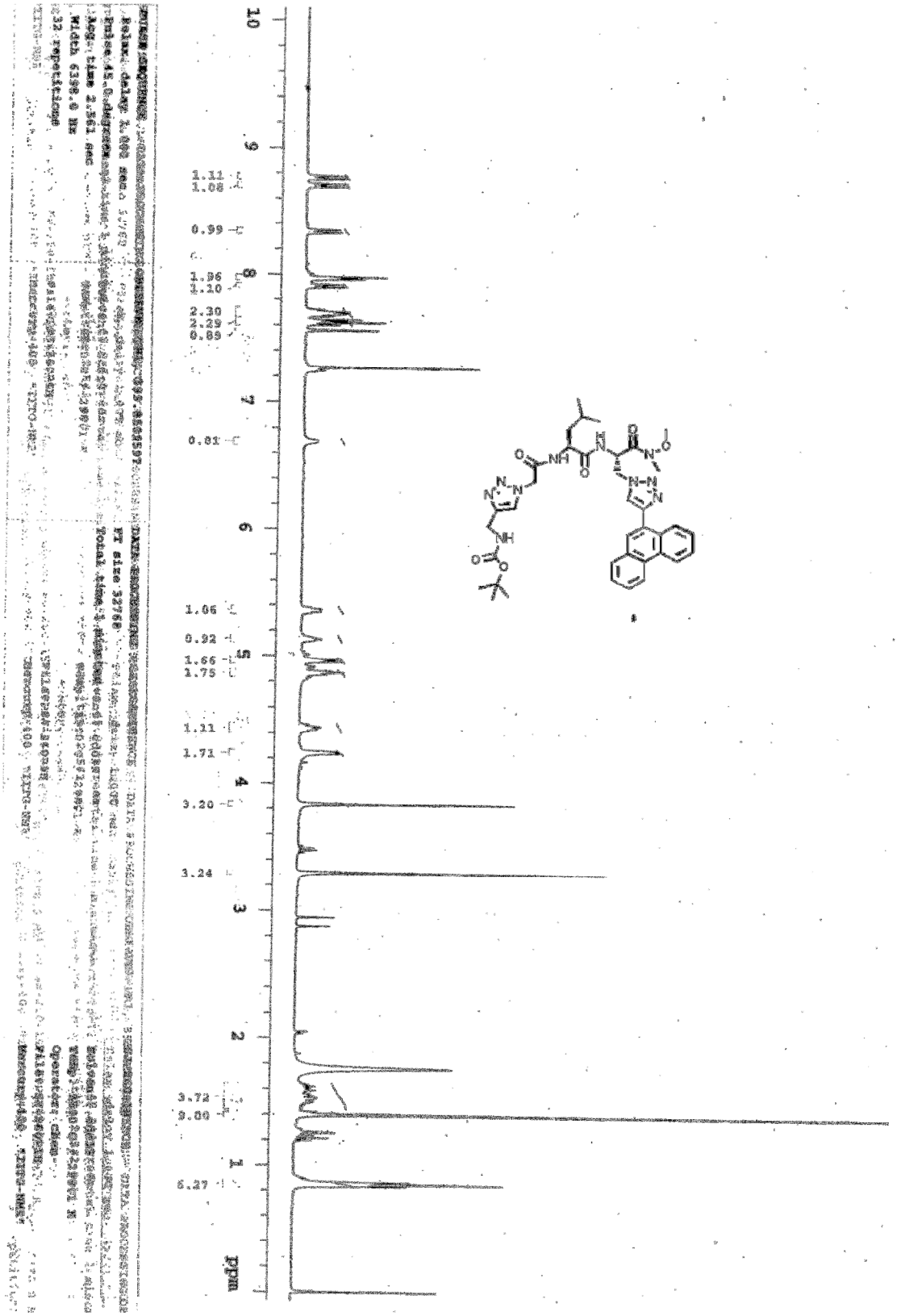

Figure S69. ^{1}H Spectra of synthesized compound **36.**

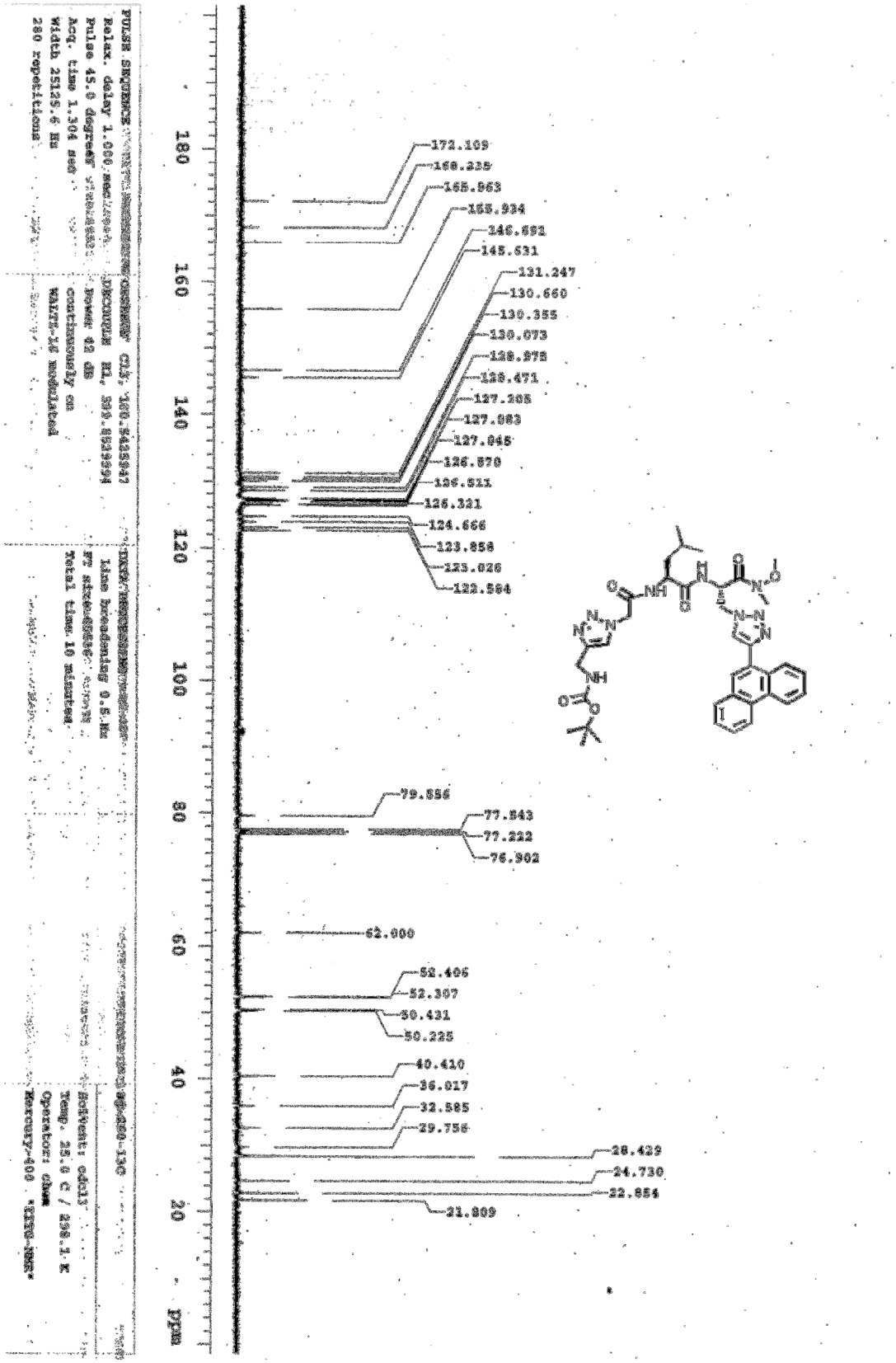

Figure S70. ^{13}C Spectra of synthesized compound **36.**

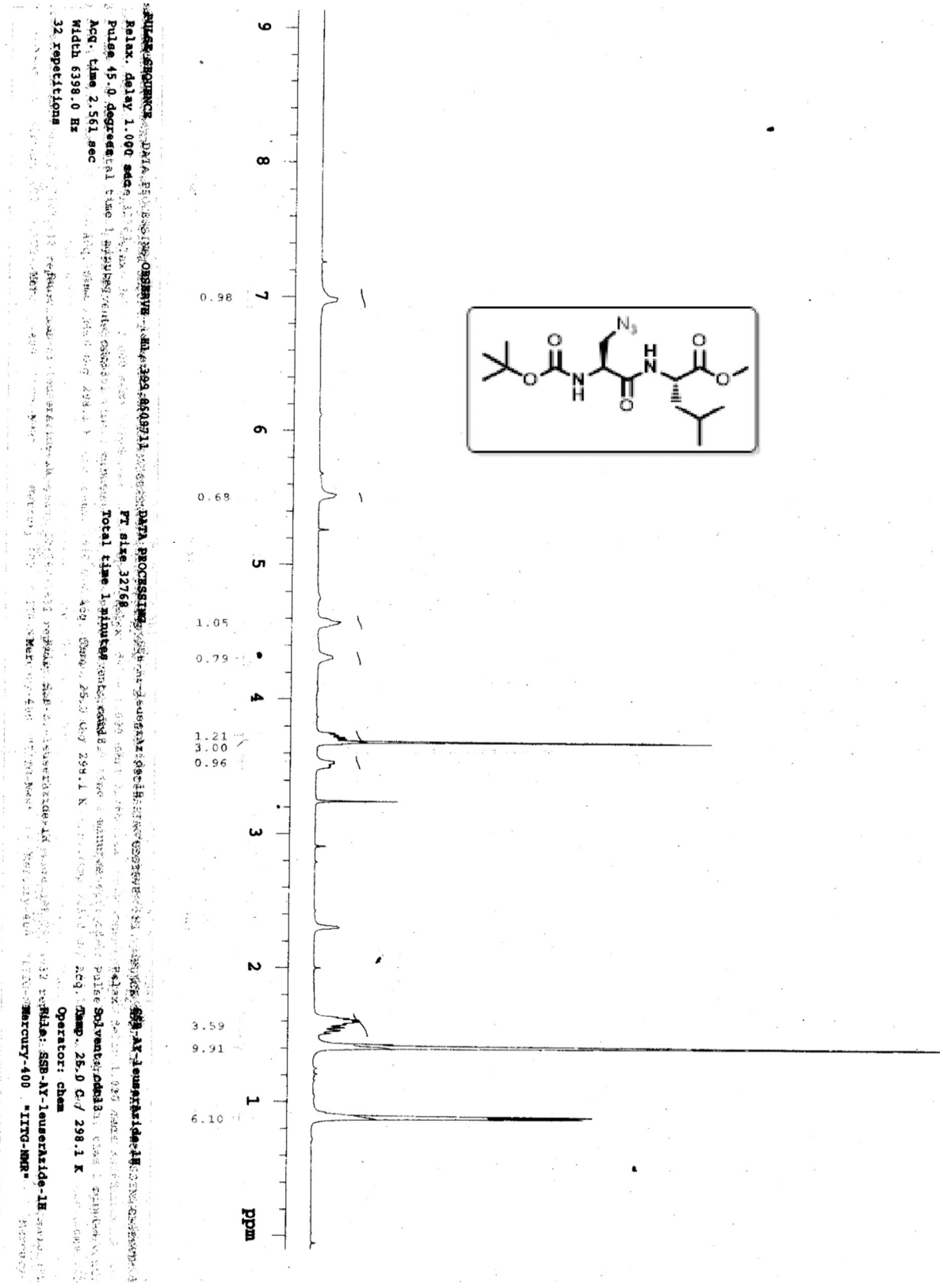

Figure S71. ^{1}H Spectra of synthesized compound **39.**

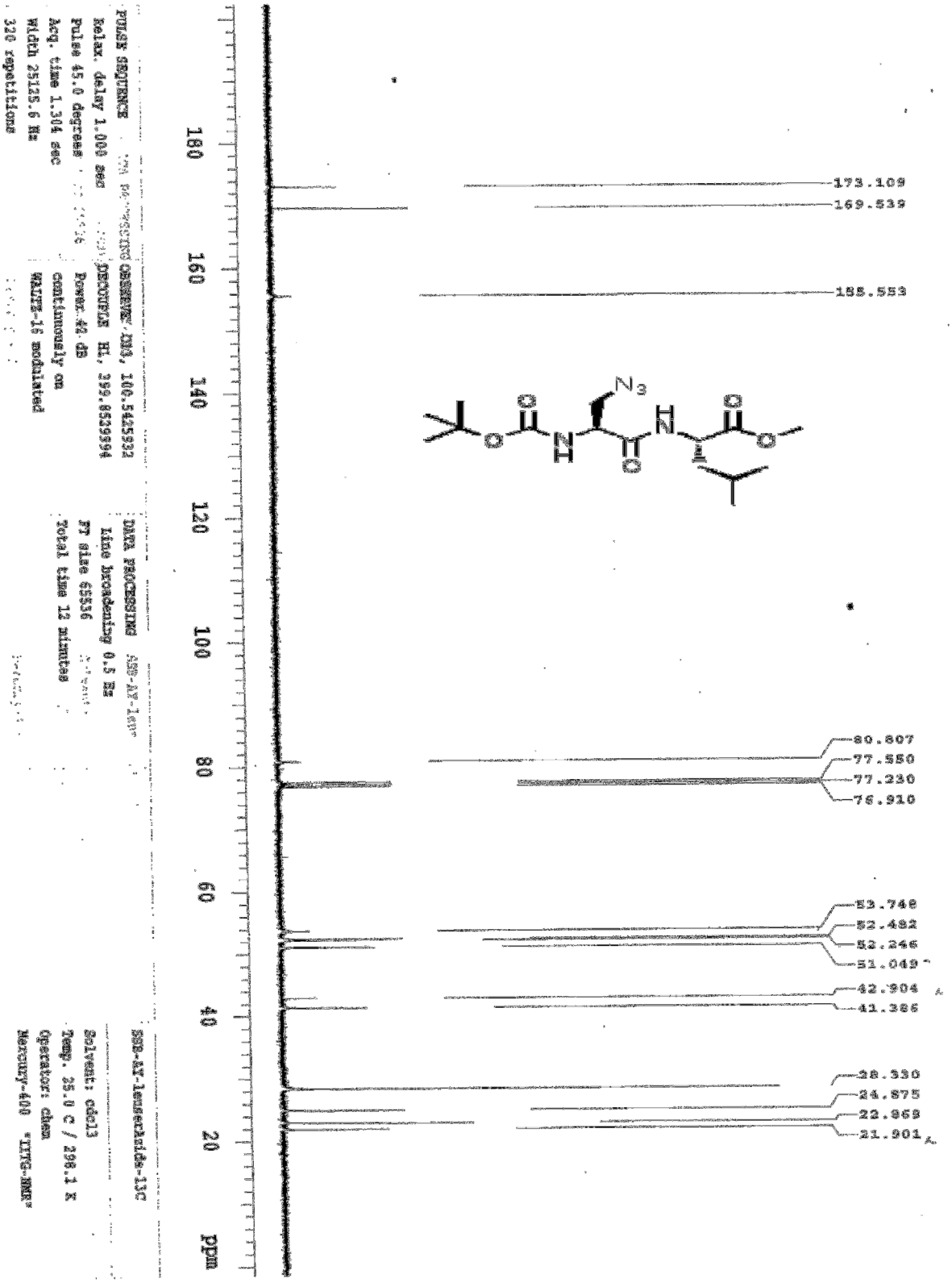

Figure S72. ^{13}C Spectra of synthesized compound **39.**

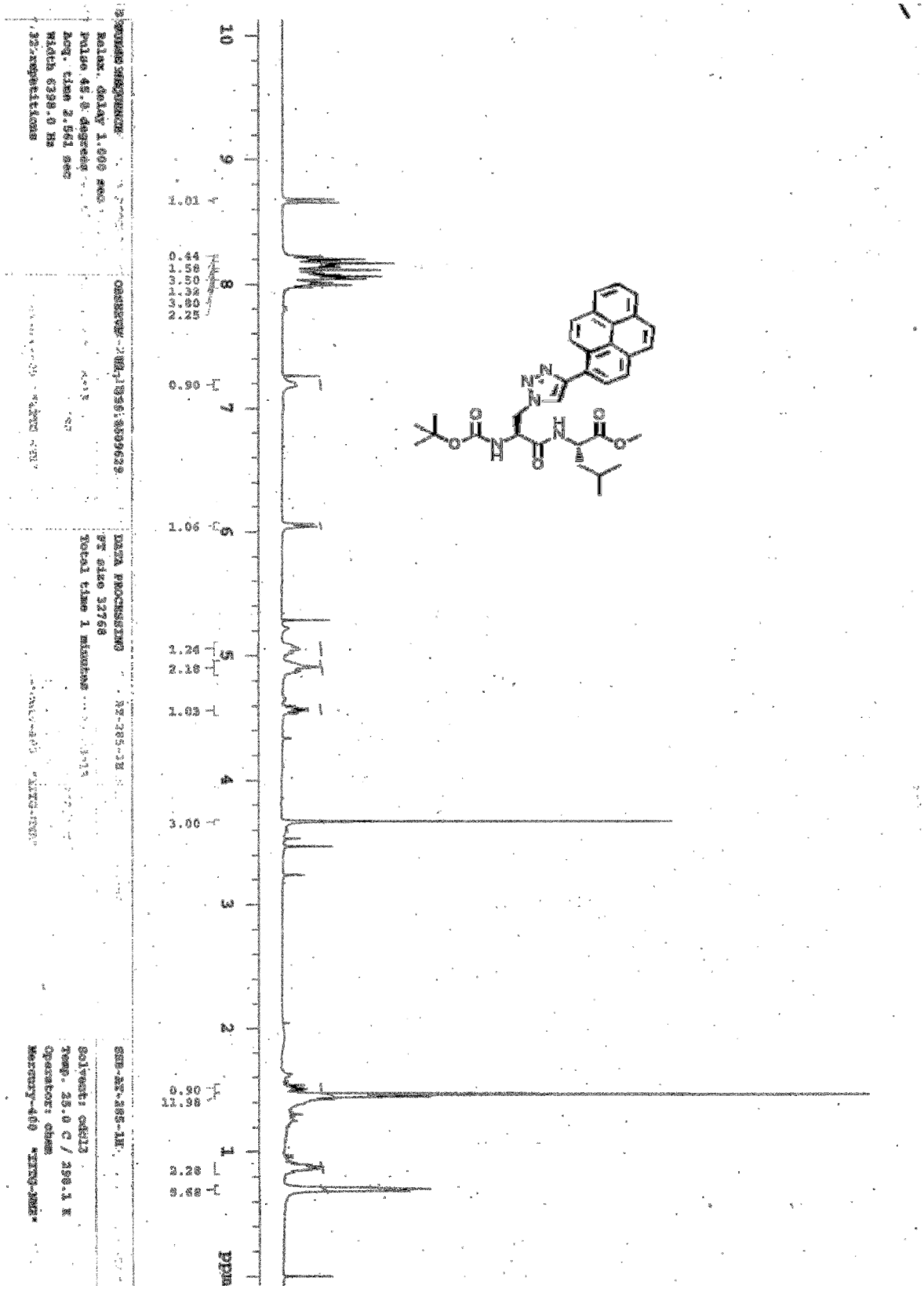

Figure S73. ^{1}H Spectra of synthesized compound **40.**

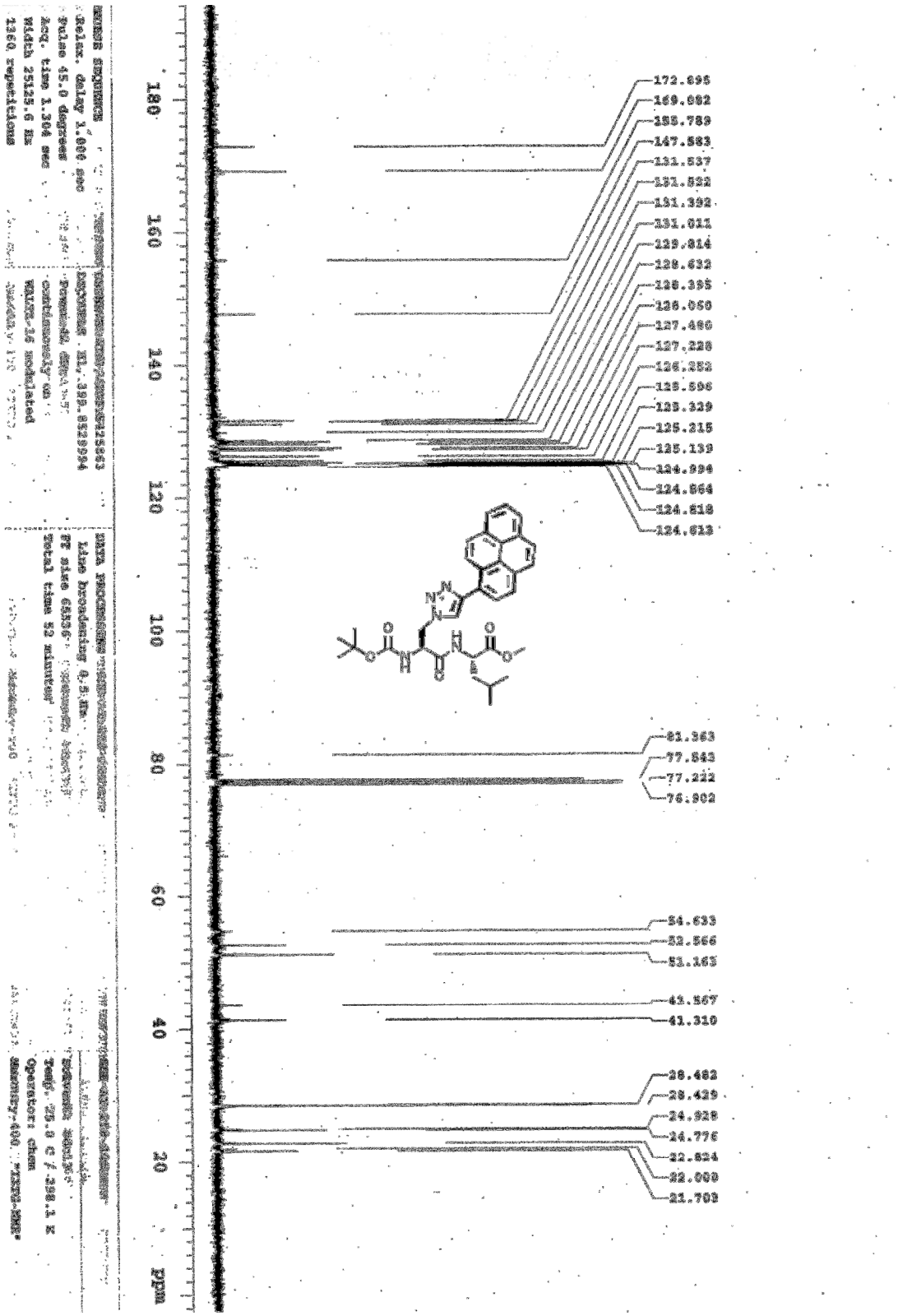

Figure S74. ^{13}C Spectra of synthesized compound **40.**

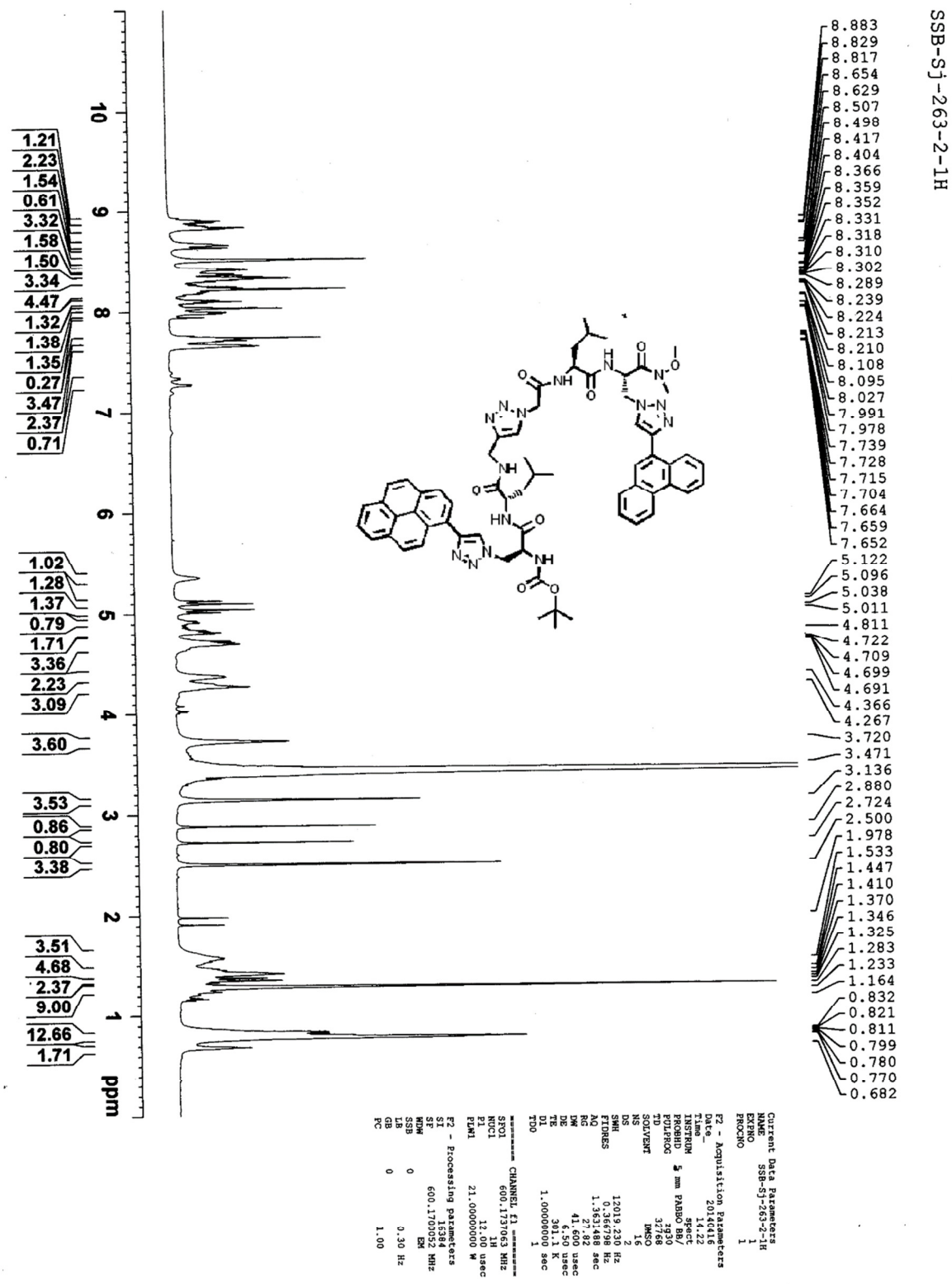

Figure S75. ^{1}H Spectra of synthesized compound **5.**

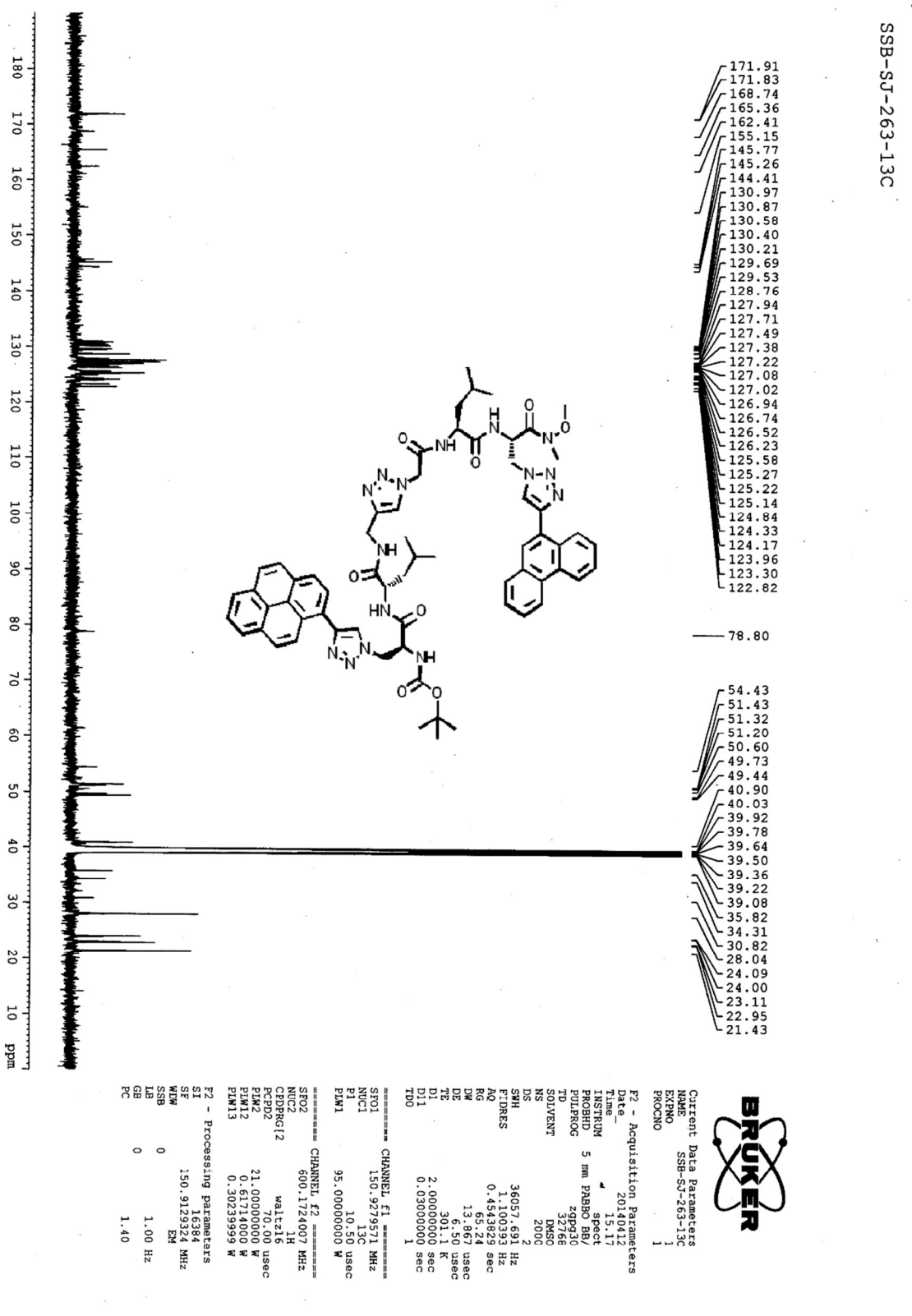

Figure S76. ^{13}C Spectra of synthesized compound **5.**

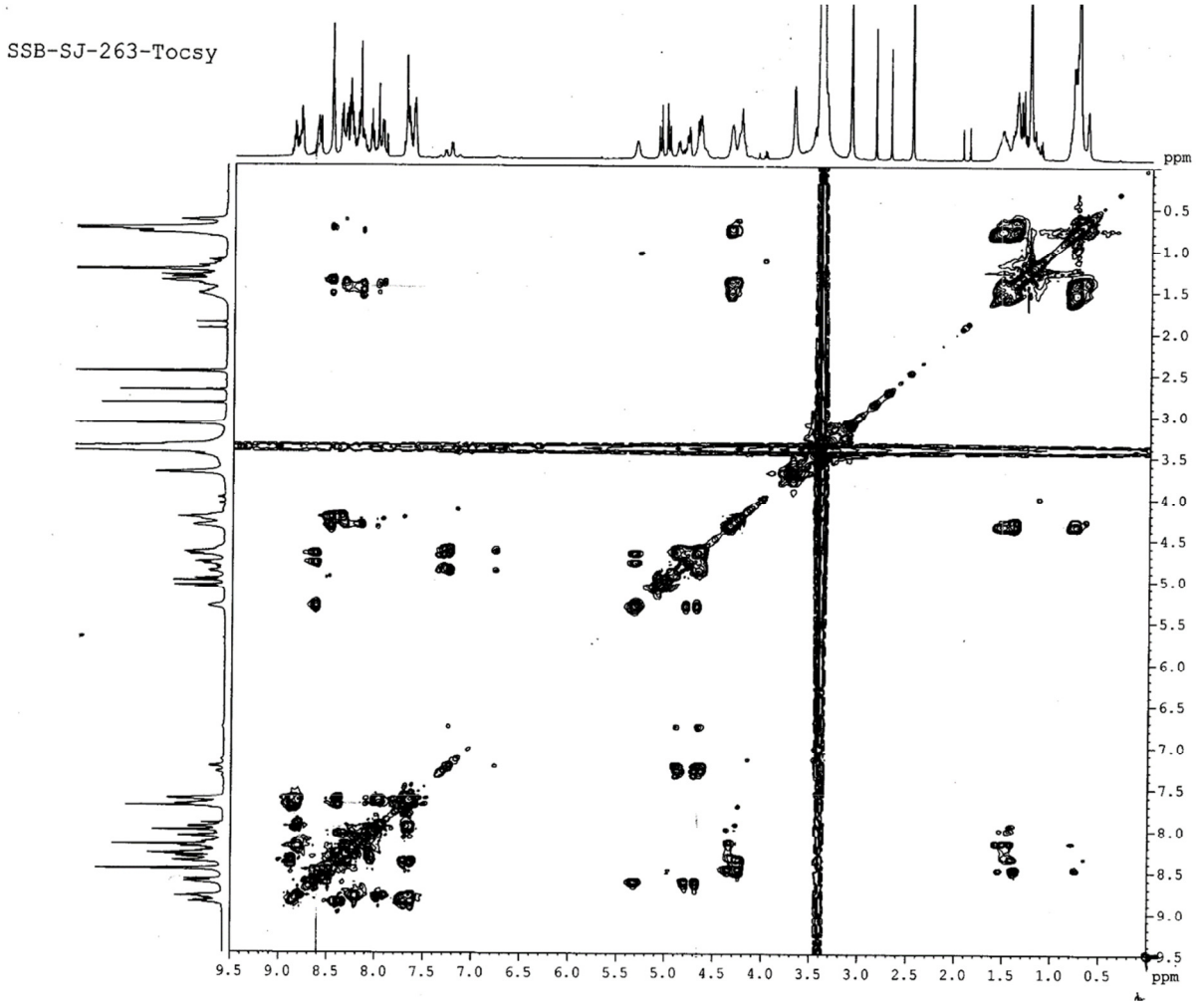

Figure S77. TOCSY spectra of **Pentapeptide 5 (BocNH-^{TPy}Ala^{Do}-Leu-^{Al}TAA-Leu-^{TPhen}Ala^{Do}-CONMe(OMe))**.