Electronic Supplementary Material (ESI) for Materials Advances.

Manuscript title - Antibacterial peptidomimetic and characterization of its efficacy as an antibacterial and biocompatible coating for bioceramic-based bone substitutes.

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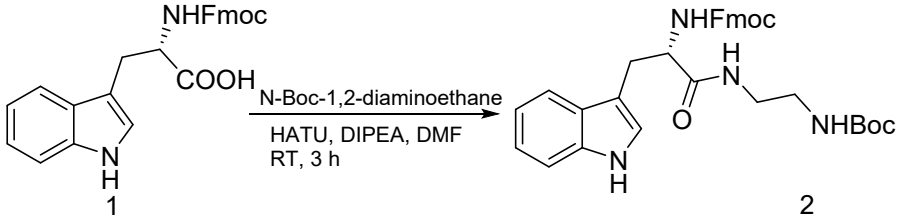
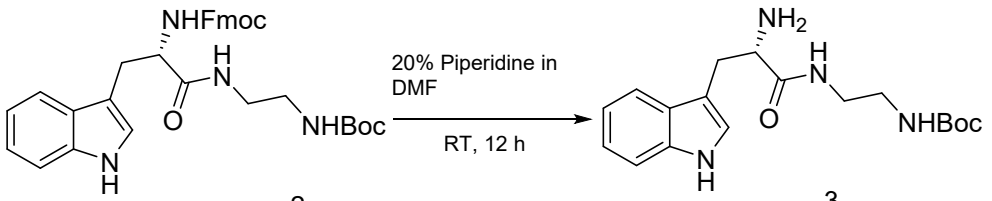
18 pages

Synthesis Protocols



Synthesis of (9H-fluoren-9-yl)methyl (S)-(1-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (2) :

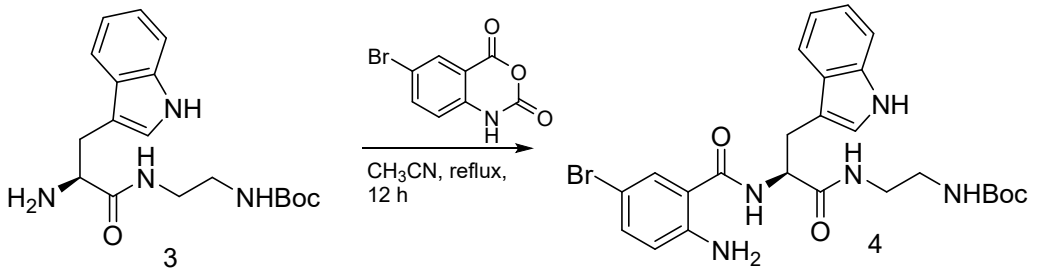
DIPEA (0.665 g, 5.14 mmol) was added to a solution of 1 (1.0 g, 2.34 mmol), N-Boc-1,2-diaminoethane (0.375 g, 2.34 mmol) and HATU (1.09 g, 2.87 mmol) in 10 ml DMF under nitrogen and stirred at room temperature for 2 h. The reaction mixture was diluted with water and extracted with ethyl acetate. Organic layer washed with saturated sodium bicarbonate, 0.5 N HCl, and brine solution. The organic layer dried under Na_2SO_4, concentrated in vacuo to yield the desired compound **2** as off-white solid (1.0 g, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.05 (t, J = 5.2 Hz, 1H), 7.89-7.87 (m, 2H), 7.68-7.63 (m, 3H), 7.51 (d, J = 8.4 Hz, 1H), 7.43-7.25 (m, 5H), 7.19 (br s, 1H), 7.08-7.06 (m, 2H), 6.76 (br s, H), 4.22-4.14 (m, 4H), 3.15-2.92 (m, 6H); ^{13}C NMR (101 MHz, DMSO-d_6) 172.4, 156.2, 156.1, 144.3, 144.2, 141.1, 136.5, 128.1, 127.7, 127.5, 125.8, 125.8, 124.2, 121.3, 120.5, 118.9, 118.6, 111.8, 110.8, 78.2, 66.1, 56.1, 47.1, 40.5, 28.6, 28.4; HRMS (ESI): m/z calcd for $C_{33}H_{36}N_4O_5$ $[M + Na]^+$: 591.2571; found: 591.2577.



2 3

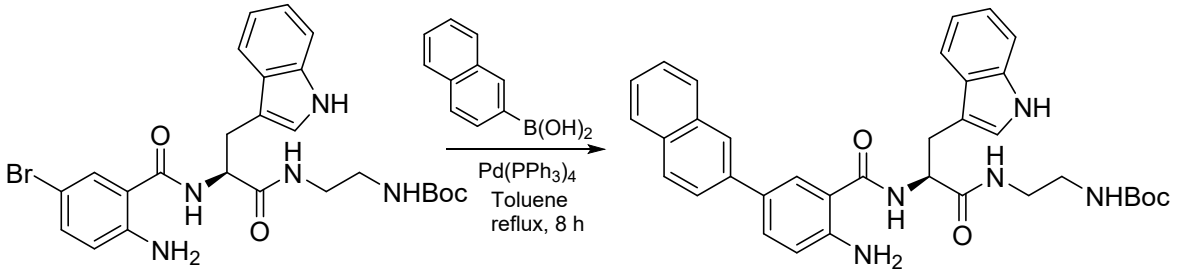
Synthesis of *tert*-butyl (S)-(2-(2-amino-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (3):

The solution of 20% piperidine in DMF (10.0 mL) was added to the starting material **2** (1.0 g) and stirred at room temperature for 12 h. The reaction mixture was concentrated under vacuo and purified using silica gel with eluent $CHCl_3$:MeOH:Ammonia solution (9:1:1). Upon concentration the product **3** isolated as white solid (0.509 g, 83%); 1H NMR (400 MHz, DMSO-d_6): δ 10.84 (s, 1H), 7.94 (t, J = 5.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.15-7.14 (m, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.81-6.78 (m, 1H), 3.13-3.05 (m, 5H), 2.78-2.72 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) 175.1, 156.1, 136.7, 127.9, 124.2, 121.3, 118.9, 118.7, 111.8, 111.0, 78.1, 55.8, 40.4, 40.1, 31.3, 28.7; HRMS (ESI): m/z calcd for $C_{18}H_{26}N_4O_3$ $[M + H]^+$: 347.2074; found: 347.2077.



Synthesis of *tert*-butyl (S)-(2-(2-(2-amino-5-bromobenzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (4):

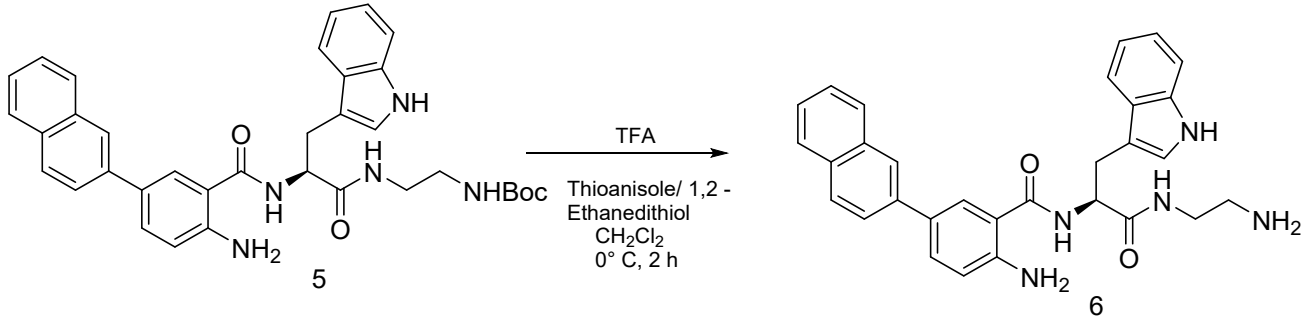
The suspension of isatoic anhydride (0.68 g, 2.8 mmol) and compound **3** (1.0 g, 2.8 mmol) in anhydrous acetonitrile (20 mL) was refluxed under an argon atmosphere for 16 h. After completion of the reaction the mixture was concentrated in *vacuo* to yield the crude compound, which was subjected to trituration using diethyl ether. The solid was filtered out and dried under *vacuo* to afford compound **4** as pale-brown solid (1.0 g, 67%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.10 (t, J = 5.8 Hz, 1H), 7.69 (dd, J = 5.1, 15.9 Hz, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.23 (dd, J = 2.4, 8.8 Hz, 1H), 7.17 (d, J = 2.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 7.4 Hz, 1H), 6.76 (t, J = 5.6 Hz, 1H), 6.62 (d, J = 8.9 Hz, 1H), 6.48 (s, 2H), 4.64 – 4.55 (m, 1H), 3.21 – 2.94 (m, 6H), 1.37 (s, 9H);^{13}C NMR(75 MHz, DMSO-d_6) 172.4, 167.9, 156.1, 149.4, 136.5, 134.7, 131.1, 127.7, 124, 121.3, 118.9, 116.1, 111.8, 111.1, 105.3, 78.2, 54.6, 40.5, 28.7, 27.8; HRMS (ESI): m/z calcd for $C_{25}H_{30}BrN_5O_4$ $[M + Na]^+$: 566.1371; found: 566.1369.



Synthesis of *tert*-butyl (S)-(2-(2-(2-amino-5-(naphthalen-2-yl)benzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (5):

To the degassed solution of the bromo compound **4** (0.5 g, 0.918 mmol) and boronic acid (0.189 g, 1.1 mmol) in toluene and ethanol (2.5:2.5 mL) were added 2N Na_2CO_3 (1.4 mL, 2.75 mmol) and $Pd(PPh_3)_4$ (53 mg, 0.05 mmol). The reaction mixture was heated at 80 ° C for 12 hours. The reaction mixture was filtered through celite, washed with ethyl acetate. The organic layer was diluted with water. The organic layer was separated and washed with brine solution and dried under anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified using silica gel column chromatography using hexane: ethyl acetate (50: 50) as eluent. Upon concentration the product **5** isolated as pale-brown solid (0.29 g, 54%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.51 – 8.49 (m, 1H), 8.16 (s, 2H), 8.00 – 7.87 (m, 4H), 7.76 (d, J = 7.8 Hz, 1H), 7.65 (dd, J = 2.2, 8.6 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.32 – 7.26 (m, 2H), 7.06 – 6.95 (m, 2H), 6.79 (dd, J = 7.1, 9.5 Hz, 2H), 6.53 (s, 2H), 4.70 – 4.64 (m, 1H), 3.25 – 3.02 (m, 6H), 1.37 (s, 9H);^{13}C NMR (101 MHz, DMSO-d_6) 172.6, 169.2, 156.1, 149.8, 137.9, 136.5, 133.9, 132.1, 130.7, 128.6, 128.3, 127.9, 127.8, 127.4, 126.7, 126.4, 125.8, 125.2, 124.1,

123.7, 121.3, 119.0, 118.6, 117.4, 114.9, 111.8, 111.3, 78.2, 65.3, 54.7, 28.7, 27.9; HRMS (ESI): m/z calcd for $C_{35}H_{37}N_5O_4$ $[M + Na]^+$: 614.2738; found: 614.2732

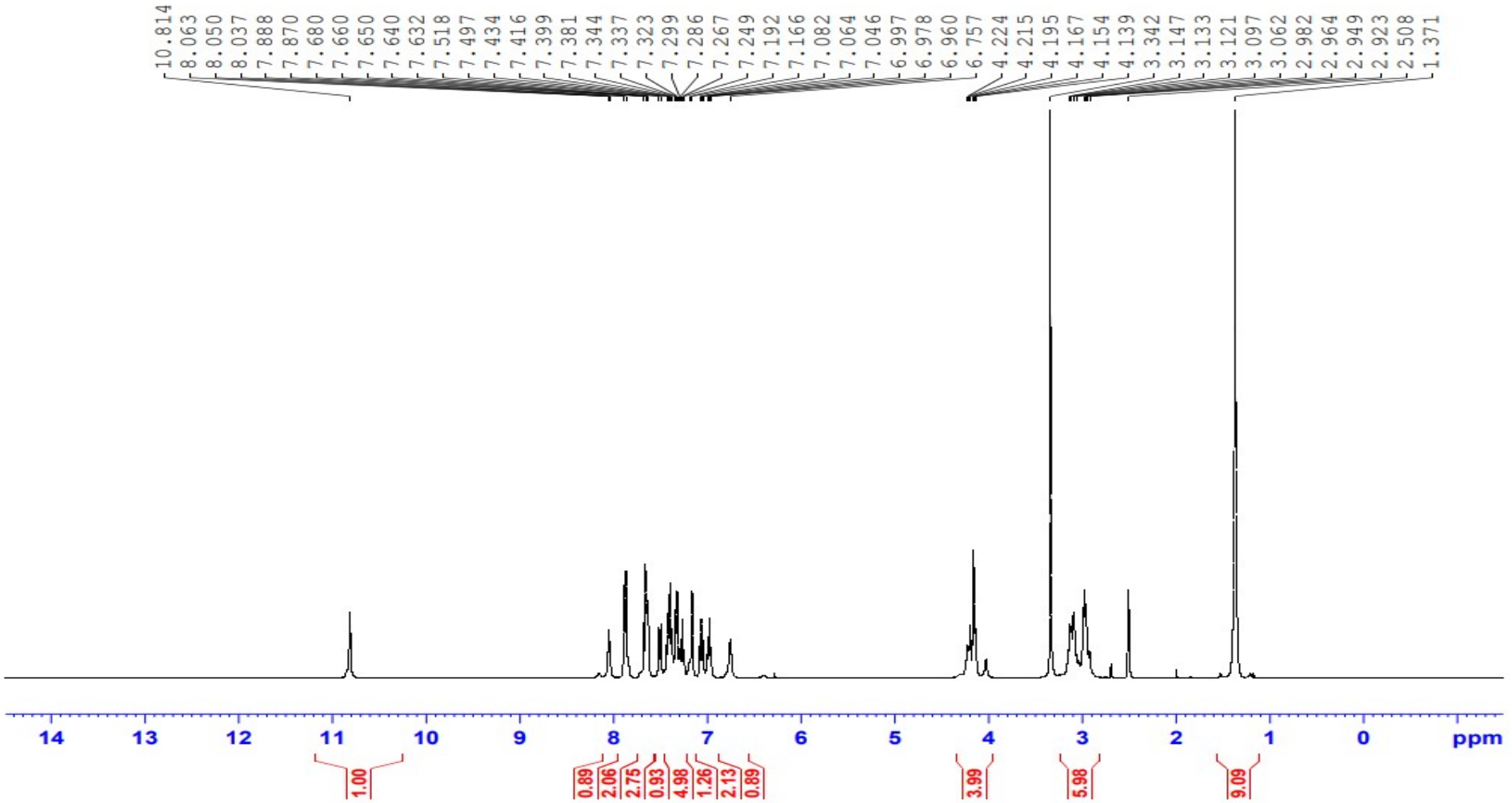


Synthesis of (*S*)-2-amino-N-(1-((2-aminoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)-5-(naphthalen-2-yl)benzamide (6):

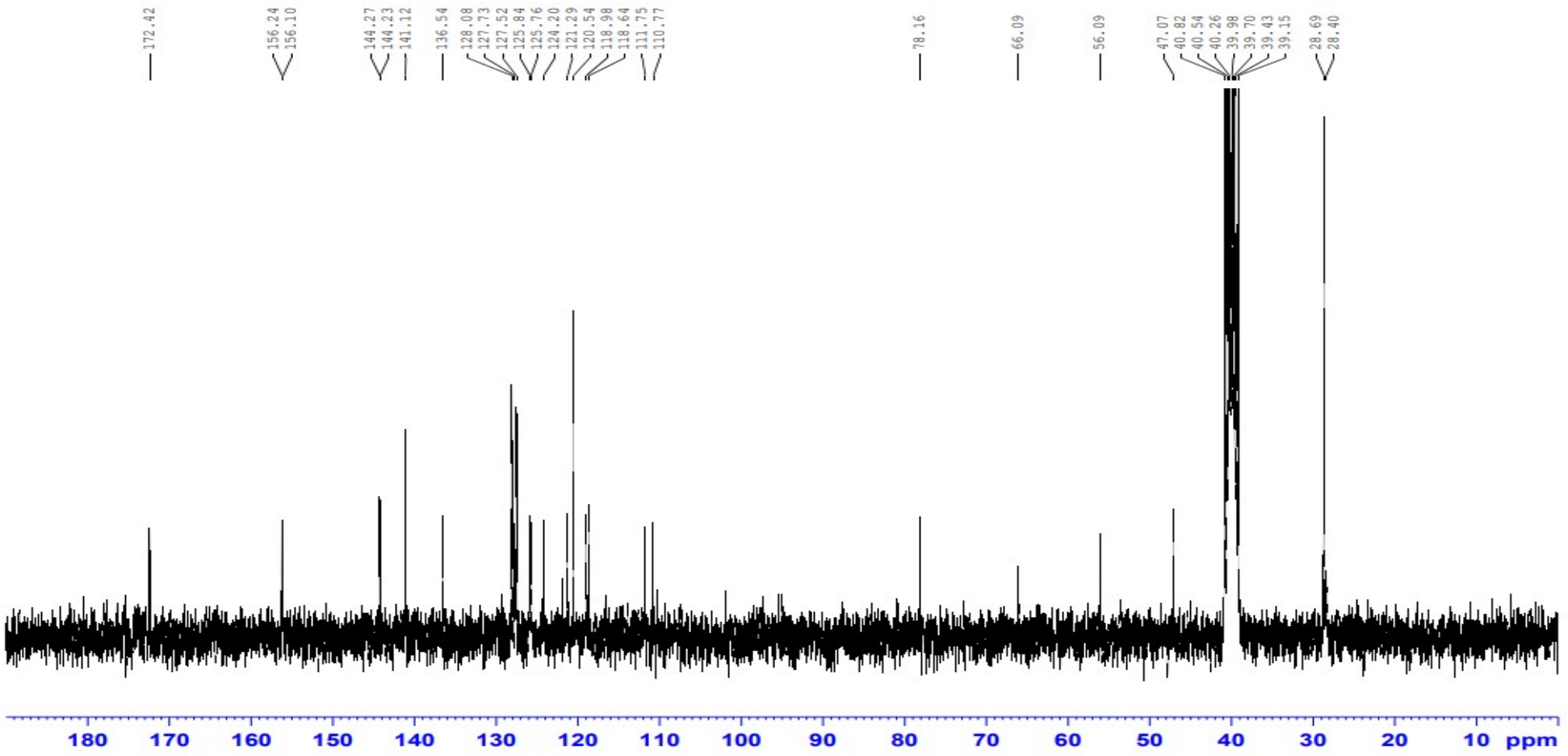
To a solution of **5** (0.1 g, 0.169 mmol) in dichloromethane (1.0 mL) Thioanisole (0.1 mL), 1,2 -Ethanedithiol (0.1) was added followed by TFA (1.0 mL) at 0 °C. The reaction mixture was stirred at same temperature for 1.5 h. After completion of the reaction, solvent was removed under reduced pressure and treated with diethyl ether and the solid filtered out and dried under high vacuum. The solid was treated with 4N HCl in dioxane and freeze dried the sample using acetonitrile and water, to yield the desired product as off-white solid (0.04 g, 48%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s,

1H), 8.97 (d, J = 8.1 Hz, 1H), 8.50 (t, J = 5.5 Hz, 1H), 8.31 – 8.26 (m, 1H), 8.16 (s, 3H), 8.09 (s, 1H), 8.04 – 7.92 (m, 4H), 7.83 – 7.78 (m, 2H), 7.58 – 7.52 (m, 2H), 7.30 – 7.20 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.02 – 6.99 (m, 1H), 6.95 – 6.91 (m, 1H), 4.75 – 4.74 (m, 1H), 3.43 – 3.26 (m, 4H), 2.89 (q, J = 6.1 Hz, 2H);^{13}C NMR δ_C (101 MHz, DMSO-d_6) 172.6, 168.1, 137.1, 136.5, 133.8, 132.4, 130.7, 128.8, 128.5, 127.9, 127.8, 127.7, 126.8, 126.3, 125.3, 124.7, 124.1, 121.2, 120.6, 119.0, 118.6, 111.8, 111.8, 111.2, 66.8, 55.0, 37.0, 27.7; HRMS (ESI): m/z calcd for $C_{30}H_{35}N_5O_2$ $[M + Na]^+$: 514.2206; found: 514.2213.

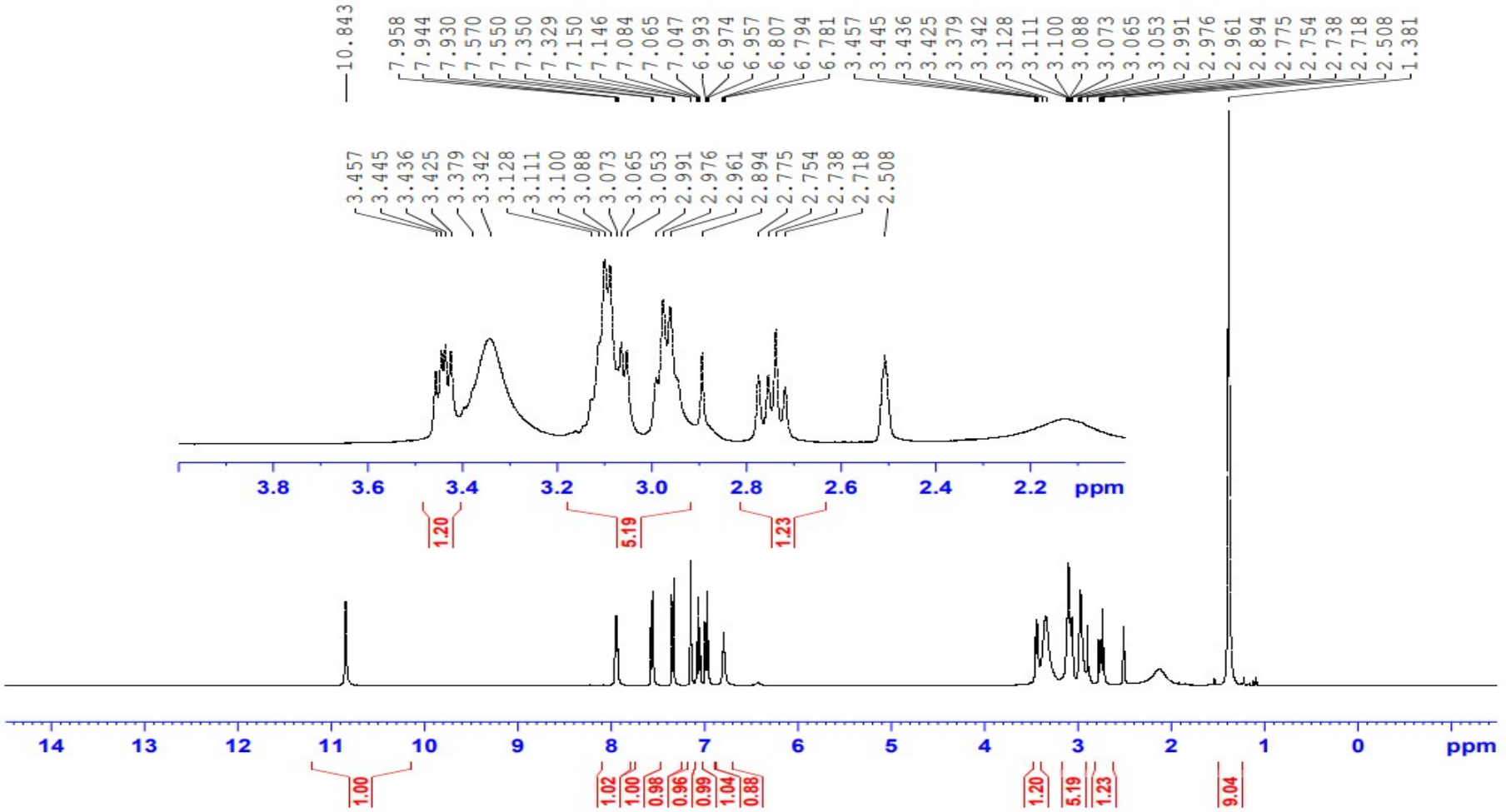
1H NMR of (9H-fluoren-9-yl)methyl (S)-(1-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (2):



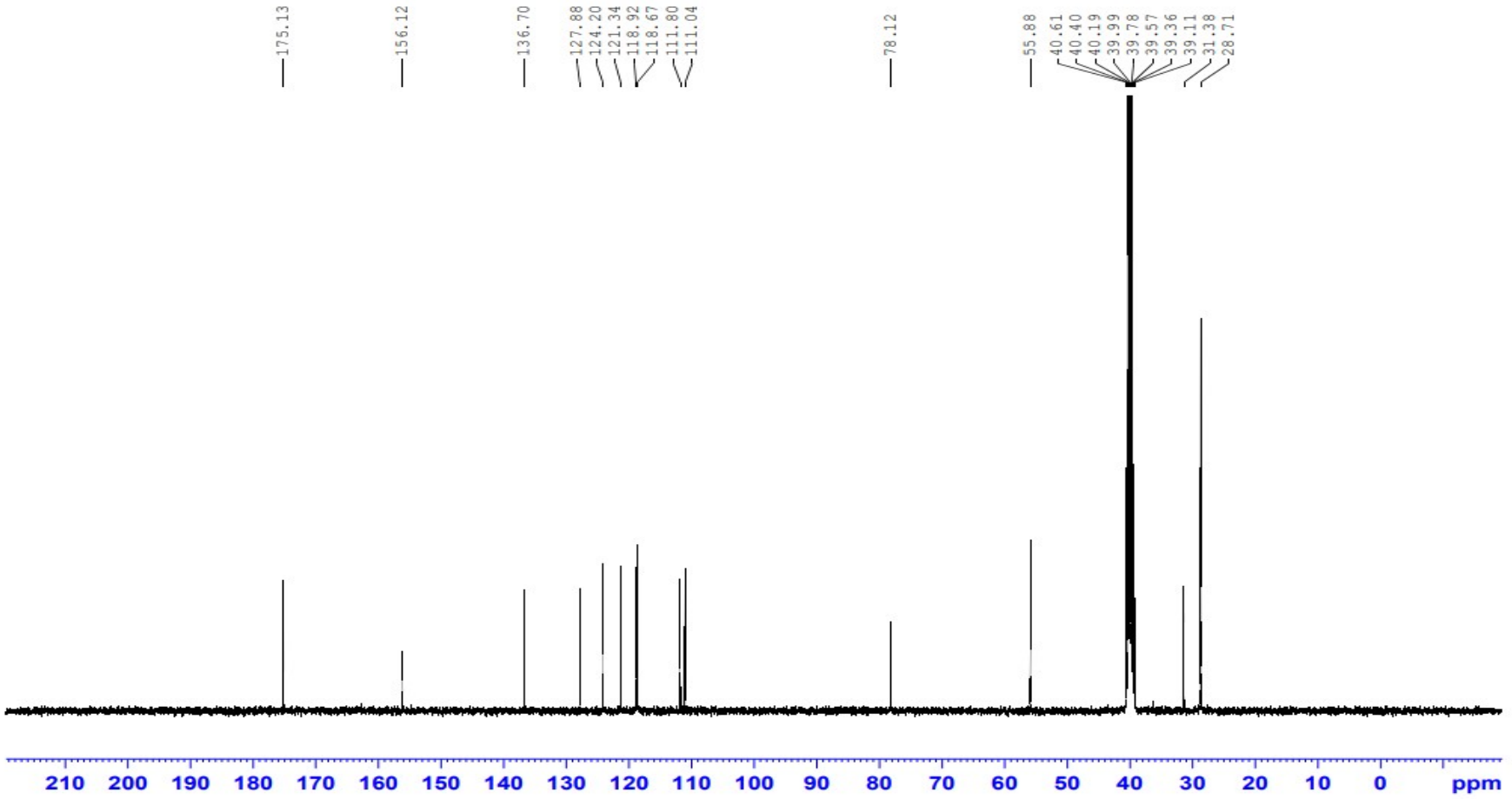
13C NMR of (9H-fluoren-9-yl)methyl (S)-(1-((2-((tert-butoxycarbonyl)amino)ethyl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate (2):



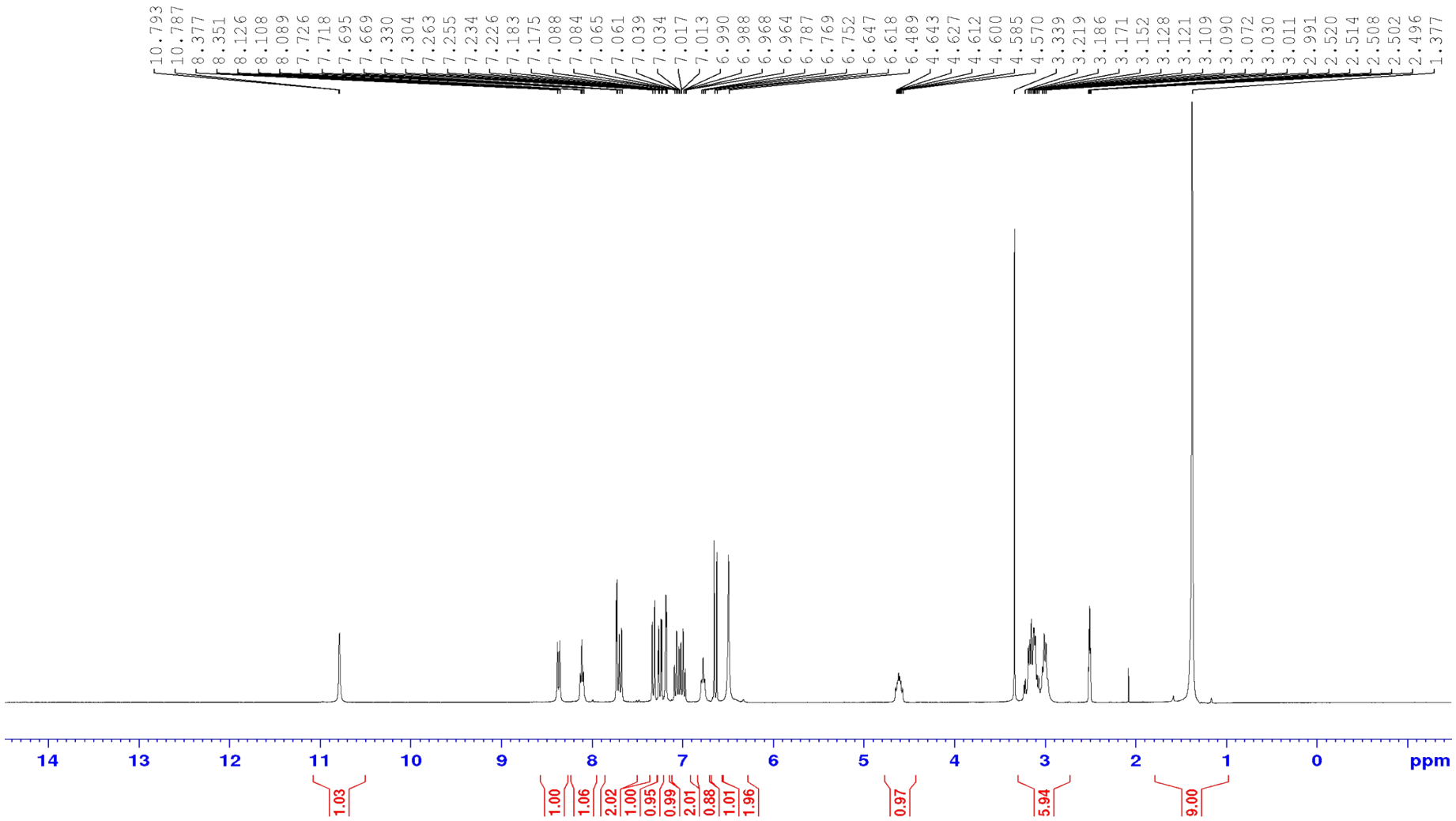
1H NMR of *tert*-butyl (S)-(2-(2-amino-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (3):



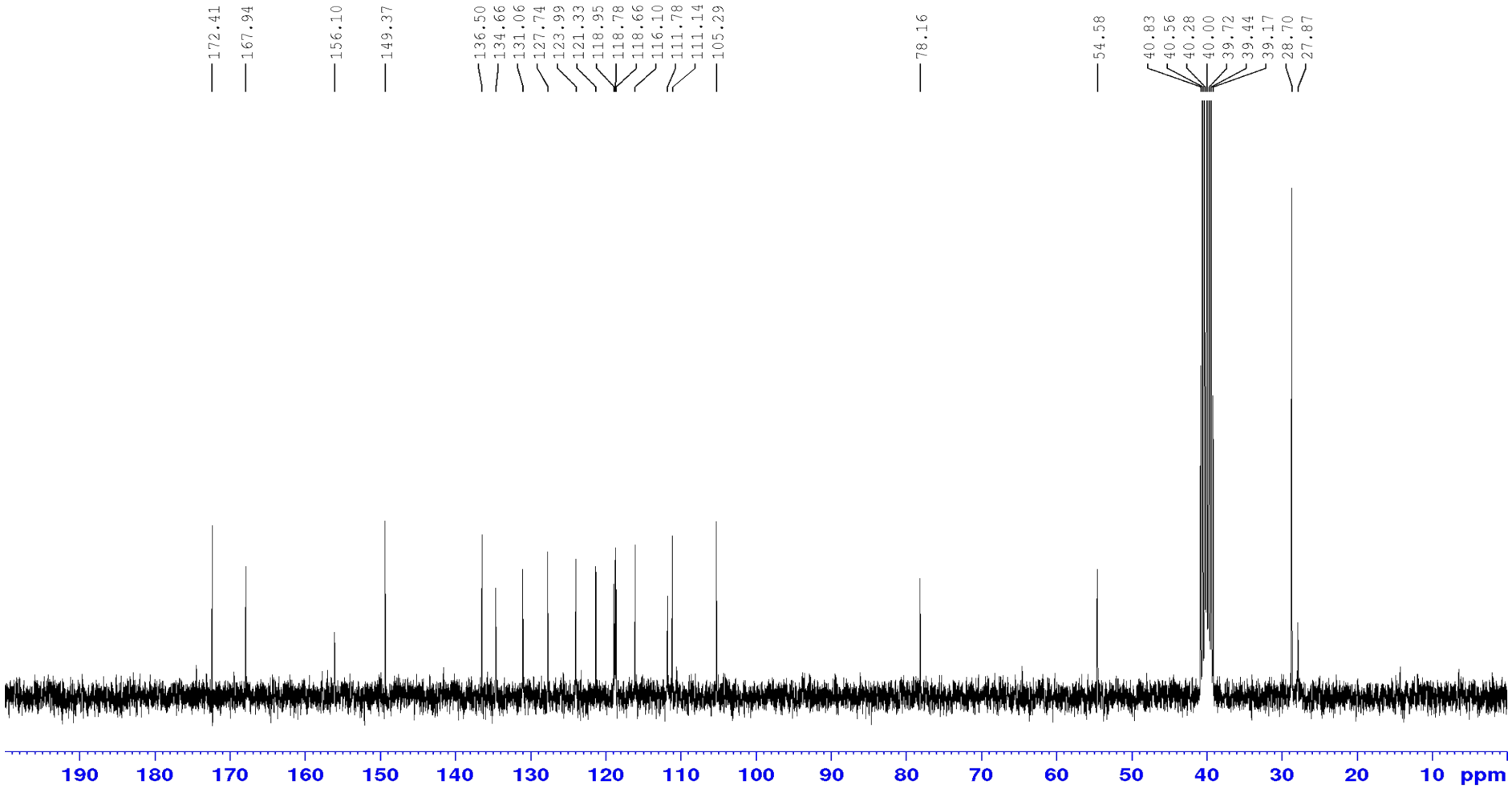
13C NMR of *tert*-butyl (S)-(2-(2-amino-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (3):



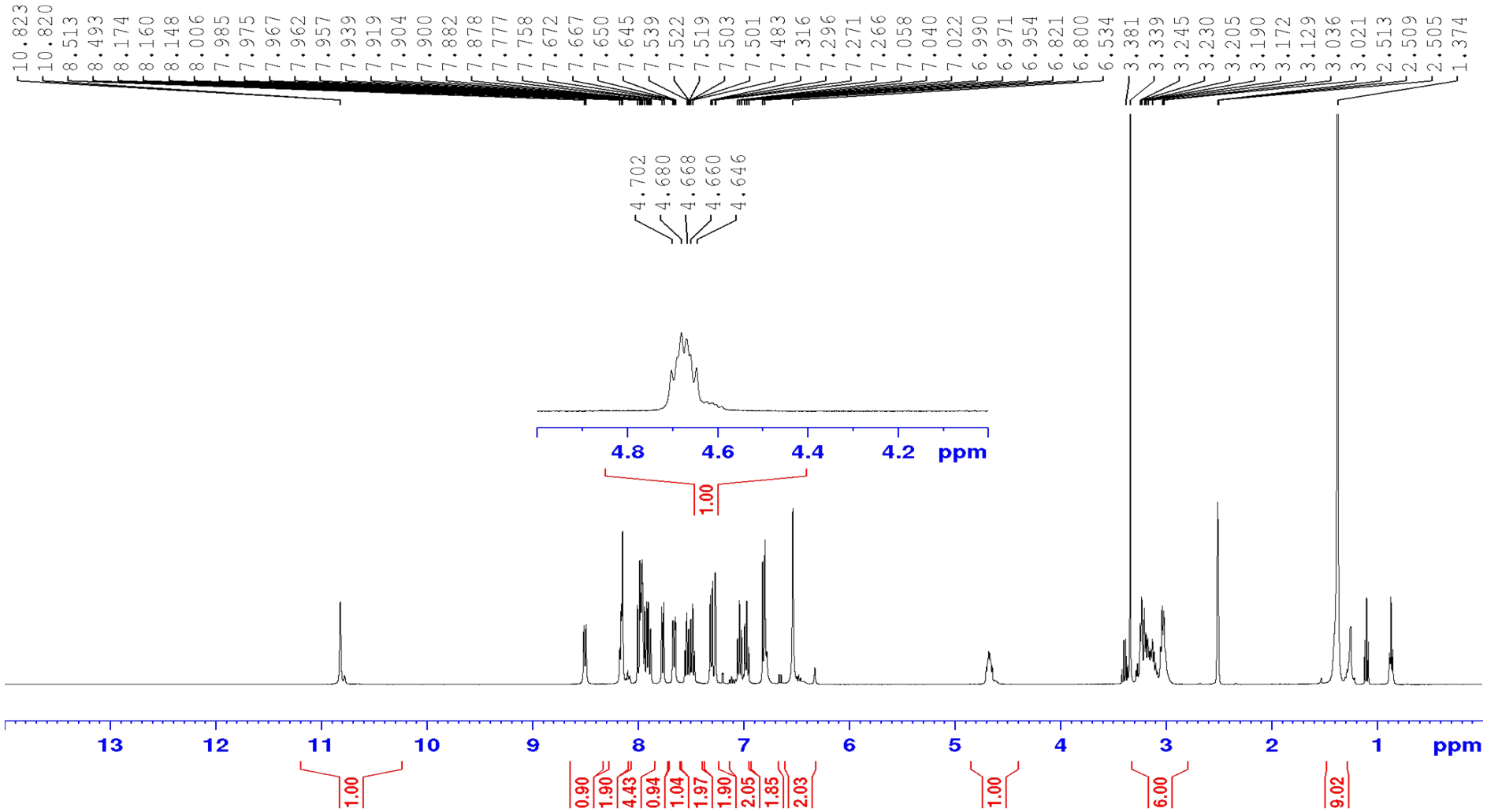
1H NMR of *tert*-butyl (S)-(2-(2-(2-amino-5-bromobenzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (4):



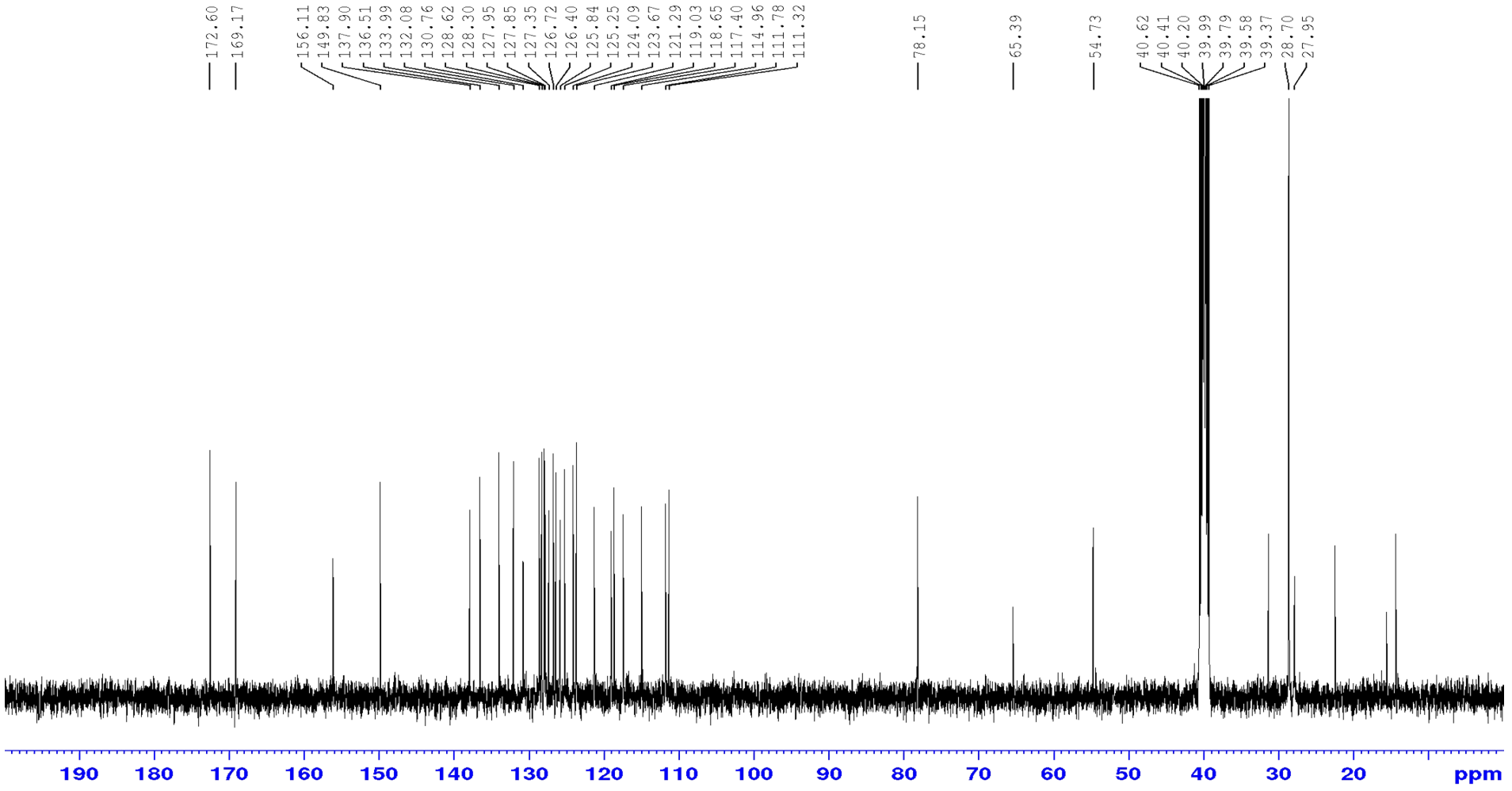
13C NMR of *tert*-butyl (S)-(2-(2-(2-amino-5-bromobenzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (4):



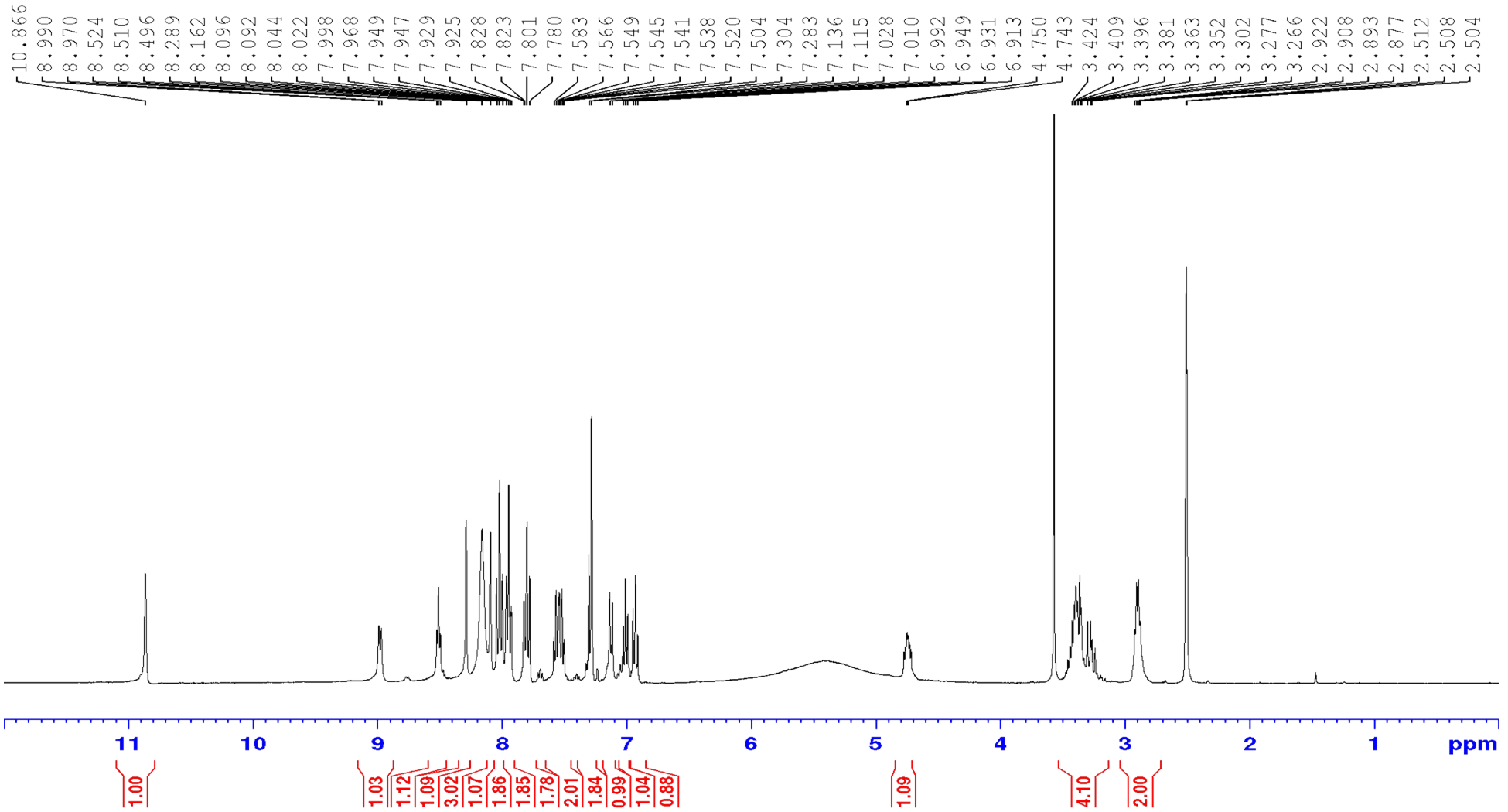
1H NMR of *tert*-butyl (S)-(2-(2-(2-amino-5-(naphthalen-2-yl)benzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (5):



13C NMR of *tert*-butyl (S)-(2-(2-(2-amino-5-(naphthalen-2-yl)benzamido)-3-(1H-indol-3-yl)propanamido)ethyl)carbamate (5):



1H NMR of (*S*)-2-amino-N-(1-((2-aminoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)-5-(naphthalen-2-yl)benzamide (6):



13CNMR of (*S*)-2-amino-N-(1-((2-aminoethyl)amino)-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)-5-(naphthalen-2-yl)benzamide (6):