Optimization of Peptidomimetics as Selective Inhibitors for the β-Catenin/T-Cell Factor Protein−Protein Interaction

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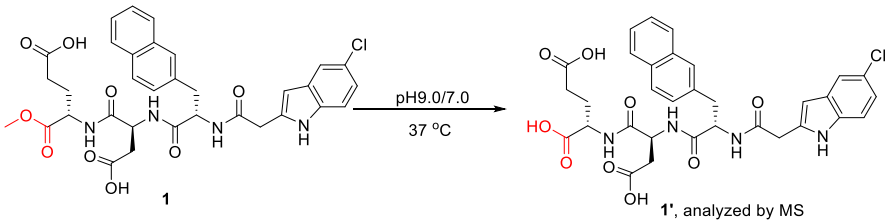
Supplementary Note 1. Chemical Stability of 1 and 21.

The chemical stability of **1** and **21** was evaluated in three buffer solutions (pH = 5.0, 7.0, and 9.0) at 37 °C. The results were shown in the table below. The remaining percentage of compound **1** in pH = 9.0 was decreased from 98.6% to 23.1% over 24 h, indicating **1** was unstable in pH = 9.0. Compound **1** decreased from ~98.5% to 96.0% over 24 h in pH = 7.0, indicating this compound was slightly unstable in pH = 7.0. The major byproduct identified was the derivative that the methyl ester of **1** was hydrolyzed, as shown in the Scheme below. The data also revealed **1** was stable in pH = 5.0. Compound **21** is stable at all the three tested pH buffers. On the other hand, it is worth noting that the indole ring of **1** is stable under three tested conditions and air at 37 °C.

	Remaining percentage (%) of **1** or **21** (pH 9.0/7.0/5.0)				
	0 h	2 h	4 h	8 h	24 h
Compound **1**	98.6/98.6/98.3	89.6/98.5/98.3	83.2/98.4/98.4	69.7/98.4/98.4	23.1/96.0/98.2
Compound **21**	99.3/100/100	99.4/100/100	99.4/100/100	99.4/100/100	99.6/100/100



Procedure. The solutions of compounds **1** (400 μg/mL) and **21** (200 μg/mL) were prepared by dissolving them in pH = 5.0 (for pH = 5 experiments, 5% DMSO was added), pH = 7.0, or pH = 9.0 buffers. These buffers were purchased from Fisher Scientific and contained different components as follows: pH = 5.0 buffer (SB102-500, potassium acid phthalate, sodium hydroxide, water), pH = 7.0 buffer (SB107-500, potassium phosphate monobasic, sodium hydroxide, water), pH = 9.0 buffer (SB114-500, boric acid potassium chloride, sodium hydroxide, water). The control buffers and the compound-containing solution were bubbled with air and kept stirring at 37 °C for 24 h.[1] Aliquots (100 μL) withdrawn at the designated time points during the 24-h incubation period were analyzed by HPLC. The HPLC condition was: elute with gradient starting with 0.1% TFA in water and end with 0.1% TFA in water and acetonitrile mixture (water with 0.1% TFA : acetonitrile = 1 : 1) in 10 min, and then change to a 5-min gradient starting with 0.1% TFA in water and acetonitrile 1 : 1 mixture and ending with 100% acetonitrile, and at last elute with 100% acetonitrile for 5 min.

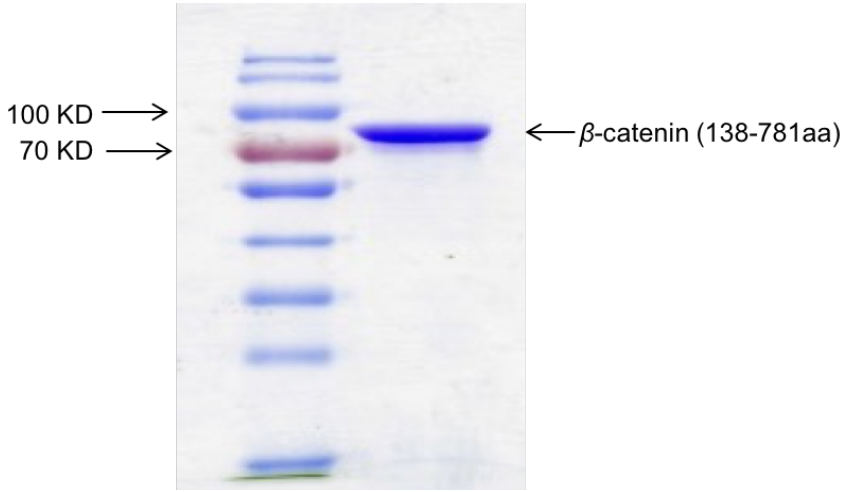
Supplementary Note 2. Determination of the Intracellular Concentrations of 53 and 56.

Following the procedure described in the previous paper (*J. Med. Chem.* **2017**, *60* ,157–169),[2] the intracellular concentrations of **53** and **56** in SW480 cells were determined. The calibration curves of **53** and **56** are shown in Supplementary Figure S6. The results of the HPLC analyses are shown in Supplementary Figures S7 and S8. Based on the IC_{50} values of **53** and **56** in MTS cell growth inhibition assays, the input concentration was set to 25 μM. The solvent extraction efficiencies were determined to be 0.5 for **53** and 0.7 for **56** in MeCN/MeOH (v/v = 1:1), respectively. The cell-bound concentrations of **53** at 37 °C were determined to be 0.17 and 0.71

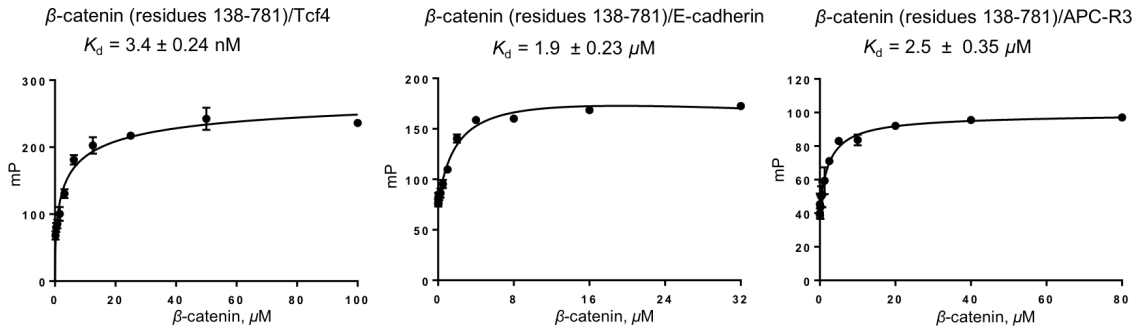
nmol/million cells for the 3-h and 24-h incubation in 5 mL of DMEM media with 10% FBS, respectively. The cell-bound concentration of **56** at 37 °C was determined to be 1.4 and 2.6 nmol/million cells for the 3-h and 24-h incubation in 5 mL of DMEM media with 10% FBS, respectively. Transformation of **56** into **53** was not detected under these conditions.

Supplementary Table S1. Peptide Sequences Used in This Study.[3]

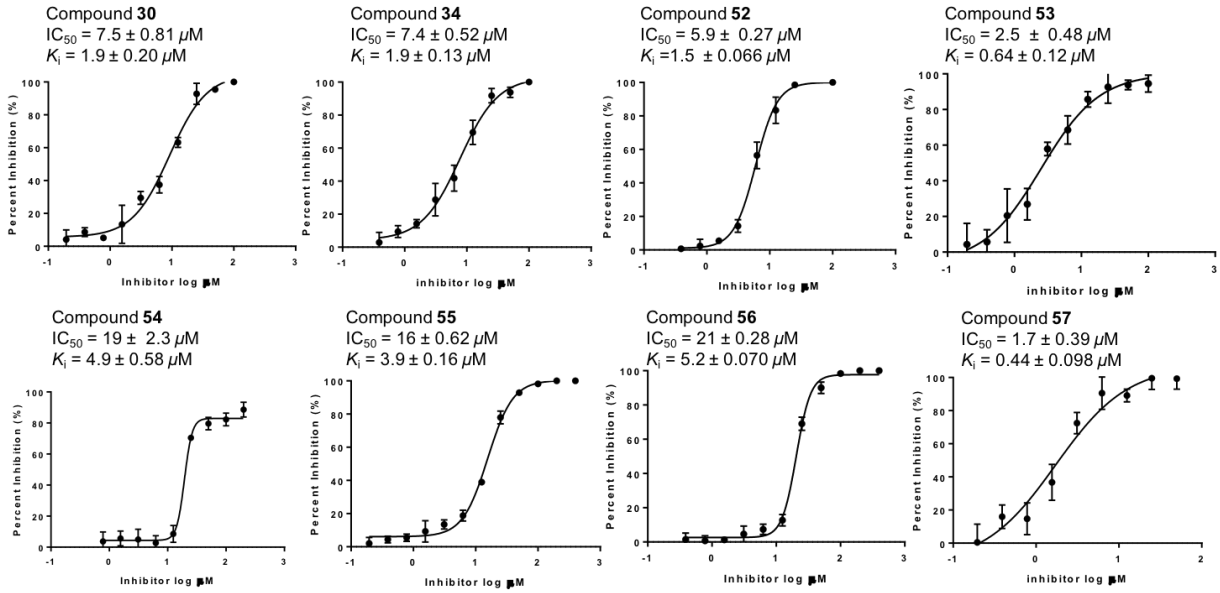
Peptides	Sequences
Fluorescein-labeled Tcf4 45-mer	H-^{7}GGGDDLGANDELISFKDEGEQEEKSSENSSAERDLADVKSSLVNE^{51}K(FITC)-NH_2
Fluorescein-labeled E-cadherin 55-mer	H-^{819}DTDPTAPPYDSLLVFDYEGSGSEAASLSSLNSSESDKDQDYDYLNEWGNRF KKLA^{873}K(FITC)-NH_2
Fluorescein-labeled APC-R3 43-mer	H-^{1477}QRVQVLPDADTLLHFATESTPDGFSCSSSLSALSLDEPFIQKD^{1519}K(FITC)-NH_2



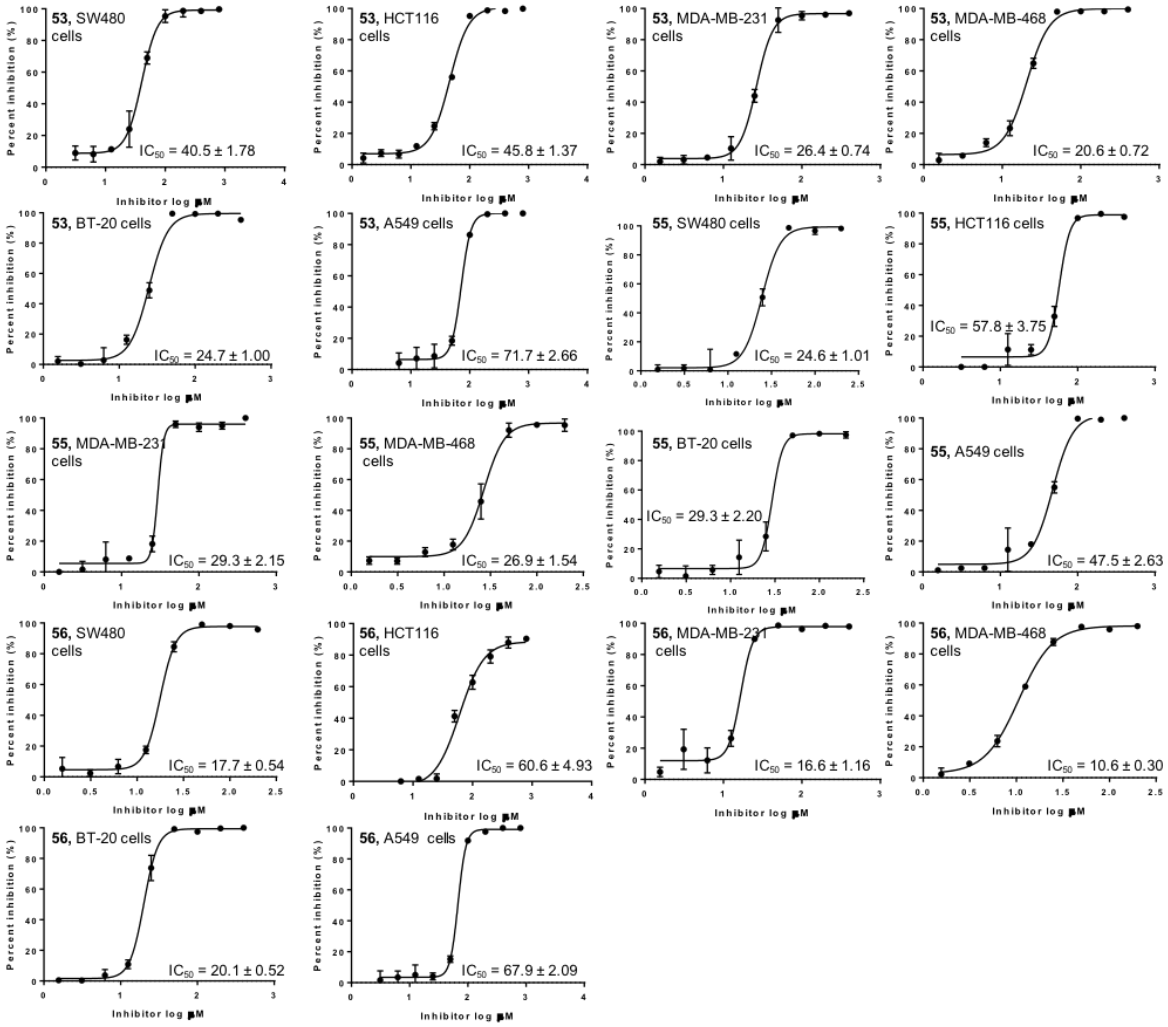
Supplementary Figure S1. The SDS-PAGE Gel of *β*-Catenin (residues 138–781) Used in the Assays.



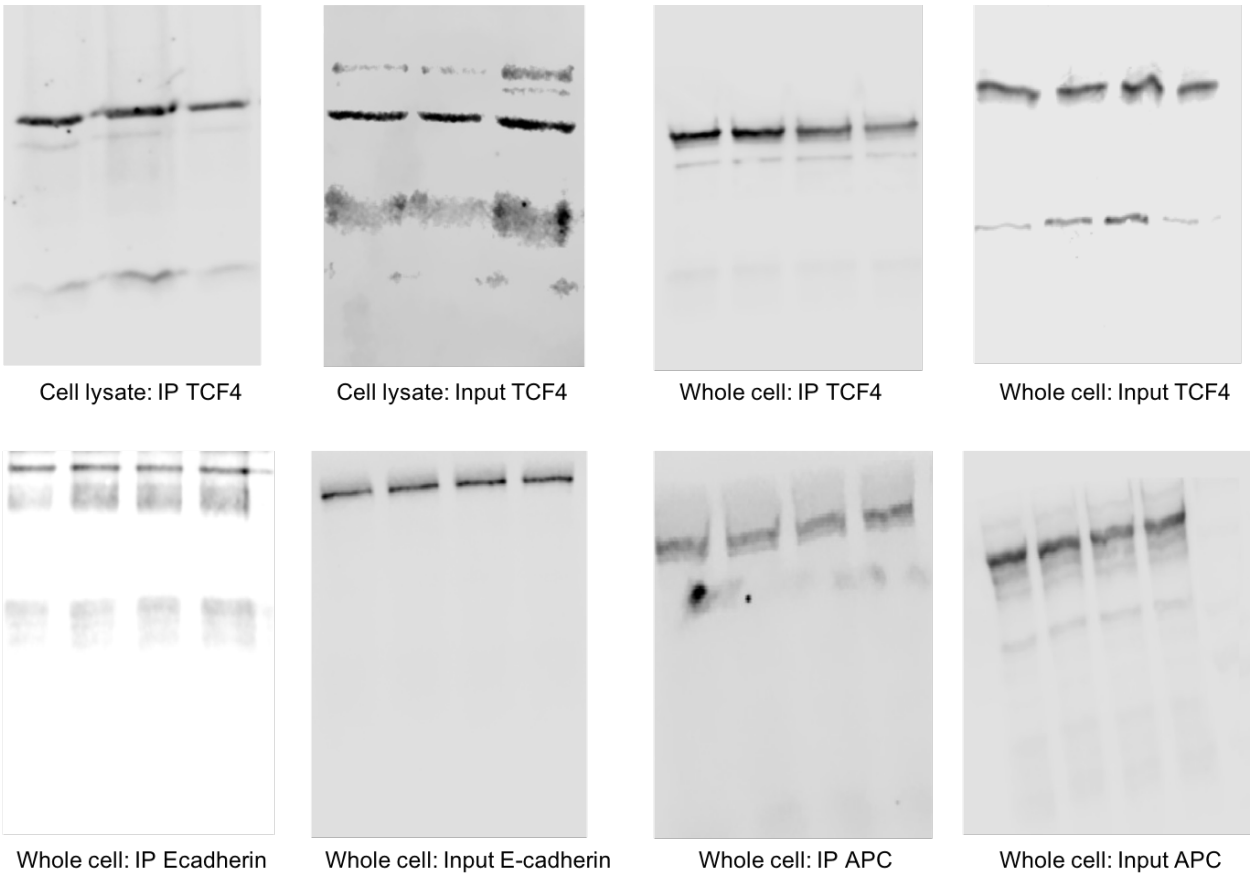
Supplementary Figure S2. Direct FP Titration of Fluorescein-Labeled Tcf4 45-mer, Fluorescein-Labeled E-cadherin 55-mer, and Fluorescein-Labeled APC-R3 43-mer with *β*-Catenin, and the Corresponding K_d Values.



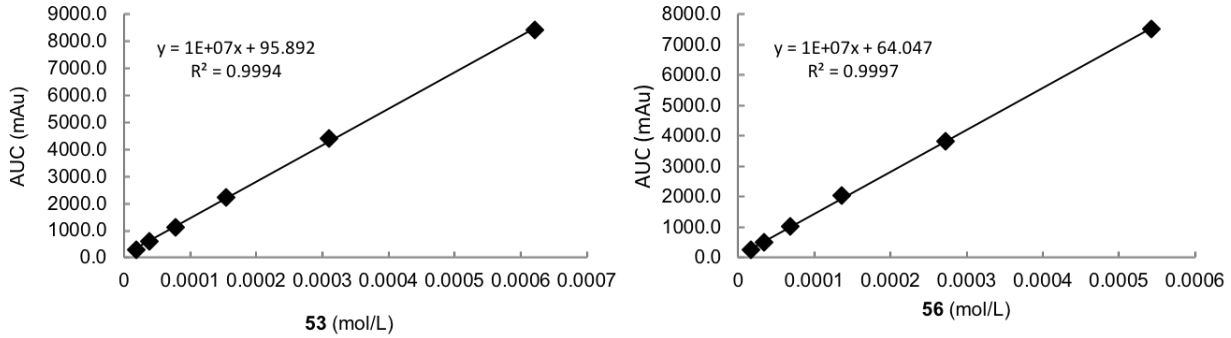
Supplementary Figure S3. Competitive FP Inhibition Assay Rsults of **30**, **34**, and **52-57**. Each set of data is expressed as mean ± standard deviation (n = 3).



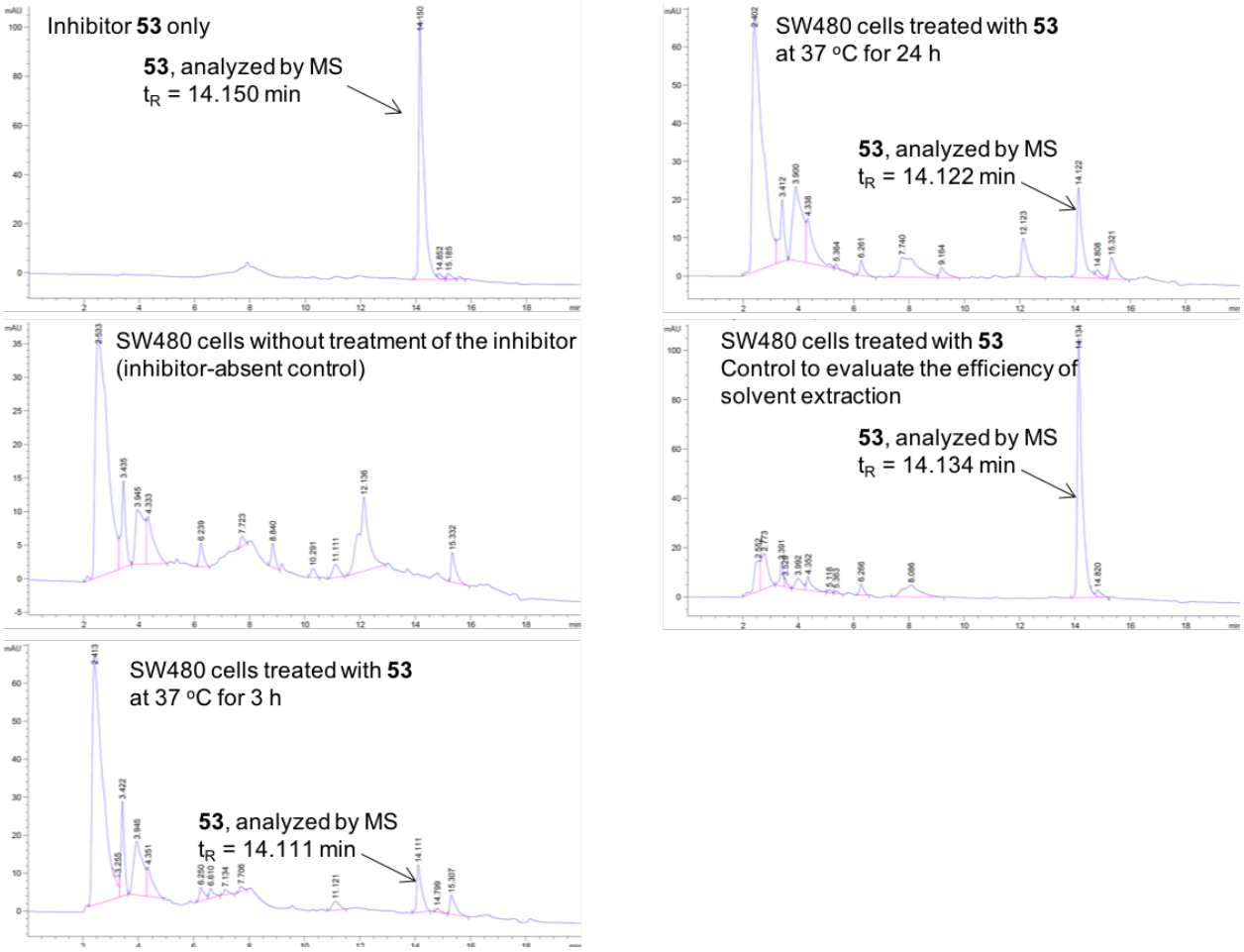
Supplementary Figure S4. The Effects of **53**, **55**, and **56** on Growth of Colorectal Cancer Cells (SW480 and HCT116), TNBC Cells (MDA-MB-231, MDA-MB-468, and BT-20), and Lung Cancer A549 Cells.



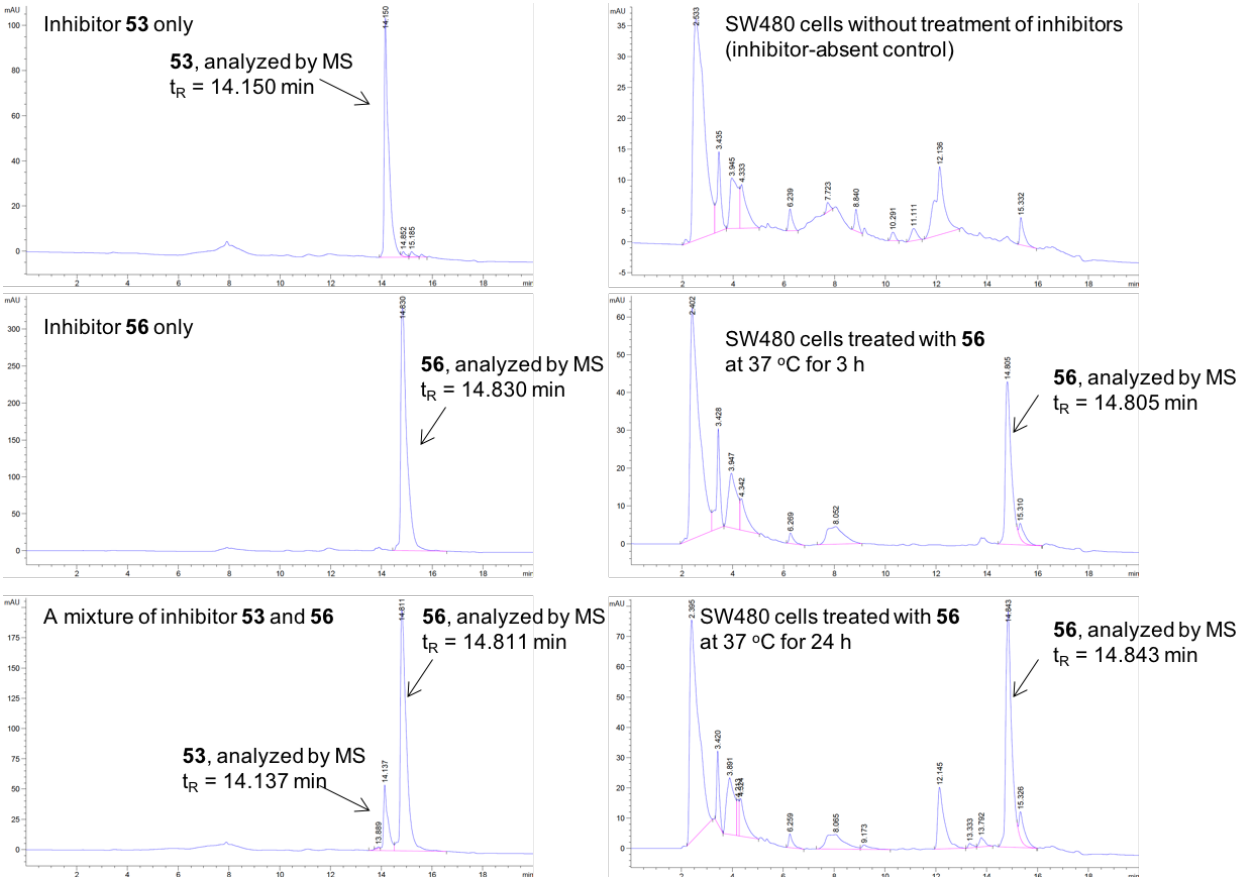
Supplementary Figure S5. The Full Western Blot Images of the Co-IP Experiments for Compounds **53** and **56**.



Supplementary Figure S6. The Calibration Curves of **53** (A) and **56** (B) for Determination of Their Intracellular Concentrations.

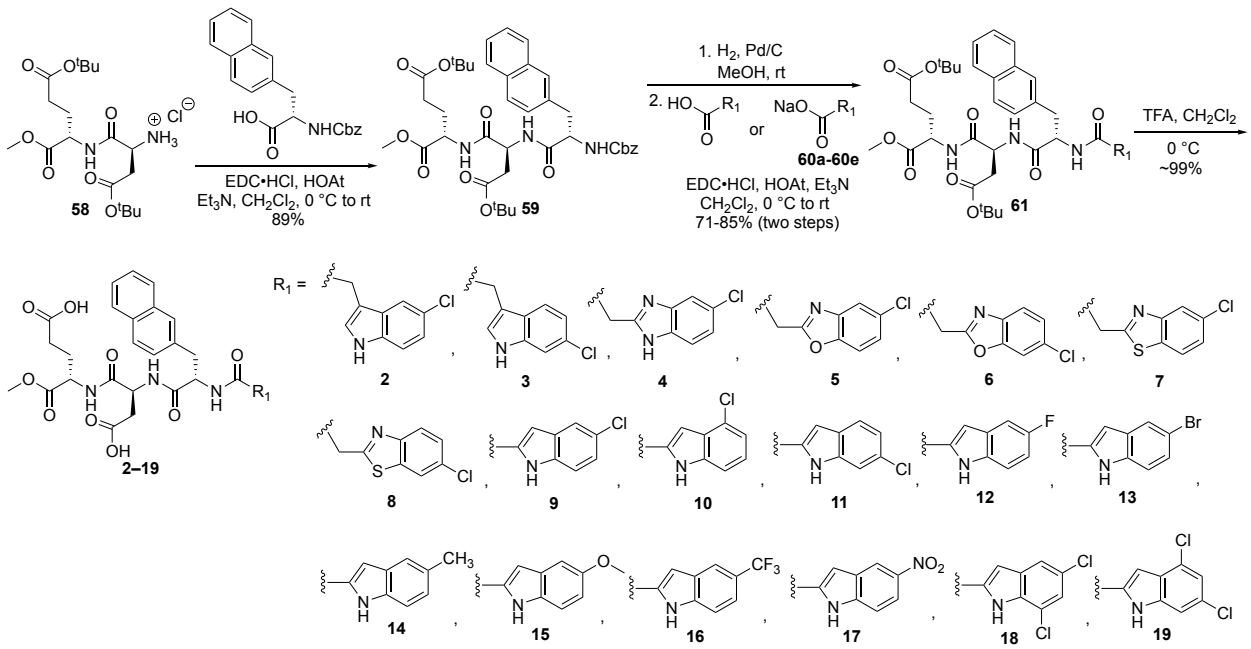


Supplementary Figure S7. HPLC/DAD Chromatograms of **53** Under Various Conditions to Determine the Intracellular Concentrations.

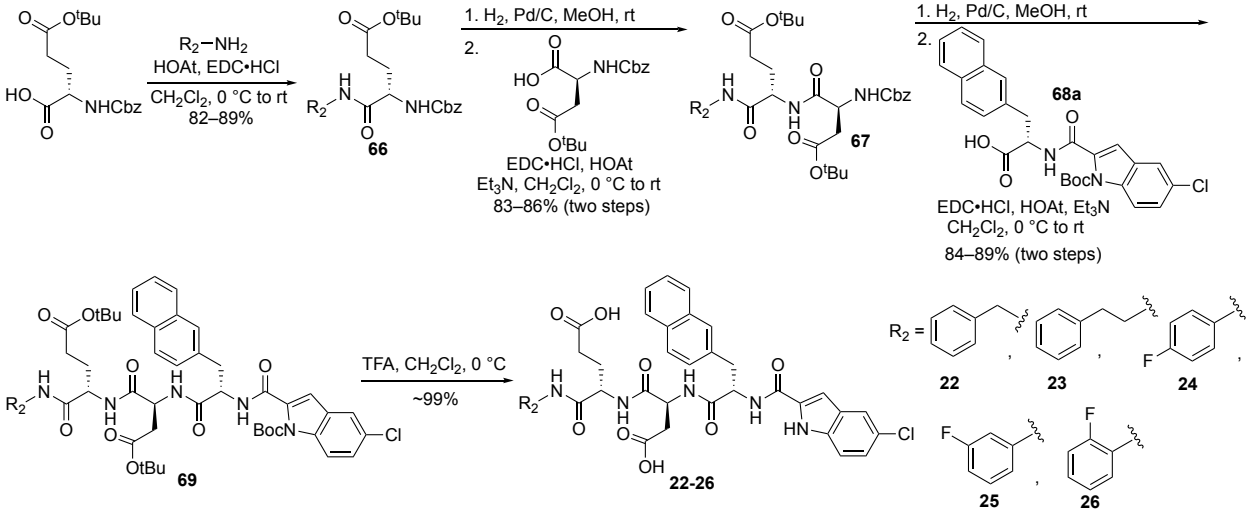


Supplementary Figure S8. HPLC/DAD Chromatograms of **56** Under Various Conditions to Determine the Intracellular Concentrations.

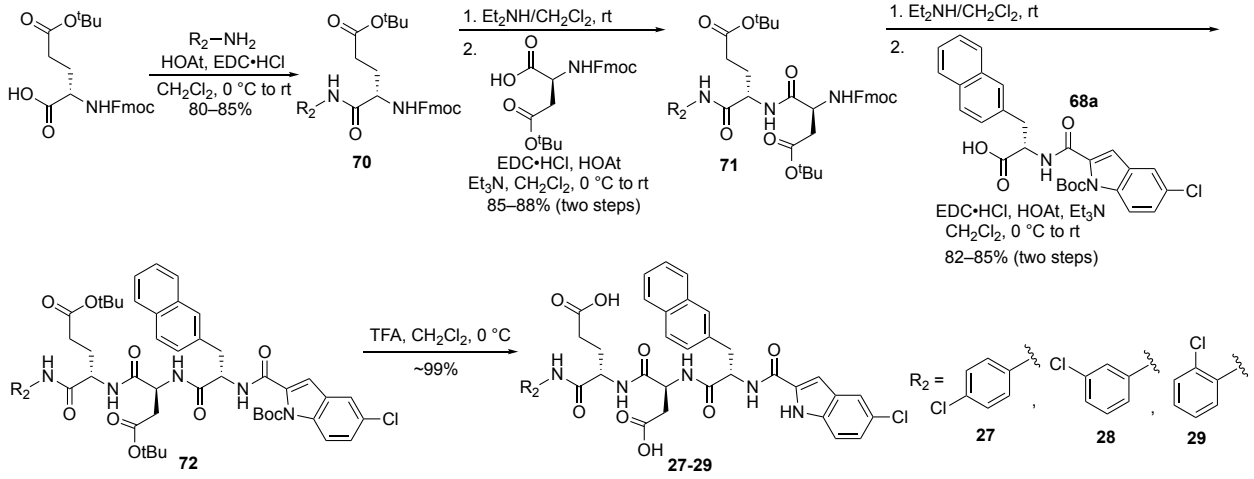
Supplementary Scheme S1. Synthesis of Final Compounds 2–19.



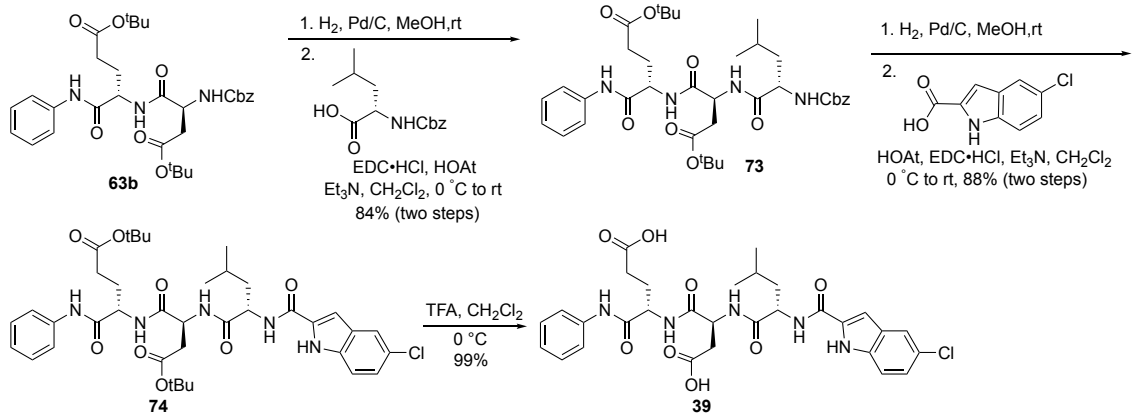
Supplementary Scheme S2. Synthesis of Final Compounds 22–26.



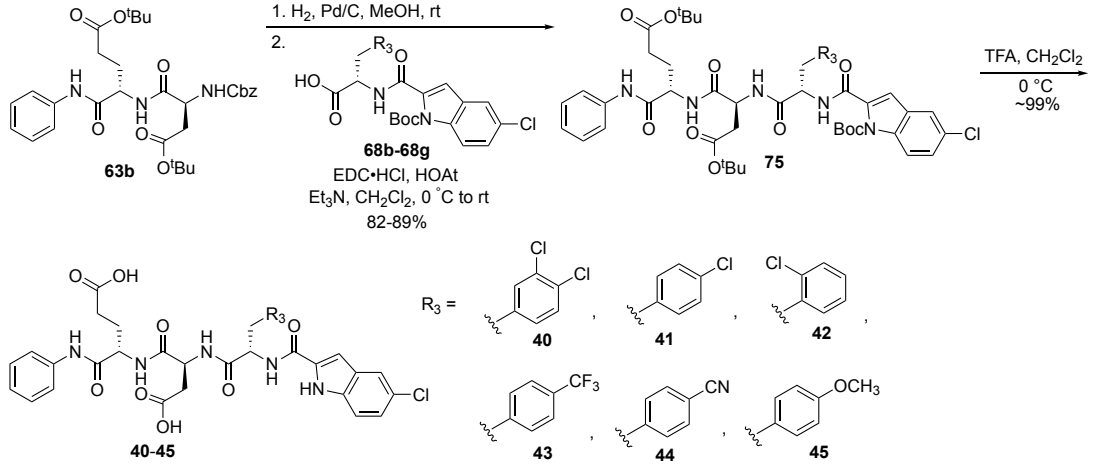
Supplementary Scheme S3. Synthesis of Final Compounds 27–29.



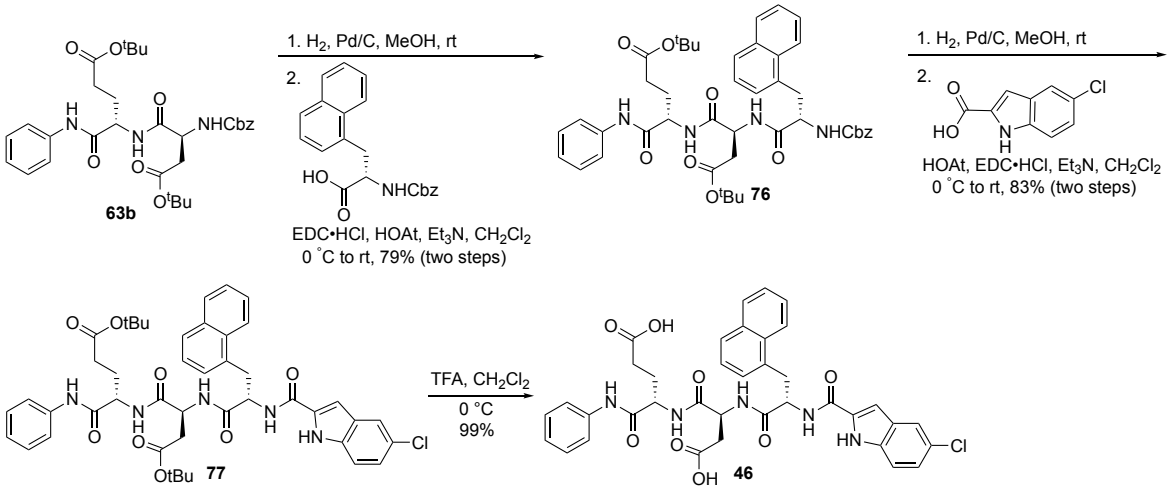
Supplementary Scheme S4. Synthesis of Final Compound 39.



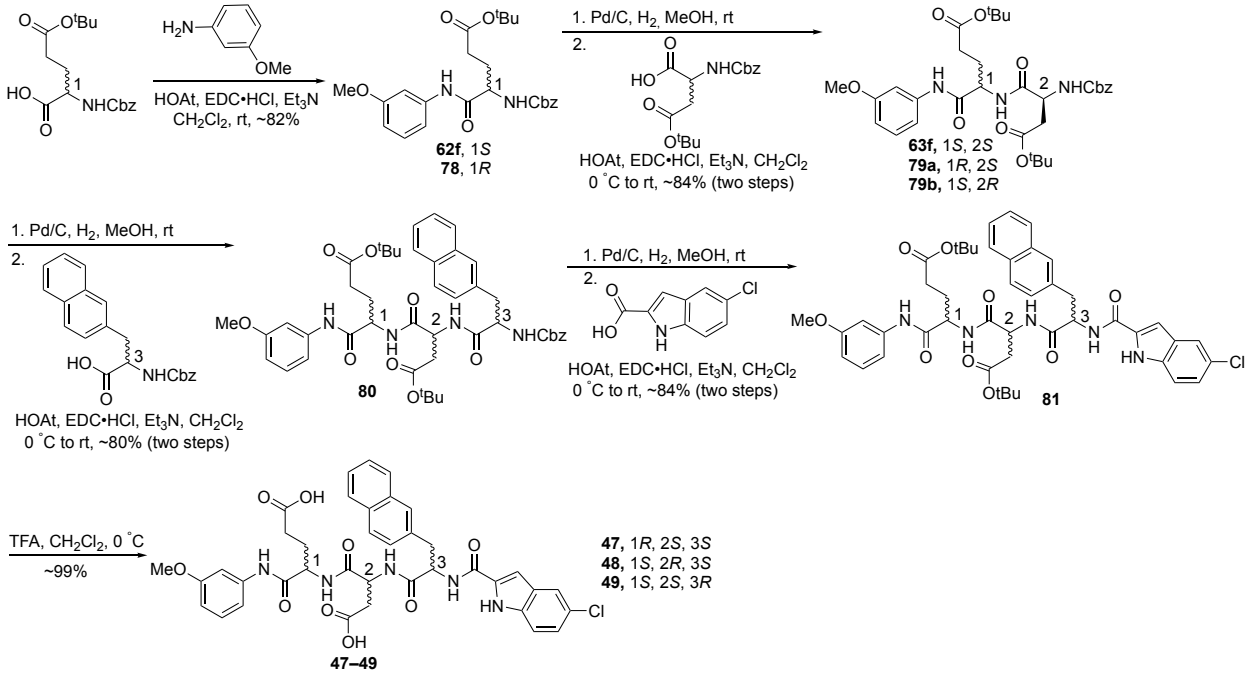
Supplementary Scheme S5. Synthesis of Final Compounds 40–45.



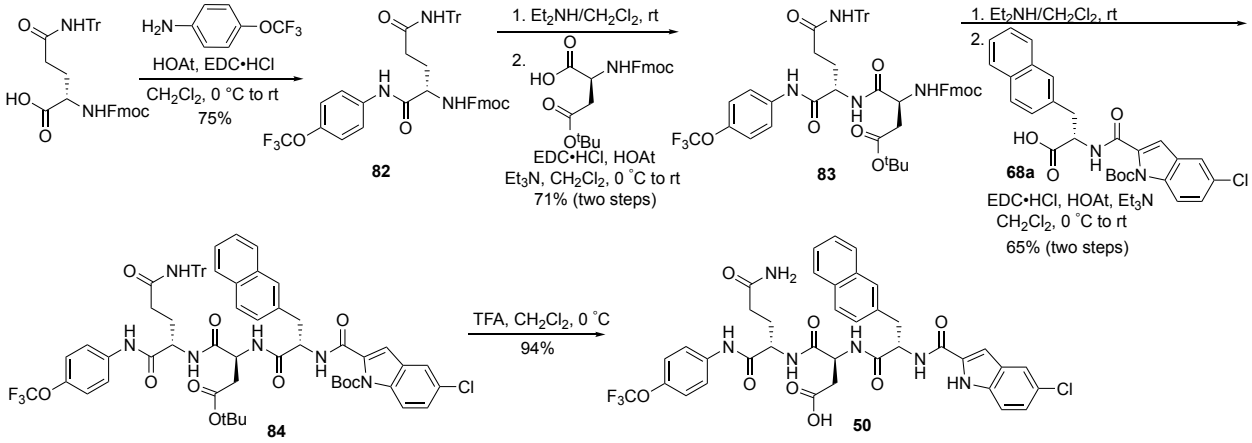
Supplementary Scheme S6. Synthesis of Final Compound 46.



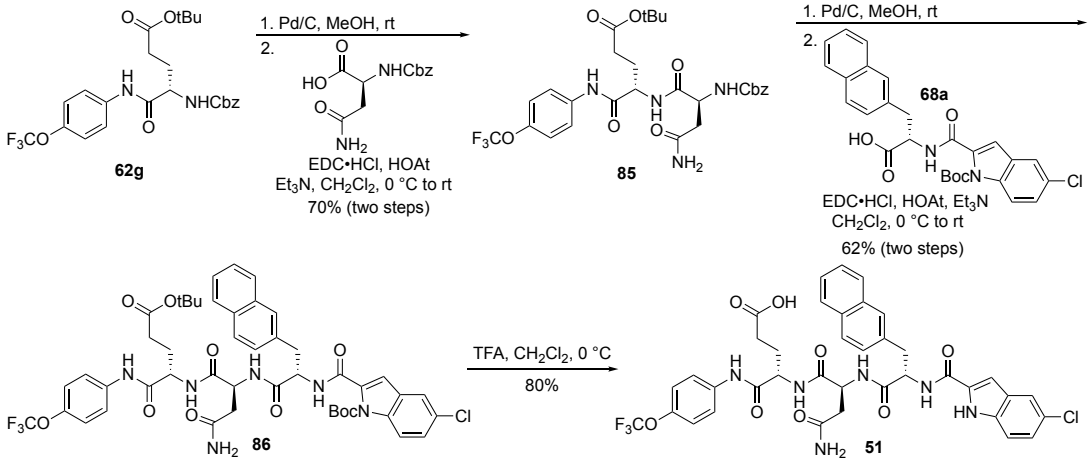
Supplementary Scheme S7. Synthesis of Final Compounds 47–49.



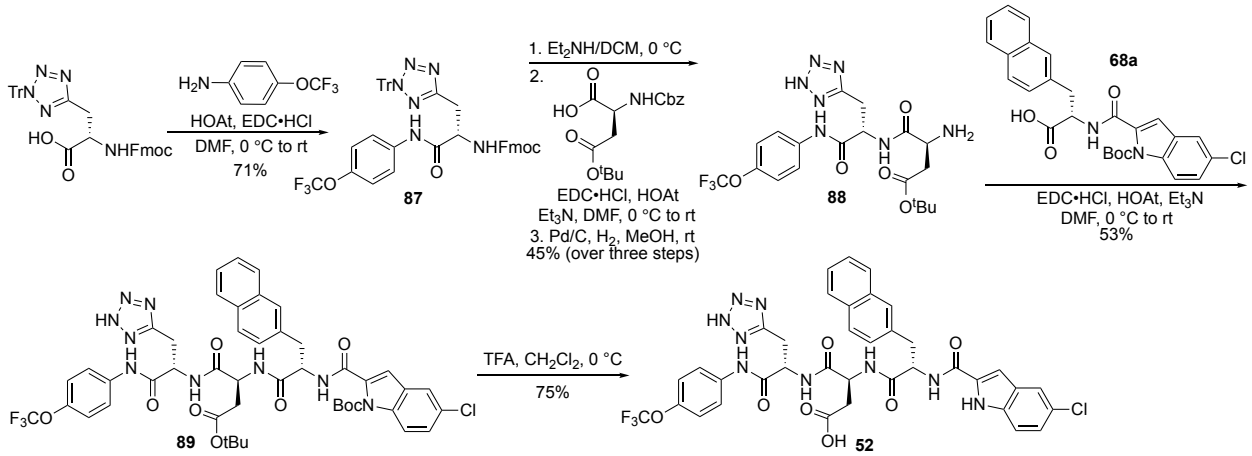
Supplementary Scheme S8. Synthesis of Final Compound 50.



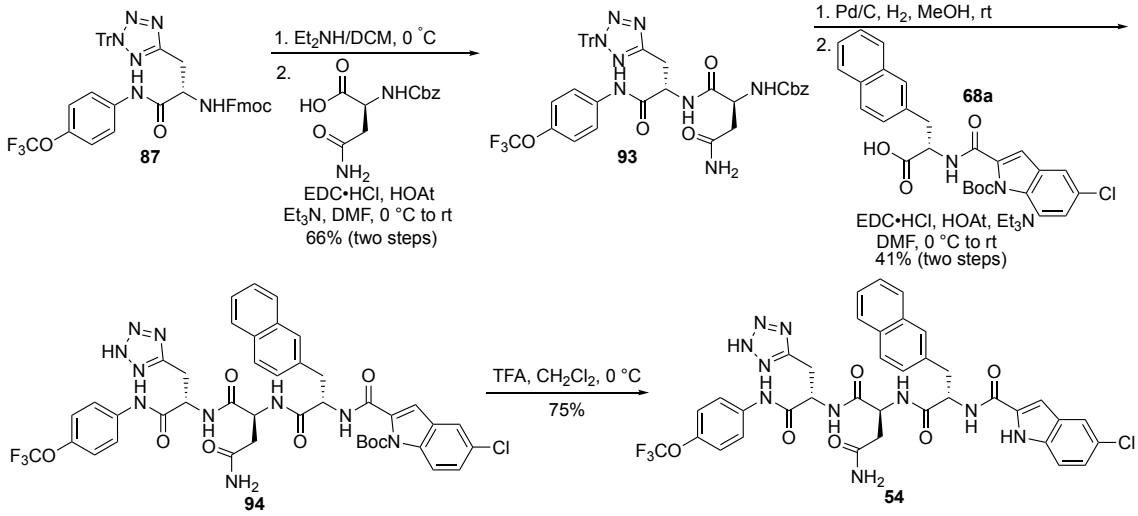
Supplementary Scheme S9. Synthesis of Final Compound 51.



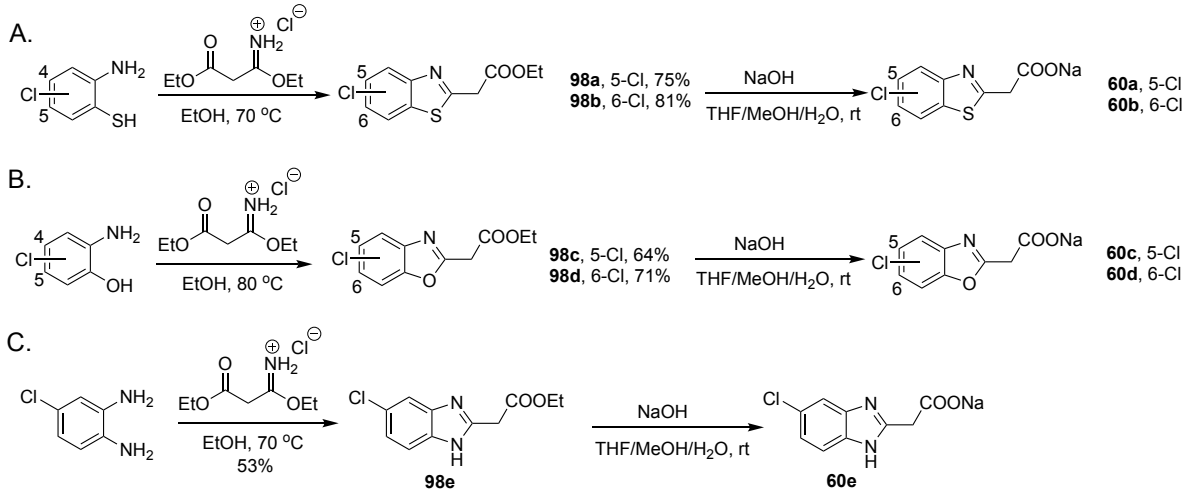
Supplementary Scheme S10. Synthesis of Final Compound 52.



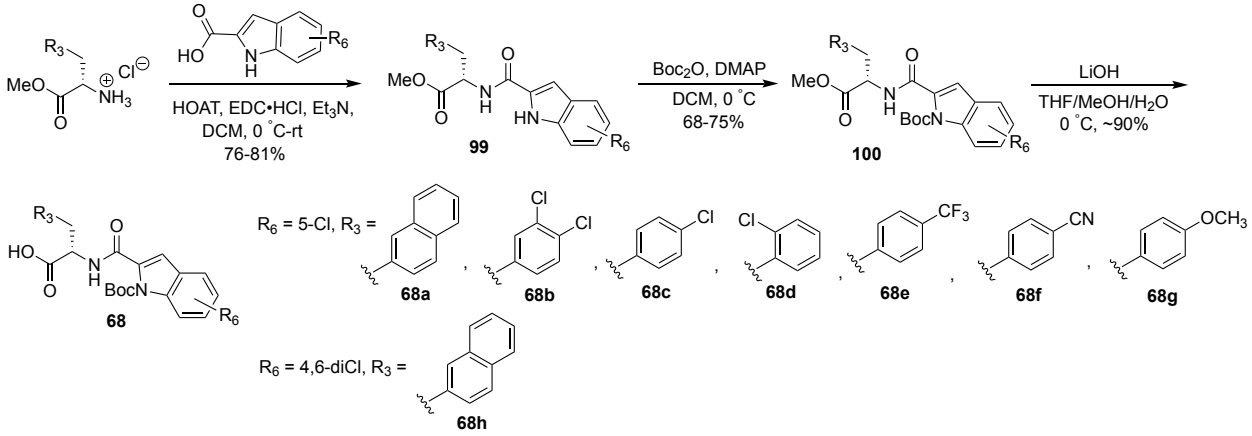
Supplementary Scheme S11. Synthesis of Final Compound 54.



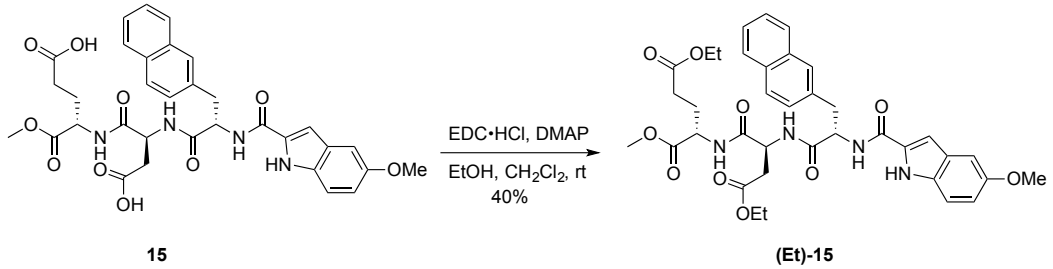
Supplementary Scheme S12. Synthesis of Intermediates 60a–60e.



Supplementary Scheme S13. Synthesis of Intermediates 68a–68h.



Supplementary Scheme S14. Synthesis of (Et)-15.



Supplemental Procedures.

The starting material **58** was prepared according to our previous paper.[4]

5-(tert-Butyl) 1-methyl ((S)-2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(naphthalen-2-yl)propanamido)-4-(tert-butoxy)-4-oxobutanoyl)-L-glutamate (59). Yield, 89%. 1H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.63 (m, 3H), 7.60 – 7.54 (m, 1H), 7.46 – 7.33 (m, 2H), 7.29 – 7.13 (m, 8H), 7.09 (d, J = 8.1 Hz, 1H), 4.99 (d, J = 2.8 Hz, 2H), 4.72 – 4.61 (m, 1H), 4.47 (q, J = 6.7 Hz, 1H), 4.39 (td, J = 8.2, 5.1 Hz, 1H), 3.64 (s, 3H), 3.26 (dd, J = 14.2, 5.8 Hz, 1H), 3.17 (dd, J = 14.2, 7.6 Hz, 1H), 2.88 (d, J = 17.3 Hz, 1H), 2.38 (dd, J = 17.2, 6.4 Hz, 1H), 2.18 – 2.09 (m, 2H), 2.04 – 1.97 (m, 1H), 1.76 (dtd, J = 14.6, 8.7, 6.1 Hz, 1H), 1.33 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 170.7, 135.9, 133.5, 133.4, 132.6, 128.7, 128.5, 128.3, 128.1, 128.0, 127.7, 127.6, 127.0, 126.3, 125.9, 82.0, 80.6, 67.3, 56.4, 52.4, 51.9, 49.1, 38.1, 36.7, 31.3, 28.1, 28.0, 27.1. MS (ESI) m/z 742.3 $[M + Na]^+$. The Cbz protecting group of compound **59** was removed by Pd/C under H_2 in MeOH. The resulting product was used directly in next step without further purification.1H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.4 Hz, 1H), 7.91 – 7.72 (m, 3H), 7.67 (d, J = 1.6 Hz, 1H), 7.47 (tt, J = 6.8, 5.2 Hz, 2H), 7.37 (dd, J = 8.4, 1.8 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 4.79 (ddd, J = 8.5, 6.6, 4.6 Hz, 1H), 4.51 (td, J = 7.9, 5.1 Hz, 1H), 3.95 – 3.77 (m, 1H), 3.71 (s, 3H), 3.42 (dd, J = 13.7, 4.0 Hz, 1H), 2.93 (dd, J = 13.7, 9.2 Hz, 1H), 2.86 (dd, J = 17.0, 4.6 Hz, 1H), 2.55 (dd, J = 17.0, 6.6 Hz, 1H), 2.27 (td, J = 8.1, 6.7 Hz, 2H), 2.19 – 2.03 (m, 1H), 1.98 – 1.80 (m, 1H), 1.42 (s, 9H), 1.42 (s, 9H). MS (ESI) m/z = 586.3 $[M + H]^+$, 608.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(2-(5-chloro-1*H*-indol-3-yl)acetamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61a). Yield, 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.5 Hz, 1H), 7.75 (dt, *J* = 7.0, 3.5 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.35 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.21 – 7.13 (m, 2H), 7.08 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.97 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.13 (d, *J* = 6.0 Hz, 1H), 4.73 (ddd, *J* = 8.5, 6.0, 3.9 Hz, 1H), 4.64 (dt, *J* = 7.8, 5.8 Hz, 1H), 4.52 (td, *J* = 8.5, 5.0 Hz, 1H), 3.69 (s, 3H), 3.68 – 3.47 (m, 2H), 3.17 (dd, *J* = 14.1, 5.6 Hz, 1H), 3.08 (dd, *J* = 14.1, 7.8 Hz, 1H), 2.97 (dd, *J* = 17.3, 3.9 Hz, 1H), 2.45 (dd, *J* = 17.3, 6.0 Hz, 1H), 2.33 – 2.21 (m, 2H), 2.12 (dtd, *J* = 13.9, 7.8, 5.0 Hz, 1H), 1.93 (dtd, *J* = 14.0, 8.4, 6.8 Hz, 1H), 1.40 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 172.1, 171.7, 171.7, 170.4, 170.2, 134.5, 133.2, 133.2, 132.3, 128.5, 127.8, 127.7, 127.6, 127.5, 126.6, 126.2, 125.8, 125.8, 125.3, 122.9, 117.7, 112.6, 107.6, 82.0, 80.6, 54.9, 52.4, 51.9, 49.2, 37.1, 36.5, 32.9, 31.4, 28.1, 28.0, 27.2. MS (ESI) m/z = 799.3 $[M + Na]^+$, 775.3 $[M - H]^-$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(2-(6-chloro-1*H*-indol-3-yl)acetamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61b). Yield, 80%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 2.4 Hz, 1H), 7.85 – 7.72 (m, 1H), 7.56 (dd, *J* = 8.8, 3.9 Hz, 2H), 7.51 – 7.46 (m, 2H), 7.38 (dd, *J* = 8.4, 6.2 Hz, 2H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.18 (d, *J* = 1.6 Hz, 1H), 6.94 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.88 (dd, *J* = 8.5, 1.8 Hz, 1H),

6.80 (d, *J* = 2.5 Hz, 1H), 6.12 (d, *J* = 5.8 Hz, 1H), 4.78 (ddd, *J* = 8.7, 5.8, 3.9 Hz, 1H), 4.63 (dt, *J* = 8.1, 5.5 Hz, 1H), 4.56 (td, *J* = 8.5, 4.8 Hz, 1H), 3.72 (s, 3H), 3.71 – 3.55 (m, 2H), 3.19 (dd, *J* = 14.1, 5.4 Hz, 1H), 3.10 – 2.95 (m, 2H), 2.44 (dd, *J* = 17.3, 5.8 Hz, 1H), 2.31 (t, *J* = 7.8 Hz, 2H), 2.18 – 2.10 (m, 1H), 1.98 (ddt, *J* = 14.2, 8.9, 7.5 Hz, 1H), 1.41 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.7, 172.1, 171.8, 170.4, 170.2, 136.5, 133.2, 133.0, 132.3, 128.5, 128.4, 127.7, 127.6, 127.5, 126.5, 126.2, 125.9, 125.3, 124.7, 120.8, 119.1, 111.5, 107.9, 82.0, 80.6, 55.0, 52.4, 51.9, 49.1, 37.0, 36.4, 32.8, 31.5, 28.1, 28.0, 27.2. MS (ESI) m/z = 799.3 $[M + Na]^+$, 775.2 $[M – H]^–$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61c). Yield, 71%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 6.4 Hz, 1H), 7.71 – 7.60 (m, 3H), 7.58 – 7.53 (m, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.43 (s, 1H), 7.35 (dtd, *J* = 6.9, 5.3, 4.7, 3.3 Hz, 3H), 7.19 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.15 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.92 – 4.70 (m, 2H), 4.46 (td, *J* = 8.4, 5.0 Hz, 1H), 3.89 (d, *J* = 16.3 Hz, 1H), 3.76 (d, *J* = 16.3 Hz, 1H), 3.68 (s, 3H), 3.23 (d, *J* = 6.4 Hz, 2H), 2.79 (dd, *J* = 17.1, 4.6 Hz, 1H), 2.35 (dd, *J* = 17.1, 6.1 Hz, 1H), 2.24 (dt, *J* = 9.3, 6.3 Hz, 2H), 2.10 (tdd, *J* = 11.6, 5.2, 3.5 Hz, 1H), 2.00 – 1.84 (m, 1H), 1.43 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.1, 171.6, 170.9, 170.5, 170.3, 168.5, 149.3, 133.3, 132.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.1, 126.2, 125.8, 123.0, 82.0, 81.3, 55.7, 53.9, 52.4, 51.9, 48.9, 37.6, 36.7, 36.3, 31.9, 28.0, 27.6. MS (ESI) m/z = 778.3 $[M + H]^+$, 800.3 $[M + Na]^+$, 776.2 $[M – H]^–$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(2-(5-chlorobenzo[*d*]oxazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61d). Yield, 74%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 6.6 Hz, 1H), 7.82 – 7.72 (m, 1H), 7.71 – 7.62 (m, 3H), 7.51 – 7.41 (m, 3H), 7.33 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.24 (dt, *J* = 8.5, 1.6 Hz, 2H), 4.92 – 4.74 (m, 2H), 4.49 (td, *J* = 8.4, 5.0 Hz, 1H), 3.95 (d, *J* = 18.1 Hz, 1H), 3.86 (d, *J* = 18.0 Hz, 1H), 3.69 (s, 3H), 3.35 (h, *J* = 7.8, 7.4 Hz, 2H), 2.92 (dd, *J* = 17.2, 4.4 Hz, 1H), 2.53 (dd, *J* = 17.2, 6.3 Hz, 1H), 2.24 (ddd, *J* = 8.5, 6.6, 5.4 Hz, 2H), 2.09 (dddd, *J* = 13.8, 8.7, 7.1, 5.0 Hz, 1H), 1.96 – 1.81 (m, 1H), 1.41 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 171.7, 171.3, 170.4, 170.1, 165.7, 162.1, 148.9, 141.4, 133.4, 133.4, 132.5, 130.1, 128.4, 128.2, 127.6, 127.5, 127.0, 126.3, 125.9, 125.6, 119.7, 111.3, 81.8, 80.6, 55.3, 52.4, 51.8, 49.3, 37.5, 36.7, 35.7, 31.3, 28.1, 27.8, 27.1. MS (ESI) m/z = 801.3 $[M + Na]^+$, 777.3 $[M – H]^–$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(2-(6-chlorobenzo[*d*]oxazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61e). Yield, 72%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 6.5 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.72 – 7.61 (m, 3H), 7.50 – 7.38 (m, 4H), 7.36 – 7.30 (m, 2H), 7.29 – 7.25 (m, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 4.98 – 4.72 (m, 2H), 4.50 (td, *J* = 8.4, 5.0 Hz, 1H), 4.06 – 3.82 (m, 2H), 3.72 (s, 3H), 3.37 (qd, *J* = 14.2, 6.7 Hz, 2H), 2.94 (dd, *J* = 17.1, 4.3 Hz, 1H), 2.52 (dd, *J* = 17.2, 6.3 Hz, 1H), 2.25 (dt, *J* = 8.6, 6.4 Hz, 2H), 2.14 – 2.07 (m, 1H), 1.98 – 1.81 (m, 1H), 1.43 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 171.7, 171.3, 170.3, 170.0, 165.6, 161.3, 150.6, 139.1, 133.4 (d, *J* = 2.7 Hz), 132.5, 131.0, 128.5, 128.1, 127.7, 127.5, 127.0, 126.3, 125.8, 125.3, 120.2, 111.2, 81.8, 80.6, 55.4, 52.4, 51.8, 49.2, 37.5, 36.7, 35.7, 31.3, 28.1, 27.9, 27.1. MS (ESI) m/z = 801.3 $[M + Na]^+$, 777.3 $[M – H]^–$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(2-(5-chlorobenzo[*d*]thiazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61f). Yield, 75%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 6.4 Hz, 1H), 7.72 – 7.64 (m, 1H), 7.63 – 7.55 (m, 3H), 7.54 – 7.48 (m, 2H), 7.38 – 7.30 (m, 2H), 7.26 (dd, *J* = 8.6, 2.0 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.14 (d, *J* = 8.1 Hz, 1H), 4.82 – 4.61 (m, 2H), 4.42 (td, *J* = 8.4, 5.0 Hz, 1H), 4.02 (d, *J* =

17.2 Hz, 1H), 3.93 (d, *J* = 17.2 Hz, 1H), 3.64 (s, 3H), 3.39 – 3.18 (m, 2H), 2.87 (dd, *J* = 17.3, 4.0 Hz, 1H), 2.38 (dd, *J* = 17.3, 6.2 Hz, 1H), 2.26 – 2.12 (m, 2H), 2.03 (tdd, *J* = 12.0, 5.2, 3.6 Hz, 1H), 1.93 – 1.76 (m, 1H), 1.35 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.0, 171.7, 171.4, 170.2, 170.0, 167.2, 166.0, 153.1, 133.3, 133.1, 132.5, 132.4, 128.5, 127.9, 127.6, 127.4, 126.9, 126.3, 126.0, 125.9, 122.5, 122.2, 81.8, 80.6, 55.4, 52.4, 51.9, 49.2, 40.5, 37.4, 36.6, 31.4, 28.1, 27.9, 27.2. MS (ESI) m/z = 817.2 $[M + Na]^+$, 793.3 $[M – H]^–$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(2-(6-chlorobenzo[*d*]thiazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61g). Yield, 72%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 6.3 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.51 (m, 3H), 7.49 – 7.38 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.23 (m, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 4.77 (ddt, *J* = 8.3, 6.1, 4.9 Hz, 2H), 4.49 (td, *J* = 8.4, 5.0 Hz, 1H), 4.07 (d, *J* = 17.2 Hz, 1H), 3.97 (d, *J* = 17.2 Hz, 1H), 3.72 (s, 3H), 3.41 – 3.18 (m, 2H), 2.95 (dd, *J* = 17.3, 4.0 Hz, 1H), 2.44 (dd, *J* = 17.3, 6.2 Hz, 1H), 2.25 (dt, *J* = 8.6, 6.3 Hz, 2H), 2.11 (dddd, *J* = 13.9, 8.9, 7.1, 4.9 Hz, 1H), 2.02 – 1.80 (m, 1H), 1.42 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.0, 171.7, 171.5, 170.2, 170.0, 167.3, 164.4, 151.1, 136.1, 133.3, 133.3, 132.4, 131.4, 128.4, 127.9, 127.6, 127.4, 127.1, 126.8, 126.3, 125.8, 123.4, 121.2, 81.9, 80.6, 55.3, 52.4, 51.9, 49.1, 40.5, 37.4, 36.6, 31.4, 28.1, 27.9, 27.2. MS (ESI) m/z = 817.2 $[M + Na]^+$, 793.3 $[M – H]^–$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61h). Yield, 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.51 (s, 1H), 7.95 (s, 1H), 7.70 – 7.30 (m, 6H), 7.27 – 6.92 (m, 5H), 6.86 (s, 1H), 5.28 (d, *J* = 11.3 Hz, 1H), 5.05 (d, *J* = 9.9 Hz, 1H), 4.39 (q, *J* = 6.8 Hz, 1H), 3.74 (s, 3H), 3.31 – 3.08 (m, 2H), 2.88 (t, *J* = 25.0 Hz, 2H), 2.48 – 2.22 (m, 2H), 2.04 (dp, *J* = 34.9, 7.5 Hz, 2H), 1.45 (d, *J* = 2.6 Hz, 9H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.6, 171.3, 170.3, 161.5, 135.2, 134.0, 133.3, 132.2, 131.5, 128.3, 128.0, 127.8, 127.2, 125.8, 125.4, 124.2, 120.9, 113.5, 101.9, 82.1, 81.0, 55.1, 52.4, 52.2, 48.7, 38.7, 36.2, 31.4, 28.1, 27.9, 27.1. MS (ESI) m/z = 785.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(4-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61i). Yield, 82%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.79 (s, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 7.57 – 7.41 (m, 6H), 7.24 – 7.07 (m, 6H), 7.05 (d, *J* = 2.2 Hz, 1H), 5.48 (q, *J* = 7.4 Hz, 1H), 4.97 (td, *J* = 8.4, 4.2 Hz, 1H), 4.36 (td, *J* = 7.8, 5.6 Hz, 1H), 3.67 (s, 3H), 3.42 – 3.17 (m, 2H), 2.83 (dd, *J* = 17.4, 4.2 Hz, 1H), 2.62 (dd, *J* = 17.3, 8.4 Hz, 1H), 2.41 – 2.25 (m, 2H), 2.11 (ddt, *J* = 14.7, 9.0, 6.0 Hz, 1H), 2.04 – 1.96 (m, 1H), 1.46 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.2, 171.6, 171.1, 170.9, 170.8, 161.3, 137.5, 133.8, 133.3, 132.3, 130.5, 128.1, 128.0, 127.4, 127.3, 126.9, 126.5, 125.9, 125.4, 124.5, 119.8, 111.2, 101.3, 81.8, 81.1, 54.6, 52.4, 52.2, 48.9, 39.3, 38.5, 31.5, 28.1, 27.9, 26.9. MS (ESI) m/z = 763.4 $[M + H]^+$, 785.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(6-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61j). Yield, 79%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.73 (s, 1H), 8.33 (d, *J* = 8.5 Hz, 1H), 7.67 – 7.41 (m, 6H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.29 – 7.16 (m, 4H), 7.08 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.91 (d, *J* = 2.1 Hz, 1H), 5.48 (q, *J* = 7.3 Hz, 1H), 4.94 (td, *J* = 8.3, 4.4 Hz, 1H), 4.34 – 4.25 (m, 1H), 3.71 (s, 3H), 3.45 – 3.21 (m, 2H), 2.79 (dd, *J* = 17.3, 4.4 Hz, 1H), 2.61 (dd, *J* = 17.3, 8.3 Hz, 1H), 2.43 – 2.24 (m, 2H), 2.11 (ddt, *J* = 14.8, 9.0, 6.3 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.46 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.2, 171.6, 171.0, 170.8, 161.4, 137.3, 133.7, 133.3, 132.3, 130.7, 130.0,

128.1, 127.9, 127.4, 127.3, 127.2, 125.9, 125.9, 125.5, 122.8, 121.2, 112.3, 102.9, 81.8, 81.1, 54.4, 52.4, 52.2, 48.9, 39.3, 38.4, 31.5, 28.1, 27.8, 26.8. MS (ESI) m/z = 785.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-fluoro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61k). Yield, 74%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.34 (s, 1H), 8.80 (s, 1H), 8.44 (s, 1H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.28 (m, 5H), 7.16 (dd, *J* = 6.3, 3.2 Hz, 2H), 7.08 – 6.88 (m, 4H), 5.40 – 5.32 (m, 1H), 5.16 (d, *J* = 7.6 Hz, 1H), 4.41 (q, *J* = 7.0 Hz, 1H), 3.77 (s, 3H), 3.31 – 2.85 (m, 4H), 2.43 – 2.24 (m, 2H), 2.12 – 2.07 (m, 1H), 2.05 – 1.90 (m, 1H), 1.46 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 172.0, 171.6, 171.3, 170.3, 161.6, 158.8, 157.0, 134.4, 133.5, 133.3, 132.2, 132.0, 125.7, 125.2, 113.3 (d, *J* = 9.6 Hz), 112.5, 112.3, 105.9, 105.7, 102.4, 82.1, 80.9, 55.3, 52.4, 52.2, 48.7, 39.6, 38.8, 31.5 28.1, 28.0, 27.3. MS (ESI) m/z = 769.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-2-((*S*)-2-(5-bromo-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-(*tert*-butoxy)-4-oxobutanoyl)-*L*-glutamate (61l). Yield, 78%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.43 (s, 1H), 8.51 (s, 1H), 7.96 (s, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.41 – 7.25 (m, 4H), 7.20 (d, *J* = 1.9 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.99 (t, *J* = 9.6 Hz, 2H), 6.89 – 6.72 (m, 1H), 5.42 – 5.24 (m, 1H), 4.97 (q, *J* = 7.3 Hz, 1H), 4.29 (q, *J* = 6.9 Hz, 1H), 3.65 (s, 3H), 3.21 – 3.00 (m, 2H), 2.77 (td, *J* = 24.2, 21.5, 9.8 Hz, 2H), 2.30 – 2.14 (m, 2H), 1.97 (d, *J* = 9.7 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.37 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 171.8, 171.6, 171.2, 170.4, 161.4, 135.4, 134.1, 133.3, 132.2, 131.4, 129.1, 128.0 127.8, 127.3, 127.2, 126.7, 125.8, 125.4, 124.1, 114.0, 113.1, 101.9, 82.0, 81.0, 55.0, 52.5, 52.2, 48.8, 39.1, 38.9, 31.4, 28.1, 28.0, 27.0. MS (ESI) m/z = 829.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-methyl-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61m). Yield, 83%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 – 10.31 (m, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.48 (ddd, *J* = 11.3, 5.9, 2.4 Hz, 4H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.24 – 7.07 (m, 5H), 7.01 (dd, *J* = 8.5, 1.6 Hz, 1H), 6.78 (dd, *J* = 2.2, 0.9 Hz, 1H), 5.41 (q, *J* = 7.2 Hz, 1H), 4.85 (td, *J* = 8.1, 4.6 Hz, 1H), 4.29 (td, *J* = 7.8, 5.7 Hz, 1H), 3.59 (s, 3H), 3.23 (qd, *J* = 13.7, 6.9 Hz, 2H), 2.71 (dd, *J* = 17.2, 4.6 Hz, 1H), 2.52 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.41 – 2.31 (m, 3H), 2.27 – 2.17 (m, 2H), 2.01 (ddt, *J* = 14.8, 9.1, 6.2 Hz, 1H), 1.87 (dtd, *J* = 9.4, 7.9, 4.6 Hz, 1H), 1.36 (s, 9H), 1.21 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 171.8, 171.1, 170.8 (d, *J* = 1.6 Hz), 161.9, 135.5, 133.8, 133.4, 132.4, 130.0, 129.5, 128.2, 128.0, 127.8, 127.5, 127.5, 127.4, 126.3, 125.9, 125.5, 121.2, 112.2, 102.6, 81.7, 81.0, 54.3, 52.4, 52.2, 49.1, 39.3, 38.2, 31.5, 28.1, 27.9, 26.9, 21.5. MS (ESI) m/z = 765.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-methoxy-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61n). Yield, 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.57 – 10.40 (m, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.63 – 7.47 (m, 4H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.28 – 7.13 (m, 4H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.79 – 6.71 (m, 1H), 5.38 (q, *J* = 7.2 Hz, 1H), 4.84 (td, *J* = 8.1, 4.5 Hz, 1H), 4.29 (td, *J* = 7.8, 5.6 Hz, 1H), 3.76 (s, 3H), 3.59 (s, 3H), 3.24 (qd, *J* = 13.8, 6.9 Hz, 2H), 2.73 (dd, *J* = 17.2, 4.4 Hz, 1H), 2.51 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.34 – 2.15 (m, 2H), 2.01 (q, *J* = 4.6, 3.2 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.37 (s, 9H), 1.21 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 171.7, 171.0, 170.9, 170.8, 161.8, 154.5, 133.8, 133.4, 132.5, 132.4, 130.3, 128.2, 128.0, 127.7, 127.53, 127.46, 127.3, 125.9, 125.5, 115.9, 113.4, 102.7, 102.0, 81.8, 81.0, 55.7, 54.3, 52.4, 52.2, 49.1, 39.3, 38.1, 31.5, 28.1, 27.9, 26.9. MS (ESI) m/z = 781.1 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-3-(naphthalen-2-yl)-2-(5-(trifluoromethyl)-1*H*-indole-2-carboxamido)propanamido)-4-oxobutanoyl)-*L*-glutamate

(61o). Yield, 75%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.87 (s, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 7.74 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.33 (m, 6H), 7.23 – 6.97 (m, 4H), 5.51 (q, *J* = 7.6, 7.1 Hz, 1H), 5.01 (td, *J* = 8.2, 4.2 Hz, 1H), 4.35 (td, *J* = 7.5, 5.8 Hz, 1H), 3.69 (s, 3H), 3.25 (ddd, *J* = 37.9, 13.5, 7.1 Hz, 2H), 2.83 (dd, *J* = 17.4, 4.2 Hz, 1H), 2.68 (dd, *J* = 17.4, 8.4 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.09 (ddt, *J* = 12.4, 8.5, 4.2 Hz, 1H), 2.01 – 1.93 (m, 1H), 1.46 (s, 9H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 171.6, 171.4, 170.9, 170.7, 161.2, 138.1, 133.9, 133.3, 132.3, 132.0, 128.5, 128.0, 127.9, 127.33, 127.28, 126.6, 126.3, 125.8, 125.4, 124.2, 122.5 (q, *J* = 31.6 Hz), 122.0, 120.5, 119.7 (d, *J* = 4.6 Hz), 112.9, 103.5, 81.9, 81.1, 54.6, 52.4, 52.3, 49.0, 39.3, 38.8, 31.5, 28.1, 27.9, 26.9. MS (ESI) m/z = 819.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-3-(naphthalen-2-yl)-2-(5-nitro-1*H*-indole-2-carboxamido)propanamido)-4-oxobutanoyl)-*L*-glutamate (61p). Yield, 71%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 11.00 (s, 1H), 8.58 (dd, *J* = 36.9, 5.3 Hz, 2H), 8.09 (dt, *J* = 13.5, 6.8 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.48 – 7.33 (m, 4H), 7.22 (d, *J* = 9.0 Hz, 1H), 7.17 – 7.03 (m, 4H), 5.49 (q, *J* = 7.7 Hz, 1H), 5.05 (td, *J* = 8.4, 4.4 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 1H), 3.71 (s, 3H), 3.27 (dd, *J* = 13.2, 7.1 Hz, 1H), 3.17 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.84 (dd, *J* = 17.6, 4.3 Hz, 1H), 2.75 (dd, *J* = 17.5, 8.6 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.10 – 1.98 (m, 2H), 1.46 (s, 9H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.0, 171.6, 171.4, 171.0, 170.7, 160.8, 142.1, 139.5, 133.9, 133.5, 133.2, 132.2, 128.0, 127.9, 127.2, 126.6, 125.8, 125.4, 119.3, 119.1, 112.5, 104.7, 82.1, 81.2, 54.9, 52.5, 52.3, 49.0, 39.2, 39.1, 31.4, 28.1, 27.9, 26.9. MS (ESI) m/z = 796.3 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5,7-dichloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61q). Yield, 79%. ^{1}H NMR (500 MHz, Acetone-d_6) δ 10.75 (s, 1H), 8.31 (d, *J* = 7.7 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.92 – 7.72 (m, 4H), 7.62 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.42 – 7.34 (m, 2H), 7.30 (d, *J* = 1.8 Hz, 1H), 5.01 (ddd, *J* = 9.5, 7.6, 5.0 Hz, 1H), 4.81 (dt, *J* = 8.2, 6.4 Hz, 1H), 4.51 (td, *J* = 8.4, 5.1 Hz, 1H), 3.70 (s, 3H), 3.50 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.30 (dd, *J* = 14.1, 9.4 Hz, 1H), 2.82 (dd, *J* = 16.4, 6.1 Hz, 1H), 2.69 (dd, *J* = 16.4, 6.6 Hz, 1H), 2.42 – 2.25 (m, 2H), 2.14 – 2.06 (m, 1H), 1.90 (dtd, *J* = 13.9, 8.7, 6.2 Hz, 1H), 1.38 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 171.8, 171.7, 171.0, 170.2, 169.9, 160.7, 135.4, 133.64, 133.59, 132.5, 132.4, 129.6, 127.9, 127.8, 127.7, 127.50, 127.49, 125.9, 125.4, 125.2, 123.3, 120.0, 117.8, 104.4, 80.4, 79.7, 55.4, 51.6, 50.0, 37.3, 37.1, 30.9, 27.4, 27.3, 27.0. MS (ESI) m/z = 818.9 $[M + Na]^+$.

5-(*tert*-Butyl) 1-methyl ((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(4,6-dichloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate (61r). Yield, 76%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.78 (s, 1H), 8.72 (d, *J* = 8.6 Hz, 1H), 8.34 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.50 – 7.29 (m, 4H), 7.20 – 6.97 (m, 6H), 5.54 (q, *J* = 7.9 Hz, 1H), 5.16 (td, *J* = 8.7, 4.5 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 1H), 3.72 (s, 3H), 3.24 (dd, *J* = 13.3, 7.3 Hz, 1H), 3.14 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.90 (dd, *J* = 17.7, 4.3 Hz, 1H), 2.79 (dd, *J* = 17.5, 9.2 Hz, 1H), 2.39 (td, *J* = 7.8, 7.3, 2.4 Hz, 2H), 2.19 – 2.08 (m, 1H), 2.08 – 1.99 (m, 1H), 1.46 (s, 9H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 172.0, 171.6, 171.0, 170.9, 160.9, 137.1, 134.2, 133.2, 132.1, 131.5, 129.1, 127.9, 127.8, 127.29, 127.26, 127.23, 127.1, 125.6, 125.3, 125.1, 120.1, 111.0, 101.2, 81.8, 81.1, 54.9, 52.4, 48.9, 39.3, 31.6, 26.8. MS (ESI) m/z = 818.9 $[M + Na]^+$.

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(2-(5-chloro-1*H*-indol-3-yl)acetamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.26 (s, 2H), 11.00 (d, *J* = 2.4 Hz, 1H), 8.50 (d, *J* = 7.7 Hz, 1H), 8.18 (dd, *J* = 18.8, 7.9 Hz, 2H), 7.88 – 7.74 (m, 1H), 7.74 – 7.58 (m, 3H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.26 (m, 2H), 7.16 – 6.91 (m, 2H), 4.64 – 4.44 (m, 2H), 4.30 (ddd, *J* = 9.2, 7.5, 5.1 Hz, 1H), 3.62 (s, 3H), 3.53 – 3.39 (m, 2H), 3.16 (dd, *J* = 13.9, 4.0 Hz, 1H), 2.94 (dd, *J* = 13.9, 9.5 Hz,

1H), 2.69 (dd, *J* = 16.6, 5.3 Hz, 1H), 2.54 (d, *J* = 8.3 Hz, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.96 (dtd, *J* = 13.1, 7.8, 5.2 Hz, 1H), 1.86 – 1.65 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 172.0, 171.7, 171.2, 171.0, 136.0, 134.99, 133.3, 132.2, 128.8, 128.4, 127.9, 127.83, 127.79, 127.70, 126.3, 126.0, 125.7, 123.5, 121.3, 118.5, 113.2, 109.0, 54.4, 52.4, 51.8, 50.0, 38.3, 36.5, 32.5, 30.2, 26.5. HRMS (ESI) Calcd for $C_{33}H_{33}ClN_4O_9$ $(M-H)^-$ 663.1858, found 663.1860. HPLC purity 96.9%, t_R = 8.95 min (condition A1); 97.8%, t_R = 11.17 min (condition B1).

(S)-4-((S)-3-Carboxy-2-((S)-2-(2-(6-chloro-1H-indol-3-yl)acetamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (3). 1H NMR (500 MHz, DMSO-d6) δ 12.27 (s, 2H), 10.89 (d, J = 2.4 Hz, 1H), 8.49 (d, J = 7.7 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.91 – 7.80 (m, 1H), 7.79 – 7.64 (m, 3H), 7.53 – 7.43 (m, 2H), 7.38 (dd, J = 8.4, 1.7 Hz, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.13 – 7.03 (m, 2H), 6.54 (dd, J = 8.4, 1.9 Hz, 1H), 4.66 – 4.55 (m, 2H), 4.31 (ddd, J = 9.3, 7.6, 5.1 Hz, 1H), 3.62 (s, 3H), 3.53 – 3.41 (m, 2H), 3.19 (dd, J = 13.9, 3.8 Hz, 1H), 2.93 (dd, J = 13.9, 10.1 Hz, 1H), 2.70 (dd, J = 16.6, 5.2 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.30 (t, J = 7.6 Hz, 2H), 1.97 (dtd, J = 13.1, 7.8, 5.1 Hz, 1H), 1.81 (ddt, J = 14.0, 9.2, 7.2 Hz, 1H). 13C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 172.0, 171.8, 171.2, 170.9, 136.8, 136.0, 133.4, 132.3, 128.3, 127.9, 127.88, 127.86, 127.82, 126.33, 126.31, 126.0, 125.8, 125.4, 120.3, 118.9, 111.2, 109.4, 54.4, 52.4, 51.8, 50.0, 38.2, 36.5, 32.6, 30.2, 26.5. HRMS (ESI) Calcd for $C_{33}H_{33}ClN_4O_9$ $(M-H)^-$ 663.1858, found 663.1865. HPLC purity 98.4%, t_R = 12.44 min (condition A2); 100%, t_R = 14.77 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (4). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (d, *J* = 8.1 Hz, 1H), 8.56 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 7.93 – 7.69 (m, 1H), 7.68 – 7.60 (m, 4H), 7.56 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.44 – 7.33 (m, 3H), 7.31 (dt, *J* = 8.8, 2.0 Hz, 1H), 4.64 (td, *J* = 8.8, 8.3, 3.8 Hz, 1H), 4.57 (td, *J* = 8.1, 5.0 Hz, 1H), 4.23 (td, *J* = 8.4, 5.2 Hz, 1H), 4.01 – 3.75 (m, 2H), 3.55 (s, 3H), 3.19 (dd, *J* = 14.0, 3.8 Hz, 1H), 2.86 (dd, *J* = 13.9, 9.9 Hz, 1H), 2.65 (dd, *J* = 16.7, 5.0 Hz, 1H), 2.56 – 2.44 (m, 1H), 2.23 (t, *J* = 7.6 Hz, 2H), 2.03 – 1.83 (m, 1H), 1.73 (ddd, *J* = 16.4, 14.0, 7.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 171.9, 171.3, 171.2, 166.0, 158.6, 150.5, 135.8, 133.3, 132.2, 128.6, 128.3, 128.0, 127.82, 127.80, 126.3, 125.8, 124.5, 116.0, 114.6, 54.7, 52.4, 51.8, 50.0, 38.5, 36.6, 34.9, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{32}ClN_5O_9$ $(M-H)^-$ 664.1810, found 664.1810. HPLC purity 99.2%, t_R = 7.47 min (condition A1); 100%, t_R = 9.54 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(2-(5-chlorobenzo[*d*]oxazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.27 (s, 2H), 8.67 (d, *J* = 8.3 Hz, 1H), 8.55 (d, *J* = 7.7 Hz, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.97 – 7.81 (m, 1H), 7.79 – 7.69 (m, 4H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.53 – 7.30 (m, 4H), 4.79 – 4.55 (m, 2H), 4.31 (ddd, *J* = 9.2, 7.6, 5.1 Hz, 1H), 3.97 – 3.79 (m, 2H), 3.62 (s, 3H), 3.24 (dd, *J* = 14.0, 3.9 Hz, 1H), 2.94 (dd, *J* = 13.9, 9.8 Hz, 1H), 2.72 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.97 (dtd, *J* = 13.1, 7.7, 5.1 Hz, 1H), 1.80 (ddt, *J* = 14.1, 9.2, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 172.0, 171.3, 171.1, 165.7, 163.7, 149.6, 142.4, 135.8, 133.4, 132.3, 129.0, 128.3, 128.0, 127.9, 127.8, 126.3, 125.8, 125.4, 119.6, 112.4, 54.5, 52.4, 51.8, 50.0, 38.4, 36.5, 36.3, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}ClN_4O_{10}$ $(M-H)^-$ 665.1650, found 665.1650. HPLC purity 97.0%, t_R = 12.43 min (condition A2); 96.6%, t_R = 14.93 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(2-(6-chlorobenzo[*d*]oxazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.27 (s, 2H), 8.67 (d, *J* = 8.3 Hz, 1H), 8.55 (d, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 7.7 Hz,

1H), 7.90 – 7.80 (m, 1H), 7.79 – 7.69 (m, 3H), 7.68 – 7.59 (m, 2H), 7.54 – 7.40 (m, 3H), 7.38 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.77 – 4.54 (m, 2H), 4.31 (ddd, *J* = 9.1, 7.5, 5.1 Hz, 1H), 3.88 (d, *J* = 1.8 Hz, 2H), 3.62 (s, 3H), 3.24 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.94 (dd, *J* = 13.9, 9.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.54 (dd, *J* = 16.8, 8.7 Hz, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.97 (dtd, *J* = 13.1, 7.7, 5.2 Hz, 1H), 1.80 (ddt, *J* = 14.0, 9.1, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 172.0, 171.3, 171.1, 165.7, 162.9, 151.1, 140.2, 135.8, 133.4, 132.3, 129.7, 128.3, 128.0, 127.9, 127.87, 127.83, 126.3, 125.8, 125.2, 120.8, 111.6, 54.5, 52.4, 51.8, 50.0, 38.4, 36.6, 36.2, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}ClN_4O_{10}$ $(M - H)^-$ 665.1650, found 665.1659. HPLC purity 98.1%, t_R = 12.42 min (condition A2); 98.0%, t_R = 14.96 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(2-(5-chlorobenzo[*d*]thiazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (7). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.26 (s, 2H), 8.70 (d, *J* = 8.3 Hz, 1H), 8.57 (d, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.04 – 7.87 (m, 2H), 7.83 – 7.74 (m, 1H), 7.75 – 7.56 (m, 3H), 7.52 – 7.18 (m, 4H), 4.70 (td, *J* = 9.2, 3.8 Hz, 1H), 4.61 (td, *J* = 7.9, 5.1 Hz, 1H), 4.31 (td, *J* = 8.3, 5.1 Hz, 1H), 4.14 – 3.91 (m, 2H), 3.62 (s, 3H), 3.24 (dd, *J* = 14.0, 3.9 Hz, 1H), 2.93 (dd, *J* = 13.9, 10.0 Hz, 1H), 2.80 – 2.65 (m, 1H), 2.61 – 2.50 (m, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.96 (ddd, *J* = 13.2, 9.4, 5.4 Hz, 1H), 1.81 (ddd, *J* = 16.4, 14.1, 7.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 172.0, 171.4, 171.1, 168.3, 167.3, 153.4, 135.8, 134.5, 133.3, 132.2, 131.1, 128.3, 128.0, 127.8, 127.8, 126.2, 125.8, 125.4, 123.8, 122.1, 54.4, 52.4, 51.8, 50.0, 41.0, 38.4, 36.5, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}ClN_4O_9S$ $(M - H)^-$ 681.1422, found 681.1432. HPLC purity 100%, t_R = 12.74 min (condition A2); 99.2%, t_R = 15.35 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(2-(6-chlorobenzo[*d*]thiazol-2-yl)acetamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (8). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (d, *J* = 8.3 Hz, 1H), 8.58 (d, *J* = 7.6 Hz, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 2.2 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.74 – 7.65 (m, 3H), 7.48 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.45 – 7.36 (m, 3H), 4.70 (ddd, *J* = 10.1, 8.4, 4.0 Hz, 1H), 4.61 (td, *J* = 8.1, 5.2 Hz, 1H), 4.30 (ddd, *J* = 9.3, 7.6, 5.1 Hz, 1H), 4.08 – 3.91 (m, 2H), 3.62 (s, 3H), 3.24 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.92 (dd, *J* = 13.9, 10.0 Hz, 1H), 2.71 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.53 (dd, *J* = 16.0, 7.8 Hz, 1H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.97 (dtd, *J* = 13.1, 7.8, 5.1 Hz, 1H), 1.80 (ddt, *J* = 14.1, 9.3, 7.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 172.0, 171.4, 171.2, 167.4, 166.9, 151.3, 137.3, 135.8, 133.3, 132.2, 129.8, 128.3, 128.0, 127.84, 127.81, 127.78, 126.7, 126.2, 125.7, 123.8, 121.9, 54.4, 52.40 51.8, 50.0, 40.9, 38.4, 36.5, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}ClN_4O_9S$ $(M - H)^-$ 681.1422, found 681.1425. HPLC purity 100%, t_R = 8.94 min (condition A1); 100%, t_R = 11.18 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (9). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 2H), 11.64 (d, *J* = 2.1 Hz, 1H), 8.79 (d, *J* = 8.5 Hz, 1H), 8.59 (d, *J* = 7.7 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 7.94 – 7.74 (m, 4H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.48 – 7.32 (m, 3H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.15 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.88 (ddd, *J* = 11.8, 8.5, 3.6 Hz, 1H), 4.65 (td, *J* = 8.0, 5.2 Hz, 1H), 4.30 (ddd, *J* = 9.2, 7.5, 5.2 Hz, 1H), 3.63 (s, 3H), 3.42 – 3.27 (m, 1H), 3.14 (dd, *J* = 13.9, 10.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.58 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.40 – 2.28 (m, 2H), 2.00 – 1.94 (m, 1H), 1.84 – 1.75 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.0, 171.8, 171.2, 161.0, 136.5, 135.2, 133.4, 133.1, 132.2, 128.5, 128.3, 127.9, 127.88, 127.85, 127.7, 126.4, 125.8, 124.6, 123.9, 121.1, 114.3, 103.3, 54.9, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}ClN_4O_9$ $(M - H)^-$

649.1701, found 649.1700. HPLC purity 97.1%, t_R = 13.34 min (condition A2); 99.5%, t_R = 15.98 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(4-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (10). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 2H), 11.80 (d, J = 2.3 Hz, 1H), 8.88 (d, J = 8.6 Hz, 1H), 8.57 (d, J = 7.7 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.94 – 7.71 (m, 4H), 7.56 (dd, J = 8.4, 1.7 Hz, 1H), 7.42 (pd, J = 6.9, 1.5 Hz, 2H), 7.39 – 7.26 (m, 2H), 7.19 – 6.97 (m, 2H), 4.96 – 4.83 (m, 1H), 4.65 (td, J = 8.0, 5.1 Hz, 1H), 4.30 (ddd, J = 9.2, 7.5, 5.2 Hz, 1H), 3.62 (s, 3H), 3.43 – 3.23 (m, 1H), 3.14 (dd, J = 13.9, 11.0 Hz, 1H), 2.72 (dd, J = 16.6, 5.2 Hz, 1H), 2.58 (dd, J = 16.6, 8.3 Hz, 1H), 2.38 – 2.21 (m, 2H), 1.98 (dtd, J = 13.0, 7.7, 5.1 Hz, 1H), 1.92 – 1.76 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.0, 171.8, 171.2, 160.9, 137.5, 136.6, 133.4, 132.4, 132.2, 128.3, 127.9, 127.86, 127.85, 127.7, 126.4, 126.1, 125.8, 124.6, 119.7, 111.9, 101.8, 54.9, 52.4, 51.8, 50.0, 37.9, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}ClN_4O_9$ (M – H)$^-$ 649.1701, found 649.1713. HPLC purity 99.7%, t_R = 13.26 min (condition A2); 100%, t_R = 16.03 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(6-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (11). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.29 (s, 2H), 11.57 (d, J = 2.2 Hz, 1H), 8.77 (d, J = 8.5 Hz, 1H), 8.59 (d, J = 7.7 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 7.93 – 7.71 (m, 4H), 7.64 (d, J = 8.5 Hz, 1H), 7.55 (dd, J = 8.5, 1.7 Hz, 1H), 7.50 – 7.33 (m, 3H), 7.24 (dd, J = 2.2, 0.9 Hz, 1H), 7.03 (dd, J = 8.5, 2.0 Hz, 1H), 5.01 – 4.77 (m, 1H), 4.65 (td, J = 8.0, 5.2 Hz, 1H), 4.30 (ddd, J = 9.2, 7.5, 5.2 Hz, 1H), 3.63 (s, 3H), 3.32 (dd, J = 13.9, 3.7 Hz, 1H), 3.13 (dd, J = 13.9, 10.9 Hz, 1H), 2.72 (dd, J = 16.6, 5.1 Hz, 1H), 2.58 (dd, J = 16.7, 8.3 Hz, 1H), 2.30 (dp, J = 9.0, 3.1, 2.6 Hz, 2H), 2.07 – 1.93 (m, 1H), 1.85 – 1.72 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.0, 171.9, 171.2, 161.1, 137.1, 136.5, 133.4, 132.6, 132.2, 128.4, 128.3, 127.9, 127.88, 127.85, 127.7, 126.4, 126.2, 125.8, 123.6, 120.7, 112.1, 103.8, 54.8, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}ClN_4O_9$ (M – H)$^-$ 649.1701, found 649.1701. HPLC purity 97.9%, t_R = 13.35 min (condition A2); 99.7%, t_R = 15.93 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-fluoro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (12). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 2H), 11.53 (d, J = 2.3 Hz, 1H), 8.74 (d, J = 8.5 Hz, 1H), 8.58 (d, J = 7.7 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.99 – 7.72 (m, 4H), 7.55 (dd, J = 8.5, 1.7 Hz, 1H), 7.50 – 7.30 (m, 4H), 7.20 (d, J = 2.1 Hz, 1H), 7.01 (td, J = 9.2, 2.6 Hz, 1H), 4.96 – 4.83 (m, 1H), 4.65 (td, J = 8.0, 5.2 Hz, 1H), 4.30 (ddd, J = 9.2, 7.5, 5.2 Hz, 1H), 3.63 (s, 3H), 3.31 (s, 1H), 3.14 (dd, J = 13.9, 10.9 Hz, 1H), 2.72 (dd, J = 16.6, 5.2 Hz, 1H), 2.58 (dd, J = 16.6, 8.3 Hz, 1H), 2.38 – 2.25 (m, 2H), 2.06 – 1.89 (m, 1H), 1.89 – 1.74 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.0, 171.9, 171.2, 161.1, 158.5, 156.6, 136.5, 133.6, 133.4, 133.3, 132.2, 128.3, 127.9, 127.88, 127.84, 127.7, 127.5, 127.4, 126.4, 125.8, 113.9, 113.8, 112.6, 112.4, 106.3, 106.1, 103.8, 103.7, 54.8, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}FN_4O_9$ (M – H)$^-$ 633.1997, found 633.2003. HPLC purity 97.3%, t_R = 12.80 min (condition A2); 100%, t_R = 15.21 min (condition B2).

(*S*)-4-((*S*)-2-((*S*)-2-(5-Bromo-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-3-carboxypropanamido)-5-methoxy-5-oxopentanoic acid (13). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 2H), 11.64 (d, J = 2.3 Hz, 1H), 8.78 (d, J = 8.5 Hz, 1H), 8.58 (d, J = 7.7 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.94 – 7.69 (m, 5H), 7.55 (dd, J = 8.5, 1.7 Hz, 1H), 7.42 (pd, J = 6.9, 1.6 Hz, 2H), 7.32 (d, J = 8.7 Hz, 1H), 7.25 (dd, J = 8.7, 1.9 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 5.12 – 4.81 (m, 1H), 4.65 (td, J = 7.9, 5.1 Hz, 1H), 4.30 (ddd, J = 9.2, 7.5, 5.1 Hz, 1H), 3.63 (s, 3H), 3.38 –

3.25 (m, 1H), 3.14 (dd, *J* = 13.9, 10.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.57 (dd, *J* = 16.6, 8.4 Hz, 1H), 2.36 – 2.26 (m, 2H), 2.05 – 1.93 (m, 1H), 1.83 (ddt, *J* = 13.9, 7.9, 4.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.0, 171.8, 171.2, 161.0, 136.5, 135.4, 133.4, 132.9, 132.2, 129.2, 128.3, 127.9, 127.88, 127.85, 127.7, 126.4, 125.8, 124.2, 114.7, 112.6, 103.2, 54.8, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}BrN_4O_9$ $(M - H)^-$ 693.1196, 695.1176, found 693.1206, 695.1195. HPLC purity 97.5%, t_R = 13.48 min (condition A2); 98.7%, t_R = 16.16 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-methyl-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (14). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 2H), 11.28 (d, *J* = 2.2 Hz, 1H), 8.59 (dd, *J* = 20.6, 8.0 Hz, 2H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.92 – 7.71 (m, 4H), 7.55 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 6.98 (dd, *J* = 8.4, 1.6 Hz, 1H), 4.87 (ddd, *J* = 11.8, 8.6, 3.7 Hz, 1H), 4.65 (td, *J* = 7.9, 5.2 Hz, 1H), 4.30 (td, *J* = 8.5, 5.4 Hz, 1H), 3.63 (s, 3H), 3.30 (d, *J* = 7.8 Hz, 1H), 3.14 (dd, *J* = 13.9, 10.8 Hz, 1H), 2.72 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.58 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.39 – 2.24 (m, 5H), 2.09 – 1.91 (m, 1H), 1.84 (ddd, *J* = 11.6, 8.6, 6.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.04, 171.96, 171.2, 161.5, 136.6, 135.3, 133.39, 132.2, 131.5, 128.7, 128.3, 127.9, 127.89, 127.84, 127.7, 127.6, 126.4, 125.8, 125.7, 121.2, 112.4, 103.3, 54.8, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.5, 21.6. HRMS (ESI) Calcd for $C_{33}H_{34}N_4O_9$ $(M - H)^-$ 629.2248, found 629.2250. HPLC purity 96.1%, t_R = 13.11 min (condition A2); 97.0%, t_R = 15.63 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-methoxy-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (15). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.29 (s, 2H), 11.26 (d, *J* = 2.2 Hz, 1H), 8.59 (dd, *J* = 21.0, 8.0 Hz, 2H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.85 – 7.70 (m, 4H), 7.55 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.49 – 7.29 (m, 2H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.09 (dd, *J* = 17.1, 2.3 Hz, 2H), 6.80 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.98 – 4.80 (m, 1H), 4.65 (td, *J* = 8.0, 5.2 Hz, 1H), 4.30 (ddd, *J* = 9.2, 7.5, 5.2 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 3.32 – 3.28 (m, 7H), 3.14 (dd, *J* = 13.9, 10.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.58 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.36 – 2.24 (m, 2H), 2.09 – 1.93 (m, 1H), 1.88 – 1.78 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.04, 171.97, 171.2, 161.4, 154.1, 136.6, 133.4, 132.2, 132.1, 131.9, 128.4, 127.9, 127.8, 127.76, 127.71, 126.4, 125.8, 115.0, 113.5, 103.5, 102.5, 55.7, 54.8, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.5. HRMS (ESI) Calcd for $C_{33}H_{34}N_4O_{10}$ $(M - H)^-$ 645.2197, found 645.2200. HPLC purity 97.3%, t_R = 12.43 min (condition A2); 97.9%, t_R = 14.81 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-3-(naphthalen-2-yl)-2-(5-(trifluoromethyl)-1*H*-indole-2-carboxamido)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (16). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.27 (s, 2H), 11.88 (d, *J* = 2.2 Hz, 1H), 8.88 (d, *J* = 8.6 Hz, 1H), 8.60 (d, *J* = 7.7 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 1.7 Hz, 1H), 7.85 (d, *J* = 1.6 Hz, 1H), 7.81 – 7.71 (m, 3H), 7.59 – 7.50 (m, 2H), 7.48 – 7.36 (m, 4H), 5.01 – 4.74 (m, 1H), 4.66 (td, *J* = 7.9, 5.1 Hz, 1H), 4.31 (ddd, *J* = 9.2, 7.5, 5.1 Hz, 1H), 3.63 (s, 3H), 3.40 – 3.31 (m, 1H), 3.15 (dd, *J* = 13.8, 10.9 Hz, 1H), 2.72 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.58 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.38 – 2.25 (m, 2H), 1.99 (td, *J* = 8.2, 4.1 Hz, 1H), 1.88 – 1.75 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.4, 172.0, 171.8, 171.2, 160.9, 138.1, 136.5, 133.7, 133.4, 132.2, 128.3, 127.9, 127.8, 127.8, 126.9, 126.7, 126.4, 125.8, 124.8, 121.1, 120.9, 120.0, 104.6, 54.9, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.6. HRMS (ESI) Calcd for $C_{33}H_{31}F_3N_4O_9$ $(M - H)^-$ 683.1965, found 683.1976. HPLC purity 98.1%, t_R = 13.60 min (condition A2); 99.0%, t_R = 16.12 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-3-(naphthalen-2-yl)-2-(5-nitro-1*H*-indole-2-carboxamido)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (17). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.21 (s, 2H), 9.03 (d, J = 8.6 Hz, 1H), 8.71 (d, J = 2.3 Hz, 1H), 8.61 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 7.5 Hz, 1H), 8.03 (dd, J = 9.2, 2.3 Hz, 1H), 7.91 – 7.70 (m, 4H), 7.56 (dd, J = 8.5, 1.7 Hz, 1H), 7.51 (t, J = 4.4 Hz, 2H), 7.42 (pd, J = 6.8, 1.6 Hz, 2H), 4.92 (ddd, J = 11.9, 8.6, 3.6 Hz, 1H), 4.65 (td, J = 7.9, 5.1 Hz, 1H), 4.30 (td, J = 8.5, 5.4 Hz, 1H), 3.63 (s, 3H), 3.15 (dd, J = 13.9, 11.0 Hz, 2H), 2.72 (dd, J = 16.6, 5.1 Hz, 1H), 2.58 (dd, J = 16.6, 8.4 Hz, 1H), 2.36 – 2.22 (m, 2H), 2.09 – 1.91 (m, 1H), 1.83 (ddd, J = 14.5, 8.7, 6.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 172.5, 172.0, 171.7, 171.2, 160.6, 141.7, 139.7, 136.5, 135.1, 133.4, 132.2, 128.3, 127.9, 127.89, 127.86, 127.76, 126.69, 126.4, 125.8, 119.7, 118.9, 113.2, 106.1, 54.9, 52.4, 51.9, 50.1, 37.9, 36.6, 30.3, 26.5. HRMS (ESI) Calcd for $C_{32}H_{31}N_5O_{11}$ $(M - H)^-$ 660.1942, found 660.1953. HPLC purity 98.1%, t_R = 12.76 min (condition A2); 97.9%, t_R = 15.30 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5,7-dichloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (18). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.30 (s, 2H), 11.90 (s, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.66 (d, J = 7.6 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.93 – 7.74 (m, 4H), 7.71 (d, J = 1.8 Hz, 1H), 7.53 (dd, J = 8.5, 1.7 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.37 (d, J = 1.8 Hz, 1H), 7.16 (d, J = 1.2 Hz, 1H), 4.93 (ddd, J = 10.6, 8.5, 3.8 Hz, 1H), 4.65 (td, J = 8.0, 5.0 Hz, 1H), 4.31 (ddd, J = 9.2, 7.4, 5.1 Hz, 1H), 3.63 (s, 3H), 3.34 (d, J = 11.8 Hz, 1H), 3.09 (dd, J = 14.0, 10.7 Hz, 1H), 2.72 (dd, J = 16.6, 5.0 Hz, 1H), 2.57 (dd, J = 16.6, 8.6 Hz, 1H), 2.38 – 2.23 (m, 2H), 1.98 (dq, J = 10.5, 4.1, 2.6 Hz, 1H), 1.89 – 1.75 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.0, 171.7, 171.2, 160.1, 136.2, 134.6, 133.4, 132.8, 132.3, 129.4, 128.3, 127.91, 127.89, 127.8, 126.4, 125.9, 124.7, 123.3, 120.4, 117.8, 106.3, 100.0, 54.7, 52.4, 51.8, 50.1, 38.3, 36.6, 30.2, 26.6. HRMS (ESI) Calcd for $C_{32}H_{30}Cl_2N_4O_9$ $(M - H)^-$ 683.1312, found 683.1312. HPLC purity 98.2%, t_R = 13.84 min (condition A2); 99.5%, t_R = 16.89 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(4,6-dichloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-methoxy-5-oxopentanoic acid (19). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.28 (s, 2H), 11.94 (s, 1H), 8.95 (d, J = 8.6 Hz, 1H), 8.58 (d, J = 7.7 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.00 – 7.73 (m, 4H), 7.55 (dd, J = 8.5, 1.7 Hz, 1H), 7.47 – 7.31 (m, 4H), 7.21 (d, J = 1.7 Hz, 1H), 5.11 – 4.82 (m, 1H), 4.65 (td, J = 8.0, 5.2 Hz, 1H), 4.30 (ddd, J = 9.2, 7.5, 5.1 Hz, 1H), 3.63 (s, 3H), 3.36 – 3.23 (m, 1H), 3.13 (dd, J = 13.9, 11.0 Hz, 1H), 2.72 (dd, J = 16.6, 5.1 Hz, 1H), 2.58 (dd, J = 16.6, 8.4 Hz, 1H), 2.30 (dt, J = 8.0, 3.4 Hz, 2H), 1.98 (dtd, J = 13.1, 7.7, 5.1 Hz, 1H), 1.88 – 1.70 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.2, 172.5, 172.0, 171.7, 171.2, 160.6, 137.2, 136.5, 133.4, 133.3, 132.2, 128.3, 128.2, 127.92, 127.88, 127.85, 127.7, 126.8, 126.4, 125.8, 125.1, 119.9, 111.5, 101.9, 54.9, 52.4, 51.8, 50.0, 38.0, 36.6, 30.2, 26.5. HRMS (ESI) Calcd for $C_{32}H_{30}Cl_2N_4O_9$ $(M - H)^-$ 683.1312, found 683.1314. HPLC purity 99.1%, t_R = 14.00 min (condition A2); 99.4%, t_R = 17.02 min (condition B2).

***tert*-Butyl (S)-5-(benzylamino)-4-(((benzyloxy)carbonyl)amino)-5-oxopentanoate (66a).** Yield, 89%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 (qd, J = 9.1, 7.7, 4.2 Hz, 7H), 7.13 – 7.09 (m, 3H), 6.99 (d, J = 6.1 Hz, 1H), 5.90 (d, J = 8.1 Hz, 1H), 4.89 (q, J = 12.3 Hz, 2H), 4.25 (tp, J = 19.5, 7.1, 6.4 Hz, 3H), 2.32 – 2.13 (m, 2H), 1.98 (dtd, J = 14.5, 7.3, 5.3 Hz, 1H), 1.83 (dt, J = 14.8, 7.4 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.6, 171.4, 156.4, 138.0, 136.2, 128.6, 128.5, 128.1, 128.00, 127.6, 127.4, 80.8, 77.2, 66.9, 54.4, 43.4, 31.6, 28.1. MS (ESI) m/z = 449.2 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-(((benzyloxy)carbonyl)amino)-5-oxo-5-(phenethylamino)pentanoate(66b).** Yield, 82%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.26 (m, 7H), 7.25 – 7.11 (m, 3H), 6.50 (d, *J* = 6.1 Hz, 1H), 5.82 (d, *J* = 7.9 Hz, 1H), 5.19 – 4.97 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 1H), 3.72 – 3.41 (m, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 2.37 (dt, *J* = 16.4, 7.2 Hz, 1H), 2.25 (dt, *J* = 16.6, 7.0 Hz, 1H), 2.13 – 1.99 (m, 1H), 1.93 (s, 1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.7, 171.2, 156.2, 138.7, 136.2, 128.7, 128.6, 128.5, 128.2, 128.0, 126.5, 80.9, 77.1, 67.0, 54.4, 40.7, 35.6, 31.7, 28.1. MS (ESI) m/z = 441.3 $[M + H]^+$, MS (ESI) m/z = 463.2 $[M + Na]^+$, MS (ESI) m/z = 903.4 $[2M + Na]^+$.

***tert*-Butyl (*S*)-4-(((benzyloxy)carbonyl)amino)-5-((4-fluorophenyl)amino)-5-oxopentanoate (66c).** Yield, 87%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 7.47 – 7.38 (m, 2H), 7.35 – 7.21 (m, 5H), 6.93 (t, *J* = 8.7 Hz, 2H), 6.03 (d, *J* = 7.8 Hz, 1H), 5.18 – 4.95 (m, 2H), 4.38 (t, *J* = 7.4 Hz, 1H), 2.48 (dt, *J* = 16.5, 7.2 Hz, 1H), 2.37 (dt, *J* = 16.7, 6.9 Hz, 1H), 2.21 – 2.10 (m, 1H), 2.07 – 1.92 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.0, 169.8, 159.4 (d, *J* = 243.5 Hz), 156.7, 136.0, 133.7, 128.5, 128.2, 128.0, 121.7 (d, *J* = 7.9 Hz), 115.5 (d, *J* = 22.5 Hz), 81.3, 67.2, 55.0, 31.8, 28.1, 28.0. MS (ESI) m/z = 453.2 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-(((benzyloxy)carbonyl)amino)-5-((3-fluorophenyl)amino)-5-oxopentanoate(66d).** Yield, 84%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.85 (s, 1H), 7.46 (dt, *J* = 11.0, 2.4 Hz, 1H), 7.32 (q, *J* = 4.3 Hz, 5H), 7.21 (td, *J* = 8.2, 6.3 Hz, 1H), 7.16 – 7.06 (m, 1H), 6.95 – 6.59 (m, 1H), 5.92 (d, *J* = 7.7 Hz, 1H), 5.11 (d, *J* = 4.3 Hz, 2H), 4.36 (d, *J* = 7.1 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.37 (ddd, *J* = 16.7, 7.3, 6.0 Hz, 1H), 2.15 (ddt, *J* = 13.8, 7.8, 6.0 Hz, 1H), 2.06 – 1.89 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.2, 169.8, 162.9 (d, *J* = 244.7 Hz), 156.6, 139.2 (d, *J* = 10.8 Hz), 136.0, 130.0 (d, *J* = 9.2 Hz), 128.6, 128.3, 128.0, 115.1 (d, *J* = 3.0 Hz), 111.1 (d, *J* = 21.3 Hz), 107.3 (d, *J* = 26.3 Hz), 81.5, 67.3, 55.0, 31.9, 28.1, 28.0. MS (ESI) m/z = 297.2 $[M + H]^+$, MS (ESI) m/z = 453.2 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-(((benzyloxy)carbonyl)amino)-5-((2-fluorophenyl)amino)-5-oxopentanoate (66e).** Yield, 88%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.37 – 8.09 (m, 1H), 7.43 – 7.28 (m, 5H), 7.06 (dtt, *J* = 14.0, 5.3, 2.6 Hz, 3H), 6.07 – 5.87 (m, 1H), 5.27 – 5.01 (m, 2H), 4.47 (t, *J* = 7.3 Hz, 1H), 2.48 (q, *J* = 8.0, 7.2 Hz, 1H), 2.38 (dt, *J* = 16.7, 6.8 Hz, 1H), 2.26 – 2.10 (m, 1H), 2.08 – 1.89 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.8, 170.0, 156.5, 152.9 (d, *J* = 243.8 Hz), 136.1, 128.5, 128.2, 128.1, 125.9 (d, *J* = 10.4 Hz), 124.8 (d, *J* = 7.4 Hz), 124.4 (d, *J* = 3.7 Hz), 122.2, 115.0 (d, *J* = 19.2 Hz), 81.2 (d, *J* = 4.1 Hz), 67.2, 55.1, 31.8, 28.0, 27.9. MS (ESI) m/z = 453.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-5-(benzylamino)-4-((*S*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-oxopentanoate (67a).** Yield, 86%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.31 (m, 7H), 7.27 (dd, *J* = 10.6, 3.4 Hz, 3H), 7.09 (d, *J* = 8.3 Hz, 1H), 5.89 (d, *J* = 8.3 Hz, 1H), 5.25 – 5.02 (m, 2H), 4.58 – 4.31 (m, 4H), 2.89 (dd, *J* = 16.9, 4.8 Hz, 1H), 2.70 (dd, *J* = 16.9, 6.1 Hz, 1H), 2.55 – 2.39 (m, 1H), 2.33 (dt, *J* = 17.0, 6.5 Hz, 1H), 2.22 – 2.12 (m, 1H), 2.02 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.44 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.5, 170.9, 170.8, 170.6, 156.1, 138.2, 136.0, 128.61, 128.56, 128.3, 128.1, 127.6, 127.3, 82.0, 81.1, 67.3, 53.3, 51.7, 43.4, 37.3, 31.7, 28.04, 27.99, 27.0. MS (ESI) m/z = 620.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*S*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-oxo-5-(phenethylamino)pentanoate (67b).** Yield, 83%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.41 – 7.27 (m, 8H), 7.24 – 7.12 (m, 3H), 6.62 (s, 1H), 5.84 (d, *J* = 8.4 Hz, 1H), 5.13 (q, *J* = 12.2 Hz, 2H), 4.45 (q, *J* = 7.3, 6.2 Hz, 1H), 4.32 (td, *J* = 8.0, 4.7 Hz, 1H), 3.49 (q, *J* = 7.3 Hz, 2H), 2.90 (dd, *J* = 17.0, 4.6 Hz, 1H), 2.85 – 2.75 (m, 2H), 2.67 (dd, *J* = 16.9, 5.9 Hz, 1H), 2.36 (ddd, *J* =

17.1, 8.0, 6.1 Hz, 1H), 2.24 (dt, *J* = 17.0, 6.5 Hz, 1H), 2.06 (dt, *J* = 10.4, 5.5 Hz, 1H), 1.91 (dd, *J* = 14.5, 7.4 Hz, 1H), 1.43 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.5, 171.0, 170.7, 170.5, 156.1, 138.8, 136.0, 128.7, 128.6, 128.3, 128.1, 126.5, 82.0, 81.0, 67.3, 53.3, 53.2, 51.6, 40.8, 37.3, 35.6, 31.6, 28.1, 28.0, 27.0. MS (ESI) m/z = 612.3 $[M + H]^+$, MS (ESI) m/z = 634.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*S*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((4-fluorophenyl)amino)-5-oxopentanoate (67c).** Yield, 86%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.78 (s, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.47 (dd, *J* = 8.9, 4.8 Hz, 2H), 7.26 – 7.12 (m, 5H), 6.94 – 6.63 (m, 2H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.14 – 4.95 (m, 2H), 4.47 (dtd, *J* = 11.2, 7.9, 5.4 Hz, 2H), 2.78 (dd, *J* = 16.9, 5.1 Hz, 1H), 2.68 (dd, *J* = 16.8, 6.3 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.27 (dt, *J* = 17.0, 6.7 Hz, 1H), 2.13 (q, *J* = 6.4, 6.0 Hz, 1H), 2.00 – 1.90 (m, 1H), 1.34 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.5, 171.2, 170.8, 169.1, 159.3 (d, *J* = 243.3 Hz), 156.2, 136.0, 133.9 (d, *J* = 2.8 Hz), 128.5, 128.3, 128.1, 121.9 (d, *J* = 7.8 Hz), 115.3 (d, *J* = 22.4 Hz), 82.0, 81.2, 67.3, 53.8, 51.8, 37.3, 31.7, 28.04, 27.98, 26.8. MS (ESI) m/z = 624.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*S*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((3-fluorophenyl)amino)-5-oxopentanoate (67d).** Yield, 84%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.91 (s, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.54 (dt, *J* = 11.2, 2.3 Hz, 1H), 7.38 – 7.25 (m, 6H), 7.21 (td, *J* = 8.2, 6.4 Hz, 1H), 6.77 (tdd, *J* = 8.3, 2.5, 1.0 Hz, 1H), 5.95 (d, *J* = 7.9 Hz, 1H), 5.21 – 5.03 (m, 2H), 4.67 – 4.41 (m, 2H), 2.88 (dd, *J* = 16.9, 4.9 Hz, 1H), 2.76 (dd, *J* = 16.9, 6.2 Hz, 1H), 2.48 (ddd, *J* = 17.1, 8.1, 5.9 Hz, 1H), 2.35 (ddd, *J* = 17.1, 7.1, 5.8 Hz, 1H), 2.20 (td, *J* = 8.4, 4.0 Hz, 1H), 2.04 (q, *J* = 5.4, 3.4 Hz, 1H), 1.43 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.7, 171.3, 170.8, 169.2, 162.9 (d, *J* = 244.2 Hz), 156.2, 139.4 (d, *J* = 10.7 Hz), 135.9, 129.8 (d, *J* = 9.3 Hz), 128.6, 128.3, 128.1, 115.4 (d, *J* = 2.8 Hz), 110.9 (d, *J* = 21.3 Hz), 107.5 (d, *J* = 26.3 Hz), 82.2, 81.4, 67.4, 53.9, 51.8, 37.2, 31.8, 28.04, 27.99, 26.7. MS (ESI) m/z = 624.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*S*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((2-fluorophenyl)amino)-5-oxopentanoate (67e).** Yield, 85%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 8.31 – 8.01 (m, 1H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.43 – 7.27 (m, 5H), 7.14 – 6.92 (m, 3H), 5.99 (d, *J* = 8.7 Hz, 1H), 5.24 – 5.01 (m, 2H), 4.61 (ddt, *J* = 15.7, 10.5, 4.8 Hz, 2H), 2.95 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.67 (dd, *J* = 17.1, 6.0 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.36 (dt, *J* = 17.0, 6.6 Hz, 1H), 2.23 – 2.15 (m, 1H), 2.09 – 1.98 (m, 1H), 1.43 (s, 9H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.3, 171.4, 170.9, 169.3, 156.0, 153.1 (d, *J* = 244.8 Hz), 136.0, 128.5, 128.2, 128.1, 125.9 (d, *J* = 10.7 Hz), 124.9 (d, *J* = 7.4 Hz), 124.3 (d, *J* = 3.6 Hz), 122.6, 115.0 (d, *J* = 19.1 Hz), 81.9, 81.1, 67.3, 53.8, 51.4, 37.4, 31.6, 28.05, 27.97, 27.0. MS (ESI) m/z = 624.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-1-(((*S*)-1-(benzylamino)-5-(*tert*-butoxy)-1,5-dioxopentan-2-yl)amino)-4-(*tert*-butoxy)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (69a).** Yield, 89%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 – 7.64 (m, 4H), 7.64 – 7.55 (m, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.45 – 7.32 (m, 4H), 7.26 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.23 – 7.17 (m, 5H), 7.16 – 7.06 (m, 2H), 6.76 (d, *J* = 5.9 Hz, 1H), 6.53 (d, *J* = 0.7 Hz, 1H), 4.79 – 4.57 (m, 2H), 4.40 (ddd, *J* = 21.0, 13.9, 7.3 Hz, 2H), 4.26 (dd, *J* = 14.9, 5.5 Hz, 1H), 3.34 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.16 (dd, *J* = 14.4, 8.3 Hz, 1H), 2.83 – 2.60 (m, 2H), 2.31 – 2.06 (m, 3H), 1.97 – 1.76 (m, 1H), 1.49 (s, 9H), 1.28 (s, 9H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.5, 171.0, 170.7, 170.4, 170.3, 163.0, 149.4, 138.4, 134.7, 134.5, 133.4, 133.3, 132.6, 129.2, 129.1, 128.9, 128.8, 128.5, 128.0, 127.9, 127.8, 127.6, 127.1, 126.9, 126.5, 126.0, 121.4, 121.3, 116.6, 116.5, 111.2, 111.1, 86.0, 81.7, 80.4, 55.6, 53.2,

53.1, 51.0, 50.9, 43.3, 37.3, 36.7, 31.9, 28.1, 28.0, 27.92, 27.88, 27.8, 27.0. MS (ESI) m/z = 960.4 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-(phenethylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (69b).** Yield, 84%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 – 7.68 (m, 4H), 7.66 – 7.58 (m, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.33 – 7.24 (m, 2H), 7.24 – 7.16 (m, 3H), 7.16 – 7.03 (m, 3H), 6.88 – 6.65 (m, 2H), 6.56 (d, *J* = 0.7 Hz, 1H), 4.81 – 4.61 (m, 2H), 4.37 – 4.20 (m, 1H), 3.57 – 3.31 (m, 3H), 3.22 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.88 – 2.64 (m, 4H), 2.13 (ddd, *J* = 11.2, 5.4, 2.5 Hz, 2H), 2.10 – 2.00 (m, 1H), 1.85 – 1.73 (m, 1H), 1.50 (s, 9H), 1.31 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.5, 171.0, 170.7, 170.35, 170.32, 163.0, 149.4, 139.1, 134.6, 134.5, 133.5, 133.2, 132.6, 129.2, 129.1, 129.0, 128.8, 128.5, 128.0, 127.9, 127.8, 127.7, 127.5, 126.90, 126.87, 126.5, 126.2, 126.1, 121.4, 121.3, 116.6, 116.5, 111.3, 111.1, 86.1, 81.7, 80.4, 55.74, 55.66, 53.3, 53.2, 51.0, 50.9, 40.9, 37.3, 36.6, 35.6, 31.9, 28.2, 28.1, 28.02, 27.97, 27.9, 27.8, 26.8. MS (ESI) m/z = 974.4 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1-((4-fluorophenyl)amino)-1,5-dioxopentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (69c).** Yield, 86%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.66 (s, 1H), 7.93 – 7.75 (m, 4H), 7.74 – 7.53 (m, 5H), 7.52 – 7.41 (m, 3H), 7.39 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.30 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.95 (t, *J* = 8.4 Hz, 2H), 6.83 (s, 1H), 6.65 (s, 1H), 4.81 (dq, *J* = 13.4, 6.9, 6.3 Hz, 2H), 4.51 (s, 1H), 3.55 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.30 (dd, *J* = 14.3, 8.6 Hz, 1H), 2.88 (qd, *J* = 16.6, 6.4 Hz, 2H), 2.52 – 2.20 (m, 3H), 2.04 – 1.95 (m, 1H), 1.58 (s, 9H), 1.39 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 171.4, 170.6, 170.2, 169.1, 163.4, 160.2, 158.2, 149.5, 134.6, 134.3, 134.29, 134.22, 133.5, 133.0, 132.7, 129.3, 129.1, 129.0, 127.9, 127.8, 127.6, 126.8, 126.7, 126.6, 126.2, 121.7, 121.6, 121.4, 116.6, 115.4, 115.2, 111.5, 86.3, 81.9, 80.5, 56.0, 53.8, 51.3, 37.2, 36.5, 32.0, 28.0, 27.96, 27.94, 26.7. MS (ESI) m/z = 964.1 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1-((3-fluorophenyl)amino)-1,5-dioxopentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (69d).** Yield, 88%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.79 (d, *J* = 24.9 Hz, 1H), 8.04 – 7.75 (m, 4H), 7.68 (d, *J* = 33.8 Hz, 4H), 7.52 – 7.35 (m, 5H), 7.30 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.18 (s, 1H), 6.75 (t, *J* = 8.0 Hz, 2H), 6.65 (s, 1H), 4.82 (s, 2H), 4.54 (s, 1H), 3.54 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.30 (dd, *J* = 14.4, 8.5 Hz, 1H), 3.05 – 2.74 (m, 2H), 2.48 – 2.19 (m, 3H), 2.09 – 1.89 (m, 1H), 1.57 (s, 9H), 1.39 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 171.3, 170.6, 170.2, 169.4, 163.3, 161.9, 149.5, 139.8, 139.7, 134.7, 134.3, 133.5, 133.0, 132.7, 129.8, 129.7, 129.3, 129.1, 129.00, 128.0, 127.8, 127.6, 126.8, 126.7, 126.5, 126.1, 121.4, 116.6, 115.3, 111.5, 110.7, 110.6, 107.4, 107.2, 86.2, 81.9, 80.5, 56.0, 53.8, 51.2, 37.3, 36.6, 31.9, 28.0, 27.9, 26.8. MS (ESI) m/z = 964.1 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1-((2-fluorophenyl)amino)-1,5-dioxopentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (69e).** Yield, 84%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 2.4 Hz, 1H), 8.11 – 7.98 (m, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.76 – 7.67 (m, 3H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.50 (dd, *J* = 21.4, 7.8 Hz, 2H), 7.41 – 7.28 (m, 4H), 7.26 – 7.15 (m, 1H), 7.10 – 6.92 (m, 3H), 6.81 (d, *J* = 6.3 Hz, 1H), 6.66 – 6.35 (m, 1H), 4.85 (dt, *J* = 7.9, 5.8 Hz, 1H), 4.80 – 4.71 (m, 1H), 4.46 (td, *J* = 8.1, 5.2 Hz, 1H), 3.43 (dd, *J* = 14.3, 5.5 Hz, 1H), 3.25 (dd, *J* = 14.3, 8.1 Hz, 1H), 2.76 (dd, *J* = 6.2, 2.2 Hz, 2H), 2.43 – 2.02 (m, 3H), 1.86 (dtd,

J = 14.4, 8.3, 6.0 Hz, 1H), 1.48 (s, 9H), 1.29 (s, 9H), 1.25 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.5, 170.9, 170.6, 170.5, 169.3, 162.9, 154.1, 152.2, 149.3, 134.8, 134.6, 133.5, 132.6, 129.10, 129.07, 128.8, 128.0, 127.7, 127.6, 127.0, 126.5, 126.4, 126.1, 126.0, 124.8 (d, *J* = 7.6 Hz), 124.2 (d, *J* = 3.7 Hz), 122.8, 121.3, 116.5, 115.1, 114.9, 111.0, 85.9, 81.7, 80.7, 55.4, 53.9, 50.3, 37.4, 36.9, 31.8, 27.98, 27.97, 27.91, 26.8. MS (ESI) m/z = 964.4 $[M + Na]^+$.

(*S*)-5-(Benzylamino)-4-((*S*)-3-carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-oxopentanoic acid (22). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.26 (s, 2H), 11.62 (d, *J* = 2.2 Hz, 1H), 8.80 (d, *J* = 8.6 Hz, 1H), 8.67 (d, *J* = 7.6 Hz, 1H), 8.36 (t, *J* = 6.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.91 – 7.73 (m, 4H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.55 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.49 – 7.37 (m, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.31 (dd, *J* = 8.1, 6.9 Hz, 2H), 7.26 – 7.18 (m, 4H), 7.15 (dd, *J* = 8.7, 2.1 Hz, 1H), 5.00 – 4.81 (m, 1H), 4.65 (td, *J* = 7.6, 6.0 Hz, 1H), 4.30 (t, *J* = 5.8 Hz, 3H), 3.28 (d, *J* = 3.5 Hz, 1H), 3.15 (dd, *J* = 13.8, 11.0 Hz, 1H), 2.81 (dd, *J* = 16.7, 6.0 Hz, 1H), 2.60 (dd, *J* = 16.7, 7.6 Hz, 1H), 2.26 (ddd, *J* = 9.2, 6.5, 3.0 Hz, 2H), 1.99 (dddd, *J* = 14.0, 9.2, 6.8, 4.9 Hz, 1H), 1.80 (dtd, *J* = 13.7, 9.0, 6.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 172.4, 172.0, 171.3, 170.9, 161.0, 139.7, 136.5, 135.2, 133.4, 133.1, 132.2, 128.7, 128.5, 128.3, 127.91, 127.90, 127.8, 127.7, 127.5, 127.2, 126.4, 125.8, 124.6, 123.9, 121.1, 114.3, 103.3, 54.8, 52.6, 50.2, 42.5, 38.0 36.4, 30.5, 27.8. HRMS (ESI) Calcd for $C_{38}H_{36}ClN_5O_8$ $(M - H)^-$ 724.2174, found 724.2178. HPLC purity 100%, t_R = 9.85 min (condition A1); 100%, t_R = 12.41 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-oxo-5-(phenethylamino)pentanoic acid (23). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.25 (s, 2H), 11.62 (d, *J* = 2.2 Hz, 1H), 8.80 (d, *J* = 8.6 Hz, 1H), 8.67 (d, *J* = 7.5 Hz, 1H), 7.92 (dd, *J* = 6.7, 4.9 Hz, 2H), 7.85 (d, *J* = 1.6 Hz, 1H), 7.83 – 7.74 (m, 3H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.27 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.22 – 7.17 (m, 4H), 7.17 – 7.09 (m, 1H), 5.00 – 4.79 (m, 1H), 4.63 (td, *J* = 7.5, 6.1 Hz, 1H), 4.21 (td, *J* = 8.2, 5.1 Hz, 1H), 3.27 (qd, *J* = 7.4, 6.7, 5.0 Hz, 3H), 3.18 – 3.05 (m, 1H), 2.79 (dd, *J* = 16.7, 6.1 Hz, 1H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.60 (dd, *J* = 16.6, 7.5 Hz, 1H), 2.20 (t, *J* = 8.0 Hz, 2H), 1.92 (dtd, *J* = 16.3, 8.0, 5.1 Hz, 1H), 1.79 – 1.65 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 172.4, 172.0, 171.0, 170.7, 161.0, 139.7, 136.5, 135.2, 133.4, 133.1, 132.2, 129.1, 128.7, 128.5, 128.3, 127.91, 127.90, 127.8, 127.7, 126.5, 126.4, 125.8, 124.6, 123.9, 121.1, 114.3, 103.3, 54.8, 52.5, 50.1, 40.7, 38.0, 36.4, 35.5, 30.4, 27.9. HRMS (ESI) Calcd for $C_{39}H_{38}ClN_5O_8$ $(M - H)^-$ 738.2331, found 738.2337. HPLC purity 99.1%, t_R = 9.96 min (condition A1); 99.5%, t_R = 12.59 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((4-fluorophenyl)amino)-5-oxopentanoic acid (24). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.31 (s, 2H), 11.80 – 11.30 (m, 1H), 9.93 (s, 1H), 8.84 (d, *J* = 8.5 Hz, 1H), 8.67 (d, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.89 – 7.73 (m, 4H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.42 (pd, *J* = 6.9, 1.6 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.18 – 7.07 (m, 3H), 4.91 (ddd, *J* = 11.7, 8.6, 3.7 Hz, 1H), 4.66 (q, *J* = 7.1 Hz, 1H), 4.39 (td, *J* = 8.2, 5.0 Hz, 1H), 3.29 (d, *J* = 3.7 Hz, 1H), 3.16 (dd, *J* = 13.9, 10.9 Hz, 1H), 2.80 (dd, *J* = 16.6, 6.1 Hz, 1H), 2.62 (dd, *J* = 16.6, 7.4 Hz, 1H), 2.31 (pt, *J* = 9.0, 4.9 Hz, 2H), 2.05 (td, *J* = 8.8, 5.0 Hz, 1H), 1.88 (ddt, *J* = 13.5, 8.7, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 172.5, 172.0, 171.2, 170.2, 161.1, 159.5, 157.6, 136.5, 135.5, 135.5, 135.2, 133.4, 133.1, 132.2, 128.5, 128.3, 127.9, 127.89, 127.85, 127.7, 126.4, 125.8, 124.6, 123.9, 121.8, 121.7, 121.1, 115.8, 115.6, 114.3, 103.3, 54.8, 53.3, 50.2, 38.0, 36.6, 30.6, 27.7.

HRMS (ESI) Calcd for $C_{37}H_{33}ClFN_5O_8$ $(M - H)^-$ 728.1923, found 728.1936. HPLC purity 95.9%, t_R = 10.03 min (condition A1); 98.6%, t_R = 12.52 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((3-fluorophenyl)amino)-5-oxopentanoic acid (25). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.31 (s, 2H), 11.62 (d, J = 2.2 Hz, 1H), 10.08 (s, 1H), 8.81 (d, J = 8.5 Hz, 1H), 8.67 (d, J = 7.5 Hz, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.93 – 7.73 (m, 4H), 7.70 (d, J = 2.1 Hz, 1H), 7.65 – 7.49 (m, 2H), 7.48 – 7.39 (m, 2H), 7.37 – 7.28 (m, 3H), 7.21 (d, J = 2.1 Hz, 1H), 7.15 (dd, J = 8.8, 2.1 Hz, 1H), 7.05 – 6.82 (m, 1H), 4.91 (ddd, J = 11.7, 8.5, 3.6 Hz, 1H), 4.67 (td, J = 7.6, 5.9 Hz, 1H), 4.41 (td, J = 8.3, 5.1 Hz, 1H), 3.30 (d, J = 3.5 Hz, 1H), 3.16 (dd, J = 13.9, 11.0 Hz, 1H), 2.81 (dd, J = 16.7, 5.8 Hz, 1H), 2.63 (dd, J = 16.7, 7.7 Hz, 1H), 2.42 – 2.20 (m, 2H), 2.05 (ddt, J = 14.7, 9.7, 5.7 Hz, 1H), 1.88 (ddt, J = 14.5, 9.1, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 172.4, 172.1, 171.2, 170.7, 163.5, 161.6, 161.1, 140.9, 140.8, 136.5, 135.2, 133.4, 133.1, 132.2, 130.9, 130.8, 128.5, 128.3, 127.9, 127.88, 127.85, 127.7, 126.4, 125.8, 124.6, 123.9, 121.1, 115.6, 114.3, 110.5, 110.4, 106.8, 106.6, 103.3, 54.8, 53.4, 50.1, 38.0, 36.4, 30.5, 27.6. HRMS (ESI) Calcd for $C_{37}H_{33}ClFN_5O_8$ $(M - H)^-$ 728.1923, found 728.1929. HPLC purity 95.6%, t_R = 10.09 min (condition A1); 97.2%, t_R = 12.61 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((2-fluorophenyl)amino)-5-oxopentanoic acid (26). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.29 (s, 2H), 11.62 (d, J = 2.2 Hz, 1H), 9.72 (s, 1H), 8.80 (d, J = 8.5 Hz, 1H), 8.67 (d, J = 7.5 Hz, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.93 – 7.74 (m, 5H), 7.70 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.6, 1.7 Hz, 1H), 7.42 (pd, J = 6.9, 1.6 Hz, 2H), 7.36 (d, J = 8.7 Hz, 1H), 7.28 – 7.01 (m, 5H), 4.91 (ddd, J = 11.8, 8.6, 3.5 Hz, 1H), 4.68 (td, J = 7.6, 5.6 Hz, 1H), 4.55 (td, J = 8.2, 5.0 Hz, 1H), 3.30 (d, J = 3.4 Hz, 1H), 3.15 (dd, J = 13.8, 11.0 Hz, 1H), 2.80 (dd, J = 16.7, 5.6 Hz, 1H), 2.61 (dd, J = 16.6, 7.8 Hz, 1H), 2.34 (dq, J = 16.6, 10.6 Hz, 2H), 2.05 (ddt, J = 14.9, 10.3, 5.5 Hz, 1H), 1.90 (ddt, J = 13.8, 8.8, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 172.2, 172.0, 171.2, 170.7, 161.0, 155.4, 153.4, 136.5, 135.2, 133.4, 133.1, 132.2, 128.5, 128.3, 127.9, 127.8, 127.7, 126.4, 126.2, 126.1, 126.0, 125.8, 125.0, 124.82, 124.79, 124.6, 123.9, 121.1, 116.1, 115.9, 114.3, 103.3, 54.8, 53.0, 50.1, 38.0, 36.4, 30.5, 27.8. HRMS (ESI) Calcd for $C_{37}H_{33}ClFN_5O_8$ $(M - H)^-$ 728.1923, found 728.1929. HPLC purity 97.1%, t_R = 9.87 min (condition A1); 99.3%, t_R = 12.31 min (condition B1).

***tert*-Butyl (*S*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((4-chlorophenyl)amino)-5-oxopentanoate (70a).** Yield, 85%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.55 – 7.41 (m, 2H), 7.40 – 7.32 (m, 2H), 7.28 (t, J = 7.5 Hz, 2H), 7.23 – 7.01 (m, 4H), 6.02 (d, J = 7.7 Hz, 1H), 4.29 (dd, J = 19.2, 7.0 Hz, 3H), 4.07 (t, J = 7.2 Hz, 1H), 2.57 – 2.37 (m, 1H), 2.29 (dt, J = 16.4, 6.7 Hz, 1H), 2.16 – 2.04 (m, 1H), 2.00 – 1.78 (m, 1H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.1, 169.9, 156.7, 143.7, 143.5, 141.3, 136.2, 129.4, 128.9, 127.8, 127.12, 127.09, 125.1, 125.0, 121.2, 120.0, 81.4, 67.4, 55.0, 47.0, 31.8, 28.1. MS (ESI) m/z = 557.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((3-chlorophenyl)amino)-5-oxopentanoate (70b).** Yield, 82%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.93 (s, 1H), 7.68 – 7.53 (m, 3H), 7.43 (dd, J = 13.0, 7.5 Hz, 2H), 7.29 – 7.18 (m, 3H), 7.15 – 7.07 (m, 2H), 7.02 (t, J = 8.1 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.14 (d, J = 7.9 Hz, 1H), 4.29 (dd, J = 42.7, 7.2 Hz, 3H), 4.13 – 3.89 (m, 1H), 2.37 (q, J = 7.9, 7.2 Hz, 1H), 2.28 (dt, J = 16.5, 6.8 Hz, 1H), 2.14 – 2.01 (m, 1H), 1.94 (h, J = 5.9, 4.6 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.0, 170.2, 156.8, 143.7, 143.5, 141.3, 138.9, 134.6, 129.9, 127.80, 127.79, 127.14, 127.10, 125.1, 125.0,

124.5, 120.1, 120.0, 117.9, 81.3, 67.5, 55.1, 47.0, 31.8, 28.1, 28.0. MS (ESI) m/z = 557.4 [M + Na]$^+$.

***tert*-Butyl (*S*)-4-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-5-((2-chlorophenyl)amino)-5-oxopentanoate (70c).** Yield, 80%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 8.21 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.32 – 7.23 (m, 3H), 7.23 – 7.10 (m, 3H), 6.95 (td, *J* = 7.7, 1.6 Hz, 1H), 5.95 (d, *J* = 7.4 Hz, 1H), 4.59 – 4.26 (m, 3H), 4.12 (t, *J* = 6.9 Hz, 1H), 2.41 (q, *J* = 8.2, 6.9 Hz, 1H), 2.30 (dt, *J* = 16.8, 6.6 Hz, 1H), 2.15 (dd, *J* = 14.5, 7.3 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.9, 169.8, 156.5, 143.8, 143.7, 141.3, 134.2, 129.1, 127.8, 127.6, 127.11, 127.09, 125.14, 125.07, 123.6, 122.0, 120.02, 120.01, 81.3, 67.3, 55.6, 47.1, 31.8, 28.10 27.5. MS (ESI) m/z = 557.3 [M + Na]$^+$.

***tert*-Butyl (*S*)-4-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((4-chlorophenyl)amino)-5-oxopentanoate (71a).** Yield, 88%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.69 (q, *J* = 6.2, 5.3 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.51 – 7.14 (m, 6H), 4.64 – 4.14 (m, 5H), 2.69 (dd, *J* = 16.2, 5.0 Hz, 1H), 2.50 (s, 1H), 2.36 – 2.16 (m, 2H), 2.00 – 1.93 (m, 1H), 1.84 (ddt, *J* = 13.6, 8.7, 4.6 Hz, 1H), 1.36 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.9, 171.3, 170.4, 169.8, 156.3, 144.3, 144.2, 141.2, 138.1, 129.1, 128.1, 127.5, 125.7, 121.4, 120.6, 80.7, 80.2, 66.2, 53.3, 51.8, 47.1, 37.9, 31.6, 31.2, 28.1, 27.5. MS (ESI) m/z = 728.3 [M + Na]$^+$.

***tert*-Butyl (*S*)-4-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((3-chlorophenyl)amino)-5-oxopentanoate (71b).** Yield, 85%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 7.87 – 7.65 (m, 4H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.40 (ddd, *J* = 9.4, 7.4, 1.8 Hz, 2H), 7.30 (tdd, *J* = 7.4, 2.4, 1.2 Hz, 2H), 7.20 (t, *J* = 8.1 Hz, 1H), 7.06 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H), 5.90 (d, *J* = 7.8 Hz, 1H), 4.72 – 4.35 (m, 4H), 4.23 (t, *J* = 6.9 Hz, 1H), 2.89 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.80 (dd, *J* = 16.9, 6.3 Hz, 1H), 2.58 – 2.49 (m, 1H), 2.38 (dt, *J* = 17.2, 6.7 Hz, 1H), 2.22 (tt, *J* = 9.0, 4.5 Hz, 1H), 2.14 – 2.07 (m, 1H), 1.44 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.0, 171.1, 170.9, 169.1, 156.2, 143.7, 143.6, 141.3, 139.1, 134.4, 129.8, 127.8, 127.1, 125.0, 124.3, 120.1, 120.0, 118.1, 82.3, 81.5, 67.4, 54.1, 51.8, 47.1, 37.4, 31.9, 29.3, 28.0, 26.5. MS (ESI) m/z = 728.3 [M + Na]$^+$.

***tert*-Butyl (*S*)-4-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((2-chlorophenyl)amino)-5-oxopentanoate (71c).** Yield, 85%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.24 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 3H), 7.48 – 7.28 (m, 5H), 7.27 – 7.19 (m, 1H), 7.04 (td, *J* = 7.7, 1.6 Hz, 1H), 5.98 (d, *J* = 8.8 Hz, 1H), 4.68 – 4.57 (m, 2H), 4.44 (d, *J* = 7.1 Hz, 2H), 4.24 (t, *J* = 7.0 Hz, 1H), 3.20 – 2.97 (m, 1H), 2.76 – 2.59 (m, 1H), 2.54 (ddd, *J* = 17.1, 8.1, 5.8 Hz, 1H), 2.39 (ddd, *J* = 17.2, 7.1, 5.7 Hz, 1H), 2.24 (ddd, *J* = 13.5, 8.4, 5.6 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.45 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.4, 171.4, 171.1, 169.1, 156.0, 143.8, 143.7, 141.32, 141.31, 134.3, 129.1, 127.8, 127.5, 127.12, 127.09, 125.1, 123.9, 122.4, 120.01, 120.00, 82.0, 81.2, 67.4, 54.1, 51.4, 47.2, 37.4, 31.6, 28.1, 28.0, 26.7. MS (ESI) m/z = 728.3 [M + Na]$^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1-((4-chlorophenyl)amino)-1,5-dioxopentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (72a).** Yield, 85%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.92 – 7.74 (m, 4H), 7.74 – 7.66 (m, 3H), 7.60 (dd, *J* = 17.5, 7.5 Hz, 2H), 7.52 – 7.46 (m, 2H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.31 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.75 (d, *J* = 5.0 Hz, 1H), 6.65 (d, *J* = 0.7 Hz, 1H), 4.78 (tt, *J* = 8.1, 3.8 Hz, 2H), 4.48 (td, *J* = 9.4, 8.8, 3.4 Hz, 1H), 3.56 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.30 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.97 – 2.77 (m, 2H), 2.40 – 2.22 (m, 3H), 2.05 – 1.84 (m, 1H), 1.58 (s,

9H), 1.39 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 171.4, 170.6, 170.2, 169.3, 163.4, 149.6, 136.9, 134.6, 134.2, 133.5, 132.9, 132.7, 129.3, 129.1, 128.9, 128.7, 127.9, 127.8, 127.6, 126.71, 126.69, 126.61, 126.2, 121.5, 121.3, 116.6, 111.5, 86.4, 81.9, 80.5, 56.2 53.8, 51.4, 37.1, 36.3, 32.0, 29.3, 28.02, 27.98, 27.93, 26.5. MS (ESI) m/z = 980.1 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1-((3-chlorophenyl)amino)-1,5-dioxopentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (72b).** Yield, 83%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 7.88 – 7.76 (m, 5H), 7.73 – 7.52 (m, 4H), 7.51 – 7.35 (m, 4H), 7.30 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.16 (t, *J* = 8.1 Hz, 1H), 7.08 – 6.96 (m, 1H), 6.86 (s, 1H), 6.65 (s, 1H), 4.88 (s, 1H), 4.85 – 4.70 (m, 1H), 4.55 (s, 1H), 3.55 (dd, *J* = 14.3, 5.3 Hz, 1H), 3.30 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.87 (qd, *J* = 16.6, 6.4 Hz, 2H), 2.48 – 2.16 (m, 3H), 2.07 – 1.87 (m, 1H), 1.57 (s, 9H), 1.39 (s, 9H), 1.31 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 171.3, 170.6, 170.2, 169.4, 163.3, 149.5, 139.4, 134.7, 134.3, 134.2, 133.5, 133.1, 132.7, 129.7, 129.3, 129.1, 129.0, 128.0, 127.8, 127.6, 126.8, 126.6, 126.5, 126.1, 124.0, 121.4, 120.0, 117.9, 116.6, 111.4, 86.2, 81.9, 80.5, 56.0, 53.8, 51.2, 37.3, 36.6, 31.9, 28.02, 27.97, 27.94, 26.8. MS (ESI) m/z = 980.4 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1-((2-chlorophenyl)amino)-1,5-dioxopentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (72c).** Yield, 82%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 8.13 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.75 – 7.66 (m, 3H), 7.66 – 7.58 (m, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.45 – 7.30 (m, 5H), 7.27 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.14 (td, *J* = 8.4, 8.0, 1.5 Hz, 1H), 6.95 (td, *J* = 7.7, 1.5 Hz, 1H), 6.78 (d, *J* = 6.3 Hz, 1H), 6.55 (s, 1H), 4.82 (dt, *J* = 8.1, 5.8 Hz, 2H), 4.47 – 4.32 (m, 1H), 3.44 (dd, *J* = 14.3, 5.6 Hz, 1H), 3.26 (dd, *J* = 14.3, 8.1 Hz, 1H), 2.86 – 2.70 (m, 2H), 2.42 – 2.06 (m, 3H), 1.89 – 1.71 (m, 1H), 1.48 (s, 9H), 1.29 (s, 9H), 1.25 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.5, 171.0, 170.6, 170.4, 169.2, 162.9, 149.3, 134.7, 134.6, 134.5, 133.49, 133.47, 132.6, 129.11, 129.09, 128.8, 128.0, 127.7, 127.6, 127.4, 127.0, 126.5, 126.4, 126.0, 125.0, 124.1, 122.6, 121.3, 116.5, 111.0, 86.0, 81.7, 80.7, 55.4, 54.1, 50.2, 37.2, 36.8, 31.7, 28.0, 27.9, 26.5. MS (ESI) m/z = 980.0 $[M + Na]^+$.

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((4-chlorophenyl)amino)-5-oxopentanoic acid (27). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.30 (s, 2H), 11.62 (d, *J* = 2.2 Hz, 1H), 10.00 (s, 1H), 8.80 (d, *J* = 8.5 Hz, 1H), 8.67 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.92 – 7.73 (m, 4H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.56 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.42 (pd, *J* = 6.9, 1.6 Hz, 2H), 7.39 – 7.29 (m, 3H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.15 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.91 (ddd, *J* = 11.8, 8.6, 3.6 Hz, 1H), 4.67 (td, *J* = 7.5, 5.8 Hz, 1H), 4.40 (td, *J* = 8.3, 5.1 Hz, 1H), 3.29 (d, *J* = 3.5 Hz, 1H), 3.16 (dd, *J* = 13.9, 11.0 Hz, 1H), 2.80 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.63 (dd, *J* = 16.7, 7.7 Hz, 1H), 2.40 – 2.18 (m, 2H), 2.04 (ddt, *J* = 14.9, 10.7, 5.7 Hz, 1H), 1.88 (ddt, *J* = 13.4, 8.7, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 172.4, 172.1, 171.1, 170.5, 161.1, 138.1, 136.5, 135.2, 133.4, 133.1, 132.2, 129.1, 128.5, 128.3, 127.9, 127.89, 127.86, 127.8, 127.6, 126.4, 125.8, 124.6, 123.9, 121.5, 121.1, 114.3, 103.3, 54.8, 53.4, 50.1, 38.0, 36.4, 30.5, 27.6. HRMS (ESI) Calcd for $C_{37}H_{33}Cl_2N_5O_8$ $(M - H)^-$ 744.1628, found 744.1632. HPLC purity 96.3%, t_R = 10.30 min (condition A1); 98.5%, t_R = 12.93 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((3-chlorophenyl)amino)-5-oxopentanoic acid (28). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.31 (s, 2H), 11.73 – 11.41 (m, 1H), 10.06 (s, 1H), 8.80 (d, *J* =

8.5 Hz, 1H), 8.67 (d, *J* = 7.5 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.93 – 7.73 (m, 5H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.60 – 7.50 (m, 1H), 7.52 – 7.22 (m, 5H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.14 (ddd, *J* = 10.7, 8.4, 2.2 Hz, 2H), 4.91 (ddd, *J* = 11.9, 8.6, 3.8 Hz, 1H), 4.67 (q, *J* = 7.1 Hz, 1H), 4.40 (td, *J* = 8.2, 5.2 Hz, 1H), 3.30 (d, *J* = 3.6 Hz, 1H), 3.16 (dd, *J* = 13.9, 11.0 Hz, 1H), 2.80 (dd, *J* = 16.7, 5.8 Hz, 1H), 2.63 (dd, *J* = 16.6, 7.8 Hz, 1H), 2.32 (dq, *J* = 16.5, 10.4 Hz, 2H), 2.04 (ddt, *J* = 15.0, 10.7, 5.8 Hz, 1H), 1.89 (dtd, *J* = 14.5, 9.1, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.2, 172.3, 172.1, 171.2, 170.7, 161.1, 140.5, 136.5, 135.2, 133.5, 133.4, 133.1, 132.2, 130.9, 128.5, 128.3, 127.9, 127.88, 127.76, 126.4, 125.8, 124.6, 123.9, 123.7, 121.1, 119.4, 118.3, 114.3, 103.3, 54.8, 53.4, 50.2, 38.0, 36.4, 30.5, 27.5. HRMS (ESI) Calcd for $C_{37}H_{33}Cl_2N_5O_8$ $(M - H)^-$ 744.1628, found 744.1627. HPLC purity 97.5%, t_R = 10.35 min (condition A1); 99.0%, t_R = 12.92 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((2-chlorophenyl)amino)-5-oxopentanoic acid (29). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.51 – 12.07 (m, 2H), 11.85 – 11.18 (m, 1H), 9.51 (s, 1H), 8.80 (d, *J* = 8.5 Hz, 1H), 8.68 (d, *J* = 7.6 Hz, 1H), 8.20 (d, *J* = 7.7 Hz, 1H), 8.02 – 7.62 (m, 6H), 7.62 – 7.26 (m, 6H), 7.25 – 6.85 (m, 3H), 4.91 (ddd, *J* = 11.9, 8.4, 3.6 Hz, 1H), 4.70 (q, *J* = 7.1 Hz, 1H), 4.54 (td, *J* = 8.2, 4.9 Hz, 1H), 3.32 – 3.27 (m, 1H), 3.16 (dd, *J* = 13.9, 11.0 Hz, 1H), 2.81 (dd, *J* = 16.7, 5.7 Hz, 1H), 2.62 (dd, *J* = 16.7, 7.8 Hz, 1H), 2.36 (tq, *J* = 16.7, 8.8, 7.1 Hz, 2H), 2.09 (ddt, *J* = 15.0, 10.5, 5.7 Hz, 1H), 1.92 (dq, *J* = 13.6, 5.7, 3.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.4, 172.2, 172.0, 171.3, 170.6, 161.0, 136.5, 135.2, 134.9, 133.4, 133.1, 132.2, 129.9, 128.5, 128.3, 127.94, 127.90, 127.8, 127.7, 127.1, 127.0, 126.5, 126.4, 125.8, 124.6, 123.9, 121.1, 114.3, 103.3, 54.8, 53.1, 50.1, 38.0, 36.5, 30.5, 27.6. HRMS (ESI) Calcd for $C_{37}H_{33}Cl_2N_5O_8$ $(M - H)^-$ 744.1628, found 744.1632. HPLC purity 96.7%, t_R = 9.99 min (condition A1); 99.2%, t_R = 12.46 min (condition B1).

***tert*-Butyl (5*S*,8*S*,11*S*)-8-(2-(*tert*-butoxy)-2-oxoethyl)-5-isobutyl-3,6,9-trioxo-1-phenyl-11-(phenylcarbamoyl)-2-oxa-4,7,10-triazatetradecan-14-oate (73).** Yield, 84%. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 9.84 (s, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.23 (m, 7H), 7.12 – 6.93 (m, 1H), 5.02 (q, *J* = 12.6 Hz, 2H), 4.57 (td, *J* = 7.9, 5.8 Hz, 1H), 4.38 (td, *J* = 8.3, 5.1 Hz, 1H), 4.04 (ddd, *J* = 9.3, 7.6, 5.7 Hz, 1H), 2.73 (dd, *J* = 16.1, 5.8 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.35 – 2.16 (m, 2H), 2.06 – 1.93 (m, 1H), 1.89 – 1.79 (m, 1H), 1.69 – 1.59 (m, 1H), 1.52 – 1.42 (m, 2H), 0.86 (dd, *J* = 9.6, 6.6 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 173.0, 171.9, 170.7, 170.1, 169.9, 156.5, 139.1, 137.4, 129.2, 128.8, 128.3, 128.2, 124.0, 119.8, 80.7, 80.2, 65.9, 53.7, 53.2, 50.1, 41.1, 37.4, 31.6, 28.2, 28.1, 27.7, 24.6, 23.4, 22.0. MS (ESI) m/z = 719.2 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-4-methylpentanamido)-4-oxobutanamido)-5-oxo-5-(phenylamino)pentanoate (74).** Yield, 88%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.97 (s, 1H), 9.00 (s, 1H), 8.65 (s, 1H), 8.54 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 3H), 7.50 (s, 1H), 7.35 – 7.25 (m, 1H), 7.25 – 7.15 (m, 3H), 7.12 – 6.99 (m, 2H), 5.04 (d, *J* = 39.7 Hz, 2H), 4.80 (s, 1H), 3.14 – 2.75 (m, 2H), 2.47 (q, *J* = 8.6, 7.9 Hz, 3H), 2.38 – 2.23 (m, 1H), 1.85 (dtd, *J* = 36.5, 12.4, 11.5, 6.7 Hz, 3H), 1.47 (s, 9H), 1.21 (s, 9H), 1.02 (dd, *J* = 18.9, 5.9 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.4, 172.7, 171.5, 170.4, 169.9, 162.2, 137.7, 135.5, 131.0, 128.7, 128.2, 126.0, 125.0, 124.5, 121.1, 120.6, 113.6, 104.0, 81.8, 81.2, 54.1, 53.2, 50.3, 41.6, 37.0, 32.6, 28.1, 27.8, 27.7, 25.2, 22.6, 22.5. MS (ESI) m/z = 762.1 $[M + Na]^+$.

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-4-methylpentanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (39). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.19 (s, 2H), 11.66 (d, *J* = 2.2 Hz, 1H), 9.75 (s, 1H), 8.53 (d, *J* = 8.1 Hz,

1H), 8.40 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.31 – 7.17 (m, 3H), 7.12 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.08 – 6.90 (m, 1H), 4.72 – 4.42 (m, 2H), 4.31 (dt, *J* = 8.4, 4.3 Hz, 1H), 2.71 (dd, *J* = 16.7, 6.2 Hz, 1H), 2.51 (dd, *J* = 16.7, 7.5 Hz, 1H), 2.20 (td, *J* = 10.4, 6.0 Hz, 2H), 2.07 – 1.92 (m, 1H), 1.79 (dt, *J* = 10.1, 5.3 Hz, 1H), 1.71 – 1.57 (m, 2H), 1.54 – 1.44 (m, 1H), 0.84 (dd, *J* = 13.6, 6.2 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 172.9, 172.4, 171.0, 170.2, 161.2, 139.1, 135.3, 133.2, 129.2, 128.5, 124.7, 124.0 (d, *J* = 3.5 Hz), 121.1, 119.9, 114.3, 103.6, 53.3, 51.8, 50.0, 40.9, 36.1, 30.5, 27.8, 24.8, 23.5, 21.9. HRMS (ESI) Calcd for $C_{30}H_{34}ClN_5O_8$ $(M-H)^-$ 626.2018, found 626.2014. HPLC purity 98.3%, t_R = 13.38 min (condition A2); 99.0%, t_R = 15.96 min (condition B2).

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-(phenylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(3,4-dichlorophenyl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (75a).** Yield, 82%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.52 (s, 1H), 8.44 (s, 2H), 7.89 (d, *J* = 8.9 Hz, 1H), 7.53 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.09 (m, 6H), 6.80 (d, *J* = 22.8 Hz, 4H), 5.58 – 4.98 (m, 3H), 3.36 (td, *J* = 19.5, 16.8, 7.8 Hz, 2H), 2.89 – 2.70 (m, 2H), 2.58 – 1.93 (m, 4H), 1.51 (s, 9H), 1.41 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 170.6, 170.1, 169.8, 169.2, 162.4, 148.7, 137.7, 136.6, 135.0, 134.7, 132.3, 131.8, 131.0, 130.5, 129.0, 128.9, 128.8, 128.4, 126.3, 123.8, 121.3, 119.3, 116.2, 111.5, 85.2, 81.5, 80.7, 54.2, 53.3, 49.6, 38.8, 38.1, 31.9, 29.1, 28.1, 27.9, 27.8. MS (ESI) m/z = 964.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-(phenylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(4-chlorophenyl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (75b).** Yield, 89%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.16 (s, 1H), 8.08 (s, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.40 – 7.04 (m, 10H), 6.96 – 6.78 (m, 3H), 6.68 (s, 1H), 5.28 – 4.76 (m, 3H), 3.27 (dd, *J* = 14.1, 6.3 Hz, 1H), 3.15 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.84 – 2.53 (m, 2H), 2.36 (dd, *J* = 9.7, 6.4 Hz, 2H), 2.28 – 2.17 (m, 1H), 2.09 – 2.05 (m, 1H), 1.47 (s, 9H), 1.30 (s, 9H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 170.6, 170.3, 169.9, 169.1, 162.6, 149.0, 137.9, 135.1, 134.62, 134.59, 133.0, 130.8, 128.99, 128.96, 128.9, 128.5, 126.5, 123.9, 121.3, 119.5, 116.4, 111.4, 85.5, 81.6, 80.7, 54.7, 53.4, 49.9, 38.2, 38.0, 31.9, 28.5, 28.0, 27.94, 27.88. MS (ESI) m/z = 930.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-(phenylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(2-chlorophenyl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (75c).** Yield, 87%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.17 (s, 1H), 8.16 (s, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.37 – 7.04 (m, 10H), 6.78 (s, 3H), 6.67 (s, 1H), 5.51 – 4.79 (m, 3H), 3.43 (dd, *J* = 14.2, 6.4 Hz, 1H), 3.32 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.88 – 2.61 (m, 2H), 2.36 (s, 2H), 2.19 (t, *J* = 8.1 Hz, 1H), 2.07 (d, *J* = 6.9 Hz, 1H), 1.44 (s, 9H), 1.29 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 170.4, 170.3, 169.8, 169.2, 162.6, 149.0, 137.9, 135.1, 134.7, 134.4, 134.2, 131.8, 129.7, 129.0, 128.9, 128.8, 128.4, 127.2, 126.4, 123.8, 121.3, 119.4, 116.4, 111.3, 85.4, 81.4, 80.4, 54.2, 53.2, 50.0, 38.3, 36.1, 31.8, 28.5, 28.0, 27.9, 27.8. MS (ESI) m/z = 930.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-(phenylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-1-oxo-3-(4-(trifluoromethyl)phenyl)propan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (75d).** Yield, 84%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.51 – 8.25 (m, 2H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.02 (m, 6H), 6.71 (d, *J* = 26.1 Hz, 4H), 5.70 – 4.91 (m, 3H), 3.37 (dd, *J* = 14.2, 5.7 Hz, 1H), 3.25 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.73 (dt, *J* = 38.6, 11.1 Hz, 2H), 2.48 – 2.18 (m, 3H), 2.12 – 2.03 (m, 1H), 1.39 (s, 9H), 1.28 (s, 9H), 1.18 (s,

9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.0, 170.8, 170.3, 169.7, 169.3, 162.5, 148.7, 140.6, 137.8, 135.1, 134.7, 130.0, 128.9, 128.8, 128.4, 126.3, 125.5 (d, *J* = 3.6 Hz), 125.3, 123.9, 123.2, 121.3, 119.4, 116.2, 111.5, 85.2, 81.4, 80.7, 54.2, 53.2, 49.6, 38.7, 31.8, 29.0, 28.2, 27.9, 27.8, 27.7. MS (ESI) m/z = 964.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-(phenylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(4-cyanophenyl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (75e).** Yield, 87%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.80 – 8.38 (m, 2H), 7.79 – 7.71 (m, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.25 – 6.87 (m, 5H), 6.79 – 6.37 (m, 5H), 5.21 (s, 3H), 3.51 – 3.24 (m, 2H), 2.94 – 2.63 (m, 2H), 2.50 – 2.24 (m, 3H), 2.17 – 2.11 (m, 1H), 1.39 (s, 9H), 1.33 (s, 9H), 1.17 (dd, *J* = 4.9, 2.5 Hz, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.1, 170.8, 170.5, 170.1, 169.61, 169.2, 162.5, 148.5, 142.1, 137.7, 134.9, 134.7, 132.4, 130.5, 128.9, 128.7, 128.4, 123.9, 121.3, 119.1, 118.8, 116.1, 111.5, 110.9, 85.1, 81.4, 81.0, 53.8, 53.1, 49.4, 39.2, 31.8, 29.7, 29.3, 28.0, 27.9, 27.8. MS (ESI) m/z = 921.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-(phenylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (75f).** Yield, 88%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.48 (dd, *J* = 45.3, 4.2 Hz, 3H), 7.26 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.13 – 7.04 (m, 2H), 7.02 – 6.91 (m, 1H), 6.86 – 6.73 (m, 2H), 6.63 (d, *J* = 0.7 Hz, 2H), 4.73 (td, *J* = 7.3, 5.3 Hz, 1H), 4.64 (dd, *J* = 8.1, 5.5 Hz, 1H), 4.48 (td, *J* = 8.6, 3.7 Hz, 1H), 3.70 (s, 3H), 3.25 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.01 (dd, *J* = 14.4, 8.3 Hz, 1H), 2.80 (qd, *J* = 16.5, 6.4 Hz, 2H), 2.33 – 2.13 (m, 3H), 2.04 – 1.85 (m, 1H), 1.54 (s, 9H), 1.33 (s, 9H), 1.23 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.4, 171.2, 170.6, 170.3, 169.1, 163.2, 159.0, 149.5, 138.2, 134.7, 134.4, 130.1, 129.3, 129.1, 128.7, 127.4, 126.6, 124.0, 121.4, 120.0, 116.6, 114.5, 111.2, 86.2, 81.8, 80.5, 56.1, 55.2, 53.8, 51.1, 36.7, 36.3, 32.0, 28.03, 27.99, 27.95, 26.89. MS (ESI) m/z = 926.3 $[M + Na]^+$.

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(3,4-dichlorophenyl)propanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (40). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.30 (s, 2H), 11.69 (s, 1H), 9.86 (s, 1H), 8.77 (d, *J* = 8.6 Hz, 1H), 8.62 (d, *J* = 7.6 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.80 – 7.55 (m, 4H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.42 – 7.25 (m, 4H), 7.24 – 7.12 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.80 (ddd, *J* = 11.9, 8.6, 3.6 Hz, 1H), 4.64 (q, *J* = 7.1 Hz, 1H), 4.41 (td, *J* = 8.2, 4.9 Hz, 1H), 3.13 (dd, *J* = 13.9, 3.5 Hz, 1H), 3.05 – 2.89 (m, 1H), 2.78 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.60 (dd, *J* = 16.7, 7.7 Hz, 1H), 2.31 (pt, *J* = 10.6, 4.5 Hz, 2H), 2.04 (ddt, *J* = 15.2, 10.7, 5.8 Hz, 1H), 1.88 (qd, *J* = 8.8, 4.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 172.3, 171.6, 171.0, 170.2, 161.1, 140.0, 139.1, 135.3, 132.9, 131.7, 131.0, 130.6, 130.1, 129.4, 129.2, 128.5, 124.7, 124.0, 121.1, 119.9, 114.3, 103.3, 54.3, 53.3, 50.1, 36.9, 36.5, 30.6, 27.8. HRMS (ESI) Calcd for $C_{33}H_{30}Cl_3N_5O_8$ $(M-H)^-$ 728.1082, 730.1052, found 728.1092, 730.1069. HPLC purity 98.1%, t_R = 14.15 min (condition A2); 99.0%, t_R = 16.80 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-chlorophenyl)propanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (41). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.30 (s, 2H), 11.96 – 11.32 (m, 1H), 9.85 (s, 1H), 8.75 (d, *J* = 8.6 Hz, 1H), 8.62 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 2H), 7.39 (dd, *J* = 8.5, 5.9 Hz, 3H), 7.29 (d, *J* = 8.0 Hz, 4H), 7.23 – 7.12 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.78 (ddd, *J* = 11.8, 8.6, 3.7 Hz, 1H), 4.64 (q, *J* = 7.1 Hz, 1H), 4.41 (td, *J* = 8.3, 5.0 Hz, 1H), 3.12 (dd, *J* = 13.9, 3.7 Hz, 1H), 2.97 (dd, *J* = 13.8, 11.1 Hz, 1H), 2.78 (dd, *J* = 16.7,

5.9 Hz, 1H), 2.60 (dd, *J* = 16.7, 7.7 Hz, 1H), 2.30 (pd, *J* = 16.5, 7.4 Hz, 2H), 2.04 (td, *J* = 9.1, 4.9 Hz, 1H), 1.87 (dtd, *J* = 14.5, 9.3, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.3, 172.3, 171.9, 171.0, 170.2, 161.0, 139.1, 137.8, 135.3, 133.0, 131.5, 131.4, 129.2, 128.5, 128.4, 124.7, 123.99, 123.98, 121.1, 119.9, 114.3, 103.3, 54.6, 53.3, 50.1, 37.1, 36.4, 30.5, 27.8. HRMS (ESI) Calcd for $C_{33}H_{31}Cl_2N_5O_8$ $(M - H)^-$ 694.1471, found 694.1470. HPLC purity 98.5%, t_R = 13.80 min (condition A2); 99.7%, t_R = 16.35 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(2-chlorophenyl)propanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (42). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.26 (s, 2H), 11.68 (s, 1H), 9.83 (s, 1H), 8.78 (d, *J* = 8.5 Hz, 1H), 8.47 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.71 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.49 – 7.36 (m, 3H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.24 – 7.14 (m, 4H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.90 (td, *J* = 9.6, 4.2 Hz, 1H), 4.64 (q, *J* = 7.0 Hz, 1H), 4.39 (td, *J* = 8.1, 4.9 Hz, 1H), 3.32 (m, 1H), 3.13 (dd, *J* = 14.4, 10.6 Hz, 1H), 2.78 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.62 (dd, *J* = 16.6, 7.3 Hz, 1H), 2.30 (tq, *J* = 16.5, 6.7, 5.4 Hz, 2H), 2.03 (ddq, *J* = 17.0, 11.9, 5.9 Hz, 1H), 1.87 (dq, *J* = 8.7, 4.5, 3.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.3, 172.4, 171.5, 170.9, 170.2, 161.1, 139.1, 135.9, 135.3, 133.9, 133.0, 131.8, 129.5, 129.2, 128.7, 128.5, 127.3, 124.7, 124.01, 123.97, 121.1, 119.9, 114.3, 103.4, 53.4, 52.7, 50.2, 36.3, 35.3, 30.6, 27.7. HRMS (ESI) Calcd for$C_{33}H_{31}Cl_2N_5O_8$ $(M - H)^-$ 694.1471, found 694.1477. HPLC purity 96.4%, t_R = 13.66 min (condition A2); 97.6%, t_R = 16.11 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-(trifluoromethyl)phenyl)propanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (43). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.27 (s, 2H), 11.67 (d, *J* = 2.2 Hz, 1H), 9.86 (s, 1H), 8.80 (d, *J* = 8.6 Hz, 1H), 8.66 (d, *J* = 7.6 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.60 (q, *J* = 8.3 Hz, 6H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.17 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.85 (ddd, *J* = 11.9, 8.6, 3.6 Hz, 1H), 4.66 (td, *J* = 7.5, 5.9 Hz, 1H), 4.42 (td, *J* = 8.3, 5.0 Hz, 1H), 3.22 (dd, *J* = 13.8, 3.6 Hz, 1H), 3.08 (dd, *J* = 13.8, 11.1 Hz, 1H), 2.79 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.61 (dd, *J* = 16.7, 7.6 Hz, 1H), 2.39 – 2.22 (m, 2H), 2.08 – 1.98 (m, 1H), 1.90 – 1.80 (m, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.3, 172.3, 171.7, 171.0, 170.2, 161.1, 143.7, 139.1, 135.3, 133.0, 130.4, 129.2, 128.5, 127.5 (d, *J* = 31.7 Hz), 125.3 (d, *J* = 4.2 Hz), 124.8 (d, *J* = 270.0 Hz), 124.7, 124.0, 121.1, 119.9, 114.3, 103.4, 54.3, 53.3, 50.2, 37.5, 36.4, 30.5, 27.8. HRMS (ESI) Calcd for $C_{34}H_{31}ClF_3N_5O_8$ $(M - H)^-$ 728.1735, found 728.1733. HPLC purity 95.3%, t_R = 14.00 min (condition A2); 95.1%, t_R = 16.44 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-cyanophenyl)propanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (44). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.28 (s, 2H), 11.67 (d, *J* = 2.2 Hz, 1H), 9.85 (s, 1H), 8.80 (d, *J* = 8.7 Hz, 1H), 8.64 (d, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.83 – 7.66 (m, 3H), 7.58 (ddd, *J* = 18.4, 7.5, 1.6 Hz, 4H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.30 (dd, *J* = 8.5, 7.4 Hz, 2H), 7.23 – 7.14 (m, 2H), 7.06 (dd, *J* = 8.1, 6.7 Hz, 1H), 4.84 (ddd, *J* = 12.0, 8.8, 3.6 Hz, 1H), 4.65 (td, *J* = 7.6, 5.9 Hz, 1H), 4.41 (td, *J* = 8.3, 5.1 Hz, 1H), 3.21 (dd, *J* = 13.8, 3.6 Hz, 1H), 3.07 (dd, *J* = 13.7, 11.1 Hz, 1H), 2.79 (dd, *J* = 16.7, 5.9 Hz, 1H), 2.61 (dd, *J* = 16.7, 7.7 Hz, 1H), 2.31 (dq, *J* = 16.6, 10.5 Hz, 2H), 2.04 (td, *J* = 9.0, 5.0 Hz, 1H), 1.88 (ddt, *J* = 13.5, 8.7, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.3, 172.3, 171.6, 171.0, 170.2, 161.1, 144.8, 139.1, 135.3, 132.9, 132.4, 130.7, 129.2, 128.5, 124.7, 124.0, 121.1, 119.9, 119.4, 114.3, 109.7, 103.4, 54.2, 53.3, 50.2, 37.8, 36.4, 30.5, 27.8. HRMS (ESI) Calcd for $C_{34}H_{31}ClN_6O_8$ $(M - H)^-$ 685.1814, found 685.1812. HPLC purity 97.1%, t_R = 13.02 min (condition A2); 96.7%, t_R = 15.12 min (condition B2).

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-methoxyphenyl)propanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (45). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.27 (s, 2H), 11.66 (s, 1H), 9.84 (s, 1H), 8.69 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 7.6 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.79 – 7.65 (m, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.7 Hz, 1H), 7.34 – 7.23 (m, 4H), 7.22 – 7.11 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 8.2 Hz, 2H), 4.72 (ddd, J = 11.8, 8.3, 3.6 Hz, 1H), 4.64 (q, J = 7.1 Hz, 1H), 4.41 (td, J = 8.3, 5.1 Hz, 1H), 3.66 (s, 3H), 3.06 (dd, J = 13.9, 3.7 Hz, 1H), 2.92 (dd, J = 14.0, 10.9 Hz, 1H), 2.78 (dd, J = 16.6, 6.1 Hz, 1H), 2.60 (dd, J = 16.7, 7.5 Hz, 1H), 2.30 (td, J = 10.0, 6.1 Hz, 2H), 2.04 (td, J = 9.2, 5.1 Hz, 1H), 1.87 (dt, J = 15.0, 4.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 172.4, 172.2, 171.0, 170.2, 161.0, 158.2, 139.1, 135.3, 133.2, 130.6, 130.5, 129.2, 128.5, 124.6, 124.0, 123.9, 121.1, 119.9, 114.3, 113.9, 103.3, 55.3, 55.1, 53.3, 50.1, 36.9, 36.4, 30.5, 27.8. HRMS (ESI) Calcd for $C_{34}H_{34}ClN_5O_9$ $(M - H)^-$ 690.1967, found 690.1963. HPLC purity 99.3%, t_R = 13.27 min (condition A2); 98.3%, t_R = 15.62 min (condition B2).

***tert*-Butyl (5*S*,8*S*,11*S*)-8-(2-(*tert*-butoxy)-2-oxoethyl)-5-(naphthalen-1-ylmethyl)-3,6,9-trioxo-1-phenyl-11-(phenylcarbamoyl)-2-oxa-4,7,10-triazatetradecan-14-oate (76).** Yield, 79%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.89 – 7.79 (m, 1H), 7.77 – 7.66 (m, 2H), 7.64 – 7.51 (m, 3H), 7.39 – 7.26 (m, 2H), 7.25 – 7.05 (m, 9H), 7.02 – 6.84 (m, 1H), 6.10 – 5.65 (m, 1H), 4.87 (s, 2H), 4.67 (dt, J = 21.2, 5.7 Hz, 2H), 4.50 (td, J = 8.9, 8.4, 4.2 Hz, 1H), 3.63 (dd, J = 14.4, 4.8 Hz, 1H), 3.26 (dd, J = 14.4, 9.1 Hz, 1H), 2.74 (dd, J = 17.3, 4.6 Hz, 1H), 2.56 – 2.39 (m, 1H), 2.17 (dt, J = 12.9, 6.6 Hz, 3H), 1.88 (d, J = 17.7 Hz, 1H), 1.25 (d, J = 6.9 Hz, 18H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.3, 172.2, 170.9, 170.7, 169.4, 156.8, 138.2, 135.8, 134.0, 132.2, 131.9, 129.0, 128.8, 128.5, 128.3, 128.2, 127.7, 126.6, 125.9, 125.4, 124.2, 123.4, 120.2, 82.1, 80.5, 67.4, 56.4, 53.7, 50.3, 36.7, 35.4, 31.9, 28.1, 28.0, 27.1. MS (ESI) m/z = 803.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-1-yl)propanamido)-4-oxobutanamido)-5-oxo-5-(phenylamino)pentanoate (77).** Yield, 83%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.70 (s, 1H), 8.70 (s, 1H), 8.25 (s, 1H), 8.09 (d, J = 7.3 Hz, 1H), 7.90 – 7.77 (m, 1H), 7.56 (dd, J = 27.2, 8.7 Hz, 4H), 7.48 – 7.40 (m, 1H), 7.30 – 7.05 (m, 9H), 6.97 (t, J = 7.4 Hz, 1H), 6.64 (s, 1H), 5.06 – 4.90 (m, 1H), 4.80 – 4.66 (m, 1H), 4.47 (dt, J = 9.1, 5.0 Hz, 1H), 3.68 (dd, J = 14.5, 5.9 Hz, 1H), 3.30 (dd, J = 14.2, 8.6 Hz, 1H), 2.77 – 2.54 (m, 2H), 2.35 (ddt, J = 17.3, 13.7, 4.7 Hz, 3H), 2.16 (d, J = 8.6 Hz, 1H), 1.34 (s, 9H), 1.08 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.8, 171.9, 171.0, 170.7, 169.4, 162.3, 137.8, 135.6, 133.9, 132.1, 131.7, 130.6, 128.9, 128.8, 128.3, 128.1, 127.5, 126.5, 126.0, 125.8, 125.23, 125.16, 124.4, 123.0, 121.0, 120.4, 113.7, 103.0, 82.2, 81.4, 55.2, 54.4, 50.3, 36.9, 35.0, 32.6, 28.1, 27.8, 27.5. MS (ESI) m/z = 846.4 $[M + Na]^+$.

(*S*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-1-yl)propanamido)propanamido)-5-oxo-5-(phenylamino)pentanoic acid (46). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.27 (s, 2H), 11.62 (d, J = 2.2 Hz, 1H), 9.86 (s, 1H), 8.83 (d, J = 8.4 Hz, 1H), 8.67 (d, J = 7.5 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.89 (dd, J = 8.3, 1.4 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.64 – 7.47 (m, 5H), 7.42 – 7.33 (m, 2H), 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 1H), 7.16 (dd, J = 8.7, 2.1 Hz, 1H), 7.11 – 7.02 (m, 1H), 4.96 (ddd, J = 10.7, 8.4, 3.9 Hz, 1H), 4.69 (td, J = 7.5, 5.9 Hz, 1H), 4.43 (td, J = 8.3, 5.1 Hz, 1H), 3.70 (dd, J = 14.4, 3.8 Hz, 1H), 3.42 (dd, J = 14.5, 10.6 Hz, 1H), 2.82 (dd, J = 16.7, 5.9 Hz, 1H), 2.65 (dd, J = 16.7, 7.6 Hz, 1H), 2.40 – 2.24 (m, 2H), 2.16 – 2.01 (m, 1H), 1.91 (ddt, J = 13.7, 8.7, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 172.4, 172.0, 171.0, 170.3, 161.1, 139.1, 135.2, 134.3, 133.8, 133.0, 132.1, 129.2, 129.0, 128.5, 127.7, 127.5, 126.6, 126.0, 125.8, 124.7,

124.3, 123.99, 123.96, 121.1, 119.9, 114.3, 103.4, 53.8, 53.3, 50.3, 36.3, 34.9, 30.6, 27.8. HRMS (ESI) Calcd for $C_{37}H_{34}ClN_5O_8$ $(M - H)^-$ 710.2018, found 710.2016. HPLC purity 96.0%, t_R = 14.00 min (condition A2); 95.6%, t_R = 16.66 min (condition B2).

***tert*-Butyl (*R*)-4-(((benzyloxy)carbonyl)amino)-5-((3-methoxyphenyl)amino)-5-oxopentanoate (78).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 7.34 – 7.12 (m, 6H), 7.06 (t, *J* = 8.2 Hz, 1H), 6.90 – 6.70 (m, 1H), 6.55 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.95 (d, *J* = 8.0 Hz, 1H), 5.00 (q, *J* = 12.3 Hz, 2H), 4.33 (q, *J* = 7.3 Hz, 1H), 3.65 (s, 3H), 2.37 (td, *J* = 9.3, 4.8 Hz, 1H), 2.28 (dt, *J* = 16.6, 6.9 Hz, 1H), 2.12 – 2.03 (m, 1H), 2.01 – 1.85 (m, 1H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.9, 169.9, 160.1, 156.6, 138.9, 136.1, 129.6, 128.5, 128.2, 128.0, 112.1, 110.5, 105.5, 81.2, 67.2, 55.2, 31.8, 28.1. MS (ESI) m/z = 443.2 $[M + H]^+$, MS (ESI) m/z = 465.3 $[M + Na]^+$.

***tert*-Butyl (*R*)-4-((*S*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoate (79a).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.65 (s, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.50 – 7.27 (m, 6H), 7.24 – 6.97 (m, 2H), 6.63 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H), 5.89 (d, *J* = 8.7 Hz, 1H), 5.19 – 5.01 (m, 2H), 4.64 – 4.33 (m, 2H), 3.76 (s, 3H), 3.05 (dd, *J* = 17.3, 5.0 Hz, 1H), 2.69 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.54 – 2.42 (m, 1H), 2.36 (dt, *J* = 17.2, 6.5 Hz, 1H), 2.26 – 2.13 (m, 1H), 2.12 – 2.04 (m, 1H), 1.42 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.6, 171.3, 171.2, 169.0, 160.0, 156.2, 139.0, 135.9, 129.3, 128.6, 128.3, 128.2, 112.5, 110.3, 105.9, 82.2, 81.2, 67.5, 55.3, 53.8, 51.6, 37.4, 31.9, 28.0, 28.0, 26.6. MS (ESI) m/z = 614.4 $[M + H]^+$, MS (ESI) m/z = 636.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*R*)-2-(((benzyloxy)carbonyl)amino)-4-(*tert*-butoxy)-4-oxobutanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoate (79b).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.60 (s, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.47 – 7.30 (m, 6H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.64 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1H), 5.80 (d, *J* = 8.9 Hz, 1H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 4.56 (ddd, *J* = 12.5, 8.4, 4.6 Hz, 2H), 3.79 (s, 3H), 3.10 (dd, *J* = 17.4, 4.8 Hz, 1H), 2.69 (dd, *J* = 17.4, 5.0 Hz, 1H), 2.56 – 2.41 (m, 1H), 2.38 (ddd, *J* = 17.1, 7.2, 5.2 Hz, 1H), 2.28 – 2.13 (m, 1H), 2.09 (dd, *J* = 14.3, 7.0 Hz, 1H), 1.44 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.8, 171.4, 171.2, 169.0, 160.0, 156.1, 138.9, 135.8, 129.3, 128.6, 128.4, 128.2, 112.5, 110.3, 105.9, 82.3, 81.3, 67.6, 55.3, 53.9, 51.6, 37.4, 32.0, 28.04, 27.97, 26.5. MS (ESI) m/z = 614.4 $[M + H]^+$, MS (ESI) m/z = 636.3 $[M + Na]^+$.

***tert*-Butyl (5*S*,8*S*,11*R*)-8-(2-(*tert*-butoxy)-2-oxoethyl)-11-((3-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazatetradecan-14-oate (80a).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 7.84 (s, 1H), 7.57 – 7.34 (m, 5H), 7.13 (dq, *J* = 13.1, 7.1, 6.1 Hz, 8H), 7.03 (d, *J* = 7.0 Hz, 2H), 6.91 – 6.79 (m, 1H), 6.79 – 6.69 (m, 1H), 6.45 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.23 – 4.60 (m, 5H), 3.51 (d, *J* = 7.1 Hz, 3H), 3.17 (dd, *J* = 14.0, 4.6 Hz, 1H), 3.10 – 2.89 (m, 2H), 2.75 (s, 1H), 2.19 (dt, *J* = 56.9, 7.5 Hz, 3H), 1.92 (d, *J* = 5.4 Hz, 1H), 1.32 (s, 9H), 1.27 (d, *J* = 11.9 Hz, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.2, 171.3, 170.8, 169.3, 159.9, 156.8, 139.1, 135.8, 133.6, 133.3, 132.4, 129.3, 128.5, 128.1, 127.8, 127.6, 127.4, 127.1, 126.1, 125.6, 112.1, 109.9, 105.5, 81.8, 80.5, 67.2, 56.3, 55.1, 53.5, 53.3, 49.5, 39.5, 38.2, 31.7, 28.1, 28.0. MS (ESI) m/z = 811.4 $[M + H]^+$, MS (ESI) m/z = 833.4 $[M + Na]^+$.

***tert*-Butyl (5*S*,8*R*,11*S*)-8-(2-(*tert*-butoxy)-2-oxoethyl)-11-((3-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazatetradecan-14-oate (80b).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.84 – 7.69 (m, 4H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.43 (t, *J* = 2.2 Hz, 1H), 7.38 – 7.20 (m, 6H), 7.19 – 6.98 (m, 2H), 6.94 (d, *J* = 9.1 Hz, 1H), 6.63 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H), 5.67 (d, *J* = 5.7 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 4.99 (d, *J* = 12.2 Hz, 1H), 4.76 (dt, *J* = 9.2, 4.6 Hz, 1H), 4.56 (ddd, *J* = 8.5, 6.6, 3.5 Hz, 1H),

4.31 (q, *J* = 7.1 Hz, 1H), 3.75 (s, 3H), 3.32 (dd, *J* = 13.5, 7.8 Hz, 1H), 3.19 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.99 (dd, *J* = 17.4, 4.2 Hz, 1H), 2.51 – 2.25 (m, 3H), 2.22 – 2.10 (m, 1H), 2.10 – 1.93 (m, 1H), 1.41 (s, 9H), 1.25 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.6, 171.5, 171.2, 171.0, 169.2, 160.0, 156.6, 139.2, 135.7, 133.4, 132.4, 129.3, 128.5 (d, *J* = 2.0 Hz), 128.2, 128.1, 128.0, 127.7, 127.6, 127.0, 126.4, 126.0, 112.5, 110.1, 105.9, 82.1, 80.7, 67.5, 57.8, 55.2, 53.8, 49.0, 37.5, 36.4, 32.0, 28.1, 27.8, 26.3. MS (ESI) m/z = 811.4 $[M + H]^+$, MS (ESI) m/z = 833.4 $[M + Na]^+$.

***tert*-Butyl (5*R*,8*S*,11*S*)-8-(2-(*tert*-butoxy)-2-oxoethyl)-11-((3-methoxyphenyl)carbamoyl)-5-(naphthalen-2-ylmethyl)-3,6,9-trioxo-1-phenyl-2-oxa-4,7,10-triazatetradecan-14-oate (80c).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 7.87 – 7.72 (m, 4H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.48 (qt, *J* = 7.1, 3.3 Hz, 3H), 7.39 – 7.21 (m, 5H), 7.21 – 7.03 (m, 4H), 6.85 – 6.45 (m, 1H), 5.73 (d, *J* = 5.8 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.76 (d, *J* = 12.1 Hz, 1H), 4.70 (dt, *J* = 8.1, 5.0 Hz, 1H), 4.67 – 4.56 (m, 1H), 4.44 (d, *J* = 6.8 Hz, 1H), 3.77 (s, 3H), 3.32 (dd, *J* = 13.5, 7.3 Hz, 1H), 3.20 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.90 (dd, *J* = 17.1, 4.3 Hz, 1H), 2.40 – 2.29 (m, 3H), 2.24 – 2.17 (m, 1H), 2.09 – 1.97 (m, 1H), 1.42 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.6, 172.2, 170.9, 170.5, 169.2, 160.0, 156.7, 139.3, 135.6, 133.4, 132.5, 129.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.7, 127.5, 127.0, 126.4, 125.9, 112.0, 110.3, 105.3, 82.1, 80.6, 67.5, 57.4, 55.2, 53.6, 50.2, 37.8, 35.7, 32.0, 28.1, 27.9, 26.8. MS (ESI) m/z = 833.4 $[M + Na]^+$.

***tert*-Butyl (*R*)-4-((*S*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoate (81a).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.18 (s, 1H), 8.61 (s, 1H), 7.96 (s, 1H), 7.71 – 7.47 (m, 4H), 7.42 (d, *J* = 1.9 Hz, 1H), 7.30 – 7.10 (m, 5H), 7.07 (dd, *J* = 8.7, 2.0 Hz, 3H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.62 (s, 1H), 6.40 (dt, *J* = 7.3, 2.2 Hz, 1H), 4.75 (d, *J* = 126.2 Hz, 3H), 3.46 (s, 3H), 3.34 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.20 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.95 (dd, *J* = 17.2, 5.8 Hz, 1H), 2.71 (d, *J* = 16.9 Hz, 1H), 2.31 (dt, *J* = 44.6, 6.9 Hz, 3H), 2.13 – 1.99 (m, 1H), 1.34 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.0, 171.1, 170.7, 169.8, 162.4, 159.8, 138.8, 135.3, 133.4, 132.4, 130.4, 129.3, 128.7, 128.2, 127.9, 127.6, 127.3, 126.9, 126.4, 126.2, 125.9, 125.3, 121.0, 113.5, 112.1, 109.9, 105.8, 103.2, 81.9, 81.0, 69.5, 55.7, 55.0, 53.8, 53.6, 49.8, 32.1, 29.3, 28.1, 27.8. MS (ESI) m/z = 876.4 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*R*)-4-(*tert*-butoxy)-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoate (81b).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.03 (d, *J* = 2.1 Hz, 1H), 8.41 (s, 1H), 8.02 (d, *J* = 6.4 Hz, 1H), 7.84 (d, *J* = 4.9 Hz, 1H), 7.77 – 7.67 (m, 3H), 7.67 – 7.55 (m, 1H), 7.50 – 7.35 (m, 4H), 7.34 – 7.24 (m, 2H), 7.09 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.99 (t, *J* = 8.1 Hz, 1H), 6.91 (ddd, *J* = 8.1, 1.9, 1.0 Hz, 1H), 6.75 (s, 1H), 6.64 (d, *J* = 9.9 Hz, 1H), 6.49 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 4.80 (dt, *J* = 9.9, 4.0 Hz, 1H), 4.35 – 4.26 (m, 2H), 3.64 (s, 3H), 3.50 – 3.28 (m, 2H), 2.98 (dd, *J* = 17.7, 3.8 Hz, 1H), 2.50 – 2.36 (m, 1H), 2.35 – 2.15 (m, 2H), 1.87 – 1.68 (m, 2H), 1.36 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.9, 171.6, 171.5, 171.4, 169.1, 162.5, 159.9, 139.0, 135.5, 133.4, 133.1, 132.5, 130.4, 129.1, 128.6, 128.1, 128.0, 127.8, 127.5, 126.9, 126.7, 126.2, 125.9, 124.9, 120.9, 113.9, 112.6, 110.1, 106.0, 103.4, 82.2, 80.9, 58.6, 55.2, 54.4, 48.4, 37.1, 36.3, 32.2, 28.1, 27.5, 26.6. MS (ESI) m/z = 876.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-4-((*S*)-4-(*tert*-butoxy)-2-((*R*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoate (81c).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.33 (s, 1H), 8.42 (s, 1H), 8.06 (s, 1H), 7.74 – 7.60 (m, 3H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.50 – 7.29 (m, 4H), 7.27 – 7.21 (m, 2H), 7.18 (d, *J* = 4.1 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.03 – 6.99 (m, 1H), 6.99 – 6.91 (m, 2H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.41 (ddd, *J* = 7.6, 2.5, 1.5 Hz, 1H), 4.81 – 4.37 (m, 3H), 3.55 (s, 3H), 3.36

(dd, *J* = 13.5, 7.6 Hz, 1H), 3.26 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.78 (dd, *J* = 17.0, 4.5 Hz, 1H), 2.46 – 2.20 (m, 3H), 2.18 – 2.05 (m, 2H), 1.35 (s, 9H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.7, 171.7, 170.9, 170.7, 169.5, 162.6, 159.8, 138.9, 135.4, 133.5, 133.4, 132.5, 130.4, 129.3, 128.6, 128.2, 128.0, 127.6, 127.5, 127.0, 126.5, 126.1, 126.0, 125.1, 121.0, 113.6, 112.2, 110.0, 105.7, 103.1, 82.1, 81.1, 57.0, 55.1, 54.0, 50.3, 37.3, 35.7, 32.2, 28.1, 27.9, 27.3. MS (ESI) m/z = 876.4 $[M + Na]^+$.

(*R*)-4-((*S*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoic acid (47). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.28 (s, 2H), 11.62 (s, 1H), 9.80 (s, 1H), 8.76 (d, *J* = 8.3 Hz, 1H), 8.66 (d, *J* = 7.2 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.72 (m, 4H), 7.72 – 7.63 (m, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.48 – 7.25 (m, 4H), 7.16 (ddd, *J* = 19.7, 9.6, 5.0 Hz, 4H), 6.78 – 6.42 (m, 1H), 4.89 (td, *J* = 9.7, 8.6, 3.7 Hz, 1H), 4.64 (q, *J* = 7.0 Hz, 1H), 4.43 (td, *J* = 8.5, 4.8 Hz, 1H), 3.67 (s, 3H), 3.46-3.24 (m, 1H), 3.16 (dd, *J* = 13.9, 10.6 Hz, 1H), 2.78 (dd, *J* = 16.5, 6.1 Hz, 1H), 2.64 (dd, *J* = 16.5, 7.6 Hz, 1H), 2.30 (ddt, *J* = 20.0, 16.4, 10.4 Hz, 2H), 2.06 (td, *J* = 9.3, 5.1 Hz, 1H), 1.88 (dq, *J* = 9.4, 5.0, 4.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.3, 172.2, 172.1, 171.0, 170.3, 161.1, 159.9, 140.2, 136.4, 135.2, 133.4, 133.0, 132.2, 129.9, 128.5, 128.3, 127.9, 127.8, 127.7, 126.4, 125.8, 124.6, 123.9, 121.1, 114.3, 112.2, 109.4, 105.7, 103.4, 55.4, 54.9, 53.3, 50.5, 37.9, 36.5, 30.6, 27.7. HRMS (ESI) Calcd for $C_{38}H_{36}ClN_5O_9$ $(M - H)^-$ 740.2123, found 740.2121. HPLC purity 96.6%, t_R = 10.13 min (condition A1); 97.1%, t_R = 12.74 min (condition B1).

(*S*)-4-((*R*)-3-Carboxy-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoic acid (48). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.26 (s, 2H), 11.56 (s, 1H), 9.77 (s, 1H), 8.77 (d, *J* = 8.2 Hz, 1H), 8.67 (d, *J* = 7.5 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 8.01 – 7.73 (m, 4H), 7.69 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.49 – 7.32 (m, 4H), 7.28 – 7.00 (m, 4H), 6.79 – 6.41 (m, 1H), 5.04 – 4.84 (m, 1H), 4.75 – 4.59 (m, 1H), 4.41 (dt, *J* = 8.7, 4.2 Hz, 1H), 3.68 (s, 3H), 3.46-3.24 (m, 1H), 3.17 (dd, *J* = 13.8, 10.4 Hz, 1H), 2.71 (dd, *J* = 16.5, 5.9 Hz, 1H), 2.58 (dd, *J* = 16.5, 7.7 Hz, 1H), 2.38 – 2.15 (m, 2H), 2.07 (ddd, *J* = 14.7, 10.0, 5.3 Hz, 1H), 1.90 (ddd, *J* = 14.1, 9.6, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.3, 172.1, 172.0, 171.0, 170.3, 161.2, 159.9, 140.2, 136.3, 135.3, 133.4, 133.0, 132.2, 129.9, 128.4, 128.3, 127.9, 127.9, 127.8, 126.4, 125.8, 124.7, 123.9, 121.1, 114.3, 112.2, 109.4, 105.7, 103.4, 55.4, 55.1, 53.4, 50.3, 37.9, 36.7, 30.5, 27.6. HRMS (ESI) Calcd for $C_{38}H_{36}ClN_5O_9$ $(M - H)^-$ 740.2123, found 740.2123. HPLC purity 95.2%, t_R = 10.14 min (condition A1); 96.1%, t_R = 12.71 min (condition B1).

(*S*)-4-((*S*)-3-Carboxy-2-((*R*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)propanamido)-5-((3-methoxyphenyl)amino)-5-oxopentanoic acid (49). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 12.27 (s, 2H), 11.55 (s, 1H), 9.75 (s, 1H), 8.80 (d, *J* = 8.1 Hz, 1H), 8.67 (d, *J* = 7.9 Hz, 1H), 8.14 (d, *J* = 7.7 Hz, 1H), 7.98 – 7.76 (m, 4H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.29 (t, *J* = 2.3 Hz, 1H), 7.25 – 6.98 (m, 4H), 6.61 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.89 (ddd, *J* = 10.6, 8.2, 4.4 Hz, 1H), 4.69 (td, *J* = 7.8, 5.3 Hz, 1H), 4.36 (td, *J* = 8.3, 5.2 Hz, 1H), 3.70 (s, 3H), 3.46-3.24 (m, 1H), 3.17 (dd, *J* = 13.8, 10.3 Hz, 1H), 2.73 (dd, *J* = 16.6, 5.4 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.36 – 2.22 (m, 2H), 2.06 – 1.99 (m, 1H), 1.92 (tt, *J* = 9.8, 5.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.4, 172.3, 172.0, 171.1, 170.3, 161.2, 159.9, 140.2, 136.3, 135.2, 133.4, 133.0, 132.3, 129.9, 128.5, 128.3, 127.91, 127.89, 127.8, 126.4, 125.9, 124.7, 124.0, 121.1, 114.3, 112.1, 109.4, 105.6, 103.5, 55.4, 55.1, 53.6, 50.1, 37.9, 36.6, 30.7, 27.6. HRMS (ESI) Calcd for $C_{38}H_{36}ClN_5O_9$ $(M - H)^-$ 740.2123, found 740.2121. HPLC purity 96.7%, t_R = 10.11 min (condition A1); 97.9%, t_R = 12.53 min (condition B1).

(9H-Fluoren-9-yl)methyl (*S*)-(1,5-dioxo-1-((4-(trifluoromethoxy)phenyl)amino)-5-(tritylamino)pentan-2-yl)carbamate (82). Yield, 75%. 1H NMR (500 MHz, Chloroform-d) δ 9.12 (s, 1H), 7.65 (dd, J = 8.2, 3.5 Hz, 2H), 7.49 (d, J = 7.5 Hz, 2H), 7.36 – 7.05 (m, 21H), 7.01 – 6.89 (m, 2H), 6.88 (s, 1H), 6.00 (d, J = 7.0 Hz, 1H), 4.30 (t, J = 6.1 Hz, 2H), 4.11 (t, J = 7.1 Hz, 1H), 4.03 (q, J = 7.1 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.42 – 2.31 (m, 1H), 2.13 – 1.99 (m, 1H), 1.90 – 1.85 (m, 1H). 13C NMR (126 MHz, Chloroform-d) δ 172.5, 169.5, 156.3, 145.08, 145.06, 144.2, 143.8, 143.7, 141.34, 141.33, 136.5, 128.7, 128.1, 127.77, 127.76, 127.2, 127.1, 125.1, 121.4, 120.9, 120.0, 119.5, 80.0, 67.0, 54.3, 47.2, 34.0, 30.5. MS (ESI) m/z = 792.3 $[M + Na]^+$.

***tert*-Butyl (*S*)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(((*S*)-1,5-dioxo-1-((4-(trifluoromethoxy)phenyl)amino)-5-(tritylamino)pentan-2-yl)amino)-4-oxobutanoate (83).** Yield, 71%. 1H NMR (500 MHz, Chloroform-d) δ 9.03 (s, 1H), 7.97 (d, J = 6.5 Hz, 1H), 7.67 (dd, J = 7.5, 4.7 Hz, 2H), 7.47 (dt, J = 6.4, 3.1 Hz, 4H), 7.31 (td, J = 7.4, 3.7 Hz, 2H), 7.23 – 7.04 (m, 17H), 7.00 (d, J = 8.6 Hz, 2H), 6.88 (s, 1H), 5.66 (d, J = 7.3 Hz, 1H), 4.44 – 4.18 (m, 4H), 4.10 (t, J = 7.1 Hz, 1H), 2.86 – 2.52 (m, 3H), 2.40 (ddd, J = 15.8, 7.4, 4.2 Hz, 1H), 2.20 – 2.00 (m, 1H), 1.65 (s, 1H), 1.34 (s, 9H). 13C NMR (126 MHz, Chloroform-d) δ 173.0, 170.9, 170.6, 169.3, 156.1, 145.1, 144.2, 143.8, 143.6, 141.3, 136.7, 128.6, 128.1, 127.7, 127.2, 127.09, 127.08, 125.1, 121.5, 121.4, 121.2, 120.0, 82.1, 70.9, 67.3, 54.0, 51.8, 47.1, 37.4, 33.9, 28.2, 28.0.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(tert-butoxy)-1-(((*S*)-1,5-dioxo-1-((4-(trifluoromethoxy)phenyl)amino)-5-(tritylamino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1H-indole-1-carboxylate (84).** Yield, 65%. 1H NMR (500 MHz, Chloroform-d) δ 8.76 (s, 1H), 7.75 (dd, J = 7.2, 3.3 Hz, 2H), 7.70 (dd, J = 9.5, 4.7 Hz, 2H), 7.60 (td, J = 5.9, 5.0, 3.3 Hz, 4H), 7.50 (d, J = 7.4 Hz, 1H), 7.46 (s, 1H), 7.41 (dd, J = 6.3, 3.3 Hz, 2H), 7.30 – 7.21 (m, 3H), 7.03 – 6.91 (m, 11H), 6.90 – 6.82 (m, 6H), 6.72 (d, J = 5.8 Hz, 1H), 5.90 (s, 1H), 4.74 (td, J = 7.9, 5.1 Hz, 1H), 4.61 (dt, J = 10.7, 5.3 Hz, 1H), 4.22 (ddd, J = 10.7, 6.6, 3.6 Hz, 1H), 3.46 (dd, J = 14.4, 4.8 Hz, 1H), 3.16 (dd, J = 14.4, 9.1 Hz, 1H), 2.91 (dd, J = 16.3, 5.1 Hz, 1H), 2.63 (dd, J = 16.3, 8.4 Hz, 1H), 2.42 (td, J = 8.9, 5.3 Hz, 1H), 2.29 – 2.15 (m, 2H), 2.04 (dt, J = 10.4, 3.8 Hz, 1H), 1.48 (s, 9H), 1.31 (s, 9H). 13C NMR (126 MHz, Chloroform-d) δ 172.0, 171.2, 170.5, 170.0, 169.5, 163.6, 149.6, 145.0 (d, *J* = 2.0 Hz), 144.4, 136.9, 134.4, 133.7, 133.5, 133.4, 132.7, 129.4, 129.1, 129.0, 128.7, 128.6, 127.9, 127.8, 127.7, 127.6, 126.85, 126.76, 126.6, 126.2, 121.6, 121.5, 121.4, 121.0, 116.4, 111.2, 86.7, 81.7, 70.2, 56.4, 54.5, 51.2, 36.7, 36.5, 34.4, 29.0, 28.04, 27.96.

(*S*)-4-(((*S*)-5-Amino-1,5-dioxo-1-((4-(trifluoromethoxy)phenyl)amino)pentan-2-yl)amino)-3-((*S*)-2-(5-chloro-1H-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoic acid (50). 1H NMR (500 MHz, DMSO-d6) δ 12.45 (s, 1H), 11.84 – 11.29 (m, 1H), 10.09 (s, 1H), 8.82 (d, J = 8.3 Hz, 1H), 8.63 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 7.94 – 7.64 (m, 7H), 7.56 (d, J = 8.4 Hz, 1H), 7.48 – 7.35 (m, 3H), 7.31 (d, J = 8.7 Hz, 3H), 7.21 (d, J = 2.1 Hz, 1H), 7.15 (dd, J = 8.7, 2.1 Hz, 1H), 6.85 (s, 1H), 4.89 (ddd, J = 11.9, 8.4, 3.8 Hz, 1H), 4.65 (q, J = 7.2 Hz, 1H), 4.35 (q, J = 7.3 Hz, 1H), 3.30-3.32 (m, 1H), 3.16 (dd, J = 13.9, 10.9 Hz, 1H), 2.81 (dd, J = 16.7, 5.5 Hz, 1H), 2.63 (dd, J = 16.6, 8.0 Hz, 1H), 2.18 (t, J = 8.2 Hz, 2H), 2.01 (q, J = 7.2, 6.7 Hz, 1H), 1.92 (p, J = 7.5, 7.0 Hz, 1H). 13C NMR (126 MHz, DMSO-d6) δ 174.1, 172.4, 172.1, 171.1, 170.7, 161.2, 144.1, 138.4, 136.5, 135.3, 133.4, 133.0, 132.2, 128.4, 128.3, 127.9, 127.8, 127.7, 126.4, 125.8, 124.7, 123.9, 122.1, 121.2, 121.1, 120.6 (t, *J* = 253.7 Hz), 114.3, 103.4, 55.0, 53.8, 50.2, 37.9, 36.4, 31.8, 28.2. HRMS (ESI) Calcd for $C_{38}H_{34}ClF_3N_6O_8$ $(M - H)^-$ 793.2000, found 793.1999. HPLC purity 100%, t_R = 10.16 min (condition A1); 100%, t_R = 12.53 min (condition B1).

***tert*-Butyl (*S*)-4-((*S*)-4-amino-2-(((benzyloxy)carbonyl)amino)-4-oxobutanamido)-5-oxo-5-((4-(trifluoromethoxy)phenyl)amino)pentanoate (85).** Yield, 70%. ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.57 (s, 1H), 7.93 (dd, J = 28.0, 8.6 Hz, 3H), 7.47 – 7.27 (m, 5H), 7.26 – 7.10 (m, 3H), 6.95 – 6.49 (m, 2H), 5.11 (d, J = 1.8 Hz, 2H), 4.51 (tdd, J = 11.2, 7.8, 4.6 Hz, 2H), 3.10 – 2.71 (m, 2H), 2.39 (dddd, J = 16.6, 14.0, 10.4, 6.1 Hz, 3H), 2.01 – 1.87 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 172.7, 171.9, 171.4, 170.1, 156.1, 144.4, 138.4, 137.1, 128.3, 127.8, 127.7, 121.6, 121.2, 121.1, 79.6, 66.1, 53.4, 52.1, 36.9, 31.5, 27.4, 26.6. MS (ESI) m/z = 611.3 $[M + H]^+$, 633.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-amino-1-(((*S*)-5-(*tert*-butoxy)-1,5-dioxo-1-((4-(trifluoromethoxy)phenyl)amino)pentan-2-yl)amino)-1,4-dioxobutan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (86).** Yield, 62%. ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.41 (s, 1H), 8.32 (d, J = 6.6 Hz, 1H), 8.24 (d, J = 7.0 Hz, 1H), 8.11 – 7.93 (m, 3H), 7.91 – 7.82 (m, 4H), 7.80 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.55 (dd, J = 8.3, 1.8 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.37 (dd, J = 8.9, 2.1 Hz, 1H), 7.32 – 7.11 (m, 3H), 6.95 (d, J = 0.8 Hz, 1H), 6.71 (s, 1H), 4.93 (ddd, J = 9.1, 6.5, 4.8 Hz, 1H), 4.71 (q, J = 6.1 Hz, 1H), 4.48 (dt, J = 9.5, 5.6 Hz, 1H), 3.51 (dd, J = 14.2, 4.8 Hz, 1H), 3.35 (dd, J = 14.2, 9.2 Hz, 1H), 2.89 (d, J = 6.0 Hz, 2H), 2.47 – 2.21 (m, 3H), 1.98 – 1.85 (m, 1H), 1.44 (s, 9H), 1.33 (s, 9H).

(*S*)-4-((*S*)-4-Amino-2-((*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanamido)-5-oxo-5-((4-(trifluoromethoxy)phenyl)amino)pentanoic acid (51). Yield, 80%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (s, 1H), 11.64 (s, 1H), 9.97 (s, 1H), 8.80 (d, J = 8.5 Hz, 1H), 8.61 (d, J = 7.5 Hz, 1H), 8.36 (d, J = 7.7 Hz, 1H), 7.94 – 7.75 (m, 5H), 7.69 (d, J = 2.1 Hz, 1H), 7.63 – 7.52 (m, 2H), 7.42 (pd, J = 6.8, 1.6 Hz, 2H), 7.36 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 2.1 Hz, 1H), 7.16 – 7.06 (m, 2H), 4.93 (ddd, J = 11.9, 8.7, 3.7 Hz, 1H), 4.64 (q, J = 7.1 Hz, 1H), 4.38 (ddd, J = 9.3, 7.6, 4.6 Hz, 1H), 3.28 (dd, J = 14.8, 4.7 Hz, 1H), 3.15 (dd, J = 13.9, 11.0 Hz, 1H), 2.69 (dd, J = 15.6, 7.6 Hz, 1H), 2.58 (dd, J = 15.5, 6.0 Hz, 1H), 2.33 (pt, J = 8.8, 5.2 Hz, 2H), 2.12 (dq, J = 9.7, 6.1 Hz, 1H), 1.86 (ddt, J = 13.5, 9.0, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 172.4, 171.8, 171.7, 170.7, 161.0, 144.2, 138.4, 136.5, 135.2, 133.4, 133.1, 132.2, 128.5, 128.3, 127.9, 127.8, 127.7, 126.4, 125.8, 124.6, 123.9, 121.9, 121.5, 121.1, 120.6 (d, J = 253.7 Hz), 114.3, 103.3, 100.0, 54.8, 53.3, 50.4, 37.9, 37.4, 30.6, 27.2. HRMS (ESI) Calcd for $C_{38}H_{34}ClF_3N_6O_8$ $(M - H)^-$ 793.2000, found 793.1998. HPLC purity 100%, t_R = 10.43 min (condition A1); 100%, t_R = 13.03 min (condition B1).

(9*H*-fluoren-9-yl)methyl (*S*)-(1-oxo-1-((4-(trifluoromethoxy)phenyl)amino)-3-(2-trityl-2*H*-tetrazol-5-yl)propan-2-yl)carbamate (87). Yield, 71%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 7.76 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 5.7 Hz, 2H), 7.43 – 7.35 (m, 4H), 7.35 – 7.31 (m, 3H), 7.31 – 7.21 (m, 8H), 7.18 – 6.81 (m, 8H), 6.17 (d, J = 8.3 Hz, 1H), 4.97 (d, J = 8.8 Hz, 1H), 4.41 (h, J = 8.6, 7.2 Hz, 2H), 4.18 (t, J = 6.9 Hz, 1H), 3.60 (dd, J = 16.0, 6.0 Hz, 1H), 3.46 (dd, J = 15.5, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 168.4, 161.8, 156.4, 145.4, 143.52, 143.49, 141.3, 141.0, 136.0, 130.1, 128.5, 127.8, 127.1, 125.0, 121.6, 121.5, 121.3, 120.0, 119.5, 83.4, 67.5, 53.7, 47.0, 28.5. MS (ESI) m/z = 803.2 $[M + Na]^+$.

***tert*-Butyl (*S*)-3-amino-4-oxo-4-(((*S*)-1-oxo-3-(2*H*-tetrazol-5-yl)-1-((4-(trifluoromethoxy)phenyl)amino)propan-2-yl)amino)butanoate (88).** Yield, 45%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.81 – 7.60 (m, 1H), 7.34 – 7.22 (m, 2H), 7.22 – 7.13 (m, 2H), 7.13 – 6.99 (m, 2H), 4.87 – 4.78 (m, 1H), 3.87 (dd, J = 7.3, 5.5 Hz, 1H), 3.43 (dd, J = 14.8, 5.2 Hz, 1H),

3.34 (d, *J* = 8.5 Hz, 1H), 2.80 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.63 (dd, *J* = 17.1, 7.5 Hz, 1H), 1.42 (s, 9H).

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-(*tert*-butoxy)-1,4-dioxo-1-(((*S*)-1-oxo-3-(2*H*-tetrazol-5-yl)-1-((4-(trifluoromethoxy)phenyl)amino)propan-2-yl)amino)butan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (89).** Yield, 53%. ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.41 (s, 1H), 8.46 (d, *J* = 6.5 Hz, 1H), 8.38 (d, *J* = 6.9 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.91 – 7.77 (m, 6H), 7.67 – 7.52 (m, 2H), 7.51 – 7.42 (m, 2H), 7.37 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.78 (s, 1H), 4.93 (dtd, *J* = 12.4, 8.7, 7.9, 4.9 Hz, 2H), 4.69 (q, *J* = 6.7 Hz, 1H), 3.66 (dd, *J* = 15.4, 4.8 Hz, 1H), 3.60 – 3.42 (m, 2H), 3.35 (dd, *J* = 14.2, 9.5 Hz, 1H), 2.97 (dd, *J* = 16.6, 6.0 Hz, 1H), 2.76 (dd, *J* = 16.6, 7.2 Hz, 1H), 1.50 (s, 9H), 1.41 (s, 9H).

(*S*)-3-((*S*)-2-(5-Chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxo-4-(((*S*)-1-oxo-3-(2*H*-tetrazol-5-yl)-1-((4-(trifluoromethoxy)phenyl)amino)propan-2-yl)amino)butanoic acid (52). Yield, 75%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.66 (s, 1H), 10.03 (s, 1H), 8.74 (dd, *J* = 40.3, 7.8 Hz, 2H), 8.42 (d, *J* = 7.6 Hz, 1H), 7.98 – 7.59 (m, 8H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.35 (m, 3H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.23 – 7.07 (m, 2H), 4.94 – 4.79 (m, 2H), 4.61 (q, *J* = 7.0 Hz, 1H), 3.45 (dd, *J* = 15.1, 6.3 Hz, 2H), 3.15 (d, *J* = 12.1 Hz, 1H), 2.77 (dd, *J* = 16.7, 5.5 Hz, 1H), 2.69 – 2.58 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3, 172.3, 171.1, 170.0, 161.1, 144.3, 138.1, 136.5, 135.2, 133.4, 133.0, 132.2, 128.4, 128.3, 127.9, 127.7, 126.4, 125.8, 124.6, 123.9, 122.0, 121.4, 121.1, 114.3, 103.3, 54.9, 52.7, 50.4, 37.8, 36.4, 26.1. HRMS (ESI) Calcd for $C_{37}H_{31}ClF_3N_9O_7$ (M-H)$^-$ 804.1909, found 793.1919. HPLC purity 97.0%, t_R = 10.61 min (condition A1); 100%, t_R = 13.03 min (condition B1).

Benzyl ((*S*)-4-amino-1,4-dioxo-1-(((*S*)-1-oxo-1-((4-(trifluoromethoxy)phenyl)amino)-3-(2-trityl-2*H*-tetrazol-5-yl)propan-2-yl)amino)butan-2-yl)carbamate (93). Yield, 66%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.09 (m, 13H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.96 – 6.80 (m, 7H), 6.13 (d, *J* = 6.4 Hz, 1H), 5.64 (s, 1H), 5.30 (s, 1H), 5.09 – 4.94 (m, 2H), 4.90 (d, *J* = 12.1 Hz, 1H), 4.32 (q, *J* = 5.9 Hz, 1H), 3.70 (dd, *J* = 15.9, 5.3 Hz, 1H), 3.26 (dd, *J* = 15.8, 5.0 Hz, 1H), 2.66 (d, *J* = 5.7 Hz, 2H). MS (ESI) m/z = 829.3 $[M + Na]^+$.

***tert*-Butyl 2-(((*S*)-1-(((*S*)-4-amino-1,4-dioxo-1-(((*S*)-1-oxo-3-(2*H*-tetrazol-5-yl)-1-((4-(trifluoromethoxy)phenyl)amino)propan-2-yl)amino)butan-2-yl)amino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-5-chloro-1*H*-indole-1-carboxylate (94).** Yield, 41%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.94 (d, *J* = 8.5 Hz, 1H), 8.60 (t, *J* = 7.6 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.87 – 7.71 (m, 6H), 7.66 (s, 1H), 7.55 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.50 – 7.35 (m, 3H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.74 (s, 1H), 4.86 (dddd, *J* = 19.4, 11.5, 8.1, 4.7 Hz, 2H), 4.59 (q, *J* = 7.0 Hz, 1H), 3.52 (dd, *J* = 15.3, 5.7 Hz, 1H), 3.29 – 3.24 (m, 1H), 3.16 (s, 1H), 3.02 (dd, *J* = 14.0, 10.8 Hz, 1H), 2.69 (dd, *J* = 15.9, 7.5 Hz, 1H), 2.57 (dd, *J* = 15.7, 5.8 Hz, 1H), 1.26 (s, 9H). MS (ESI) m/z = 905.3 $[M + H]^+$, 903.3 $[M – H]^–$.

(*S*)-2-((*S*)-2-(5-Chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-*N*^{1}-((*S*)-1-oxo-3-(2*H*-tetrazol-5-yl)-1-((4-(trifluoromethoxy)phenyl)amino)propan-2-yl)succinamide (54). Yield, 75%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.63 (d, *J* = 2.2 Hz, 1H), 9.99 (s, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.59 (t, *J* = 8.2 Hz, 2H), 7.94 – 7.73 (m, 6H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.64 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.33 (m, 3H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.22 – 7.06 (m, 3H), 5.00 – 4.75 (m, 2H), 4.60 (q, *J* = 6.9 Hz, 1H), 3.52 (dd, *J* = 15.2, 5.8 Hz, 1H), 3.24 (dd, *J* = 14.0, 3.7 Hz, 2H), 3.12 (dd, *J* = 14.0, 11.0 Hz, 1H), 2.69 (dd, *J* = 15.7, 7.2 Hz, 1H), 2.59 (dd, *J* = 15.7, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.5, 172.0, 171.5, 161.1,

144.3, 138.1, 136.5, 135.2, 133.4, 133.0, 132.2, 128.4, 128.3, 127.9, 127.8, 127.7, 126.4, 125.8, 124.6, 123.9, 121.9, 121.6, 121.1, 120.6 (d, J = 253.8 Hz), 114.3, 103.3, 54.8, 52.4, 50.4, 37.9, 37.4, 25.9. HRMS (ESI) Calcd for $C_{37}H_{32}ClF_3N_{10}O_6$ $(M - H)^-$ 803.2069, found 803.2065. HPLC purity 98.9%, t_R = 10.60 min (condition A1); 100%, t_R = 13.17 min (condition B1).

General procedure for synthesis of 60a and 60b. A mixture of 2-amino-4-chlorobenzenethiol (1eq) or 2-amino-5-chlorobenzenethiol (1eq) and ethyl 3-ethoxy-3-iminopropanoate hydrochloride (1eq) in EtOH was stirred at 70 °C for 16 h. The mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine and concentrated. The residue was further purified on silica gel.

Ethyl 2-(5-chlorobenzo[d]thiazol-2-yl)acetate (98a). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (dd, J = 8.5, 0.4 Hz, 1H), 8.06 (dd, J = 2.0, 0.5 Hz, 1H), 7.49 (dd, J = 8.6, 2.1 Hz, 1H), 4.34 (s, 2H), 4.17 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.9, 166.5, 153.6, 134.5, 131.4, 125.8, 124.1, 122.4, 61.6, 14.4. MS (ESI) m/z = 256.1 $[M + H]^+$, 278.1 $[M + Na]^+$, 533.1 $[2M + Na]^+$.

Ethyl 2-(6-chlorobenzo[d]thiazol-2-yl)acetate (98b). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.90 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 2.1 Hz, 1H), 7.43 (dd, J = 8.7, 2.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 168.3, 163.3, 151.2, 137.0, 131.2, 126.9, 123.7, 121.1, 61.9, 39.7, 14.1.

General procedure for synthesis of 60a and 60b. To a solution of **98a** or **98b** (1eq) in THF/MeOH/H_2O (4/2/1) was added NaOH (1.2eq). The mixture was stirred at rt for 6 h and was concentrated under reduced pressure and dried on the lyophilizer overnight. The resulting solid was used in the next step without further purification. For **60a**, MS (ESI) m/z = 228.1 $[M + H]^+$, 250.0 $[M + Na]^+$, 477.0 $[2M + Na]^+$.

The procedure for synthesis of **60c** and **60d** was similar to **60a** and **60b**, with the modified temperature of 80 °C in the first step.

Ethyl 2-(5-chlorobenzo[*d*]oxazol-2-yl)acetate (98c). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (dd, J = 2.2, 0.5 Hz, 1H), 7.77 (dd, J = 8.7, 0.6 Hz, 1H), 7.45 (dd, J = 8.7, 2.2 Hz, 1H), 4.23 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.5, 162.4, 149.7, 142.4, 129.3, 125.9, 119.9, 112.6, 61.8, 35.2, 14.4. Hydrolysis of 101a yielded compound 102a. MS (ESI) m/z = 212.1 $[M + H]^+$, 234.1 $[M + Na]^+$, 445.1 $[2M + Na]^+$.

Ethyl 2-(6-chlorobenzo[*d*]oxazol-2-yl)acetate (98d). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 (dd, J = 8.5, 0.5 Hz, 1H), 7.53 (dd, J = 2.0, 0.5 Hz, 1H), 7.31 (dd, J = 8.5, 2.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.99 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.7, 160.3, 151.3, 139.9, 130.9, 125.2, 120.6, 111.3, 62.0, 35.3, 14.1. MS (ESI) m/z = 240.1 $[M + H]^+$, 262.1 $[M + Na]^+$, 501.1 $[2M + Na]^+$. Hydrolysis of **98d** yielded compound **60d**. MS (ESI) m/z = 212.1 $[M + H]^+$, 234.1 $[M + Na]^+$.

The procedure for synthesis of **60e** was similar to **60a**.

Ethyl 2-(5-chloro-1*H*-benzo[*d*]imidazol-2-yl)acetate (98e). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.54 (s, 1H), 7.55 (d, J = 30.1 Hz, 2H), 7.29 – 7.00 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.98 (s, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.0, 149.9, 126.1, 122.5, 120.0, 118.3, 112.9, 111.5, 100.0, 61.3, 35.5, 14.5. Hydrolysis of **98e** yielded compound **60e**. MS (ESI) m/z = 211.1 $[M + H]^+$, 209.1 $[M - H]^-$.

The coupling reaction described in the main text was used to prepare compound **99**.

Methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanoate (99a). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.66 (s, 1H), 7.91 – 7.71 (m, 3H), 7.63 – 7.59 (m, 1H), 7.57 (d, J = 1.9 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.35 (dt, J = 8.8, 0.8 Hz, 1H), 7.28 (dd, J = 8.4, 1.8 Hz, 1H),

7.23 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.84 – 6.71 (m, 2H), 5.21 (dt, *J* = 7.9, 5.7 Hz, 1H), 3.78 (s, 3H), 3.60 – 3.31 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.8, 160.8, 134.8, 133.5, 133.1, 132.6, 131.1, 128.48, 128.47, 128.2, 127.7, 127.6, 127.2, 126.3, 125.9, 125.2, 121.2, 113.1, 102.4, 53.4, 52.6, 38.3. MS (ESI) m/z = 429.1 $[M + Na]^+$.

Methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(3,4-dichlorophenyl)propanoate (99b). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.27 (s, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.29 (d, *J* = 2.1 Hz, 1H), 7.21 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.81 (dd, *J* = 2.3, 0.9 Hz, 1H), 5.12 (dt, *J* = 7.7, 6.1 Hz, 1H), 3.82 (s, 3H), 3.27 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.18 (dd, *J* = 14.0, 6.4 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 161.4, 136.0, 135.1, 132.7, 131.5, 131.2, 130.8, 130.6, 128.6, 128.3, 126.3, 125.2, 121.2, 113.3, 102.8, 53.4, 52.9, 37.2. MS (ESI) m/z = 447.0 $[M + Na]^+$.

Methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-chlorophenyl)propanoate (99c). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.18 (s, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.17 – 7.08 (m, 3H), 7.05 – 6.96 (m, 2H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.75 – 6.46 (m, 1H), 5.03 (dt, *J* = 7.7, 6.0 Hz, 1H), 3.71 (s, 3H), 3.20 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.12 (dd, *J* = 14.0, 6.2 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.0, 161.2, 135.1, 134.1, 133.3, 130.9, 130.6, 128.9, 128.3, 126.3, 125.2, 121.2, 113.3, 102.6, 53.5, 52.8, 37.4. MS (ESI) m/z = 391.1 $[M + H]^+$, 413.1 $[M + Na]^+$, 389.0 $[M – H]^–$.

Methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(2-chlorophenyl)propanoate (99d). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.43 (s, 1H), 7.56 (d, *J* = 2.1 Hz, 1H), 7.40 (dd, *J* = 5.8, 3.5 Hz, 1H), 7.37 – 7.06 (m, 6H), 6.83 (d, *J* = 2.0 Hz, 1H), 5.22 (qd, *J* = 7.0, 6.1, 2.4 Hz, 1H), 3.82 (s, 3H), 3.50 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.38 (dd, *J* = 13.9, 8.3 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.4, 161.5, 135.1, 134.3, 134.0, 131.4, 131.0, 129.8, 128.9, 128.3, 127.1, 126.1, 125.0, 121.1, 113.4, 102.59, 102.56, 52.9, 52.8, 35.6. MS (ESI) m/z = 391.1 $[M + H]^+$, 413.1 $[M + Na]^+$.

Methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-(trifluoromethyl)phenyl)propanoate (99e). ^{1}H NMR (500 MHz, Acetone-d_6) δ 11.09 (s, 1H), 8.26 (d, *J* = 8.3 Hz, 1H), 7.72 – 7.48 (m, 6H), 7.23 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.17 (dd, *J* = 2.2, 0.9 Hz, 1H), 5.06 (ddd, *J* = 9.4, 8.2, 5.3 Hz, 1H), 3.72 (s, 3H), 3.43 (dd, *J* = 14.0, 5.3 Hz, 1H), 3.29 (dd, *J* = 14.0, 9.4 Hz, 1H).^{13}C NMR (126 MHz, Acetone-d_6) δ 171.5, 161.1, 142.3, 135.3, 132.2, 130.0, 128.7, 128.5, 128.2, 125.6, 125.3, 125.2 (q, *J* = 3.8 Hz), 124.2, 123.4, 120.9, 113.8, 102.6, 53.7, 51.7, 36.9. MS (ESI) m/z = 425.1 $[M + H]^+$, 447.1 $[M + Na]^+$.

Methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-cyanophenyl)propanoate (99f). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.36 (d, *J* = 2.2 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.1 Hz, 3H), 7.33 – 7.14 (m, 4H), 7.09 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.74 (dd, *J* = 2.3, 0.9 Hz, 1H), 5.04 (td, *J* = 7.4, 5.7 Hz, 1H), 3.70 (s, 3H), 3.28 (dd, *J* = 13.9, 5.7 Hz, 1H), 3.16 (dd, *J* = 13.9, 7.1 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.9, 161.5, 141.6, 135.2, 132.4, 130.8, 130.1, 128.3, 126.2, 125.1, 121.2, 118.6, 113.4, 111.1, 102.9, 53.4, 52.9, 38.0. MS (ESI) m/z = 382.1 $[M + H]^+$, 404.1 $[M + Na]^+$, 380.1 $[M – H]^–$.

Methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3-(4-methoxyphenyl)propanoate (99g). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.82 (d, *J* = 2.3 Hz, 1H), 7.52 (d, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.34 (dt, *J* = 8.7, 0.8 Hz, 1H), 7.21 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.18 (s, 1H), 7.16 (s, 1H), 7.05 – 6.68 (m, 3H), 5.16 (ddd, *J* = 7.9, 6.9, 5.7 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.31 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.23 (dd, *J* = 14.0, 7.0 Hz, 1H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.8, 161.7, 158.8, 135.3, 131.2, 130.3, 128.3, 127.8, 126.0, 124.8, 121.0, 114.2, 113.5, 102.7, 55.2, 54.1, 52.7, 37.1. MS (ESI) m/z = 387.1 $[M + H]^+$, 409.1 $[M + Na]^+$.

***tert*-Butyl (*S*)-5-chloro-2-((1-methoxy-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamoyl)-1*H*-indole-1-carboxylate (100a).** To the solution of methyl (*S*)-2-(5-chloro-1*H*-indole-2-carboxamido)-3 (naphthalen-2-yl)propanoate (1eq) in DCM at 0 °C was added Boc_2O (1.5eq) and DMAP (0.01eq). The mixture was stirred at 0 °C for 4 h. Water was added to the mixture. The organic layer was concentrated and the residue was further purified by silica column. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 8.9 Hz, 1H), 7.89 – 7.70 (m, 3H), 7.67 – 7.54 (m, 1H), 7.52 – 7.39 (m, 3H), 7.31 (ddd, *J* = 9.1, 7.6, 1.9 Hz, 2H), 6.62 (d, *J* = 0.7 Hz, 1H), 6.59 – 6.50 (m, 1H), 5.16 (dt, *J* = 7.9, 5.7 Hz, 1H), 3.79 (s, 3H), 3.50 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.39 (dd, *J* = 13.9, 5.5 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.6, 161.3, 148.8, 135.5, 135.1, 133.4, 133.1, 132.6, 128.82, 128.77, 128.4, 128.3, 127.7, 127.5, 127.3, 126.4, 126.3, 125.9, 121.0, 116.3, 110.4, 85.2, 53.4, 52.5, 38.0, 27.8. MS (ESI) m/z = 529.2 $[M + Na]^+$, 505.2 $[M - H]^-$. Hydrolysis of **100a** yielded compound **68a**.

***tert*-Butyl (*S*)-5-chloro-2-((3-(3,4-dichlorophenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-1*H*-indole-1-carboxylate (100b).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.03 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.88 – 6.43 (m, 2H), 5.03 (dt, *J* = 7.5, 5.6 Hz, 1H), 3.78 (s, 3H), 3.30 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.15 (dd, *J* = 14.0, 5.4 Hz, 1H), 1.60 (s, 10H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.2, 161.4, 148.8, 136.0, 135.3, 134.9, 132.5, 131.52, 131.48, 130.5, 128.9, 128.8, 128.7, 126.5, 121.1, 116.4, 110.6, 85.3, 53.3, 52.7, 36.9, 27.8. MS (ESI) m/z = 547.1 $[M + Na]^+$, 523.1 $[M - H]^-$. Hydrolysis of **100b** yielded compound **68b**.

***tert*-Butyl (*S*)-5-chloro-2-((3-(4-chlorophenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-1*H*-indole-1-carboxylate (100c).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.02 (d, *J* = 8.9 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.23 (m, 3H), 7.18 – 7.03 (m, 2H), 6.68 (d, *J* = 21.6 Hz, 2H), 5.07 (dt, *J* = 7.7, 5.6 Hz, 1H), 3.78 (s, 3H), 3.31 (dd, *J* = 14.0, 5.8 Hz, 1H), 3.20 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.61 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.4, 161.3, 148.8, 135.4, 135.0, 134.2, 133.3, 130.7, 128.9, 128.79, 128.77, 126.4, 121.1, 116.4, 110.5, 85.2, 53.3, 52.6, 37.2, 27.8. MS (ESI) m/z = 513.1 $[M + Na]^+$, 489.2 $[M - H]^-$. Hydrolysis of **100c** yielded compound **68c**.

***tert*-Butyl (*S*)-5-chloro-2-((3-(2-chlorophenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-1*H*-indole-1-carboxylate (100d).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 9.0 Hz, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 7.32 – 7.25 (m, 1H), 7.23 – 7.16 (m, 2H), 7.15 – 7.01 (m, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 0.7 Hz, 1H), 5.02 (td, *J* = 7.9, 6.1 Hz, 1H), 3.65 (s, 3H), 3.30 (d, *J* = 6.1 Hz, 1H), 3.21 (dd, *J* = 13.9, 7.6 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.8, 161.4, 148.8, 135.4, 135.0, 134.5, 133.9, 131.5, 129.7, 128.8, 128.73, 128.71, 127.0, 126.3, 121.0, 116.3, 110.4, 85.1, 52.6, 52.5, 35.6, 27.7. MS (ESI) m/z = 513.1 $[M + Na]^+$, Hydrolysis of **100d** yielded compound **68d**.

***tert*-Butyl (*S*)-5-chloro-2-((1-methoxy-1-oxo-3-(4-(trifluoromethyl)phenyl)propan-2-yl)carbamoyl)-1*H*-indole-1-carboxylate (100e).** ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.22 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.78 – 7.50 (m, 5H), 7.37 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.85 (s, 1H), 5.01 (td, *J* = 8.7, 5.3 Hz, 1H), 3.74 (s, 3H), 3.41 (dd, *J* = 13.9, 5.3 Hz, 1H), 3.25 (dd, *J* = 13.9, 8.9 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (126 MHz, Acetone-d_6) δ 171.4, 161.3, 148.8, 142.0, 135.7, 135.3, 130.2, 129.1, 128.5 (d, *J* = 32.0 Hz), 128.2, 125.8, 125.6, 125.2 (q, *J* = 3.8 Hz), 123.5, 121.1, 115.9, 109.9, 84.6, 53.7, 51.8, 37.1, 26.8. MS (ESI) m/z = 547.1 $[M + Na]^+$, 523.1 $[M – H]^–$, Hydrolysis of **100e** yielded compound **68e**.

***tert*-Butyl (*S*)-5-chloro-2-((3-(4-cyanophenyl)-1-methoxy-1-oxopropan-2-yl)carbamoyl)-1*H*-indole-1-carboxylate (100f).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.46 (dd, *J* = 8.3, 2.0 Hz, 2H), 7.33 (d, *J* = 2.2 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.16 (dt, *J* = 9.0, 2.3

Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 4.95 (dt, *J* = 8.0, 6.0 Hz, 1H), 3.64 (d, *J* = 2.0 Hz, 3H), 3.25 (ddd, *J* = 14.0, 5.9, 2.2 Hz, 1H), 3.11 (dd, *J* = 13.9, 6.4 Hz, 1H), 1.47 (d, *J* = 2.4 Hz, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.1, 161.5, 148.8, 141.7, 135.2, 134.8, 132.2, 130.2, 128.73, 128.69, 126.3, 121.1, 118.6, 116.2, 111.0, 110.5, 85.2, 53.2, 52.6, 37.9, 27.7. MS (ESI) m/z = 504.2 $[M + Na]^+$, 480.2 $[M - H]^-$, Hydrolysis of **100f** yielded compound **68f**.

***tert*-Butyl (*S*)-5-chloro-2-((1-methoxy-3-(4-methoxyphenyl)-1-oxopropan-2-yl)carbamoyl)-1*H*-indole-1-carboxylate (100g).** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.20 – 7.82 (m, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.30 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.12 – 7.00 (m, 2H), 6.92 – 6.74 (m, 2H), 6.69 – 6.50 (m, 2H), 5.03 (dt, *J* = 8.0, 5.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.23 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.15 (dd, *J* = 14.0, 5.6 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.7, 161.3, 158.8, 148.8, 135.4, 135.2, 130.4, 128.78, 128.76, 127.5, 126.3, 121.0, 116.3, 114.1, 110.3, 85.1, 55.2, 53.5, 52.5, 37.1, 27.8. MS (ESI) m/z = 509.1 $[M + Na]^+$, Hydrolysis of **100g** yielded compound **68g**.

Methyl (*S*)-2-(4,6-dichloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanoate (99h). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.04 (s, 1H), 9.15 (d, *J* = 8.0 Hz, 1H), 7.91 – 7.77 (m, 4H), 7.55 – 7.41 (m, 3H), 7.41 – 7.31 (m, 2H), 7.23 (d, *J* = 1.7 Hz, 1H), 4.86 (ddd, *J* = 10.1, 8.0, 5.3 Hz, 1H), 3.66 (s, 3H), 3.38 (dd, *J* = 13.9, 5.3 Hz, 1H), 3.26 (dd, *J* = 13.9, 10.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3, 160.7, 137.3, 135.6, 133.4, 133.0, 132.3, 128.4, 128.2, 128.0, 127.93, 127.87, 127.8, 126.9, 126.5, 126.0, 125.1, 120.0, 111.6, 101.9, 54.4, 52.6, 37.0. MS (ESI) m/z = 463.1 $[M + Na]^+$

(*S*)-2-(4,6-Dichloro-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanoic acid (68h). ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.01 (s, 1H), 8.86 (s, 1H), 7.82 – 7.66 (m, 4H), 7.60 (d, *J* = 6.4 Hz, 1H), 7.49 – 7.30 (m, 3H), 7.14 (d, *J* = 1.7 Hz, 1H), 6.96 (d, *J* = 3.2 Hz, 1H), 4.70 – 4.45 (m, 1H), 3.37-3.32 (m, 1H), 3.14 (dd, *J* = 13.5, 8.0 Hz, 1H). MS (ESI) m/z = 449.1 $[M + Na]^+$

5-Ethyl 1-methyl ((*S*)-4-ethoxy-2-((*S*)-2-(5-methoxy-1*H*-indole-2-carboxamido)-3-(naphthalen-2-yl)propanamido)-4-oxobutanoyl)-*L*-glutamate ((Et)-15). To a solution of compound **15** (60 mg, 0.09 mmol), EtOH (52 uL, 0.9 mmol) and EDC·HCl (69 mg, 0.36 mmol) in CH_2Cl_2, was added DMAP (1 mg, 0.009 mmol). The mixture was stirred at rt overnight. Then the organic phase was washed with water and dried over Na_2SO_4. The pure compound was obtained by column chromatography (40% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.25 – 10.13 (m, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.72 – 7.62 (m, 4H), 7.40 – 7.29 (m, 5H), 7.02 – 6.91 (m, 2H), 6.80 (d, *J* = 6.4 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 5.12 (q, *J* = 6.6 Hz, 1H), 4.90 (ddd, *J* = 8.7, 6.3, 4.4 Hz, 1H), 4.43 (td, *J* = 8.0, 5.3 Hz, 1H), 4.13 (qd, *J* = 7.1, 1.8 Hz, 2H), 3.95 (qd, *J* = 7.1, 2.5 Hz, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 3.43 (dd, *J* = 13.9, 6.1 Hz, 1H), 3.33 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.01 (dd, *J* = 17.4, 4.4 Hz, 1H), 2.62 (dd, *J* = 17.3, 6.4 Hz, 1H), 2.45 – 2.28 (m, 2H), 2.17 (ddt, *J* = 11.6, 9.6, 5.9 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.4, 171.8, 171.6, 170.7, 170.4, 154.6, 133.5, 132.5, 132.4, 129.8, 128.7, 127.9, 127.6, 127.5, 127.0, 126.3, 125.8, 116.3, 113.3, 102.9, 102.0, 77.2, 61.1, 60.9, 55.7, 55.0, 52.4, 52.1, 49.1, 38.3, 35.9, 30.4, 26.9, 14.1, 13.9. HRMS (ESI) Calcd for $C_{37}H_{42}N_4O_{10}$ $(M+Na)^+$ 725.2793, found 725.2776. HPLC purity 98.4%, t_R = 13.73 min (condition A2); 98.1%, t_R = 15.42 min (condition B2).

HPLC Conditions and Traces:. The purity of final compounds **2–57** and **(Et)-15** was determined by HPLC analysis. The instrument was an Agilent 1260 Infinity II HPLC system with a quaternary pump, a vial sampler, and a DAD detector. A Kromasil 300–5–C18 column (4.6 × 250 mm) was used. The DAD detector was set to 220, 254, and 280 nm. The purity of all tested compounds was >95%. Some HPLC traces are shown below.

Condition A1. Elute with gradient starting with 0.1% TFA in water and end with 0.1% TFA in water and acetonitrile mixture (water with 0.1% TFA : acetonitrile = 1 : 1) in 6 min, and then change to a 5 min-gradient starting with 0.1% TFA in water and acetonitrile 1 : 1 mixture and ending with 100% acetonitrile, and at last elute with 100% acetonitrile for 9 min.

Condition A2. Elute with gradient starting with 0.1% TFA in water and end with 0.1% TFA in water and acetonitrile mixture (water with 0.1% TFA : acetonitrile = 1 : 1) in 10 min, and then change to a 5-min gradient starting with 0.1% TFA in water and acetonitrile 1 : 1 mixture and ending with 100% acetonitrile, and at last elute with 100% acetonitrile for 5 min.

Condition B1. Elute with gradient starting with 0.1% TFA in water and end with 0.1% TFA in water and methanol mixture (water with 0.1% TFA : methanol = 30 : 70) in 8 min, and then change to a 4-min gradient starting with 0.1% TFA in water and methanol 30 : 70 mixture and ending with 0.1% TFA in water and methanol 5 : 95 mixture, and at last elute with 0.1% TFA in water and methanol 5 : 95 mixture for 8 min.

Condition B2. Elute with gradient starting with 0.1% TFA in water and end with 0.1% TFA in water and methanol mixture (water with 0.1% TFA : methanol = 30 : 70) in 12 min, and then change to a 4-min gradient starting with 0.1% TFA in water and methanol 30 : 70 mixture and ending with 0.1% TFA in water and methanol 5 : 95 mixture, and at last elute with 0.1% TFA in water and methanol 5 : 95 mixture for 4 min.

Compound 52, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-05-20 09-06-40\001-P1-F1-ZW-5-64-4-2.D
Sample Name: ZW-5-64-4-2

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Acq. Instrument : HPLC                           Location :   P1-F1
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Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-05-20 09-06-40\Zhen.M-2.M (Sequence Method)
Last changed    : 5/20/2018 9:06:40 AM by SYSTEM
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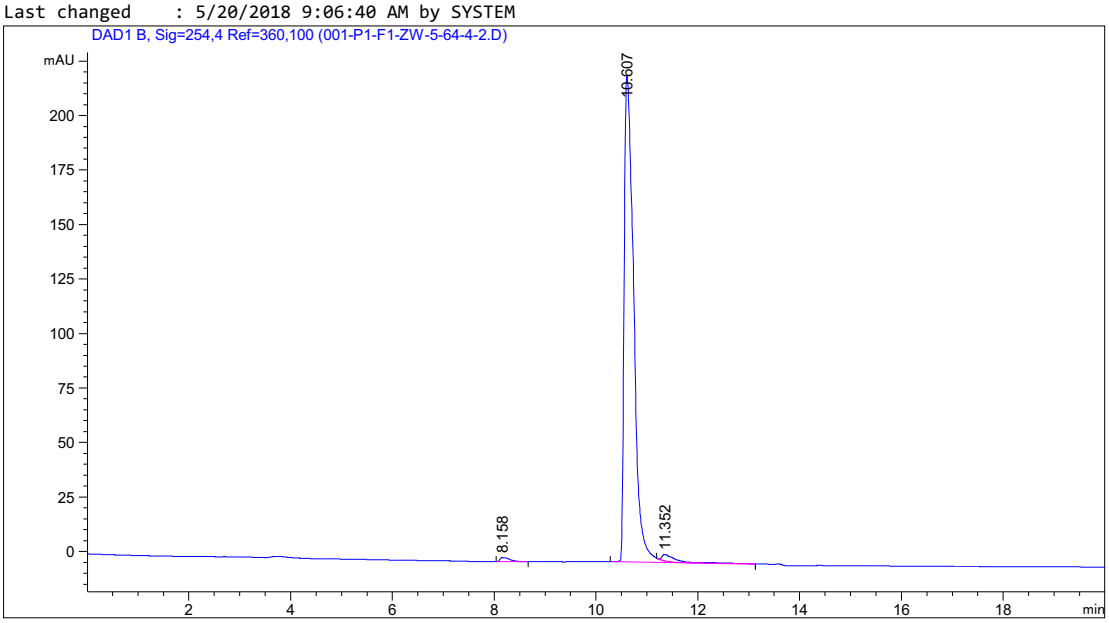



```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.158 BB    0.1776   24.20502    1.79153   0.8092
   2  10.607 BV R  0.1879 2902.11816  222.82851  97.0210
   3  11.352 VB E  0.2875   64.90414    2.98676   2.1698

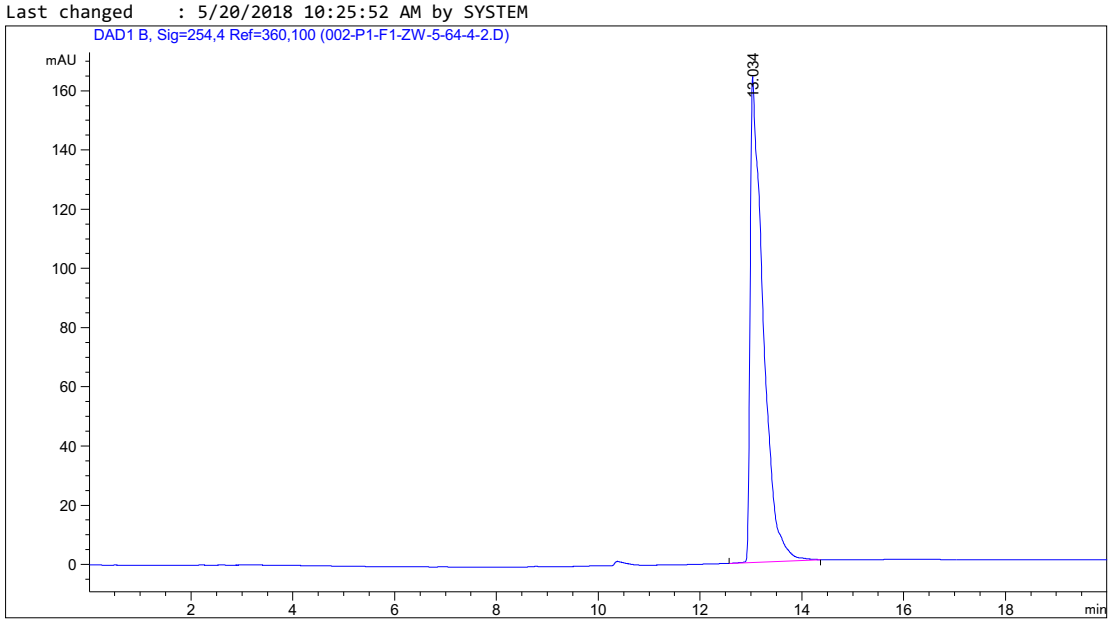
Totals :                  2991.22733  227.60679


==========================================================================
                        *** End of Report ***
```

Compound 52, condition B1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-05-20 10-25-31\002-P1-F1-ZW-5-64-4-2.D
Sample Name: ZW-5-64-4-2

```
==================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : HPLC                           Location :   P1-F1
Injection Date  : 5/20/2018 10:57:47 AM               Inj :   1
                                                Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-05-20 10-25-31\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-05-20 10-25-31\Zhen_MeOH.M-2.M (Sequence
                  Method)
Last changed    : 5/20/2018 10:25:52 AM by SYSTEM
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.034 BB    0.2302 2899.89136  164.08179 100.0000

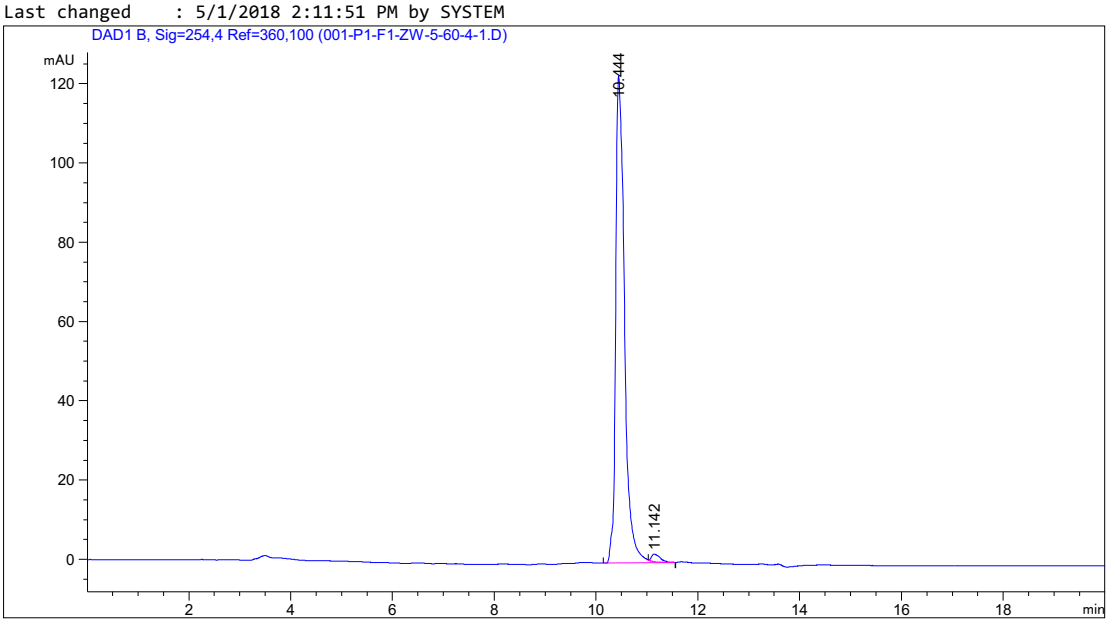
Totals :                  2899.89136  164.08179


==================================================================
                        *** End of Report ***
```

Compound 53, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-05-01 14-11-51\001-P1-F1-ZW-5-60-4-1.D
Sample Name: ZW-5-60-4-1

```
======================================================================
Acq. Operator   : SYSTEM                       Seq. Line :   1
Acq. Instrument : HPLC                          Location :   P1-F1
Injection Date  : 5/1/2018 2:15:27 PM                Inj :   1
                                               Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-05-01 14-11-51\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-05-01 14-11-51\Zhen.M-2.M (Sequence Method)
Last changed    : 5/1/2018 2:11:51 PM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.444 BV R  0.1663 1476.01453  122.70236  98.4698
   2  11.142 VB E  0.1667   22.93664    1.92876   1.5302

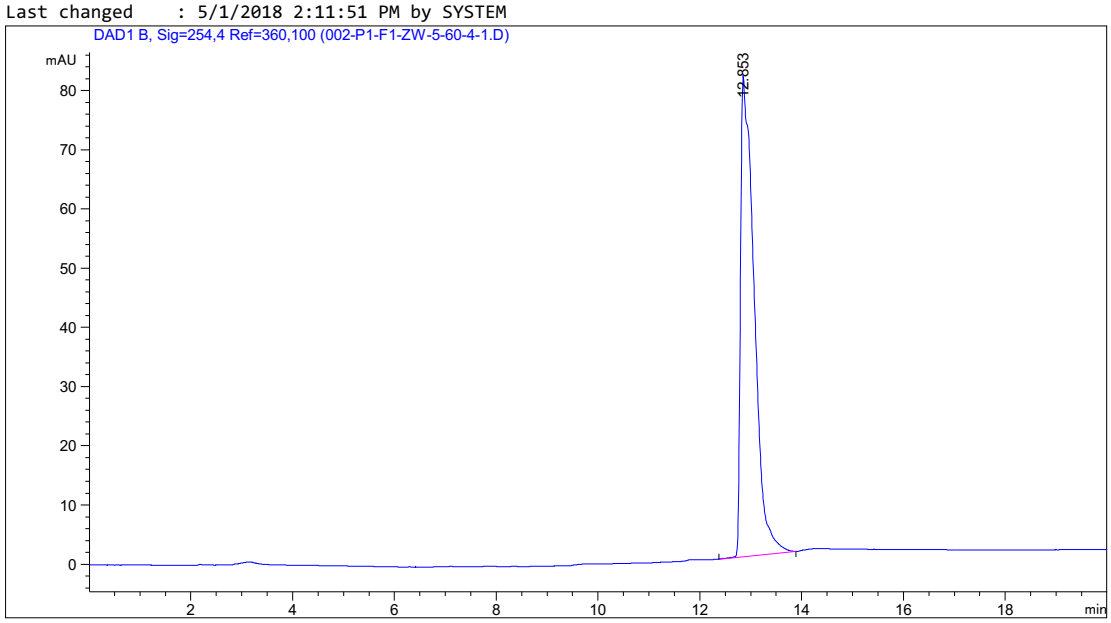
Totals :                  1498.95116  124.63113


======================================================================
                        *** End of Report ***
```

Compound 53, condition B1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-05-01 14-11-51\002-P1-F1-ZW-5-60-4-1.D
Sample Name: ZW-5-60-4-1

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : HPLC                           Location :   P1-F1
Injection Date  : 5/1/2018 2:44:04 PM                 Inj :   1
                                                Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-05-01 14-11-51\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-05-01 14-11-51\Zhen_MeOH.M-2.M (Sequence
                  Method)
Last changed    : 5/1/2018 2:11:51 PM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.853 BB    0.2422 1502.99744   81.10352 100.0000

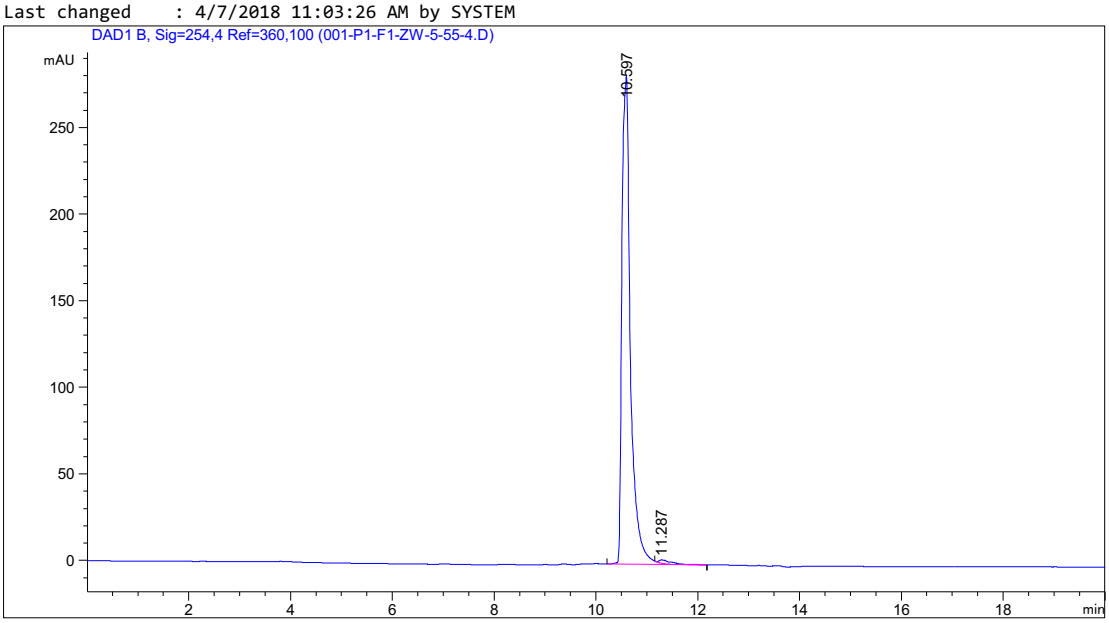
Totals :                  1502.99744   81.10352


======================================================================
                        *** End of Report ***
```

Compound 54, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-04-07 11-03-26\001-P1-F1-ZW-5-55-4.D
Sample Name: ZW-5-55-4

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : HPLC                           Location :   P1-F1
Injection Date  : 4/7/2018 11:07:21 AM                Inj :   1
                                                Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-04-07 11-03-26\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-04-07 11-03-26\Zhen.M-2.M (Sequence Method)
Last changed    : 4/7/2018 11:03:26 AM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.597 BV R  0.1802 3291.28394  281.87790  98.8742
   2  11.287 VB E  0.2503   37.47647    1.89877   1.1258

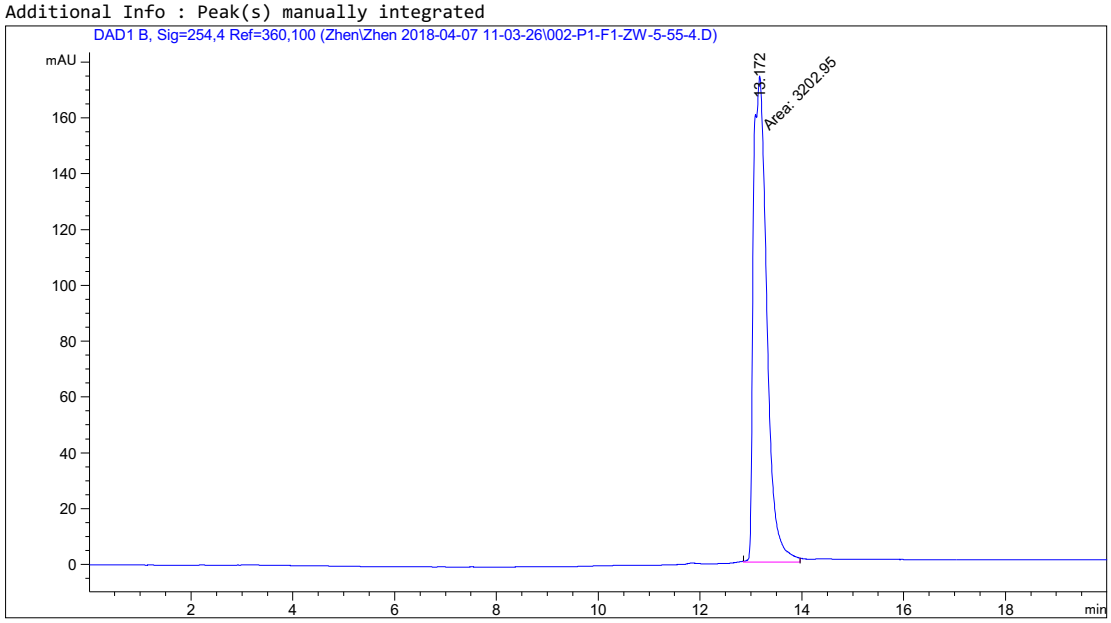
Totals :                  3328.76041  283.77667


======================================================================
                        *** End of Report ***
```

Compound 54, condition B1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-04-07 11-03-26\002-P1-F1-ZW-5-55-4.D
Sample Name: ZW-5-55-4

```
======================================================================
Acq. Operator   : SYSTEM                       Seq. Line :   2
Acq. Instrument : HPLC                          Location :   P1-F1
Injection Date  : 4/7/2018 11:35:58 AM               Inj :   1
                                               Inj Volume : 20.000 µl
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-04-07 11-03-26\Zhen_MeOH.M-2.M (Sequence
                  Method)
Last changed    : 4/7/2018 11:27:18 AM by SYSTEM
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.172 MM    0.3068 3202.94531  173.99074 100.0000

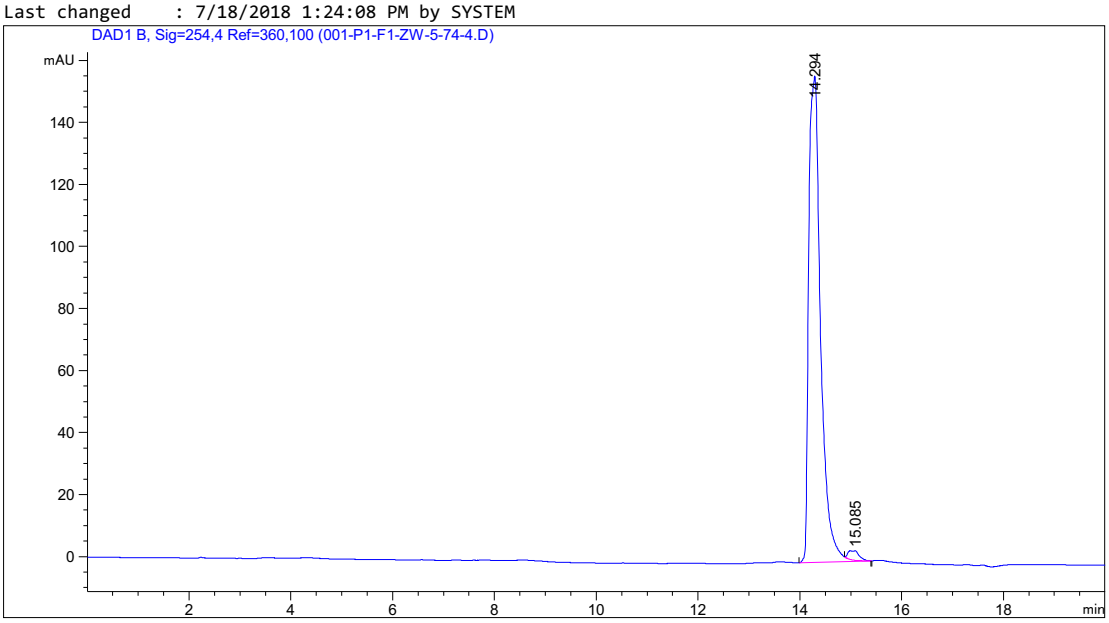
Totals :                  3202.94531  173.99074


======================================================================
                        *** End of Report ***
```

Compound 55, condition A2.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-07-18 13-24-08\001-P1-F1-ZW-5-74-4.D
Sample Name: ZW-5-74-4

```
======================================================================
Acq. Operator   : SYSTEM                       Seq. Line :   1
Acq. Instrument : HPLC                          Location :   P1-F1
Injection Date  : 7/18/2018 1:27:45 PM               Inj :   1
                                               Inj Volume : 80.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-07-18 13-24-08\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-07-18 13-24-08\Zhen.M (Sequence Method)
Last changed    : 7/18/2018 1:24:08 PM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.294 BV R  0.2148 2534.75439  156.64259  98.2732
   2  15.085 VB E  0.1882   44.53917    3.05366   1.7268

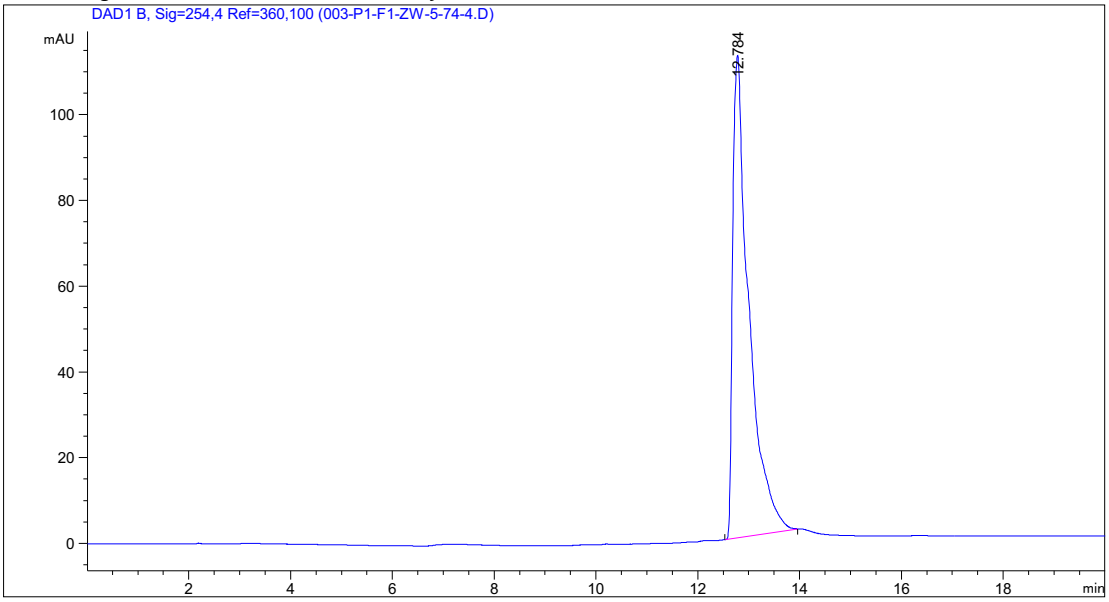
Totals :                  2579.29356  159.69625


======================================================================
                          *** End of Report ***
```

Compound 55, condition B1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-07-18 13-24-08\003-P1-F1-ZW-5-74-4.D
Sample Name: ZW-5-74-4

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   3
Acq. Instrument : HPLC                           Location :   P1-F1
Injection Date  : 7/18/2018 2:24:58 PM                Inj :   1
                                                Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-07-18 13-24-08\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-07-18 13-24-08\Zhen_MeOH.M-2.M (Sequence
                  Method)
Last changed    : 7/18/2018 1:40:14 PM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.784 BB    0.3094 2480.26758  112.43984 100.0000

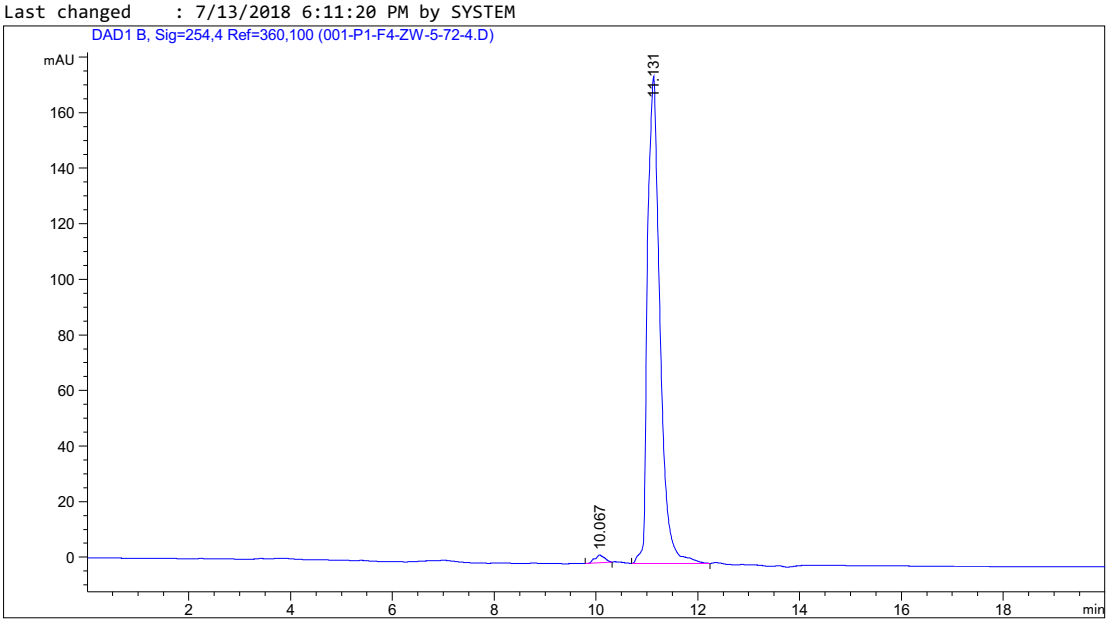
Totals :                  2480.26758  112.43984


======================================================================
                        *** End of Report ***
```

Compound 56, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-07-13 18-11-19\001-P1-F4-ZW-5-72-4.D
Sample Name: ZW-5-72-4

```
==========================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : HPLC                          Location :   P1-F4
Injection Date  : 7/13/2018 6:14:57 PM               Inj :   1
                                               Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-07-13 18-11-19\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-07-13 18-11-19\Zhen.M-2.M (Sequence Method)
Last changed    : 7/13/2018 6:11:20 PM by SYSTEM
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.067 BB    0.1715   36.76062    2.83132   1.2274
   2  11.131 BB    0.2270 2958.34180  175.15872  98.7726

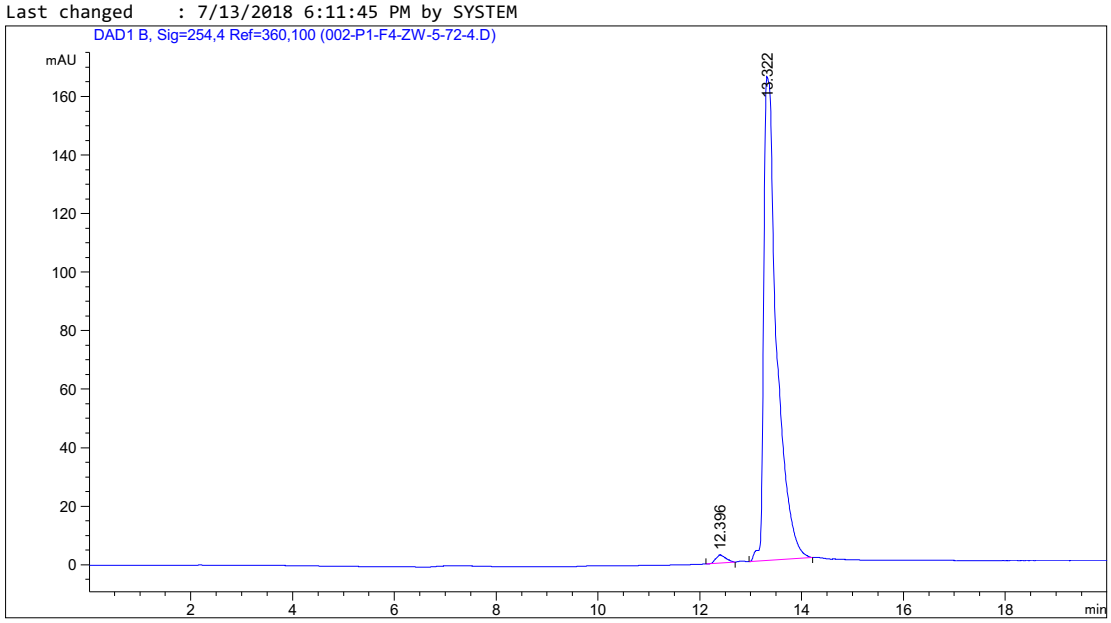
Totals :                  2995.10241  177.99004


==========================================================================
                        *** End of Report ***
```

Compound 56, condition B1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-07-13 18-11-19\002-P1-F4-ZW-5-72-4.D
Sample Name: ZW-5-72-4

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   2
Acq. Instrument : HPLC                           Location :   P1-F4
Injection Date  : 7/13/2018 6:43:36 PM                Inj :   1
                                                Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-07-13 18-11-19\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-07-13 18-11-19\Zhen_MeOH.M-2.M (Sequence
                  Method)
Last changed    : 7/13/2018 6:11:45 PM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.396 BB    0.1781   37.51956    2.80441   1.2655
   2  13.322 BB    0.2305 2927.27856  165.38649  98.7345

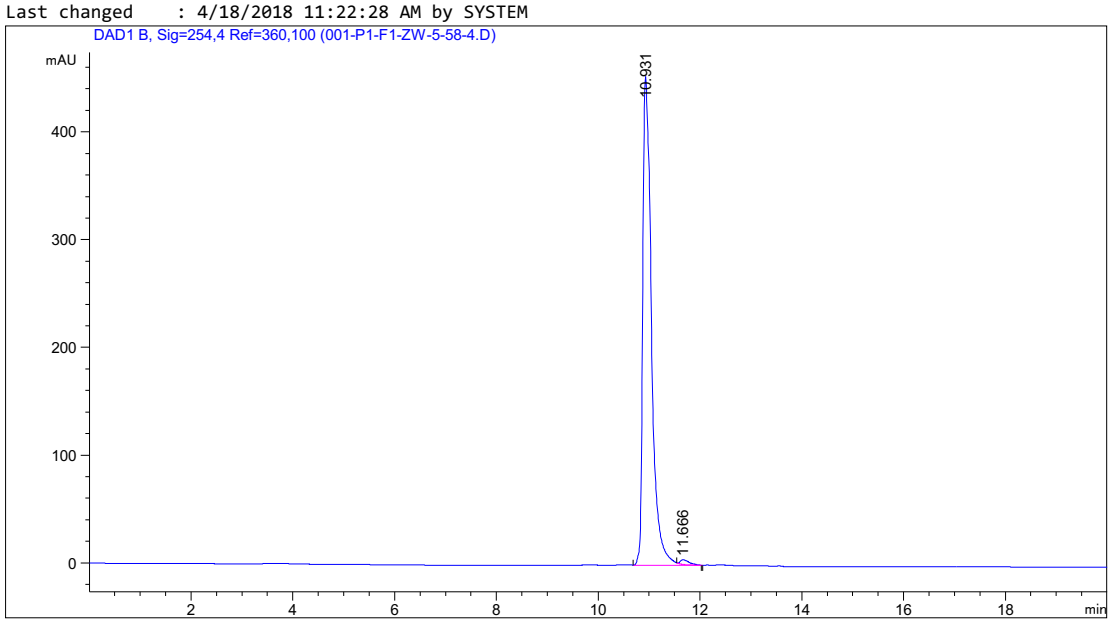
Totals :                  2964.79812  168.19090


======================================================================
                        *** End of Report ***
```

Compound 57, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-04-18 11-22-28\001-P1-F1-ZW-5-58-4.D
Sample Name: ZW-5-58-4

```
==================================================================
Acq. Operator   : SYSTEM                       Seq. Line :   1
Acq. Instrument : HPLC                          Location :   P1-F1
Injection Date  : 4/18/2018 11:25:58 AM              Inj :   1
                                                Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-04-18 11-22-28\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-04-18 11-22-28\Zhen.M-2.M (Sequence Method)
Last changed    : 4/18/2018 11:22:28 AM by SYSTEM
```




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  10.931 BV R  0.1650 5406.46191  453.77237  99.0072
   2  11.666 VB E  0.1705   54.21277    4.37616   0.9928

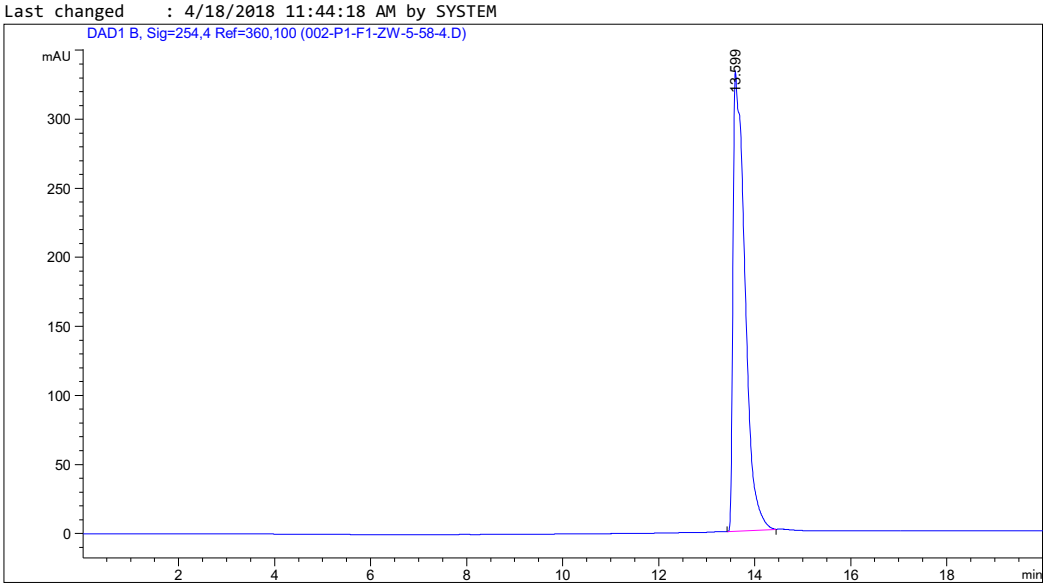
Totals :                  5460.67468  458.14853


==================================================================
                        *** End of Report ***
```

Compound 57, condition B1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-04-18 11-22-28\002-P1-F1-ZW-5-58-4.D
Sample Name: ZW-5-58-4

```
=====================================================================
Acq. Operator   : SYSTEM                       Seq. Line :   2
Acq. Instrument : HPLC                          Location :   P1-F1
Injection Date  : 4/18/2018 11:54:37 AM              Inj :   1
                                               Inj Volume : 20.000 µl
Sequence File   : C:\Chem32\1\Data\Zhen\Zhen 2018-04-18 11-22-28\Zhen.S
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-04-18 11-22-28\Zhen_MeOH.M-2.M (Sequence
                  Method)
Last changed    : 4/18/2018 11:44:18 AM by SYSTEM
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.599 BB    0.2259 5754.13232  332.48322 100.0000

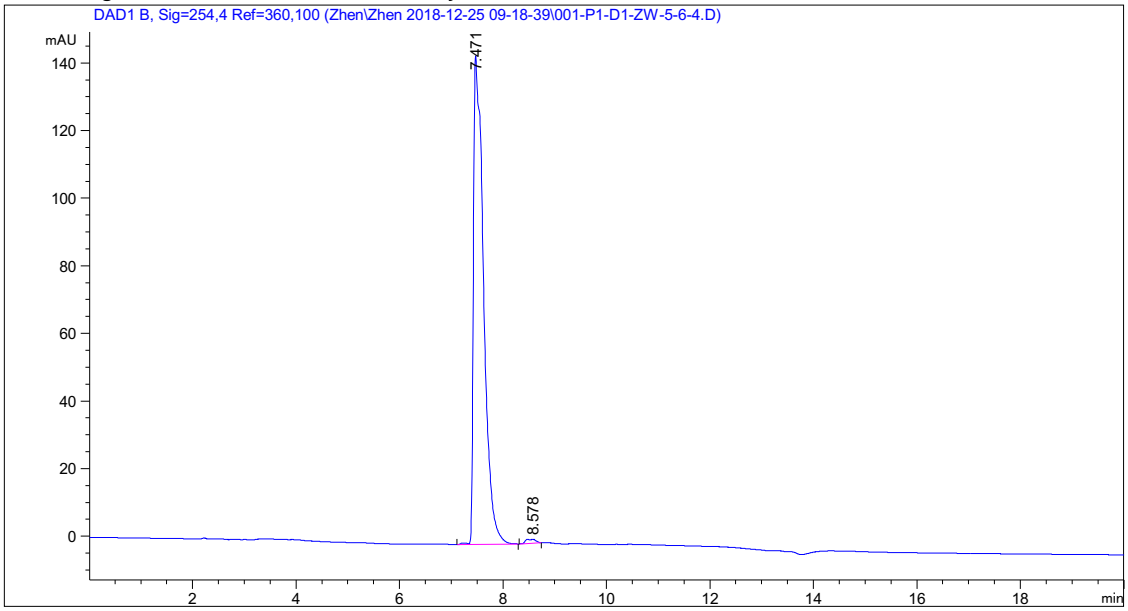
Totals :                  5754.13232  332.48322


=====================================================================
                        *** End of Report ***
```

Compound 4, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2018-12-25 09-18-39\001-P1-D1-ZW-5-6-4.D
Sample Name: ZW-5-6-4

```
======================================================================
Acq. Operator   : SYSTEM                       Seq. Line :   1
Acq. Instrument : HPLC                          Location :   P1-D1
Injection Date  : 12/25/2018 9:25:09 AM              Inj :   1
                                               Inj Volume : 20.000 µl
Method          : C:\Chem32\1\Data\Zhen\Zhen 2018-12-25 09-18-39\Zhen.M-2.M (Sequence Method)
Last changed    : 12/25/2018 9:18:40 AM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.471 BB    0.1788 1965.25171  144.38025  99.2124
   2   8.578 BB    0.1819   15.60179    1.13865   0.7876

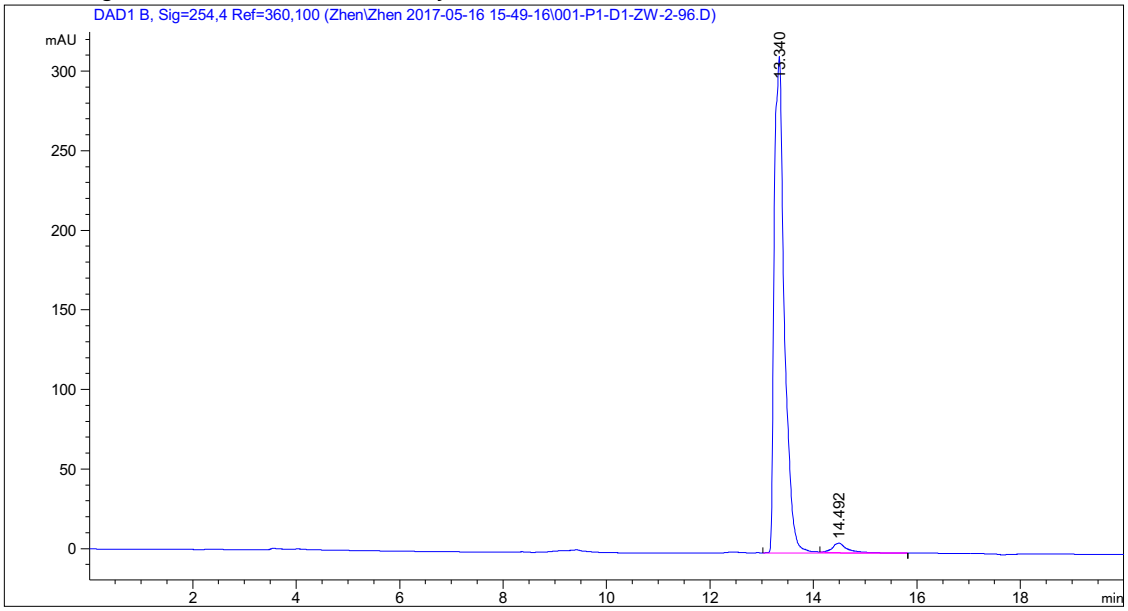
Totals :                  1980.85350  145.51890


======================================================================
                        *** End of Report ***
```

Compound 9, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2017-05-16 15-49-16\001-P1-D1-ZW-2-96.D
Sample Name: ZW-2-96

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   1
Acq. Instrument : HPLC                           Location :   P1-D1
Injection Date  : 5/16/2017 3:53:44 PM               Inj :   1
                                                Inj Volume : 20.000 µl
Method          : C:\Chem32\1\Data\Zhen\Zhen 2017-05-16 15-49-16\Zhen.M (Sequence Method)
Last changed    : 5/16/2017 3:49:16 PM by SYSTEM
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.340 BV R  0.1785 4240.89209  312.07471  97.0886
   2  14.492 VB E  0.3019  127.17232    6.03380   2.9114

Totals :                  4368.06441  318.10851


======================================================================
                        *** End of Report ***
```

Compound (Et)-15, condition A1.

Data File C:\Chem32\1\Data\Zhen\Zhen 2019-01-20 15-43-12\001-P1-F1-ZW-5-91.D
Sample Name: ZW-5-91

```
======================================================================
Acq. Operator   : SYSTEM                       Seq. Line :   1
Acq. Instrument : HPLC                         Location :   P1-F1
Injection Date  : 1/20/2019 3:49:44 PM              Inj :   1
                                              Inj Volume : 80.000 µl
Different Inj Volume from Sample Entry!  Actual Inj Volume : 20.000 µl
Method          : C:\Chem32\1\Data\Zhen\Zhen 2019-01-20 15-43-12\Zhen.M (Sequence Method)
Last changed    : 1/20/2019 3:43:12 PM by SYSTEM
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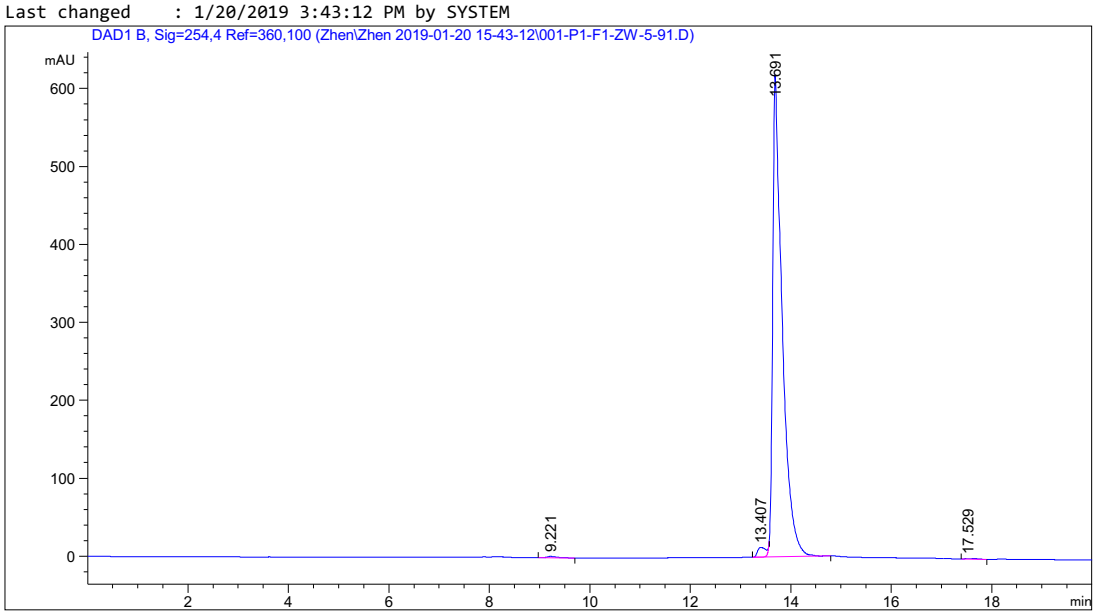


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======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=254,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   9.221 BB    0.2021   24.24774    1.74552   0.2924
   2  13.407 BV E  0.1805  140.65938   12.57143   1.6963
   3  13.691 VV R  0.1752 8108.86035  617.41132  97.7916
   4  17.529 BB    0.1914   18.21508    1.31701   0.2197

Totals :                  8291.98256  633.04528


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                        *** End of Report ***
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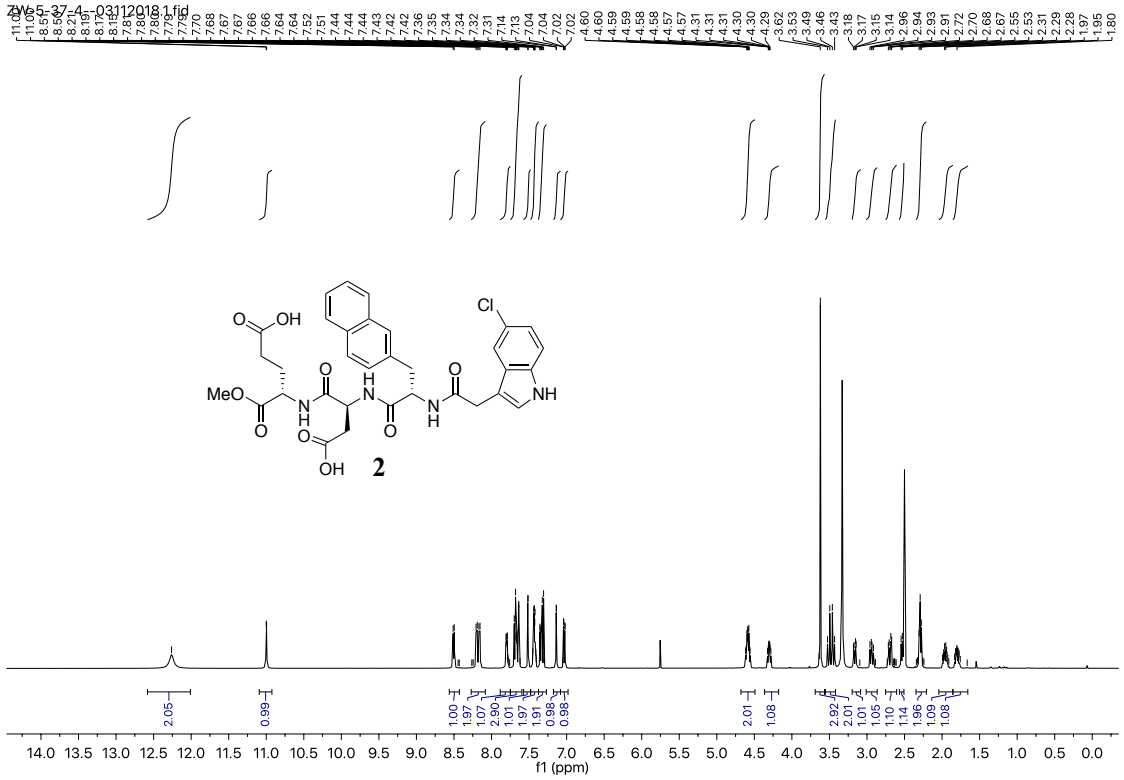
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OH
Cl
NH
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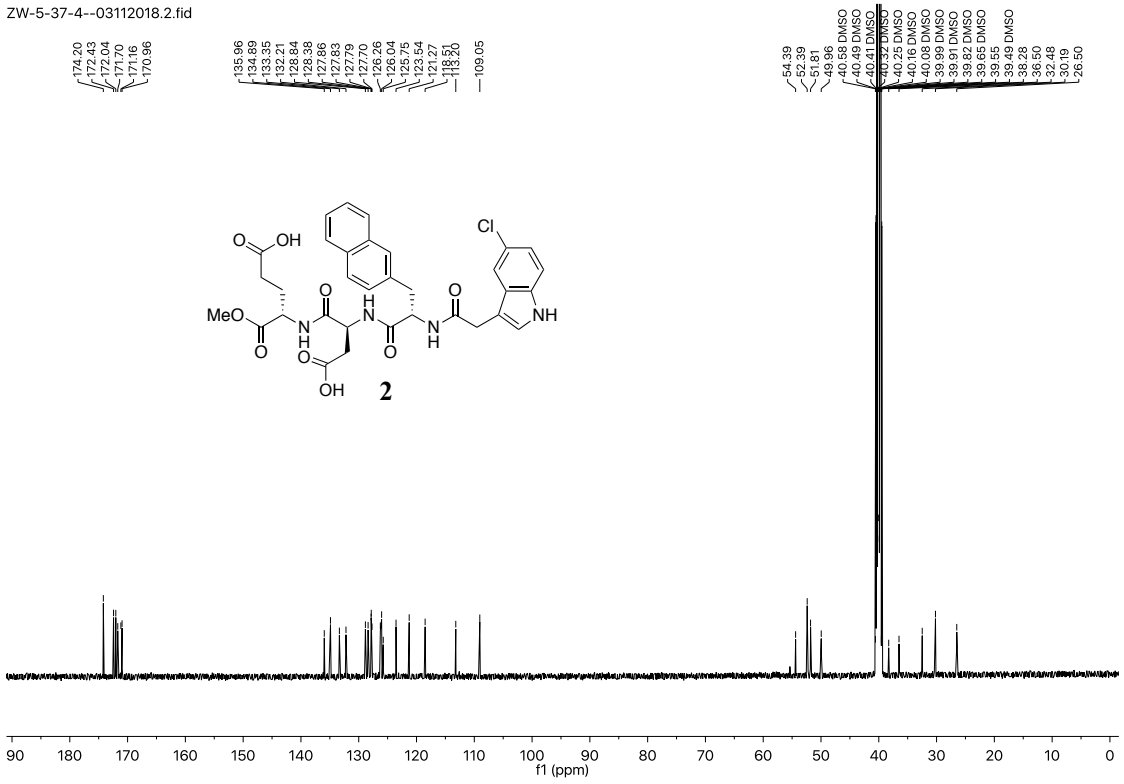
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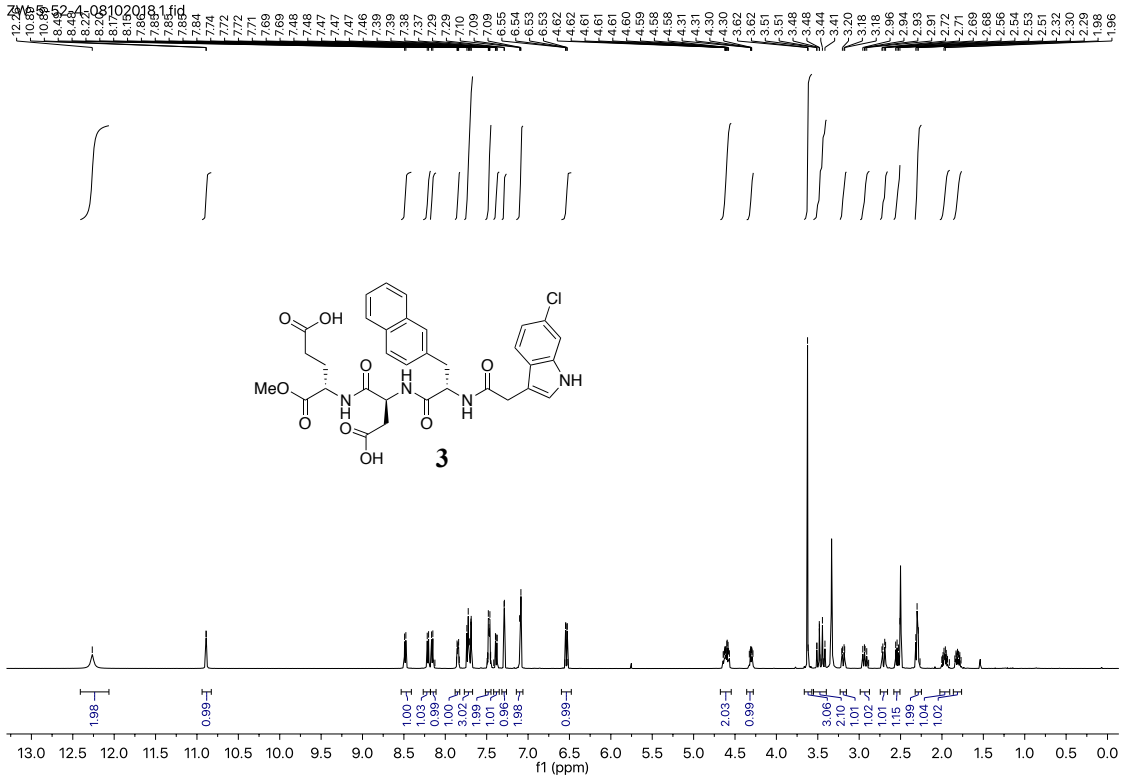
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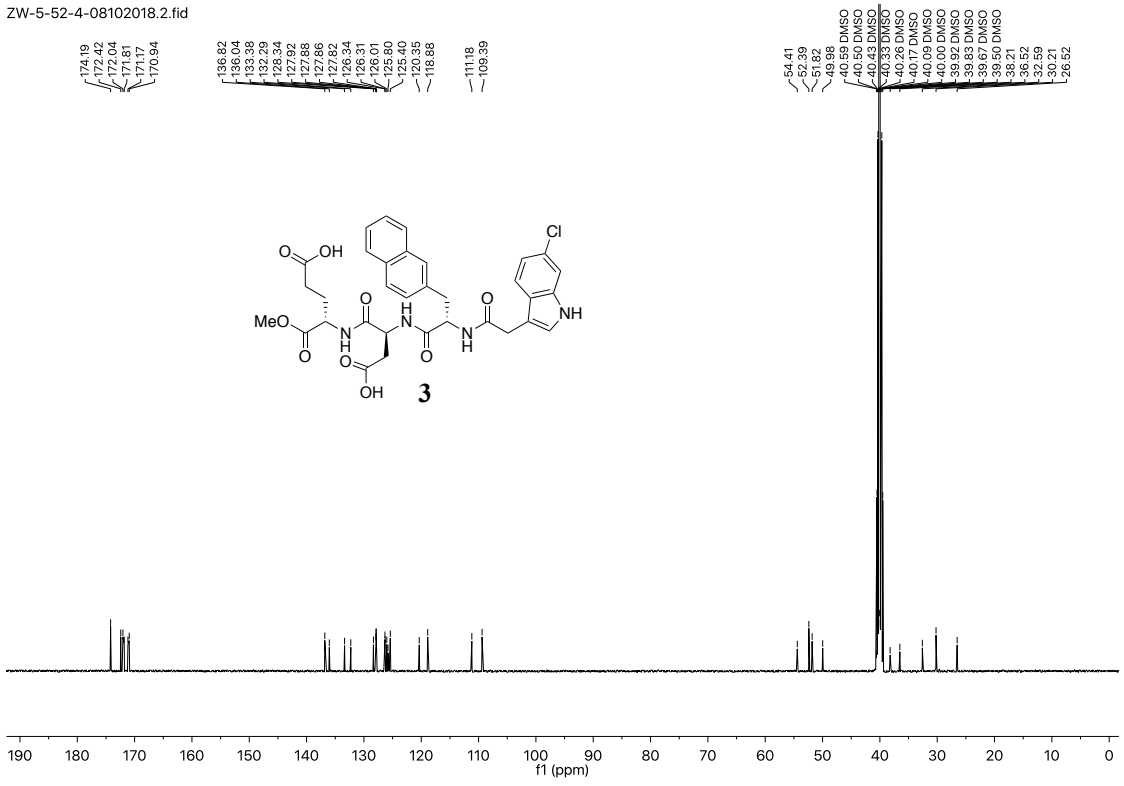
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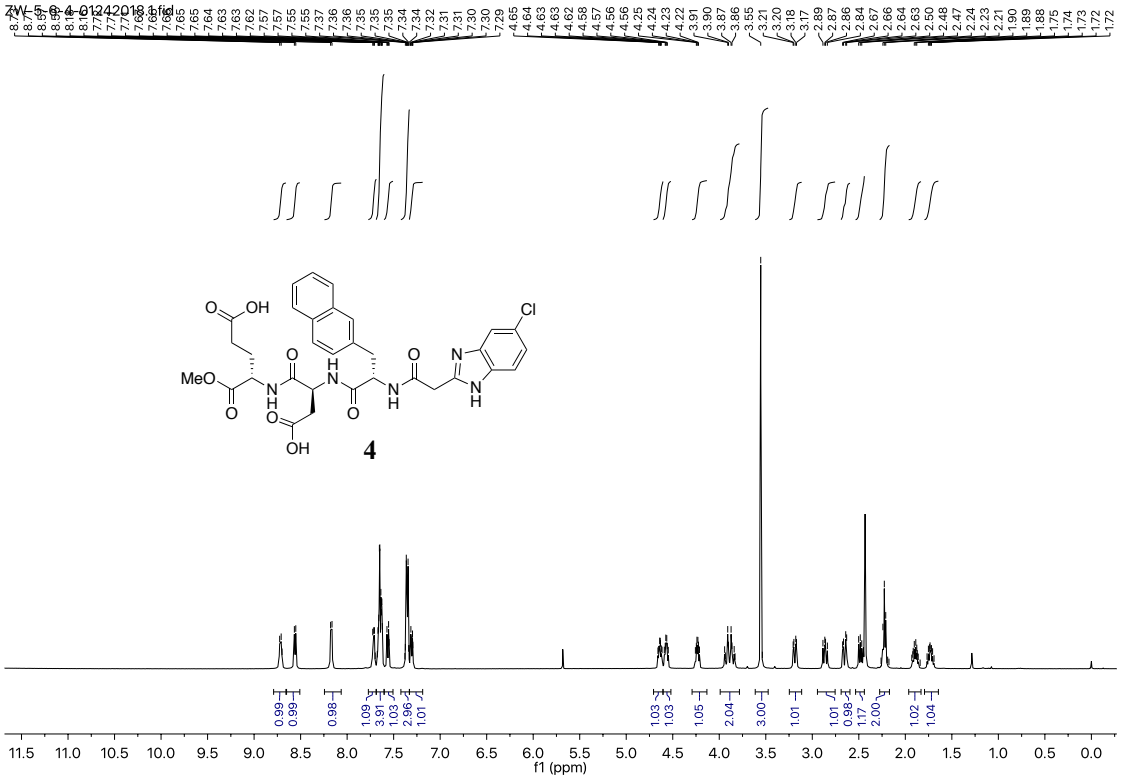

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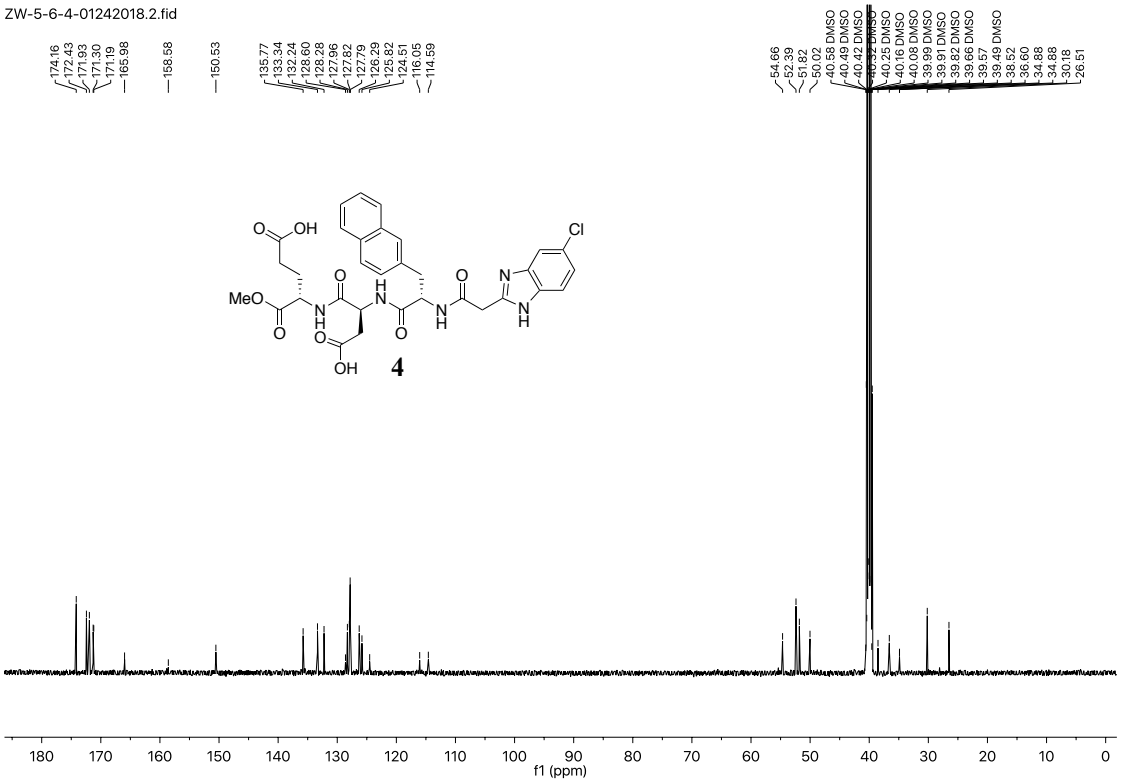

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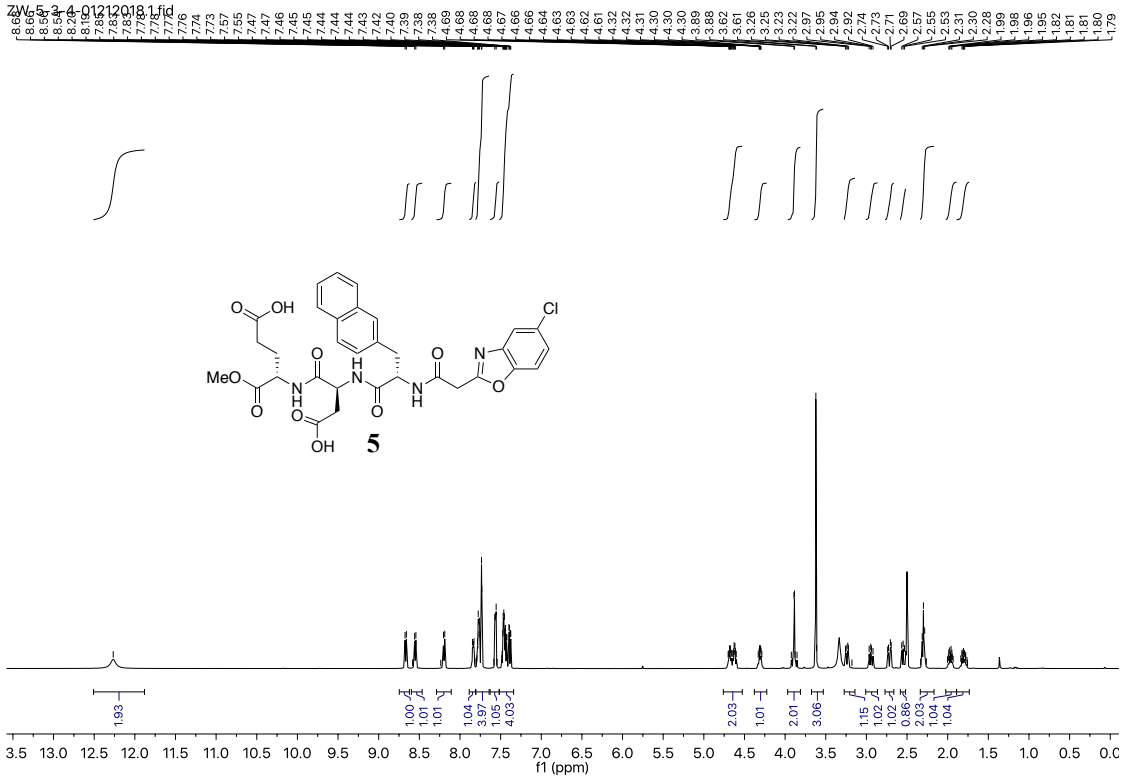
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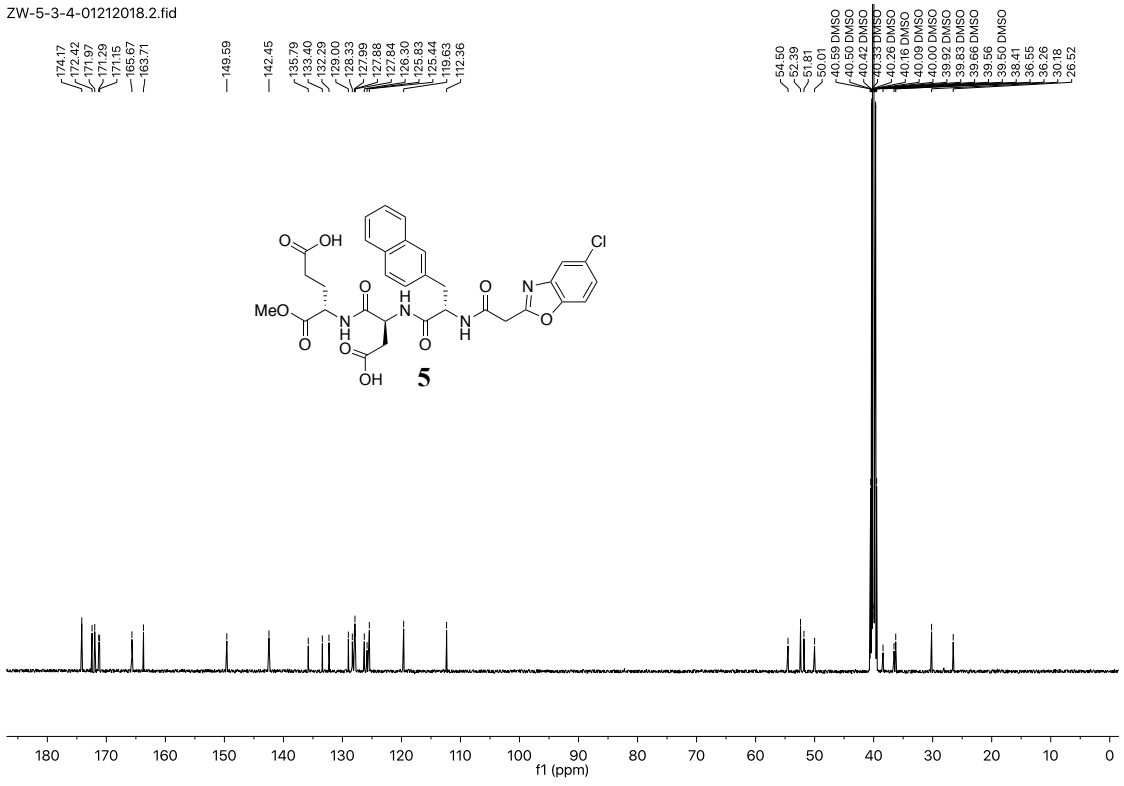
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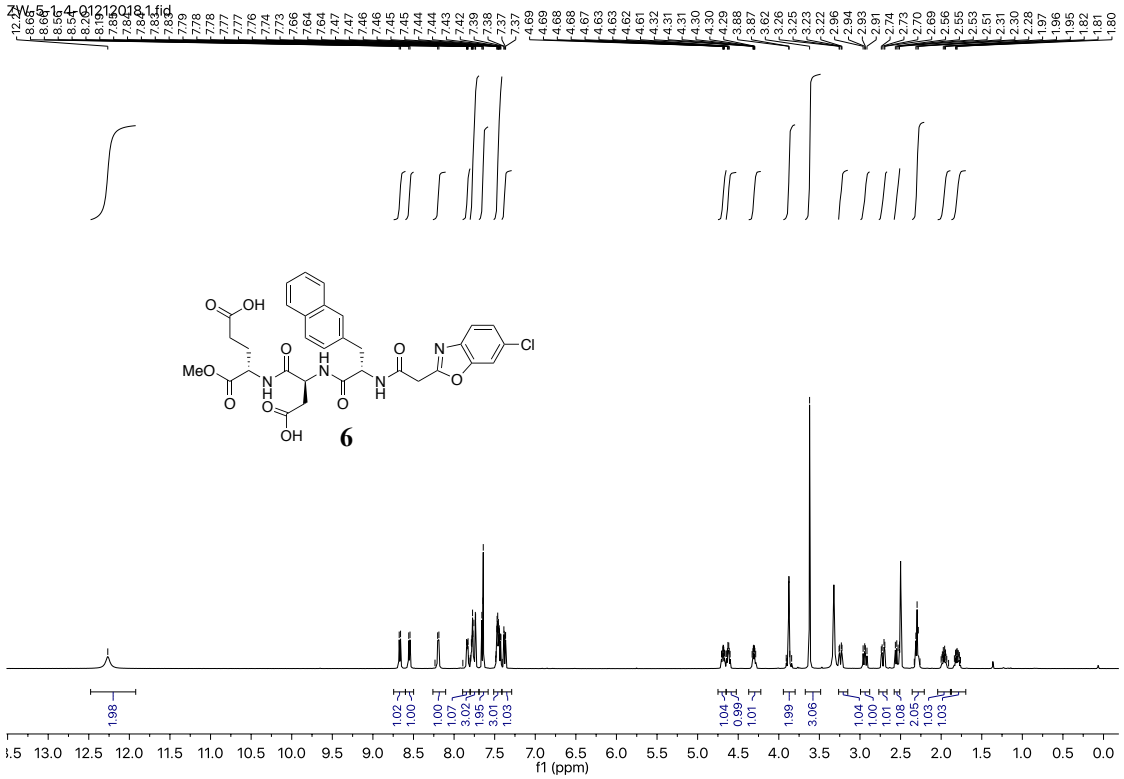
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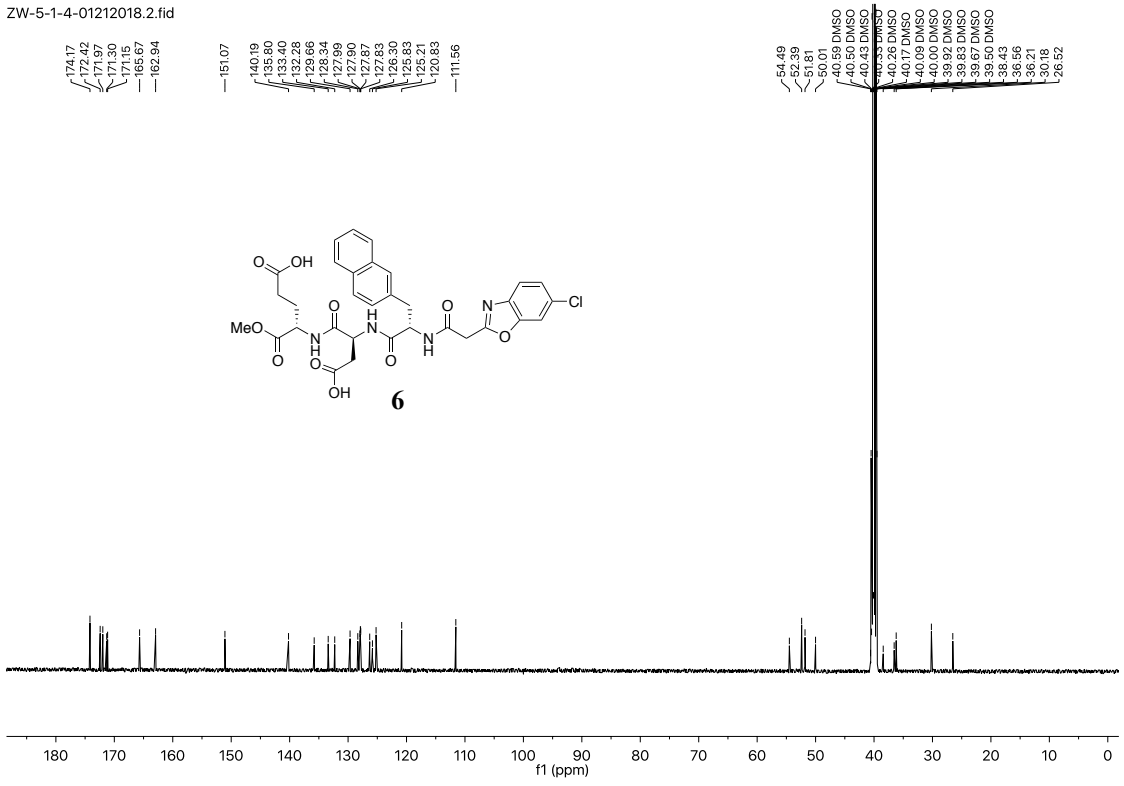
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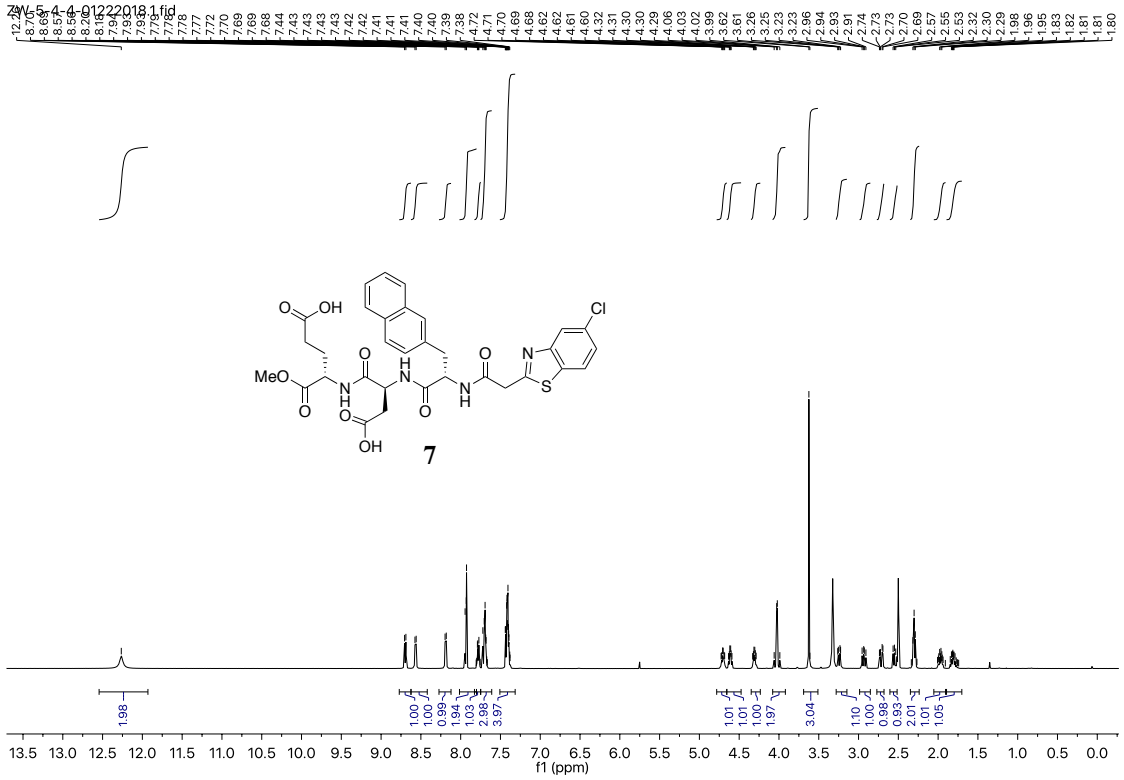
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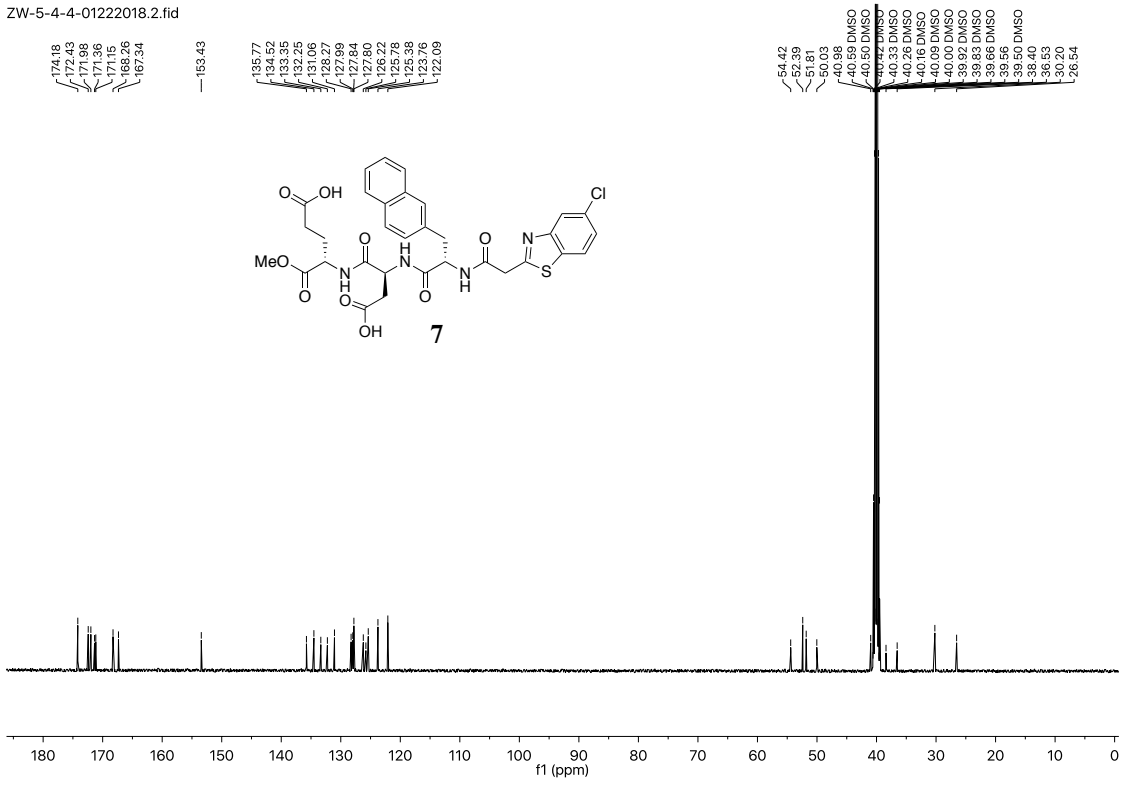
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Cl
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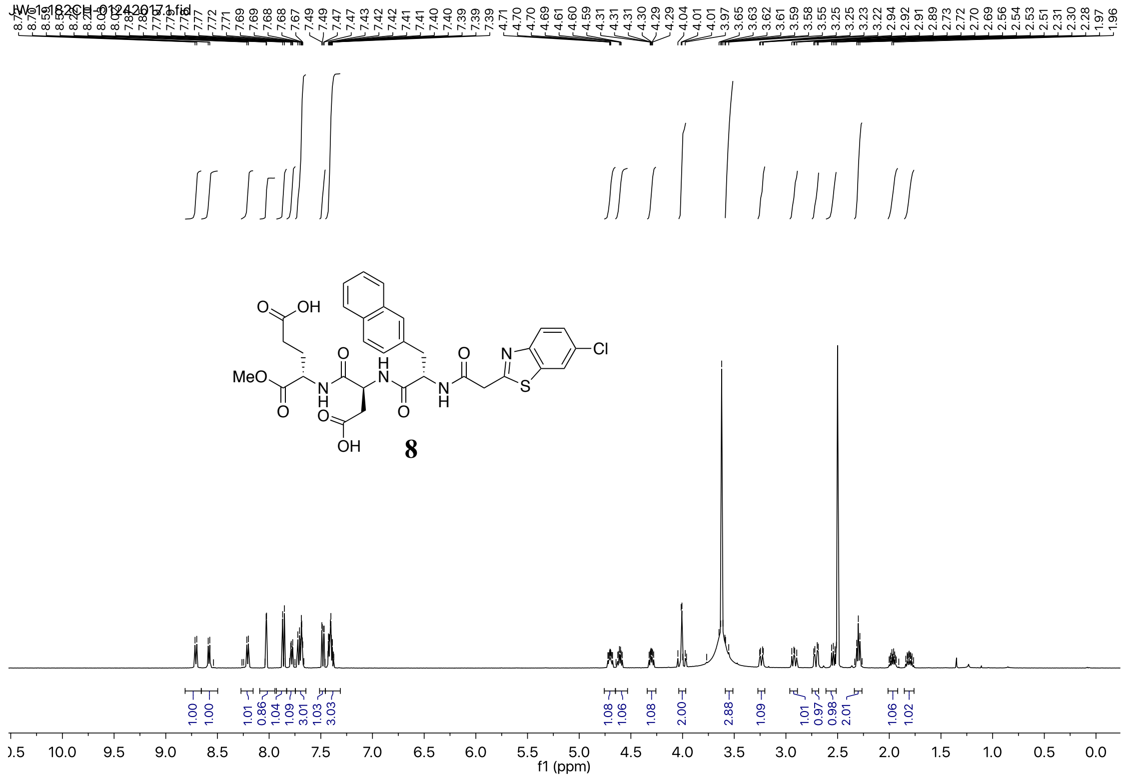
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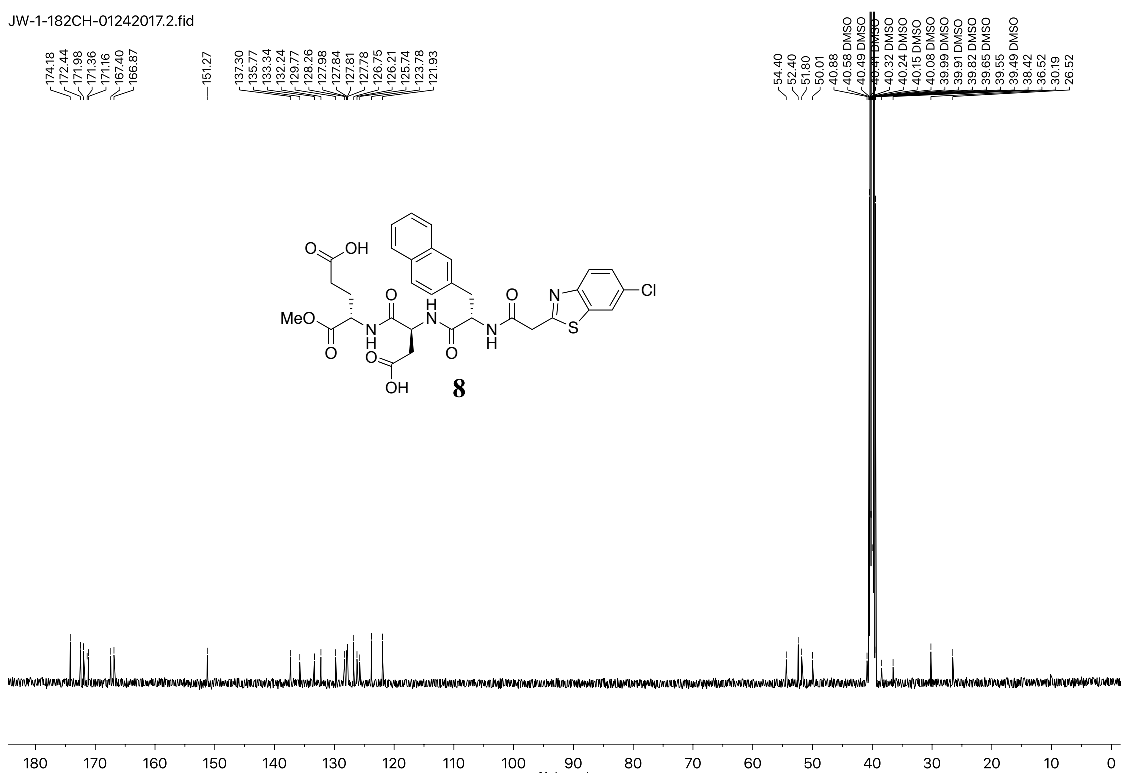
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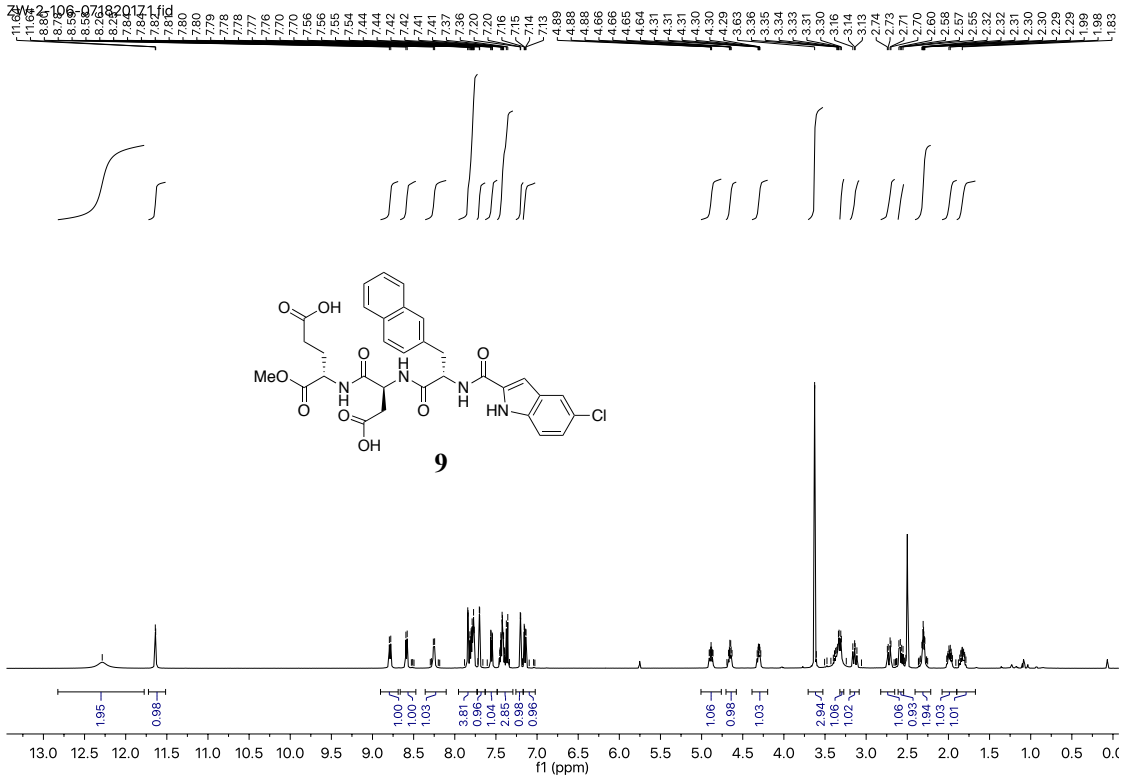
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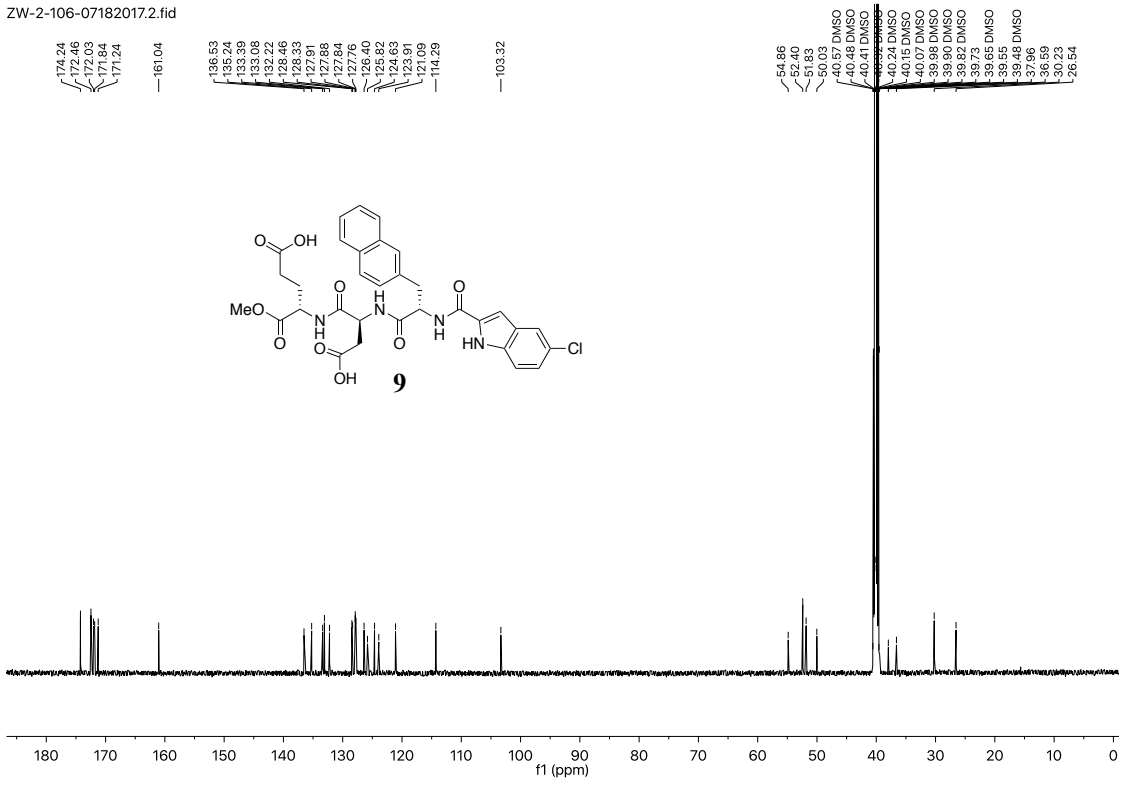
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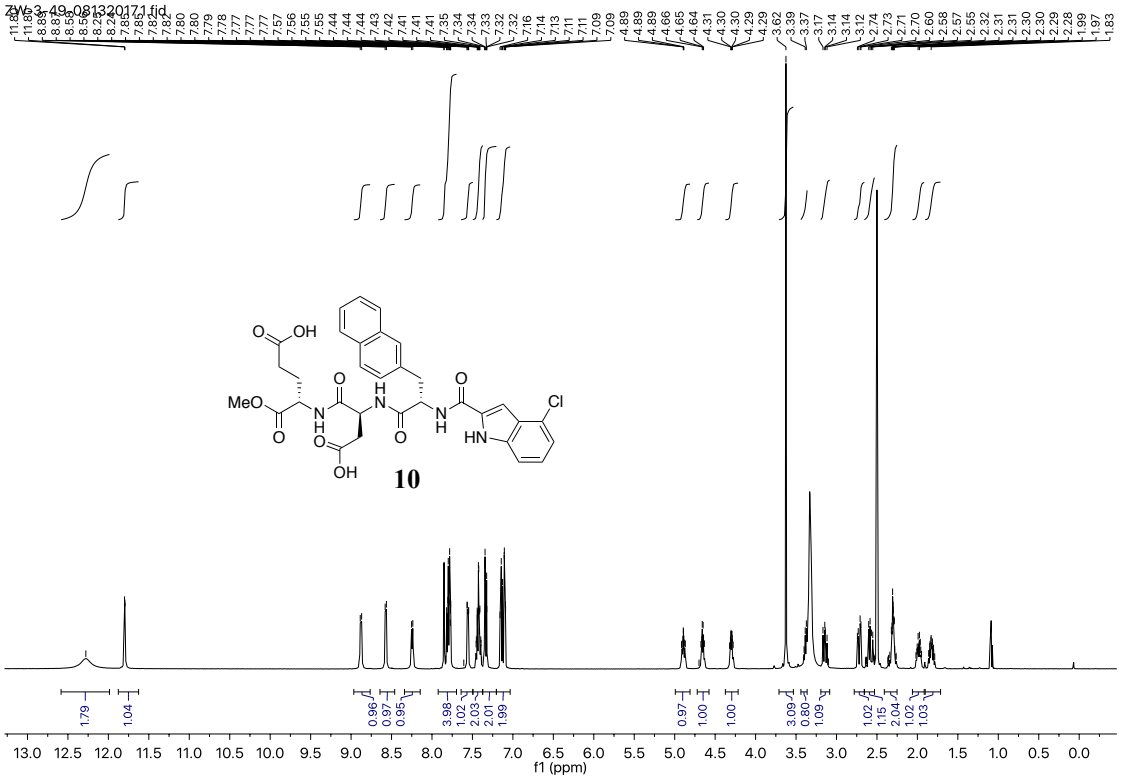
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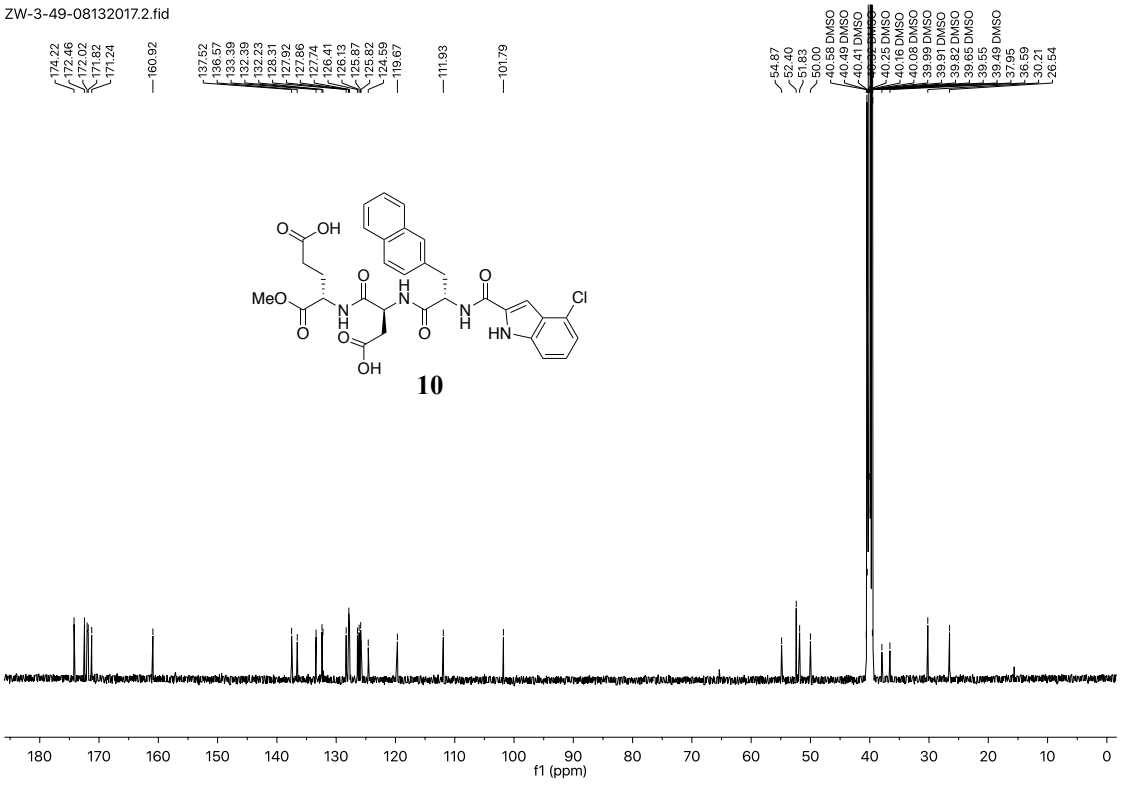
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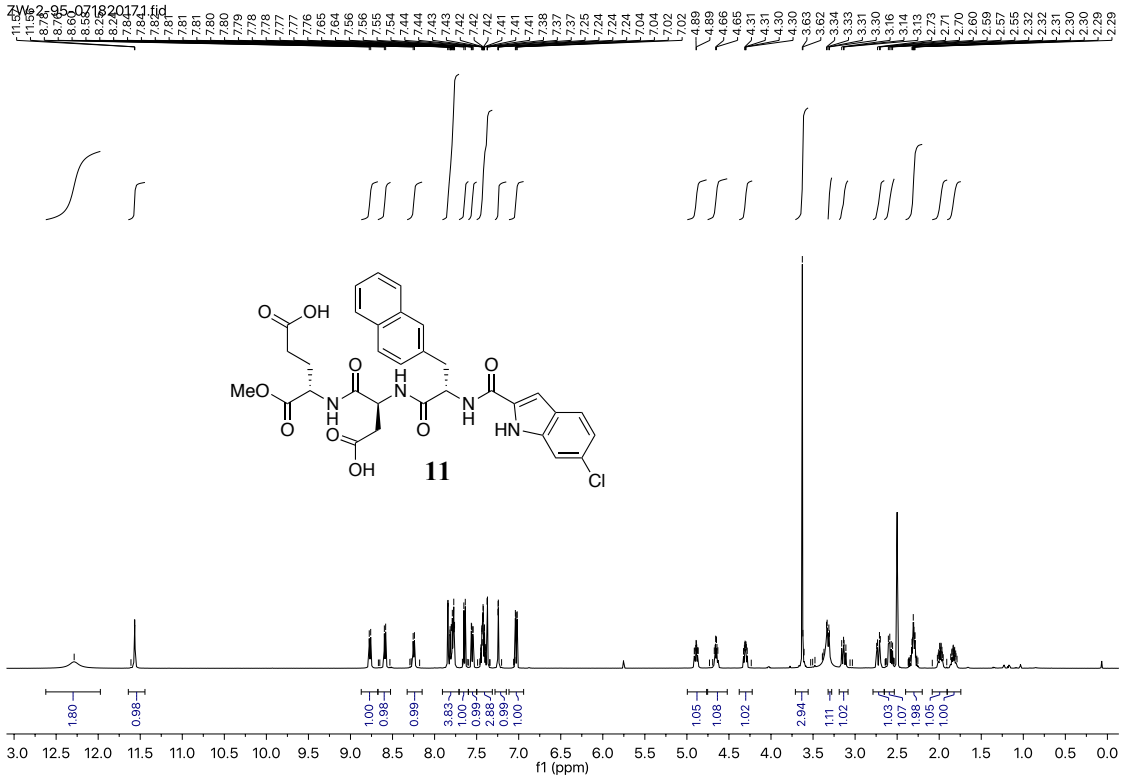
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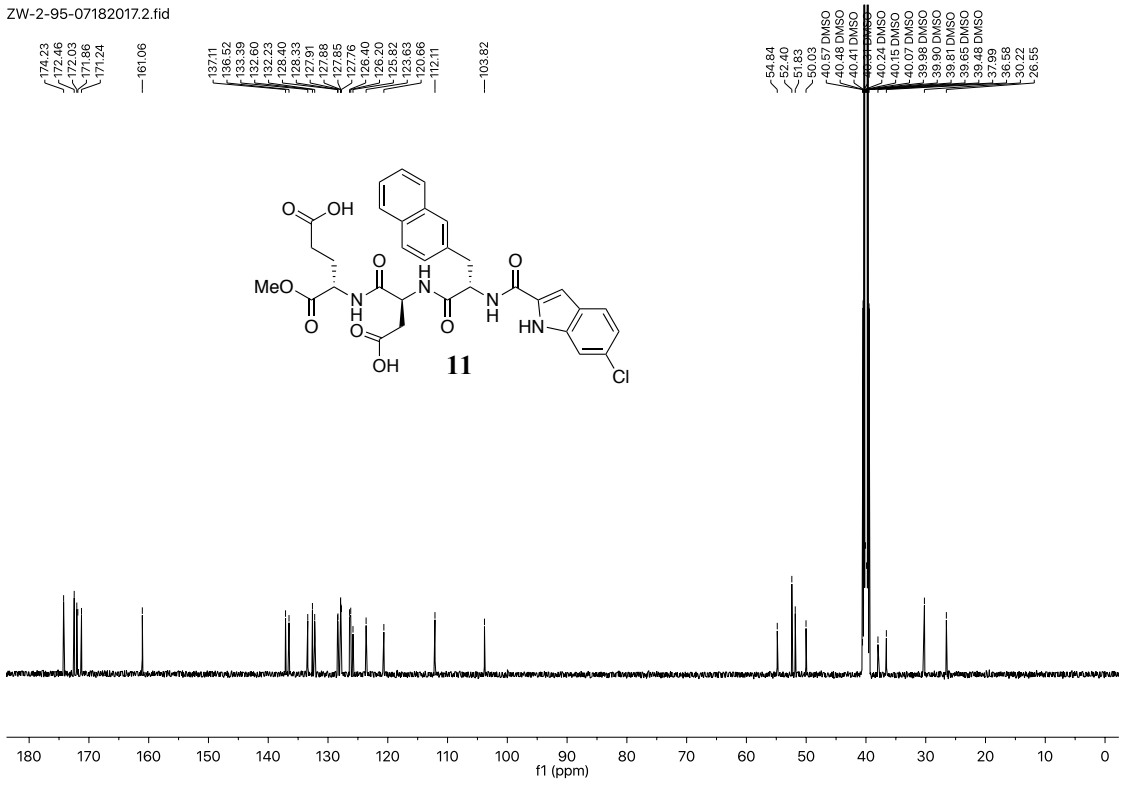
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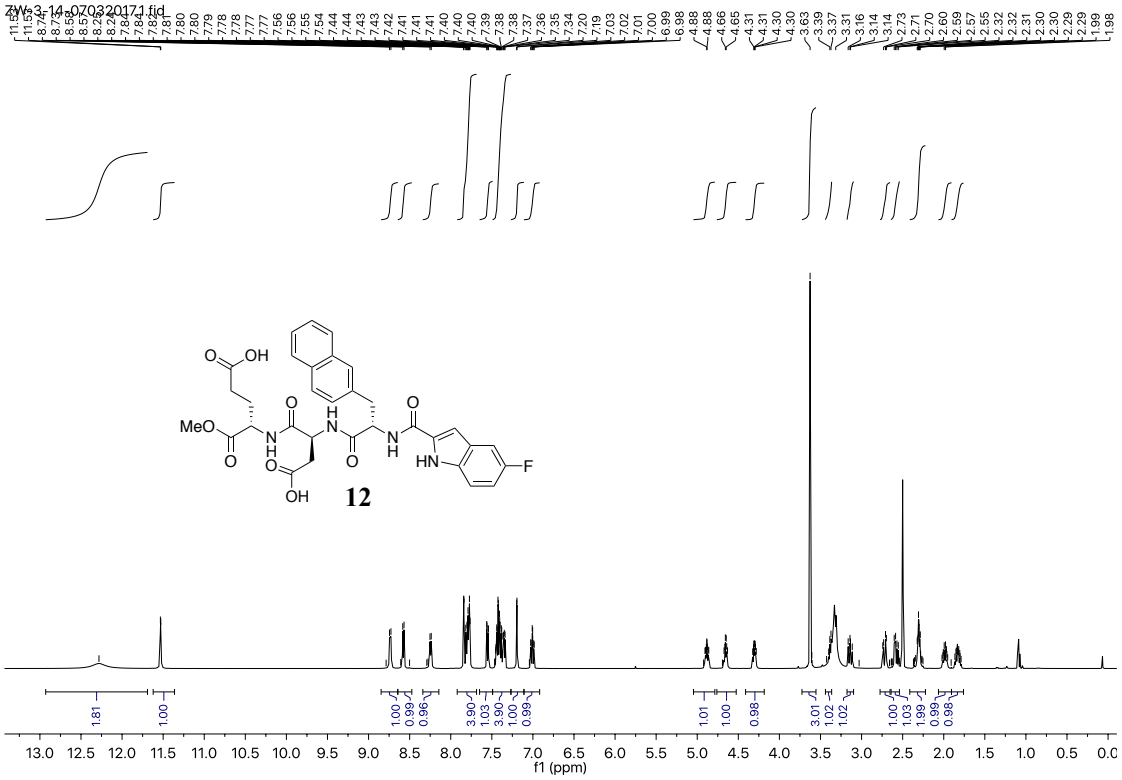
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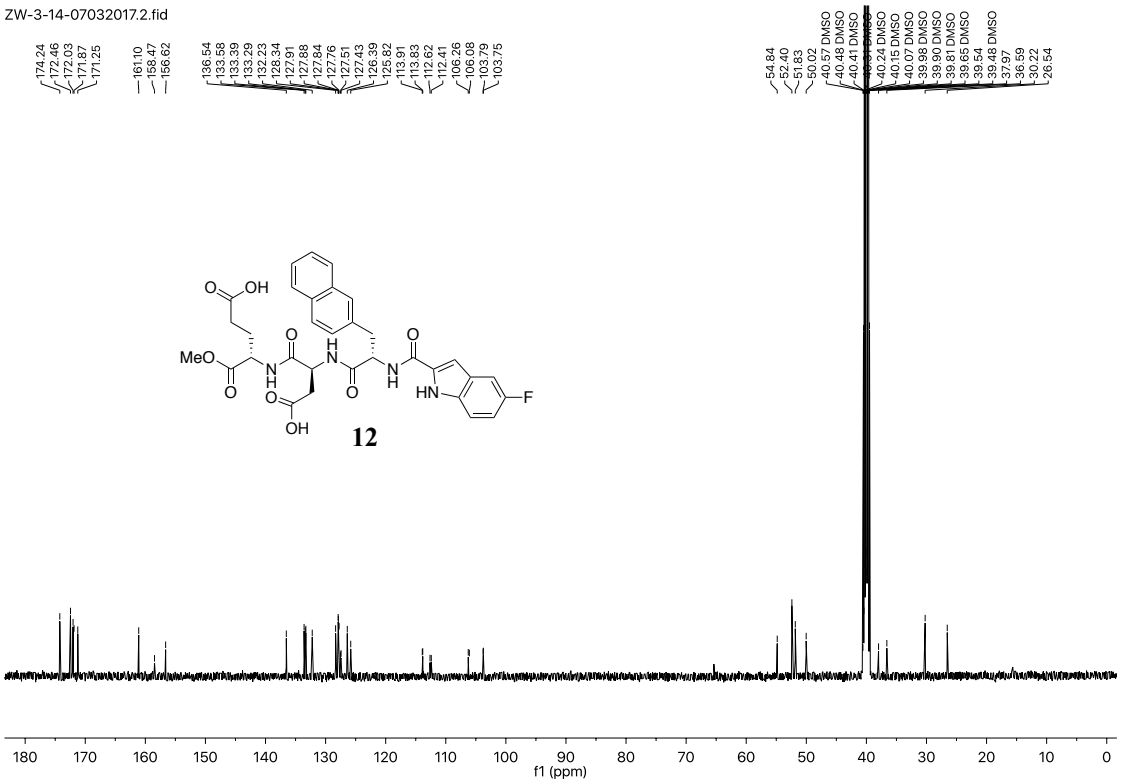
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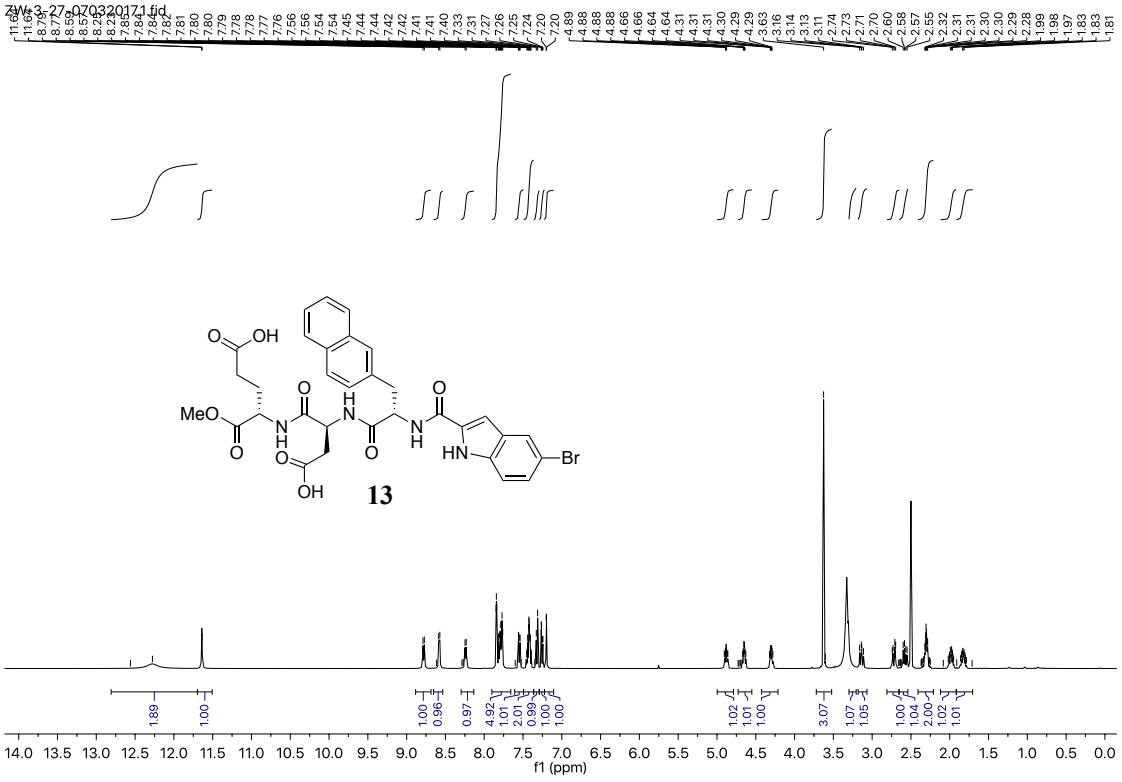
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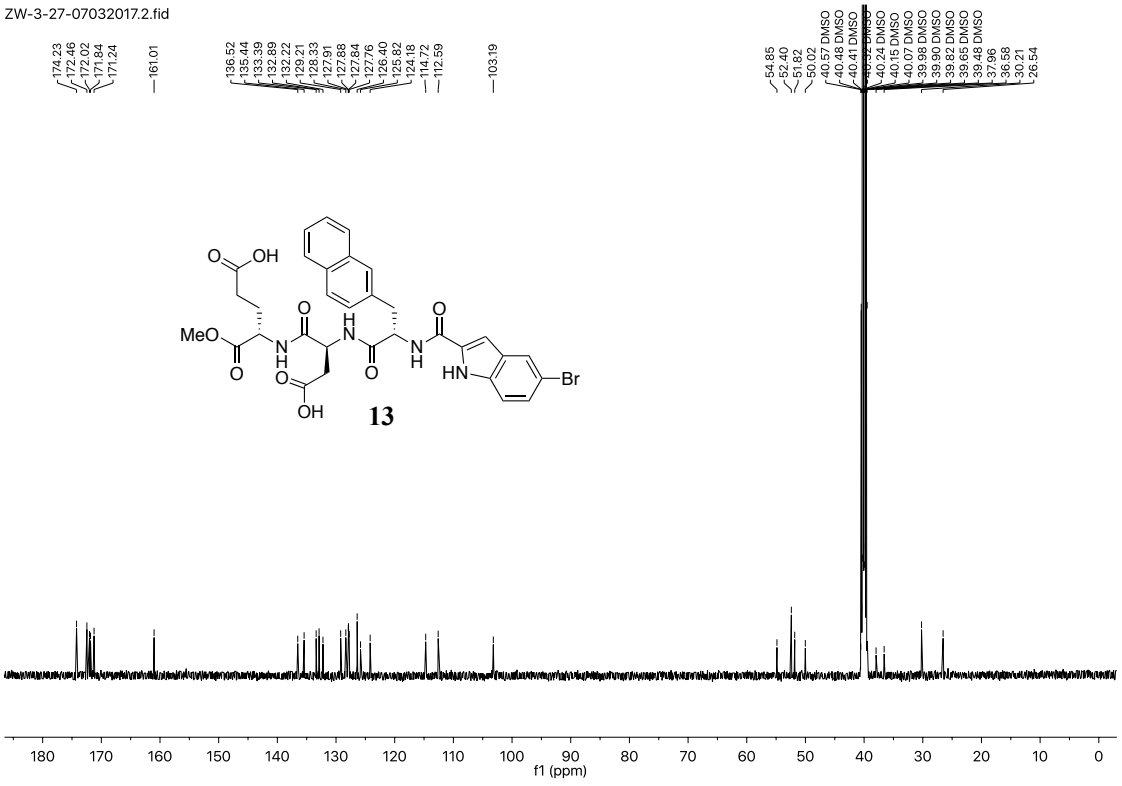
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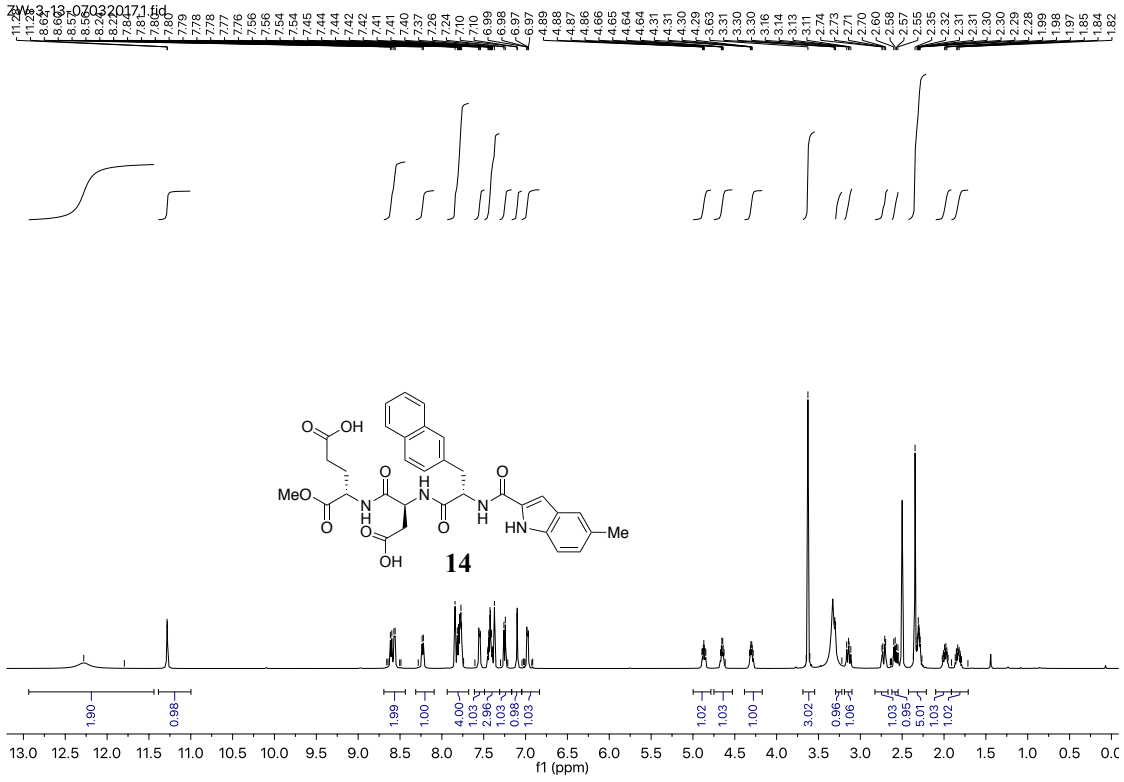
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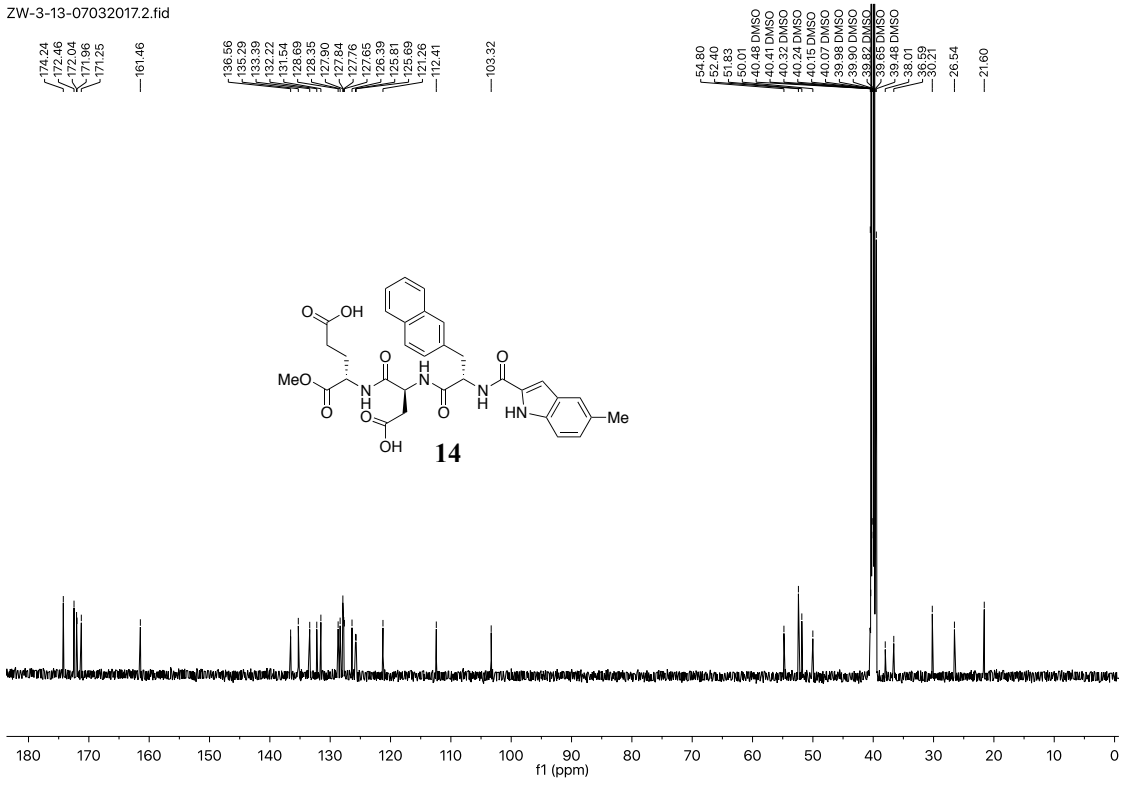
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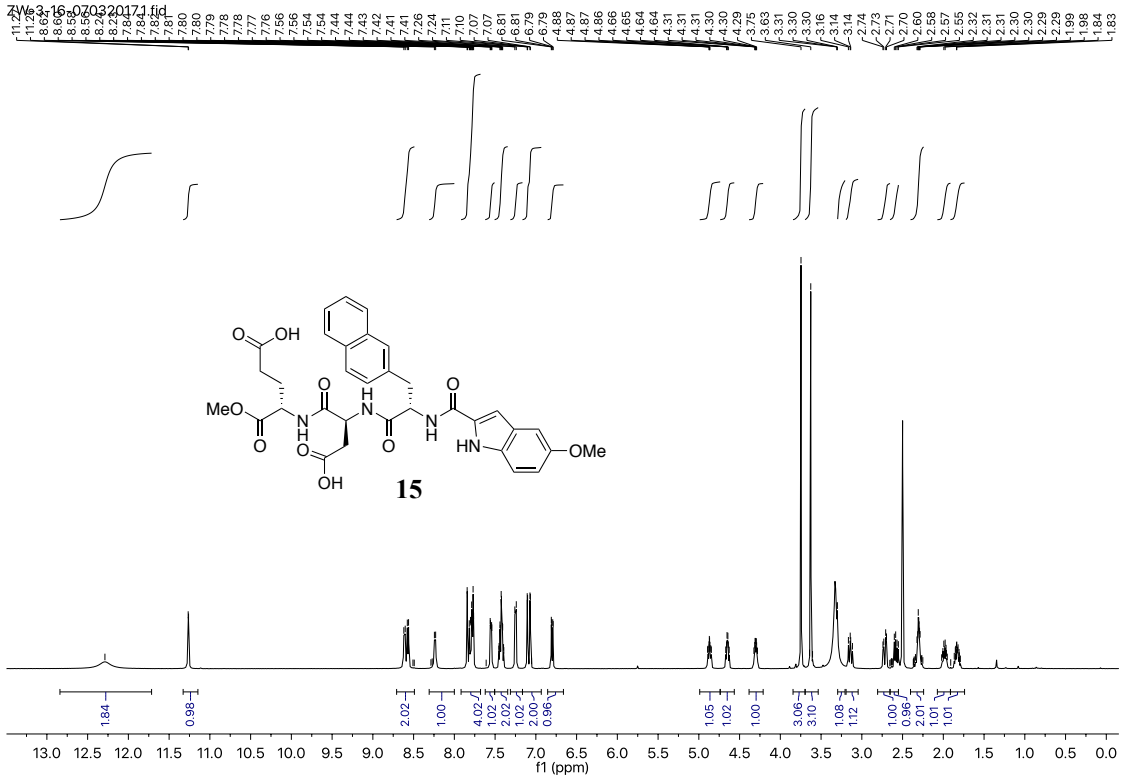
f1 (ppm)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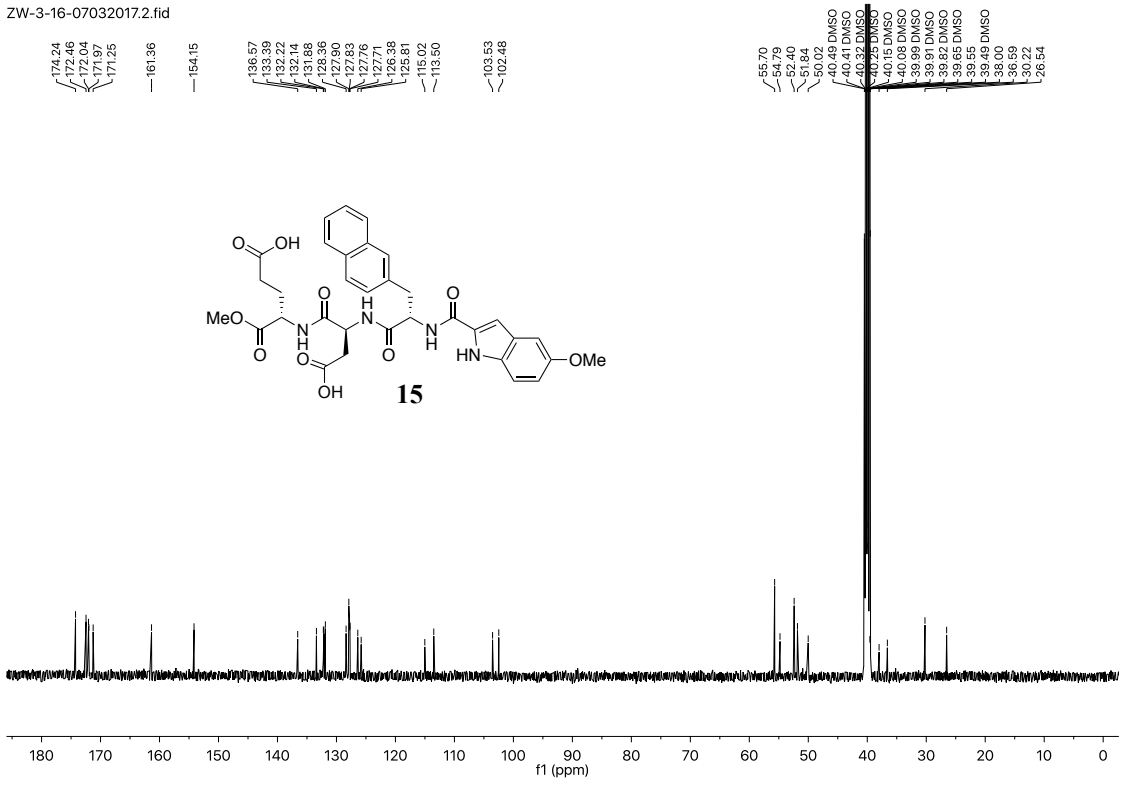
f1 (ppm)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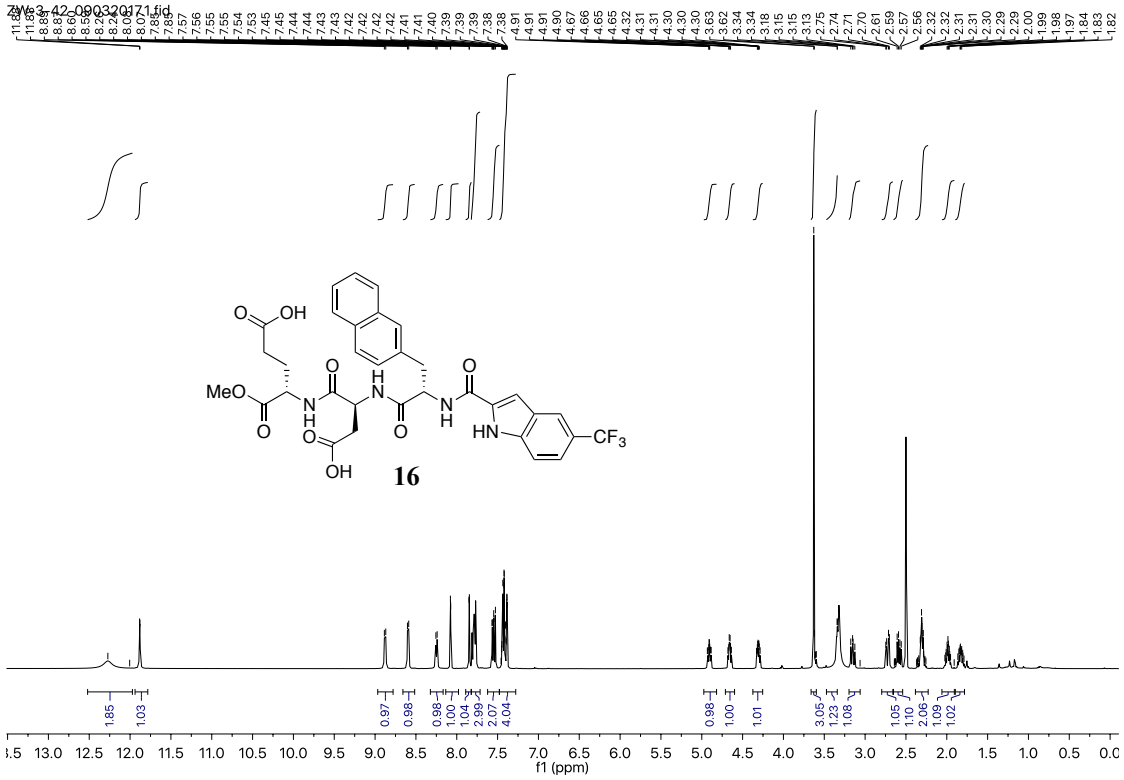

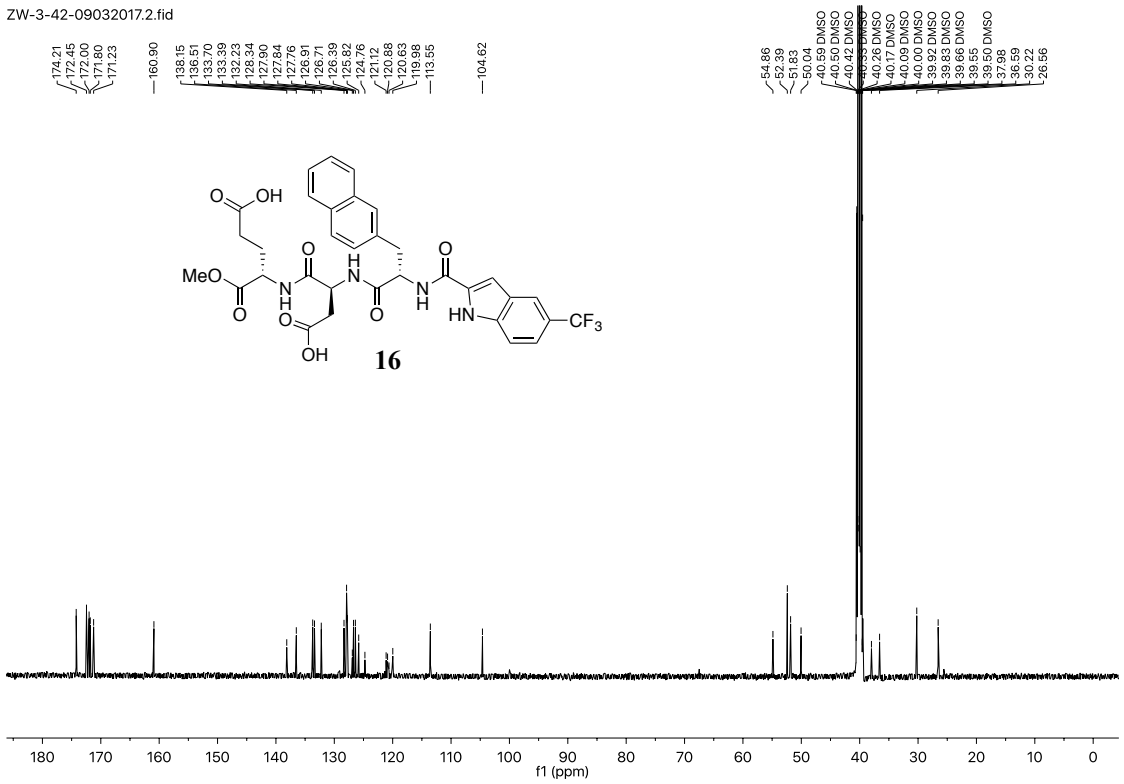

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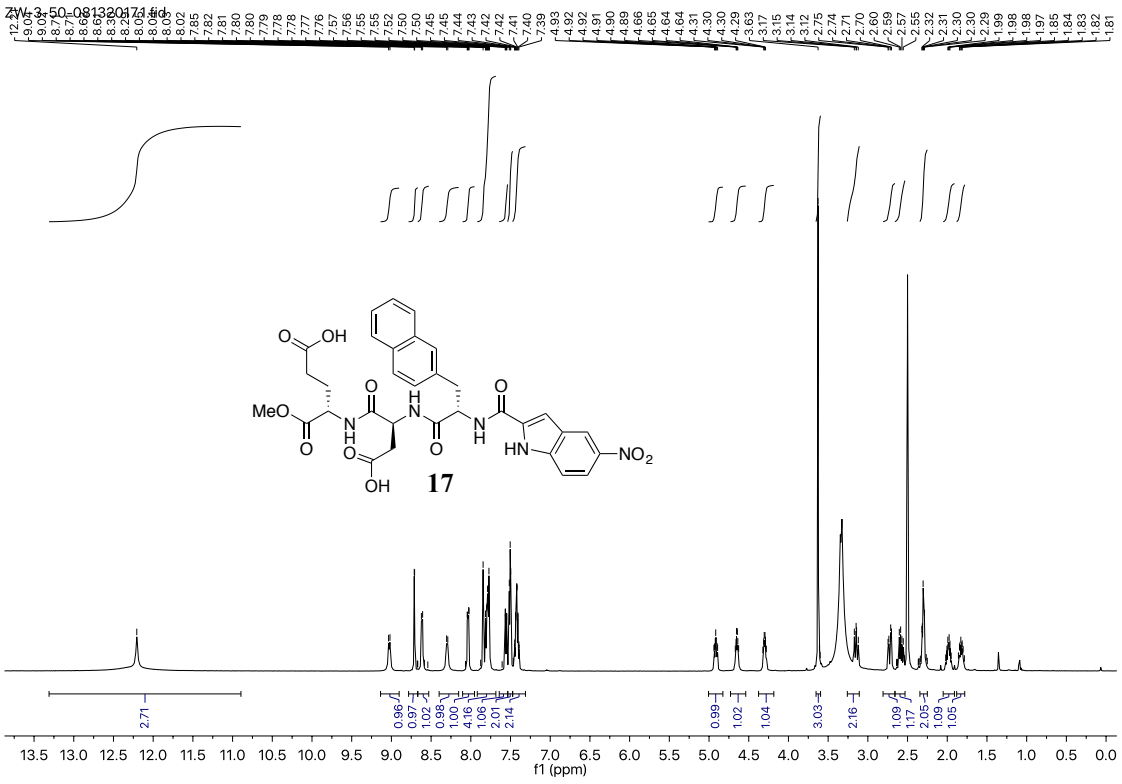
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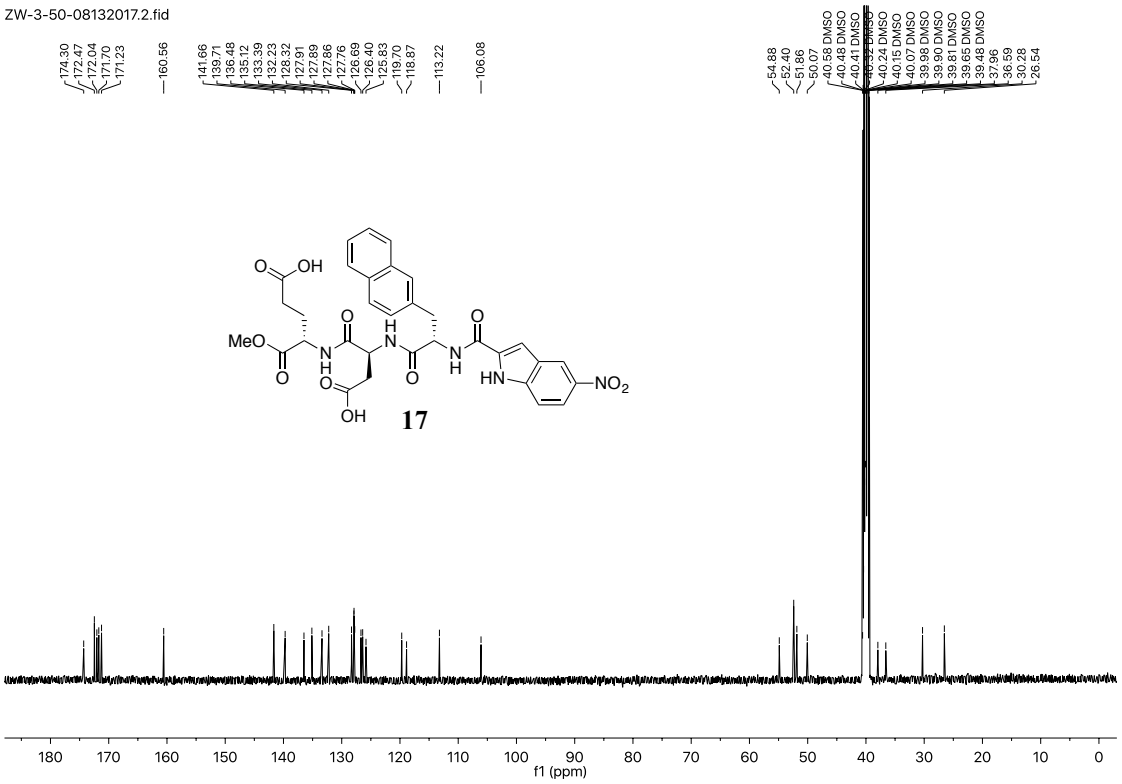
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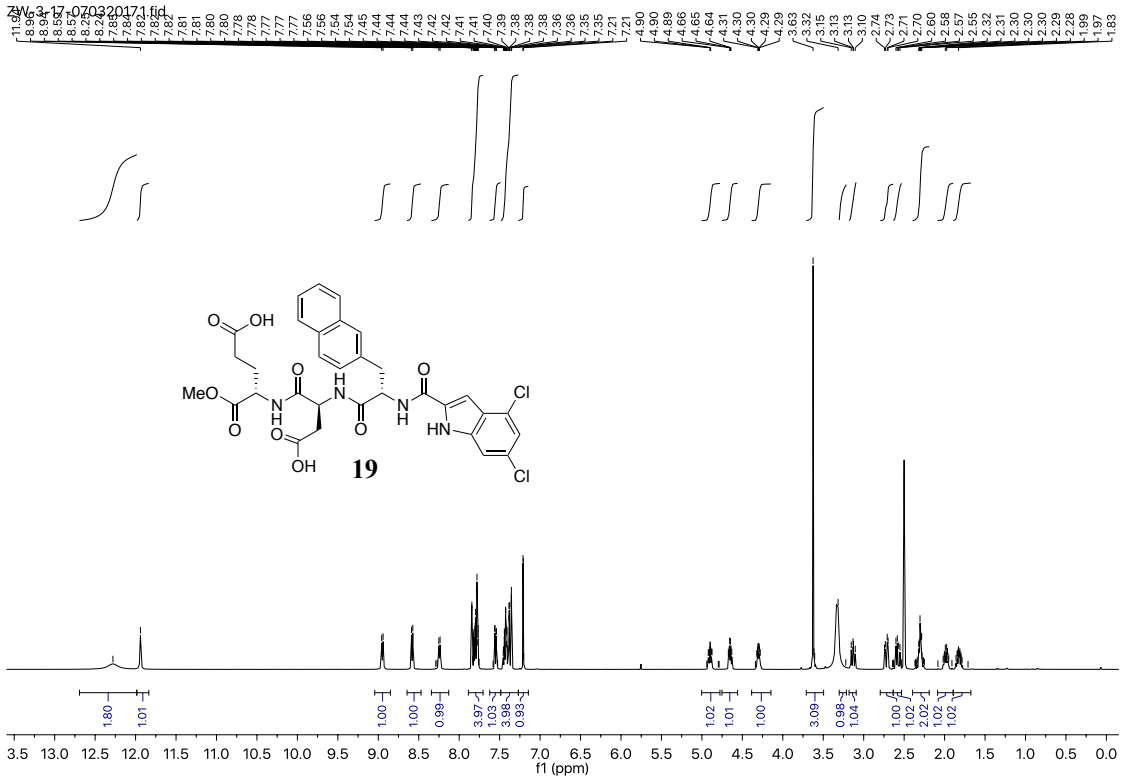
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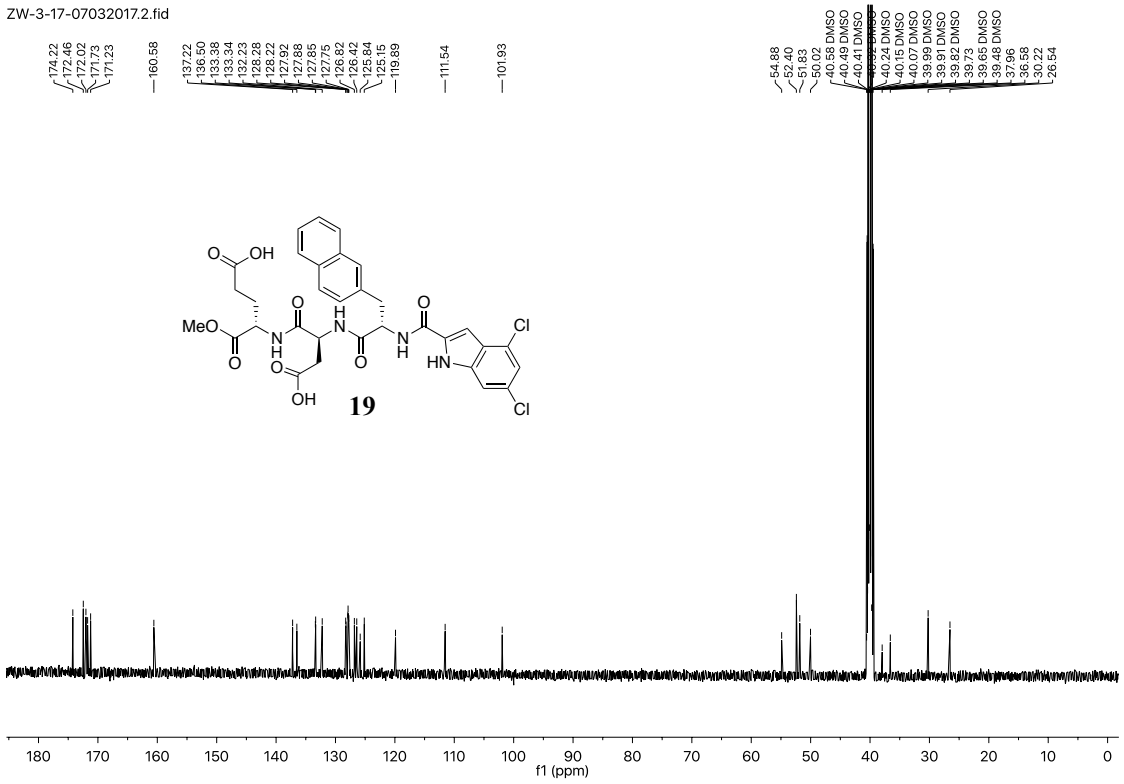
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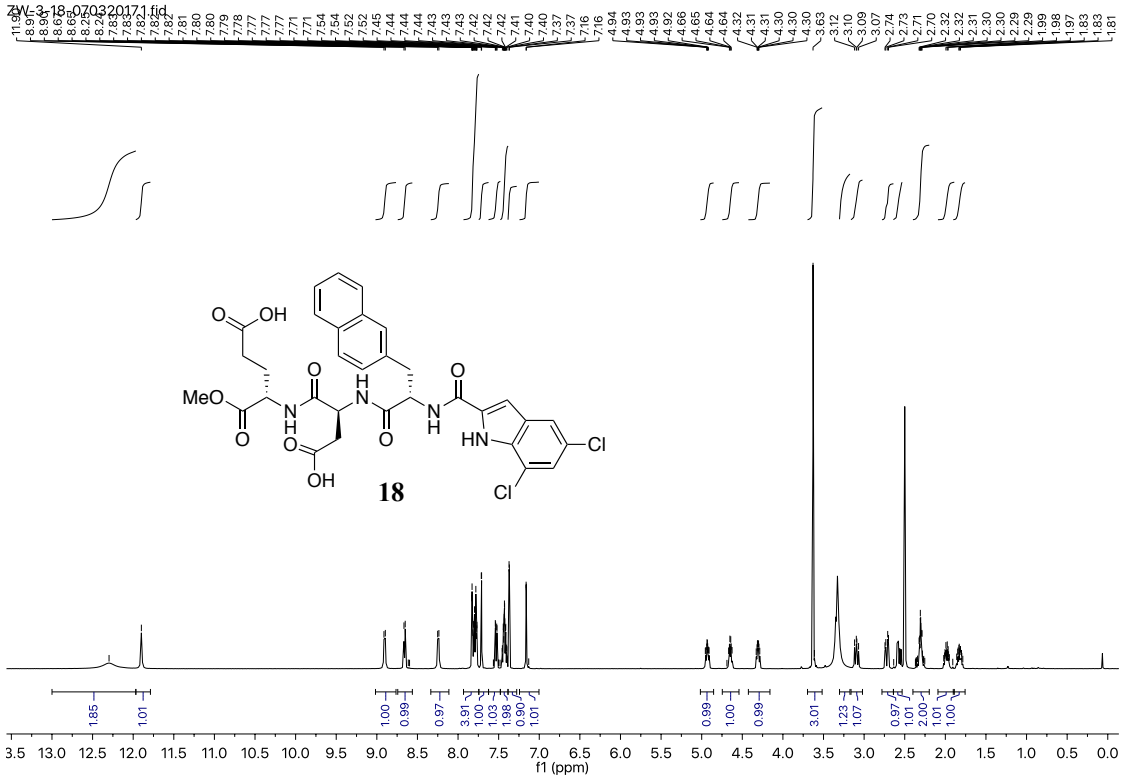
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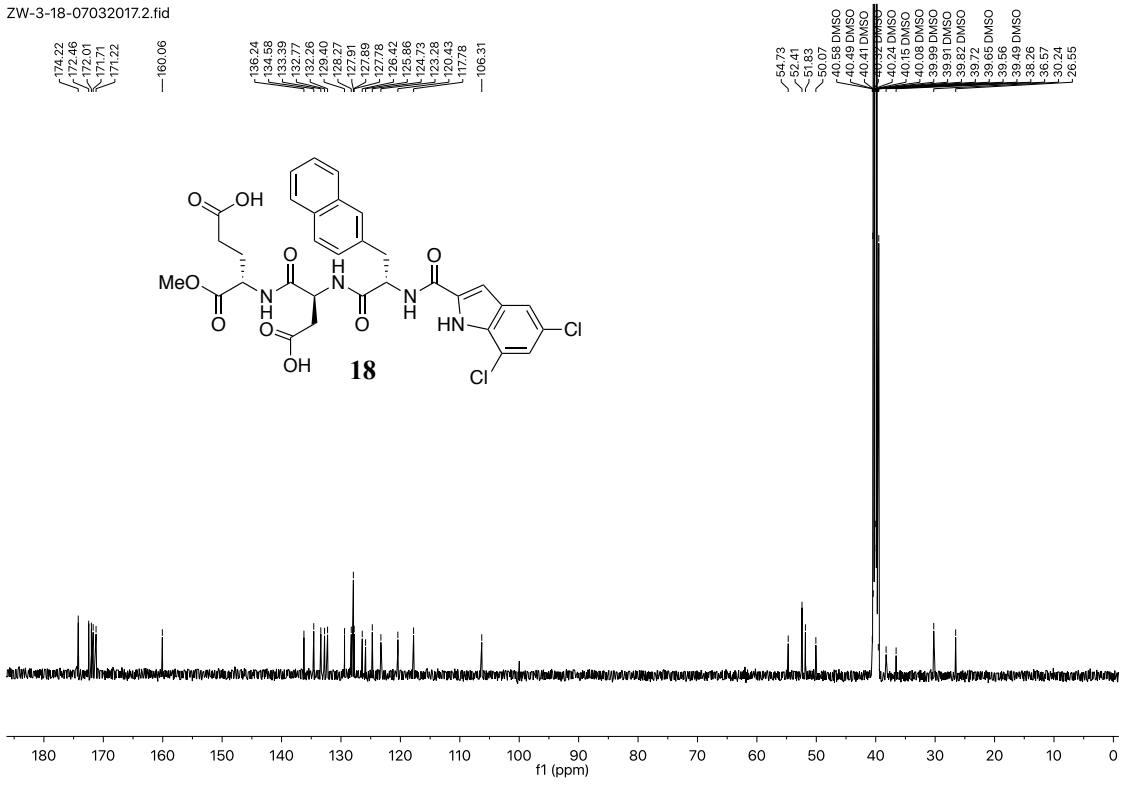
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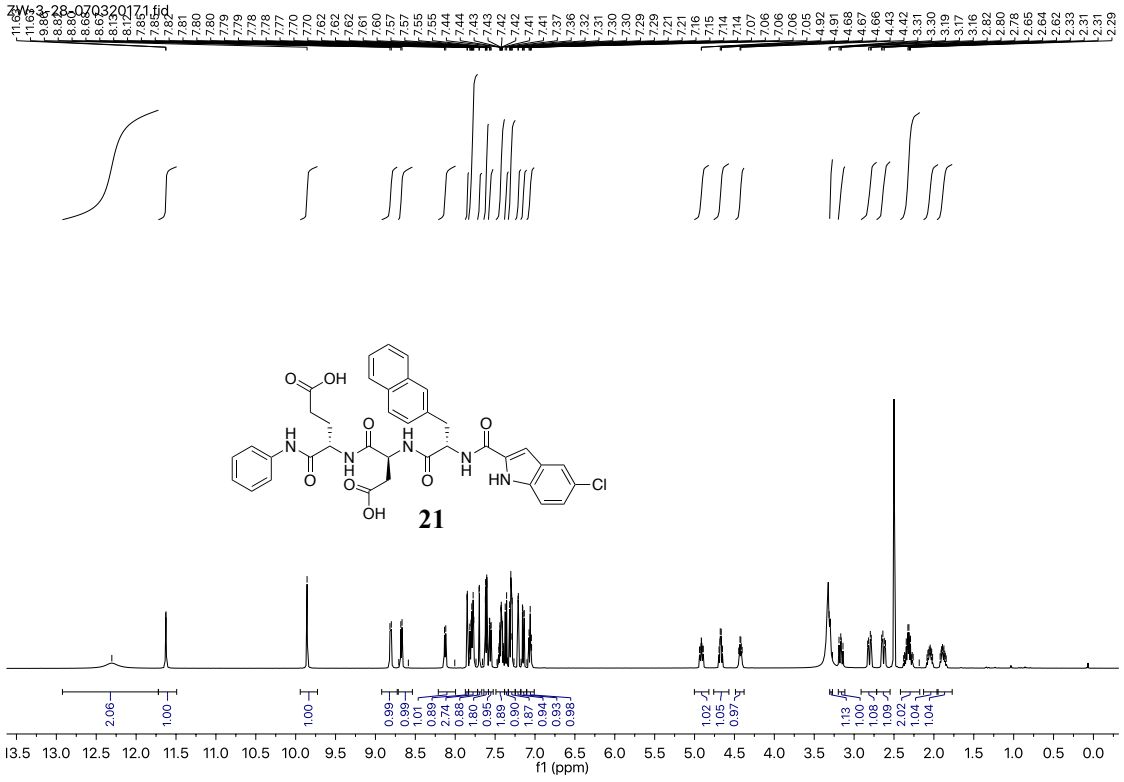
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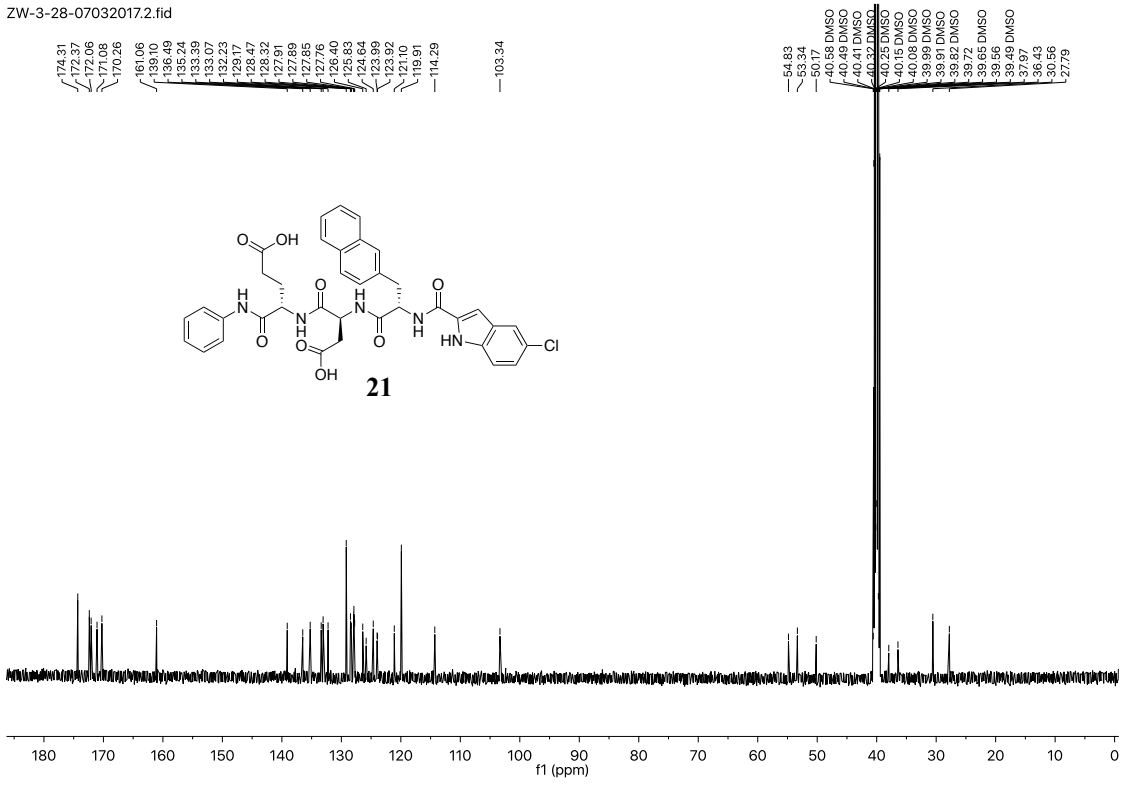
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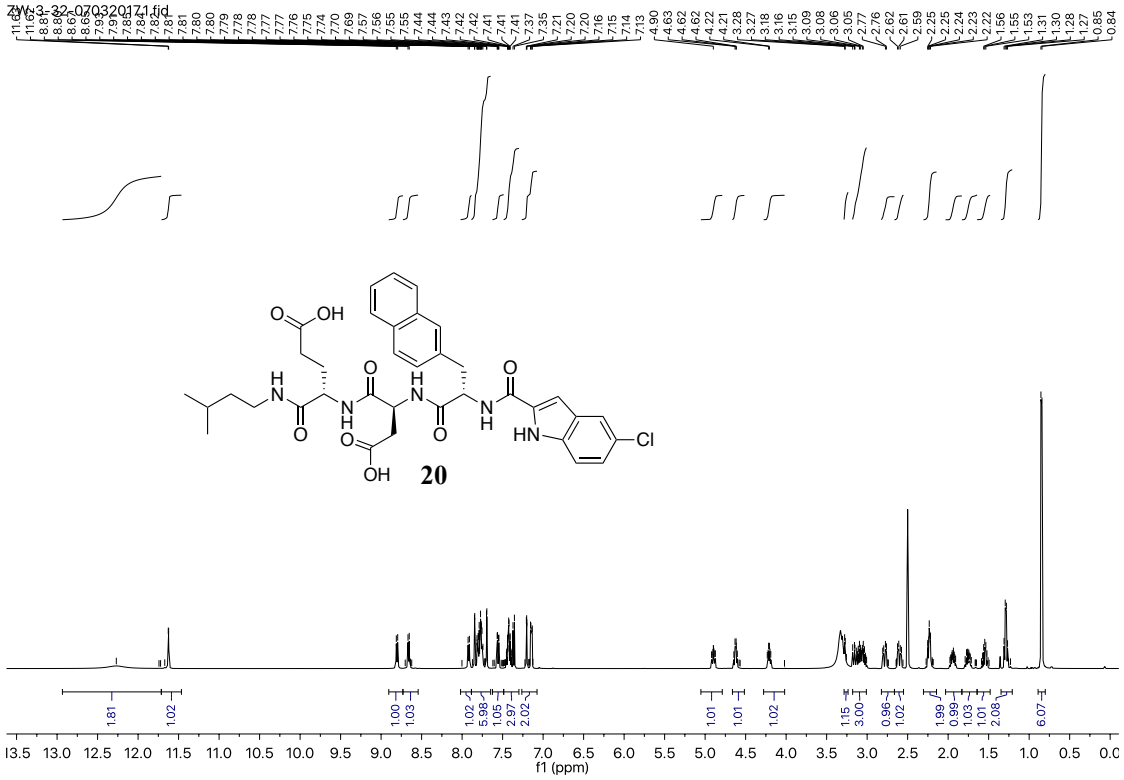
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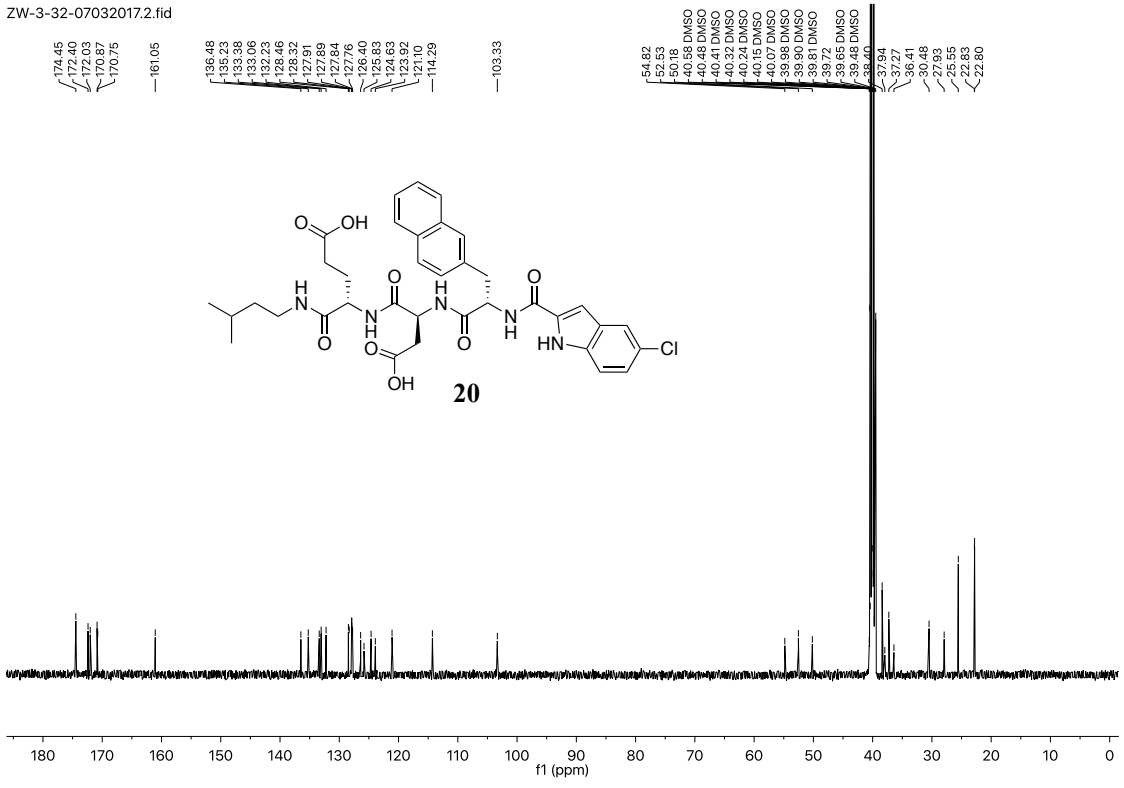
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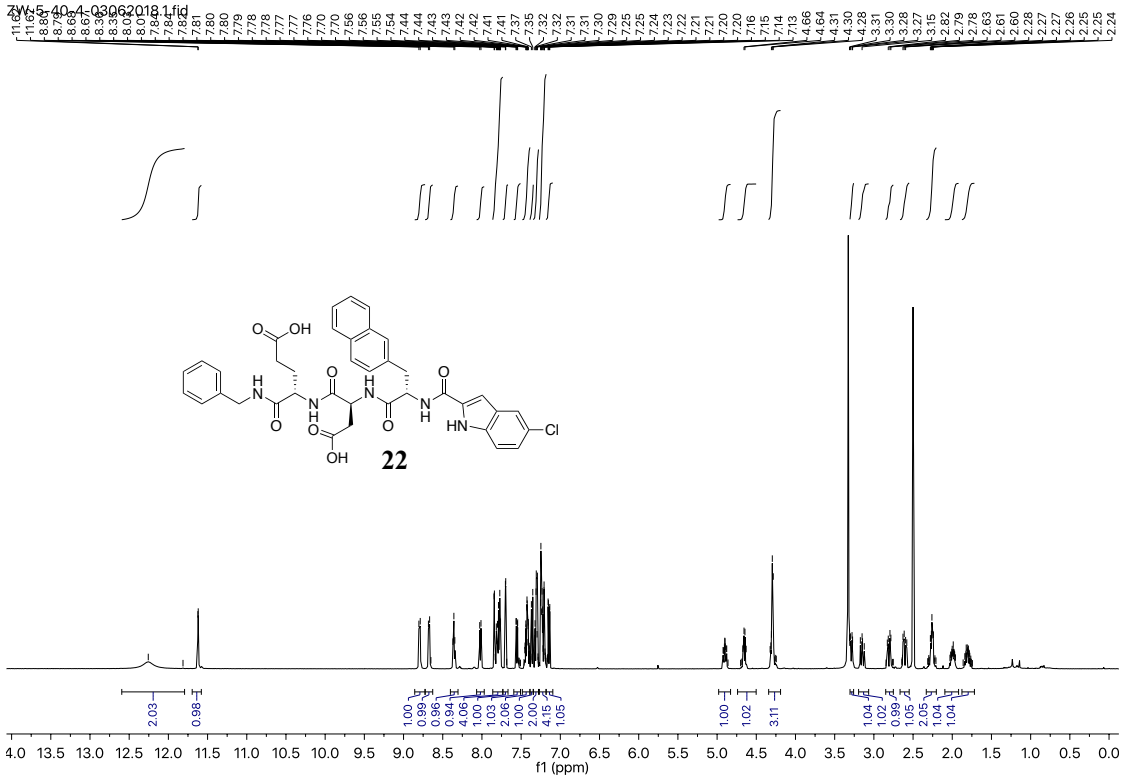
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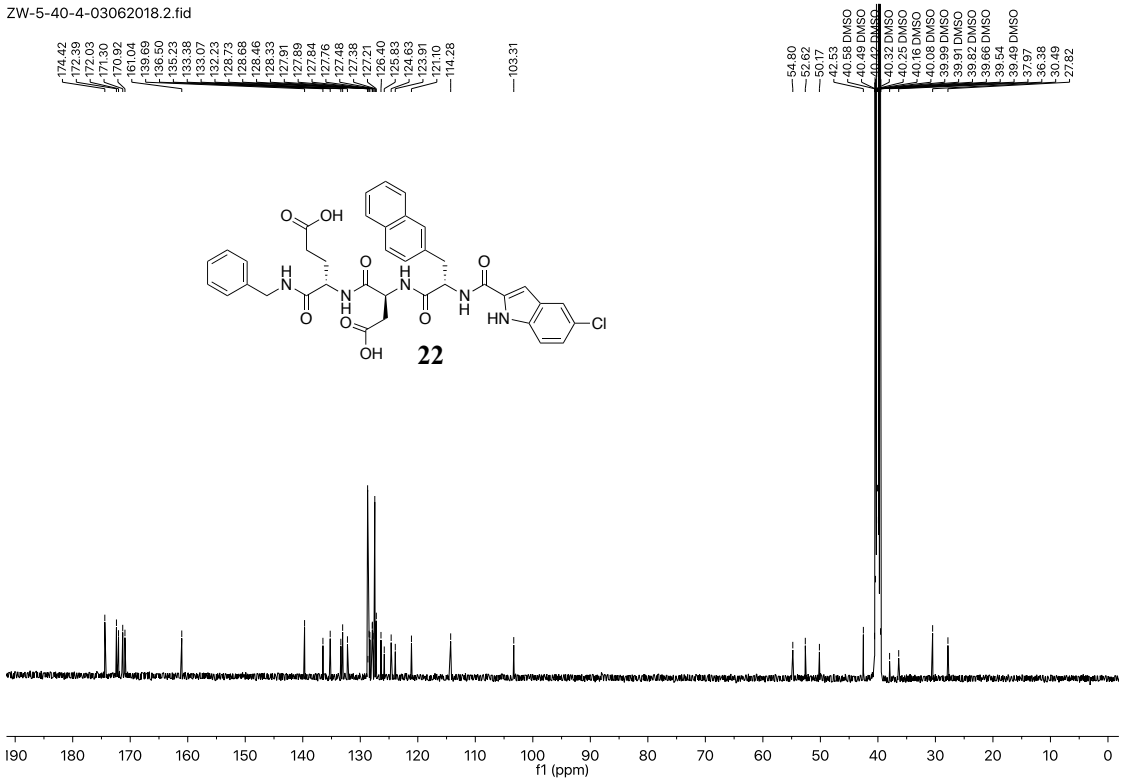
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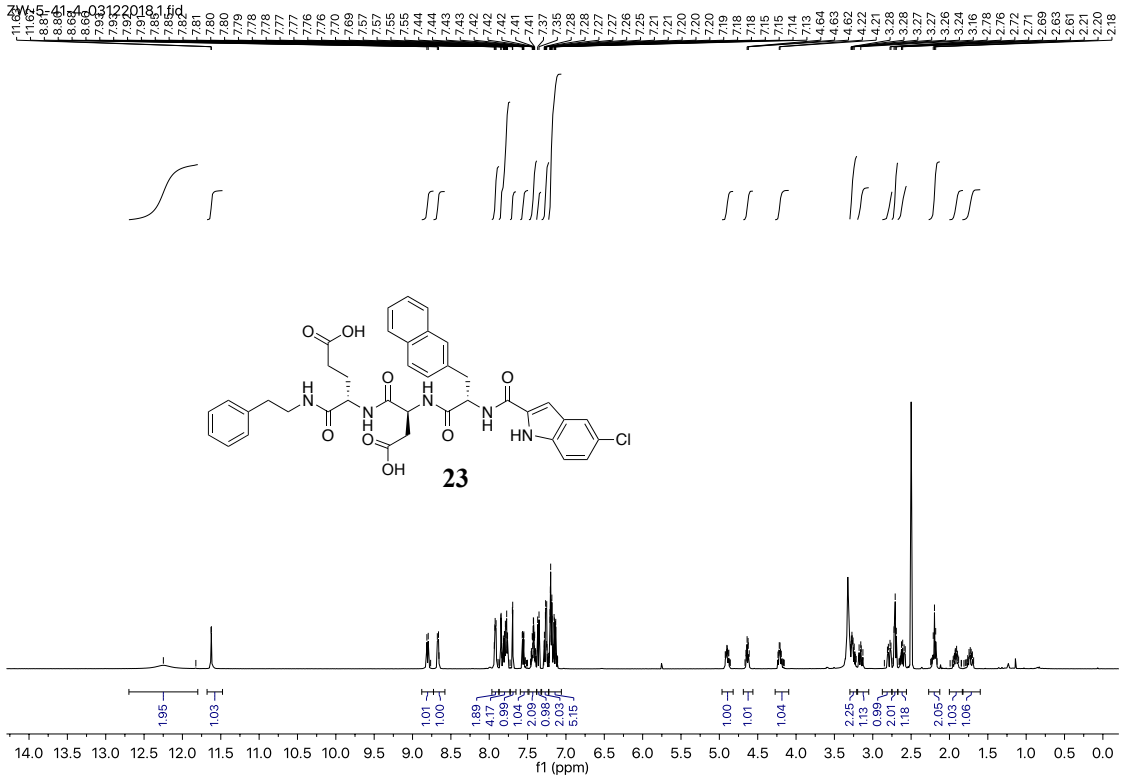
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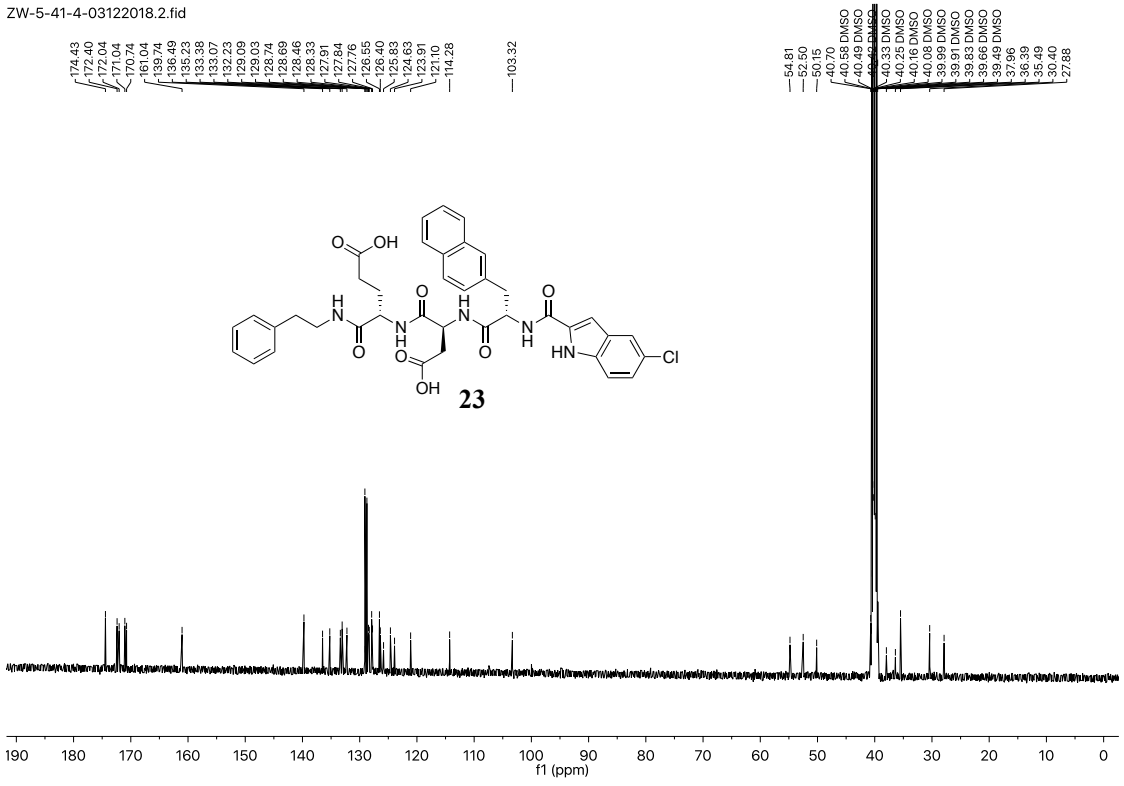
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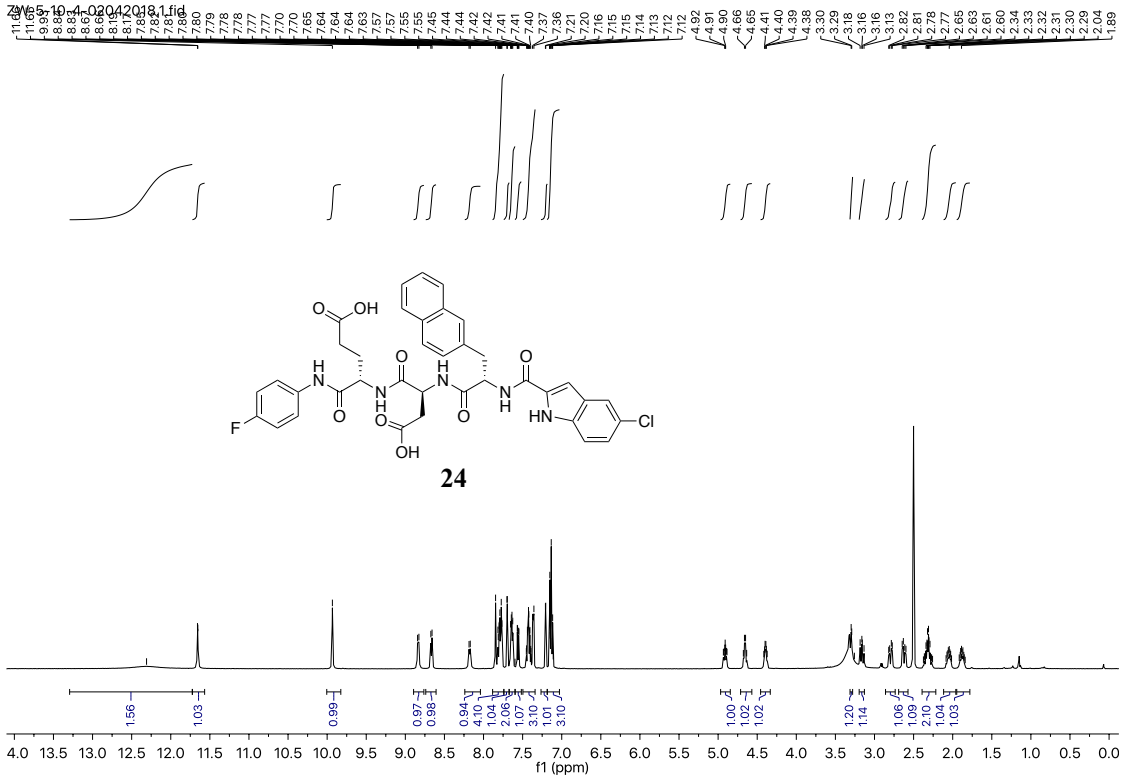
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1.07
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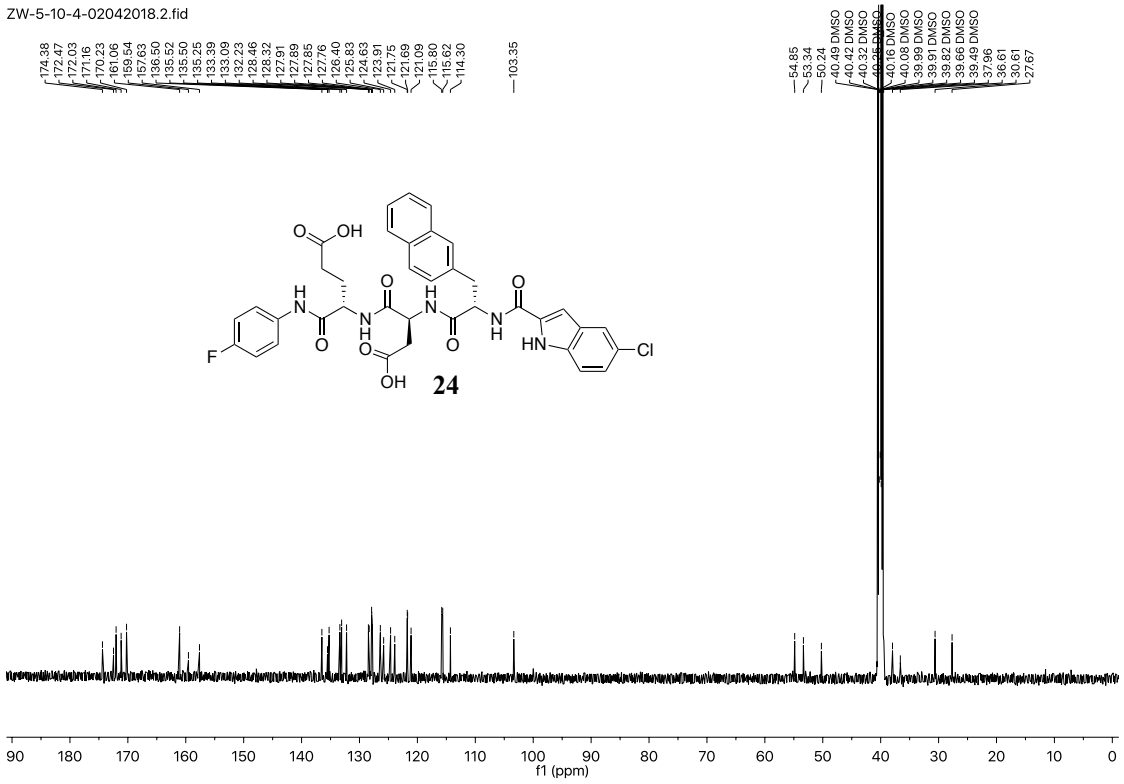
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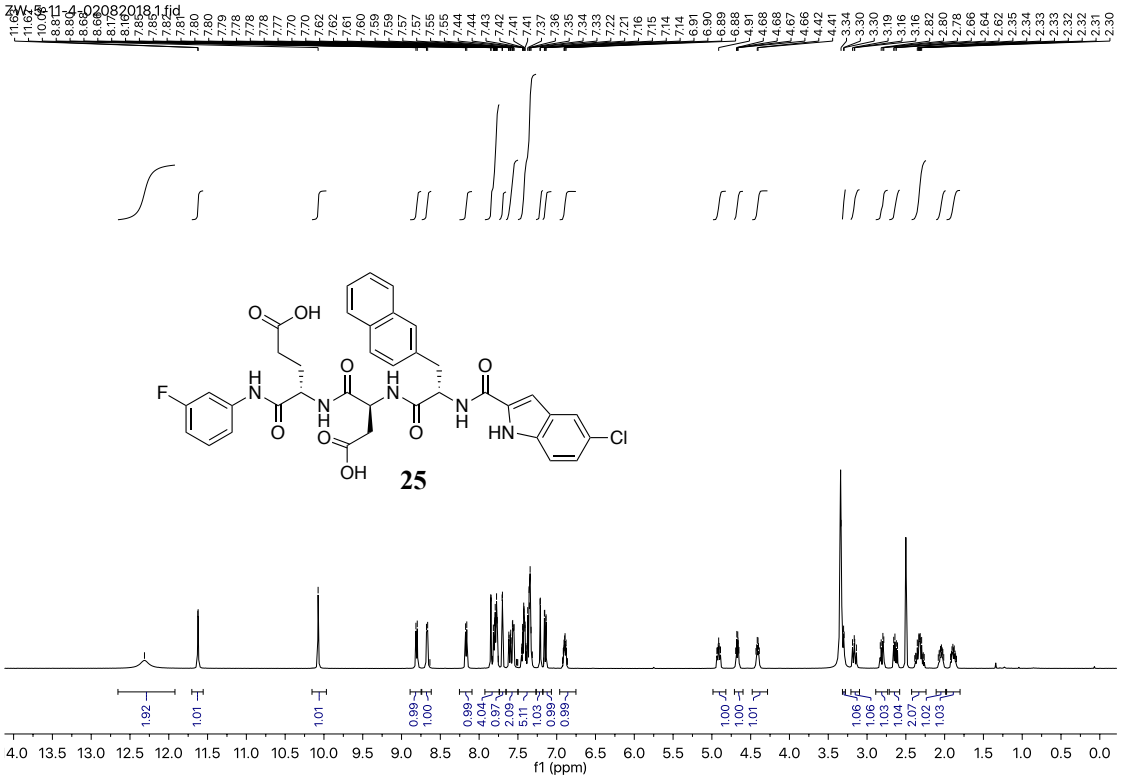
24
f1 (ppm)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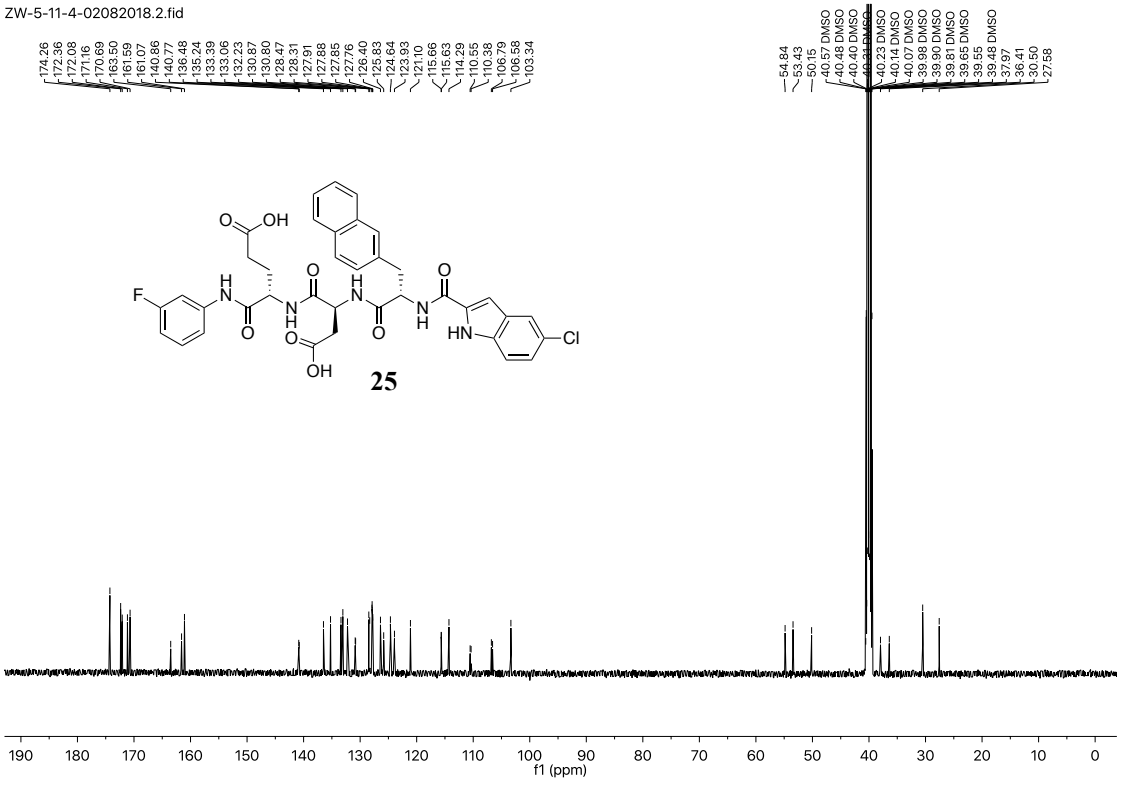
25
f1 (ppm)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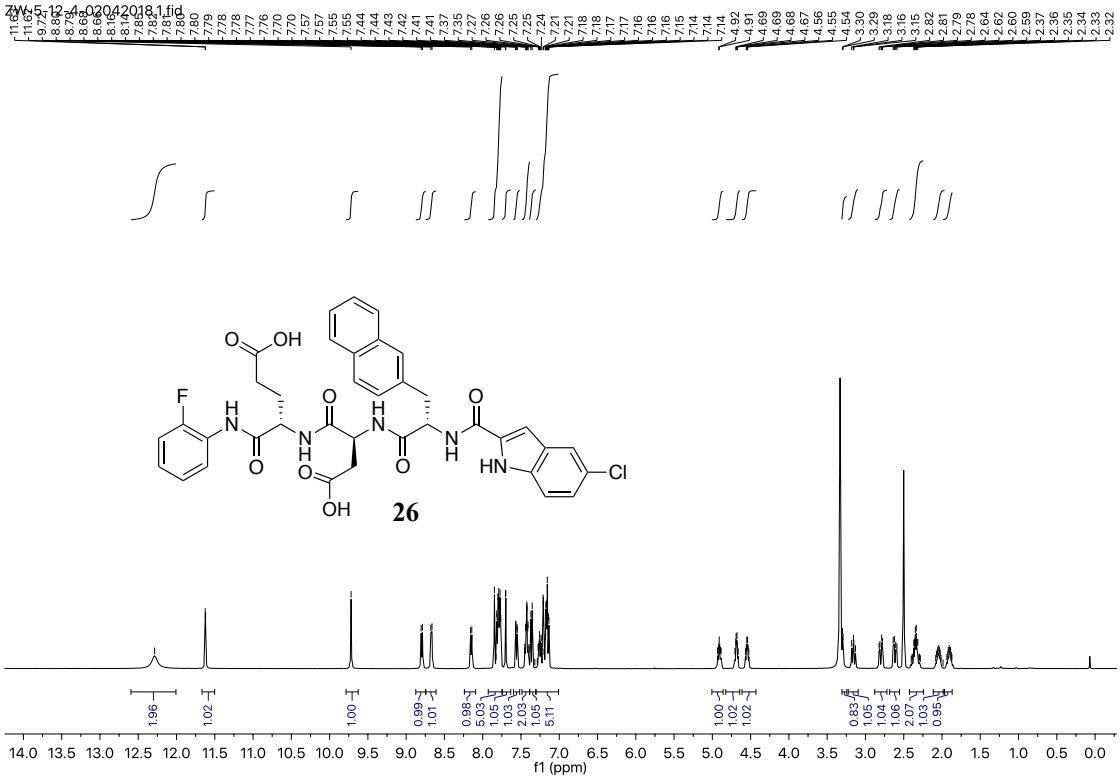
25
f1 (ppm)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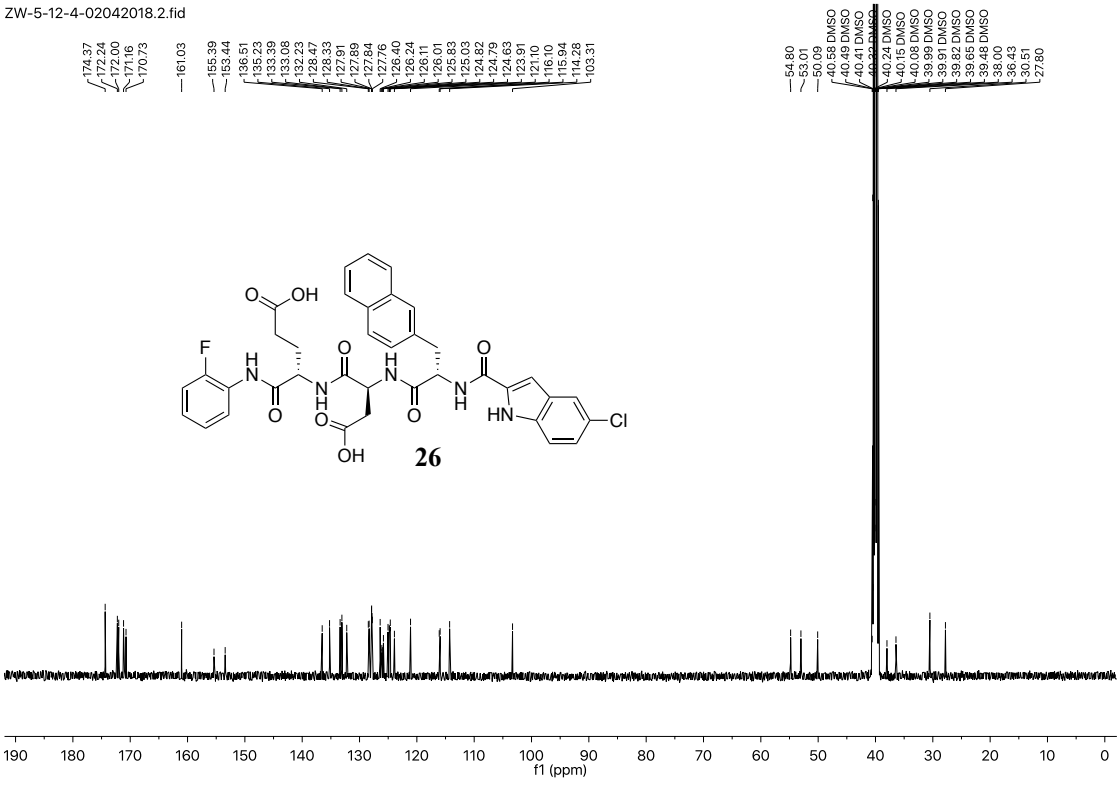
26
f1 (ppm)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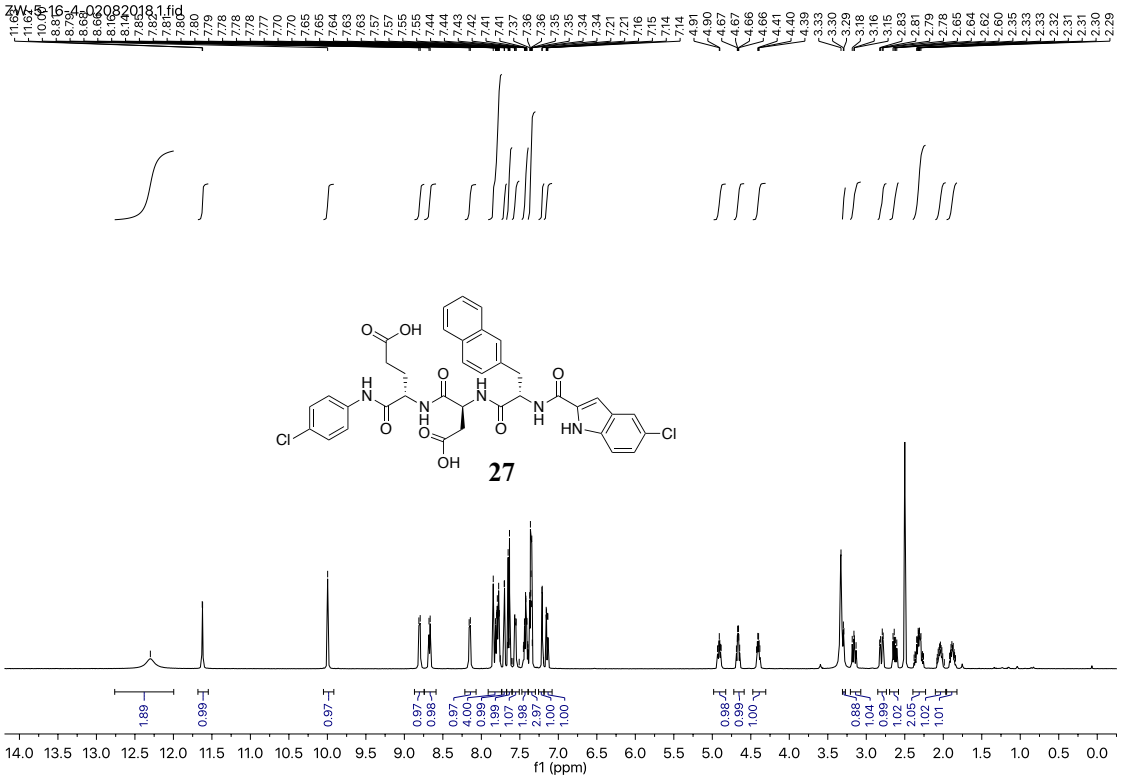
26
f1 (ppm)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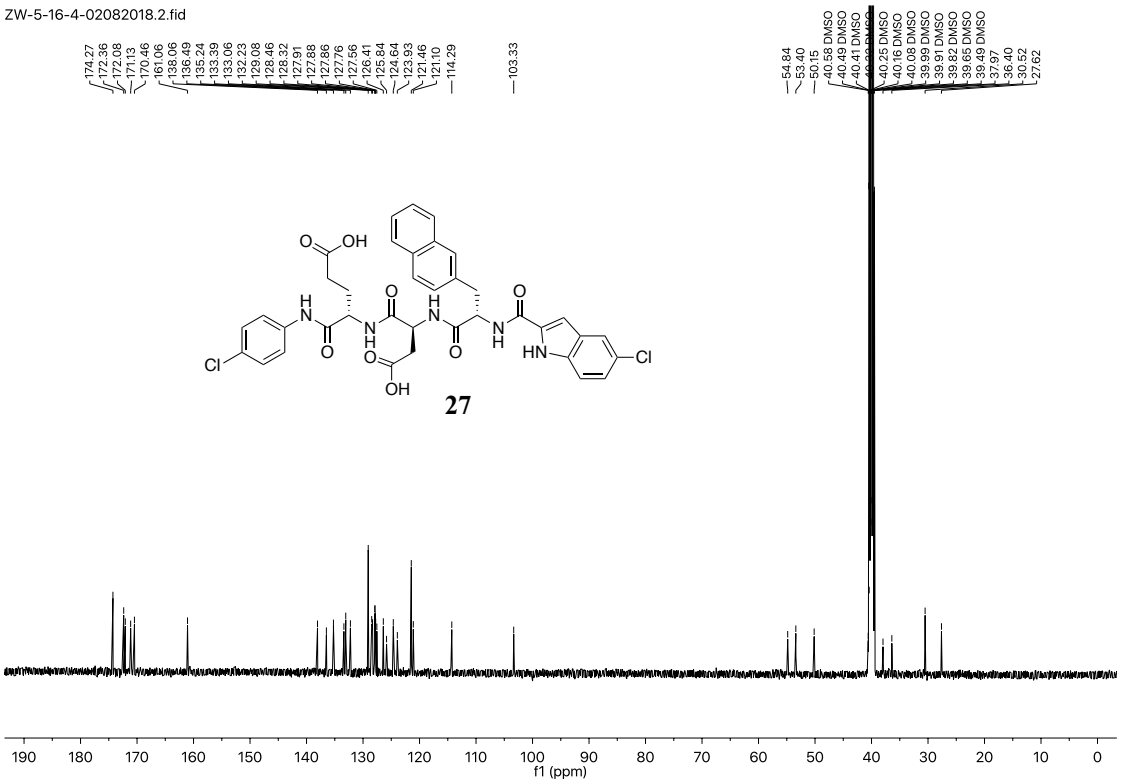
27
f1 (ppm)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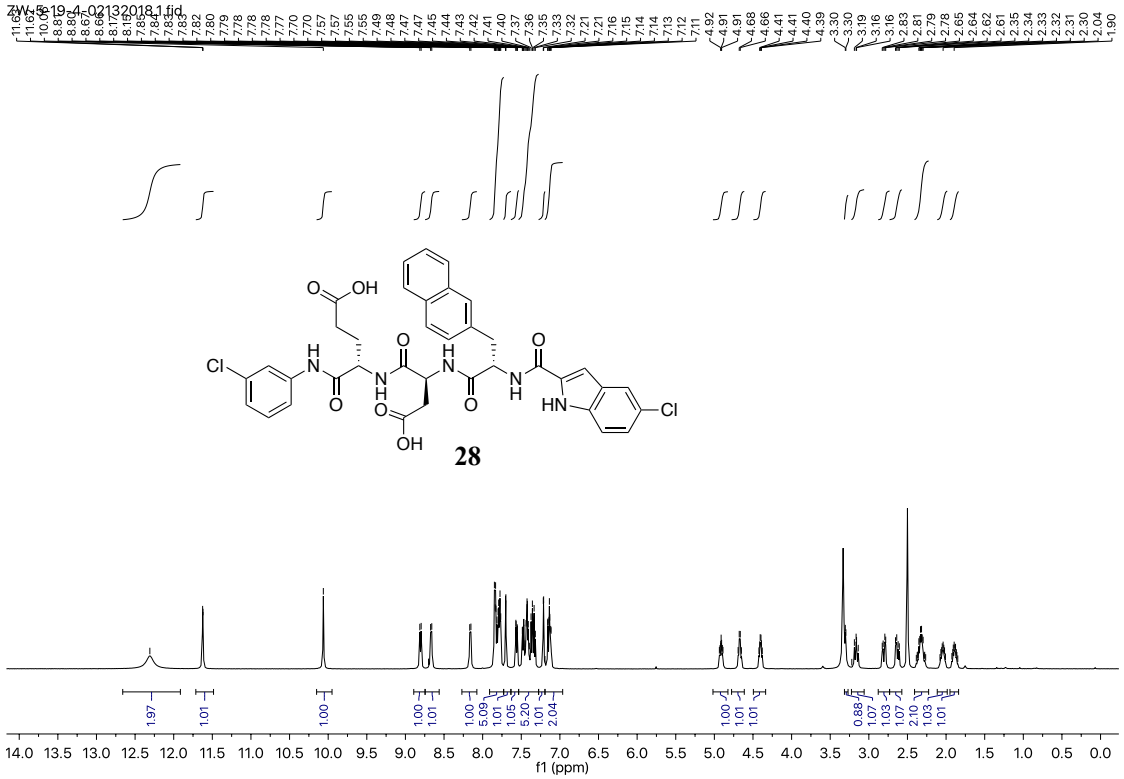
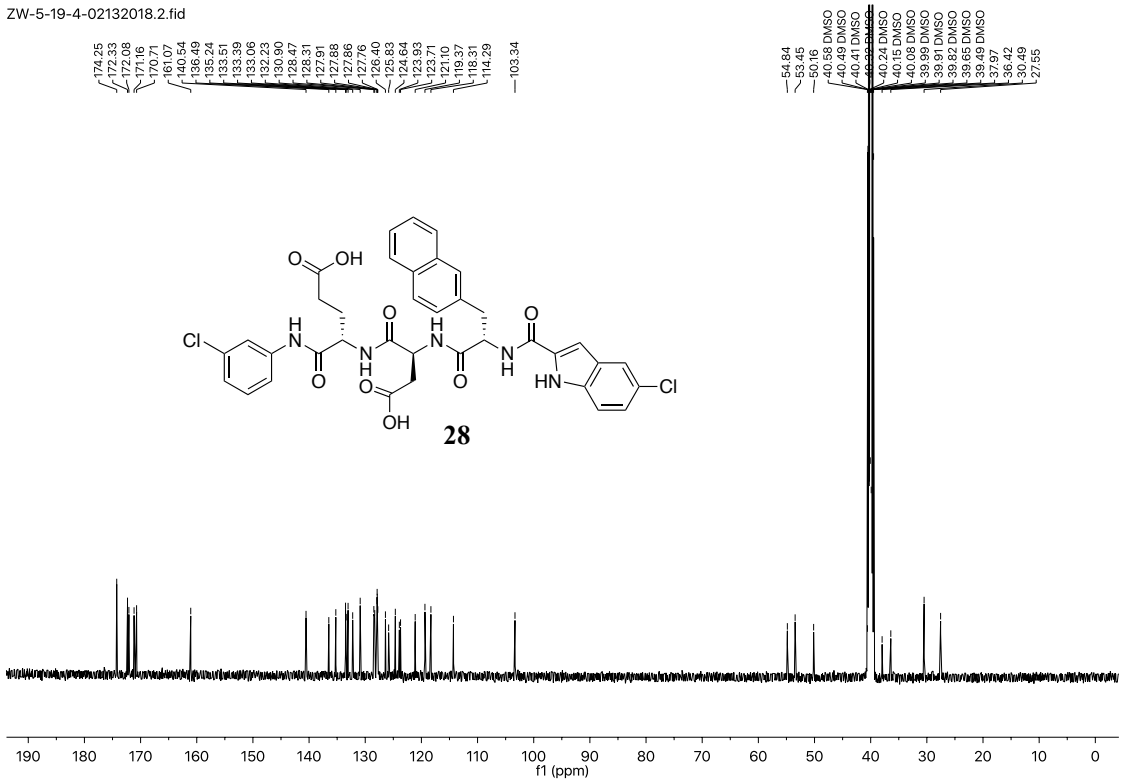
27
f1 (ppm)


ZW-5-19-4-02132018.1.fid
28
f1 (ppm)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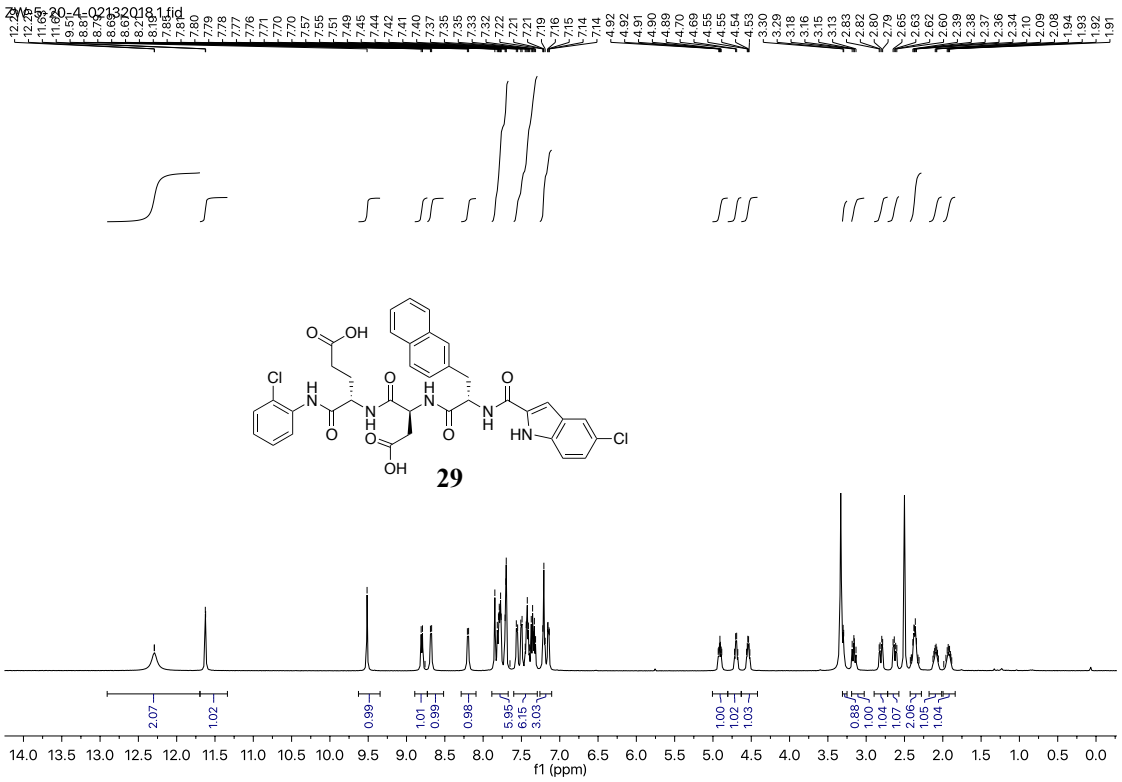
28
f1 (ppm)

ZW-5-20-4-02132018.1.fid



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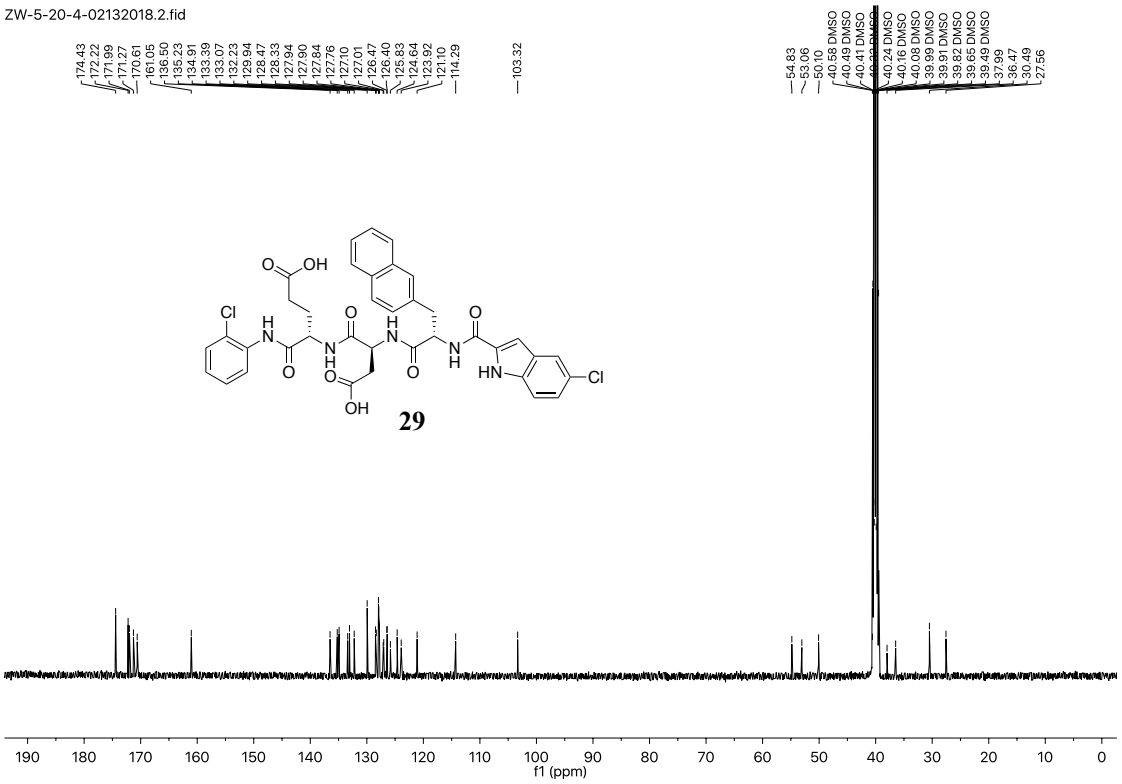
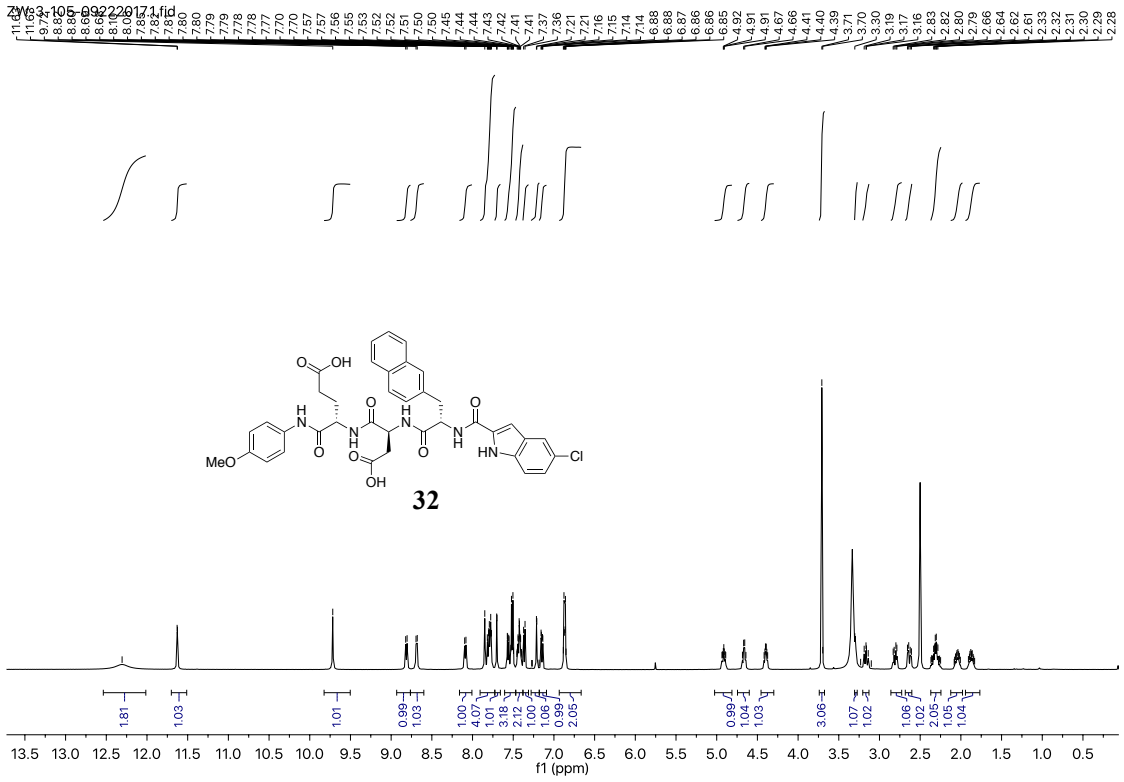
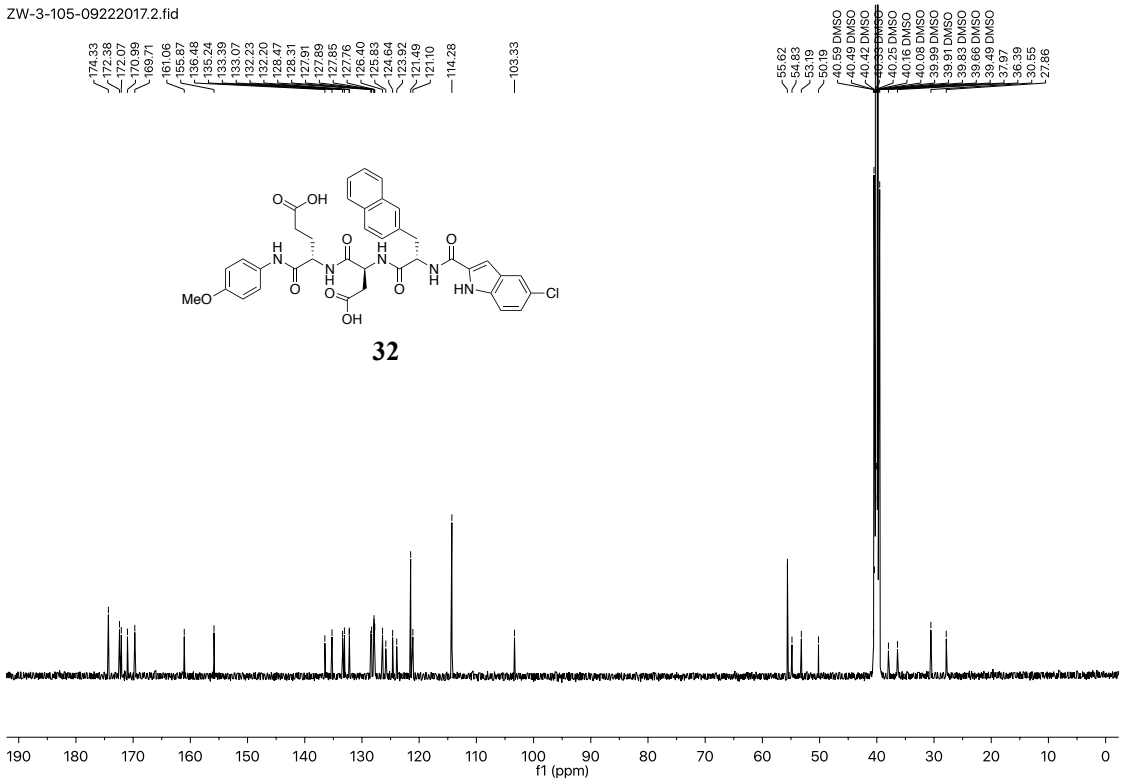
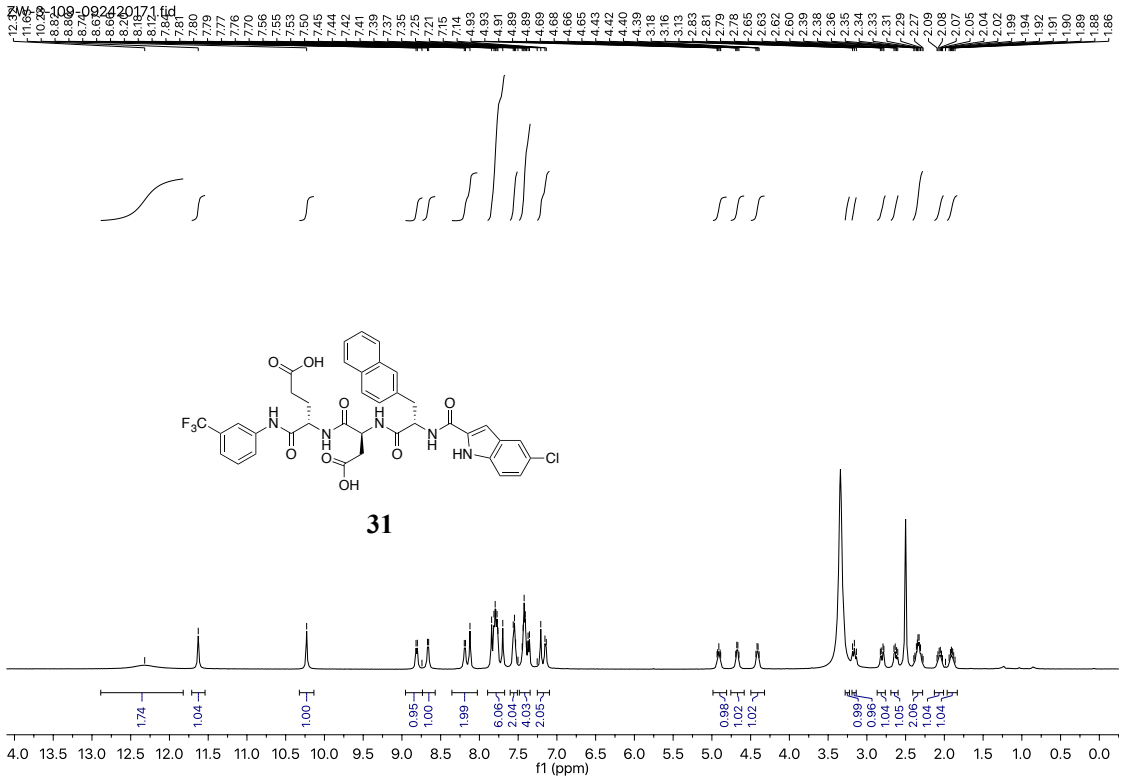



ZW-3-105-09222017.1.fid
MeO
HN
Cl
f1 (ppm)

32


ZW-3-105-09222017.2.fid
MeO
HN
Cl
f1 (ppm)

32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31
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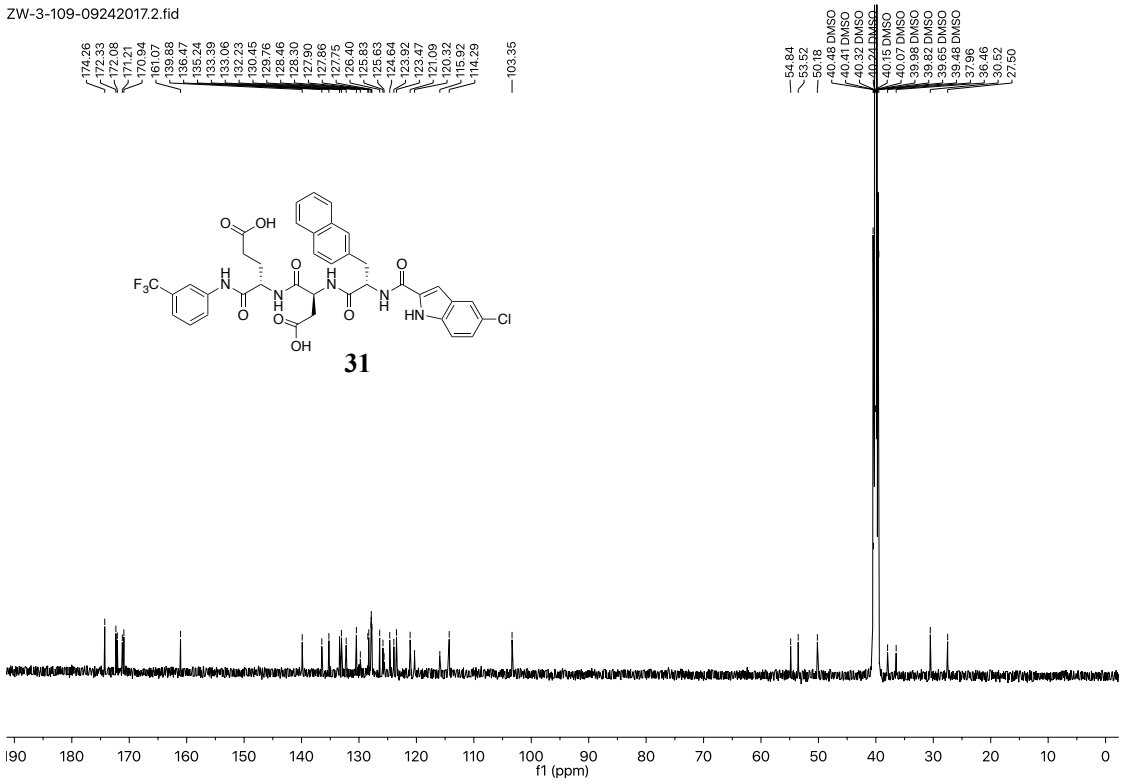
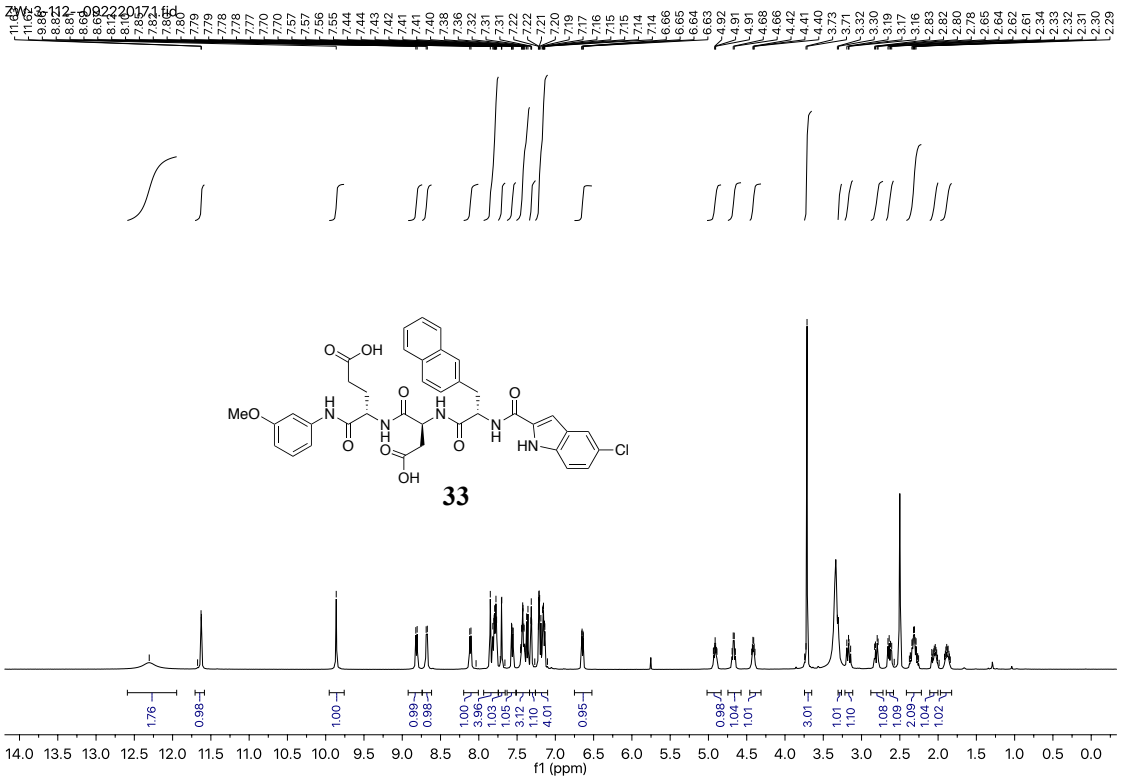
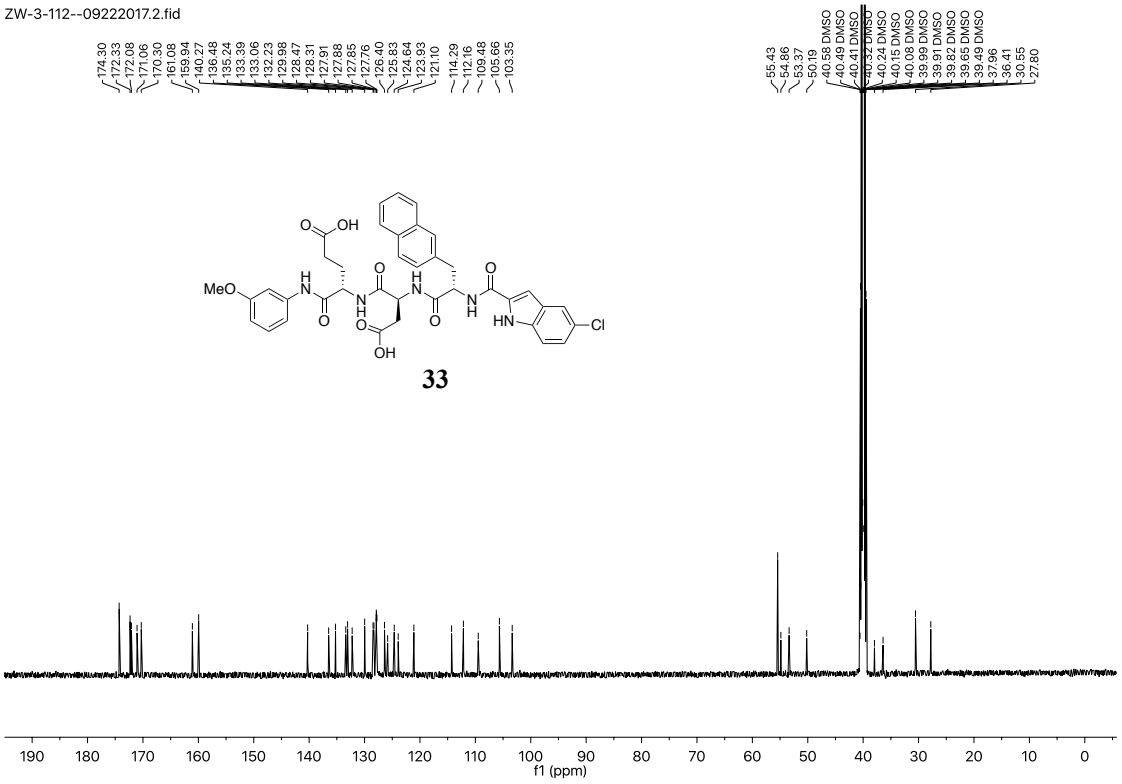
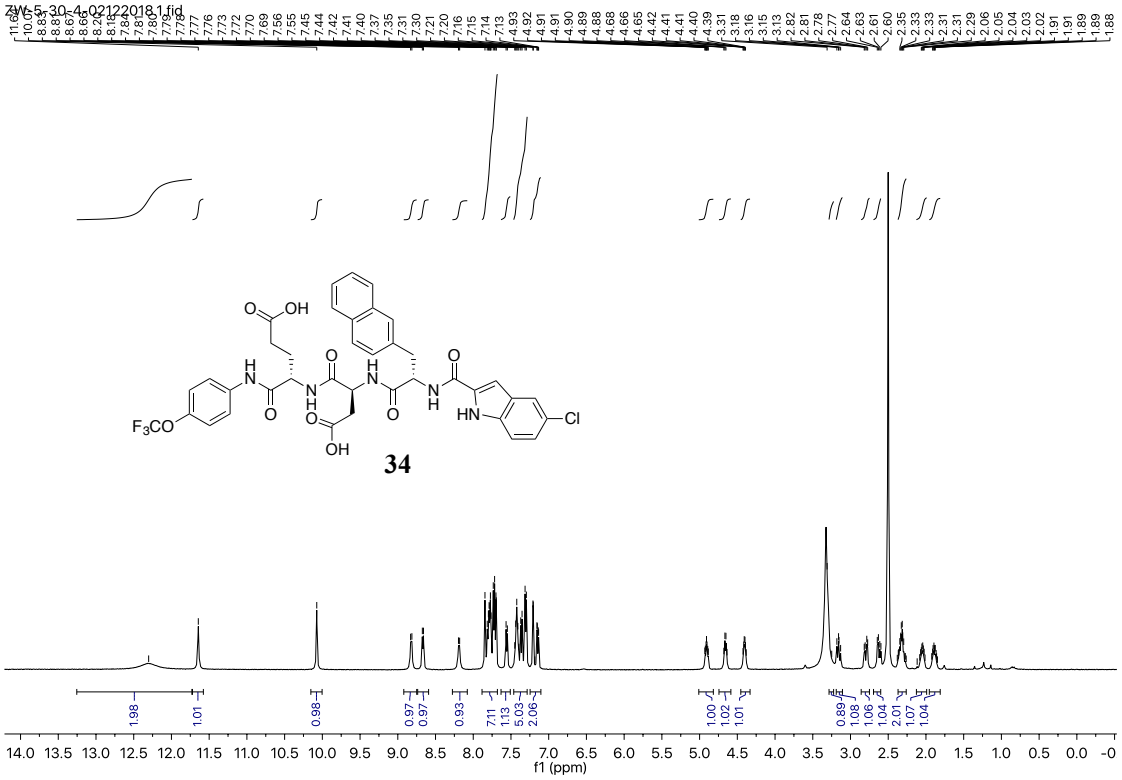
1.04
1.00
0.95
1.00
1.99
6.06
2.04
4.03
2.05
0.98
1.02
1.02
0.99
0.96
1.04
1.05
2.06
1.04
1.04
f1 (ppm)


ZW-3-109-09242017.2.fid
31
f1 (ppm)


ZW-3-112--09222017.1.fid
MeO
Cl
HN
OH
33
f1 (ppm)


ZW-3-112--09222017.2.fid
MeO
Cl
HN
OH
33
f1 (ppm)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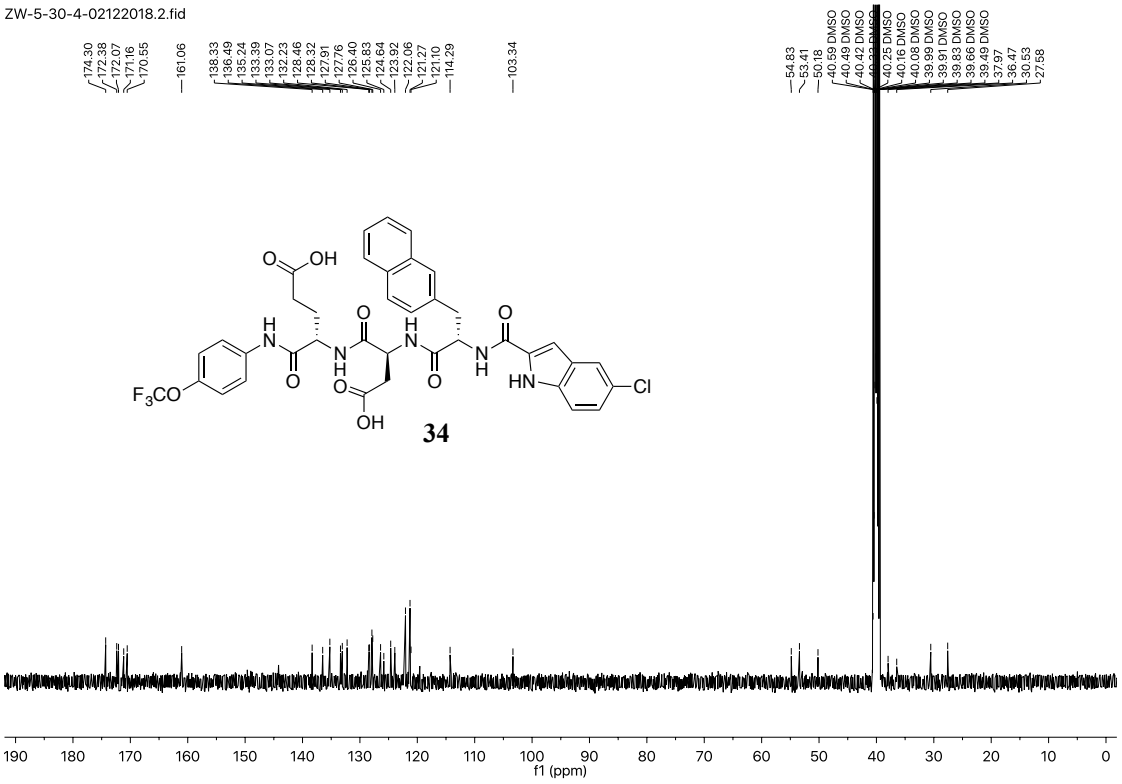
34
f1 (ppm)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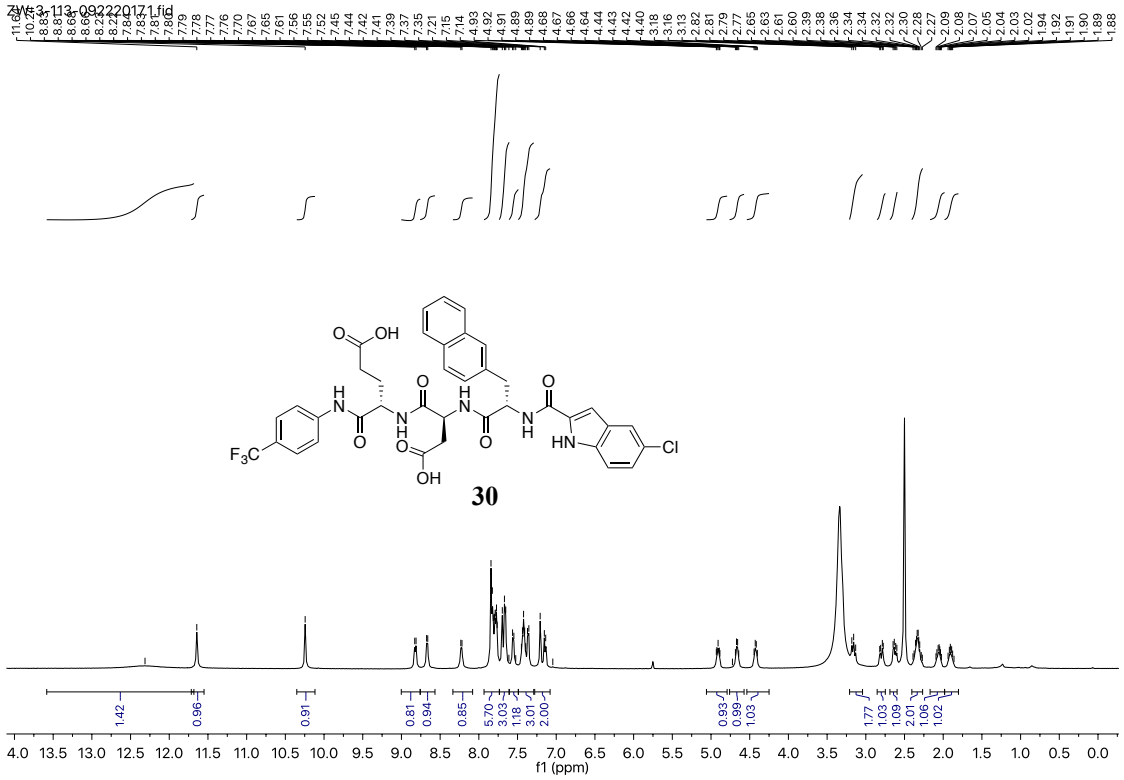
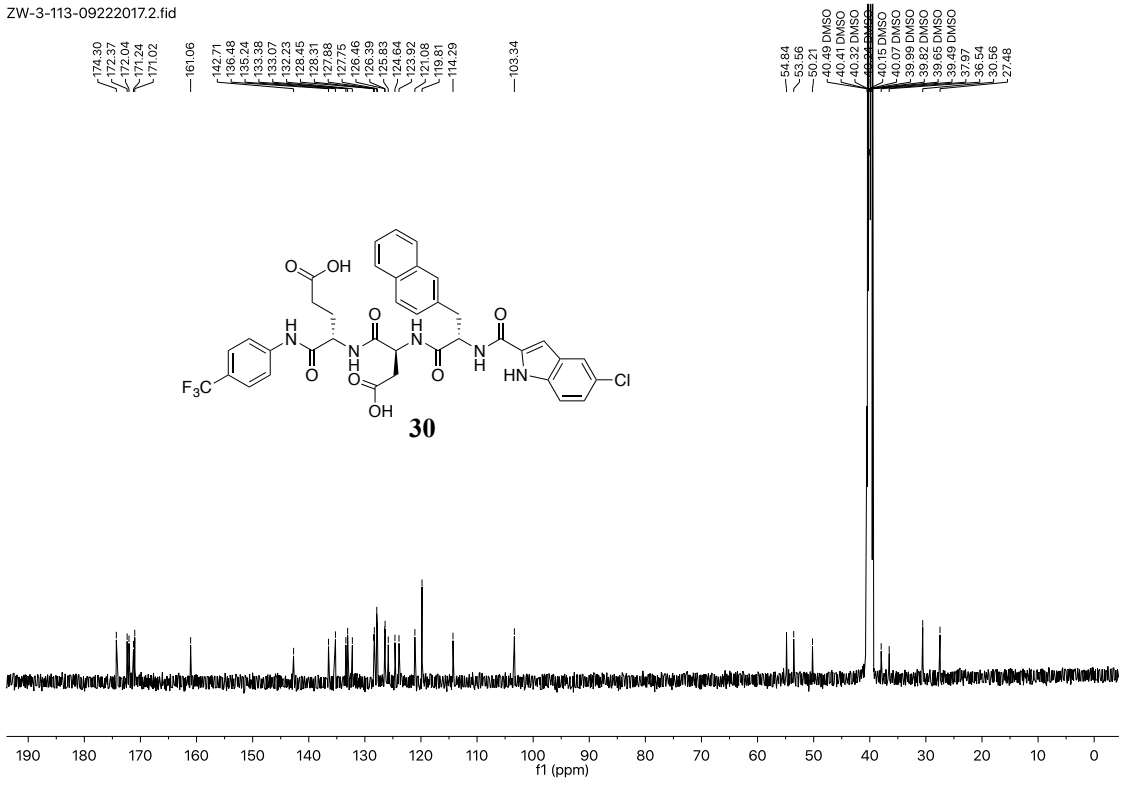
34
f1 (ppm)


ZW-3-113-092220171.fid
30
f1 (ppm)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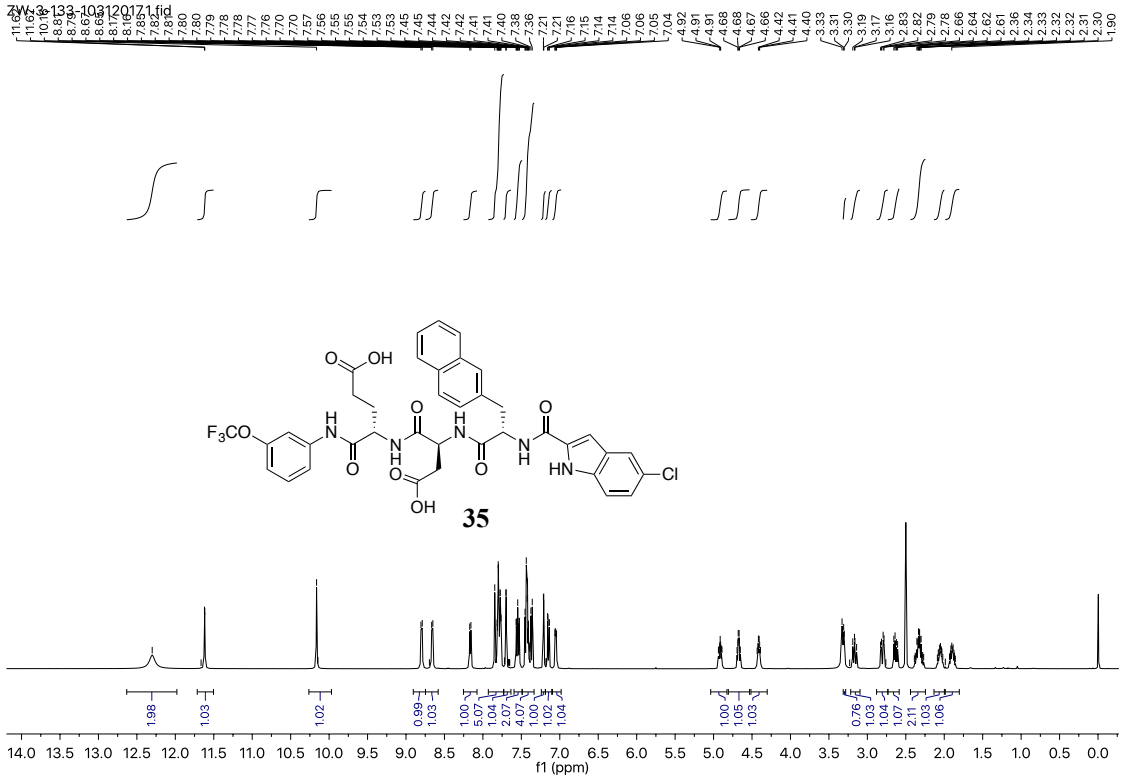
30
f1 (ppm)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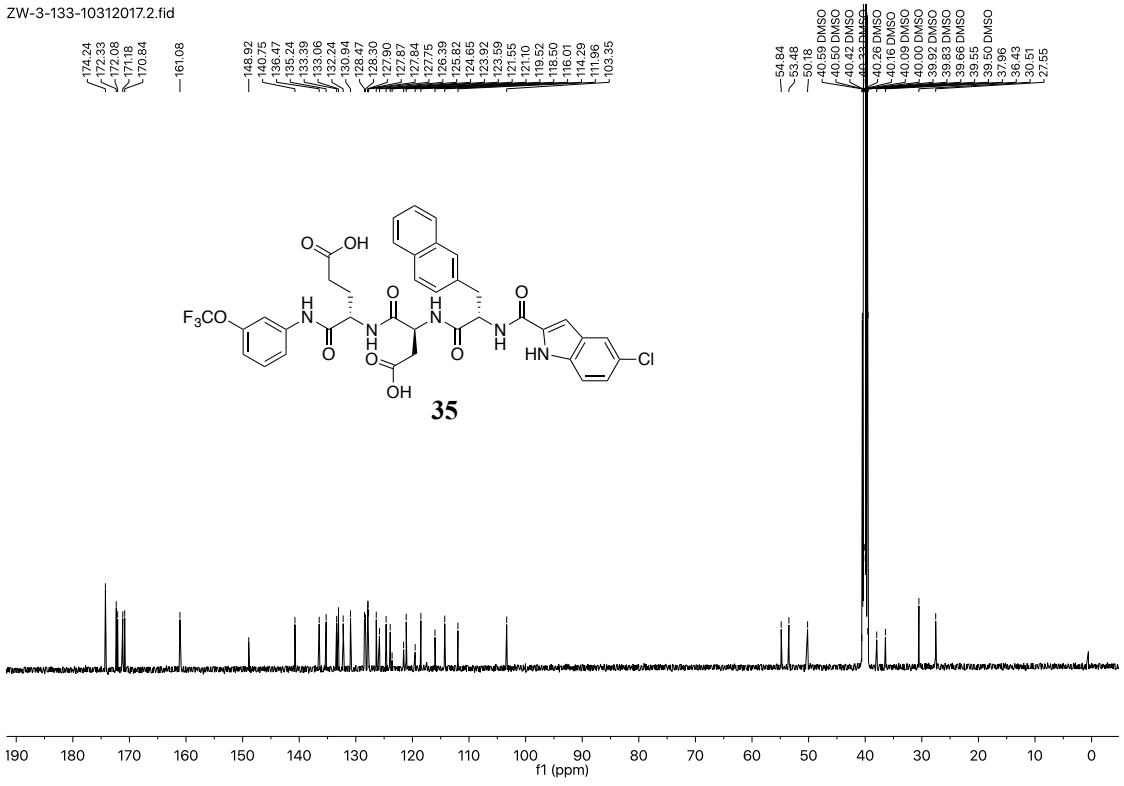
35
f1 (ppm)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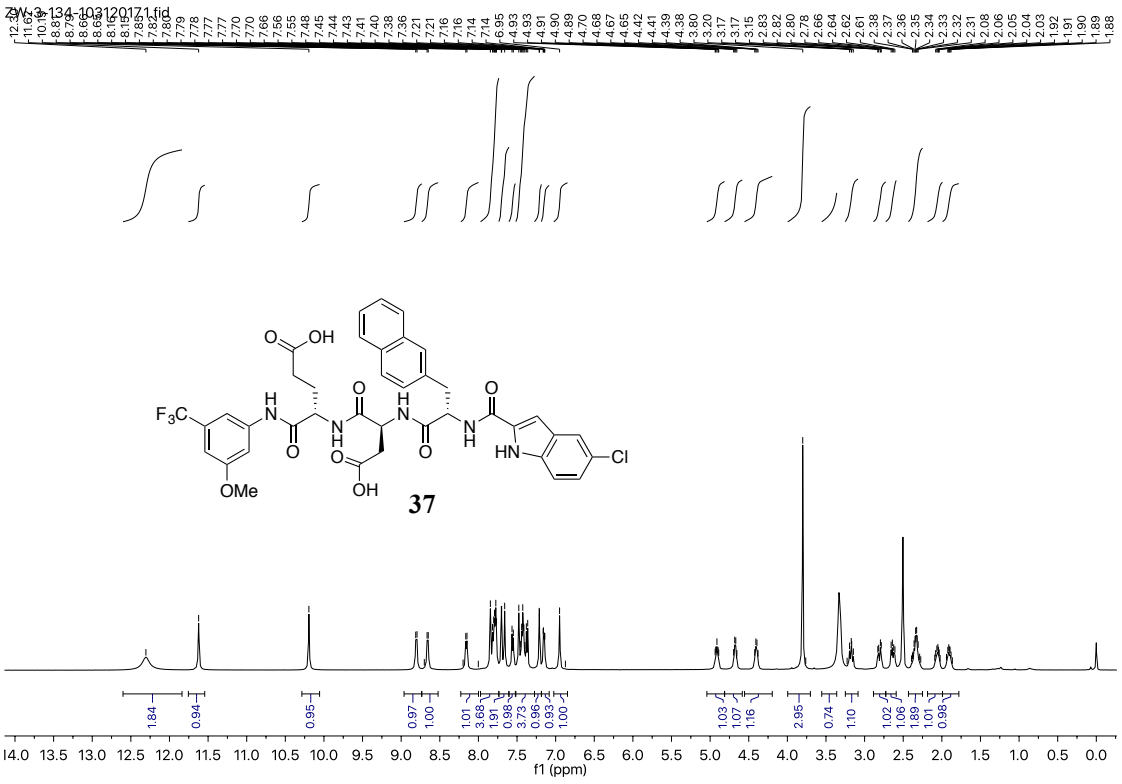
35
f1 (ppm)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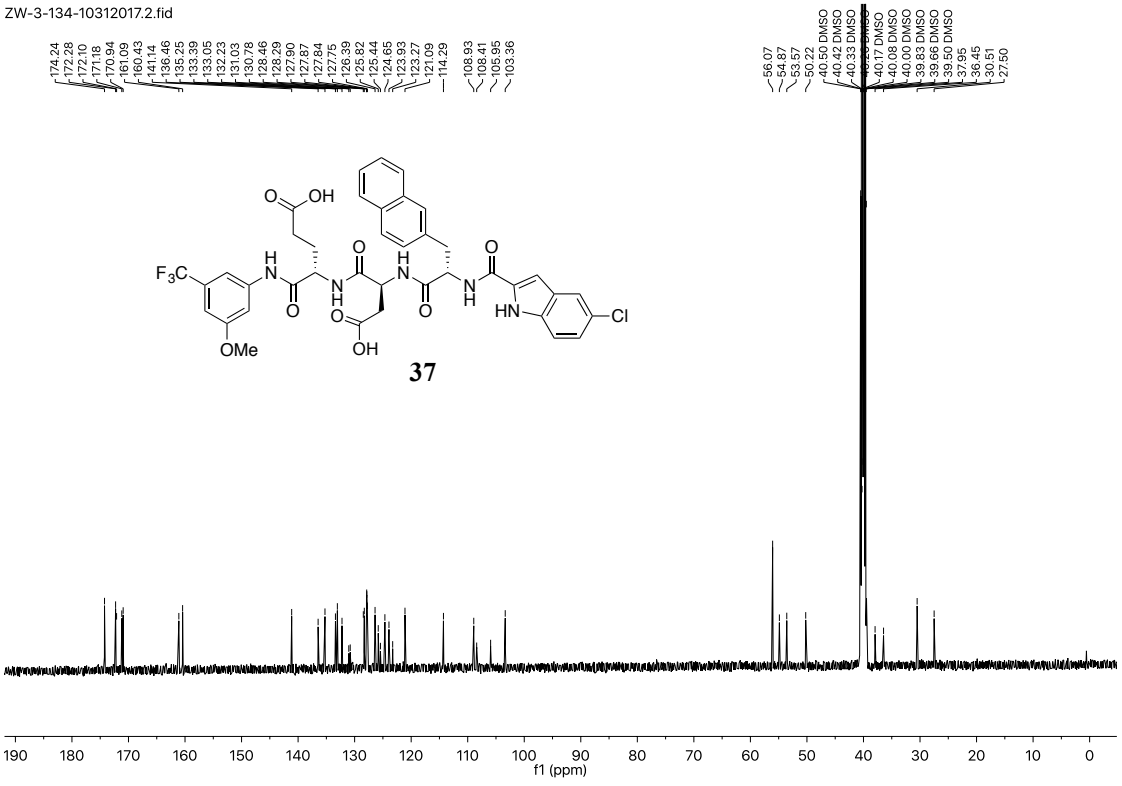
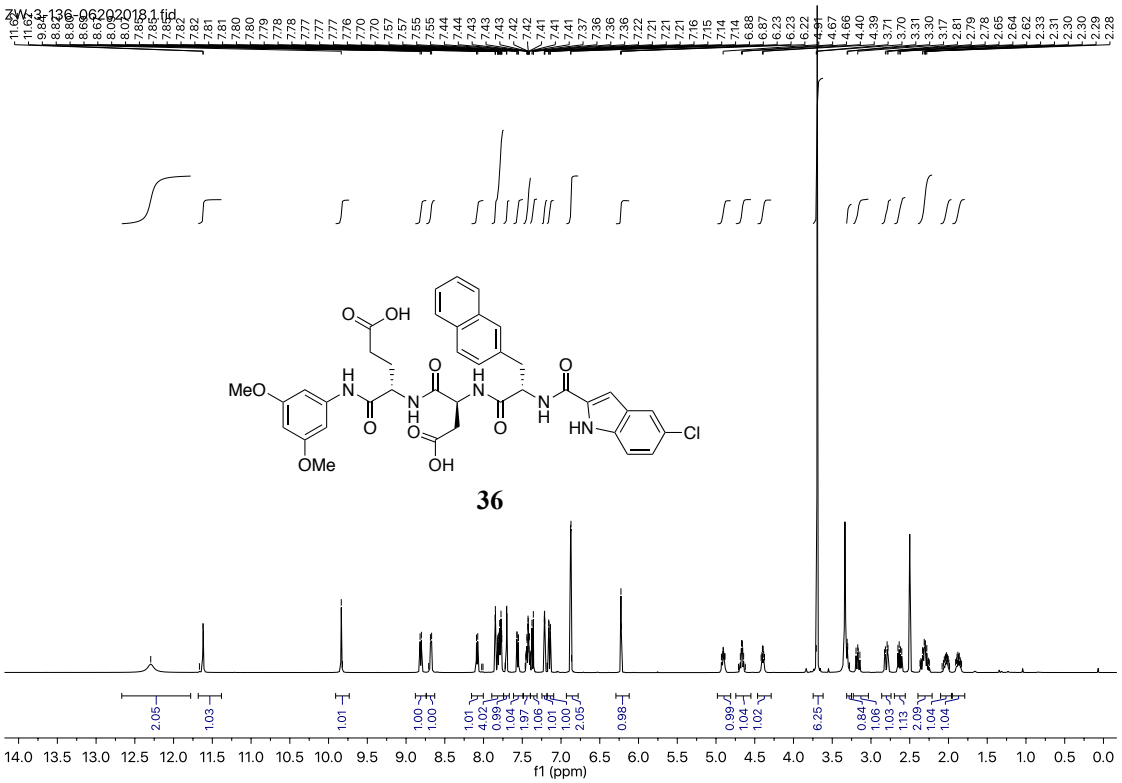
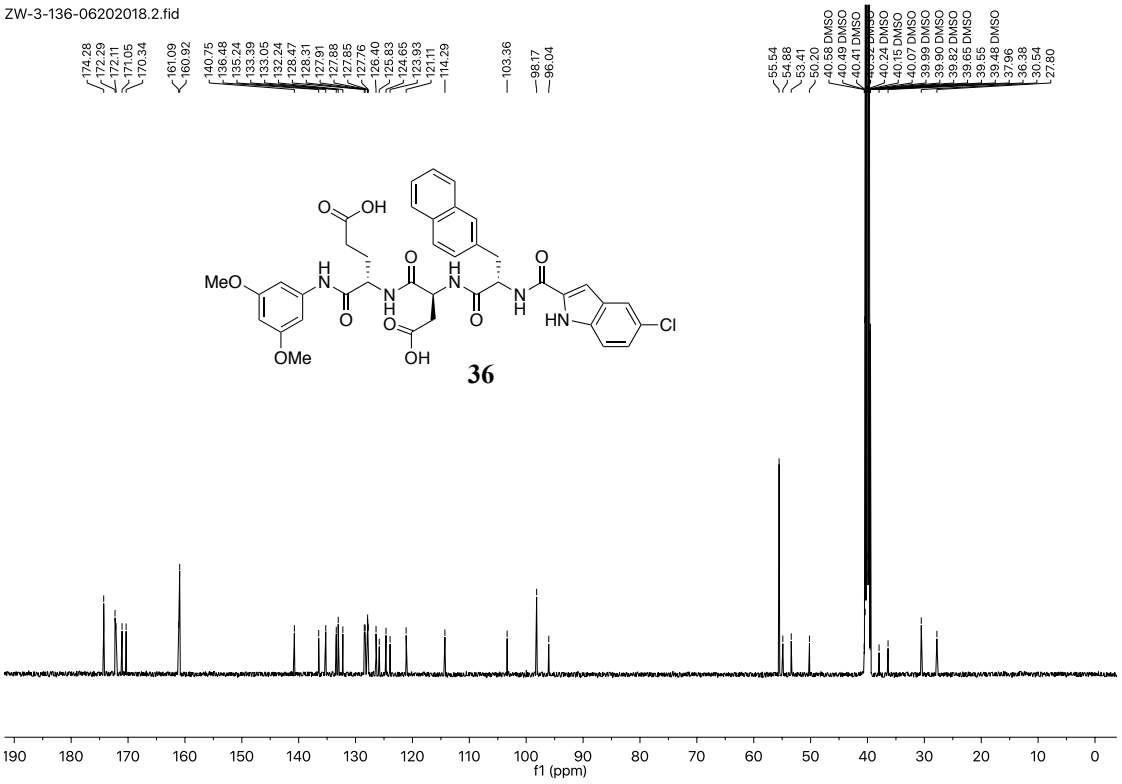
37
f1 (ppm)


ZW-3-134-10312017.2.fid
37
f1 (ppm)

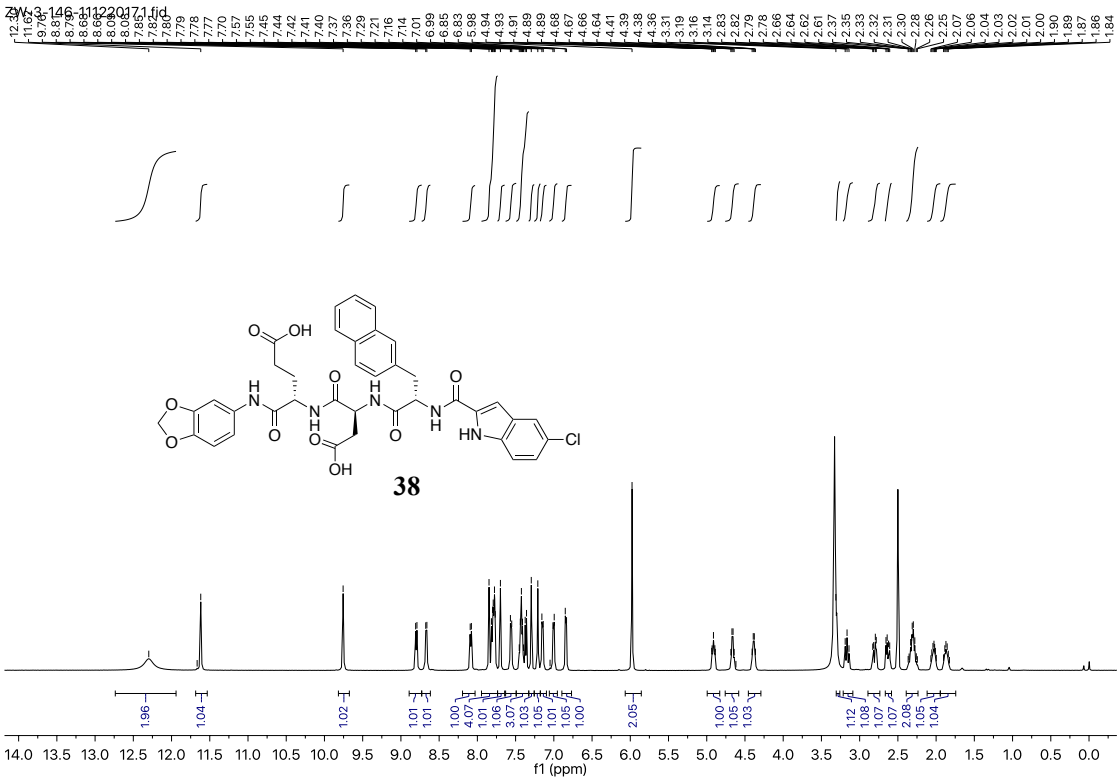


36

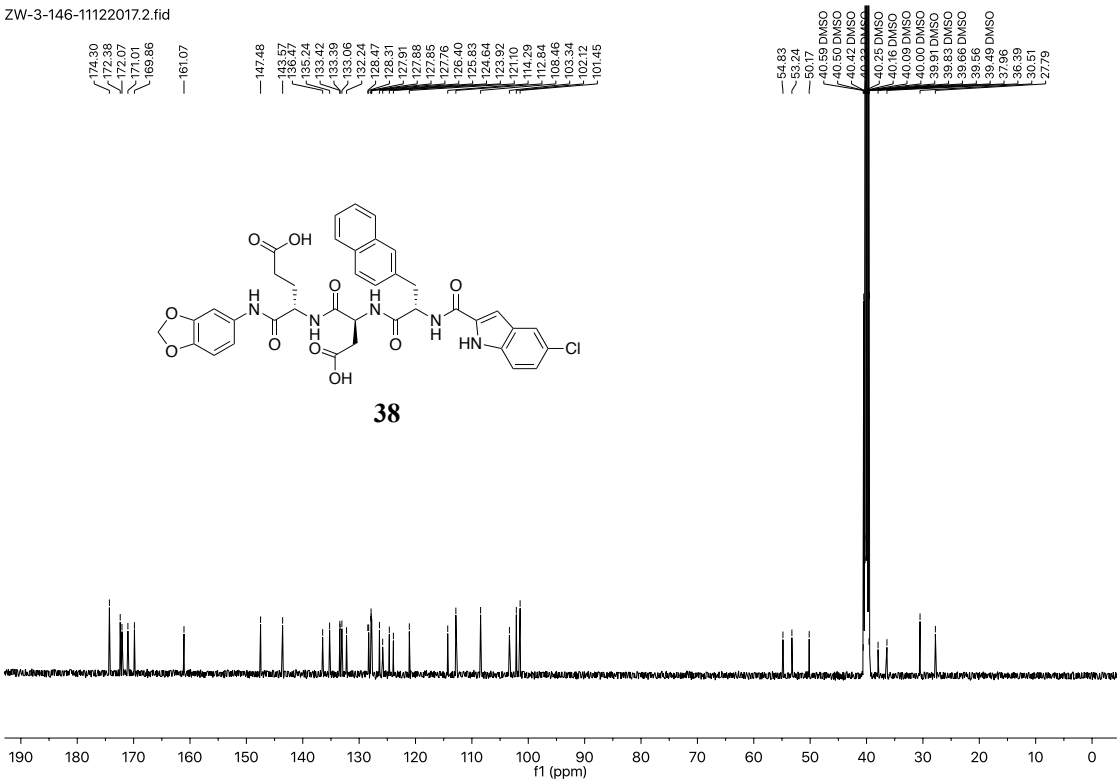


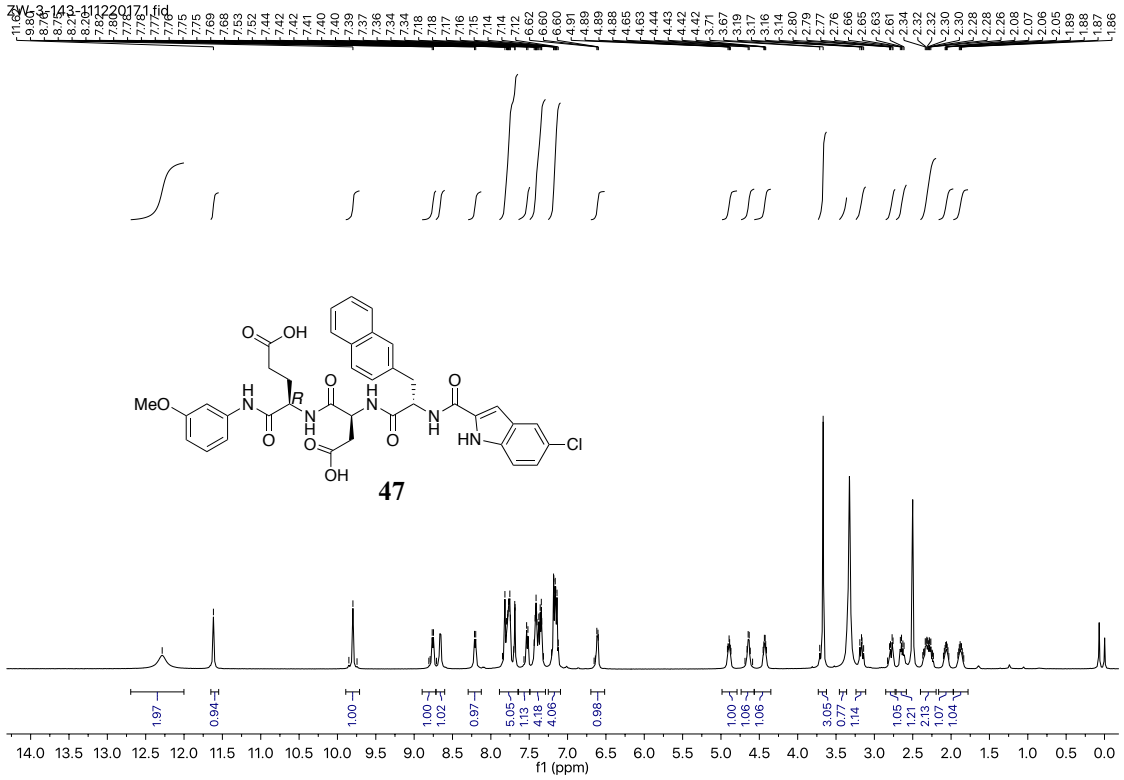
36

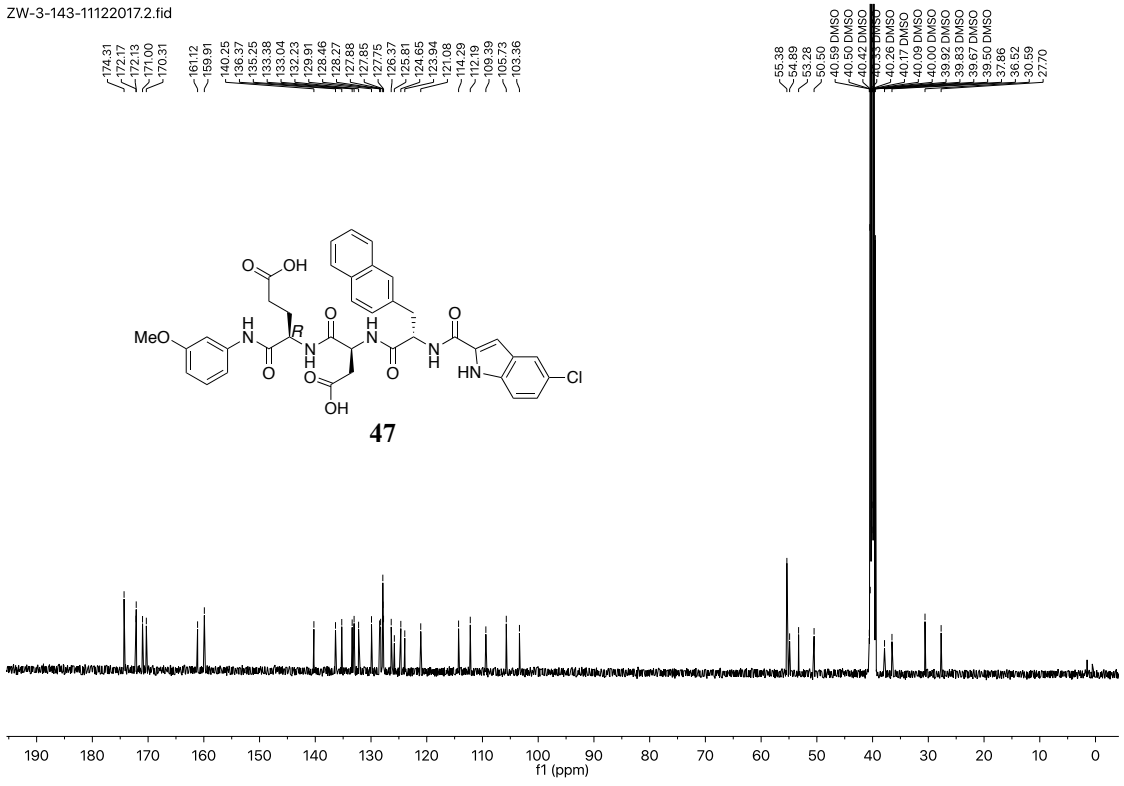
ZW-3-146-11122017.1.fid

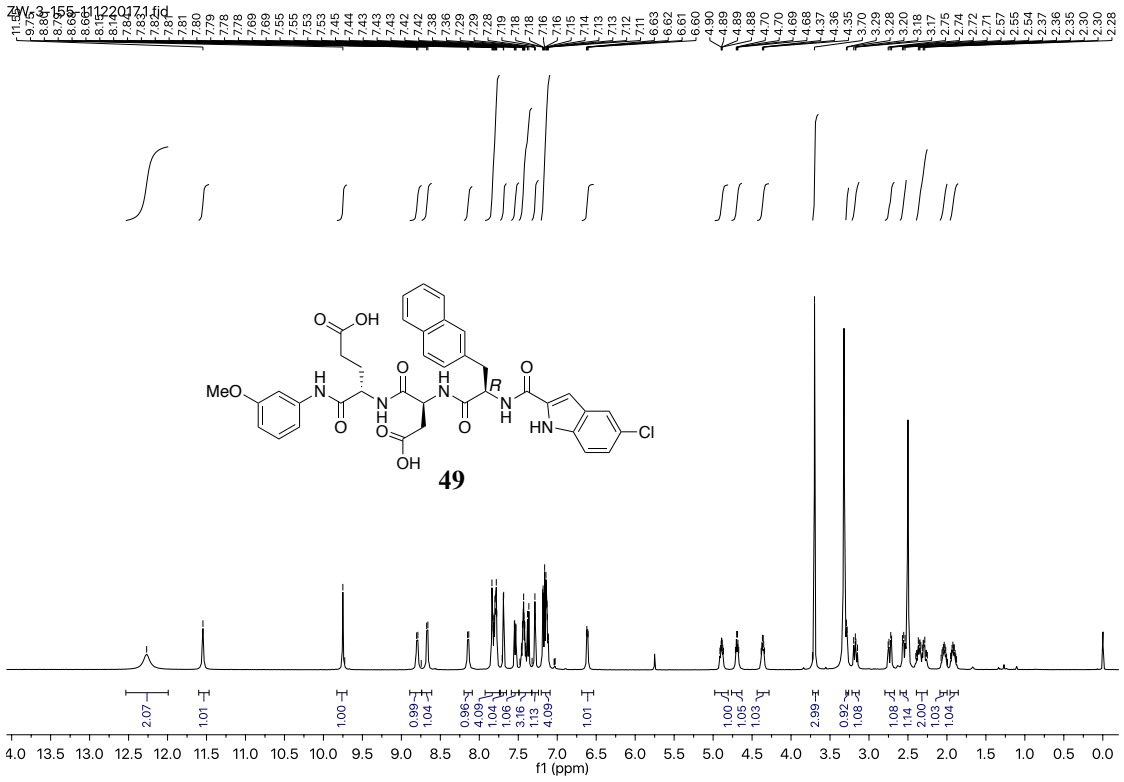


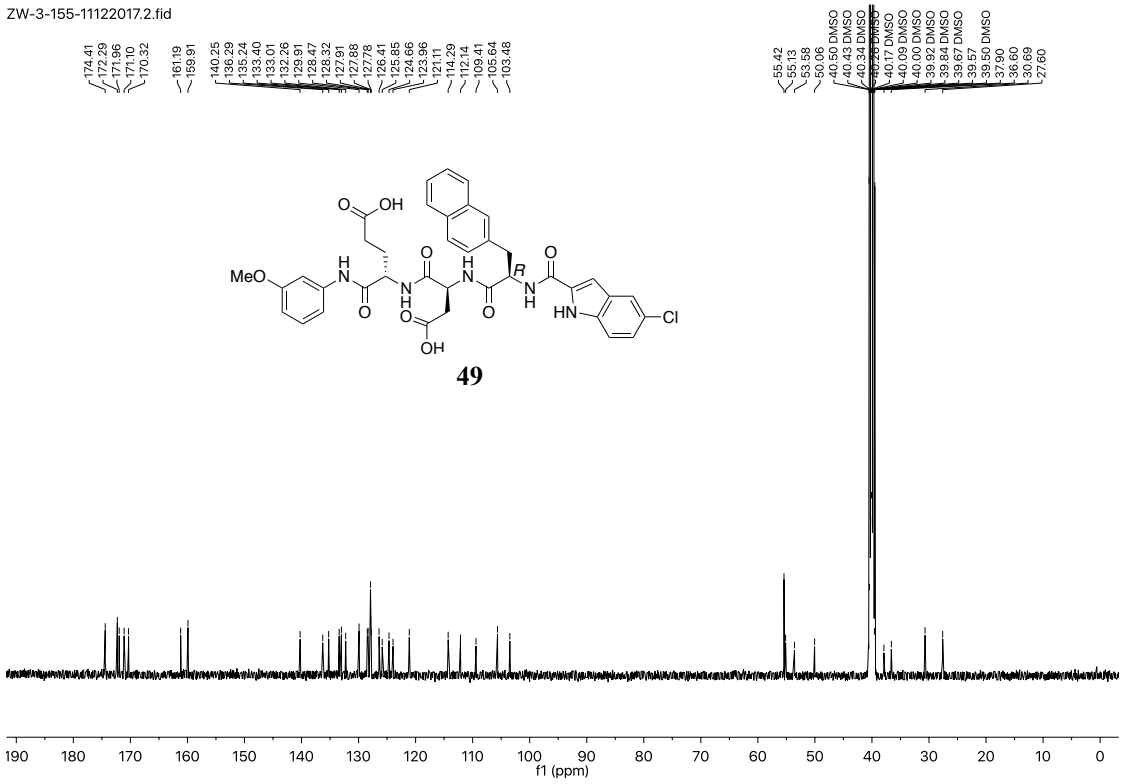
ZW-3-146-11122017.2.fid




ZW-3-143-11122017.1.fid
MeO
HN
Cl
47
f1 (ppm)


ZW-3-143-11122017.2.fid
MeO
HN
Cl
47
f1 (ppm)


ZW-3-155-11122017.1.fid
MeO
HN
Cl
OH
49
f1 (ppm)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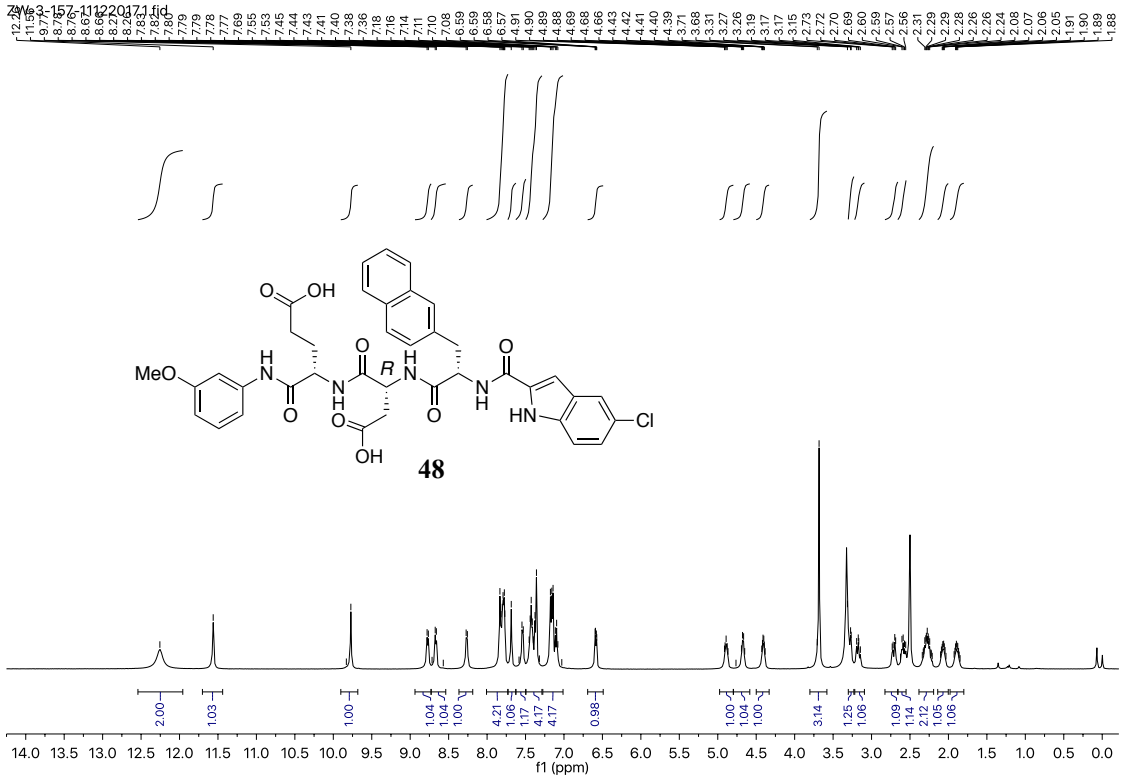
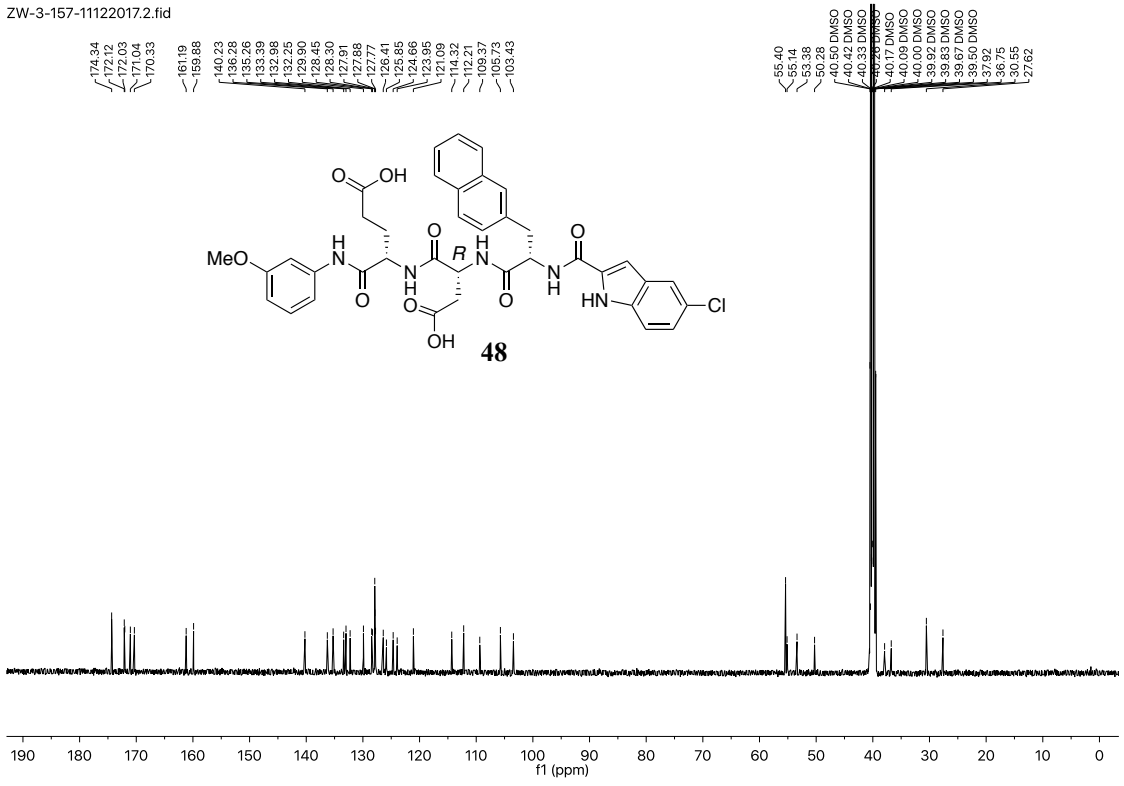
MeO
HN
Cl
OH
49
f1 (ppm)


ZW-3-157-11122017.1.fid
MeO
HN
Cl
48
f1 (ppm)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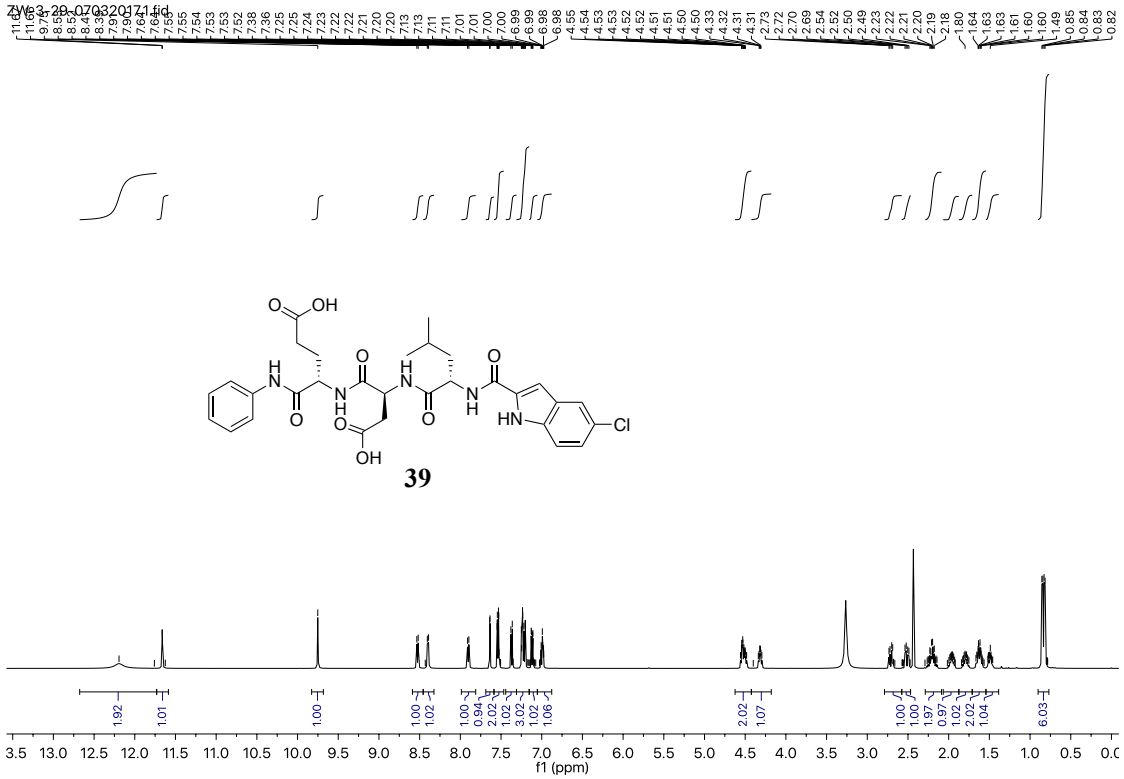
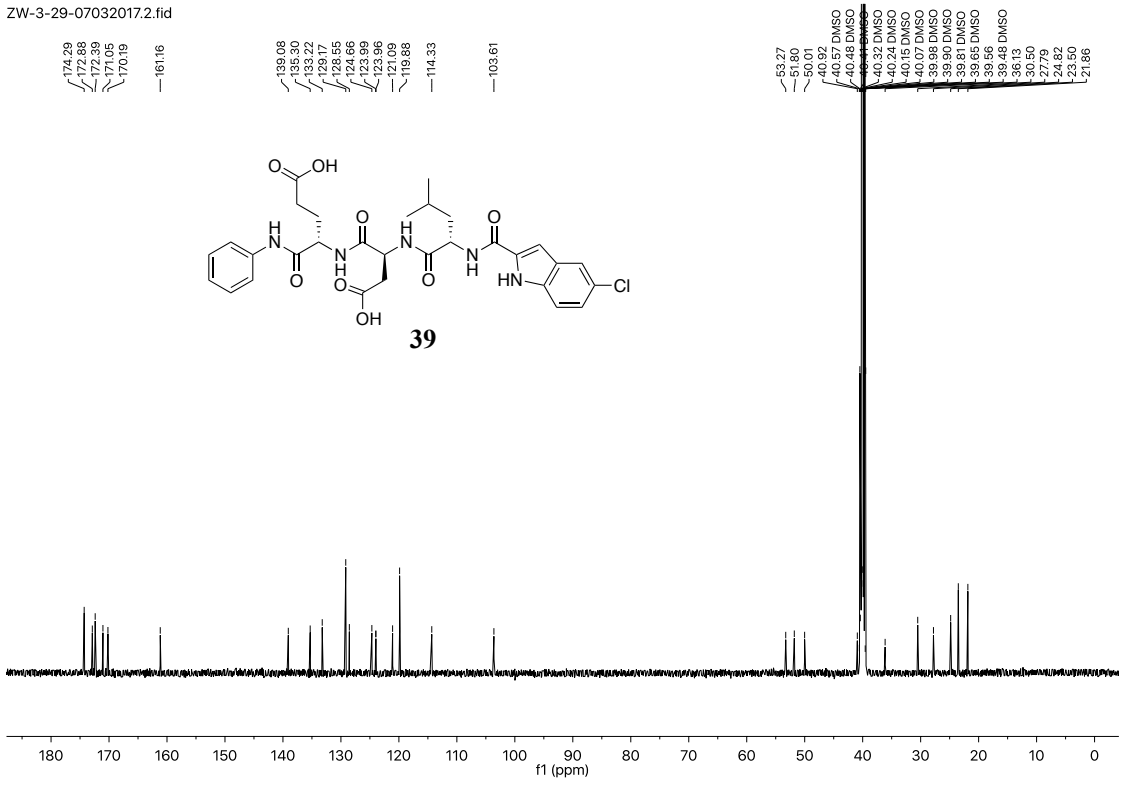
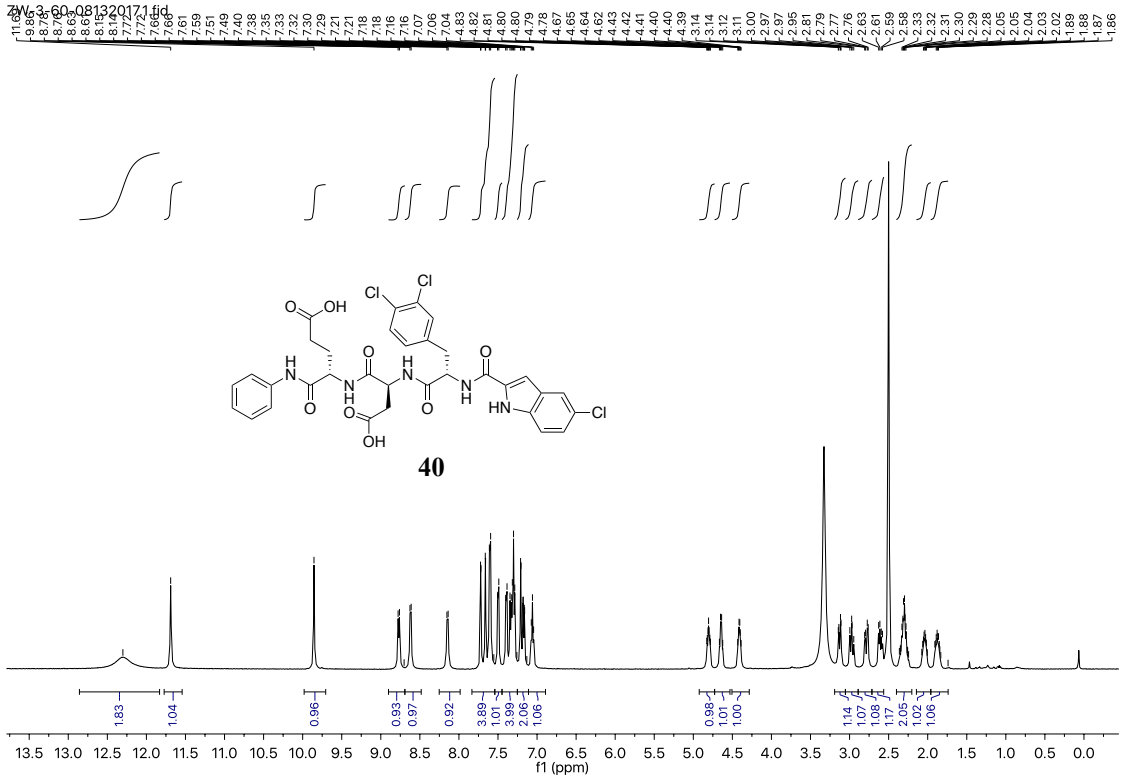
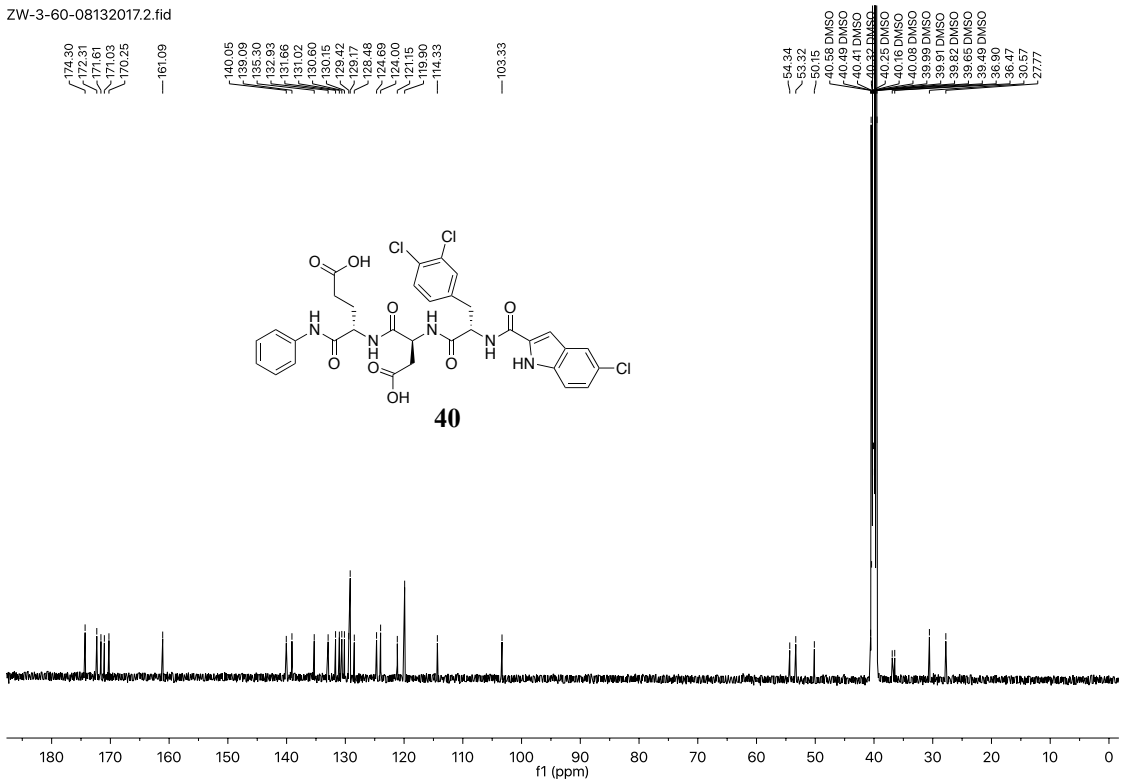
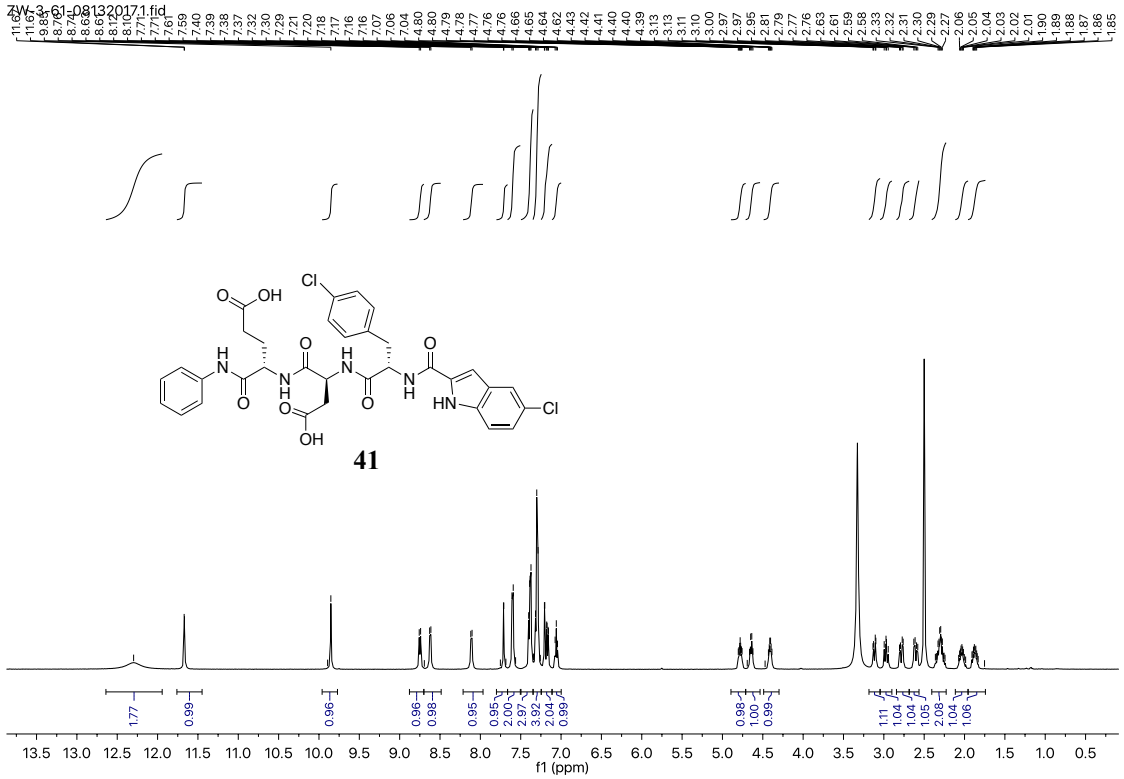
MeO
HN
Cl
48
f1 (ppm)


ZW3-29-07032017.1.fid
39
f1 (ppm)

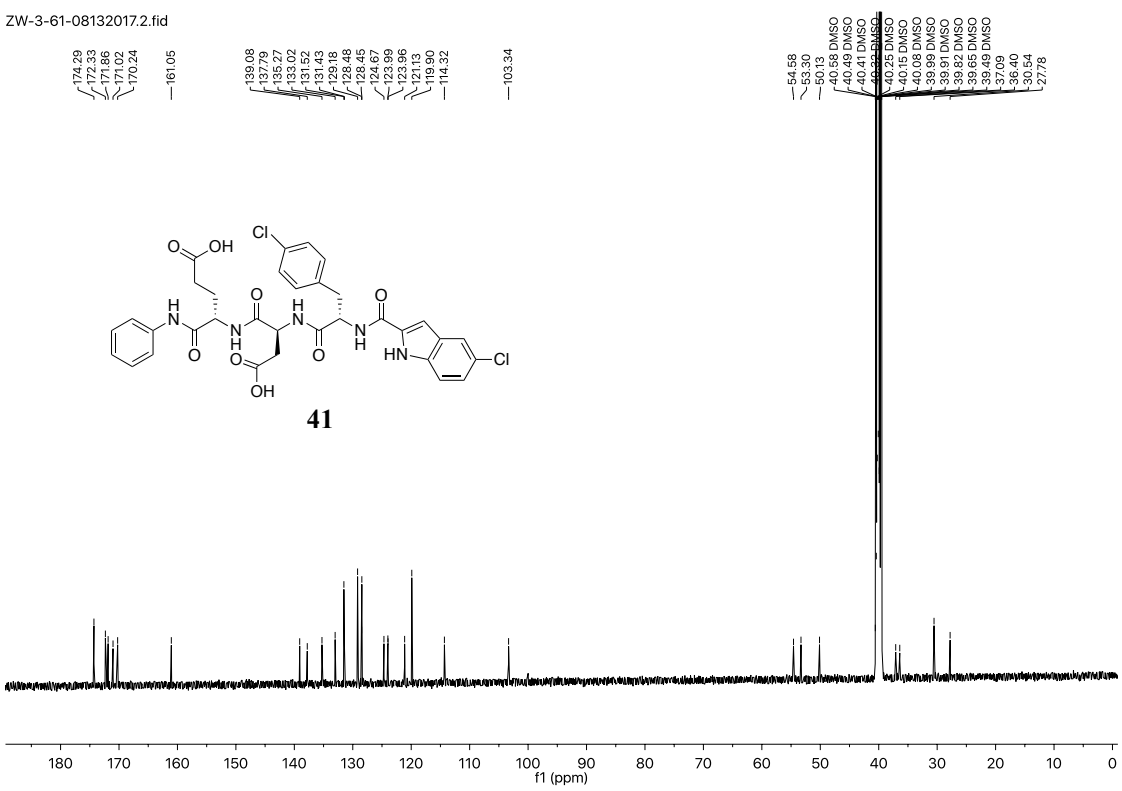

ZW-3-29-07032017.2.fid
39
f1 (ppm)


ZW-3-60-081320171.fid
40
1.83
1.04
0.96
0.93
0.97
0.92
3.89
1.01
3.99
2.06
1.06
0.98
1.01
1.00
1.14
1.07
1.08
1.17
2.05
1.02
1.06
f1 (ppm)

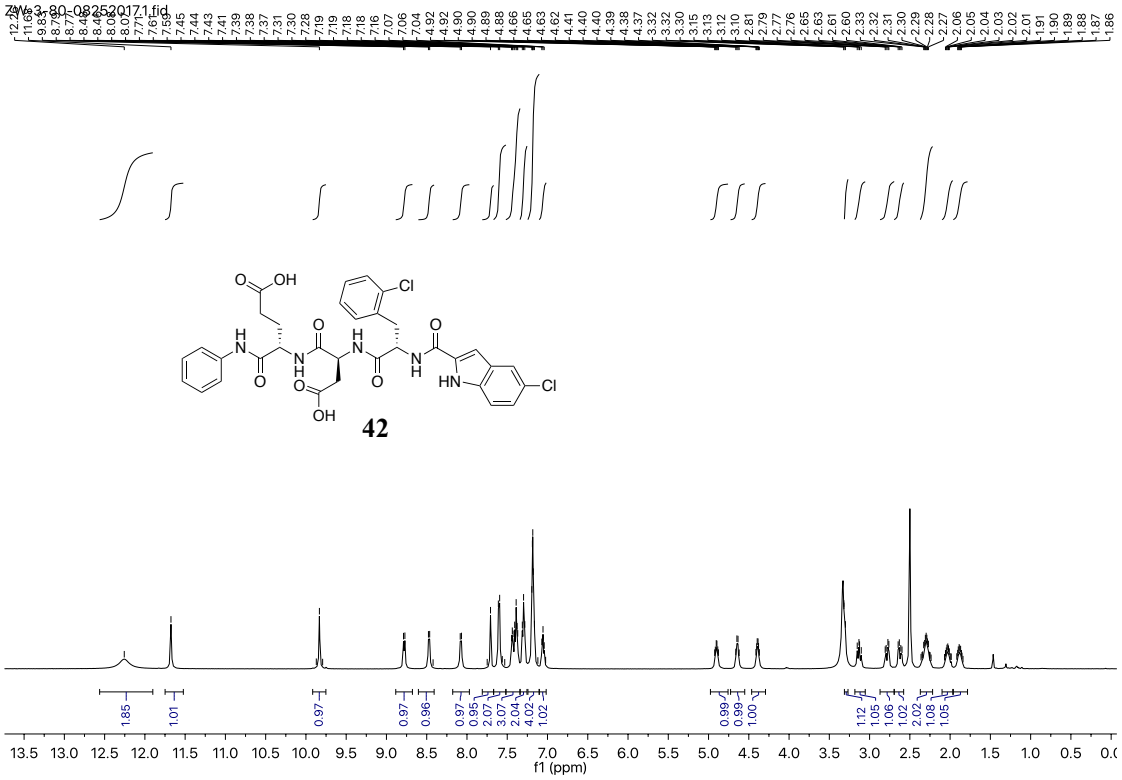

ZW-3-60-08132017.2.fid
40
f1 (ppm)

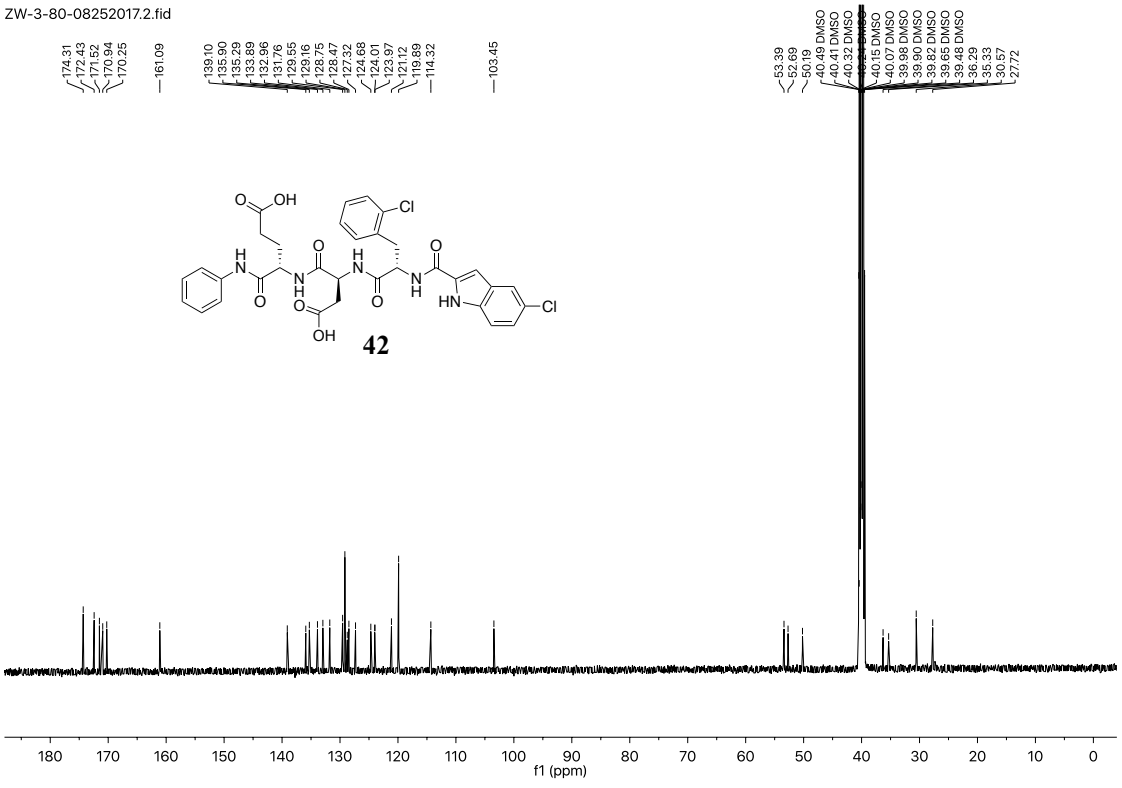


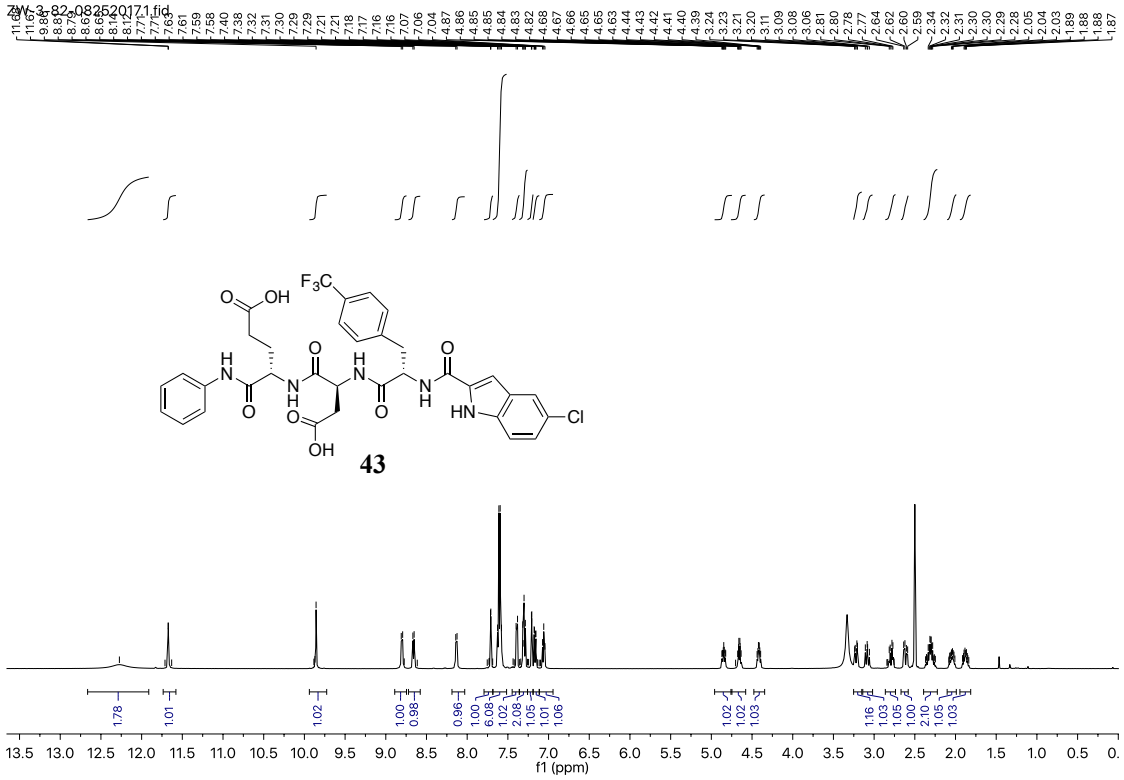
41

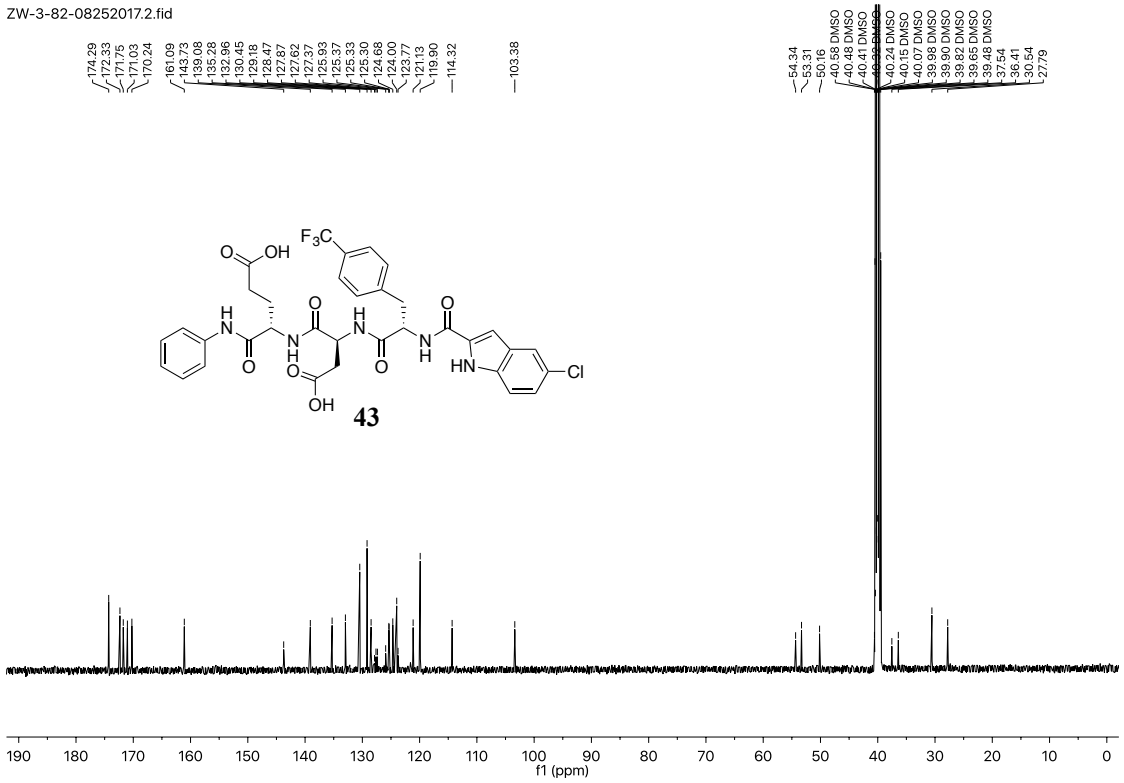


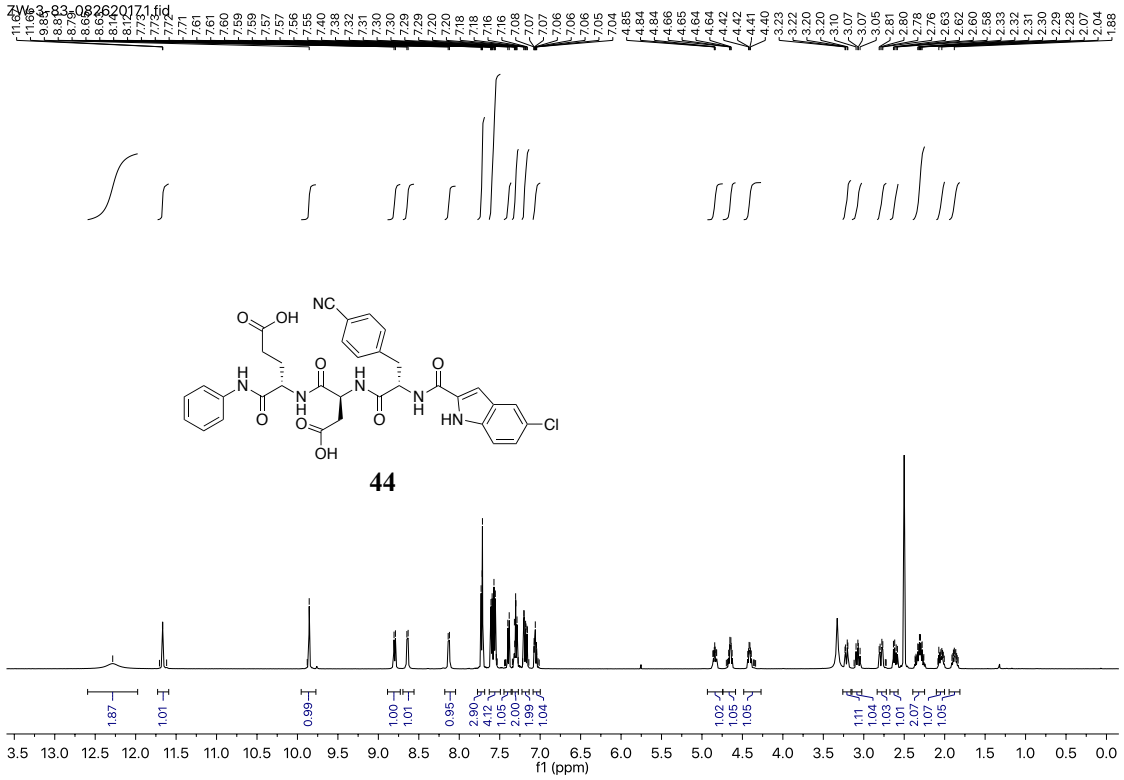
41

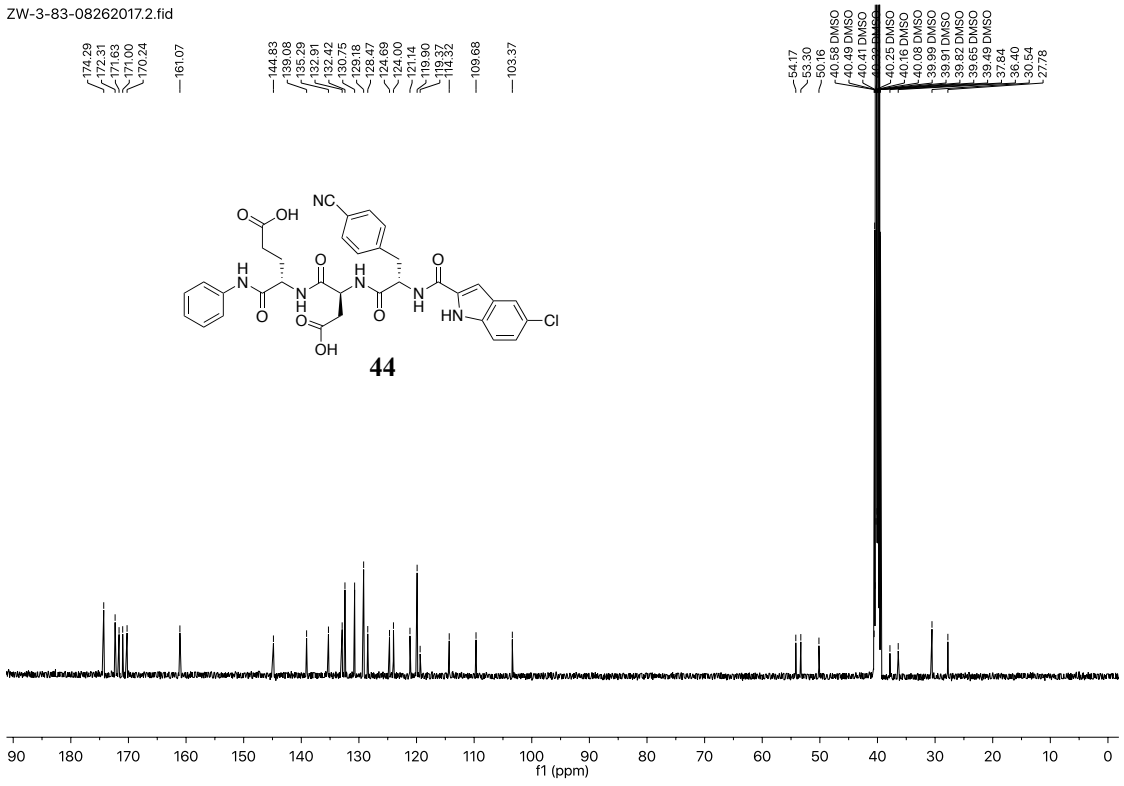

ZW-3-80-08252017.1.fid
42

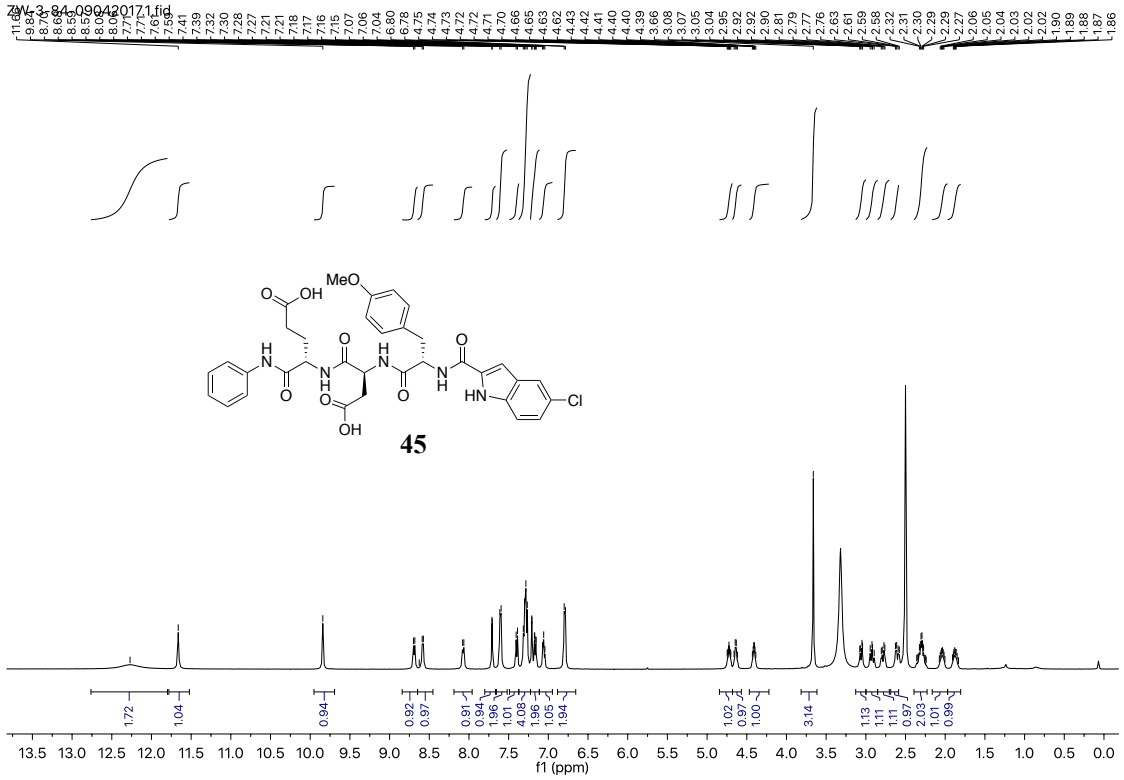

ZW-3-80-08252017.2.fid
42

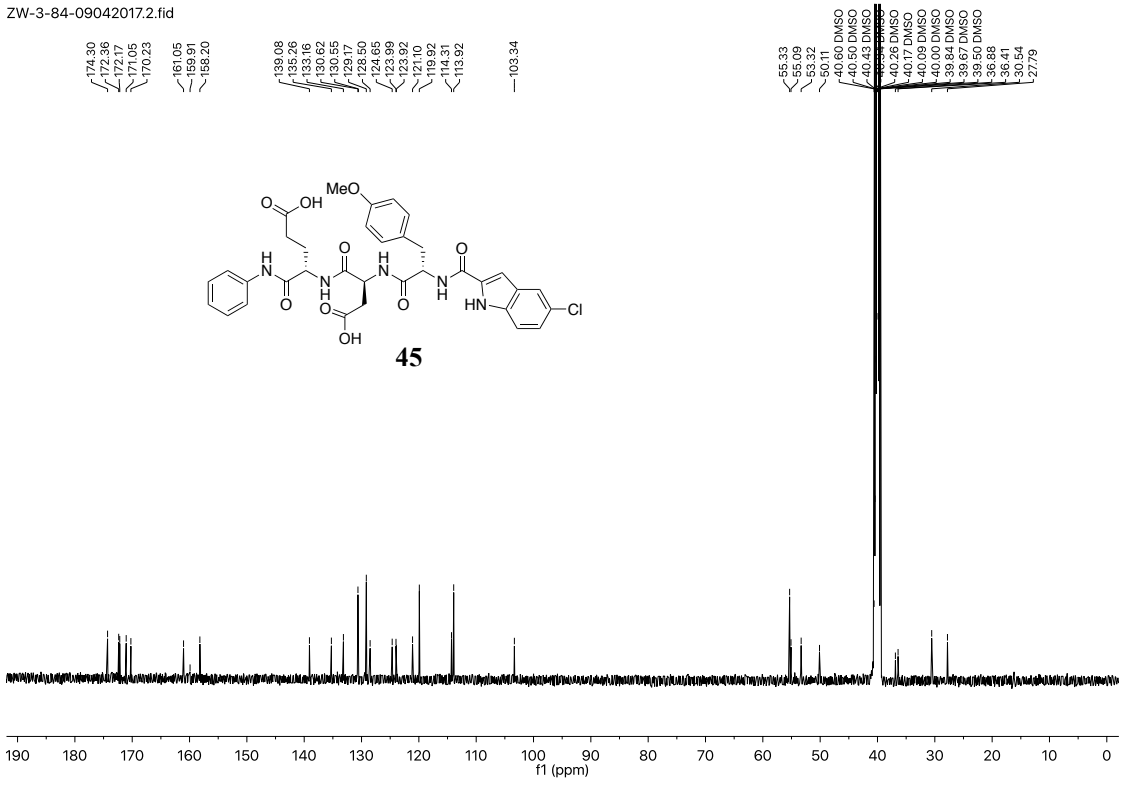

ZW-3-82-08252017.1.fid
F3C
O
OH
H
N
O
N
H
O
HN
Cl
OH
43
1.78
1.01
1.02
1.00
0.98
0.96
1.00
6.08
1.02
2.08
1.05
1.01
1.06
1.02
1.02
1.03
1.16
1.03
1.05
1.00
2.10
1.05
1.03
f1 (ppm)

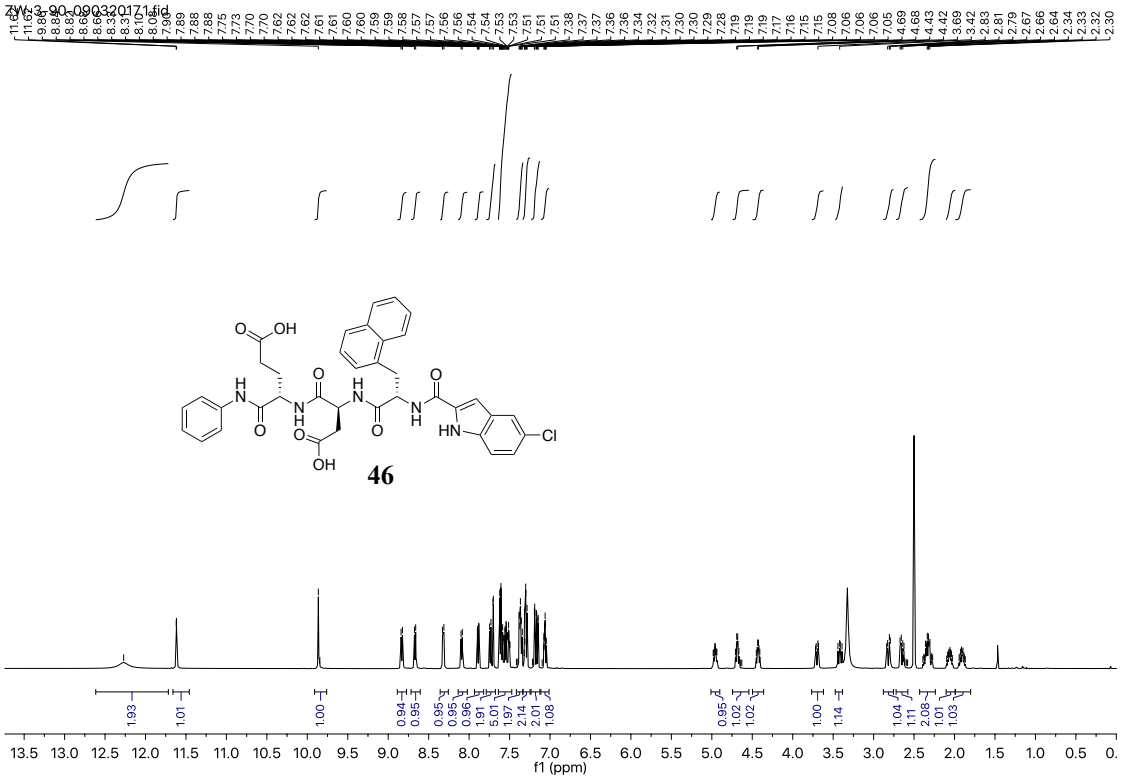

ZW-3-82-08252017.2.fid
F3C
O
OH
H
N
O
N
H
O
HN
Cl
OH
43
DMSO
f1 (ppm)

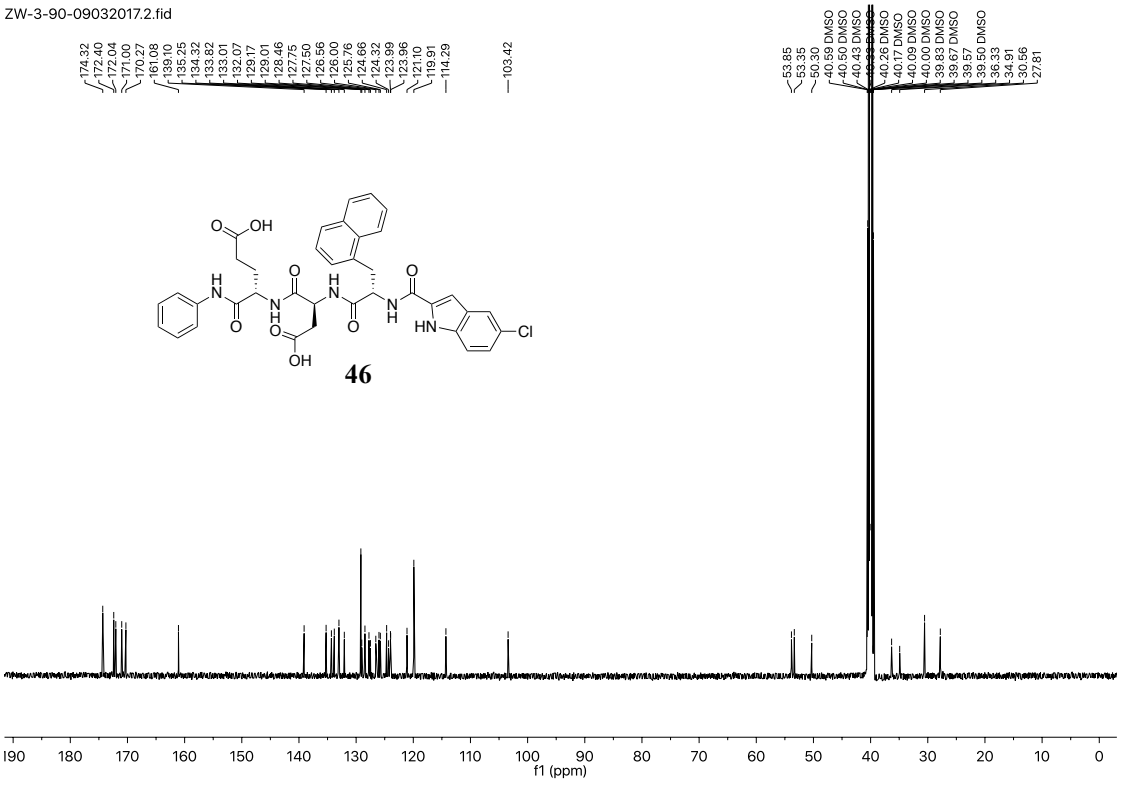

ZW-3-83-08262017.1.fid
44
f1 (ppm)


ZW-3-83-08262017.2.fid
44
f1 (ppm)


ZW-3-84-09042017.1.fid
MeO
OH
O
N
H
Cl
45
1.72
1.04
0.94
0.92
0.97
0.91
0.94
1.96
1.01
4.08
1.96
1.05
1.94
1.02
0.97
1.00
3.14
1.13
1.11
1.11
0.97
2.03
1.01
0.99
f1 (ppm)


ZW-3-84-09042017.2.fid
174.30
172.36
172.17
171.05
170.23
161.05
159.91
158.20
139.08
135.26
133.16
130.62
130.55
129.17
128.50
124.65
123.99
123.92
121.10
119.92
114.31
113.92
103.34
55.33
55.09
53.32
50.11
40.60 DMSO
40.50 DMSO
40.43 DMSO
40.26 DMSO
40.17 DMSO
40.09 DMSO
40.00 DMSO
39.84 DMSO
39.67 DMSO
39.50 DMSO
36.88
36.41
30.54
27.79
MeO
OH
O
N
H
Cl
45
f1 (ppm)


ZW-3-90-09032017.1.fid
46
f1 (ppm)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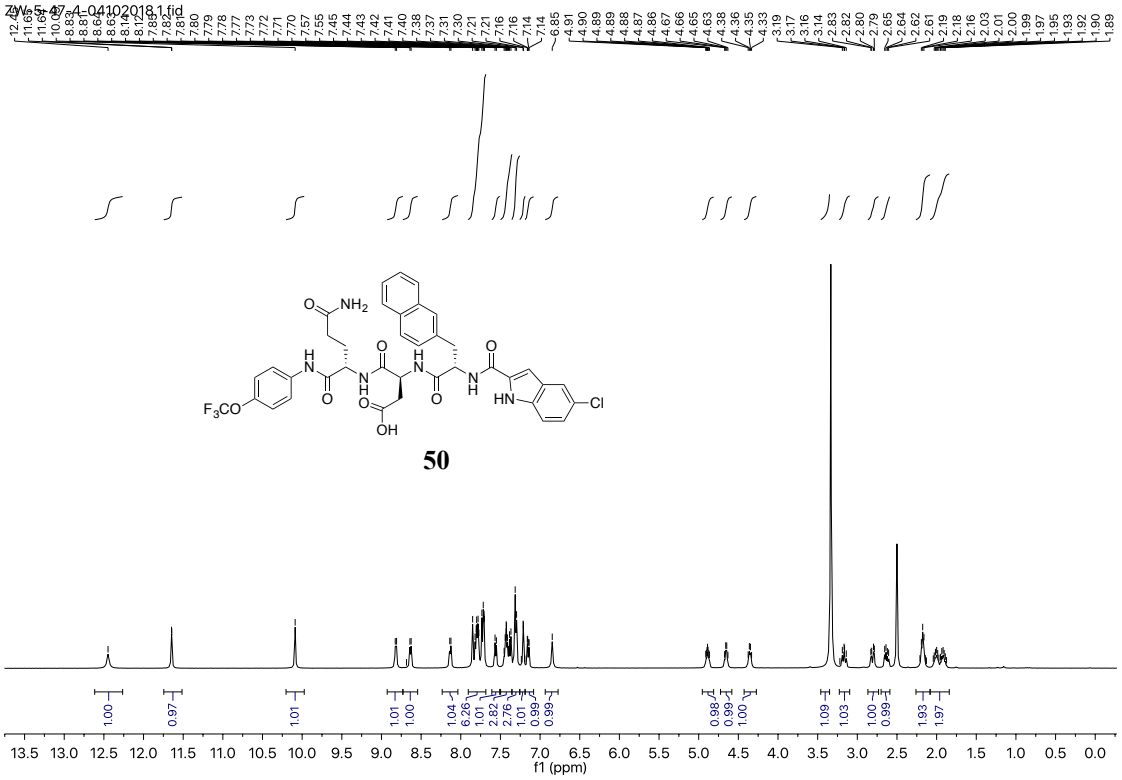
46
f1 (ppm)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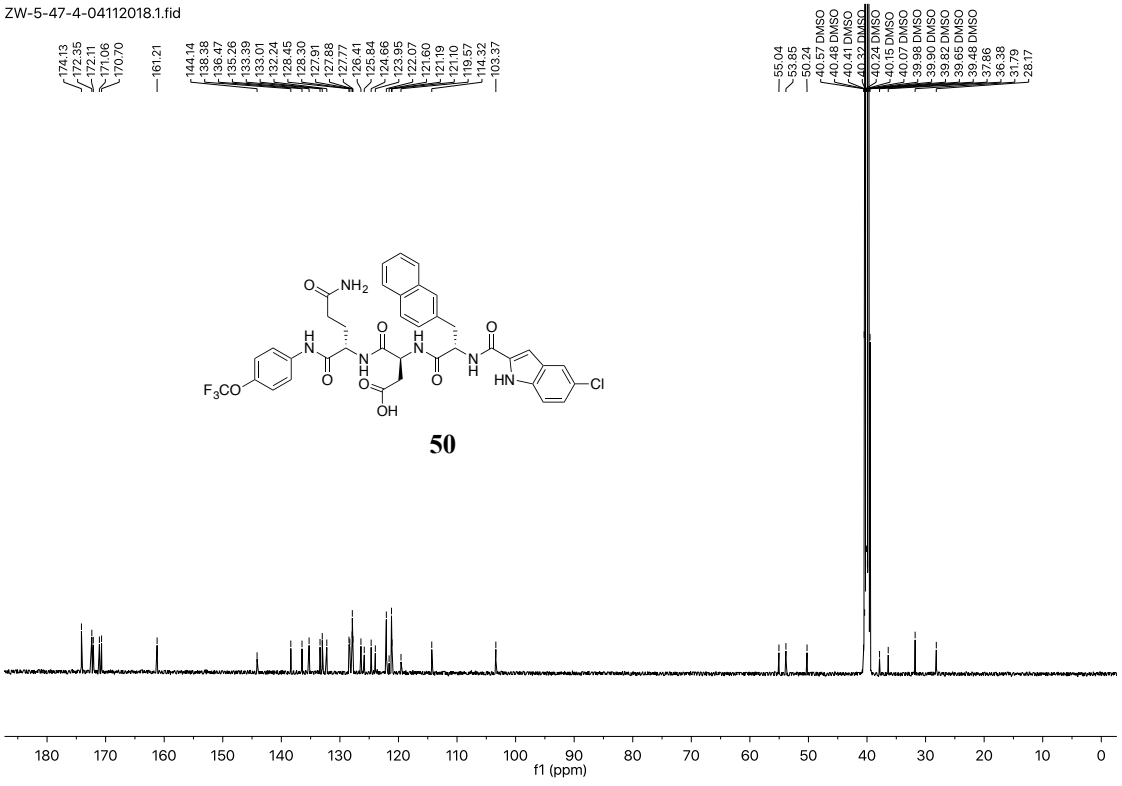
50
f1 (ppm)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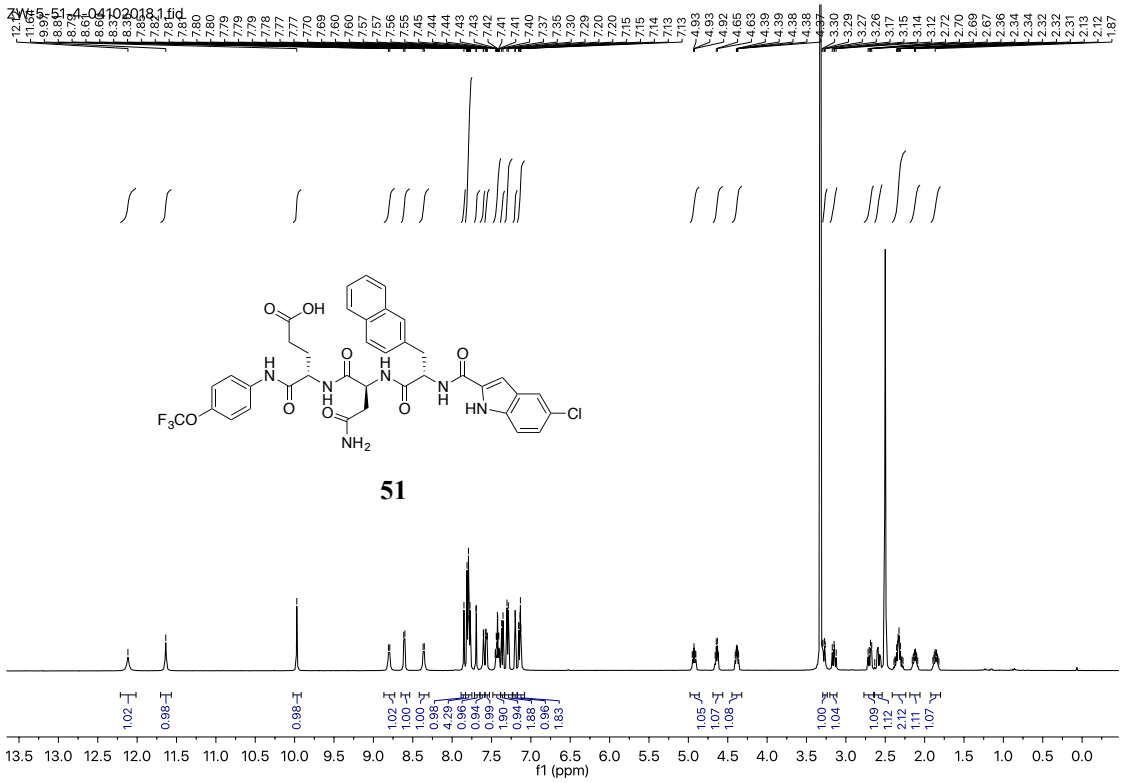
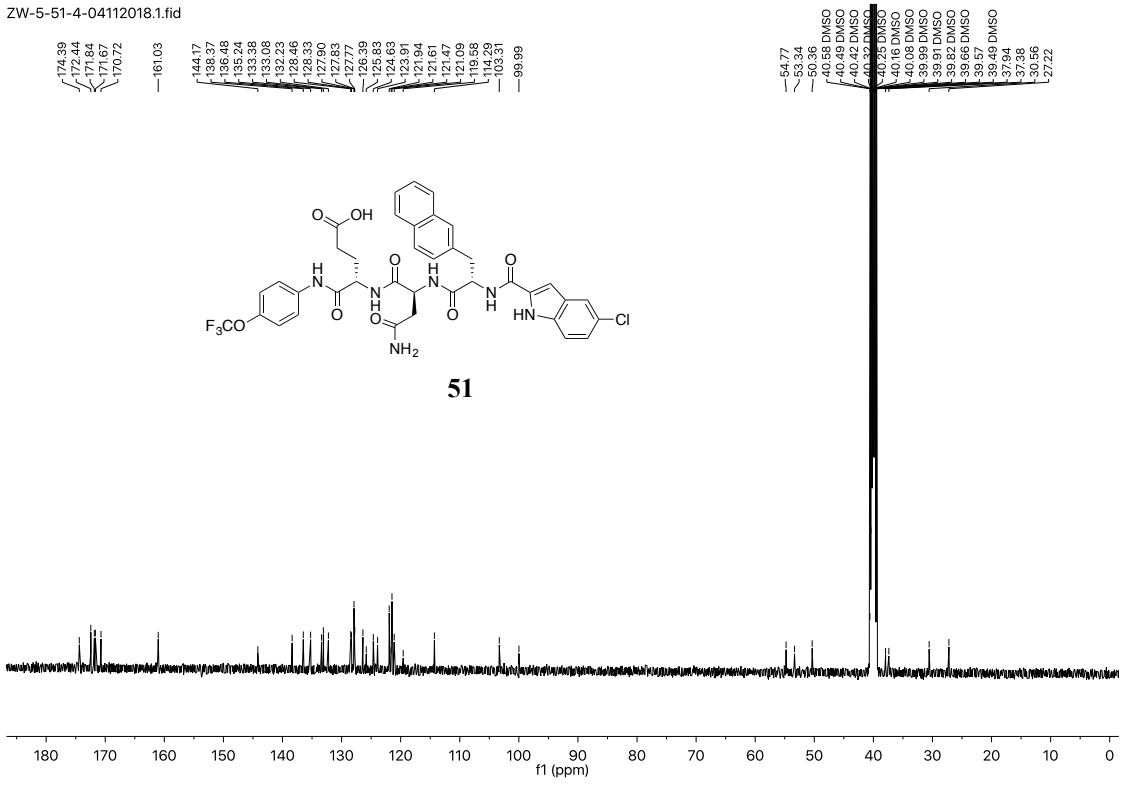
50
f1 (ppm)



51



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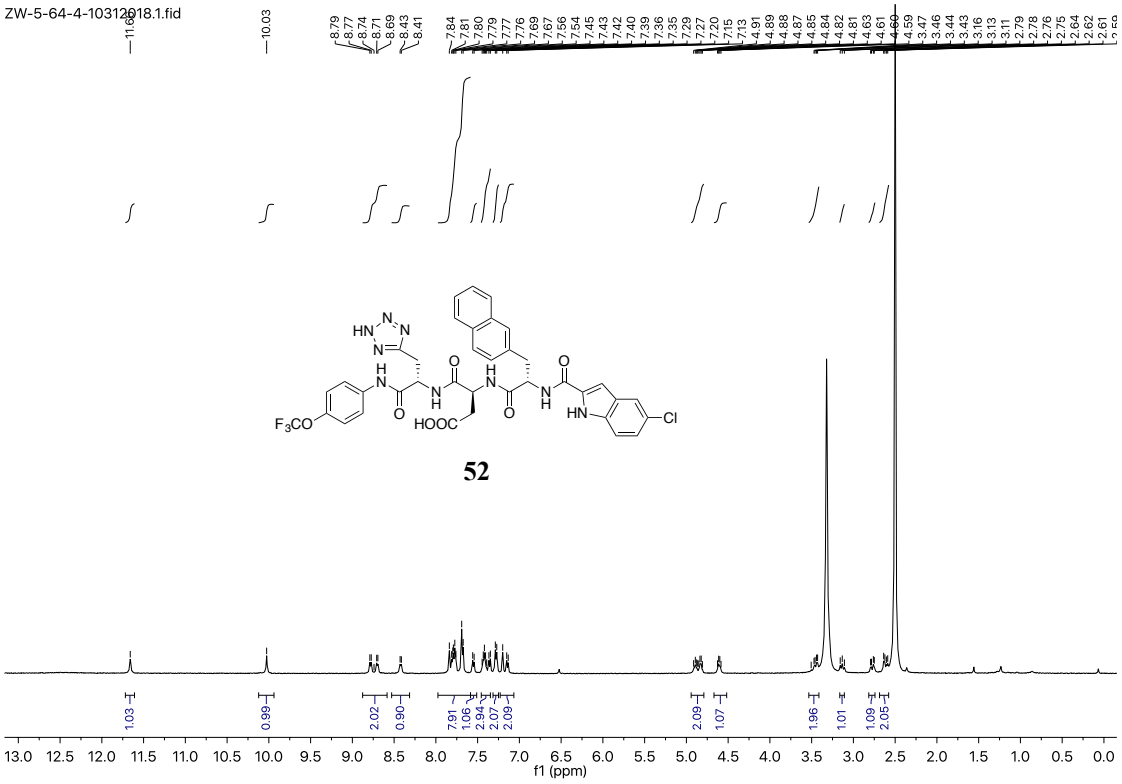
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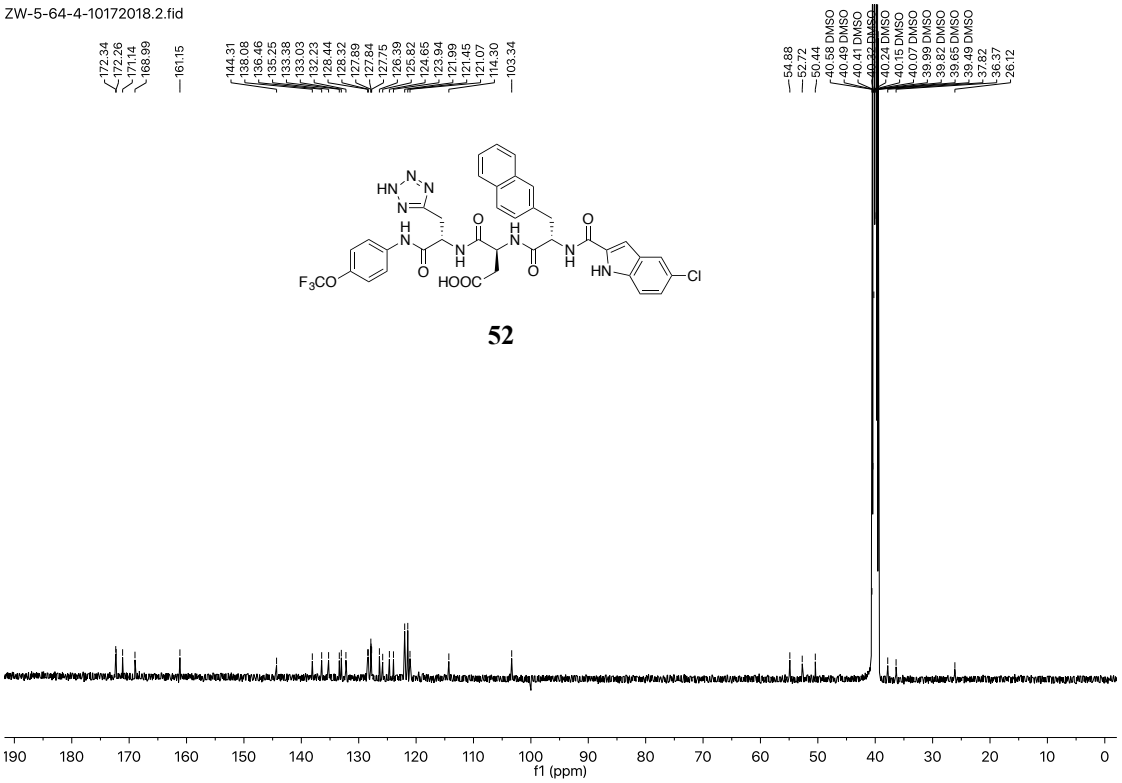
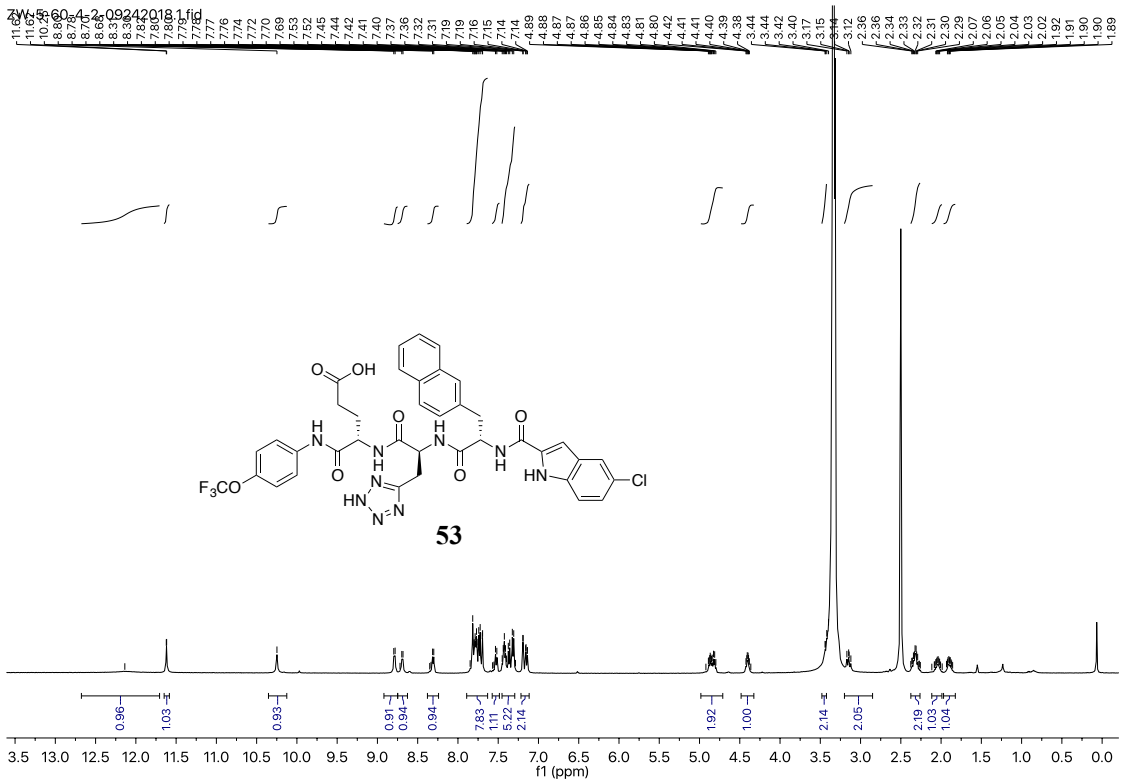
11.60
10.03
8.79
8.77
8.74
8.71
8.69
8.43
8.41
7.84
7.81
7.80
7.79
7.77
7.76
7.69
7.67
7.56
7.54
7.45
7.43
7.42
7.40
7.39
7.36
7.35
7.29
7.27
7.20
7.15
7.13
4.91
4.89
4.88
4.87
4.85
4.84
4.82
4.81
4.63
4.61
4.60
4.59
3.47
3.46
3.44
3.43
3.16
3.13
3.11
2.79
2.78
2.76
2.75
2.64
2.62
2.61
1.03
0.99
2.02
0.90
7.91
1.06
2.94
2.07
2.09
2.09
1.07
1.96
1.01
1.09
2.05
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

52


ZW-5-64-4-10172018.2.fid
172.34
172.26
171.14
168.99
161.15
144.31
138.08
136.46
135.25
133.38
133.03
132.23
128.44
128.32
127.89
127.84
127.75
126.39
125.82
124.65
123.94
121.99
121.45
121.07
114.30
103.34
54.88
52.72
50.44
40.58 DMSO
40.49 DMSO
40.41 DMSO
40.24 DMSO
40.15 DMSO
40.07 DMSO
39.99 DMSO
39.82 DMSO
39.65 DMSO
39.49 DMSO
37.82
36.37
26.12
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

52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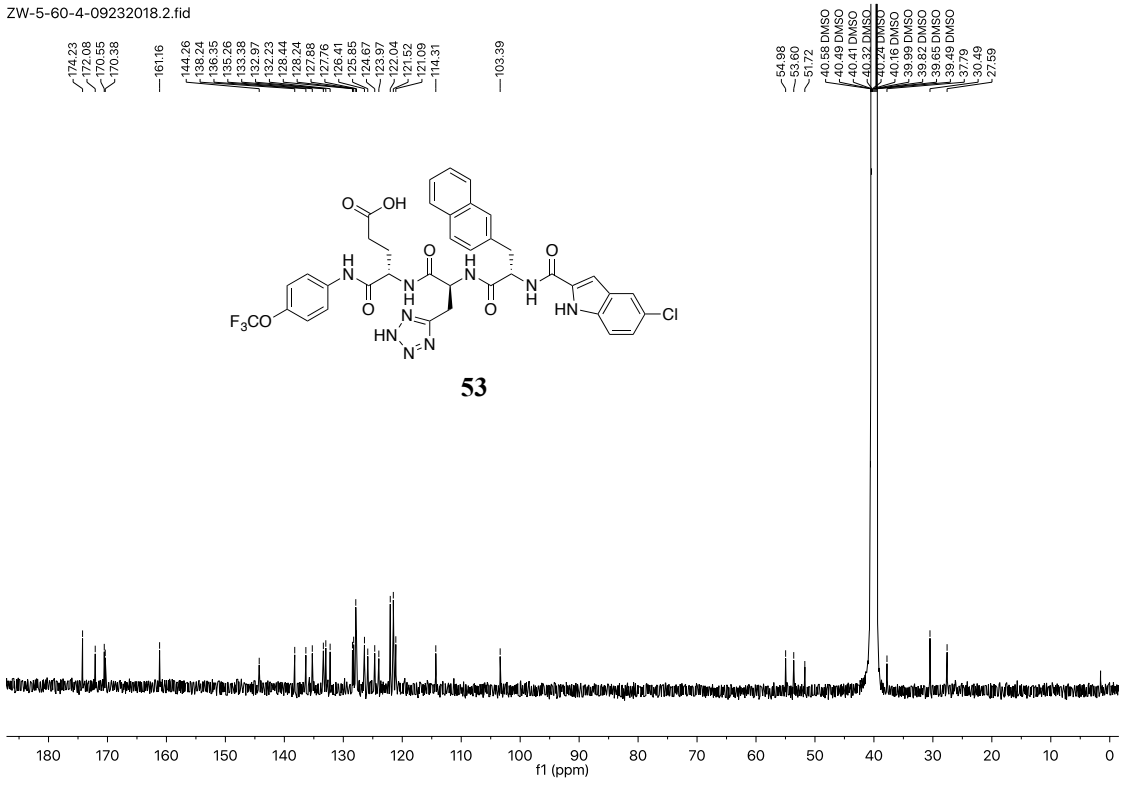
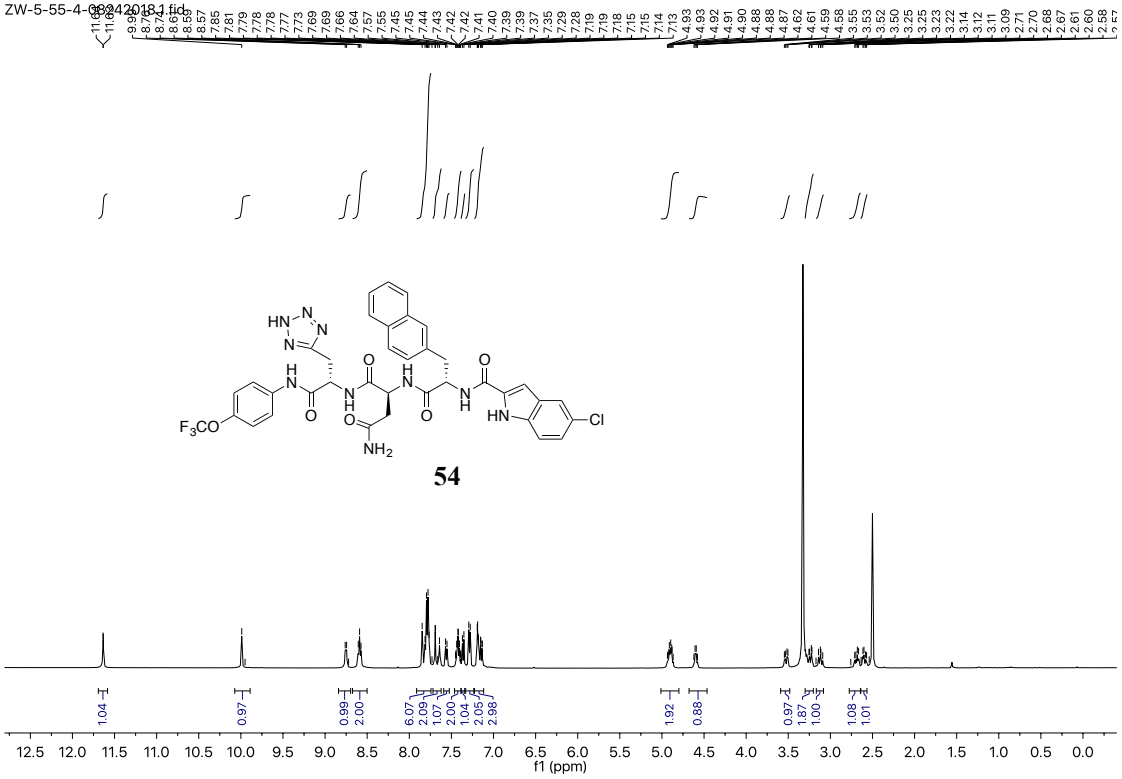
53

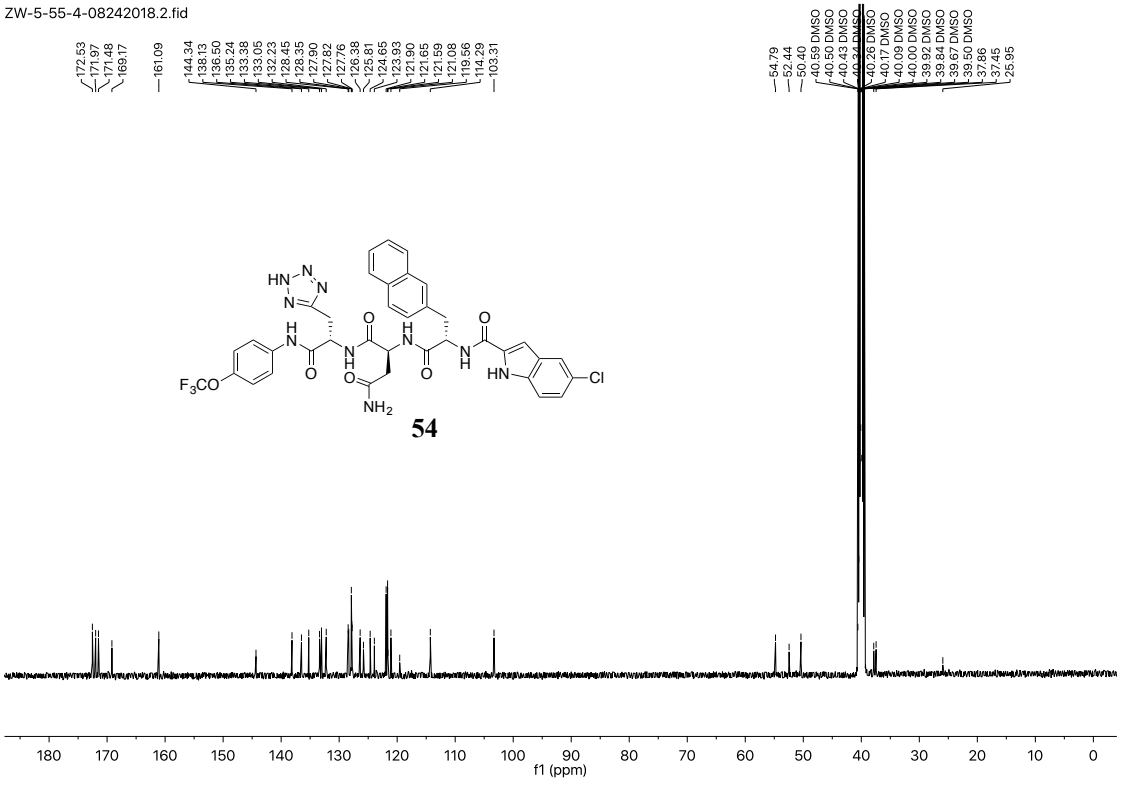

ZW-5-60-4-09232018.2.fid
53

ZW-5-55-4-08242018.1.fid

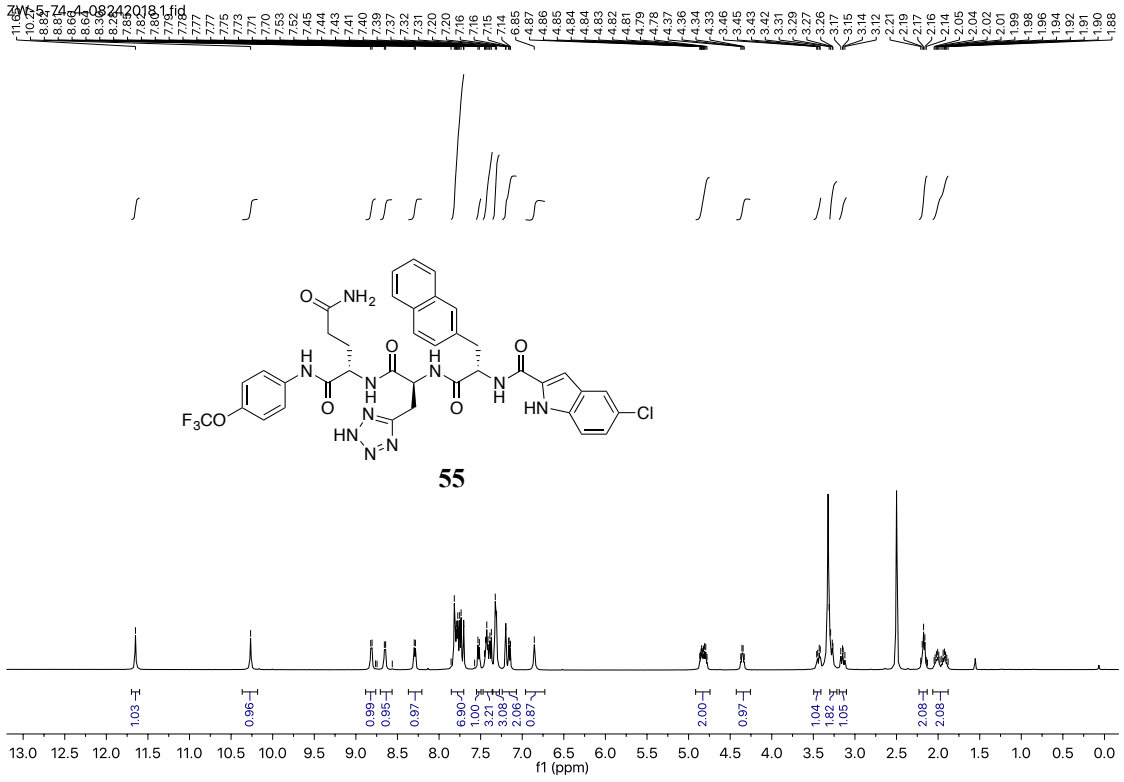


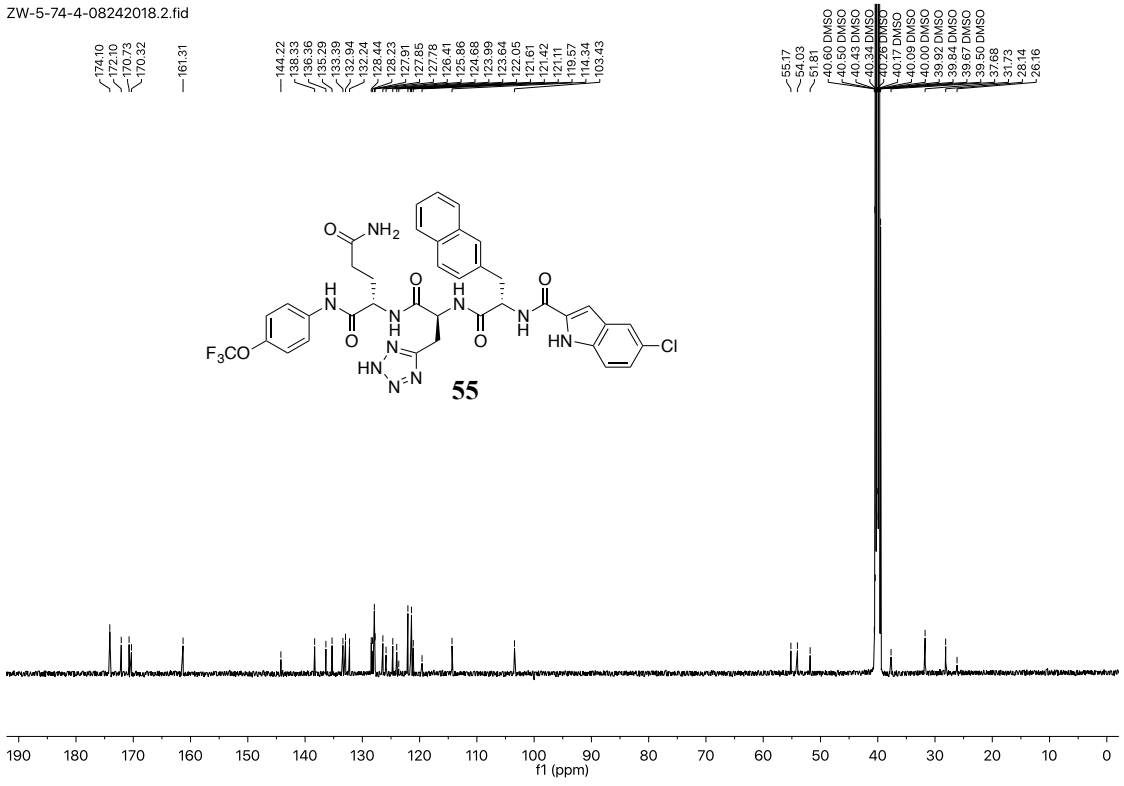
54

ZW-5-55-4-08242018.2.fid



54


ZW-5-74-4-08242018.1.fid
55
1.03
0.96
0.99
0.95
0.97
6.90
1.00
3.21
3.08
2.06
0.87
2.00
0.97
1.04
1.82
1.05
2.08
2.08
f1 (ppm)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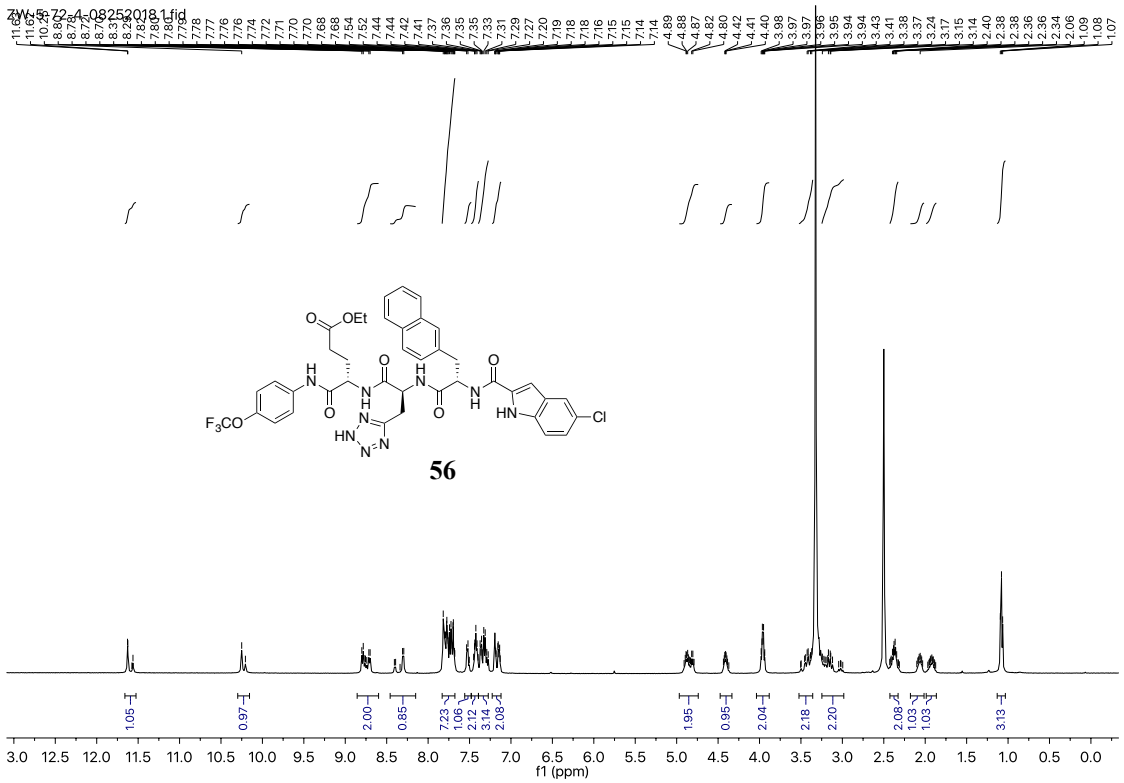
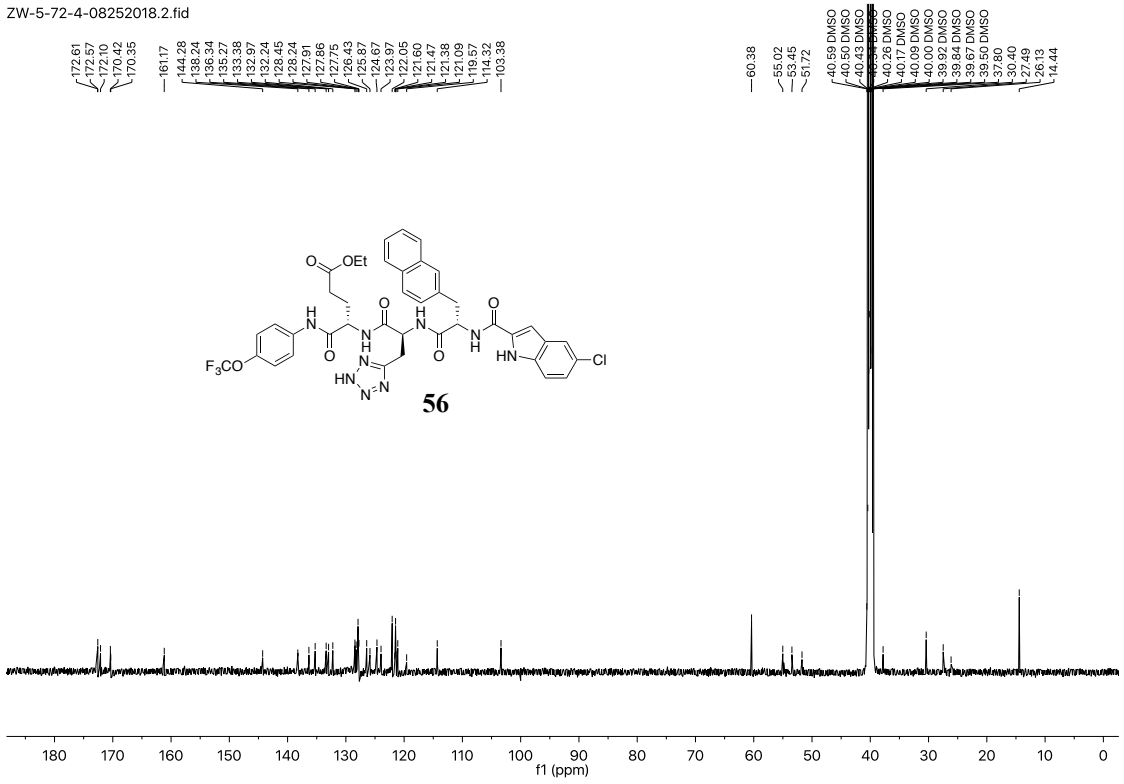
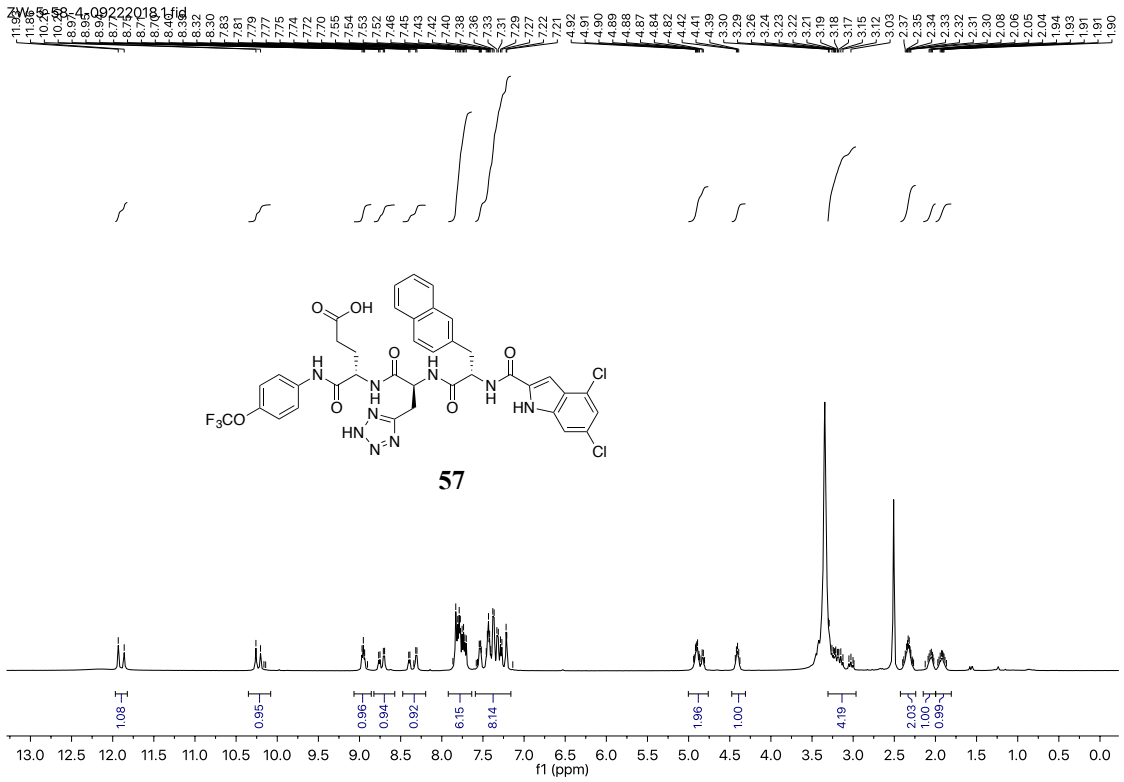
55
f1 (ppm)



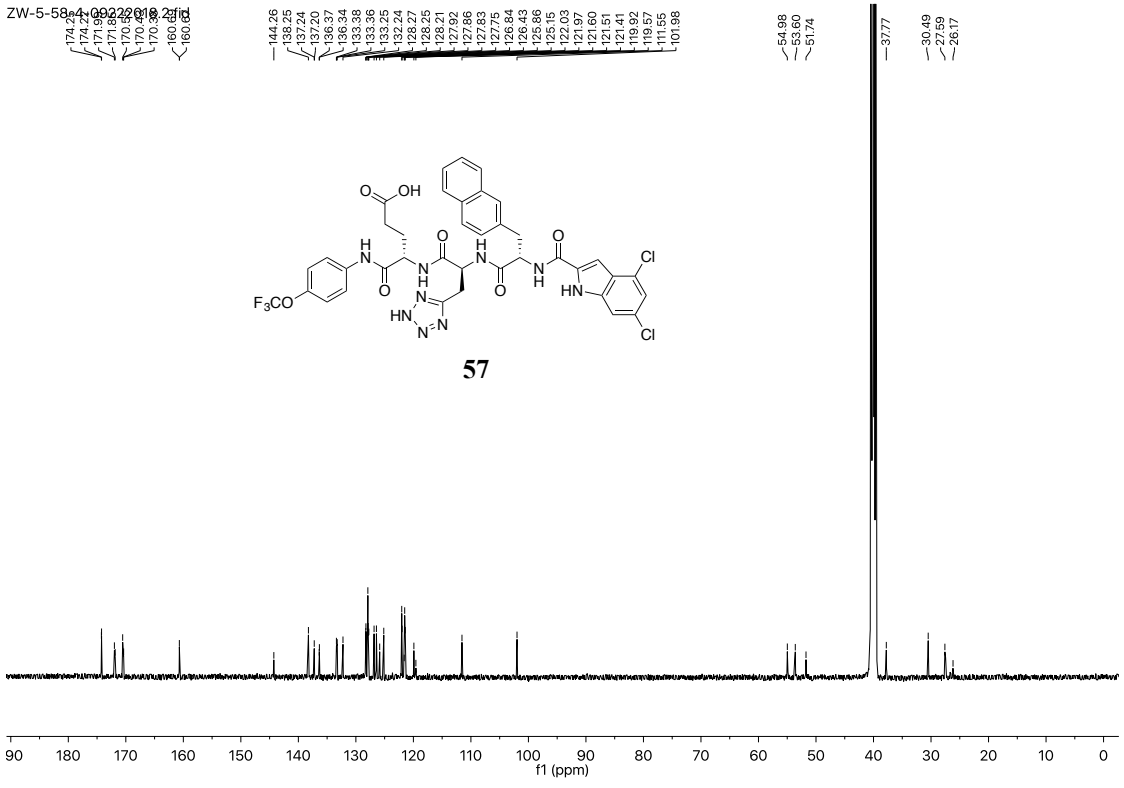
56



56

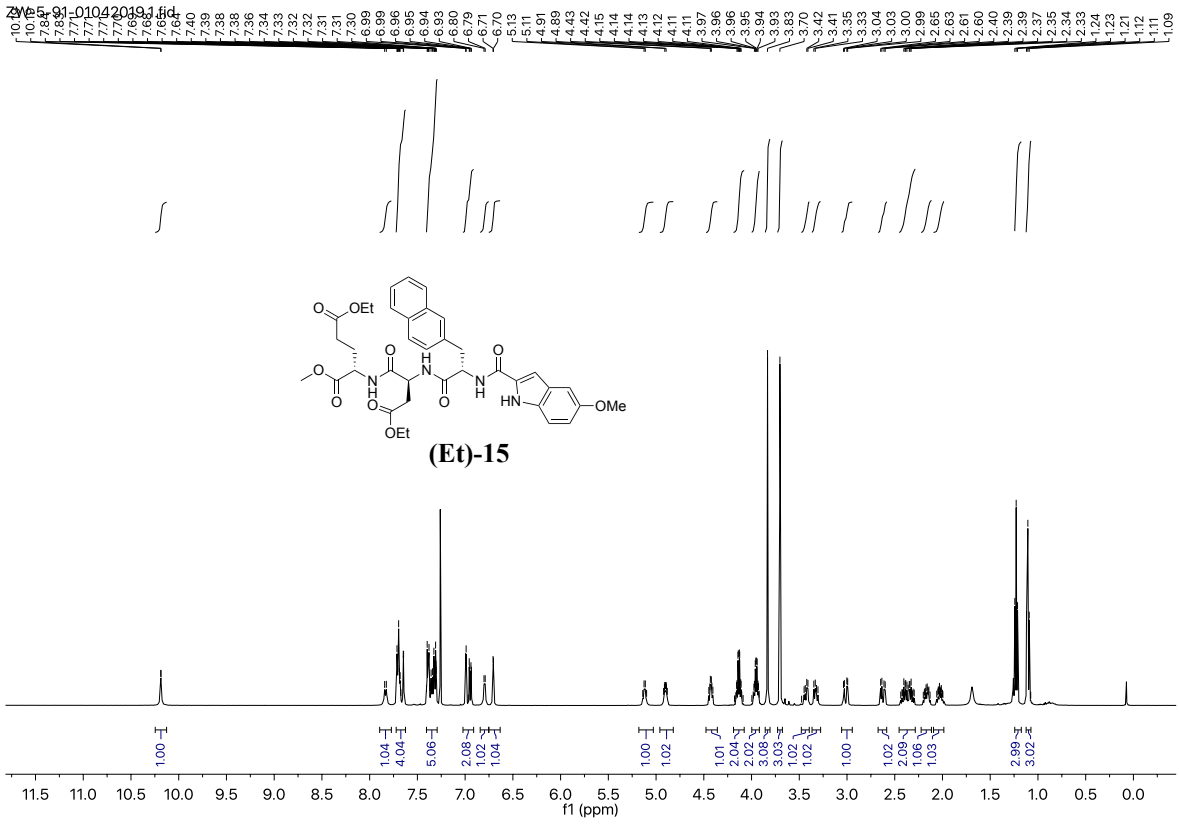

ZW-5-58-4-09222018.1.fid
1.08
0.95
0.96
0.94
0.92
6.15
8.14
1.96
1.00
4.19
2.03
1.00
0.99
f1 (ppm)

57


ZW-5-58-4-09222018.2.fid
f1 (ppm)

57

ZW-5-91-01042019.1.fid



(Et)-15

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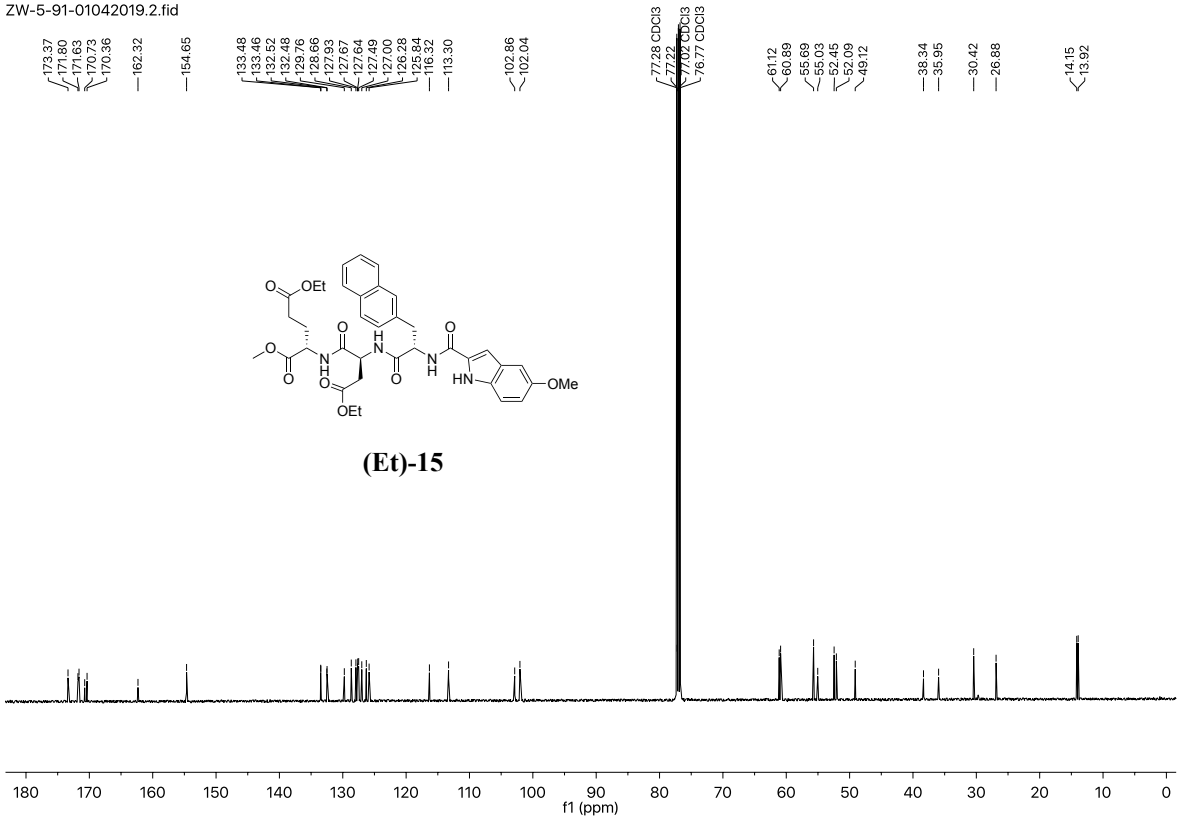

(Et)-15

Supplementary References:

1. Curcio, A.; Sasso, O.; Melisi, D.; Nieddu, M.; La Rana, G.; Russo, R.; Gavini, E.; Boatto, G.; Abignente, E.; Calignano, A.; Rimoli, M. G. Galactosyl prodrug of ketorolac: synthesis, stability, and pharmacological and pharmacokinetic evaluations. *J. Med. Chem.* **2009,** *52*, 3794–3800.
2. Teuscher, K. B.; Zhang, M.; Ji, H. A versatile method to determine the cellular bioavailability of small-molecule inhibitors. *J. Med. Chem.* **2017**, *60*, 157-169.
3. Zhang, M.; Catrow, J. L.; Ji, H. High-throughput selectivity assays for small-molecule inhibitors of *β*-catenin/T-cell factor protein-protein interactions. *ACS Med. Chem. Lett.* **2013**, *4*, 306-311.
4. Huang, Z.; Zhang, M.; Burton, S. D.; Katsakhyan, L. N.; Ji, H. Targeting the Tcf4 $G^{13}ANDE^{17}$ binding site to selectively disrupt beta-catenin/T-cell factor protein-protein interactions. *ACS Chem. Biol.* **2014,** *9*, 193–201.