

Supplementary Table 1. Summary of binding affinities between the designed lead compounds and indicated DCN recombinant proteins.

	DCN1 (FP, K_i , nM)	DCN2 (FP, K_i , nM)	DCN3 (BLI) (BLI, K_d , nM)	DCN4 (BLI, K_d , nM)	DCN5 (BLI, K_d , nM)
DI-591	12.4 ± 1.2	10.4 ± 2.1	> 10000	> 10000	> 10000
DI-591DD	6403 ± 213	4631 ± 455	> 10000	> 10000	> 10000
46	21.9±2.3	10.6 ± 0.9	> 10000	> 10000	> 10000

Supplementary Table 2. Crystallography Data Collection and Refinement Statistics.

Data Collection		DCN1-591
PDBID		5UFI
SpaceGroup		P2 ₁ 2 ₁ 2 ₁
Unit Cell (Å)	a = 62.142 b= 101.647 c = 173.521	
	$\alpha = \beta = \gamma = 90^\circ$	
Wavelength (Å)		0.9787
Resolution (Å) ¹		2.58 (2.58-2.62)
Rsym ²		0.084 (0.616)
<I/σI> ³		10 (2)
Completeness (%) ⁴		99.9 (99.7)
Redundancy		5.3 (5.2)
Refinement		
Resolution (Å)		2.58
R-Factor ⁵		0.2246
Rfree ⁶		0.2606
Protein atoms		6185
Ligands		4
Water Molecules		15
Unique Reflections		35332
R.m.s.d. ⁷		
Bonds		0.01
Angles		1.1
MolProbity Score ⁸		1.43
Clash Score ⁸		2.02

¹Statistics for highest resolution bin of reflections in parentheses.

² $R_{\text{sym}} = \sum_h \sum_j |I_{hj} - \langle I_h \rangle| / \sum_h \sum_j I_{hj}$, where I_{hj} is the intensity of observation j of reflection h and $\langle I_h \rangle$ is the mean intensity for multiply recorded reflections.

³Intensity signal-to-noise ratio.

⁴Completeness of the unique diffraction data.

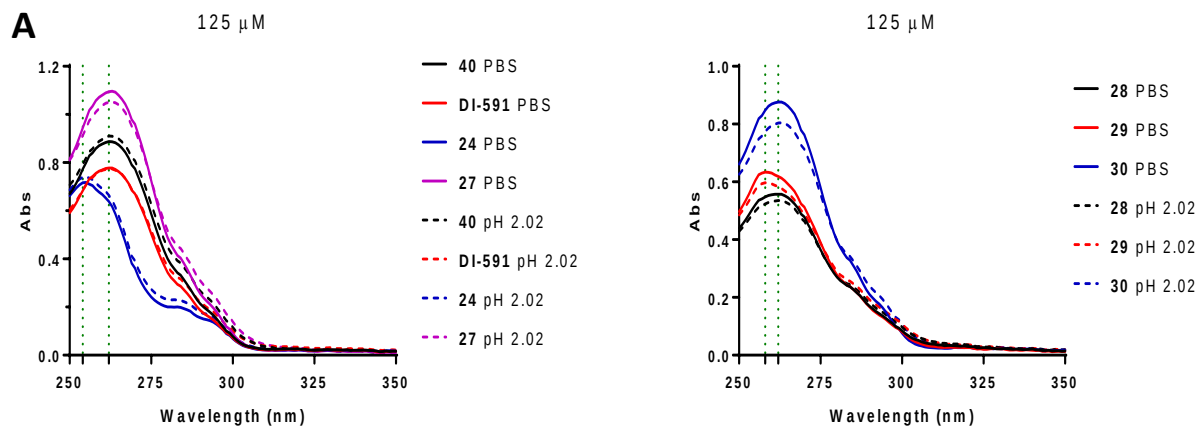
⁵R-factor = $\sum_h |F_o I - F_c I| / \sum_h |F_o|$, where F_o and F_c are the observed and calculated structure factor amplitudes for reflection h.

⁶ R_{free} is calculated against a 5% random sampling of the reflections that were removed before structure refinement.

⁷Root mean square deviation of bond lengths and bond angles.

⁸Chen et al. (2010) MolProbity: all-atom structure validation for macromolecular crystallography. Acta Crystallographica D66:12-21.

1 **Supplementary Figure 1:**



B

	24	27	28	29	30	40	DI-591
pH 2.02 (μ M)	1476 $\pm$ 38	227 $\pm$ 10	> 20000	1052 $\pm$ 21	> 20000	4754 $\pm$ 77	> 20000
pH 7.4 (μ M)	251 $\pm$ 5	31 $\pm$ 2	7472 $\pm$ 98	1279 $\pm$ 15	> 20000	1906 $\pm$ 43	> 20000

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3 **Supplementary Figure 1. Solubility of representative compounds. (a)** UV-Vis absorption

4 spectra of seven compounds at pH values of 2.0 and 7.4. **(b)** Solubility (μ M) of seven

5 compounds at pH values of 2.0 and 7.4.

1 **Supplementary Figure 2:**



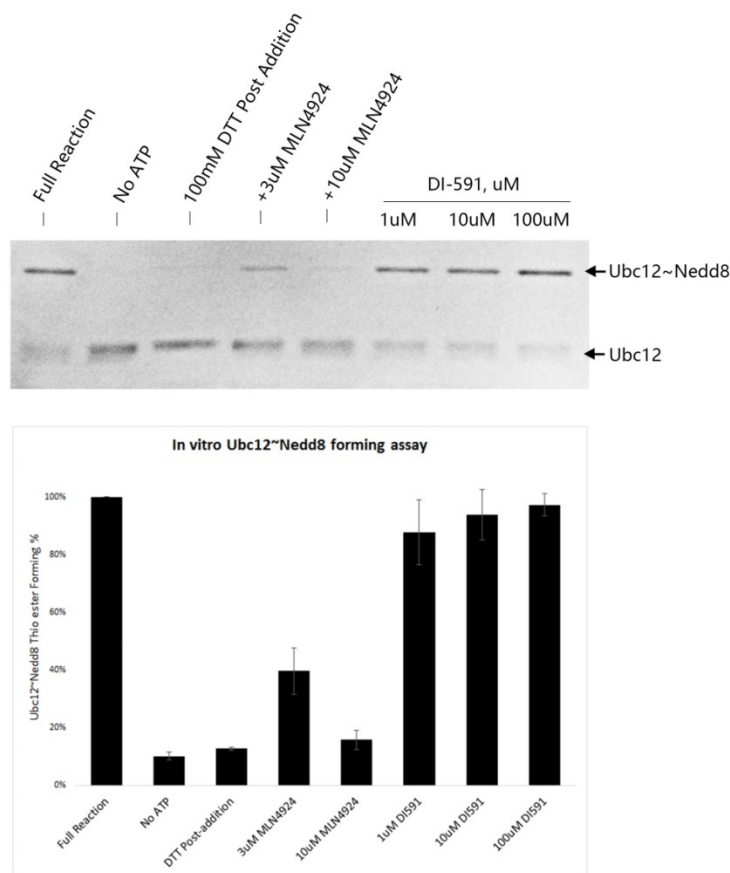
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Percent Identity Matrix created by Clustal2.1					
sp Q92564 DCNL4	100	70.69	29.28	29.34	31.4
sp Q9BTE7 DCNL5	70.69	100	29.57	29.74	30.17
sp Q8IWE4 DCNL3	29.28	29.57	100	37.55	39.92
sp Q96GG9 DCNL1	29.34	29.74	37.55	100	77.61
sp Q6PH85 DCNL2	31.4	30.17	39.92	77.61	100

3

4 **Supplementary Figure 2. Sequence alignment of DCN protein family.** Multiple sequence
 5 alignment of DCN1-5 (also known as DCNL1-5) by ClustalW. Rectangular boxes indicate the
 6 residues forming the binding site for DI-591. Uniprot accession numbers for each protein are
 7 listed in the sequence alignment.

1 **Supplementary Figure 3:**



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3 **Supplementary Figure 3. In vitro UBC12~NEDD8 thio ester forming assay.** NEDD8,

4 NEDD8 E1 (APP-BP1/Uba3) and UBC12 were purchased from Boston Biochem. 10μM

5 NEDD8, 25nM NEDD8 E1, and 2μM UBC12 were incubated in 50mM Tris-HCl (pH 7.4), 5mM

6 MgCl₂, 0.5mM DTT, and 0.1mg/ml BSA, with indicated compounds at 25°C for 10min.

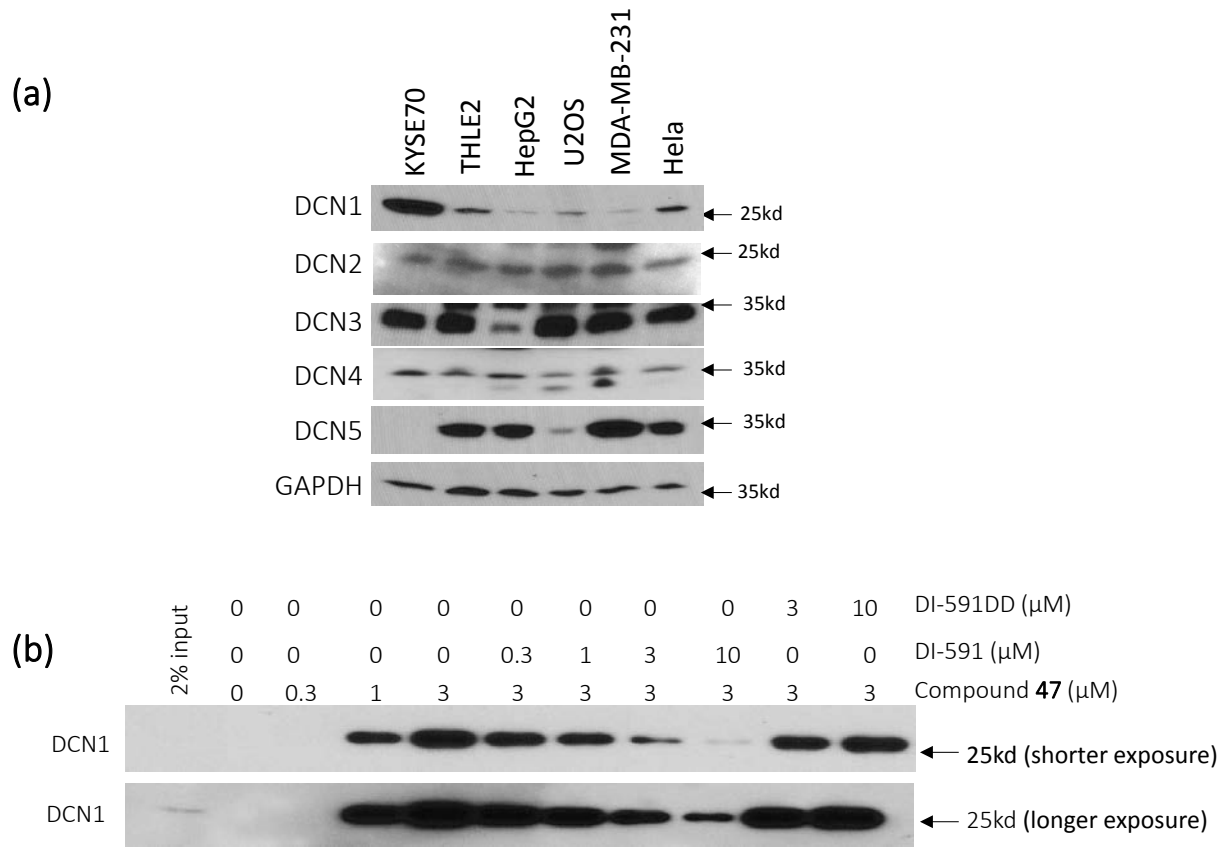
7 Reactions were initiated by addition of 2mM ATP (or dH₂O) and were run for 5min at 25°C.

8 Reaction mixtures were then added with 1M DTT (or dH₂O) and kept on ice for 1min followed

9 by addition of SDS Loading buffer (without DTT). The products were separated by SDS-PAGE,

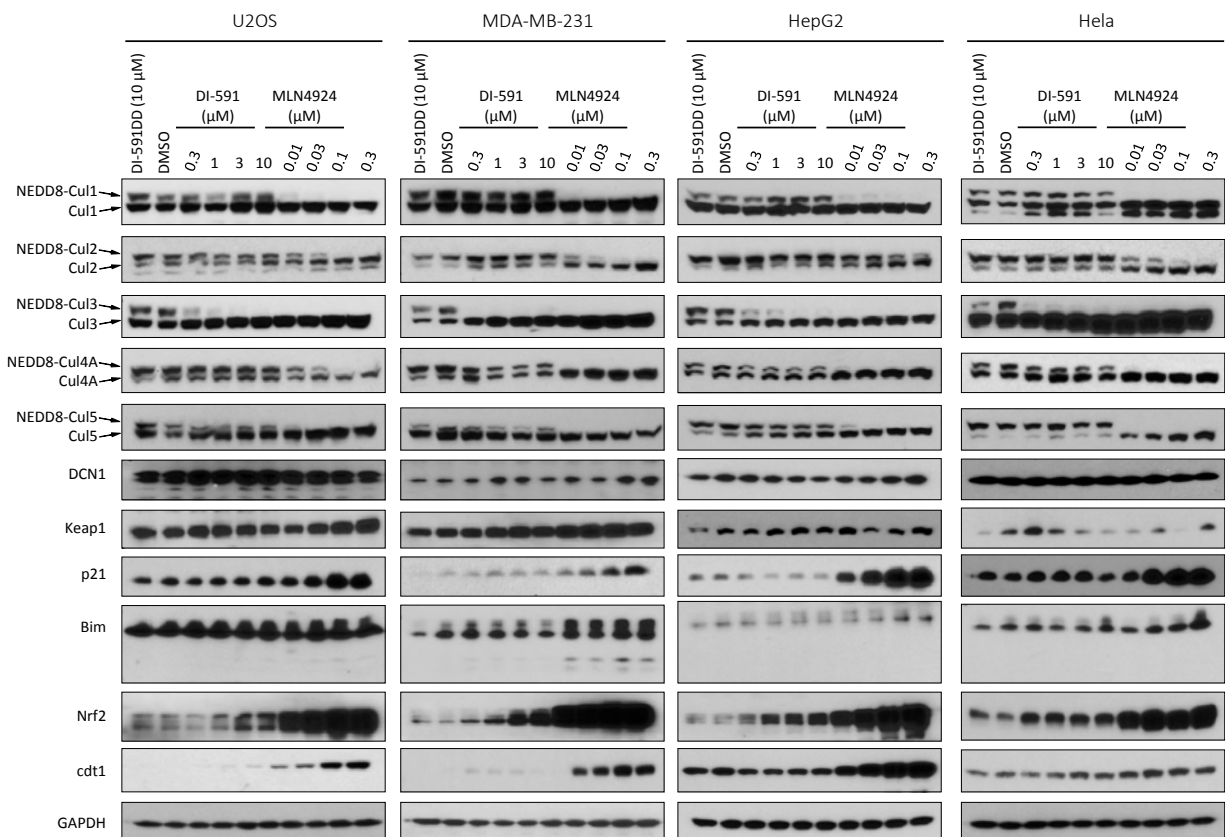
10 visualized by Coomassie stain and quantified using an ImageLab imager (Bio-Rad).

1 **Supplementary Figure 4:**



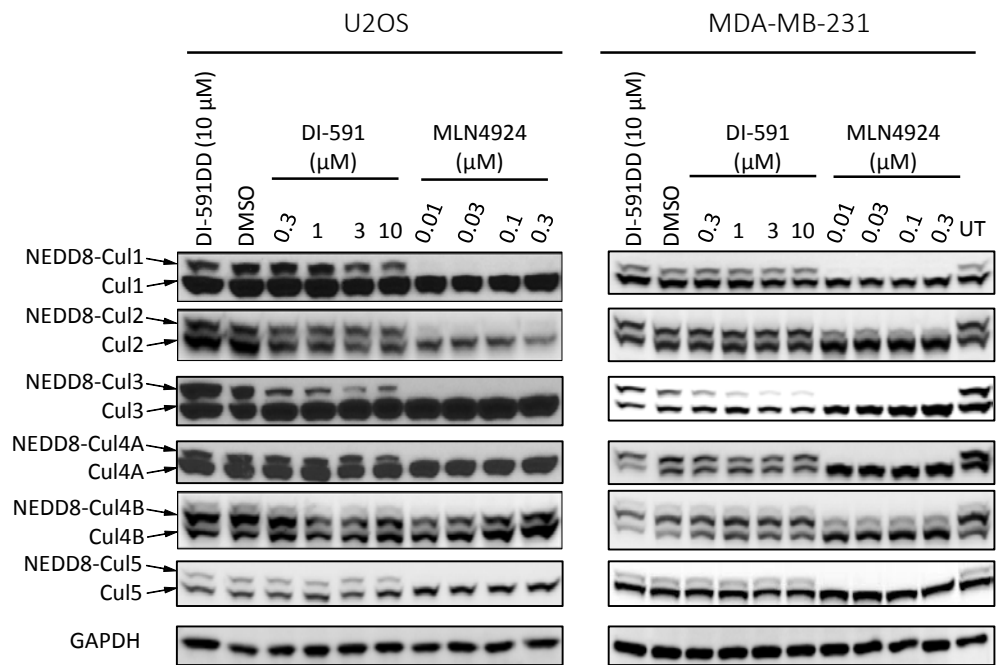
Supplementary Figure 4. (a) Esophageal cancer KYSE70, immortalized liver THLE2, hepatoma HepG2, osteosarcoma U2OS, breast cancer MDA-MB-231 and ovarian cancer Hela cells growing in exponential phase were harvested and lysed. The cell lysates were analyzed by western blotting for the expression of DCN1 (#GWB-E3D700, GenWay Biotech), DCN2 (#ARP68256_P050, Aviva Systems, San Diego, CA), DCN3 (#GWB-MS982A, GenWay Biotech) DCN4 (#PA5-28562, Thermo Fisher Scientific) and DCN5 (#PA5-62257, Thermo Fisher Scientific) proteins. GAPDH was used as a loading control. **(b)** Biotinylated compound **47** pulls down DCN1 protein from KYSE140 cell lysates in a dose-dependent manner. DI-591 but not its enantiomeric control, DI-591DD, effectively competes off the binding of **47** to DCN1 protein.

Supplementary Figure 5:



Supplementary Figure 5. U2OS, MDA-MB-231, HepG2 and HeLa cell lines were treated as indicated for 24 h, the expression level and neddylation state of the cullin family of proteins and the abundance of their CRL substrates was examined by western blotting. GAPDH was used as a loading control.

1 **Supplementary Figure 6:**



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3 **Supplementary Figure 6.** The expression level and neddylation state of the cullin family of
4 proteins were examined by western blotting in U2OS and MDA-MB-231 cells treated as
5 indicated for 24 h. GAPDH was used as a loading control. These experiments were performed by
6 a second scientist independently.

1 **Supplementary Figure 7:**

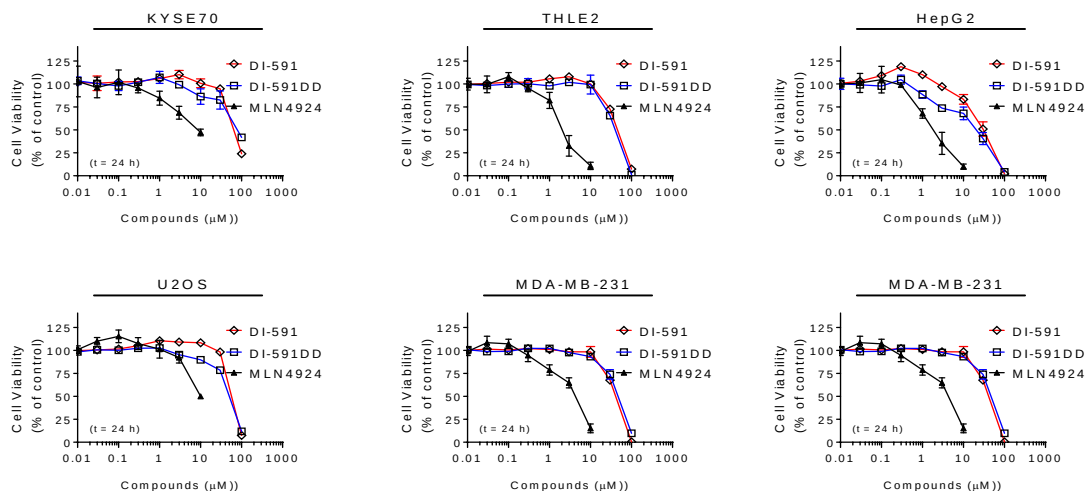


3 **Supplementary Figure 7.** Detection of NRF2 protein by IHC (immunohistochemical staining)
4 demonstrates that DI-591 increases the levels of NRF2 in liver cells. THLE2 liver cells were
5 grown in chamber slides and treated with DI-591 at 10 μ M or DI-591DD at 10 μ M for 16 h,
6 DMSO was used as a treatment control.

1 **Supplementary Figure 8:**

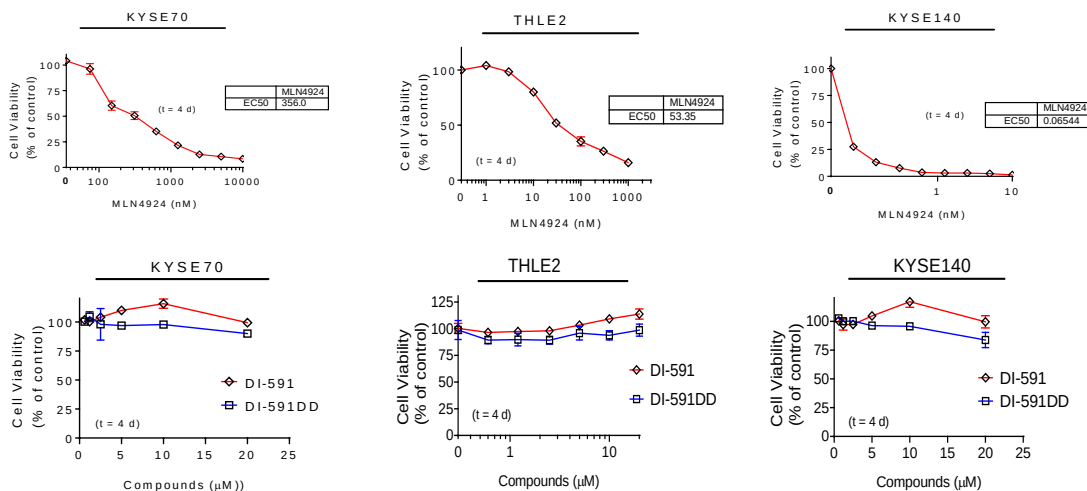
(a)

(t = 24 h)



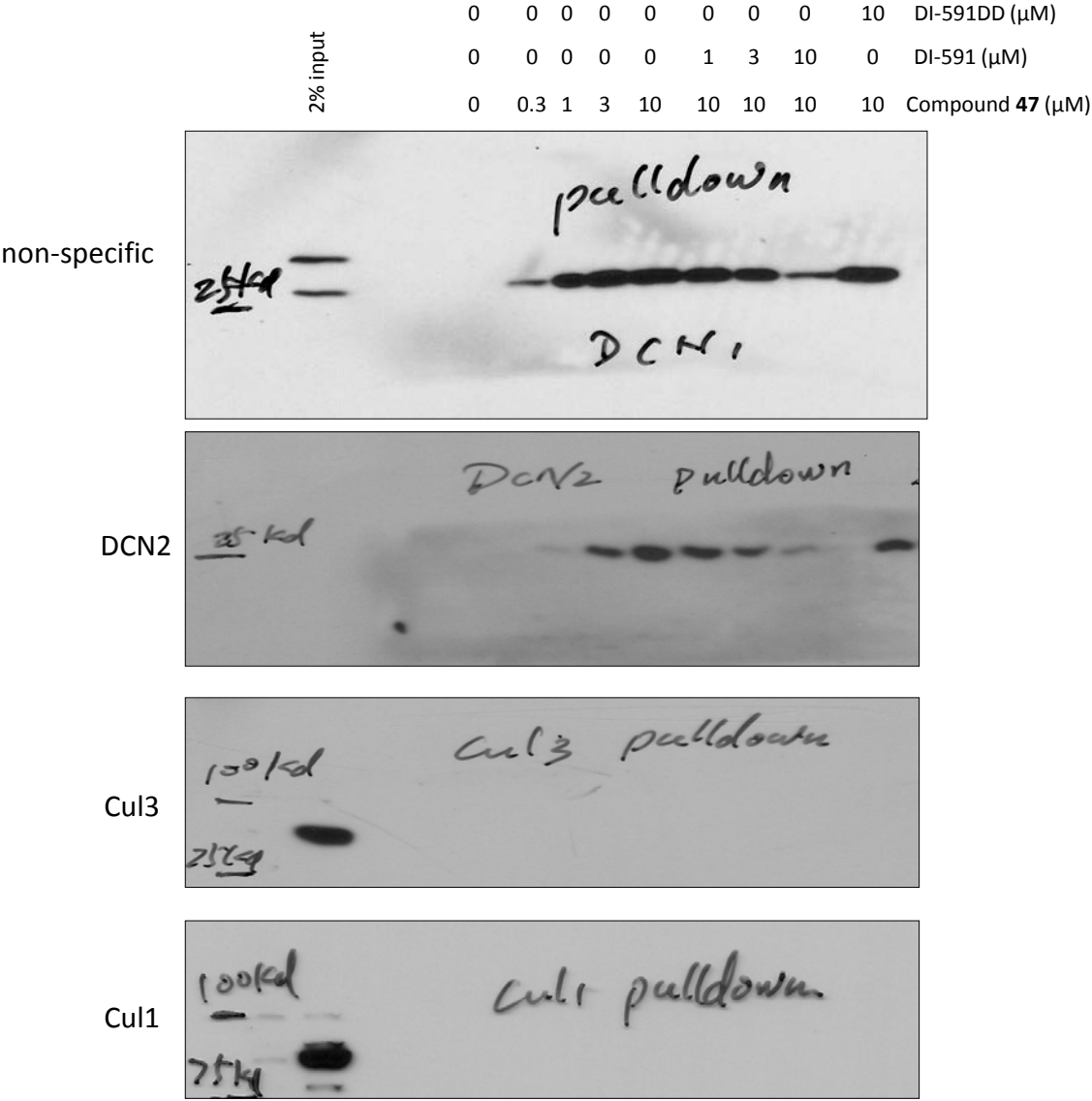
(b)

(t = 96 h)



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3 **Supplementary Figure 8. Cell growth inhibitory activity of DI-591, DI-591DD, and**
4 **MLN49224 in a panel of 6 cell lines.** (a) The indicated cell lines were treated with MLN4924,
5 DI-591 or DI-591DD for 24 h. Cell viability was determined with a WST assay. (b) The
6 indicated cell lines were treated with MLN4924, DI-591 or DI-591DD for 4 days. Cell viability
7 was determined with a WST assay.

1 **Supplementary Figure 9:**

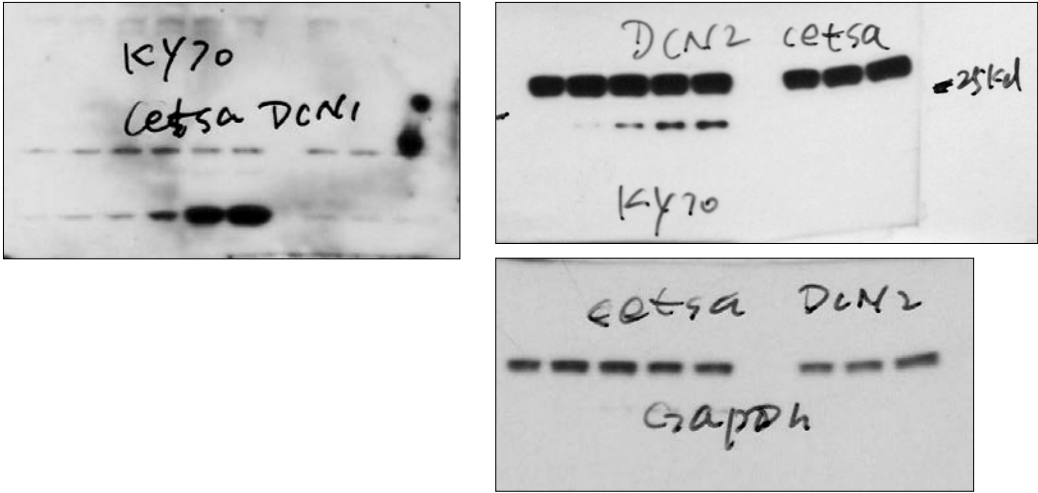
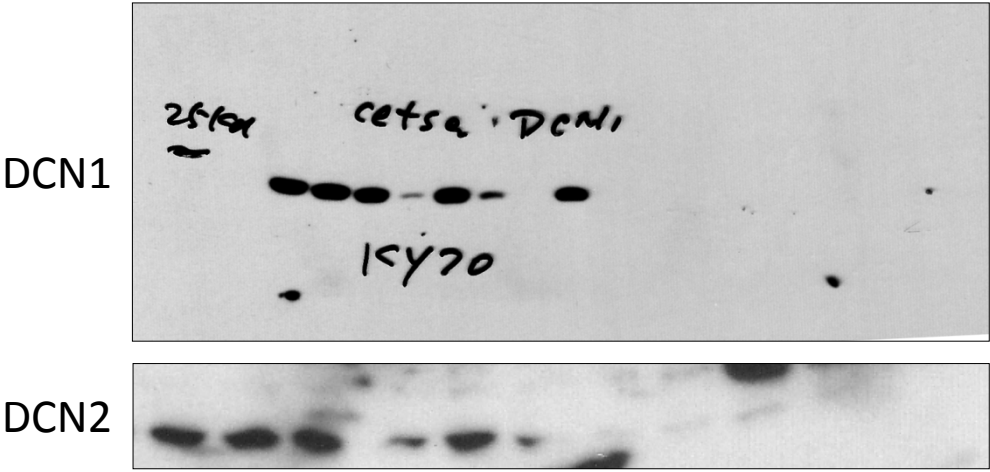


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3 **Supplementary Figure 9.** Uncropped western blot images for Figure 4b.

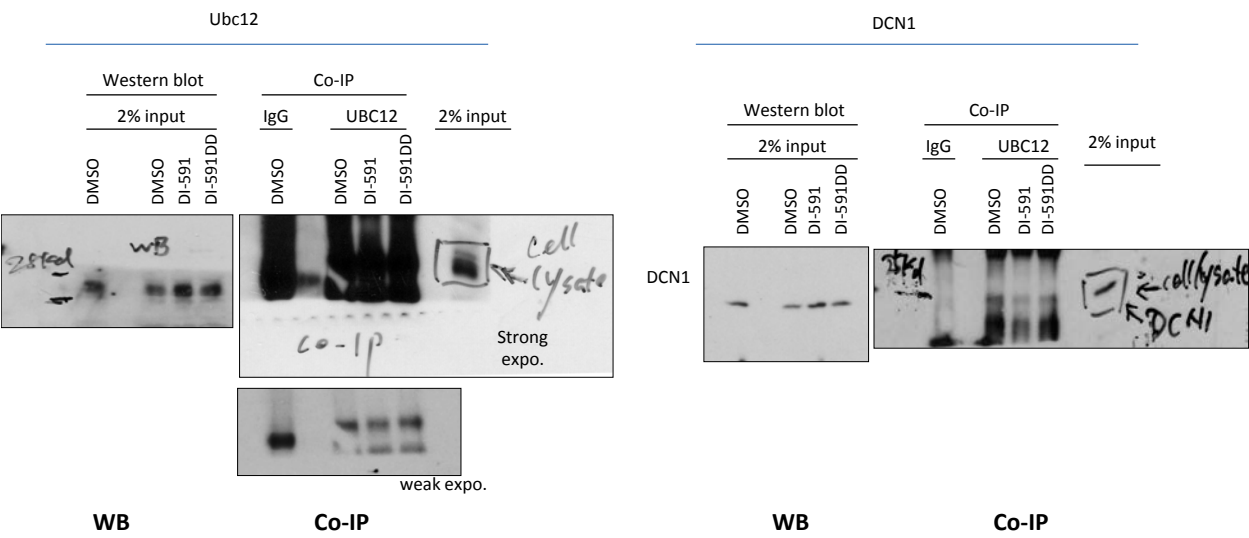
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1 **Supplementary Figure 10:**



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3 **Supplementary Figure 10.** Uncropped western blot images for Figures 4c, 4d and 4e,
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1 **Supplementary Figure 11:**

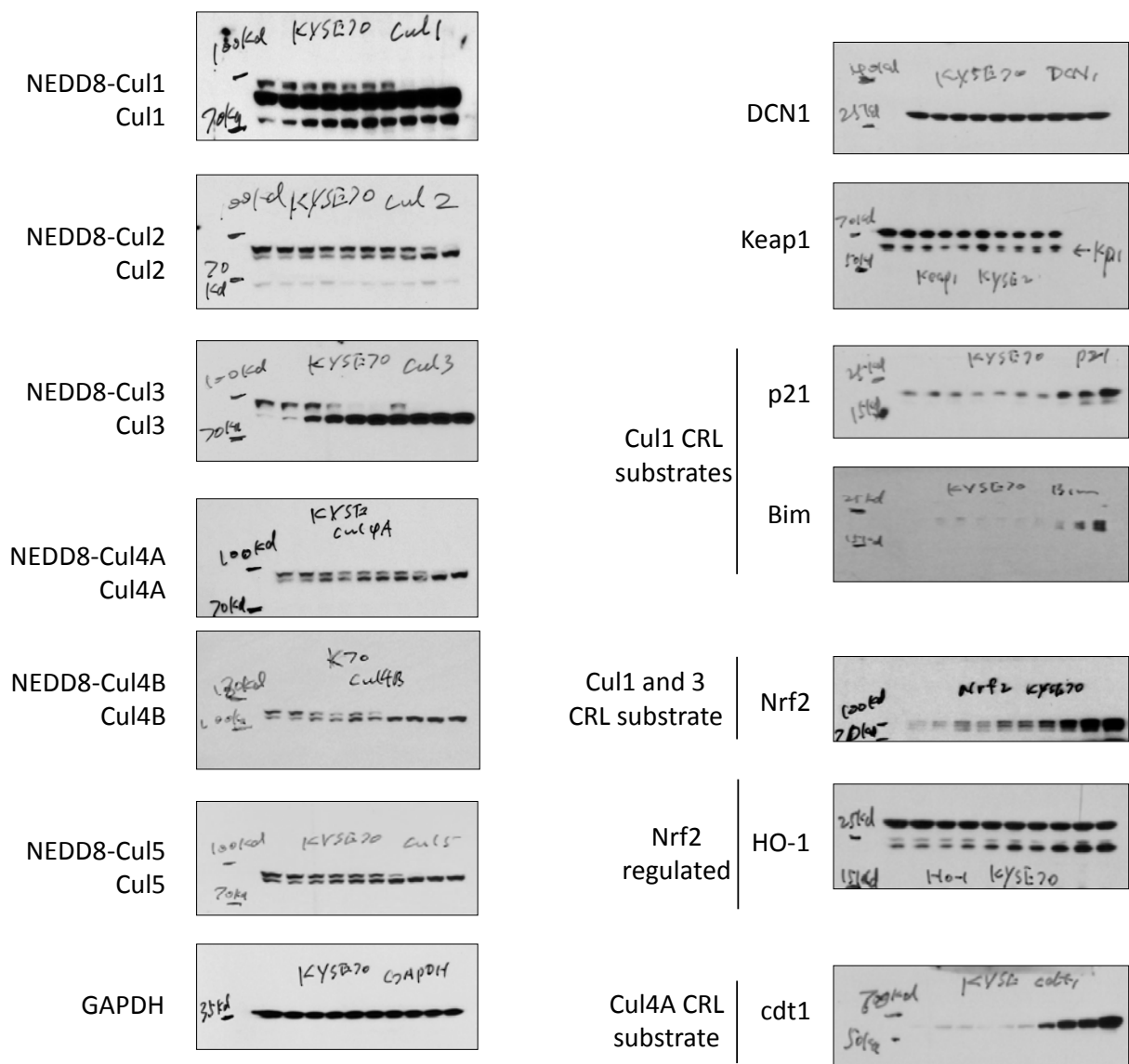


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3 **Supplementary Figure 11.** Uncropped Western blot images for Figure 4f.

4

1 **Supplementary Figure 12:**

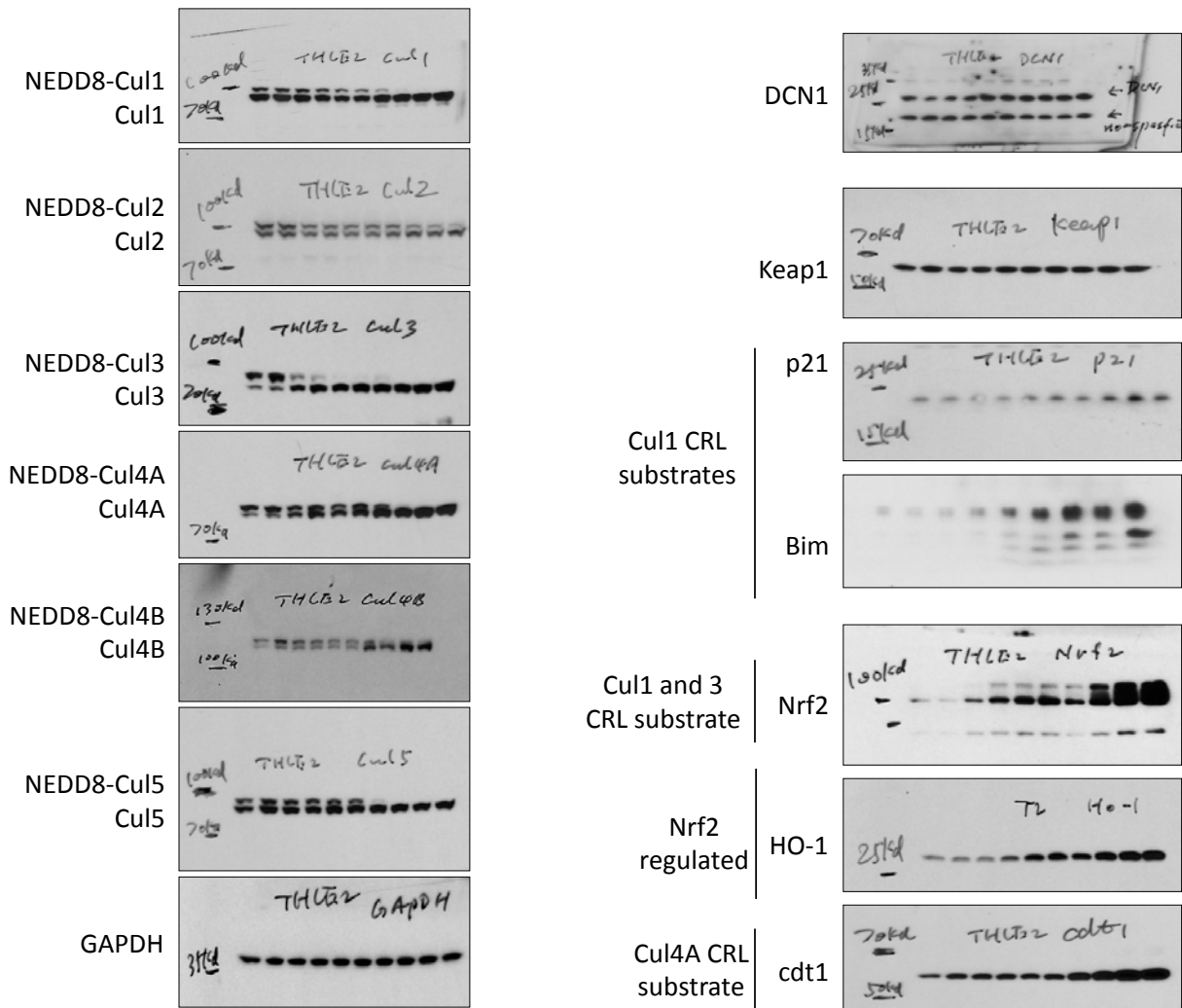


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3 **Supplementary Figure 12.** Uncropped western blot images for Figure 5a (KYSE70 cell line).

4

1 **Supplementary Figure 13:**

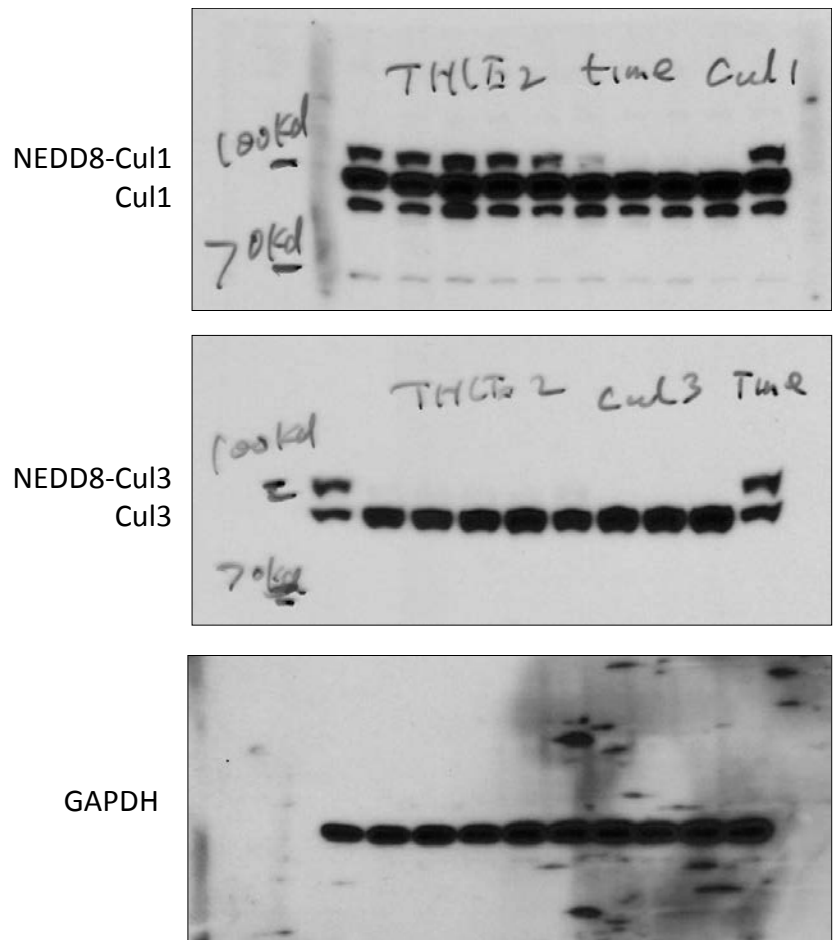


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3 **Supplementary Figure 13.** Uncropped western blot images for Figure 5a (THLE2 cell line).

4

1 **Supplementary Figure 14:**

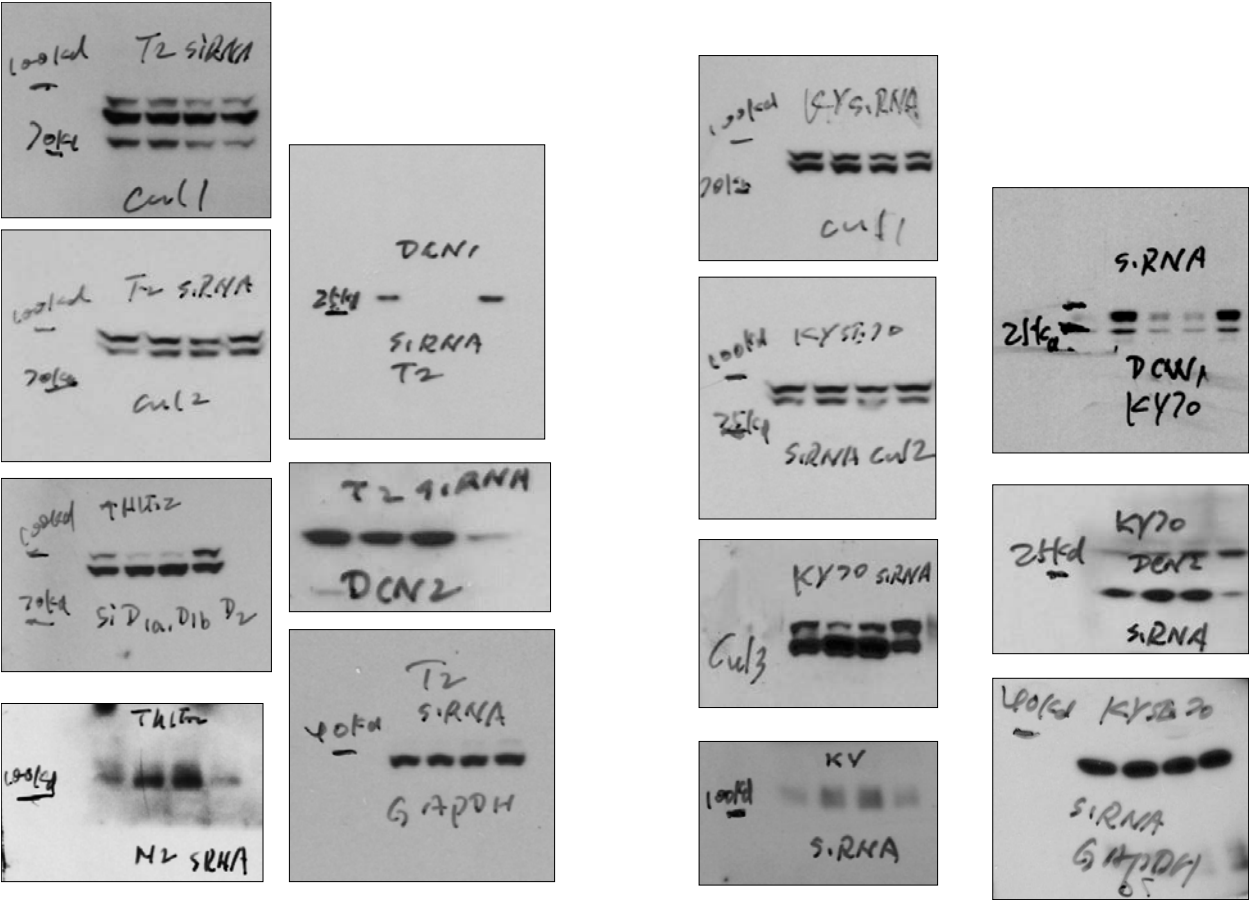


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3 **Supplementary Figure 14.** Uncropped western blot images for repeat experiment for Figure 5b.

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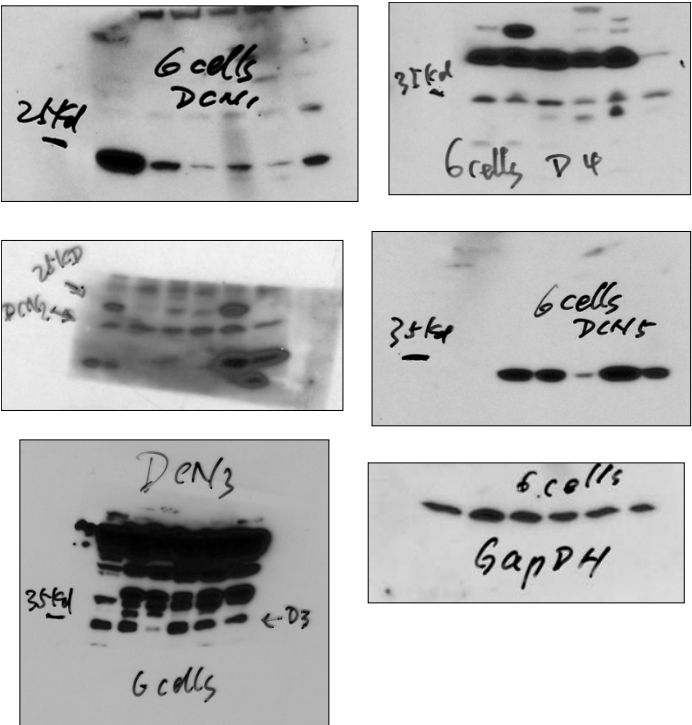
1 **Supplementary Figure 15:**



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3 **Supplementary Figure 15.** Uncropped western blot images Figure 5d.

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1 **Supplementary Figure 16:**

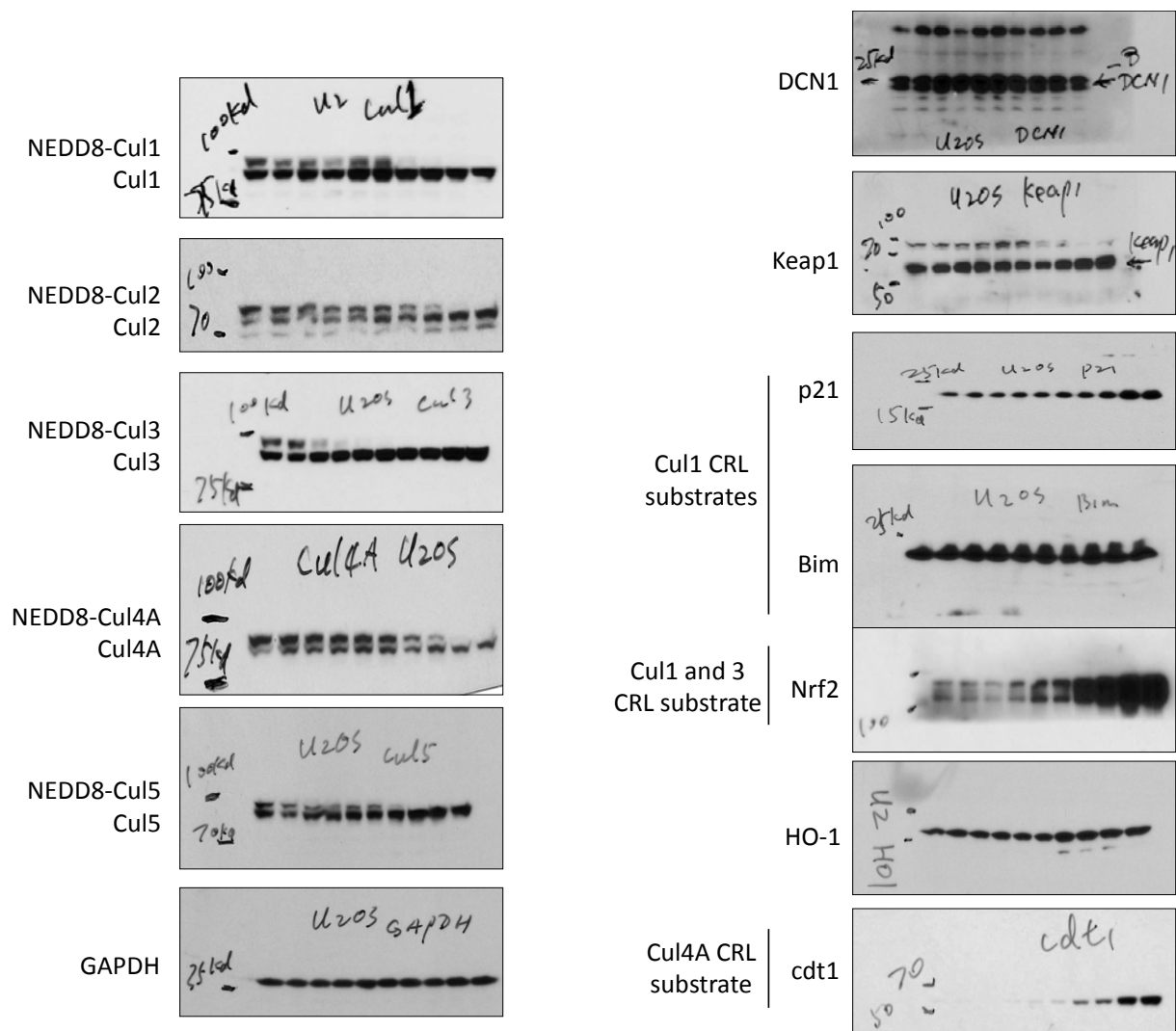


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3 **Supplementary Figure 16.** Uncropped western blot images for Supplementary Figure 4a.

4

1 **Supplementary Figure 17:**

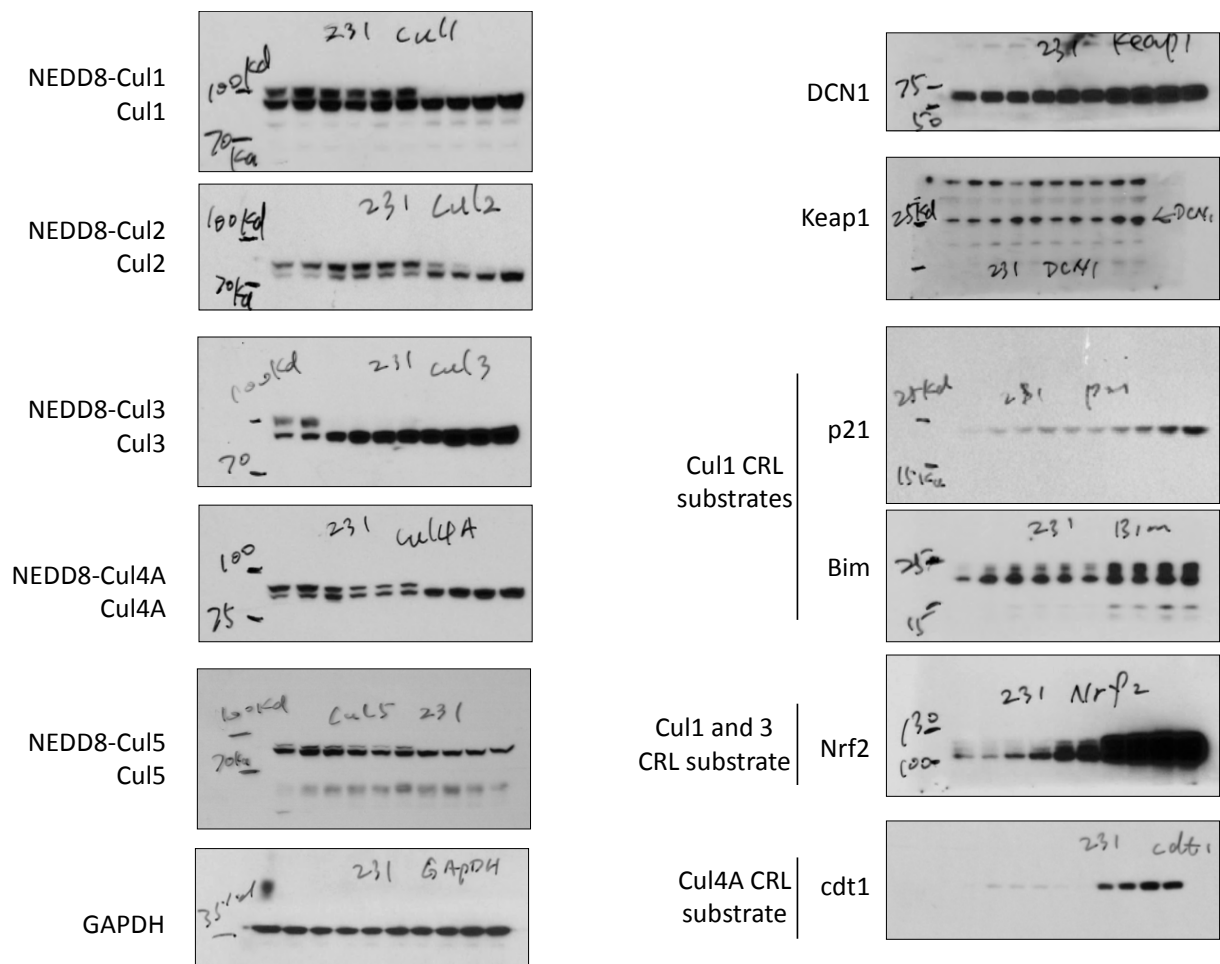


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3 **Supplementary Figure 17.** Uncropped western blot images for Supplementary Figure 5 (U2OS
4 cell line).

5

1 **Supplementary Figure 18:**



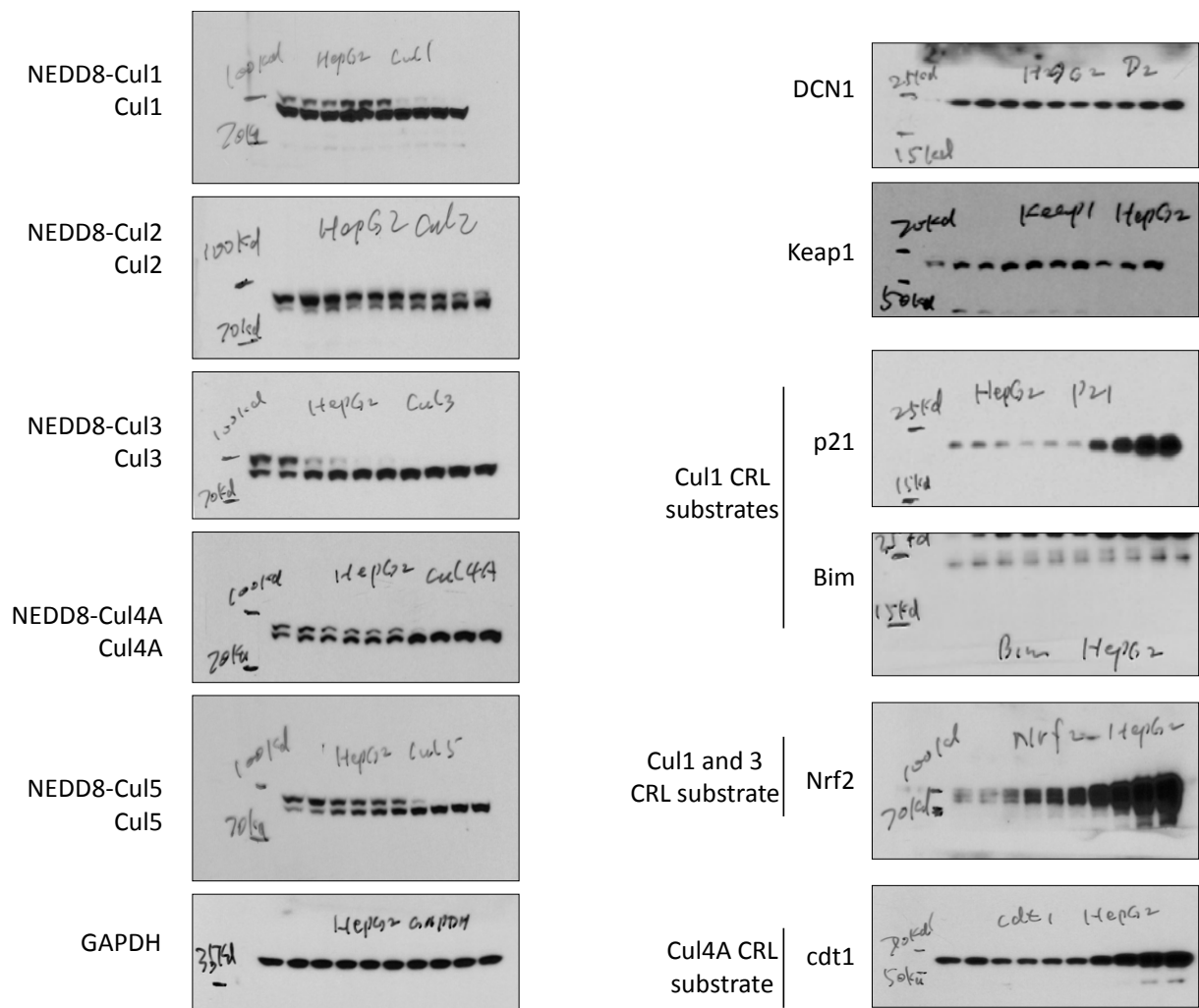
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3 **Supplementary Figure 18.** Uncropped western blot images for Supplementary Figure 5 (MDA-

4 MB-231 cell line).

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1 **Supplementary Figure 19:**



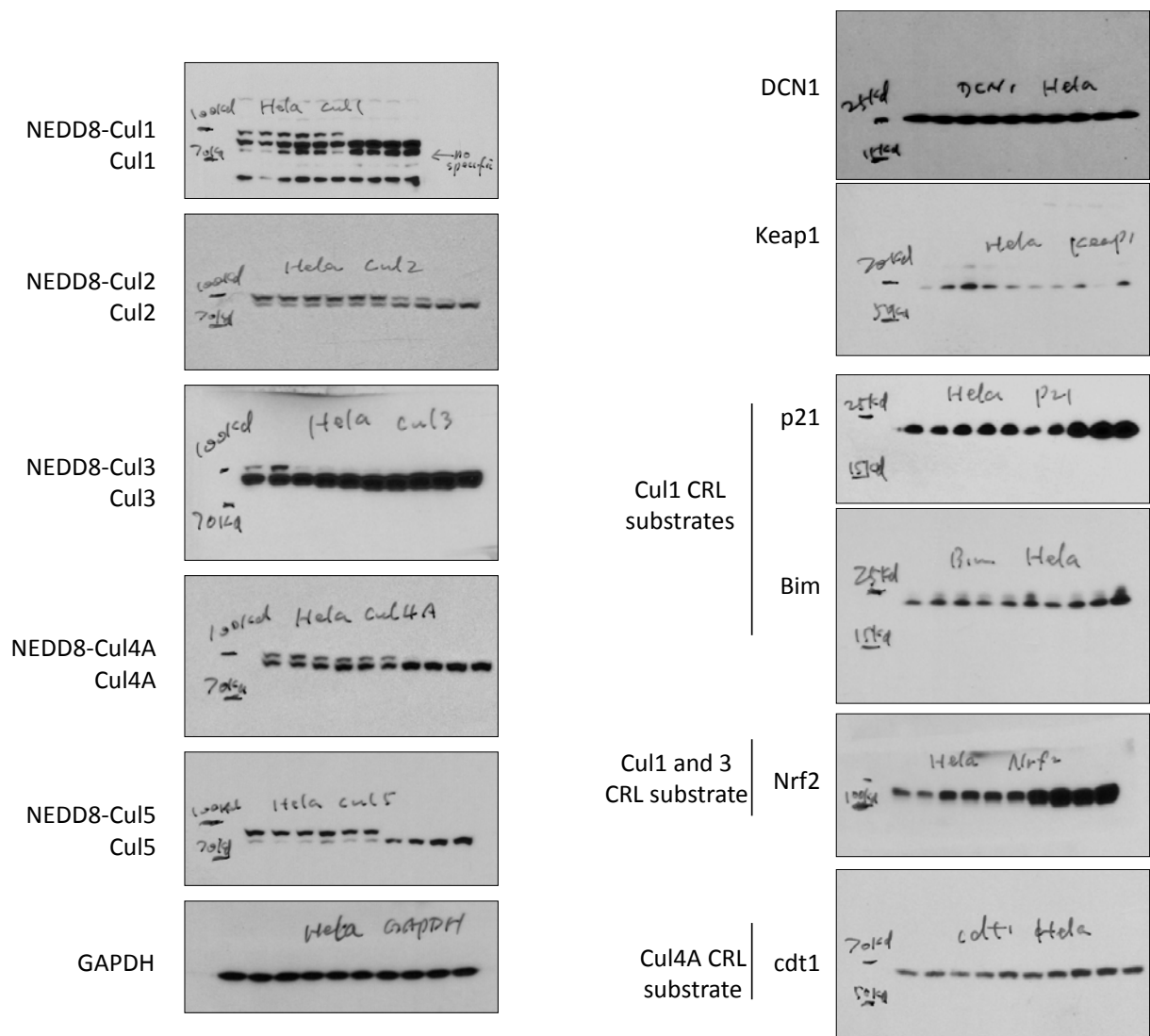
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3 **Supplementary Figure 19.** Uncropped western blot images for Supplementary Figure 5 (HepG2

4 cell line).

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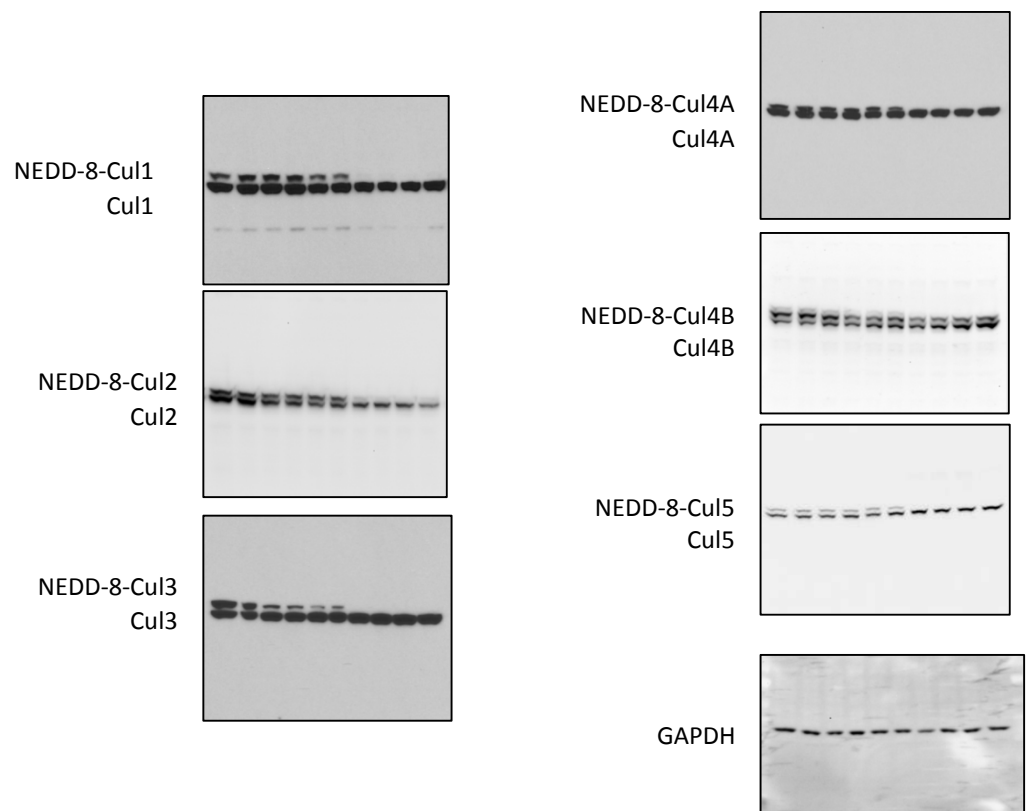
1 **Supplementary Figure 20:**



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3 **Supplementary Figure 20.** Uncropped western blot images for Supplementary Figure 5 (HeLa
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1 **Supplementary Figure 21:**

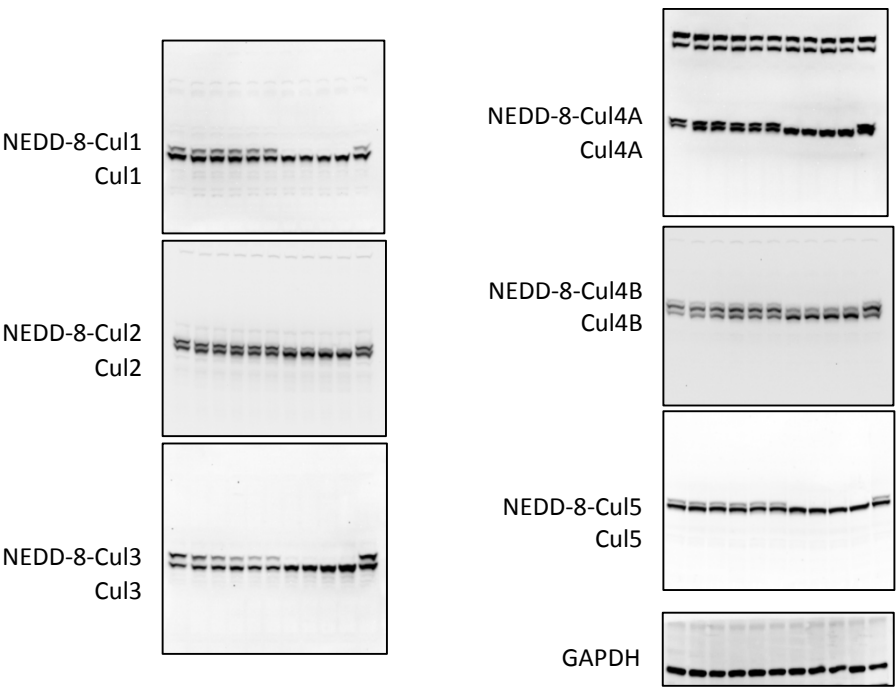


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3 **Supplementary Figure 21.** Uncropped western blot images for Supplementary Figure 6 (U2OS
4 cell line).

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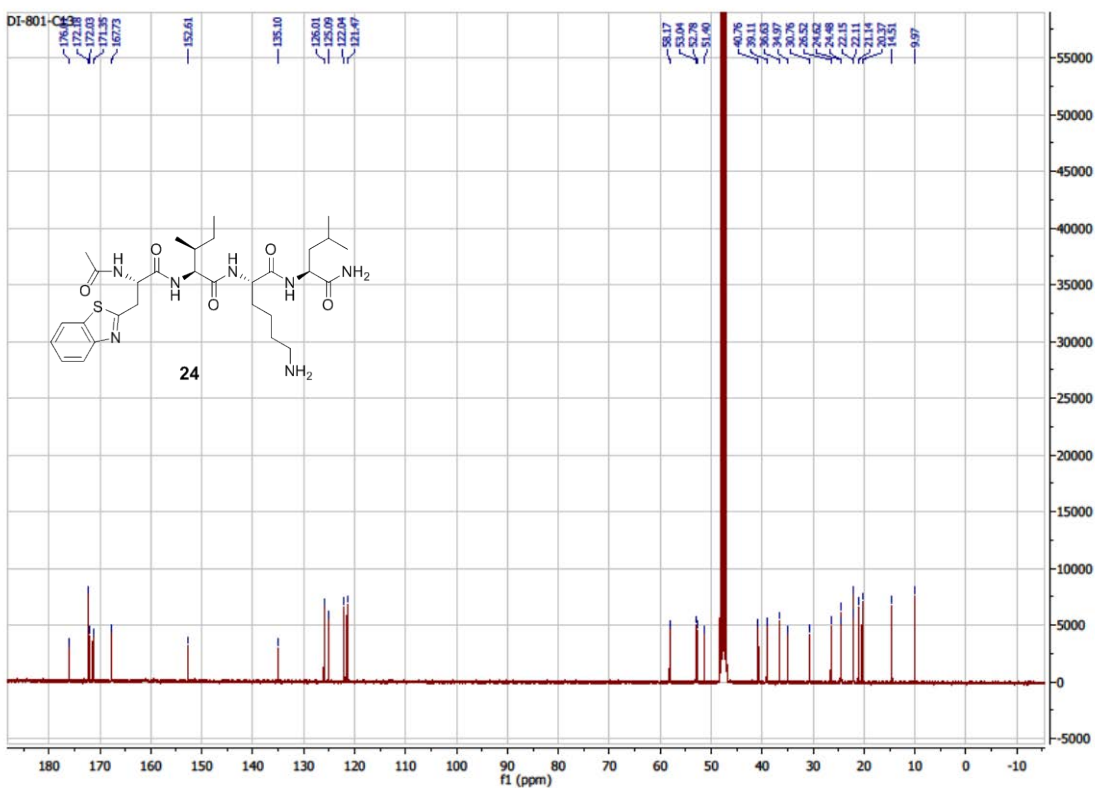
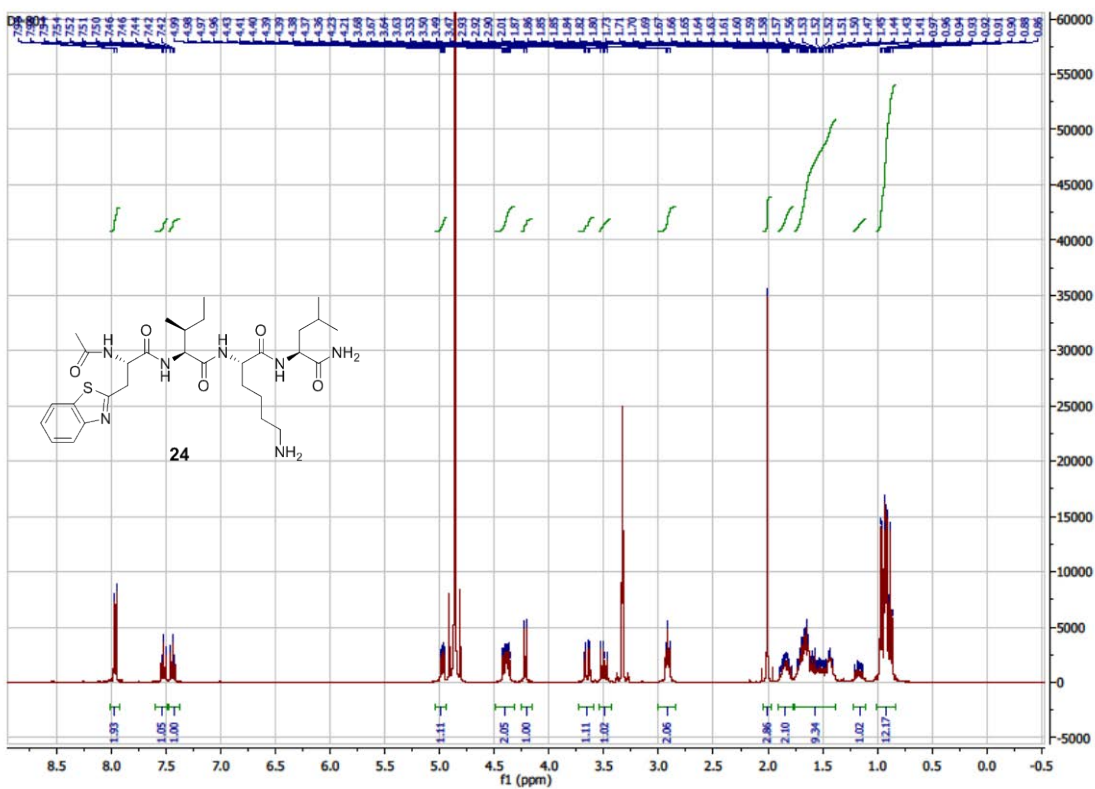
1 **Supplementary Figure 22:**



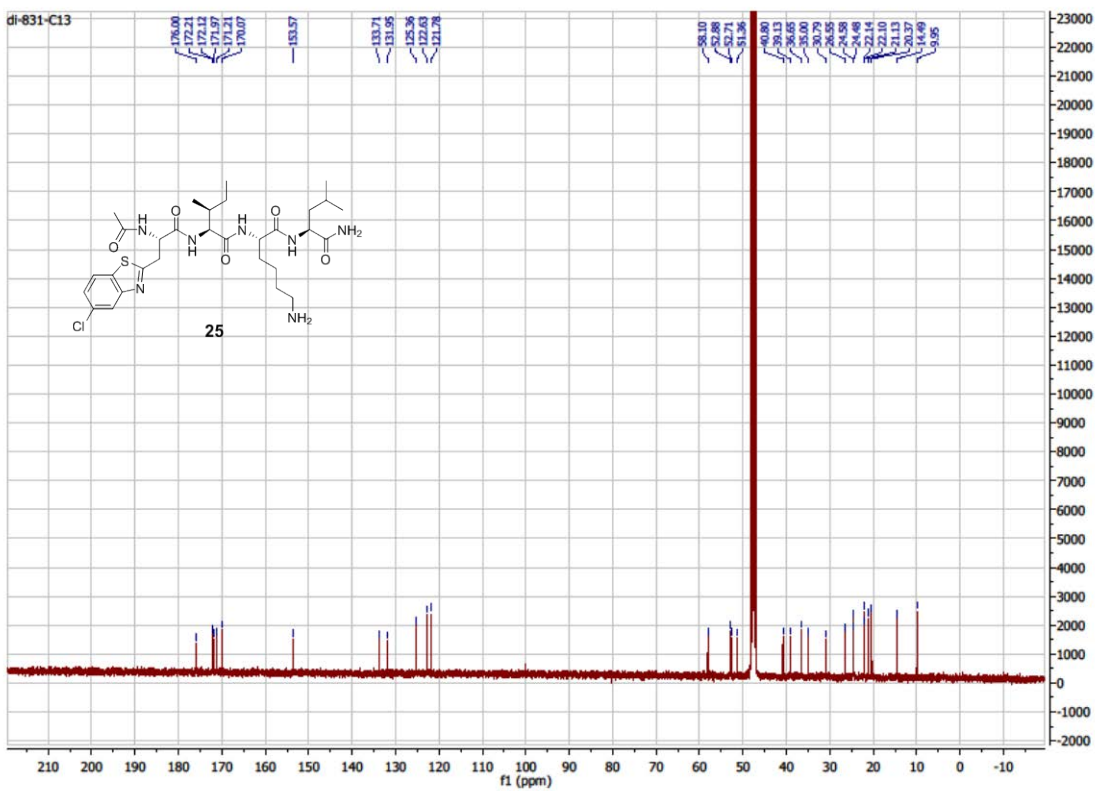
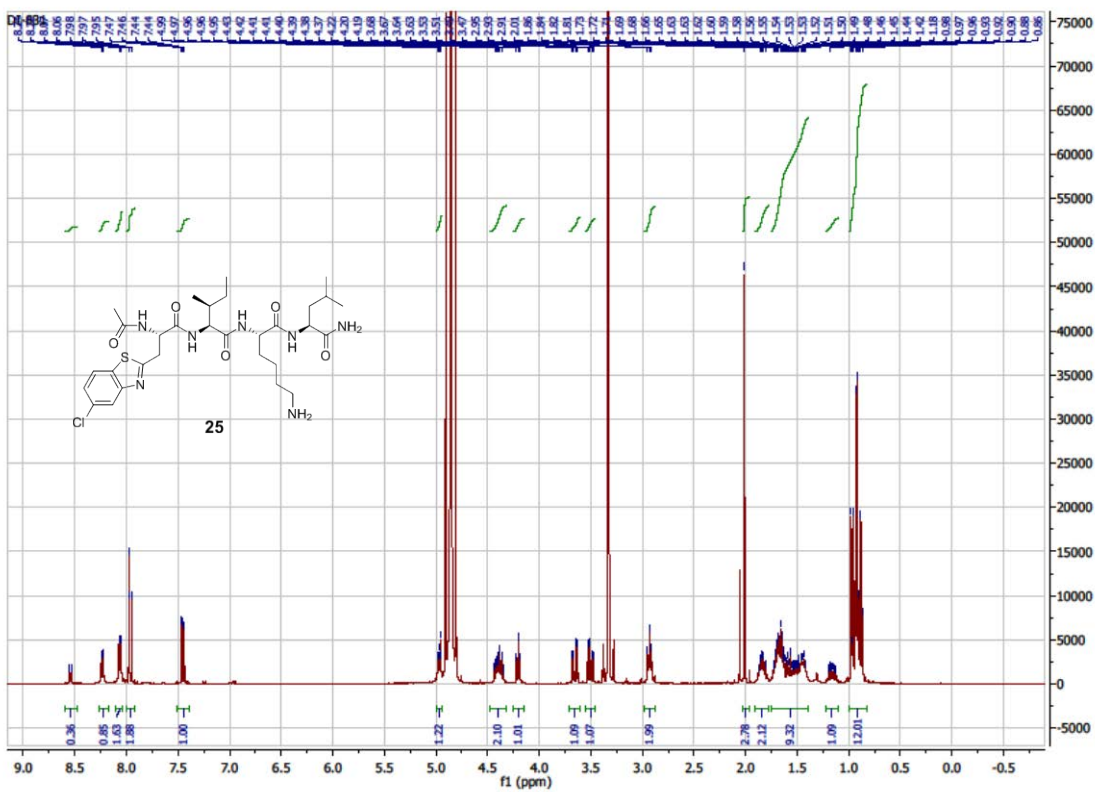
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3 **Supplementary Figure 22.** Uncropped western blot images for Supplementary Figure 6 (MDA-
4 MB-231 cell line).

1 **Supplementary Figure 23.** ^1H NMR and ^{13}C NMR for Compound 24.



1 **Supplementary Figure 24.** ^1H NMR and ^{13}C NMR for Compound 25.



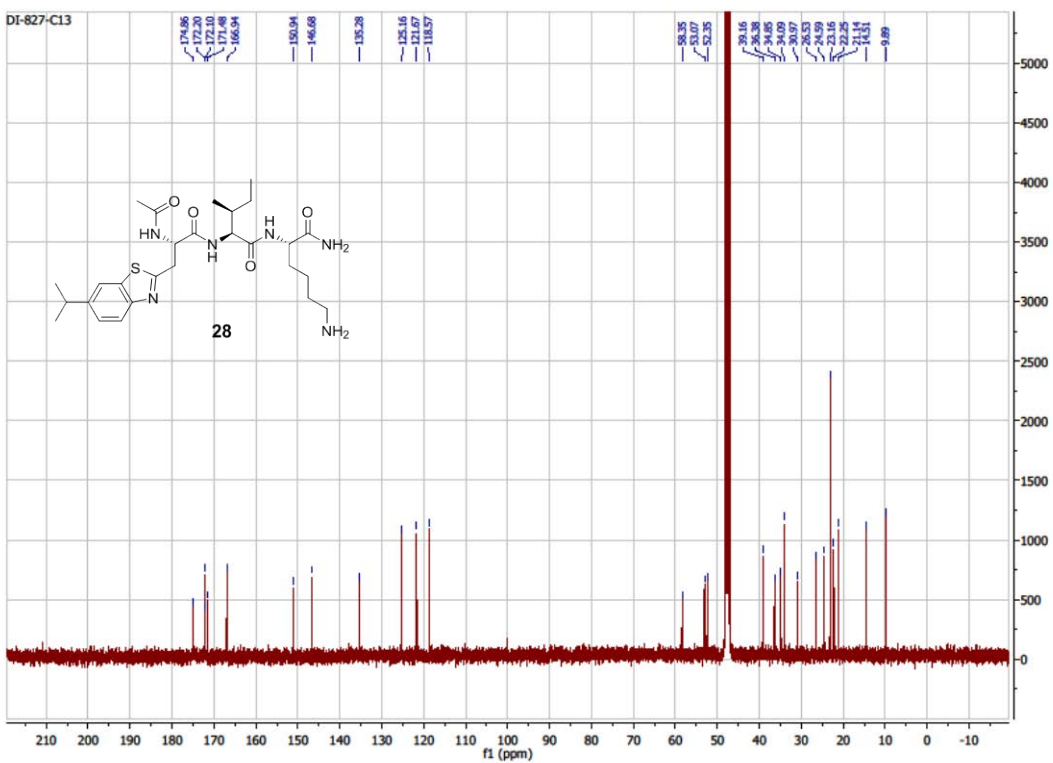
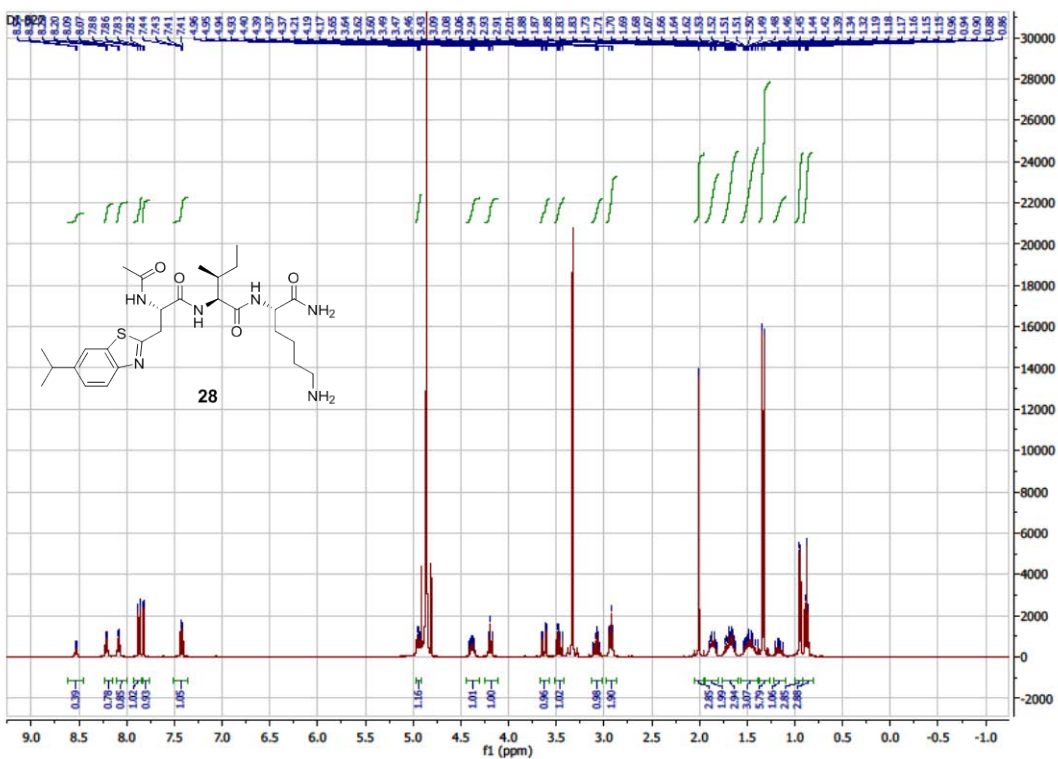
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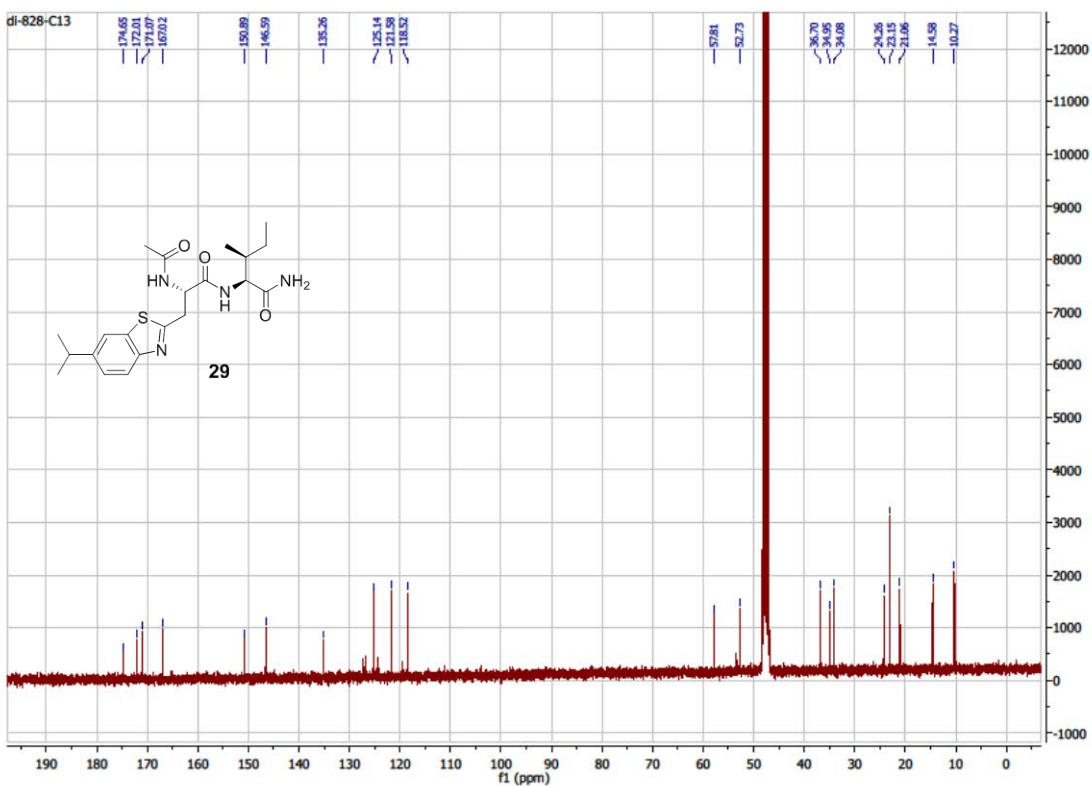
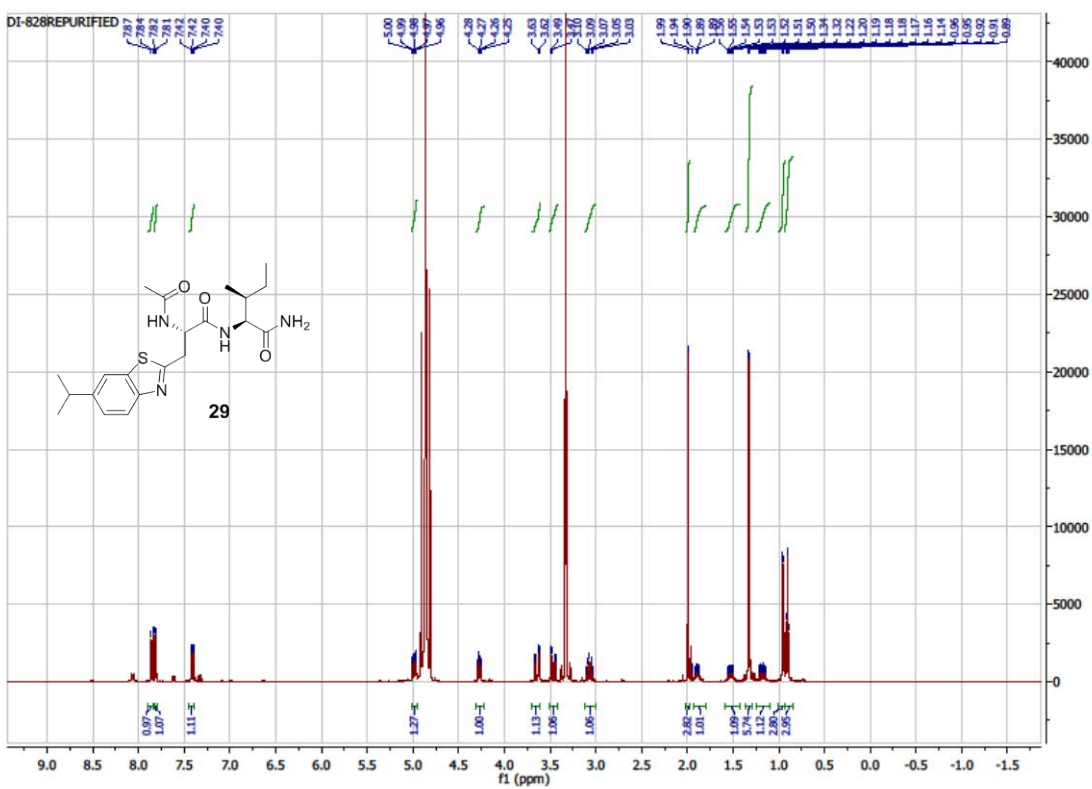
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1 **Supplementary Figure 27.** ^1H NMR and ^{13}C NMR for Compound **28**.



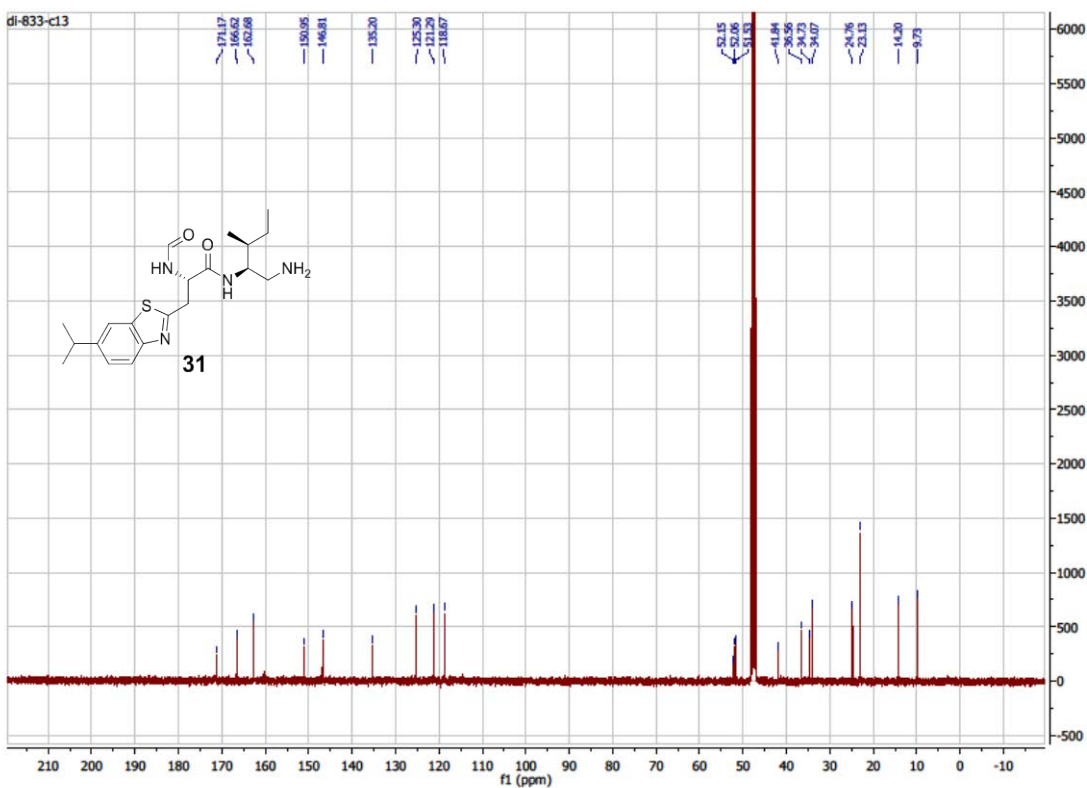
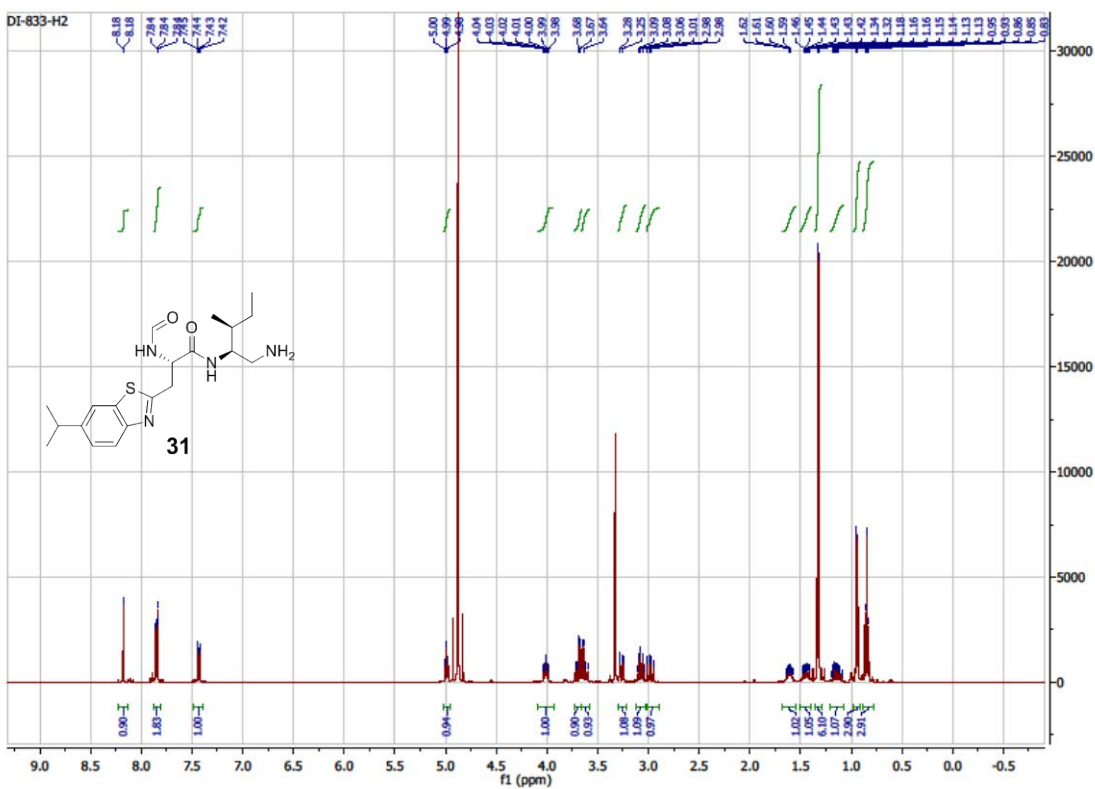
1 **Supplementary Figure 28.** ^1H NMR and ^{13}C NMR for Compound 29.



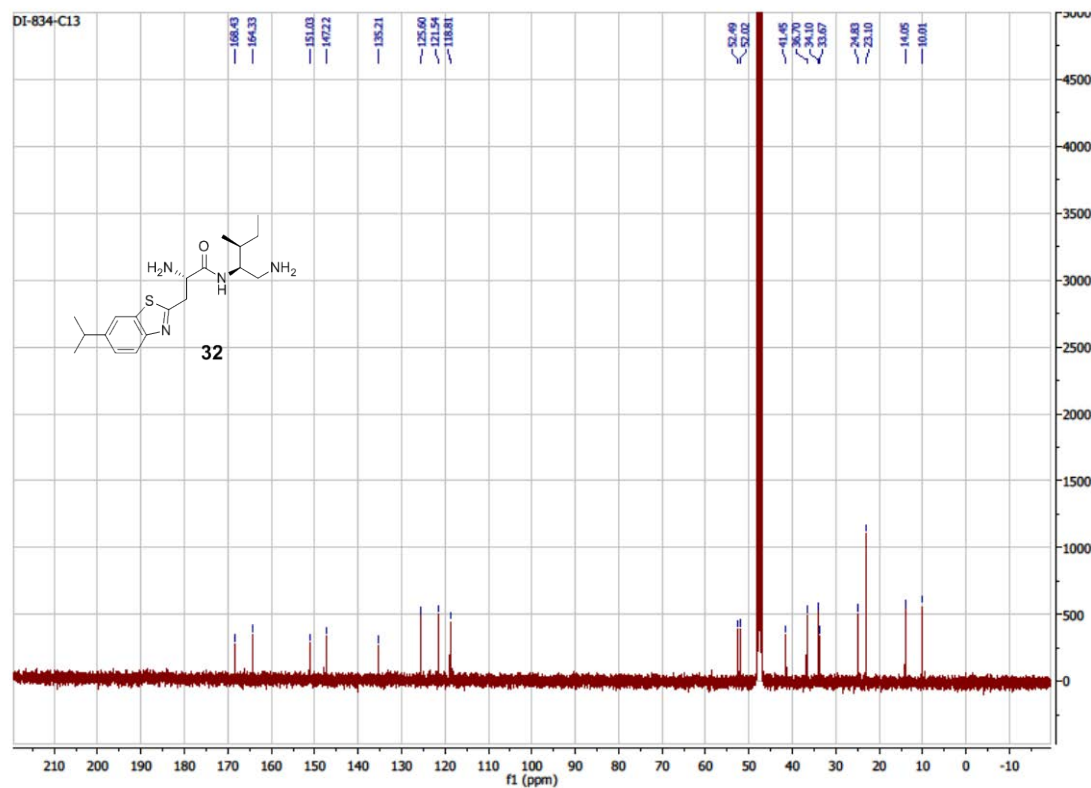
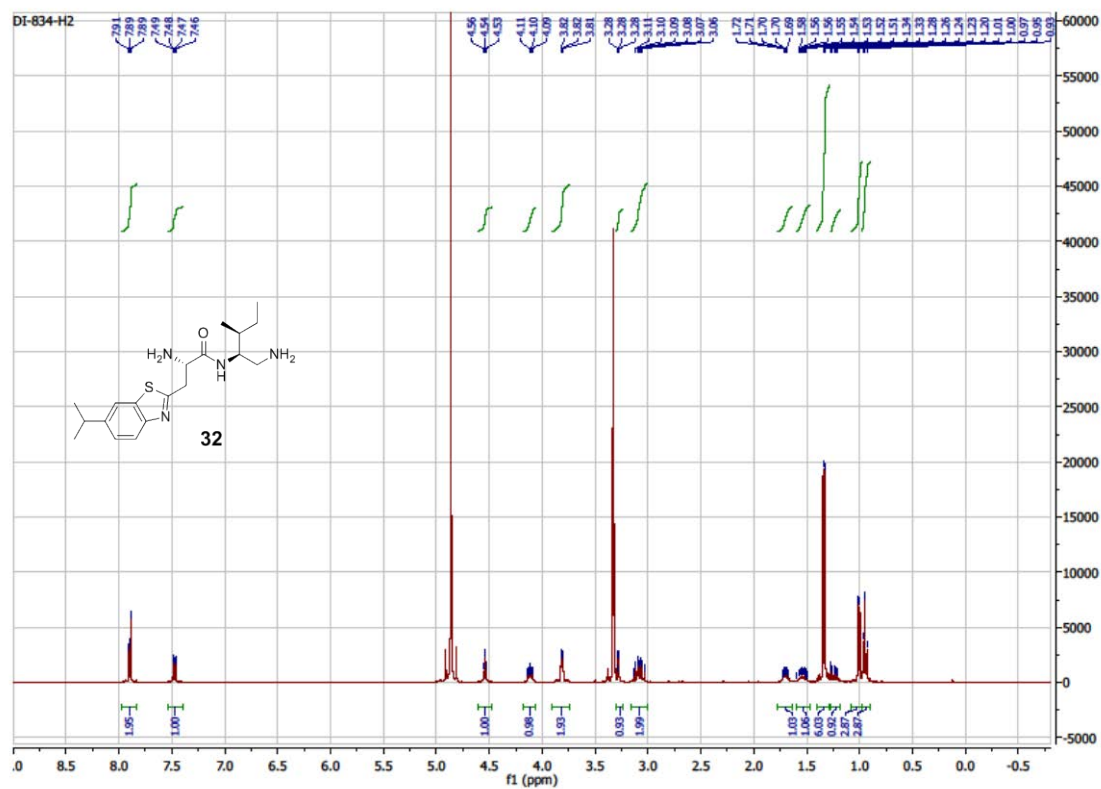
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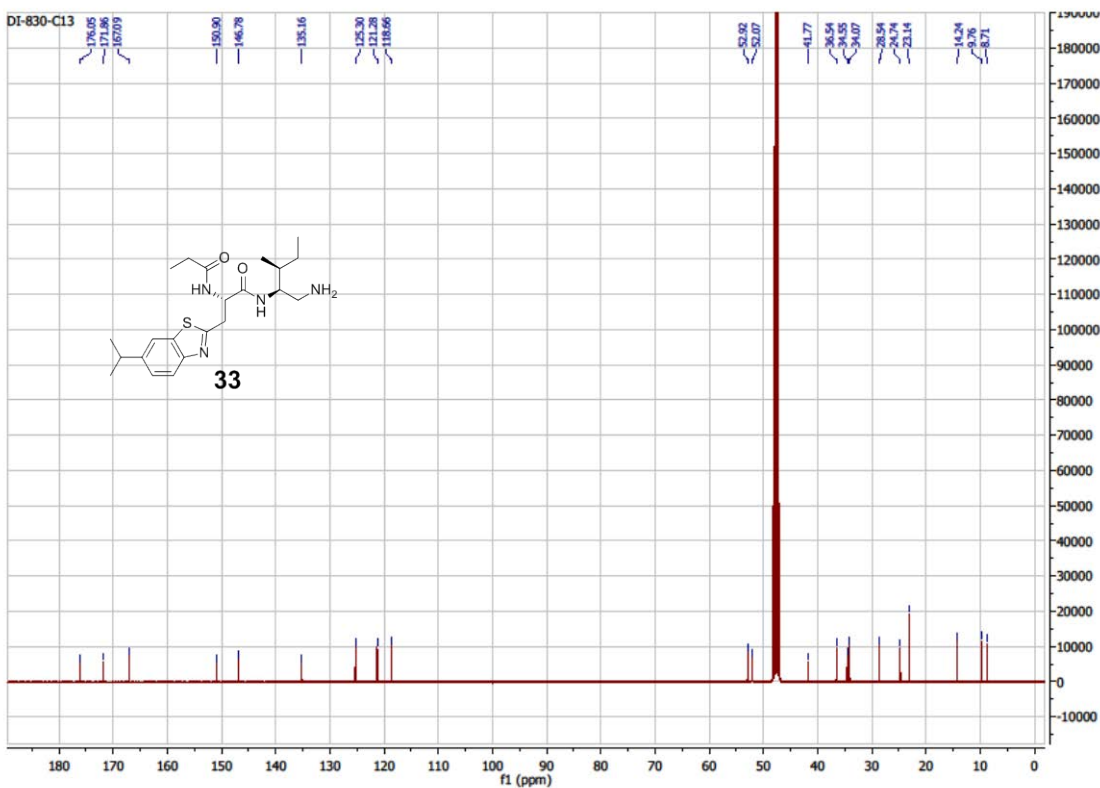
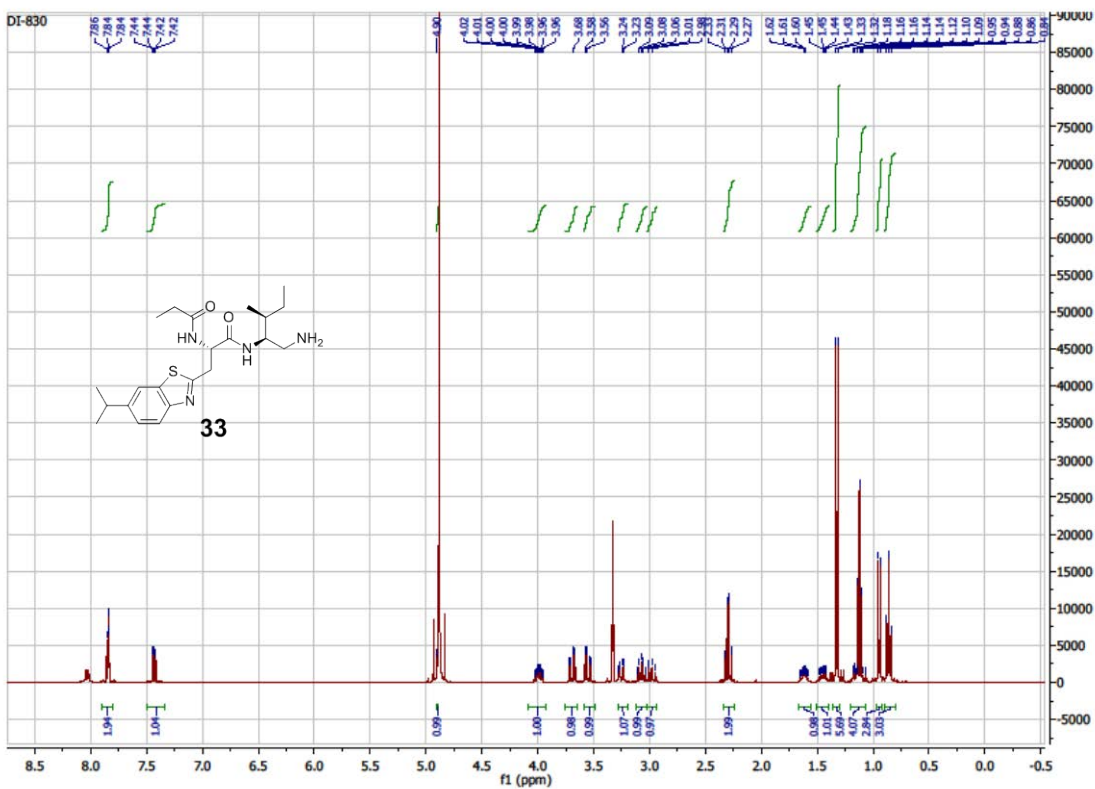
1 **Supplementary Figure 30.** ^1H NMR and ^{13}C NMR for Compound **31**.



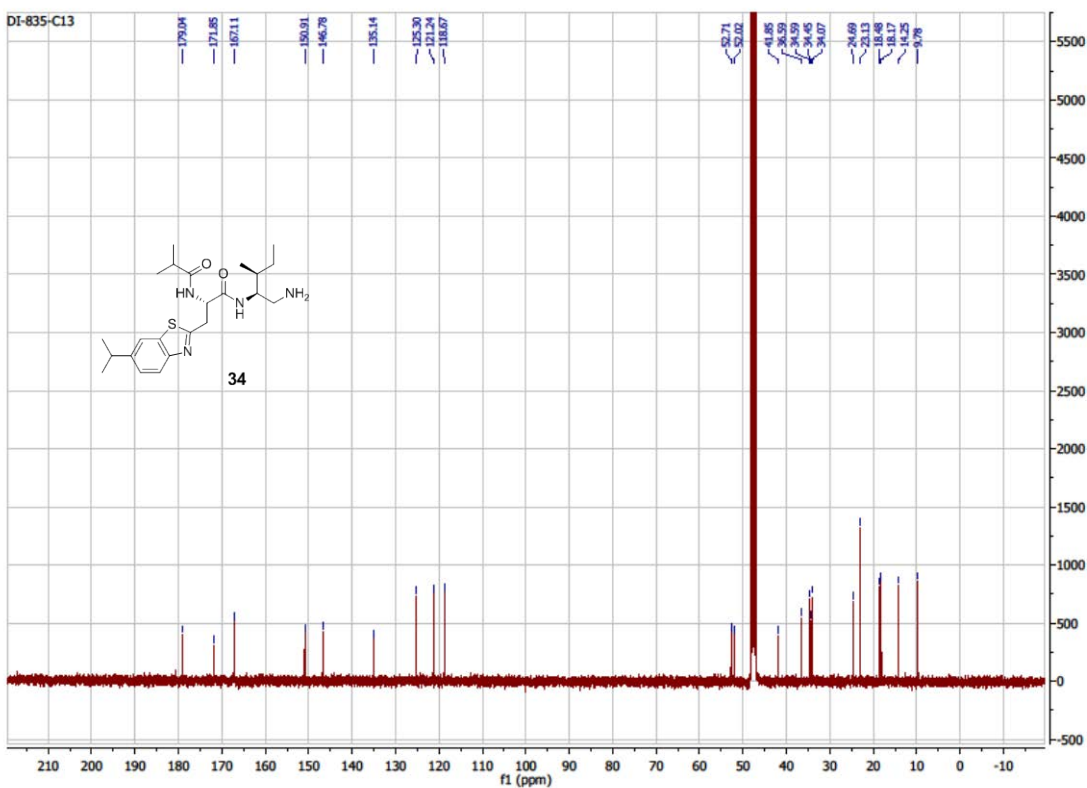
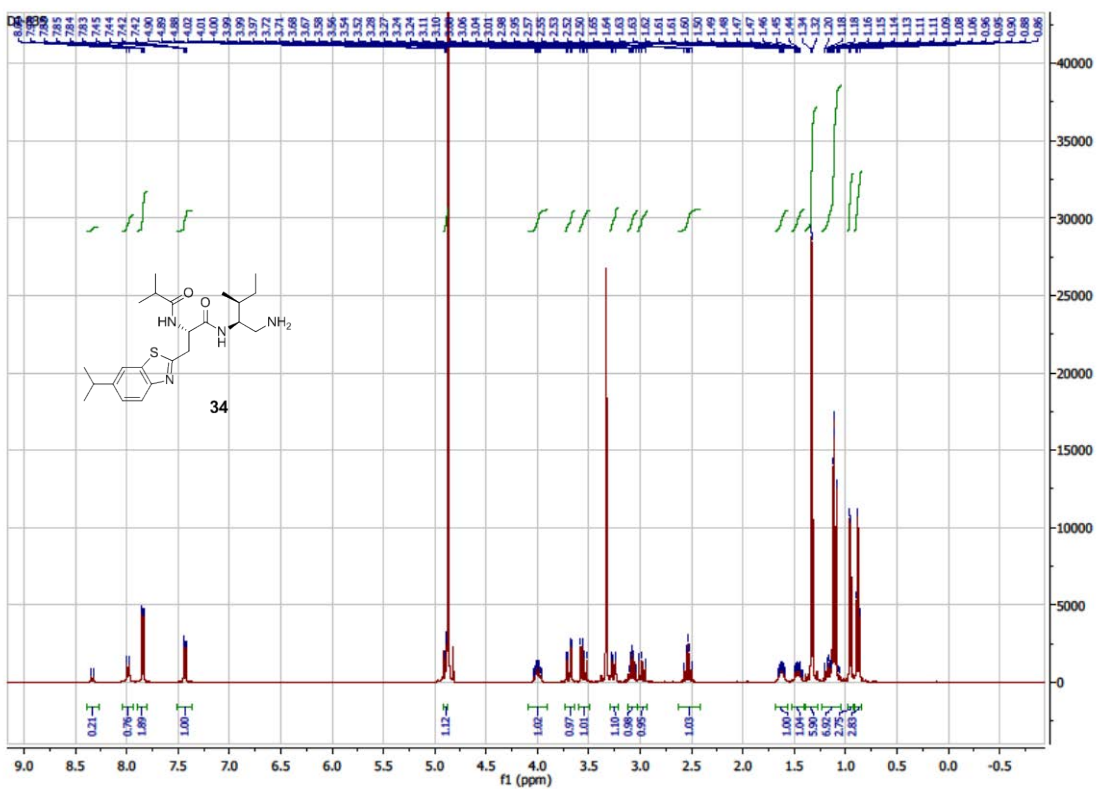
1 **Supplementary Figure 31.** ^1H NMR and ^{13}C NMR for Compound 32.



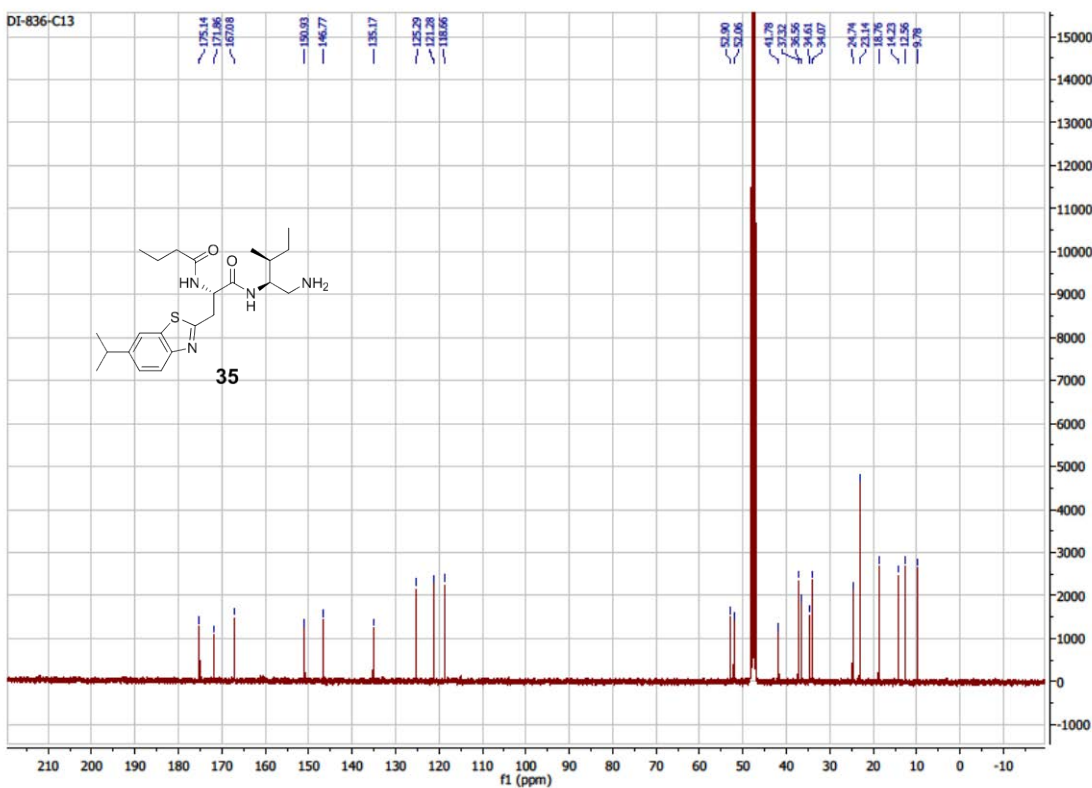
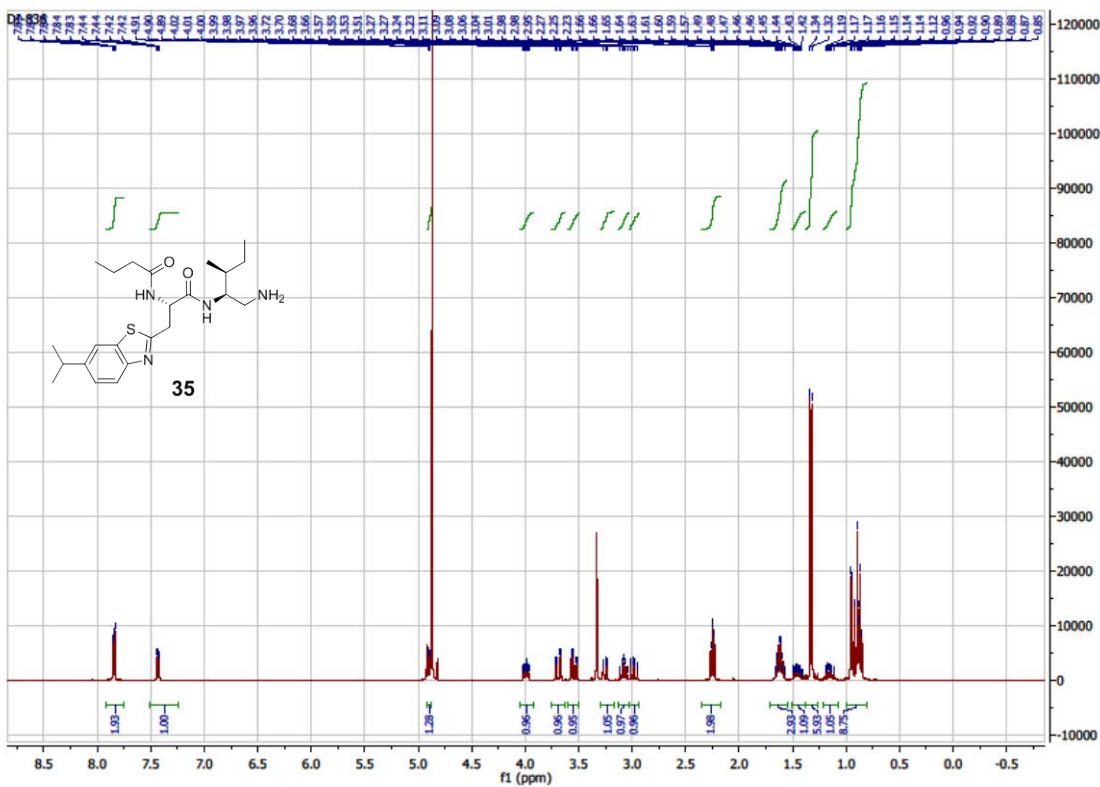
1 **Supplementary Figure 32.** ^1H NMR and ^{13}C NMR for Compound 33.



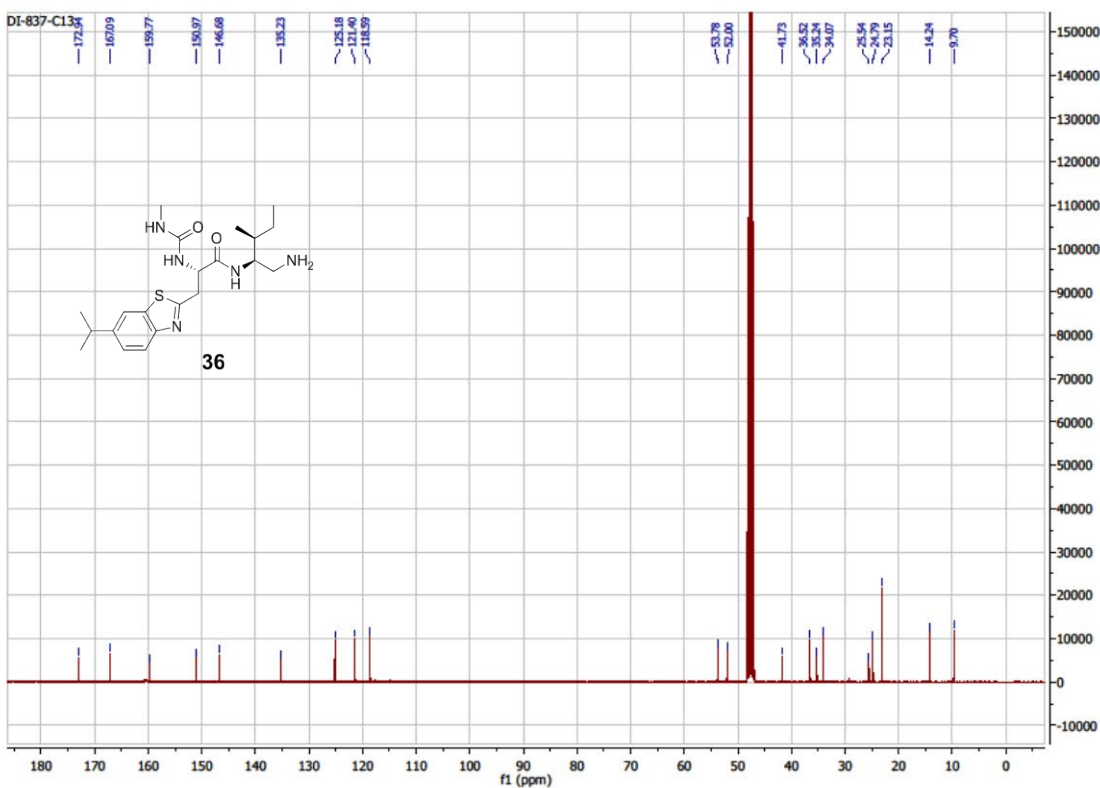
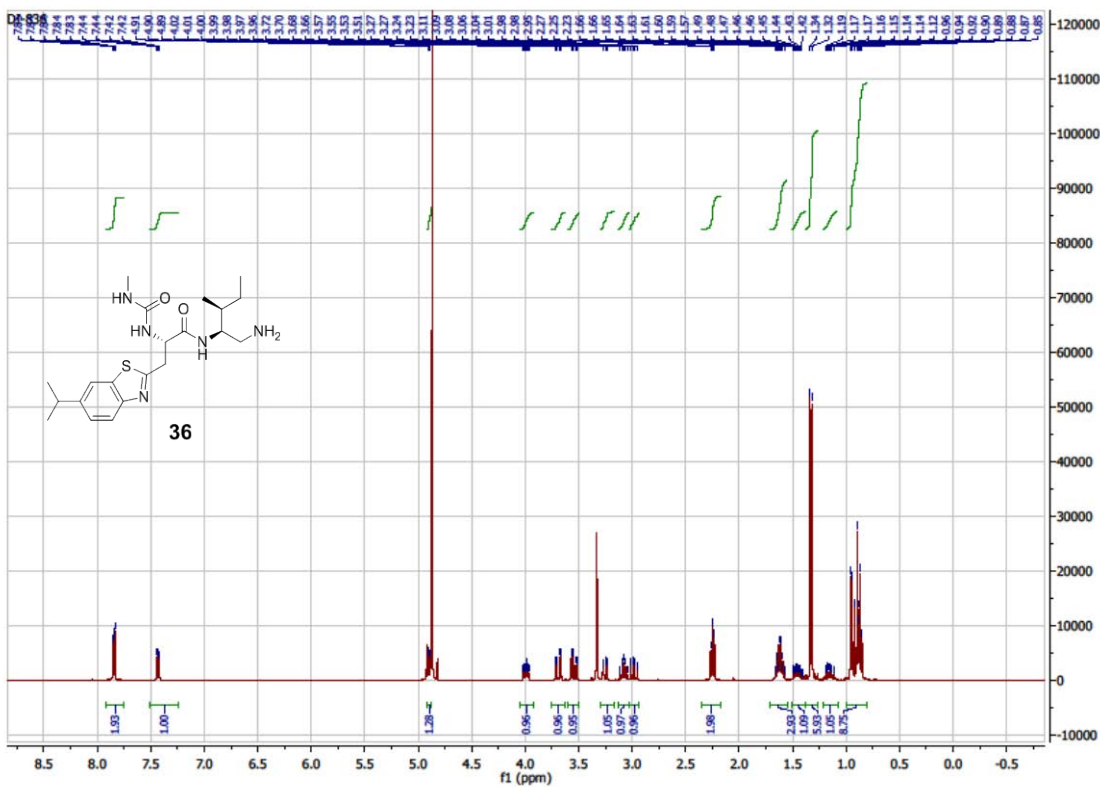
1 **Supplementary Figure 33.** ^1H NMR and ^{13}C NMR for Compound **34**.



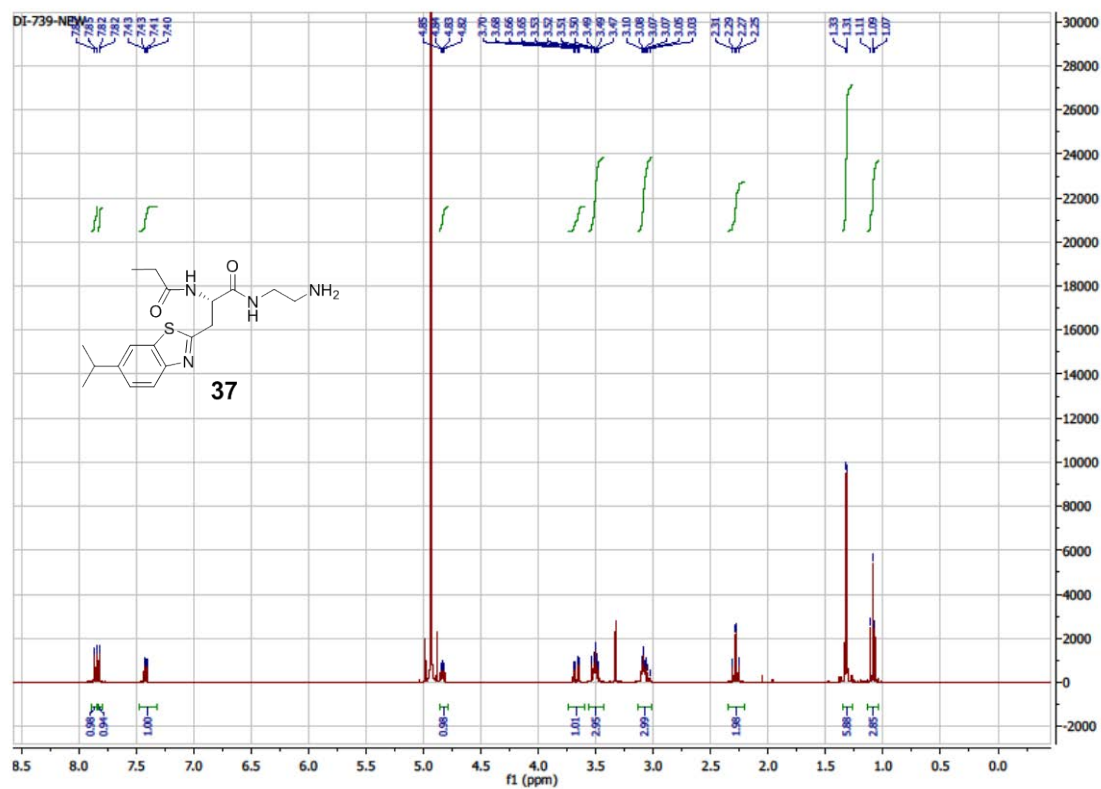
1 **Supplementary Figure 34.** ^1H NMR and ^{13}C NMR for Compound 35.



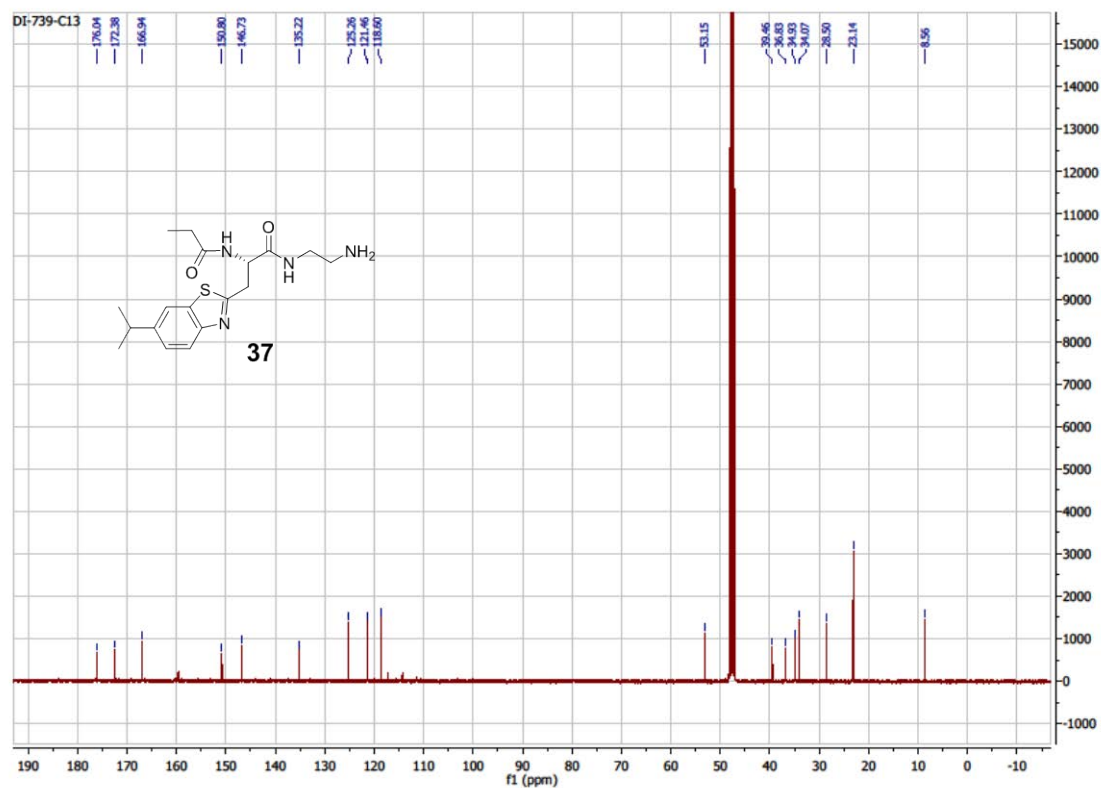
1 **Supplementary Figure 35.** ^1H NMR and ^{13}C NMR for Compound **36**.



1 **Supplementary Figure 36.** ^1H NMR and ^{13}C NMR for Compound 37.

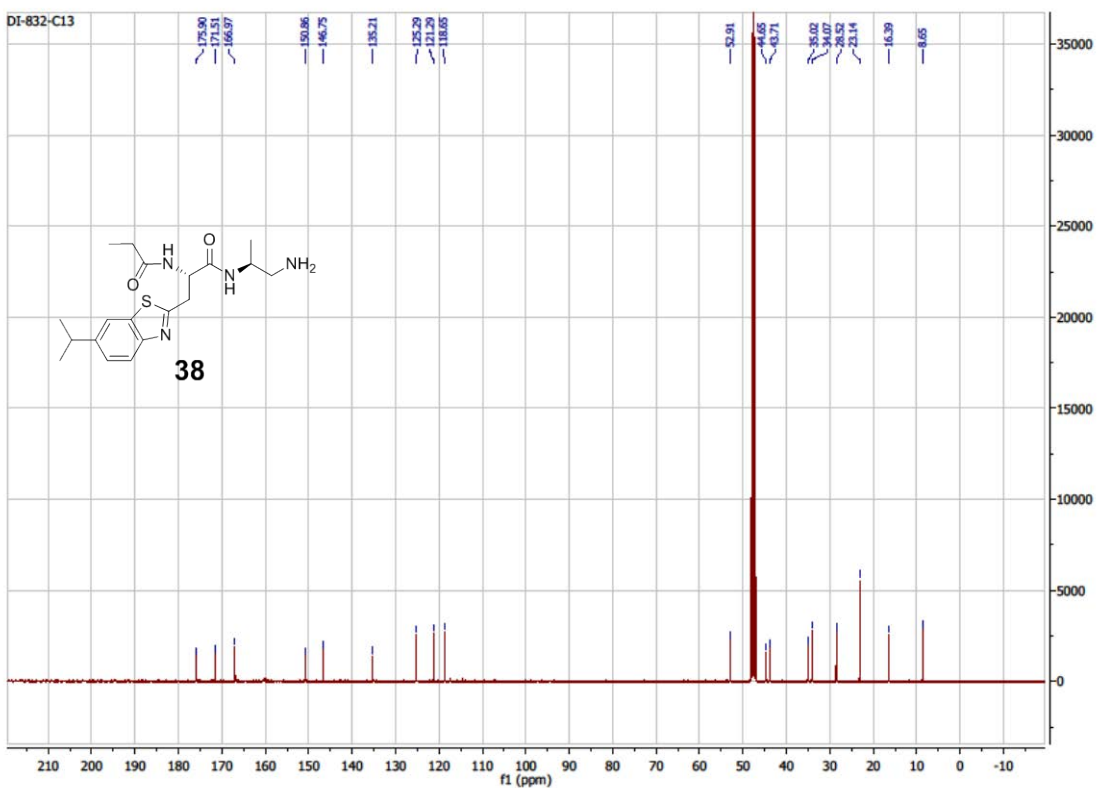
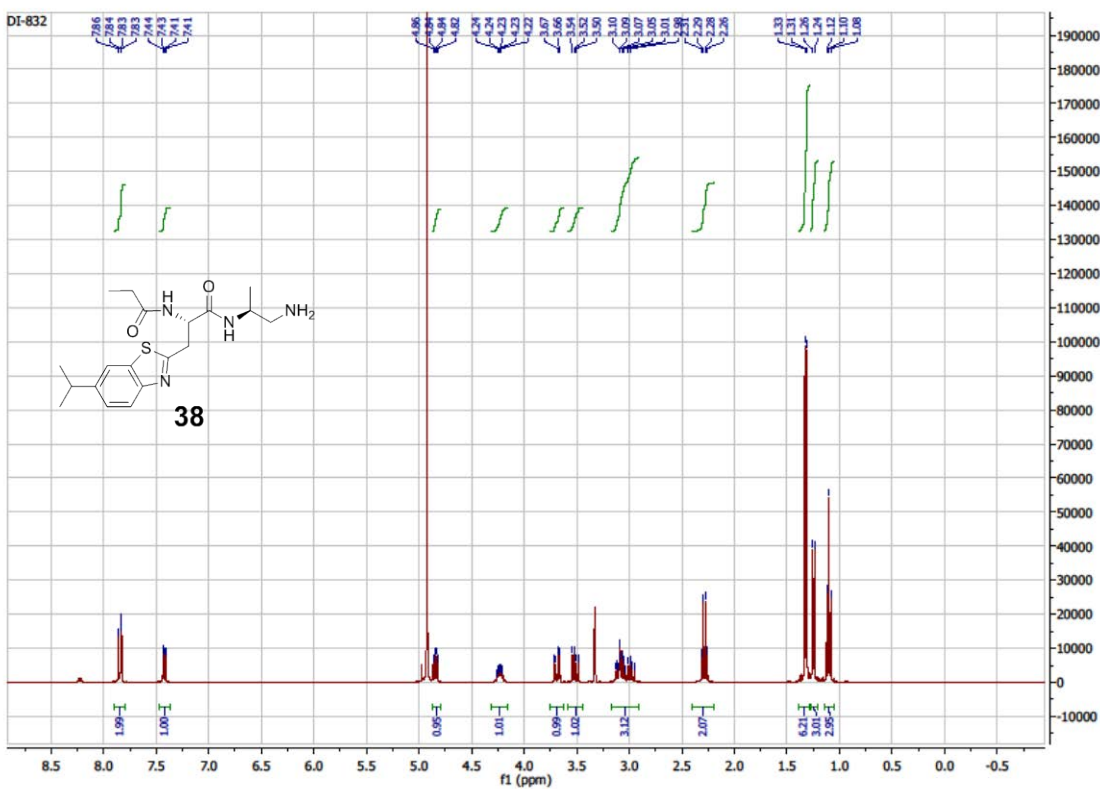


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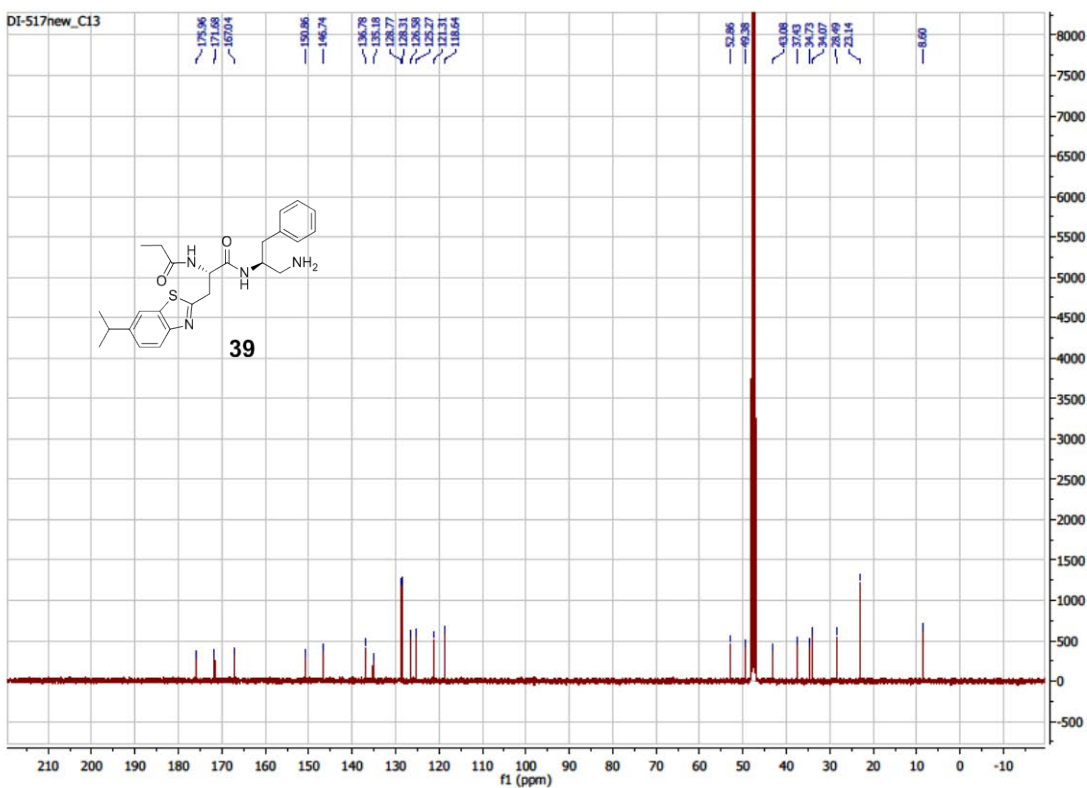
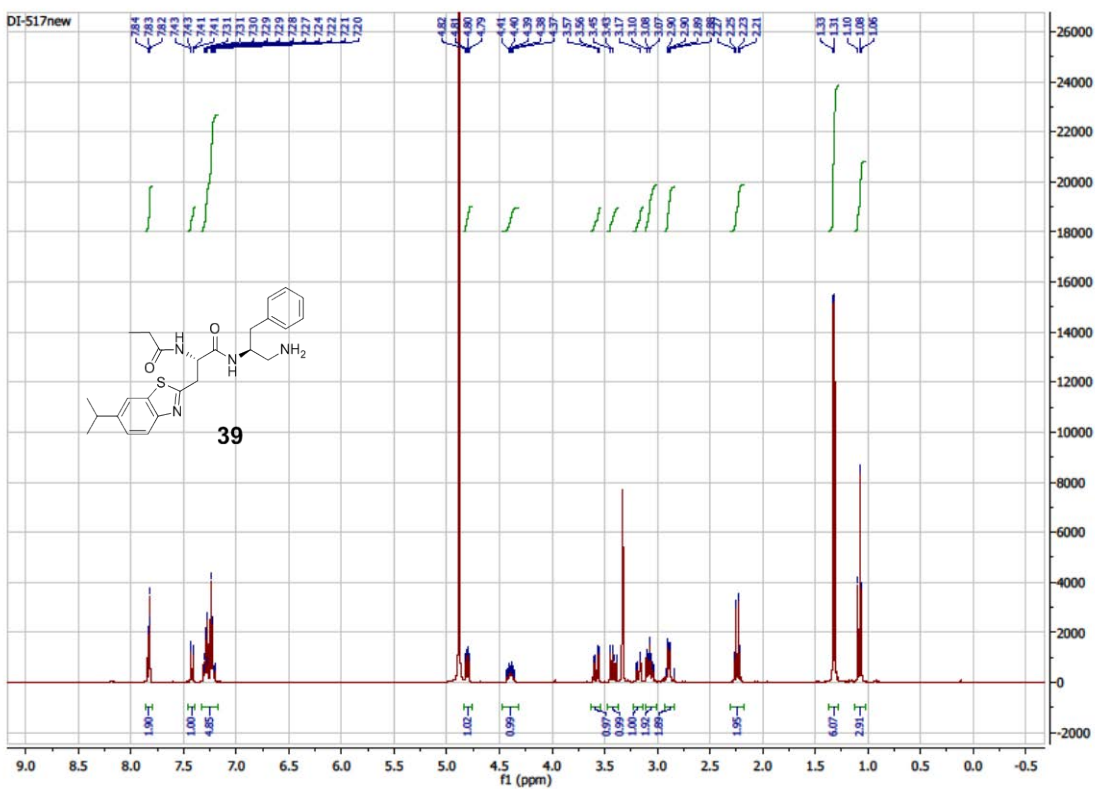


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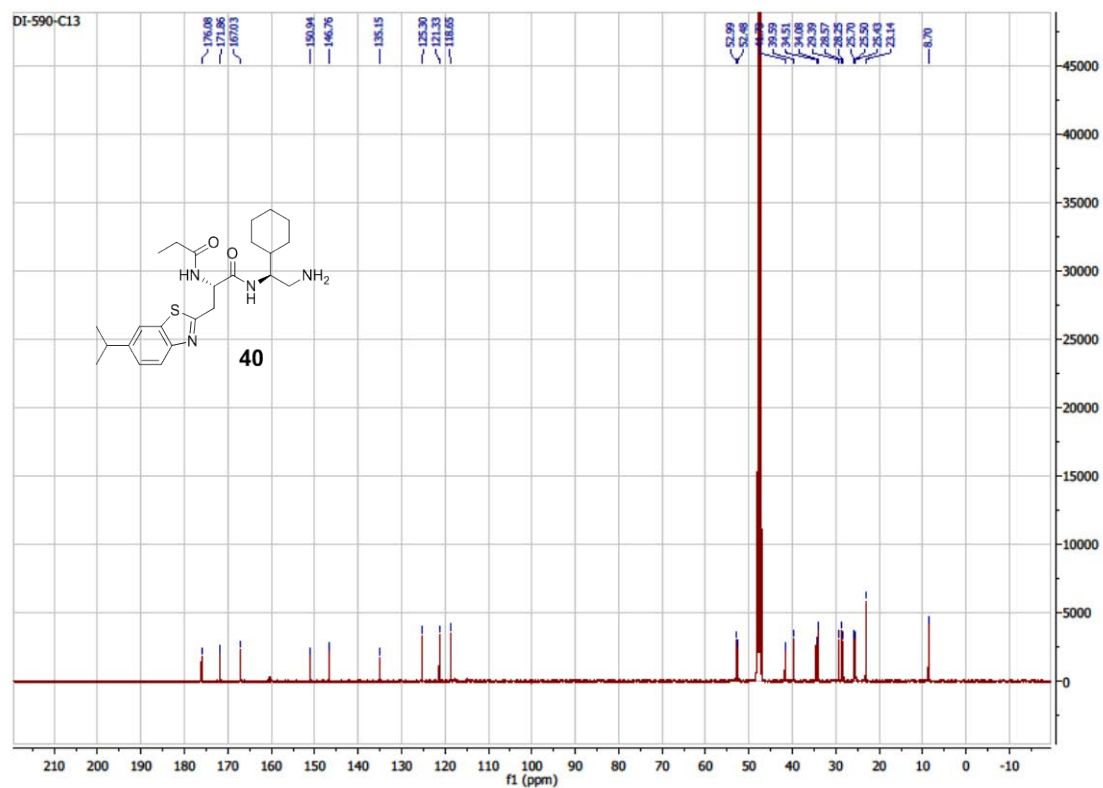
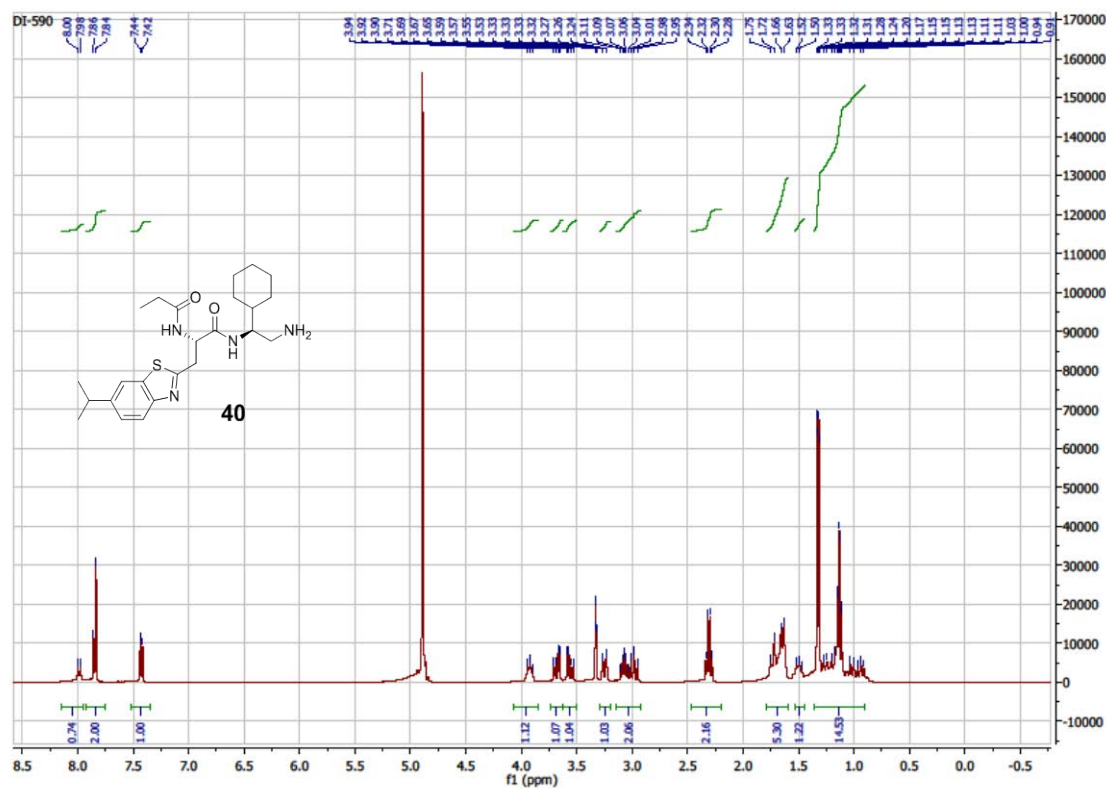
1 **Supplementary Figure 37.** ^1H NMR and ^{13}C NMR for Compound **38**.



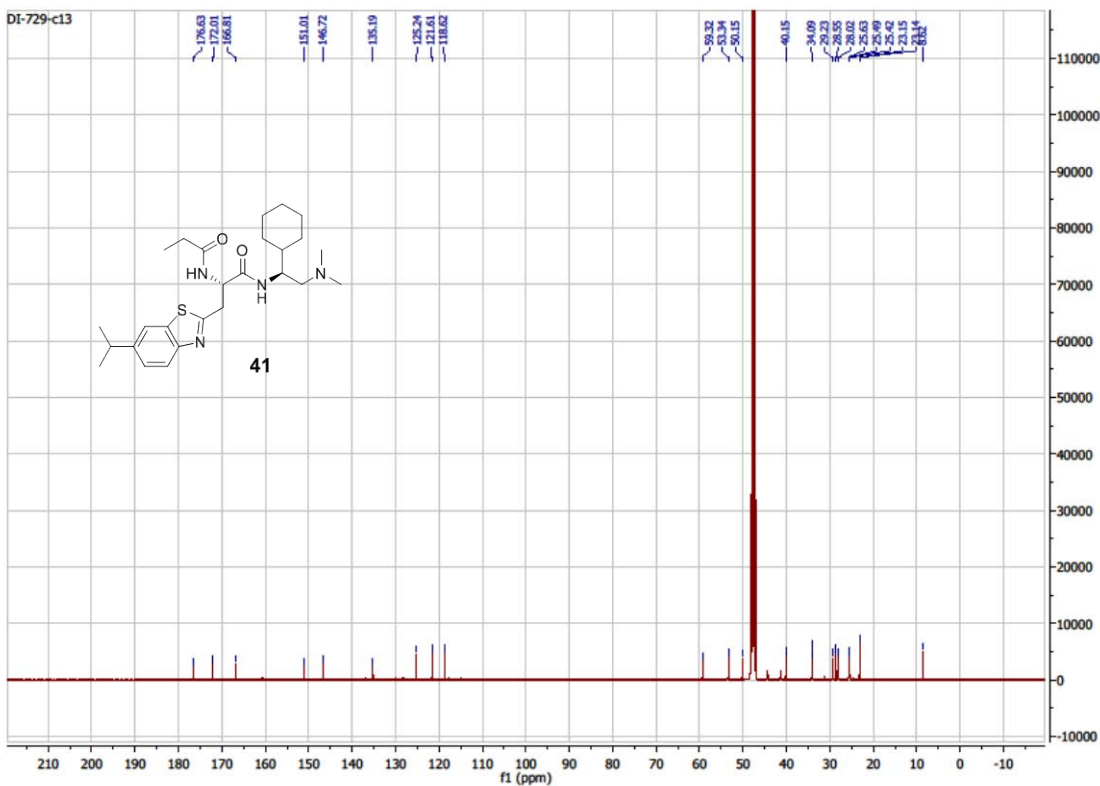
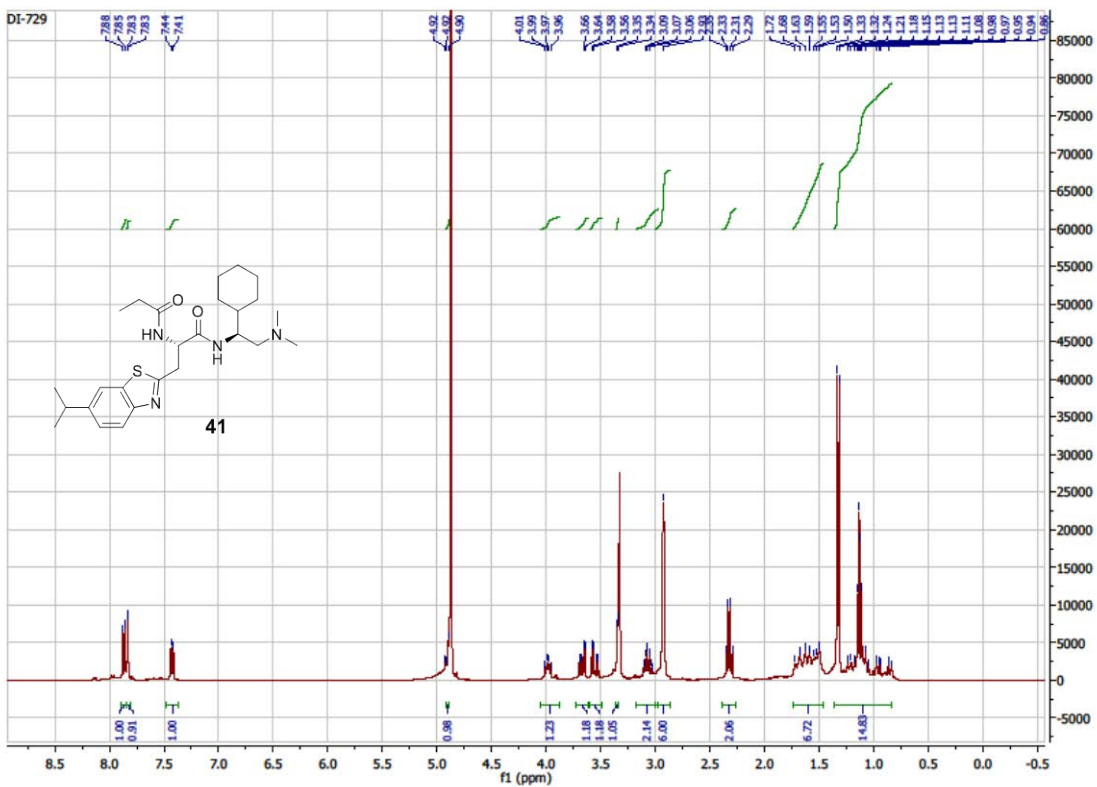
1 **Supplementary Figure 38.** ^1H NMR and ^{13}C NMR for Compound **39**.



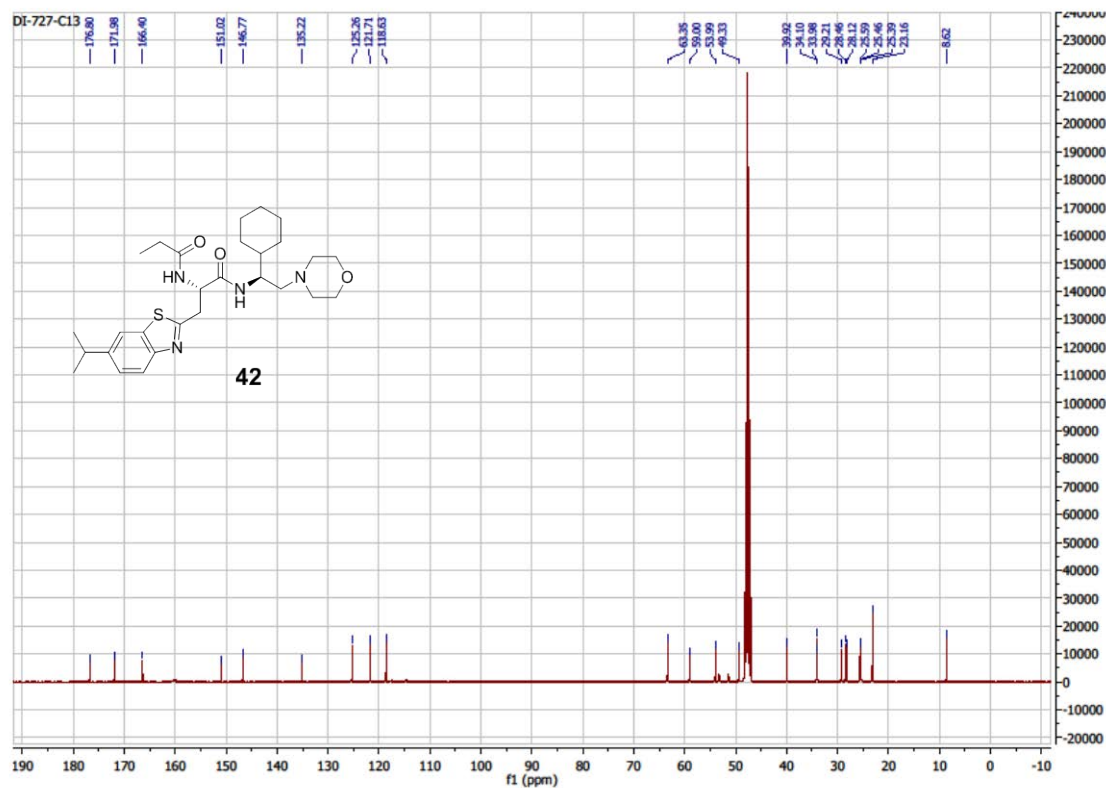
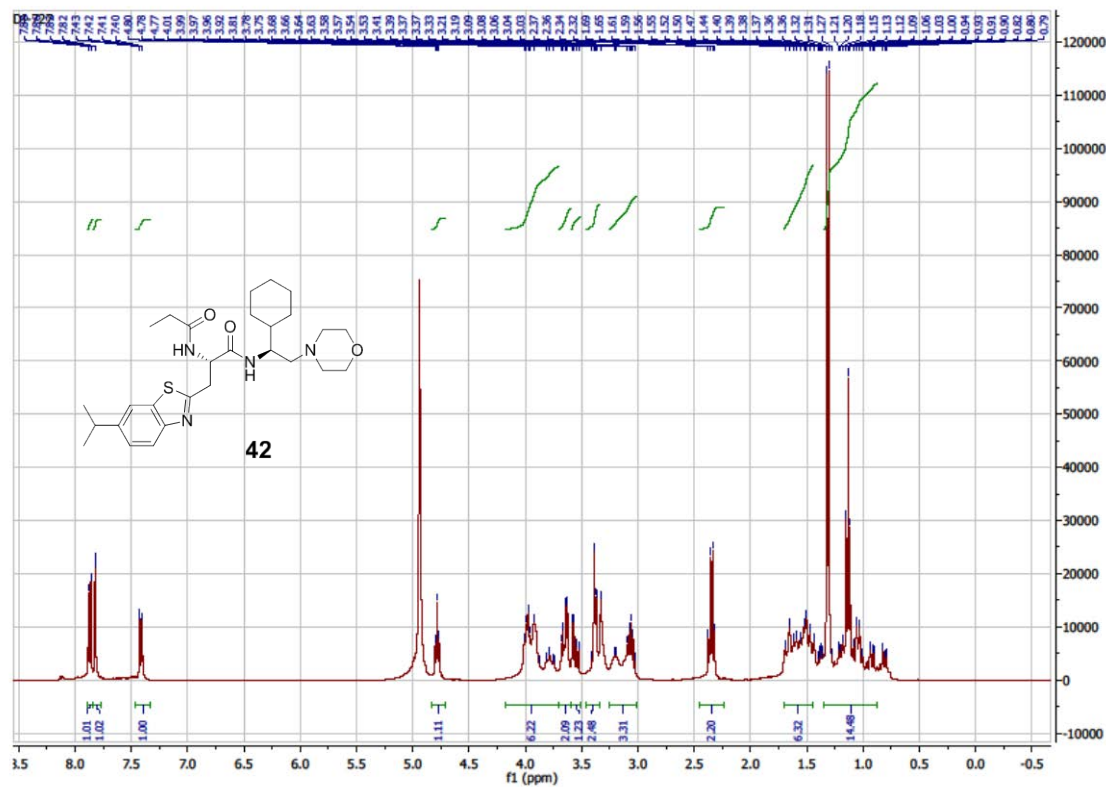
1 **Supplementary Figure 39.** ^1H NMR and ^{13}C NMR for Compound **40**.



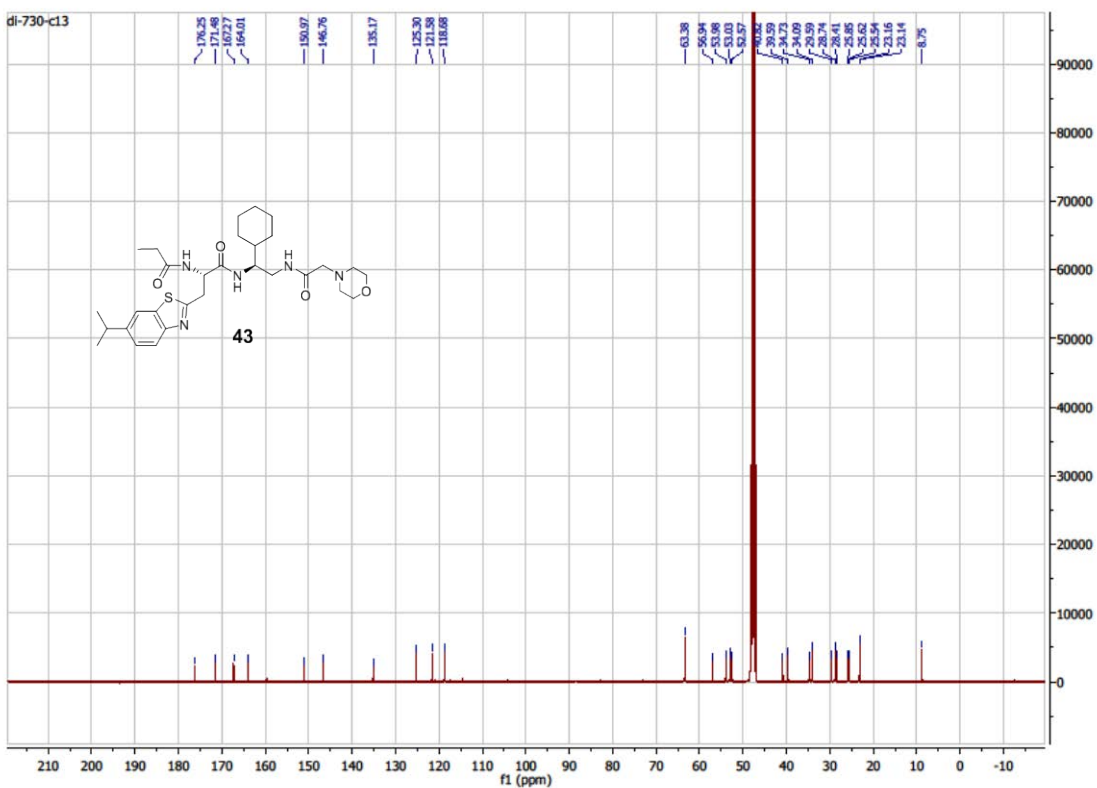
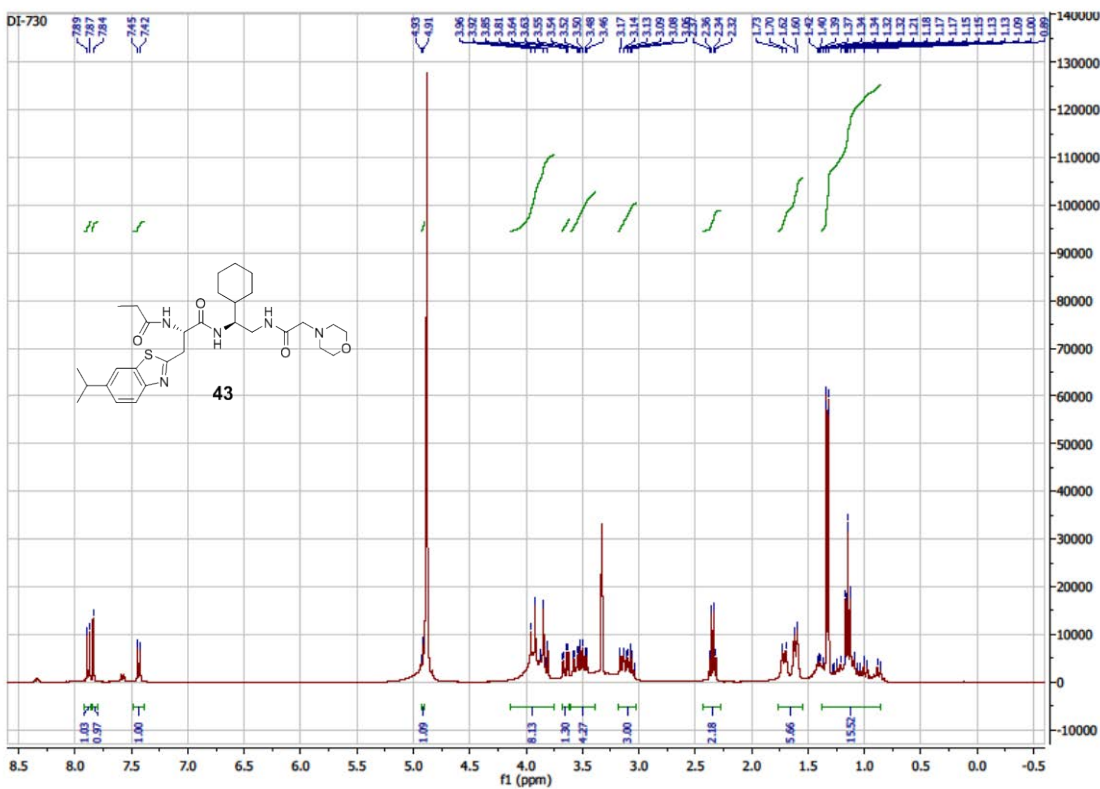
1 **Supplementary Figure 40.** ^1H NMR and ^{13}C NMR for Compound **41**.



1 **Supplementary Figure 41.** ^1H NMR and ^{13}C NMR for Compound 42.



1 **Supplementary Figure 42.** ^1H NMR and ^{13}C NMR for Compound 43.



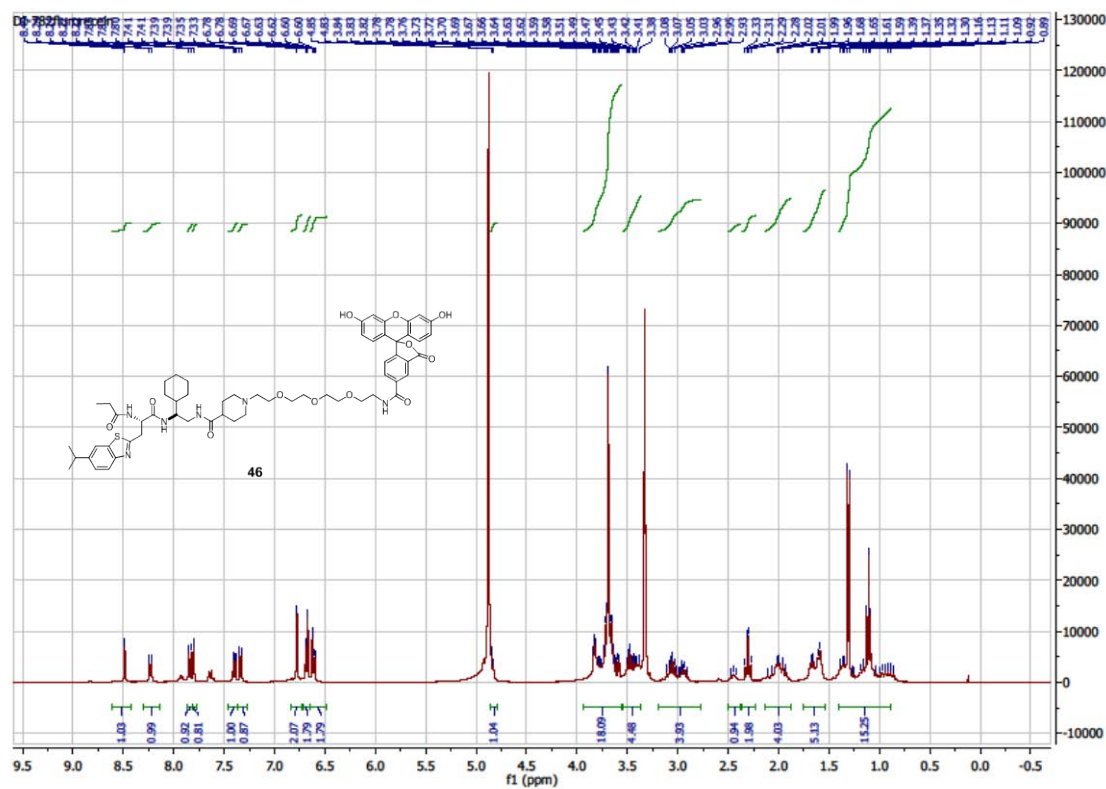
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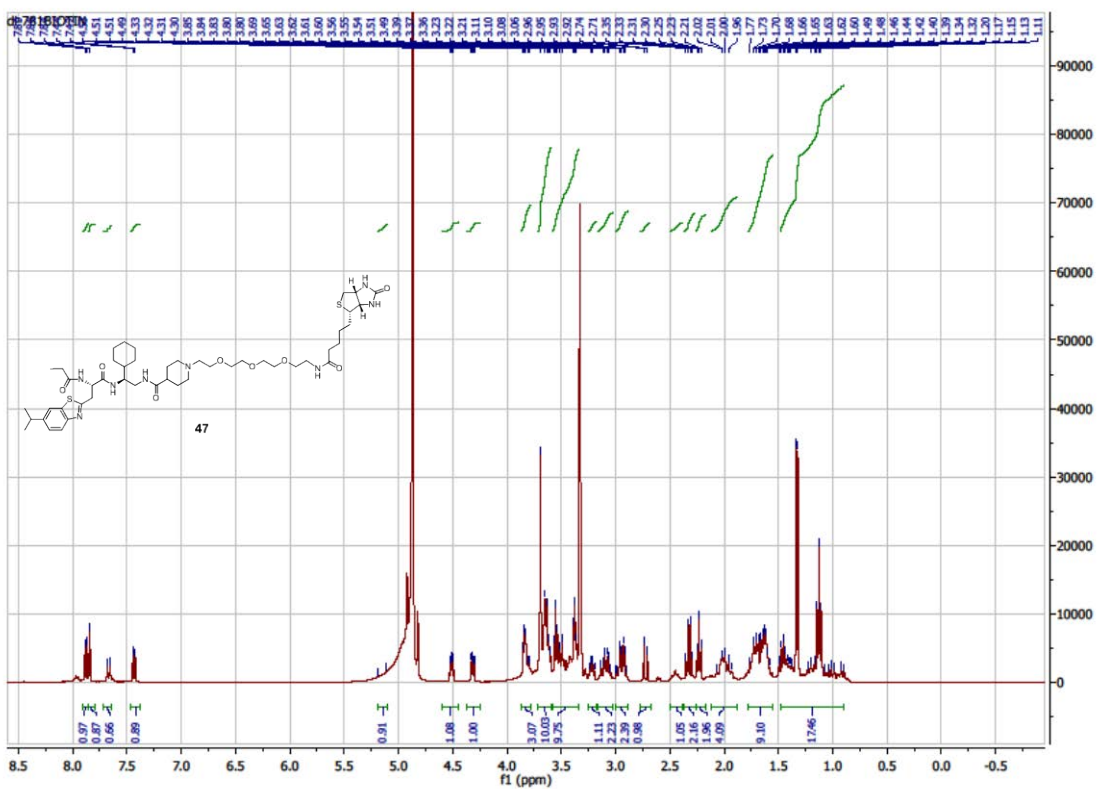
1 **Supplementary Figure 45.** ^1H NMR for Compound **46**.



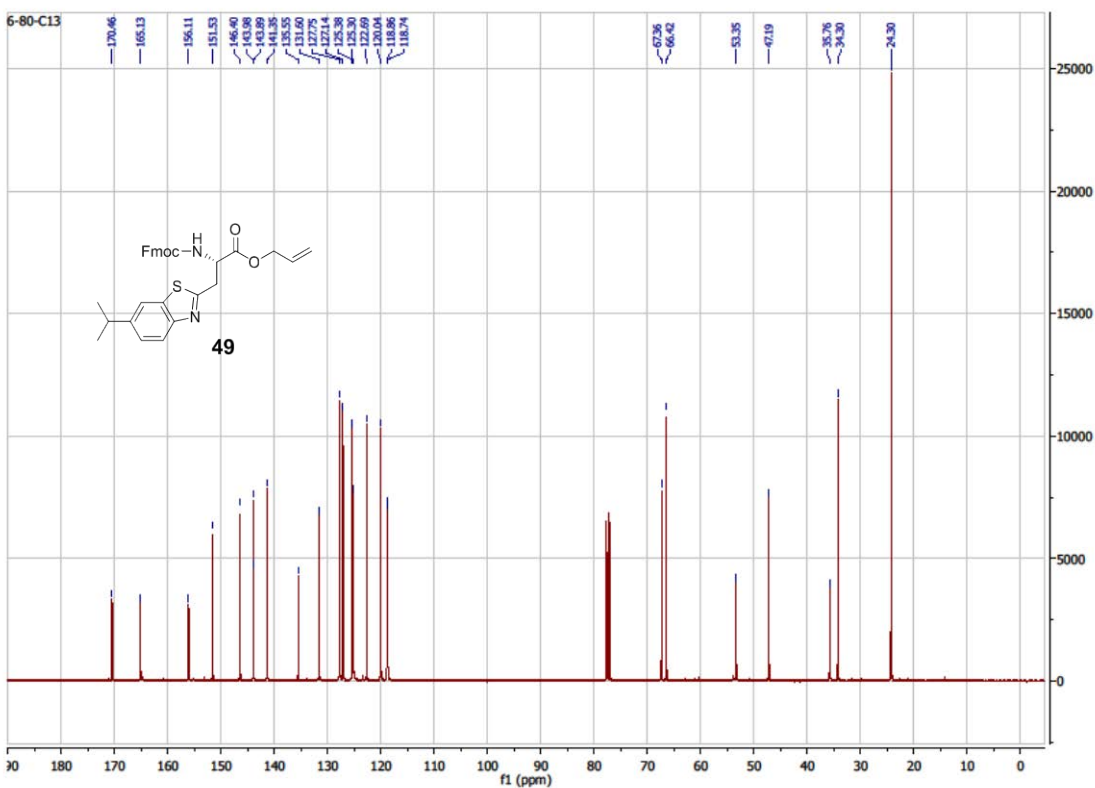
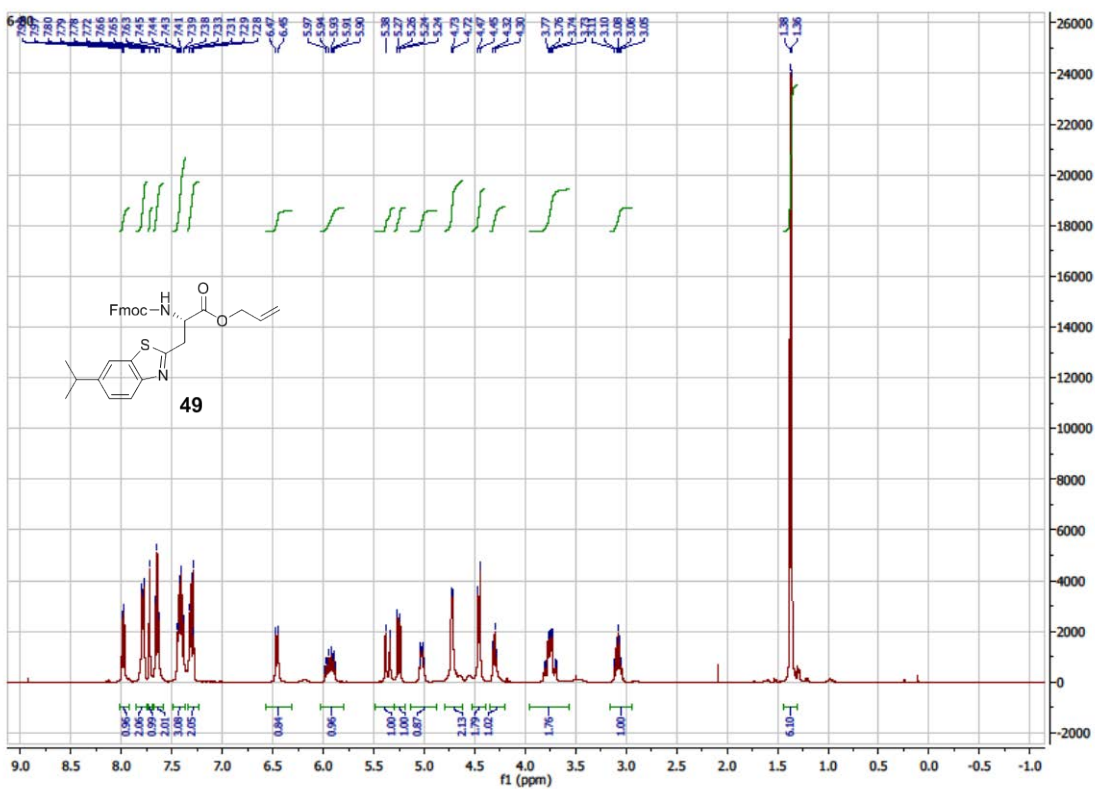
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3

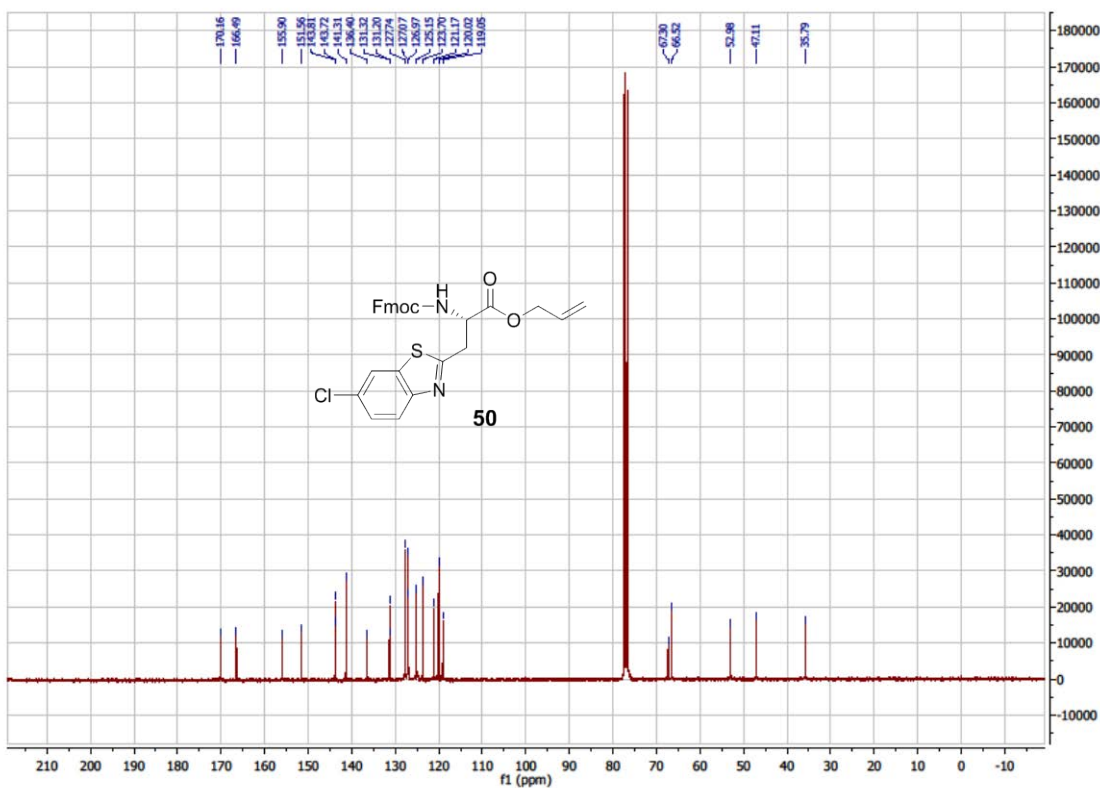
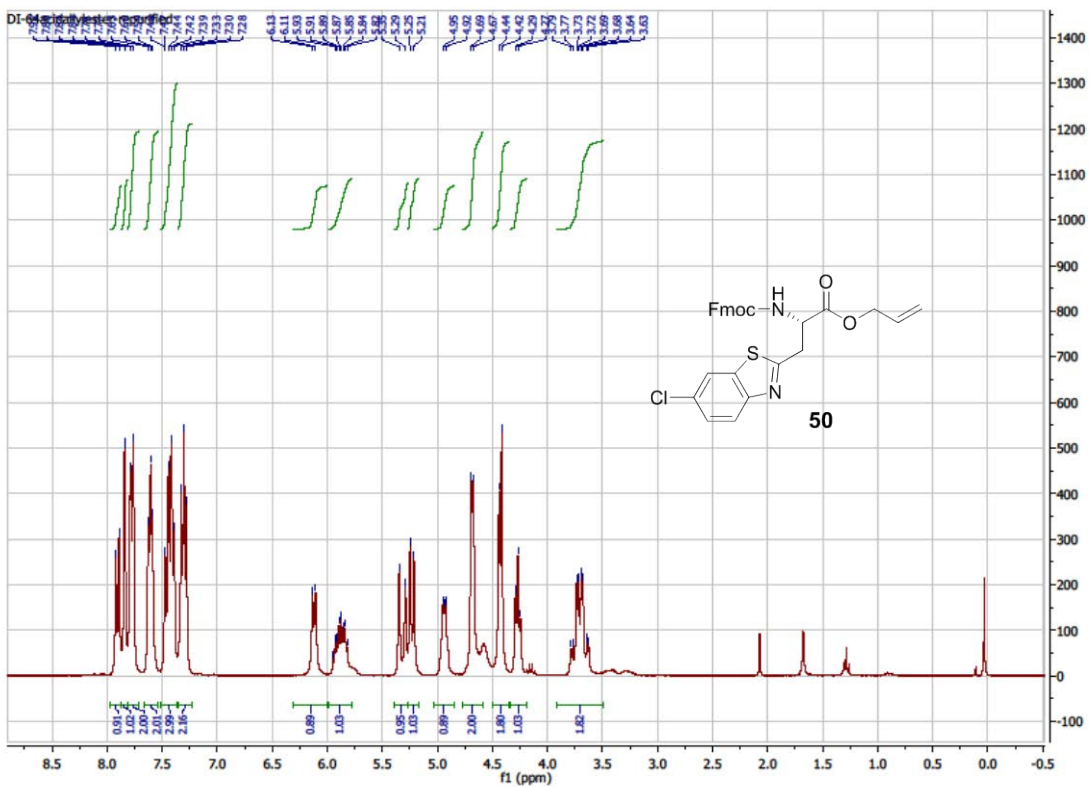
1 **Supplementary Figure 46.** ^1H NMR for Compound 47.



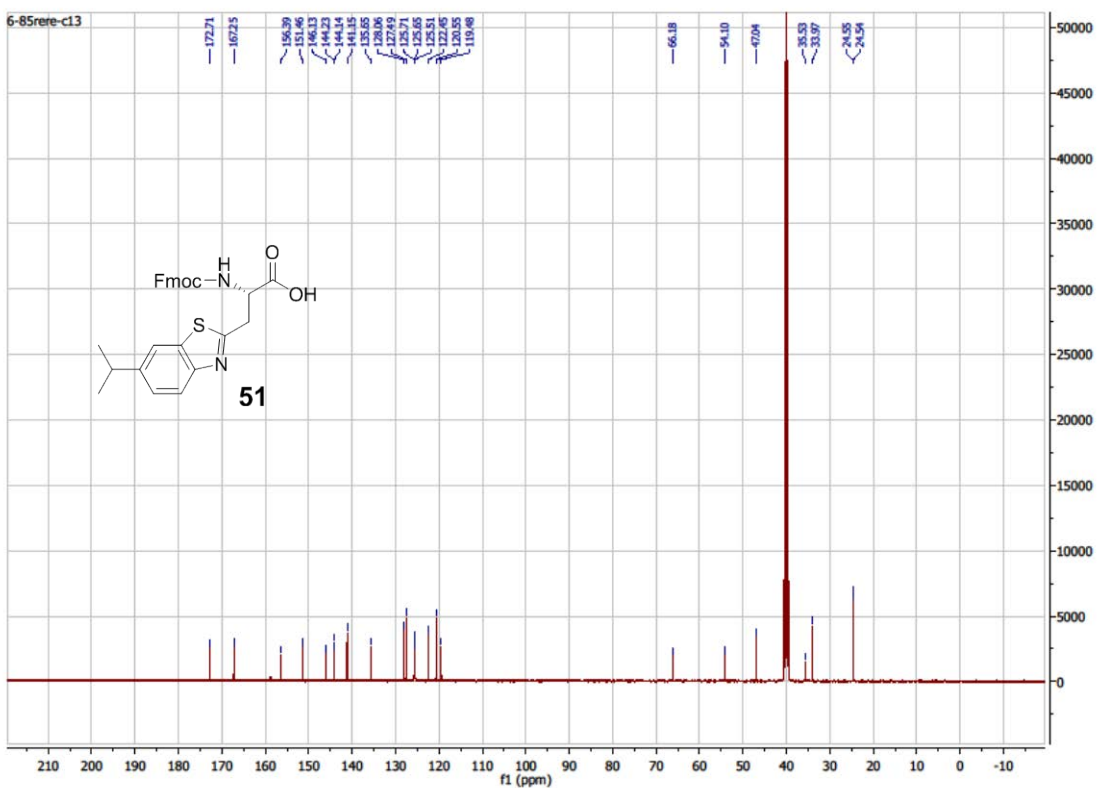
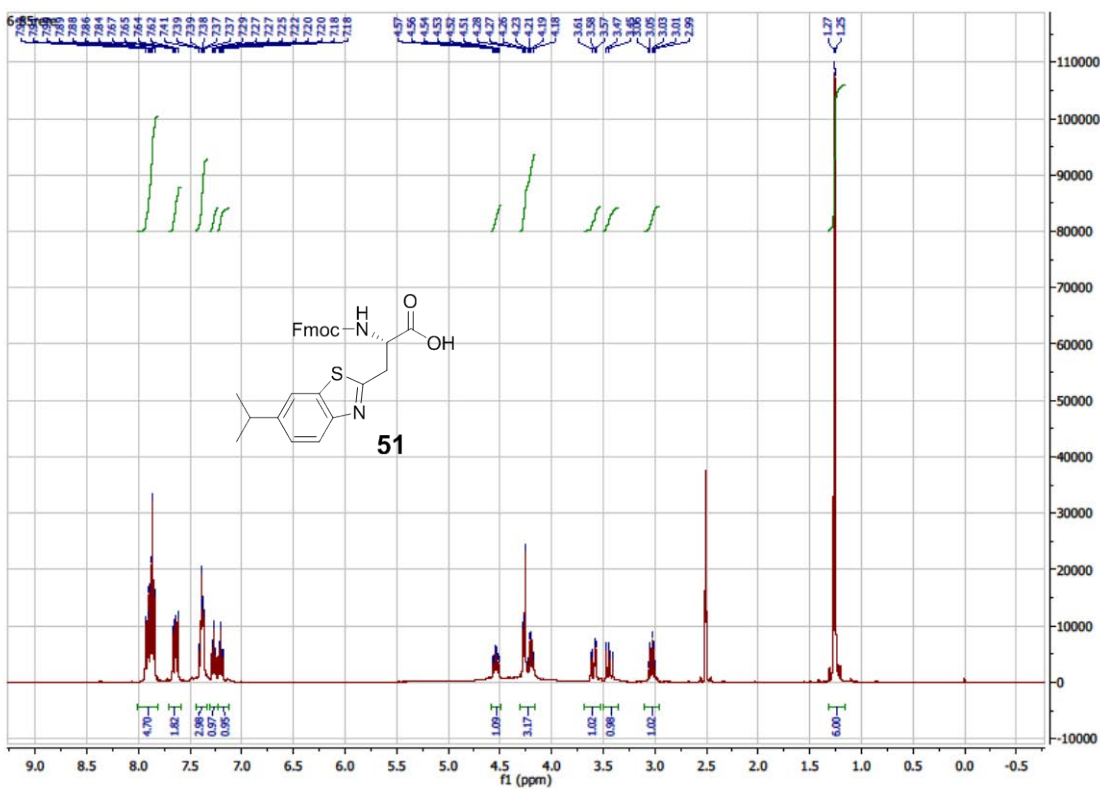
1 **Supplementary Figure 47.** ^1H NMR and ^{13}C NMR for Compound **49**.



1 **Supplementary Figure 48.** ^1H NMR and ^{13}C NMR for Compound **50**.



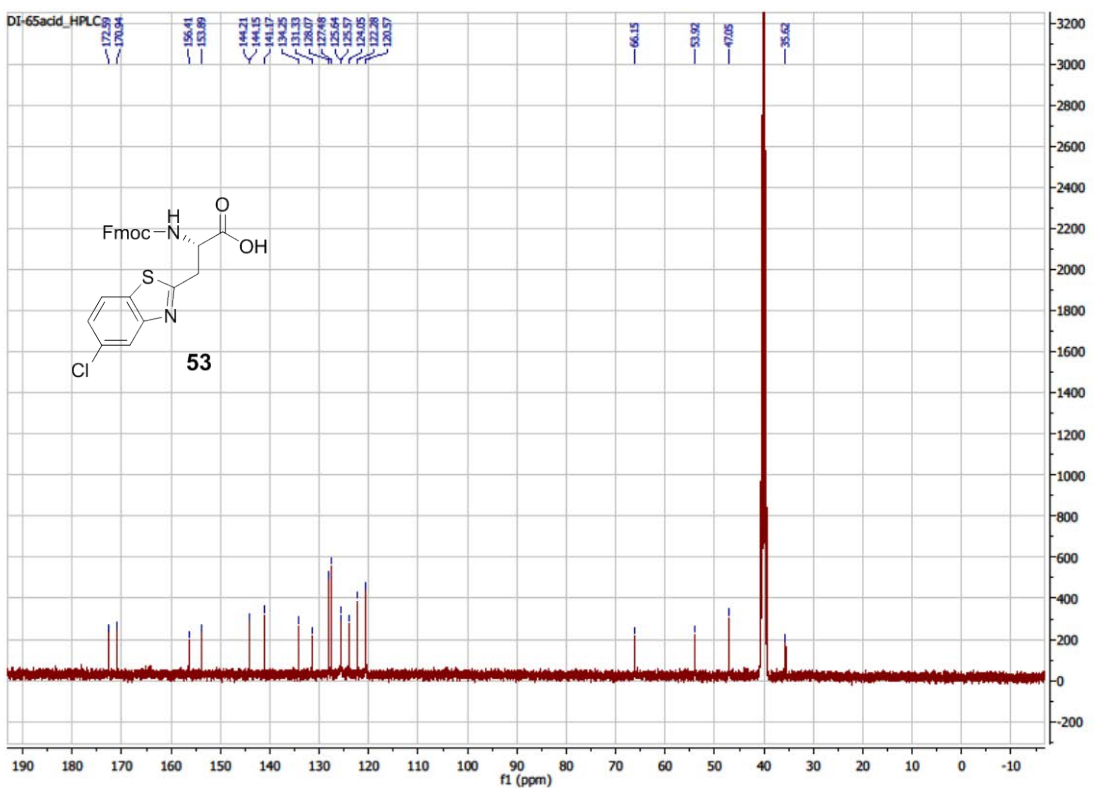
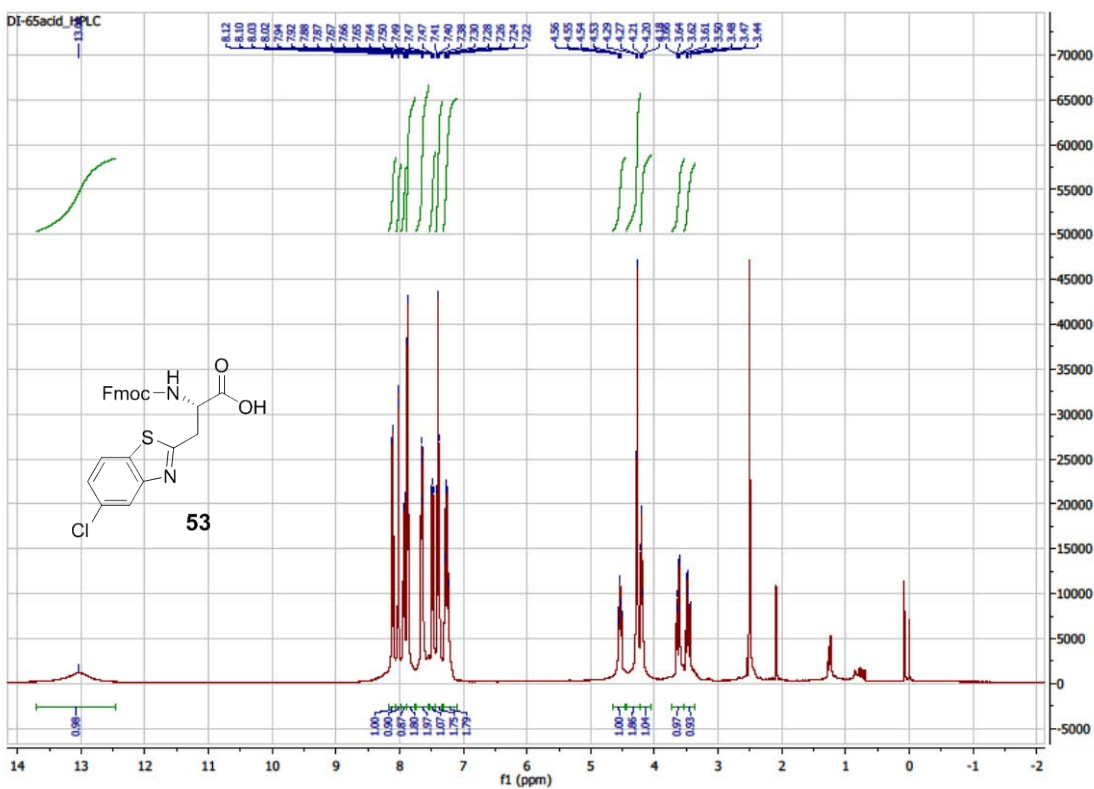
1 **Supplementary Figure 49.** ^1H NMR and ^{13}C NMR for Compound 51.



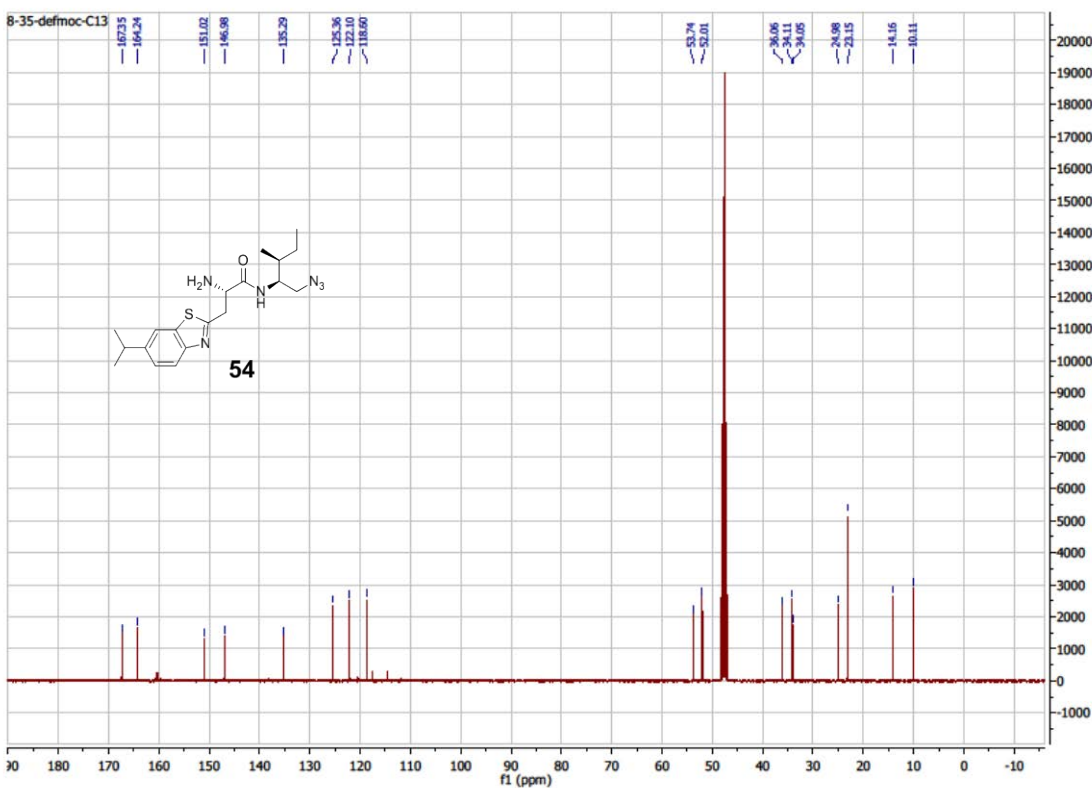
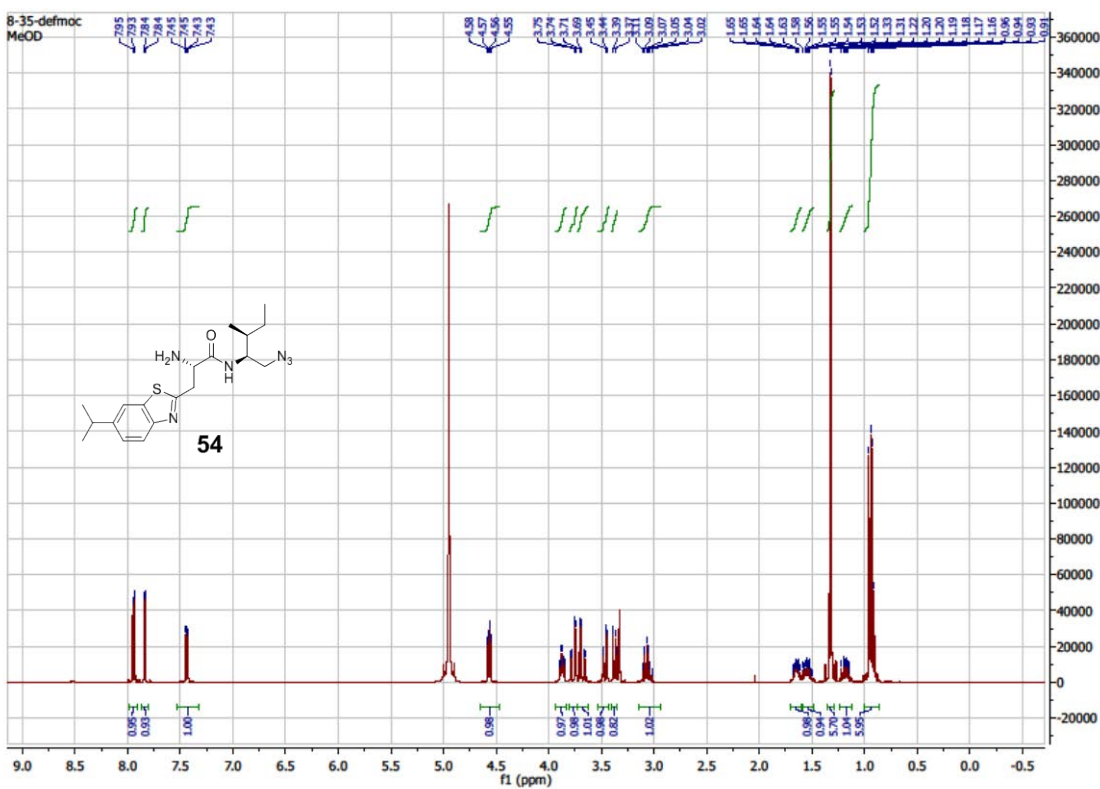
2



1 **Supplementary Figure 51.** ^1H NMR and ^{13}C NMR for Compound 53.



1 **Supplementary Figure 52.** ^1H NMR and ^{13}C NMR for Compound 54.



2



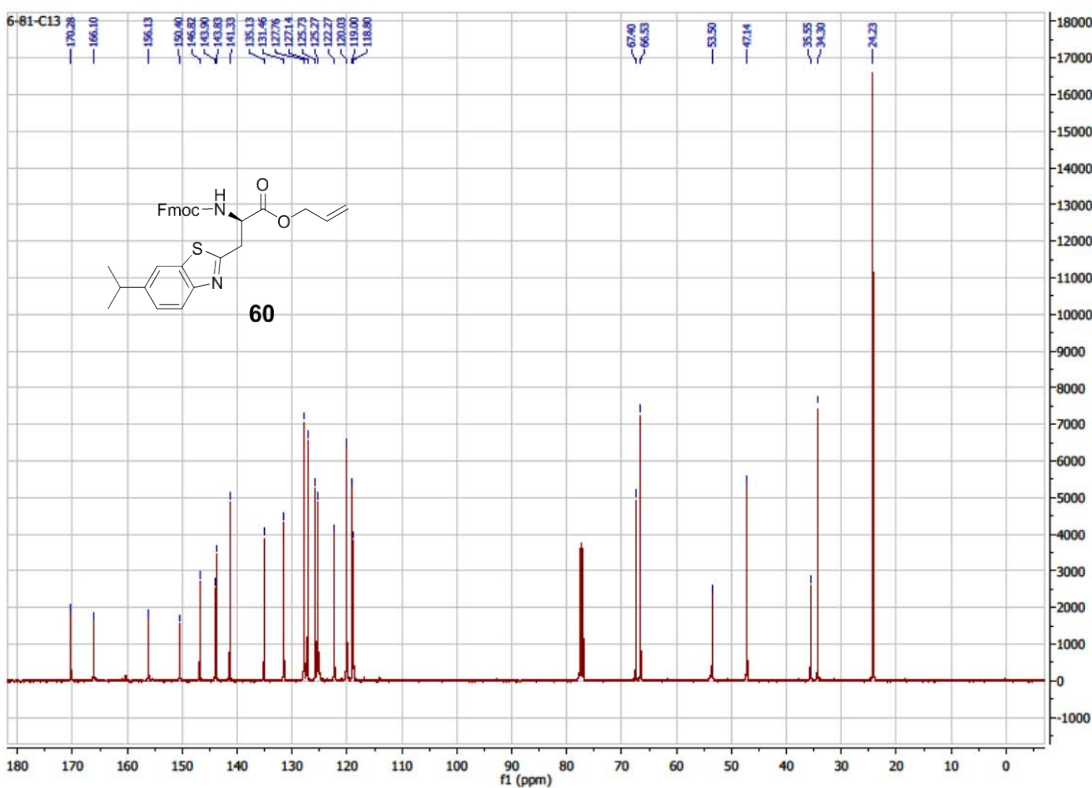
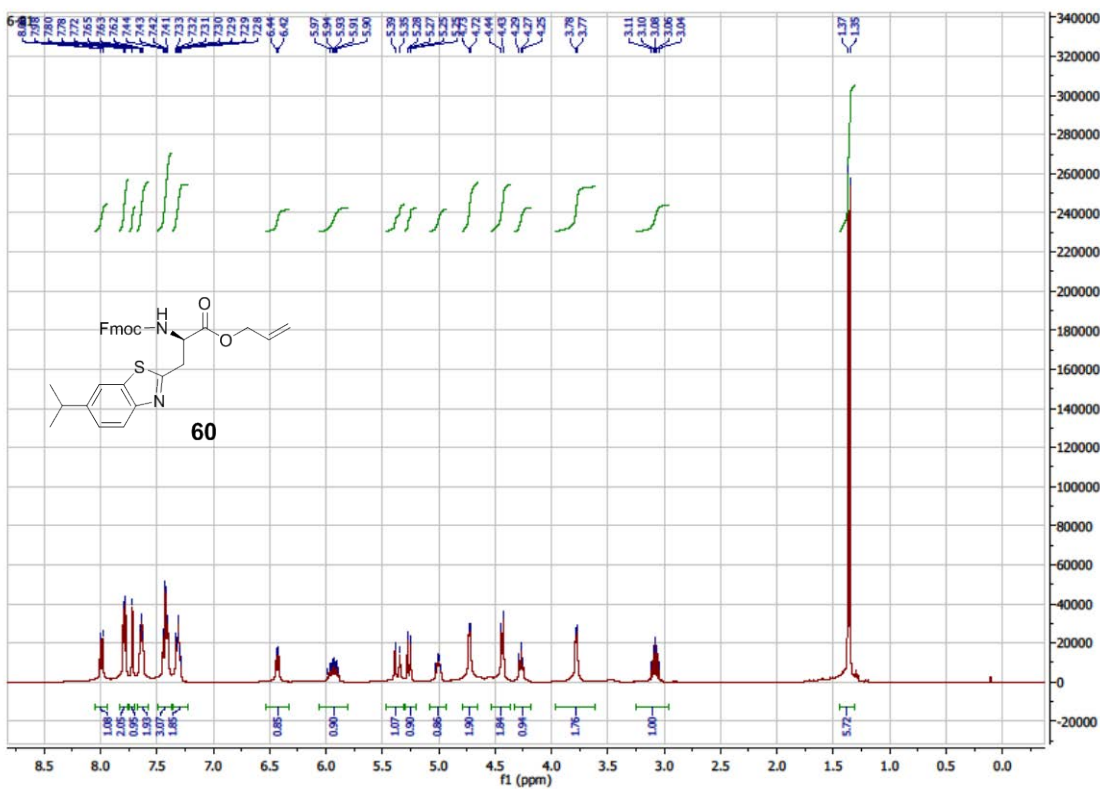
2



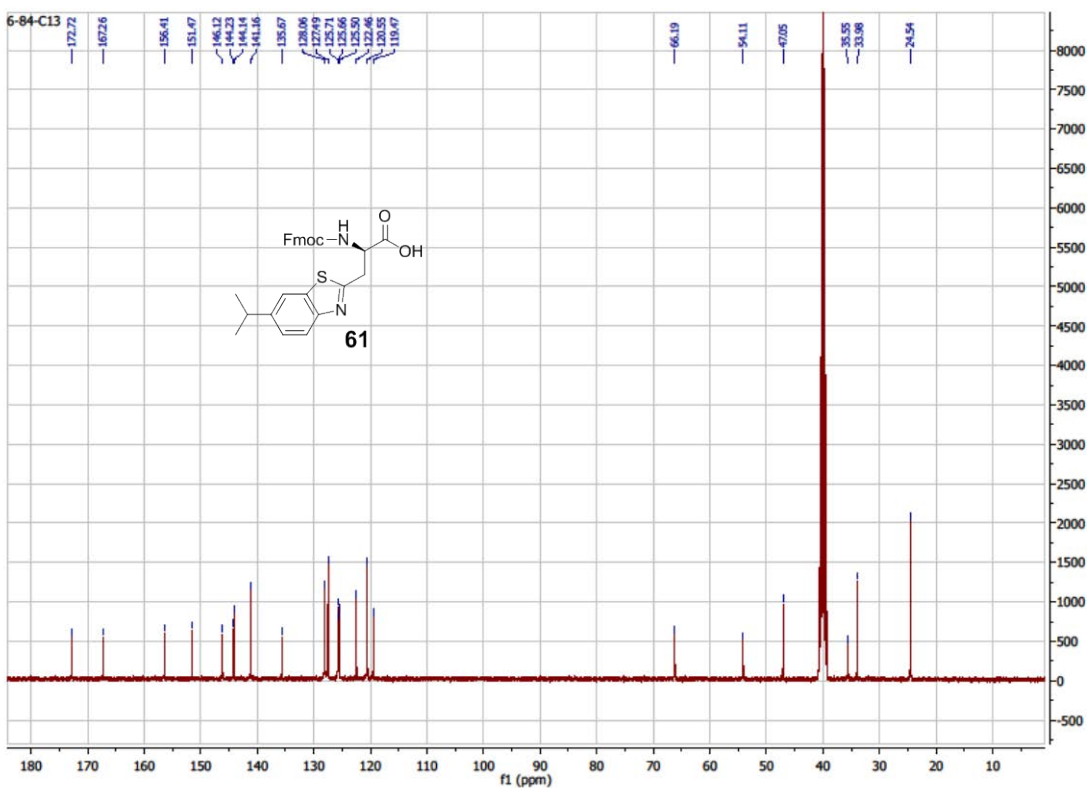
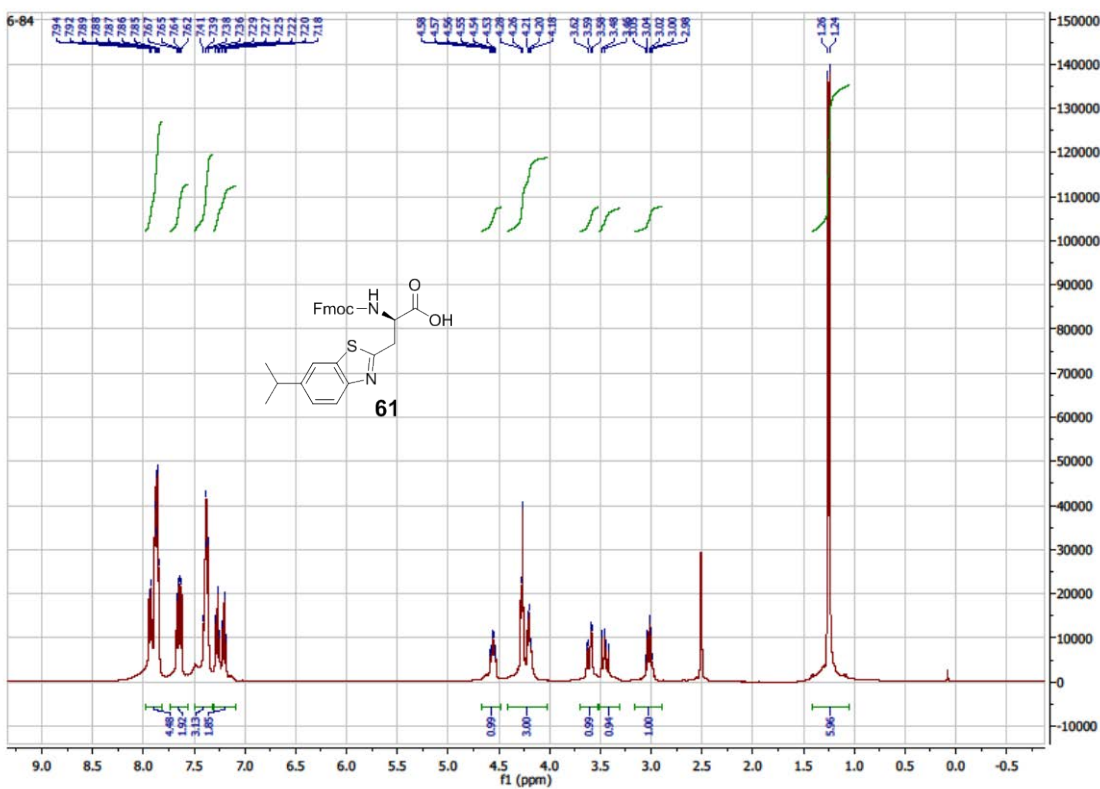
2



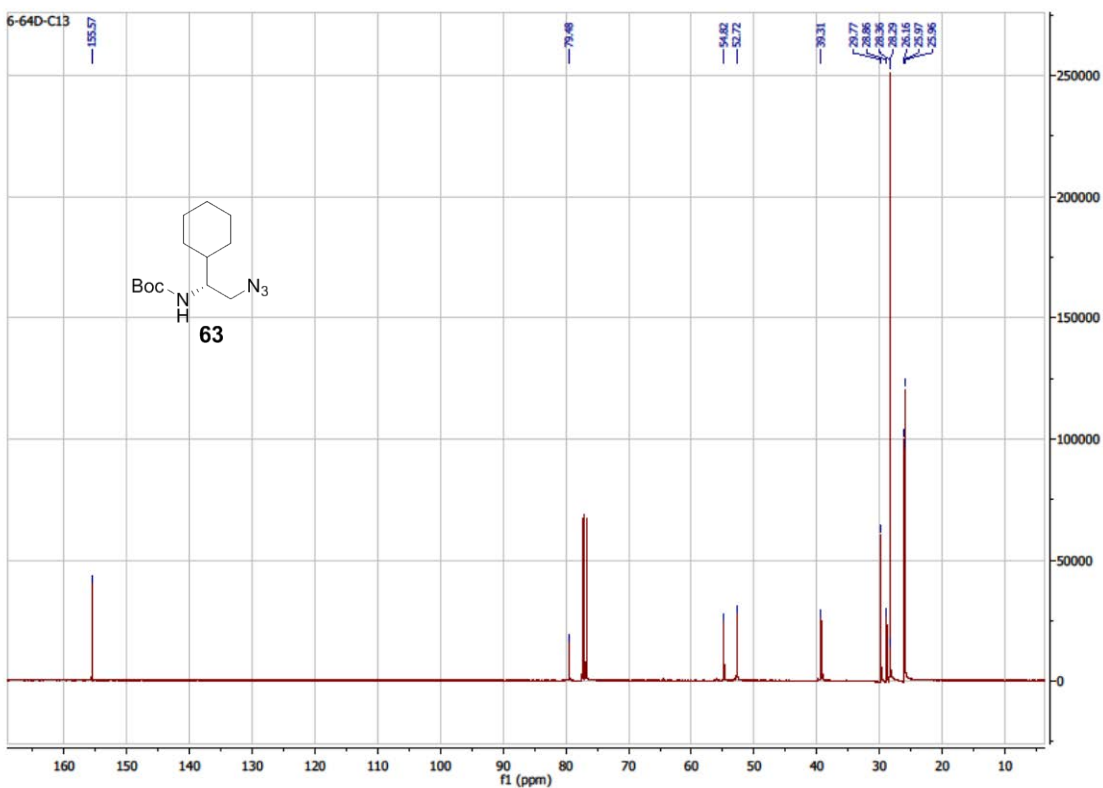
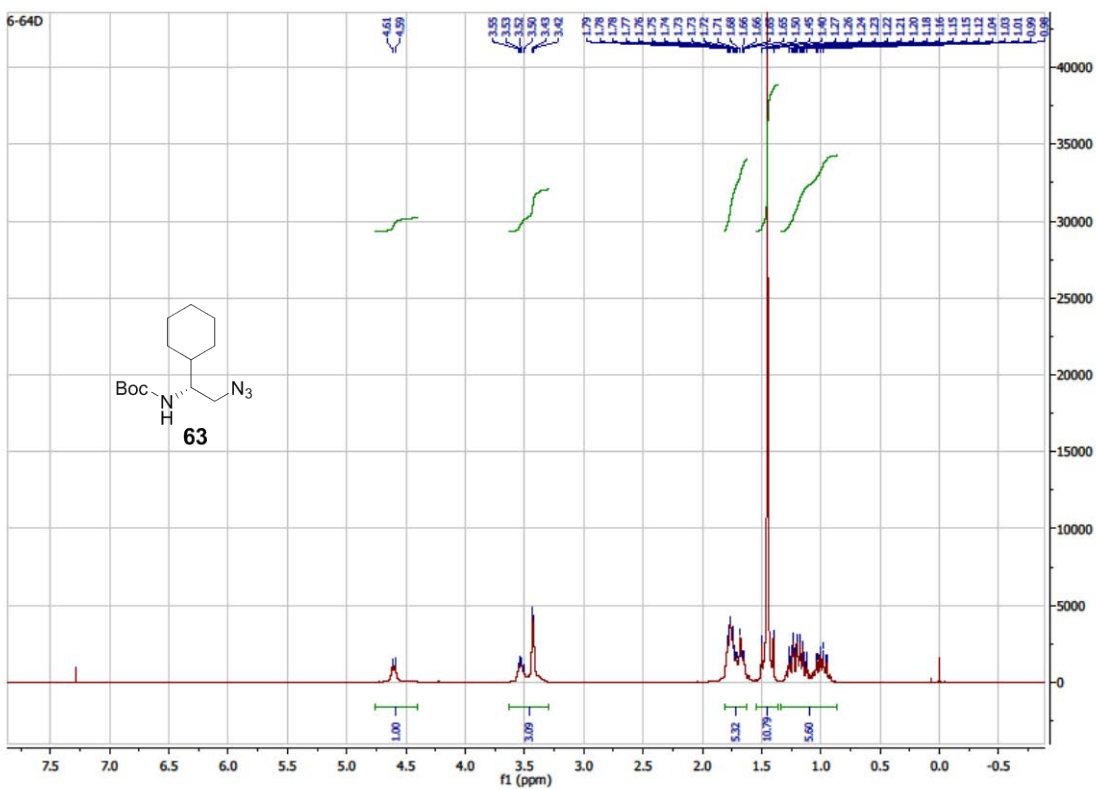
1 **Supplementary Figure 56.** ^1H NMR and ^{13}C NMR for Compound **60**.



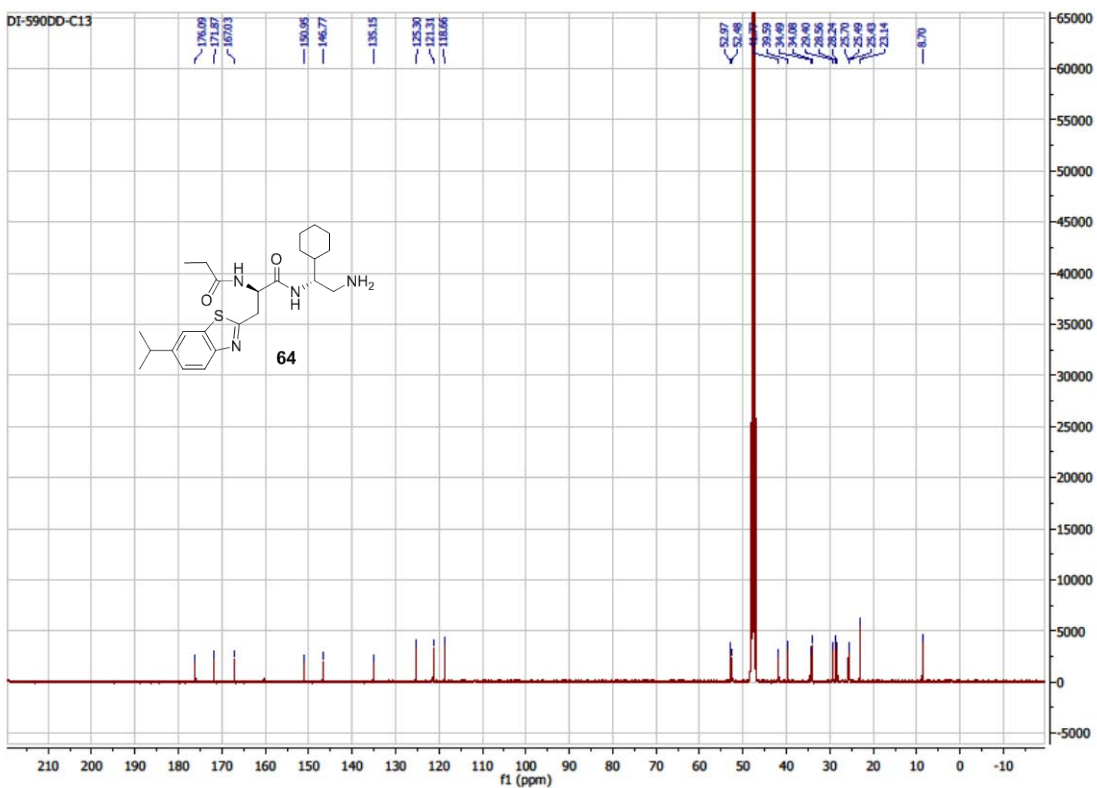
1 **Supplementary Figure 57.** ^1H NMR and ^{13}C NMR for Compound **61**.



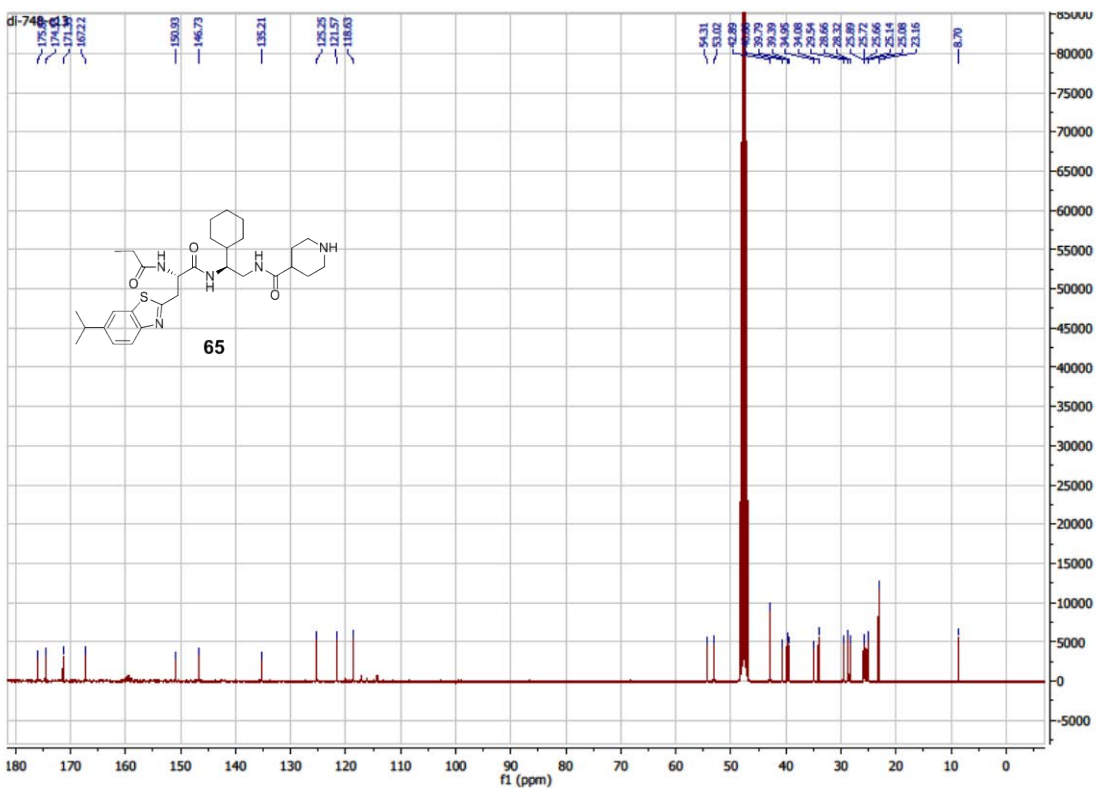
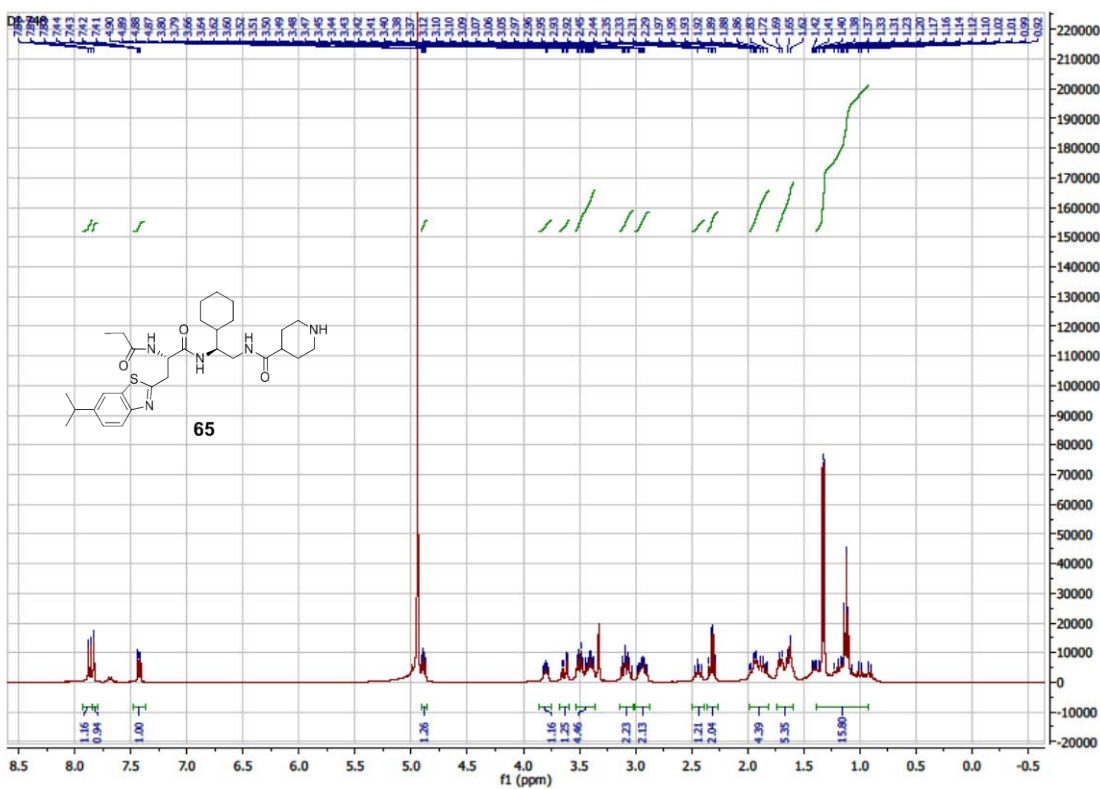
1 **Supplementary Figure 58.** ^1H NMR and ^{13}C NMR for Compound **63**.



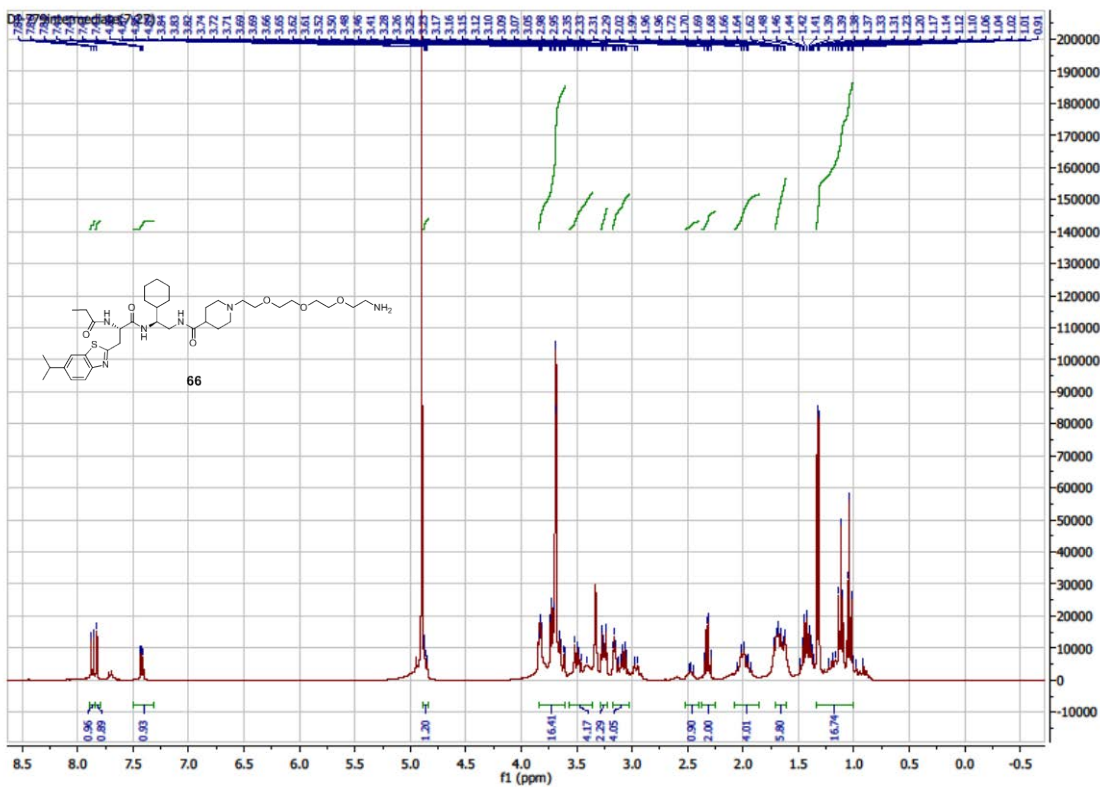
2



1 **Supplementary Figure 60.** ^1H NMR and ^{13}C NMR for Compound 65.



1 **Supplementary Figure 61.** ^1H NMR for Compound **66**.



2

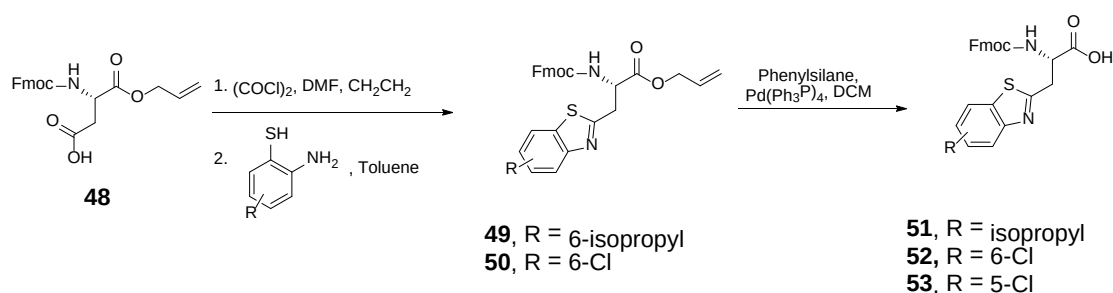
3

Supplementary Methods:

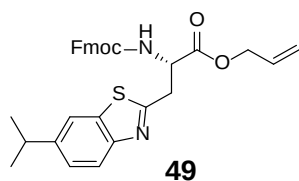
General Information

Unless otherwise noted, all reagents and solvents were used as supplied without further purification and the reactions were performed under nitrogen atmosphere in anhydrous solvents. The final products were purified by a reverse phase HPLC (RP-HPLC) with solvent A (0.1% of TFA in water) and solvent B (0.1% of TFA in CH₃CN) as eluents. The purity was determined by Waters ACQUITY UPLC and all the final compounds were > 95% pure. ¹H-NMR, ¹³C-NMR spectra of the synthetic compounds were acquired at a proton frequency of 300 or 400 MHz and chemical shifts are reported in parts per million (ppm) relative to an internal standard. High resolution mass spectra (HRMS) were obtained from Agilent Q-TOF Electrospray mass spectrometer and low resolution mass spectra analyses were determined by Waters ACQUITY UPLC-MS or by a Thermo-Scientific LCQ Fleet mass spectrometer.

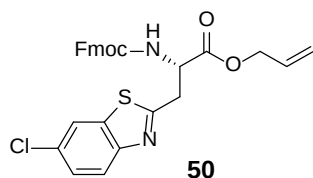
Synthesis of intermediates 51-53:



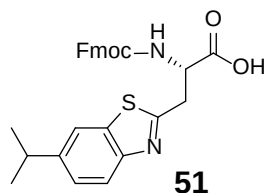
Compounds **49** and **50** were afforded by transforming the carboxylic acid of compound **48** to benzothiazoles. A reported method¹ was employed for forming the benzothiazole ring.



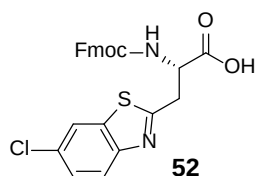
Allyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-isopropylbenzo[d]thiazol-2-yl)propanoate (49): To a solution of (S)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(allyloxy)-4-oxobutanoic acid (**48**, 5 g, 12.6 mmol) in CH₂Cl₂ (300 mL), oxalyl chloride (3.3 mL, 38.0 mmol) and catalytic amounts of DMF were added at 0°C. The reaction mixture was concentrated after being stirred for 0.5 h. The residue was suspended in toluene (250 mL) and treated with 2-amino-5-isopropylbenzenethiol (2.1 g, 12.6 mmol). The resultant mixture was stirred overnight at room temperature. The solution was diluted with EtOAc and washed with saturated sodium bicarbonate, 1.0 M HCl, brine and dried over sodium sulfate. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel to afford intermediate **49** (3.5 g, 53%). ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.86 – 7.75 (m, 2H), 7.72 (s, 1H), 7.65 (t, *J* = 7.1 Hz, 2H), 7.49 – 7.36 (m, 3H), 7.33-7.27 (m, 2H), 6.46 (d, *J* = 8.5 Hz, 1H), 5.98-5.88 (m, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.25 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.02 (dt, *J* = 8.5, 5.3 Hz, 1H), 4.72 (d, *J* = 4.9 Hz, 2H), 4.46 (d, *J* = 7.3 Hz, 2H), 4.30 (t, *J* = 7.3 Hz, 1H), 3.75 (qd, *J* = 15.7, 5.3 Hz, 2H), 3.08 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 170.46, 165.13, 156.11, 151.53, 146.40, 143.98, 143.89, 141.35, 135.55, 131.60, 127.75, 127.14, 125.38, 125.30, 122.69, 120.04, 118.86, 118.74, 67.36, 66.42, 53.35, 47.19, 35.76, 34.30, 24.30. UPLC-MS (ESI-MS) *m/z*: calculated for C₃₁H₃₁N₂O₄S⁺ 527.20, found 527.26 [M+H]⁺.



Allyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chlorobenzo[d]thiazol-2-yl)propanoate (50): Intermediate **50** was prepared in 46% yield by a similar procedure as that for **49**. ¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 1.4 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 2H), 7.67 – 7.54 (m, 2H), 7.52 – 7.37 (m, 3H), 7.36 – 7.22 (m, 2H), 6.12 (d, *J* = 8.1 Hz, 1H), 5.95-5.82(m, 1H), 5.32 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 10.3 Hz, 1H), 5.03 – 4.85 (m, 1H), 4.68 (d, *J* = 5.1 Hz, 2H), 4.43 (d, *J* = 7.1 Hz, 2H), 4.27 (t, *J* = 7.0 Hz, 1H), 3.71 (qd, *J* = 15.8, 4.9 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 170.16, 166.49, 155.90, 151.56, 143.72, 141.31, 136.40, 131.32, 131.20, 127.74, 127.07, 126.97, 125.15, 123.70, 121.17, 120.02, 119.05, 67.30, 66.52, 52.98, 47.11, 35.79.

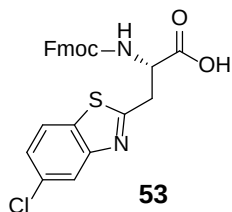


(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-isopropylbenzo[d]thiazol-2-yl)propanoic acid (51): Phenylsilane (1.9 g, 17.1 mmol) was added to a solution of **49** (3.0 g, 5.7 mmol) and Tetrakis(triphenylphosphine)palladium(0) (658 mg, 0.57mmol) in DCM. The resultant solution was stirred 1 h before being concentrated. The residue was purified by flash chromatography on silica gel to afford **51** (2.24 g, 81%). ¹H NMR (400 MHz, DMSO) δ 8.01 – 7.82 (m, 5H), 7.64 (dd, *J* = 11.7, 7.6 Hz, 2H), 7.41-7.37 (m, 3H), 7.29-7.25 (m, 1H), 7.23 – 7.13 (m, 1H), 4.57-4.51 (m, 1H), 4.30 – 4.16 (m, 3H), 3.60 (dd, *J* = 15.1, 4.6 Hz, 1H), 3.44 (dd, *J* = 15.0, 9.9 Hz, 1H), 3.03 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). ¹³C NMR (101 MHz, DMSO) δ 172.71, 167.25, 156.39, 151.46, 146.13, 144.23, 144.14, 141.15, 135.65, 128.06, 127.49, 125.71, 125.65, 125.51, 122.45, 120.55, 119.48, 66.18, 54.10, 47.04, 35.53, 33.97, 24.55, 24.54. UPLC-MS (ESI-MS) *m/z*: calculated for C₂₈H₂₇N₂O₄S⁺ 487.17, found 487.19 [M+H]⁺.



(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chlorobenzo[d]thiazol-2-

yl)propanoic acid (52): Intermediate **52** was prepared from **50** in 79% yield by a similar procedure as that for **51**. ^1H NMR (300 MHz, $\text{CD}_3\text{OD}:\text{CCl}_3\text{D}=1:10$) δ 7.84 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.57-7.54 (m, 2H), 7.43 – 7.30 (m, 3H), 7.24 (t, J = 7.4 Hz, 2H), 4.95 – 4.66 (m, 1H), 4.45 – 4.25 (m, 2H), 4.19 (t, J = 7.0 Hz, 1H), 3.67-3.64 (m, 2H). ^{13}C NMR (75 MHz, $\text{CD}_3\text{OD}:\text{CCl}_3\text{D}=1:10$) δ 172.19, 167.48, 156.13, 151.13, 143.72, 143.66, 141.24, 136.32, 131.19, 127.68, 127.02, 126.96, 125.06, 123.37, 121.15, 119.93, 67.15, 52.92, 47.03, 35.67. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{25}\text{H}_{20}\text{ClN}_2\text{O}_4\text{S}^+$ 479.08, found 479.19 $[\text{M}+\text{H}]^+$.



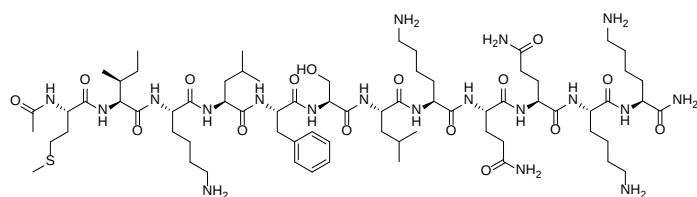
(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(5-chlorobenzo[d]thiazol-2-

yl)propanoic acid (53): Intermediate **53** was prepared from **48** in 41% yield in two steps using a similar procedure as that for **51**. ^1H NMR (400 MHz, DMSO) δ 13.04 (br, 1H), 8.11 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.67-7.94 (m, 2H), 7.48 (dd, J = 8.6, 2.0 Hz, 1H), 7.41-7.38 (m, 2H), 7.30-7.22 (m, 2H), 4.54 (td, J = 9.5, 4.6 Hz, 1H), 4.29 – 4.27 (m, 2H), 4.20 (t, J = 6.8 Hz, 1H), 3.63 (dd, J = 15.2, 4.5 Hz, 1H), 3.47 (dd, J = 15.1, 9.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 172.59, 170.94, 156.41, 153.89,

1 144.21, 144.15, 141.17, 134.25, 131.33, 128.07, 127.48, 125.64, 125.57, 124.05, 122.28, 120.57,
2 66.15, 53.92, 47.05, 35.62. UPLC-MS (ESI-MS) m/z : calculated for $C_{25}H_{20}ClN_2O_4S^+$ 479.08,
3 found 479.22[M+H]⁺.

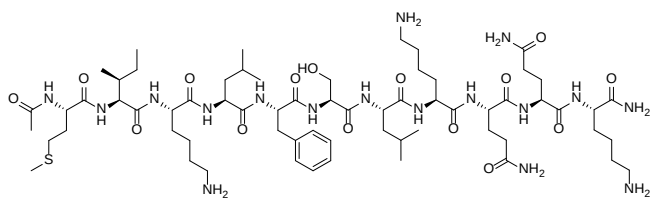
5 Solid-phase synthesis of peptides 1-29.

6 General method for synthesis of peptides 1-29: The peptides **1-29** were synthesized on an ABI
7 433 Peptide Synthesizer using Fmoc chemistry. Rink amide resin was used as the solid support
8 and the coupling reagents were HBTU (*O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium
9 hexafluorophosphate) and HOBT (1-Hydroxybenzotriazole hydrate). The crude peptides were cleaved
10 from the resin by cleavage cocktail (TFA:TES:H₂O, 18 mL:0.5 mL:1 mL), which also led to
11 removal of the protecting groups. The solution containing the cleaved peptides was evaporated
12 and purified by RP-HPLC to give peptides **1-29**.



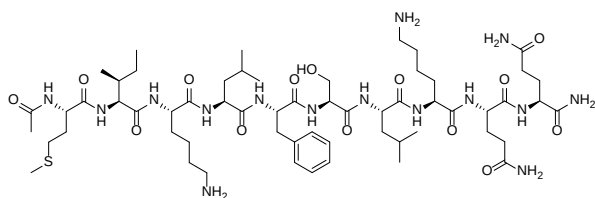
14 **1**

15 **(S)-2-((5S,8S,11S,14S,17S,20S,23S,26S)-5-acetamido-11,26-bis(4-aminobutyl)-17-benzyl-8-**
16 **((S)-sec-butyl)-20-(hydroxymethyl)-14,23-diisobutyl-6,9,12,15,18,21,24-hepta-2-thia-**
17 **7,10,13,16,19,22,25-heptaazaheptacosan-27-amido)-N1-((S)-5-amino-1-(((S)-6-amino-1-**
18 **(((S)-1,6-diamino-1-oxohexan-2-yl)amino)-1-oxohexan-2-yl)amino)-1,5-dioxopentan-2-**
19 **yl)pentanediamide (1):** HRMS (ESI-MS) m/z : calculated for $C_{71}H_{127}N_{19}O_{16}S^{2+}$ 766.9709, found
20 766.9711 [M+2H]²⁺.



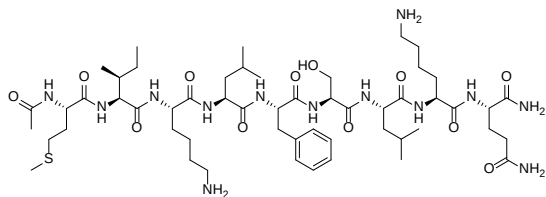
2

(S)-2-((5S,8S,11S,14S,17S,20S,23S,26S)-5-acetamido-11,26-bis(4-aminobutyl)-17-benzyl-8-((S)-sec-butyl)-20-(hydroxymethyl)-14,23-diisobutyl-6,9,12,15,18,21,24-heptaoxo-2-thia-7,10,13,16,19,22,25-heptaazaheptacosan-27-amido)-N1-(((S)-5-amino-1-(((S)-1,6-diamino-1-oxohexan-2-yl)amino)-1,5-dioxopentan-2-yl)pentanediamide (2): HRMS (ESI-MS) m/z : calculated for $C_{65}H_{114}N_{17}O_{15}S^+$ 1404.8396, found 1404.8443 $[M+H]^+$.



3

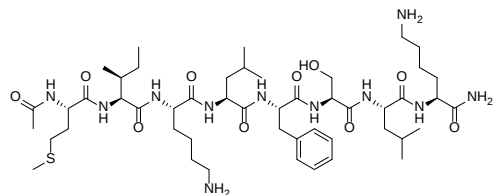
(S)-2-((5S,8S,11S,14S,17S,20S,23S,26S)-5-acetamido-11,26-bis(4-aminobutyl)-17-benzyl-8-((S)-sec-butyl)-20-(hydroxymethyl)-14,23-diisobutyl-6,9,12,15,18,21,24-heptaoxo-2-thia-7,10,13,16,19,22,25-heptaazaheptacosan-27-amido)-N1-((S)-1,5-diamino-1,5-dioxopentan-2-yl)pentanediamide (3): HRMS (ESI-MS) m/z : calculated for $C_{59}H_{102}N_{15}O_{14}S^+$ 1276.7446, found 1276.7440 $[M+H]^+$.



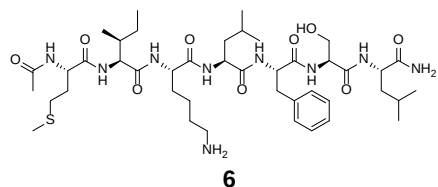
4

(S)-2-((5S,8S,11S,14S,17S,20S,23S,26S)-5-acetamido-11,26-bis(4-aminobutyl)-17-benzyl-8-((S)-sec-butyl)-20-(hydroxymethyl)-14,23-diisobutyl-6,9,12,15,18,21,24-heptaoxo-2-thia-7,10,13,16,19,22,25-

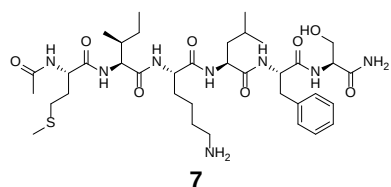
heptaazaheptacosan-27-amido)pentanediamide (4): HRMS (ESI-MS) m/z : calculated for $C_{54}H_{94}N_{13}O_{12}S^+$ 1148.6860, found 1148.6858 $[M+H]^+$.



(S)-2-((2S,3S)-2-((S)-2-acetamido-4-(methylthio)butanamido)-3-methylpentanamido)-6-amino-N-((4S,7S,10S,13S,16S)-20-amino-7-benzyl-16-carbamoyl-10-(hydroxymethyl)-13-isobutyl-2-methyl-5,8,11,14-tetraoxo-6,9,12,15-tetraazaicosan-4-yl)hexanamide (5): HRMS (ESI-MS) m/z : calculated for $C_{49}H_{86}N_{11}O_{10}S^+$ 1020.6274, found 1020.6273 $[M+H]^+$.

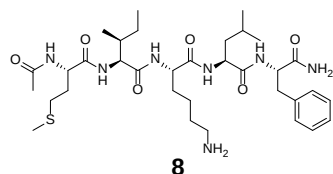


(S)-2-((2S,3S)-2-((S)-2-acetamido-4-(methylthio)butanamido)-3-methylpentanamido)-6-amino-N-(((S)-1-(((S)-1-(((S)-1-(((S)-1-amino-4-methyl-1-oxopentan-2-yl)amino)-3-hydroxy-1-oxopropan-2-yl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)hexanamide (6): UPLC-MS (ESI-MS) m/z : calculated for $C_{43}H_{74}N_9O_9S^+$ 892.5325, found 892.5324 $[M+H]^+$.

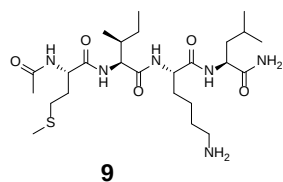


(S)-2-((2S,3S)-2-((S)-2-acetamido-4-(methylthio)butanamido)-3-methylpentanamido)-6-amino-N-(((S)-1-(((S)-1-(((S)-1-amino-3-hydroxy-1-oxopropan-2-yl)amino)-1-oxo-3-phenylpropan-2-

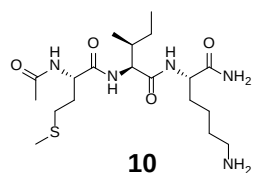
yl)amino)-4-methyl-1-oxopentan-2-yl)hexanamide (7): HRMS (ESI-MS) m/z : calculated for $C_{37}H_{63}N_8O_8S^+$ 779.4484, found 779.4488 $[M+H]^+$.



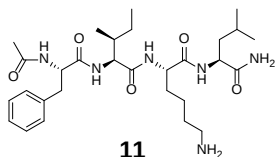
(S)-2-((2S,3S)-2-((S)-2-acetamido-4-(methylthio)butanamido)-3-methylpentanamido)-6-amino-N-((S)-1-(((S)-1-amino-1-oxo-3-phenylpropan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)hexanamide (8): HRMS (ESI-MS) m/z : calculated for $C_{34}H_{58}N_7O_6S^+$ 692.4164, found 692.4164 $[M+H]^+$.



(S)-2-((2S,3S)-2-((S)-2-acetamido-4-(methylthio)butanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (9): HRMS (ESI-MS) m/z : calculated for $C_{25}H_{49}N_6O_5S^+$ 545.3480, found 545.3481 $[M+H]^+$.

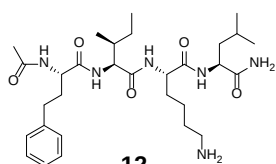


(S)-2-((2S,3S)-2-((S)-2-acetamido-4-(methylthio)butanamido)-3-methylpentanamido)-6-aminohexanamide (10): UPLC-MS (ESI-MS) m/z : calculated for $C_{19}H_{38}N_5O_4S^+$ 432.2639, found 432.2643 $[M+H]^+$.



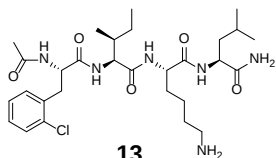
11

(S)-2-((2S,3S)-2-((S)-2-acetamido-3-phenylpropanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (11): HRMS (ESI-MS) m/z : calculated for $C_{29}H_{49}N_6O_5^+$ 561.3759, found 561.3760 $[M+H]^+$.



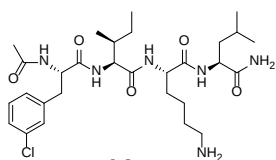
12

(S)-2-((2S,3S)-2-((S)-2-acetamido-4-phenylbutanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (12): HRMS (ESI-MS) m/z : calculated for $C_{30}H_{51}N_6O_5^+$ 575.3915, found 575.3918 $[M+H]^+$.



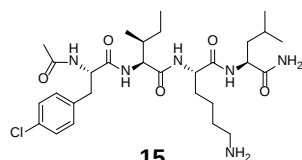
13

(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(2-chlorophenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (13): HRMS (ESI-MS) m/z : calculated for $C_{29}H_{48}ClN_6O_5^+$ 595.3369, found 595.3374 $[M+H]^+$.

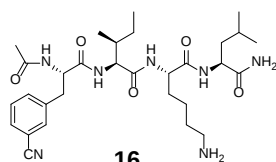


14

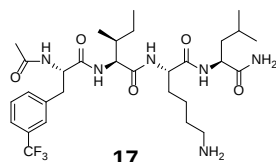
(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(3-chlorophenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (14): HRMS (ESI-MS) m/z : calculated for $C_{29}H_{48}ClN_6O_5^+$ 595.3369, found 595.3372 $[M+H]^+$.



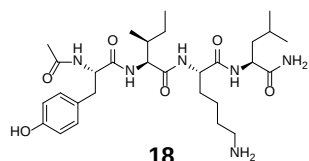
(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(4-chlorophenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (15): HRMS (ESI-MS) m/z : calculated for $C_{29}H_{48}ClN_6O_5^+$ 595.3369, found 595.3375 $[M+H]^+$.



(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(3-cyanophenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (16): HRMS (ESI-MS) m/z : calculated for $C_{30}H_{48}N_7O_5^+$ 586.3711, found 586.3713 $[M+H]^+$.

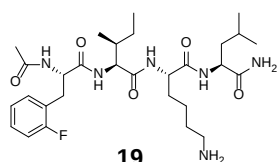


(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(3-(trifluoromethyl)phenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (17): HRMS (ESI-MS) m/z : calculated for $C_{30}H_{48}F_3N_6O_5^+$ 629.3633, found 629.3636 $[M+H]^+$.



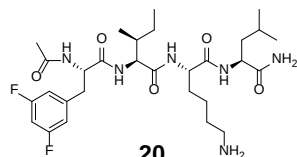
18

(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(4-hydroxyphenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (18): HRMS (ESI-MS) m/z : calculated for $C_{29}H_{49}N_6O_6^+$ 577.3708, found 577.3713 $[M+H]^+$.



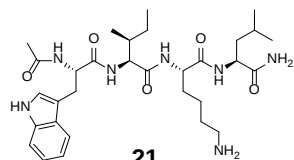
19

(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(2-fluorophenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (19): HRMS (ESI-MS) m/z : calculated for $C_{29}H_{48}FN_6O_5^+$ 579.3665, found 579.3671 $[M+H]^+$.



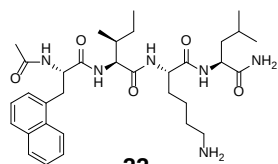
20

(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(3,5-difluorophenyl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (20): HRMS (ESI-MS) m/z : calculated for $C_{29}H_{47}F_2N_6O_5^+$ 597.3571, found 597.3570 $[M+H]^+$.

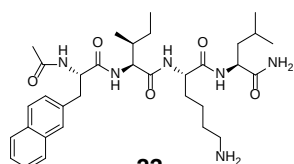


21

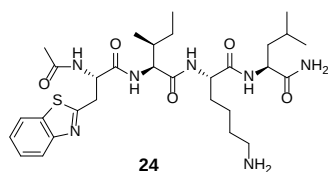
(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(1H-indol-3-yl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (21): HRMS (ESI-MS) m/z : calculated for $C_{31}H_{50}N_7O_5^+$ 600.3868, found 600.3867 $[M+H]^+$.



(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(naphthalen-1-yl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (22): HRMS (ESI-MS) m/z : calculated for $C_{33}H_{51}N_6O_5^+$ 611.3915, found 611.3916 $[M+H]^+$.

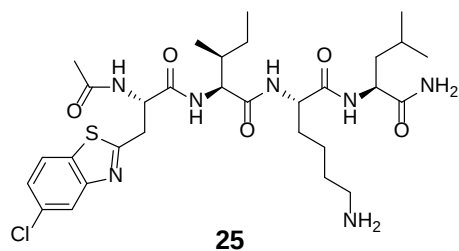


(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(naphthalen-2-yl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (23): HRMS (ESI-MS) m/z : calculated for $C_{33}H_{51}N_6O_5^+$ 611.3915, found 611.3914 $[M+H]^+$.

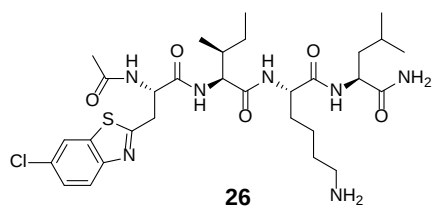


(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(benzo[d]thiazol-2-yl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (24): 1H NMR (400 MHz, MeOD) δ 7.97 (d, J = 9.0 Hz, 2H), 7.60 – 7.48 (m, 1H), 7.48 – 7.38 (m, 1H), 4.98 (dd, J = 8.5, 5.2 Hz, 1H), 4.39 (ddd, J = 12.5, 9.2, 5.6 Hz, 2H), 4.22 (d, J = 7.6 Hz, 1H), 3.65 (dd, J = 15.4, 5.2 Hz, 1H), 3.50 (dd, J = 15.4, 8.5 Hz, 1H), 2.92 (t, J = 7.4 Hz, 2H), 2.01 (s,

3H), 1.91 – 1.77 (m, 2H), 1.76 – 1.38 (m, 9H), 1.21-1.15 (m, 1H), 1.01 – 0.83 (m, 12H). ¹³C
 NMR (101 MHz, MeOD) δ 176.01, 172.18, 172.03, 171.35, 167.73, 152.61, 135.10, 126.01,
 125.09, 122.04, 121.47, 58.17, 53.04, 52.78, 51.40, 40.76, 39.11, 36.63, 34.97, 30.76, 26.52,
 24.62, 24.48, 22.15, 22.11, 21.14, 20.37, 14.51, 9.97. UPLC-MS (ESI-MS) *m/z*: calculated for
 C₃₀H₄₈N₇O₅S⁺ 618.34, found 618.29 [M+H]⁺.

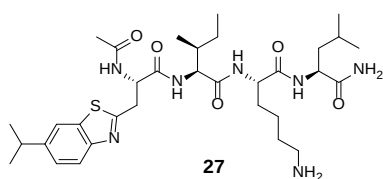


(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(5-chlorobenzo[d]thiazol-2-yl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (25):
¹H NMR (400 MHz, MeOD) δ 8.54 (d, *J* = 7.7 Hz, 1H), 8.23 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 7.0
 Hz, 2H), 7.98-7.95 (m, 2H), 7.45 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.00 – 4.95 (m, 1H), 4.48 – 4.32 (m,
 2H), 4.20 (t, *J* = 7.7 Hz, 1H), 3.65 (dd, *J* = 15.5, 5.3 Hz, 1H), 3.50 (dd, *J* = 15.5, 8.4 Hz, 1H),
 2.93 (t, *J* = 7.4 Hz, 2H), 2.01 (s, 3H), 1.91 – 1.77 (m, 2H), 1.74 – 1.39 (m, 9H), 1.20-1.12 (m,
 1H), 1.00 – 0.82 (m, 12H). ¹³C NMR (101 MHz, MeOD) δ 176.00, 172.21, 172.12, 171.97,
 171.21, 170.07, 153.57, 133.71, 131.95, 125.36, 122.63, 121.78, 58.10, 52.88, 52.71, 51.36,
 40.80, 39.13, 36.65, 35.00, 30.79, 26.55, 24.58, 24.48, 22.14, 22.10, 21.13, 20.37, 14.49, 9.95.
 UPLC-MS (ESI-MS) *m/z*: calculated for C₃₀H₄₇ClN₇O₅S⁺ 652.30, found 652.25 [M+H]⁺.



(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(6-chlorobenzo[d]thiazol-2-yl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (26):

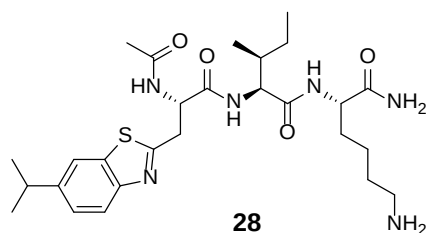
^1H NMR (400 MHz, MeOD) δ 8.53 (d, J = 7.6 Hz, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.08-8.06 (m, 2H), 8.03 (d, J = 2.0 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.52 (dd, J = 8.7, 2.1 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.50 – 4.30 (m, 2H), 4.20 (t, J = 7.7 Hz, 1H), 3.64 (dd, J = 15.5, 5.2 Hz, 1H), 3.48 (dd, J = 15.5, 8.4 Hz, 1H), 2.93 (t, J = 7.4 Hz, 2H), 2.01 (s, 3H), 1.90 – 1.78 (m, 2H), 1.75 – 1.34 (m, 9H), 1.23 – 1.09 (m, 1H), 1.06 – 0.73 (m, 12H). ^{13}C NMR (101 MHz, MeOD) δ 176.00, 172.18, 172.13, 171.96, 171.22, 168.56, 151.37, 136.58, 130.86, 126.64, 123.07, 121.14, 58.10, 52.90, 52.73, 51.36, 40.79, 39.13, 36.63, 34.92, 30.77, 26.55, 24.58, 24.47, 22.14, 22.10, 21.12, 20.36, 14.49, 9.95. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{30}\text{H}_{47}\text{ClN}_7\text{O}_5\text{S}^+$ 652.30, found 652.28 $[\text{M}+\text{H}]^+$.



(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(6-isopropylbenzo[d]thiazol-2-yl)propanamido)-3-methylpentanamido)-6-amino-N-((S)-1-amino-4-methyl-1-oxopentan-2-yl)hexanamide (27):

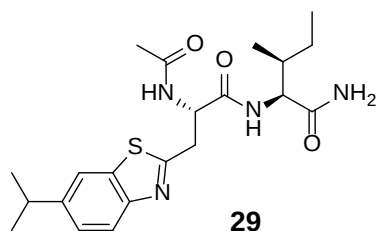
^1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 1.7 Hz, 1H), 7.42 (dd, J = 8.5, 1.7 Hz, 1H), 4.94 (dd, J = 8.6, 5.0 Hz, 1H), 4.43-4.36 (m, 2H), 4.20 (d, J = 7.6 Hz, 1H), 3.62 (dd, J = 15.4, 5.0 Hz, 1H), 3.47 (dd, J = 15.4, 8.7 Hz, 1H), 3.08 (dt, J = 13.8, 6.9 Hz, 1H), 2.93 (t,

$J = 7.4$ Hz, 2H), 2.01 (s, 3H), 1.90 – 1.79 (m, 2H), 1.77 – 1.39 (m, 9H), 1.33 (d, $J = 6.9$ Hz, 6H),
 1.19-1.12 (m, 1H), 0.98-0.85 (m, 12H). ^{13}C NMR (101 MHz, MeOD) δ 176.00, 172.19, 172.15,
 172.05, 171.39, 166.88, 150.96, 146.66, 135.29, 125.15, 121.69, 118.56, 58.20, 53.11, 52.73,
 51.36, 40.79, 39.13, 36.56, 34.88, 34.09, 30.74, 26.51, 24.60, 24.48, 23.16, 22.15, 22.09, 21.13,
 20.36, 14.50, 9.95. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{33}\text{H}_{54}\text{N}_7\text{O}_5\text{S}^+$ 660.39, found 661.01
 $[\text{M}+\text{H}]^+$.



(S)-2-((2S,3S)-2-((S)-2-acetamido-3-(6-isopropylbenzo[d]thiazol-2-yl)propanamido)-3-
methylpentanamido)-6-aminohexanamide (28): ^1H NMR (400 MHz, MeOD) δ 8.53 (d, $J = 7.7$

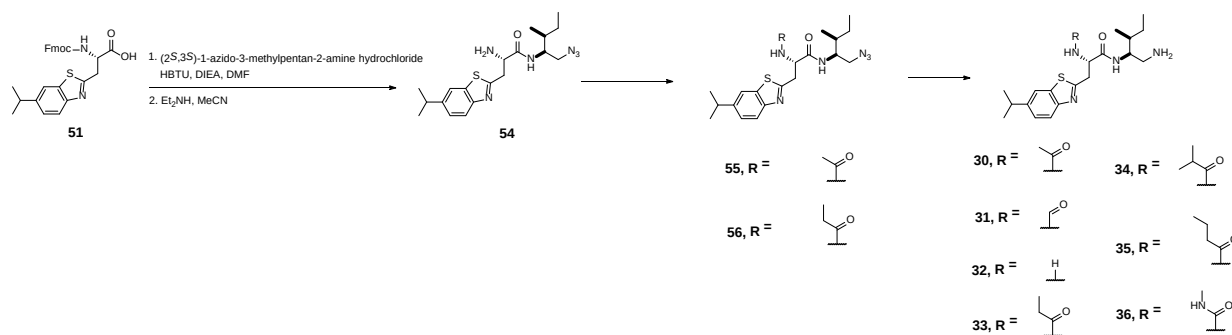
Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 7.7$ Hz, 1H), 7.87 (d, $J = 8.5$ Hz, 1H), 7.82 (d, $J =$
 1.7 Hz, 1H), 7.42 (dd, $J = 8.5, 1.7$ Hz, 1H), 4.94 (dd, $J = 8.6, 5.1$ Hz, 1H), 4.44 – 4.30 (m, 1H),
 4.19 (t, $J = 7.7$ Hz, 1H), 3.63 (dd, $J = 15.4, 5.1$ Hz, 1H), 3.46 (dd, $J = 15.4, 8.6$ Hz, 1H), 3.08 (dt,
 $J = 13.8, 6.9$ Hz, 1H), 2.93 (t, $J = 7.5$ Hz, 2H), 2.01 (s, 3H), 1.94 – 1.80 (m, 2H), 1.76 – 1.60 (m,
 3H), 1.56 – 1.38 (m, 3H), 1.33 (d, $J = 6.9$ Hz, 6H), 1.20-1.13 (m, 1H), 0.95 (d, $J = 6.8$ Hz, 3H),
 0.88 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 174.86, 172.20, 172.10, 171.48, 166.94,
 150.94, 146.68, 135.28, 125.16, 121.67, 118.57, 58.35, 53.07, 52.35, 39.16, 36.38, 34.85, 34.09,
 30.97, 26.53, 24.59, 23.16, 22.25, 21.14, 14.51, 9.89. UPLC-MS (ESI-MS) m/z : calculated for
 $\text{C}_{27}\text{H}_{43}\text{N}_6\text{O}_4\text{S}^+$ 547.31, found 547.22 $[\text{M}+\text{H}]^+$.



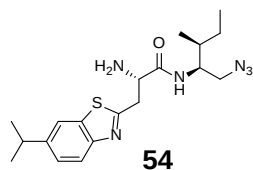
(2S,3S)-2-((S)-2-acetamido-3-(6-isopropylbenzo[d]thiazol-2-yl)propanamido)-3-

methylpentanamide (29): ^1H NMR (400 MHz, MeOD) δ 7.86 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 1.7 Hz, 1H), 7.41 (dd, J = 8.5, 1.7 Hz, 1H), 5.01 – 4.95 (m, 1H), 4.32 – 4.22 (m, 1H), 3.64 (dd, J = 15.3, 5.7 Hz, 1H), 3.46 (dd, J = 15.3, 8.0 Hz, 1H), 3.07 (dt, J = 13.8, 6.9 Hz, 1H), 1.99 (s, 3H), 1.93 – 1.80 (m, 1H), 1.56-1.50 (m, 1H), 1.33 (d, J = 6.9 Hz, 6H), 1.22-1.14 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 174.65, 172.01, 171.07, 167.02, 150.89, 146.59, 135.26, 125.14, 121.58, 118.52, 57.81, 52.73, 36.70, 34.95, 34.08, 24.26, 23.15, 21.06, 14.58, 10.27. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{21}\text{H}_{31}\text{N}_4\text{O}_3\text{S}^+$ 419.21, found 419.27 $[\text{M}+\text{H}]^+$.

Synthesis of compounds 30-36.



(2S,3S)-1-azido-3-methylpentan-2-amine hydrochloride was synthesized as reported².



1 **(S)-2-amino-N-((2S,3S)-1-azido-3-methylpentan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-**

2 **yl)propanamide (54):** To a solution of **51** (2.0 g, 4.1 mmol, 1 equiv.), HBTU (2.3 g, 6.2 mmol,

3 1.5 equiv.) and DIEA (2.1 mL, 12.3 mmol, 3 equiv.) in DMF (20 mL) was added (2S,3S)-1-

4 azido-3-methylpentan-2-amine hydrochloride (0.8 g, 4.5 mmol, 1.1 equiv.). The resultant

5 mixture was stirred at room temperature for 1 h. The solution was diluted with EtOAc and

6 washed with H₂O, saturated sodium bicarbonate, 1.0 M HCl, brine and dried over sodium sulfate.

7 After removal of the solvent under vacuum, the residue was treated with 3 mL diethylamine in

8 Actonitrile (27 mL) for 1 h. The reaction mixture was evaporated and the residue was purified by

9 flash chromatography on silica gel to afford **54** (1.2 g 77%). ¹H NMR (400 MHz, MeOD) δ 7.94

10 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 1.7 Hz, 1H), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.57 (dd, *J* = 7.8, 5.2

11 Hz, 1H), 3.87 (td, *J* = 7.3, 3.8 Hz, 1H), 3.77 (dd, *J* = 16.6, 5.2 Hz, 1H), 3.68 (dd, *J* = 16.6, 7.8 Hz,

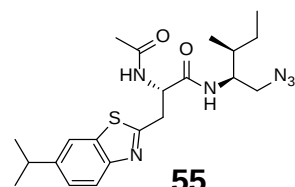
12 1H), 3.47 (dd, *J* = 12.8, 3.9 Hz, 1H), 3.41 – 3.35 (m, 1H), 3.06 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.70 –

13 1.60 (m, 1H), 1.58-1.50 (m, 1H), 1.32 (d, *J* = 6.9 Hz, 6H), 1.24 – 1.12 (m, 1H), 0.96-0.91 (m,

14 6H). ¹³C NMR (101 MHz, MeOD) δ 167.35, 164.24, 151.02, 146.98, 135.29, 125.36, 122.10,

15 118.60, 53.74, 52.01, 36.06, 34.11, 34.05, 24.98, 23.15, 14.16, 10.11. UPLC-MS (ESI-MS) *m/z*:

16 calculated for C₁₉H₂₉N₆O⁺ 389.21, found 389.36[M+H]⁺.

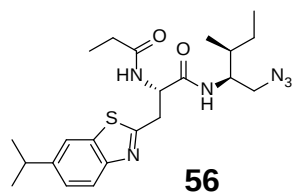


19 **(S)-2-acetamido-N-((2S,3S)-1-azido-3-methylpentan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-**

20 **yl)propanamide (55):** Acetic anhydride (46 mg, 0.45 mmol, 2 equiv.) was added to a solution

21 of **54** (87 mg, 0.22 mmol, 1 equiv.) and DIEA (156 μL, 0.89 mmol, 4 equiv.) in DCM (10 mL).

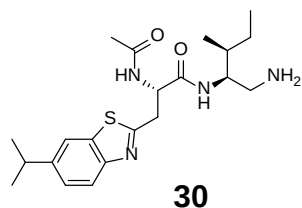
The resulting reaction mixture was stirred for half an hour and then was evaporated. The residue was purified by flash chromatography on silica gel to afford compound **55** (89 mg, 92% yields). ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.59 (d, J = 9.1 Hz, 1H), 7.47 – 7.36 (m, 2H), 5.06 (q, J = 6.4 Hz, 1H), 4.02 – 3.82 (m, 1H), 3.64 (d, J = 6.3 Hz, 2H), 3.37 (qd, J = 12.6, 5.3 Hz, 2H), 3.08 (dt, J = 13.8, 6.9 Hz, 1H), 2.08 (s, 3H), 1.65-1.58 (m, 1H), 1.51 – 1.39 (m, 1H), 1.33 (d, J = 6.9 Hz, 6H), 1.21 – 1.03 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.12, 169.86, 168.43, 148.60, 147.43, 134.34, 126.28, 121.25, 118.98, 53.54, 52.41, 52.37, 36.15, 35.62, 34.29, 25.06, 24.10, 22.97, 15.39, 11.19. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{21}\text{H}_{31}\text{N}_6\text{O}_2\text{S}^+$ 431.22, found 431.36[M+H] $^+$.



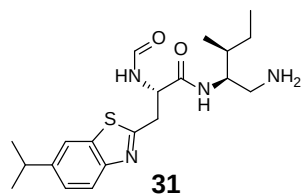
(S)-N-((2S,3S)-1-azido-3-methylpentan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-

propionamidopropionamide (56): Propionic anhydride (58 mg, 0.45 mmol, 2 equiv.) was added to a solution of **54** (87 mg, 0.22 mmol, 1 equiv.) and DIEA (156 μL , 0.89 mmol, 4 equiv.) in DCM (10 mL). The resulting reaction mixture was stirred for half an hour and then was evaporated. The residue was purified by flash chromatography on silica gel to afford compound **56** (86 mg, 89% yields). ^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 1.0 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 7.0 Hz, 1H), 7.45 (dd, J = 8.4, 1.5 Hz, 1H), 5.08 (dd, J = 12.7, 6.8 Hz, 1H), 4.00 – 3.88 (m, 1H), 3.75 (dd, J = 15.3, 5.3 Hz, 1H), 3.63 (dd, J = 15.3, 7.2 Hz, 1H), 3.39 (qd, J = 12.6, 5.4 Hz, 2H), 3.08 (dt, J = 13.8, 6.9 Hz, 1H), 2.31 (q, J = 7.6 Hz, 2H), 1.68 – 1.56 (m, 1H), 1.48-1.42 (m, 1H), 1.33 (d, J = 6.9 Hz, 6H), 1.20 – 1.05 (m, 4H),

0.92 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.27, 169.85, 169.08, 147.86, 147.47, 133.89, 126.67, 120.89, 119.04, 53.65, 52.49, 52.36, 36.20, 35.35, 34.30, 29.42, 25.07, 24.05, 24.04, 15.32, 11.17, 9.61. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{22}\text{H}_{33}\text{N}_6\text{O}_2\text{S}^+$ 445.24, found 445.37 $[\text{M}+\text{H}]^+$.



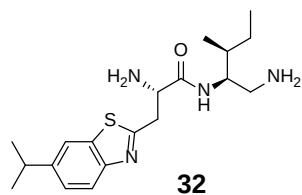
(S)-2-acetamido-N-((2S,3S)-1-amino-3-methylpentan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-yl)propanamide, (30): To a solution of compound 55 (45 mg, 0.11 mmol) in MeOH (10 mL), 10% Pd-C (20 mg) was added. The solution was stirred under 1 atm of H_2 at room temperature for 3 hours before filtering through celite and being concentrated. The resulting amine was purified by HPLC to afford compound **30** (38 mg, 91%). ^1H NMR (400 MHz, MeOD) δ 7.92 – 7.77 (m, 2H), 7.49 – 7.36 (m, 1H), 4.87-4.85 (m, 1H), 4.01-3.96 (m, 1H), 3.69 (dd, $J = 15.2, 5.9$ Hz, 1H), 3.55 (dd, $J = 15.2, 6.9$ Hz, 1H), 3.30 – 3.19 (m, 1H), 3.08 (dt, $J = 13.8, 6.9$ Hz, 1H), 2.97 (dd, $J = 12.6, 11.3$ Hz, 1H), 2.03 (s, 3H), 1.68 – 1.54 (m, 1H), 1.48-1.41 (m, 1H), 1.33 (d, $J = 6.9$ Hz, 6H), 1.21 – 1.06 (m, 1H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.45, 171.81, 167.06, 150.90, 146.80, 135.18, 125.31, 121.29, 118.67, 53.09, 52.09, 41.76, 36.51, 34.60, 34.08, 24.77, 23.14, 21.18, 14.22, 9.75. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{21}\text{H}_{33}\text{N}_4\text{O}_2\text{S}^+$ 405.23, found 405.25 $[\text{M}+\text{H}]^+$.



(S)-N-((2S,3S)-1-amino-3-methylpentan-2-yl)-2-formamido-3-(6-isopropylbenzo[d]thiazol-2-yl)propanamide (31):

Compound **54** (100 mg, 0.26 mmol) was dissolved in a mixture of DIEA (1 mL) and Ethyl formate (5 mL) and the resulting reaction mixture was left stirring for 3 days at room temperature. The solvents were removed *in vacuo* and the residue was dissolved in MeOH (10ml). Then 10% Pd-C (20 mg) was added and the resulting reaction mixture was stirred under 1 atm of H₂ at room temperature for 3 hours before filtering through celite and being concentrated. The resulting amine was purified by HPLC to afford compound **31** (58 mg, 58%).

¹H NMR (400 MHz, MeOD) δ 8.18 (d, *J* = 0.7 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.43 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.99 (t, *J* = 5.6 Hz, 1H), 4.04-3.98 (m, 1H), 3.69 (dd, *J* = 15.3, 5.8 Hz, 1H), 3.63 (dd, *J* = 15.3, 6.1 Hz, 1H), 3.27 (dd, *J* = 12.9, 2.4 Hz, 1H), 3.08 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.98 (dd, *J* = 12.9, 11.1 Hz, 1H), 1.68 – 1.55 (m, 1H), 1.48-1.42 (m, 1H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.21 – 1.08 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, MeOD) δ 171.17, 166.62, 162.68, 150.95, 146.81, 135.20, 125.30, 121.29, 118.67, 52.15, 52.06, 51.53, 41.84, 36.56, 34.73, 34.07, 24.76, 23.13, 14.20, 9.73. UPLC-MS (ESI-MS) *m/z*: calculated for C₂₀H₃₁N₄O₂S⁺ 391.22, found 391.22 [M+H]⁺.



1 **(S)-2-amino-N-((2S,3S)-1-amino-3-methylpentan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-**

2 **yl)propanamide (32):** To a solution of compound **54** (36 mg, 0.09 mmol) in MeOH (10 mL),

3 was added 10% Pd-C (20 mg). The solution was stirred under 1 atm of H₂ at room temperature

4 for 3 hours before filtering through celite and being concentrated. The resulting amine was

5 purified by HPLC to afford **32** (28 mg, 83%). ¹H NMR (400 MHz, MeOD) δ 7.97 – 7.83 (m,

6 2H), 7.48 (dd, *J* = 8.6, 1.6 Hz, 1H), 4.54 (t, *J* = 5.8 Hz, 1H), 4.14-4.09 (m, 1H), 3.82-3.80(m, 2H),

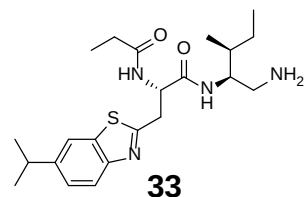
7 3.29-3.28 (m, 1H), 3.13-3.03 (m, 2H), 1.73-1.67 (m, 1H), 1.60 – 1.47 (m, 1H), 1.34 (d, *J* = 6.9

8 Hz, 6H), 1.28-1.20 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101

9 MHz, MeOD) δ 168.43, 164.33, 151.03, 147.22, 135.21, 125.60, 121.54, 118.81, 52.49, 52.02,

10 41.45, 36.70, 34.10, 33.67, 24.83, 23.10, 14.05, 10.01. UPLC-MS (ESI-MS) *m/z*: calculated for

11 C₁₉H₃₂N₄OS²⁺ 182.11, found 182.21 [M+2H]²⁺.



14 **33**

15 **(S)-N-((2S,3S)-1-amino-3-methylpentan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-**

16 **propionamidopropanamide (33):** To a solution of compound **56** (52 mg, 0.12 mmol) in MeOH

17 (10 mL) was added 10% Pd-C (20 mg). The solution was stirred under 1 atm of H₂ at room

18 temperature for 3 hours before filtering through celite and being concentrated. The resulting

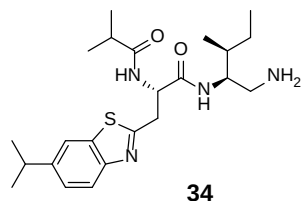
19 amine was purified by HPLC to afford compound **33** (36 mg, 86%). ¹H NMR (400 MHz, MeOD)

20 δ 7.90 – 7.80 (m, 2H), 7.43 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.91-4.89 (m, 1H), 4.09 – 3.92 (m, 1H),

21 3.69 (dd, *J* = 15.2, 5.9 Hz, 1H), 3.55 (dd, *J* = 15.2, 7.0 Hz, 1H), 3.29 – 3.20 (m, 1H), 3.08 (dt, *J* =

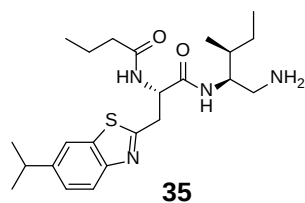
22 13.8, 6.9 Hz, 1H), 3.02 – 2.93 (m, 1H), 2.30 (q, *J* = 7.6 Hz, 2H), 1.67 – 1.56 (m, 1H), 1.48-1.42

(m, 1H), 1.33 (d, $J = 6.9$ Hz, 6H), 1.20 – 1.07 (m, 4H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.05, 171.86, 167.09, 150.90, 146.78, 135.16, 125.30, 121.28, 118.66, 52.92, 52.07, 41.77, 36.54, 34.55, 34.07, 28.54, 24.74, 23.14, 14.24, 9.76, 8.71. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{22}\text{H}_{35}\text{N}_4\text{O}_2\text{S}^+$ 419.25, found 419.29 $[\text{M}+\text{H}]^+$.

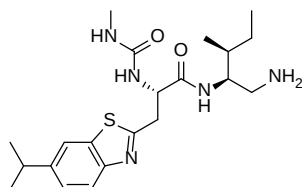


(S)-N-((2S,3S)-1-amino-3-methylpentan-2-yl)-2-isobutyramido-3-(6-

isopropylbenzo[d]thiazol-2-yl)propanamide (34): Compound **34** was prepared from **54** in 72% yield over two steps by a similar procedure as that for compound **30**. ^1H NMR (400 MHz, MeOD) δ 8.33 (d, $J = 7.3$ Hz, 1H), 7.99 (d, $J = 8.9$ Hz, 1H), 7.85-7.83 (m, 2H), 7.43 (dd, $J = 8.6, 1.6$ Hz, 1H), 4.91 – 4.88 (m, 1H), 4.09 – 3.90 (m, 1H), 3.69 (dd, $J = 15.2, 5.9$ Hz, 1H), 3.55 (dd, $J = 15.2, 7.1$ Hz, 1H), 3.26 (dd, $J = 13.4, 3.1$ Hz, 1H), 3.08 (dt, $J = 13.8, 6.9$ Hz, 1H), 3.02 – 2.93 (m, 1H), 2.53 (dt, $J = 13.7, 6.9$ Hz, 1H), 1.68 – 1.57 (m, 1H), 1.50-1.42 (m, 1H), 1.33 (d, $J = 6.9$ Hz, 6H), 1.23 – 1.04 (m, 7H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.88 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 179.04, 171.85, 167.11, 150.91, 146.78, 135.14, 125.30, 121.24, 118.67, 52.71, 52.02, 41.85, 36.59, 34.59, 34.45, 34.07, 24.69, 23.13, 18.48, 18.17, 14.25, 9.78. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{23}\text{H}_{37}\text{N}_4\text{O}_2\text{S}^+$ 433.26, found 433.29 $[\text{M}+\text{H}]^+$.



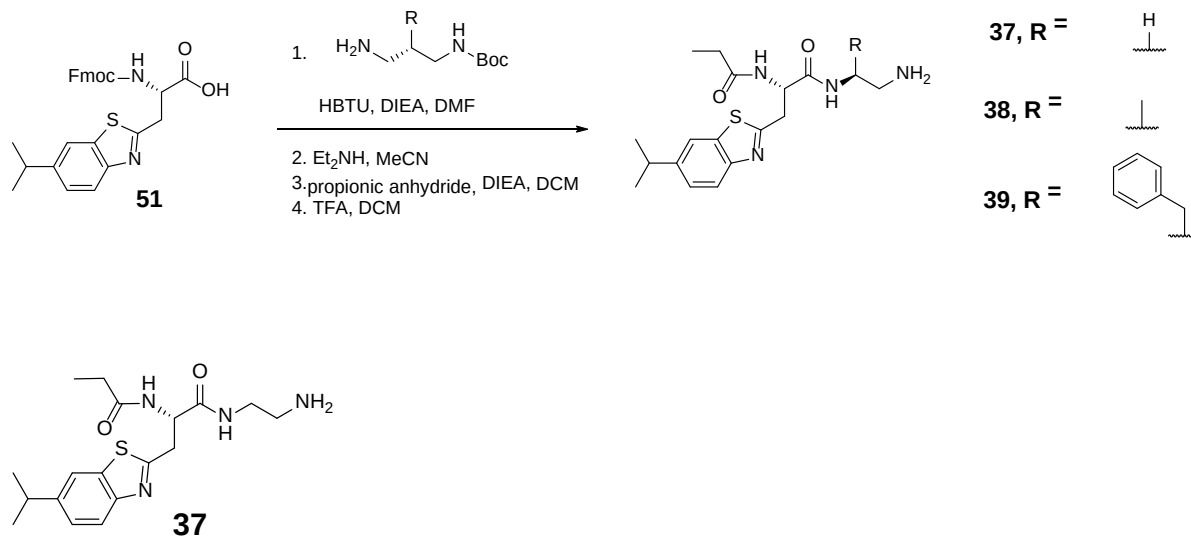
N-((S)-1-(((2S,3S)-1-amino-3-methylpentan-2-yl)amino)-3-(6-isopropylbenzo[d]thiazol-2-yl)-1-oxopropan-2-yl)butyramide (35): Compound **35** was prepared from **54** in 70% yield over two steps by a similar procedure as that for compound **30**. ¹H NMR (400 MHz, MeOD) δ 7.91 – 7.75 (m, 2H), 7.43 (dd, *J* = 8.6, 1.6 Hz, 1H), 4.91 – 4.88 (m, 1H), 4.02-3.96 (m, 1H), 3.69 (dd, *J* = 15.2, 5.9 Hz, 1H), 3.54 (dd, *J* = 15.2, 7.2 Hz, 1H), 3.25 (dd, *J* = 13.1, 3.1 Hz, 1H), 3.08 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.98 (dd, *J* = 12.8, 11.1 Hz, 1H), 2.35 – 2.18 (m, 2H), 1.71 – 1.55 (m, 3H), 1.49-1.41 (m, 1H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.19-1.12 (m, 1H), 0.96-0.85 (m, 9H). ¹³C NMR (101 MHz, MeOD) δ 175.14, 171.86, 167.08, 150.93, 146.77, 135.17, 125.29, 121.28, 118.66, 52.90, 52.06, 41.78, 37.32, 36.56, 34.61, 34.07, 24.74, 23.14, 18.76, 14.23, 12.56, 9.78. UPLC-MS (ESI-MS) *m/z*: calculated for C₂₃H₃₇N₄O₂S⁺ 433.26, found 433.29 [M+H]⁺.



(S)-N-((2S,3S)-1-amino-3-methylpentan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-(3-methylureido)propanamide (36): Methyl isocyanate (18 mg, 0.31 mmol, 2 equiv.) was added to a solution of **54** (60 mg, 0.15 mmol, 1 equiv.) and DIEA (54 μL, 0.31 mmol, 2 equiv.) in CH₂Cl₂ (5 mL) and the resulting solution was stirred at room temperature overnight. The reaction mixture was concentrated and the residue was dissolved in MeOH (10ml). Then 10% Pd-C (20 mg) was added and the resulting reaction mixture was stirred under 1 atm of H₂ at room temperature for 3 hours before filtering through celite and being concentrated. The resulting amine was purified by HPLC to afford compound **36** (58 mg, 74%). ¹H NMR (400 MHz, MeOD) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 1.7 Hz, 1H), 7.42 (dd, *J* = 8.5, 1.7 Hz, 1H),

4.74 (t, $J = 5.8$ Hz, 1H), 3.99-3.94 (m, 1H), 3.61 (d, $J = 5.8$ Hz, 2H), 3.24 (dd, $J = 12.9, 3.0$ Hz, 1H), 3.07 (dt, $J = 13.8, 6.9$ Hz, 1H), 2.98 (dd, $J = 12.8, 11.3$ Hz, 1H), 2.74 (s, 3H), 1.58 (dtd, $J = 8.8, 7.3, 3.7$ Hz, 1H), 1.44 – 1.35 (m, 1H), 1.32 (d, $J = 6.9$ Hz, 6H), 1.12-1.04 (m, 1H), 0.91 (d, $J = 6.8$ Hz, 3H), 0.79 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.94, 167.09, 159.77, 150.97, 146.68, 135.23, 125.18, 121.40, 118.59, 53.78, 52.00, 41.73, 36.52, 35.24, 34.07, 25.54, 24.79, 23.15, 14.24, 9.70. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{21}\text{H}_{34}\text{N}_5\text{O}_2\text{S}^+$ 420.24, found 419.29 $[\text{M}+\text{H}]^+$.

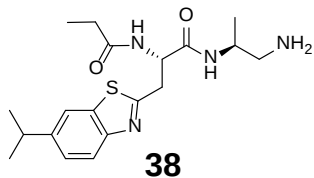
Synthesis of compounds 37-39.



(S)-N-(2-aminoethyl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-propionamidopropanamide (37):

To a solution of **51** (120 mg, 0.25 mmol, 1 equiv.), HBTU (140 mg, 0.37 mmol, 1.5 equiv.) and DIEA (129 μL , 0.74 mmol, 3 equiv.) in DMF (5 mL) was added tert-butyl (2-aminoethyl)carbamate (43 mg, 0.27 mmol, 1.1 equiv.). The resultant mixture was stirred at room temperature for 1 h. The solution was diluted with EtOAc and washed with H_2O , saturated

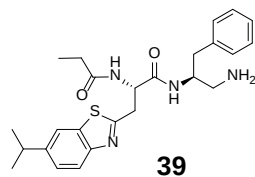
sodium bicarbonate, 1.0 M HCl, brine and dried over sodium sulfate. After removal of the solvent under vacuum, the residue was treated with 1 mL diethylamine in Actonitrile (9 mL) for 1 h. The reaction mixture was evaporated and dissolved in DCM (5 mL). This solution was treated with propionic anhydride (64 mg, 0.49 mmol, 2 equiv.) and DIEA (171 μ L, 0.99 mmol, 4 equiv.). The resulting reaction mixture was stirred for half an hour and then was evaporated. The residue was treated with TFA (1 mL) in DCM (5 mL) and stirred for 5 h. This reaction mixture was concentrated and purified by HPLC to afford **37** (54 mg, 61%). ^1H NMR (400 MHz, MeOD) δ 7.86 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 1.7 Hz, 1H), 7.42 (dd, J = 8.5, 1.7 Hz, 1H), 4.83 (dd, J = 8.2, 5.5 Hz, 1H), 3.67 (dd, J = 15.1, 5.5 Hz, 1H), 3.56 – 3.43 (m, 3H), 3.10-3.03 (m, 3H), 2.28 (q, J = 7.6 Hz, 2H), 1.32 (d, J = 6.9 Hz, 6H), 1.09 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 176.04, 172.38, 166.94, 150.80, 146.73, 135.22, 125.26, 121.46, 118.60, 53.15, 39.46, 36.83, 34.93, 34.07, 28.50, 23.14, 8.56. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{18}\text{H}_{27}\text{N}_4\text{O}_2\text{S}^+$ 363.18, found 363.18 $[\text{M}+\text{H}]^+$.



(S)-N-((S)-1-aminopropan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-

propionamidopropanamide (38): Compound **38** was prepared from **51** in 57% yield over four steps by a similar procedure as that for compound **37**. ^1H NMR (400 MHz, MeOD) δ 7.86-7.83 (m, 2H), 7.42 (dd, J = 8.5, 1.7 Hz, 1H), 4.84 (dd, J = 7.1, 5.8 Hz, 1H), 4.31 – 4.15 (m, 1H), 3.69 (dd, J = 15.0, 5.8 Hz, 1H), 3.51 (dd, J = 15.0, 7.2 Hz, 1H), 3.17 – 2.91 (m, 3H), 2.28 (q, J = 7.6 Hz, 2H), 1.32 (d, J = 6.9 Hz, 6H), 1.25 (d, J = 6.9 Hz, 3H), 1.10 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.90, 171.51, 166.97, 150.86, 146.75, 135.21, 125.29, 121.29, 118.65,

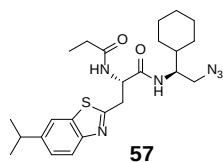
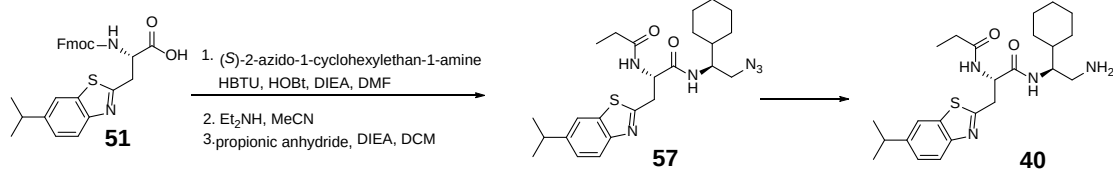
52.91, 44.65, 43.71, 35.02, 34.07, 28.52, 23.14, 16.39, 8.65. UPLC-MS (ESI-MS) m/z : calculated for $C_{19}H_{29}N_4O_2S^+$ 377.20, found 377.23 $[M+H]^+$.



(S)-N-((S)-1-amino-3-phenylpropan-2-yl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-

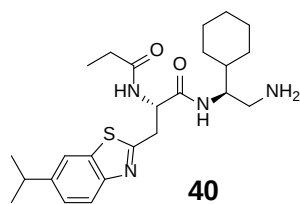
propionamidopropanamide (39): Compound **39** was prepared from **51** in 53% yield over four steps by a similar procedure as that for compound **37**. 1H NMR (400 MHz, MeOD) δ 7.86 – 7.80 (m, 2H), 7.42 (dd, J = 8.5, 1.6 Hz, 1H), 7.33 – 7.18 (m, 5H), 4.81 (dd, J = 7.6, 5.5 Hz, 1H), 4.47 – 4.32 (m, 1H), 3.58 (dd, J = 15.2, 5.5 Hz, 1H), 3.42 (dd, J = 15.2, 7.6 Hz, 1H), 3.18 (dd, J = 13.0, 3.6 Hz, 1H), 3.10–3.04 (m, 2H), 2.93 – 2.84 (m, 2H), 2.24 (q, J = 7.6 Hz, 2H), 1.32 (d, J = 6.9 Hz, 6H), 1.08 (t, J = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 175.96, 171.68, 167.04, 150.86, 146.74, 136.78, 135.18, 128.77, 128.31, 126.58, 125.27, 121.31, 118.64, 52.86, 49.38, 43.08, 37.43, 34.73, 34.07, 28.49, 23.14, 8.60. UPLC-MS (ESI-MS) m/z : calculated for $C_{25}H_{33}N_4O_2S^+$ 453.23, found 453.24 $[M+H]^+$.

Synthesis of compound 40.



1 **(S)-N-((S)-2-azido-1-cyclohexylethyl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-**

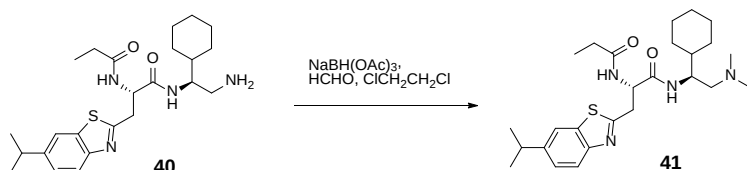
2 **propionamidopropanamide (57):** Compound **57** was prepared from **51** in 65% yield over three
3 steps by a similar procedure as that for compound **56**. ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, J =
4 8.4 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 9.1 Hz, 1H), 7.39 (d, J = 7.1 Hz, 1H), 7.34 (dd,
5 J = 8.5, 1.7 Hz, 1H), 5.04 (td, J = 7.0, 4.8 Hz, 1H), 3.91 – 3.76 (m, 1H), 3.66 (dd, J = 15.9, 4.7
6 Hz, 1H), 3.43 (dd, J = 15.9, 7.0 Hz, 1H), 3.35 (dd, J = 5.0, 1.1 Hz, 2H), 3.04 (dt, J = 13.8, 6.9 Hz,
7 1H), 2.32 (q, J = 7.6 Hz, 2H), 1.70-1.60 (dd, J = 28.1, 15.3 Hz, 6H), 1.52 – 1.41 (m, 1H), 1.32 –
8 0.87 (m, 14H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.11, 170.30, 167.09, 150.97, 146.46, 135.25,
9 125.39, 121.98, 118.79, 53.54, 52.31, 51.92, 38.95, 35.50, 34.24, 29.69, 29.65, 28.51, 26.09,
10 25.91, 25.85, 24.18, 9.68. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{24}\text{H}_{35}\text{N}_6\text{O}_2\text{S}^+$ 471.25, found
11 471.27 $[\text{M}+\text{H}]^+$.



16 **(S)-N-((S)-2-amino-1-cyclohexylethyl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-**

17 **propionamidopropanamide (40):** Compound **40** was prepared from **57** in 88% yield by a
18 similar procedure as that for compound **33**. ^1H NMR (400 MHz, MeOD) δ 7.99 (d, J = 8.9 Hz,
19 1H), 7.86-7.84 (m, 2H), 7.43 (d, J = 8.5 Hz, 1H), 4.87-4.84 (m, 1H), 3.94-3.90 (m, 1H), 3.68 (dd,
20 J = 15.3, 5.8 Hz, 1H), 3.56 (dd, J = 15.2, 6.9 Hz, 1H), 3.29 – 3.20 (m, 1H), 3.12-2.91 (m, 2H),
21 2.31 (q, J = 7.6 Hz, 2H), 1.75-1.63 (m, 5H), 1.54 – 1.46 (m, 1H), 1.36 – 0.90 (m, 14H). ^{13}C
22 NMR (101 MHz, MeOD) δ 176.08, 171.86, 167.03, 150.94, 146.76, 135.15, 125.30, 121.33,
23 118.65, 52.99, 52.48, 41.73, 39.59, 34.51, 34.08, 29.39, 28.57, 28.25, 25.70, 25.50, 25.43, 23.14,
8.70. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{24}\text{H}_{37}\text{N}_4\text{O}_2\text{S}^+$ 445.26, found 445.27 $[\text{M}+\text{H}]^+$.

Synthesis of compound 41.



(S)-N-((S)-1-cyclohexyl-2-(dimethylamino)ethyl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-

propionamidopropanamide (41): Compound **40** (45 mg, 0.1 mmol) and formaldehyde solution

37 wt. % in H₂O (66 mg, 0.8 mmol) were mixed in 1,2-dichloroethane (5 mL) and then treated

with sodium triacetoxyborohydride (86 mg, 0.4 mmol). The mixture was stirred at room

temperature for 3 h until compound **40** was consumed. Then the reaction mixture was quenched

by adding 1N NaOH, and concentrated. The residue was purified by HPLC to give compound **41**

(40 mg, 83%). ¹H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 0.5 Hz, 1H),

7.42 (d, *J* = 8.4 Hz, 1H), 4.92-4.90 (m, 1H), 4.01-3.96 (m, 1H), 3.67 (dd, *J* = 15.5, 6.1 Hz, 1H),

3.55 (dd, *J* = 15.4, 7.6 Hz, 1H), 3.36-3.33 (m, 1H), 3.11-3.02 (m, 2H), 2.93 (s, 6H), 2.32 (q, *J* =

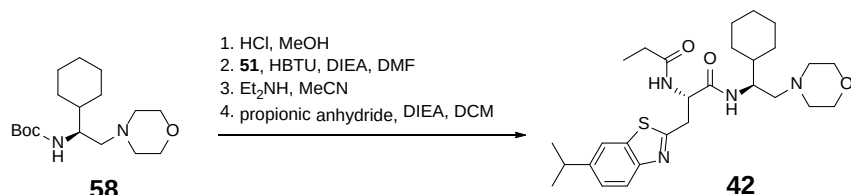
7.6 Hz, 2H), 1.74 – 1.47 (m, 6H), 1.36 – 0.84 (m, 14H). ¹³C NMR (101 MHz, MeOD) δ 176.63,

172.01, 166.81, 151.01, 146.72, 135.19, 125.24, 121.61, 118.62, 59.32, 53.34, 50.15, 40.15,

34.09, 34.06, 29.23, 28.55, 28.02, 25.63, 25.49, 25.42, 23.15, 23.14, 8.62. UPLC-MS (ESI-MS)

m/z: calculated for C₂₆H₄₁N₄O₂S⁺ 473.29, found 473.32 [M+H]⁺.

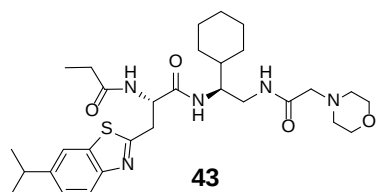
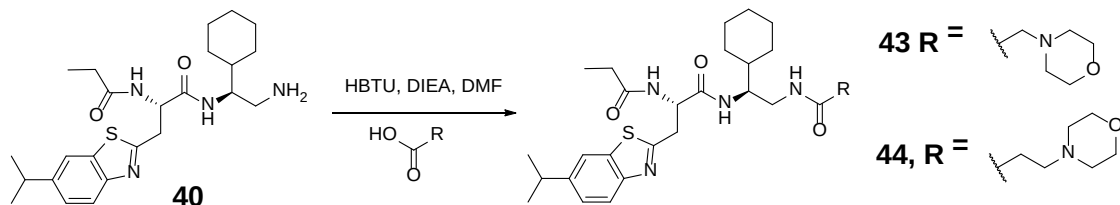
Synthesis of compound 42.



(S)-N-((S)-1-cyclohexyl-2-morpholinoethyl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-

propionamidopropanamide (42): The synthesis of tert-butyl (S)-(1-cyclohexyl-2-morpholinoethyl)carbamate (**58**) has been reported previously.³ Hydrogen chloride solution (4.0 M in dioxane, 1 mL) was added to a solution of **58** (30 mg, 0.1 mmol, 1 equiv.) in MeOH (5 mL). The solution was stirred overnight and concentrated. The residue in DMF (2 mL) was added to a solution of **51** (47 mg, 0.1 mmol, 1 equiv.), HBTU (55 mg, 0.14 mmol, 1.5 equiv.) and DIEA (50 μ L, 0.29 mmol, 3 equiv.) in DMF (20 mL). The resultant mixture was stirred at room temperature for 1 h. The solution was diluted with EtOAc and washed with H₂O, saturated sodium bicarbonate, 1.0 M HCl, brine and dried over sodium sulfate. After removal of the solvent under vacuum, the residue was treated with 0.5 mL diethylamine in Acetonitrile (5 mL) for 1 h. The reaction mixture was evaporated and dissolved in DCM (5 mL). This solution was treated with propionic anhydride (25 mg, 0.2 mmol, 2 equiv.) and DIEA (69 μ L, 0.4 mmol, 4 equiv.). The resulting reaction mixture was stirred for half an hour and then was evaporated. The residue was purified by HPLC to afford compound **42** (31 mg, 63%). ¹H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.41 (dd, J = 8.4, 1.5 Hz, 1H), 4.78 (t, J = 6.9 Hz, 1H), 4.18 – 3.71 (m, 6H), 3.68-3.63 (m, 2H), 3.56 (dd, J = 15.4, 7.0 Hz, 1H), 3.41-3.33 (m, 2H), 3.25 – 3.01 (m, 3H), 2.35 (q, J = 7.6 Hz, 2H), 1.70 – 1.45 (m, 6H), 1.35 – 0.87 (m, 14H). ¹³C NMR (101 MHz, MeOD) δ 176.80, 171.98, 166.40, 151.02, 146.77, 135.22, 125.26, 121.71, 118.63, 63.35, 59.00, 53.99, 49.33, 39.92, 34.10, 33.98, 29.21, 28.46, 28.12, 25.59, 25.46, 25.39, 23.16, 8.62. UPLC-MS (ESI-MS) m/z : calculated for C₂₈H₄₃N₄O₃S⁺ 515.31, found 515.26 [M+H]⁺.

Synthesis of compounds 43 and 44.



(S)-N-((S)-1-cyclohexyl-2-(2-morpholinoacetamido)ethyl)-3-(6-isopropylbenzo[d]thiazol-2-

yl)-2-propionamidopropanamide (43): Compound **40** (40 mg, 0.09 mmol, 1 equiv.) was added

to a solution of 2-morpholinoacetic acid (16 mg, 0.11 mmol, 1.2 equiv.), HBTU (51 mg, 0.13

mmol, 1.5 equiv.) and DIEA (47 μ L, 0.27 mmol, 3 equiv.) in DCM (5 mL). The resultant

mixture was stirred at room temperature for 1 h and concentrated. The residue was purified by

HPLC to afford compound **43** (45 mg, 87%). ^1H NMR (400 MHz, MeOD) δ 7.88 (d, J = 8.4 Hz,

1H), 7.84 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 4.93-4.91 (s, 1H), 4.14 – 3.75 (m, 8H), 3.65 (dd, J =

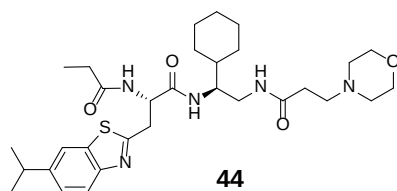
15.5, 5.4 Hz, 1H), 3.58-3.46 (m, 4H), 3.17-3.04 (m, 3H), 2.35 (q, J = 7.5 Hz, 2H), 1.73-1.62 (m,

6H), 1.38 – 0.86 (m, 15H). ^{13}C NMR (101 MHz, MeOD) δ 176.25, 171.48, 167.27, 164.01,

150.97, 146.76, 135.17, 125.30, 121.58, 118.68, 63.38, 56.94, 53.98, 53.03, 52.57, 40.82, 39.59,

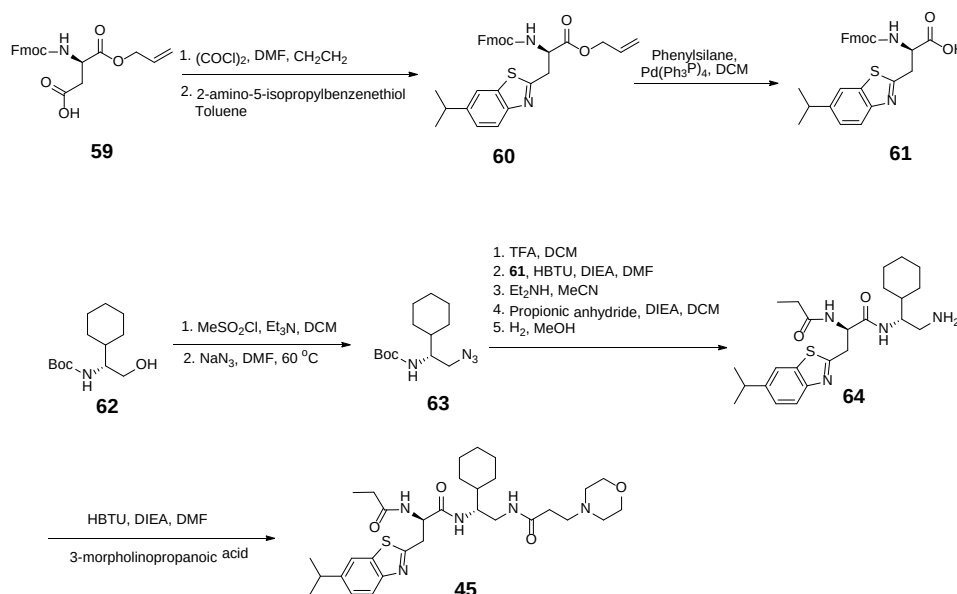
34.73, 34.09, 29.59, 28.74, 28.41, 25.85, 25.62, 25.54, 23.16, 23.14, 8.75. UPLC-MS (ESI-MS)

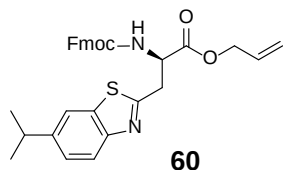
m/z : calculated for $\text{C}_{30}\text{H}_{46}\text{N}_5\text{O}_4\text{S}^+$ 572.33, found 572.21 $[\text{M}+\text{H}]^+$.



(S)-N-((S)-1-cyclohexyl-2-(3-morpholinopropanamido)ethyl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-propionamidopropanamide (44): Compound **44** was prepared from **40** in 81% yield by a similar procedure as that for compound **43**. ¹H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 1.6 Hz, 1H), 7.43 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.86 (dd, *J* = 7.8, 5.4 Hz, 1H), 4.07-4.04 (m, 2H), 3.88 – 3.76 (m, 3H), 3.64 (dd, *J* = 15.4, 5.3 Hz, 1H), 3.57 – 3.37 (m, 6H), 3.17-3.06 (m, 4H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.34 (q, *J* = 7.5 Hz, 2H), 1.72-1.60 (m, 5H), 1.39 – 0.86 (m, 15H). ¹³C NMR (101 MHz, MeOD) δ 176.00, 171.58, 170.51, 167.14, 150.98, 146.74, 135.17, 125.28, 121.57, 118.63, 63.61, 54.19, 53.25, 53.18, 51.89, 40.78, 39.66, 34.80, 34.09, 29.55, 28.72, 28.47, 28.43, 25.87, 25.66, 25.58, 23.16, 23.15, 8.73. UPLC-MS (ESI-MS) *m/z*: calculated for C₃₁H₄₈N₅O₄S⁺ 586.34, found 586.29 [M+H]⁺.

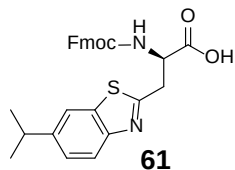
Synthesis of compounds 45.





60

Allyl (R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-isopropylbenzo[d]thiazol-2-yl)propanoate (60): Intermediate **60** was prepared from (R)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(allyloxy)-4-oxobutanoic acid (**59**) in 56% yield by a similar procedure as that for **49**. ^1H NMR (400 MHz, CDCl_3) δ 7.99 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.72 (s, 1H), 7.68 – 7.58 (m, 2H), 7.45–7.40 (m, 3H), 7.36 – 7.22 (m, 2H), 6.43 (d, J = 8.4 Hz, 1H), 5.98–5.89 (m, 1H), 5.37 (d, J = 17.2 Hz, 1H), 5.26 (dd, J = 10.4, 0.9 Hz, 1H), 5.08 – 4.94 (m, 1H), 4.73 (d, J = 4.5 Hz, 2H), 4.44 (d, J = 7.3 Hz, 2H), 4.27 (t, J = 7.2 Hz, 1H), 3.78 (d, J = 5.0 Hz, 2H), 3.08 (dt, J = 13.8, 6.9 Hz, 1H), 1.36 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.28, 166.10, 156.13, 150.40, 146.82, 143.90, 143.83, 141.33, 135.13, 131.46, 127.76, 127.14, 125.73, 125.27, 122.27, 120.03, 119.00, 118.80, 67.40, 66.53, 53.50, 47.14, 35.55, 34.30, 24.23. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{31}\text{H}_{31}\text{N}_2\text{O}_4\text{S}^+$ 527.20, found 527.15 $[\text{M}+\text{H}]^+$.



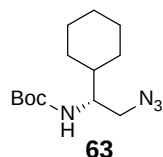
61

(R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-isopropylbenzo[d]thiazol-2-yl)propanoic acid (61): Intermediate **61** was prepared from **60** in 84% yield by a similar

procedure as that for **51**. ^1H NMR (400 MHz, DMSO) δ 8.08 – 7.79 (m, 5H), 7.65 (dd, J = 11.4, 7.7 Hz, 2H), 7.41–7.36 (m, 3H), 7.27 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 4.56 (td, J = 9.1, 4.6 Hz, 1H), 4.28–4.18 (m, 3H), 3.61 (dd, J = 15.0, 4.2 Hz, 1H), 3.45 (dd, J = 14.9, 10.0 Hz, 1H), 3.02 (dt, J = 13.6, 6.8 Hz, 1H), 1.25 (d, J = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 172.72, 167.26, 156.41, 151.47, 146.12, 144.23, 144.14, 141.16, 135.67, 128.06, 127.49, 125.71,

1 125.66, 125.50, 122.46, 120.55, 119.47, 66.19, 54.11, 47.05, 35.55, 33.98, 24.54. UPLC-MS

2 (ESI-MS) m/z : calculated for $C_{28}H_{27}N_2O_4S^+$ 487.17, found 487.18 $[M+H]^+$.



5 **tert-butyl (R)-(2-azido-1-cyclohexylethyl)carbamate (63):** Compound **63** was made by

6 utilizing a reported method.² MsCl (710 mg, 6.2 mmol, 1.5 equiv.) was added dropwise to a

7 solution of N-Boc-D-cyclohexylglycinol (1.00 g, 4.1 mmol, 1 equiv.) and Et₃N (1.7 mL, 12.3

8 mmol, 3 equiv.) in CH₂Cl₂ (20 mL) at 0 °C. The mixture was stirred 3 h at 0 °C and diluted with

9 CH₂Cl₂. The mixture was washed with sat. aq NaHCO₃ (2 x 20 mL), 1M HCl, and brine. The

10 organic layer was dried (Na₂SO₄) and the solvent was removed *in vacuo*. The residue was

11 dissolved in DMF and NaN₃ (802 mg, 12.3 mmol, 3 equiv.) was added. This reaction mixture

12 was stirred at 60°C overnight and cooled to room temperature. EtOAc and H₂O were added to

13 this mixture and the aqueous layer was extracted with EtOAc. The organic layer was washed

14 with H₂O and brine. The organic layer was dried (Na₂SO₄) and the solvent was removed under

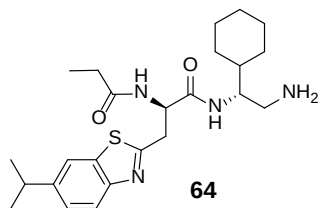
15 vacuum. The crude product was purified by flash chromatography to produce compound **63** (617

16 mg, 56% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 4.60 (d, *J* = 8.6 Hz, 1H), 3.63 – 3.29 (m,

17 3H), 1.79-1.65 (m, 5H), 1.54 – 1.36 (m, 11H), 1.33 – 0.86 (m, 6H). ¹³C NMR (101 MHz, CDCl₃)

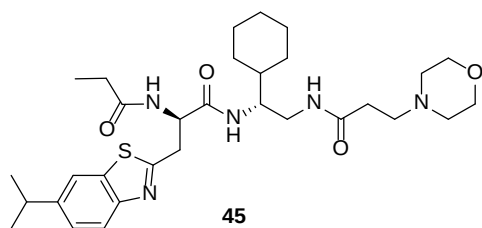
18 δ 155.57, 79.48, 54.82, 52.72, 39.31, 29.77, 28.86, 28.36, 28.29, 26.16, 25.97, 25.96. UPLC-MS

19 (ESI-MS) m/z : calculated for $C_{13}H_{25}N_4O_2^+$ 269.20, found $[M+H]^+$.



(R)-N-((R)-2-amino-1-cyclohexylethyl)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-

propionamidopropanamide (64): Compound **64** was prepared from **61** and **62** in 51% yield over 5 steps by a similar procedure as that for compound **40**. ^1H NMR (400 MHz, MeOD) δ 7.97 (d, J = 9.0 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.43 (dd, J = 8.6, 1.5 Hz, 1H), 4.91 (m, 1H), 3.97 – 3.87 (m, 1H), 3.68 (dd, J = 15.3, 5.9 Hz, 1H), 3.56 (dd, J = 15.2, 6.9 Hz, 1H), 3.25 (dd, J = 12.9, 3.0 Hz, 1H), 3.08 (dt, J = 13.8, 6.9 Hz, 1H), 3.01 – 2.93 (m, 1H), 2.31 (q, J = 7.6 Hz, 2H), 1.76 – 1.61 (m, 5H), 1.55 – 1.47 (m, 1H), 1.34 – 0.90 (m, 14H). ^{13}C NMR (101 MHz, MeOD) δ 176.09, 171.87, 167.03, 150.95, 146.77, 135.15, 125.30, 121.31, 118.66, 52.97, 52.48, 41.77, 39.59, 34.49, 34.08, 29.40, 28.56, 28.24, 25.70, 25.49, 25.43, 23.14, 8.70. UPLC-MS (ESI-MS) m/z : calculated for $\text{C}_{24}\text{H}_{37}\text{N}_4\text{O}_2\text{S}^+$ 445.26, found 445.41 $[\text{M}+\text{H}]^+$.

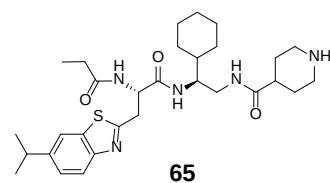
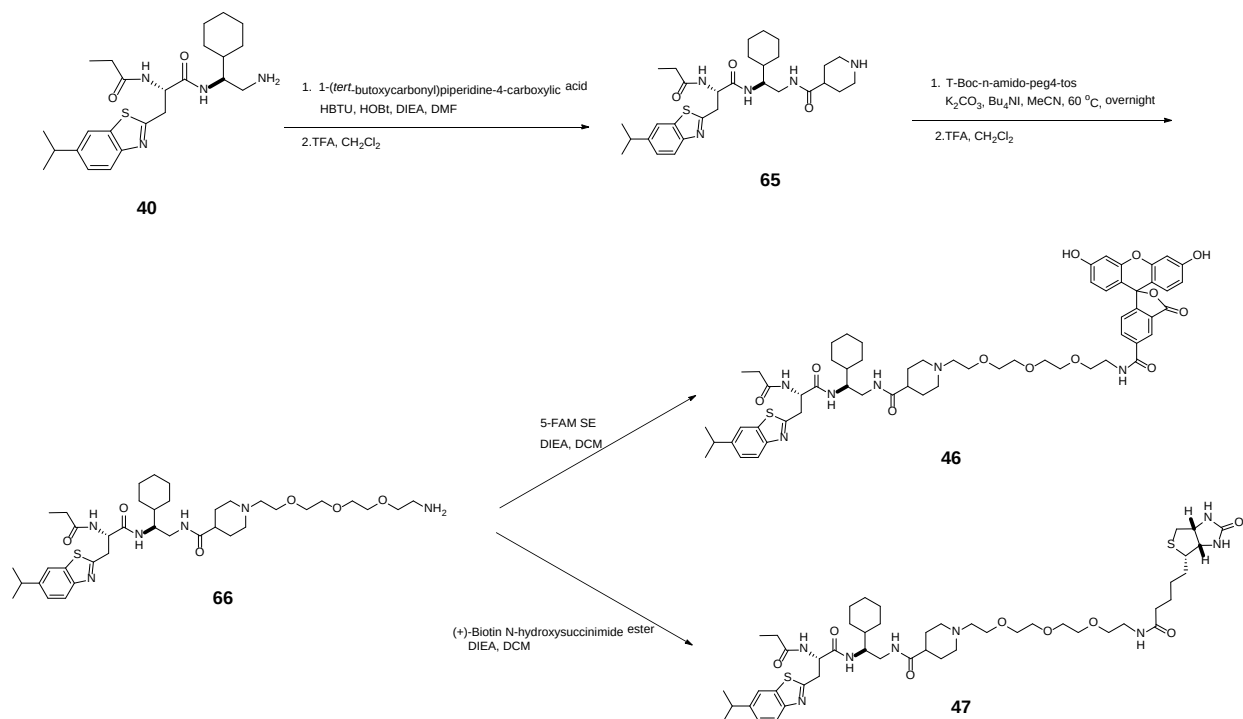


(R)-N-((R)-1-cyclohexyl-2-(3-morpholinopropanamido)ethyl)-3-(6-

isopropylbenzo[d]thiazol-2-yl)-2-propionamidopropanamide (45): Compound **45** was prepared from **64** in 83% yield by a similar procedure as that for compound **44**. ^1H NMR (400 MHz, MeOD) δ 7.87 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.43 (dd, J = 8.5, 1.6 Hz, 1H), 4.87 – 4.82 (m, 1H), 4.08-4.05 (m, 2H), 3.87 – 3.76 (m, 3H), 3.64 (dd, J = 15.4, 5.4 Hz, 1H), 3.56 – 3.37 (m, 6H), 3.20 – 3.03 (m, 4H), 2.69 (t, J = 6.3 Hz, 2H), 2.34 (q, J = 7.6 Hz, 2H), 1.72-1.60 (m, 5H), 1.38 – 0.87 (m, 16H). ^{13}C NMR (101 MHz, MeOD) δ 176.01, 171.60, 170.52, 167.11, 151.01, 146.74, 135.17, 125.28, 121.57, 118.63, 63.61, 54.19, 53.25, 53.20, 51.89, 40.80,

39.67, 34.78, 34.09, 29.55, 28.72, 28.47, 28.38, 25.86, 25.65, 25.58, 23.15, 8.73. UPLC-MS
(ESI-MS) m/z : calculated for $C_{31}H_{48}N_5O_4S^+$ 586.34, found 586.28 $[M+H]^+$.

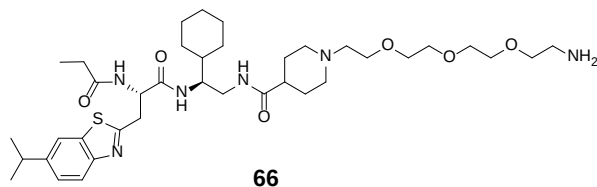
Synthesis of compounds 46 and 47.



N-((S)-2-cyclohexyl-2-((S)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-

propionamidopropylamido)ethyl)piperidine-4-carboxamide (65): Compound 40 (150 mg, 0.34 mmol, 1 equiv.) was added to a solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (93 mg, 0.40 mmol, 1.2 equiv.), HBTU (192 mg, 0.51 mmol, 1.5 equiv.) and DIEA (176 μ L, 1.01 mmol, 3 equiv.) in DCM (10 mL). The resultant mixture was stirred at room temperature for 1 h and concentrated. The residue was dissolve in EtOAc and washed with H_2O , saturated

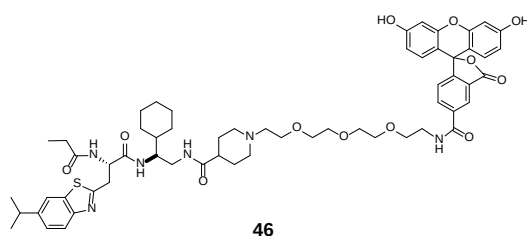
sodium bicarbonate, 1.0 M HCl, brine and dried over sodium sulfate. After removal of the solvent under vacuum, the residue was treated with TFA (2 ml) in DCM (10 mL) and stirred for 5 h. This reaction mixture was concentrated and purified by HPLC to afford compound **65** (139 mg, 74%). ¹H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.42 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.89 (dd, *J* = 7.8, 5.4 Hz, 1H), 3.80 (ddd, *J* = 10.2, 7.0, 3.5 Hz, 1H), 3.63 (dd, *J* = 15.4, 5.5 Hz, 1H), 3.53 – 3.36 (m, 4H), 3.12-3.04 (m, 2H), 2.98-2.90 (m, 2H), 2.49 – 2.38 (m, 1H), 2.32 (q, *J* = 7.6 Hz, 2H), 1.98 – 1.81 (m, 4H), 1.72-1.62 (m, 5H), 1.39 – 0.92 (m, 15H). ¹³C NMR (101 MHz, MeOD) δ 175.87, 174.55, 171.35, 167.22, 150.93, 146.73, 135.21, 125.25, 121.57, 118.63, 54.31, 53.02, 42.89, 40.66, 39.79, 39.39, 34.95, 34.08, 29.54, 28.66, 28.32, 25.89, 25.72, 25.66, 25.14, 25.08, 23.16, 8.70. UPLC-MS (ESI-MS) *m/z*: calculated for C₃₀H₄₆N₅O₃S⁺ 556.33, found 556.22 [M+H]⁺.



1-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl)-N-((S)-2-cyclohexyl-2-((S)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-propionamidopropanamido)ethyl)piperidine-4-

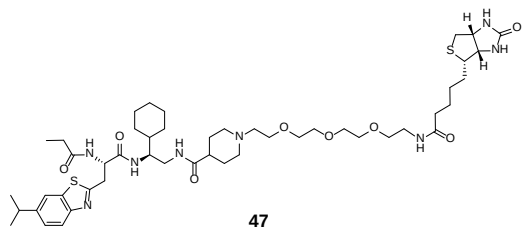
carboxamide (66): A suspension of compound **65** (120 mg, 0.22 mmol, 1 equiv.), T-Boc-n-amido-peg4-tos (126 mg, 0.28 mmol, 1.3 equiv.), K₂CO₃ (89 mg, 0.65 mmol, 3 equiv.) and Tetrabutylammonium iodide (8.0 mg, 0.02 mmol, 0.1 equiv.) in DMF (10 mL) was stirred at 60°C overnight. The reaction was cooled and diluted with EtOAc and H₂O. The organic layer was washed with saturated sodium bicarbonate, 1.0 M HCl, brine and dried over sodium sulfate. After removal of the solvent under vacuum, the residue was treated with TFA (2 ml) in DCM (10

mL) and stirred for 5 h at room temperature. This reaction mixture was concentrated and purified by HPLC to afford compound **66** (103 mg, 65%). ¹H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 7.42 (dd, *J* = 8.5, 1.4 Hz, 1H), 4.86 (dd, *J* = 8.9, 3.5 Hz, 1H), 3.85 – 3.60 (m, 16H), 3.57 – 3.36 (m, 4H), 3.28-3.23 (m, 2H), 3.17-3.05 (m, 4H), 2.53 – 2.40 (m, 1H), 2.32 (q, *J* = 7.6 Hz, 2H), 2.08 – 1.86 (m, 4H), 1.78 – 1.56 (m, 5H), 1.50 – 0.86 (m, 15H). HRMS (ESI-MS) *m/z*: calculated for C₃₈H₆₃N₆O₆S⁺ 731.4524, found 731.4515 [M+H]⁺.



N-((S)-2-cyclohexyl-2-((S)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-propionamidopropionamido)ethyl)-1-(1-(3',6'-dihydroxy-3-oxo-3H-spiro[isobenzofuran-1,9'-xanthen]-5-yl)-1-oxo-5,8,11-trioxa-2-azatridecan-13-yl)piperidine-4-carboxamide (46):

To a solution of **66** (30 mg, 0.04 mmol, 1 equiv.) and 5-Carboxyfluorescein N-hydroxysuccinimide ester (29 mg, 0.06 mmol, 1.5 equiv.) in DCM (5 mL) was added DIEA (21 μL, 0.12 mmol, 3 equiv.). The reaction was stirred at room temperature overnight and concentrated. The residue was purified by HPLC to get compound **46** (22 mg, 49%). ¹H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 8.23 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 7.40 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 2.2 Hz, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.61 (dd, *J* = 8.7, 2.1 Hz, 2H), 4.85-4.83 (m, 1H), 3.94 – 3.56 (m, 18H), 3.51-3.38 (m, 4H), 3.19 – 2.77 (m, 4H), 2.48-2.42 (m, 1H), 2.30 (q, *J* = 7.6 Hz, 2H), 2.13 – 1.87 (m, 4H), 1.68-1.59 (m, 5H), 1.40 – 0.88 (m, 15H). HRMS (ESI-MS) *m/z*: calculated for C₅₉H₇₃N₆O₁₂S⁺ 1089.5002, found 1089.4994 [M+H]⁺.



N-((S)-2-cyclohexyl-2-((S)-3-(6-isopropylbenzo[d]thiazol-2-yl)-2-propionamidopropanamido)ethyl)-1-(13-oxo-17-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-3,6,9-trioxa-12-azaheptadecyl)piperidine-4-carboxamide (47):

To a solution of **66** (30 mg, 0.04 mmol, 1 equiv.) and (+)-Biotin N-hydroxysuccinimide ester (21 mg, 0.06 mmol, 1.5 equiv.) in DCM (5 mL) was added DIEA (21 μ L, 0.12 mmol, 3 equiv.). The reaction was stirred at room temperature overnight and concentrated. The residue was purified by HPLC to get compound **47** (25 mg, 64%). ^1H NMR (400 MHz, MeOD) δ 7.88 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.67 (d, J = 9.5 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 5.18-5.11 (m, 1H), 4.51 (dd, J = 7.8, 5.0 Hz, 1H), 4.31 (dd, J = 7.8, 4.5 Hz, 1H), 3.87 – 3.79 (m, 3H), 3.71 – 3.59 (m, 10H), 3.56-3.36 (m, 10H), 3.26 – 3.18 (m, 1H), 3.13-3.04 (m, 2H), 3.00 – 2.89 (m, 2H), 2.72 (d, J = 12.8 Hz, 1H), 2.48-2.41 (m, 1H), 2.32 (q, J = 7.6 Hz, 2H), 2.23 (t, J = 7.3 Hz, 2H), 2.07-1.93 (m, 4H), 1.78 – 1.55 (m, 9H), 1.48 – 0.90 (m, 17H). HRMS (ESI-MS) m/z : calculated for $\text{C}_{48}\text{H}_{77}\text{N}_8\text{O}_8\text{S}_2^+$ 957.5300, found 957.5298 $[\text{M}+\text{H}]^+$.

Supplementary References

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