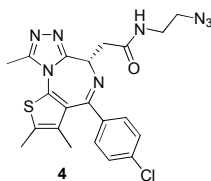


Supporting Information

A “Click Chemistry Platform” for the Rapid Synthesis of Bispecific Molecules for Inducing Protein Degradation.

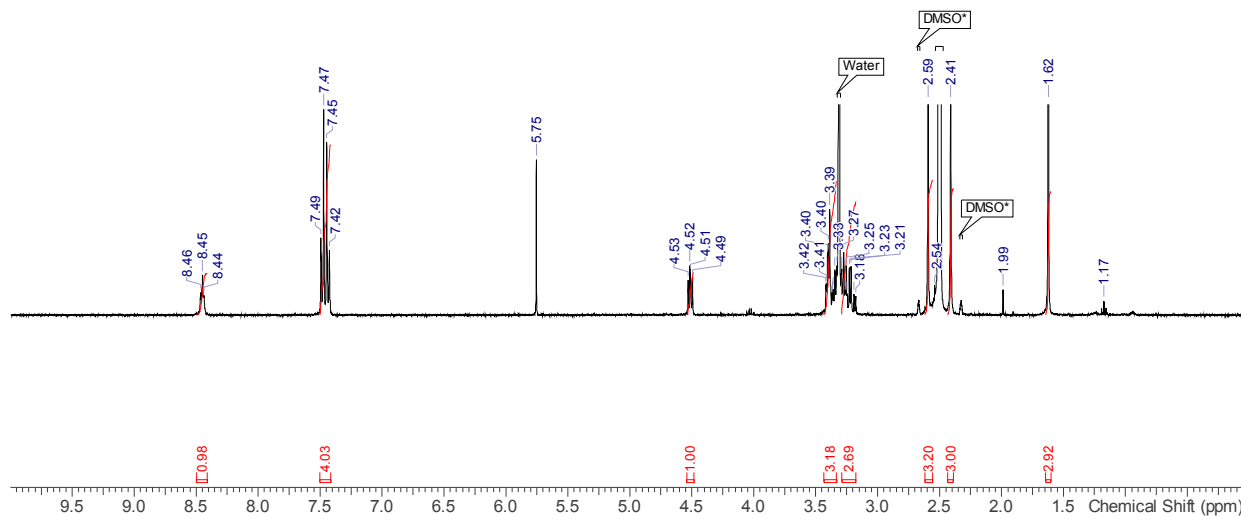
Ryan P. Wurz,* Ken Dellamaggiore, Hannah Dou, Noelle Javier, Mei-Chu Lo, Dane Mohl, Christine Sastri, J. Russell Lipford, and Victor J. Cee.

Spectra for JQ-1-azide (4)	S2
Synthesis of IMiD 0-4 (8a-e) and VHL 0-4 (10a-e) Alkynes	S3
¹ H NMR and ¹³ C NMR spectra for PROTACs	S28
Table 1: BRD4 protein degradation in the NCI-H838 cell line	S48



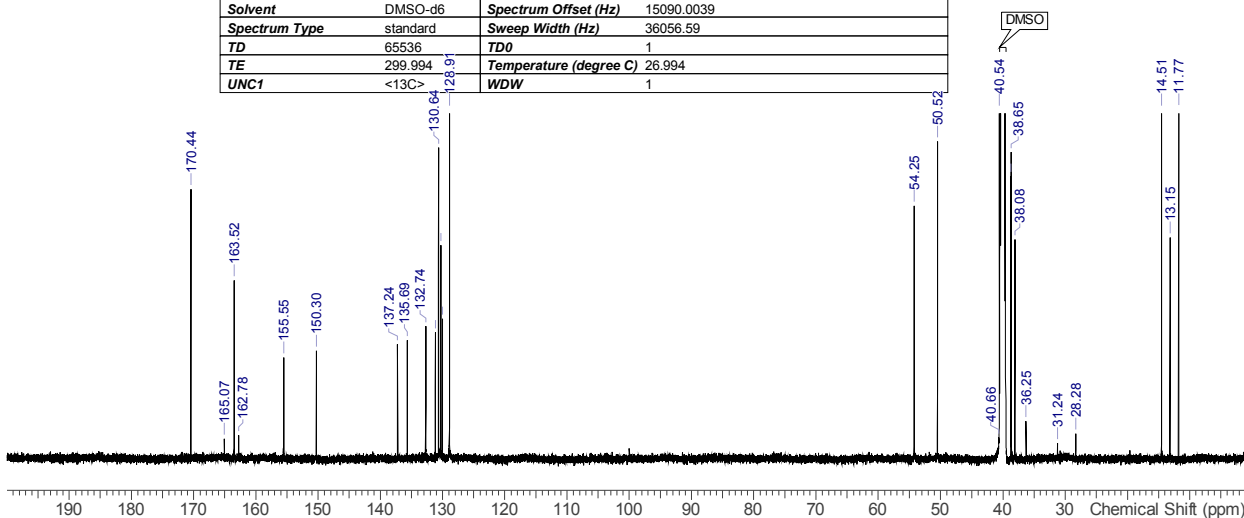
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Spectrum Offset (Hz)	2398.9685	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.45 (1 H, br t, *J*=5.2 Hz), 7.42 - 7.50 (4 H, m), 5.75 (1 H, s), 4.51 (1 H, dd, *J*=8.2, 5.9 Hz), 3.33 - 3.44 (3 H, m), 3.17 - 3.29 (3 H, m), 2.59 (3 H, s), 2.41 (3 H, s), 1.62 (3 H, s)

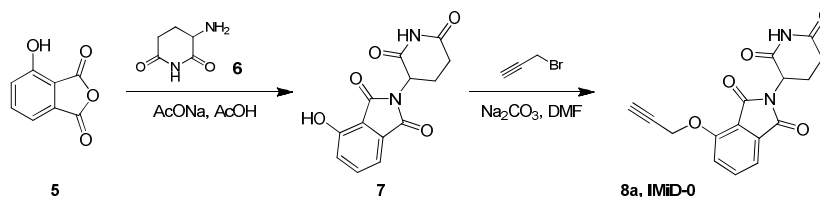




Acquisition Time (sec)	0.9088	
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Date Stamp	04 Jul 2016 18:50:34	
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SI	131072	SSB
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Solvent	DMSO-d6	Spectrum Offset (Hz)
Spectrum Type	standard	Sweep Width (Hz)
TD	65536	TD0
TE	299.994	Temperature (degree C)
UNC1	<13C>	WDW



2-(2,6-dioxopiperidin-3-yl)-4-(prop-2-yn-1-yloxy)isoindoline-1,3-dione (8a, IMiD-0).



Step 1: A mixture of **5** (50 g, 304 mmol), **6** (50.1 g, 304 mmol, HCl salt) and NaOAc (50 g, 609 mmol) in HOAc (600 mL) was stirred at 110 °C for 12 h. The solvent was evaporated, water (250 mL) was added, and the resulting solution was stirred for 15 min. The solid was filtered and concentrated to give compound **7** (73 g, 266 mmol, 87% yield) as a black solid which was used in subsequent steps without further purification.

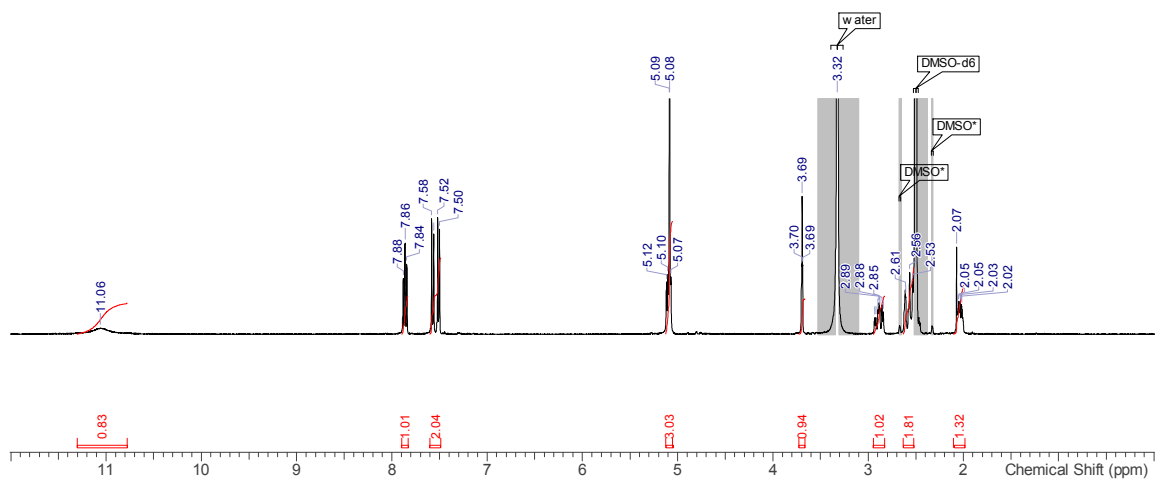
Step 2: Intermediate **7** (10 g, 36.5 mmol), propargyl bromide (6.1 g, 51.1 mmol) and Na₂CO₃ (5.8 g, 54.7 mmol) in DMF (80 mL) was stirred at 60 °C for 24 h. HPLC analysis of the reaction mixture showed ~50% of desired product was detected. The

solvent was evaporated, water (150 mL) was added, and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The crude residue was purified by reverse phase column chromatography (RP-18, H₂O/MeOH = 1:1) to furnish the title compound (**8a**, **IMiD-0**, 6.0 g, 19.2 mmol, 53% yield) as a tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.06 (1 H, br s), 7.86 (1 H, t, *J*=7.9 Hz), 7.57 (1 H, d, *J*=8.1 Hz), 7.51 (1 H, d, *J*=7.1 Hz), 5.05 - 5.13 (3 H, m), 3.69 (1 H, t, *J*=2.2 Hz), 2.82 - 2.95 (1 H, m), 2.52 - 2.63 (2 H, m), 1.99 - 2.10 (1 H, m). ¹³C NMR (151 MHz, DMSO-*d*₆) δ ppm 173.25, 170.37, 167.18, 165.64, 154.76, 137.32, 133.83, 120.73, 117.33, 116.51, 79.90, 78.74, 56.94, 49.29, 31.41, 22.43. *m/z* (ESI, +ve) 313.0 (M+H)⁺.



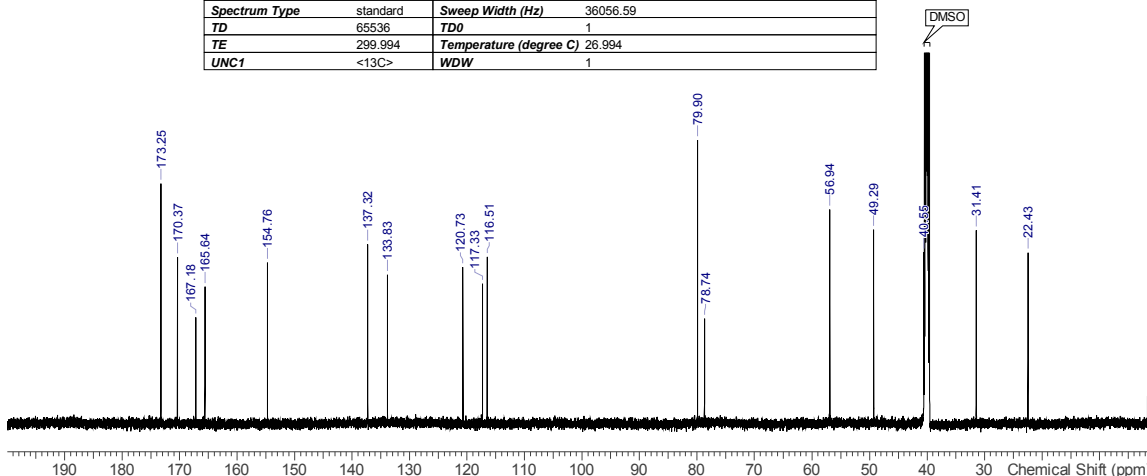
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Spectrum Offset (Hz)	2877.5083	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.06 (1 H, br s), 7.86 (1 H, t, *J*=7.9 Hz), 7.57 (1 H, d, *J*=8.1 Hz), 7.51 (1 H, d, *J*=7.1 Hz), 5.05 - 5.13 (3 H, m), 3.69 (1 H, t, *J*=2.2 Hz), 2.82 - 2.95 (1 H, m), 2.52 - 2.63 (2 H, m), 1.99 - 2.10 (1 H, m)

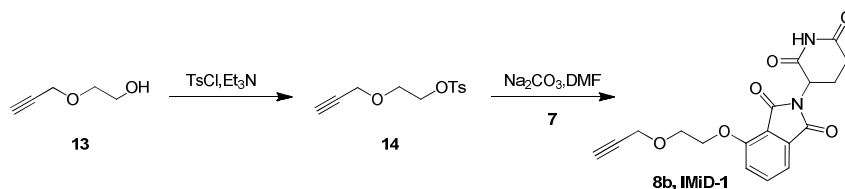




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Date Stamp	14 Oct 2016 00:02:27		
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Pulse Sequence	zpgg30	Receiver Gain	2050.00
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Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
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TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



2-(2,6-dioxopiperidin-3-yl)-4-(2-(prop-2-yn-1-yloxy)ethoxy)isoindoline-1,3-dione (8b, IMiD-1).



Step 1: To a solution of **13** (10 g, 100 mmol) in DCM (150 mL) was added Et₃N (30 g, 300 mmol, 41 mL) and 4-methylbenzenesulfonyl chloride (29 g, 150 mmol). The mixture was stirred at 25 °C for 1 h then concentrated under reduced pressure to remove the solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc = 20/1 to 3:1) to afford compound **14** (19 g, 75 mmol, 75% yield) as a yellow oil.

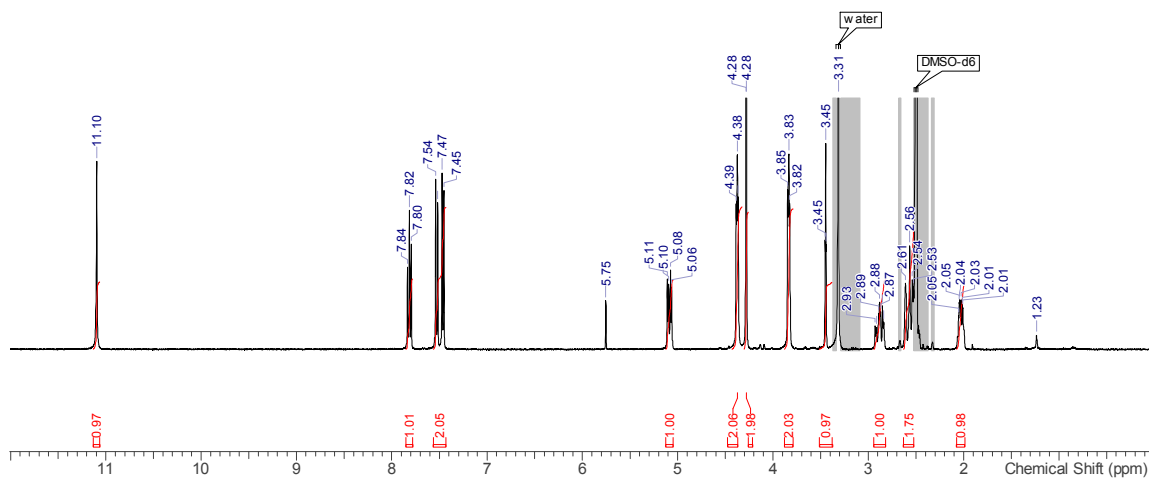
Step 2: A mixture of compound **14** (8.9 g, 35 mmol), **7** (8 g, 29 mmol) and Na₂CO₃ (4.6 g, 44 mmol) in DMF (100 mL) was stirred at 80 °C for 42 h. HPLC showed completion

of the reaction. The mixture was added to H₂O (300 mL), extracted with DCM (3 x 300 mL) and the combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ filtered and concentrated under reduced pressure. The crude residue was purified by reverse phase HPLC (using a gradient of 5-95% 0.1% TFA/AcCN and 0.1% TFA/H₂O) to furnish the title compound (**8b**, **IMiD-1**, 6.7 g, 18.4 mmol, 63% yield) as a white solid. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 11.10 (1 H, s), 7.82 (1 H, t, *J*=7.9 Hz), 7.53 (1 H, d, *J*=8.7 Hz), 7.46 (1 H, d, *J*=7.0 Hz), 5.09 (1 H, dd, *J*=12.9, 5.4 Hz), 4.32 - 4.43 (2 H, m), 4.28 (2 H, d, *J*=2.3 Hz), 3.79 - 3.88 (2 H, m), 3.38 - 3.51 (1 H, m), 2.82 - 2.94 (1 H, m), 2.52 - 2.63 (2 H, m), 1.99 - 2.07 (1 H, m). ¹³C NMR (151 MHz, *DMSO-d*₆) δ ppm 173.25, 170.40, 167.28, 165.76, 156.20, 137.49, 133.74, 120.43, 116.84, 115.93, 80.73, 77.78, 69.08, 67.82, 58.37, 49.24, 31.43, 22.47. *m/z* (ESI, +ve) 357.2 (M+H)⁺.

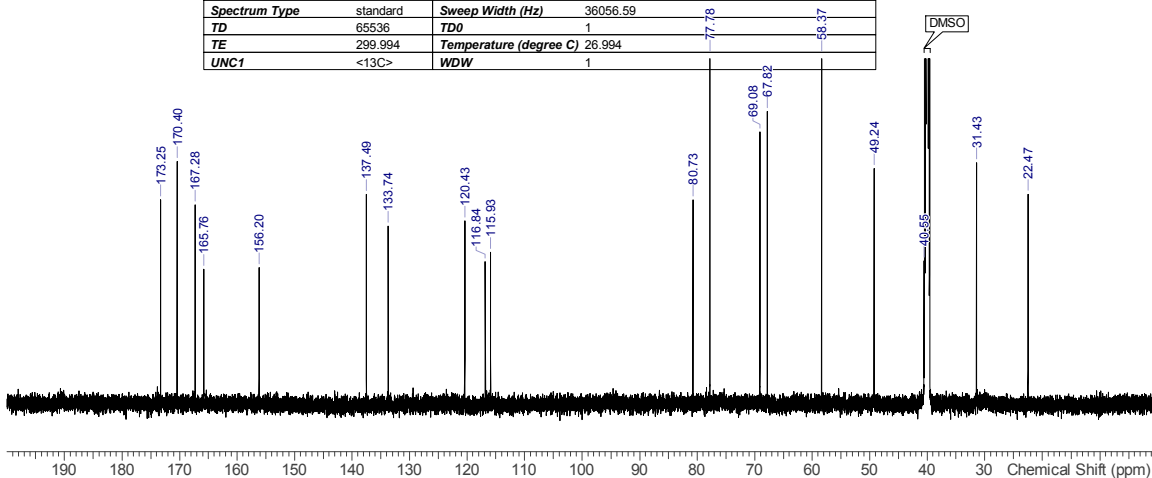


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Sweep Width (Hz)	6793.27		

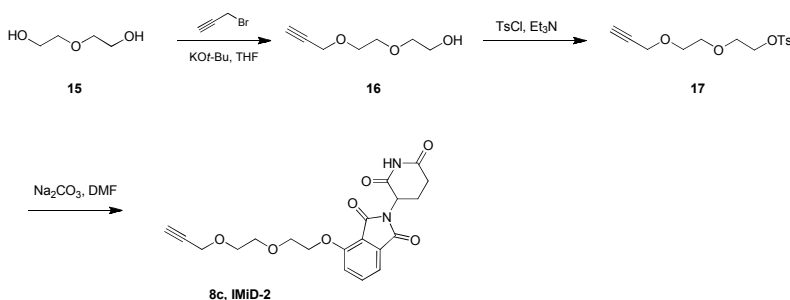
¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.10 (1 H, s), 7.82 (1 H, t, *J*=7.9 Hz), 7.53 (1 H, d, *J*=8.7 Hz), 7.46 (1 H, d, *J*=7.0 Hz), 5.09 (1 H, dd, *J*=12.9, 5.4 Hz), 4.32 - 4.43 (2 H, m), 4.28 (2 H, d, *J*=2.3 Hz), 3.79 - 3.88 (2 H, m), 3.38 - 3.51 (1 H, m), 2.82 - 2.94 (1 H, m), 2.52 - 2.63 (2 H, m), 1.99 - 2.07 (1 H, m)



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SI	32768	SSB	0
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Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



2-(2,6-dioxopiperidin-3-yl)-4-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethoxy)isoindoline-1,3-dione (8c, IMiD-2).



Step 1: To a suspension of KO t -Bu (116 g, 1 mol) in dry THF (1 L) was added compound **15** (200 g, 1.9 mol, 179 mL) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to stir at 20 °C for 30 min then propargyl bromide (140 g, 940 mmol, 101 mL) was added dropwise. The resulting mixture was allowed to stir at 80 °C for 18 h. The mixture was filtered and concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc = 50/1 to 0:1) furnish compound **16** (40 g, 277 mmol, 15% yield) as a yellow oil.

Step 2: To a solution of compound **16** (10 g, 69 mmol) in DCM (100 mL) was added Et₃N (21 g, 208 mmol, 29 mL) and 4-methylbenzenesulfonyl chloride (20 g, 104 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove solvent and the crude residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc = 20/1 to 3:1) to furnish compound **17** (20 g, 67 mmol, 97% yield) as a yellow oil.

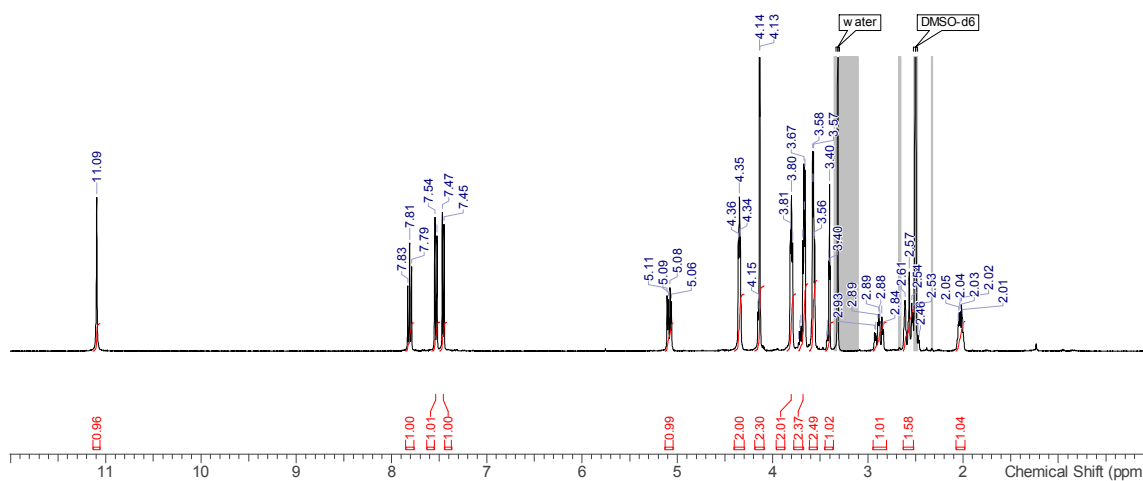
Step 3: A mixture of compound **17** (10 g, 35 mmol), **7** (8 g, 29 mmol) and Na₂CO₃ (4.6 g, 44 mmol) in DMF (100 mL) was stirred at 80 °C for 42 h. The reaction mixture was added to H₂O (300 mL), extracted with DCM (3 x 300 mL) and the combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ filtered and concentrated under reduced pressure. The crude residue was purified by reverse phase HPLC (using a gradient of 5-95% 0.1% TFA/AcCN and 0.1% TFA/H₂O) to afford the title compound (**8b**, **IMiD-2**, 6.7 g, 16 mmol, 55% yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.09 (1 H, s), 7.81 (1 H, t, *J*=7.9 Hz), 7.53 (1 H, d, *J*=8.5 Hz), 7.46 (1

H, d, $J=7.0$ Hz), 5.08 (1 H, dd, $J=12.9, 5.4$ Hz), 4.30 - 4.40 (2 H, m), 4.09 - 4.19 (2 H, m), 3.76 - 3.85 (2 H, m), 3.63 - 3.73 (2 H, m), 3.53 - 3.61 (2 H, m), 3.36 - 3.45 (1 H, m), 2.80 - 2.94 (1 H, m), 2.52 - 2.63 (2 H, m), 1.98 - 2.08 (1 H, m). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ ppm 173.25, 170.41, 167.29, 165.75, 156.31, 137.46, 133.73, 120.55, 116.83, 115.89, 80.82, 77.57, 70.36, 69.35, 69.17, 69.05, 57.98, 49.24, 31.43, 22.47. m/z (ESI, +ve) 401.2 ($\text{M}+\text{H}$) $^+$.



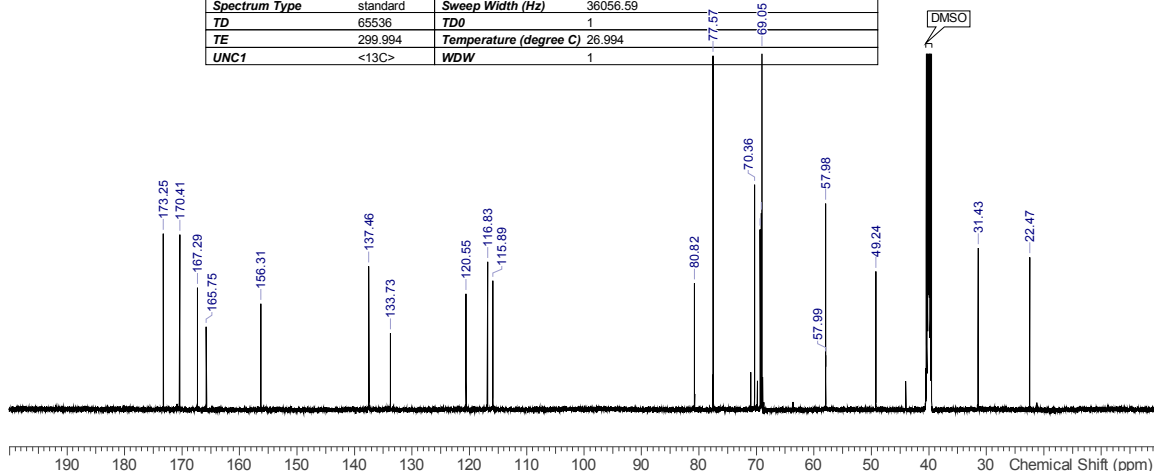
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Spectrum Offset (Hz)	2877.5083	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.09 (1 H, s), 7.81 (1 H, t, $J=7.9$ Hz), 7.53 (1 H, d, $J=8.5$ Hz), 7.46 (1 H, d, $J=7.0$ Hz), 5.08 (1 H, dd, $J=12.9, 5.4$ Hz), 4.30 - 4.40 (2 H, m), 4.09 - 4.19 (2 H, m), 3.76 - 3.85 (2 H, m), 3.63 - 3.73 (2 H, m), 3.53 - 3.61 (2 H, m), 3.36 - 3.45 (1 H, m), 2.80 - 2.94 (1 H, m), 2.52 - 2.63 (2 H, m), 2.38 - 2.48 (1 H, m), 1.98 - 2.08 (1 H, m)

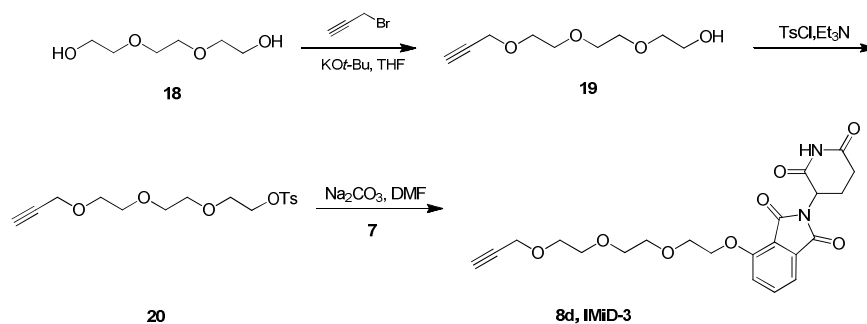




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Pulse Sequence	zpgpg30	Receiver Gain	2050.00
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Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



2-(2,6-dioxopiperidin-3-yl)-4-(2-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethoxy)ethoxy)isoindoline-1,3-dione (**8d**, IMiD-3).



Step 1: To a suspension of KOt-Bu (82 g, 731 mmol) in dry THF (1 L) was added compound **18** (200 g, 1.3 mol) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to stir at 20 °C for 30 min then treated with propargyl bromide (79 g, 665 mmol, 57 mL) slowly dropwise. The resulting mixture was allowed to stir at 80 °C for

18 h. The mixture was filtered and concentrated under reduced pressure and the crude residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc = 50/1 to 0:1) to afford compound **19** (54 g, crude) as a yellow oil.

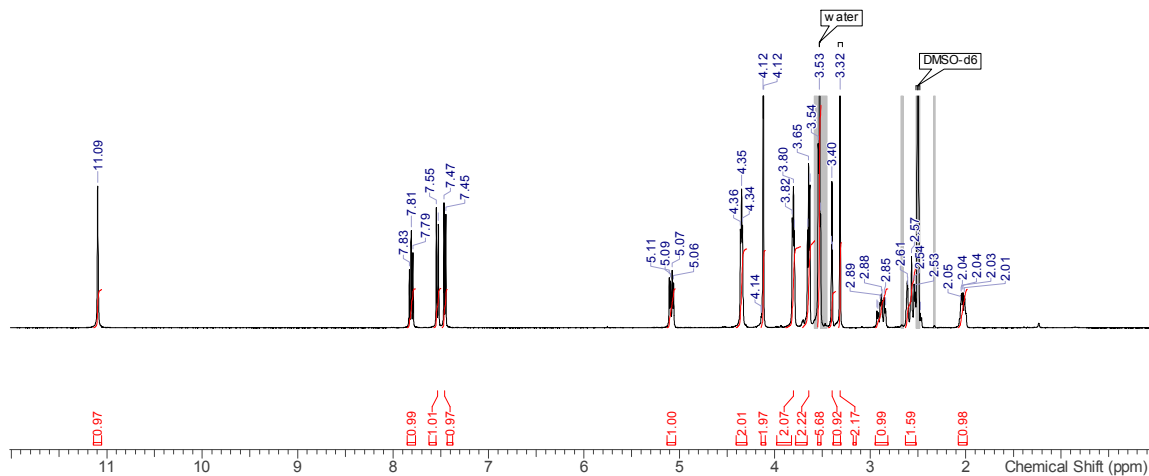
Step 2: To a solution of compound **19** (10 g, 53 mmol) in DCM (100 mL) was added Et₃N (16 g, 160 mmol, 22 mL) and 4-methylbenzenesulfonyl chloride (15 g, 80 mmol). The mixture was stirred at 25 °C for 1 h then the reaction mixture was concentrated under reduced pressure to remove solvent and the crude residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc = 20/1 to 3:1) to furnish compound **20** (11 g, 32 mmol, 60% yield) as a yellow oil.

Step 3: A mixture of compound **20** (12 g, 35 mmol), **7** (8 g, 29 mmol) and Na₂CO₃ (4.6 g, 44 mmol) in DMF (100 mL) was stirred at 80 °C for 42 h. The reaction mixture was added to H₂O (300 mL), extracted with DCM (3 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ filtered and concentrated under reduced pressure. The crude residue was purified by reverse phase HPLC (using a gradient of 5-95% 0.1% TFA/AcCN and 0.1% TFA/H₂O) to afford the title compound (**8d**, **IMiD-3**, 5.4 g, 12 mmol, 41% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.09 (1 H, s), 7.81 (1 H, t, *J*=7.9 Hz), 7.53 (1 H, d, *J*=8.5 Hz), 7.46 (1 H, d, *J*=7.3 Hz), 5.08 (1 H, dd, *J*=12.9, 5.4 Hz), 4.29 - 4.40 (2 H, m), 4.12 (2 H, d, *J*=2.3 Hz), 3.73 - 3.88 (2 H, m), 3.58 - 3.71 (2 H, m), 3.52 - 3.55 (6 H, m), 3.40 (1 H, t, *J*=2.3 Hz), 3.32 (2 H, s), 2.82 - 2.95 (1 H, m), 2.52 - 2.63 (2 H, m), 1.98 - 2.08 (1 H, m). ¹³C NMR (151 MHz, DMSO-*d*₆) δ ppm 173.25, 170.40, 167.29, 165.75, 156.33, 137.46, 133.73, 120.55, 116.82, 115.87, 80.82, 77.54, 70.63, 70.29, 69.97, 69.35, 69.17, 68.99, 57.95, 49.24, 31.44, 22.47. *m/z* (ESI, +ve) 445.2 (M+H)⁺.

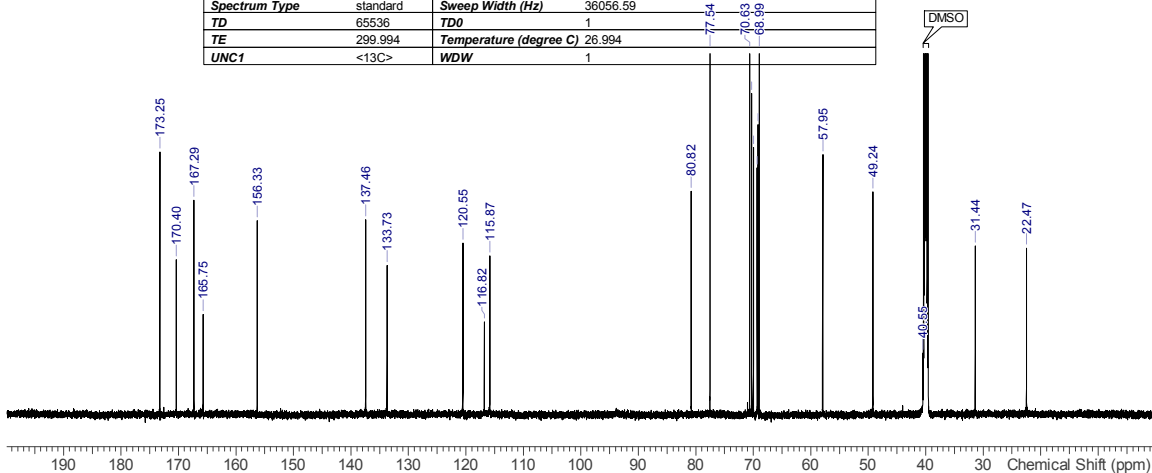


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Sweep Width (Hz)	6793.27		

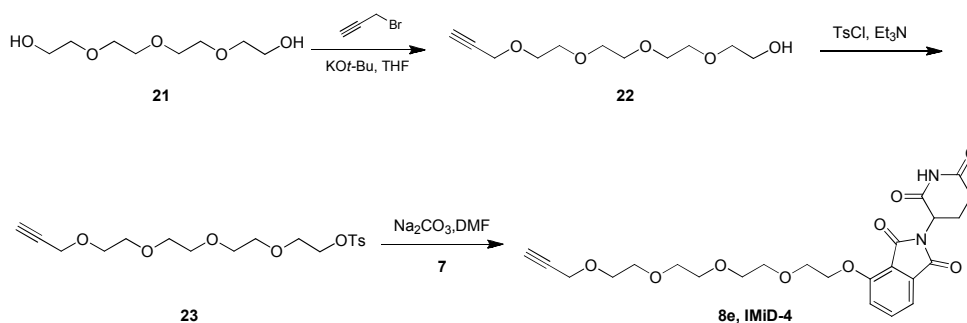
¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.09 (1 H, s), 7.81 (1 H, t, *J*=7.9 Hz), 7.53 (1 H, d, *J*=8.5 Hz), 7.46 (1 H, d, *J*=7.3 Hz), 5.08 (1 H, dd, *J*=12.9, 5.4 Hz), 4.29 - 4.40 (2 H, m), 4.12 (2 H, d, *J*=2.3 Hz), 3.73 - 3.88 (2 H, m), 3.58 - 3.71 (2 H, m), 3.52 - 3.55 (6 H, m), 3.40 (1 H, t, *J*=2.3 Hz), 3.32 (2 H, s), 2.82 - 2.95 (1 H, m), 2.52 - 2.63 (2 H, m), 1.98 - 2.08 (1 H, m)



Acquisition Time (sec)	0.9088	Comment	123691-15-9 in DMSO-d6
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SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



4-(3,6,9,12-tetraoxapentadec-14-yn-1-yloxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (8e, IMiD-4).



Step 1: To a suspension of KO t -Bu (64 g, 566 mmol) in dry THF (1 L) was added compound **21** (200 g, 1 mol, 177 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to stir at 20 °C for 30 min then propargyl bromide (77 g, 515 mmol, 55 mL) was added dropwise. The resulting mixture was allowed to stir at 80 °C for 18 h then the reaction mixture was filtered and concentrated under reduced pressure and the resulting crude residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc = 50/1 to 0:1) to furnish compound **22** (19 g, crude) as a yellow oil.

Step 2: To a solution of compound **22** (10 g, 43 mmol) in DCM (100 mL) was added Et₃N (13 g, 129 mmol, 18 mL) and 4-methylbenzenesulfonyl chloride (12 g, 65 mmol). The mixture was stirred at 25 °C for 1 h then the reaction mixture was concentrated under reduced pressure to remove solvent and the crude residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc = 20/1 to 2:1) to furnish compound **23** (15 g, 39 mmol, 90% yield) as a yellow oil.

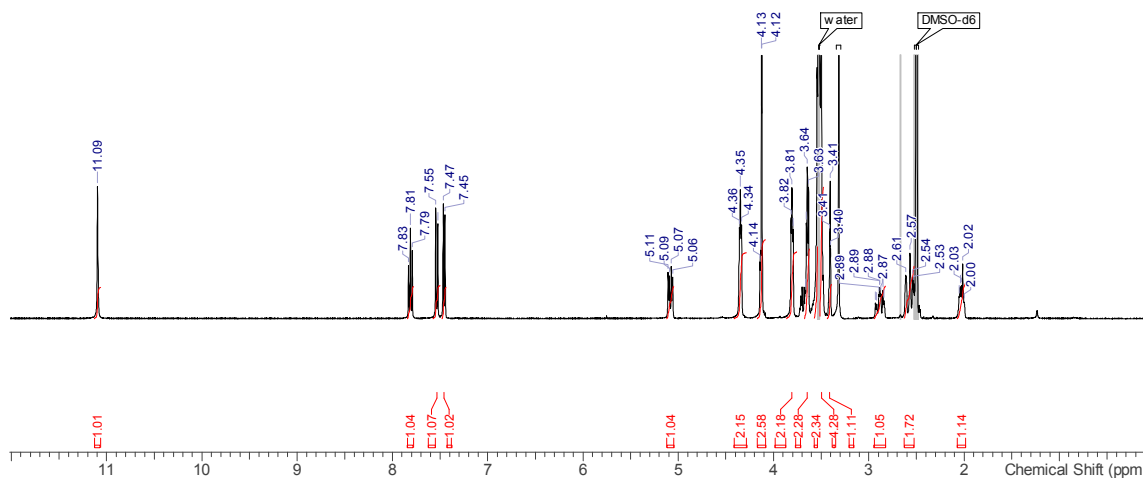
Step 3: A mixture of compound **23** (13 g, 35 mmol), **7** (8 g, 29 mmol) and Na₂CO₃ (4.6 g, 44 mmol) in DMF (100 mL) was stirred at 80 °C for 42 h. The mixture was added to H₂O (300 mL), extracted with DCM (3 x 300 mL) and the combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ filtered and concentrated under reduced pressure. The crude residue was purified by reverse phase HPLC (using a gradient of 5-95% 0.1% TFA/AcCN and 0.1% TFA/H₂O) to afford the title compound (**8e**, IMiD-4,

6.8 g, 13.3 mmol, 45% yield) as a pale yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.09 (1 H, s), 7.81 (1 H, t, $J=7.9$ Hz), 7.53 (1 H, d, $J=8.5$ Hz), 7.46 (1 H, d, $J=7.3$ Hz), 5.08 (1 H, dd, $J=12.6, 5.4$ Hz), 4.28 - 4.41 (3 H, m), 4.08 - 4.17 (3 H, m), 3.75 - 3.86 (3 H, m), 3.62 - 3.67 (3 H, m), 3.54 - 3.57 (2 H, m), 3.39 - 3.44 (1 H, m), 2.82 - 2.94 (1 H, m), 2.52 - 2.63 (2 H, m), 1.98 - 2.07 (1 H, m). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ ppm 173.25, 170.40, 167.29, 165.74, 156.33, 137.46, 133.73, 120.55, 116.82, 115.87, 80.82, 77.55, 70.64, 70.31, 70.23, 69.95, 69.35, 69.17, 68.98, 57.95, 49.24, 31.43, 22.47. m/z (ESI, +ve) 489.2 ($\text{M}+\text{H}$) $^+$.



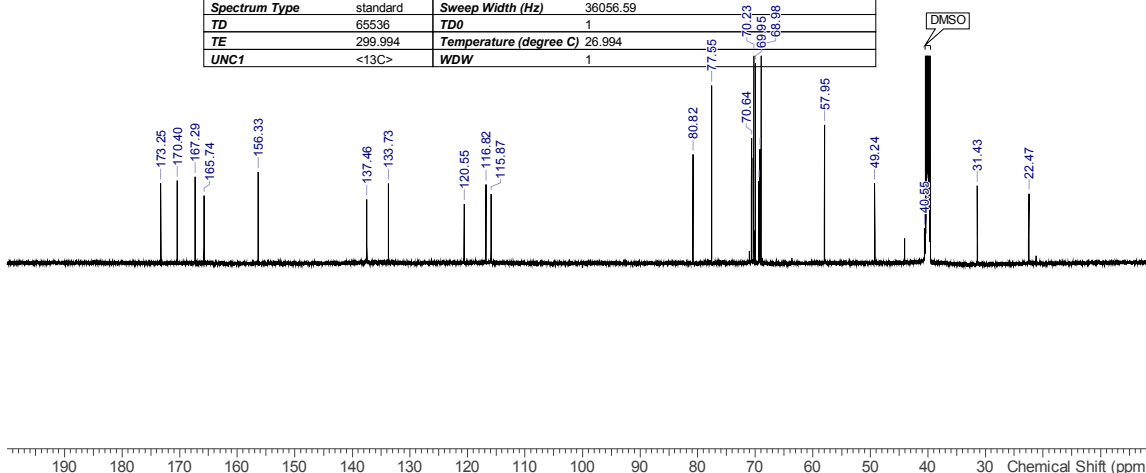
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Original Points Count	32768	Points Count	32768
SW (cyclical) (Hz)	6793.48	Solvent	$\text{DMSO}-d_6$
Spectrum Offset (Hz)	2877.5083	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 11.09 (1 H, s), 7.81 (1 H, t, $J=7.9$ Hz), 7.53 (1 H, d, $J=8.5$ Hz), 7.46 (1 H, d, $J=7.3$ Hz), 5.08 (1 H, dd, $J=12.6, 5.4$ Hz), 4.28 - 4.41 (3 H, m), 4.08 - 4.17 (3 H, m), 3.75 - 3.86 (3 H, m), 3.62 - 3.67 (3 H, m), 3.54 - 3.57 (2 H, m), 3.39 - 3.44 (1 H, m), 2.82 - 2.94 (1 H, m), 2.52 - 2.63 (2 H, m), 1.98 - 2.07 (1 H, m)

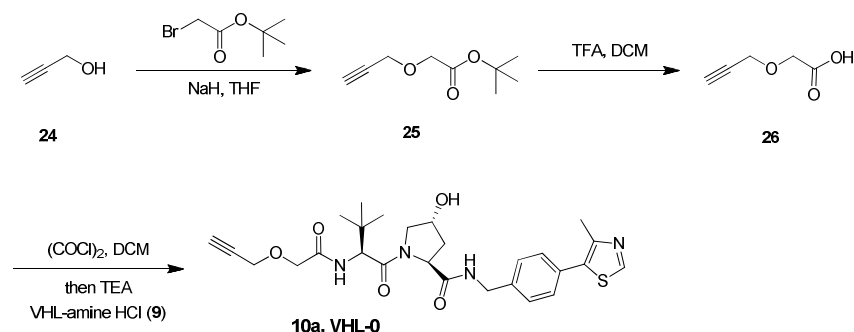




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Number of Transients	4096	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
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Pulse Sequence	zpgpg30	Receiver Gain	2050.00
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SFO1	150.91789806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(2-(prop-2-yn-1-yloxy)acetamido)butanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (10a (VHL-0)).



Step 1: To a solution of propargyl alcohol (**24**, 10 g, 178 mmol, 10 mL, 1.0 equiv.) in THF (150 mL) was added NaH (60 wt%, 12 g, 303 mmol, 1.7 equiv.) portion-wise at 0 °C. After addition, the mixture was stirred at 0 °C for 1 h then *tert*-butyl 2-bromoacetate (34.8 g, 178 mmol, 26 mL, 1.0 equiv.) was added to the mixture at 0 °C. The mixture

was stirred at 15 °C for 12 h. The mixture was quenched with a saturation solution of NH₄Cl (100 mL), extracted with EtOAc (2 x 80 mL) and the combined organic layers, were washed with brine (2 x 80 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO₂, Petroleum ether / EtOAc =10:1 to 5:1) to furnish (**25**, 12 g, 70 mmol, 40% yield) as a colorless oil.

Step 2: To a solution of **25** (5 g, 29 mmol, 1.0 equiv.) in DCM (60 mL) was added TFA (33.5 g, 294 mmol, 22 mL, 10 equiv.) drop-wise. After addition, the mixture was stirred at 15 °C for 1 h. The mixture was concentrated in vacuum to give carboxylic acid **26** (3.5 g, crude) as a brown oil.

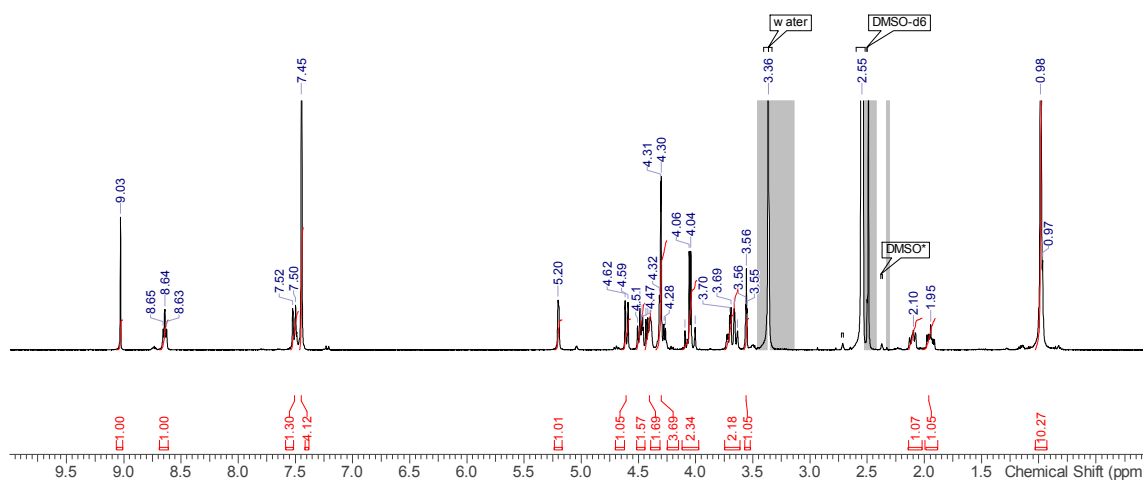
Step 3: To a solution of crude carboxylic acid **26** (684 mg, 6.0 mmol, 1.0 equiv.) in DCM (50 mL) was added (COCl)₂ (1.9 g, 15 mmol, 1.31 mL, 2.5 equiv.) followed by DMF (438 mg, 6 mmol, 0.5 mL, 1.0 equiv.) drop-wise. After addition, the mixture was stirred at 15 °C for 1 h, then the reaction mixture was concentrated under reduced pressure, the residue was diluted with THF (50 mL), VHL-amine HCl salt (**9**, 2.8 g, 6.0 mmol, 1.0 equiv.) and TEA (3.04 g, 30 mmol, 4.16 mL, 5.0 equiv.) were added to the mixture, then it was stirred at 40 °C for 12 h. The reaction mixture was quenched with water (80 mL), extracted with EtOAc (2 x 80 mL), the combined organic phase was washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (using a gradient of 5-95% 0.1% TFA/AcCN and 0.1% TFA/H₂O) to afford the title compound (**10a**, **VHL-0**, 1.40 g, 2.64 mmol, 44% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.03 (1 H, s), 8.64 (1 H, t, *J*=5.9 Hz), 7.47 - 7.54 (1 H, m), 7.45 (4 H, s), 5.20 (1 H, br s), 4.60 (1 H, d, *J*=9.5 Hz), 4.44 - 4.52 (1 H, m), 4.37 - 4.44 (2 H, m), 4.25 - 4.35 (4 H, m), 3.97 - 4.12 (2 H, m), 3.61 - 3.75 (2 H, m), 3.56 (1 H, t, *J*=2.3 Hz), 2.10 (1 H, br s), 1.95 (1 H, s), 0.93 - 1.03 (9 H, m). ¹³C NMR (151 MHz, DMSO-*d*₆) δ ppm 172.23, 169.60, 168.42, 151.93,

148.23, 139.92, 131.61, 130.18, 129.36, 129.17, 127.94, 79.99, 78.44, 69.36, 68.50,
59.21, 58.41, 57.06, 56.27, 42.16, 38.39, 36.23, 26.75, 26.67, 16.41. m/z (ESI, +ve)
527.2 (M+H)⁺.



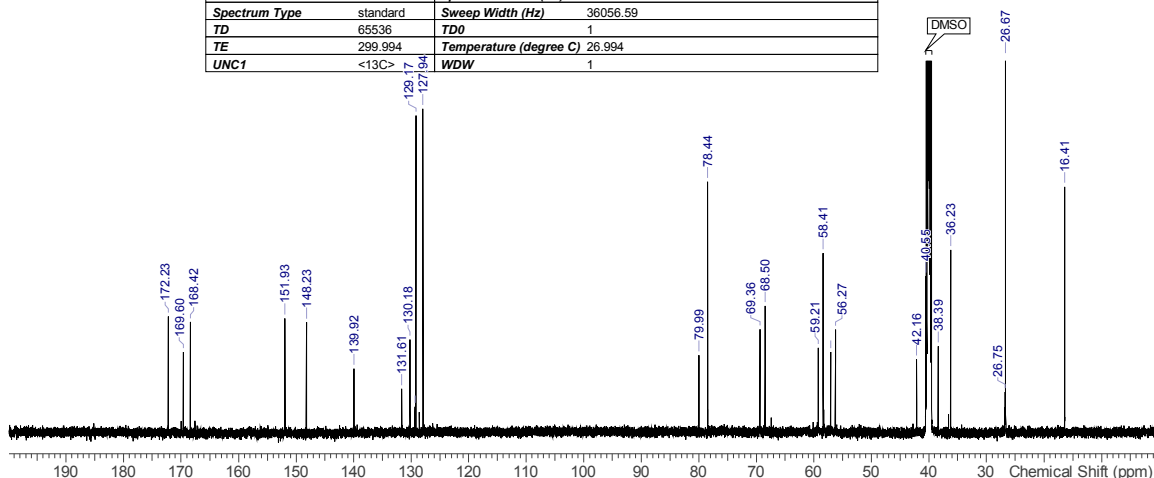
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Spectrum Offset (Hz)	2895.7527	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.03 (1 H, s), 8.64 (1 H, t, *J*=5.9 Hz), 7.47 - 7.54 (1 H, m), 7.45 (4 H, s), 5.20 (1 H, br s), 4.60 (1 H, d, *J*=9.5 Hz), 4.44 - 4.52 (1 H, m), 4.37 - 4.44 (2 H, m), 4.25 - 4.35 (4 H, m), 3.97 - 4.12 (2 H, m), 3.61 - 3.75 (2 H, m), 3.56 (1 H, t, *J*=2.3 Hz), 2.10 (1 H, br s), 1.95 (1 H, s), 0.93 - 1.03 (9 H, m)

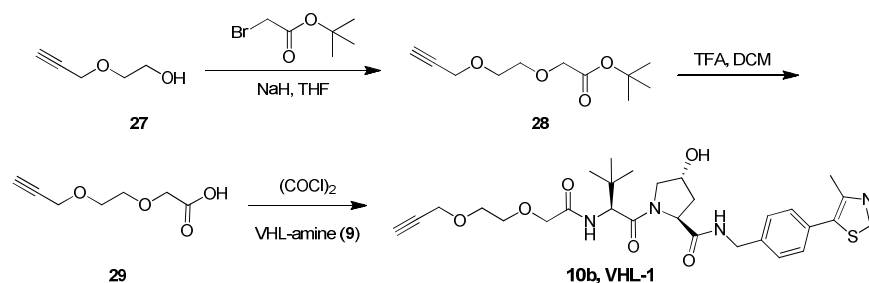




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Number of Transients	4096	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
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Pulse Sequence	zpgg30	Receiver Gain	181.00
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SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(2-(2-(prop-2-yn-1-yloxy)ethoxy)acetamido)butanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**10b**, VHL-1)



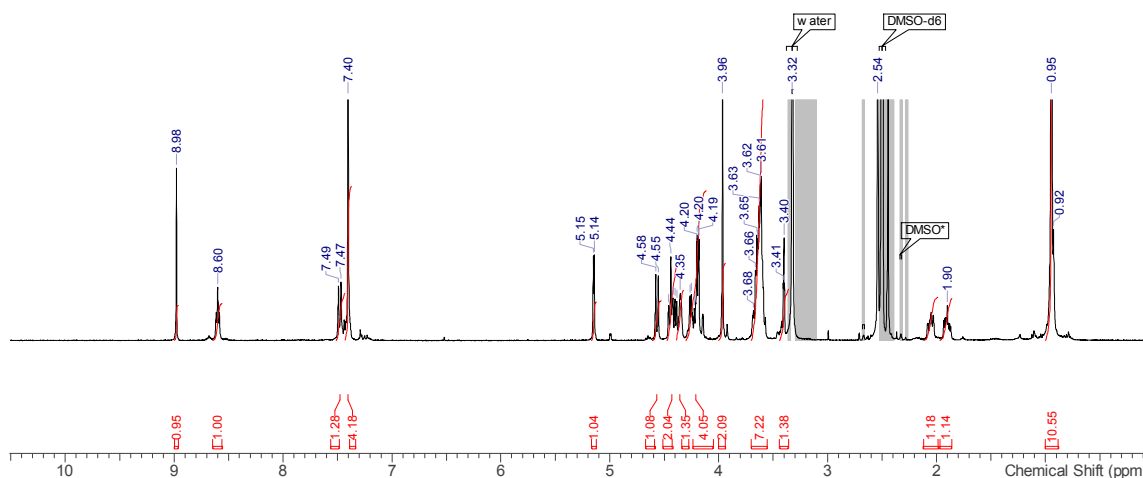
Steps 1 and 2: Prepared according to the procedure used for the synthesis of **10a**, VHL-0 affording the carboxylic acid **29** (34 g, 53% yield) from *tert*-butyl-ester **28** (30 g).

Step 3: Prepared according to the same procedure for the synthesis of **10a**, **VHL-0** affording the title compound (**10b**, **VHL-1**, 2.0 g, 40% yield) as a light yellow syrup. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.98 (1 H, s), 8.60 (1 H, t, $J=6.1$ Hz), 7.48 (1 H, br d, $J=9.5$ Hz), 7.40 (4 H, s), 5.15 (1 H, d, $J=3.5$ Hz), 4.57 (1 H, d, $J=9.5$ Hz), 4.39 - 4.47 (2 H, m), 4.37 (1 H, br d, $J=13.7$ Hz), 4.12 - 4.30 (4 H, m), 3.96 (2 H, s), 3.56 - 3.70 (7 H, m), 3.36 - 3.44 (1 H, m), 1.90 (1 H, br s), 0.88 - 1.00 (9 H, m). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ ppm 172.25, 169.61, 169.09, 151.92, 148.23, 139.93, 131.61, 130.18, 129.35, 129.16, 128.60, 127.92, 80.64, 77.73, 77.70, 70.67, 70.51, 70.03, 69.36, 68.66, 59.21, 58.02, 57.04, 56.21, 42.15, 40.92, 38.39, 36.17, 26.76, 26.66, 16.44, 16.41. m/z (ESI, +ve) 571.2 ($\text{M}+\text{H}$) $^+$.



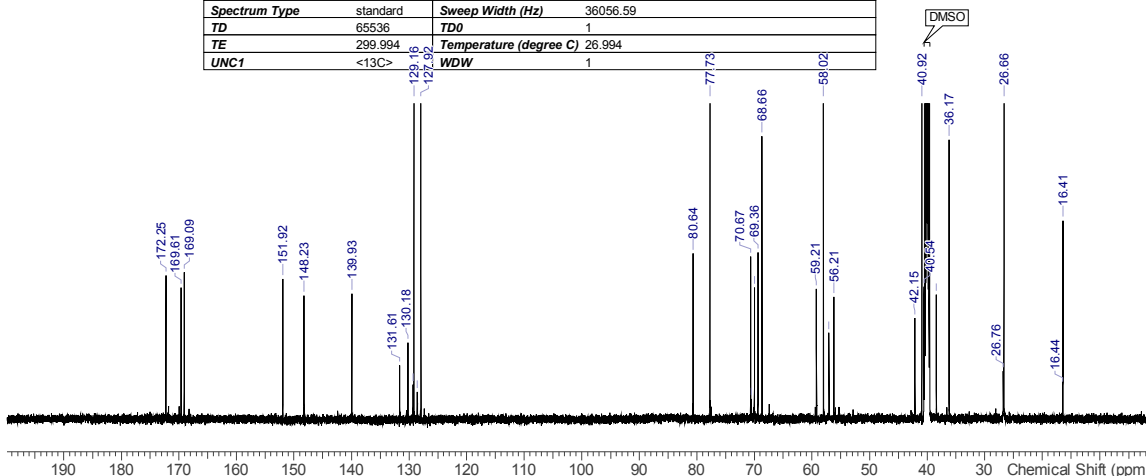
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Spectrum Offset (Hz)	2877.5083	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.98 (1 H, s), 8.60 (1 H, t, $J=6.1$ Hz), 7.48 (1 H, br d, $J=9.5$ Hz), 7.40 (4 H, s), 5.15 (1 H, d, $J=3.5$ Hz), 4.57 (1 H, d, $J=9.5$ Hz), 4.39 - 4.47 (2 H, m), 4.37 (1 H, br d, $J=13.7$ Hz), 4.12 - 4.30 (4 H, m), 3.96 (2 H, s), 3.56 - 3.70 (7 H, m), 3.36 - 3.44 (1 H, m), 1.90 (1 H, br s), 0.88 - 1.00 (9 H, m)

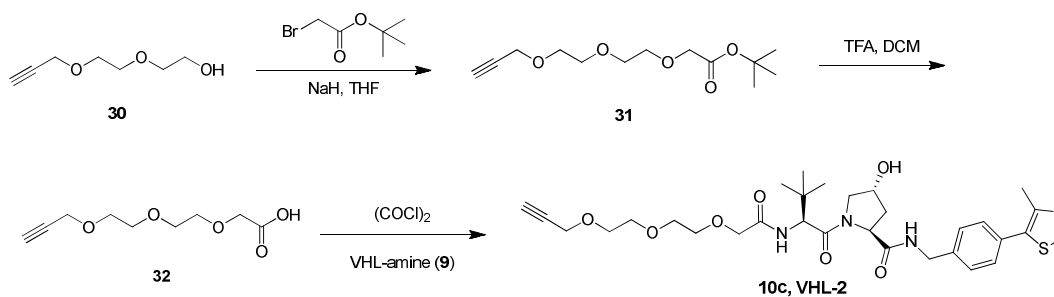




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Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
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SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-4-oxo-6,9,12-trioxa-3-azapentadec-14-yn-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**10c**, VHL-2).



Step 1: Prepared according to the same procedure used for the synthesis of **10a**, VHL-0 affording the *tert*-butyl ester **31** (13.5 g, 50% yield) from propargyl alcohol **30** (15 g).

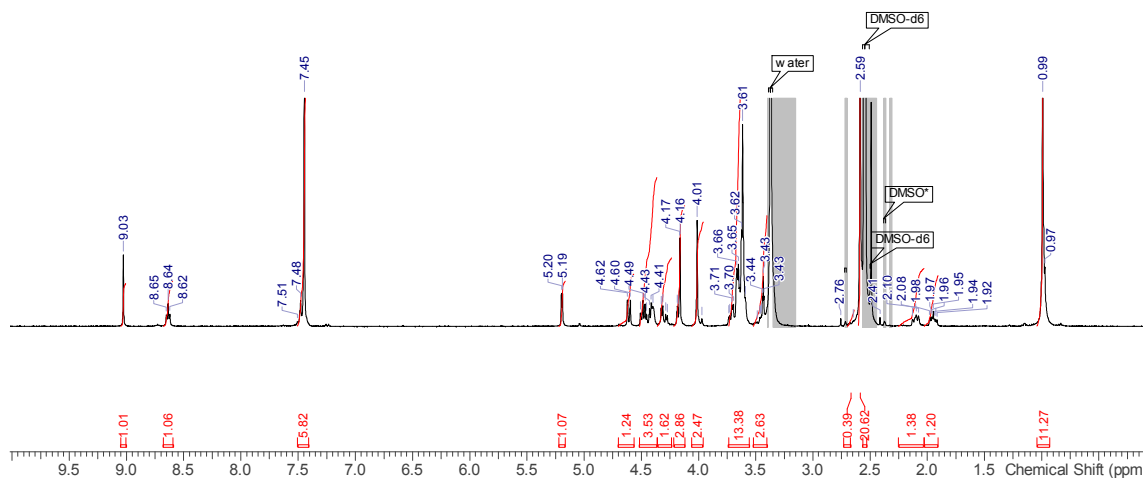
Step 2: Prepared according to the same procedure used for the synthesis of **10a**, **VHL-0** affording the carboxylic acid **32** (0.8 g, crude) from *tert*-butyl ester **31** (1 g).

Step 3: Prepared according to the same procedure for the synthesis of **10a**, **VHL-0** affording the title compound (**10c**, **VHL-2**, 1.0 g, 40% yield) as a light yellow syrup. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 9.03 (1 H, s), 8.64 (1 H, br t, *J*=6.0 Hz), 7.41 - 7.51 (6 H, m), 5.19 (1 H, d, *J*=3.5 Hz), 4.61 (1 H, d, *J*=9.5 Hz), 4.36 - 4.52 (4 H, m), 4.24 - 4.36 (2 H, m), 4.12 - 4.22 (3 H, m), 4.01 (2 H, s), 3.56 - 3.74 (13 H, m), 3.40 - 3.52 (3 H, m), 2.65 (1 H, br s), 2.57 - 2.60 (21 H, m), 2.03 - 2.25 (1 H, m), 1.95 (1 H, ddd, *J*=12.9, 8.7, 4.6 Hz), 0.93 - 1.04 (9 H, m). ¹³C NMR (151 MHz, *DMSO-d*₆) δ ppm 172.23, 169.61, 169.05, 151.93, 148.23, 139.92, 131.61, 130.19, 129.35, 129.17, 127.94, 80.77, 77.55, 70.89, 70.07, 70.03, 69.35, 69.01, 68.99, 59.20, 57.97, 57.04, 56.18, 42.16, 38.39, 36.18, 26.81, 26.75, 26.66, 16.44, 16.40. *m/z* (ESI, +ve) 615.2 (M+H)⁺.



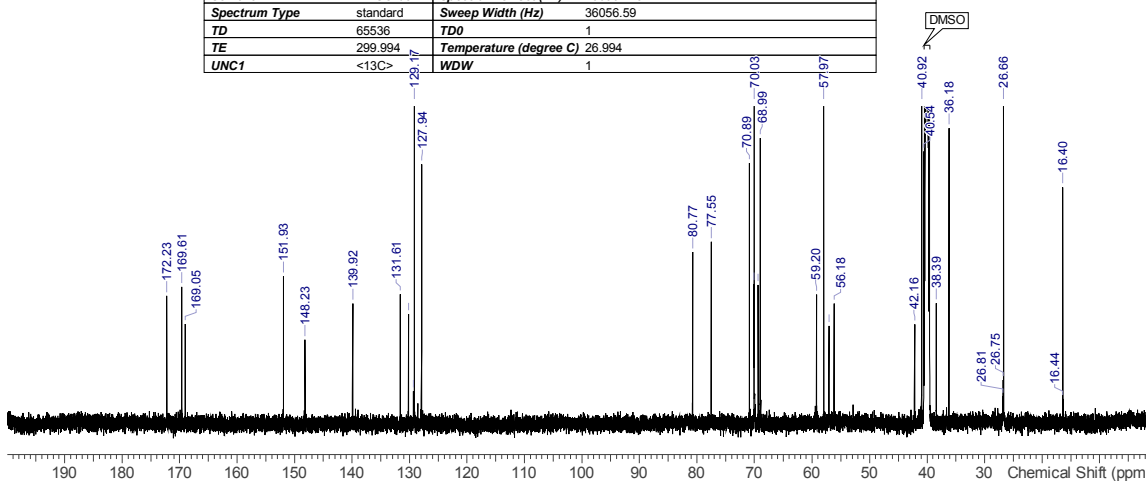
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Spectrum Offset (Hz)	2896.3745	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 9.03 (1 H, s), 8.64 (1 H, br t, *J*=6.0 Hz), 7.41 - 7.51 (6 H, m), 5.19 (1 H, d, *J*=3.5 Hz), 4.61 (1 H, d, *J*=9.5 Hz), 4.36 - 4.52 (4 H, m), 4.24 - 4.36 (2 H, m), 4.12 - 4.22 (3 H, m), 4.01 (2 H, s), 3.56 - 3.74 (13 H, m), 3.40 - 3.52 (3 H, m), 2.65 (1 H, br s), 2.57 - 2.60 (21 H, m), 2.03 - 2.25 (1 H, m), 1.95 (1 H, ddd, *J*=12.9, 8.7, 4.6 Hz), 0.93 - 1.04 (9 H, m)

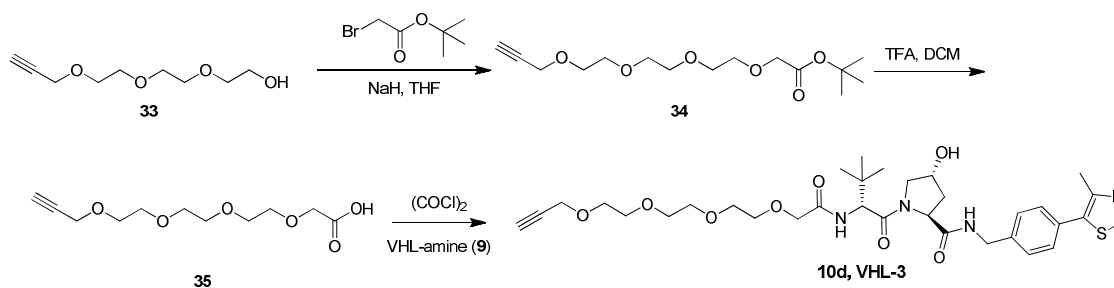




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Number of Transients	4096	Origin	spect
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SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-4-oxo-6,9,12,15-tetraoxa-3-azaoctadec-17-yn-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**10d**, VHL-3).



Step 1: Prepared according to the same procedure used for the synthesis of **10a**, VHL-0 affording the *tert*-butyl ester **34** (16 g, 33% yield) as a colorless oil from propargyl alcohol **33** (30 g).

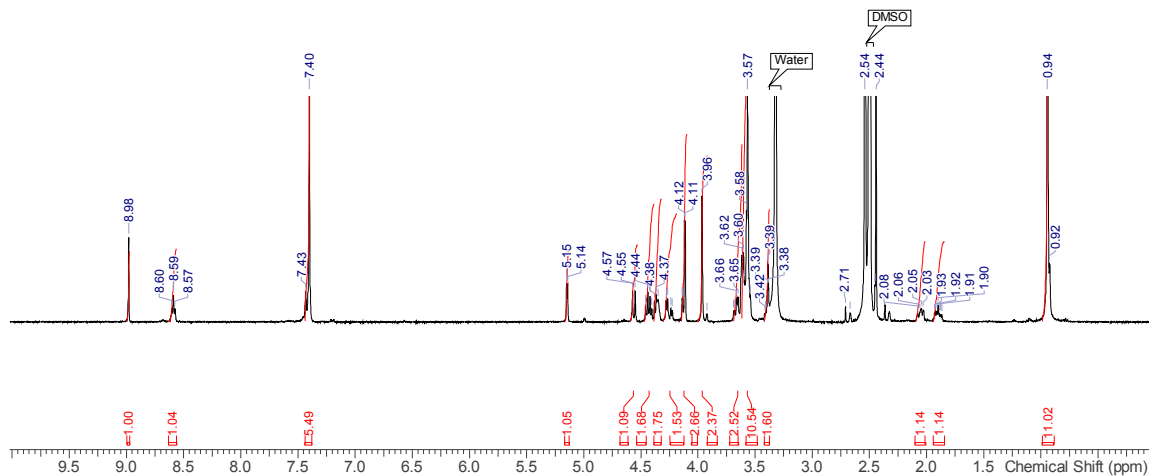
Step 2: Prepared according to the same procedure used for the synthesis of **10a**, **VHL-0** affording the carboxylic acid **35** (4.1 g, crude) as a brown oil from *tert*-butyl ester **34** (5 g).

Step 3: Prepared according to the same procedure for the synthesis of **10a**, **VHL-0** affording the title compound (**10d**, **VHL-3**, 3.6 g, 32% yield) as a light yellow syrup. ¹H NMR (400 MHz, *DMSO-d*₆) δ ppm 8.98 (1 H, s), 8.59 (1 H, t, *J*=6.1 Hz), 7.40 (5 H, s), 5.15 (1 H, d, *J*=3.5 Hz), 4.56 (1 H, d, *J*=9.5 Hz), 4.39 - 4.47 (2 H, m), 4.32 - 4.39 (2 H, m), 4.19 - 4.31 (2 H, m), 4.10 - 4.15 (3 H, m), 3.96 (2 H, s), 3.62 - 3.69 (3 H, m), 3.52 - 3.62 (11 H, m), 3.38 - 3.42 (2 H, m), 2.53 - 2.55 (35 H, m), 2.42 - 2.47 (4 H, m), 2.05 (1 H, br dd, *J*=12.5, 7.8 Hz), 1.90 (1 H, ddd, *J*=12.8, 8.7, 4.5 Hz), 0.89 - 0.99 (9 H, m). ¹³C NMR (151 MHz, *DMSO-d*₆) δ ppm 172.23, 169.61, 169.05, 151.93, 148.23, 139.92, 131.61, 130.19, 129.17, 128.61, 127.94, 80.77, 77.55, 70.89, 70.07, 70.03, 70.00, 69.35, 69.01, 68.99, 59.20, 57.97, 57.04, 56.18, 42.16, 38.39, 36.18, 26.76, 26.66, 16.40. *m/z* (ESI, +ve) 637.2 (M+H)⁺.

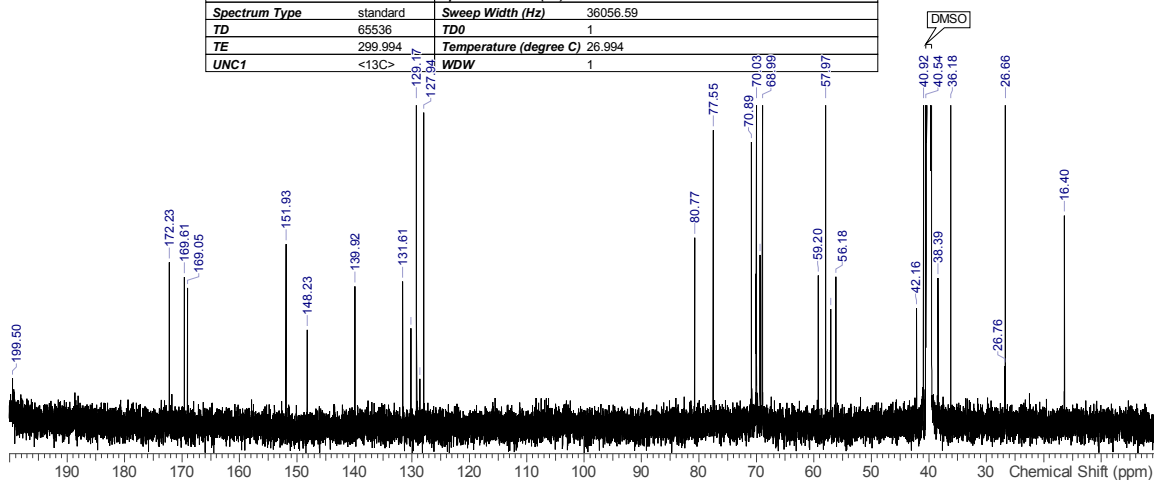


Acquisition Time (sec)	4.8234	Comment	rwurz
File Name	\\SCONE\NMR-Archive\campirwurz\2016\123691-15-4_10.JDX		
Frequency (MHz)	400.1300	Nucleus	¹ H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6793.48	Solvent	DMSO-d6
Spectrum Offset (Hz)	2877.5066	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

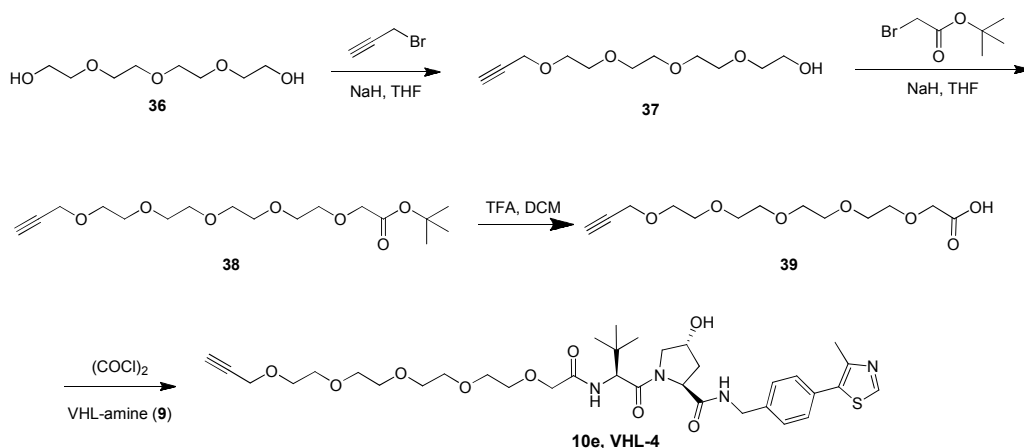
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.98 (1 H, s), 8.59 (1 H, t, *J*=6.1 Hz), 7.40 (5 H, s), 5.15 (1 H, d, *J*=3.5 Hz), 4.56 (1 H, d, *J*=9.5 Hz), 4.39 - 4.47 (2 H, m), 4.32 - 4.39 (2 H, m), 4.19 - 4.31 (2 H, m), 4.10 - 4.15 (3 H, m), 3.96 (2 H, s), 3.62 - 3.69 (3 H, m), 3.52 - 3.62 (11 H, m), 3.38 - 3.42 (2 H, m), 2.53 - 2.55 (35 H, m), 2.42 - 2.47 (4 H, m), 2.05 (1 H, br dd, *J*=12.5, 7.8 Hz), 1.90 (1 H, ddd, *J*=12.8, 8.7, 4.5 Hz), 0.89 - 0.99 (9 H, m)



Acquisition Time (sec)	0.9088	Comment	123691-15-4 in DMSO-d6
D	0.03	D1	1
DE	18	DS	2
Date	13 Oct 2016 19:25:54		
Date Stamp	13 Oct 2016 19:25:54		
File Name	\\SCONE\NMR-Archive\processed-data\campirwurz\Test ID 262608\4\fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	4096	Nucleus	¹³ C
Number of Transients	4096	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047>		
PULPROG	<zpgpg30>	Points Count	32768
Pulse Sequence	zpgpg30	Receiver Gain	2050.00
SF	150.902808526		
SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1



(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-4-oxo-6,9,12,15,18-pentaoxa-3-azahenicos-20-yn-1-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (10e, VHL-4).



Step 2: Prepared according to the same procedure for the synthesis of **10a, VHL-0** affording the *tert*-butyl ester **38** (8 g, 38% yield) as a colorless oil from propargyl alcohol **37** (14 g).

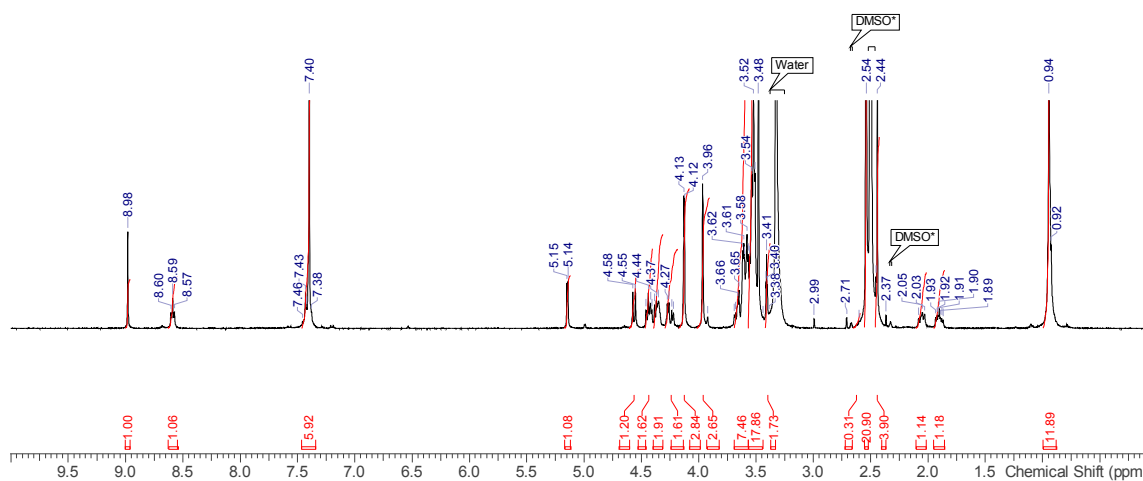
Step 4: Prepared according to the same procedure for the synthesis of **10a, VHL-0** affording the title compound (**10e, VHL-4**, 6.0 g, 39% yield) as a light yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.98 (1 H, s), 8.59 (1 H, br t, $J=5.9$ Hz), 7.34 - 7.46 (6 H, m), 5.15 (1 H, d, $J=3.3$ Hz), 4.56 (1 H, d, $J=9.7$ Hz), 4.40 - 4.47 (2 H, m), 4.31 - 4.39 (2 H, m), 4.19 - 4.29 (2 H, m), 4.13 (3 H, d, $J=2.3$ Hz), 3.96 (2 H, s), 3.57 - 3.69 (7 H, m), 3.44 - 3.57 (18 H, m), 3.38 - 3.42 (2 H, m), 2.60 (1 H, br s), 2.52 - 2.55 (21 H, m), 2.42 - 2.46 (4 H, m), 2.01 - 2.11 (1 H, m), 1.90 (1 H, ddd, $J=12.9, 8.8, 4.5$ Hz), 0.88 - 0.99 (9 H, m). ^{13}C NMR (151 MHz, $\text{DMSO}-d_6$) δ ppm 172.24, 169.61, 169.07, 151.93, 148.23, 139.92, 131.61, 130.17, 129.35, 129.16, 128.61, 127.94, 80.81, 77.55, 70.94,

70.27, 70.23, 70.14, 69.35, 68.98, 59.21, 57.96, 57.04, 56.16, 42.16, 40.92, 38.39, 36.19, 26.81, 26.75, 26.65, 16.39. m/z (ESI, +ve) 703.4 (M+H)⁺.



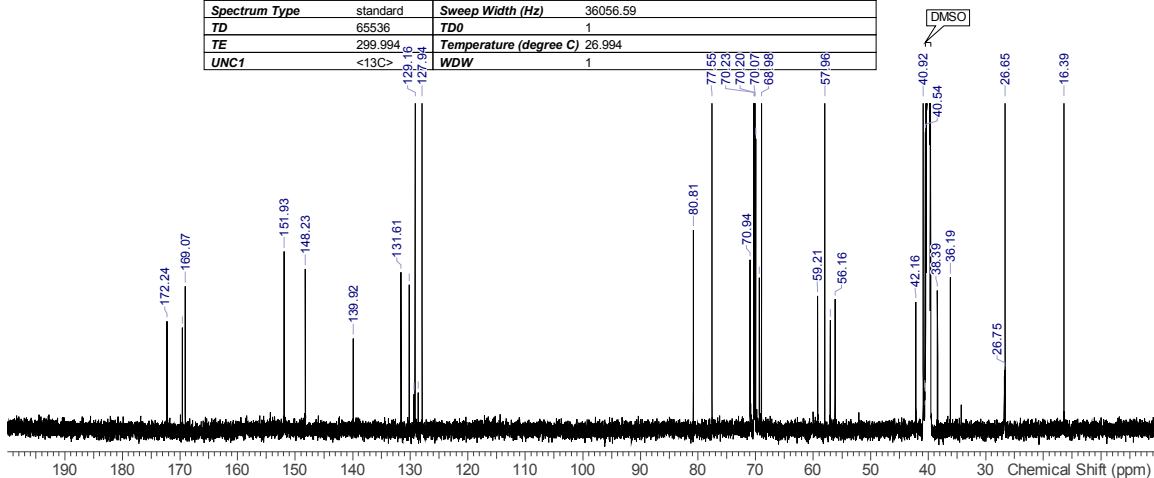
Acquisition Time (sec)	4.8234	Comment	rwurz
File Name	\\SCONE\NMR-Archive\jcamp\rwurz\2016\123691-15-5_10.JDX		
Frequency (MHz)	400.1300	Nucleus	1H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6793.48	Solvent	DMSO-d6
Spectrum Offset (Hz)	2877.3066	Spectrum Type	undefined
Sweep Width (Hz)	6793.27		

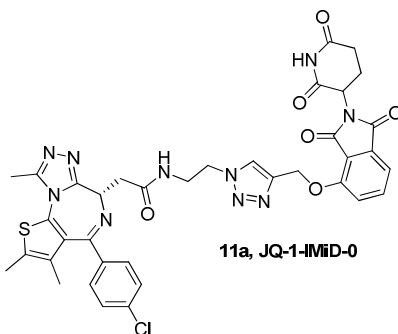
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.98 (1 H, s), 8.59 (1 H, br t, *J*=5.9 Hz), 7.34 - 7.46 (6 H, m), 5.15 (1 H, d, *J*=3.3 Hz), 4.56 (1 H, d, *J*=9.7 Hz), 4.40 - 4.47 (2 H, m), 4.31 - 4.39 (2 H, m), 4.19 - 4.29 (2 H, m), 4.13 (3 H, d, *J*=2.3 Hz), 3.96 (2 H, s), 3.57 - 3.69 (7 H, m), 3.44 - 3.57 (18 H, m), 3.38 - 3.42 (2 H, m), 2.60 (1 H, br s), 2.52 - 2.55 (21 H, m), 2.42 - 2.46 (4 H, m), 2.01 - 2.11 (1 H, m), 1.90 (1 H, ddd, *J*=12.9, 8.8, 4.5 Hz), 0.88 - 0.99 (9 H, m)





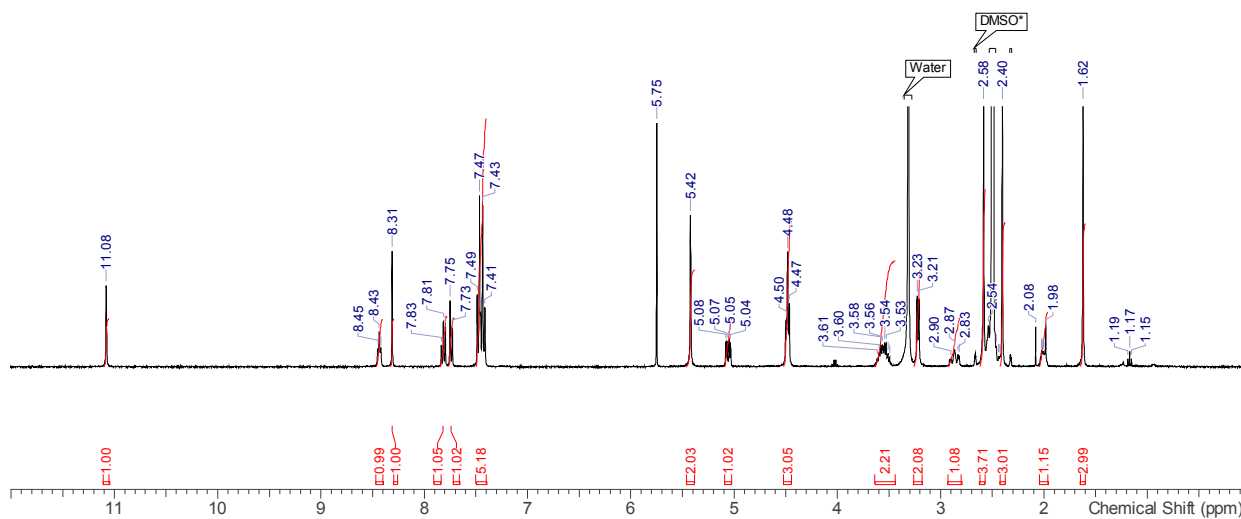
Acquisition Time (sec)	0.9088	Comment	123691-15-5 in DMSO-d6
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DE	18	DS	2
Date	13 Oct 2016 21:44:08		
Date Stamp	13 Oct 2016 21:44:08		
File Name	\\SCONE\NMR-Archive\processed-data\rwurz\Test ID 262608\5\fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	4096	Nucleus	13C
Number of Transients	4096	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zpgpg30>	Points Count	32768
Pulse Sequence	zpgpg30	Receiver Gain	2050.00
SF	150.902808526		
SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





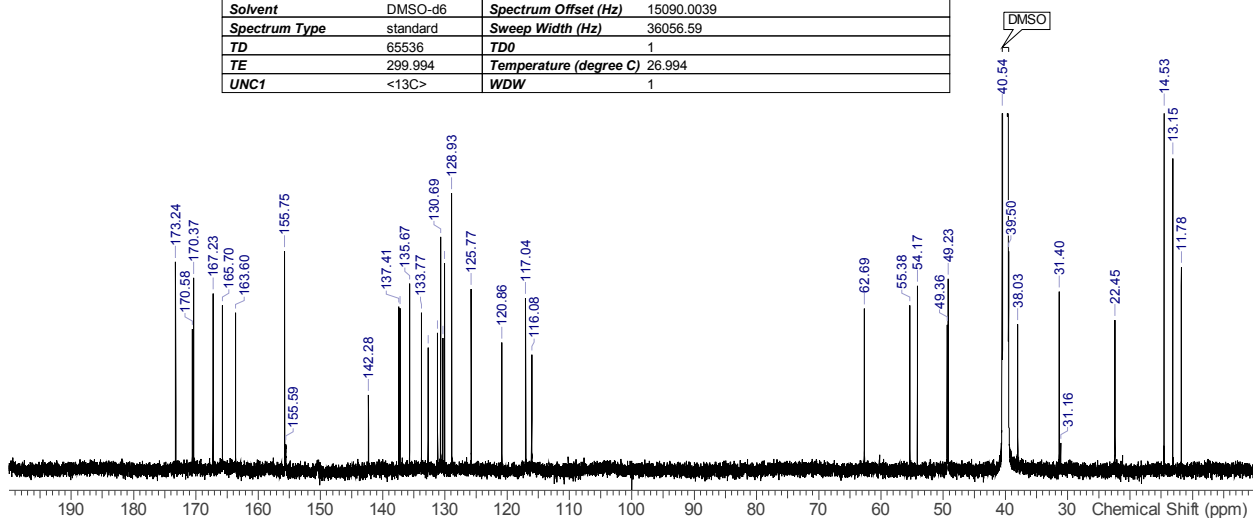
Acquisition Time (sec)	5.1118	Comment	rwurz
File Name	\\SCONE\NMR-Archive\camp\rwurz\2016\123369-22-2_10_JDX		
Frequency (MHz)	400.1300	Nucleus	¹ H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d ₆
Spectrum Offset (Hz)	2397.0078	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

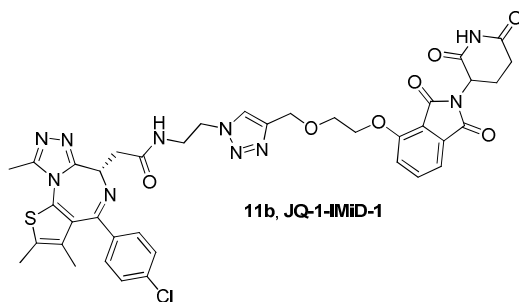
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.08 (1 H, s), 8.44 (1 H, br t, *J*=5.4 Hz), 8.31 (1 H, s), 7.72 - 7.84 (2 H, m), 7.40 - 7.50 (5 H, m), 5.75 (1 H, s), 5.42 (2 H, s), 5.06 (1 H, dd, *J*=12.7, 5.5 Hz), 4.44 - 4.52 (3 H, m), 3.44 - 3.64 (2 H, m), 3.22 (2 H, br d, *J*=7.0 Hz), 2.80 - 2.93 (1 H, m), 2.52 - 2.62 (5 H, m), 2.38 - 2.47 (4 H, m), 1.96 - 2.05 (1 H, m), 1.62 (3 H, s)





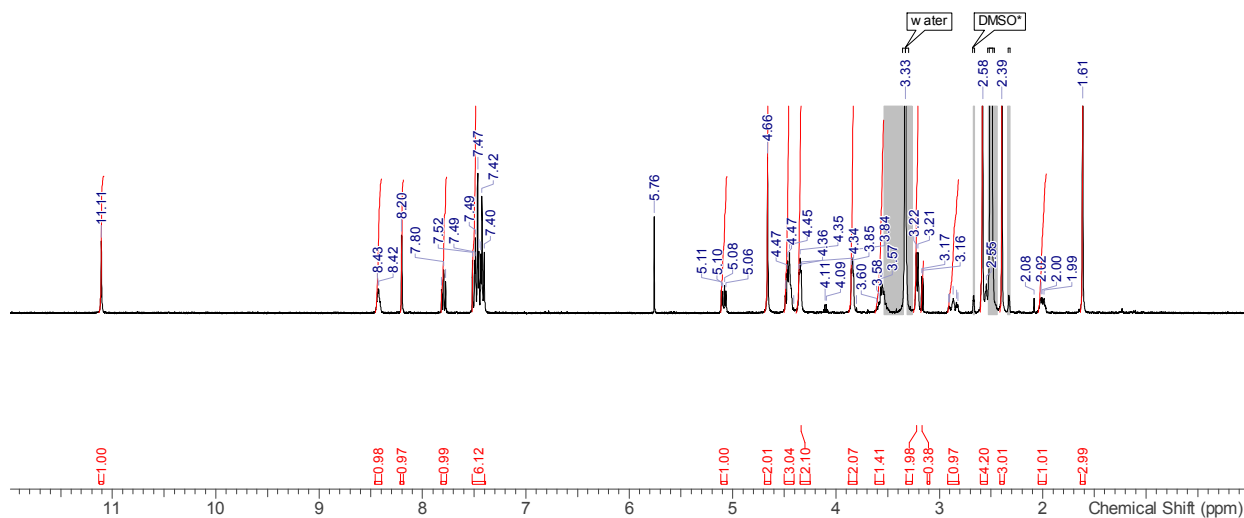
Acquisition Time (sec)	0.9088		
Comment	Test ID 256280; Request 256271-1; Targeted Proteolysis; Ryan Wurz; 123429-22-2 (3347647 in DMSO-d6		
D	1.2	D1	1.2
DE	18	DS	8
Date	09 Jul 2016 17:50:06		
Date Stamp	09 Jul 2016 17:50:06		
File Name	\\SCONE\NMR-Archive\processed-data\rywurz\BRD4 BILEs\10\fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	32768	Nucleus	13C
Number of Transients	32768	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zgdc30>	Points Count	32768
Pulse Sequence	zgdc30	Receiver Gain	2050.00
SF	150.902809	SFO1	150.917899
SI	131072	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.0039
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





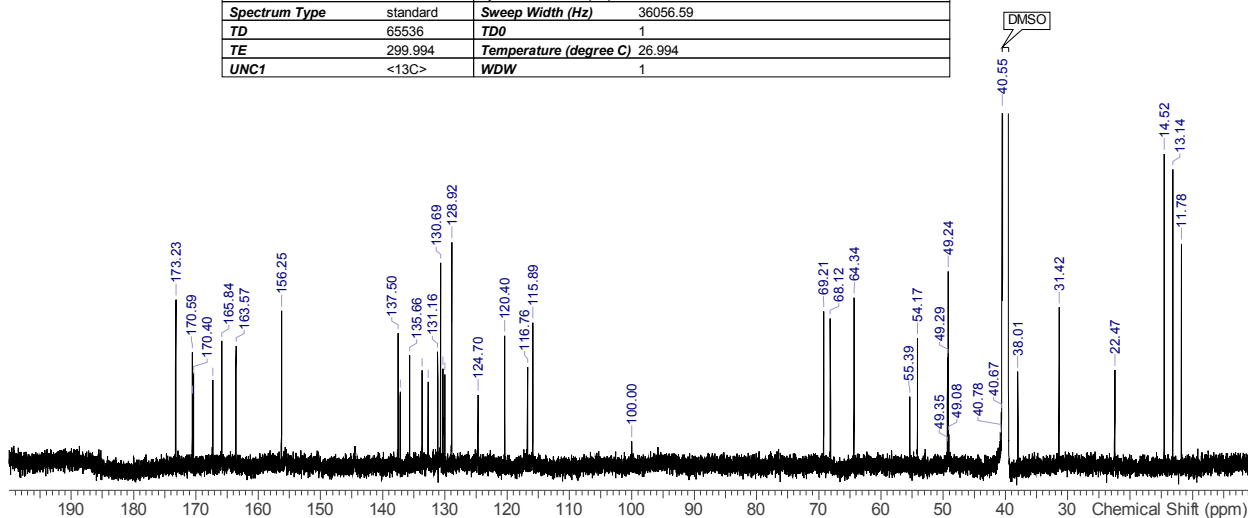
Acquisition Time (sec)	5.1118	Comment	rwurz
File Name	\\SCONE\NMR-Archive\camp\rwurz\2016\123570-13-2_10_JDX		
Frequency (MHz)	400.1300	Nucleus	¹ H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d ₆
Spectrum Offset (Hz)	2398.7539	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

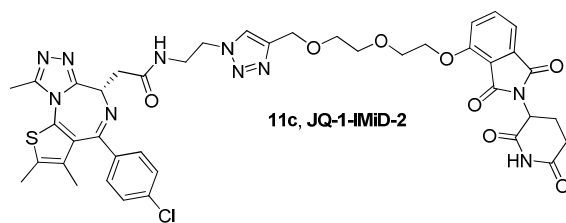
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.11 (1 H, s), 8.40 - 8.46 (1 H, m), 8.20 (1 H, s), 7.79 (1 H, t, *J*=7.5 Hz), 7.40 - 7.52 (6 H, m), 5.09 (1 H, dd, *J*=12.8, 5.4 Hz), 4.66 (2 H, s), 4.41 - 4.50 (3 H, m), 4.29 - 4.38 (2 H, m), 3.80 - 3.88 (2 H, m), 3.54 - 3.62 (1 H, m), 3.22 (2 H, br d, *J*=7.2 Hz), 2.81 - 2.92 (1 H, m), 2.54 - 2.60 (4 H, m), 2.39 (3 H, s), 1.97 - 2.05 (1 H, m), 1.61 (3 H, s)





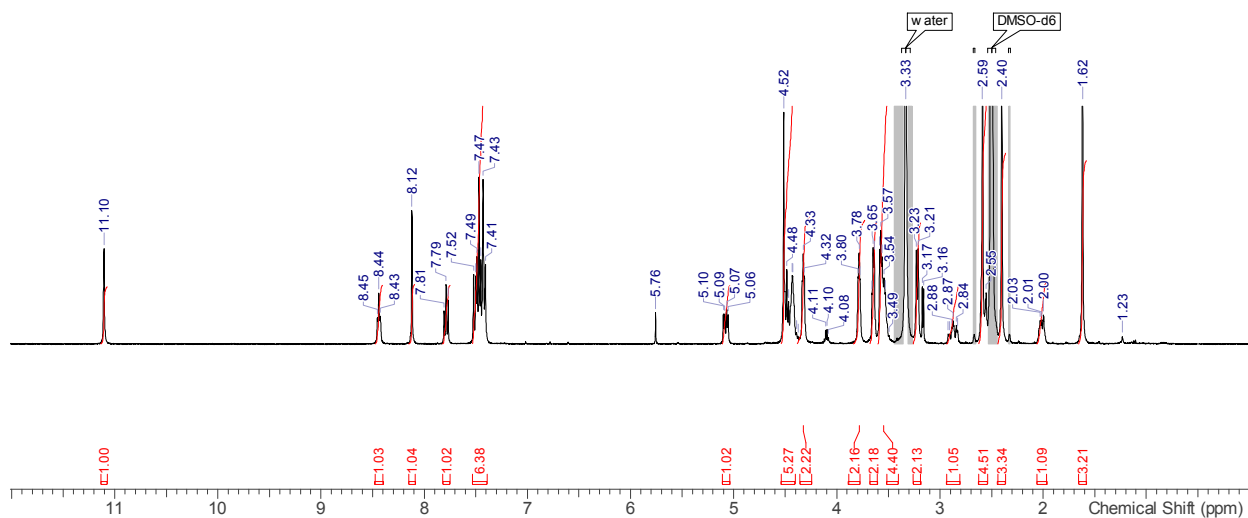
Acquisition Time (sec)	0.9088	Comment	123570-13-2 (AMG#3352579) in DMSO-d6
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DE	18	DS	2
Date	09 Sep 2016 16:36:11		
Date Stamp	09 Sep 2016 16:36:11		
File Name	\\SCONE\NMR-Archive\processed-data\wurzl\BRD4BILES (2)\9\fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	32768	Nucleus	13C
Number of Transients	32768	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zpgpg30>	Points Count	32768
Pulse Sequence	zpgpg30	Receiver Gain	2050.00
SF	150.902808526		
SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





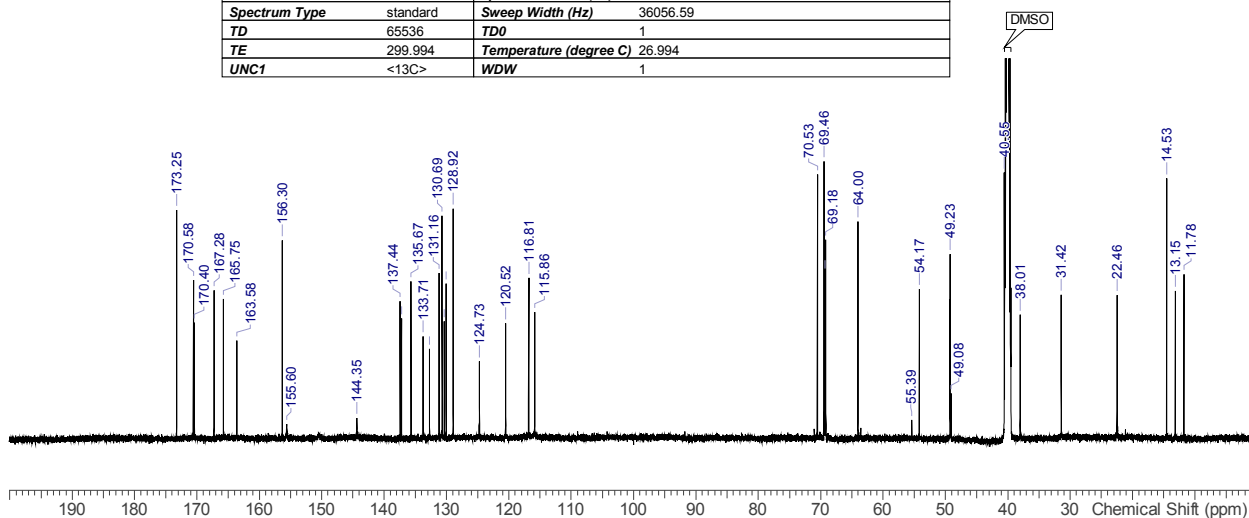
Acquisition Time (sec)	5.1118	Comment	rwurz
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Frequency (MHz)	400.1300	Nucleus	¹ H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d ₆
Spectrum Offset (Hz)	2398.7539	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

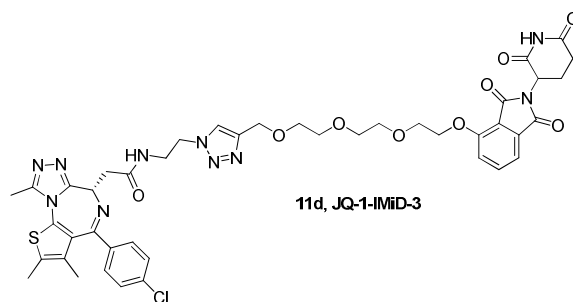
¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.10 (1 H, s), 8.44 (1 H, br t, *J*=5.6 Hz), 8.12 (1 H, s), 7.79 (1 H, t, *J*=7.8 Hz), 7.39 - 7.53 (6 H, m), 5.08 (1 H, dd, *J*=12.7, 5.3 Hz), 4.40 - 4.54 (5 H, m), 4.27 - 4.35 (2 H, m), 3.73 - 3.84 (2 H, m), 3.61 - 3.68 (2 H, m), 3.49 - 3.60 (4 H, m), 3.22 (2 H, br d, *J*=7.0 Hz), 2.81 - 2.93 (1 H, m), 2.54 - 2.62 (4 H, m), 2.37 - 2.44 (3 H, m), 1.96 - 2.06 (1 H, m), 1.62 (3 H, s)





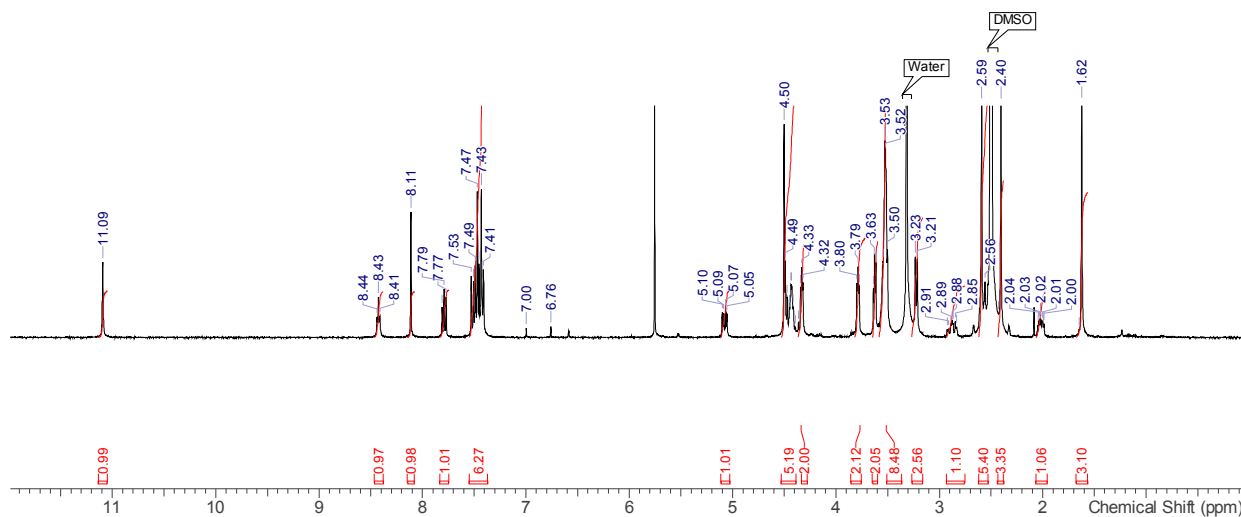
Acquisition Time (sec)	0.9088	Comment	123570-14-2 (AMG#3352580) in DMSO-d6
D	0.03	D1	1
DE	18	DS	2
Date	10 Sep 2016 10:36:47		
Date Stamp	10 Sep 2016 10:36:47		
File Name	\\SCONE\NMR-Archive\processed-data\wurzl\BRD4BILES (2)\10\fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	32768	Nucleus	13C
Number of Transients	32768	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zpgpg30>	Points Count	32768
Pulse Sequence	zpgpg30	Receiver Gain	2050.00
SF	150.902808526		
SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





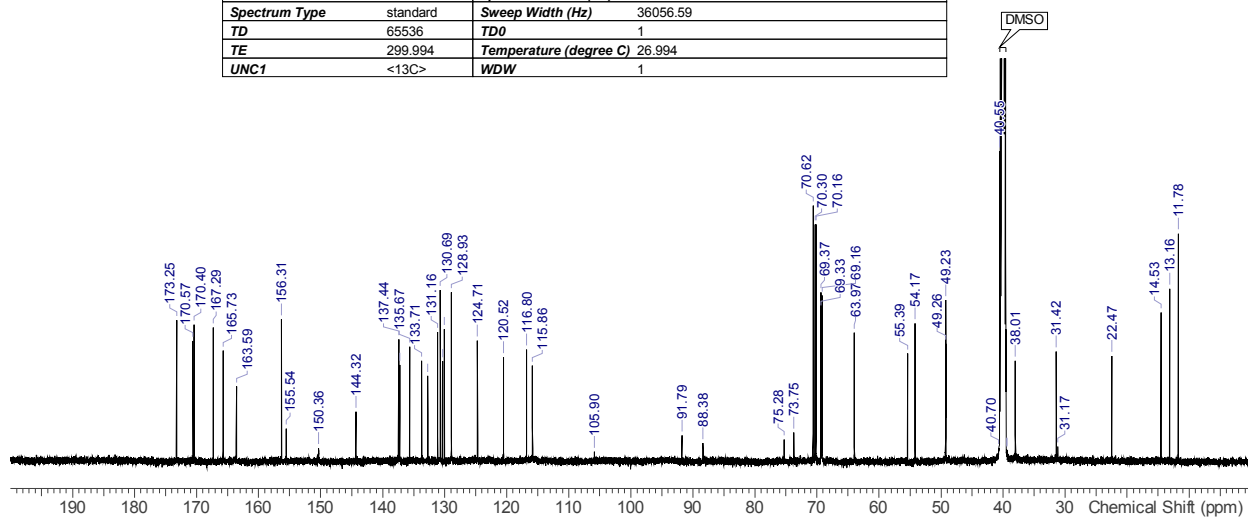
Acquisition Time (sec)	5.1118	Comment	rwurz
File Name	\\SCONE\NMR-Archive\camp\rwurz\2016\123570-15-2_10.JDX		
Frequency (MHz)	400.1300	Nucleus	¹ H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d ₆
Spectrum Offset (Hz)	2398.5681	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

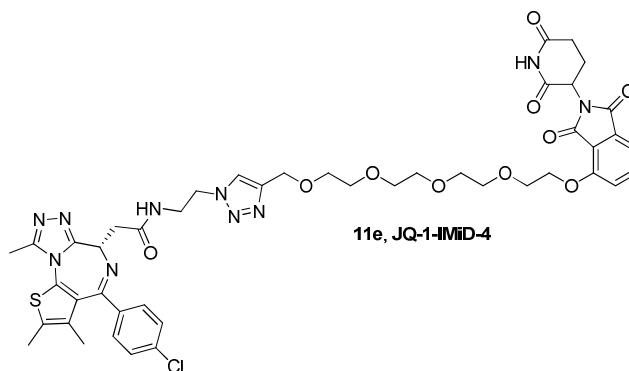
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.09 (1 H, s), 8.43 (1 H, br t, *J*=5.7 Hz), 8.11 (1 H, s), 7.79 (1 H, t, *J*=7.8 Hz), 7.37 - 7.55 (6 H, m), 5.08 (1 H, dd, *J*=12.8, 5.4 Hz), 4.38 - 4.53 (5 H, m), 4.31 - 4.37 (2 H, m), 3.72 - 3.82 (2 H, m), 3.60 - 3.65 (2 H, m), 3.44 - 3.58 (8 H, m), 3.16 - 3.27 (3 H, m), 2.75 - 2.93 (1 H, m), 2.53 - 2.62 (5 H, m), 2.38 - 2.43 (3 H, m), 1.96 - 2.06 (1 H, m), 1.62 (3 H, s)





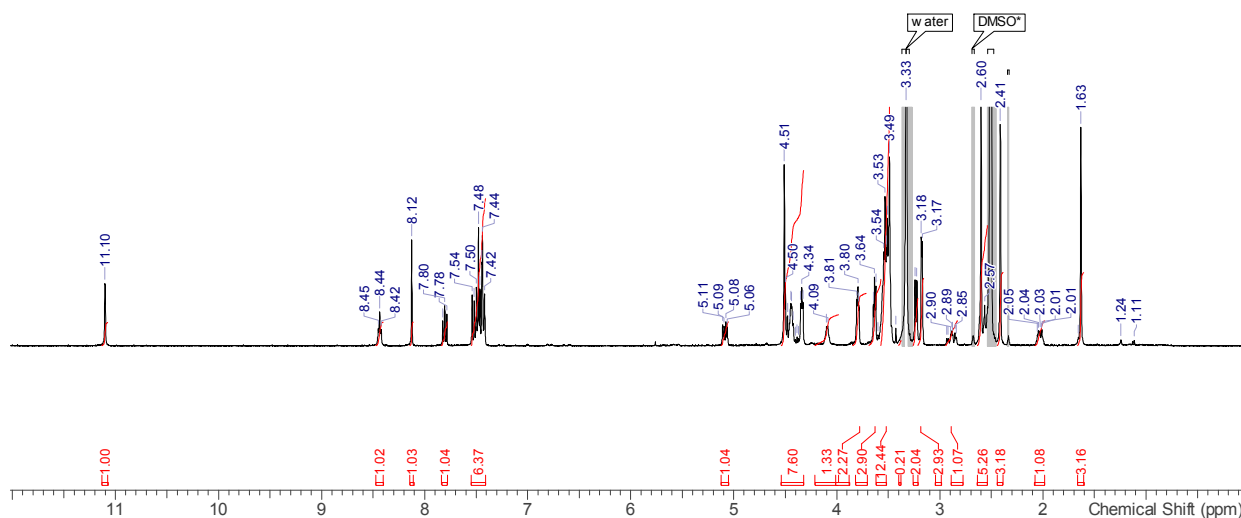
Acquisition Time (sec)	0.9088	Comment	123570-15-2 (AMG#3352521) in DMSO-d6
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Date	11 Sep 2016 04:37:18		
Date Stamp	11 Sep 2016 04:37:18		
File Name	\\SCONE\NMR-Archive\processed-data\wurzl\BRD4BILes (2)\11fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	32768	Nucleus	13C
Number of Transients	32768	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zpgpg30>	Points Count	32768
Pulse Sequence	zpgpg30	Receiver Gain	2050.00
SF	150.902808526		
SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





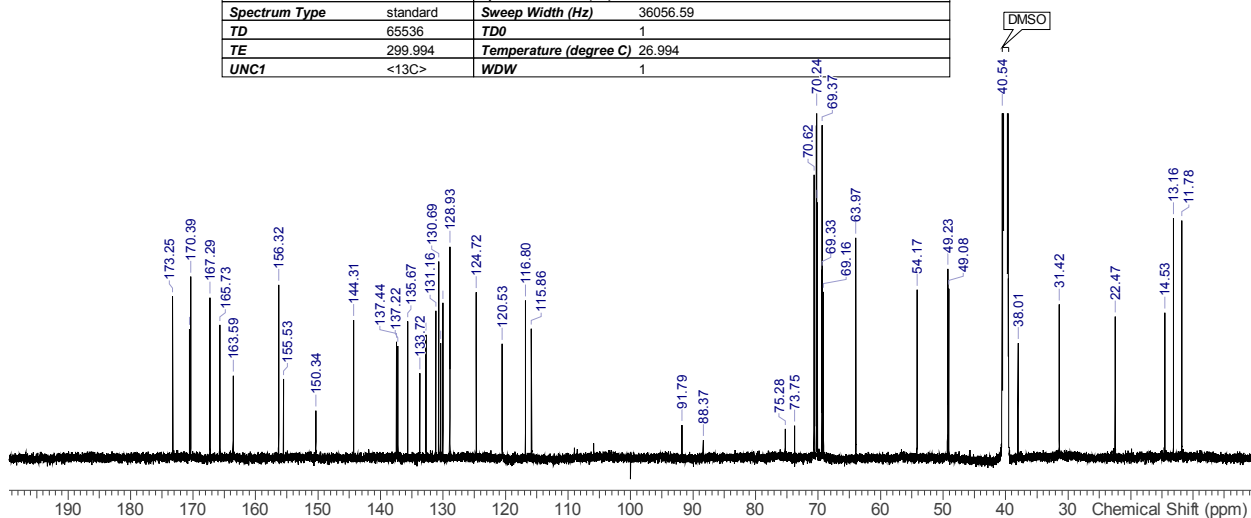
Acquisition Time (sec)	5.1118	Comment	rwurz
File Name	\\SCONE\NMR-Archive\camp\rwurz\2016\123570-16-2_10_JDX		
Frequency (MHz)	400.1300	Nucleus	1H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d6
Spectrum Offset (Hz)	2402.0093	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.10 (1 H, s), 8.44 (1 H, br t, *J*=5.5 Hz), 8.12 (1 H, s), 7.80 (1 H, t, *J*=7.9 Hz), 7.41 - 7.55 (6 H, m), 5.09 (1 H, dd, *J*=12.8, 5.4 Hz), 4.32 - 4.54 (7 H, m), 4.09 (1 H, br d, *J*=5.1 Hz), 3.72 - 3.84 (2 H, m), 3.57 - 3.69 (3 H, m), 3.47 - 3.57 (12 H, m), 3.23 (2 H, br d, *J*=7.0 Hz), 3.18 (3 H, d, *J*=3.7 Hz), 2.83 - 2.95 (1 H, m), 2.54 - 2.63 (5 H, m), 2.41 (3 H, s), 1.98 - 2.08 (1 H, m), 1.63 (3 H, s)



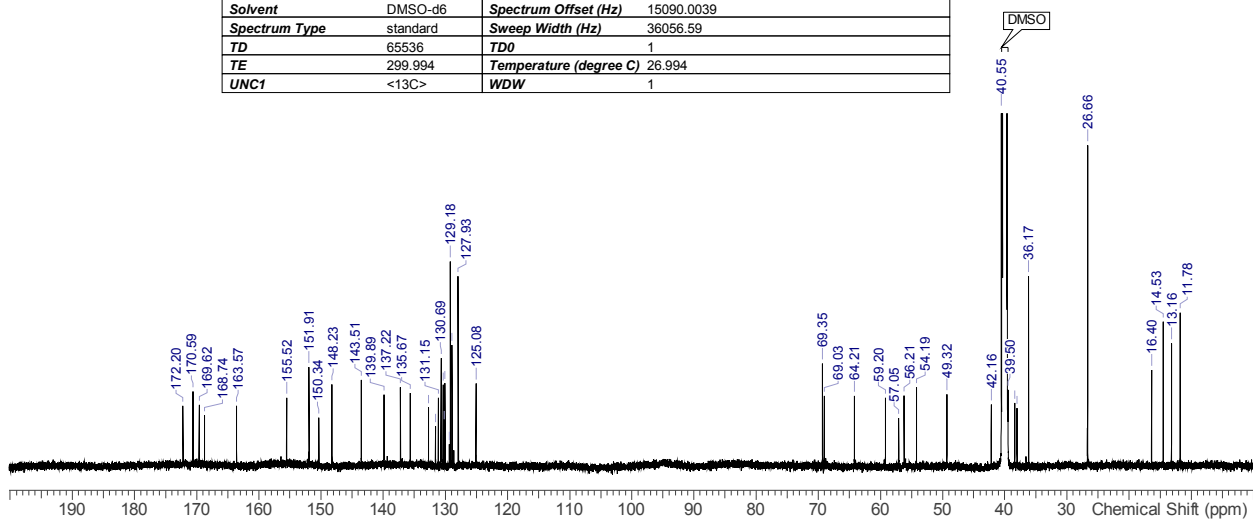


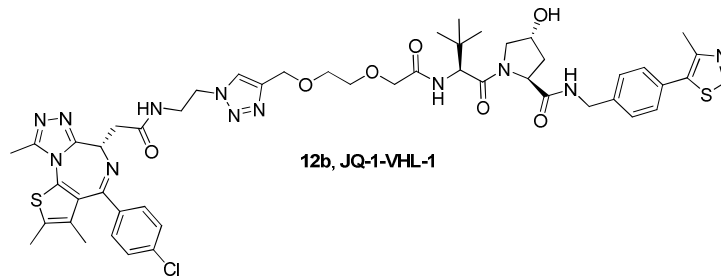
Acquisition Time (sec)	0.9088	Comment	123570-16-2 (AMG#3352522) in DMSO-d6
D	0.03	D1	1
DE	18	DS	2
Date	11 Sep 2016 22:37:58		
Date Stamp	11 Sep 2016 22:37:58		
File Name	\\SCONE\NMR-Archive\processed-data\wurzl\BRD4BILES (2)\12\fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	32768	Nucleus	13C
Number of Transients	32768	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zpgpg30>	Points Count	32768
Pulse Sequence	zpgpg30	Receiver Gain	2050.00
SF	150.902808526		
SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





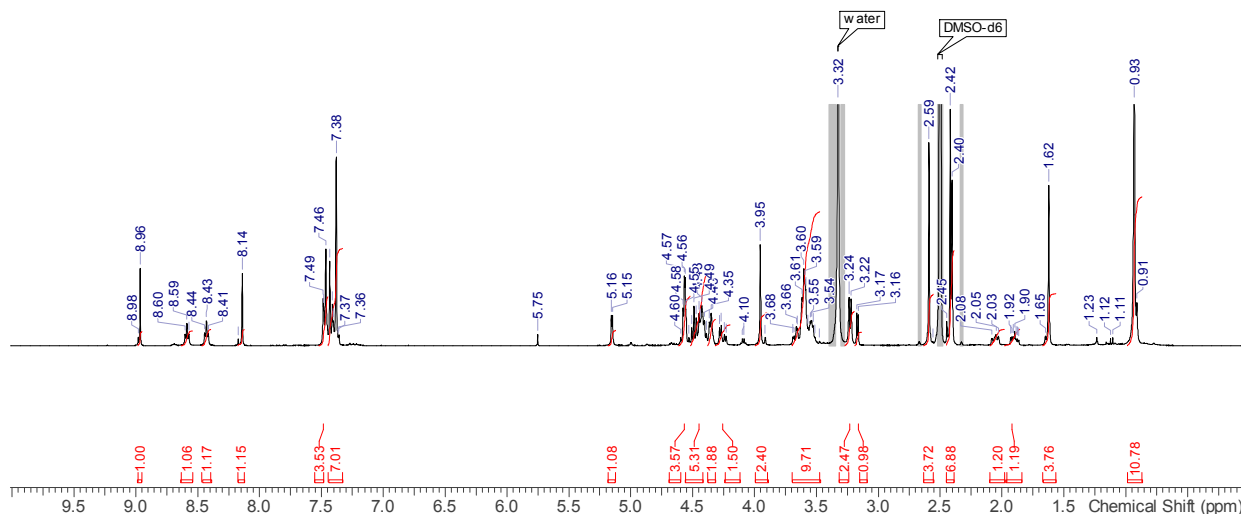
Acquisition Time (sec)	0.9088		
Comment	Test ID 256280; Request 256271-1; Targeted Proteolysis; Ryan Wurz; 123429-15-2 (3348508) in DMSO-d6		
D	1.2	D1	1.2
DE	18	DS	8
Date	01 Jul 2016 11:44:20		
Date Stamp	01 Jul 2016 11:44:20		
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Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	32768	Nucleus	13C
Number of Transients	32768	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zgdc30>	Points Count	32768
Pulse Sequence	zgdc30	Receiver Gain	2050.00
SF	150.902809	SFO1	150.917899
SI	131072	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.0039
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





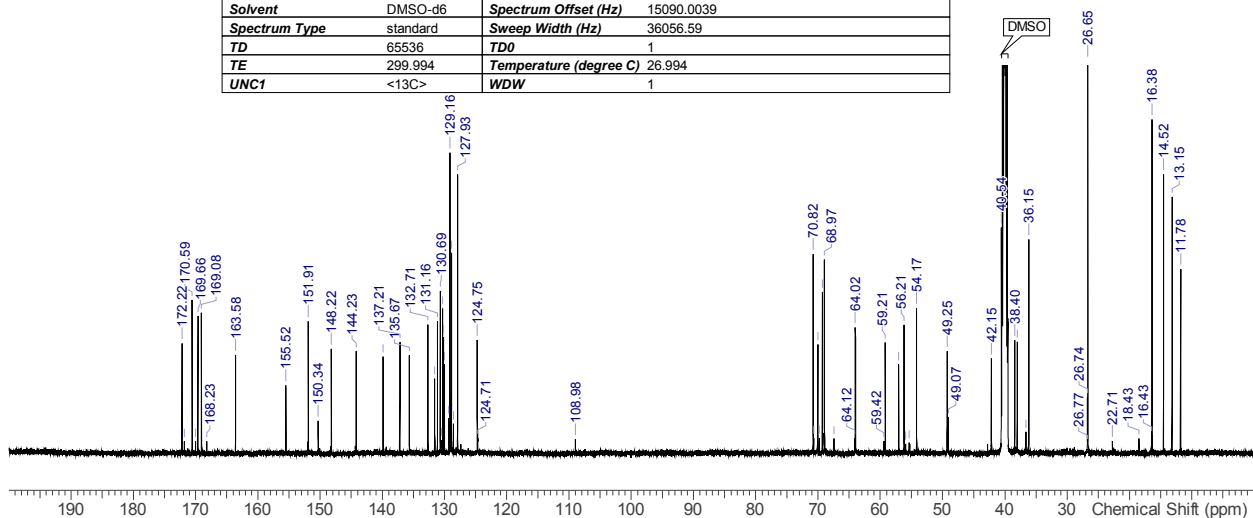
Acquisition Time (sec)	5.1118	Comment	rwurz
File Name	\\SCONE\NMR-Archive\camp\rwurz\2016\123429-12-2_10.JDX		
Frequency (MHz)	400.1300	Nucleus	1H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d6
Spectrum Offset (Hz)	2398.7539	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

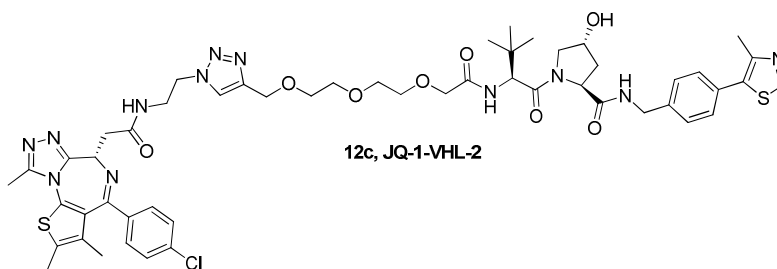
¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.95 - 8.98 (1 H, m), 8.59 (1 H, t, *J*=6.0 Hz), 8.43 (1 H, br t, *J*=5.7 Hz), 8.14 (1 H, s), 7.45 - 7.52 (3 H, m), 7.33 - 7.45 (6 H, m), 5.15 (1 H, d, *J*=3.5 Hz), 4.52 - 4.61 (3 H, m), 4.38 - 4.52 (4 H, m), 4.36 (2 H, br d, *J*=6.1 Hz), 4.20 - 4.32 (1 H, m), 3.95 (2 H, s), 3.47 - 3.70 (8 H, m), 3.19 - 3.27 (2 H, m), 3.17 (1 H, d, *J*=5.1 Hz), 2.59 (3 H, s), 2.39 - 2.45 (6 H, m), 1.98 - 2.10 (1 H, m), 1.90 (1 H, ddd, *J*=12.9, 8.7, 4.5 Hz), 1.62 (3 H, s), 0.87 - 0.99 (9 H, m)





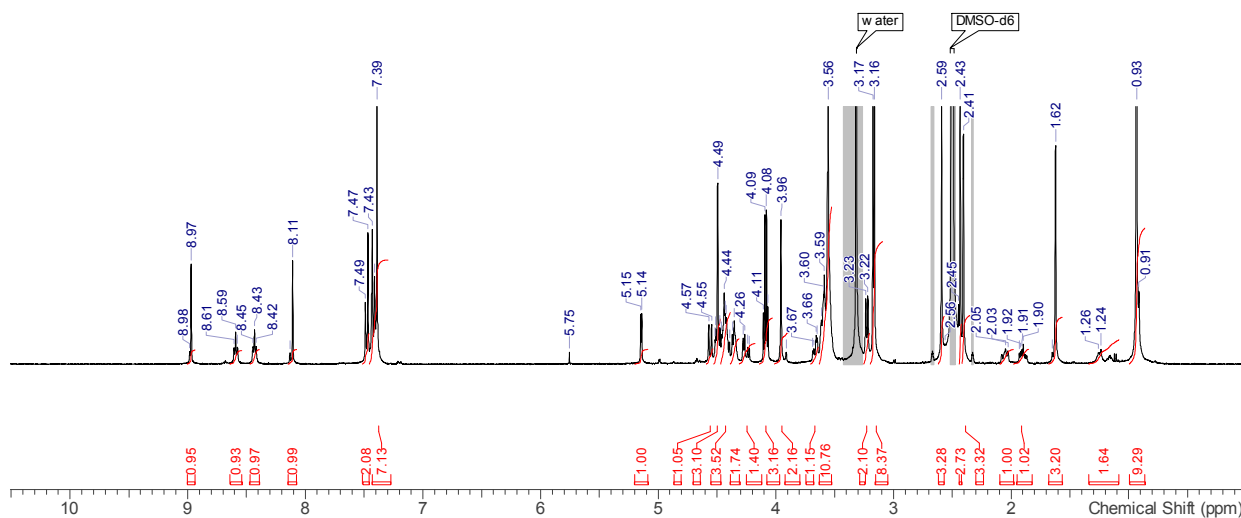
Acquisition Time (sec)	0.9088		
Comment	Test ID 256280; Request 256271-1; Targeted Proteolysis; Ryan Wurz; 123429-12-2 (3348487) in DMSO-d6		
D	1.2	D1	1.2
DE	18	DS	8
Date	07 Jul 2016 06:20:11		
Date Stamp	07 Jul 2016 06:20:11		
File Name	\\SCONE\NMR-Archive\processed-data\rywurz\BRD4 BiLEs\7\fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	32768	Nucleus	13C
Number of Transients	32768	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zgdc30>	Points Count	32768
Pulse Sequence	zgdc30	Receiver Gain	2050.00
SF	150.902809	SFO1	150.917899
SI	131072	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.0039
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





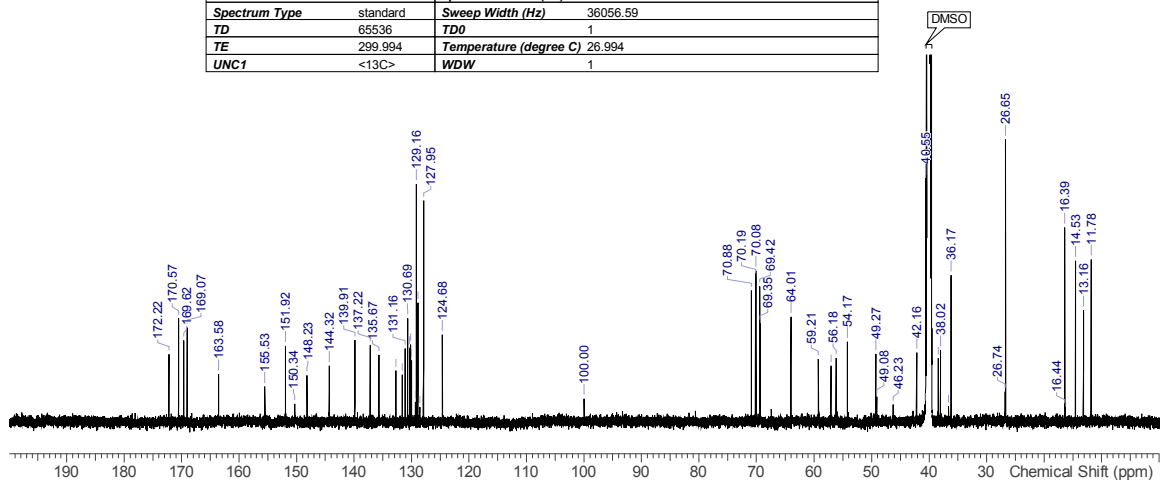
Acquisition Time (sec)	5.1118	Comment	rwurz
File Name	\\SCONE\NMR-Archive\camp\rwurz\2016\123429-11-2_10.JDX		
Frequency (MHz)	400.1300	Nucleus	¹ H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d ₆
Spectrum Offset (Hz)	2398.7539	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

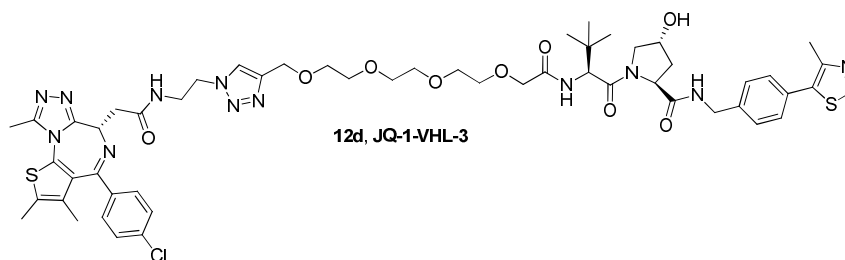
¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.94 - 9.00 (1 H, m), 8.59 (1 H, t, *J*=6.0 Hz), 8.43 (1 H, t, *J*=5.7 Hz), 8.07 - 8.14 (1 H, m), 7.46 - 7.51 (2 H, m), 7.30 - 7.45 (7 H, m), 5.14 (1 H, d, *J*=3.5 Hz), 4.56 (1 H, d, *J*=9.8 Hz), 4.47 - 4.53 (3 H, m), 4.39 - 4.47 (4 H, m), 4.36 (2 H, br d, *J*=6.3 Hz), 4.25 (1 H, br dd, *J*=15.7, 5.8 Hz), 4.09 (3 H, q, *J*=5.3 Hz), 3.96 (2 H, s), 3.64 - 3.70 (1 H, m), 3.53 - 3.63 (11 H, m), 3.23 (2 H, br d, *J*=7.0 Hz), 3.17 (9 H, d, *J*=5.3 Hz), 2.59 (3 H, s), 2.43 (3 H, s), 2.41 (3 H, s), 2.04 (1 H, br d, *J*=8.4 Hz), 1.85 - 1.98 (1 H, m), 1.62 (3 H, s), 1.25 (2 H, br d, *J*=8.2 Hz), 0.93 (9 H, s)





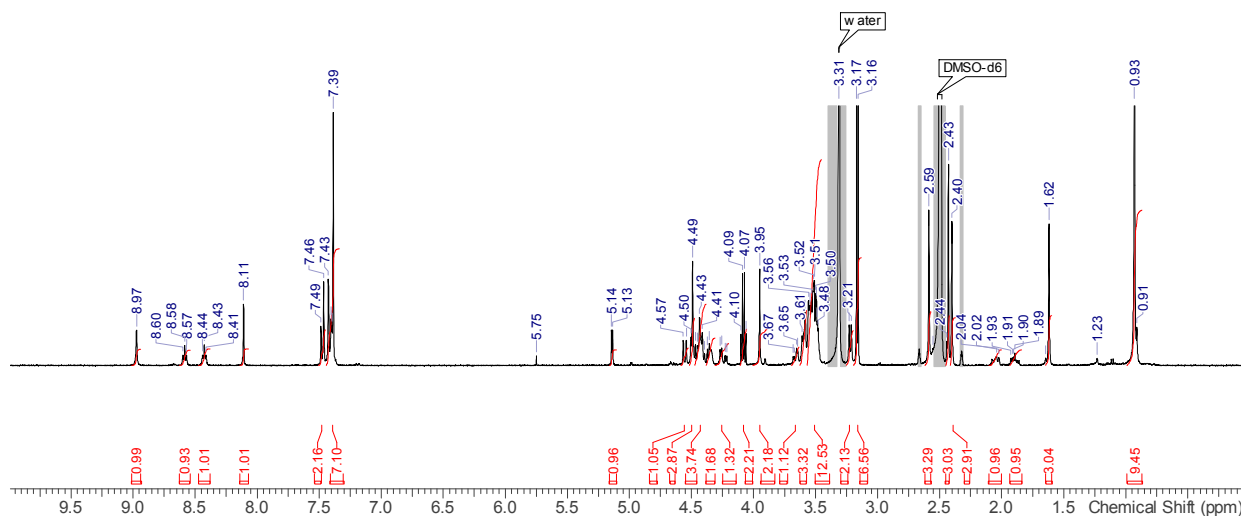
Acquisition Time (sec)	0.9088	Comment	3348488 in DMSO-d6
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Date	14 Oct 2016 18:18:14		
Date Stamp	14 Oct 2016 18:18:14		
File Name	\\SCONE\NMR-Archive\processed-data\raw\urzlTest ID 262608\11fid		
Frequency (MHz)	150.9028	GB	0
INSTRUM	<spect>	LB	1
NS	16384	Nucleus	¹³ C
Number of Transients	16384	Origin	spect
Original Points Count	32768	Owner	shr-ato-nmr1
PC	1.4		
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >		
PULPROG	<zpgpg30>	Points Count	32768
Pulse Sequence	zpgpg30	Receiver Gain	2050.00
SF	150.902808526		
SFO1	150.917898806853		
SI	32768	SSB	0
SW(cyclical) (Hz)	36057.69	SWH	36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz)	15090.2754
Spectrum Type	standard	Sweep Width (Hz)	36056.59
TD	65536	TD0	1
TE	299.994	Temperature (degree C)	26.994
UNC1	<13C>	WDW	1





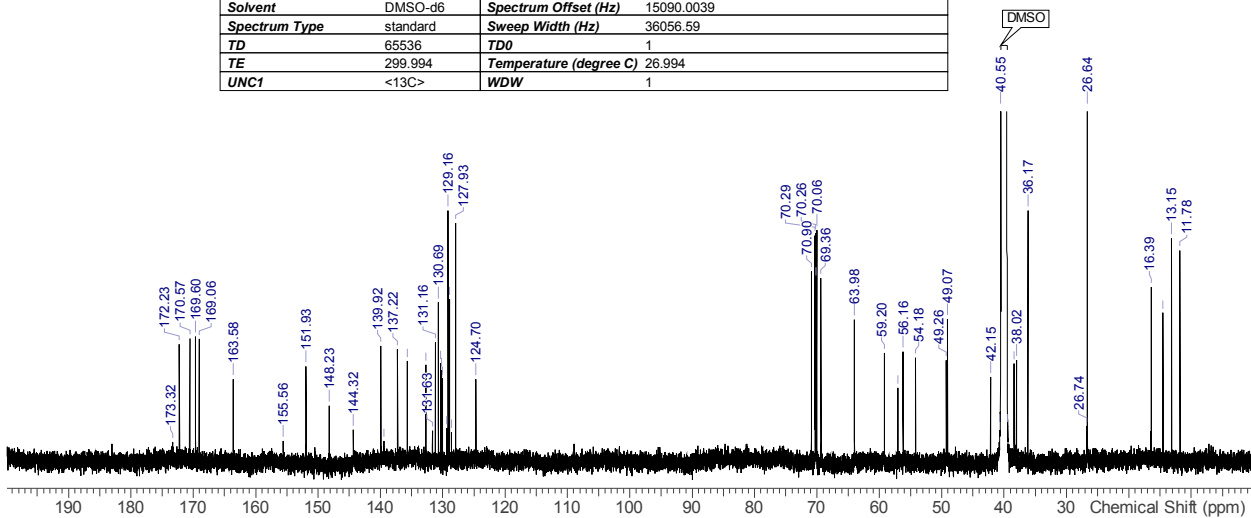
Acquisition Time (sec)	5.1118	Comment	rwurz
File Name	\\SCONE\NMR-Archive\camp\rwurz\2016\123429-10-2_10.JDX		
Frequency (MHz)	400.1300	Nucleus	1H
Original Points Count	32768	Points Count	32768
SW(cyclical) (Hz)	6410.26	Solvent	DMSO-d6
Spectrum Offset (Hz)	2396.9932	Spectrum Type	undefined
Sweep Width (Hz)	6410.06		

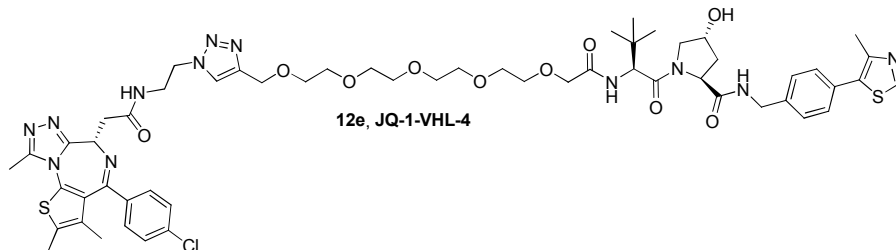
¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.97 (1 H, s), 8.58 (1 H, t, *J*=5.9 Hz), 8.43 (1 H, t, *J*=5.6 Hz), 8.11 (1 H, s), 7.45 - 7.51 (2 H, m), 7.34 - 7.44 (7 H, m), 5.14 (1 H, d, *J*=3.5 Hz), 4.55 (1 H, d, *J*=9.6 Hz), 4.48 - 4.52 (3 H, m), 4.38 - 4.47 (4 H, m), 4.36 (2 H, br d, *J*=6.5 Hz), 4.20 - 4.31 (1 H, m), 4.08 (2 H, q, *J*=5.3 Hz), 3.95 (2 H, s), 3.63 - 3.69 (1 H, m), 3.57 - 3.63 (3 H, m), 3.45 - 3.57 (13 H, m), 3.22 (2 H, d, *J*=7.2 Hz), 3.16 (7 H, d, *J*=5.3 Hz), 2.59 (3 H, s), 2.42 - 2.45 (3 H, m), 2.40 (3 H, s), 2.03 (1 H, br d, *J*=8.2 Hz), 1.84 - 1.94 (1 H, m), 1.62 (3 H, s), 0.93 (9 H, s)





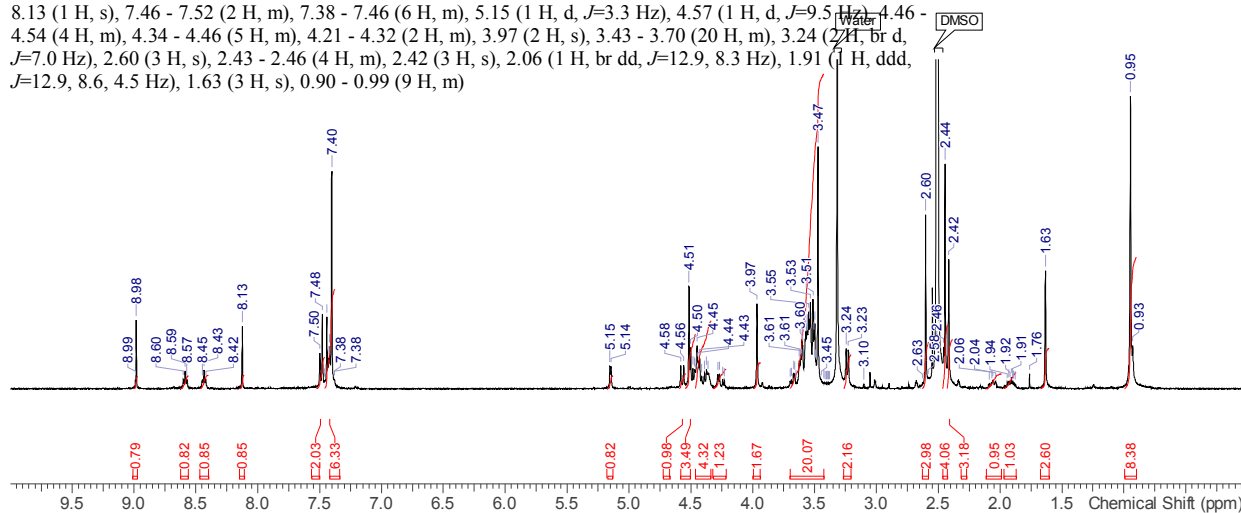
Acquisition Time (sec)	0.9088	
Comment	Test ID 256280; Request 256271-1; Targeted Proteolysis; Ryan Wurz; 123429-10-2 (3348486) in DMSO-d6	
D	1.2	D1 1.2
DE	18	DS 8
Date	05 Jul 2016 14:40:20	
Date Stamp	05 Jul 2016 14:40:20	
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Frequency (MHz)	150.9028	GB 0
INSTRUM	<spect>	LB 1
NS	32768	Nucleus 13C
Number of Transients	32768	Origin spect
Original Points Count	32768	Owner shr-ato-nmr1
PC	1.4	
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >	
PULPROG	<zgdc30>	Points Count 32768
Pulse Sequence	zgdc30	Receiver Gain 2050.00
SF	150.902809	SFO1 150.917899
SI	131072	SSB 0
SW(cyclical) (Hz)	36057.69	SWH 36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz) 15090.0039
Spectrum Type	standard	Sweep Width (Hz) 36056.59
TD	65536	TD0 1
TE	299.994	Temperature (degree C) 26.994
UNC1	<13C>	WDW 1





Acquisition Time (sec)	4.8234	Comment	rwurz	D	0.06
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Date	16 Feb 2017 09:12:04				
Date Stamp	16 Feb 2017 09:12:04				
File Name	\\scone\NMR-Archive\data\rwurz\nmr\123971-13-2\10.fid				
Frequency (MHz)	400.1300	GB	0	INSTRUM	<spect>
LB	0.3	NS	64	Nucleus	1H
Number of Transients	64	Origin	spect	Original Points Count	32768
Owner	shr-ato-nmr1			PC	1
PROBHD	<5 mm PABBO BB/19F-1H/D Z-GRD Z104450/0036 >				
PULPROG	<zg30>	Points Count	32768	Pulse Sequence	zg30
Receiver Gain	287.00	SF	400.13		
SFO1	400.132880936				
SSB	0	SW(cyclical) (Hz)	6793.48	SI	32768
SWH	6793.47826086957			Solvent	DMSO-d6
Spectrum Offset (Hz)	2880.9365	Spectrum Type	standard	Sweep Width (Hz)	6793.27
TD	65536	TD0	1	TE	300
Temperature (degree C)	27.000	UNC1	<1H>	WDW	1

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.97 - 9.01 (1 H, m), 8.59 (1 H, br t, *J*=6.0 Hz), 8.43 (1 H, br t, *J*=5.6 Hz), 8.13 (1 H, s), 7.46 - 7.52 (2 H, m), 7.38 - 7.46 (6 H, m), 5.15 (1 H, d, *J*=3.3 Hz), 4.57 (1 H, d, *J*=9.5 Hz), 4.46 - 4.54 (4 H, m), 4.34 - 4.46 (5 H, m), 4.21 - 4.32 (2 H, m), 3.97 (2 H, s), 3.43 - 3.70 (20 H, m), 3.24 (2 H, br d, *J*=7.0 Hz), 2.60 (3 H, s), 2.43 - 2.46 (4 H, m), 2.42 (3 H, s), 2.06 (1 H, br dd, *J*=12.9, 8.3 Hz), 1.91 (1 H, ddd, *J*=12.9, 8.6, 4.5 Hz), 1.63 (3 H, s), 0.90 - 0.99 (9 H, m)





Acquisition Time (sec)	0.9088	
Comment	Test ID 256280; Request 256271-1; Targeted Proteolysis; Ryan Wurz; 123429-9-2 (3348348) in DMSO-d6	
D	1.2	D1 1.2
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Date	08 Jul 2016 02:10:15	
Date Stamp	08 Jul 2016 02:10:15	
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Frequency (MHz)	150.9028	GB 0
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NS	32768	Nucleus 13C
Number of Transients	32768	Origin spect
Original Points Count	32768	Owner shr-ato-nmr1
PC	1.4	
PROBHD	<5 mm CPTCI 1H-13C/15N/D Z-GRD Z44896/0047 >	
PULPROG	<zgdc30>	Points Count 32768
Pulse Sequence	zgdc30	Receiver Gain 2050.00
SF	150.902809	SFO1 150.917899
SI	131072	SSB 0
SW(cyclical) (Hz)	36057.69	SWH 36057.6923076923
Solvent	DMSO-d6	Spectrum Offset (Hz) 15090.0039
Spectrum Type	standard	Sweep Width (Hz) 36056.59
TD	65536	TD0 1
TE	299.994	Temperature (degree C) 26.994
UNC1	<13C>	WDW 1

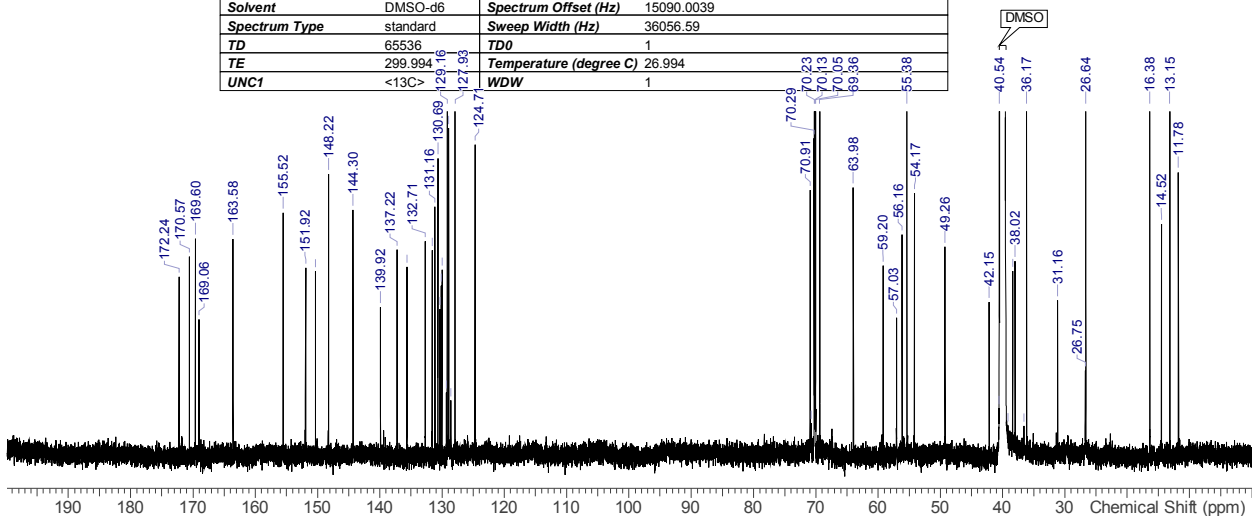


Table 1. BRD4 Degradation in a NCI-H838 Cell Line for Cereblon/BRD4 and VHL/BRD4 PROTACs.

Compound	Protein Degradation H838 Cells (4 h) DC₅₀ (μM)^a
3 ((+)-JQ-1)	>5
2 (dBET1)	0.13
11a	0.50
11b	0.13 ^b
11c	1.26
11d	0.25
11e	0.15
1 (MZ-1)	0.023
12a	0.55
12b	0.47
12c	1.67
12d	3.66
12e	2.73

^a Data represents an average of at least 2 separate determinations. ^b Data represents a single determination.