Supporting Information

Heterobivalent Inhibitors of Acetyl-CoA Carboxylase: Drug Target Residence Time and Time-Dependent Antibacterial Activity

Matthew T. Cifone,[†,‡] YongLe He,[†,‡] Rajeswari Basu,[†,‡] Nan Wang,[†] Shabnam Davoodi,[†,‡] Lauren A. Spagnuolo,[‡] Yuanyuan Si, [‡] Taraneh Daryaee, [‡] Craig E. Stivala,[§] Stephen G. Walker,[#] and Peter J. Tonge[†,‡,¶,*]

[†]Center for Advanced Study of Drug Action, and Departments of [‡]Chemistry, [#]Oral Biology and Pathology, and [¶]Radiology, John S. Toll Drive, Stony Brook University, Stony Brook, NY 11794-3400, United States

[§]Discovery Chemistry, Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, United States

*Email: peter.tonge@stonybrook.edu

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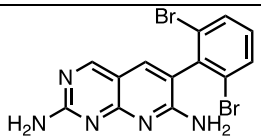
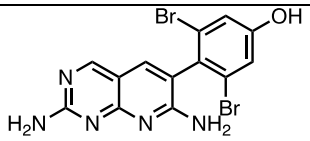
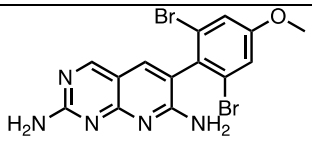
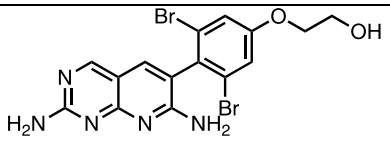
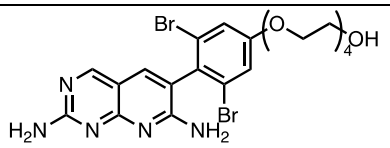
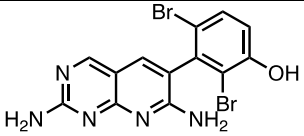
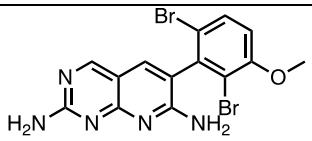
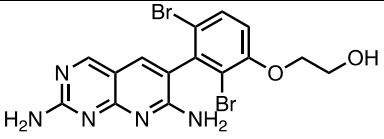
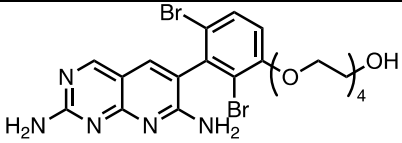
Table S1: SAR for the biotin carboxylase inhibitor analogs			
Cpd	**Structure**	**MIC *E. coli* ΔacrAB (μg/mL)**	**Biotin carboxylase K_i^{app} (nM)[a]**
1		0.5	≤ 250
S10		16	783 ± 151
S8		64	1200 ± 400
S12		32	730 ± 200
S14		≥64	≥1000
S9		8	614 ± 152
S7		2	≤ 250
S11		4	550 ± 88
S13		≥64	774 ± 320

Table S1. [a]Biotin carboxylase (BC) activity was determined at 25°C using a coupled assay in which the production of ADP was coupled to the oxidation of NADH using pyruvate kinase and lactate dehydrogenase. Reactions were initiated by adding BC (final concentration 500 nM) to a solution (0.5 mL total volume) of 100 mM HEPES buffer pH 8.0 containing 35-55 units of lactate dehydrogenase, 24-40 units of pyruvate kinase, 0.5 mM NADH, 1 mM phosphoenolpyruvate, 20 mM $MgCl_2$, 15 mM $KHCO_3$, 8 mM biotin and 3 mM ATP. The oxidation of NADH was followed at 340 nM using an Agilent Cary 100 UV-Vis spectrophotometer. Experiments were performed in triplicate, and errors are the standard deviation from mean. Data were fit to the Morrison equation in GraphPad Prism 7 (San Diego, California). MIC values were determined as described in the main manuscript.

Table S2: Primers for expression plasmid construction		
Primer	Sequence (5'-3' direction)	Restriction Enzyme
accA-f	GTTCTCCATATGAGTCTGAATTTCCTTGATTTTGAAC	NdeI
accA-r	CTTCTTAGGATCCCTTACGCGTAACCGTAGCTCATC	BamHI
accD-f	TAACACGGATCCTATGAGCTGGATTGAACGAATTAAAAGC	BamHI
accD-r	CTTCTTCTCGAGTCAGGCCTCAGGTTCC	XhoI
accC-f	CATCTTCATATGCTGGATAAAATTGTTATTGC	NdeI
accC-r	CATCAAGGATCCATTATTTTTCCTGAAGACCG	BamHI
accB-f	CTTCTTCATATGGATATTCGTAAGATTAAAAAA	NdeI
accB-r	CTTCTTGGATCCACCTCCTTACTCGATGACGACCAGCGGCTC	BamHI
Endonuclease sites are underlined.		

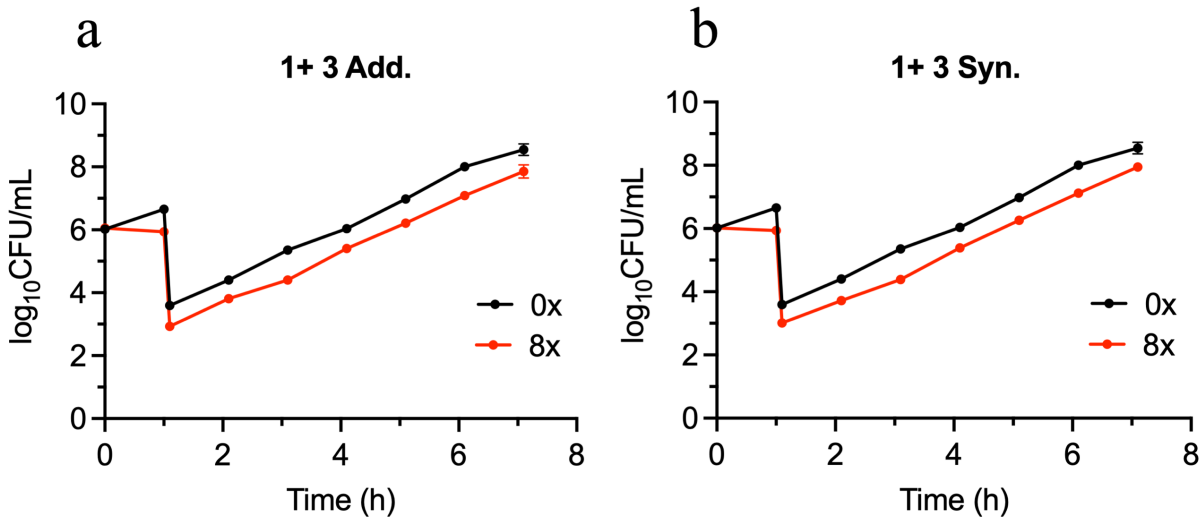
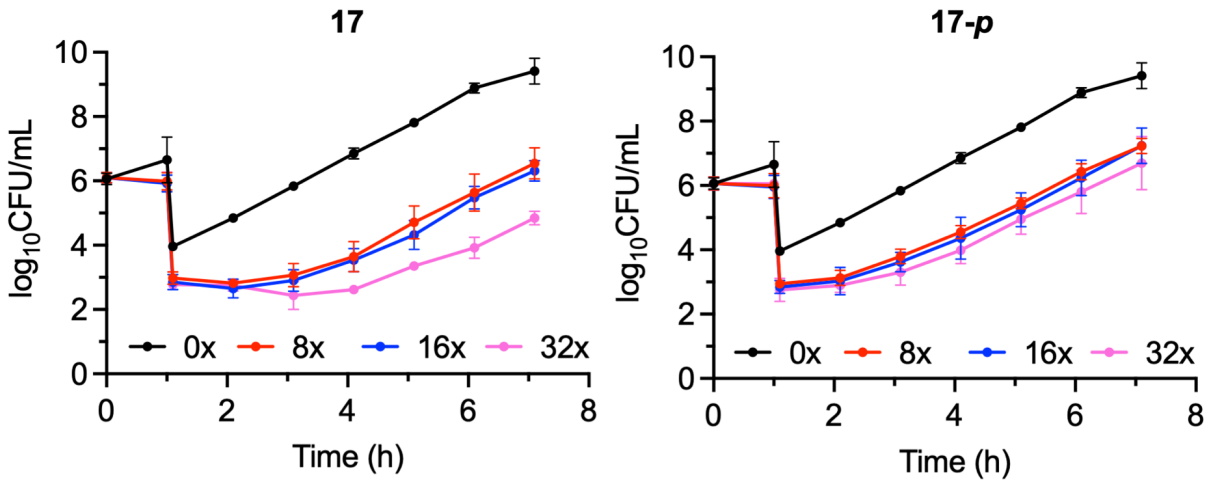


Figure S1. PAE of 1 and 3. a) **1+3** at 8x the FIC determined in the FIC experiments (0.025 µM **3**, 0.195 µM **1**) in which the two compounds acted additively, does not display a PAE against *E. coli* ΔtolC in the presence of PMBN. b) **1+3** at 8x FIC determined in the FIC experiments (0.025 µM **3**, 0.1 µM **1**) in which the two compounds acted synergistically, does not display a PAE against *E. coli* ΔtolC in the presence of PMBN. Experiments were performed with technical triplicates and performed in two independent experiments.



Compound	*E. coli* ΔtolC + PMBN MIC (μM)	PAE (h)		
		8x	16x	32x
17	0.39	1.65 ± 0.31	1.73 ± 0.23	3.41 ± 0.21
17-*p*	0.78	0.86 ± 0.18	0.92 ± 0.31	1.13 ± 0.17

Figure S2. Comparison of the PAE values generated by heterobivalent ACC inhibitors with a linker at the m or p position. The PAE generated by **17** in which the linker is coupled to the meta position of the dibromophenyl ring is 2-3-fold longer than for the regioisomer with the linker at the p position (**17-*p***).

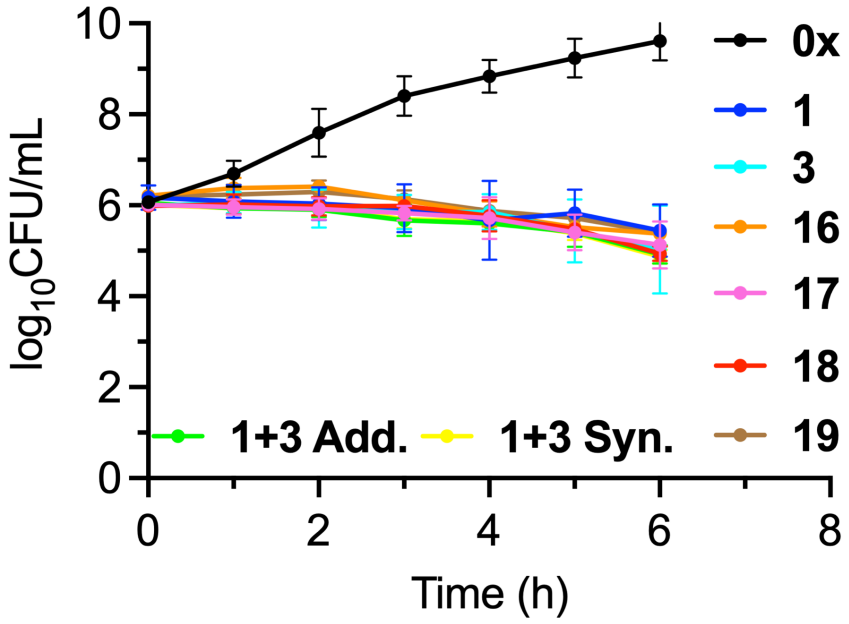


Figure S3. Time kill assays. Cultures of *E. coli* ΔtolC (10^6 CFU/mL) were grown to mid log phase (OD_{600} of 0.6-0.7) in CaMH media at 37 °C and then exposed to 0.008 μM PMBN and 32x MIC of ACC inhibitors, 8x FIC, or vehicle (DMSO). Subsequently, 0.1 mL aliquots were withdrawn at 1 h time intervals and plated in serial dilutions on Muller-Hinton agar plates. The CFUs were determined by counting colonies after overnight incubation at 37 °C. The experimental data points are the mean values from duplicate, independent measurements, and the error bars represent the standard deviation from the mean.

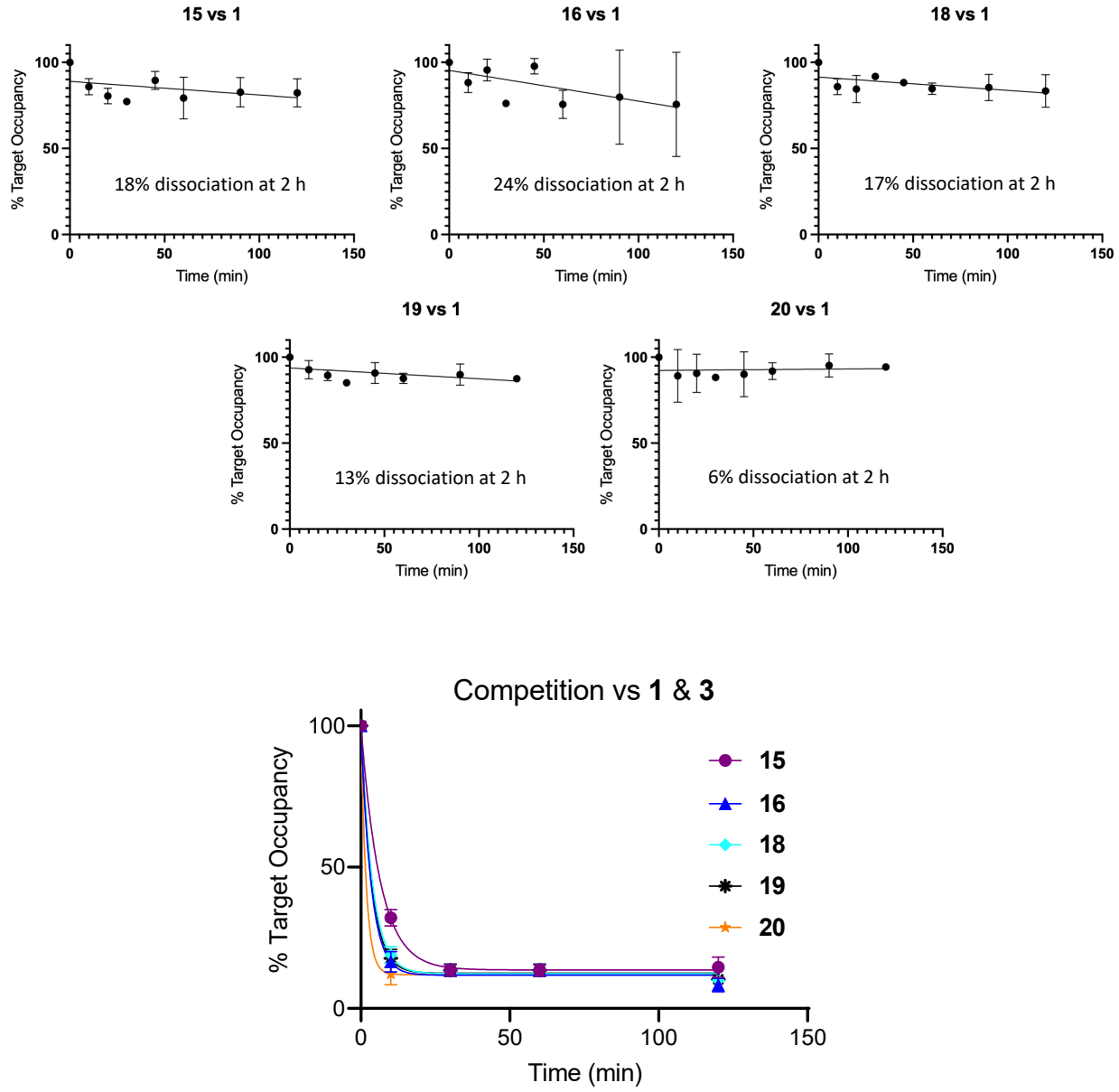


Figure S4. Competitive dissociation of the heterobivalent inhibitors from ACC. A 1 μM solution of ACC and heterobivalent inhibitor (**15, 16, 18-20**) were incubated together for 1 h before addition of 100 μM of competitor **1**, or 50 μM **1** & **3**. Subsequently, 100 μL aliquots were subjected to gel filtration chromatography using SpinTrap columns and the concentration of bivalent inhibitor in the flow though was quantified by LC/MSMS. The change in concentration of the bound bivalent inhibitor was monitored for 2 h, and the results are the average of two independent experiments performed at 22°C. (A) Competition with **1**. Linear regression gave

estimates of 5-15% dissociation of **15** and **18-20** over the 2 h incubation period and a slightly larger fractional dissociation of **16** albeit with larger errors vs **1**. (B) Competition with **1** and **3**. Addition of both **1** and **3** to the ACC:inhibitor complexes resulted in rapid dissociation of the heterobivalent inhibitors from ACC. Fitting data to a single exponential equation gave residence times of 1-5 min. The results for compounds **15, 16, 18-20** are in broadly agreement with data presented for heterobivalent inhibitor **17** (**Figure 5**) where a combination of **1** and **3** causes rapid dissociation of **17** whereas only limited dissociation is observed when **1** alone is used.

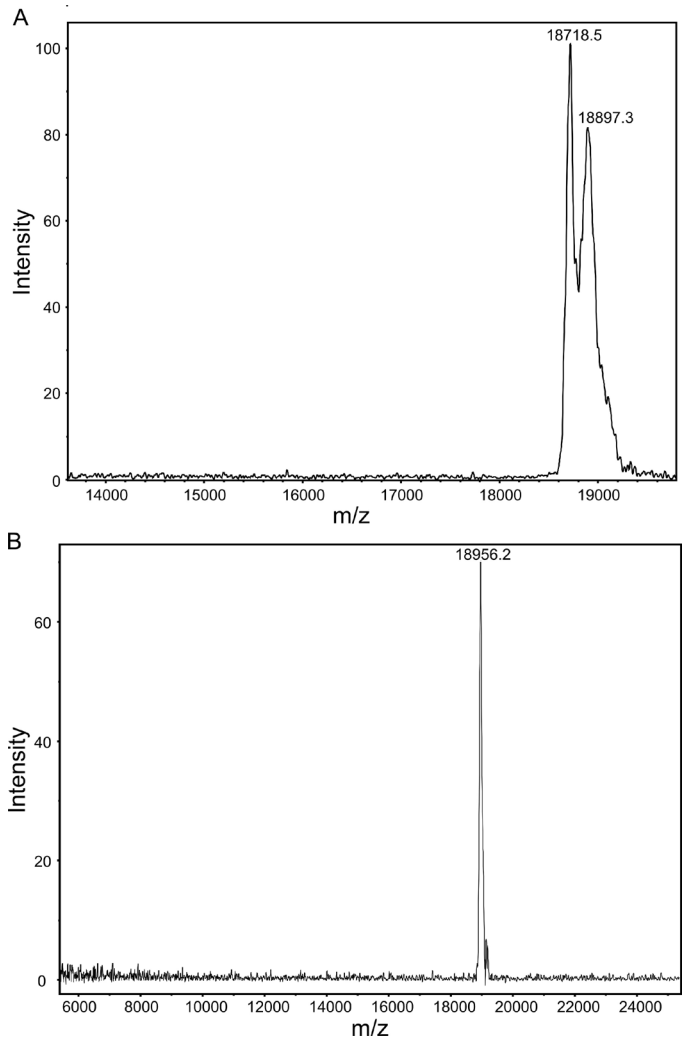


Figure S5: MALDI-TOF of BCCP. A) MALDI spectrum of BCCP prior to in vitro biotinylation. B) MALDI spectrum of BCCP after *in vitro* biotinylation. Apo-BCCP is observed to have a mass of 18718.5 whereas fully biotinylated BCCP has a mass of 18956.2. *E. coli* BCCP was expressed with an N-terminal His-tag and has the sequence shown below (sequence of endogenous BCCP is highlighted in yellow):

```
        10         20         30         40         50         60
MGSSHHHHHH SSGLVPRGSH MDIRKIKKLI ELVEESGISE LEISEGEESV RISRAAPAAS

        70         80         90        100        110        120
FPVMQQAYAA PMMQQPAQSN AAAPATVPSM EAPAAAEISG HIVRSPMVGT FYRTPSPDAK

       130        140        150        160        170
AFIEVGQKVN VGDTLCIVEA MKMMNQIEAD KSGTVKAILV ESGQPVEFDE PLVVIE
```

The theoretical mass of apo-BCCP is 18850.53 and that of holo-BCCP is 19076.53. These masses match, within experimental error (± 15 Da), the observed masses assuming that the N-terminal Met has been cleaved during protein expression (18719.34 and 18945.34).

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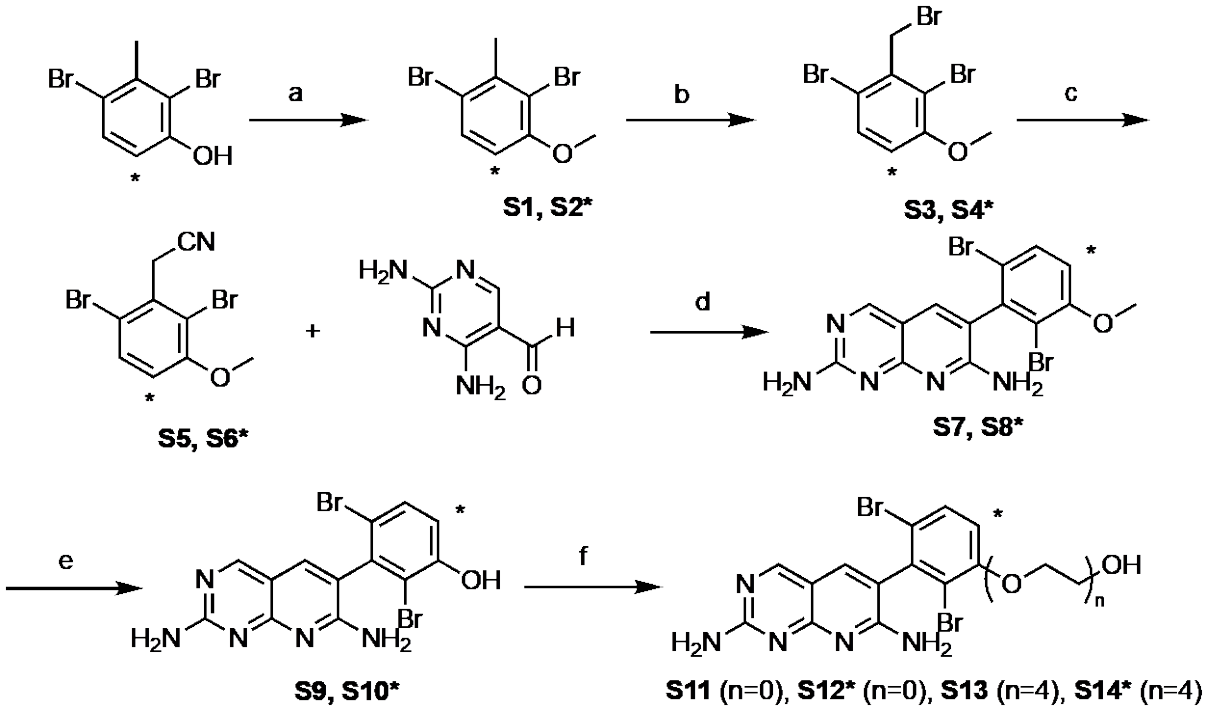


Scheme S1. Synthetic scheme for *meta* and *para* analogues of pyridopyrimidine 1.

Reagents and conditions: * Denotes *para* analogue (a) K_2CO_3, CH_3I, acetone, reflux, 89-96%; (b) NBS, benzoyl peroxide, CCl_4, reflux, 96-97%; (c) TMSCN, TBAF, CH_3CN, 22°C, 56-94%; (d) NaH, 2-ethoxyethanol, reflux, 29-33%; (e) BBr_3, CH_2Cl_2, -78°C to 22°C, 23-92%; (f) K_2CO_3, 2-bromoethanol or 2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethanol, DMF, 90°C, 18-39%.

Experimental details for Scheme S1

1,3-dibromo-4-methoxy-2-methylbenzene (S1)

To a RBF containing 2,4-dibromo-3-methylphenol (0.96 g, 3.6 mmol), 12 mL of acetone, which had been previously dried over K_2CO_3, was added. K_2CO_3 (1.1 g, 8.0 mmol) was also added, and the reaction was stirred for 10 minutes at which point CH_3I (0.3 mL, 4.8 mmol) was added. The reaction was set to reflux, and TLC showed reaction completion after 3.5 h. Acetone was removed under reduced pressure, and ethyl acetate and water were added. The layers were separated, and the aqueous layer was washed 2x with 10 mL ethyl acetate. The combined organic layers were washed with 2 mL of 10 M NaOH followed by brine. The organic layer was dried over $MgSO_4$ and concentrated and to yield a white solid (0.90 g, 89%). The product was used without further purification. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.47 (d, J = 9.03 Hz, 1H), 6.65 (d, J = 8.60 Hz, 1H), 3.88 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.4, 138.6, 131.3, 115.8, 115.1, 110.3, 56.5, 24.0.

1,3-dibromo-2-(bromomethyl)-4-methoxybenzene (S3)

To a RBF containing 1,3-dibromo-4-methoxy-2-methylbenzene (**1**) (0.900 g, 3.2 mmol), 25 mL of CCl_4 was added, followed by *N*-bromo-succinimide (0.85 g, 4.8 mmol) and benzoyl peroxide (0.020 g, 0.083 mmol). The reaction set to reflux. After 5.5 h, TLC showed reaction completion, and 10 mL saturated sodium thiosulfate was added. The layers were separated, and the aqueous layer was washed 2x with DCM (10 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated, which afforded a brown solid (1.10 g, 96%). The product was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, J = 8.85 Hz, 1H), 6.76 (d, J = 9.16 Hz, 1H), 4.87 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.8, 137.2, 132.3, 115.68, 115.62, 112.9, 56.7, 34.3.

2-(2,6-dibromo-3-methoxyphenyl)acetonitrile (S5)

TBAF (1 M in THF, 4.2 mL) was added slowly via a syringe to a solution of 3-dibromo-2-(bromomethyl)-4-methoxybenzene (**3)** (1.15 g, 3.2 mmol) in 35 mL of acetonitrile and TMSCN (0.52 mL, 4.2 mmol) in an ice-bath. After the addition, the ice-bath was removed, and the reaction was left to stir at RT. After 18 h, the solvent was removed under reduced pressure, and ethyl acetate (10 mL) and water (10 mL) were added. The layers were separated, and the aqueous phase was

washed 2x with ethyl acetate (5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude solid was purified by flash chromatography; petroleum ether:ethyl acetate 95:5 to 85:15) to yield **2-(2,6-dibromo-3-methoxyphenyl)acetonitrile** (**5**) as a white solid (0.92 g, 94%). ^{1}H NMR (500 MHz, Chloroform -*d*): δ 7.47 (d, *J* = 8.85 Hz, 1H), 6.75 (d, *J* = 8.85 Hz, 1H), 4.08 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, Chloroform -*d*): δ 155.7, 132.1, 130.7, 115.4, 114.9, 114.7, 112.8, 56.5, 25.9. Positive LR-MS (*m/z*): $[M+NH_4]^+$ calc. 322.92, found 322.92.

2,4-dibromo-3-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenol (S9)

15 mL DCM was added to **6-(2,6-dibromo-3-methoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine (S7)** (0.18 g, 0.42 mmol) and placed in a dry ice/acetone bath at -78°C. BBr_3 (1 M solution in THF, 2.2 mL) was then added dropwise. After 18 h, water was added to quench the reaction, and the layers were separated. The organic layer was washed 2x with water (5 mL each wash), and the combined aqueous layers were washed with 10 mL DCM. The aqueous layer was then neutralized with a saturated sodium bicarbonate solution, and the product precipitated from the solution. The material was placed on the lyophilizer to dry and yielded a white solid (0.16 g, 92%). ^{1}H NMR (400 MHz, Methanol-d_4): δ 7.26 (s, 1H), 6.20 (s, 1H), 6.03 (d, *J* = 8.78 Hz, 1H), 5.44 (d, *J* = 8.78 Hz, 1H). ^{13}C NMR (101 MHz, Methanol-d_4): δ 163.33, 163.30, 163.2, 161.2, 156.2, 140.7, 137.9, 133.6, 123.9, 119.1, 114.6, 114.5, 109.0. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 411.92, found 411.92.

6-(2,6-dibromo-3-methoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine (S7)

2-ethoxyethanol (10 mL) was chilled, and 55 % oil dispersion of NaH (94 mg) was added. The reaction was allowed to warm to RT, and 2,4-diaminopyrimidine-5-carbaldehyde (0.226 g, 1.6 mmol) and **2-(2,6-dibromo-3-methoxyphenyl)acetonitrile** (**S5**) (0.50 g, 1.6 mmol) were added. The reaction was set to reflux. After 4.5 h, TLC indicated reaction completion, and volatiles were removed under reduced pressure. The crude solid was purified by flash chromatography (SiO_2; DCM:MeOH 96:4 to 90:10) to yield **6-(2,6-dibromo-3-methoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine** as a white solid (0.20 g, 29%). ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.67 (s, 1H), 7.71 (d, *J* = 8.85 Hz, 1H), 7.56 (s, 1H), 7.09 (d, *J* = 9.16 Hz, 1H), 3.94 (s, 3H). ^{13}C

NMR (126 MHz, Methanol-d_4): δ 164.9, 162.5, 162.4, 161.9, 158.0, 139.6, 139.4, 133.8, 123.7, 116.5, 115.0, 110.0, 57.3. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 425.93, found 425.94.

2-(2,4-dibromo-3-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethanol] (S11)

To **2,4-dibromo-3-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenol** (0.025 g, 0.061 mmol) dissolved in 3 mL of DMF, K_2CO_3 (0.030 g, 0.22 mmol) and 2-bromoethanol (0.018 g, 0.14 mmol) were added. The reaction was left to stir at 90°C for 11 h, at which point TLC indicated reaction completion. The volatiles were removed under reduced pressure, and the crude solid was purified by flash chromatography (DCM:MeOH 95:5 to 90:10) to yield **2-(2,4-dibromo-3-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethanol** as a white solid (0.0060 g, 18%). ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.67 (s, 1H), 7.69 (d, J = 8.85 Hz, 1H), 7.56 (s, 1H), 7.11 (d, J = 8.85 Hz, 1H), 4.19 (t, J = 1.00 Hz, 2H), 3.94 (t, J = 1.00 Hz, 2H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 164.9, 162.5, 162.4, 161.9, 157.4, 139.7, 139.4, 133.8, 123.8, 117.1, 116.8, 116.4, 110.0, 72.6, 61.7. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 455.94, found 455.95.

2-(2-(2-(2-(2,4-dibromo-3-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethanol (S13)

To **2,4-dibromo-3-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenol** (0.025 g, 0.061 mmol) dissolved in 3 mL of DMF, K_2CO_3 (0.030 g, 0.22 mmol) and 2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethanol (0.016 g, 0.063 mmol) were added. The reaction was left to stir at 90°C for 11 h, at which point TLC indicated reaction completion. The volatiles were removed under reduced pressure, and the crude solid was purified by flash chromatography (DCM:MeOH 95:5 to 90:10) to yield **2-(2-(2-(2-(2,4-dibromo-3-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethanol** as a white solid (0.014 g, 39%). ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.68 (s, 1H), 7.69 (d, J = 8.85 Hz, 1H), 7.57 (s, 1H), 7.12 (d, J = 9.16 Hz, 1H), 4.23 - 4.31 (m, 2H), 3.87 - 3.95 (m, 2H), 3.75 - 3.78 (m, 2H), 3.60 - 3.69 (m, 8H), 3.53 - 3.58 (m, 2H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 162.5, 162.4, 161.9, 157.4, 154.4, 139.7, 139.4, 133.8, 117.0, 116.9, 116.4, 110.0, 101.5, 73.8, 72.2, 71.81, 71.79, 71.8, 71.6, 70.9, 70.8. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 588.02, found 588.03.

1,3-dibromo-5-methoxy-2-methylbenzene (S2)

To a RBF containing 3,5-dibromo-4-methylphenol (1.0 g, 3.8 mmol), 10 mL of acetone, which had been previously dried over K_2CO_3, was added. K_2CO_3 (1.1 g, 8.0 mmol) was then added, and the reaction was stirred for 10 minutes at which point CH_3I (0.3 mL, 4.8 mmol) was added. The reaction was set to heat to reflux, and TLC showed reaction completion after 3.5 h. Acetone was removed under reduced pressure, and ethyl acetate and water were added. Layers were separated, and the aqueous layer was washed 2x with 10 mL ethyl acetate. The combined organic layers were washed with 2 mL of 10 M NaOH followed by brine. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to yield a white solid (1.01 g, 96%). The product was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 2H), 3.77 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.0, 129.2, 125.0, 117.8, 55.7, 22.6.

1,3-dibromo-2-(bromomethyl)-5-methoxybenzene (S4)

To a RBF containing **1,3-dibromo-5-methoxy-2-methylbenzene** (1.15 g, 4.1 mmol), 25 mL CCl_4 was added, followed by *N*-bromo-succinimide (1.01 g, 5.7 mmol) and benzoyl peroxide (0.020 g, 0.083 mmol). The reaction set to heat to reflux. After 18 h, TLC showed reaction completion, and 10 mL saturated sodium thiosulfate was added. The layers were separated, and the aqueous layer was washed 2x with DCM (10 mL). The combined organic layers were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to yield a brown solid (1.25 g, 97%). The product was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (s, 2H), 4.83 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.0, 128.2, 125.8, 118.5, 55.9, 34.3.

2-(2,6-dibromo-4-methoxyphenyl)acetonitrile (S6)

TBAF (1 M in THF, 6.0 mL) was added slowly via a syringe to a solution of **1,3-dibromo-2-(bromomethyl)-5-methoxybenzene** (1.45 g, 4.0 mmol) in 20 mL of acetonitrile and TMSCN (0.76 mL, 6.1 mmol) in an ice-bath. After the addition, the ice-bath was removed, and the reaction was left to stir at RT. After 18 h, the solvent was removed under reduced pressure, and ethyl acetate (10 mL) and water (10 mL) were added. The layers were separated, and the aqueous phase was washed 2x with ethyl acetate (5 mL each wash). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude solid was purified by flash chromatography (petroleum ether:ethyl acetate 95:5 to 85:15) to yield **2-(2,6-dibromo-4-**

methoxyphenyl)acetonitrile as a white solid (0.60 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 2H), 4.04 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.1, 125.2, 121.9, 118.5, 115.9, 55.9, 25.0. Positive LR-MS (*m/z*): $[M+NH_4]^+$ calc. 322.92, found 322.92.

3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenol (S10)

15 mL DCM was added to **6-(2,6-dibromo-4-methoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine** (0.26 g, 0.61 mmol) and placed in a dry ice/acetone bath at -78°C. BBr_3 (1 M solution in THF, 1.8 mL) was then added dropwise. After 18 h, water was added to quench the reaction, a saturated sodium bicarbonate solution was added, and the layers were separated. The organic layer was washed 2x with water (5 mL each wash), and the combined aqueous layers were washed once with 10 mL DCM. Product partitioned in the aqueous layer, which was placed on the lyophilizer to dry and yield an off-white solid. The crude solid was purified by flash chromatography (DCM:MeOH 93:7 to 90:10) to yield **3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenol** as a yellow solid (0.058 g, 23%). ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.91 (s, 1H), 7.91 (s, 1H), 7.23 (s, 2H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 164.4, 161.4, 154.6, 142.9, 126.6, 126.5, 123.7, 121.0, 119.8, 108.5. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 411.92, found 411.92.

6-(2,6-dibromo-4-methoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine (S8)

To chilled 2-ethoxyethanol (20 mL), 208 mg of a 55% oil dispersion of NaH was added. The reaction was allowed to warm to RT, and 2,4-diaminopyrimidine-5-carbaldehyde (0.50 g, 3.6 mmol) and **2-(2,6-dibromo-4-methoxyphenyl)acetonitrile** (1.1 g, 3.6 mmol) were added. The reaction was set to heat to reflux. After 4.5 h, TLC indicated reaction completion, and the volatiles were removed under reduced pressure. The crude solid was purified by flash chromatography (DCM:MeOH 96:4 to 90:10) to yield **6-(2,6-dibromo-4-methoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,7-diamine** as a white solid (0.63 g, 33%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.63 (s, 1H), 7.49 (s, 1H), 7.38 (br. s, 2H), 6.68 (s, 2H), 6.52 (br. s., 2H), 3.84 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 163.7, 161.2, 160.6, 160.1, 160.0, 137.5, 129.6, 125.5, 120.0, 118.0, 108.1, 56.1. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 425.93, found 425.94.

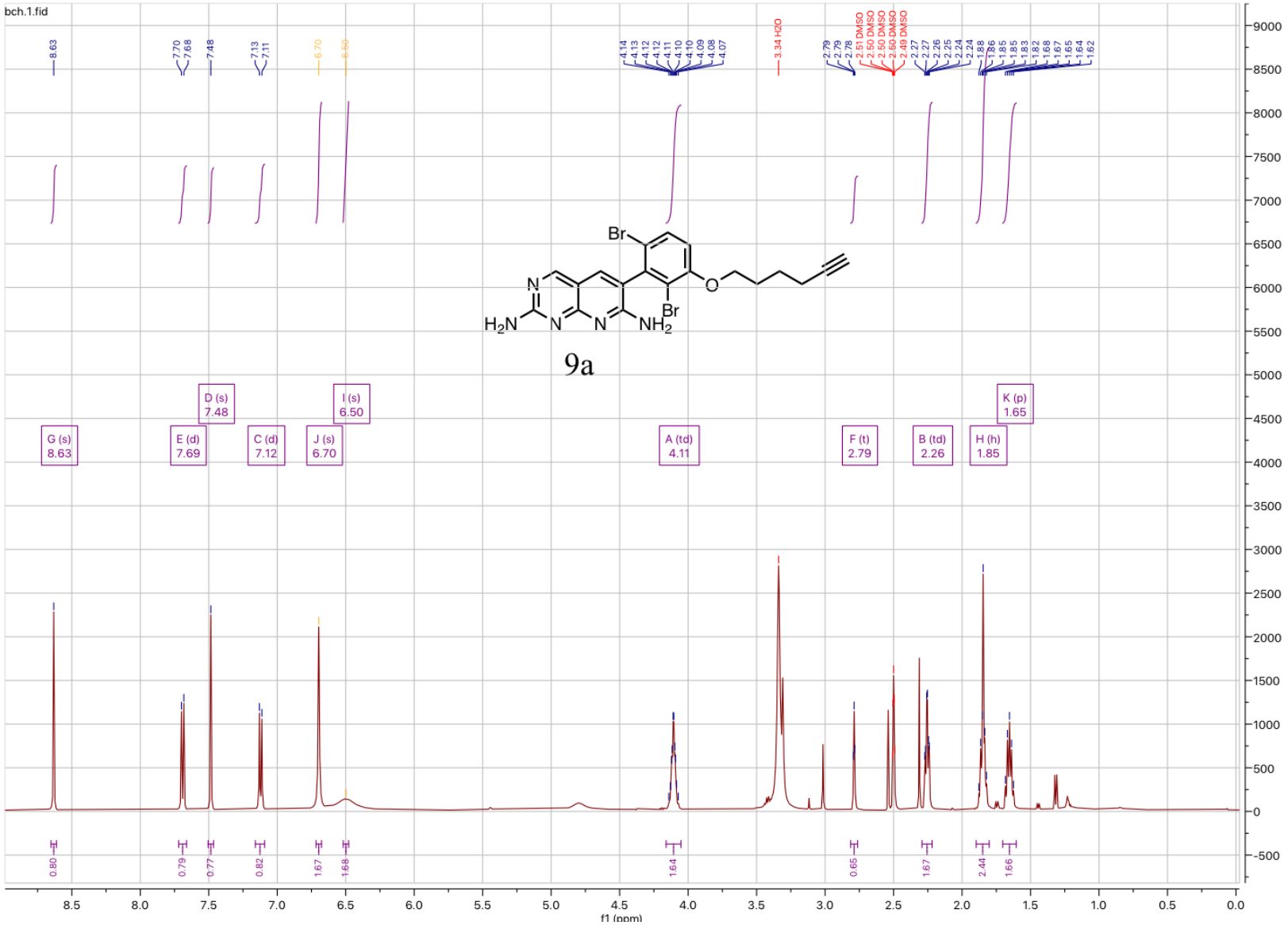
2-(3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethanol (S12)

To **3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenol** (0.025 g, 0.061 mmol) dissolved in 3 mL of DMF, K_2CO_3 (0.030 g, 0.22 mmol) and 2-bromoethanol (0.018 g, 0.14 mmol) were added. The reaction was left to stir at 90°C for 3 h, at which point TLC indicated reaction completion. The volatiles were removed under reduced pressure, and the crude solid was purified by flash chromatography (DCM:MeOH 95:5 to 90:10) to yield **2-(3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethanol** as a white solid (0.0083 g, 30%). ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.83 (s, 1H), 7.77 (s, 1H), 7.37 (s, 2H), 4.17 (t, J = 4.73 Hz, 2H), 3.88 (t, J = 4.73 Hz, 2H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 161.8, 161.7, 140.1, 130.7, 126.9, 120.2, 71.7, 61.5. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 455.94, found 455.95.

2-(2-(2-(2-(3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethanol (14)

To **3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenol** (0.025 g, 0.061 mmol) dissolved in 3 mL of DMF, K_2CO_3 (0.030 g, 0.22 mmol) and 2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethanol (0.028 g, 0.11 mmol), were added. The reaction was left to stir at 90°C for 4.5 h, at which point TLC indicated reaction completion. The volatiles were removed under reduced pressure, and the crude solid was purified by flash chromatography (DCM:MeOH 95:5 to 90:10) to yield **2-(2-(2-(2-(3,5-dibromo-4-(2,7-diaminopyrido[2,3-*d*]pyrimidin-6-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethanol** as a white solid (0.0082 g, 23%). ^{1}H NMR (500 MHz, Methanol-d_4): δ 8.68 (s, 1H), 7.59 (s, 1H), 7.39 (s, 2H), 4.20 - 4.24 (m, 2H), 3.86 - 3.91 (m, 2H), 3.72 - 3.75 (m, 2H), 3.64 - 3.71 (m, 8H), 3.56 - 3.60 (m, 2H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 163.0, 162.5, 161.8, 161.6, 140.1, 130.7, 126.9, 123.2, 120.2, 110.0, 73.8, 71.9, 71.8, 71.7, 71.6, 70.7, 69.7, 62.4. Positive LR-MS (*m/z*): $[M+H]^+$ calc. 588.02, found 588.03

NMR Spectra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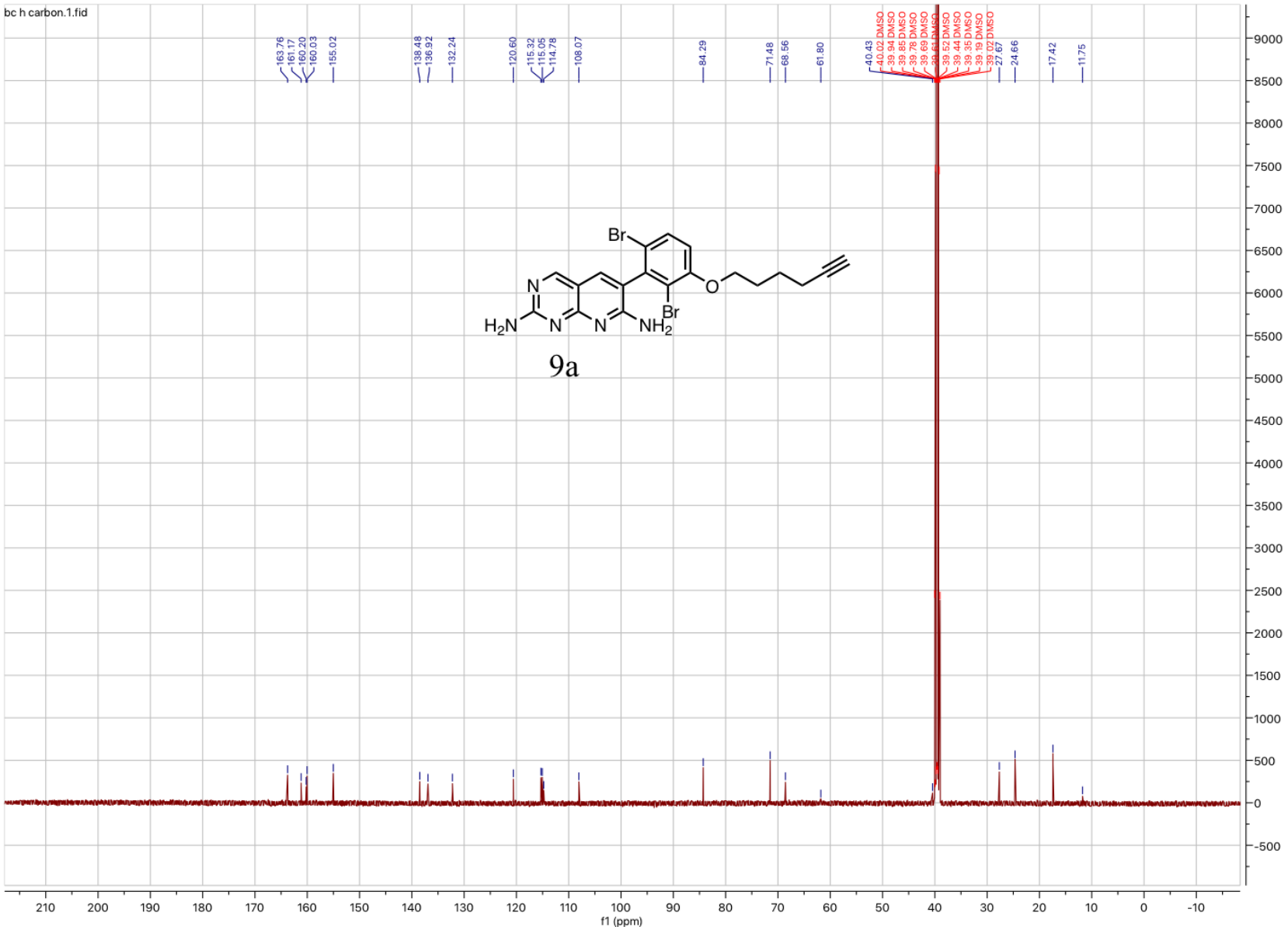
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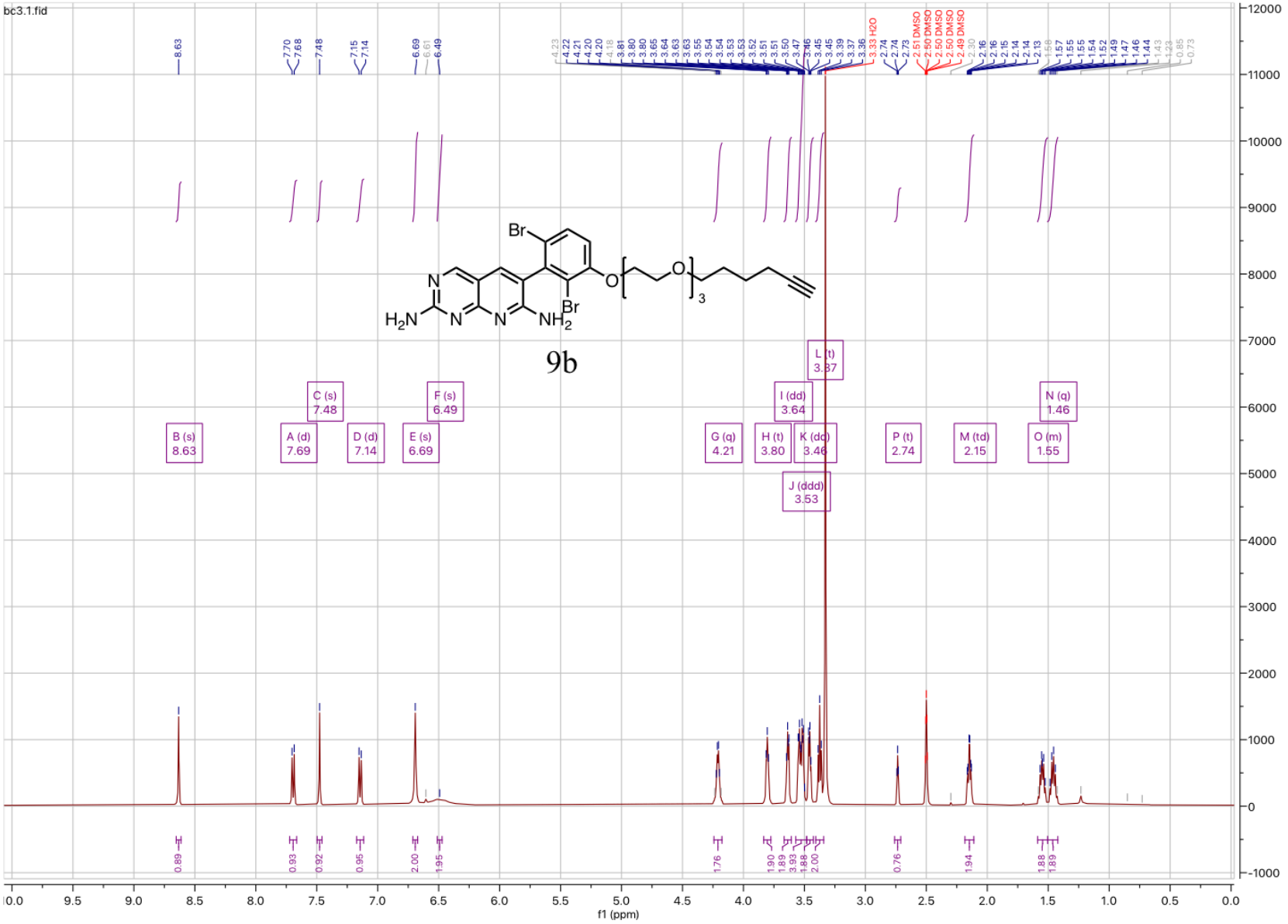
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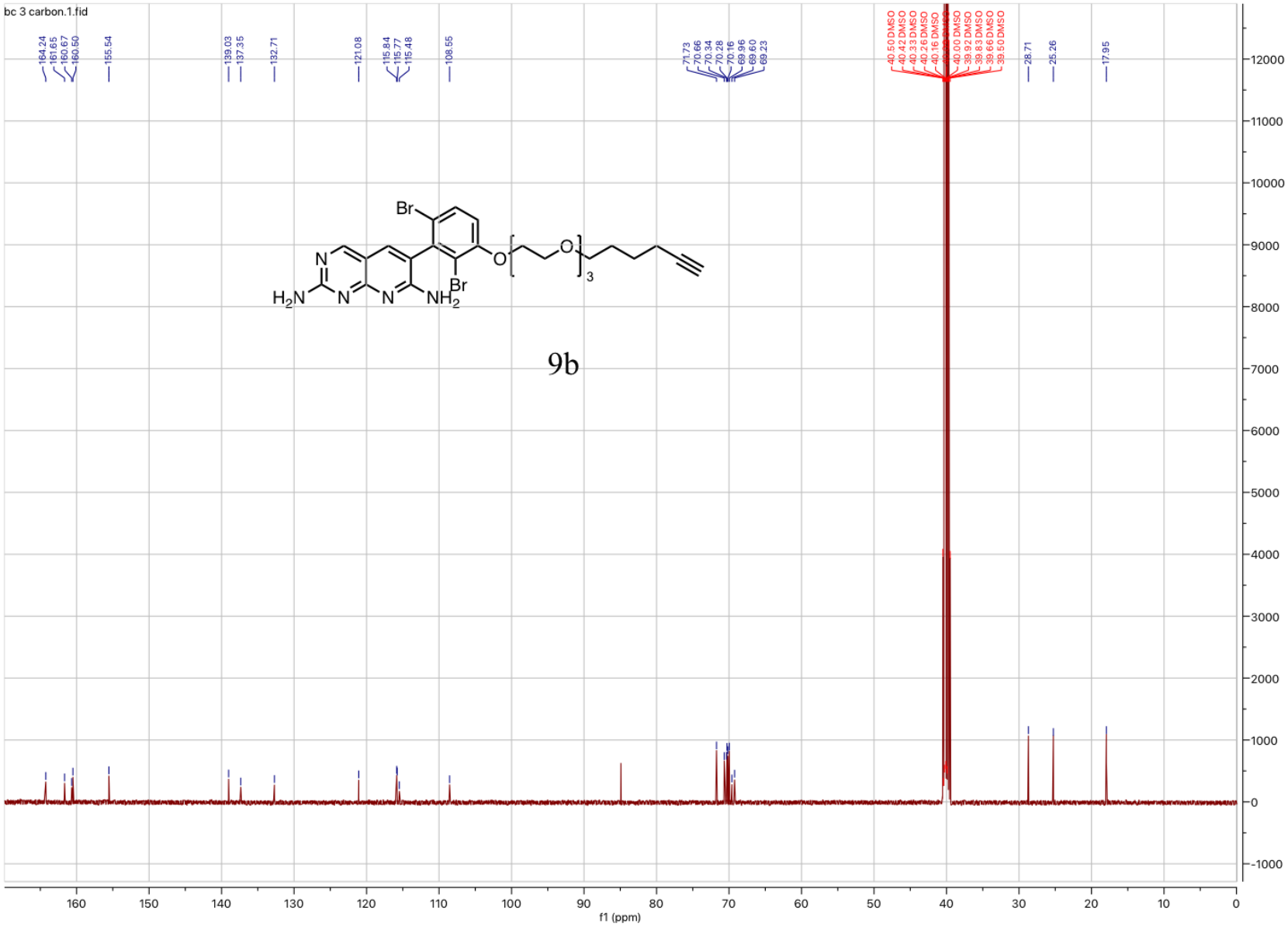
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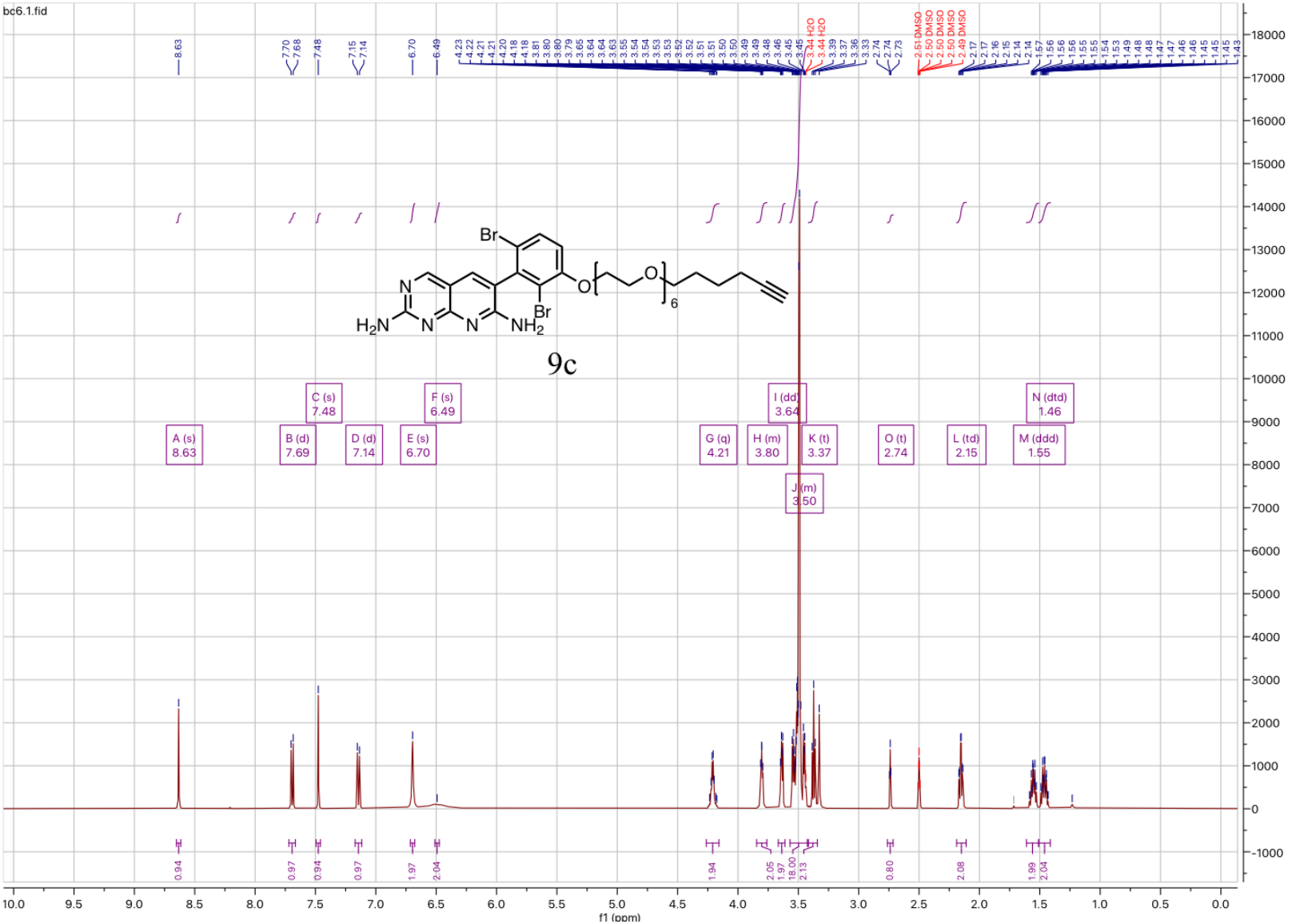
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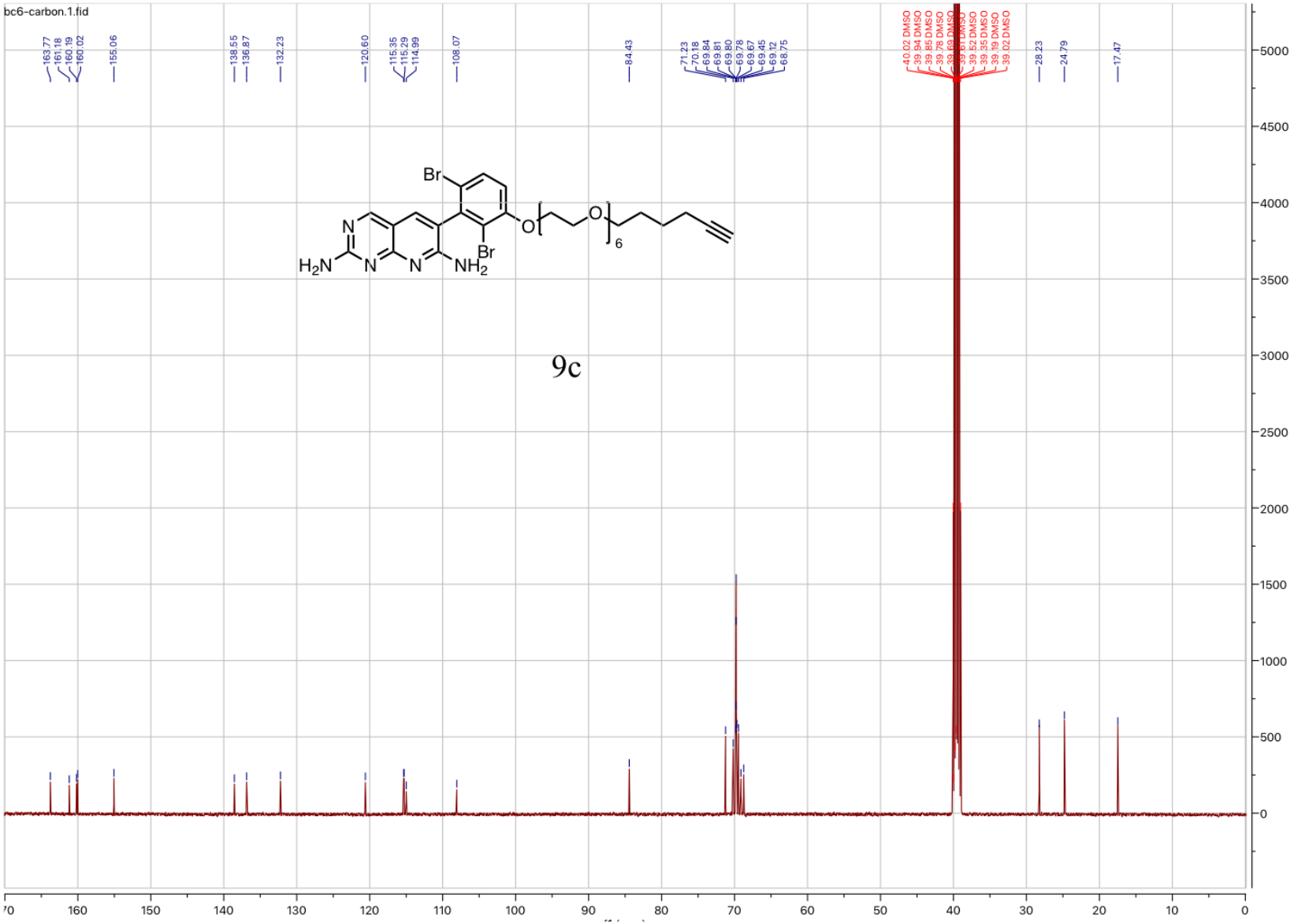
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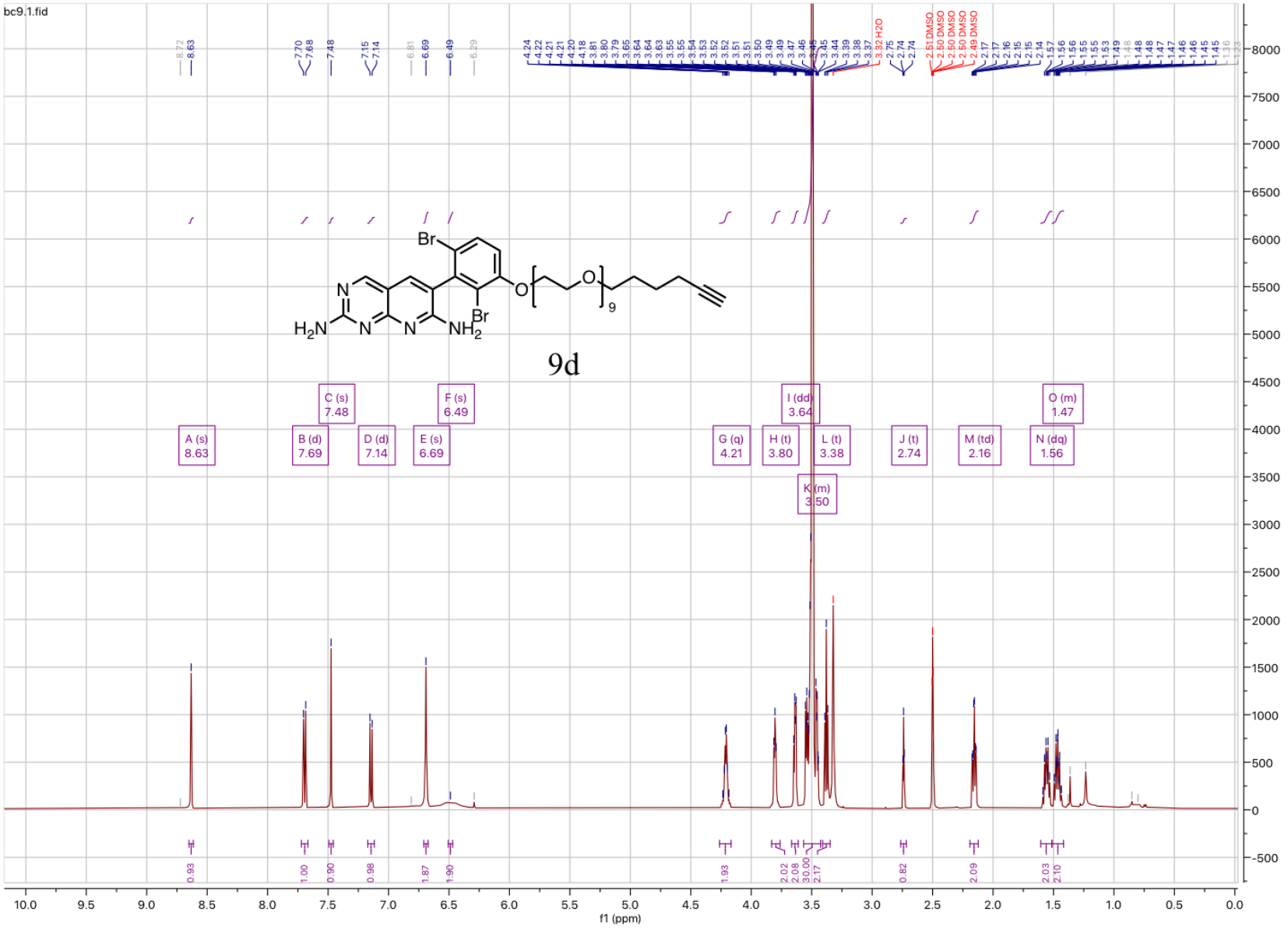
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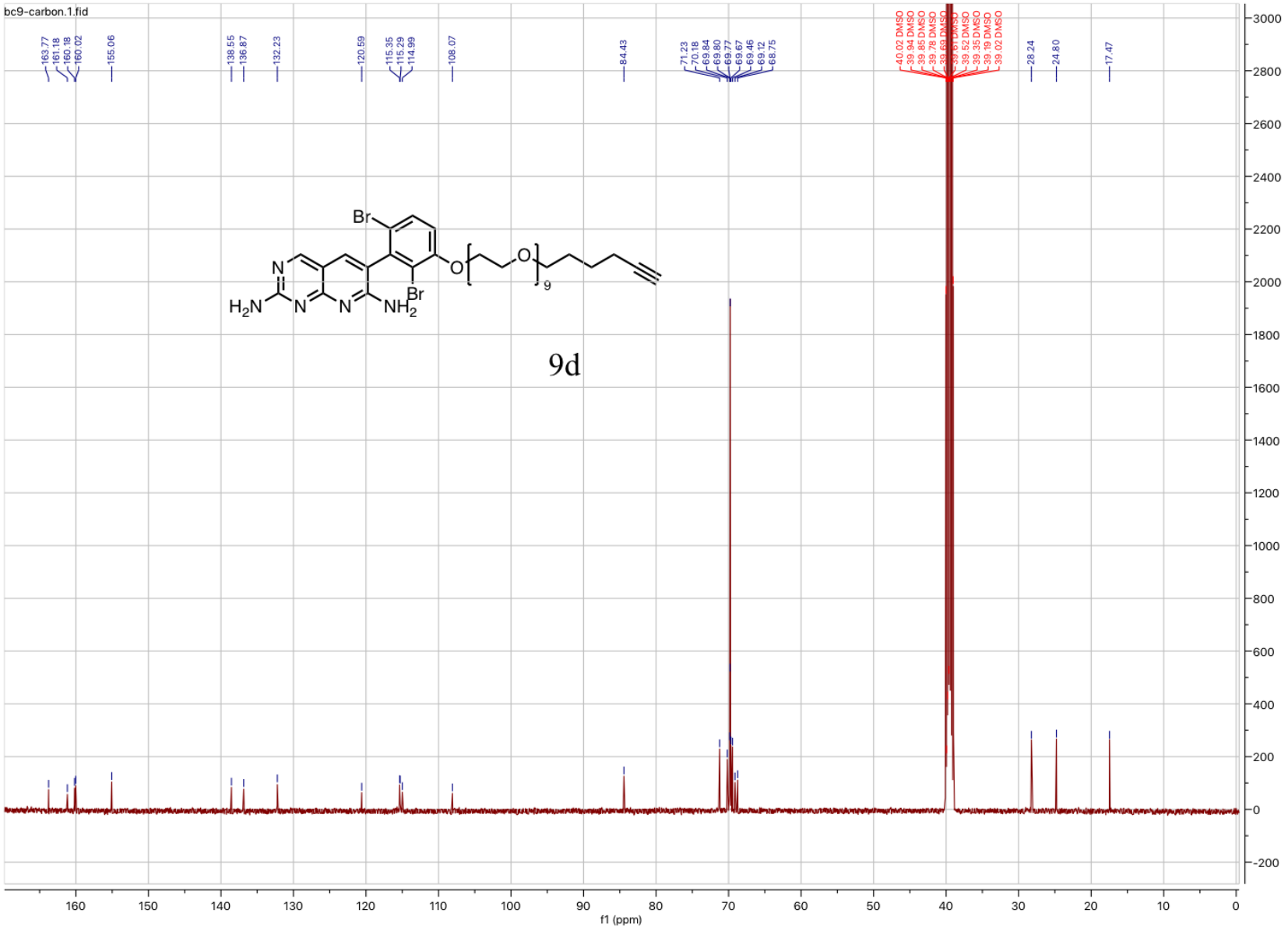
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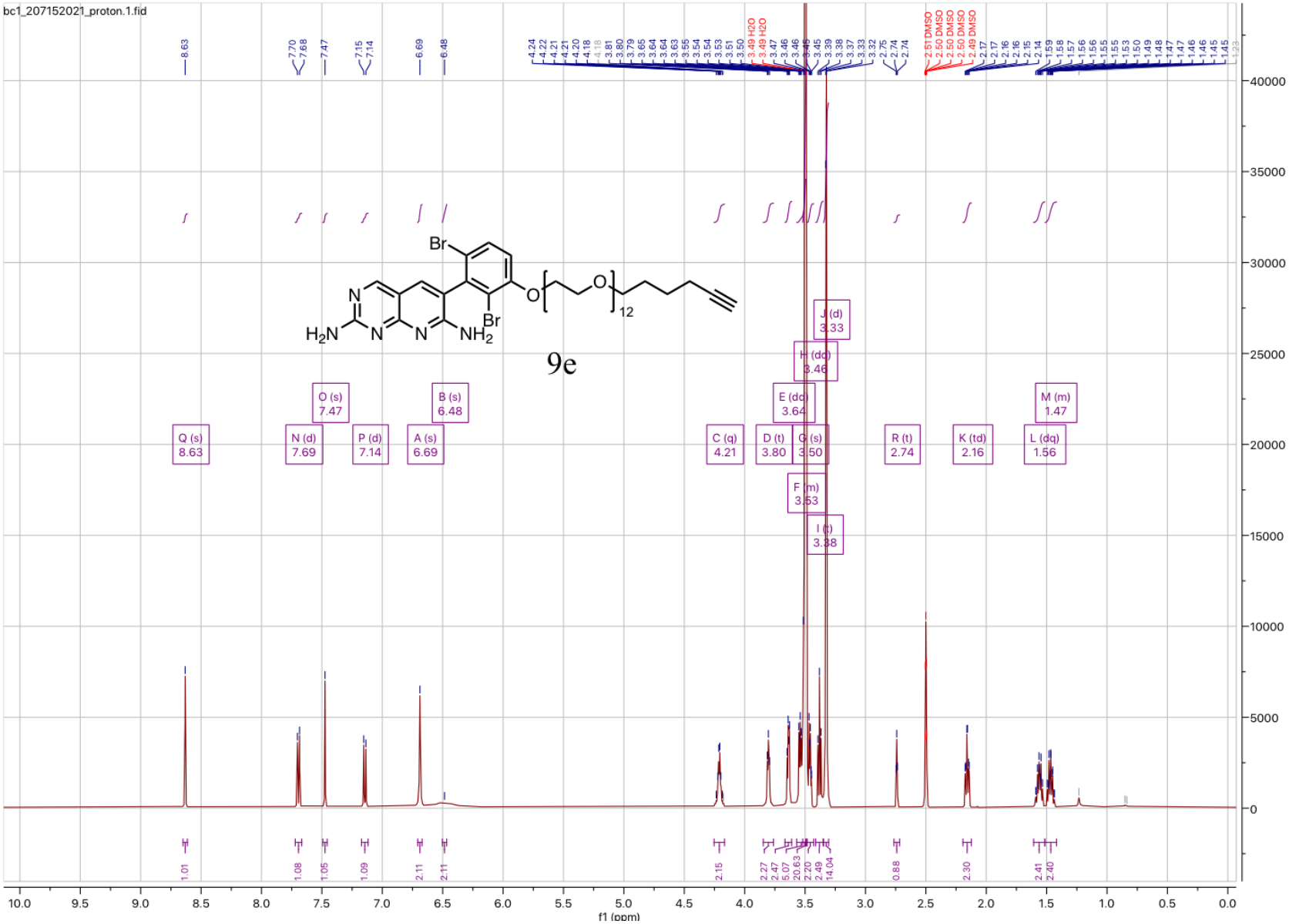
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D (t) 3.80
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F (m) 3.53
G (s) 3.50
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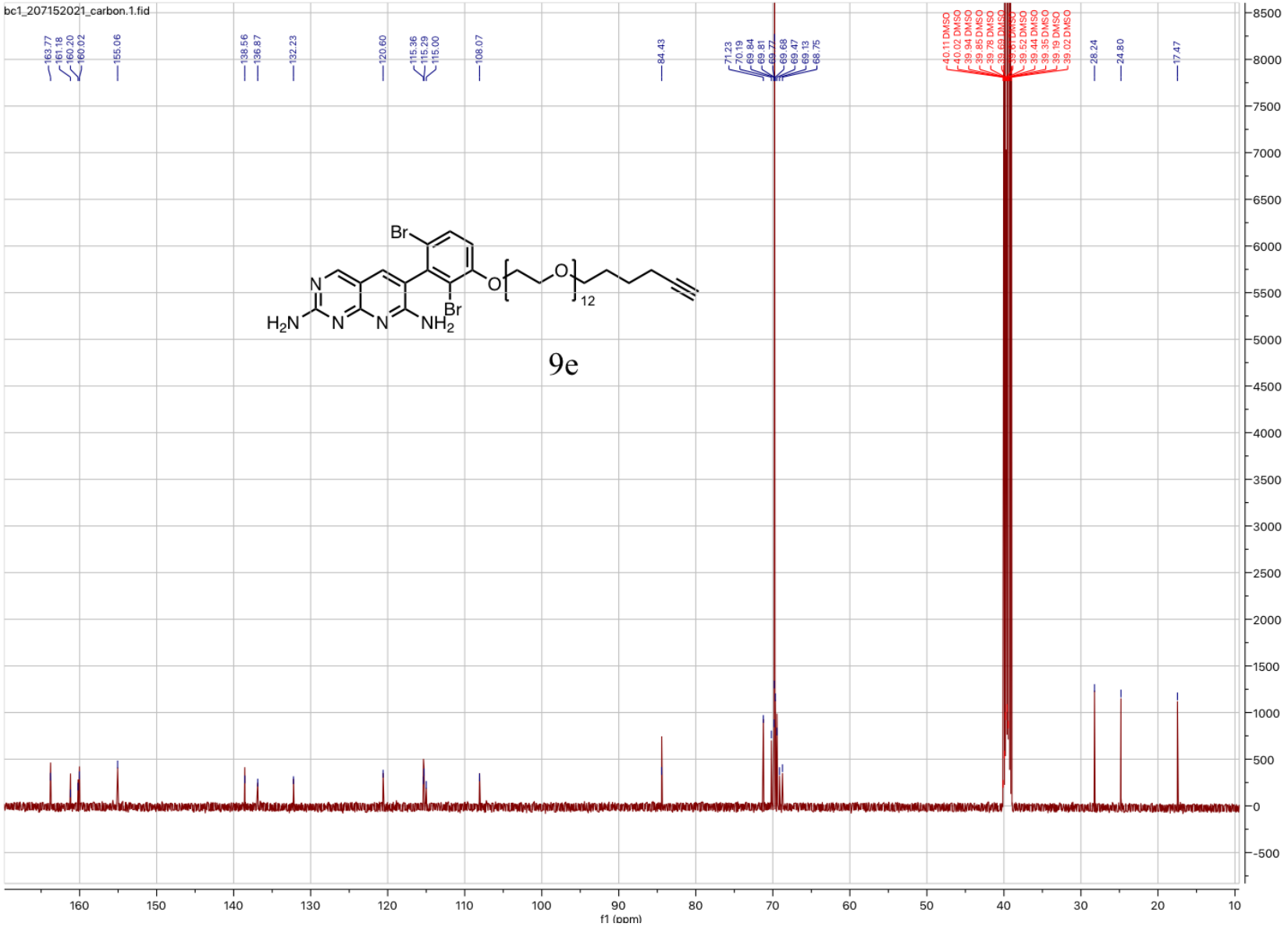
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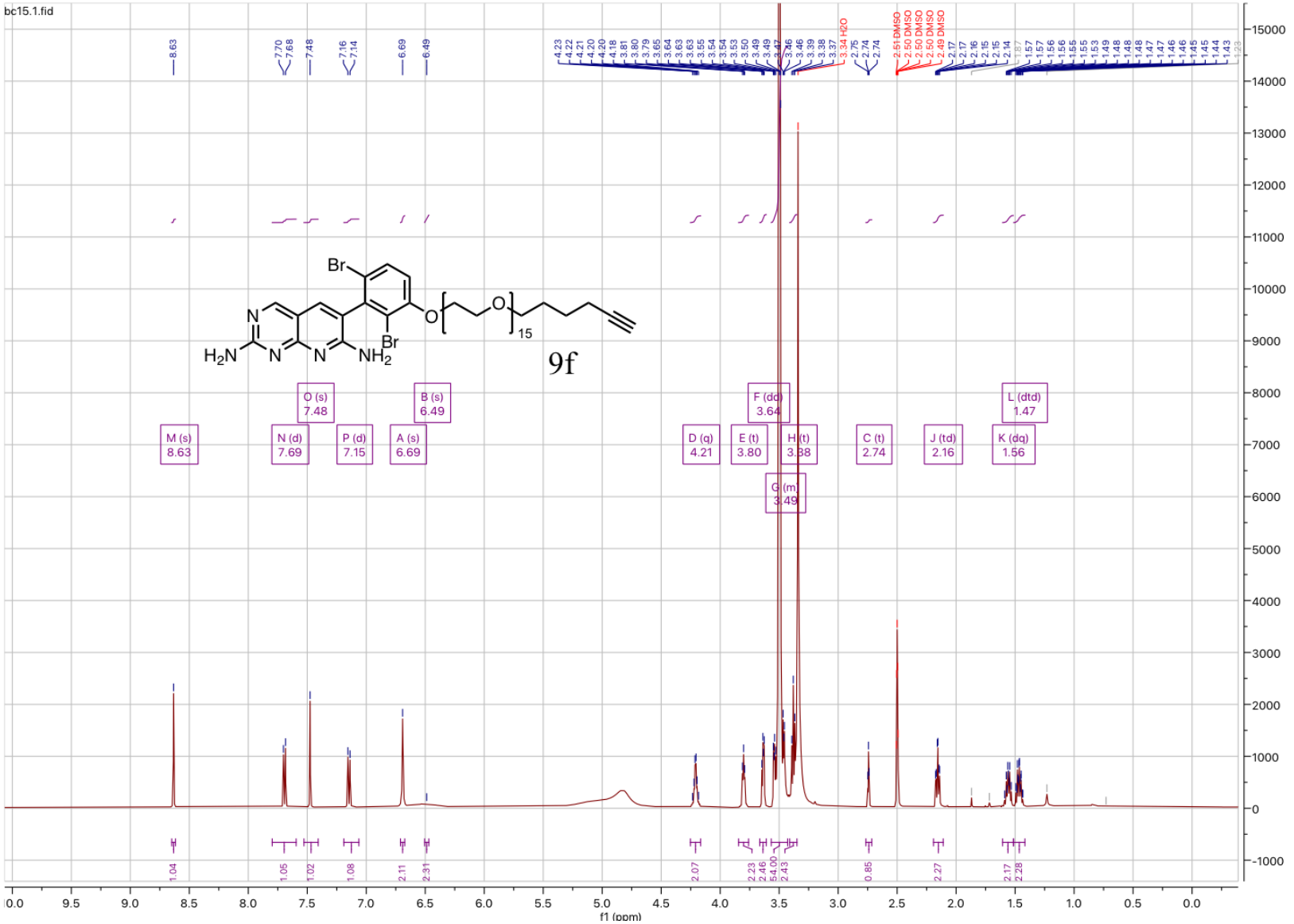
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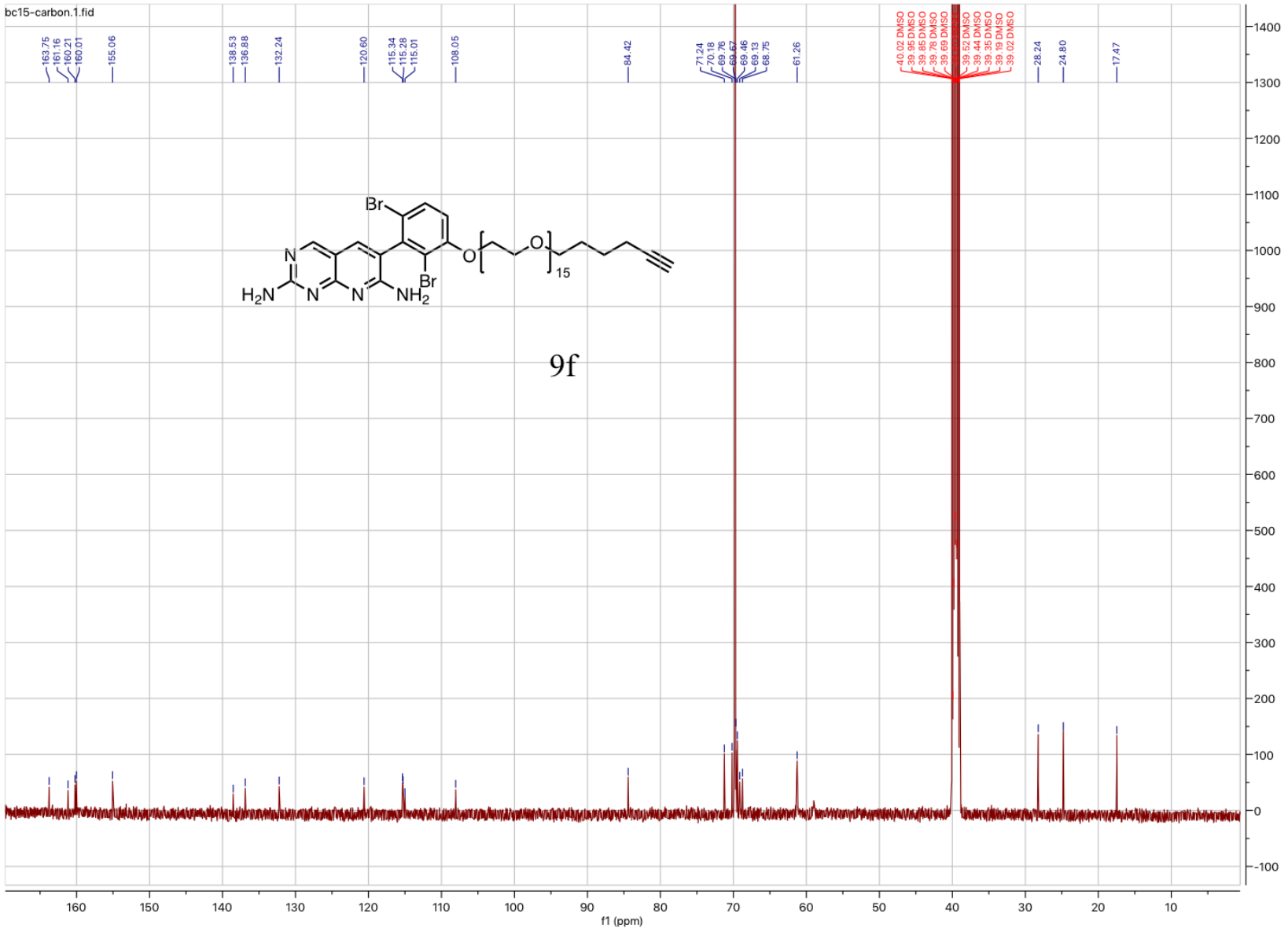
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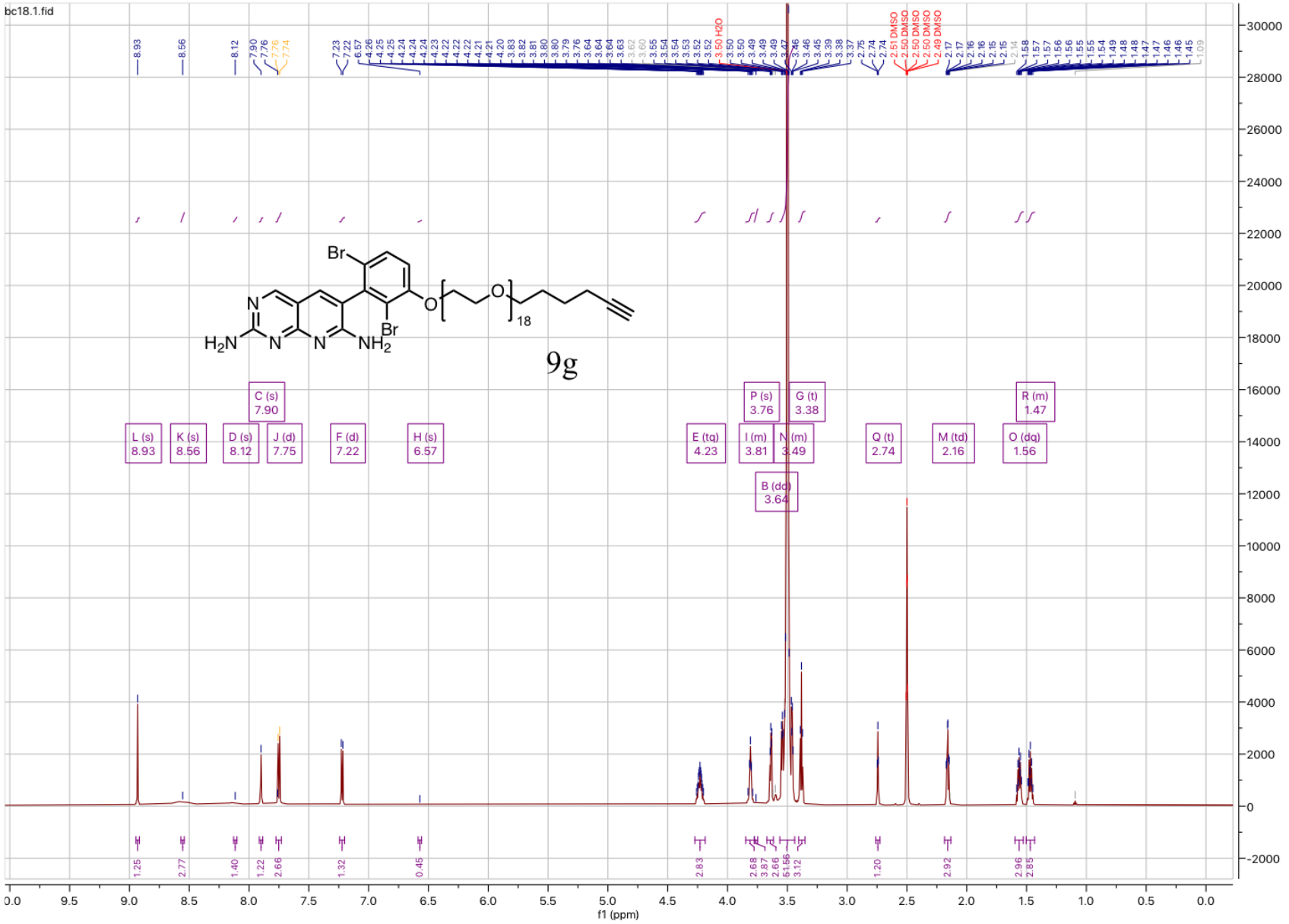
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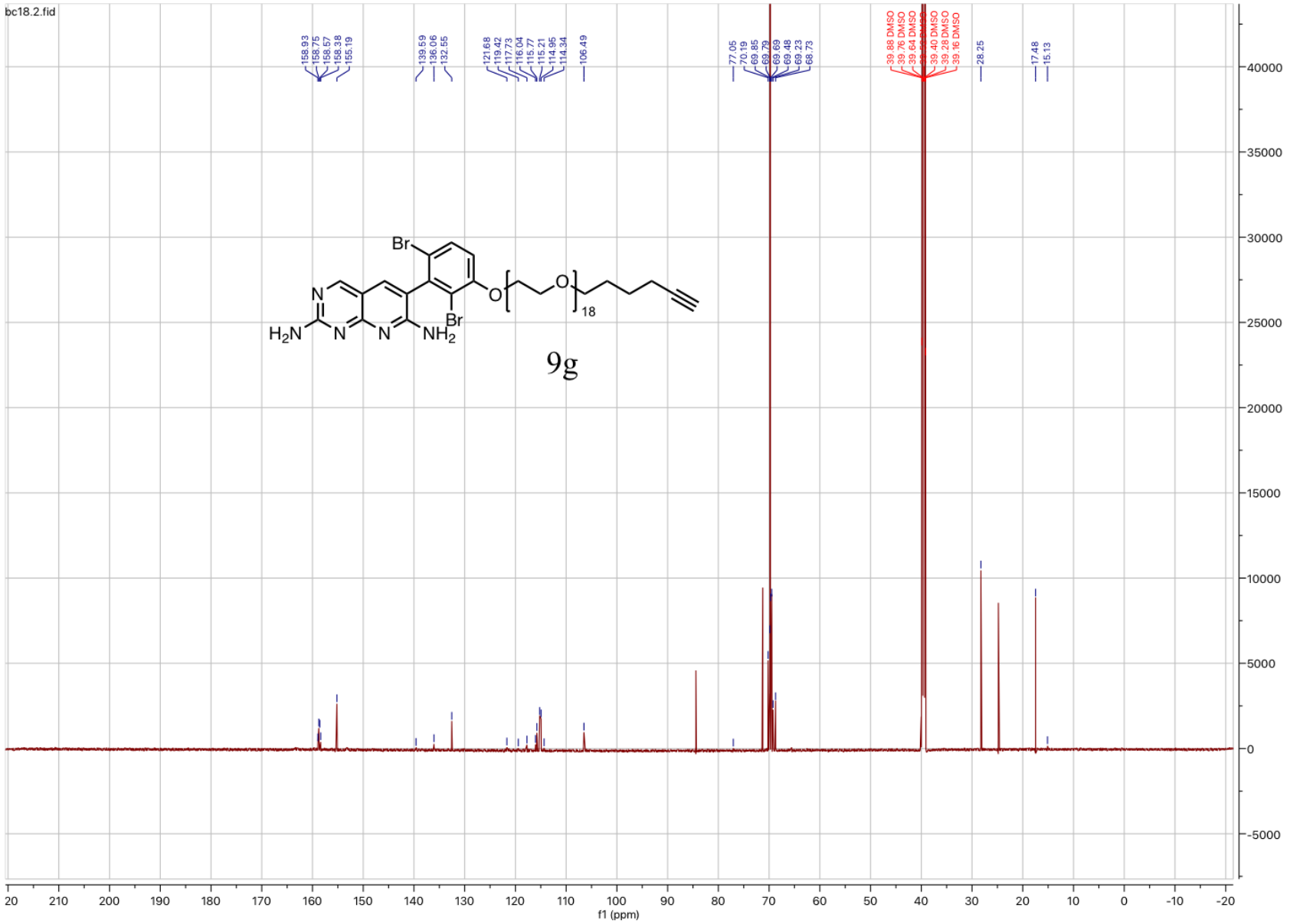
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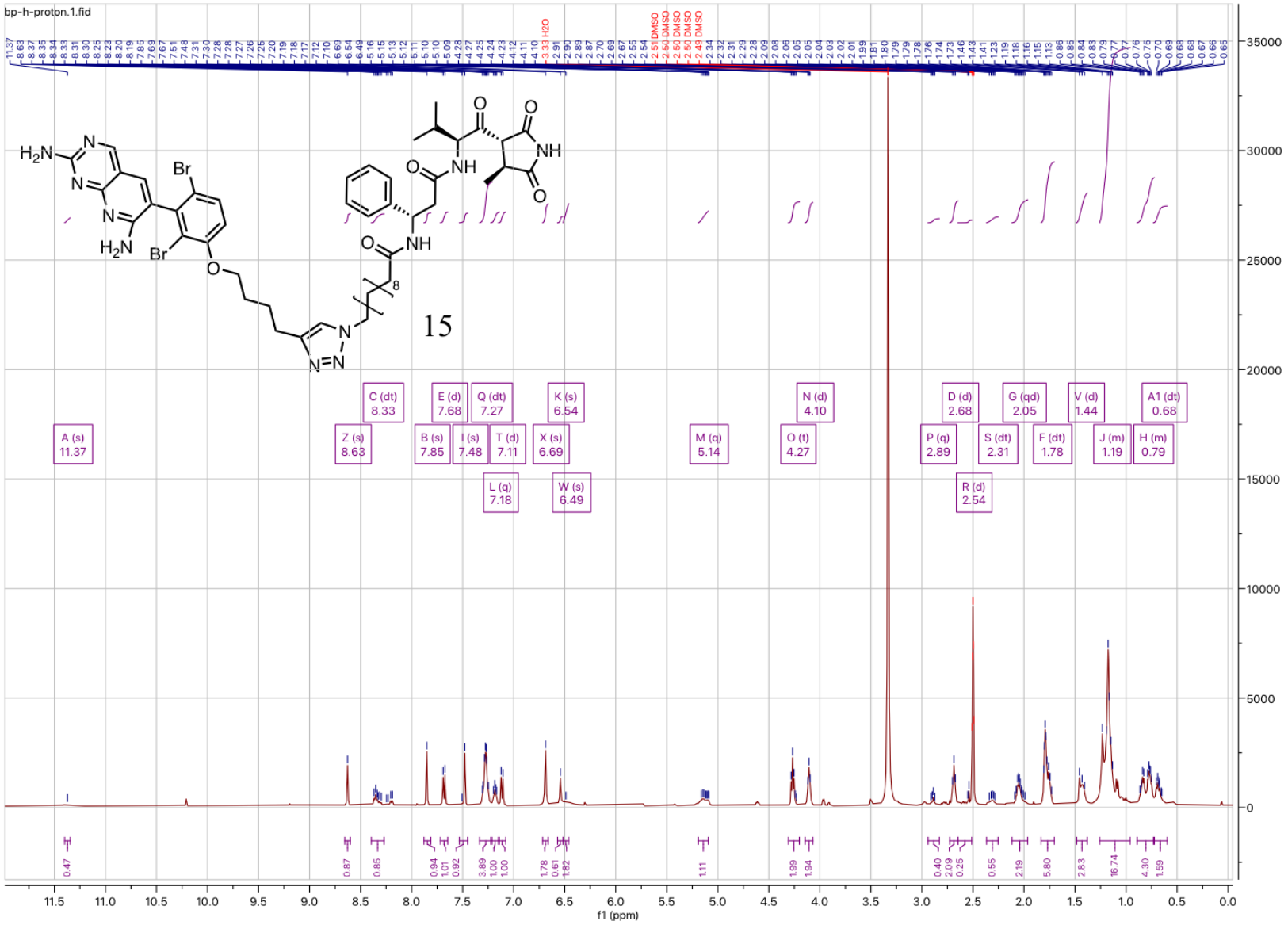
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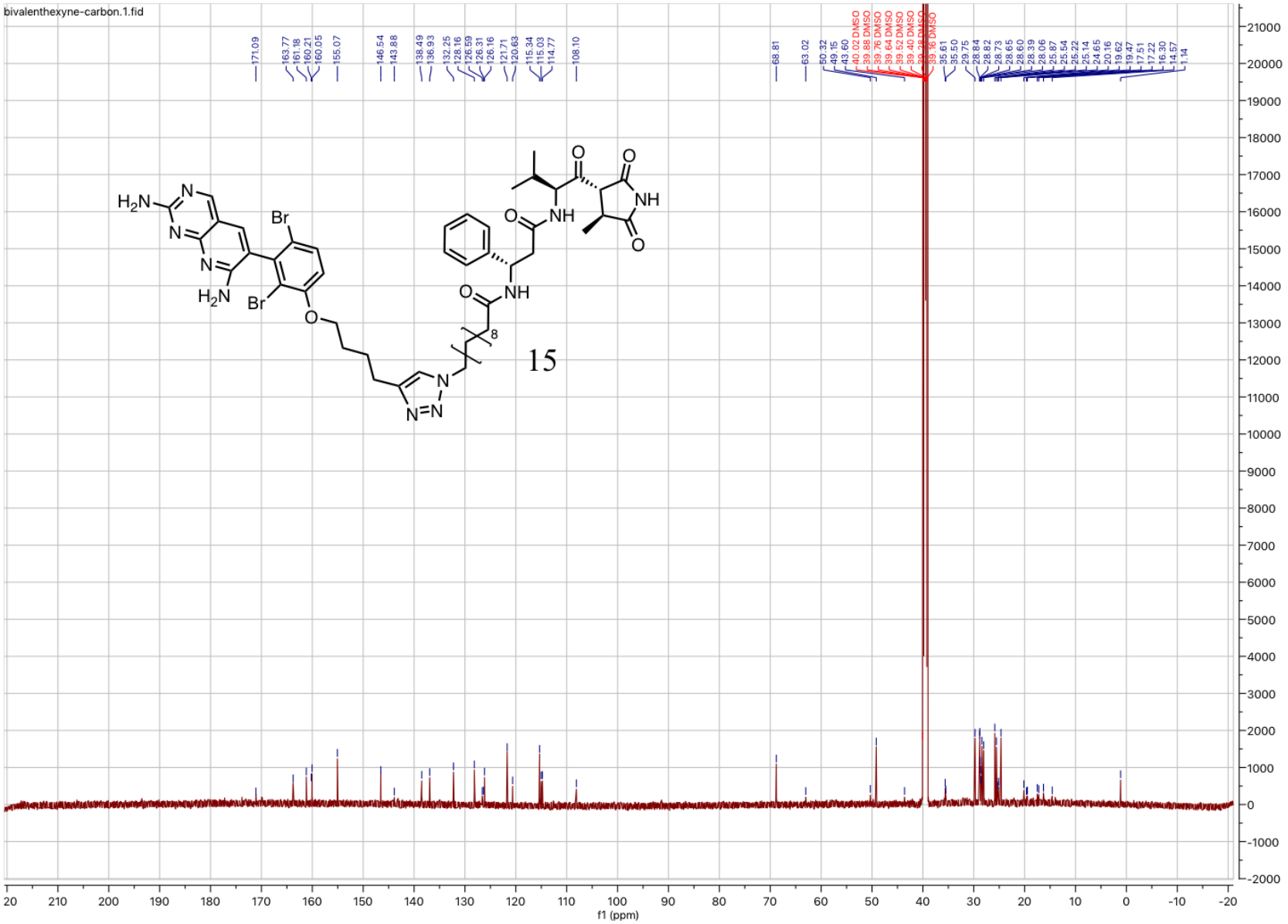
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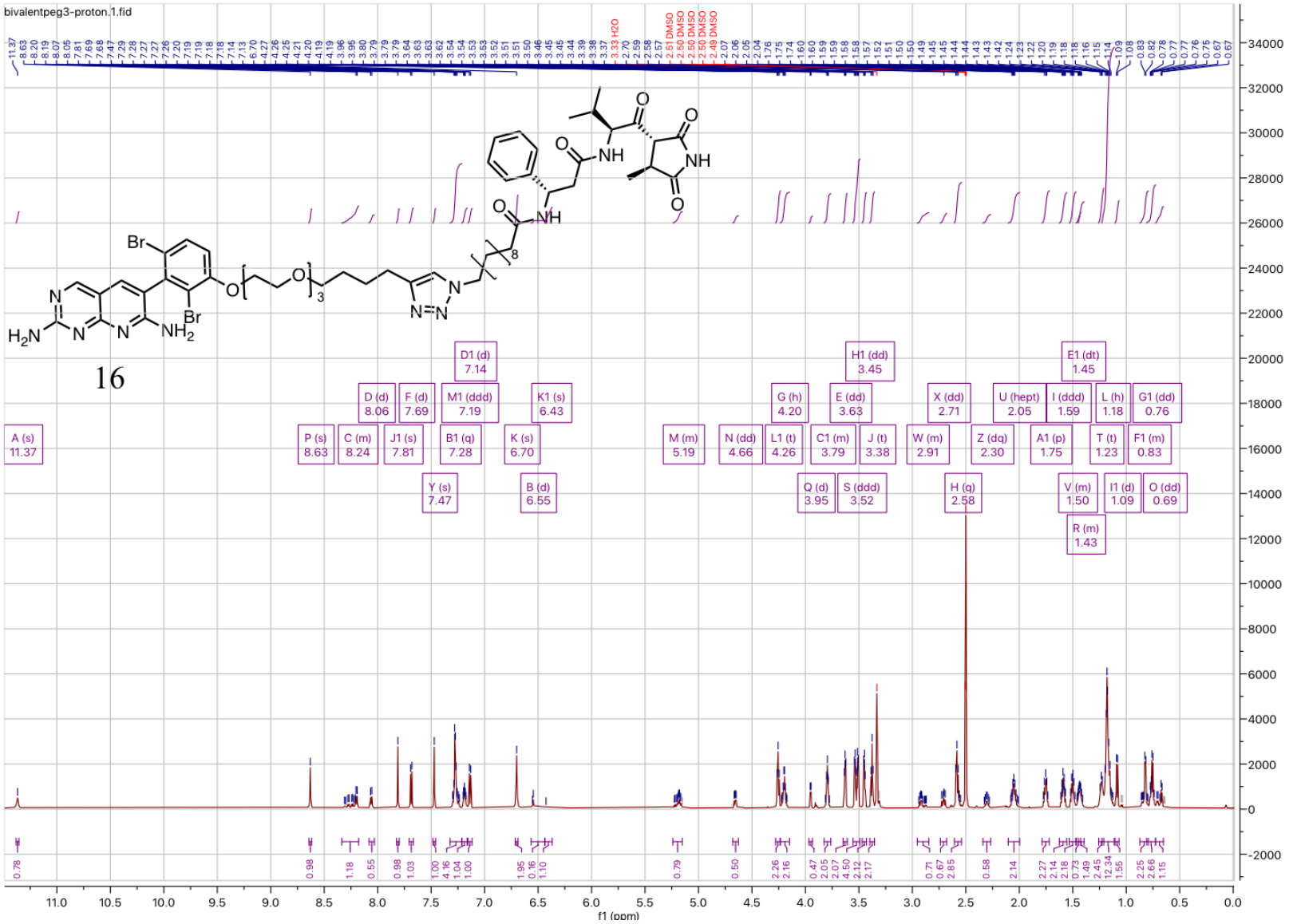
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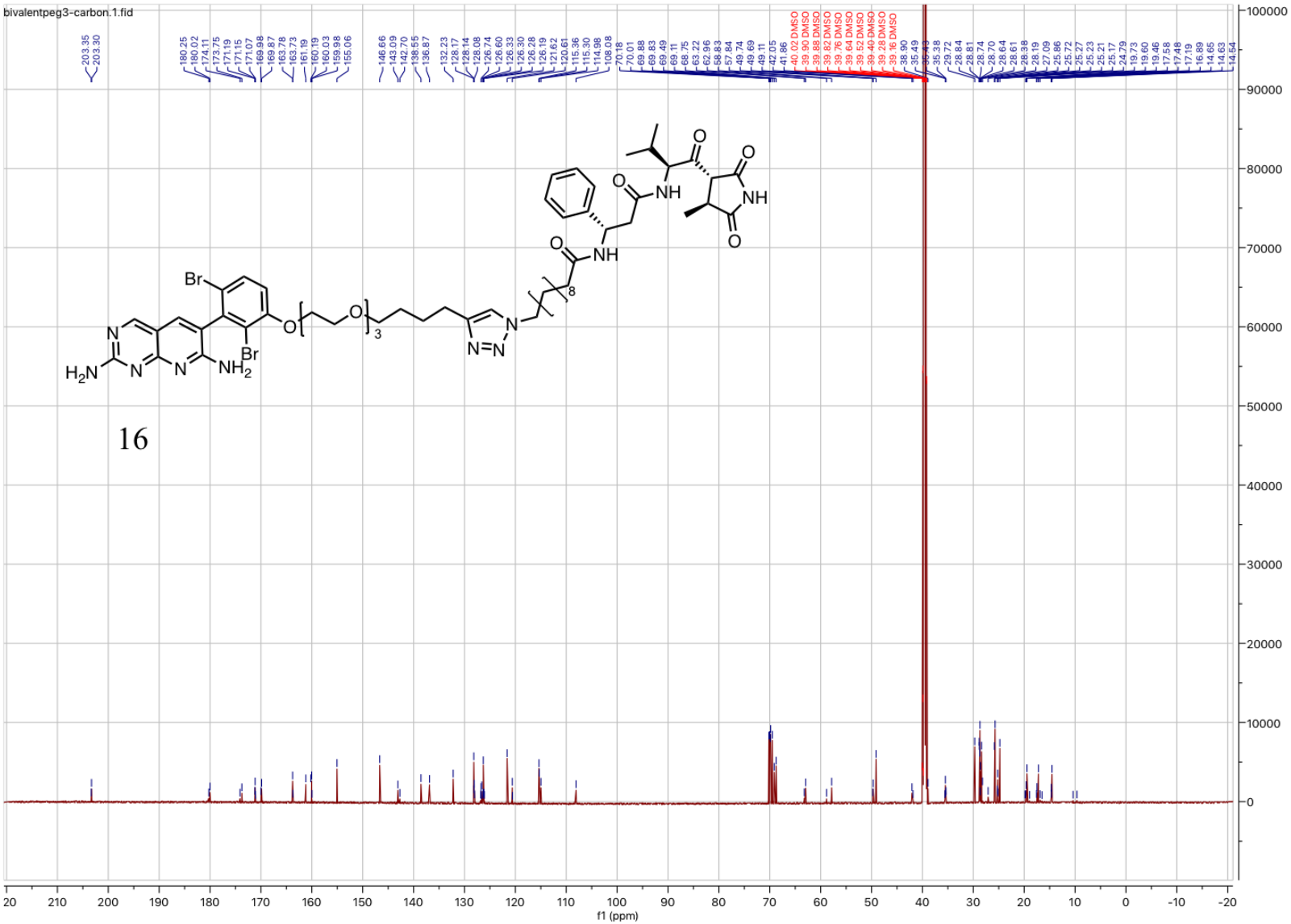
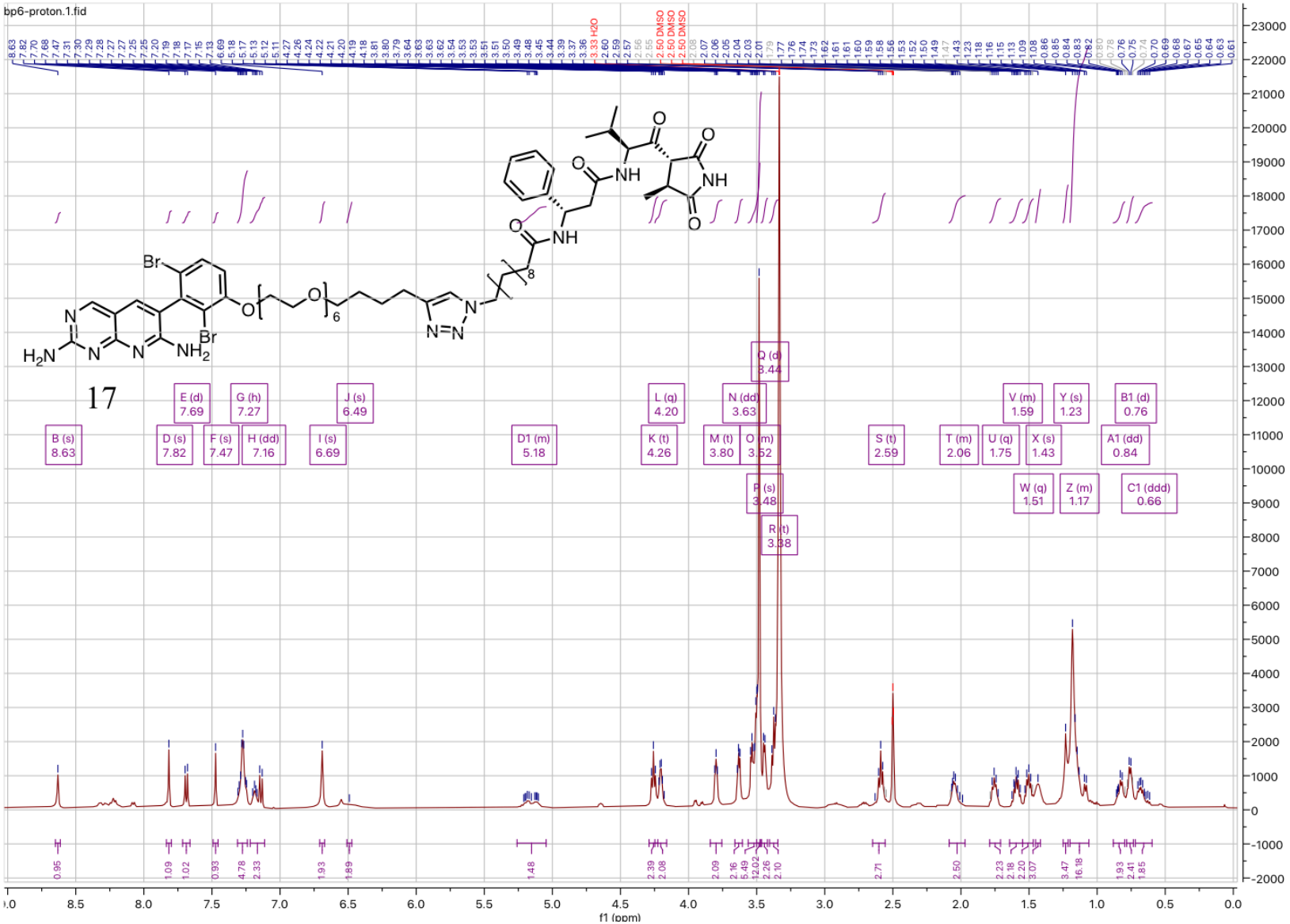
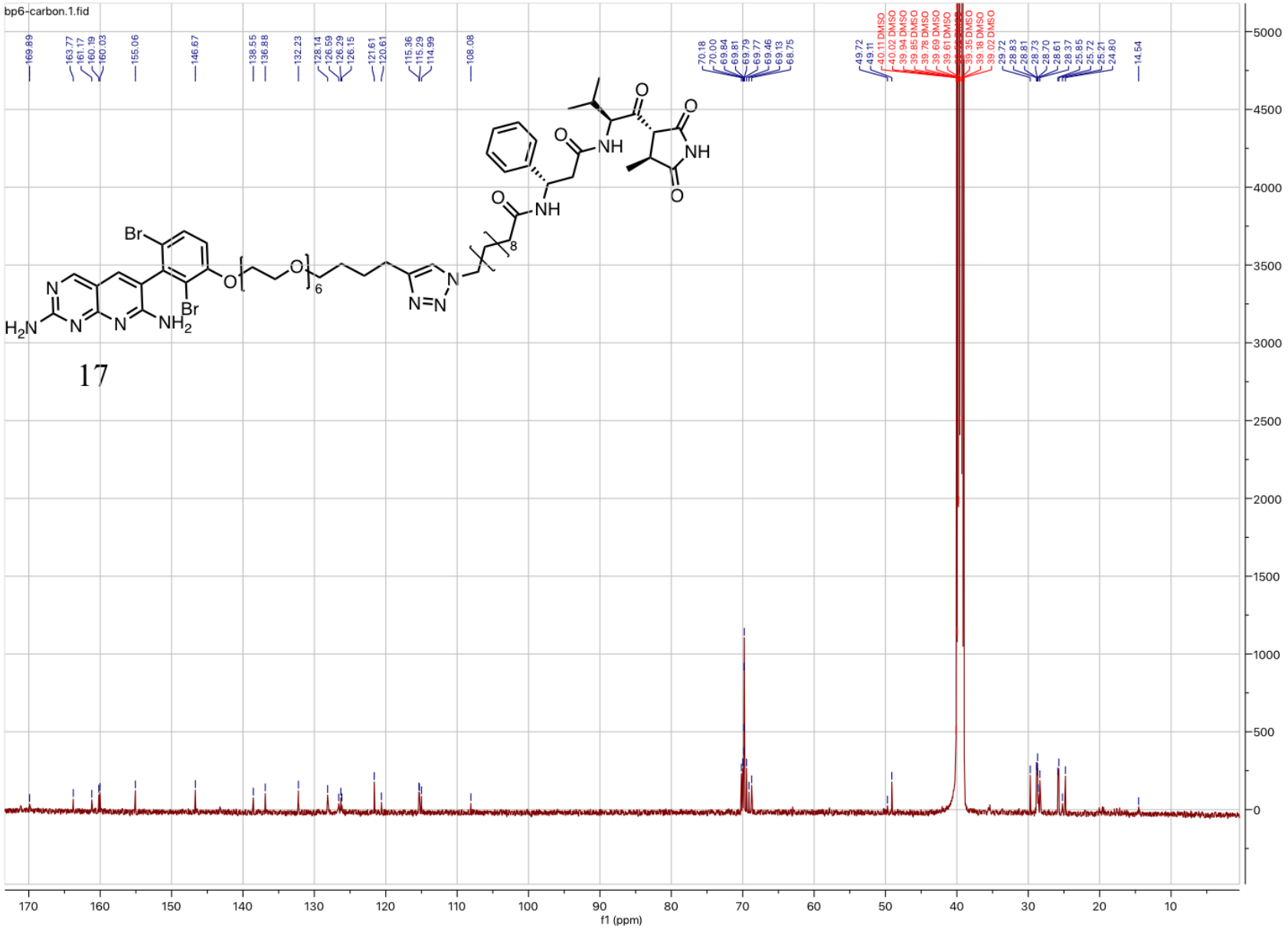
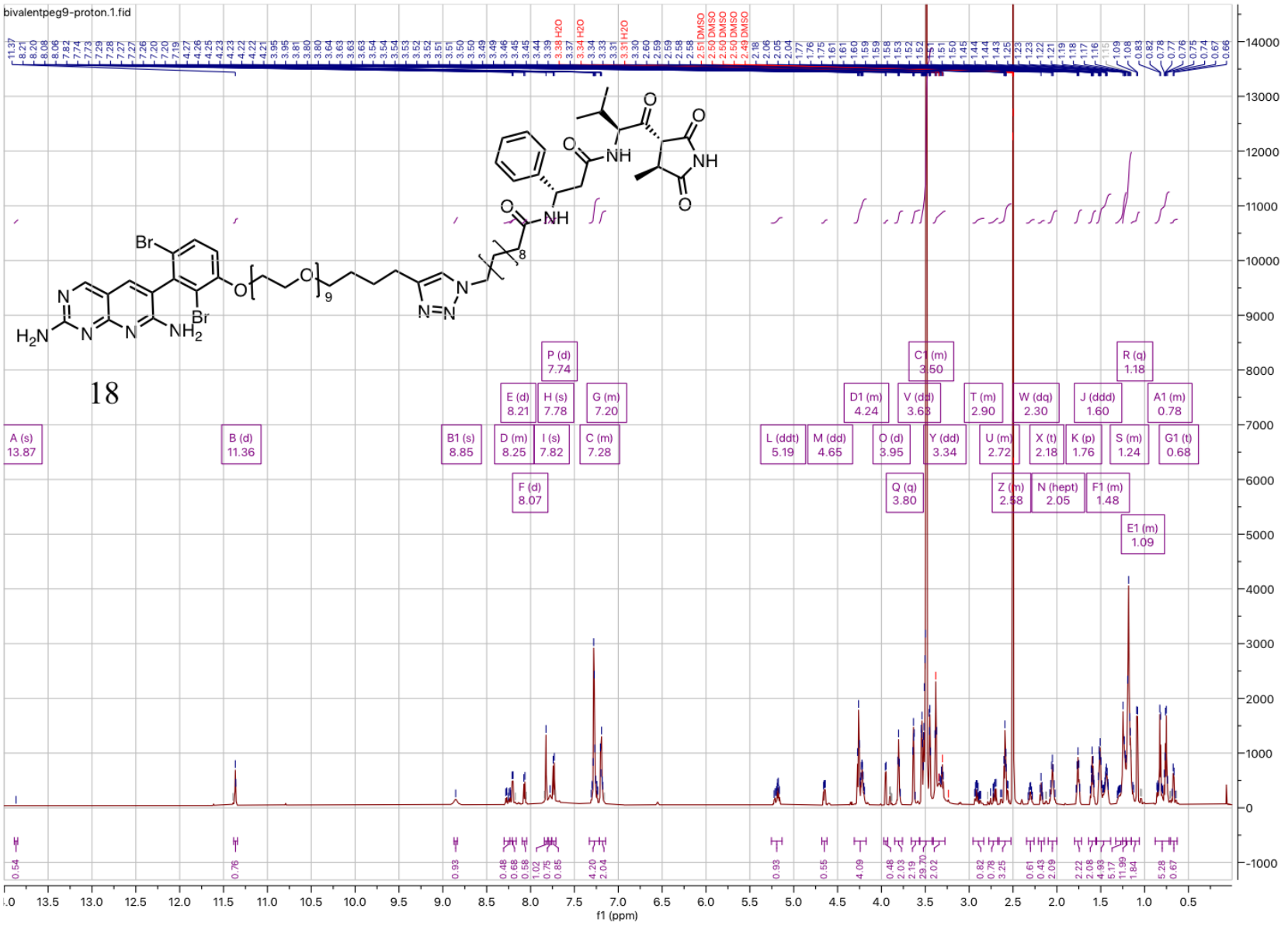
D1 (d) 7.14
B (d) 6.55
K (s) 6.70
K1 (s) 6.43
M (m) 5.19
N (dd) 4.66
L1 (t) 4.26
G (h) 4.20
Q (d) 3.95
S (ddd) 3.52
C1 (m) 3.79
J (t) 3.38
E (dd) 3.63
H1 (dd) 3.45
W (m) 2.91
X (dd) 2.71
H (q) 2.58
Z (dq) 2.30
U (hept) 2.05
A1 (p) 1.75
I (ddd) 1.59
R (m) 1.43
L (h) 1.18
T (t) 1.23
V (m) 1.50
E1 (dt) 1.45
I1 (d) 1.09
F1 (m) 0.83
G1 (dd) 0.76
O (dd) 0.69
f1 (ppm)

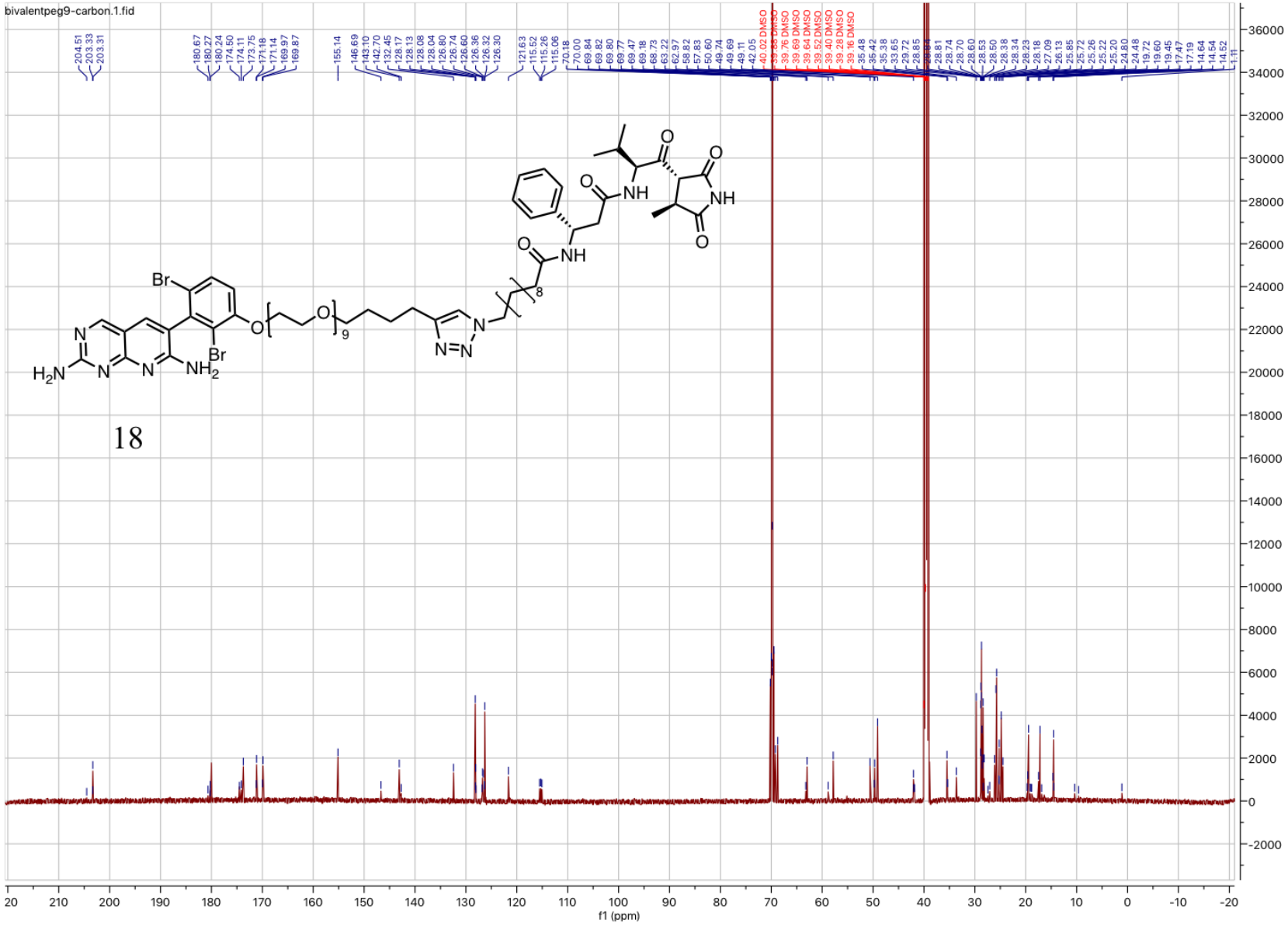

bivalentpeg3-carbon.1.fid
16
f1 (ppm)

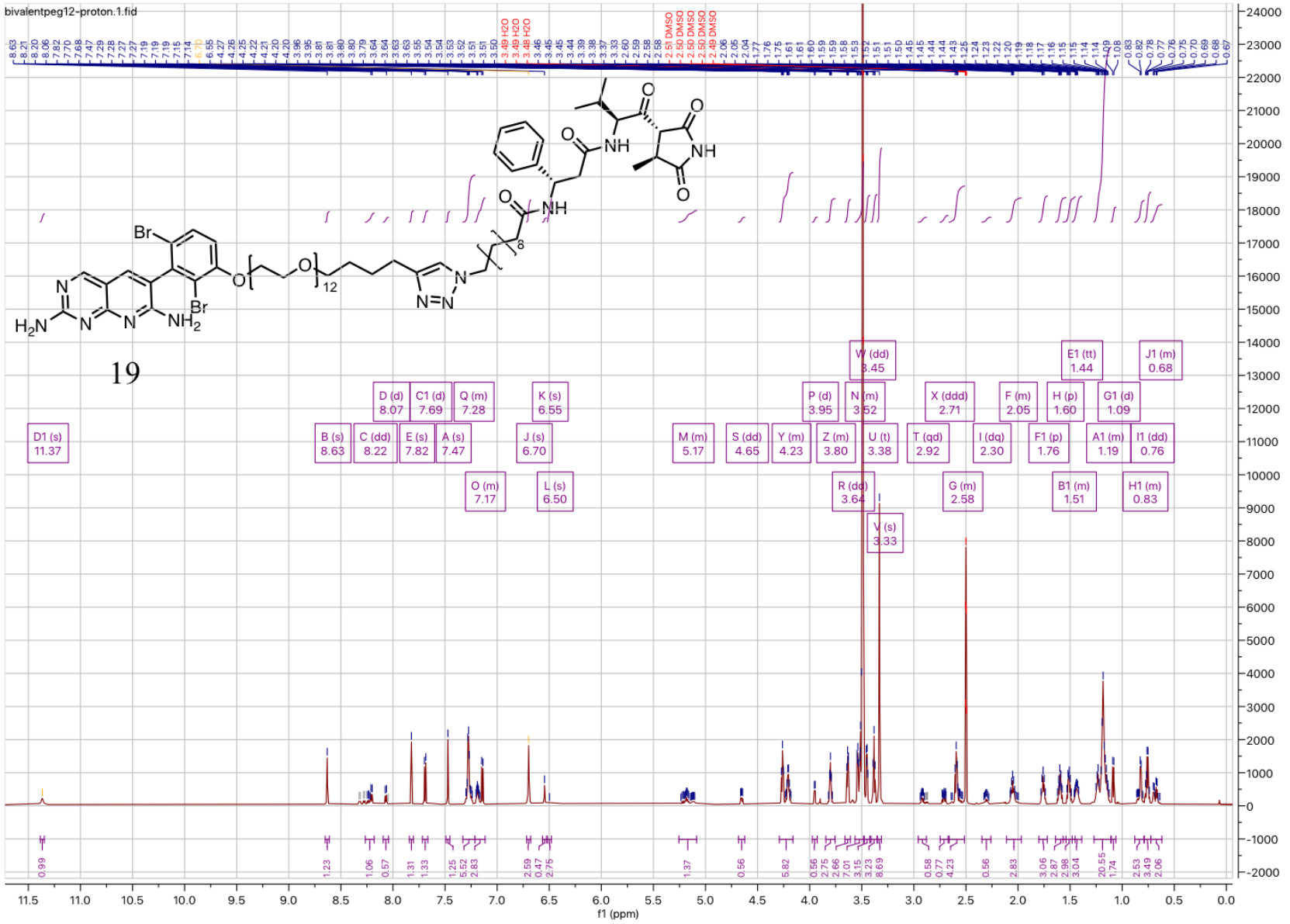

bp6-proton.1.fid
17
B (s) 8.63
D (s) 7.82
E (d) 7.69
F (s) 7.47
G (h) 7.27
H (dd) 7.16
I (s) 6.69
J (s) 6.49
D1 (m) 5.18
K (t) 4.26
L (q) 4.20
M (t) 3.80
N (dd) 3.63
O (m) 3.52
P (s) 3.48
Q (d) 3.44
R (t) 3.38
S (t) 2.59
T (m) 2.06
U (q) 1.75
V (m) 1.59
W (q) 1.51
X (s) 1.43
Y (s) 1.23
Z (m) 1.17
A1 (dd) 0.84
B1 (d) 0.76
C1 (ddd) 0.66
f1 (ppm)

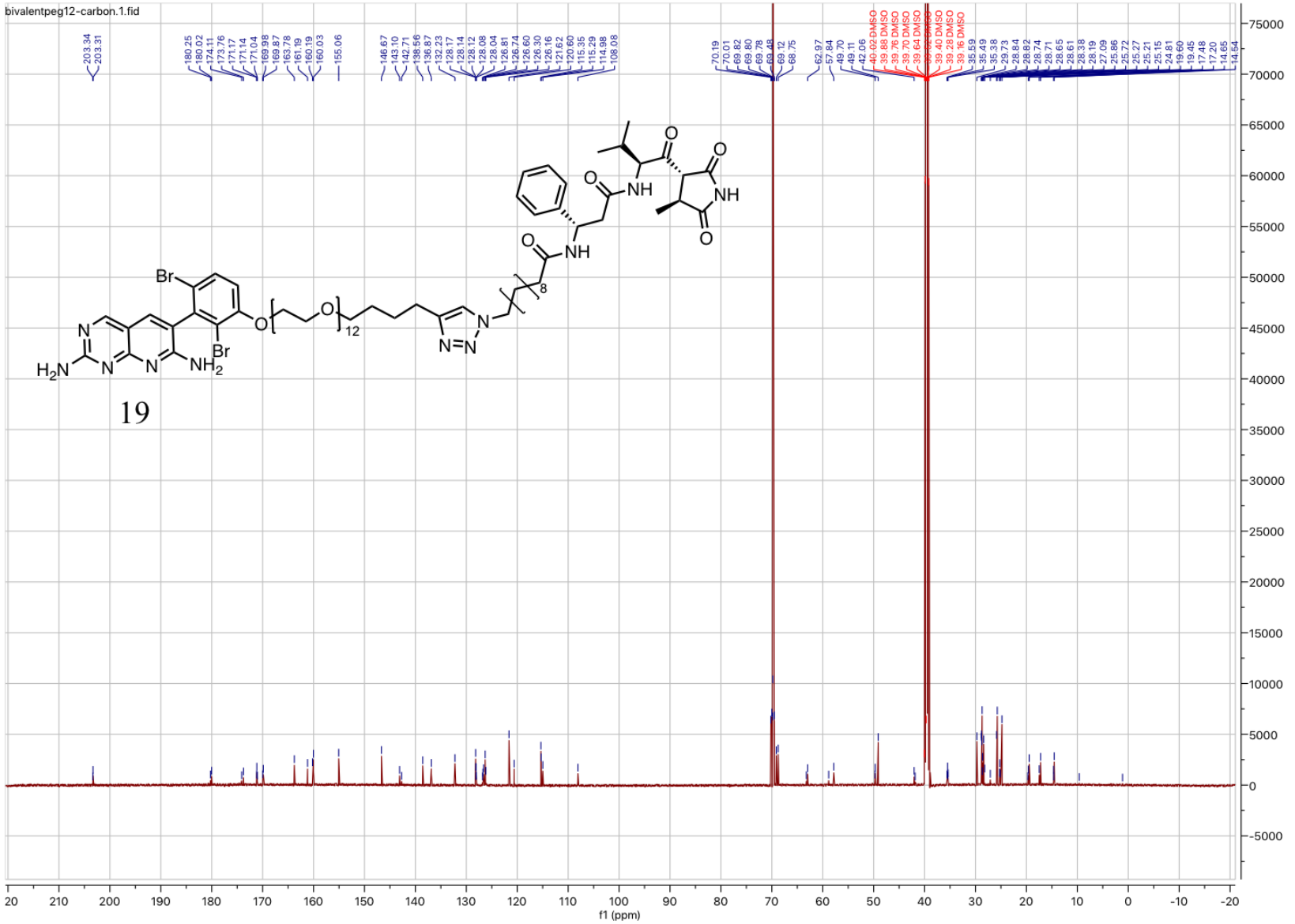

bp6-carbon.1.fid
169.89
163.77
161.17
160.19
160.03
155.06
146.67
138.55
136.88
132.23
128.14
126.59
126.29
126.15
121.61
120.61
115.36
115.29
114.99
108.08
70.18
70.00
69.84
69.81
69.79
69.77
69.46
69.13
68.75
49.72
49.11
40.11 DMSO
40.02 DMSO
39.94 DMSO
39.85 DMSO
39.78 DMSO
39.69 DMSO
39.61 DMSO
39.35 DMSO
39.18 DMSO
39.02 DMSO
29.72
28.83
28.81
28.73
28.70
28.61
28.37
25.85
25.72
25.21
24.80
14.54
f1 (ppm)

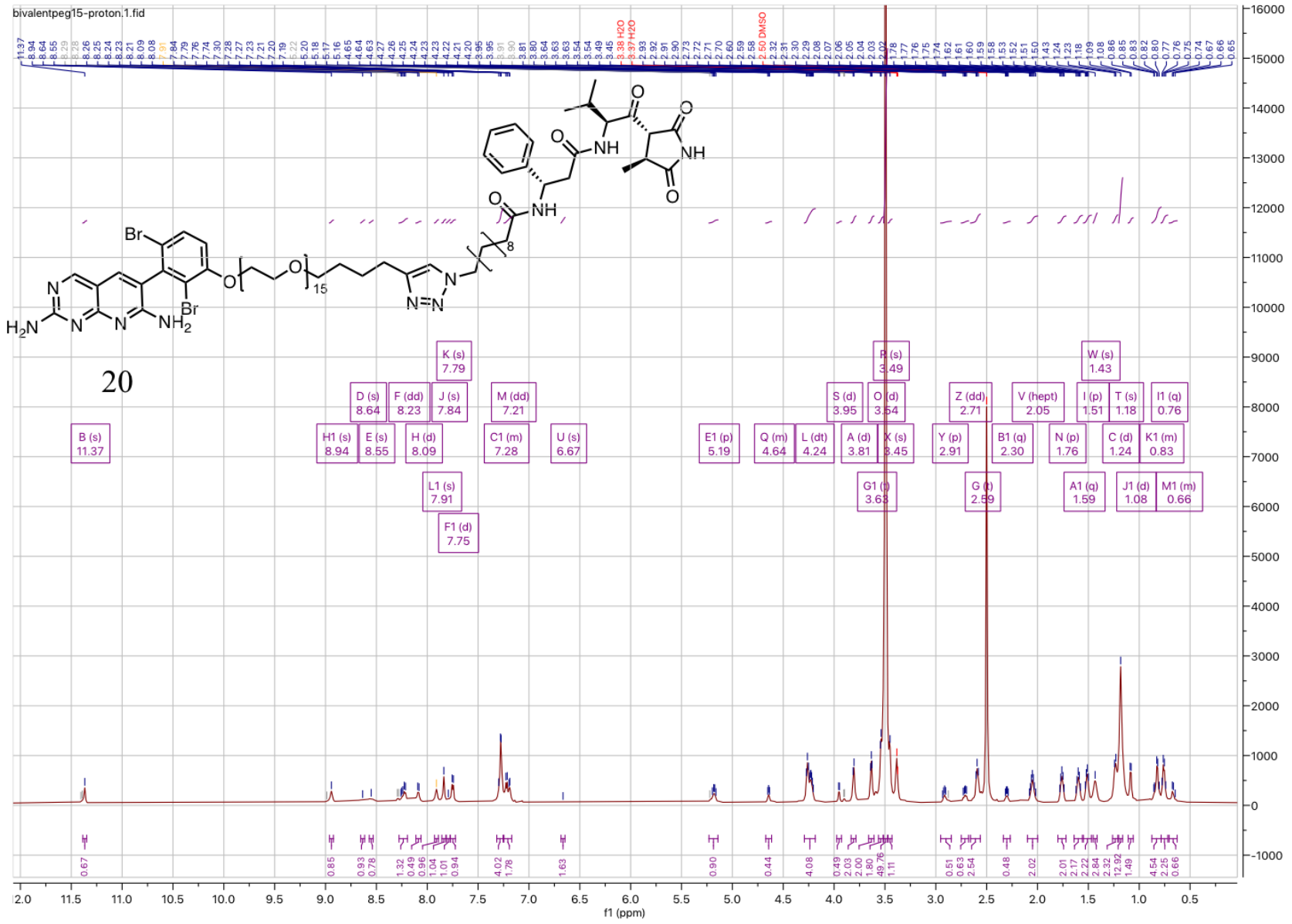
17

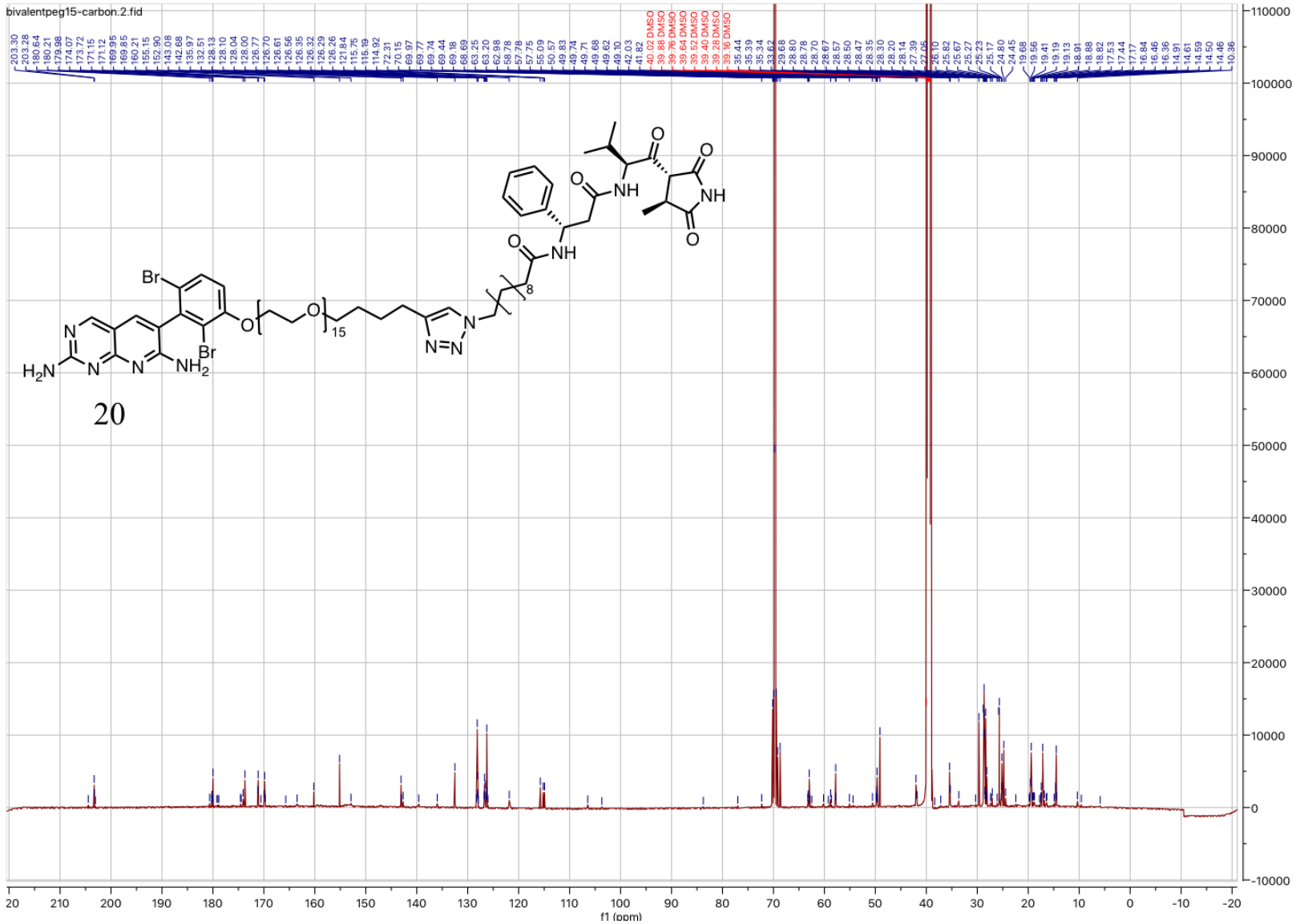

bivalentpeg9-proton.1.fid
18
A (s) 13.87
B (d) 11.36
B1 (s) 8.85
D (m) 8.25
E (d) 8.21
F (d) 8.07
G (m) 7.20
H (s) 7.78
I (s) 7.82
P (d) 7.74
C (m) 7.28
L (ddt) 5.19
M (dd) 4.65
O (d) 3.95
Q (q) 3.80
D1 (m) 4.24
Y (dd) 3.34
V (dd) 3.63
C1 (m) 3.50
T (m) 2.90
U (m) 2.72
Z (m) 2.58
W (dq) 2.30
X (t) 2.18
N (hept) 2.05
K (p) 1.76
J (ddd) 1.60
F1 (m) 1.48
S (m) 1.24
R (q) 1.18
E1 (m) 1.09
A1 (m) 0.78
G1 (t) 0.68
f1 (ppm)

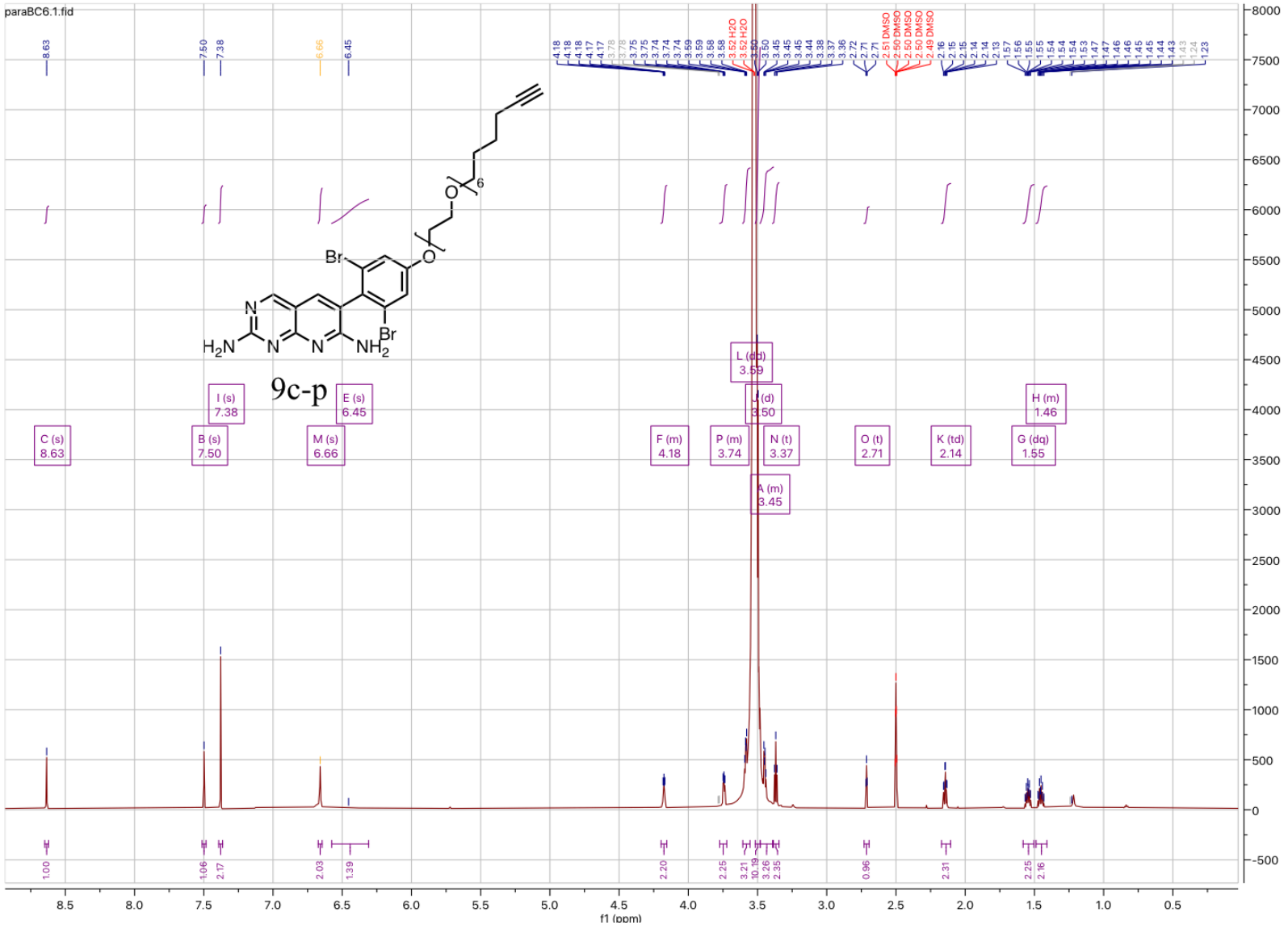

bivalentpeg9-carbon.1.fid
18
f1 (ppm)

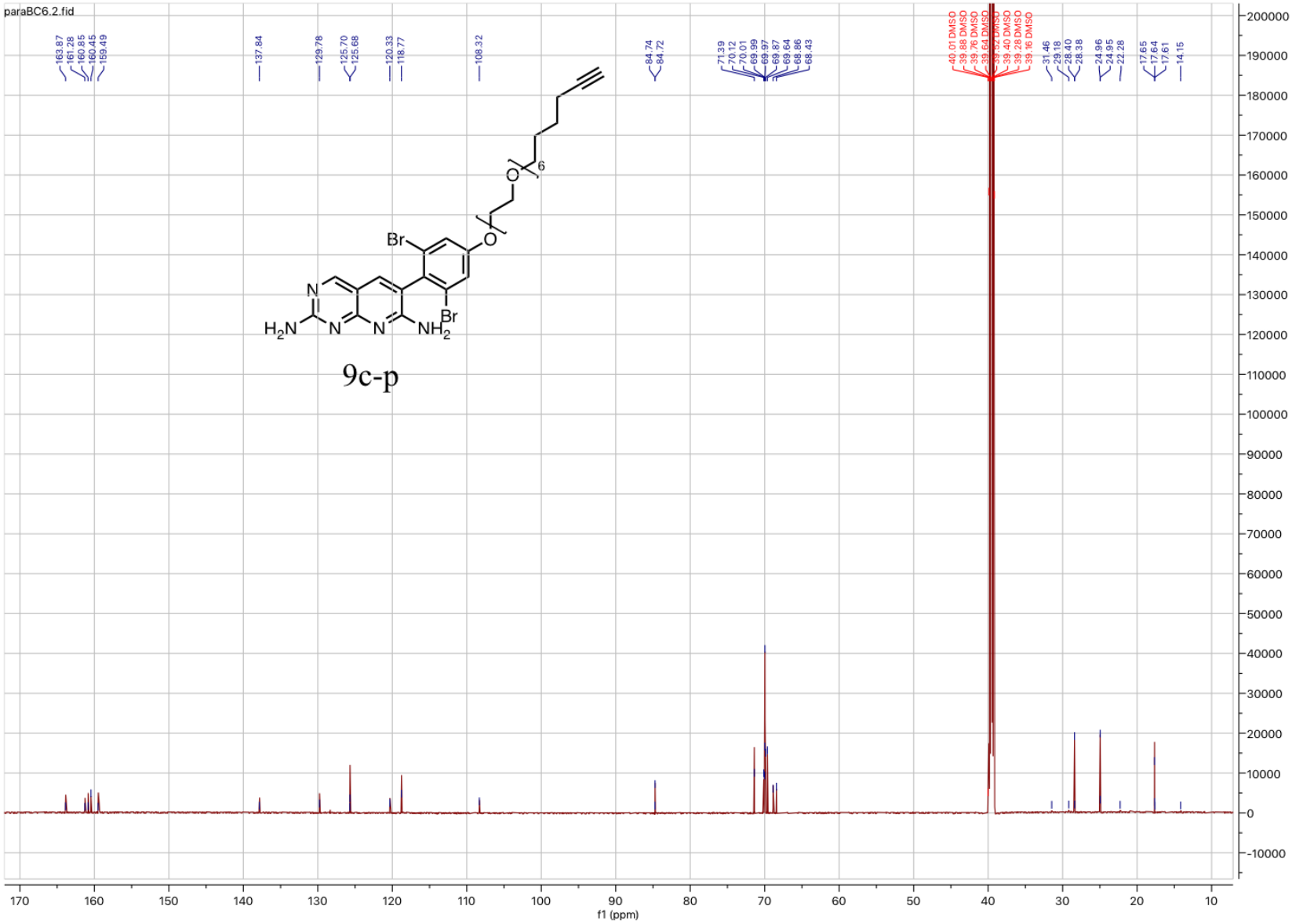

bivalentpeg12-proton.1.fid
19
D1 (s) 11.37
B (s) 8.63
C (dd) 8.22
E (s) 7.82
A (s) 7.47
D (d) 8.07
C1 (d) 7.69
Q (m) 7.28
O (m) 7.17
K (s) 6.55
J (s) 6.70
L (s) 6.50
M (m) 5.17
S (dd) 4.65
Y (m) 4.23
Z (m) 3.80
U (t) 3.38
V (s) 3.33
R (dd) 3.64
W (dd) 3.45
N (m) 3.52
P (d) 3.95
T (qd) 2.92
X (ddd) 2.71
G (m) 2.58
I (dq) 2.30
F (m) 2.05
F1 (p) 1.76
H (p) 1.60
B1 (m) 1.51
E1 (tt) 1.44
G1 (d) 1.09
A1 (m) 1.19
I1 (dd) 0.76
H1 (m) 0.83
J1 (m) 0.68
f1 (ppm)

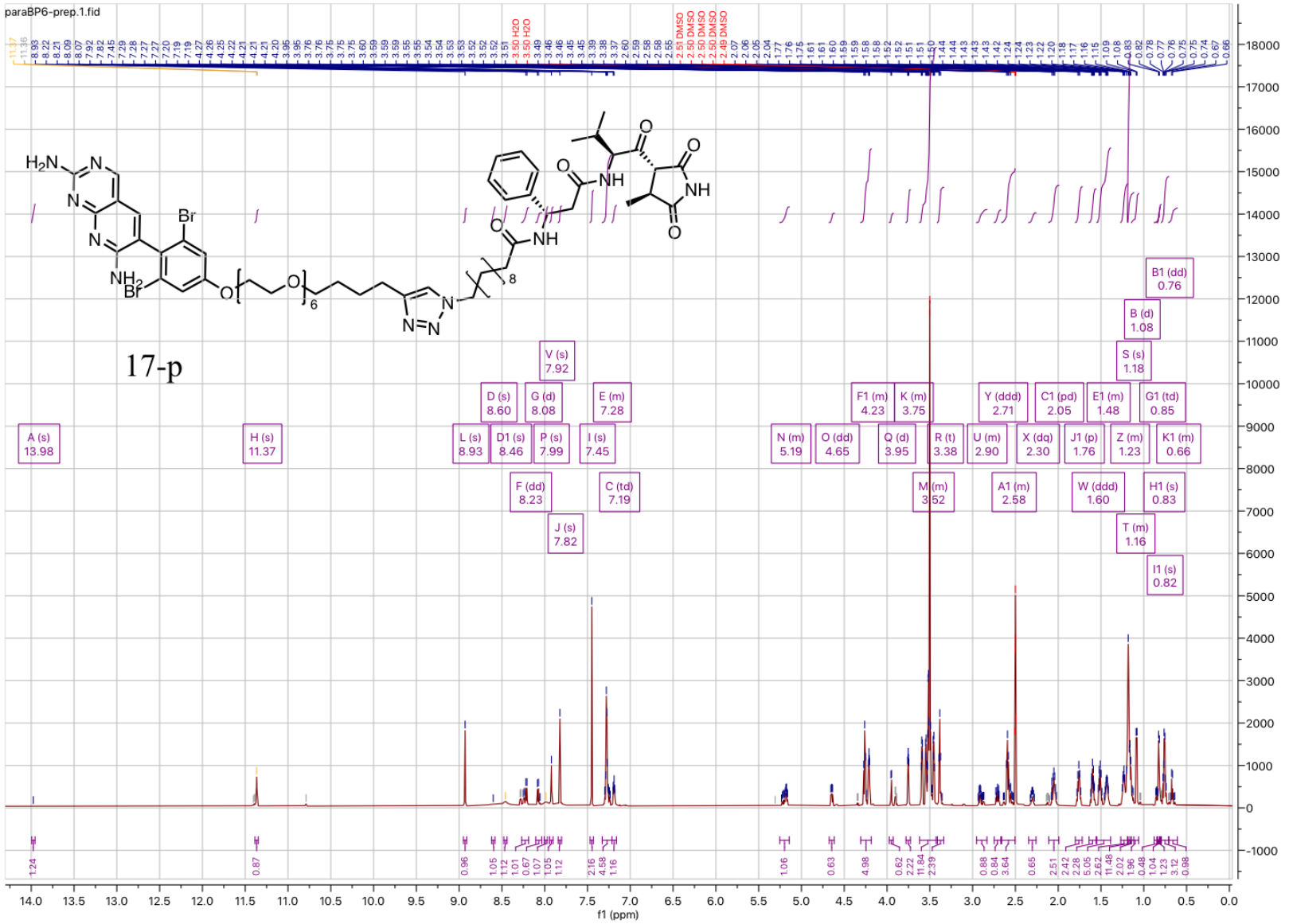

bivalentpeg12-carbon.1.fid
19
f1 (ppm)

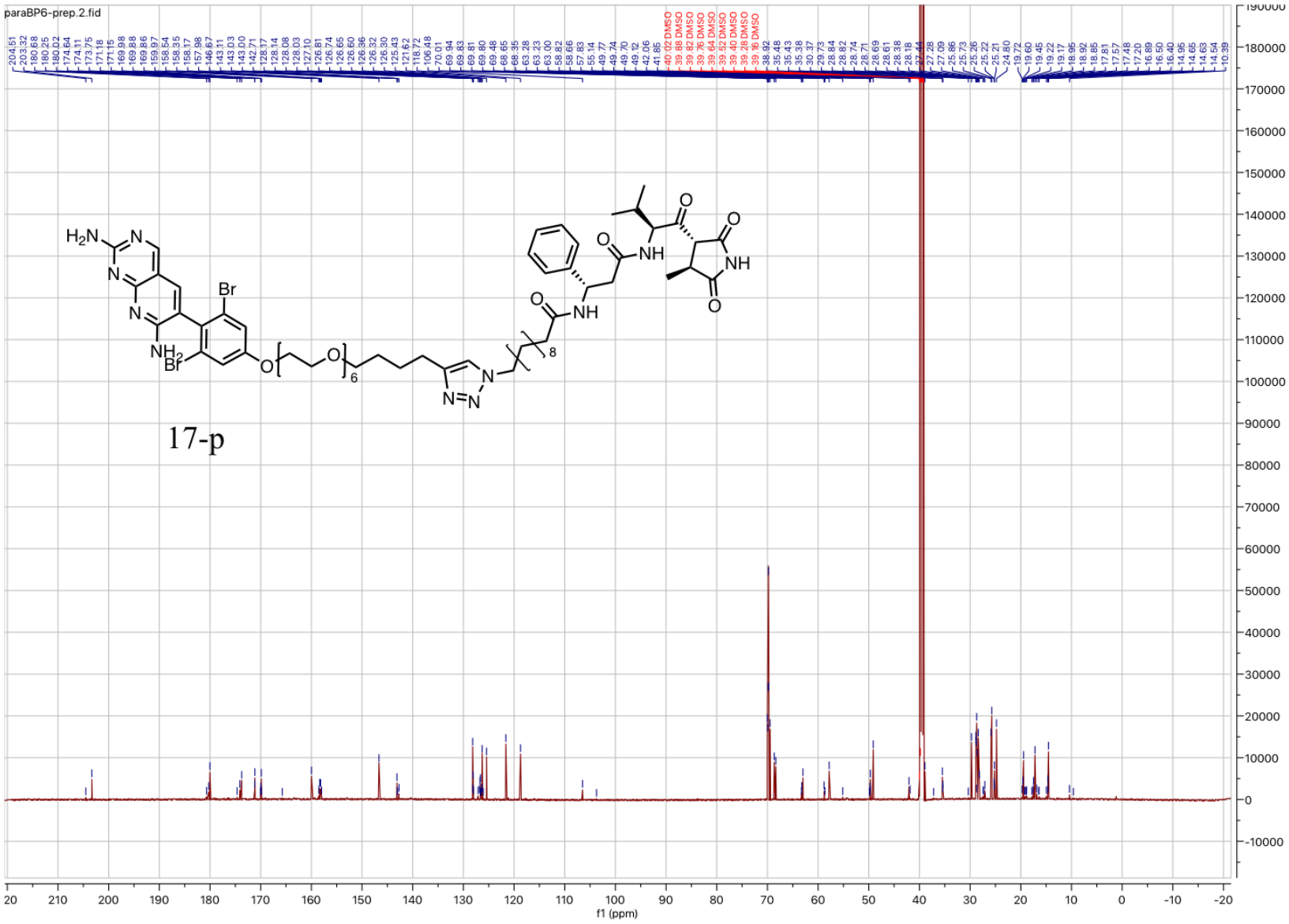

bivalentpeg15-proton.1.fid
20
B (s) 11.37
H1 (s) 8.94
E (s) 8.55
H (d) 8.09
D (s) 8.64
F (dd) 8.23
J (s) 7.84
K (s) 7.79
L1 (s) 7.91
F1 (d) 7.75
C1 (m) 7.28
M (dd) 7.21
U (s) 6.67
E1 (p) 5.19
Q (m) 4.64
L (dt) 4.24
A (d) 3.81
X (s) 3.45
G1 (t) 3.63
S (d) 3.95
O (d) 3.54
R (s) 3.49
Y (p) 2.91
G (t) 2.59
Z (dd) 2.71
B1 (q) 2.30
V (hept) 2.05
N (p) 1.76
A1 (q) 1.59
I (p) 1.51
W (s) 1.43
C (d) 1.24
T (s) 1.18
J1 (d) 1.08
K1 (m) 0.83
I1 (q) 0.76
M1 (m) 0.66
f1 (ppm)

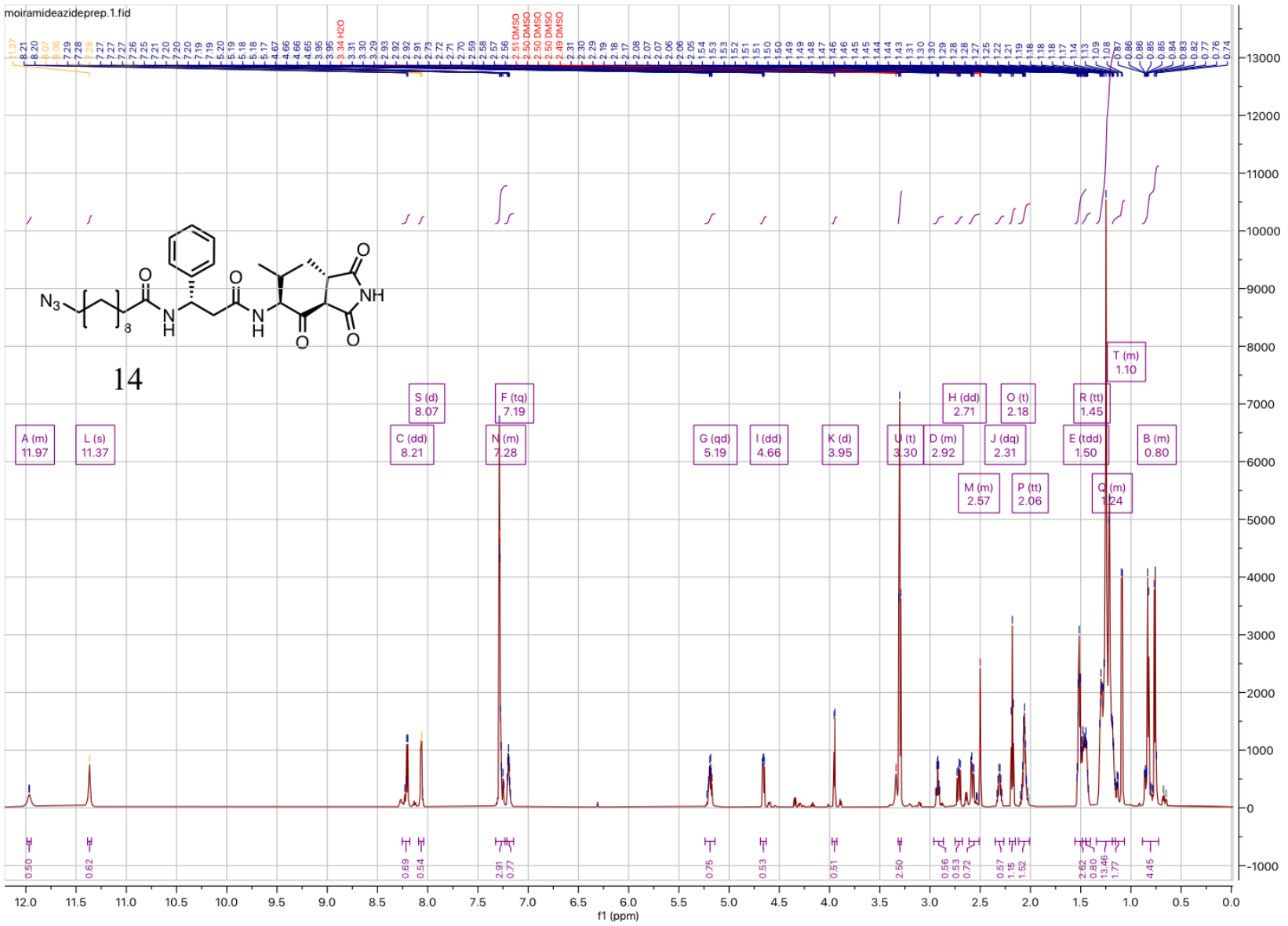

bivalentpeg15-carbon.2.fid
20
f1 (ppm)

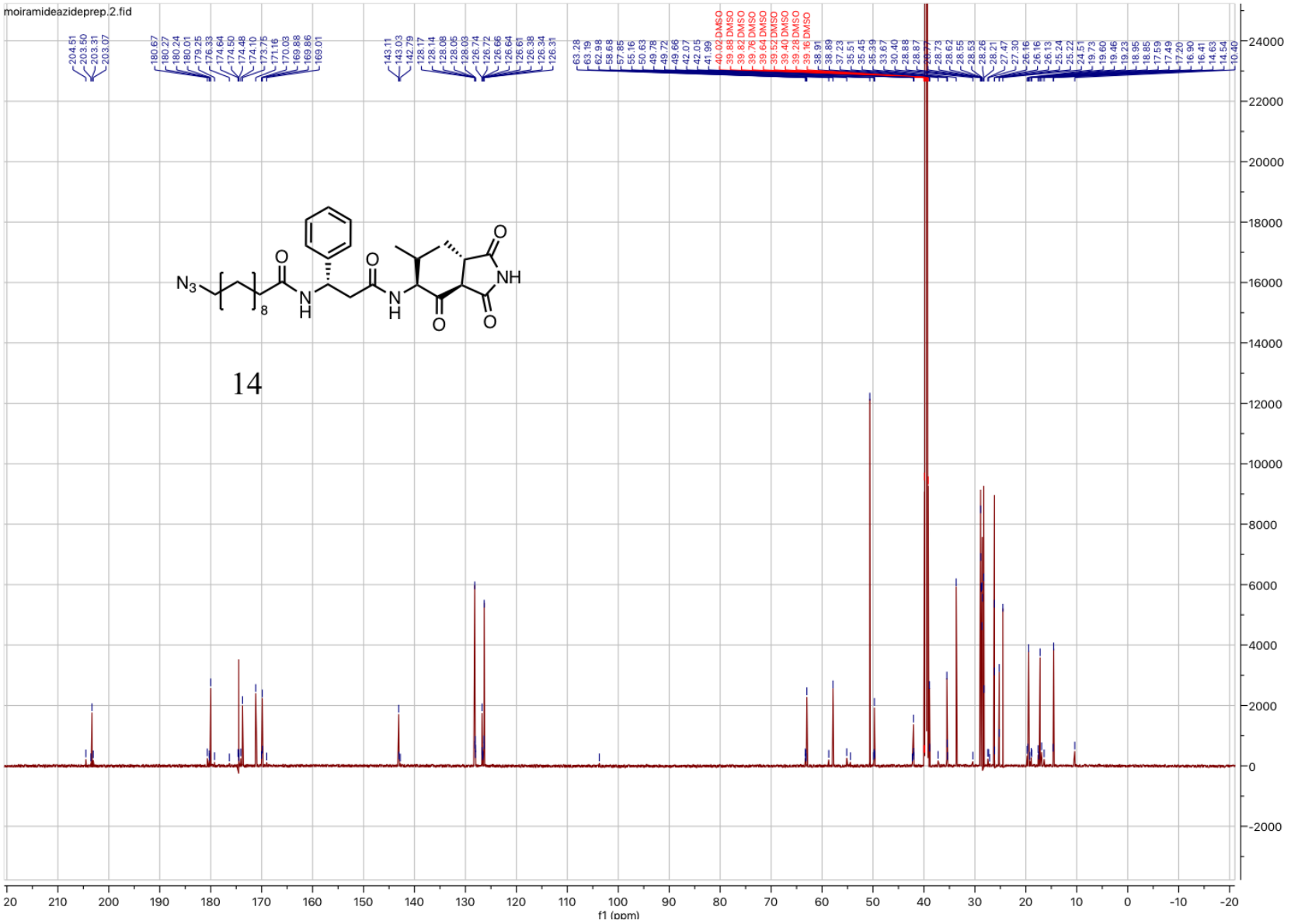

paraBC6.1.fid
9c-p
C (s) 8.63
B (s) 7.50
I (s) 7.38
M (s) 6.66
E (s) 6.45
F (m) 4.18
P (m) 3.74
A (m) 3.45
N (t) 3.37
L (dd) 3.59
J (d) 3.50
O (t) 2.71
K (td) 2.14
H (m) 1.46
G (dq) 1.55
f1 (ppm)


paraBC6.2.fid
163.87
161.28
160.85
160.45
159.49
137.84
129.78
125.70
125.68
120.33
118.77
108.32
84.74
84.72
71.39
70.12
70.01
69.99
69.97
69.87
69.64
68.86
68.43
40.01 DMSO
39.88 DMSO
39.76 DMSO
39.64 DMSO
39.40 DMSO
39.28 DMSO
39.16 DMSO
31.46
29.18
28.40
28.38
24.96
24.95
22.28
17.65
17.64
17.61
14.15
Br
O
6
O
N
N
N
N
H_2N
NH_2
Br
9c-p
f1 (ppm)

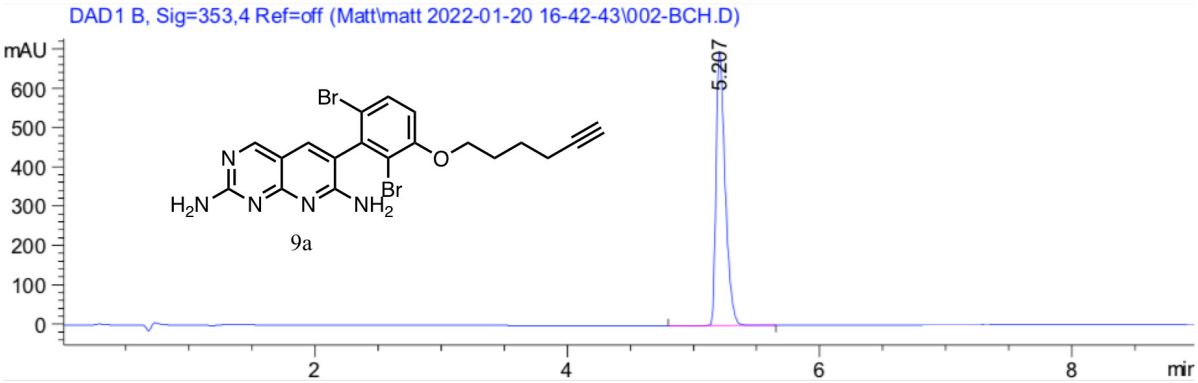

paraBP6-prep.1.fid
17-p
A (s) 13.98
H (s) 11.37
L (s) 8.93
D1 (s) 8.46
P (s) 7.99
I (s) 7.45
D (s) 8.60
G (d) 8.08
E (m) 7.28
V (s) 7.92
F (dd) 8.23
J (s) 7.82
C (td) 7.19
N (m) 5.19
O (dd) 4.65
Q (d) 3.95
R (t) 3.38
F1 (m) 4.23
K (m) 3.75
M (m) 3.52
U (m) 2.90
Y (ddd) 2.71
A1 (m) 2.58
X (dq) 2.30
C1 (pd) 2.05
J1 (p) 1.76
E1 (m) 1.48
W (ddd) 1.60
Z (m) 1.23
G1 (td) 0.85
K1 (m) 0.66
B1 (dd) 0.76
B (d) 1.08
S (s) 1.18
T (m) 1.16
H1 (s) 0.83
I1 (s) 0.82
f1 (ppm)

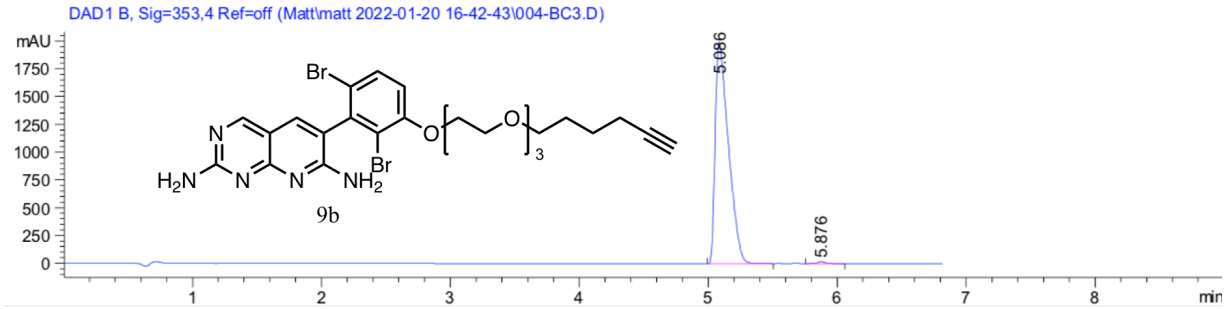

paraBP6-prep.2.fid
17-p
f1 (ppm)

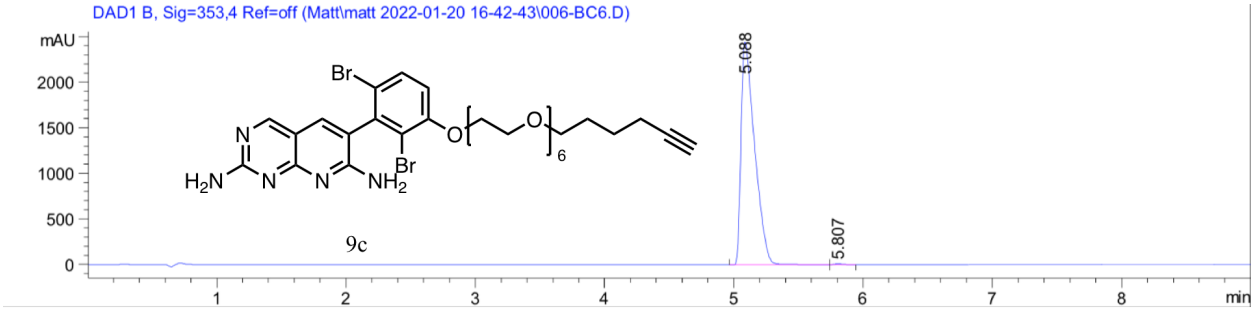

moiramideazideprep.1.fid
14
A (m) 11.97
L (s) 11.37
S (d) 8.07
C (dd) 8.21
F (tq) 7.19
N (m) 7.28
G (qd) 5.19
I (dd) 4.66
K (d) 3.95
U (t) 3.30
D (m) 2.92
H (dd) 2.71
M (m) 2.57
J (dq) 2.31
O (t) 2.18
P (tt) 2.06
E (tdd) 1.50
R (tt) 1.45
Q (m) 1.24
T (m) 1.10
B (m) 0.80
f1 (ppm)

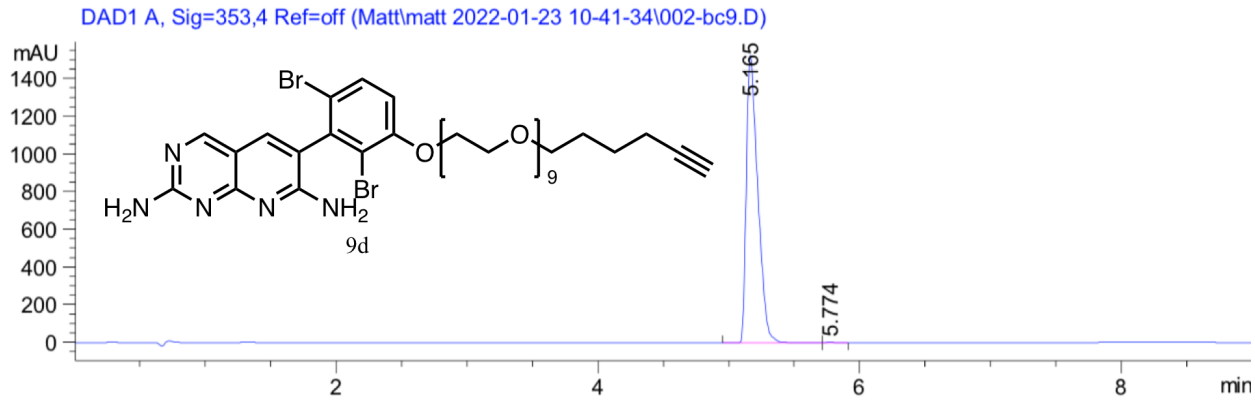

moiramideazideprep.2.fid
14
f1 (ppm)

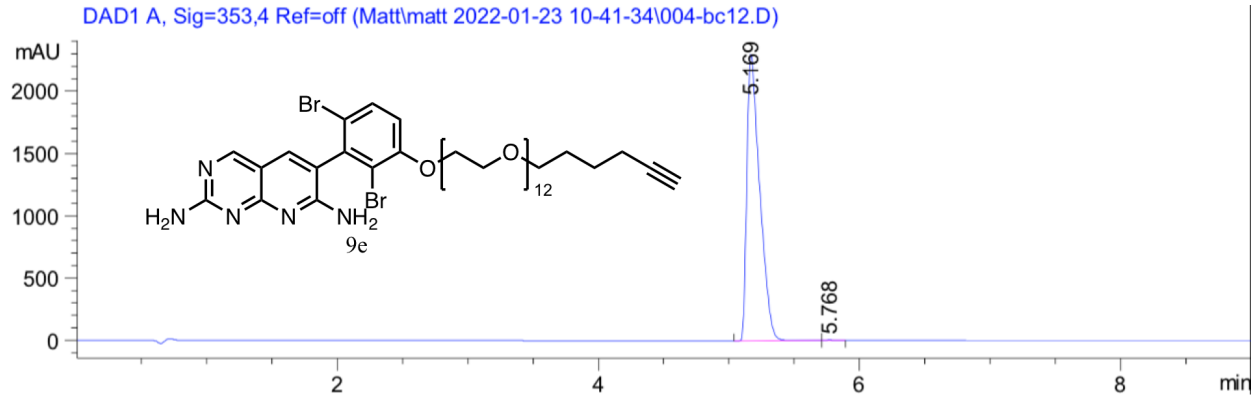
HPLC Traces


DAD1 B, Sig=353,4 Ref=off (Matt\matt 2022-01-20 16-42-43\002-BCH.D)
mAU
5.207
9a
min

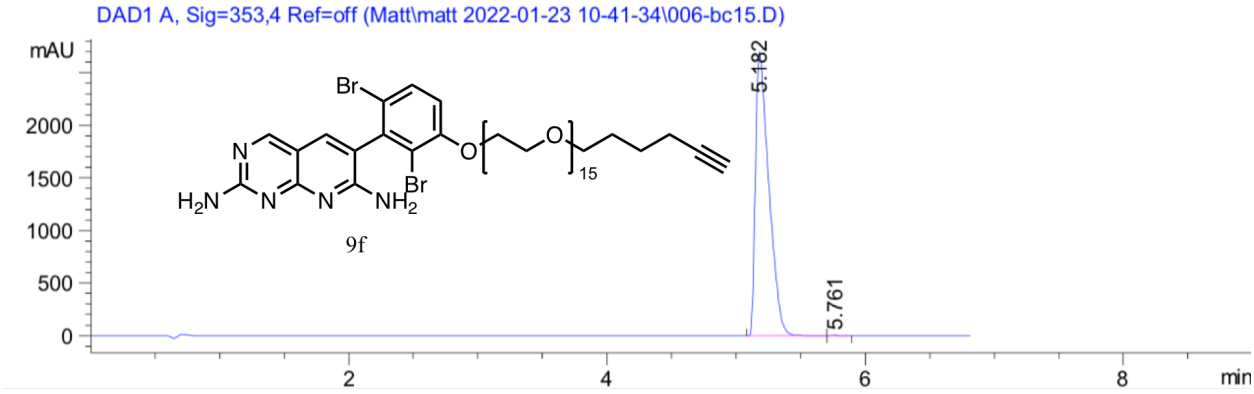

DAD1 B, Sig=353,4 Ref=off (Matt\matt 2022-01-20 16-42-43\004-BC3.D)
mAU
5.086
5.876
9b
min


DAD1 B, Sig=353,4 Ref=off (Matt\matt 2022-01-20 16-42-43\006-BC6.D)
mAU
5.088
5.807
9c
min

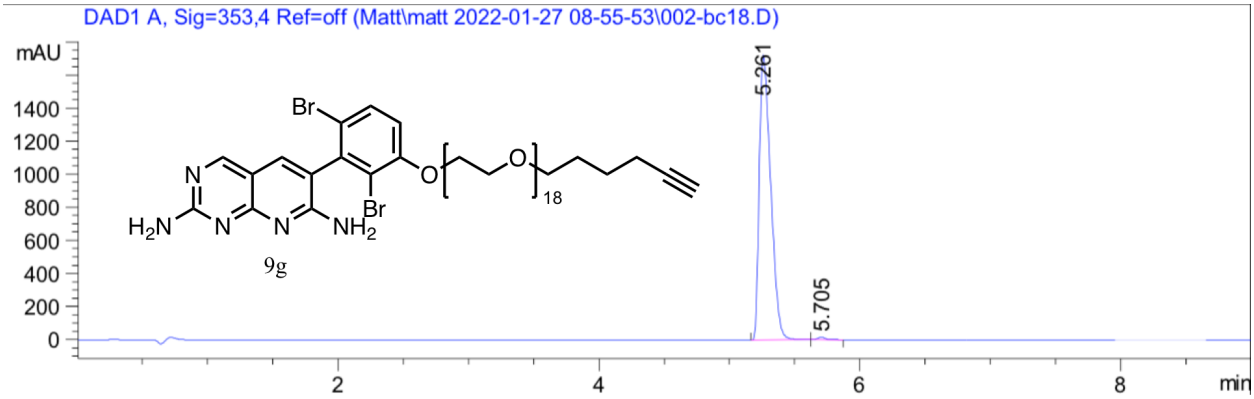

DAD1 A, Sig=353,4 Ref=off (Matt\matt 2022-01-23 10-41-34\002-bc9.D)
mAU
5.165
5.774
9d
min


DAD1 A, Sig=353,4 Ref=off (Matt\matt 2022-01-23 10-41-34\004-bc12.D)
mAU
2000
1500
1000
500
0
5.169
5.768
2
4
6
8
min
Br
N
O
12
H_2N
N
N
NH_2
Br

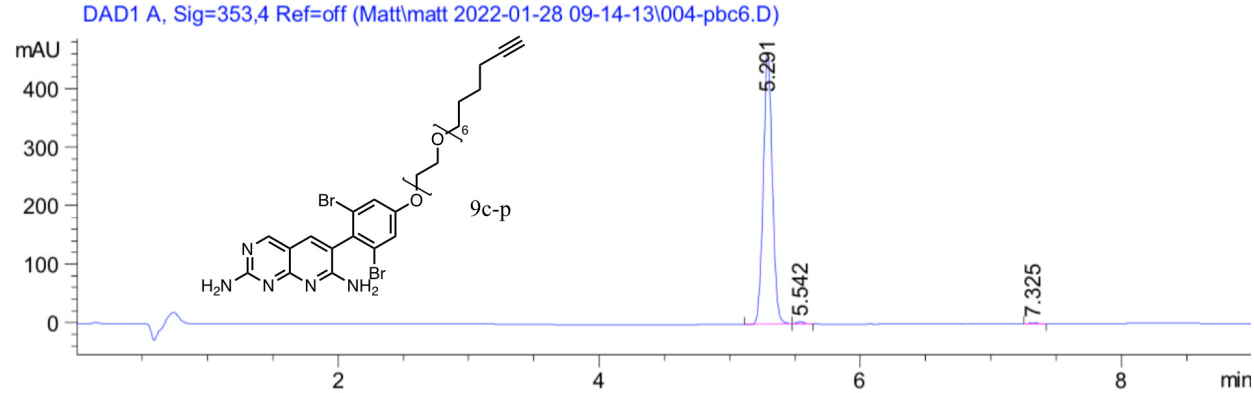
9e


DAD1 A, Sig=353,4 Ref=off (Matt\matt 2022-01-23 10-41-34\006-bc15.D)
mAU
2000
1500
1000
500
0
5.182
5.761
2
4
6
8
min
Br
N
O
15
H_2N
N
N
NH_2
Br

9f

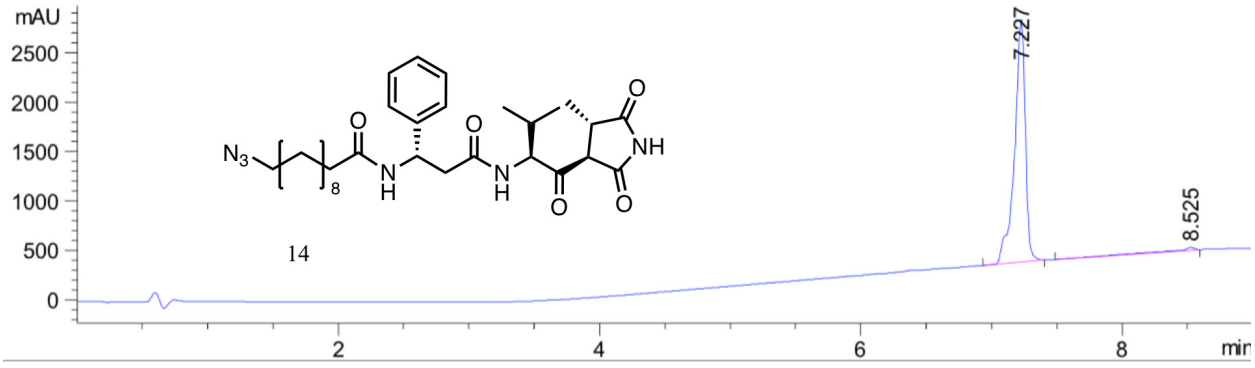

DAD1 A, Sig=353,4 Ref=off (Matt\matt 2022-01-27 08-55-53\002-bc18.D)
mAU
1400
1200
1000
800
600
400
200
0
5.261
5.705
2
4
6
8
min
Br
N
O
18
H_2N
N
N
NH_2
Br

9g

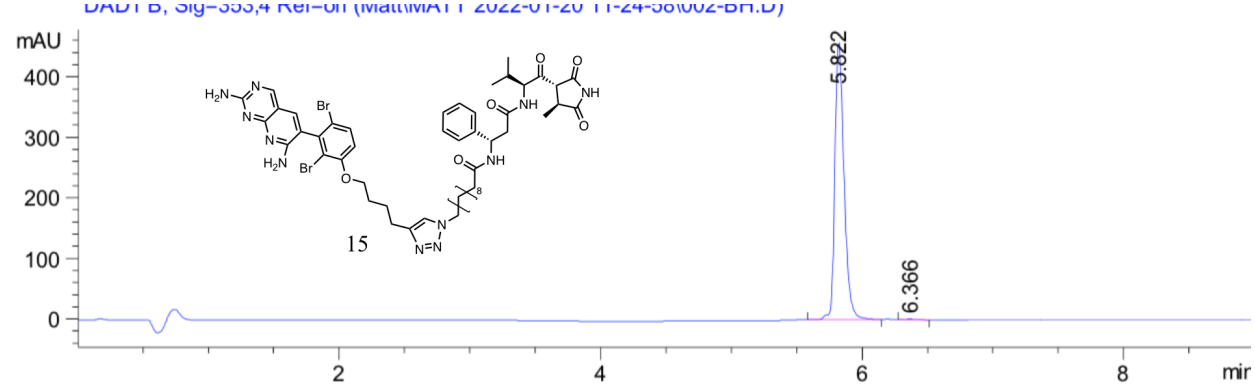

DAD1 A, Sig=353,4 Ref=off (Matt\matt 2022-01-28 09-14-13\004-pbc6.D)
mAU
400
300
200
100
0
5.291
5.542
7.325
2
4
6
8
min
O
6
Br
O
N
H_2N
N
N
NH_2
Br

9c-p

DAD1 C, Sig=213,4 Ref=off (Matt\matt 2022-01-22 14-17-17\004-mapeak.D)

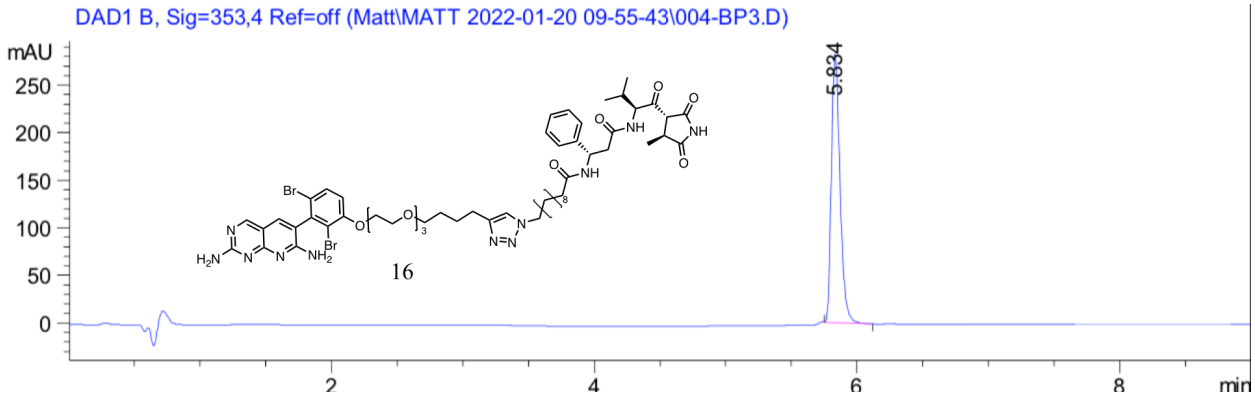


14



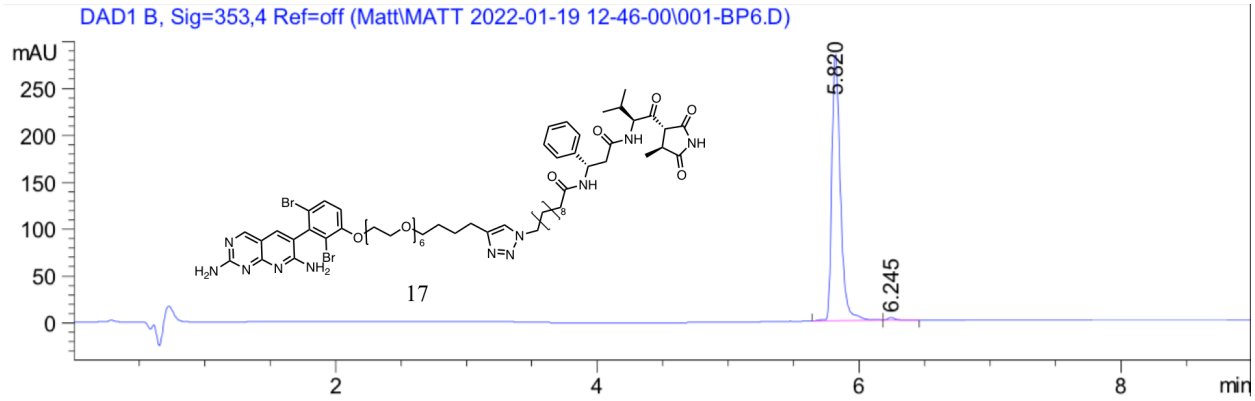
15

DAD1 B, Sig=353,4 Ref=off (Matt\MATT 2022-01-20 09-55-43\004-BP3.D)

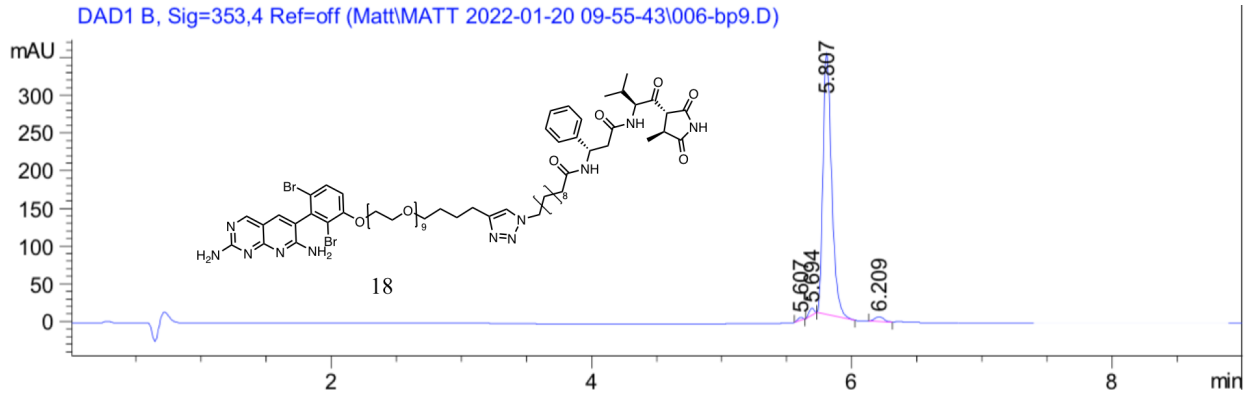


16

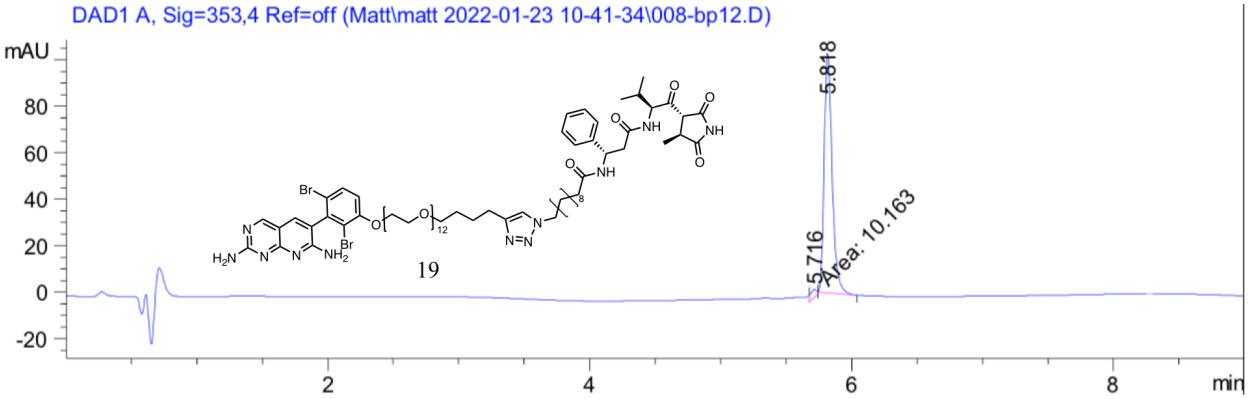
DAD1 B, Sig=353,4 Ref=off (Matt\MATT 2022-01-19 12-46-00\001-BP6.D)



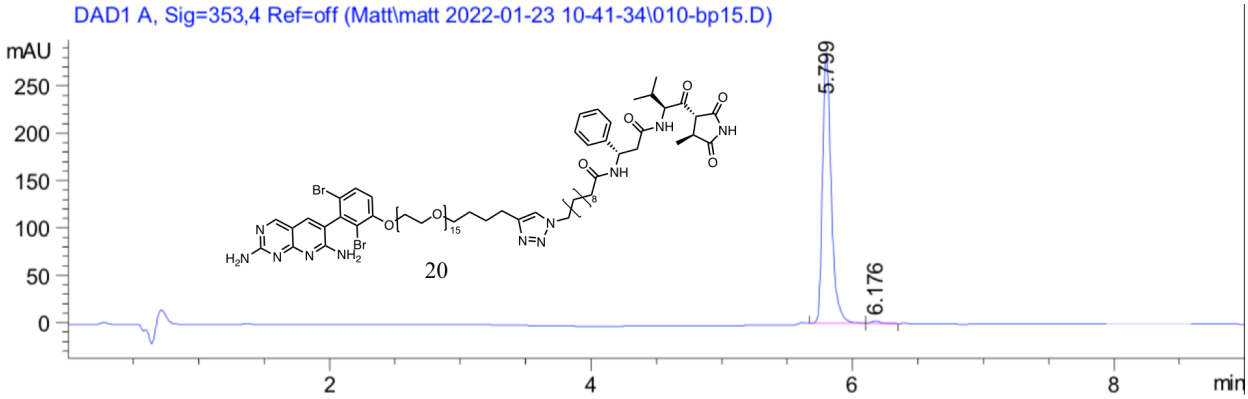
17


DAD1 B, Sig=353,4 Ref=off (Matt\MATT 2022-01-20 09-55-43\006-bp9.D)
mAU
300
250
200
150
100
50
0
5.807
5.607
5.894
6.209
2
4
6
8
min

18


DAD1 A, Sig=353,4 Ref=off (Matt\matt 2022-01-23 10-41-34\008-bp12.D)
mAU
80
60
40
20
0
-20
5.818
5.716
Area: 10.163
2
4
6
8
min

19


DAD1 A, Sig=353,4 Ref=off (Matt\matt 2022-01-23 10-41-34\010-bp15.D)
mAU
250
200
150
100
50
0
5.799
6.176
2
4
6
8
min

20