Supporting Information

DNA and aptamer stabilized gold nanoparticles for targeted delivery of anticancer therapeutics.

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Supporting figures

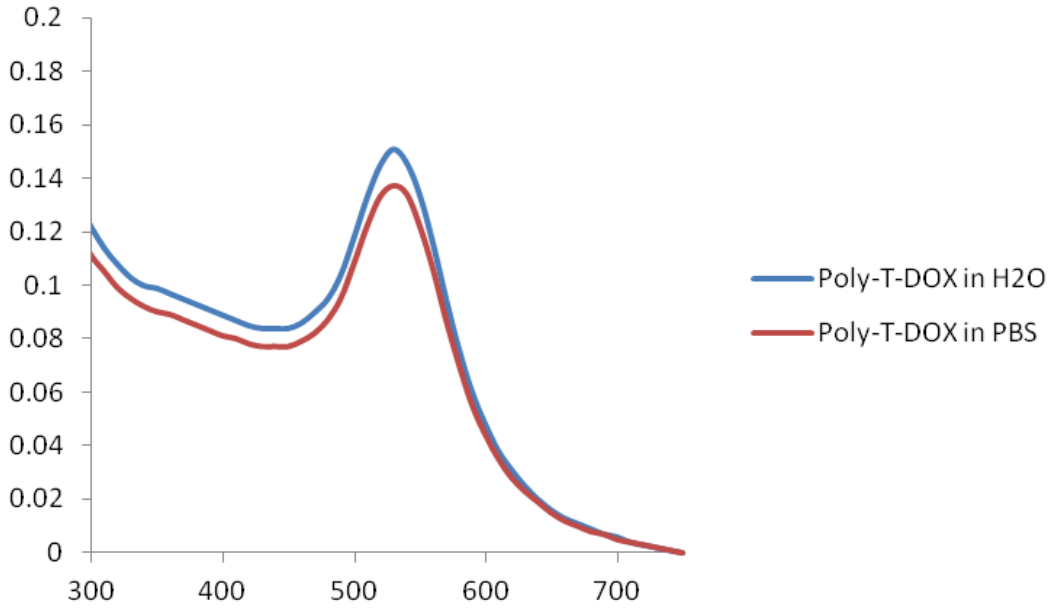


Figure S1. UV spectra of Poly-T-DOX in water and PBS. There are no significant differences in the plasmon band.

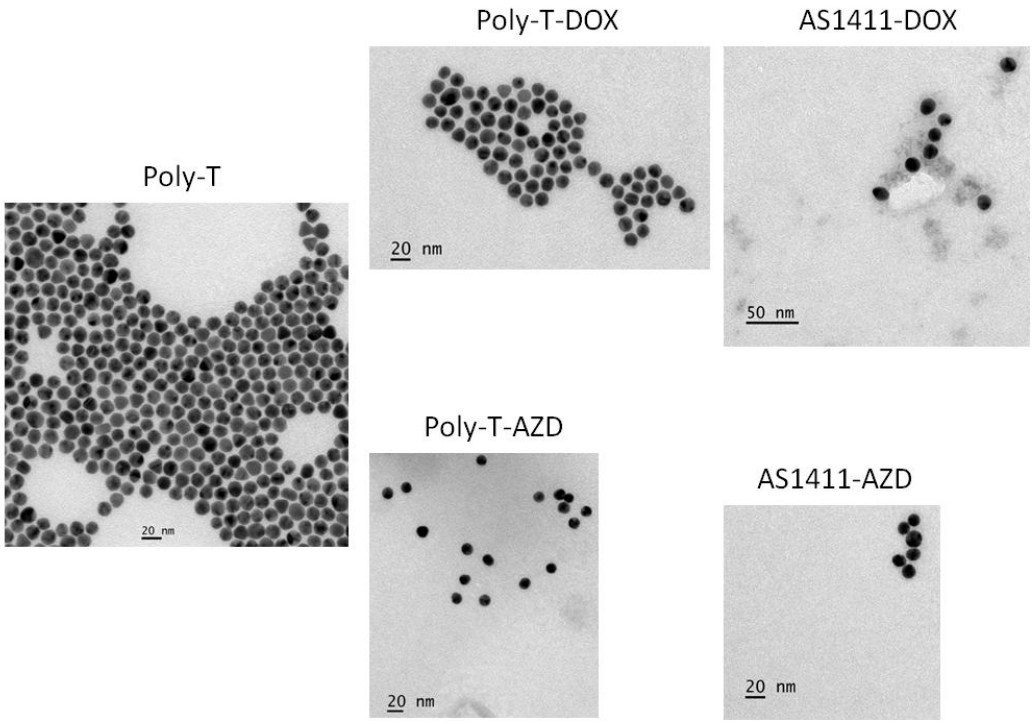


Figure S2. Transmission electron microscopy (TEM) images of GNPs.

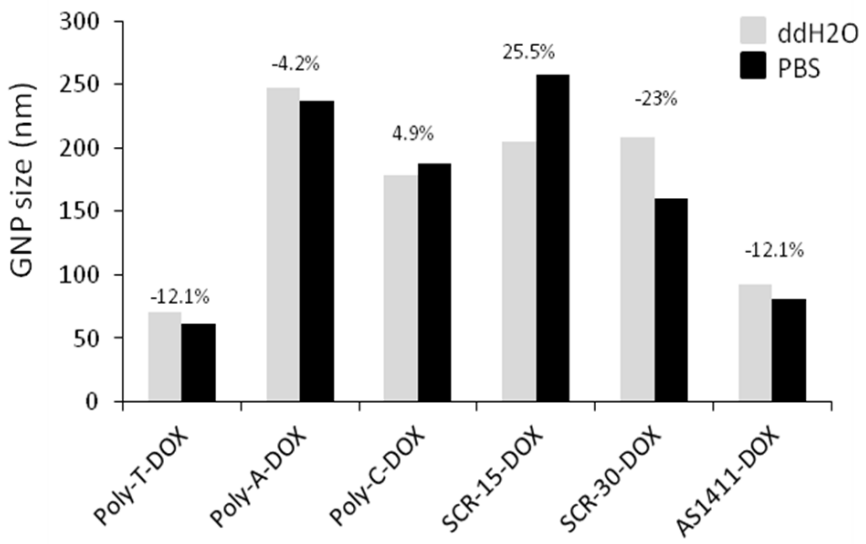


Figure S3. Hydrodynamic sizes of Poly-T, Poly-A, Poly-C, SCR-15 and SCR-30 GNP loaded with DOX and dispersed in water and PBS buffer. GNPs are stable when resuspended in ddH_2O or PBS buffer.

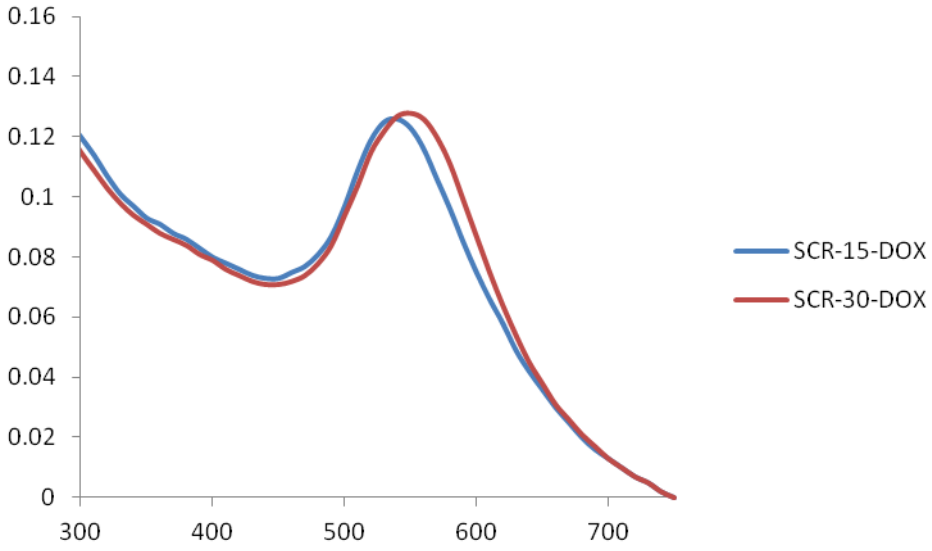


Figure S4. UV-VIS spectra of SCR-15-DOX and SCR-30-DOX. There are no significant changes in the plasmon band.

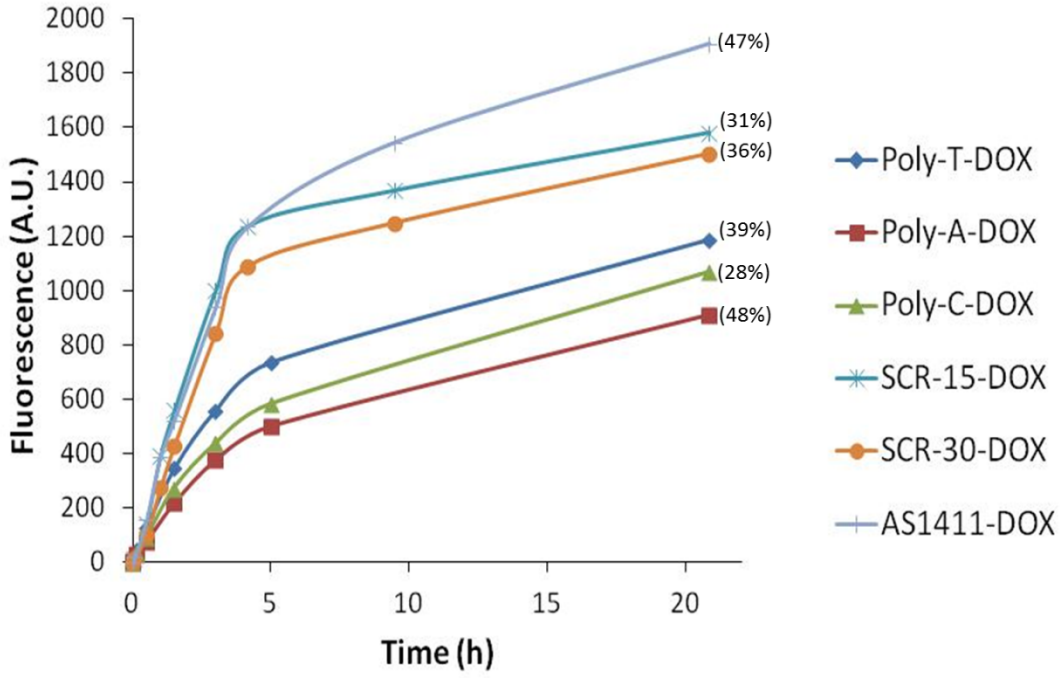


Figure S5. Cumulative DOX release of 1nM GNPs incubated with 1mM GSH, measured by fluorescence (λexc = 495 nm, λem = 595 nm). Designs used are: Poly-T, Poly-A, Poly-C, SCR-15, SCR-30 and AS1411 modified GNP bearing DOX. The released DOX relative to the initial concentration of every design is indicated in brackets (%) after 20 h.

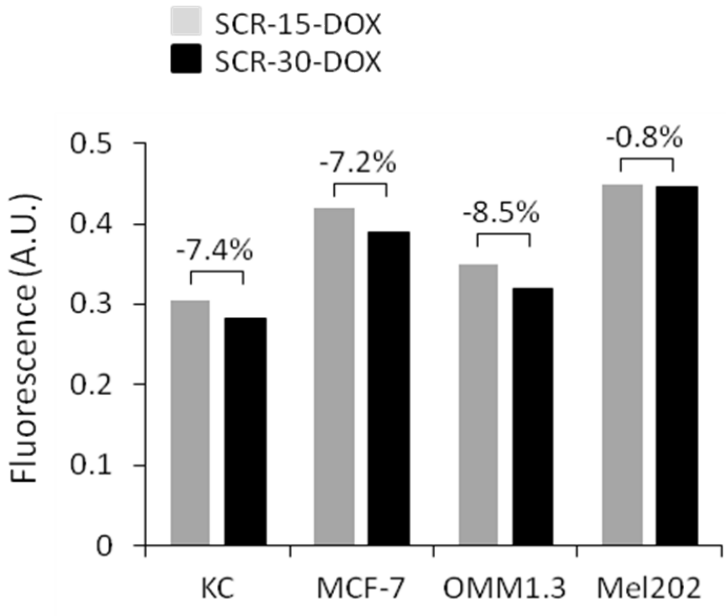


Figure S6. Modifications of GNPs with oligonucleotide sequences of 15 or 30 nucleotides has no influence on DOX release measured with flow cytometric analysis.

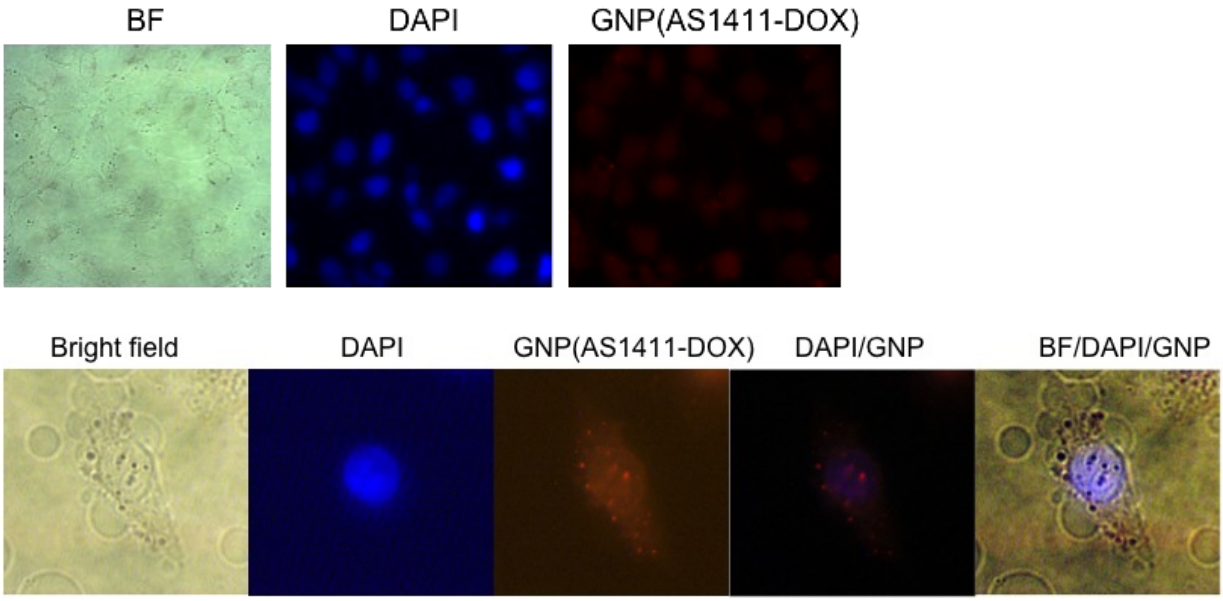


Figure S7. Fluorescence microscopy of OMM1.3 cells incubated with AS1411-DOX GNPs. Vacuolic changes of the cells indicate a pre-apoptotic state which is related to AS1411-DOX GNP incubation (second row).

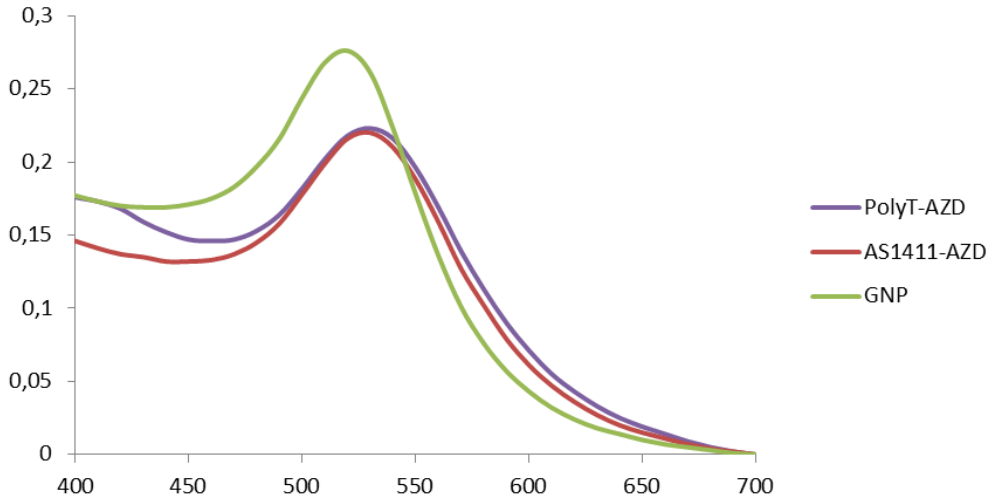


Figure S8. UV-VIS spectra of Poly-T-AZD and AS1411-AZD.

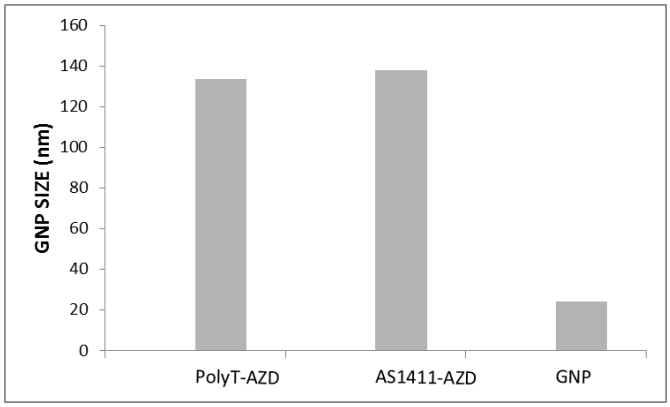


Figure S9. Hydrodynamic size of Poly-T-AZD, AS1411-AZD and non-modified GNP dispersed in water.

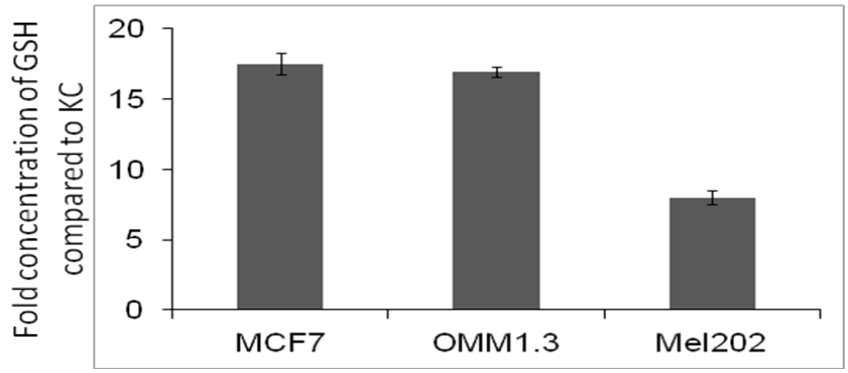


Figure S10. GSH measurement of cells used in this study.

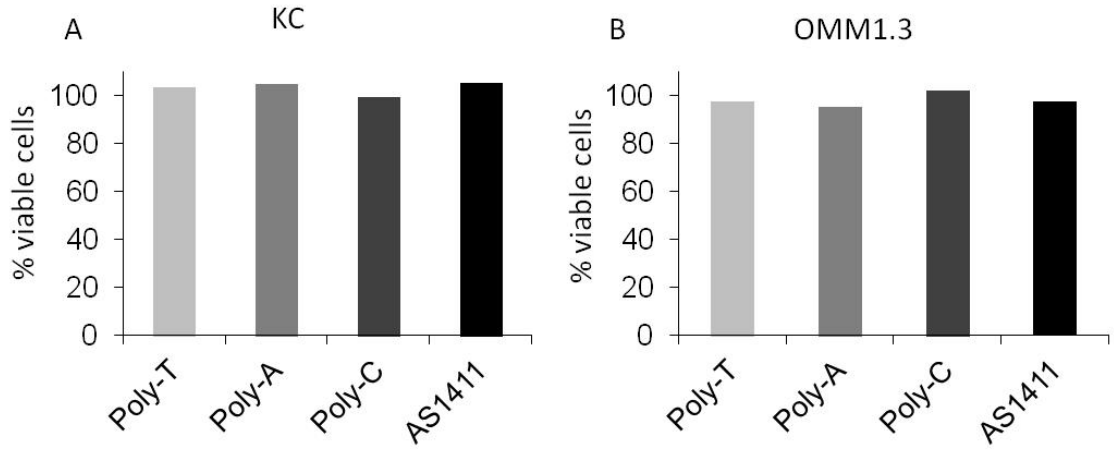


Figure S11. Modified GNP do not influence cell viability in **a.** primary human keratinocytes and **b.** uveal melanoma cells OMM1.3

Nanostructure	DOX (μM)	Oligonucleotide (μM)	Ratio DOX/Oligonucleotide	Stability
PolyA-DOX	30.6	12.8	2.4	Low
PolyT-DOX	23.0	9.7	2.4	High
PolyC-DOX	24.5	15.3	1.6	Medium
AS1411-DOX	32.1	11.6	2.8	High

Table 1. Concentration of DOX and oligonucleotides in different nanoparticle designs. The stability of GNPs does not correlate with the concentration of DOX or oligonucleotides.

Preparation of DNA stabilized GNP loaded with AZD

1mL of GNPs were incubated with modified oligonucleotides (17nmol). After 30min, NaCl 5M (20µL) was added and stirred for 5min. Then, 18.5 µL of a solution modified AZD (**2**) in DMF (2 mM) were added and stirred for 16 h. Then, GNPs were centrifuged at 13200 rpm at 4°C, the supernatant was removed and the reddish pellet was resuspended in water. This process was repeated three times to remove unattached AZD. The stability of GNPs were evaluated comparing the surface plasmon band by UV-Vis.

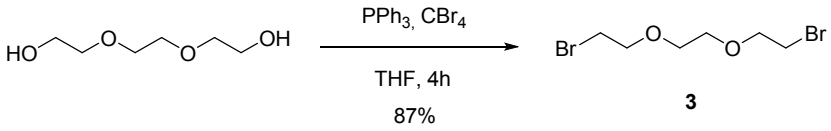
The concentration of AZD was determined using fluorescence spectrometry. 50µL of DNA stabilized GNP loaded with AZD were diluted with 1442.5µL of PBS, and 7.5µL of GSH 1M. The mix was stirred for 24h followed by measurement of fluorescence at λexc = 390 nm, λem = 450 nm. The concentration was calculated by interpolation from a standard linear calibration curve. The AZD concentration determined for GNPs stabilized with polyT and AS1411 were 12.9 µM and 2 µM respectively.

Synthesis of intermediates and self-immolative linkers

Materials and methods

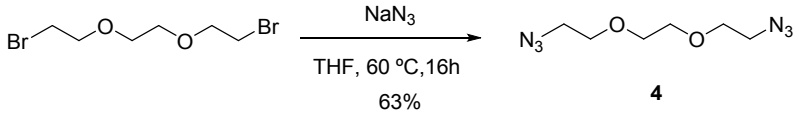
^{1}H and ^{13}C NMR spectra of intermediates were recorded in $CDCl_3$ at 300 and 75MHz, respectively. ^{1}H and ^{13}C NMR spectra of compounds 1, 2, 11 and 12, were recorded at 500 and 125MHz, respectively. All reactions were monitored by thin layer chromatography using precoated sheets of silica gel 60. Flash column chromatography was done using silica gel 60 (230-400 mesh, Merck). Eluting solvents are indicated in the text. All other reagents were purchased from Sigma-Aldrich and used without further purification.

1,2-Bis(2-bromoethoxy)ethane (3).[1]



To a solution of tetraethylene glicol (2 g, 13.3 mmol) and PPh_3 (6.99 g, 26.6 mmol) in THF (20 mL), CBr_4 (8.83 g, 26.6 mmol) was added in small portions and stirred for 4 h. The white solid appeared was filtrated and the solution concentrated in vacuo. The solid residue was suspended in the minimal amount of CH_2Cl_2 and Hexane was added. The white solid appeared was filtrated and the solution concentrated. This operation was repeated three times. Compound **3** was obtained as yellow oil in 87% and was used in the next step without further purification. ^{1}H NMR (300 MHz, CDCl3) δ 3.83 (t, J = 6.3 Hz, 4H), 3.69 (s, 4H), 3.48 (t, J = 6.2 Hz, 4H).

1,2-Bis(2-azidoethoxy)ethane (4). [2]



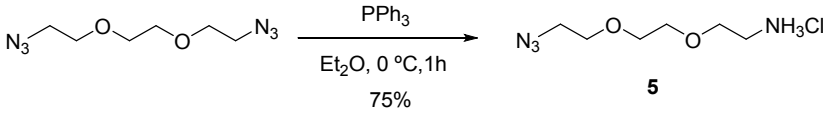
To a solution of dibromide **3** (735 mg, 2.67mmol) in DMF (3.3 mL), NaN_3 (706 mg, 10.7 mmol) was added and stirred at 60 ºC for 16 h. After this time, the mixture was diluted with water and extracted

[1] Zhu,J.; Waengler, C.; Lennox, R.B.; Schirrmacher R. Preparation of Water-Soluble Maleimide-Functionalized 3 nm Gold Nanoparticles: A New Bioconjugation Template. *Langmuir* **2012**, *28*, 5508-5512.

[2] Budin, G.; Dimala,M. M.; Lamour, V.; Oudet, P.; Mioskowski, C.; Meunier, S.; Brino, L.; Wagner A. A Chemical Labeling Strategy for Proteomics under Nondenaturing Conditions. *ChemBioChem*, **2010**, *11*, 79-82.

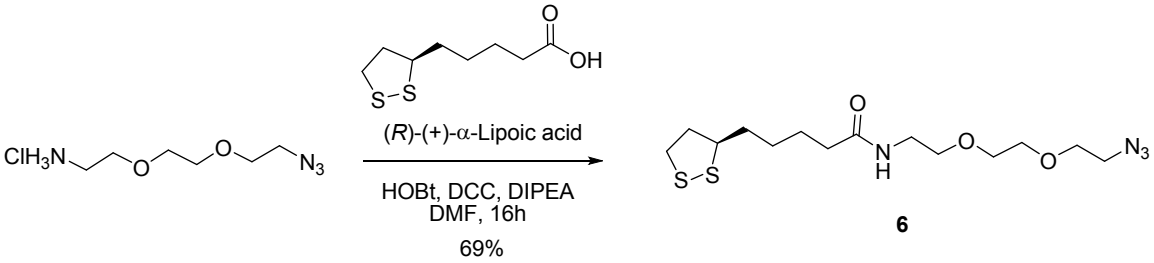
with Et_2O. After solvent evaporation, compound **4** was obtained as colorless oil in 63% yield and was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71-3.68 (m, 8H), 3.39 (t, *J* = 5.0 Hz, 4H).

2-(2-(2-azidoethoxy)ethoxy)ethanamine chlorohydrate (5).[3]



To a solution of diazide **4** (285 mg, 1.42 mmol) in AcOEt (1.4 mL) and Et_2O (1.4 mL) at 0ºC, HCl 5% (1.4 mL) was added. Then, PPh_3 (354 mg, 1.35 mmol) was added during 1 h and stirred for 16 h. The aqueous phase was evaporated to obtain compound **5** as colorless oil in 75% yield and was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (bs, 3H), 3.77-3.74 (m, 2H), 3.71-3.67 (m, 6H), 3.45-3.41 (m, 2H), 3.16-3.13 (m, 2H).

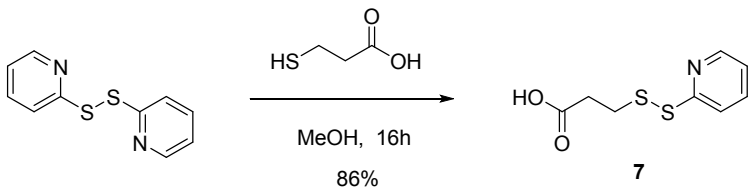
(*R*)-N-(2-(2-(2-azidoethoxy)ethoxy)ethyl)-5-(1,2-dithiolan-3-yl)pentanamide (6).



To a suspension of azide **5** (226 mg, 1.07 mmol) in DMF (3.2 mL), HOBt (157 mg, 1.17 mmol), DCC (241 mg, 1.17 mmol), (*R*)-(+)-α-Lipoic acid (241 mg, 1.17 mmol) and DIPEA (200 µL, 1.17 mmol) were added and stirred for 16 h. After this time, the mixture was filtered and solvent removed in vacuum. Then, the residue was purified by flash chromatography (eluent Hexane/AcOEt 1:2) to give the compound **6** in 69% yield as pallid yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (bs, 1H), 3.70-3.64 (m, 6H), 3.58-3.54 (m, 3H), 3.48 – 3.38 (m, 4H), 3.21-3.06 (m, 2H), 2.45 (td, *J* = 12.4, 6.4 Hz, 1H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.90 (td, *J* = 13.8, 6.9 Hz, 1H), 1.73-1.58 (m, 4H), 1.53-1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 70.9, 70.6, 70.5, 70.4, 56.8, 51.0, 40.6, 39.5, 38.9, 36.7, 35.0, 29.3, 25.7; MS (ESI): *m/z* (%) 232 (51), 363 (M^++H, 100), 385 (M^++Na, 83); HRMS (ESI) calcd for $C_{14}H_{27}N_4O_3S_2$ (M^++H) 363.1532, found 363.1519; HRMS (ESI) calcd for C14H26N4O3NaS$_2$ (M^++Na) 385.1328, found 385.1338.

3-(2-Pyridyl)-dithiopropionic acid (PDP-OH) (7). [3]

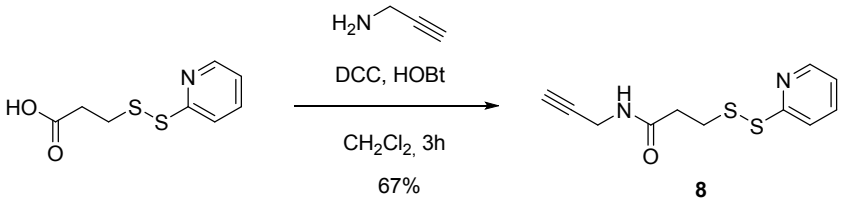
[3] Xie, H.; Braha, O.; Gu, L.Q.; Cheley, S.; Bayley, H. Single-Molecule Observation of the CatalyticSubunit of cAMP-Dependent Protein Kinase Binding to an Inhibitor Peptide. *Chemistry & Biology* **2005**, *12*, 109-120.



7

Compound **7** was obtained following the protocol found in literature with some modifications. Briefly, to a solution of aldrithiol (958 mg, 4.3 mmol) in MeOH (5 mL) under N_2, mercaptopropionic acid (0.35 mL, 3.95 mmol) was added at room temperature and stirred for 16 h. After solvent evaporation and flash chromatography (eluent Hexane/AcOEt 1:2 with AcOH 1%) compound **3** was obtained in 85% yield as colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 – 8.33 (m, 1H), 7.95 – 7.43 (m, 2H), 7.16 (ddd, *J* = 6.7, 5.0, 1.6 Hz, 1H), 3.07 (t, *J* = 6.8 Hz, 1H), 2.80 (t, *J* = 6.8 Hz, 2H).

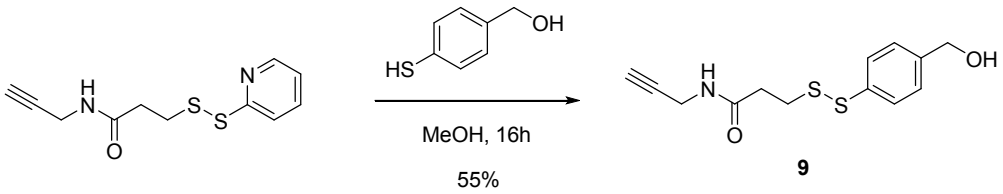
***N*-(Prop-2-ynyl)-3-(pyridin-2-yldisulfanyl)propanamide (8).**



8

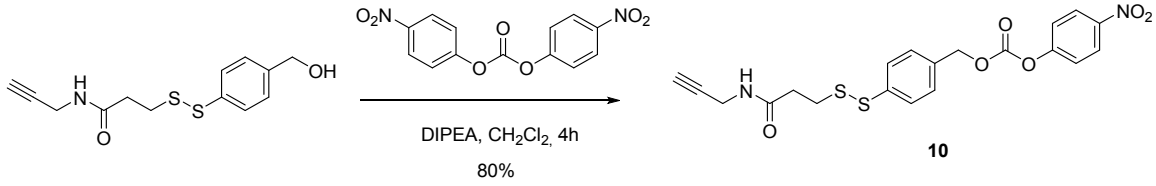
To a mixture of compound **7** (518 mg, 2.4 mmol), *N*-hydroxybenzotriazole (357 mg, 2.65 mmol) and *N*,*N*′-Dicyclohexylcarbodiimide (DCC) (545 mg, 2.65 mmol) in CH_2Cl_2 (6 mL), propargylamine (108μL, 2.65mmol) was added at room temperature and stirred during 3 h. After this time, the mixture was filtered and solvent removed in vacuum. Then, the residue was purified by flash chromatography (eluent Hexane/AcOEt 1:2) to give the compound **8** in 67% yield as pallid yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.5 Hz, 1H), 7.62-7.55 (m, 2H), 7.24 (s, 1H), 7.20 – 7.01 (m, 1H), 4.10 (dd, J= 5.2, 2.5 Hz, 2H), 3.08 (t, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 6.6 Hz, 2H), 2.25 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 159.2, 149.5, 137.0, 121.0, 120.4, 79.7, 71.5, 35.5, 35.0, 29.1. MS (ESI): *m/z* (%) 225 (11), 253 (M^++H, 99),; HRMS (ESI) calcd for $C_{11}H_{13}N_2OS_2$ (M^++H) 253.0463, found 253.0469.

3-((4-(Hydroxymethyl)phenyl)disulfanyl)-N-(prop-2-ynyl)propanamide (9).



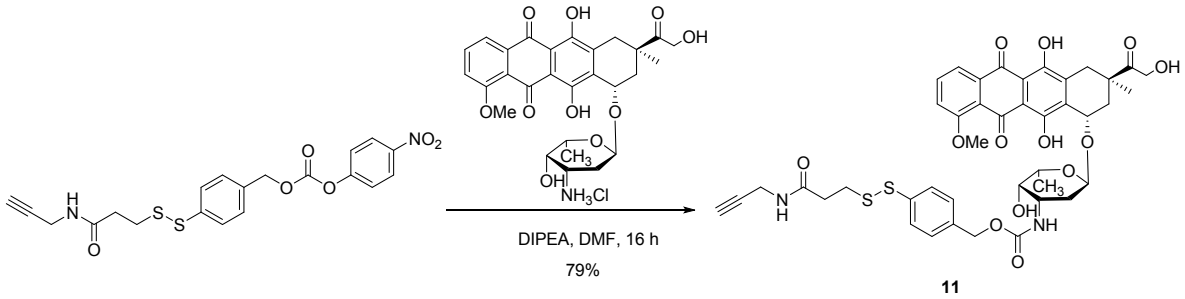
To a solution of disulfide **8** (60 mg, 0.23 mmol) in MeOH (1.5 mL) under N_2, a solution of (4-mercaptophenyl)methanol (35 mg, 0.25 mmol) in MeOH (1.5 mL) was added at room temperature and stirred for 16h. After solvent evaporation and flash chromatography (eluent CH2CL2/MeOH 30:1), compound **9** was obtained in 55% yield as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 4.69 (s, 2H), 4.02 (dd, *J* = 5.1, 2.5 Hz, 2H), 3.02 (t, *J* = 6.9 Hz, 2H), 2.56 (t, *J* = 6.9 Hz, 2H), 2.25 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 140.3, 135.4, 128.1, 127.7, 79.4, 71.6, 64.5, 35.1, 33.9, 29.1. MS (ESI): *m/z* (%) 264 (M^+-OH, 11), 304 (M^++Na, 100); HRMS (ESI) calcd for $C_{13}H_{14}NOS_2$ (M^+-OH) 264.0511, found 264.0529 and calcd for $C_{13}H_{15}NO_2NaS_2$ (M^++Na) 304.0433, found 304.0434.

4-Nitrophenyl 4-((3-oxo-3-(prop-2-ynylamino)propyl)disulfanyl)benzyl carbonate (10).



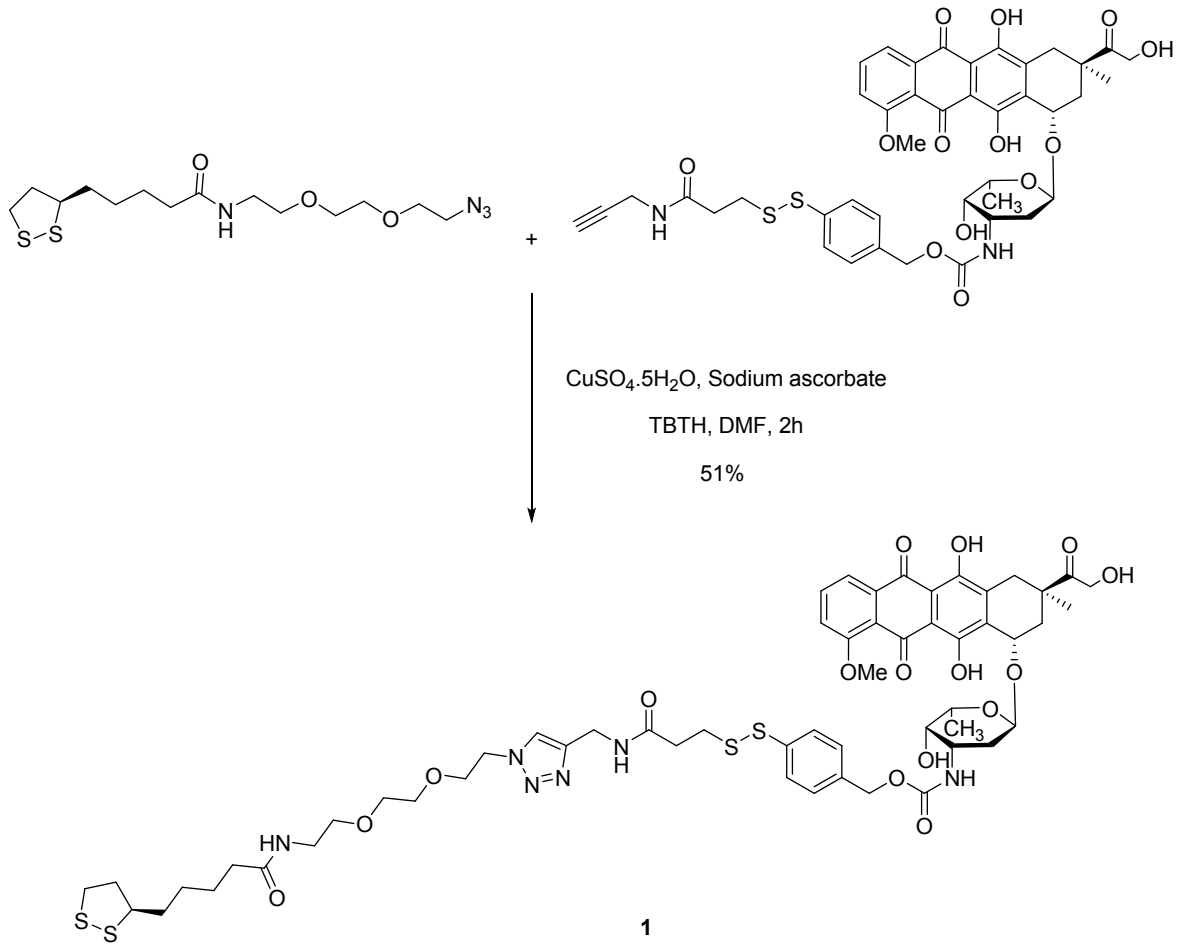
To a suspension of benzyl alcohol **9** (144 mg, 0.51 mmol) in CH_2Cl_2 (4 mL) under N_2, bis(4-nitrophenyl) carbonate (232 mg, 0.76 mmol) and DIPEA (122 µL, 0.66 mmol) were added and stirred during 4h. After solvent evaporation and flash chromatography (eluent Hexane/AcOEt 1:1) compound **10** was obtained in 80% yield as a pallid yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.9 Hz, 2H), 7.56 (d, *J* = 8.5Hz, 2H), 7.39 (dd, *J* = 8.9, 8.5 Hz, 4H), 5.80 (bs, 1H), 5.26 (s, 2H), 4.02 (dd, *J* = 5.2, 2.5 Hz, 2H), 3.02 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.24 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 165.0, 152.4, 145.5, 138.2, 129.4, 127.6, 125.2, 121.7, 79.3, 71.7, 70.3, 35.2, 33.7, 29.2, 27.6. (ESI): *m/z* (%) 225 (15), 447 (M^++H, 2), 469 (M^++Na, 100); HRMS (ESI) calcd for $C_{20}H_{18}N_2O_6NaS_2$ (M^++H) 469.0498, found 469.0517.

4-((3-oxo-3-(prop-2-ynylamino)propyl)disulfanyl)benzyl(2S,3S,4S,6R)-6-((1S,3R)-5,12-dihydroxy-3-(2-hydroxyacetyl)-10-methoxy-3-methyl-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yloxy)-3-hydroxy-2-methyltetrahydro-2H-pyran-4-ylcarbamate (11).



To a solution of carbonate **10** (9 mg, 0.02 mmol) and Doxorubicin hydrochloridrate (5 mg, 0.0086 mmol) in DMF (1 mL), DIPEA (14 µL, 0.08 mmol) was added and stirred for 16 h. After solvent evaporation and flash chromatography (eluent CH_2Cl_2/MeOH 20:1) compound **11** was obtained as a red solid in 79% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.98 (s, 1H), 13.25 (s, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.79 (dd, *J* = 7.7, 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 2H), 5.56 (bs, 1H), 5.51- 5.50 (m, 1H), 5.30 (s, 2H), 5.15 (d, *J* = 8.2 Hz, 1H), 5.01 (s, 2H), 4.80 – 4.72 (m, 2H), 4.53 (s, 1H), 4.18 – 4.10 (m, 1H), 4.08 (s, 3H), 3.99 (dd, *J* = 5.2, 2.5 Hz, 1H), 3.92 – 3.80 (m, 1H), 3.66 (d, *J* = 4.9 Hz, 1H), 3.29 (d, *J* = 18.7 Hz, 1H), 3.19 (s, 1H), 3.08 – 2.91 (m, 3H), 2.52 (t, *J* = 6.8 Hz, 2H), 2.33 (d, *J* = 14.6 Hz, 1H), 2.24 (t, *J* = 2.5 Hz, 1H), 2.19 (m, 1H), 1.97 (d, *J* = 7.4 Hz, 1H), 1.88 (dd, *J* = 13.0, 4.9 Hz, 1H), 1.77 (td, *J* = 13.0, 3.3 Hz, 1H), 1.58 (s, 3H), 1.29 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 211.7, 187.2, 186.7, 170.1, 161.1, 156.2, 155.7, 155.3, 137.2, 135.8, 135.5, 133.6, 133.5, 128.9, 127.9, 120.9, 119.9, 118.5, 111.6, 111.4, 100.7, 79.3, 71.8, 69.7, 69.5, 67.2, 66.1, 65.5, 56.7, 53.4, 48.3, 47.0, 35.6, 35.2, 34.0, 33.9, 30.9, 30.2, 29.2, 23.9, 16.8; MS (MALDI-TOF): *m/z* 873.3 (M^++2).

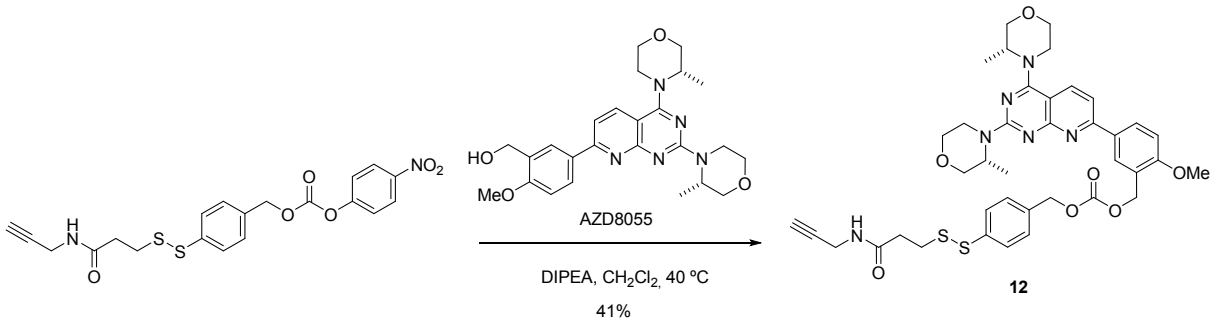
4-((3-((1-(2-(2-(2-(5-((R)-1,2-dithiolan-3-yl)pentanamido)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methylamino)-3-oxopropyl)disulfanyl)benzyl (2S,3S,4S,6R)-6-((1S,3R)-5,12-dihydroxy-3-(2-hydroxyacetyl)-10-methoxy-3-methyl-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yloxy)-3-hydroxy-2-methyltetrahydro-2H-pyran-4-ylcarbamate (1).



A mixture of alkyne **11** (11 mg, 0.013 mmol), azide **6** (5 mg, 0.014 mmol), CuSO4.5H_2O (0.18 mg, 5 % mol), sodium ascorbate (2.5 mg, 0.013 mmol), TBTH (1.6 mg, 10% mol) under argon, was dissolved with DMF (1 mL) and stirred for 2h. After solvent evaporation and flash chromatography using deactivated SiO_2 (eluent CH_2Cl_2/MeOH 15:1), compound **1** was obtained as a red solid in 51% yield; ^{1}H NMR (500 MHz, CDCl3) δ ^{1}H NMR (500 MHz, CDCl3) δ 13.97 (s, 1H), 13.25 (s, 1H), 8.09 (d, *J*= 9.2 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.80-7.76 (dd, *J*= 8.4, 7.6 Hz, 1H), 7.76 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.99-6.95 (m, 1H), 6.50 (s, 1H), 6.14 (t, *J*= 5.5 Hz, 1H), 5.88 (d, *J* = 8.4 Hz, 1H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.52 (d, *J* = 3.4 Hz, 1H), 5.30 (d, *J* = 2.2 Hz, 1H), 5.08-5.03 (m, 1H), 5.00 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.97 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.91 (dd, *J* = 15.9, 6.8 Hz, 2H), 4.76 (d, *J* = 2.4 Hz, 2H), 4.67 (s, 1H), 4.52-4.49 (m,

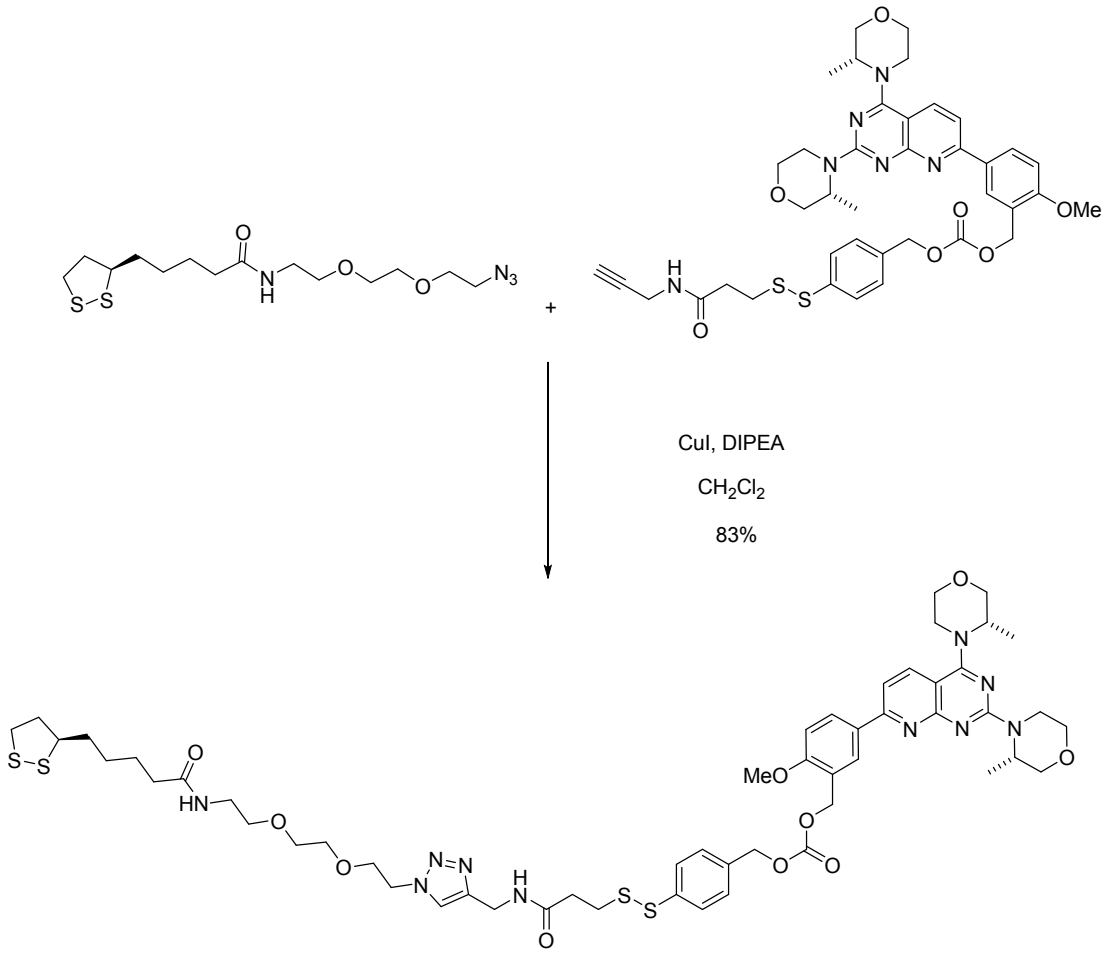
2H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.13 (dd, *J* = 12.6, 6.6 Hz, 1H), 4.08 (s, 3H), 3.91-3.87 (m, 1H), 3.86-3.82 (m, 2H), 3.70 (bs, 1H), 3.61-3.52 (m, 6H), 3.46 (t, *J* = 5.1 Hz, 2H), 3.36 (dd, *J* = 10.3, 5.2 Hz, 2H), 3.28 (dd, *J* = 18.8, 1.6 Hz, 1H), 3.18-3.13 (m, 1), 3.09 (dt, J= 11.0, 6.9 Hz, 1H), 3.06-2.98 (m, 4H), 2.47 (t, *J* = 6.1 Hz, 2H), 2.46-2.40 (m, 1H), 2.36 (d, *J* = 14.6 Hz, 1H), 2.17-2.14 (m, 3H), 2.06-2.00 (m, 2H), 1.92-1.84 (m, 3H), 1.71-1.56 (m, 5H), 1.49 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (126 MHz, CDCl3) δ 213.9, 187.1, 186.7, 173.3, 170.0, 161.0, 156.3, 155.7, 155.5, 144.7, 139.3, 137.9, 135.7, 135.6, 135.5, 133.7, 133.6, 129.0, 128.2, 126.0, 123.8, 120.9, 119.8, 118.4, 115.8, 114.0, 111.5, 111.4, 100.9, 70.5, 70.1, 69.9, 69.2, 67.6, 66.0, 65.5, 56.7, 56.5, 50.3, 40.2, 39.4, 38.4, 36.2, 34.90, 34.59, 33.8, 31.9, 29.60, 29.5, 29.3, 29.1, 29.0, 28.9, 25.4, 22.7, 17.0; MS (MALDI-TOF): *m/z* 1235.3 (M^++2).

5-(2,4-Bis((*R*)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-2-methoxybenzyl 4-((3-oxo-3-(prop-2-ynylamino)propyl)disulfanyl)benzyl carbonate (12).



To a mixture of carbonate **10** (10 mg, 0.022 mmol) and AZD8055 (6 mg, 0.012 mmol) in CH_2Cl_2 (0.5 mL), DIPEA (25 µL, 0.13 mmol) was added and stirred for 16h at 45 ºC. After solvent evaporation and flash chromatography (eluent Hex/AcOEt 1:2) compound **12** was obtained in 60% as a yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 1H), 5.74 (s, 1H), 5.30 (s, 2H), 5.16 (s, 2H), 4.94 – 4.87 (m, 1H), 4.61 (d, *J* = 13.0 Hz, 1H), 4.36 (q, *J* = 6.6 Hz, 1H), 4.03 – 3.94 (m, 4H), 3.89 (s, 3H), 3.88 – 3.83 (m, 2H), 3.80 – 3.65 (m, 5H), 3.56 (td, *J* = 12.0, 2.9 Hz, 1H), 3.40 – 3.33 (m, 1H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.52 (t, *J* = 7.0 Hz, 2H), 2.23 (t, *J* = 2.6 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl3) δ 170.06, 165.36, 162.85, 161.52, 159.92, 159.28, 155.06, 137.67, 134.56, 134.35, 130.90, 129.99, 129.71, 129.05, 127.68, 123.44, 112.75, 110.49, 104.48, 79.29, 71.74, 71.27, 70.89, 68.93, 67.24, 66.90, 65.38, 55.66, 52.79, 46.86, 44.36, 39.27, 35.21, 34.00, 31.91, 29.68, 29.24, 14.70, 14.31; MS (ESI): *m/z* (%) 205 (15), 464 (19), 773 (M^++H, 100); HRMS (ESI) calcd for $C_{39}H_{45}N_6O_7S_2$ (M^++H) 773.2815, found 773.2785.

4-((3-((1-(2-(2-(2-(5-((*R*)-1,2-Dithiolan-3-yl)pentanamido)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methylamino)-3-oxopropyl)disulfanyl)benzyl 5-(2,4-bis((*S*)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-2-methoxybenzyl carbonate (2).



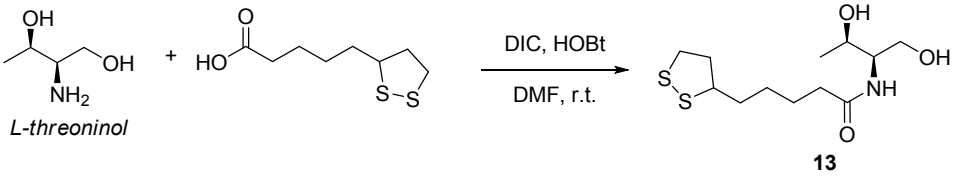
2

To a mixture of alkyne **12** (3.5 mg, 0.004 mmol) and azide **6** (1.6 mg, 0.004mmol) in CH_2Cl_2 (0.6 mL) under Ar, CuI (cat amount) and DIPEA (10 µL, 0.05 mmol) were added and stirred for 2 h. After solvent evaporation and flash chromathography (CH_2Cl_2/MeOH 25:1) compound **2** was obtained in 83% yield as a yellow solid ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.20 (m, 2H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.47 (d, *J*= 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.68 (t, *J*= 4.9Hz, 1H), 6.32 (t, J = 4.8Hz, 1H), 5.15 (s, 2H), 5.01–4.90 (m, 1H), 4.62 (m, 1H), 4.51–4.46 (m, 4H), 4.37 (q, *J* = 6.5 Hz, 1H), 4.00-3.95 (m, 2H), 3.89 (s, 3H), 3.84 (m, 4H), 3.79–3.65 (m, 5H), 3.59 – 3.52 (m, 6H), 3.47 (t, *J* = 5.3 Hz, 2H), 3.4–3.32 (m, 3H), 3.20–3.07 (m, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 2.44 (dt, *J* = 12.0, 6.5 Hz, 1H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.89 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.72–1.58 (m, 8H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 170.6, 165.1, 162.8, 161.3, 159.6, 159.4, 155.0, 144.7, 139.3, 137.6, 134.6, 134.3, 130.7, 130.1, 129.9, 129.1, 127.7, 123.3, 114.0, 113.1, 110.4, 104.6, 71.2,

70.9, 70.5, 70.1, 69.9, 69.1, 68.9, 67.2, 66.9, 65.3, 56.6, 55.7, 52.8, 50.3, 46.9, 44.3, 40.2, 39.3, 38.6, 36.3, 35.2, 34.6, 34.1, 31.9, 29.3, 28.9, 25.4, 14.7, 14.4; MS (ESI): *m/z* (%) 308 (61), 331 (100), 363 (79), 386 (32), 1135 (M^++H, 65); HRMS (ESI) calcd for $C_{53}H_{71}N_{10}O_{10}S_4$ (M^++H) 1135.4276, found 1135.4232.

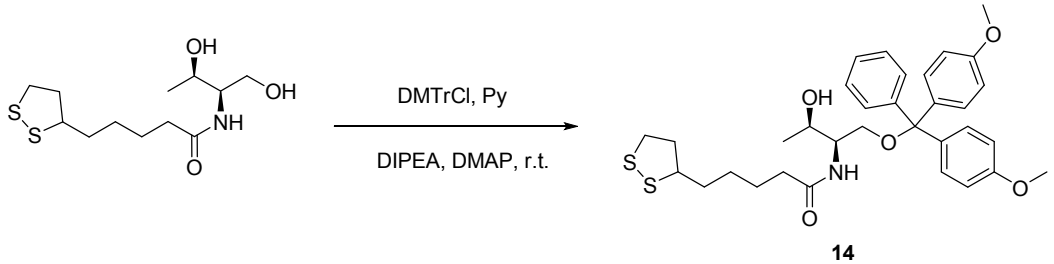
Synthesis of modified CPG

5-[(3S)-1,2-dithiolan-3-yl]-N-[(1R,2S)-2-hydroxy-1-(hydroxymethyl)propyl]pentanamide (13).



To a solution of (*R*)-(+)-α-lipoic acid (3.301 mmol, 680 mg, 1.2 eq.) in DMF (0.5 M) at room temperature, *N*- hydroxybenzotriazole (3.027 mmol, 409 mg, 1.1 eq.) and diisopropylcarbodiimide (3.026 mmol, 468 µl, 1.1 eq.) were added. After stirring the mixture 10 min. L- threoninol (2.752 mmol, 289 mg, 1 eq.) was added. The resulting mixture was stirred overnight and then quenched by the addiction of methanol. The solvent was evaporated under vacuum and the residue purified by flash chromatography 20:1 (CH_2Cl_2: MeOH) to yield **13** as a pale yellow oil (82%).^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.26 (d, *J* = 6.7 Hz, 1H), 4.21- 4.14 (m, 1H), 3.87 – 3.78 (m, 3H), 3.58 (dt, *J* = 13.1, 6.5 Hz, 1H),3.48 (s,1H), 3.26 – 3.04 (m, 2H), 2.46 (td, *J* = 12.4, 6.4 Hz, 1H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.91 (dq, *J* = 13.7, 6.9 Hz, 1H), 1.80 – 1.60 (m, 5H), 1.57 – 1.41 (m, 2H), 1.19 (d, *J* = 6.4 Hz, 3H). ^{13}C-NMR (75MHz, $CDCl_3$): δ 174.1, 68.6, 64.8, 56.2, 54.5, 40.1, 38.3, 36.4, 34.4, 28.6, 25.3, 20.4. HR-MS (ESI): *m/z* calculated for $C_{12}H_{24}NO_3S_2$ 294.1192 $[M+H]^+$, found 294.1186.

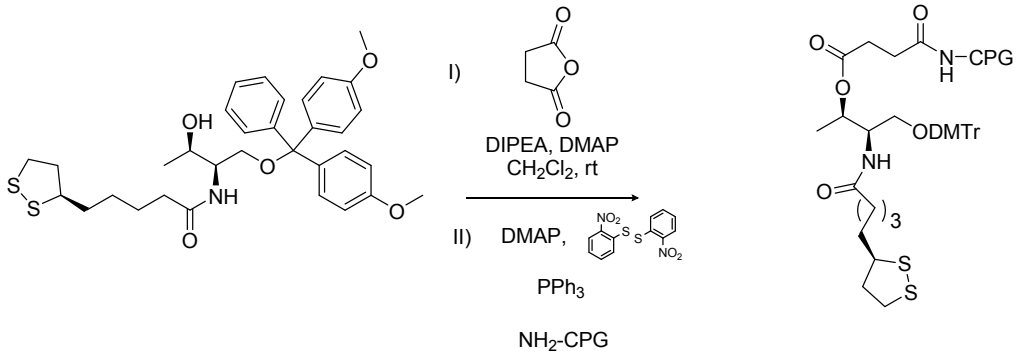
N-((1R,2S)-1-{[bis(4-methoxyphenyl)(phenyl)methoxy]methyl}-2-hydroxypropyl)-5-[(3S)-1,2-dithiolan-3-yl]pentanamide (14).



To a solution of the diol **13** (0.682 mmol, 200 mg, 1 eq.) in pyridine (0.2 M) at 0°C, diisopropylethylamine (1.023 mmol, 179 µl, 1.5 eq), 4,4´-dimethoxyltritylchloride (0.819 mmol, 277 mg, 1.2 eq) and dimethylaminopyridine (catalytic amount) were added. After 15 min. the mixture was

allowed to reach room temperature. The mixture was stirred overnight and then quenched by the addiction of methanol. The solvent was evaporated under vacuum and the residue purified by flash chromatography 1:2 (hexane: EtOAc) to yield **14** as a white to light yellow foam (66%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 9H), 6.83 (d, *J* = 8.8 Hz, 4H), 6.03 (d, *J* = 8.7 Hz, 1H),4.10 (m, 1H), 3.93 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.79 (s, 6H), 3.62 – 3.48 (m, 1H), 3.41 (dd, *J* = 9.6, 4.3 Hz, 1H), 3.29 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.23 – 3.05 (m, 3H), 2.44 (td, *J* = 12.4, 6.4 Hz, 1H), 2.23 (t, *J* = 7.3 Hz, 2H), 1.90 (td, *J* = 13.7, 6.9 Hz, 1H), 1.76 – 1.62 (m, 4H), 1.56 – 1.41 (m, 2H), 1.12 (d, *J* = 6.4 Hz, 3H). ^{13}C-NMR (75MHz, $CDCl_3$): δ 173.0 (C), 158.6 (2C) (C), 144.3 (C), 135.5 (C), 135.3 (C), 129.9 (2C) (CH), 129.8 (2C) (CH), 127.9 (2C) (CH), 127.8 (2C) (CH), 127.0(CH), 113.3 (4C) (CH_3), 86.7, 68.6(CH), 65.2(CH_2), 60.3, 56.3(CH), 55.2(CH), 53.3(CH), 40.2(CH_2), 38.4(CH_2), 36.5(CH_2), 34.6(CH_2), 28.9(CH_2), 25.5(CH_2), 19.9(CH_3). HR-MS (ESI): *m/z* calculated for $C_{33}H_{41}NNaO_5S_2$ 618.2324 $[M+Na]^+$, found 618.2296.

CPG Functionalization (two steps)



I

To a solution of **14** (0.084 mmol, 50 mg, 1 eq) in anhydrous dichloromethane (0.2 M) succinic anhydride (0.109 mmol, 10.9 mg, 1.3 eq), diisopropylethylamine (0.118 mmol, 20.5 µl, 1.4 eq) dimethylaminopyridine (catalytic amount) were added. The solution was stirred for 16 h at room temperature. The solution was washed with water and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, filtered and evaporated under vacuum to yield yellowish oil.

II

To a solution of DMAP (0.126 mmol, 15.4 mg, 1.5 eq) in acetronitrile (60 mM) the product obtained in the step II was added (0.084 mmol, 58.3 mg, 1 eq). After mixing it well in vortex, the solution was added to a solution of 2,2´-dithiobis-(5-nitropyridine) (0.126 mmol, 39.0 mg, 1.5 eq) in anhydrous CH_2Cl_2 (300 µl). The solution was mixed well and added to triphenyl posphine (0.126 mmol, 33.0 mg, 1.5 eq). The mixture was vortexed till all reagents were dissolved giving rise to a reddish

solution, which was added to 500 mg of CPG (500 Å). After 2h at room temperature, the solution was removed and the CPG washed with methanol (3 x 20 ml) and dry acetronitrile (3 x 20 ml). Once the CPG was dry, 2 ml of a 1:1 mixture of the capping reagents (CAP A: 600 µl pyridine, 500 µl dry THF, 400 µl acetic anhydride; CAP B: 1 ml dry THF, 400 µl 1-methylimidazole) was added. After 20 min at room temperature, the CPG was washed with dry acetonitrile (6 x 20 ml) and dried well.

The CPG loading was calculated by detrytylation of the sample as follow: 10 mg of CPG were treated with 5 ml of detrytylation solution (3 ml of perchloric acid and 2 ml of ethanol) for 1 hour. Then 500 µl of the mixture were dissolved in 2 ml of the detrytylation solution and absorbance was measured at 498 nm. Functionalization (F) was determined by Lambert-Beer law:

$F = (ABS \times V) / (\varepsilon \times g) = M / g$

Sequences and MALDI data of oligonucleotides

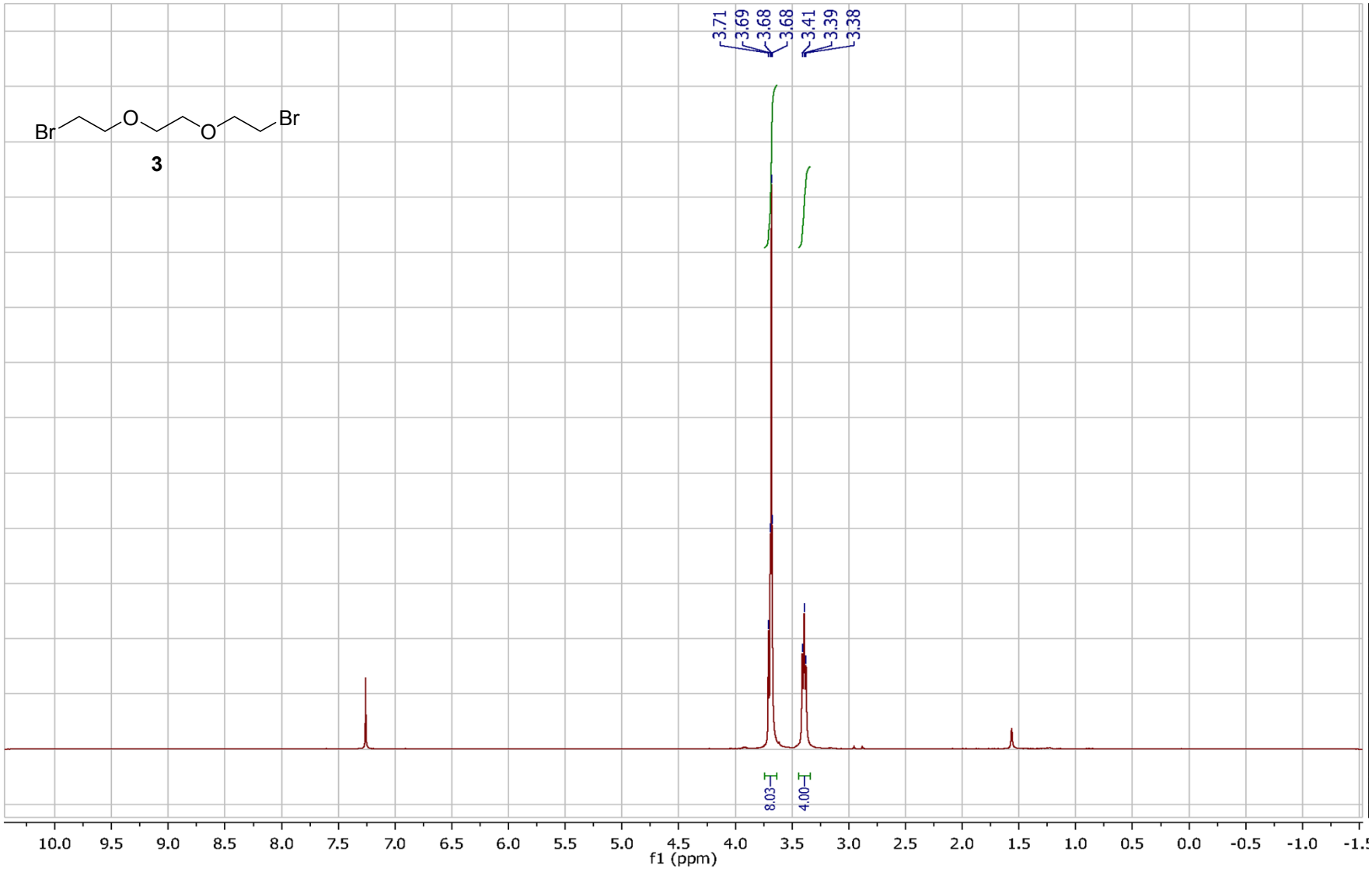
Sequences

Entry	Name	Sequence 5'-3'
1	Poly-A	5'-AAAAAAAAAAAAAAA-Modification-3'
2	Poly-T	5'-TTTTTTTTTTTTTTT- Modification -3'
3	Poly-C	5'-CCCCCCCCCCCCCCC-Modification-3'
5	SCR-15	5'- TGACAGAGAATAGAA – Modification -3'
6	SCR-30	5'- TTCTAATACGACTCACTATAGGTGCGACTA – Modification -3'
7	AS1411	5'- GGTGGTGGTGGTTGTGGTGGTGGTGGTTTT TT -3'- Modification -3'

MALDI data

Oligonucleotide	Calculated mass	Found mass
Poly-A	4991.2	4977.6
Poly-T	4856.1	4842.8
Poly-C	4630.9	4626.3
SCR-15	5013.2	5005.8
SCR-30	9520.1	9525.9
AS1411	10452.6	10447.0

NMR SPECTRA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O
Br
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3.69
3.68
3.68
3.41
3.39
3.38
8.03
4.00
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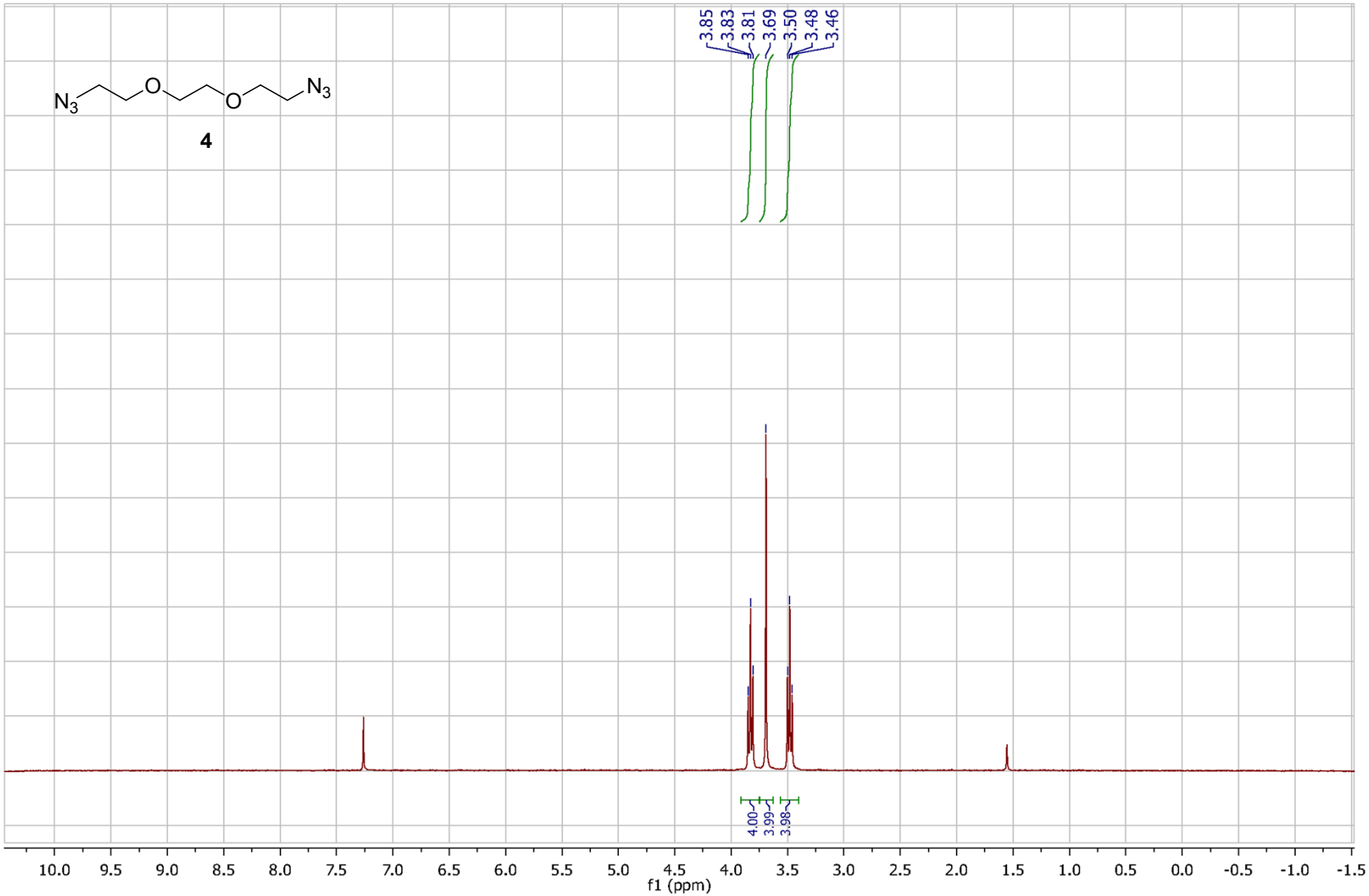
f1 (ppm)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3.48
3.46
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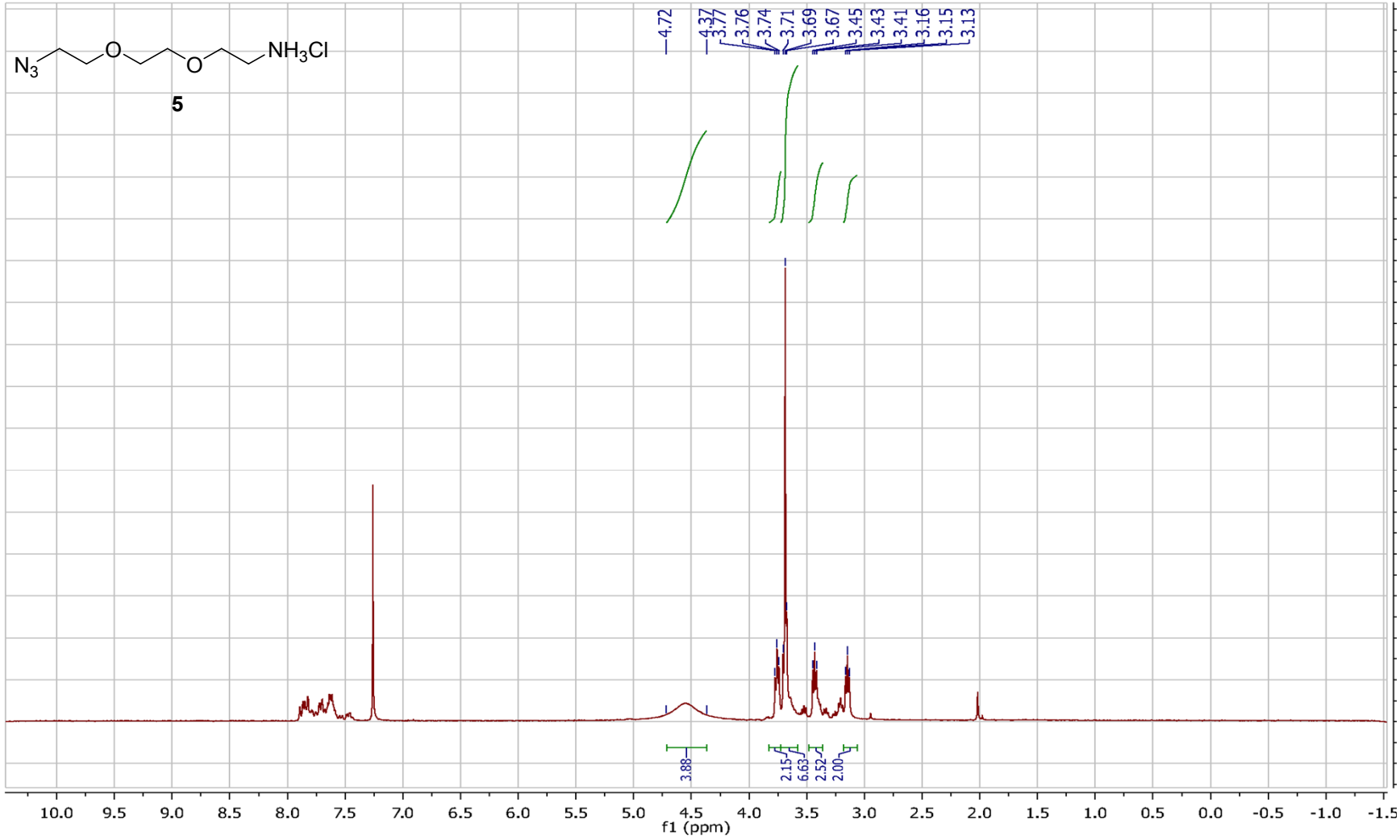
3.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)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3.13
3.88
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2.52
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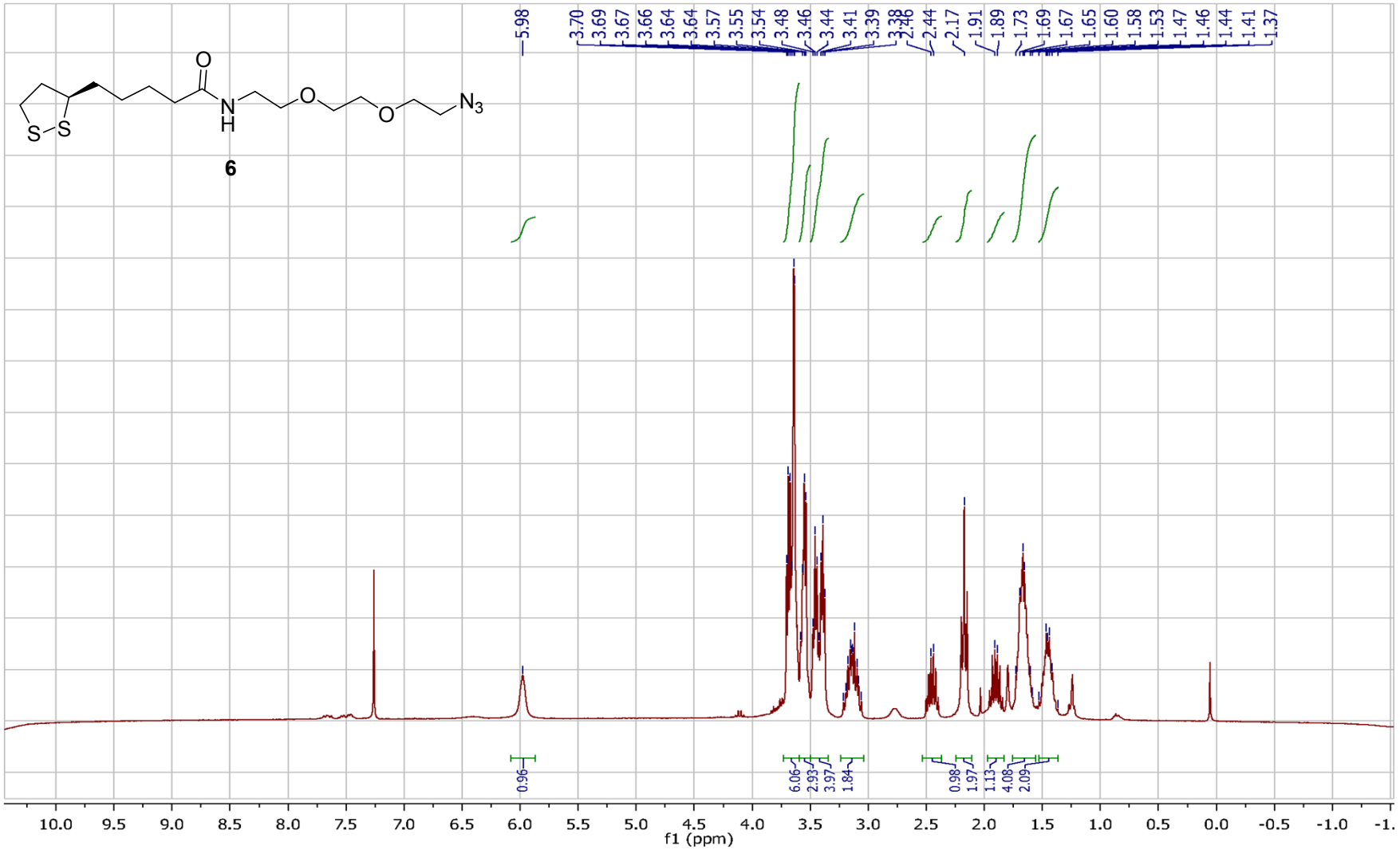
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)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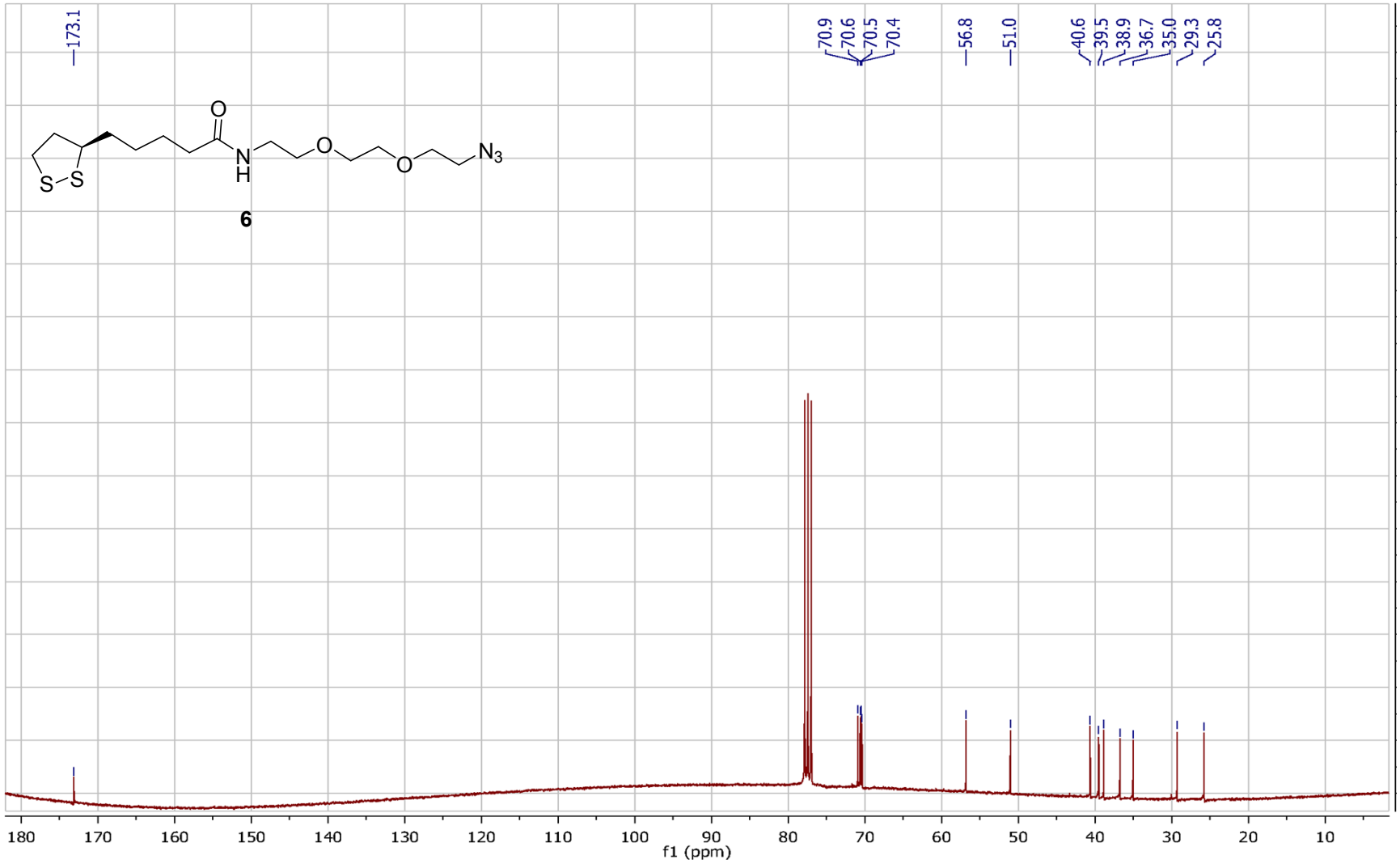
1.89
1.73
1.69
1.67
1.65
1.60
1.58
1.53
1.47
1.46
1.44
1.41
1.37
0.96
6.06
2.93
3.97
1.84
0.98
1.97
1.13
4.08
2.09
f1 (ppm)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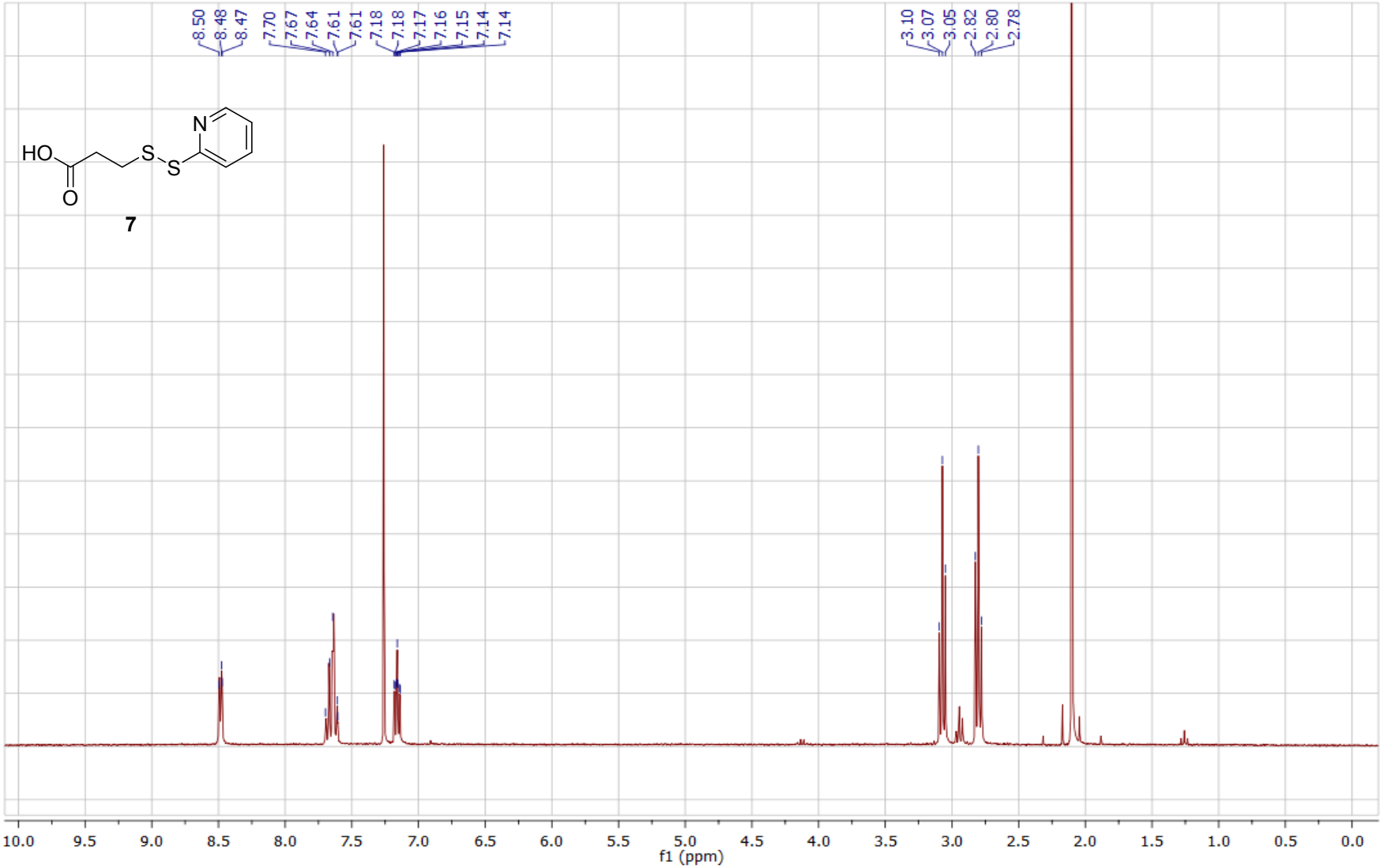
70.6
70.5
70.4
56.8
51.0
40.6
39.5
38.9
36.7
35.0
29.3
25.8
O
N
H
O
O
N_3
S
S
6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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8.48
8.47
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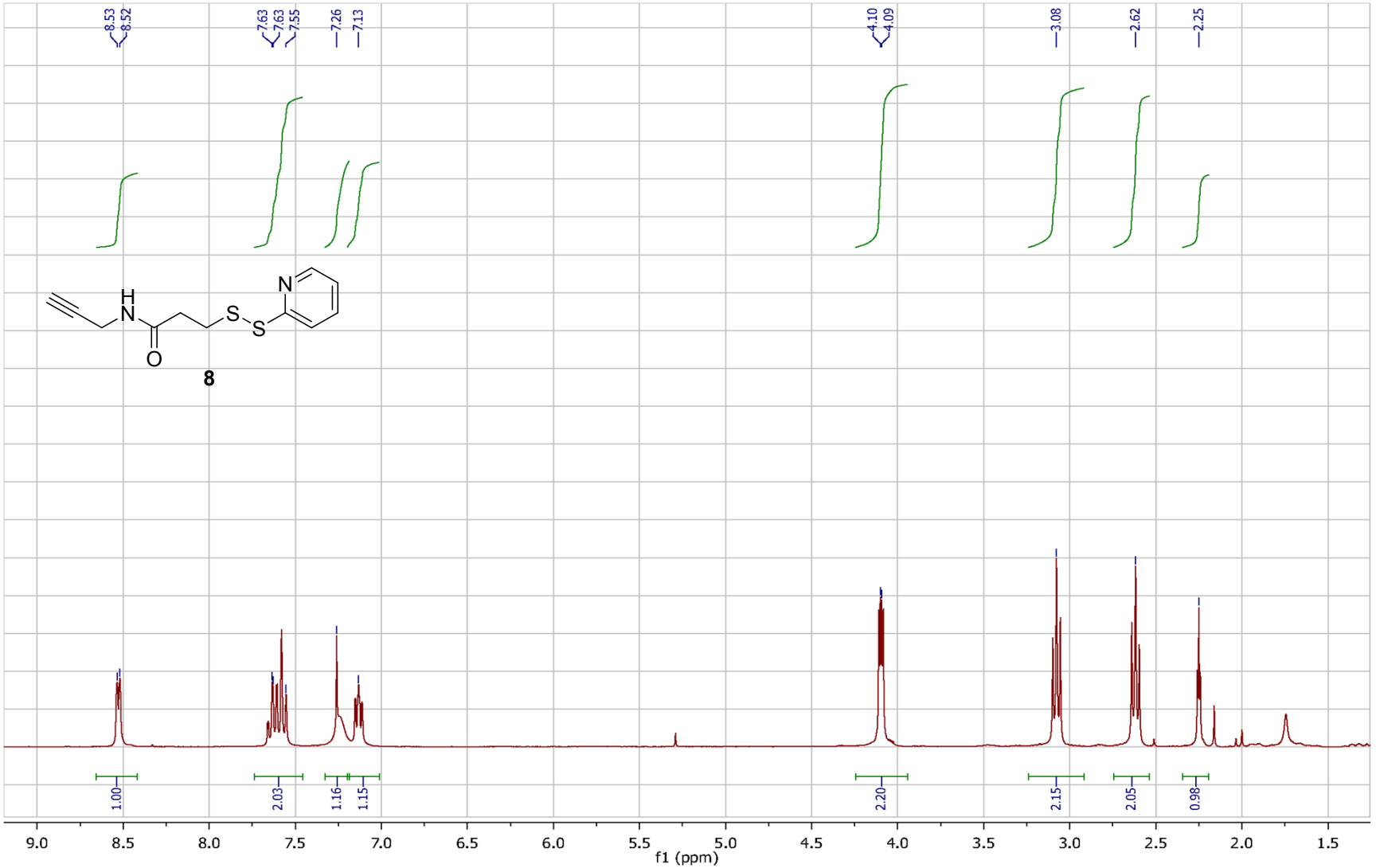
7.61
7.61
7.18
7.18
7.17
7.16
7.15
7.14
7.14
3.10
3.07
3.05
2.82
2.80
2.78
HO
O
S
S
N
7
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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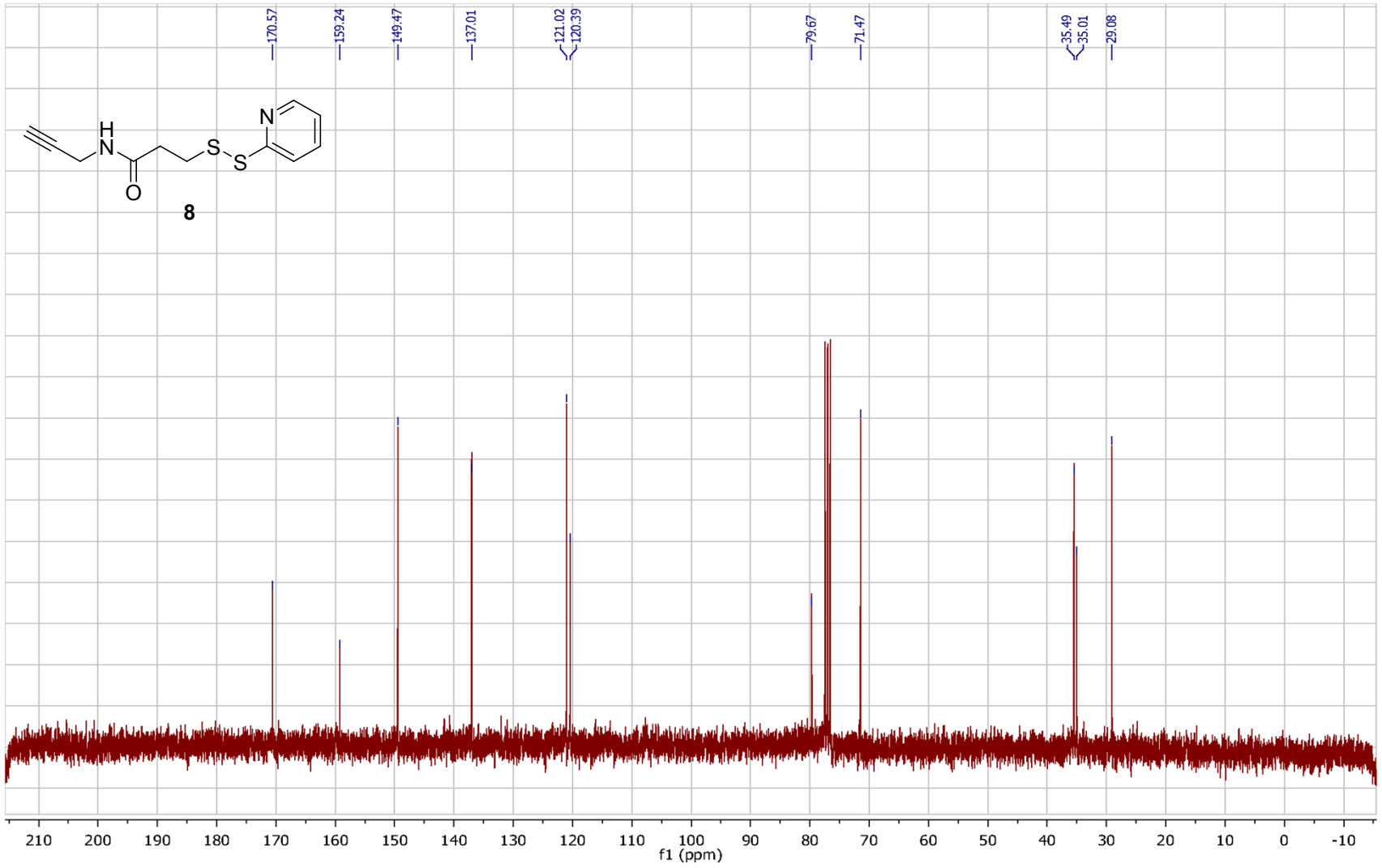
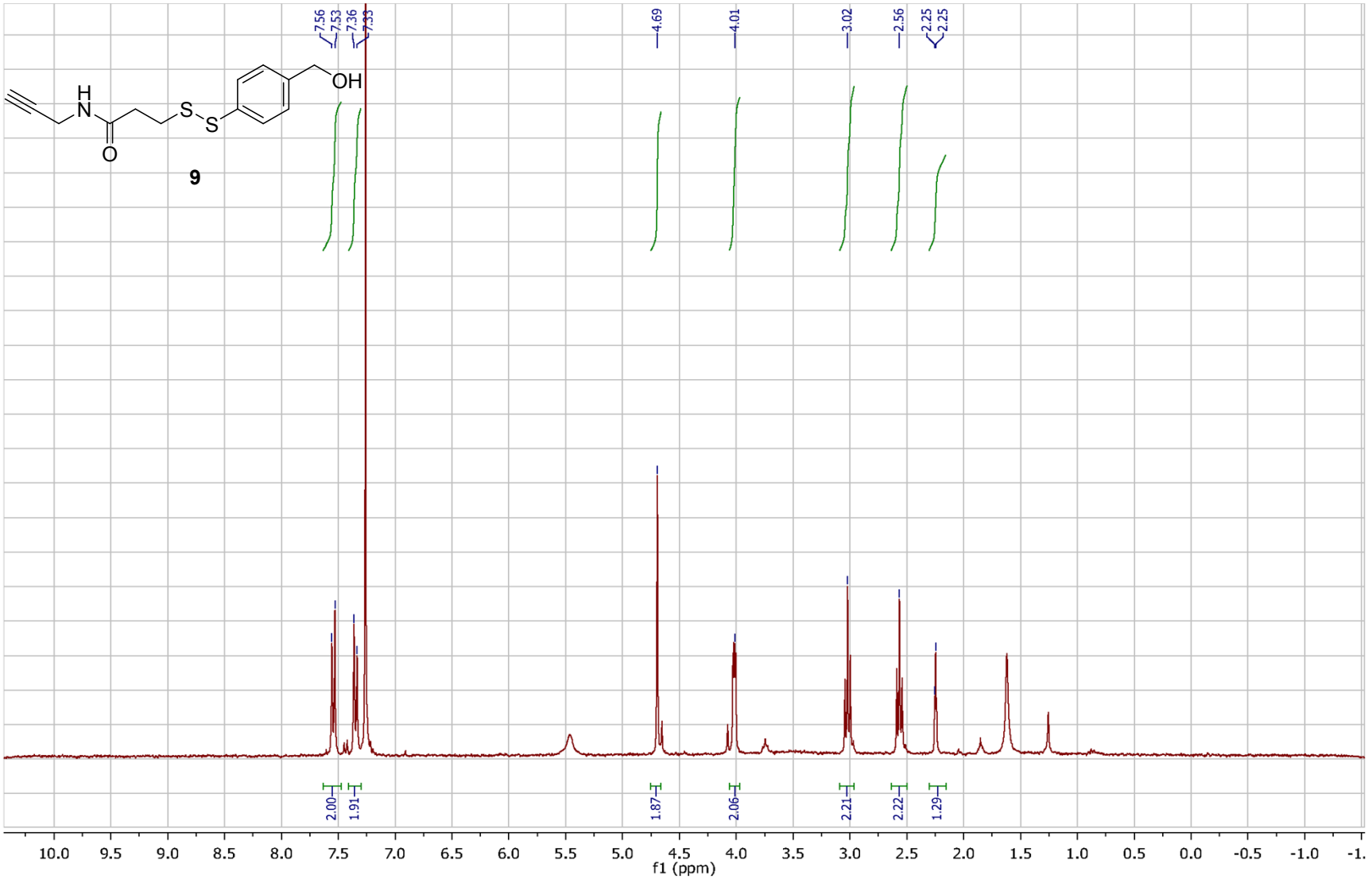
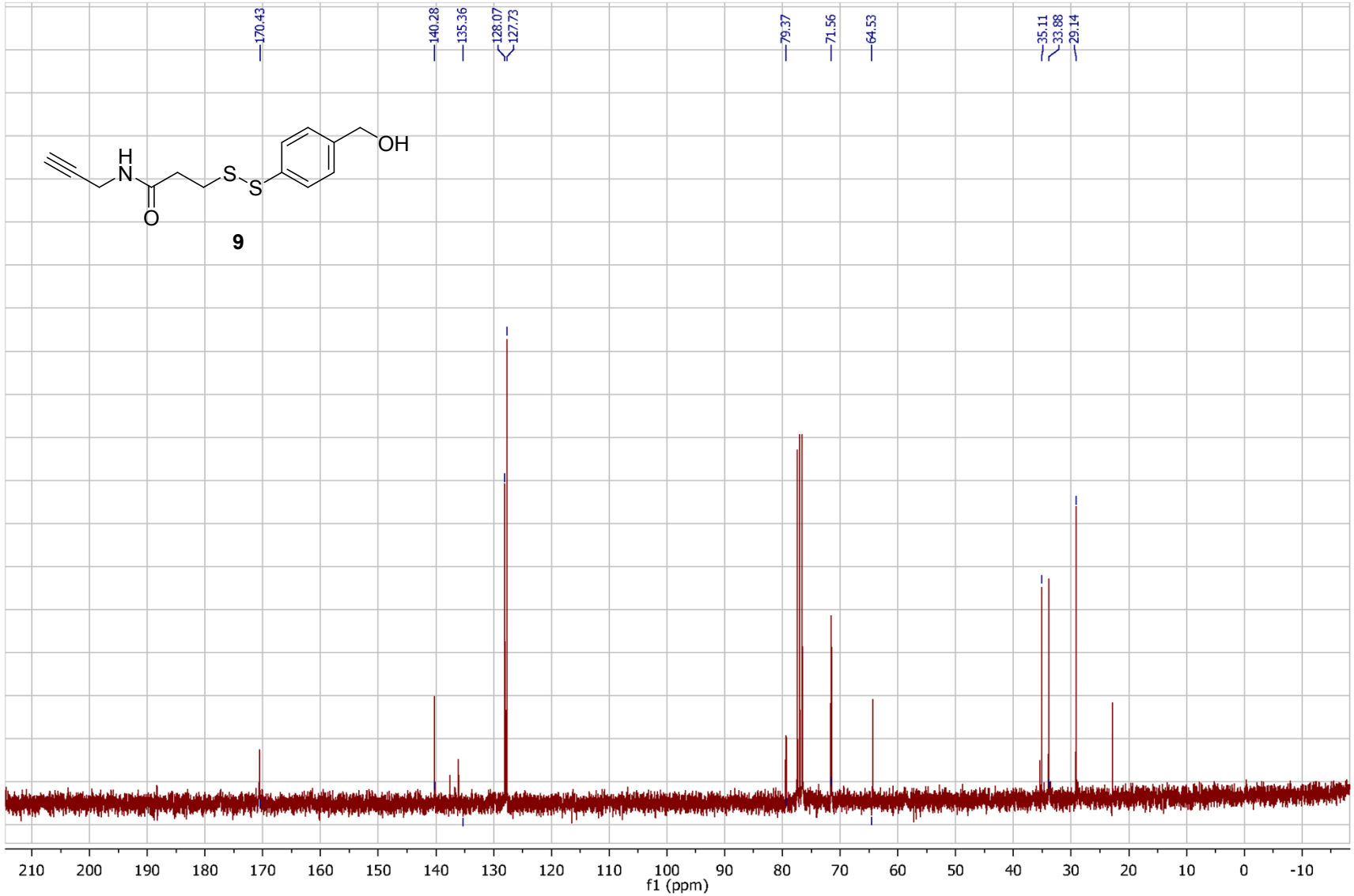
8.52
7.63
7.63
7.55
7.26
7.13
4.10
4.09
3.08
2.62
2.25
H
N
O
S
S
N
8
1.00
2.03
1.16
1.15
2.20
2.15
2.05
0.98
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


170.57
159.24
149.47
137.01
121.02
120.39
79.67
71.47
35.49
35.01
29.08
H
N
O
S
S
N
8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.56
7.53
7.36
7.33
4.69
4.01
3.02
2.56
2.25
2.25
OH
H
N
O
S
S
9
2.00
1.91
1.87
2.06
2.21
2.22
1.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.
f1 (ppm)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135.36
128.07
127.73
79.37
71.56
64.53
35.11
33.88
29.14
OH
H
N
O
S
S
9
210
200
190
180
170
160
150
140
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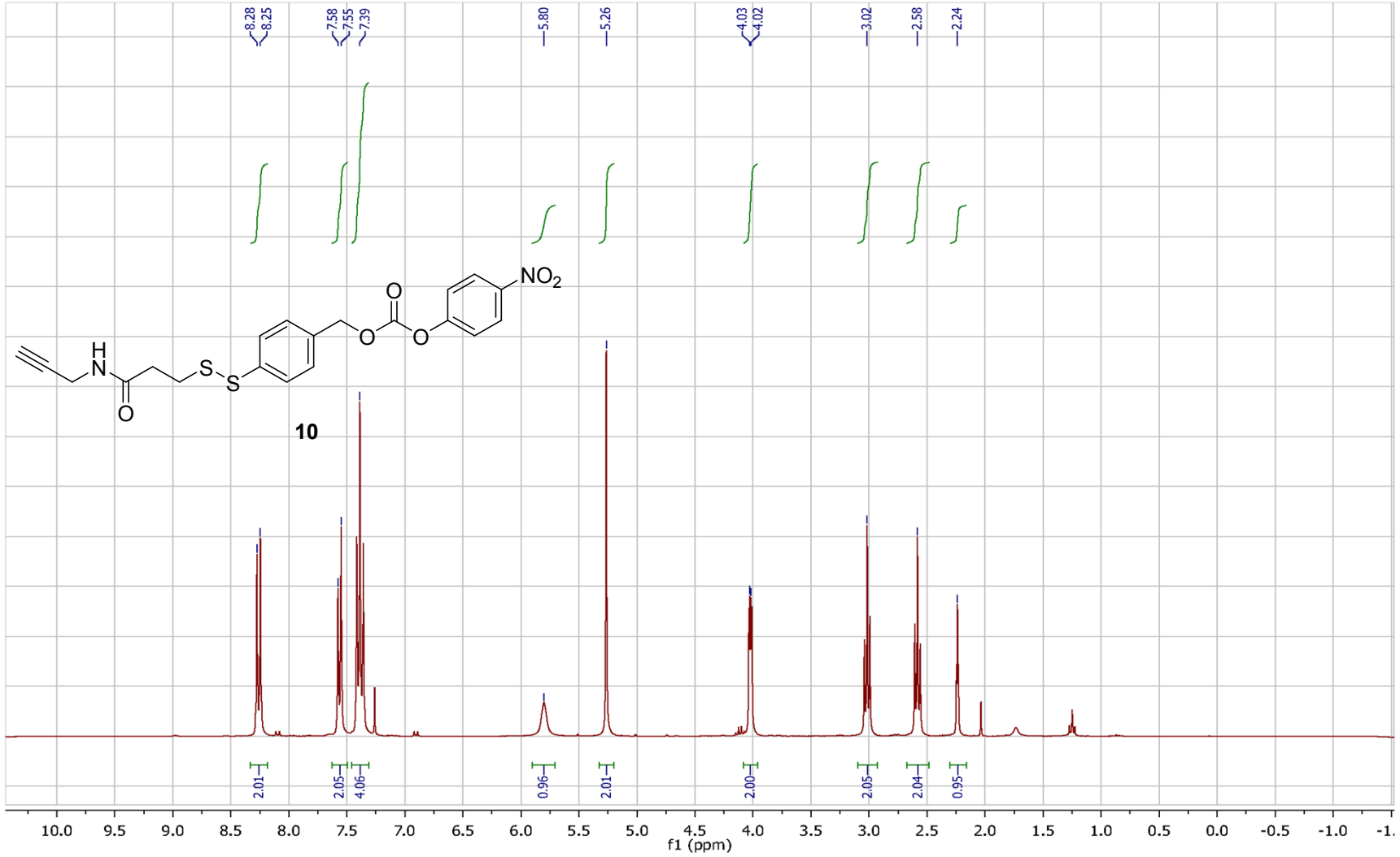
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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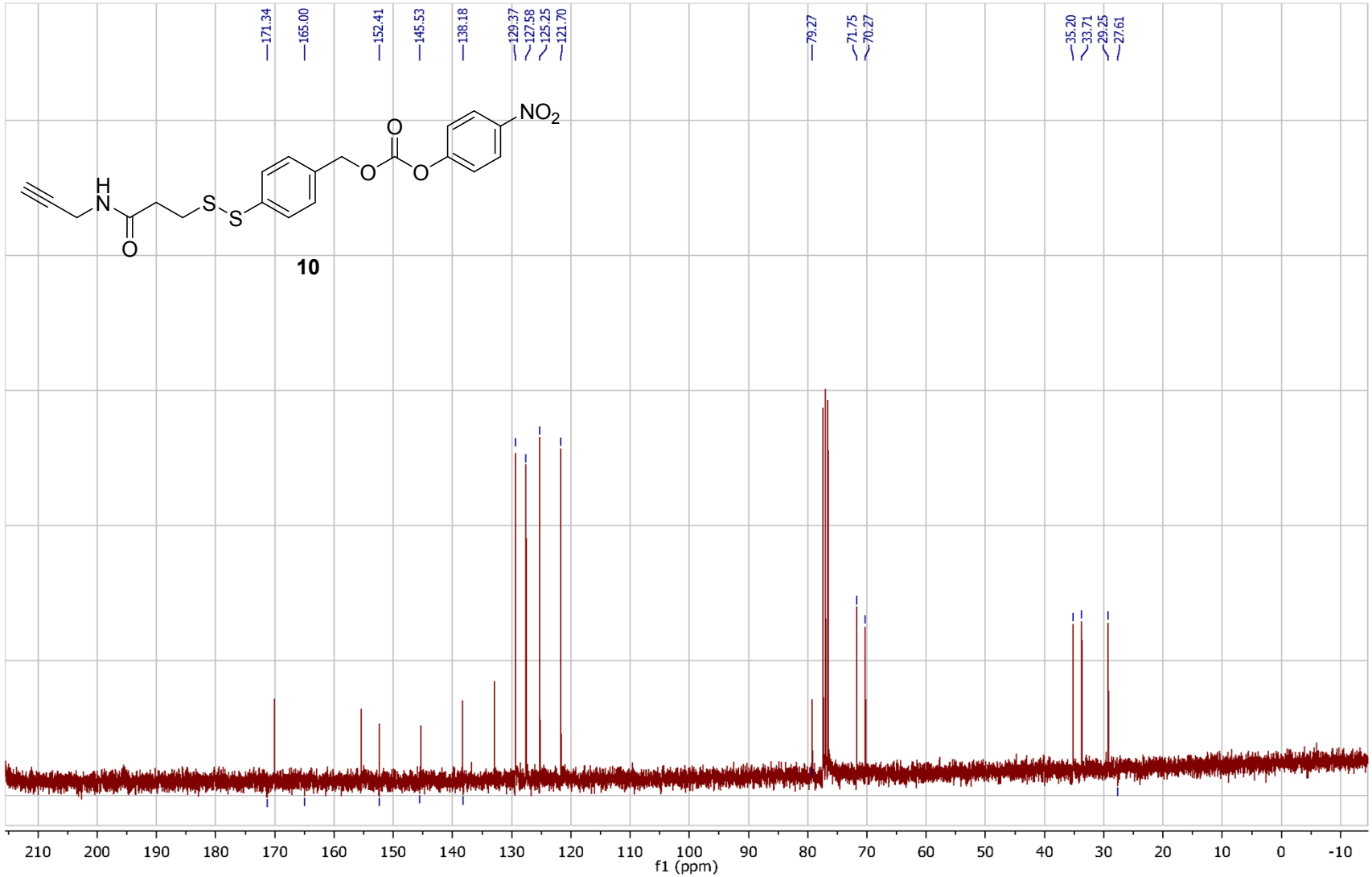
8.25
7.58
7.55
7.39
5.80
5.26
4.03
4.02
3.02
2.58
2.24
NO2
O
O
O
H
N
O
S
S
10
2.01
2.05
4.06
0.96
2.01
2.00
2.05
2.04
0.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.
f1 (ppm)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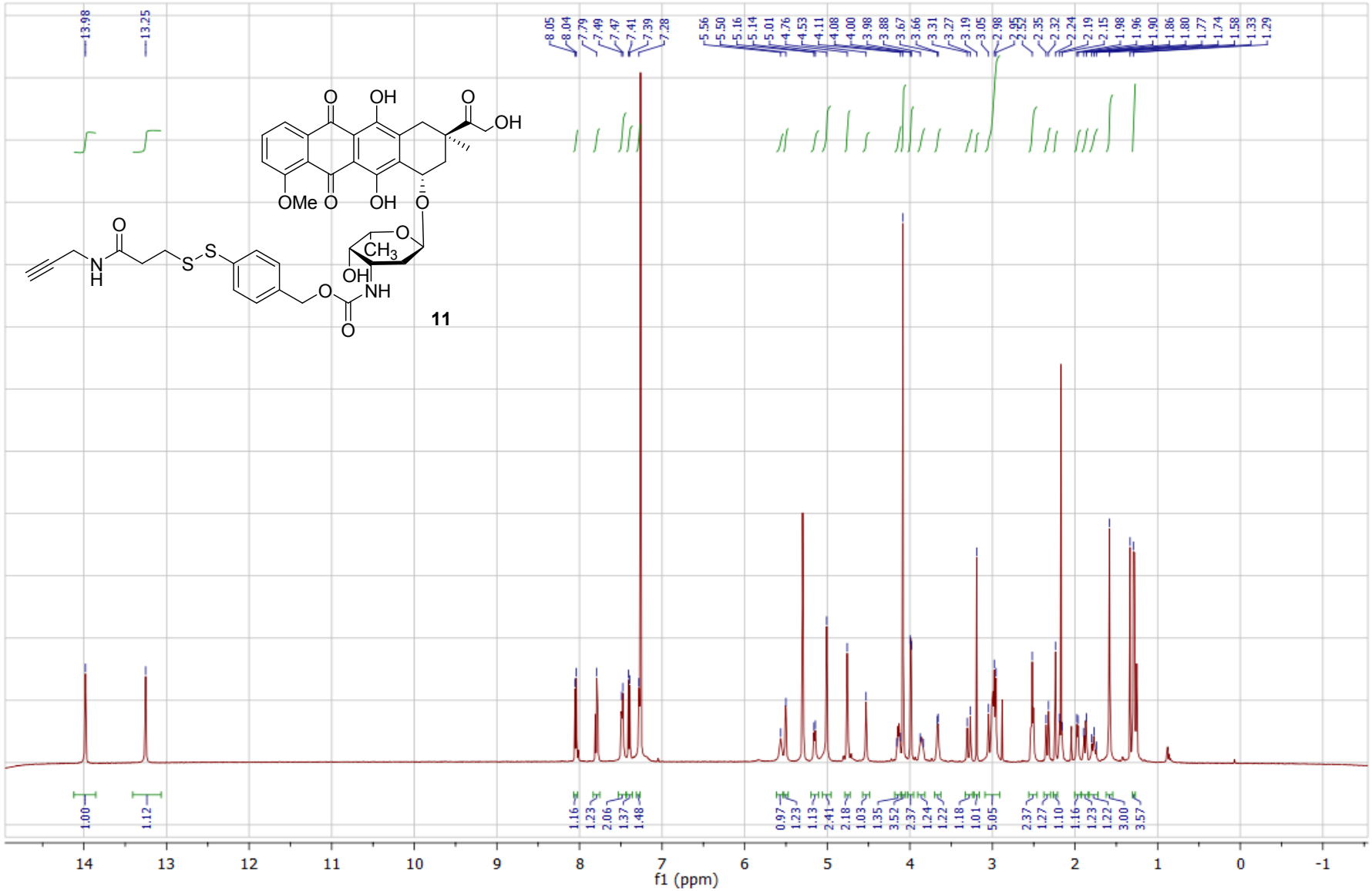
165.00
152.41
145.53
138.18
129.37
127.58
125.25
121.70
79.27
71.75
70.27
35.20
33.71
29.25
27.61
NO2
O
O
O
H
N
O
S
S
10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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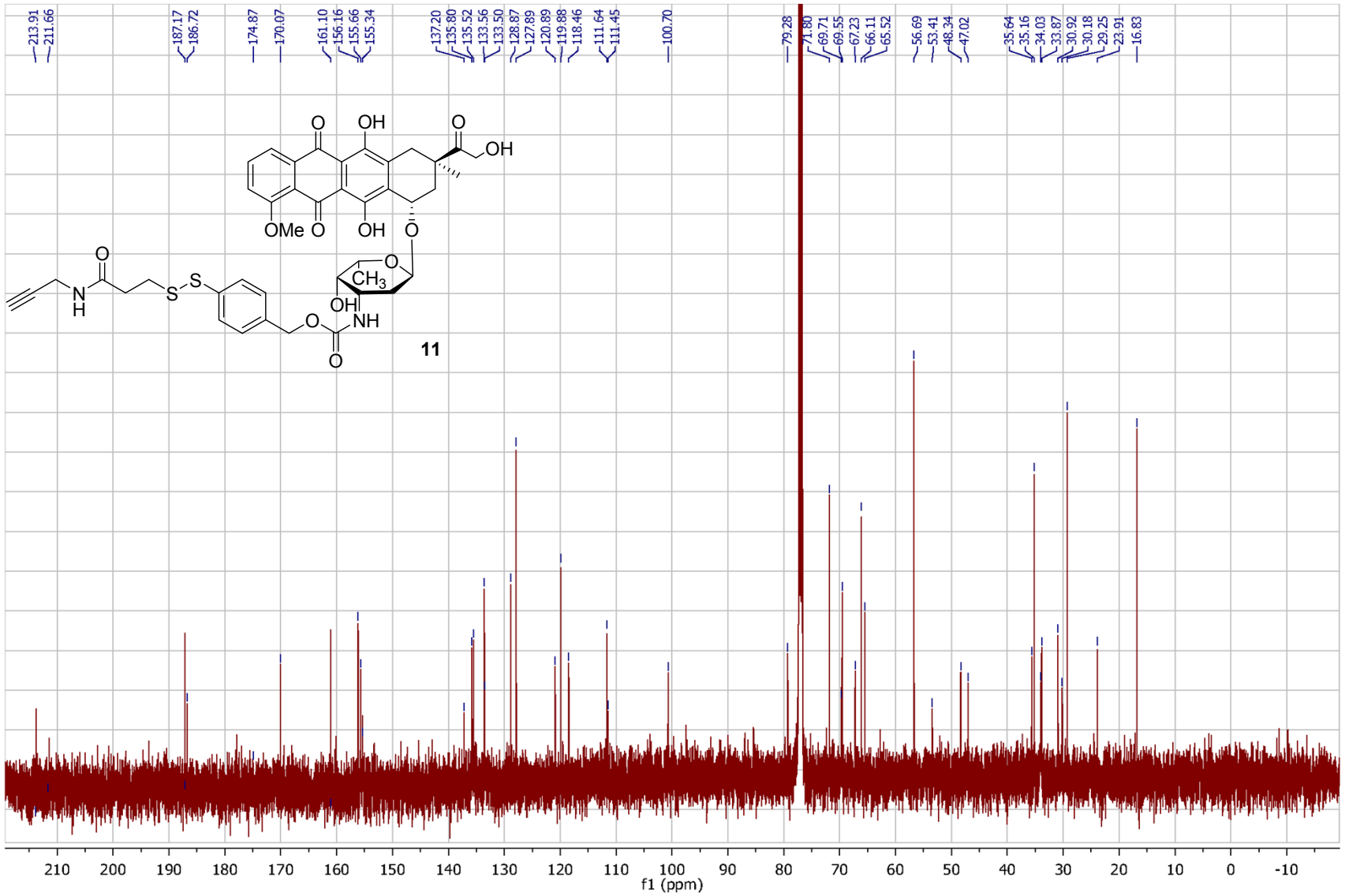
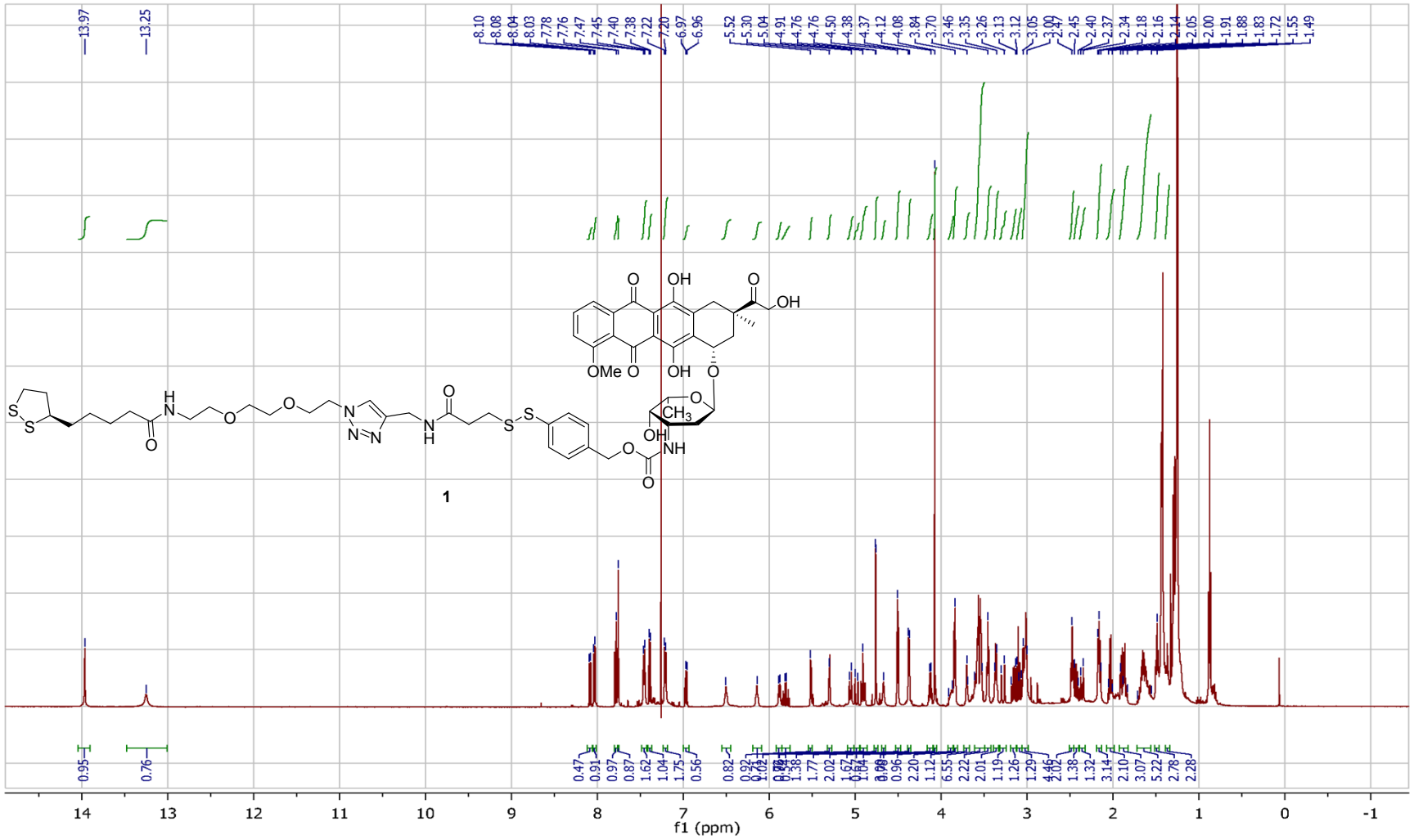
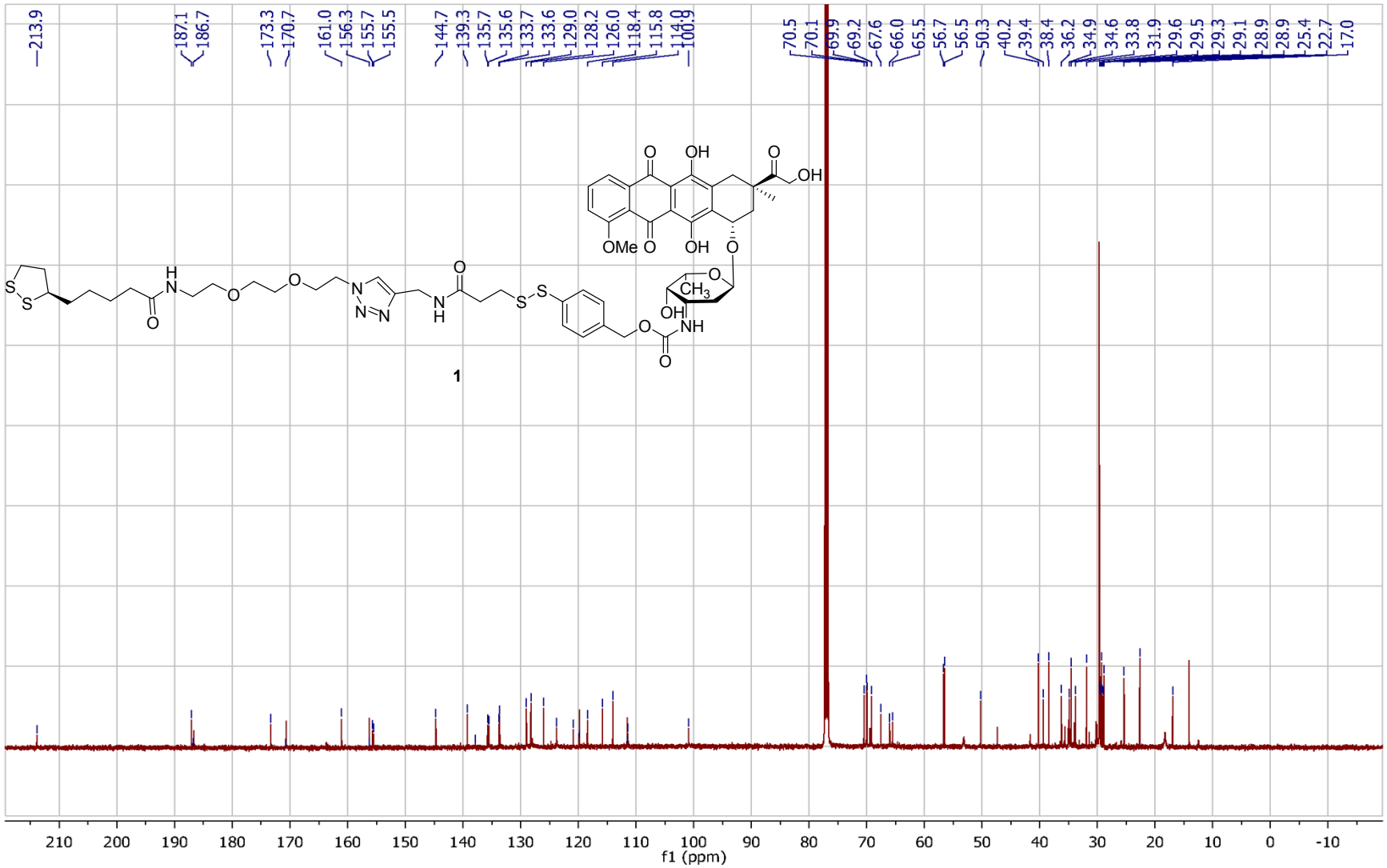
7.79
7.49
7.47
7.41
7.39
7.28
5.56
5.50
5.16
5.14
5.01
4.76
4.53
4.11
4.08
4.00
3.98
3.88
3.67
3.66
3.31
3.27
3.19
3.05
2.98
2.95
2.52
2.35
2.32
2.24
2.19
2.15
1.98
1.96
1.90
1.86
1.80
1.77
1.74
1.58
1.33
1.29
OH
O
OH
OMe
O
OH
O
O
CH3
OH
NH
O
N
H
O
S
S
O
11
1.00
1.12
1.16
1.23
2.06
1.37
1.48
0.97
1.23
1.13
2.41
2.18
1.03
1.35
3.52
2.37
1.24
1.22
1.18
1.01
5.05
2.37
1.27
1.10
1.16
1.23
1.22
3.00
3.57
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


213.91
211.66
187.17
186.72
174.87
170.07
161.10
156.16
155.66
155.34
137.20
135.80
135.52
133.56
133.50
128.87
127.89
120.89
119.88
118.46
111.64
111.45
100.70
79.28
71.80
69.71
69.55
67.23
66.11
65.52
56.69
53.41
48.34
47.02
35.64
35.16
34.03
33.87
30.92
30.18
29.25
23.91
16.83
11
f1 (ppm)


f1 (ppm)
1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173.3
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161.0
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155.7
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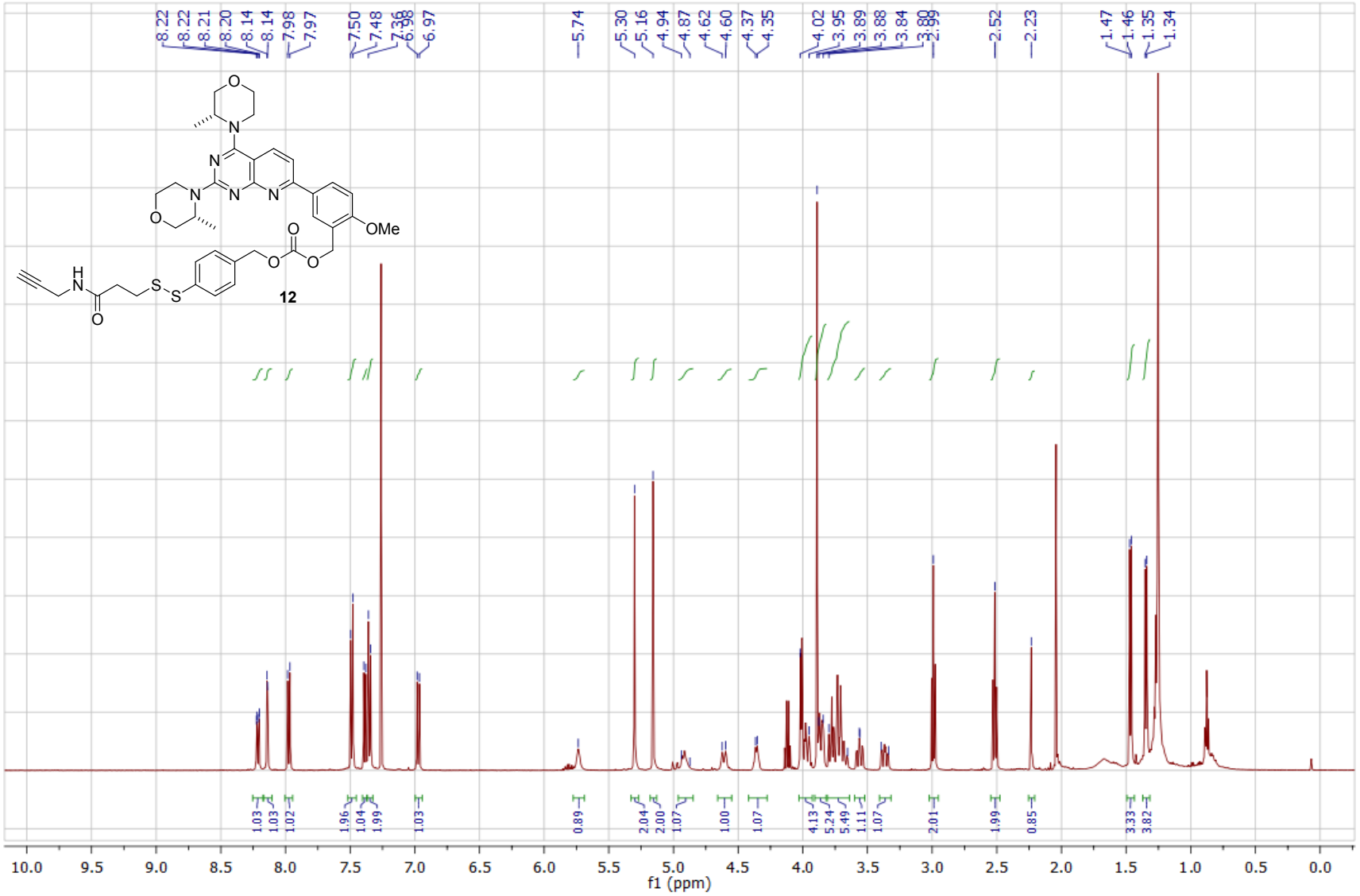
144.7
139.3
135.7
135.6
133.7
133.6
129.0
128.2
126.0
118.4
115.8
114.0
100.9
70.5
70.1
69.9
69.2
67.6
66.0
65.5
56.7
56.5
50.3
40.2
39.4
38.4
36.2
34.9
34.6
33.8
31.9
29.6
29.5
29.3
29.1
28.9
28.9
25.4
22.7
17.0
OMe
OH
NH
CH3
1
f1 (ppm)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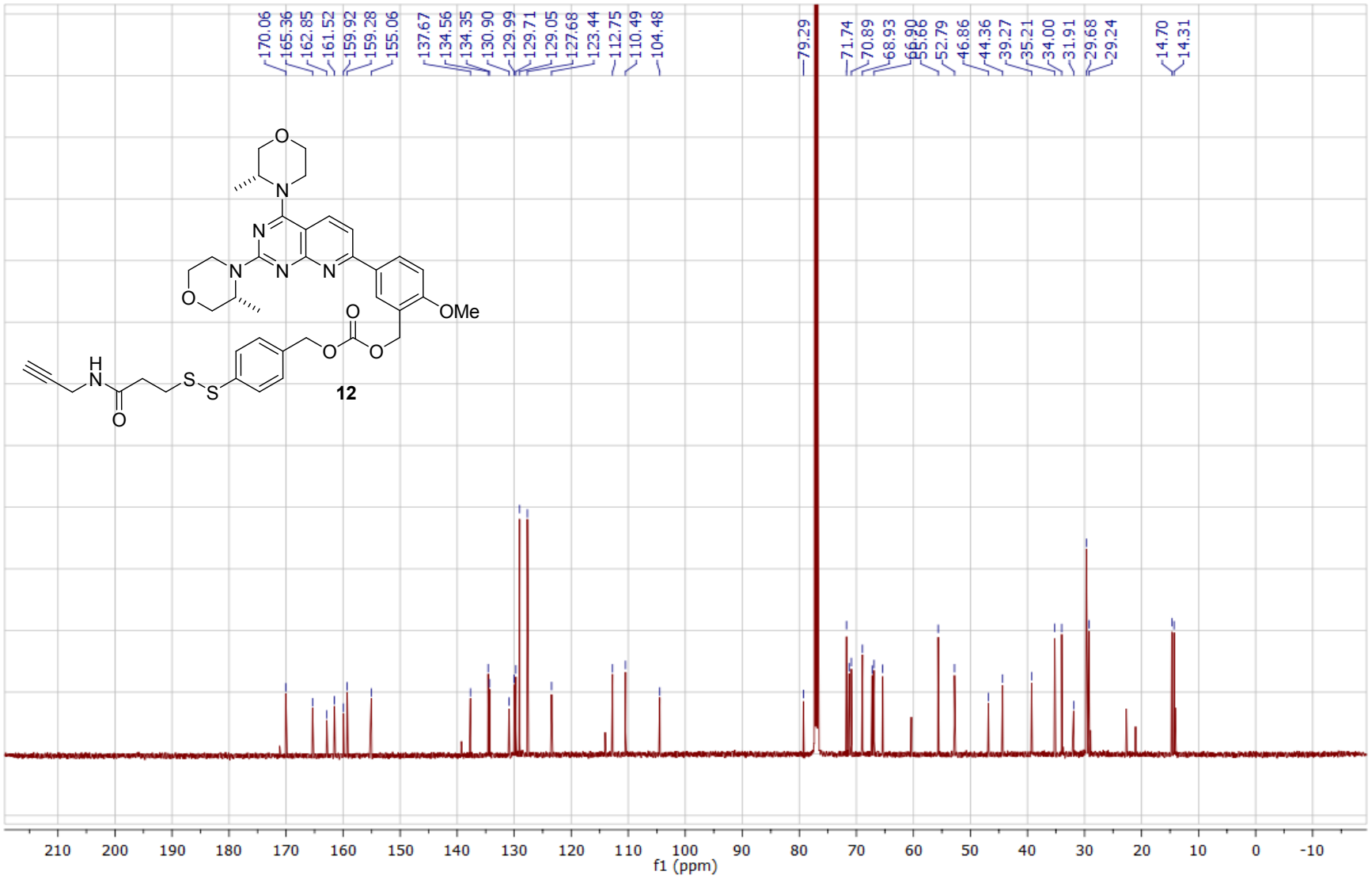
8.22
8.21
8.20
8.14
8.14
7.98
7.97
7.50
7.48
7.36
6.98
6.97
5.74
5.30
5.16
4.94
4.87
4.62
4.60
4.37
4.35
4.02
3.95
3.89
3.88
3.84
3.80
2.99
2.52
2.23
1.47
1.46
1.35
1.34
OMe
12
1.03
1.03
1.02
1.96
1.04
1.99
1.03
0.89
2.04
2.00
1.07
1.00
1.07
4.13
5.24
5.49
1.11
1.07
2.01
1.99
0.85
3.33
3.82
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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165.36
162.85
161.52
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159.28
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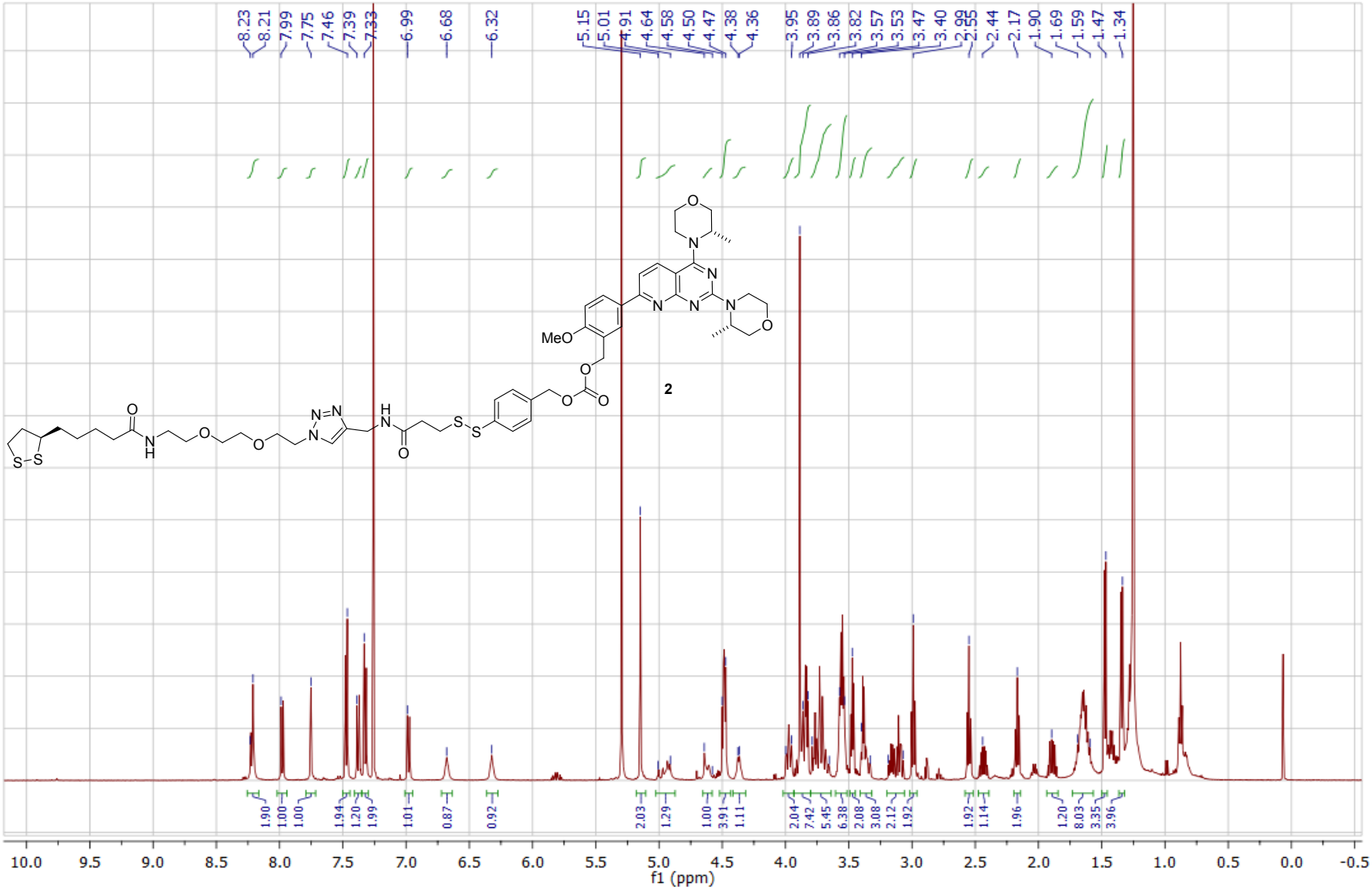
137.67
134.56
134.35
130.90
129.99
129.71
129.05
127.68
123.44
112.75
110.49
104.48
79.29
71.74
70.89
68.93
66.90
55.66
52.79
46.86
44.36
39.27
35.21
34.00
31.91
29.68
29.24
14.70
14.31
OMe
12
f1 (ppm)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7.39
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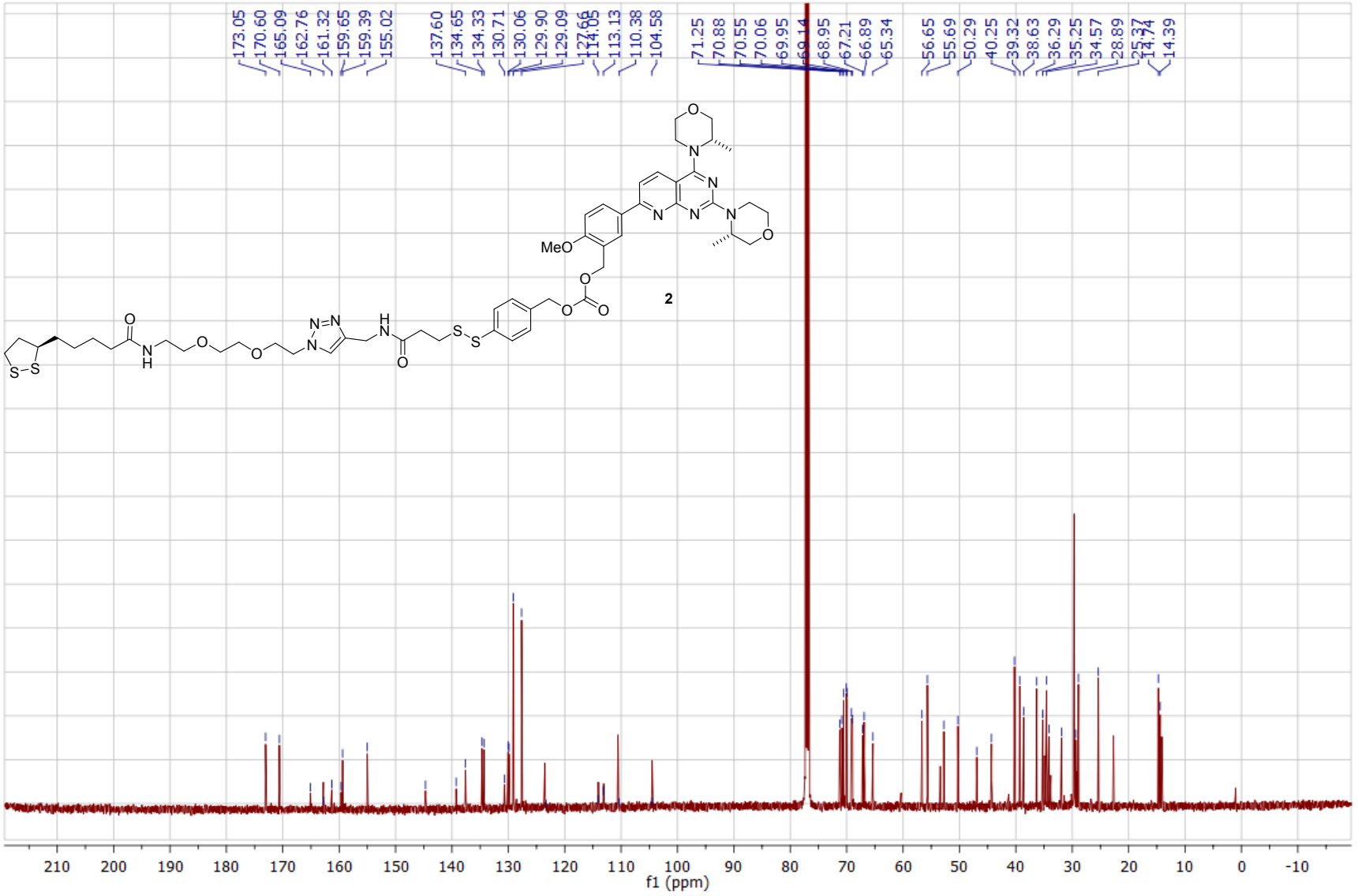
6.99
6.68
6.32
5.15
5.01
4.91
4.64
4.58
4.50
4.47
4.38
4.36
3.95
3.89
3.86
3.82
3.57
3.53
3.47
3.40
2.99
2.55
2.44
2.17
1.90
1.69
1.59
1.47
1.34
MeO
2
1.90
1.00
1.00
1.94
1.20
1.99
1.01
0.87
0.92
2.03
1.29
1.00
3.91
1.11
2.04
7.42
5.45
6.38
2.08
3.08
2.12
1.92
1.92
1.14
1.96
1.20
8.03
3.35
3.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


173.05
170.60
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162.76
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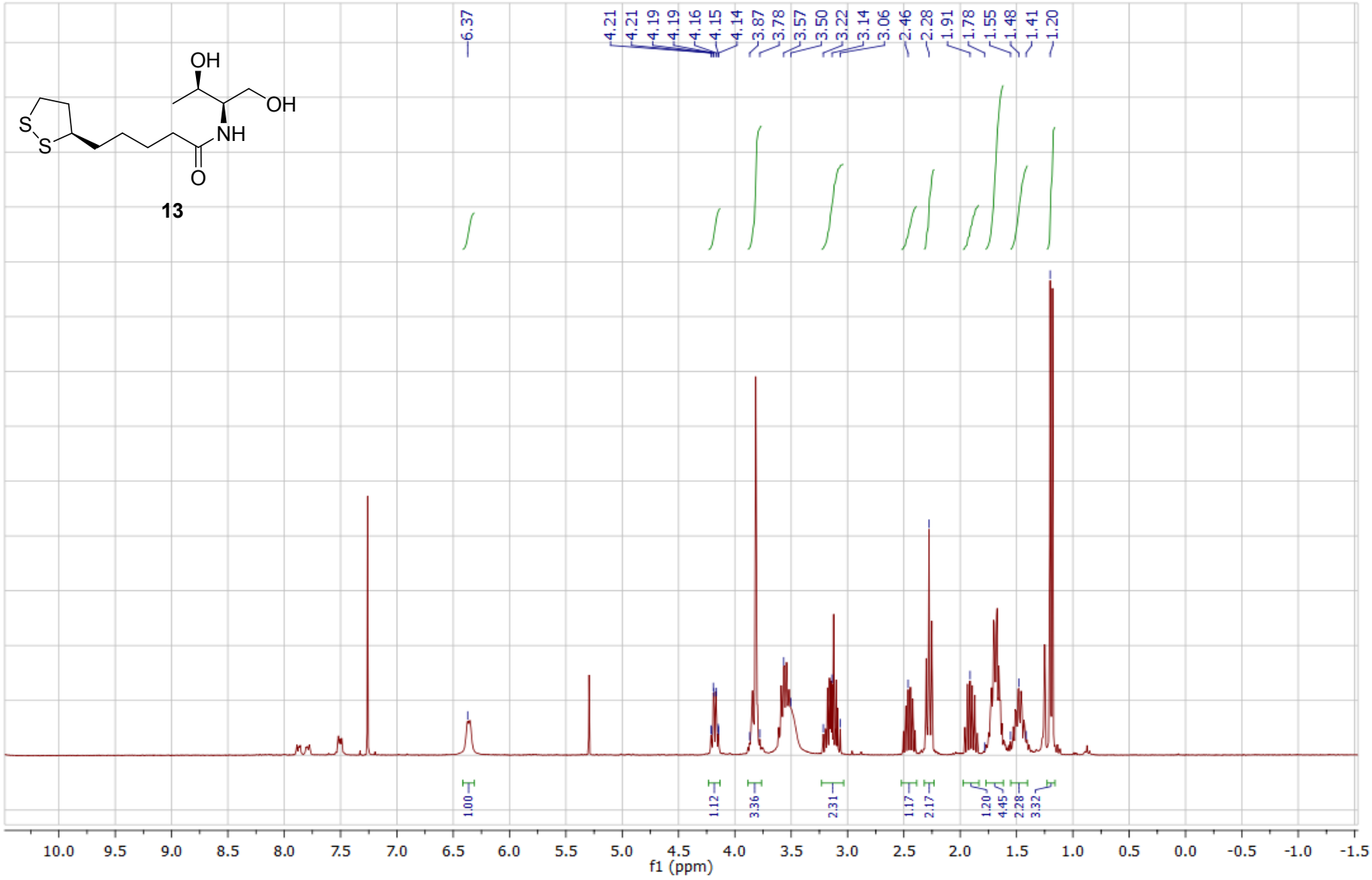
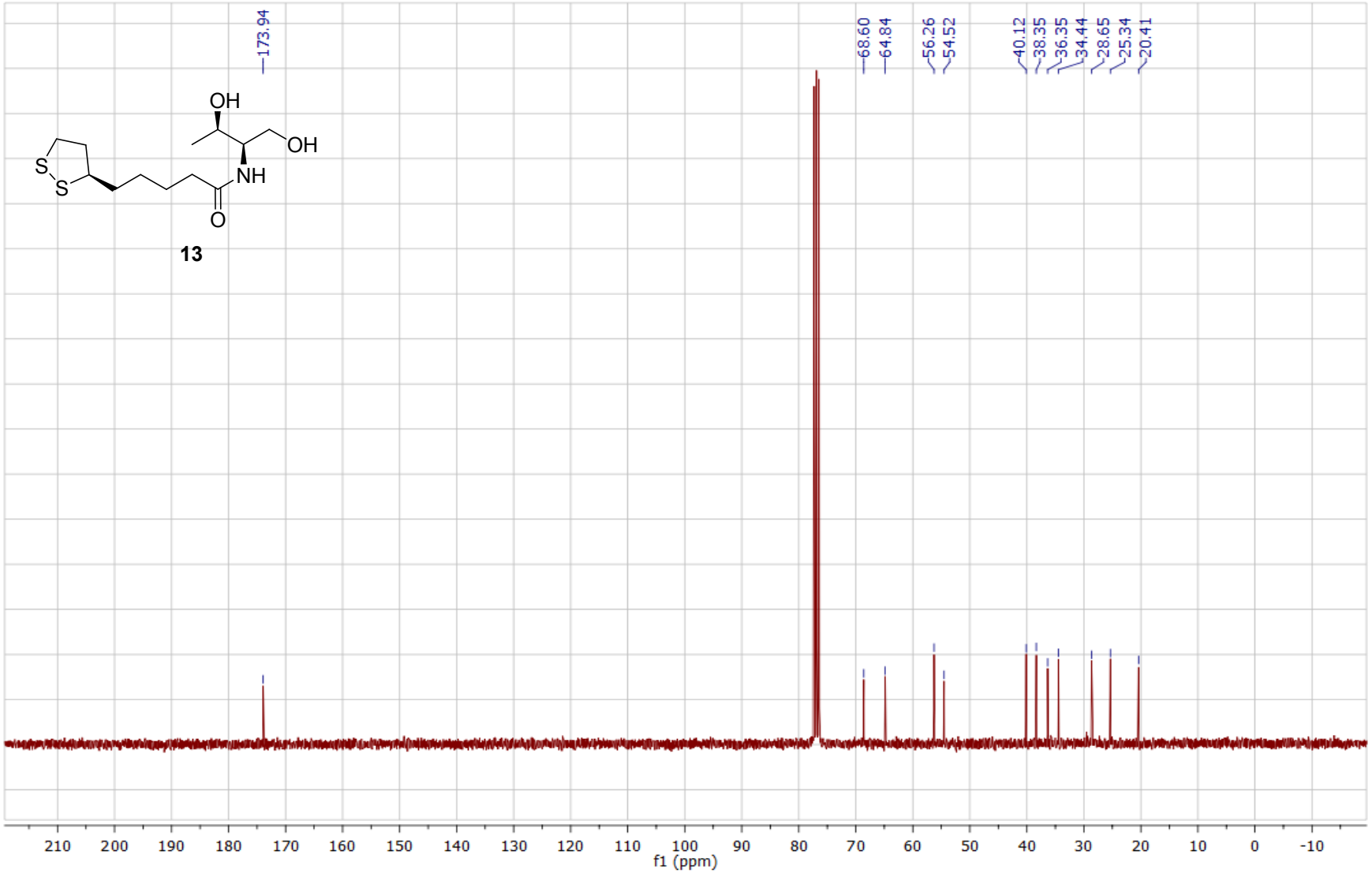
159.65
159.39
155.02
137.60
134.65
134.33
130.71
130.06
129.90
129.09
127.66
114.05
113.13
110.38
104.58
71.25
70.88
70.55
70.06
69.95
69.14
68.95
67.21
66.89
65.34
56.65
55.69
50.29
40.25
39.32
38.63
36.29
35.25
34.57
28.89
25.37
14.74
14.39
MeO
2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
OH
NH
O
S
S
13
6.37
4.21
4.21
4.19
4.19
4.16
4.15
4.14
3.87
3.78
3.57
3.50
3.22
3.14
3.06
2.46
2.28
1.91
1.78
1.55
1.48
1.41
1.20
1.00
1.12
3.36
2.31
1.17
2.17
1.20
4.45
2.28
3.32
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
f1 (ppm)


173.94
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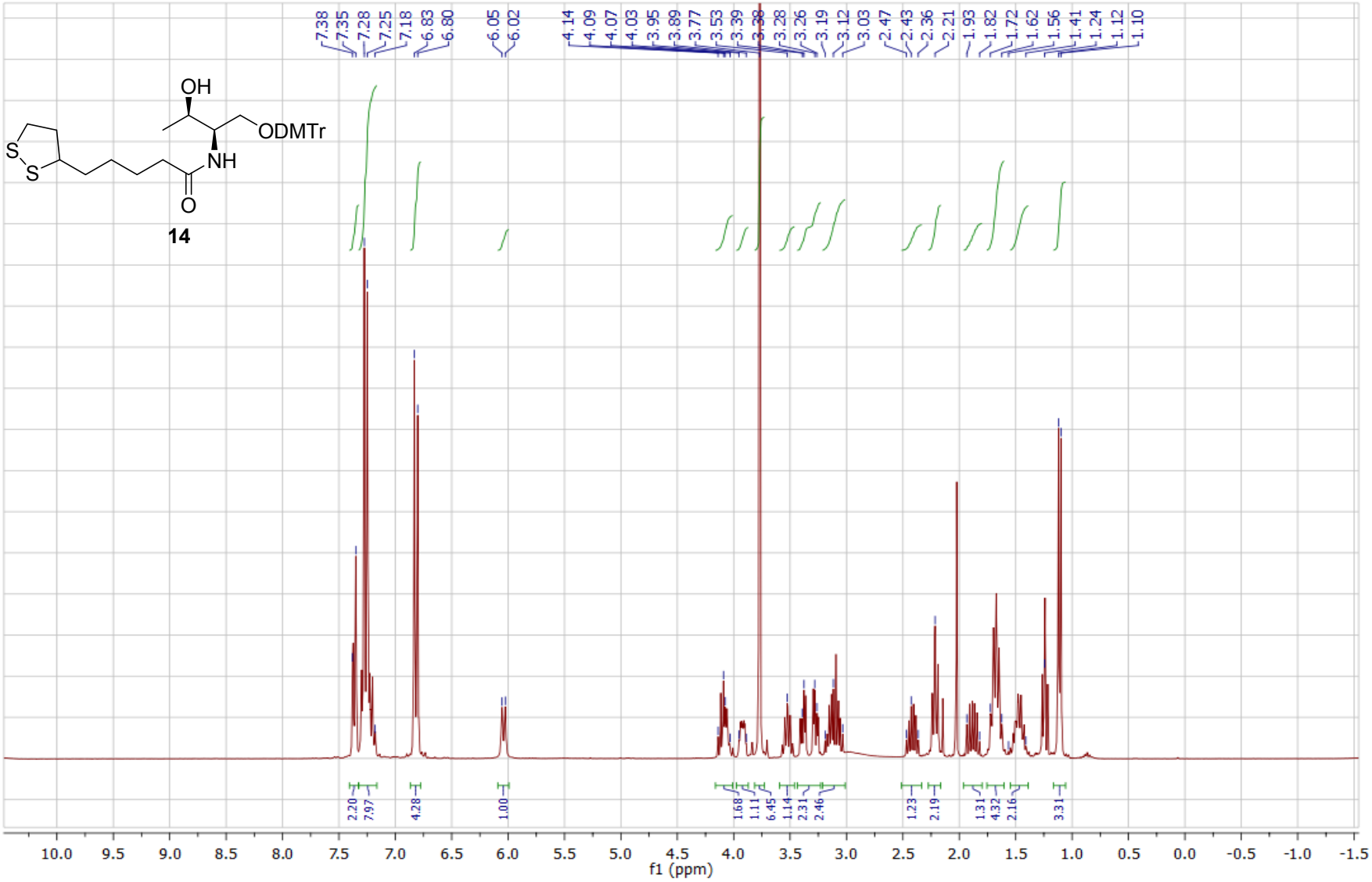
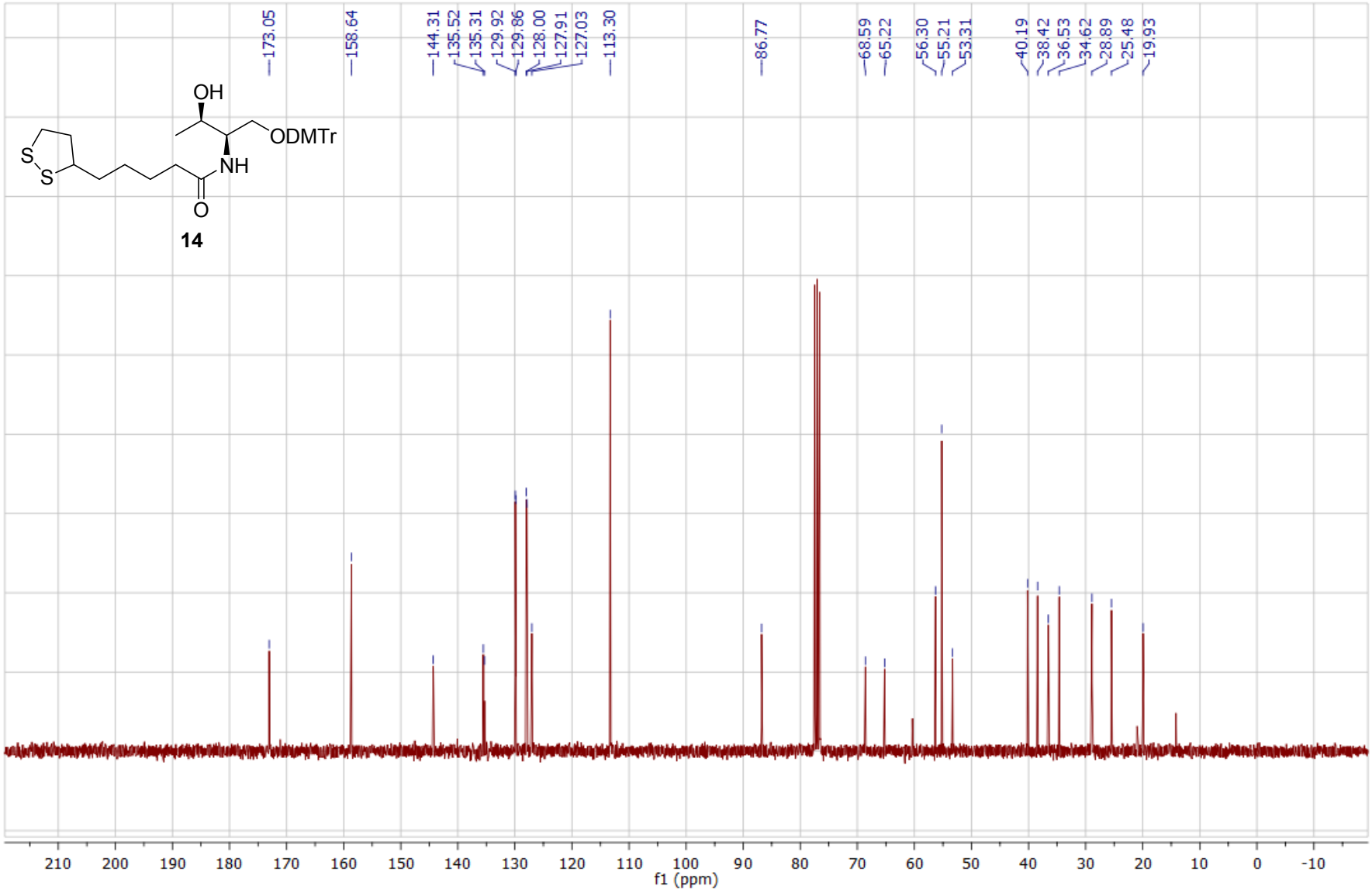
64.84
56.26
54.52
40.12
38.35
36.35
34.44
28.65
25.34
20.41
OH
OH
NH
S
S
O
13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
ODMTr
NH
O
S
S
14
7.38
7.35
7.28
7.25
7.18
6.83
6.80
6.05
6.02
4.14
4.09
4.07
4.03
3.95
3.89
3.77
3.53
3.39
3.38
3.28
3.26
3.19
3.12
3.03
2.47
2.43
2.36
2.21
1.93
1.82
1.72
1.62
1.56
1.41
1.24
1.12
1.10
2.20
7.97
4.28
1.00
1.68
1.11
6.45
1.14
2.31
2.46
1.23
2.19
1.31
4.32
2.16
3.31
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
f1 (ppm)


173.05
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128.00
127.91
127.03
113.30
86.77
68.59
65.22
56.30
55.21
53.31
40.19
38.42
36.53
34.62
28.89
25.48
19.93
OH
ODMTr
NH
S
S
O
14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)