Supporting Information For

The Development of a One Pot, Regiocontrolled, Three-Component Reaction for the Synthesis of Thieno[2,3-c]pyrroles

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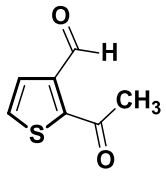
Context

General information:

Methanol (ACS grade), ethyl acetate (ACS grade, and HPLC grade), hexane (ACS grade), acetonitrile (ACS grade), chloroform (ACS grade) and acetone (ACS grade) were purchased from Fisher Scientific and used without further purification. Dichloromethane and benzene were purified by passing over activated alumina. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using Whatman precoated silica gel plates. Flash column chromatography was performed over ultra pure silica gel (230-400 mesh) from Silicycle. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III 500 MHz spectrometers using residual solvent peaks as an internal standard.

Optical rotations were measured with JASCO DIP-1000 digital polarimeter, using the sodium D line. Mass spectra were recorded with Agilent 6210 LC-TOF; API-ES, POS, SCAN, 70, with methanol or dichloromethane as the eluting solvent. Melting points were measured with Sigma-Aldrich MEL-TEMP 3.0 capillary melting point apparatus.

Synthesis and Characterization of Starting Materials 3a and 3b:



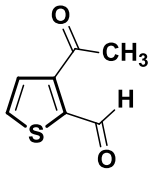
3a

Compound 3a. A flask equipped with a Dean-Stark trap was charged with a solution of thiophene-3-carboxaldehyde (1 eq., 4.2 mL, 45 mmol), ethylene glycol (5 eq., 12.6 mL, 225 mmol), and *p*-toluenesulfonic acid (0.01 eq., 85.6 mg, 0.45 mmol) in benzene (50 mL). The reaction mixture was refluxed for 4 h, cooled to RT, and washed with $NaHCO_3$ (saturated solution, 25 mL). The organic layer was collected and aqueous layer extracted with EtOAc (3x10 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was used in the next step without further purification.

To a flask charged with the resulting 2-(thiophen-3-yl)-1,3-dioxolane (1 eq., 45 mmol) in THF (50 mL) was added n-butyllithium 1.6M (1.2 eq., 33.8 mL, 54 mmol) dropwise at -78 ^{o}C. The resulting reaction mixture was stirred for 30 min at 0 ^{o}C. N-methoxy-N-methyl-acetamide (1.4 eq., 6.7 mL, 63 mmol) was then added dropwise at -78 ^{o}C and the resulting mixture was stirred for 1 h at -78 ^{o}C. The reaction mixture was quenched with methanol (30 mL) at -78 ^{o}C, washed with H_2O (25 mL), and the organic layer separated. The aqueous layer was extracted with EtOAc (3x20 mL) and combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was used in the next step without further purification.

A solution of 1-[3-(1,3-dioxolan-2-yl)thiophen-2-yl]ethanone (1 eq., 45 mmol) in 1:1 acetonitrile and water (200 mL) was treated with trifluoroacetic acid (2.5 eq., 8.6 mL, 113 mmol) dropwise and stirred for 30 min at RT. The resulting reaction mixture was washed with $NaHCO_3$ (saturated solution, 100 mL) and the aqueous layer was extracted with EtOAc (3x25 mL). The

organic layers were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*, and then purified via silica gel flash chromatography (elution with EtOAc:hexane = 1:5) to give compound **3a** as a yellow solid (3.49 g, 51% yield). mp 46-48 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.66 (s, 3H), 7.47 (dd, 1H, *J* = 5.0, 5.2 Hz), 7.64 (d, 1H, *J* = 5.2 Hz), 10.56 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.8, 187.6, 145.7, 144.2, 129.8, 128.8, 30.0. HRMS(ESI-MS) calculated for ($C_7H_6O_2S+H^+$), 155.0161, found 155.0153.



3b

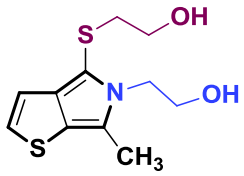
Compound 3b. A flask equipped with a Dean-Stark trap was charged with a solution of 3-acetylthiophene (1 eq., 7.0 g, 55 mmol), ethylene glycol (7 eq., 21.9 mL, 388 mmol), and *p*-toluenesulfonic acid (0.01 eq., 99.5 mg, 0.55 mmol) in benzene (70 mL). The reaction mixture was refluxed for 4 h, cooled to RT, and washed with $NaHCO_3$ (saturated solution, 50 mL).The organic layer was separated, and the aqueous layer was extracted with EtOAc (3x25 mL). Combined organic layers were washed with NaCl (saturated solution, 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was purified via silica gel flash chromatography (elution with EtOAc:hexanes = 1:5, 1% TEA) to give 2-methyl-2-(thiophen-3-yl)-1,3-dioxolane as a white solid (5.40 g, 57% yield). mp 34-36 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.68 (s, 3H), 3.86-3.89 (m, 2H), 4.02-4.05 (m, 2H), 7.06 (dd, 1H, *J* = 5.0, 1.3 Hz), 7.25-7.29 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.3, 126.1, 125.9, 121.6, 107.5, 64.8, 27.1. MS(ESI- MS) calculated for $C_8H_{10}O_2S(M+H^+)$ 171.1, found 171.1 ($M+H^+$).

To a flask charged with 2-methyl-2-(thiophen-3-yl)-1,3-dioxolane (1 eq., 1.0 g, 6 mmol) in THF (40 mL) was added n-butyllithium 2.5M (1.2 eq., 2.8 mL, 7 mmol) dropwise at -78 ^oC. The resulting reaction mixture was stirred for 30 min at 0 ^oC. Dimethylformamide (1.4 eq., 0.6 mL, 8 mmol) was added dropwise at -78 ^oC and the resulting mixture was stirred for 1 h at 0 ^oC. The reaction mixture was quenched with methanol (15 mL) at -78 ^oC, washed with H_2O (30 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (3x15 mL), and combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was used in the next step without further purification.

A solution of 3-(2-methyl-1,3-dioxolan-2-yl)thiophene-2-carbaldehyde (1 eq., 0.5 g, 3 mmol) in 1:1 EtOAc and HCl 3M (20 mL) was stirred for 1.5 h at 40 ^oC. The resulting reaction mixture was diluted with 1:1 EtOAc and H_2O (20 mL) and cooled to RT. The aqueous layer was removed and extracted with EtOAc (2x10 mL). Organic layers were combined, washed with $NaHCO_3$ (saturated solution, 50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*, and then purified via silica gel flash chromatography (elution with EtOAc:Hexane = 1:5) to give compound **3b** as a yellow solid (0.32 g, 69% yield). mp 57-59 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.63 (s, 3H), 7.51 (d, 1H, *J* = 5.1 Hz), 7.68 (dd, 1H, *J* = 5.1, 1.0 Hz), 10.49 (d, 1H, *J* = 0.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 193.9, 185.5, 147.2, 143.9, 133.4, 130.1, 30.0. HRMS(ESI-MS) calculated for ($C_7H_6O_2S+H^+$), 155.0161, found 155.0150.

General Procedure for the Synthesis of Thieno[2,3-c]pyrrole Products 8-28:

A solution of 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.1 g, 0.65 mmol) in methanol (3 mL) in a disposable glass vial was treated with amine (1 eq., 0.65 mmol) and thiol (1 eq., 0.65 mmol).The resulting reaction mixture was stirred overnight at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion, the mixture was concentrated under reduced pressure and purified by silica gel flash column chromatography to yield compounds **8-28**.

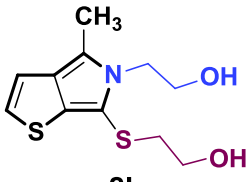


8a

General Procedure for Compound 8a. A solution of 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.1 g, 0.65 mmol) dissolved in 1:1 acetonitrile and water (3 mL) in a disposable glass vial was treated with ethanolamine (1 eq., 39 µL, 0.65 mmol) and β-mercaptoethanol (1 eq., 46 µL, 0.65 mmol). The resulting reaction mixture was stirred for 30 minutes at room temperature and the progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion at 30 min, the crude product was extracted with EtOAc (3x5 mL), washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, then purified via silica gel flash column chromatography (elution with EtOAc:hexane = 1:1) to give compound **8a** as a dark orange oil (0.146 g, 88% yield).

Solvent Free Procedure for Compound 8a. To powdered 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.5 g, 3.25 mmol) in a disposable glass vial was added ethanolamine (1 eq., 197 µL, 3.25 mmol) followed by β-mercaptoethanol (1 eq., 229 µL, 3.25 mmol). The reaction mixture was sonicated for 5 minutes and the reaction progress was monitored by thin layer chromatography (TLC). After reaction completion at 30 min, the crude red oil showed 95% conversion by ^{1}H NMR.

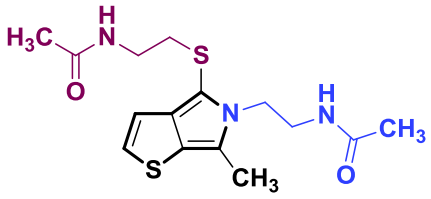
Compound 8a. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.84 (s, 1H), 2.08 (s, 1H), 2.46 (s, 3H), 2.78 (t, 2H, *J* = 5.9 Hz), 3.67 (t, 2H, *J* = 5.7 Hz), 3.91 (t, 2H, *J* = 5.7 Hz), 4.38 (t, 2H, *J* = 5.9 Hz), 6.95 (d, 1H, *J* = 5.3 Hz), 7.04 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.9, 127.7, 122.0, 121.9, 116.1, 105.3, 62.9, 61.0, 46.9, 41.0, 13.0. HRMS(ESI-MS) calculated for ($C_{11}H_{15}NO_2S_2$+H^+), 258.0617, found 258.0612.



8b

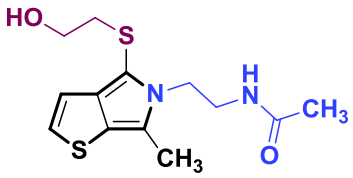
Compound 8b. A solution of 2-acetylthiophene-3-carboxaldehyde **3b** (1 eq., 0.1 g, 0.65 mmol) dissolved in 1:1 acetonitrile and water (3 mL) in a disposable glass vial was treated with ethanolamine (1 eq., 39 µL, 0.65 mmol) and β-mercaptoethanol (1 eq., 46 µL, 0.65 mmol). The

resulting reaction mixture was stirred for 30 minutes at room temperature and the progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion at 30 min, the crude product was extracted with EtOAc (3x5 mL), washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, then purified by silica gel flash column chromatography (elution with EtOAc:hexane = 1:1) to give compound **8b** as a dark orange oil (0.108 g, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.01 (s, 1H), 2.20 (s, 1H), 2.50 (s, 3H), 2.81 (t, 2H, *J* = 5.8 Hz), 3.69 (t, 2H, *J* = 5.8 Hz), 3.90 (t, 2H, *J* = 5.8 Hz), 4.34 (t, 2H, *J* = 5.8 Hz), 6.87 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 133.0, 130.4, 124.4, 122.6, 116.5, 105.2, 62.8, 61.3, 47.0, 40.4, 12.7. HRMS(ESI-MS) calculated for ($C_{11}H_{15}NO_2S_2$ +H^+), 258.0617, found 258.0605.



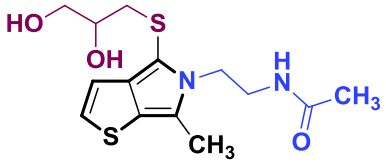
9

Compound 9. A solution of 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.1 g, 0.65 mmol) in 1:1 acetonitrile and water (3 mL) in a disposable glass vial was treated with N-(2-aminoethyl)acetamide (1 eq., 63 µL, 0.65 mmol) and N-acetylcysteamine (1 eq., 69 µL, 0.65 mmol). The resulting mixture was stirred overnight at room temperature and the progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion, the crude product was extracted with EtOAc (3x5 mL), washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*, then purified by flash chromatography on silica gel (elution with $CHCl_3$:CH_3OH = 15:1) to give compound **9** as a dark green oil (0.171 g, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.92 (s, 3H), 1.97 (s, 3H), 2.43 (s, 3H), 2.72 (t, 2H, *J* = 6.3 Hz), 3.35 (q, 2H, *J* = 6.0 Hz), 3.50 (q, 2H, *J* = 6.3 Hz), 4.30 (t, 2H, *J* = 6.4 Hz), 5.95 (s, 1H), 6.15 (s, 1H), 6.92 (d, 1H, *J* = 5.3 Hz), 7.05 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.1, 170.5, 138.8, 128.0, 122.1, 121.6, 116.0, 105.6, 43.8, 40.8, 39.4, 37.9, 23.4, 23.3, 12.7. HRMS(ESI-MS) calculated for ($C_{15}H_{21}N_3O_2S_2$ +H^+), 340.1148, found 340.1158.



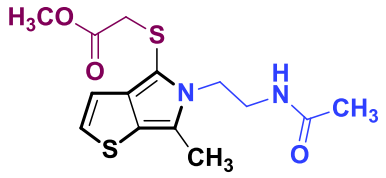
10

Compound 10. Compound **10** was prepared according to the general procedure. The reaction mixture was purified by silica gel flash column chromatography (elution with CH_2Cl_2:acetone = 2:1) to give compound **10** as a yellow solid (0.141 g, 73% yield). mp 129-131 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.96 (s, 3H), 2.38 (t, 1H, *J* = 6.0 Hz), 2.43 (s, 3H), 2.76 (t, 2H, *J* = 5.9 Hz), 3.53 (q, 2H, *J* = 6.2 Hz), 3.65 (q, 2H, *J* = 5.8 Hz), 4.34 (t, 2H, *J* = 6.3 Hz), 5.75 (s, 1H), 6.94 (d, 1H, *J* = 5.3 Hz), 7.04 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.9, 138.9, 127.8, 122.1, 121.4, 116.1, 105.5, 60.9, 43.8, 41.4, 40.8, 23.4, 12.7. HRMS(ESI-MS) calculated for ($C_{13}H_{18}N_2O_2S_2$ +H^+), 299.0882, found 299.0885.



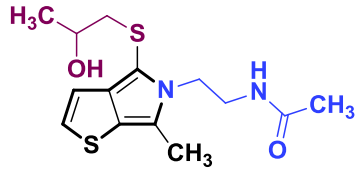
11

Compound 11. Compound **11** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with $CHCl_3$:CH_3OH = 10:1) to give compound **11** as a red solid (0.208 g, 98% yield). mp 88-90 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.95 (s, 3H), 2.42 (s, 3H), 2.62-2.77 (m, 3H), 3.48-3.52 (m, 4H), 3.64-3.69 (m, 2H), 4.32 (t, 2H, *J* = 7.5 Hz), 5.97 (t, 1H, *J* = 5.8 Hz), 6.94 (d, 1H, *J* = 5.3 Hz), 7.03 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.4, 138.6, 127.8, 122.2, 121.4, 116.1, 105.9, 70.6, 65.3, 43.8, 42.0, 40.8, 23.3, 12.7. HRMS(ESI-MS) calculated for ($C_{14}H_{20}N_2O_3S_2$ +H^+), 329.0988, found 329.1003.



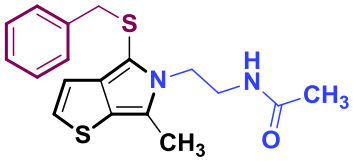
12

Compound 12. Compound **12** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc) to give compound **12** as a grey solid (0.141 g, 67% yield). mp 111-113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.95 (s, 3H), 2.44 (s, 3H), 3.31 (s, 2H), 3.52 (q, 2H, *J* = 6.2 Hz), 3.58 (s, 3H), 4.34 (t, 2H, *J* = 6.3 Hz), 5.81 (s, 1H), 6.93 (d, 1H, *J* = 5.3 Hz), 7.05 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 170.5, 139.3, 127.9, 122.5, 122.4, 116.3, 104.6, 52.6, 44.0, 40.6, 40.3, 23.3, 12.8. HRMS(ESI-MS) calculated for ($C_{14}H_{18}N_2O_3S_2$ +H^+), 327.0832, found 327.0833.



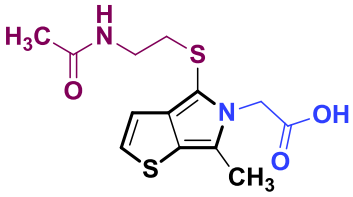
13

Compound 13. Compound **13** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc) to give compound **13** as a brown oil (0.179 g, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.19 (d, 3H, *J* = 6.3 Hz), 1.96 (s, 3H), 2.43 (s, 3H), 2.50-2.54 (m, 1H), 2.70-2.78 (m, 2H), 3.48-3.55 (m, 2H), 3.71-3.76 (m, 1H), 4.33 (t, 2H, *J* = 6.3 Hz), 5.84 (s, 1H), 6.94 (d, 1H, *J* = 5.3 Hz), 7.04 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.0, 138.6, 127.7, 122.0, 121.4, 116.1, 105.8, 66.2, 47.7, 43.8, 40.8, 23.3, 21.9, 12.7. HRMS(ESI-MS) calculated for ($C_{14}H_{20}N_2O_2S_2$+H^+), 313.1039, found 313.1042.



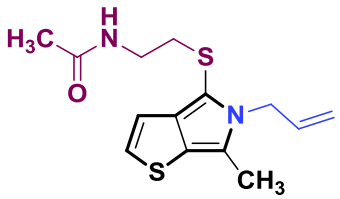
14

Compound 14. Compound **14** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **14** as a beige solid (0.171g, 77% yield). mp 141-143 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.89 (s, 3H), 2.36 (s, 3H), 3.30 (q, 2H, *J* = 6.1 Hz), 3.74 (s, 2H), 3.85 (t, 2H, *J* = 6.1 Hz), 5.45 (s, 1H), 6.78 (d, 1H, *J* = 5.3 Hz), 6.91-6.93 (m, 2H), 6.99 (d, 1H, *J* = 5.3 Hz), 7.16-7.20 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.6, 138.6, 138.4, 129.0, 128.5, 127.2, 127.2, 122.0, 121.3, 116.4, 106.2, 43.5, 43.3, 40.6, 23.3, 12.7. HRMS(ESI-MS) calculated for ($C_{18}H_{20}N_2OS_2$+H^+), 345.1090, found 345.1096.



15

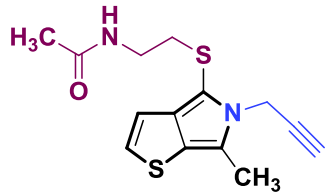
Compound 15. A solution of 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.1 g, 0.65 mmol) in H_2O (3 mL) in a disposable glass vial was treated with glycine (1 eq., 49 mg, 0.65 mmol) and N-acetylcysteamine (1 eq., 69 µL, 0.65 mmol). The resulting mixture was stirred overnight at room temperature and the progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion, the crystalline product was filtered, rinsed with water (3x1 mL), and dried under vacuum to give compound **15** as a beige solid (0.148 g, 73% yield) which decomposed upon heating to 180 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.19 (s, 3H), 2.72 (s, 3H), 2.97 (t, 2H, *J* = 7.2 Hz), 3.51 (d, 2H, *J* = 6.4 Hz), 5.40 (s, 2H), 7.41 (d, 1H, *J* = 5.3 Hz), 7.64 (d, 1H, *J* = 5.3 Hz), 8.40 (t, 1H, *J* = 5.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 170.3, 169.2, 138.1, 127.7, 121.9, 120.6, 116.4, 105.9, 45.9, 38.8, 36.9, 22.6, 12.2. HRMS(ESI-MS) calculated for ($C_{13}H_{16}N_2O_3S_2$+H^+), 313.0675, found 313.0675.



16

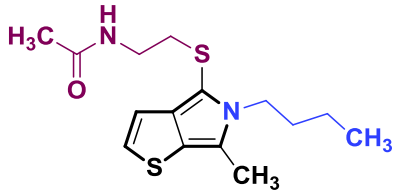
Compound 16. Compound **16** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **16** as a beige solid (0.164 g, 86% yield). mp 87-89 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.88 (s, 3H), 2.38 (s, 3H), 2.67 (t, 2H, *J* = 6.3 Hz), 3.35 (q, 2H, *J* = 6.0 Hz), 4.72 (d, 1H, *J* = 17.1 Hz), 4.83 (t, 2H, *J* = 2.5 Hz), 5.14 (d, 1H, *J* = 10.4 Hz), 5.82 (s, 1H), 5.93 (ddt, 1H,

J = 17.1, 9.1, 3.4 Hz), 6.93 (d, 1H, *J* = 5.3 Hz), 7.05 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1, 138.6, 134.1, 127.7, 121.9, 121.7, 116.2, 116.0, 105.1, 46.9, 39.3, 37.6, 23.3, 12.5. HRMS(ESI-MS) calculated for ($C_{14}H_{18}N_2OS_2$+H^+), 295.0933, found 295.0922.



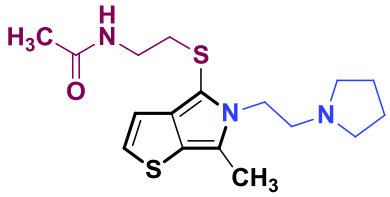
17

Compound 17. Compound **17** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **17** as a yellow solid (0.158 g, 84% yield). mp 120-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.87 (s, 3H), 2.34 (s, 1H) 2.51 (s, 3H), 2.78 (t, 2H, *J* = 6.2 Hz), 3.36 (q, 2H, *J* = 6.0 Hz), 5.00 (d, 2H, *J* = 2.5 Hz), 5.77 (s, 1H), 6.92 (d, 1H, *J* = 5.3 Hz), 7.06 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2, 138.8, 128.3, 122.2, 121.9, 115.9, 105.4, 78.8, 72.9, 39.4, 37.4, 34.0, 23.3, 12.6. HRMS(ESI-MS) calculated for ($C_{14}H_{16}N_2OS_2$+H^+), 293.0777, found 293.0772.



18

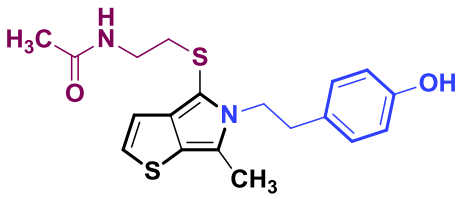
Compound 18. Compound **18** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **18** as a brown solid (0.143 g, 71% yield). mp 102-104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (t, 3H, *J* = 7.4 Hz), 1.35-1.43 (m, 2H), 1.63-1.69 (m, 2H), 1.87 (s, 3H), 2.42 (s, 3H), 2.68 (t, 2H, *J* = 6.2 Hz), 3.37 (q, 2H, *J* = 6.1 Hz), 4.13 (t, 2H, *J* = 7.8 Hz), 5.72 (s, 1H), 6.92 (d, 1H, *J* = 5.3 Hz), 7.03 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1, 138.4, 127.4, 121.7, 121.2, 115.9, 104.9, 44.9, 39.6, 37.7, 33.9, 23.3, 20.2, 14.0, 12.8. HRMS(ESI-MS) calculated for ($C_{15}H_{22}N_2OS_2$+H^+), 311.1246, found 311.1250.



19

Compound 19. Compound **19** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with acetone) to give compound **19** as a red oil (0.174 g, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.79-1.84 (m, 4H), 1.87 (s, 3H), 2.44 (s, 3H), 2.60-2.63 (m, 4H), 2.71-2.74 (m, 4H), 3.37 (q, 2H, *J* = 6.0 Hz),

4.32 (t, 2H, *J* = 7.8 Hz), 5.95 (s, 1H), 6.91 (d, 1H, *J* = 5.3 Hz), 7.03 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2, 138.5, 127.6, 121.9, 121.2, 115.9, 105.3, 57.0, 54.6, 44.2, 39.6, 37.8, 23.6, 23.3, 12.8. HRMS(ESI-MS) calculated for ($C_{17}H_{25}N_3OS_2$+H^+), 352.1512, found 352.1512.

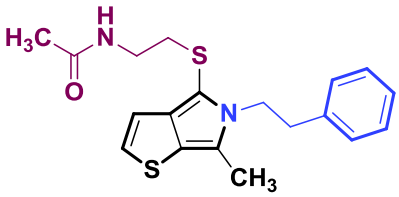


20

General Procedure for Compound 20. Compound **20** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 3:1) to give compound **20** as a yellow solid (0.227 g, 94% yield) which decomposed upon heating to 160 °C.

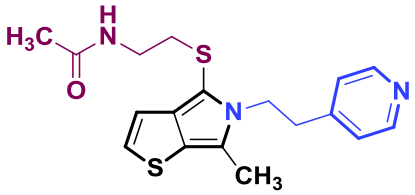
Solvent Free Procedure for Compound 20. To powdered 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.5 g, 3.25 mmol) was added tyramine (1 eq., 0.45 g, 3.25 mmol) with grinding with mortar and pestle. The rust colored reaction powder was transferred to a disposable glass vial then treated with N-acetylcysteamine (1 eq., 345 μL, 3.25 mmol). The reaction mixture was sonicated for 5 minutes and the reaction progress was monitored by thin layer chromatography (TLC). After reaction completion at 45 min, the crude orange colored oil showed 92% conversion by ^{1}H NMR.

Compound 20. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.77 (s, 3H), 2.26 (s, 3H), 2.60 (t, 2H, *J* = 6.9 Hz), 2.81 (t, 2H, *J* = 7.7 Hz), 3.12 (q, 2H, *J* = 6.3 Hz), 4.28 (t, 2H, *J* = 7.8 Hz), 6.67 (d, 2H, *J* = 8.4 Hz), 6.96 (d, 2H, *J* = 8.4 Hz), 6.99 (d, 1H, *J* = 5.3 Hz), 7.18 (d, 1H, *J* = 5.3 Hz), 7.98 (t, 1H, *J* = 5.5 Hz), 9.27 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.2, 156.0, 138.1, 129.8, 128.3, 127.2, 120.9, 120.5, 116.5, 115.3, 104.8, 46.3, 38.9, 37.1, 36.6, 22.6, 12.2. HRMS(ESI-MS) calculated for ($C_{19}H_{22}N_2O_2S_2$+H^+), 375.1195, found 375.1199.



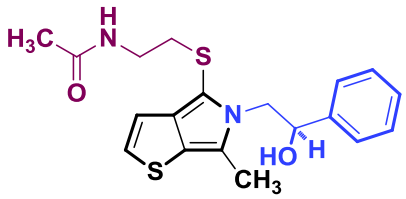
21

Compound 21. Compound **21** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 1:2) to give compound **21** as a yellow solid (0.189 g, 85% yield). mp 99-101 °C. ^{1}H NMR (500 MHz, CD_3CN) δ: 1.79 (s, 3H), 2.25 (s, 3H), 2.60 (t, 2H, *J* = 7.1 Hz), 2.98 (t, 2H, *J* = 7.6 Hz), 3.19 (q, 2H, *J* = 6.6 Hz), 4.39 (t, 2H, *J* = 7.5 Hz), 6.43 (s, 1H), 6.96 (d, 1H, *J* = 5.3 Hz), 7.07 (d, 1H, *J* = 5.3 Hz), 7.13-7.15 (m, 2H), 7.21-7.29 (m, 3H). ^{13}C NMR (125 MHz, CD_3CN) δ: 170.5, 139.5, 139.3, 129.9, 129.4, 127.9, 127.5, 122.1, 121.9, 117.2, 106.2, 47.1, 39.9, 38.4, 38.0, 22.8, 12.4. HRMS(ESI-MS) calculated for ($C_{19}H_{22}N_2OS_2$+H^+), 359.1246, found 359.1250.



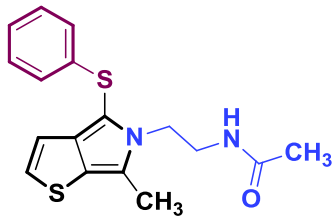
22

Compound 22. Compound **22** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with $CHCl_3$:CH_3OH = 20:1) to give compound **22** as a yellow solid (0.223 g, 96% yield). mp 111-113 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.87 (s, 3H), 2.29 (s, 3H), 2.64 (t, 2H, *J* = 6.4 Hz), 2.98 (t, 2H, *J* = 7.6 Hz), 3.35 (q, 2H, *J* = 6.2Hz), 4.37 (t, 2H, *J* = 7.5 Hz), 5.73 (s, 1H), 6.92 (d, 2H, *J* = 5.3 Hz), 7.02 (d, 2H, *J* = 5.8 Hz), 7.06 (d, 1H, *J* = 5.3 Hz), 8.50 (d, 2H, *J* = 5.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2, 150.2, 147.0, 138.9, 128.0, 124.3, 122.1, 121.2, 115.9, 105.0, 45.4, 39.6, 37.6, 37.5, 23.3, 12.7. HRMS(ESI-MS) calculated for ($C_{18}H_{21}N_3OS_2$+H^+), 360.1199, found 360.1204.



23

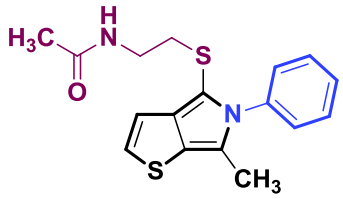
Compound 23. Compound **23** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 4:1) to give compound **23** as a yellow oil (0.165 g, 68% yield). α^{25}_D – 41.2, (c 0.4, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ: 1.76 (s, 3H), 2.28 (s, 3H), 2.57-2.71 (m, 2H), 3.13 (q, 2H, *J* = 6.6 Hz), 4.24-4.26 (m, 2H), 4.84-4.88 (m, 1H), 5.67 (d, 1H, *J* = 4.4 Hz), 7.00 (d, 1H, *J* = 5.3 Hz), 7.19 (d, 1H, *J* = 5.3 Hz), 7.27-7.31 (m, 1H), 7.34-7.37 (m, 4H), 7.98 (t, 1H, *J* = 5.5 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.2, 143.1, 138.0, 128.2, 127.5, 127.2, 125.8, 122.0, 120.3, 116.5, 105.5, 79.2, 72.9, 52.3, 37.0, 22.6, 12.7. HRMS(ESI-MS) calculated for ($C_{19}H_{22}N_2O_2S_2$+H^+), 375.1195, found 375.1195.



24

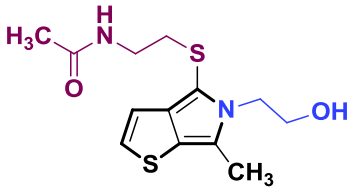
Compound 24. Compound **24** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 3:1) to give compound **24** as a blue solid (0.128 g, 60% yield) which decomposed upon heating to 160 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.85 (s, 3H), 2.49 (s, 3H), 3.44 (q, 2H, *J* = 6.2 Hz), 4.22 (t, 2H, *J* = 6.3 Hz), 5.54 (s, 1H), 6.93-6.95 (m, 3H), 7.07-7.10 (m, 2H), 7.18-7.20 (m, 2H). ^{13}C

NMR (125 MHz, $CDCl_3$) δ: 170.7, 139.9, 139.5, 129.3, 128.2, 125.6, 125.3, 122.8, 122.5, 116.4, 102.6, 44.2, 40.6, 23.2, 12.8. HRMS(ESI-MS) calculated for ($C_{17}H_{18}N_2OS_2$ +H^+), 331.0933, found 331.0934.



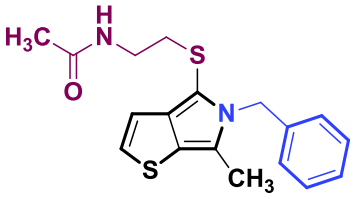
25

Compound 25. Compound **25** was prepared according to the general procedure. The crude product was filtered, rinsed with CH_3OH (3x1 mL), and dried under vacuum. The remaining reaction mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **25** as a yellow solid (0.116 g, 54% yield) which decomposed upon heating to 150 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.70 (s, 3H), 2.17 (s, 3H), 2.40 (t, 2H, *J* = 5.8 Hz), 3.07 (q, 2H, *J* = 5.9 Hz), 5.24 (s, 1H), 6.92 (d, 1H, *J* = 5.3 Hz), 7.04 (d, 1H, *J* = 5.3 Hz), 7.19-7.23 (m, 2H), 7.42-7.49 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.9, 139.1, 138.2, 129.1, 129.1, 128.6, 128.4, 122.8, 122.4, 116.1, 107.1, 38.6, 37.8, 23.3, 13.3. HRMS(ESI-MS) calculated for ($C_{17}H_{18}N_2OS_2$ +H^+), 331.0933, found 331.0936.



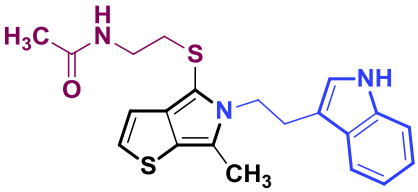
26

Compound 26. A solution of 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.1 g, 0.65 mmol) dissolved in water (3 mL) was treated with ethanolamine (1 eq., 39 μL, 0.65 mmol) and N-acetylcysteamine (1 eq., 69 μL, 0.65 mmol). The resulting mixture was stirred for 30 min. at room temperature and the progress of the reaction was monitored by thin layer chromatography (TLC). After the reaction completion, the crude product was sonicated, filtered, rinsed with water (3x1 mL) and dried under vacuum to give compound **26** as a yellow solid (0.171 g, 88% yield). mp 110-112 ^oC. ^1H NMR (500 MHz, DMSO-d_6) δ: 1.78 (s, 3H), 2.42 (s, 3H), 2.62 (t, 2H, *J* = 7.4 Hz), 3.13 (q, 2H, *J* = 7.5Hz), 3.62 (q, 2H, *J* = 5.8 Hz), 4.24 (t, 2H, *J* = 6.2 Hz), 5.01 (t, 1H, *J* = 5.6 Hz), 6.99 (d, 1H, *J* = 5.3 Hz), 7.19 (d, 1H, *J* = 5.2 Hz), 7.99 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.2, 138.1, 127.1, 121.5, 120.5, 116.5, 105.2, 61.1, 46.8, 38.9, 37.0, 22.6, 12.6. HRMS(ESI-MS) calculated for ($C_{13}H_{18}N_2O_2S_2$ +H^+), 299.0882, found 299.0879.



27

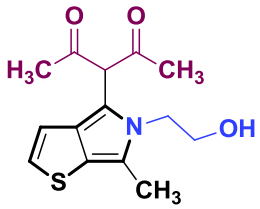
Compound 27. Compound **27** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **27** as a tan solid (0.177 g, 79% yield). mp 116-118 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.76 (s, 3H), 2.25 (s, 3H), 2.45 (t, 2H, *J* = 6.9 Hz), 3.08 (q, 2H, *J* = 6.3 Hz), 5.48 (s, 2H), 6.90 (d, 2H, *J* = 7.4 Hz), 7.03 (d, 1H, *J* = 5.3 Hz), 7.22-7.25 (m, 2H), 7.29-7.32 (m, 2H), 7.95 (t, 1H, *J* = 5.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.2, 138.3, 128.7, 127.7, 127.1, 125.8, 121.3, 121.0, 116.5, 105.9, 47.4, 38.7, 37.0, 22.6, 12.4. HRMS(ESI-MS) calculated for ($C_{18}H_{20}N_2OS_2$+H^+), 345.1090, found 345.1092.



28

Compound 28. Compound **28** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **28** as a green solid (0.218 g, 85% yield). mp 78-80 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.84 (s, 3H), 2.37 (s, 3H), 2.60 (t, 2H, *J* = 6.3 Hz), 3.14 (t, 2H, *J* = 7.9 Hz), 3.33 (q, 2H, *J* = 6.2 Hz), 4.42 (t, 2H, *J* = 7.9 Hz), 5.70 (s, 1H), 6.93 (d, 1H, *J* = 2.2 Hz), 6.97 (d, 1H, *J* = 5.3 Hz), 7.08 (d, 1H, *J* = 5.3 Hz), 7.15 (t, 1H, *J* = 7.8 Hz), 7.22 (t, 1H, *J* = 7.9 Hz), 7.37 (d, 1H, *J* = 8.0 Hz), 7.66 (d, 1H, *J* = 7.9 Hz), 8.16 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.2, 138.7, 136.3, 127.5, 127.4, 122.4, 122.3, 121.8, 121.4, 119.7, 118.7, 116.0, 112.4, 111.4, 104.9, 45.9, 39.5, 37.7, 27.8, 23.3, 12.8. HRMS(ESI-MS) calculated for ($C_{21}H_{23}N_3OS_2$ +H^+), 398.1355, found 398.1357.

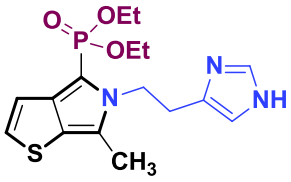
Synthesis and Characterization of Thieno[2,3-c]pyrrole Product 29



29

Compound 29. 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 50 mg, 0.33 mmol) was mixed with ethanolamine (1 eq., 20 μL, 0.33 mmol) and acetylacetone (1 eq., 34 μL, 0.33 mmol) neat, and the resulting mixture was left for thirty minutes at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion, the crude product was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 1:2) to give compound **29** as a yellow solid (0.069 g, 77% yield) which decomposed upon heating to 120 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.74 (s, 1H), 1.89 (s, 6H), 2.46 (s, 3H), 3.73 (s, 2H), 3.96 (t, 2H, *J* = 6.1 Hz), 6.68 (d, 1H, *J* = 5.3 Hz), 6.92 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 194.1, 131.9, 126.1, 121.4, 117.4, 116.0, 114.8, 105.2, 62.3, 46.6, 24.0, 12.6. HRMS(ESI-MS) calculated for ($C_{14}H_{17}NO_3S+H^+$), 280.1007, found 280.0994.

Synthesis and Characterization of Thieno[2,3-c]pyrrole Product 30



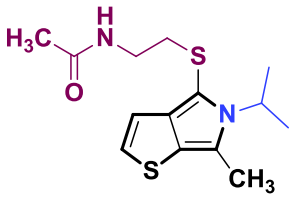
30

Procedure A for Compound 30. A solution of 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.1 g, 0.65 mmol) in ethanol (1 mL) in a disposable glass vial was treated with histamine (1 eq., 72 mg, 0.65 mmol) and diethyl phosphite (1 eq., 84 μL, 0.65 mmol). The resulting reaction mixture was stirred for three hours at 40^{o}C (oil bath) and the progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion, the crude product was purified by flash chromatography on silica gel (elution with $CHCl_3$:CH_3OH = 50:1) to give compound **30** as an orange oil (0.061 g, 25% yield).

Procedure B for Compound 30. A solution of 2-acetylthiophene-3-carboxaldehyde **3a** (1 eq., 0.1 g, 0.65 mmol) in ethanol (1 mL) in a disposable glass vial was treated with histamine (1 eq., 72 mg, 0.65 mmol), diethyl phosphite (1 eq., 84 μL, 0.65 mmol), and magnesium perchlorate (15 mg, 0.065 mmol, 10% mol.). The resulting reaction mixture was stirred for three hours at 40^{o}C (oil bath) and the progress of the reaction was monitored by thin layer chromatography (TLC). After reaction completion, the crude product was purified by flash chromatography on silica gel (elution with $CHCl_3$:CH_3OH = 50:1) to give compound **30** as an orange oil (0.233 g, 49% yield).

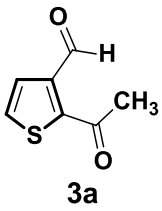
Compound 30. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (t, 6H, *J* = 7.1 Hz), 2.45 (s, 3H), 3.10 (t, 2H, *J* = 8.0 Hz), 4.06-4.14 (m, 4H), 4.48 (t, 2H, *J* = 7.8 Hz), 6.85 (s, 1H), 7.01 (d, 1H, *J* = 5.3 Hz), 7.19 (d, 1H, *J* = 5.3 Hz), 7.64 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 140.7 (d, *J* = 16.7 Hz), 135.4, 129.8, 125.5 (d, *J* = 9.6 Hz), 123.3 (d, *J* = 14.5 Hz), 122.7, 116.9, 104.4, 102.5, 62.6 (d, *J* = 5.5 Hz), 47.3, 28.6, 16.4 (d, *J* = 7.0 Hz), 12.0. HRMS(ESI-MS) calculated for ($C_{16}H_{22}N_3O_3PS+H^+$), 368.1192, found 368.1192.

Synthesis and Characterization of Thieno[2,3-c]pyrrole Product 35



35

Compound 35. Compound **35** was prepared according to the general procedure. The reaction mixture was purified by flash chromatography on silica gel (elution with EtOAc:hexane = 2:1) to give compound **35** as a brown oil (0.043 g, 22% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.55 (d, 6H, *J* = 7.1 Hz), 1.86 (s, 3H), 2.52 (s, 3H), 2.67 (t, 2H, *J* = 6.1 Hz), 3.36 (q, 2H, *J* = 6.2 Hz), 5.21 (s, 1H), 5.81 (s, 1H), 6.90 (d, 1H, *J* = 5.3 Hz), 7.02 (d, 1H, *J* = 5.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.1, 138.4, 127.3, 123.0, 121.1, 116.1, 105.2, 48.5, 39.5, 37.8, 31.0, 23.3, 22.5, 14.4. HRMS(ESI-MS) calculated for ($C_{14}H_{20}N_2OS_2$ +H^+), 297.1090, found 297.1090.



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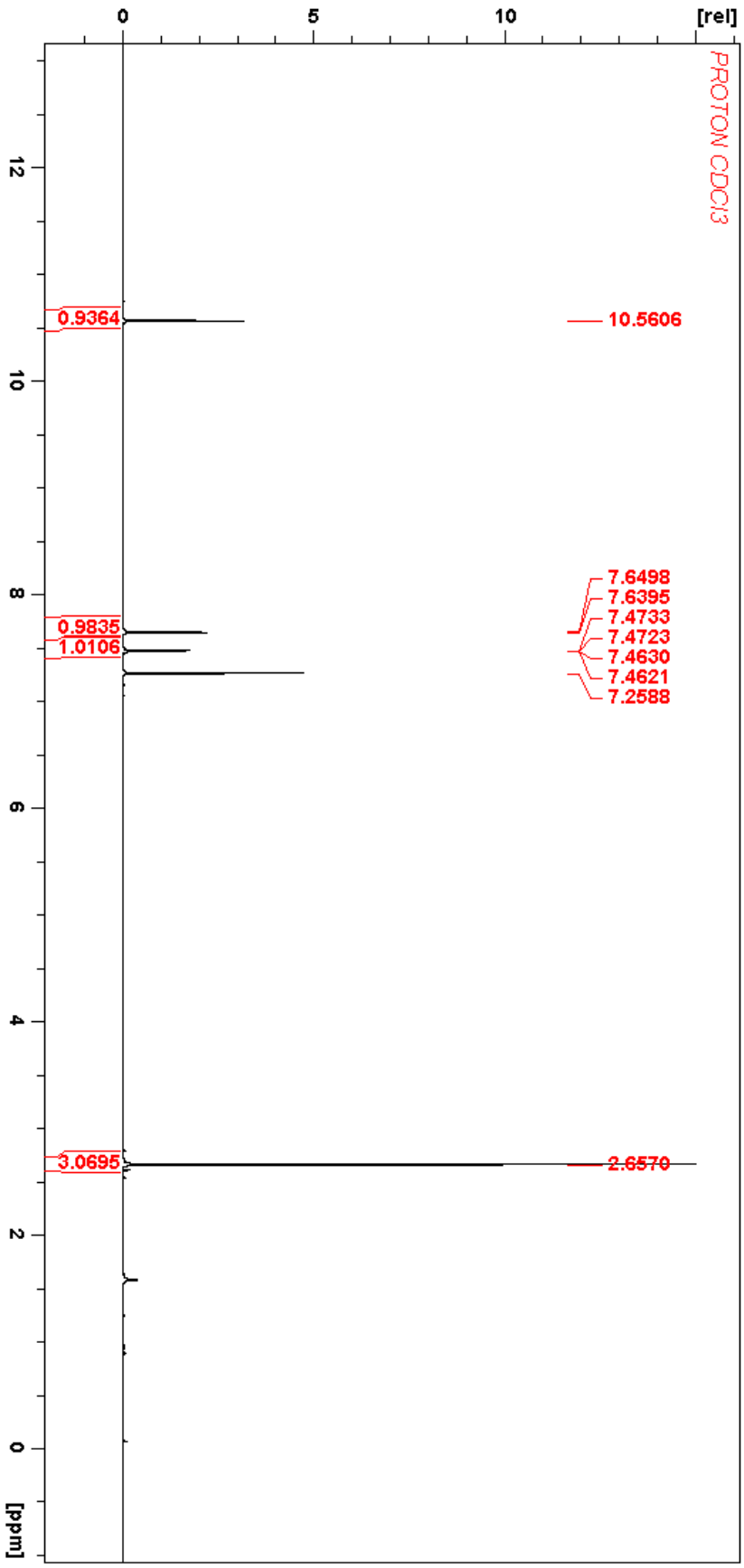

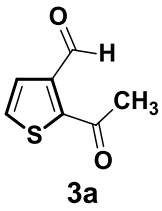

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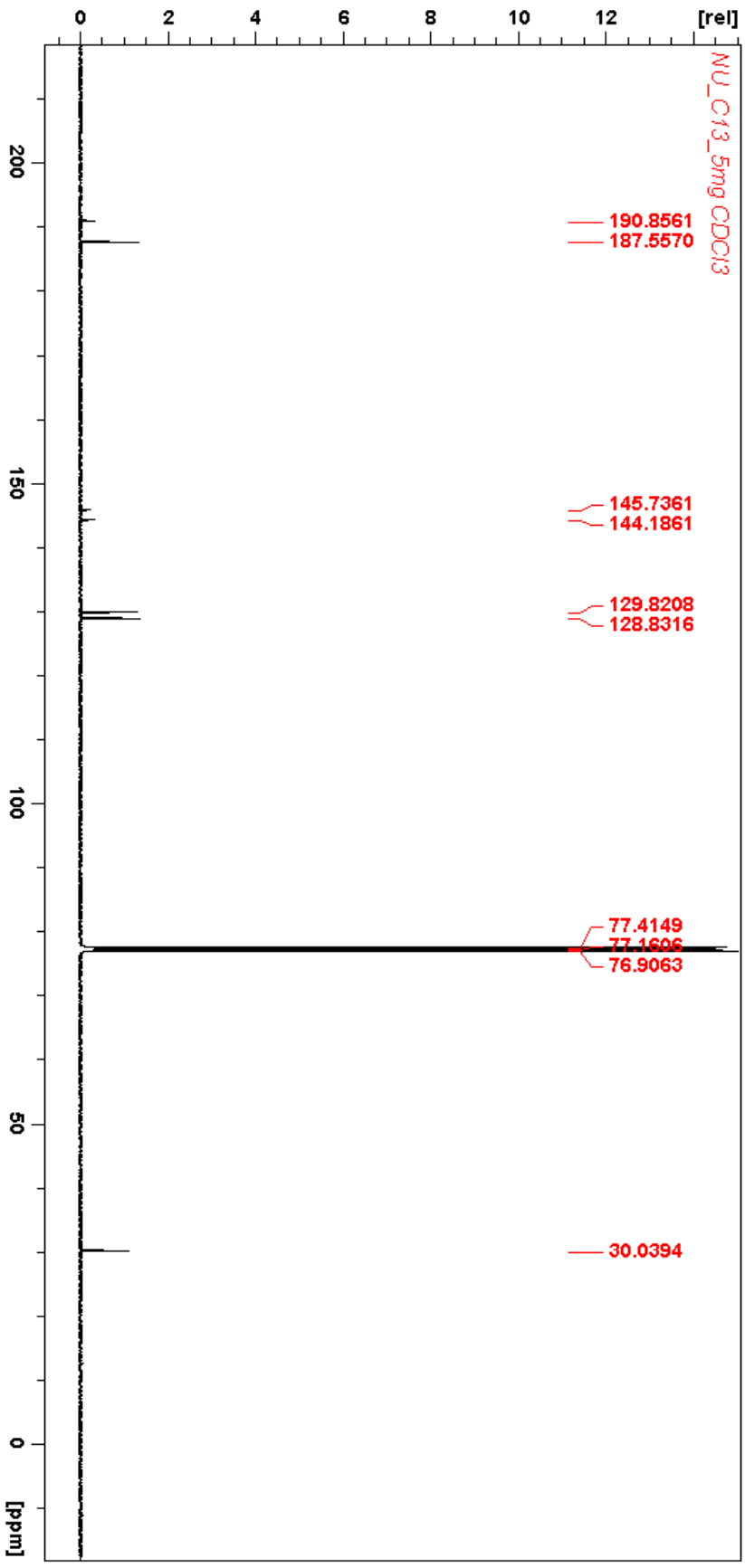

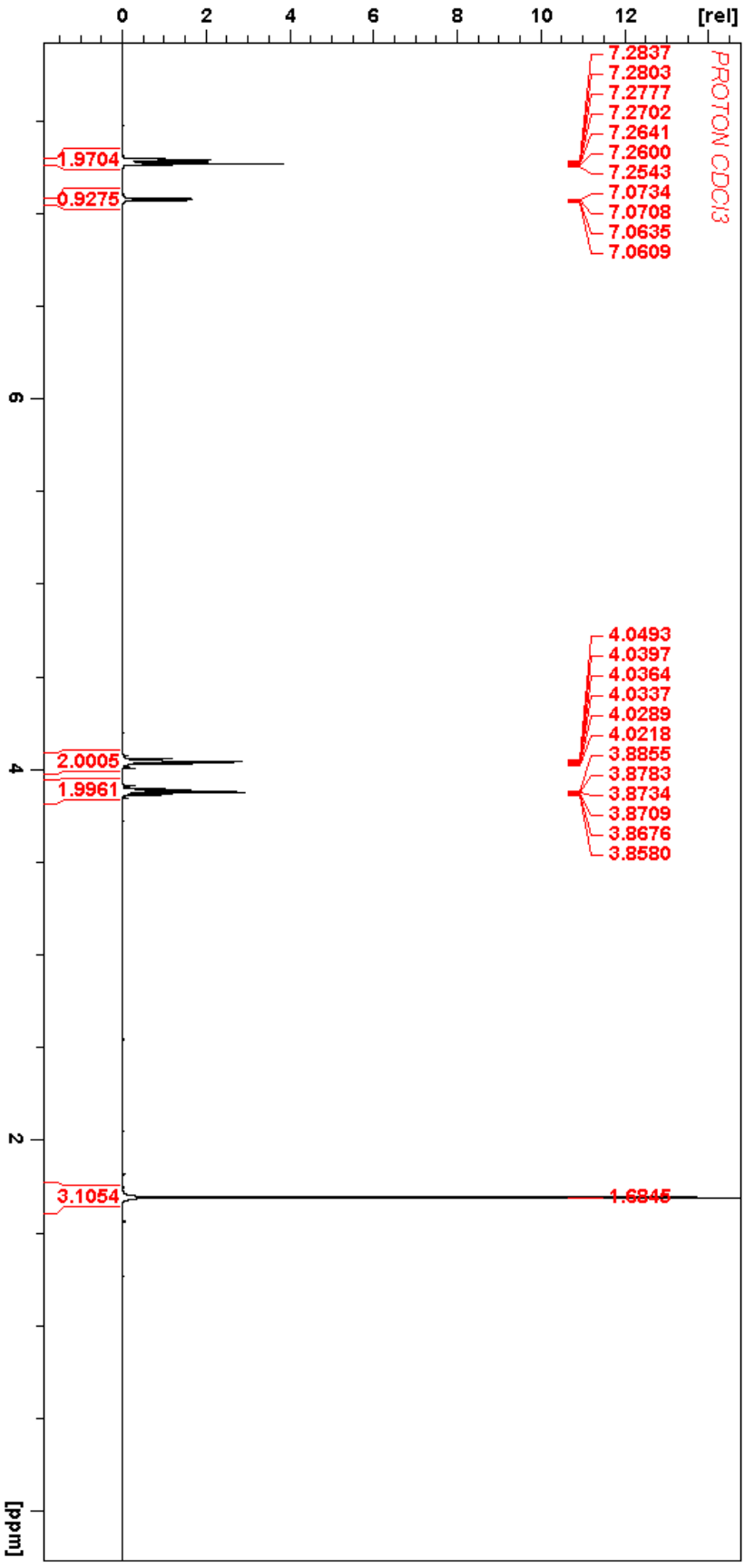

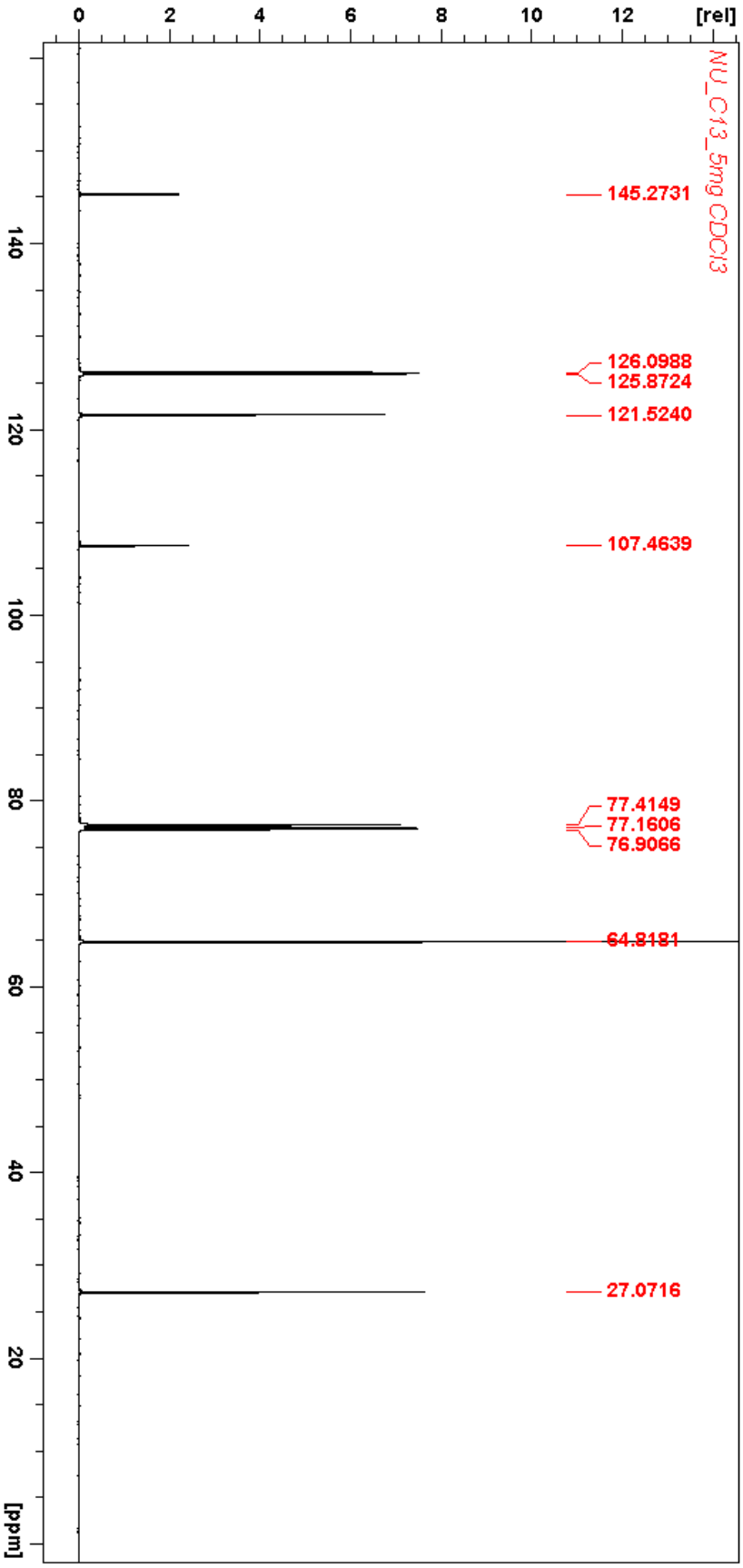

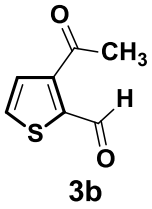

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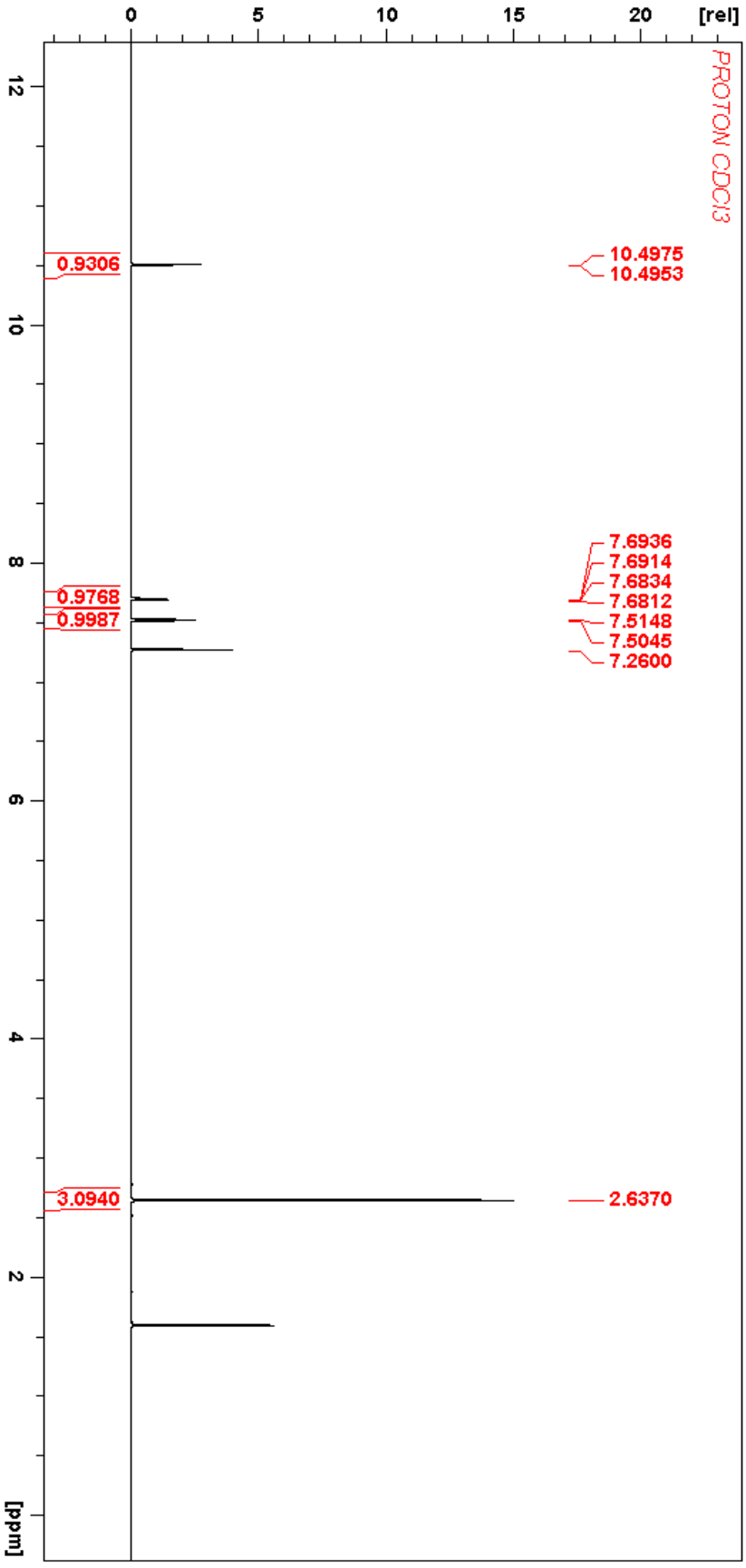

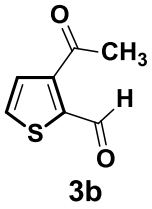

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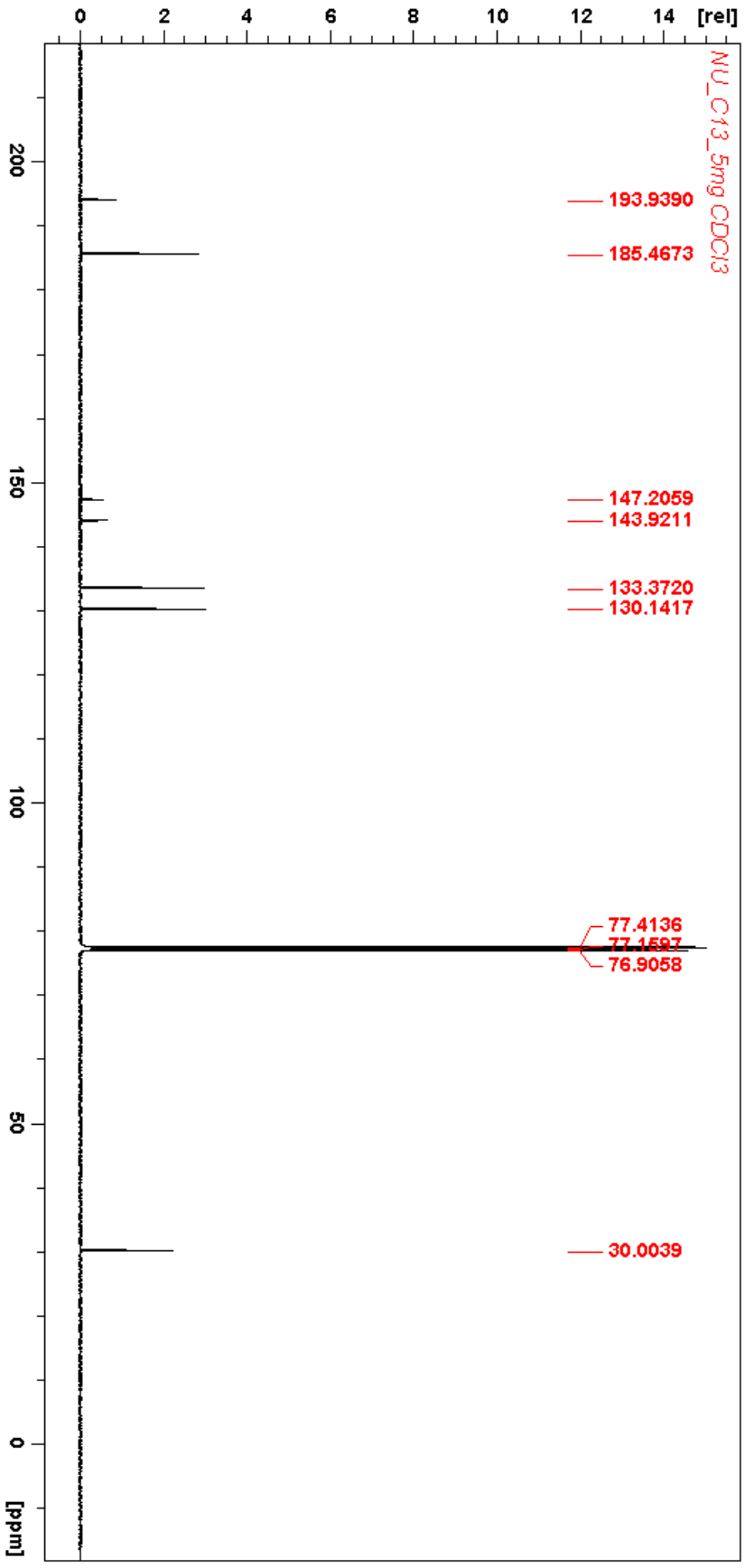

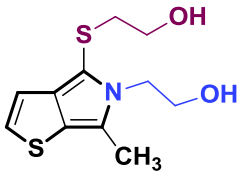

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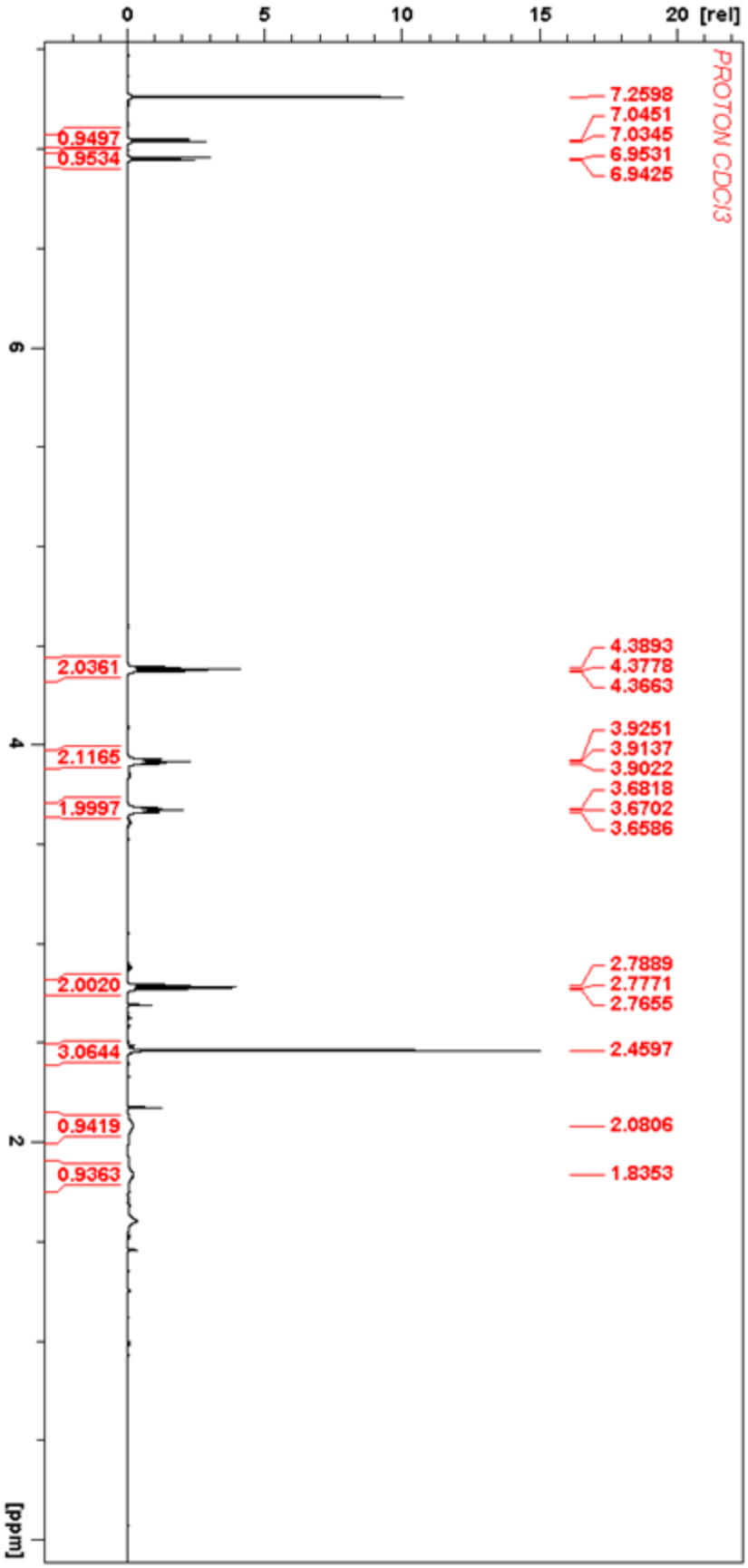

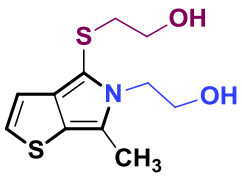

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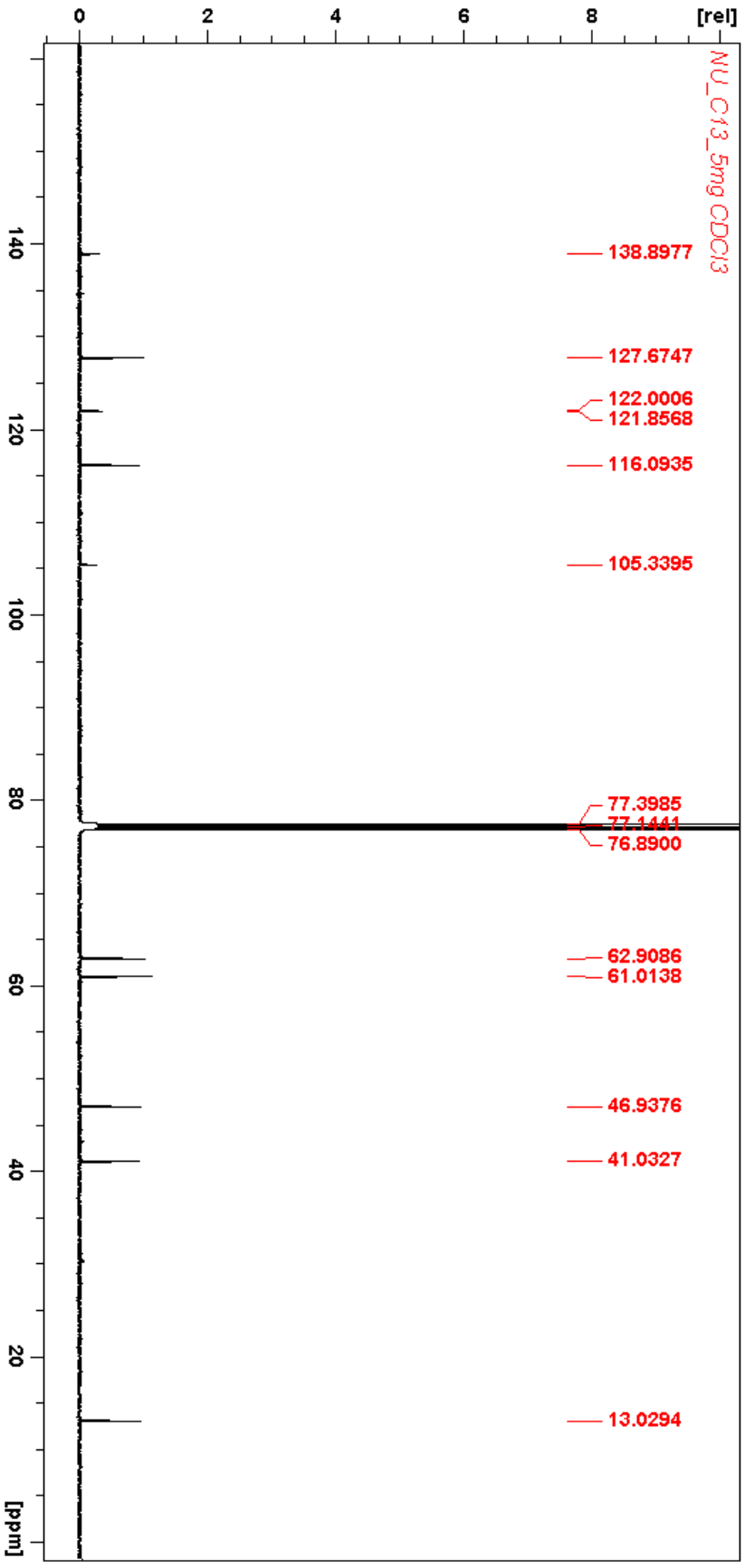

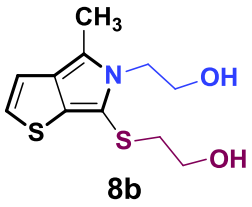

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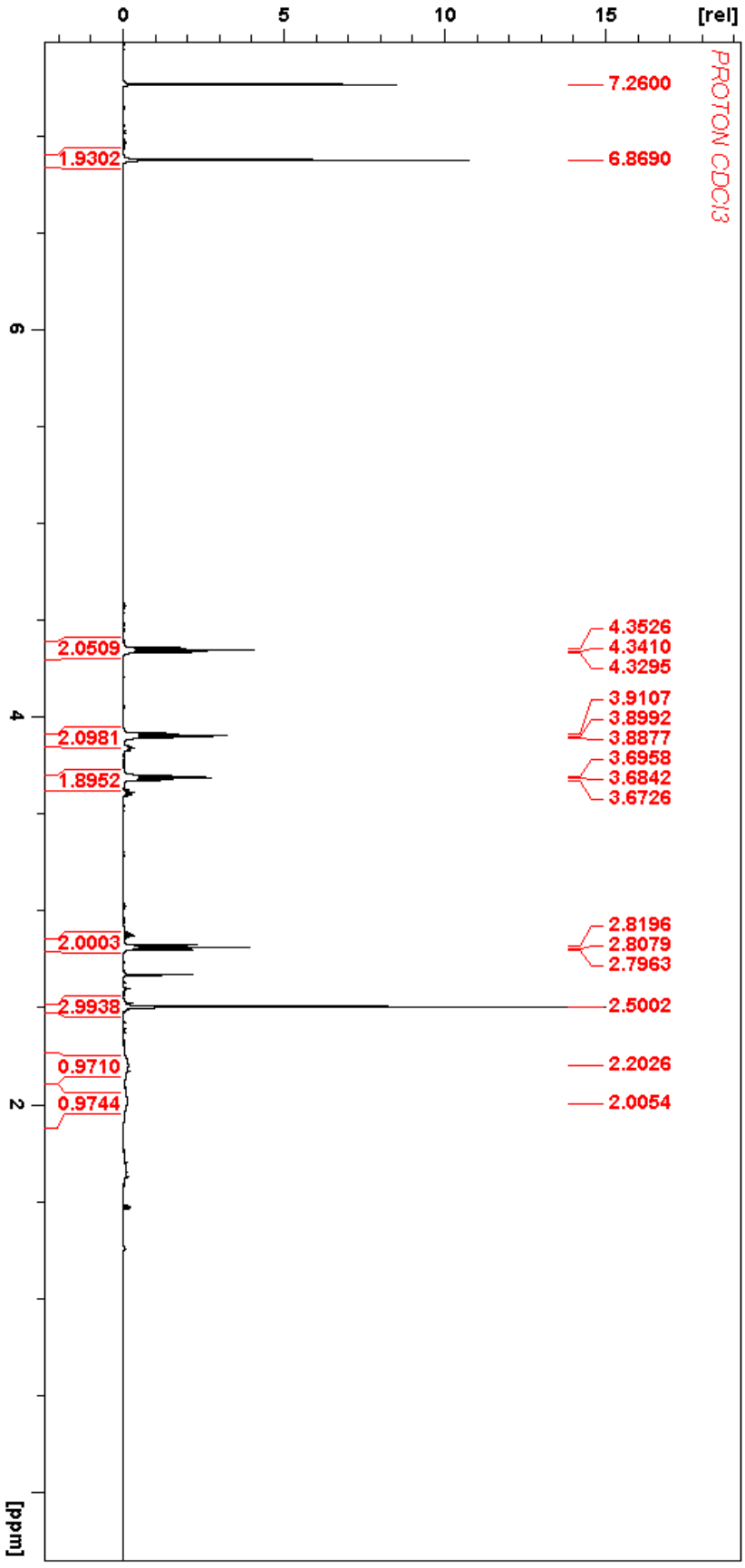

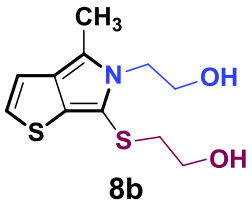

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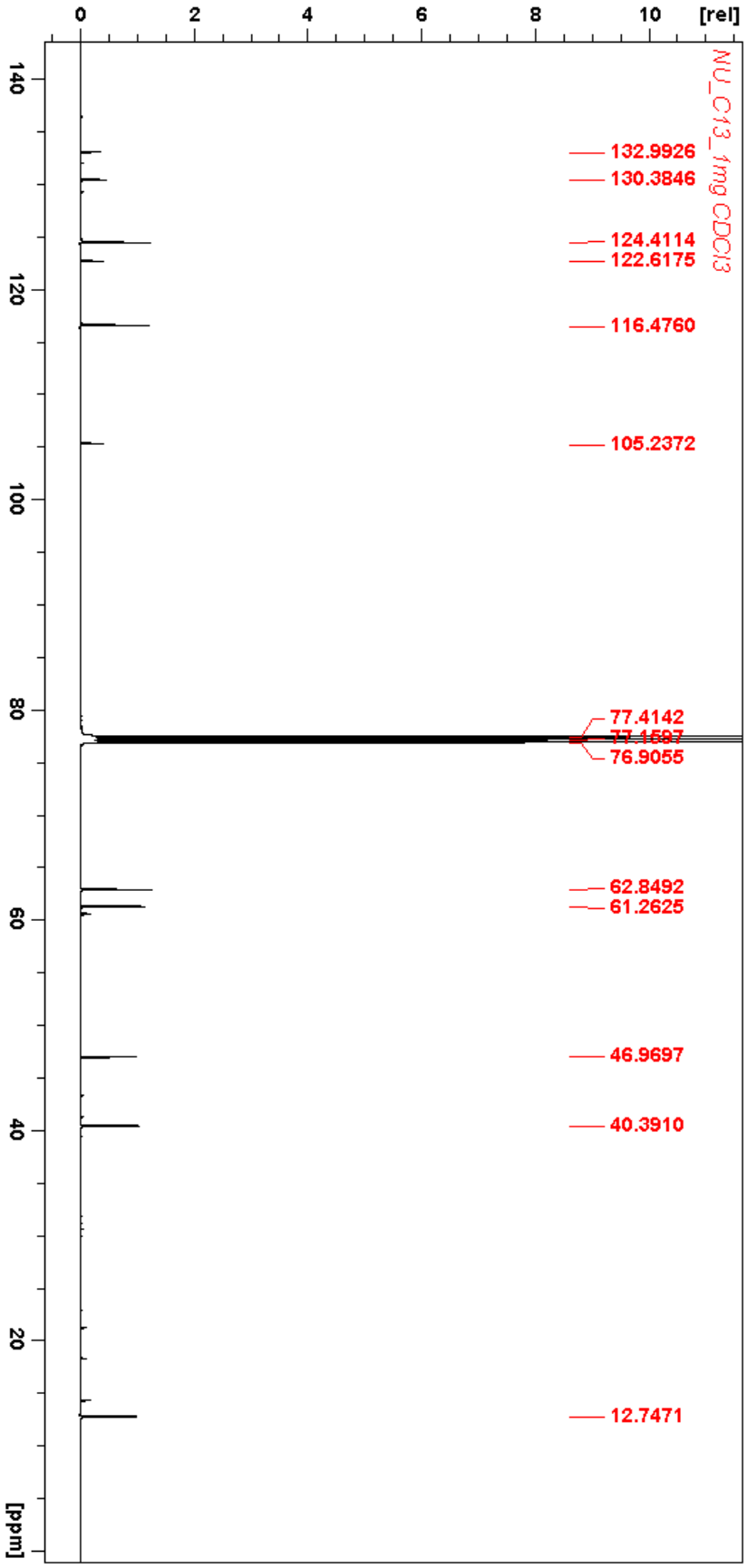

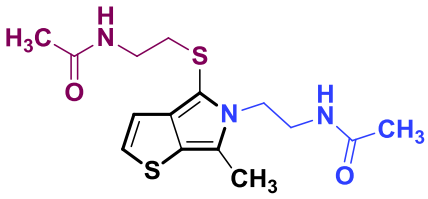

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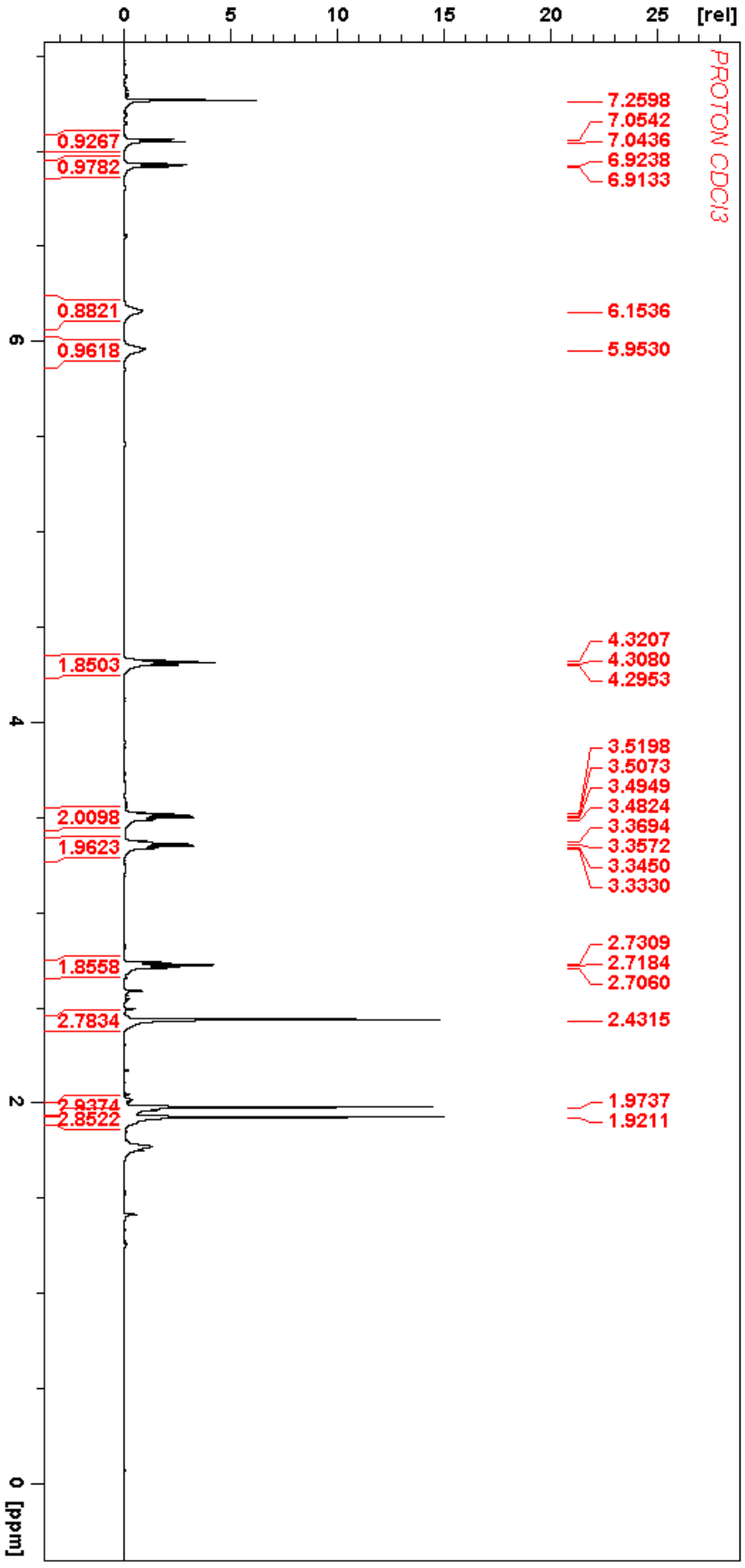

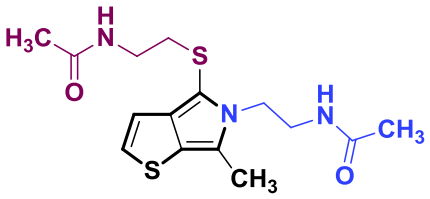

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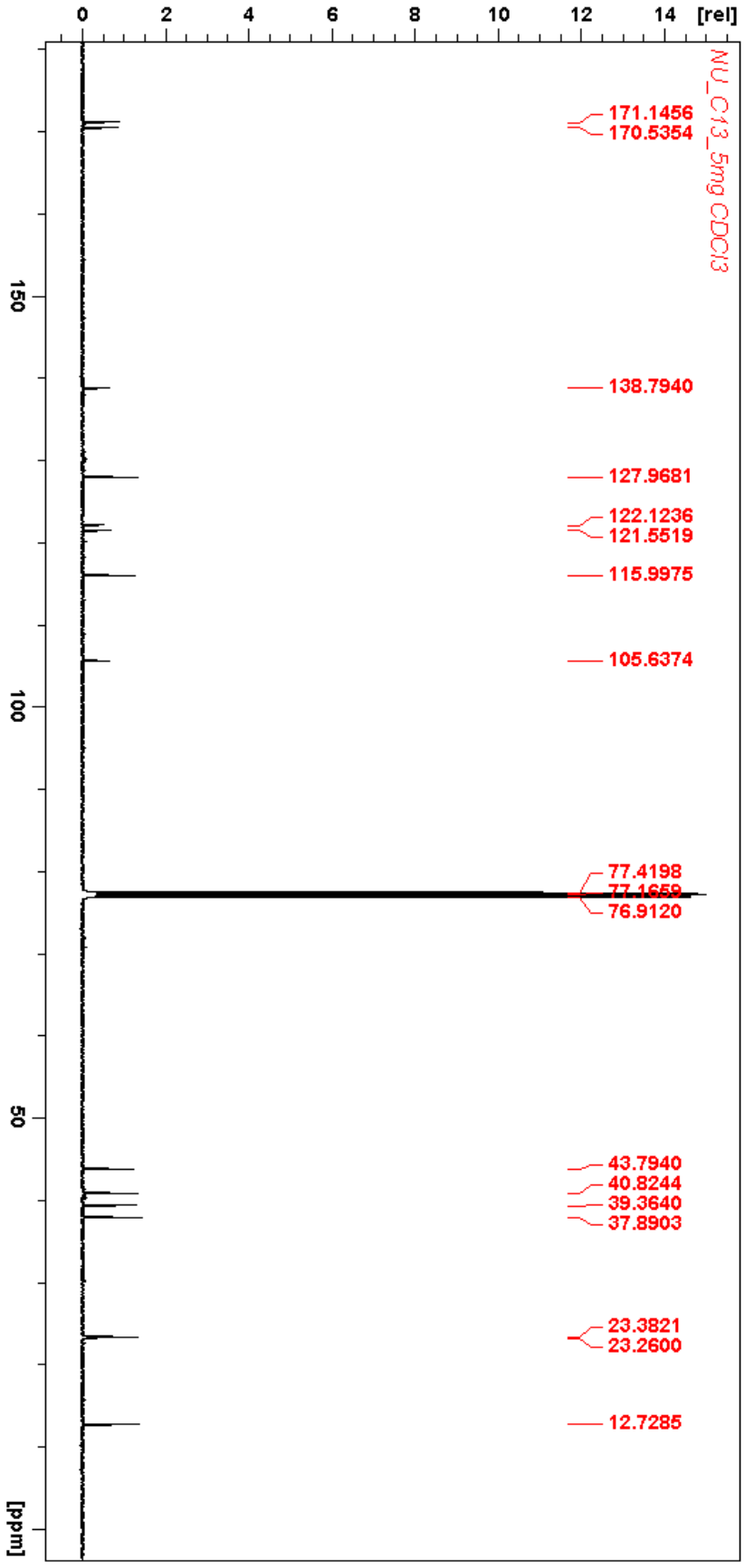

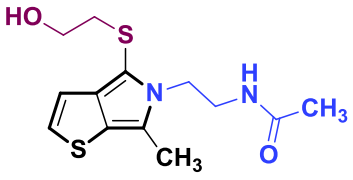

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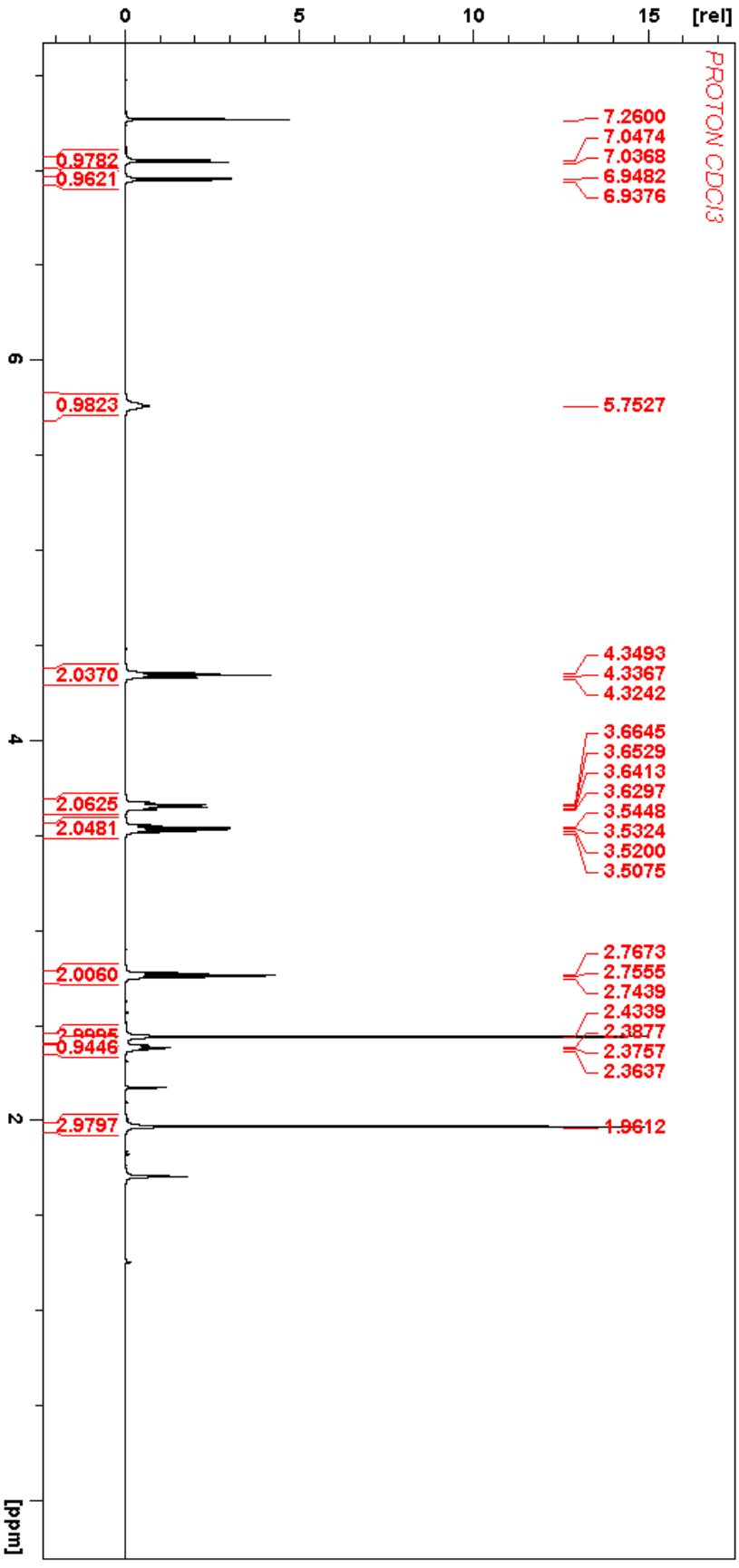

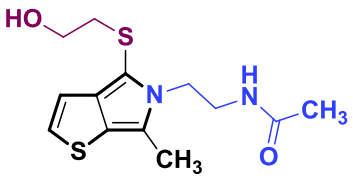

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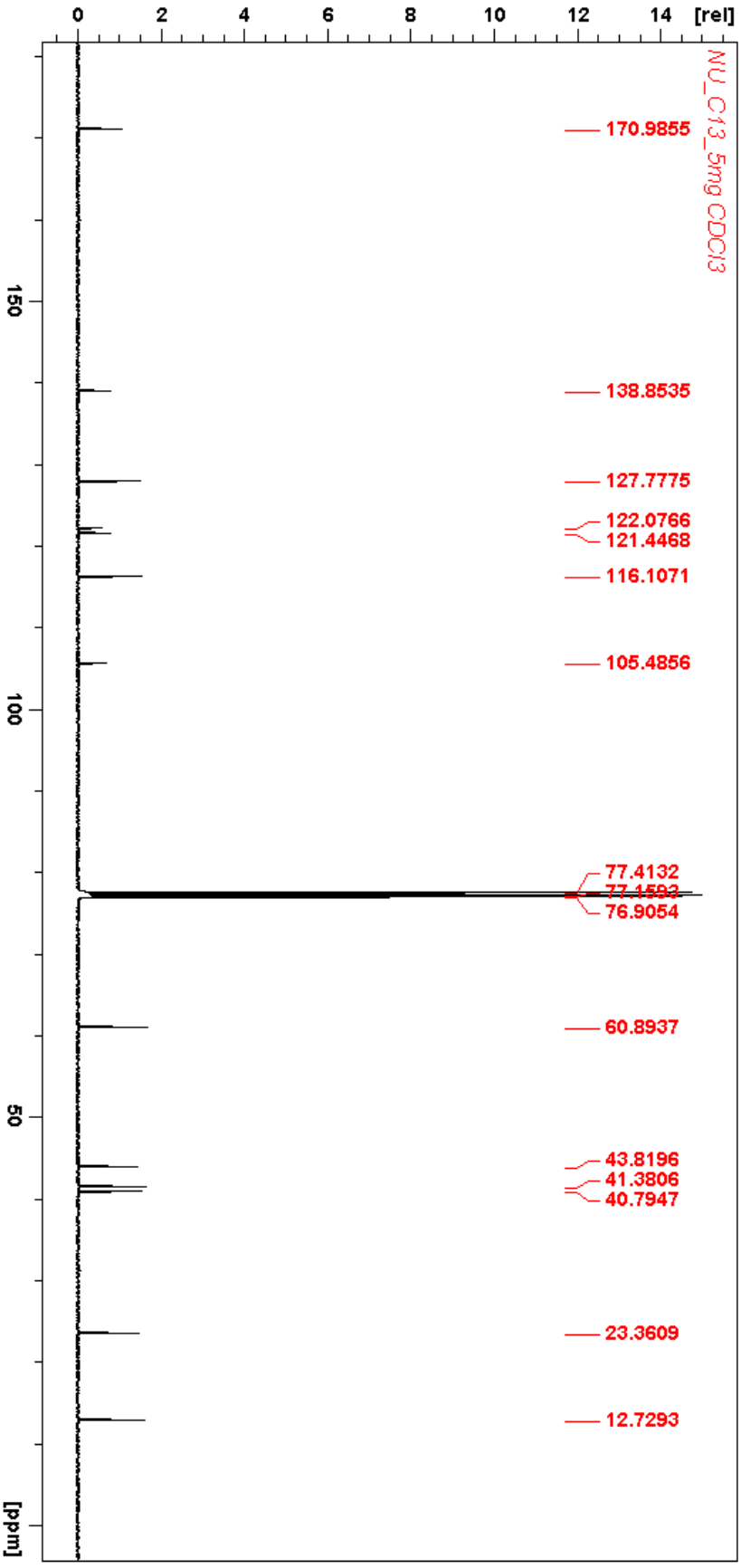

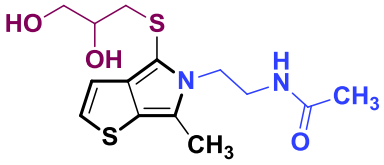

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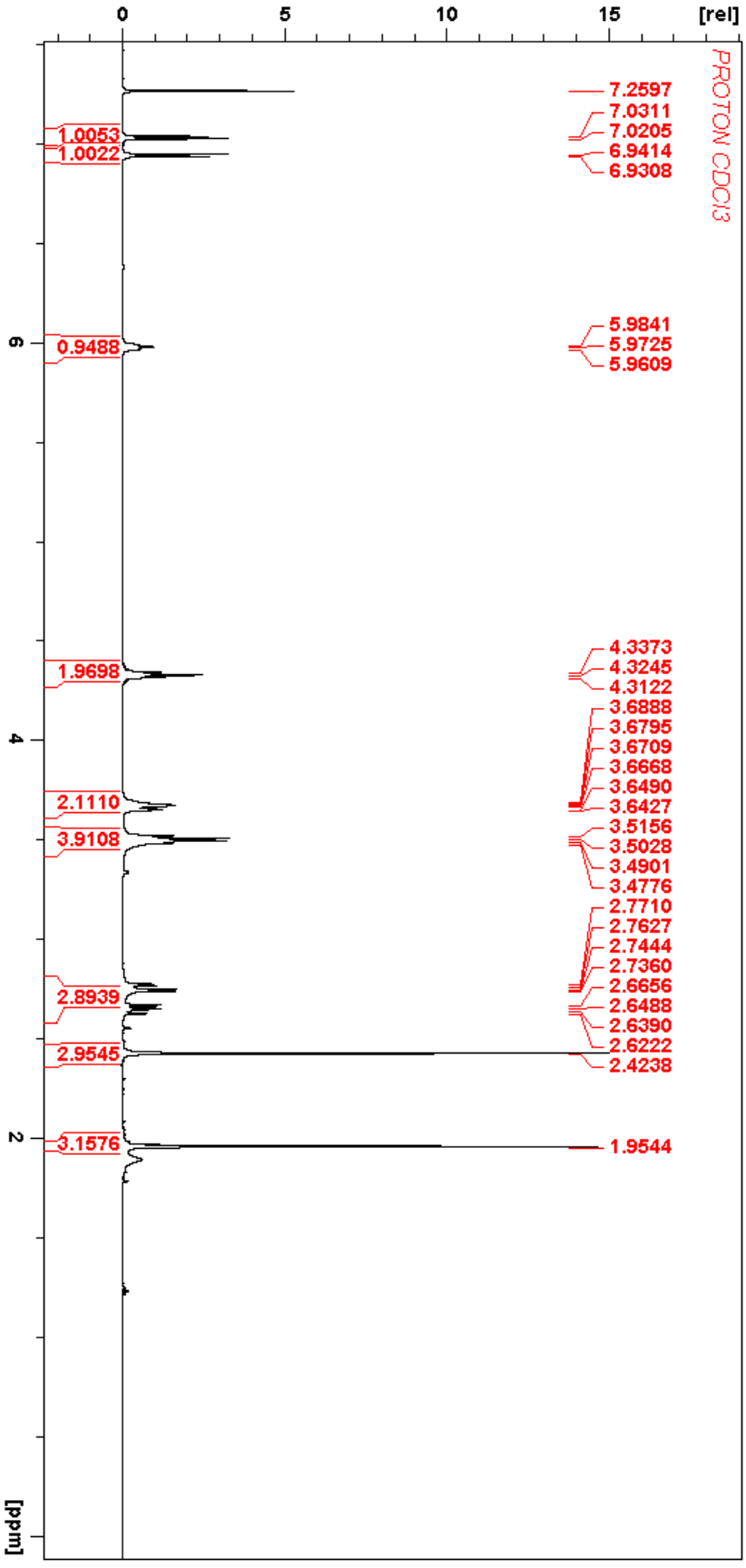

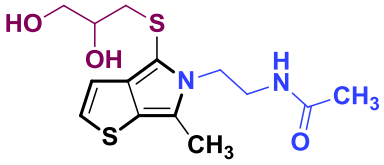

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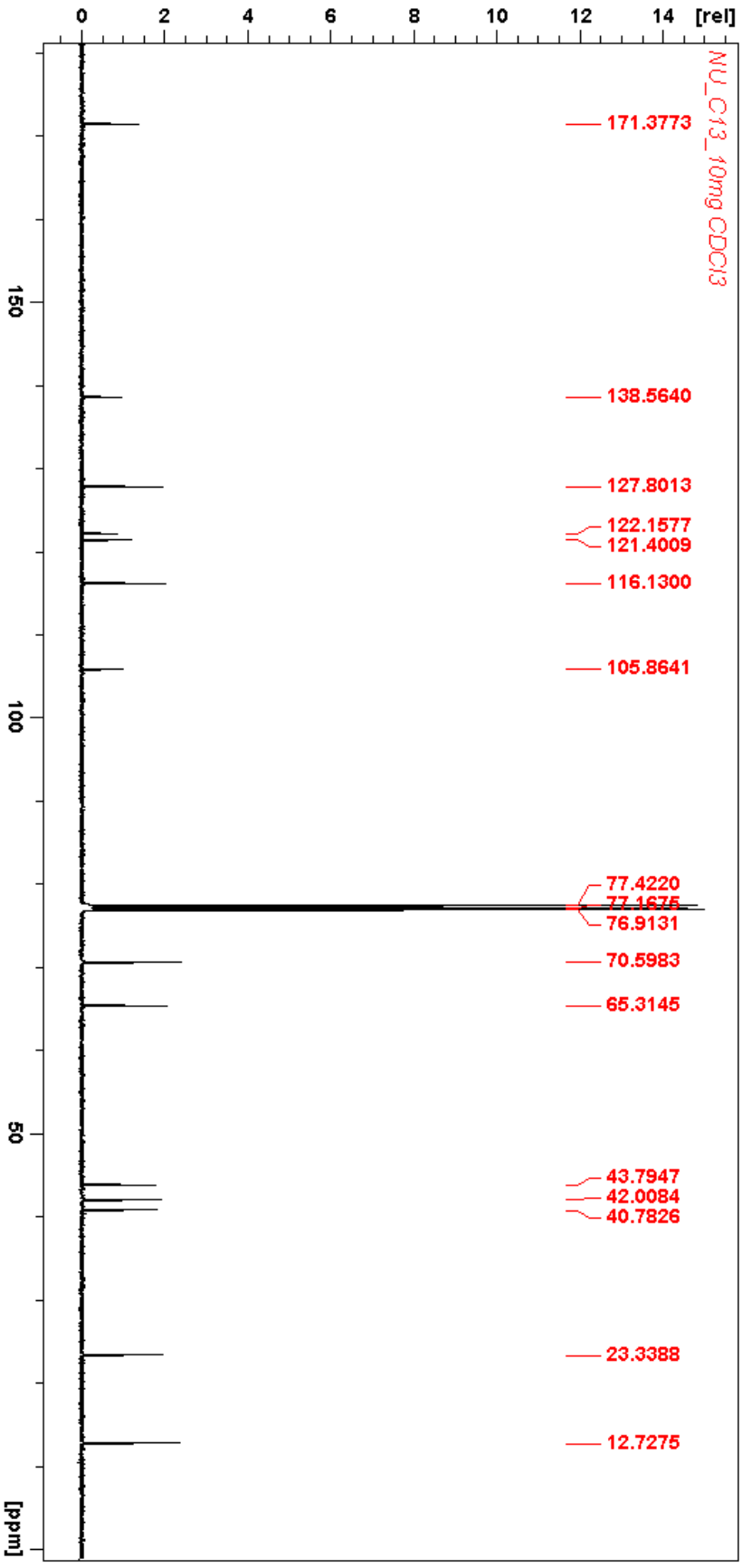

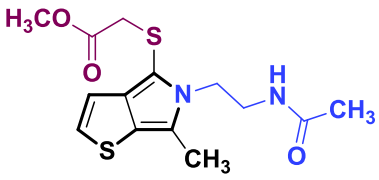

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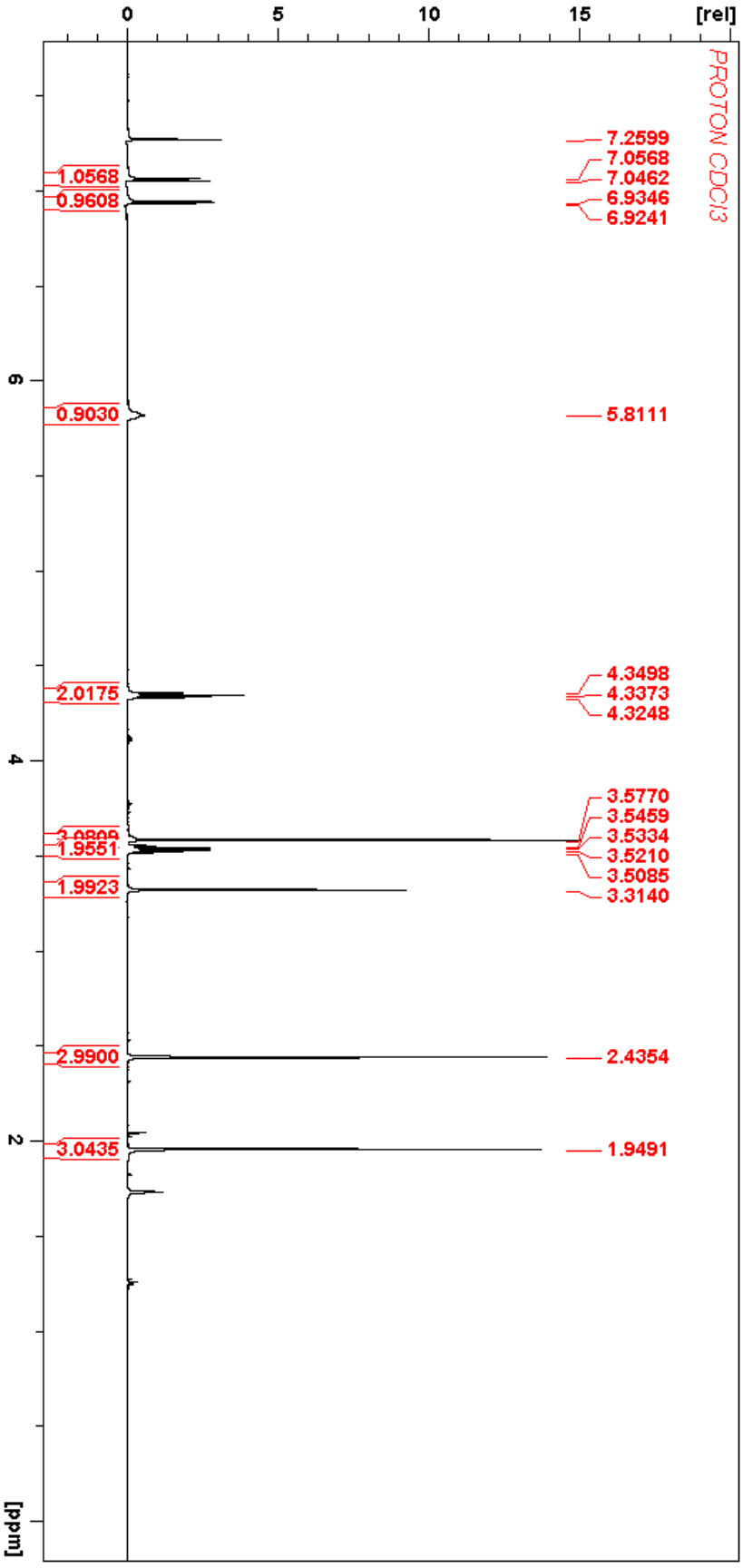

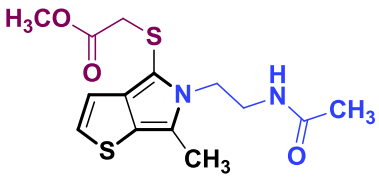

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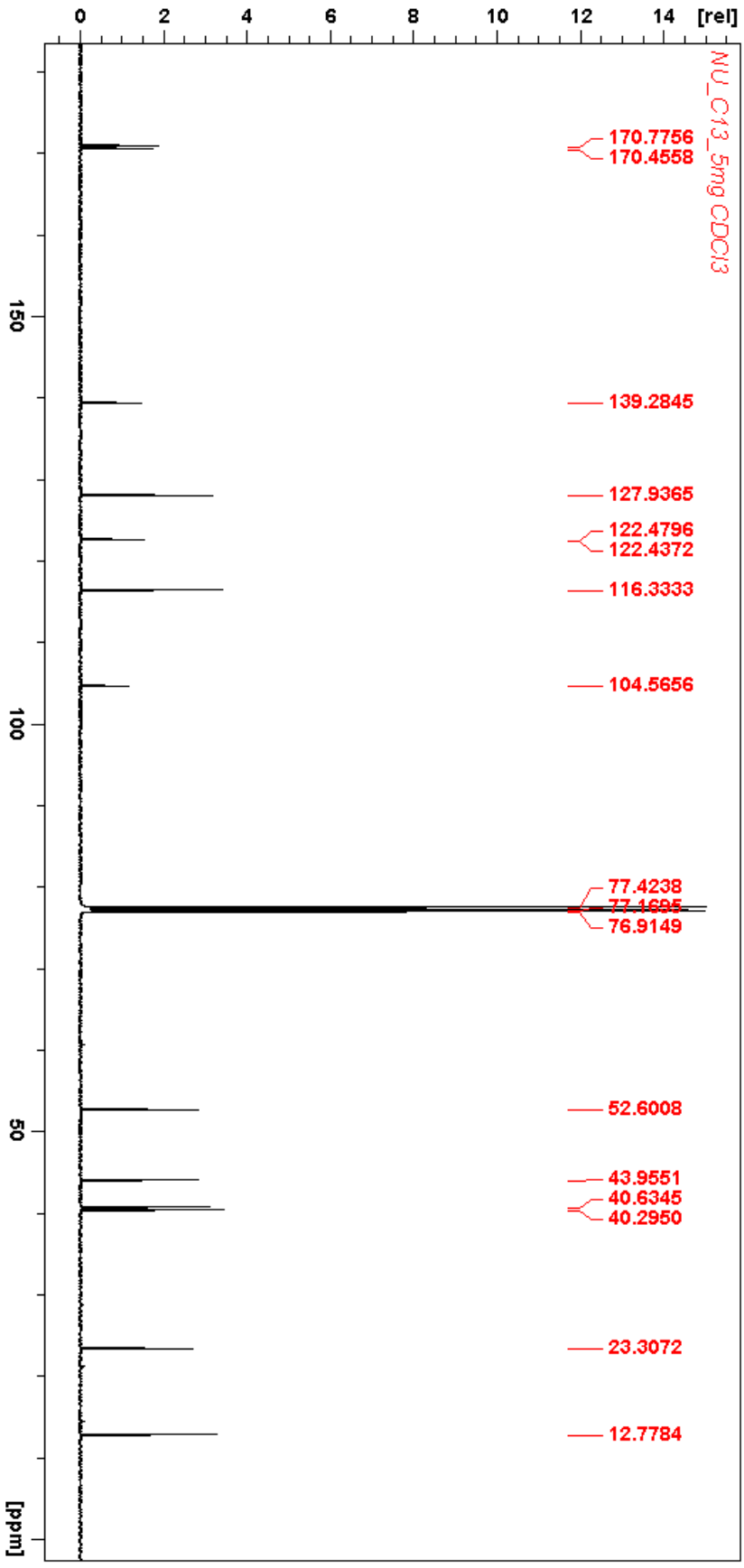

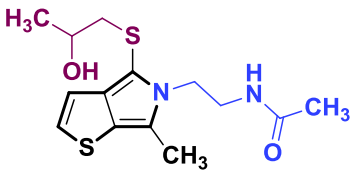

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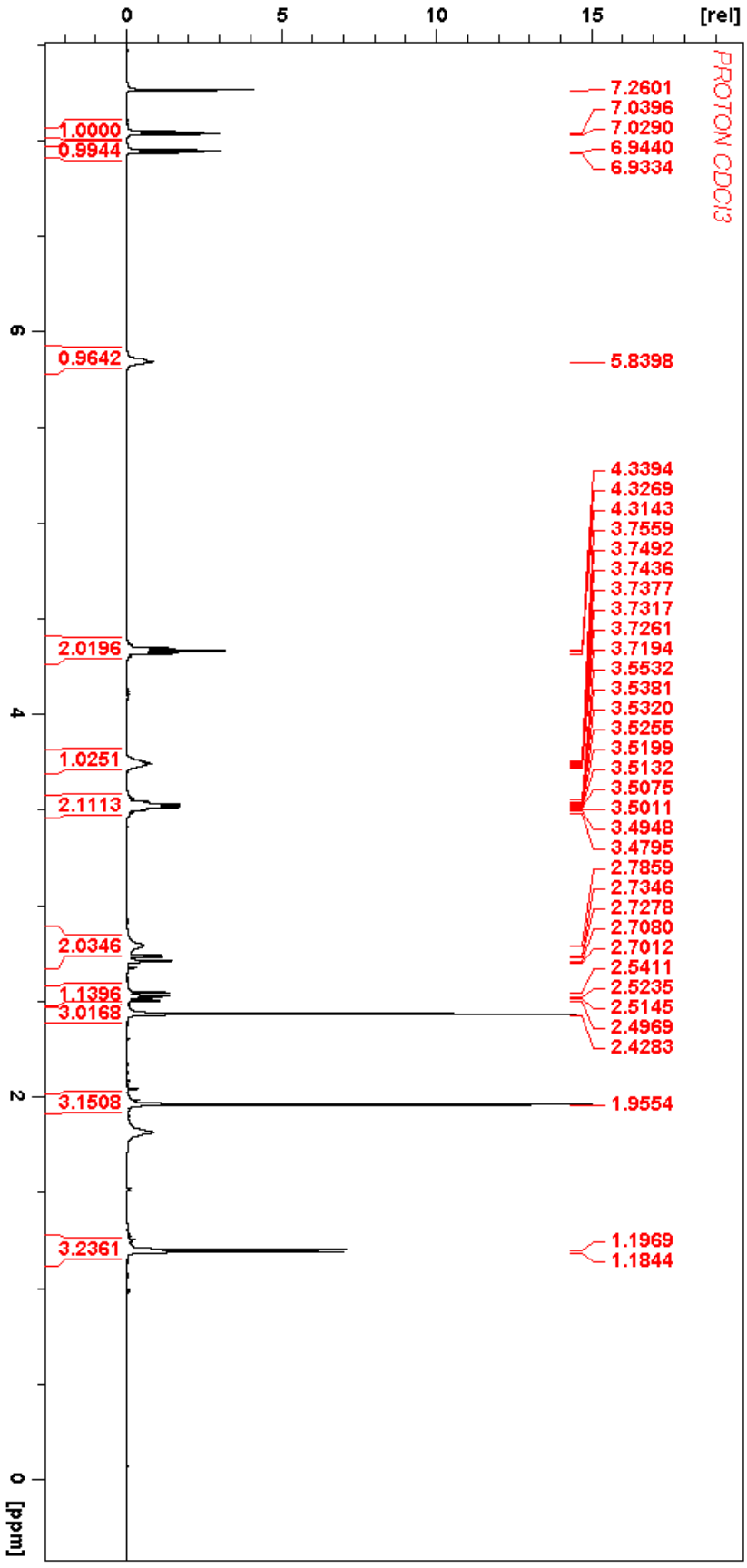

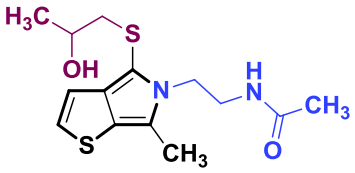

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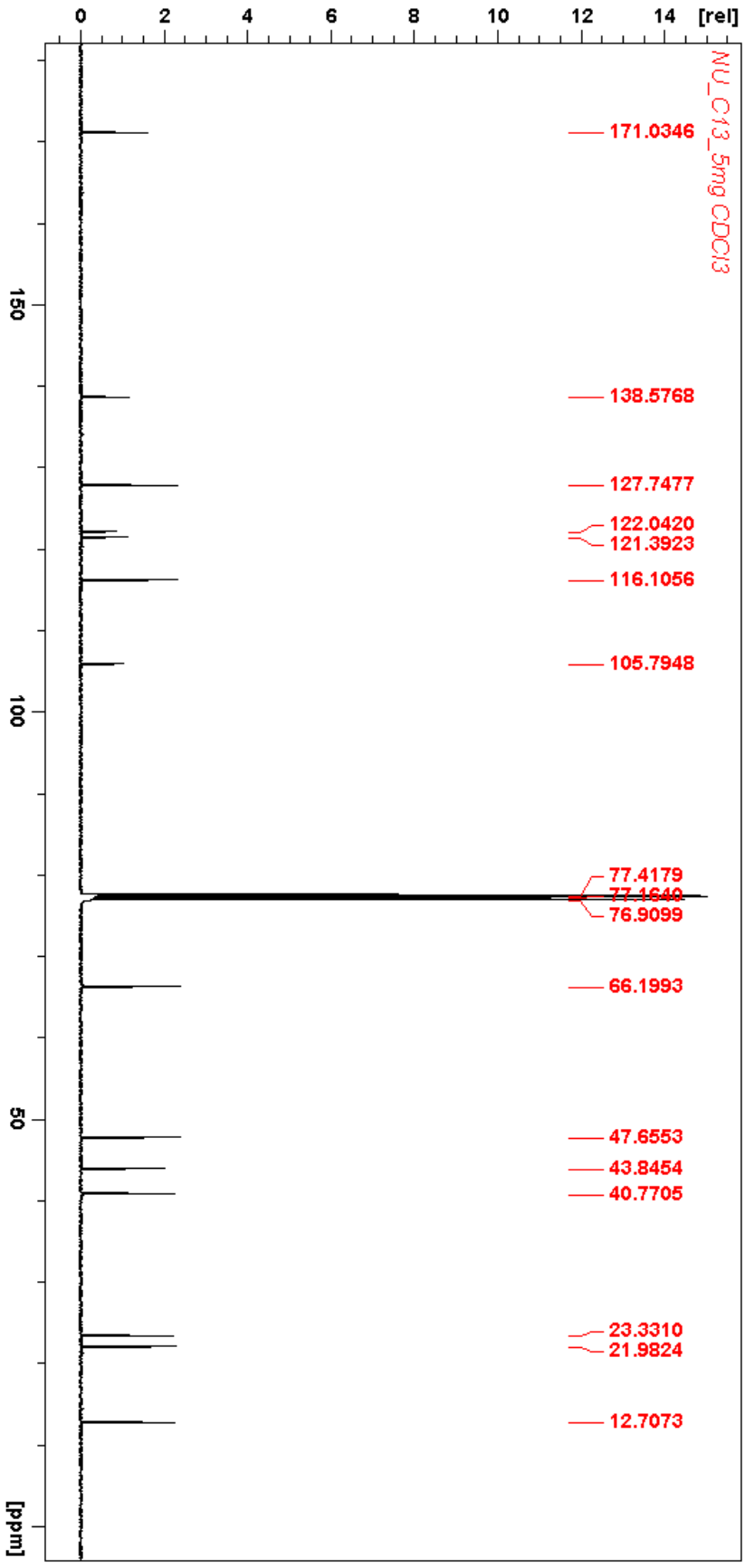

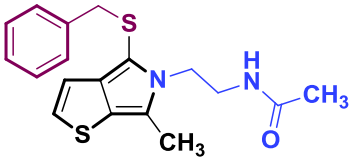

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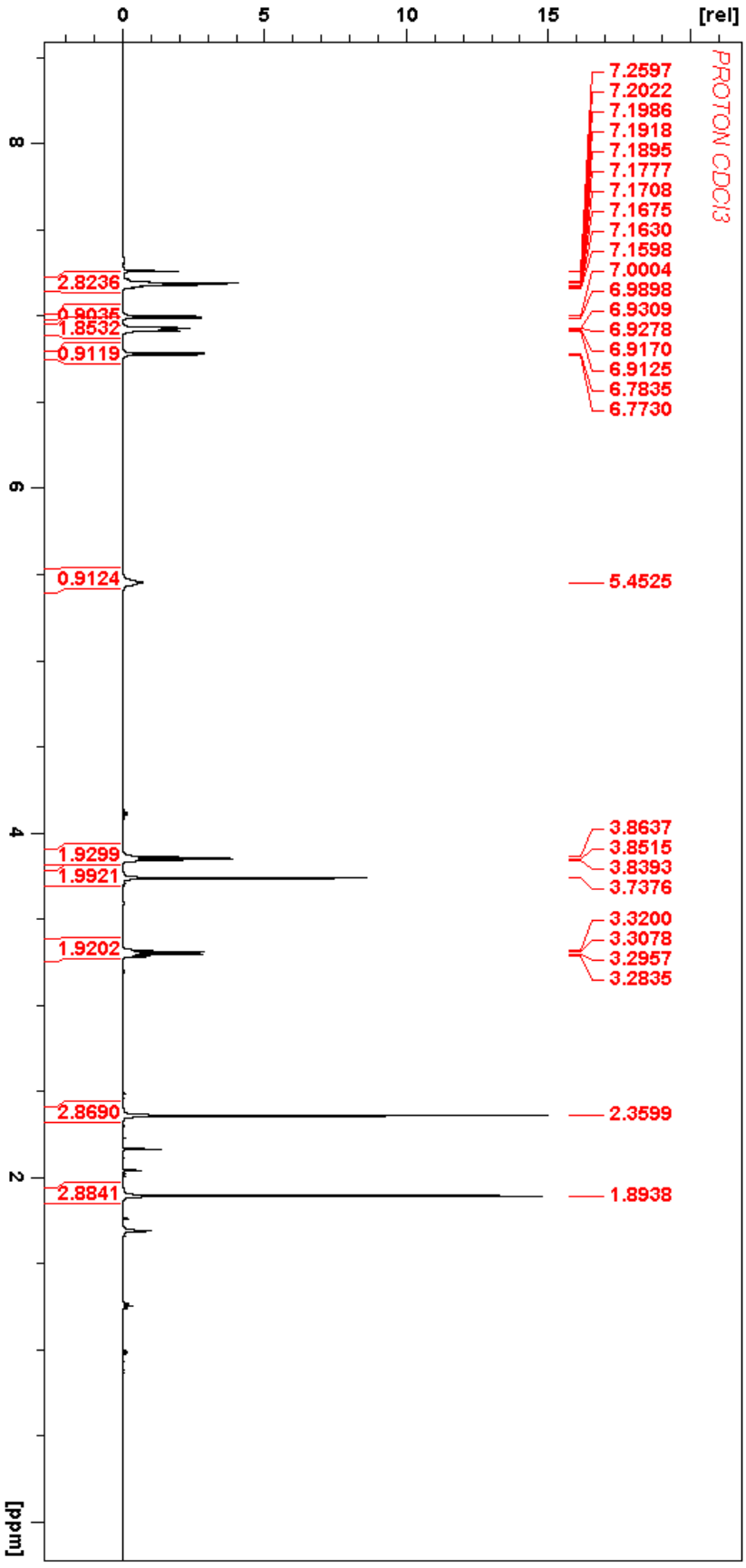

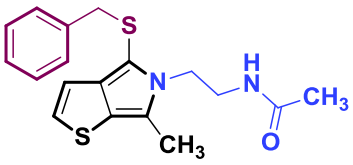

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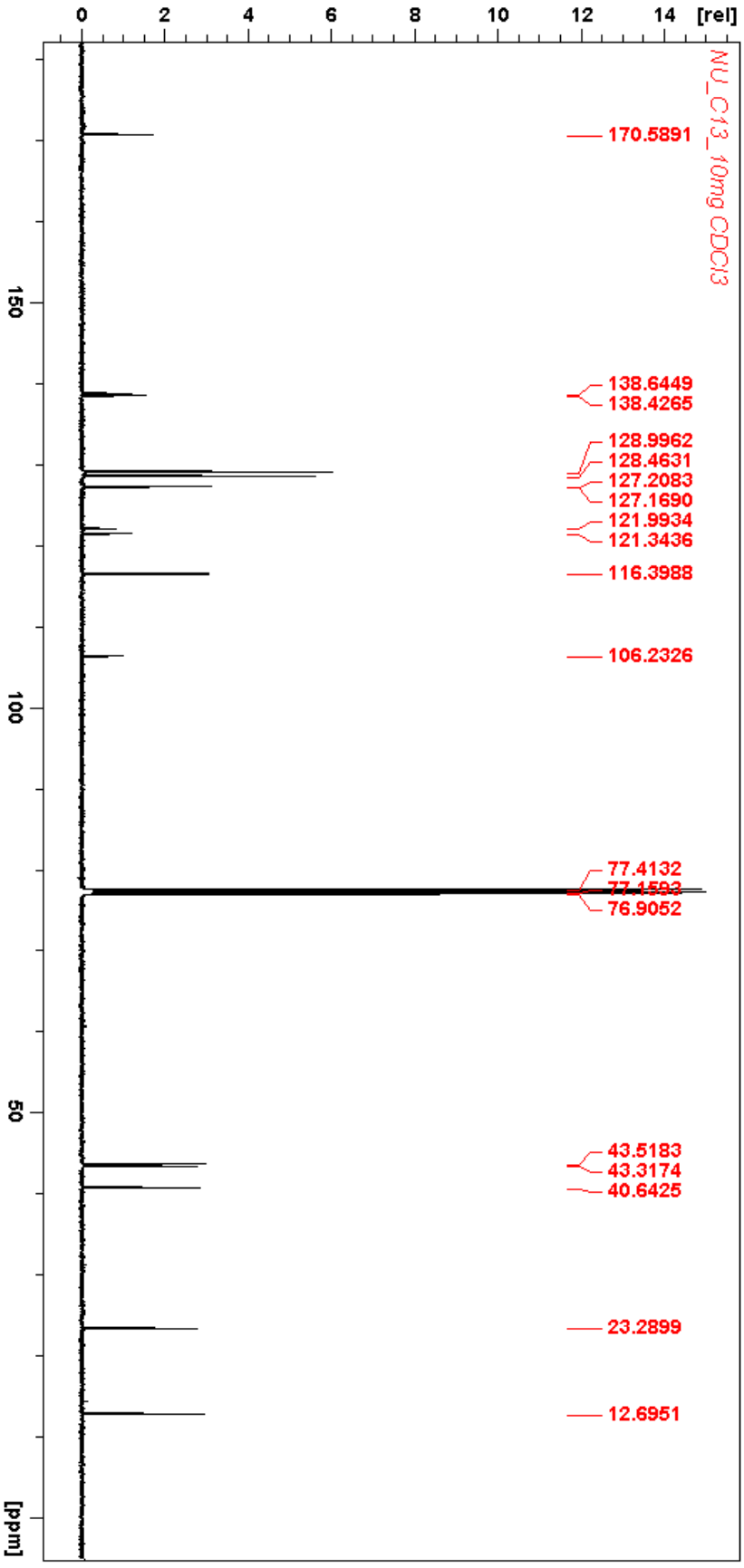

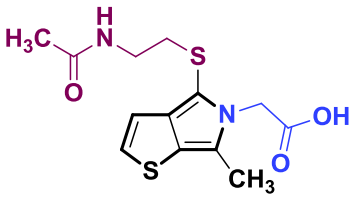

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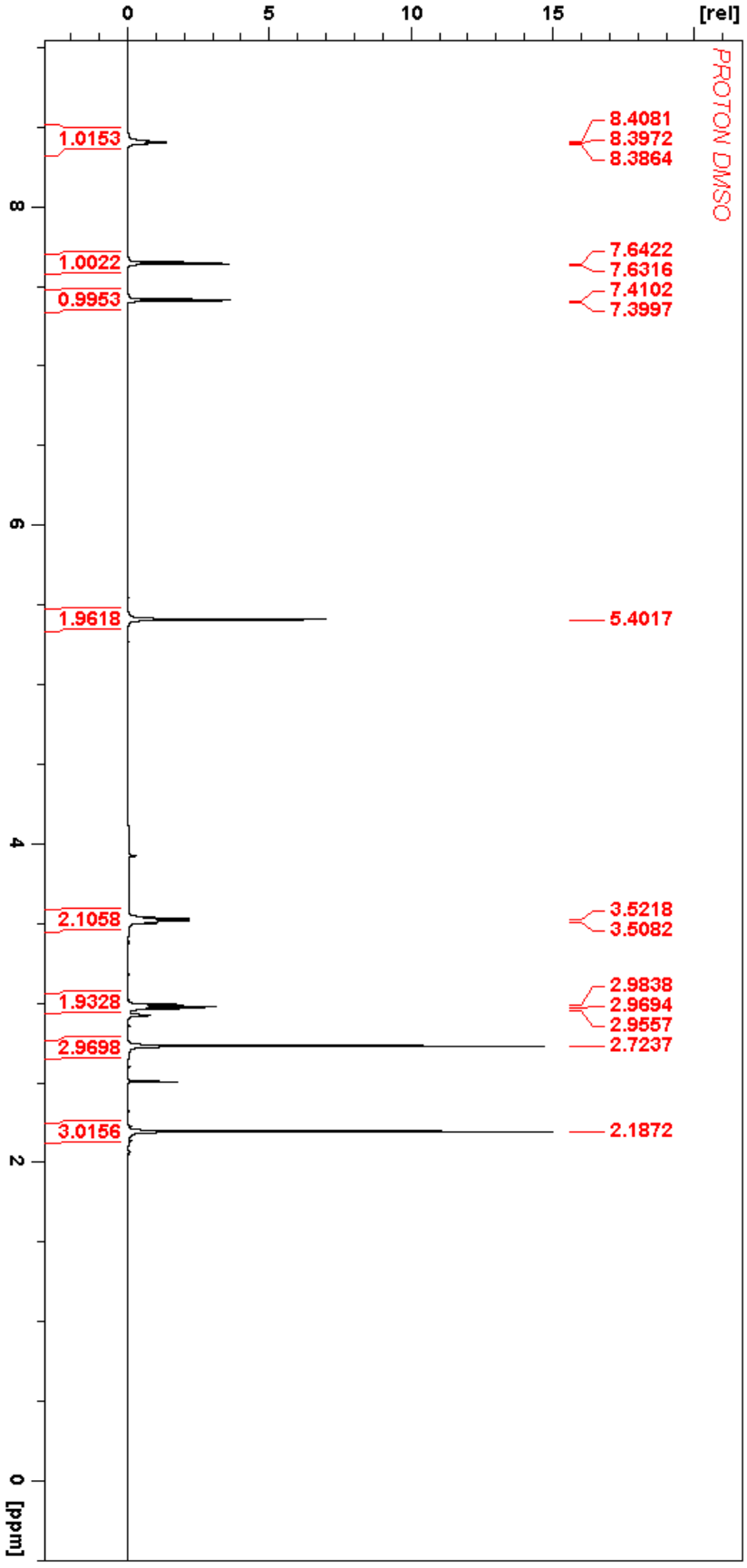

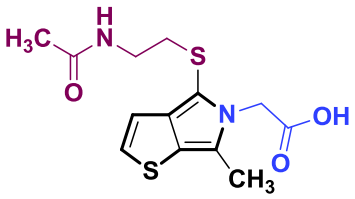
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CH3

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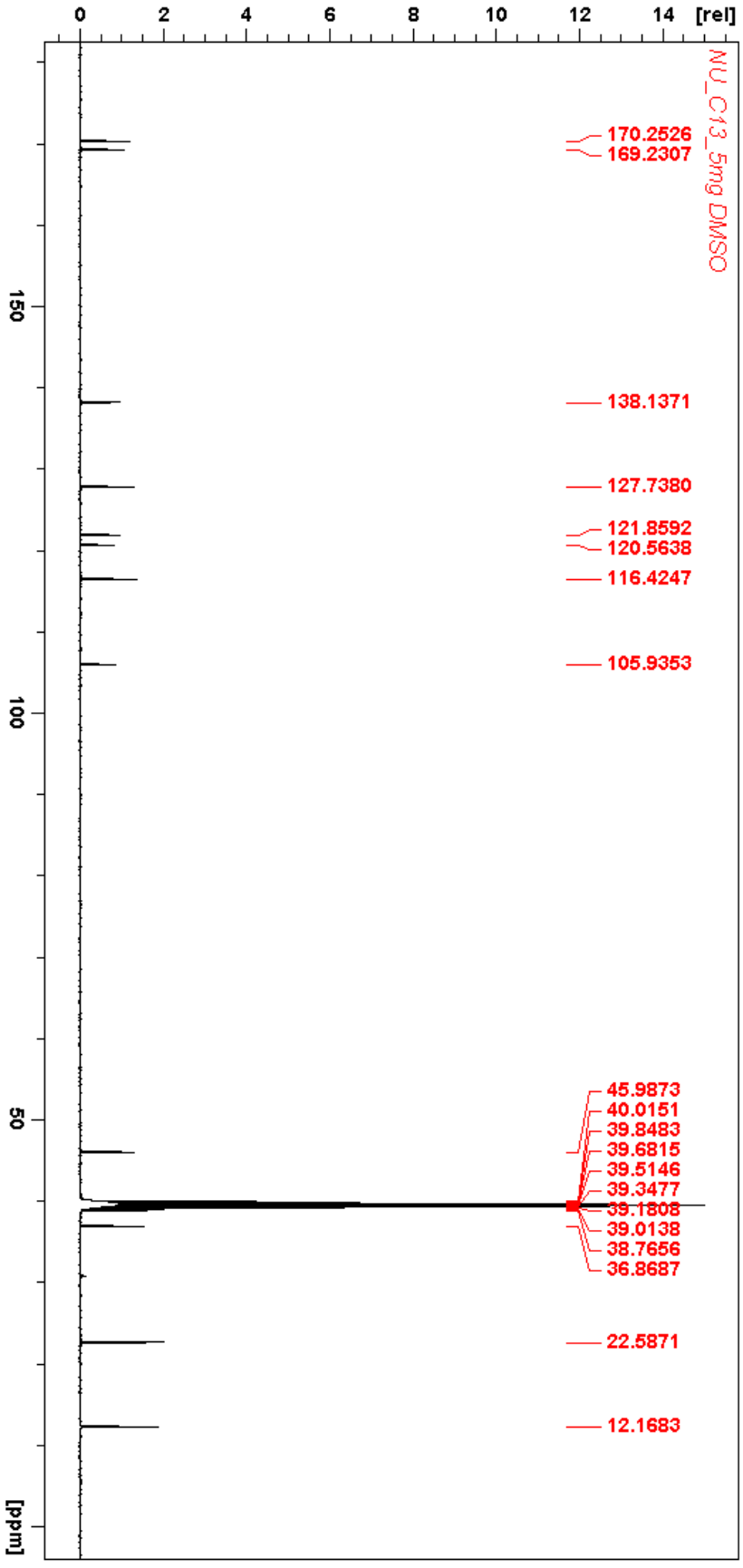
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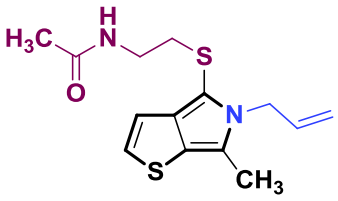

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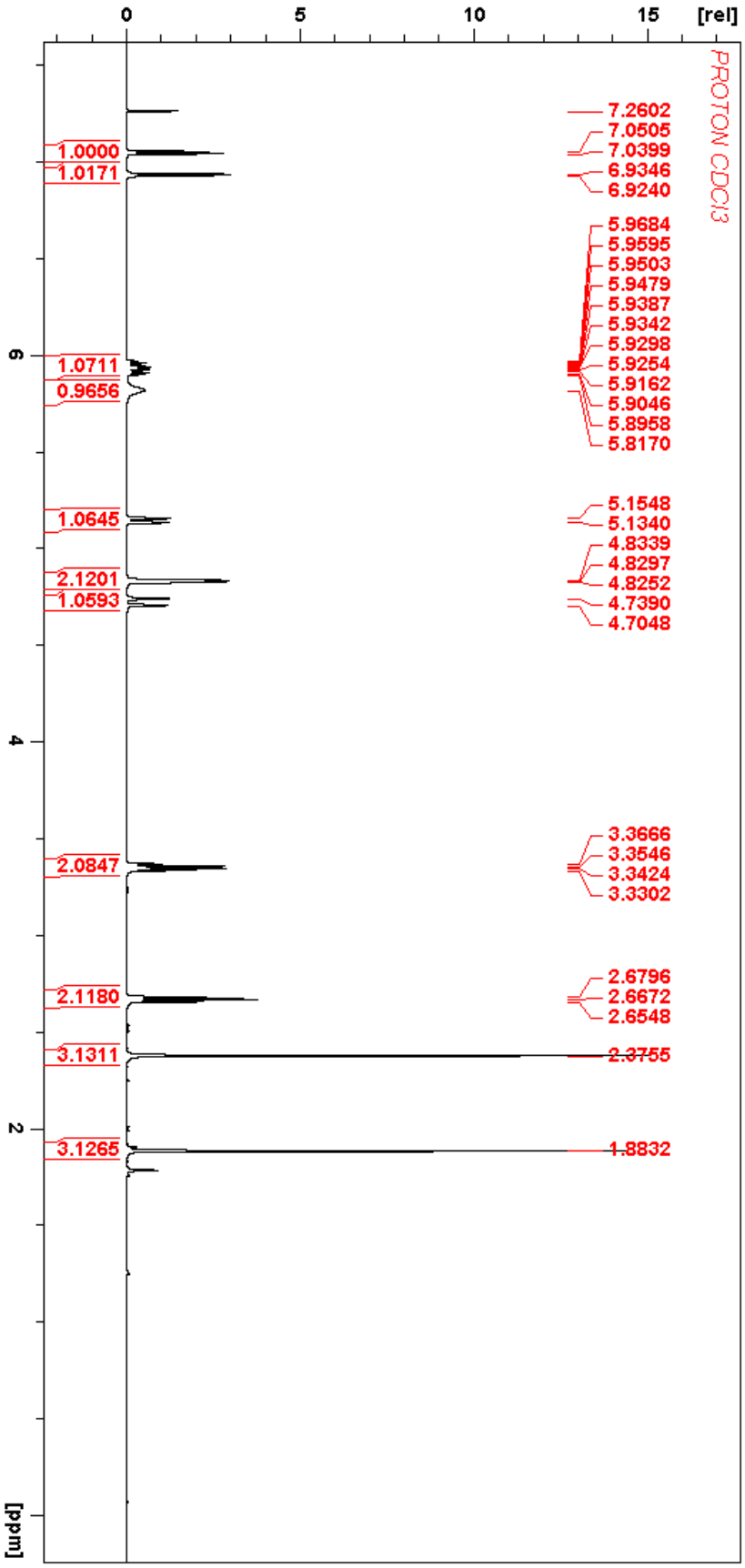

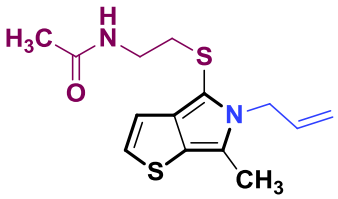

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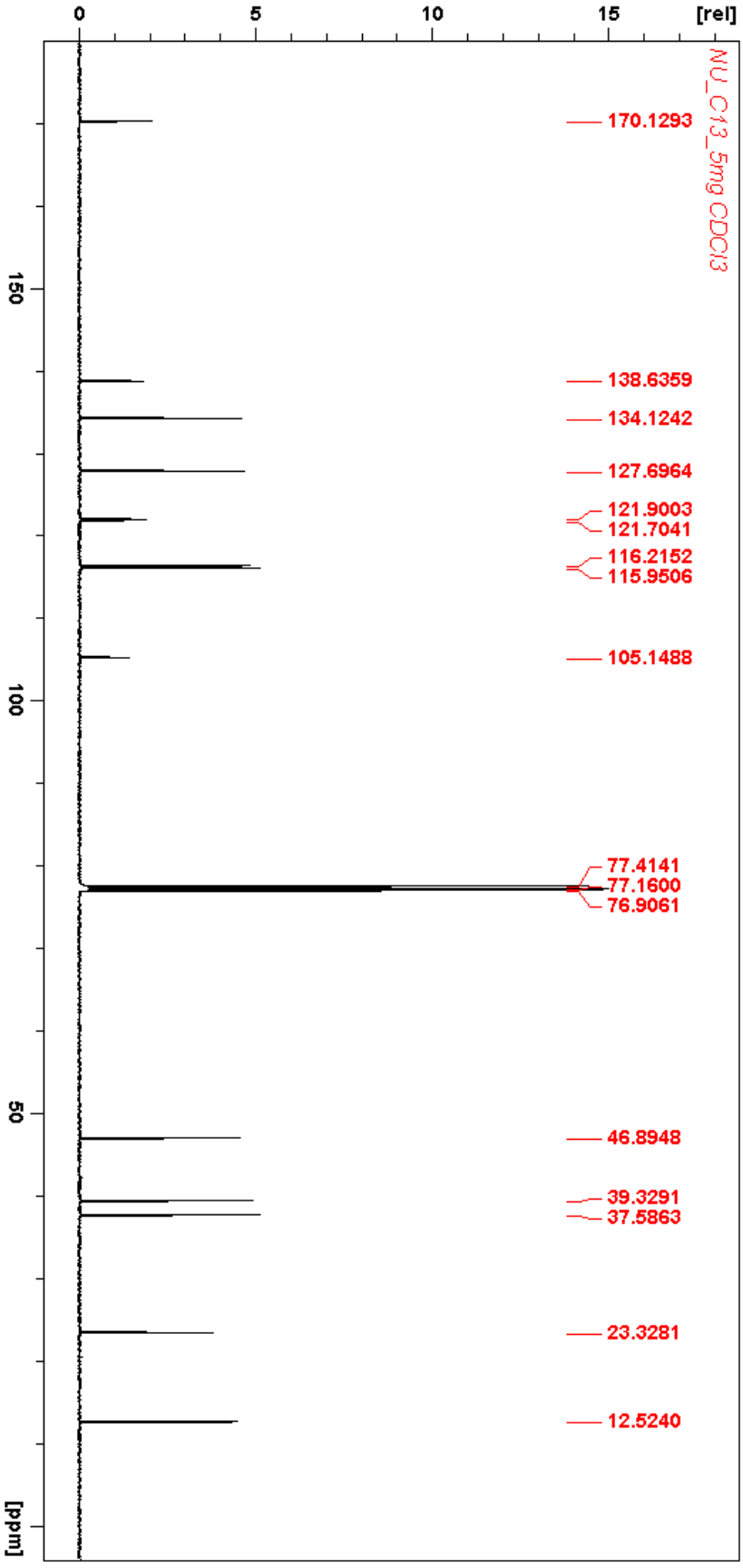

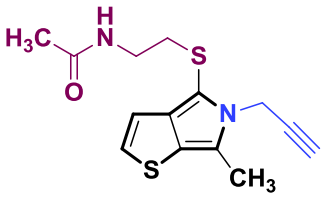

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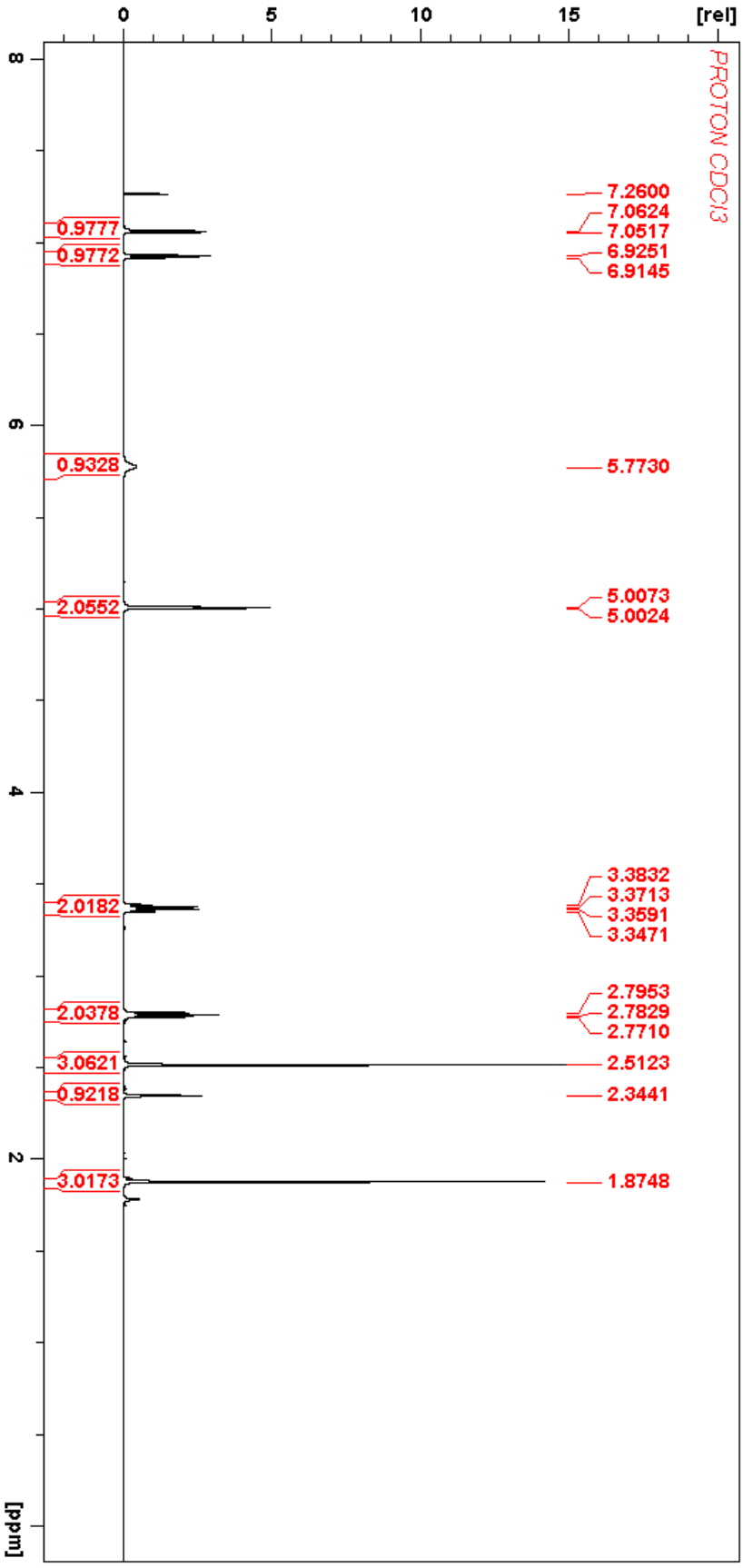

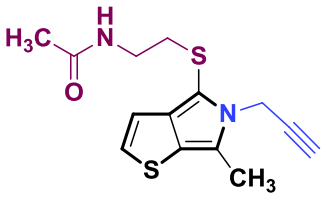

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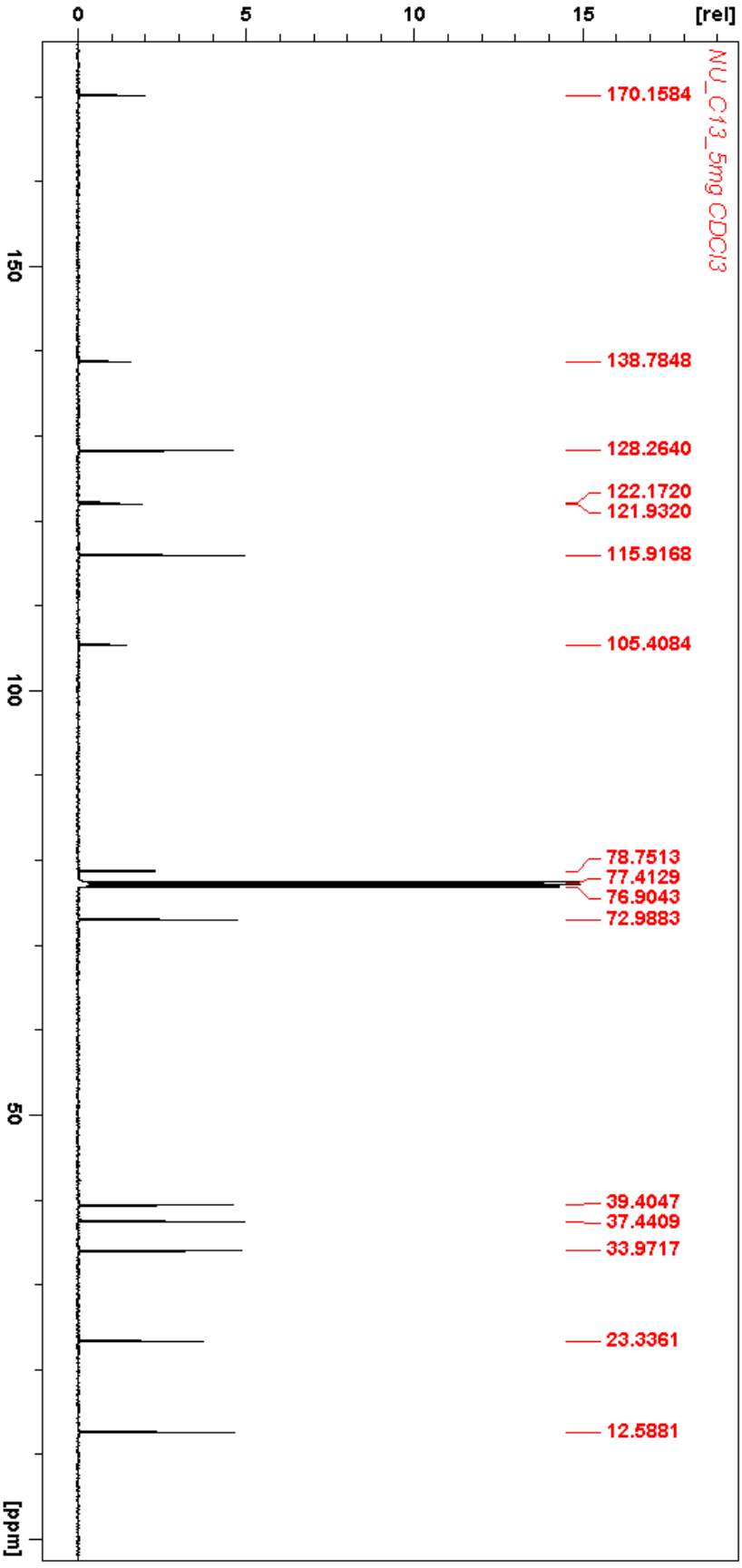

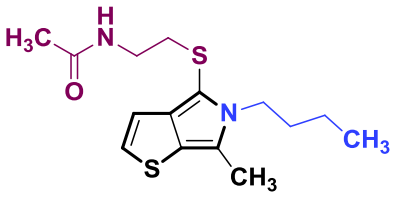

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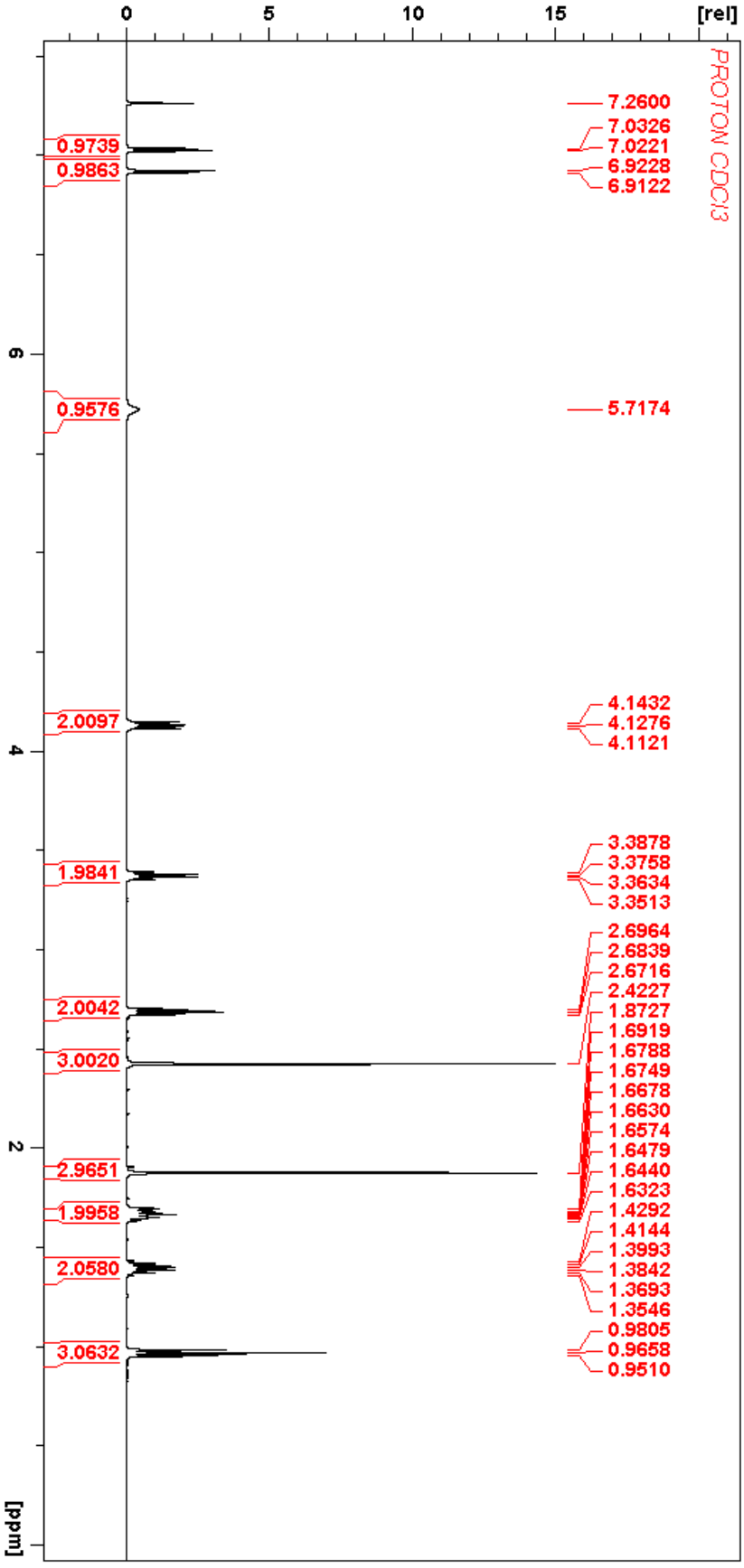

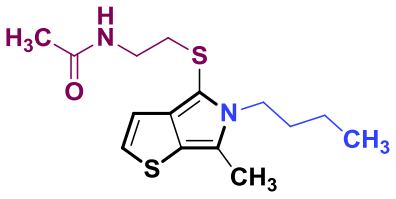

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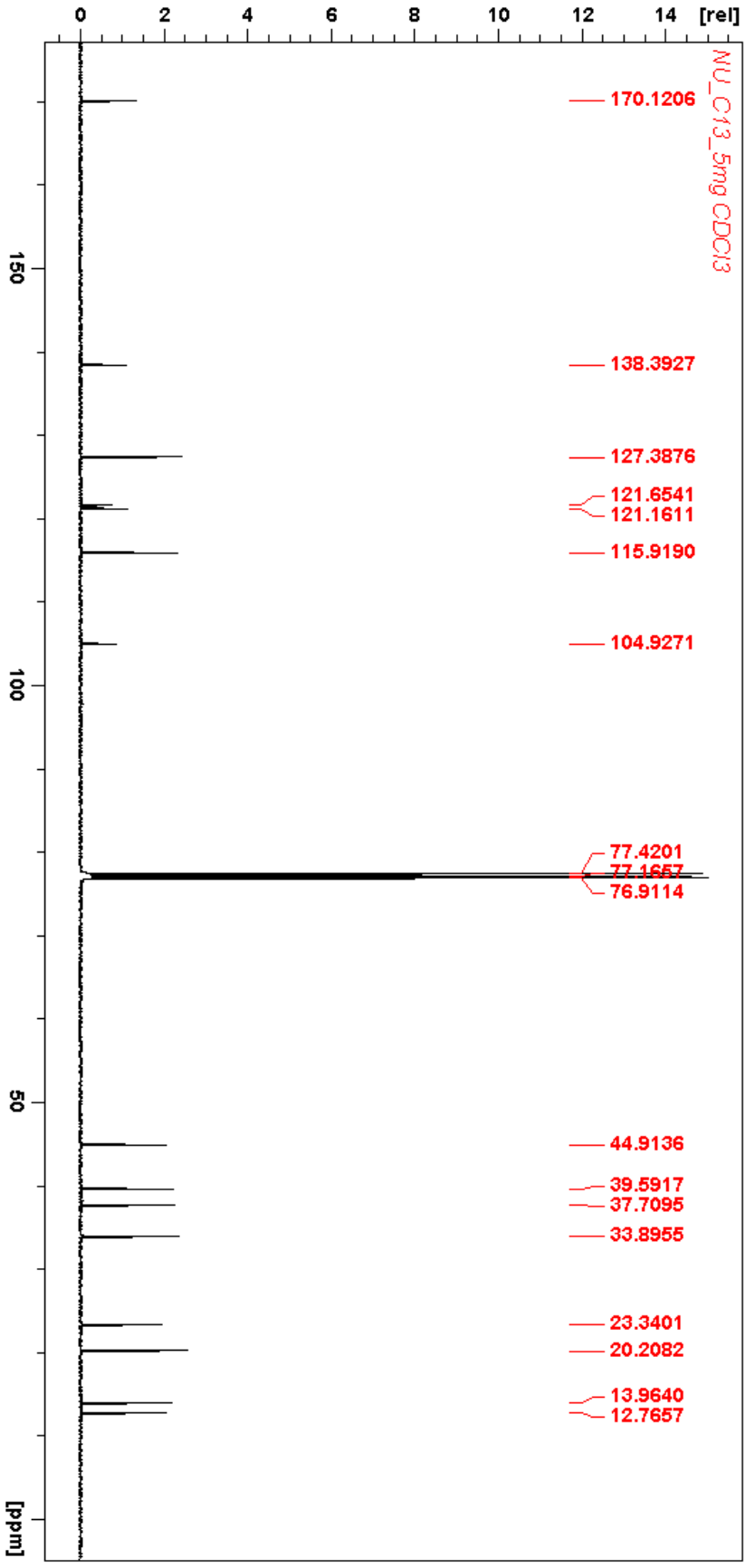

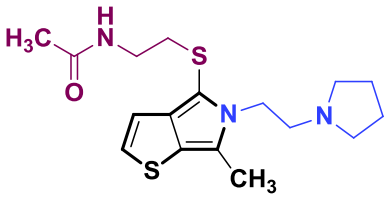

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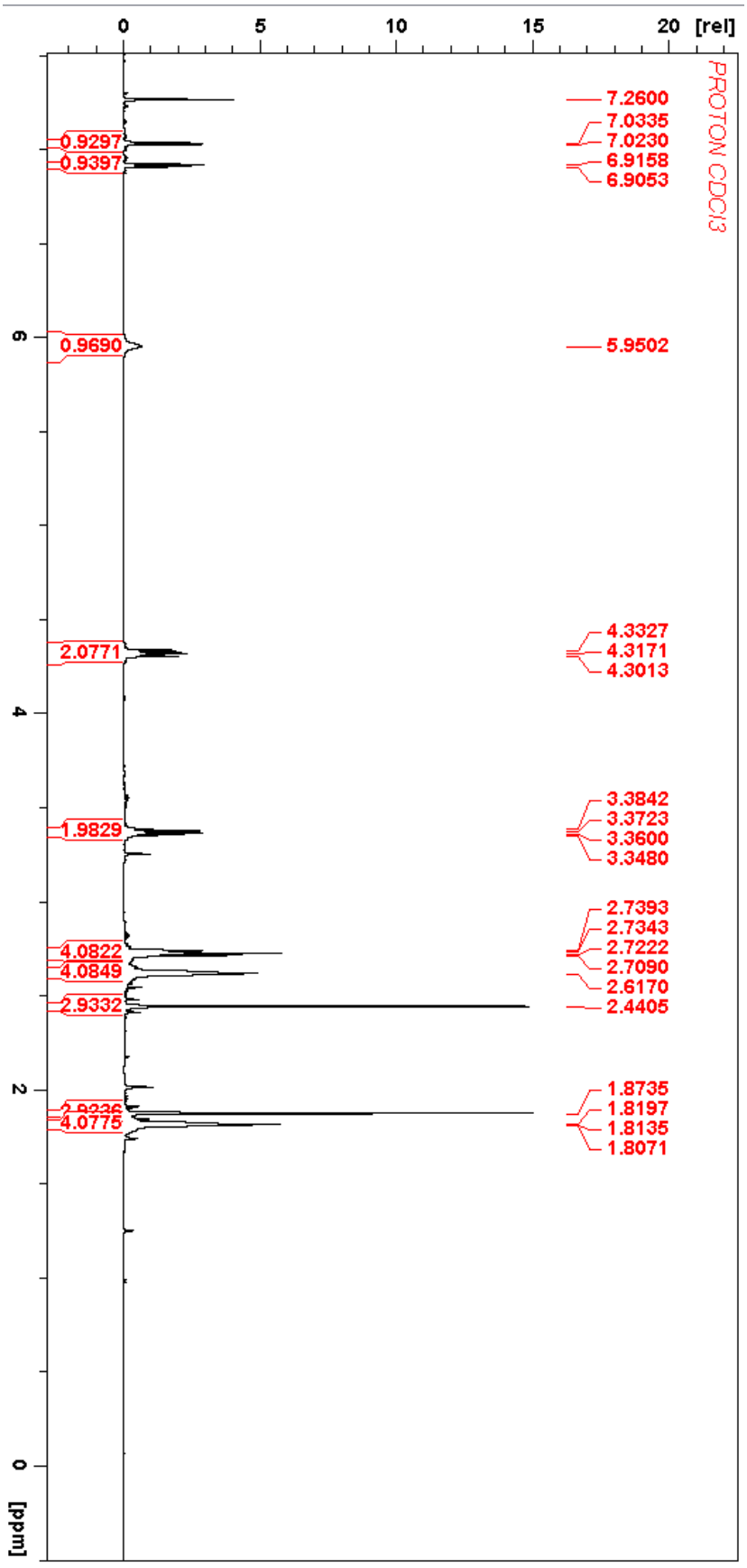

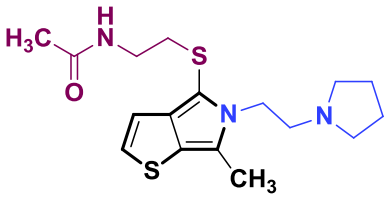

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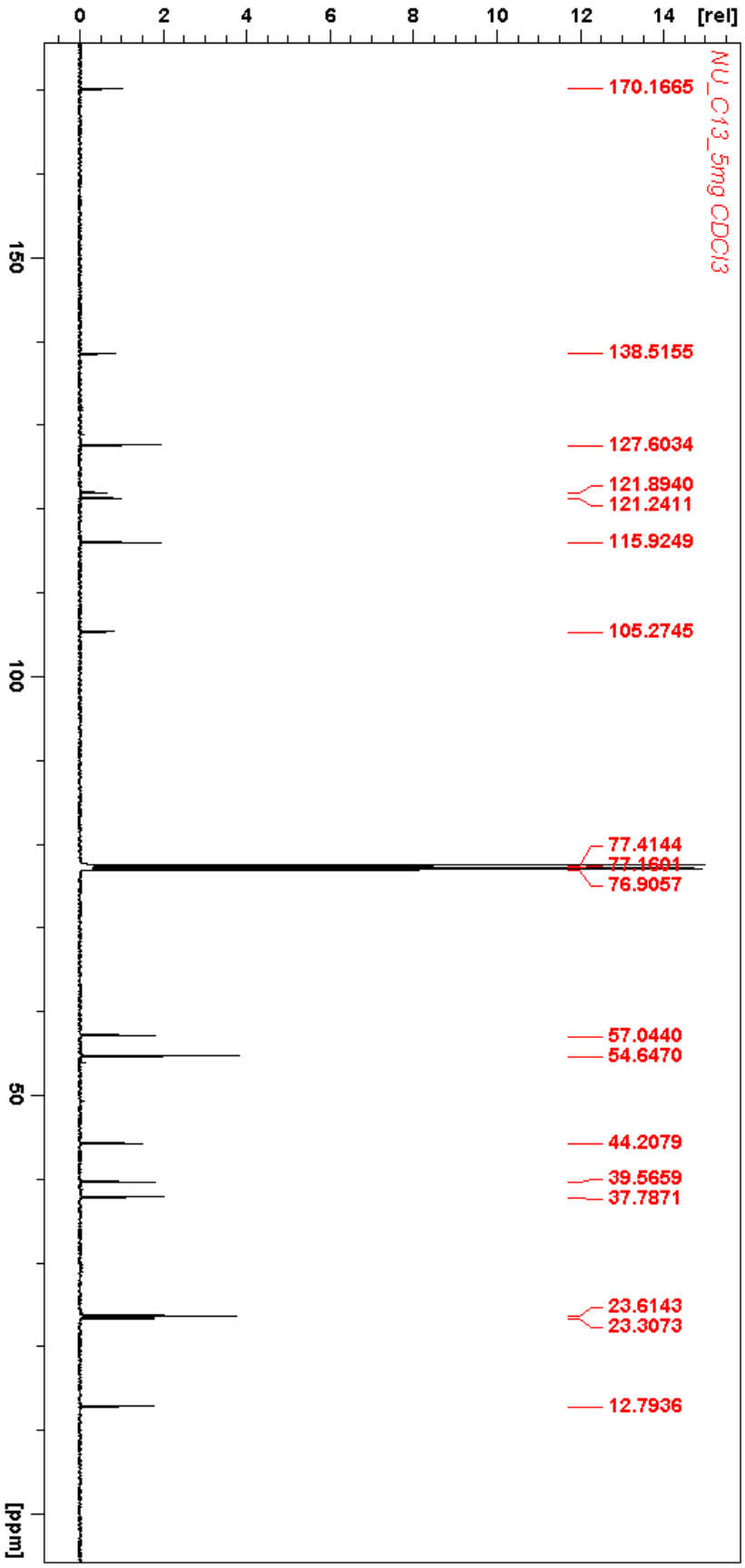

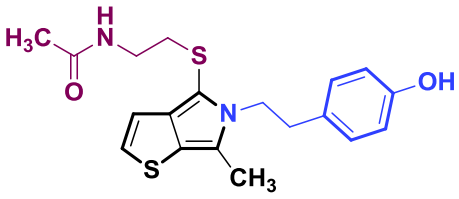

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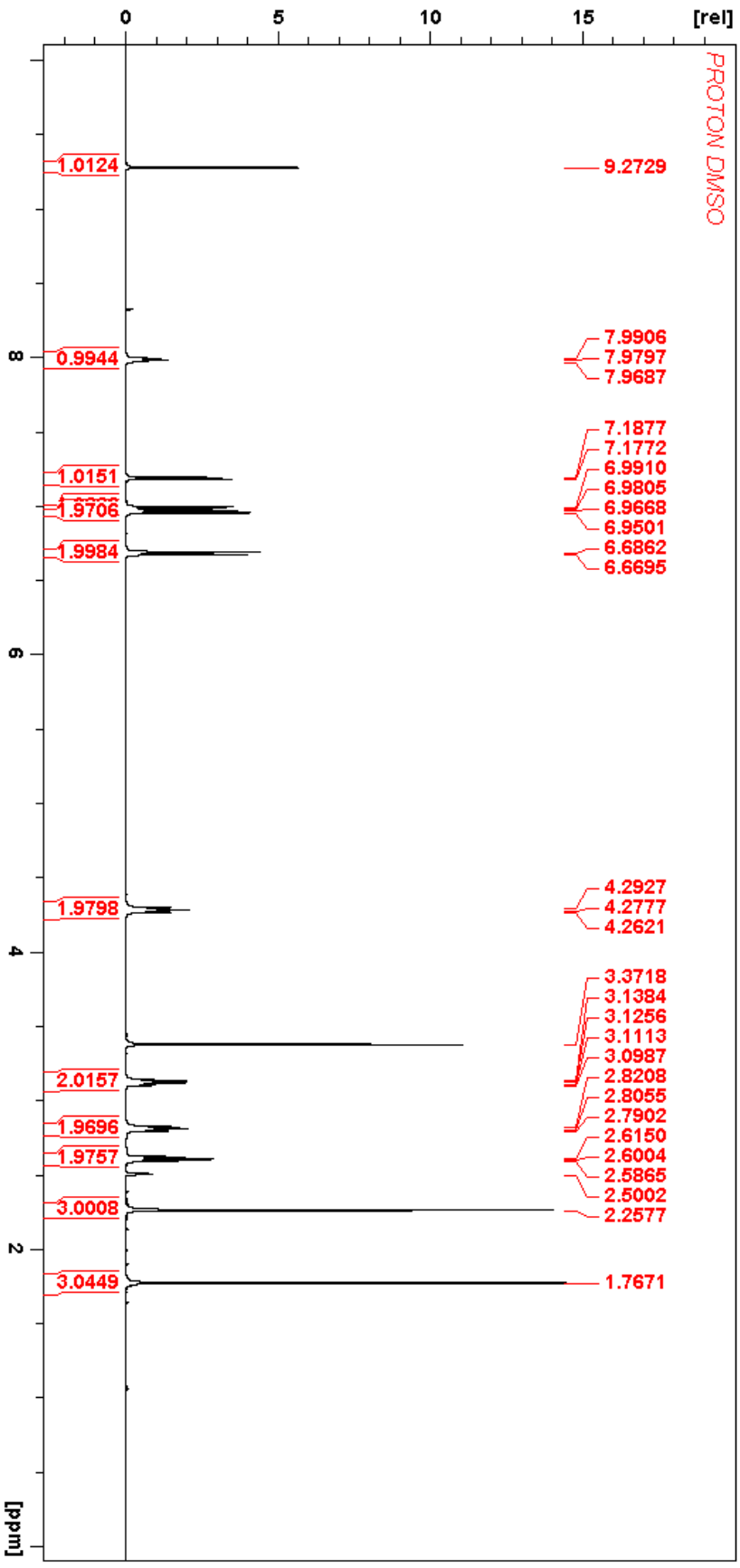

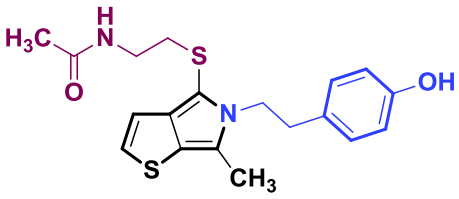

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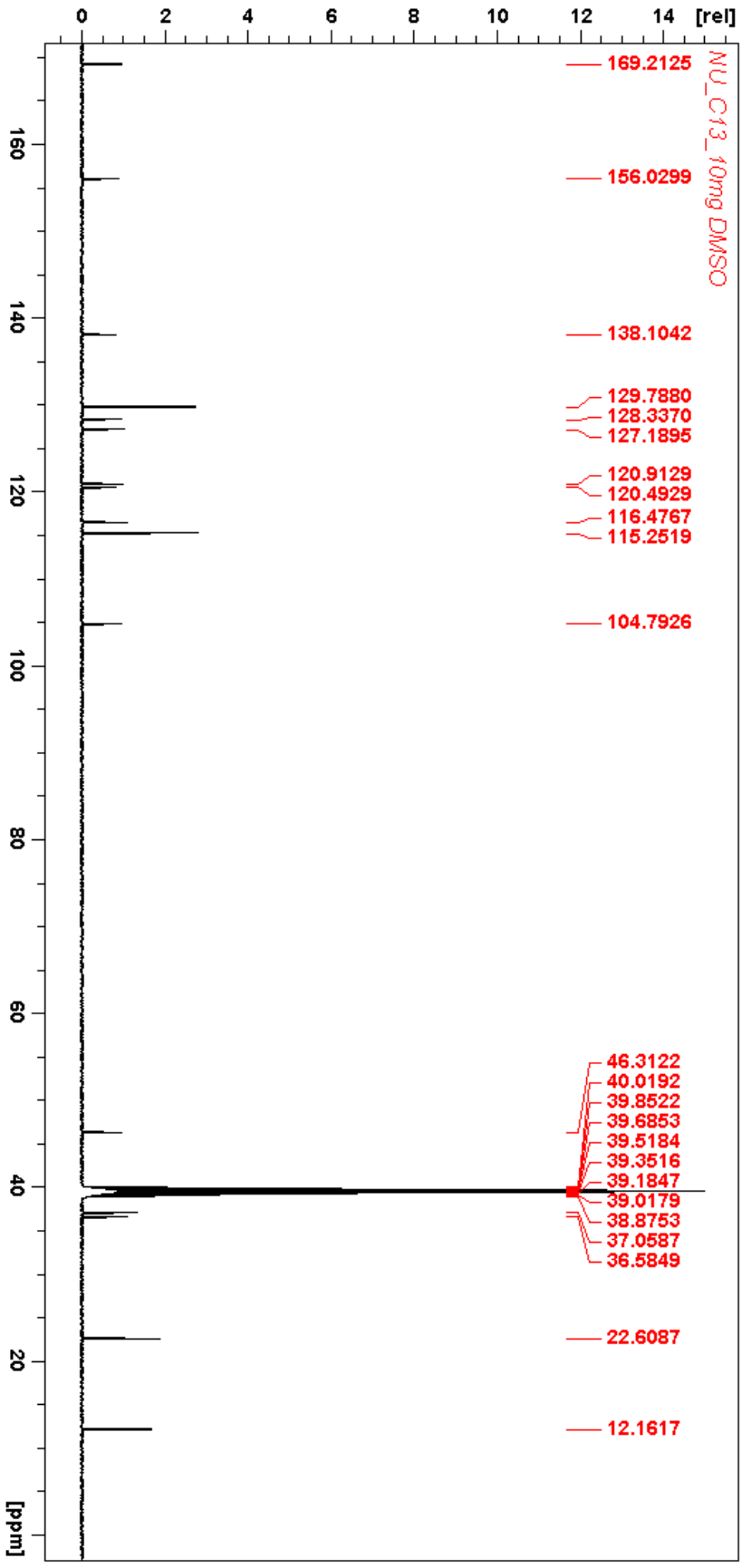

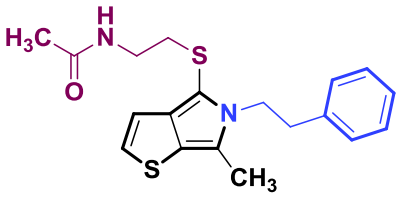

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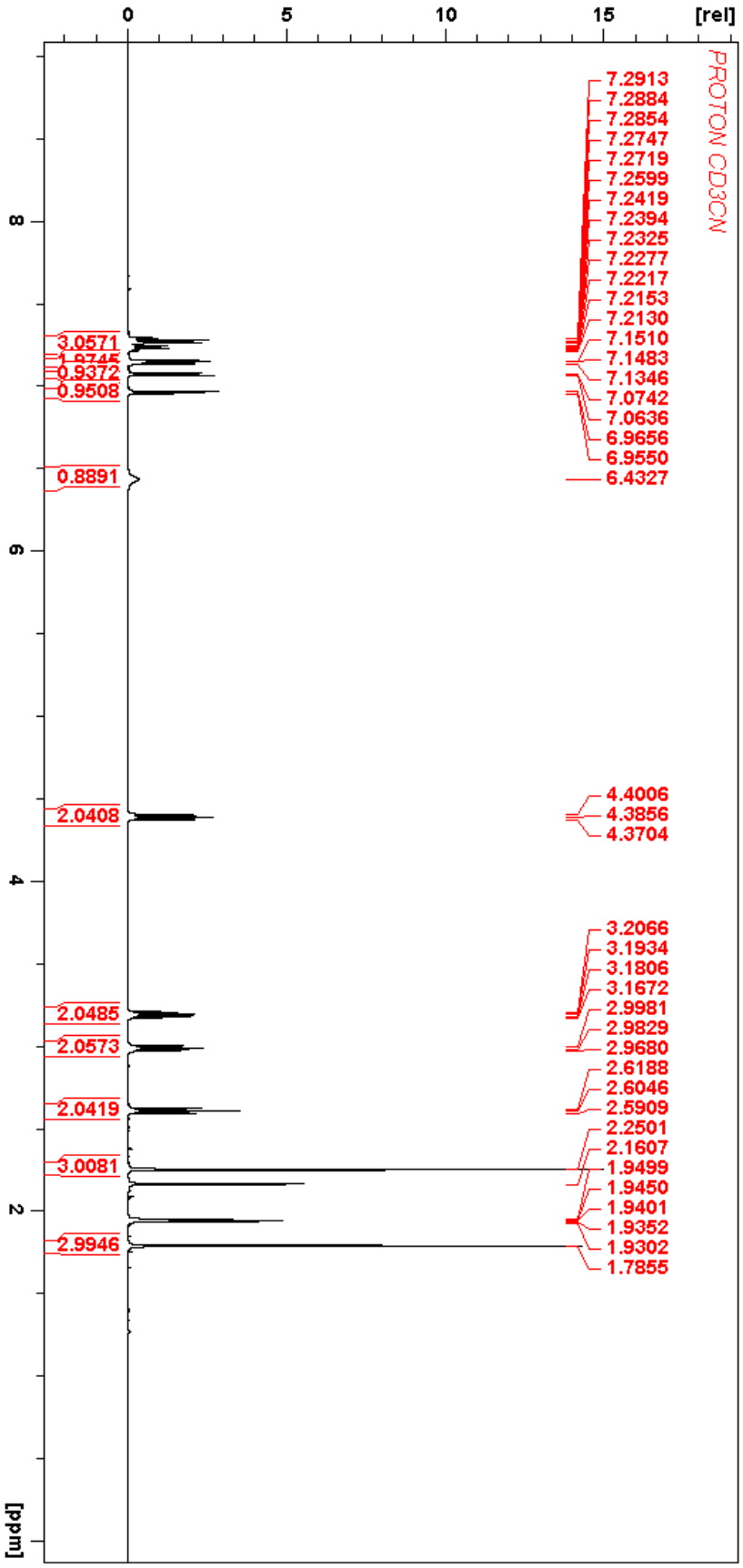

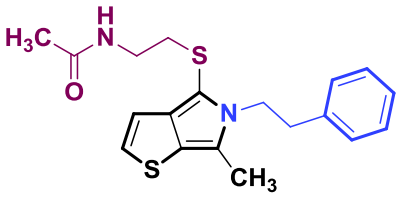

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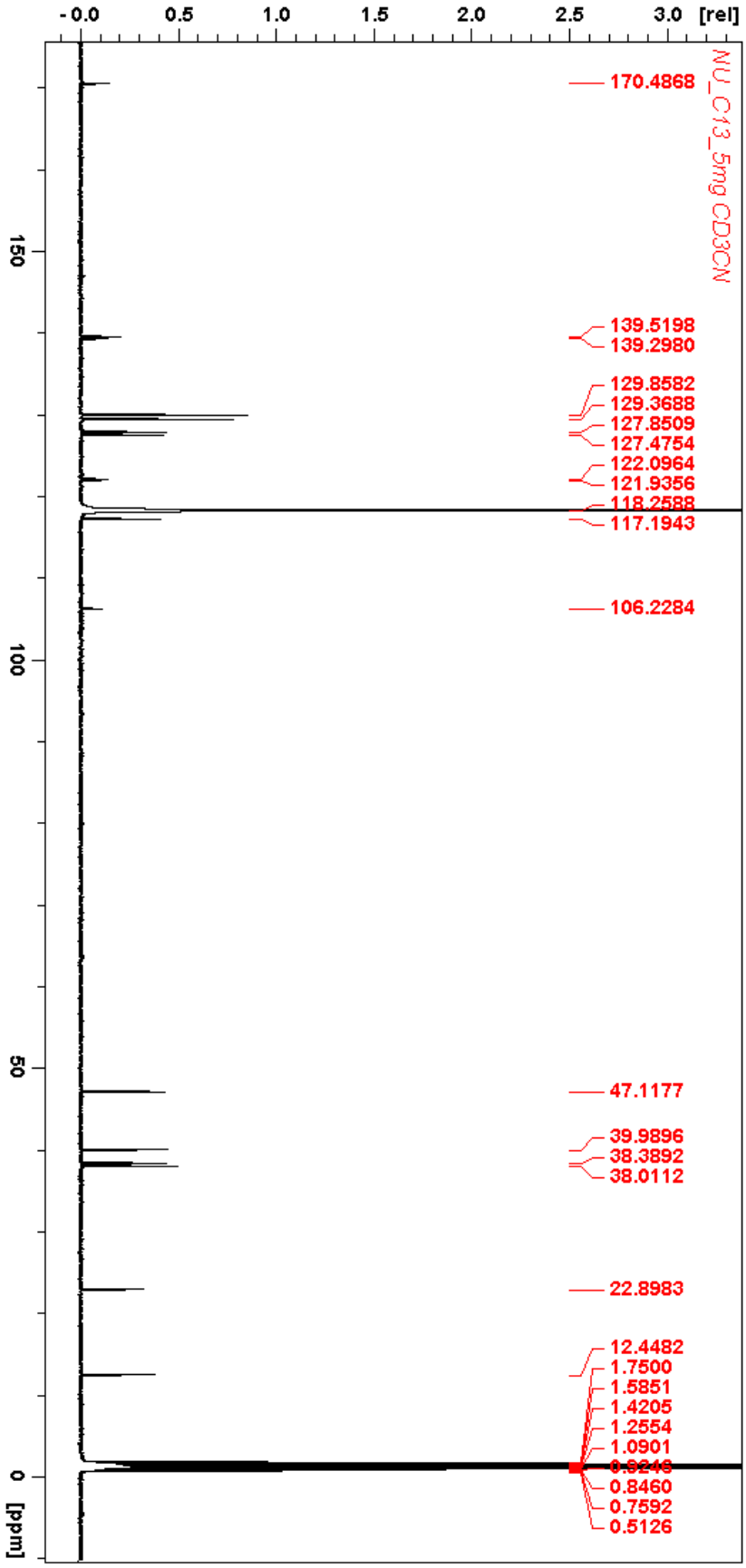

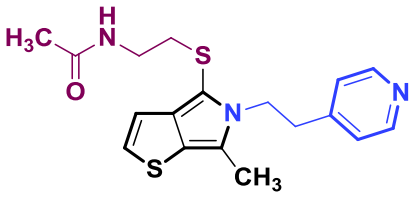

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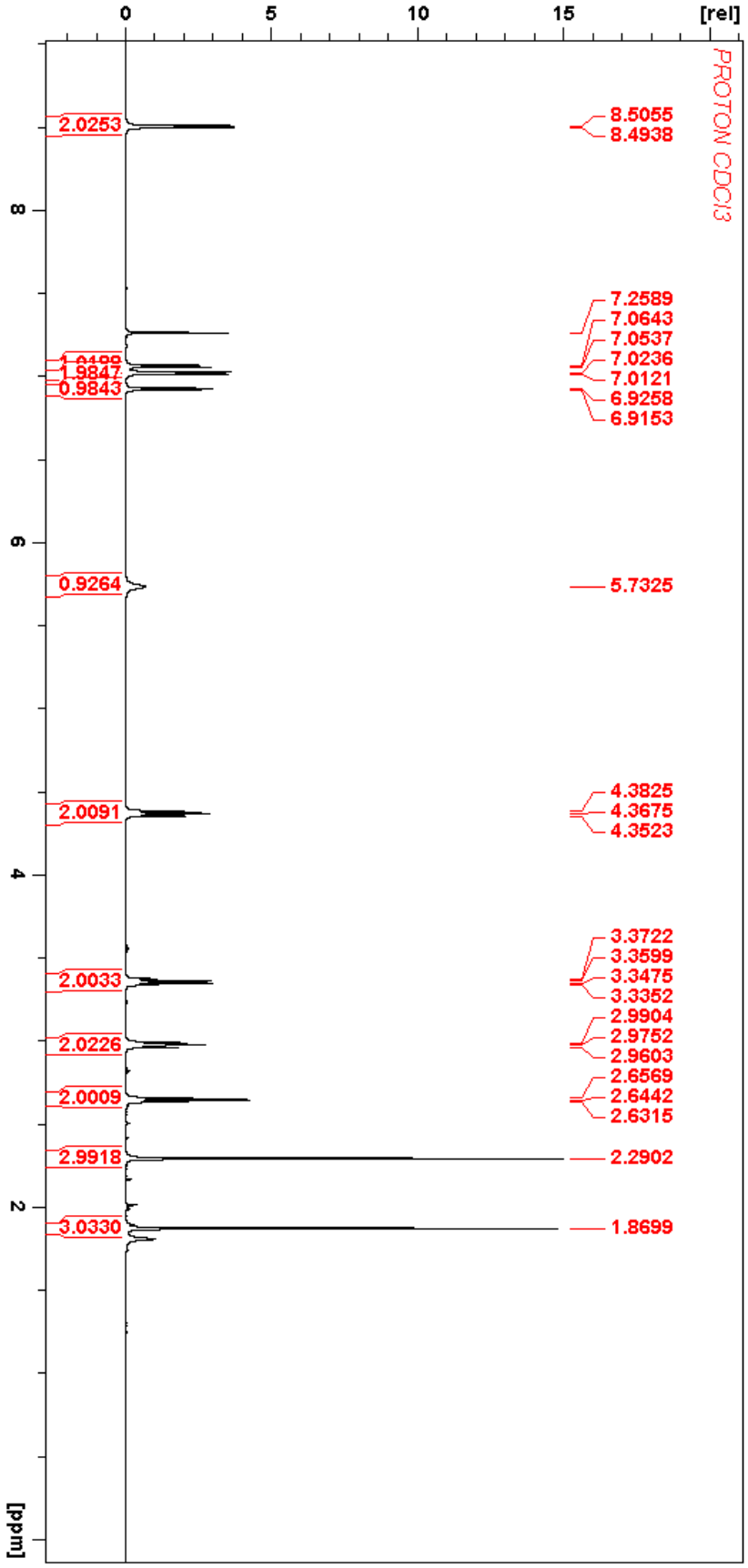

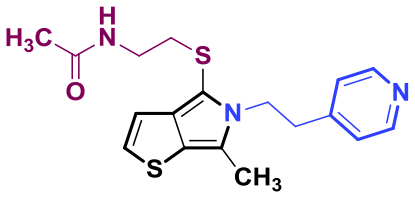

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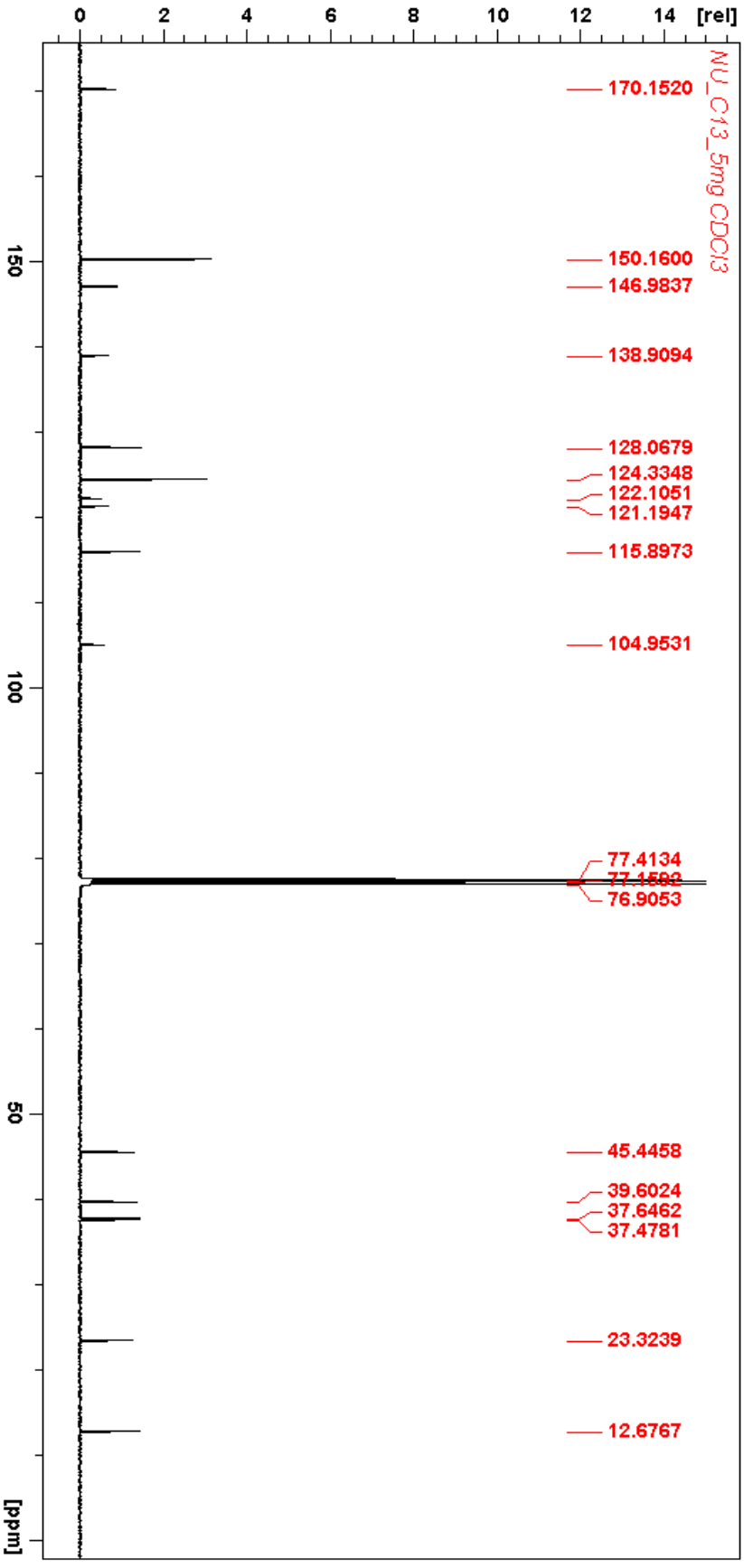

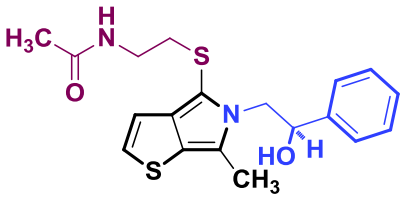

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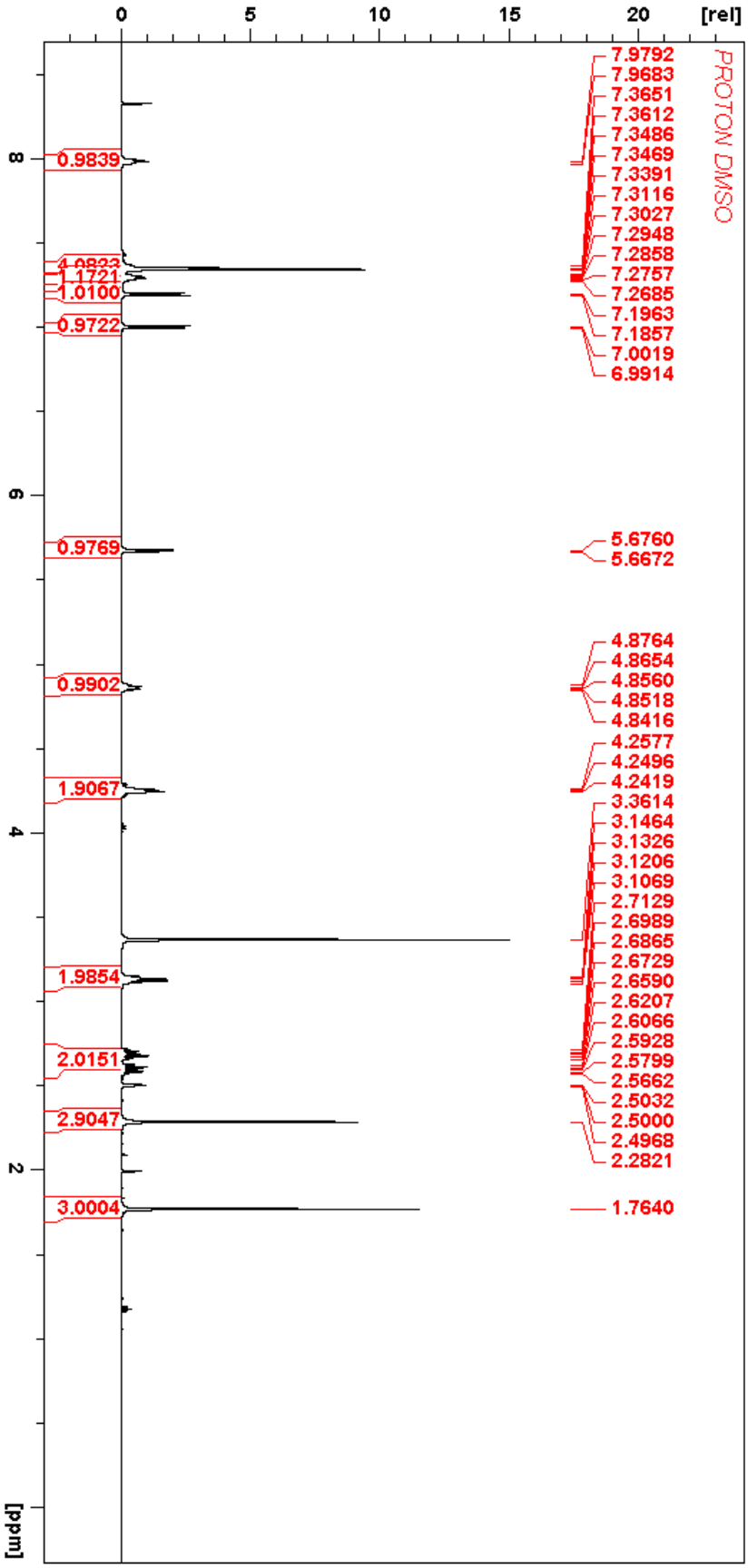

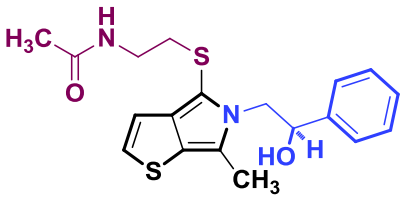

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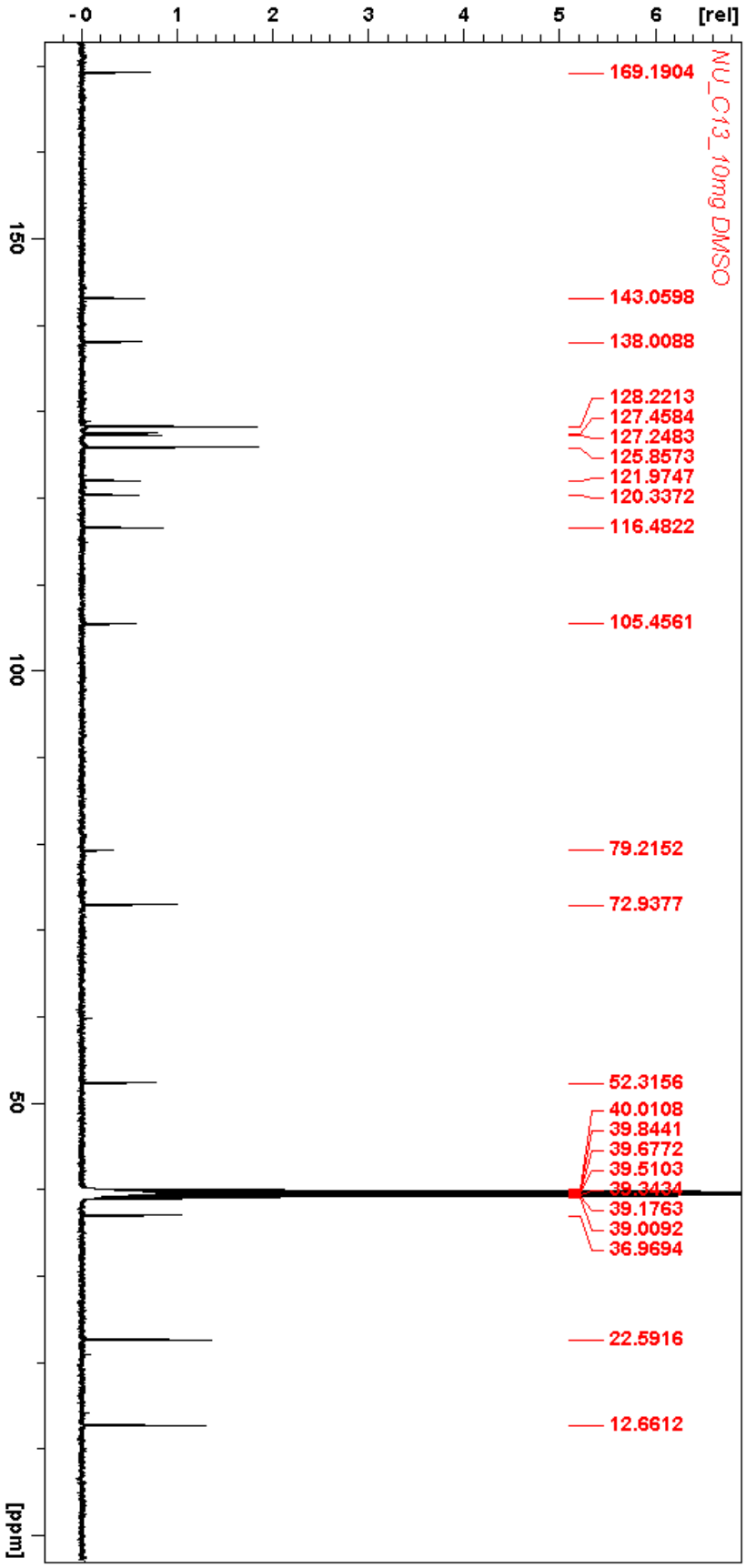

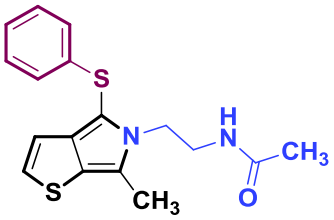

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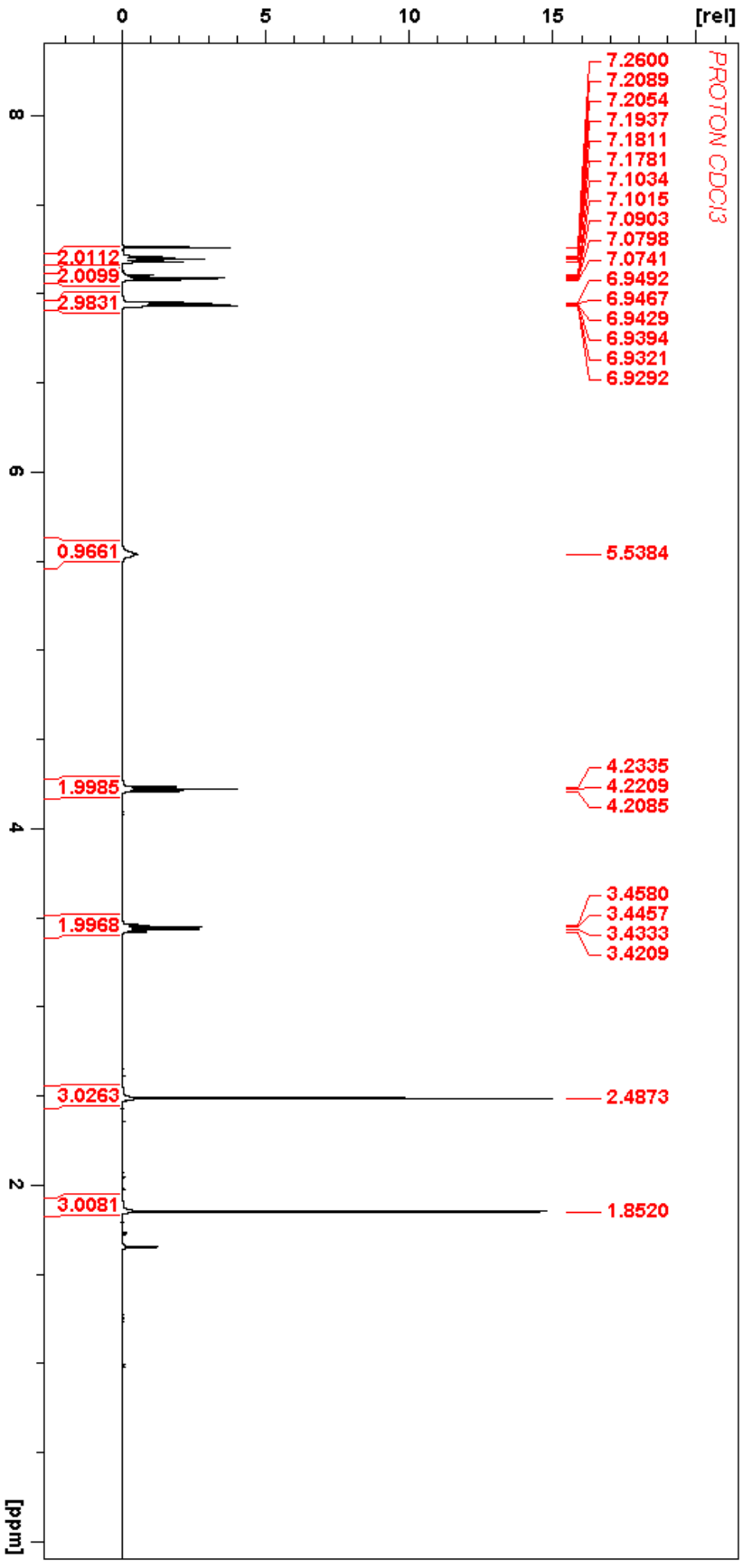

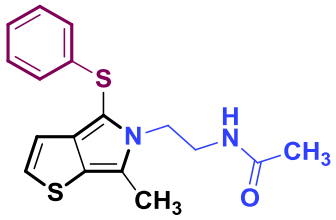

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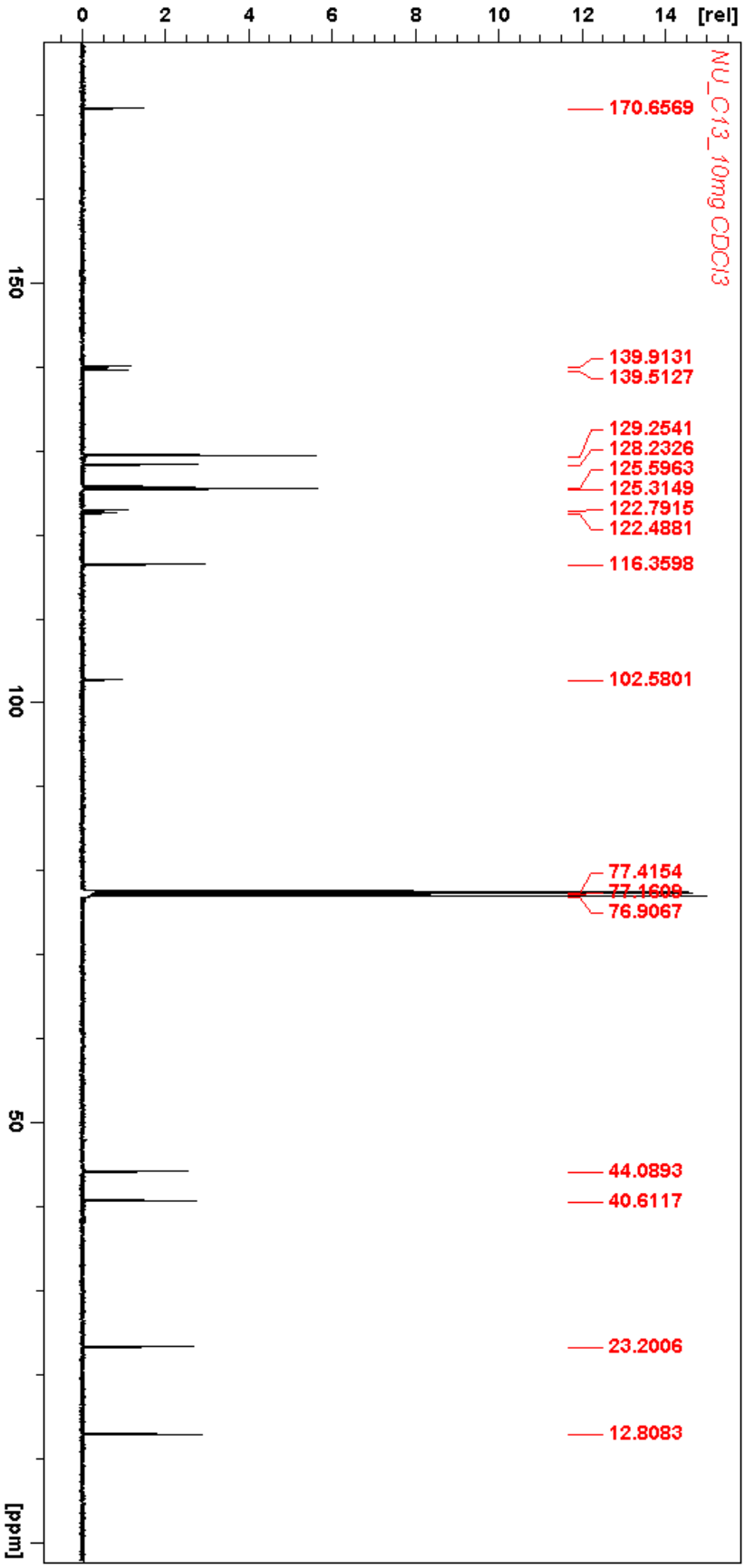

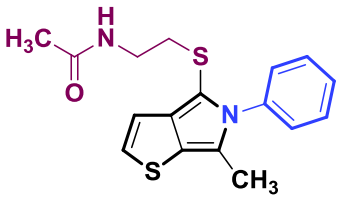

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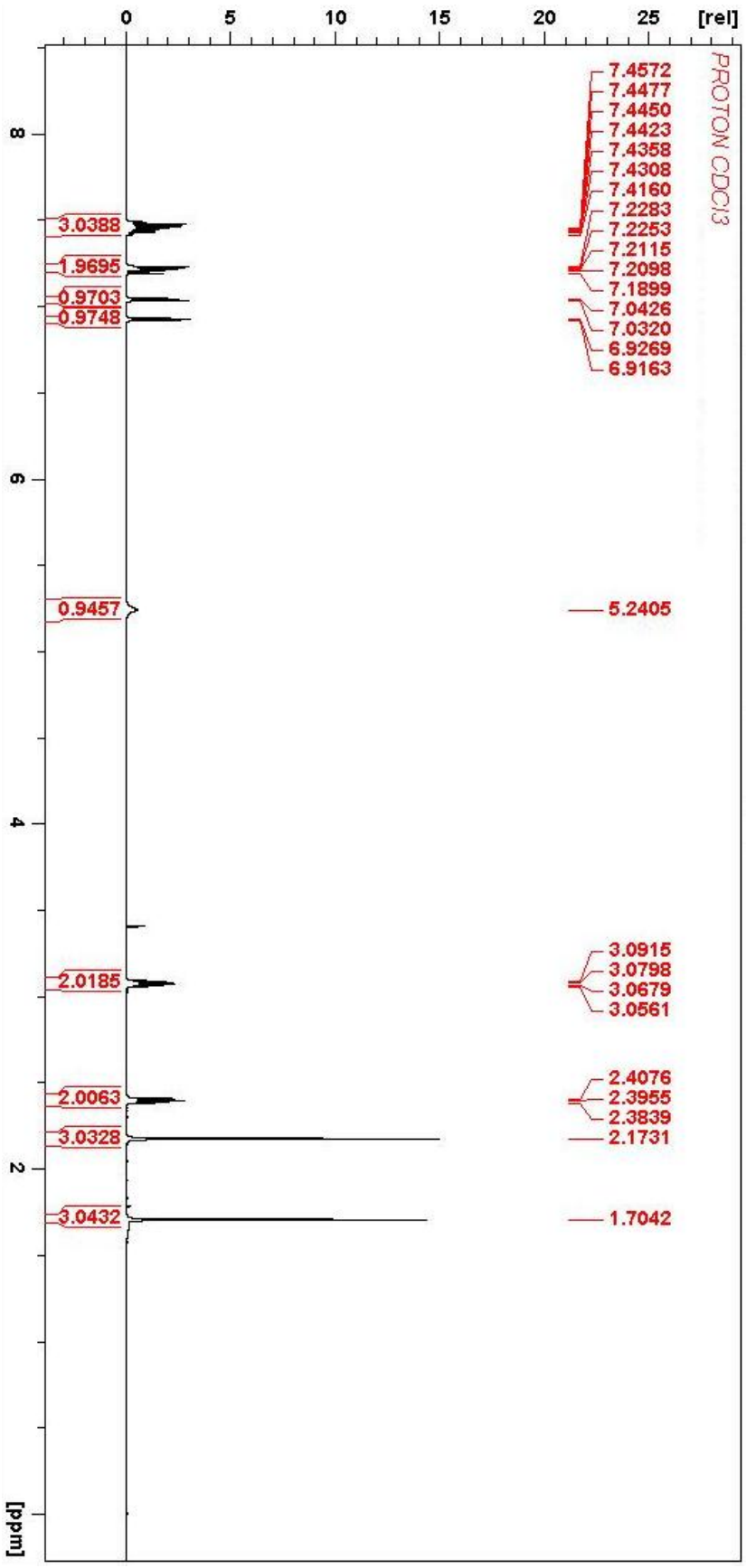

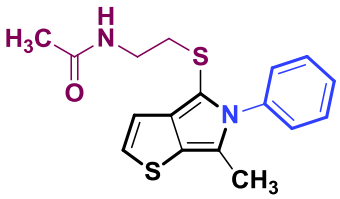

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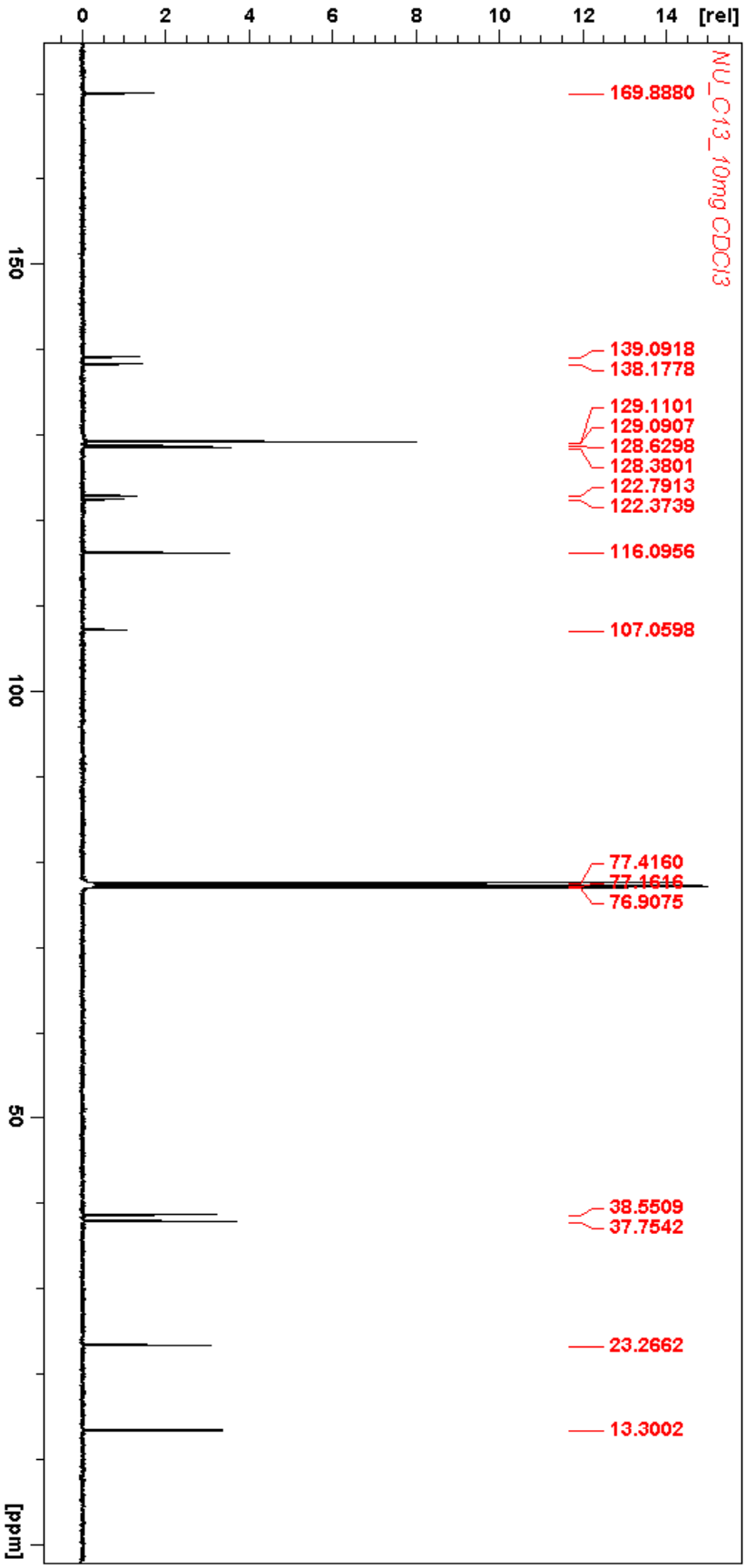

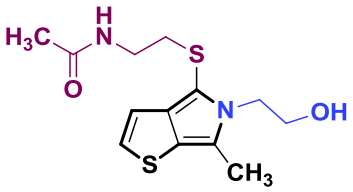

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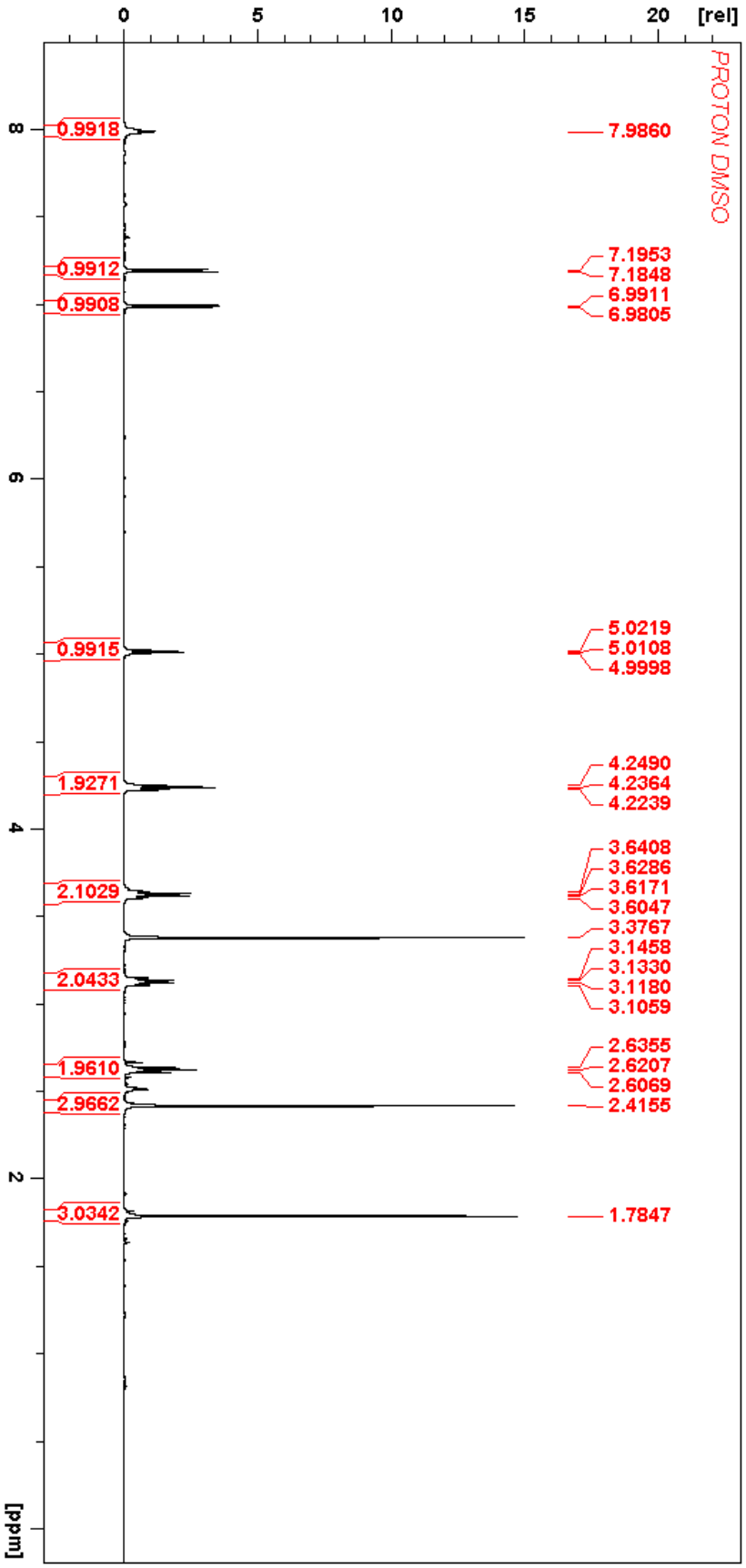

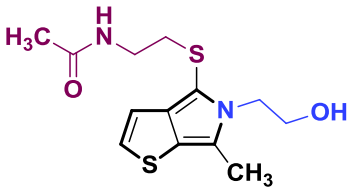

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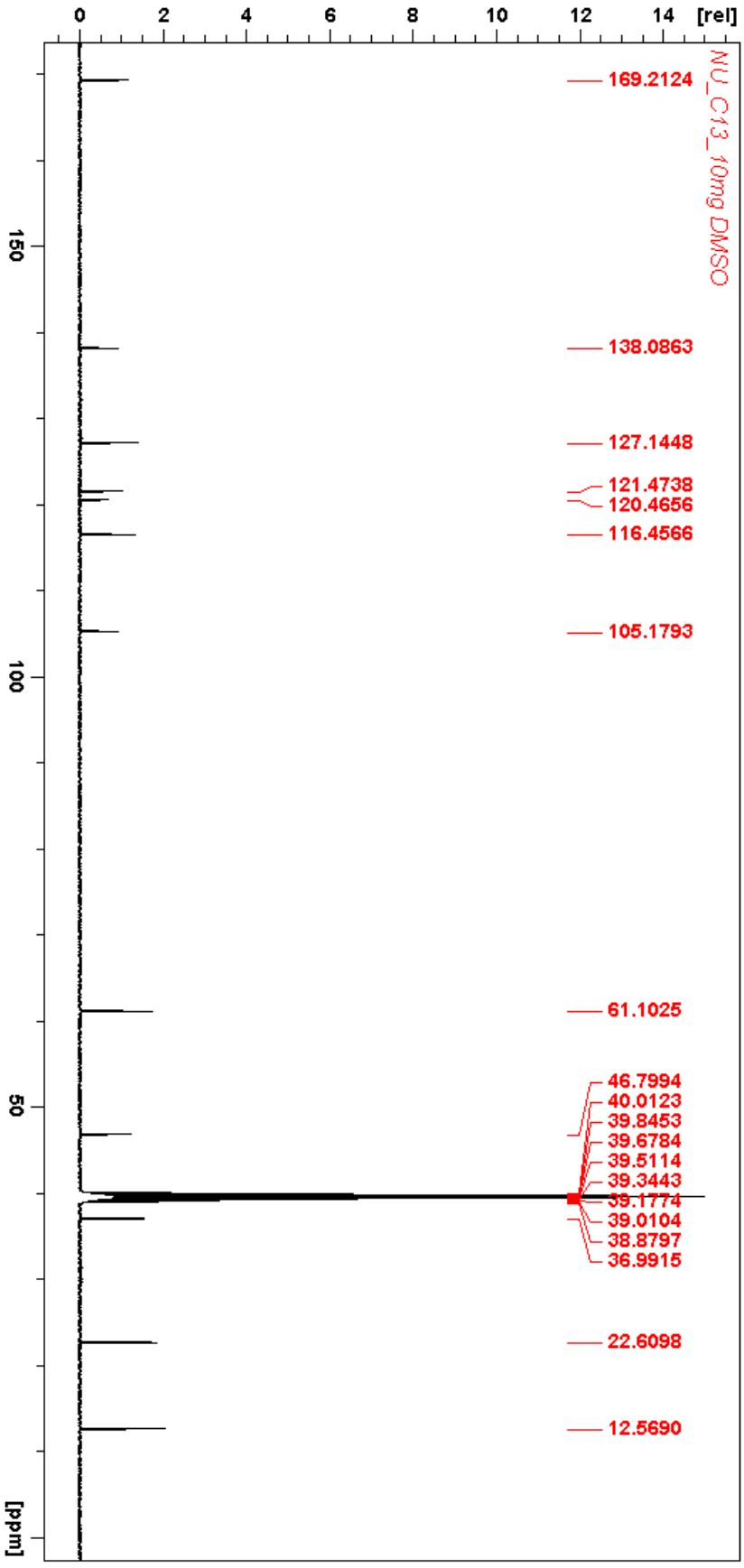

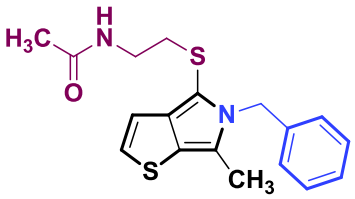

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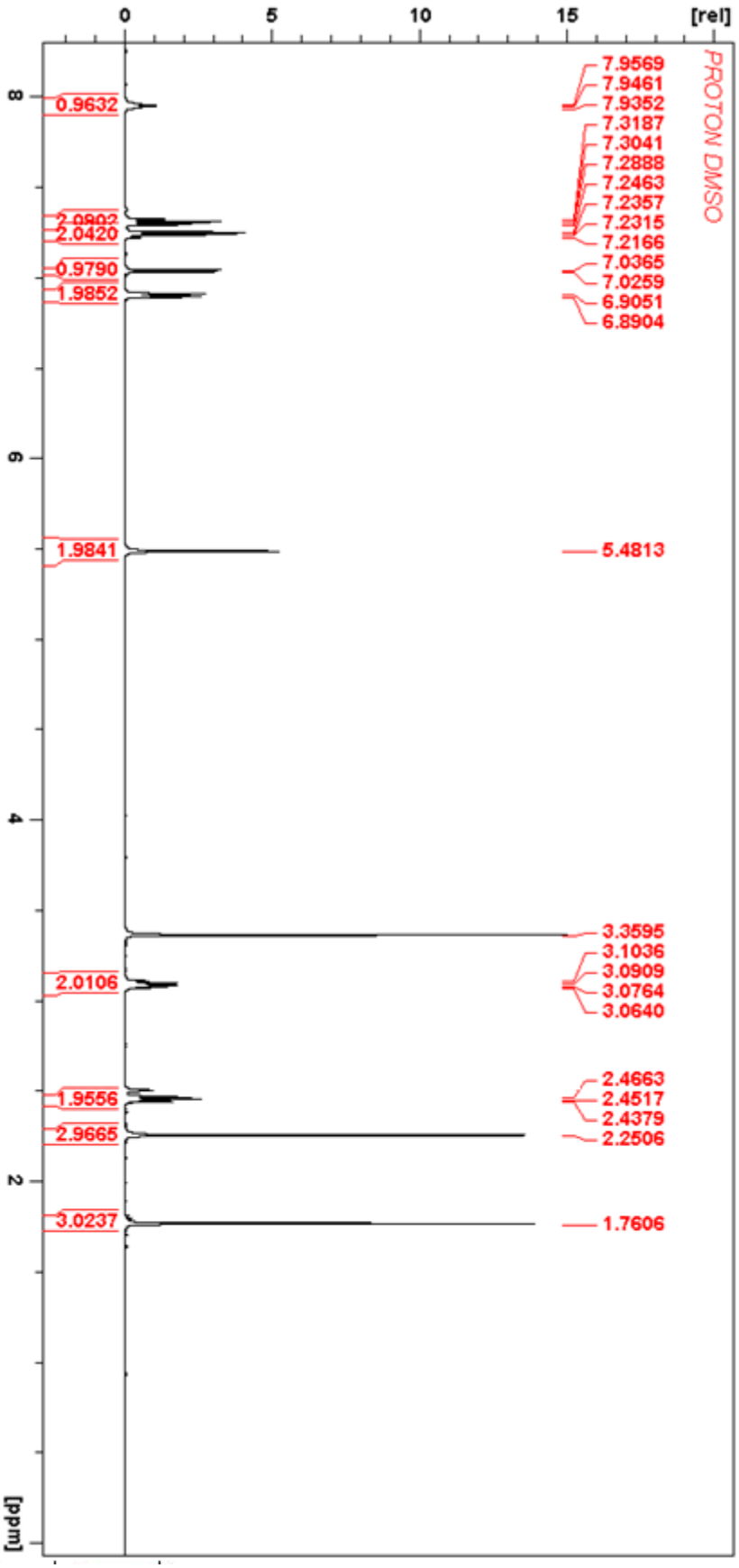

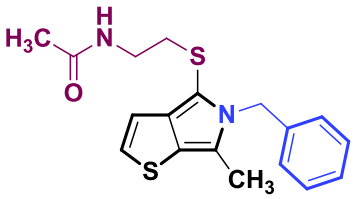

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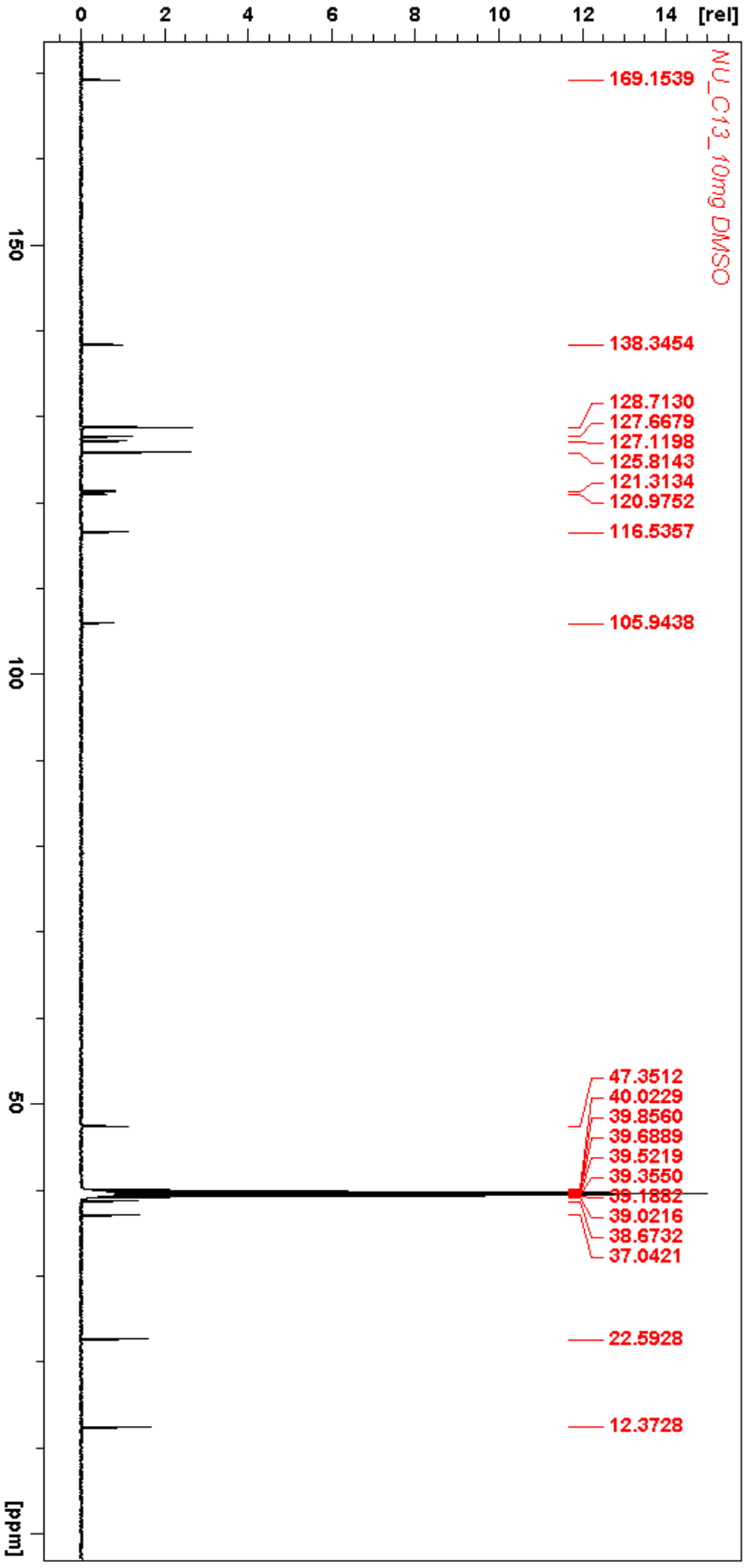

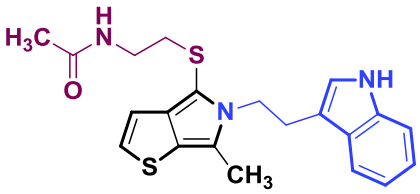

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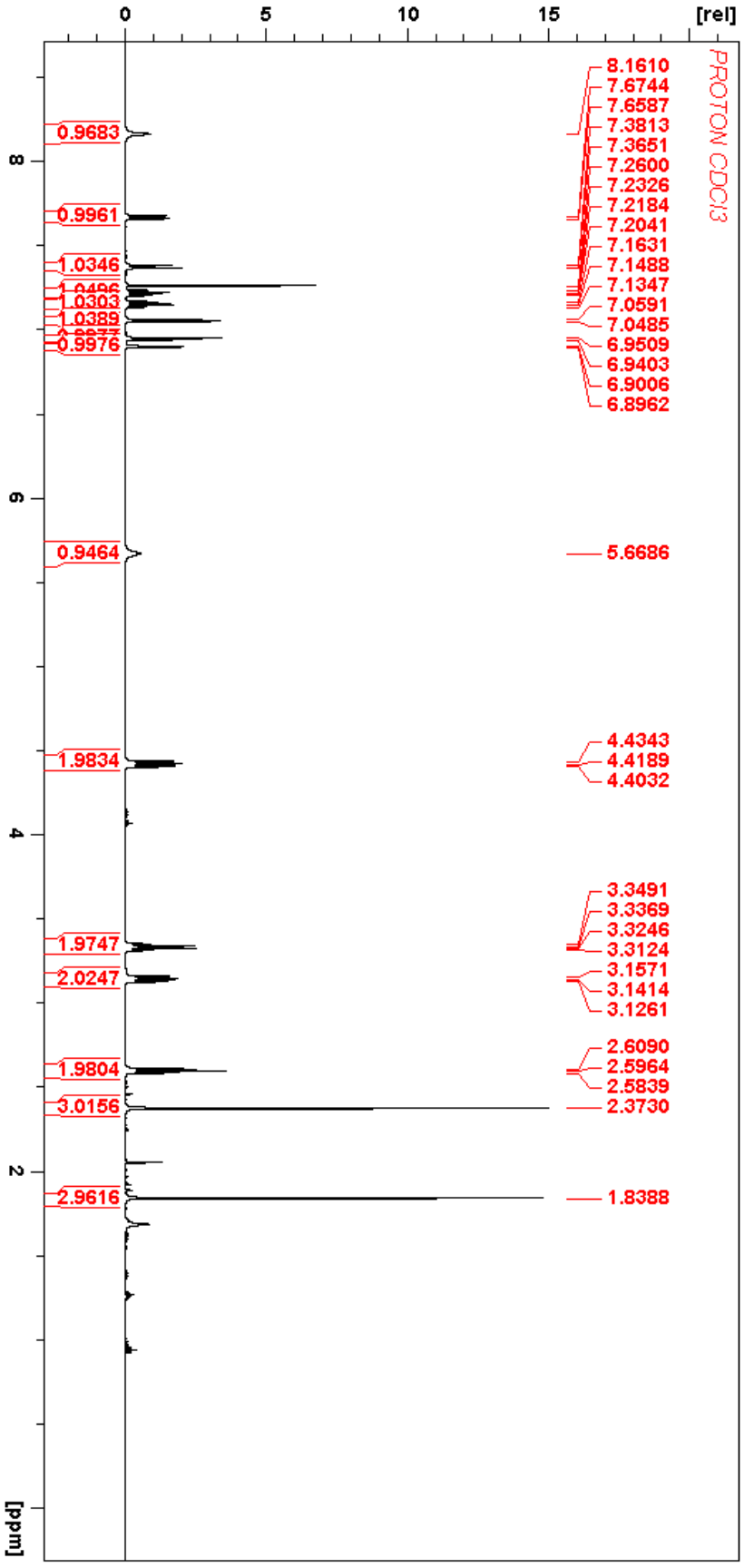

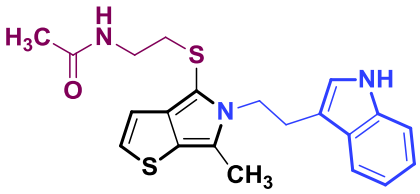

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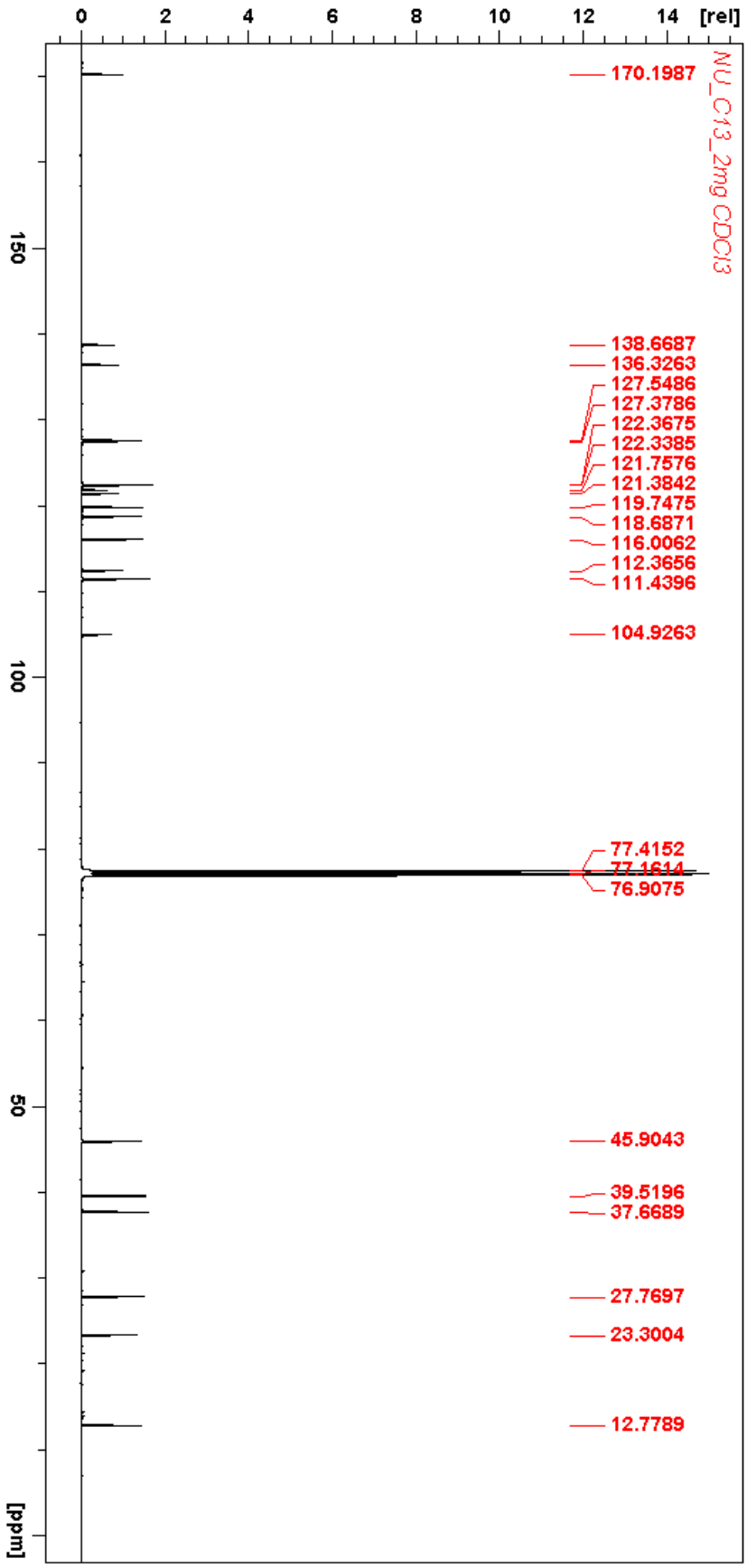

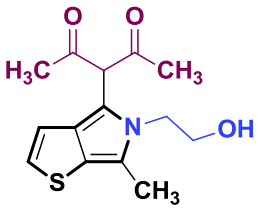

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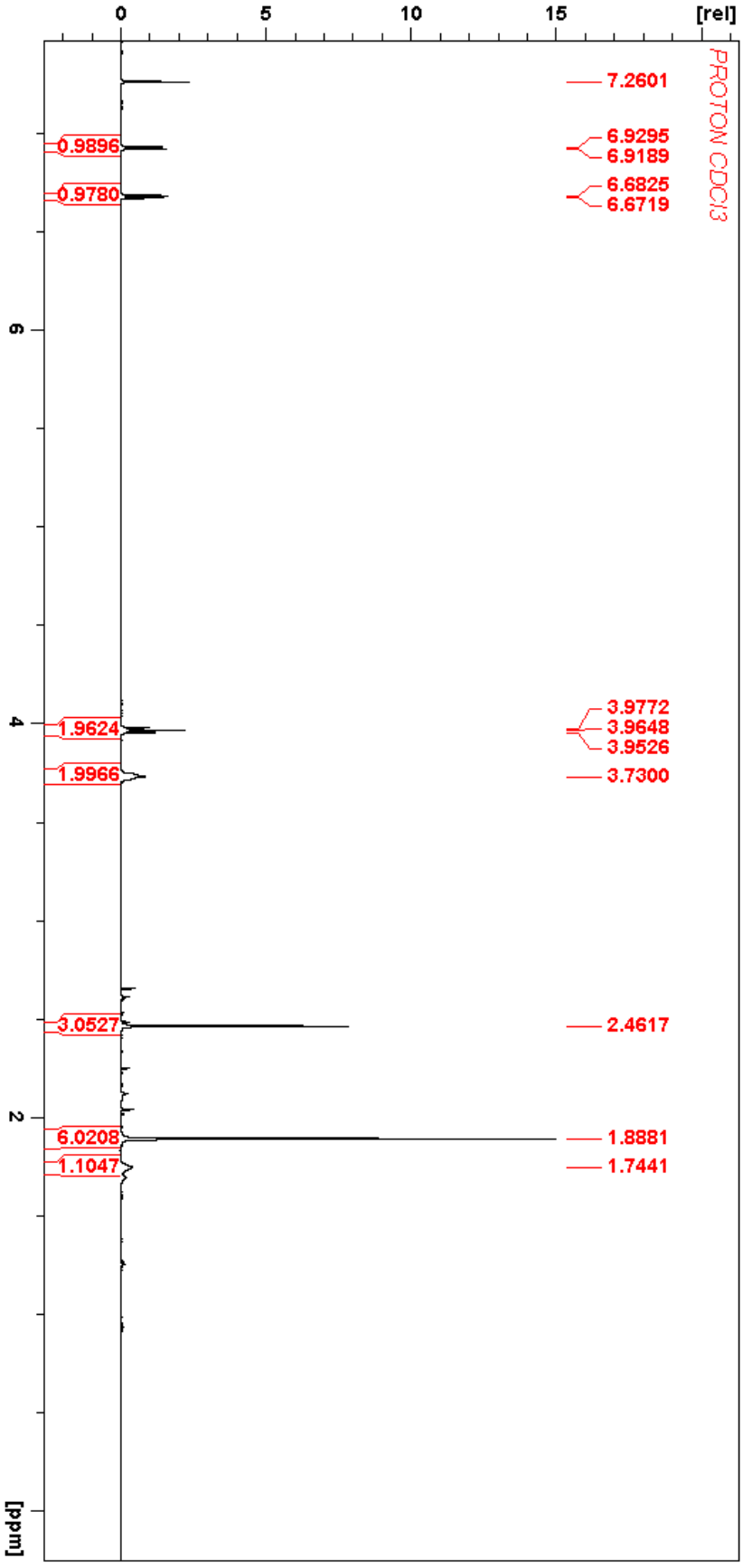

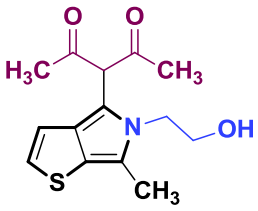
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N
OH
S
CH3

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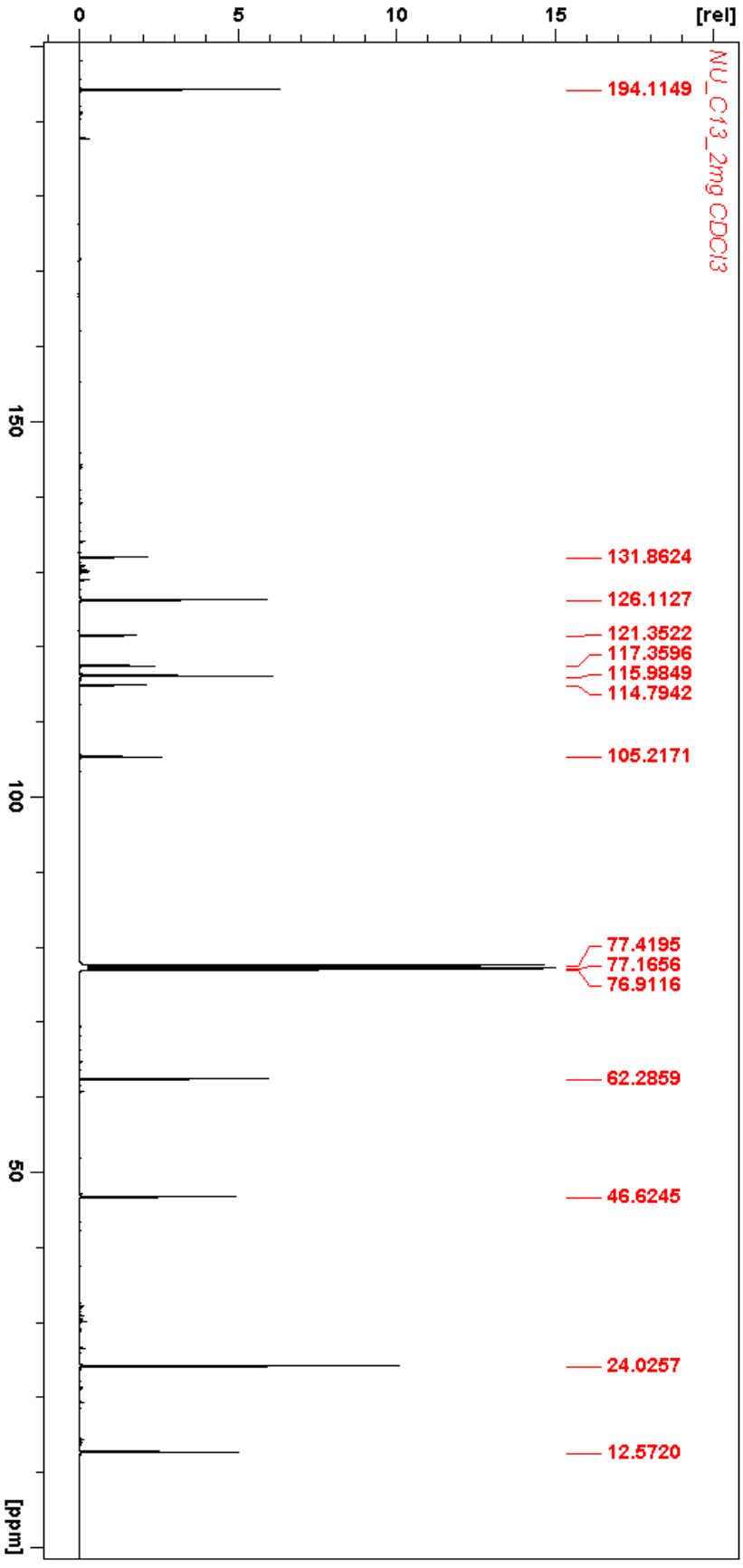
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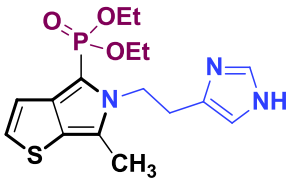

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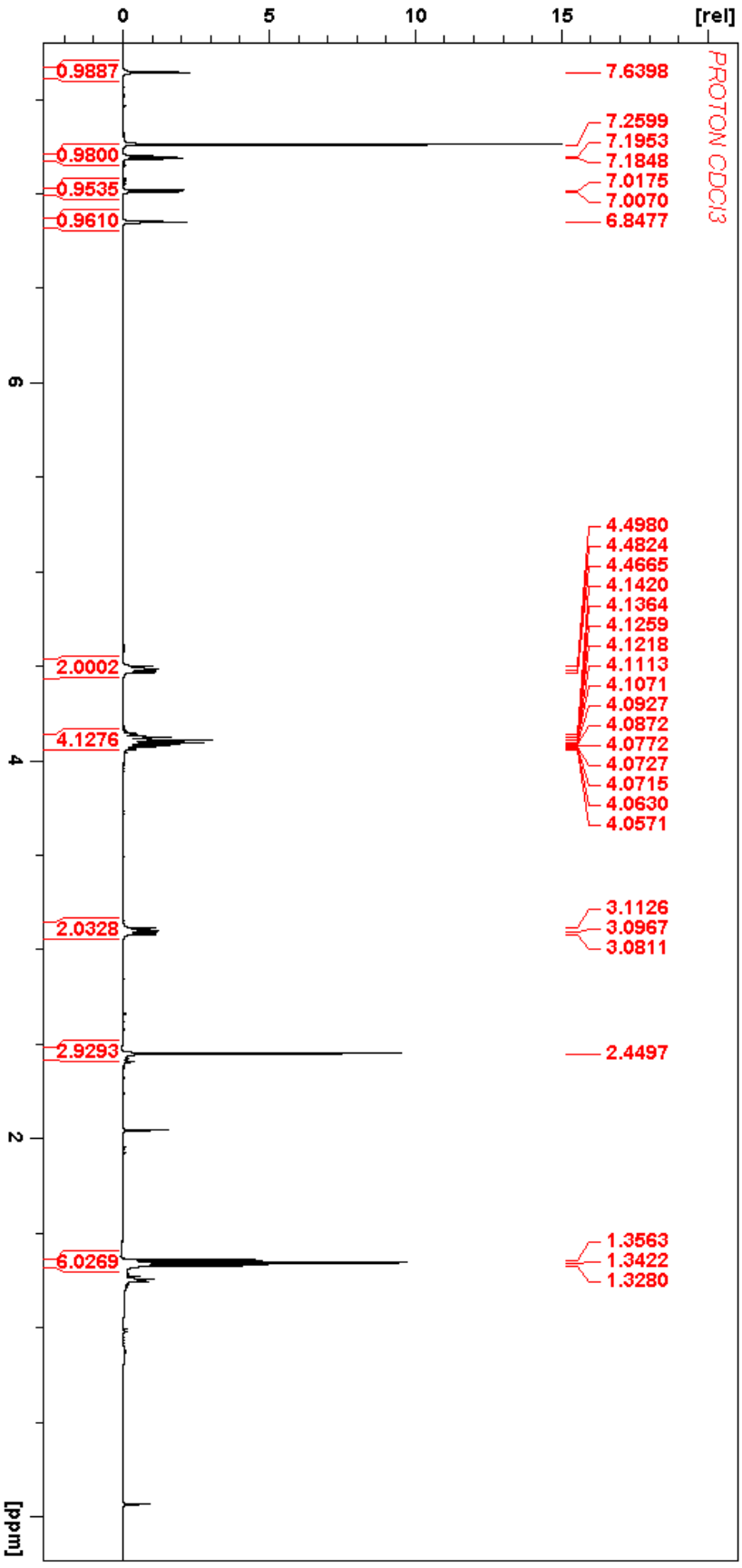

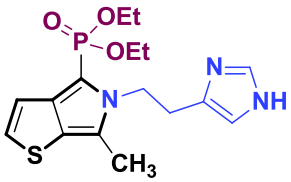

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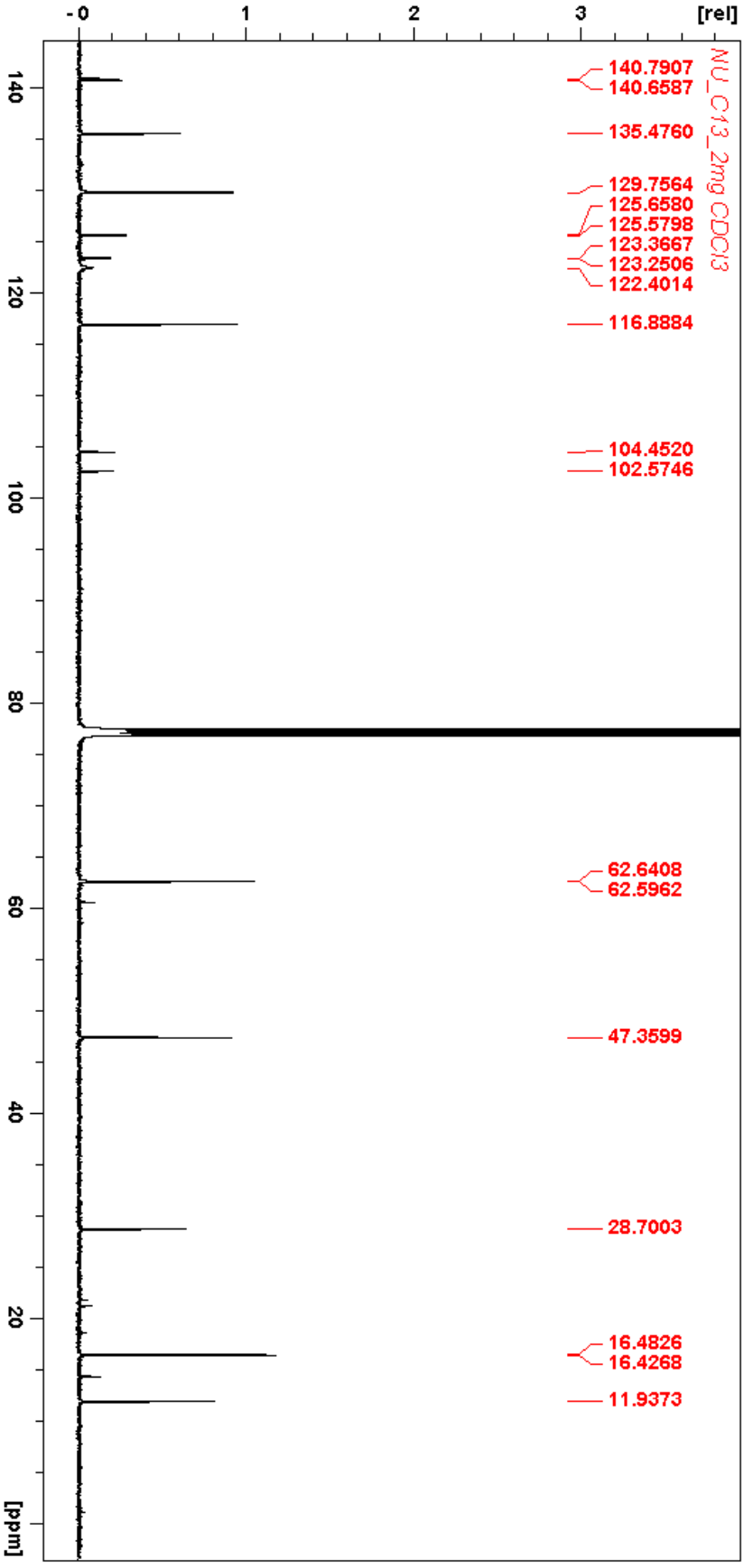

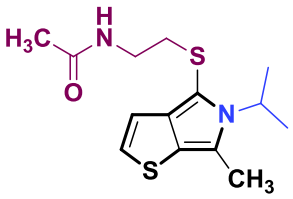
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N
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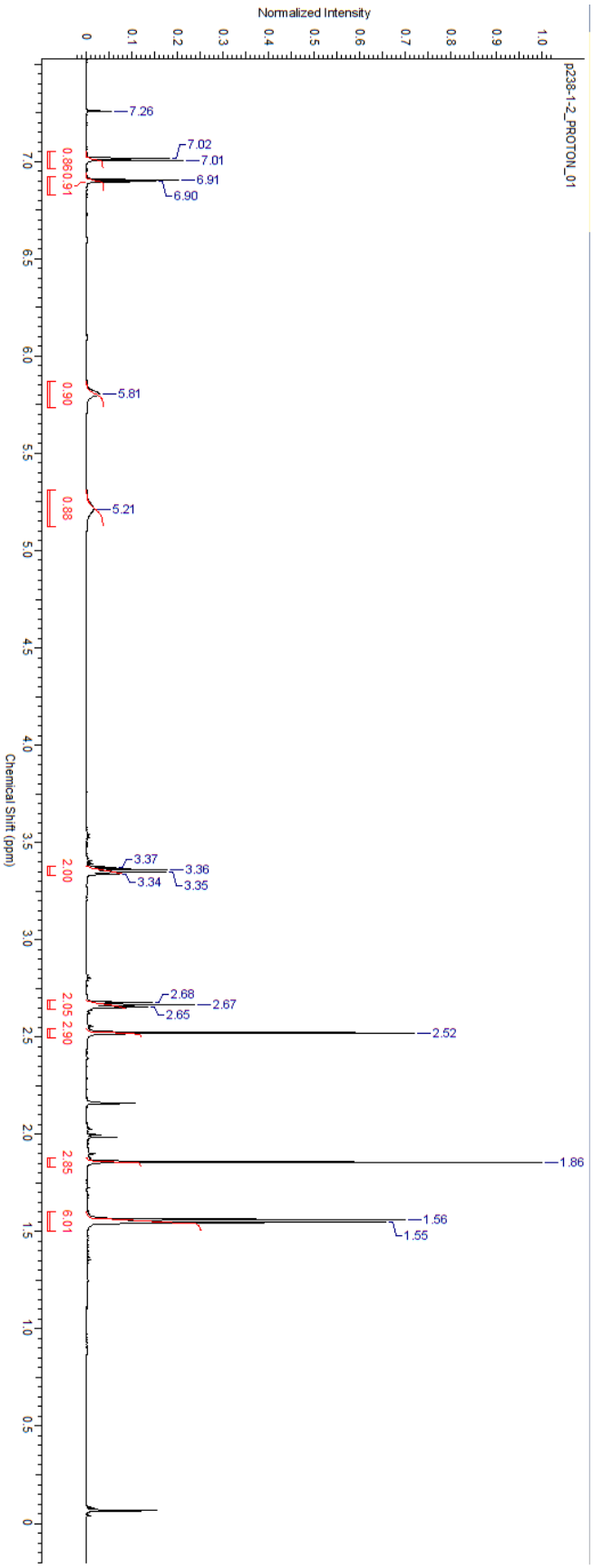
CH3

35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3.34
3.35
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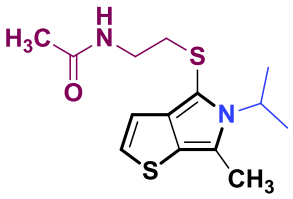

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