Supporting Information for

Repositioning Salirasib as new antimalarial agent.

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List of Supporting Information

Material and methods.

General Information.

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II 300 MHz (75.13 MHz) using $CDCl_3$ as solvent. Chemical shifts (δ) were reported in ppm downfield from tetramethylsilane (TMS) at 0 ppm as internal standard and coupling constants (*J*) are in hertz (Hz). Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relatives to the center line of the $CDCl_3$ triplet at 76.9 ppm. The following abbreviations are used to indicate NMR signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, p = pentet, br = broad signal. High-resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF II with lock spray source. IR spectra were obtained using an FTIR Shimadzu spectrometer and only partial spectral data are listed. Chemical reagents were purchased from commercial suppliers and used without further purification, unless otherwise noted. Solvents were analytical grade or were purified by standard procedures prior to use. Yields were calculated for material judged homogeneous by thin layer chromatography (TLC) and nuclear magnetic resonance (^{1}H-NMR). All reactions were monitored by thin layer chromatography performed on silica gel 60 F_{254} pre-coated aluminum sheets, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 4-anisaldehyde. Column flash chromatography was performed using silica gel 60 (230–400 mesh).

***Plasmodium falciparum* asexual stages *in vitro* culture.**

The P. falciparum 3D7 strain and its nLuc-transfected version exporting the exogenous protein to the red blood cell[1] are cultured *in vitro* using the Trager and Jensen culture methodology[2,3] in 75 mL cell-culture flasks containing RPMI-1640® medium (Thermo Fisher Scientific, San Jose, California, USA) complemented with Albumax I® (0.5%)[2] (Thermo Fisher Scientific). A gas mixture of 5% CO_2, 5% O_2, and 90% N_2 is employed for the parasite culture,[4] and synchronization at the ring stage (1–10 h after invasion) is performed with 5% (w/v) D-sorbitol solution, as previously described by Lambros and Vanderberg.[5] The parasitic stages and parasitaemia are monitored by Giemsa-stained thin-smear microscopy. PCR for mycoplasma and optic microscopy are employed to avoid culture contamination.[6]

***In vitro* activity against *P. falciparum*.**

To determine the IC_{50} value, the method of Desjardins *et al*.[7] is applied, starting at 1% ring stage, with 2% hematocrit and using 96-well cell-culture plates. The parasites are cultured without added drugs (untreated controls) or with various drug concentrations and prepared using serial dilution in solely the RPMI culture medium. We also perform solvent controls using the maximum percentage of ethanol. Parasitic stages are monitored using Giemsa smears, and parasite growth is monitored using Syber green I DNA staining[8] and nLuc assays (described below).[8] The drug's effects on the parasite are evaluated at time zero and on subsequent days (up to 72 h after the treatment) and results were confirmed by Giemsa stained smears. All experiments are performed three times, with three technical replicates each. The 20 mM stock solutions for FTS and its analogues are prepared in ethanol, 200 μM artesunate (Guiling Pharmaceutical Factory, Guiling City, Guangxi, China) diluted in ethanol, 200 μM chloroquine diphosphate salt (Sigma, St. Louis, Missouri, USA)

diluted in water and 200 μM clindamycin hydrochloride Sigma) diluted in complete RPMI medium. Then Luc assays are performed similarly, as previously described by Azevedo et al.[1] In this process, 100 μL of parasite culture (2% hematocrit) is lysed with the same volume of 0.02% saponin (w/v) lysis buffer containing 0.01% (v/v) of the standard Nano-Glo Luciferase® (Promega®, Madison, USA) containing 100 fold diluted Nano-Glo Luciferase Assay Substrate® (Promega®).[1] Luminescence measurement is performed immediately afterward for 30s on a FLUOstar Omega®luminometer (Thermo Fisher Scientific). The gain is reduced by 10% in relation to the sample with the highest signal on the plate to prevent saturation.[1]

DNA staining by Syber Green I® (Thermo Fisher Scientific) is performed, as previously described by Smilkstain *et al*.[8] In this process, 100 μL of parasite culture (2% hematocrit) is incubated in a 96-well cell plate in darkness and at room temperature after adding 100 μL of Syber Green I in a lysis buffer at 2/10.000 (v/v) [20 mMTris, pH 7.5; 5 mM EDTA; 0.008%

saponin (w/v); 0.08% Triton X-100 (v/v)]. Fluorescence is measured in an Omega BMG Labtech® Polarstar fluorimeter at a 485 nm and 520 nm excitation and emission wavelengths, respectively.[8]

Statistical analysis.

The parasite IC_{50} analysis is performed, and the inhibition percentage is measured, using GraphPad Prism®software (GraphPad Software®, Inc., California, USA). Inhibition of parasite growth is analyzed in relation to the logarithm of the concentration of the used compound. Finally, we adjust the curves using nonlinear regression (dose-response slope / variable sigmoid equation). For IC_{50} assays it is calculated the Z_{value} as described by Zhang et al.[9] and the R- squared value (R^2). The initial value of Z is given as $Z_0 = 1 - [(3\sigma(+) + 3\sigma(-)) / \mu(+) - \mu(-)]$, where $\mu(+)$ and $\sigma(+)$ are the mean and its standard deviation and where $\mu(-)$ and $\sigma(-)$ are the value and its standard

deviation for a 200 μM artesunate supralethal control. We consider those assays with $R^2 > 0.9$ to have a dose-response relationship and as those assays with $Z > 0.5$ to be robust.

Cell culture and cytotoxicity assay in Vero cell line.

The Vero cell line (African green monkey kidney), was cultured in Dulbecco's modified Eagle's medium (DMEM, Gibco) supplemented with 10% fetal bovine serum, penicillin G (100 units/ml, Sigma), and streptomycin (100 μg/mL, Sigma) and maintained in a 5% CO_2 humidified incubator at 37 °C. Cell viability was analyzed using the MTT assay.[10] Briefly, cells were seeded in 96-well plates at a density of 3000 cells per well. The synthesized compounds were dissolved in DMSO (Merck) at 27 mM or 25 mM and then diluted in culture medium to achieve the final concentration for the different treatments. As negative controls, cells were incubated with the corresponding concentration of DMSO (Merck), according to the dilution. After 72 h of treatment, cells were stained with 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) (0.5 mg/mL; Sigma) for 4 h at 37 °C. After the removal of the culture medium, formazan crystals were dissolved in DMSO and the absorbance was measured at 562 nm using a microplate reader.

ADME/toxicity predictions.

Computational modeling to estimate the bioavailability, aqueous solubility, blood brain barrier potential, human intestinal absorption, mutagenicity, and toxicity for the compounds was performed using the ChemAxon, SwissAdme, Molinspiration and Osiris Property.

General method for the preparation of S-alkylated thiosalicylic acid compounds.

Thiosalicylic acid (1 equivalent) was dissolved in anhydrous acetone (10 mL/eq), under constant stirring and inert atmosphere. Next, guanidinium carbonate (1 equivalent) and organobromide compound (1 equivalent) were added. The reaction mixture was brought to reflux for 8 hours. To finish the reaction, a solution of 1M HCl was added, continuing to extract the compound of interest with ethyl ether (3 x 25 mL). Combined organic extracts were dried with sodium sulfate and evaporated. Products were purified by column chromatography in silica gel with increasing hexanes/ethyl acetate gradients.

General procedure for the Cu(I) mediated 1,3-dipolar cycloaddition (CuAAC).

Alkyne (1 equivalent) and azide (1.5 equivalent) were suspended in 10 mL/eq of *t*BuOH:H_2O (1:1). Then, 1 M $CuSO_4$ solution (0.05 equivalents) and 1 M sodium ascorbate solution (0.2 equivalents) were added, and the mixture stirred overnight at room temperature. Brine (30 mL) was added and the solution was extracted with dichloromethane (3 x 25 mL). Combined organic extracts were dried over sodium sulfate and evaporated. Products were purified by column chromatography in silica gel with increasing hexane/ethyl acetate gradients.

Synthesis of 2-(prop-2-ynylthio)benzoic acid (1).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 567 mg of a light yellow solid (isolated yield: 81%). ^{1}H NMR ($CDCl_3$) δ 8.14 (d, 1H, $^3J_{H2\text{-}H3}$ = 7.2 Hz, Ar2-H); 7.55 (dt, 1H, $^3J_{H4\text{-}H5}$ = 7.2 Hz, $^4J_{H4\text{-}H2}$ = 0.7 Hz, Ar4-H); 7.50 (d, 1H, $^3J_{H5\text{-}H4}$ = 7.5 Hz, Ar5-H); 7.26 (m, 1H, Ar3-H); 3.68 (d, 2H, $^4J_{H8\text{-}H10}$ =

2.6 Hz, C8-H); 2.24 (t, 1H, $^{4}J_{H10\text{-}H8}$ = 2.6 Hz, C10-H). ^{13}C NMR ($CDCl_3$) δ 171.7 (C=O); 142.8 (C); 133.4 (CH); 132.4 (CH); 126.7 (C); 126.7 (CH); 124.5 (CH); 83.6 (C); 71.7 (CH) 31.4 (CH_2). ESI-HRMS calculated mass for $C_{10}H_8O_2SNa$ ($M+Na^+$) 215.01372; found m/z 215.01355. IR υ_{max} 3505 (O-H); 3282 (-C≡H); 1712 (C=O); 1484 (C=C aromatic) cm^{-1}.

Synthesis of 2-(cyclohexylthio)benzoic acid (1a).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 65 mg of a light yellow solid (isolated yield: 87%). ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, 1H, $^{3}J_{H2\text{-}H3}$ = 7.2 Hz, $^{4}J_{H2\text{-}H4}$ = 1.0 Hz, Ar2-H); 7.48 (t, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz, Ar4-H); 7.35 (d, 1H, $^{3}J_{H5\text{-}H4}$ = 8.0 Hz, Ar5-H); 7.19 (t, 1H, $^{3}J_{H3\text{-}H4}$ = 7.5 Hz, Ar3-H); 2.78 (m, 1H, C8-H); 2.27 to 1.18 (m, 10H, C9-H to C13-H). ^{13}C NMR ($CDCl_3$) δ 170.3 (C=O); 139.3 (C); 133.3 (CH); 132.6 (CH); 131.0 (C); 124.8 (CH); 124.6 (CH); 48.2 (CH); 33.4 (CH_2); 33.4 (CH_2); 25.1 (CH_2); 25.1 (CH_2); 25.0 (CH_2). HRMS calculated mass for $C_{13}H_{16}O_2SNa$ ($M+Na^+$) 259.07632; found m/z 259.07641. IR υ_{max} 3444 (O-H); 2925 (-C-H); 1675 (C=O) cm^{-1}.

Synthesis of 2-(benzylthio)benzoic acid (1b).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 69 mg of a light yellow solid (isolated yield: 73%). ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1H, $^{3}J_{H2\text{-}H3}$ = 7.2 Hz, Ar2-H); 7.50 to 7.19 (m, 8H, Ar-H); 4.17 (s, 2H, CH_2-Ar). ^{13}C NMR ($CDCl_3$) δ 170.3 (C=O); 141.3 (C); 134.3 (C); 133.2 (CH); 133.2 (CH); 132.6 (CH); 129.1 (CH); 128.7 (CH); 128.0 (CH); 126.7 (CH); 126.1 (C); 40.0 (CH_2). HRMS calculated mass for $C_{14}H_{13}O_2S$ ($M+H^+$) 245.06308; found m/z 245.06301. IR υ_{max} 3423 (O-H); 1681 (C=O); 1451 (C=C aromatic) cm^{-1}.

Synthesis of 2-((3-phenylpropyl)thio)benzoic acid (1c).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 80 mg of a light yellow solid (isolated yield: 75%). ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1H, $^{3}J_{H2\text{-}H3}$ = 7.8 Hz, Ar2-H); 7.44 (t, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz, Ar4-H); 7.33 to 7.16 (m, 7H, Ar-H); 2.94 (t, 2H, $^{3}J_{H8\text{-}H9}$ = 7.4 Hz, C8-H); 2.82 (t, 2H, $^{3}J_{H10\text{-}H9}$ = 7.4 Hz, C10- H); 2.07 (q, 2H, $^{3}J_{H9\text{-}H10}$ = 7.3 Hz, C9-H). ^{13}C NMR ($CDCl_3$) δ 170.9 (C=O); 141.3 (C); 140.3 (C); 133.2 (CH); 133.1 (CH); 132.6 (C); 128.6 (CH); 128.4 (CH); 126.7 (CH); 126.3 (CH); 126.0 (CH); 36.4 (CH_2); 32.4 (CH_2); 27.1 (CH_2). HRMS calculated mass for $C_{16}H_{16}O_2SNa$ ($M+Na^+$) 295.07632; found m/z 295.07633. IR υ_{max} 3385 (O-H); 2929 (-C-H); 1677 (C=O); 1483 (C=C aromatic) cm^{-1}.

Synthesis of 2-(cinnamylthio)benzoic acid (1d).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 71 mg of a light yellow solid (isolated yield: 68%). ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, 1H, $^{3}J_{H2\text{-}H3}$ = 7.5 Hz, $^{4}J_{H2\text{-}H4}$ = 0.9 Hz, Ar2 -H); 7.48 to 7.28 (m, 8H, aromatic protons); 7.22 (t, 1H, $^{3}J_{H3\text{-}H4}$ = 7.9 Hz, Ar3-H); 6.67 (d, 1H, $^{3}J_{H10\text{-}H9}$ = 15.8 Hz, C10-H); 6.34 (dt, 1H, $^{3}J_{H9\text{-}H10}$ = 15.8 Hz and $^{3}J_{H9\text{-}H8}$ = 6.7 Hz, C9-H); 3.60 (dd, 2H, $^{3}J_{H8\text{-}H9}$ = 6.7 Hz and $^{4}J_{H8\text{-}H10}$ = 1.3 Hz, C8-H). ^{13}C NMR ($CDCl_3$) δ 170.3 (C=O); 139.3 (C); 135.6 (C); 133.3 (CH); 132.6 (CH); 131.0 (CH); 129.4 (CH); 129.1 (CH); 128.8 (CH); 128.8 (CH); 126.8 (CH); 126.8 (C); 124.6 (CH); 124.6 (C); 121.5 (CH); 31.5 (CH_2). HRMS calculated mass for $C_{16}H_{15}O_2S$ ($M+H^+$) = 271.07873; found m/z 271.07877. IR υ_{max} 3562 (O-H); 2962 (=CH-); 2923 (-C-H); 1645 (C=O); 1487 (C=C aromatic) cm^{-1}.

Synthesis of 2-(octylthio)benzoic acid (1e).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 86 mg of a light yellow solid (isolated yield: 83%). ^{1}H NMR ($CDCl_3$) δ 8.12 (dd, 1H, $^{3}J_{H2\text{-}H3}$ = 7.2 Hz, $^{4}J_{H2\text{-}H4}$ = 0.7 Hz, Ar2-H); 7.48 (dt, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz , $^{4}J_{H4\text{-}H2}$ = 0.7 Hz, Ar4-H); 7.36 (d, 1H, $^{3}J_{H5\text{-}H4}$ = 8.0 Hz, Ar5-H); 7.21 (t, 1H, $^{3}J_{H3\text{-}H4}$ = 7.7 Hz, Ar3-H); 2.92 (t, 2H, $^{3}J_{H8\text{-}H9}$ = 7.5 Hz, C8-H); 1.72 (q, 2H, $^{3}J_{H9\text{-}H10}$ = 7.5 Hz, C9-H); 1.47 (m, 10H, C10-H to C14-H); 0.88 (t, 3H, $^{3}J_{H15\text{-}H14}$ = 6.7 Hz, C15-H). ^{13}C NMR ($CDCl_3$) δ 169.6 (C=O); 142.2 (C); 136.3 (C); 133.0 (CH); 132.6 (CH); 126.7 (CH); 124.3 (CH); 32.8 (CH_2); 31.8 (CH_2); 29.2 (CH_2); 29.2 (CH_2); 29.2 (CH_2); 29.2 (CH_2); 22.6 (CH_2); 14.1 (CH_3). ESI-HRMS calculated mass for $C_{15}H_{22}O_2SNa$ ($M+Na^+$) 289.12327, found m/z 289.12354. IR υ_{max} 3442 (O-H); 2924 (-C-H); 1697 (C = O); 1456 (C=C aromatic) cm^{-1}.

Synthesis of 2-(decylthio)benzoic acid (1f).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 92 mg of a light yellow solid (isolated yield: 81%). ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1H, $^{3}J_{H2\text{-}H3}$ = 7.2 Hz, Ar 2 -H); 7.48 (t, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz, Ar4-H); 7.35 (d, 1H, $^{3}J_{H5\text{-}H4}$ = 8.0 Hz, Ar5-H); 7.19 (t, 1H, $^{3}J_{H3\text{-}H4}$ = 7.5 Hz, Ar3-H); 2.93 (t, 2H, $^{3}J_{H8\text{-}H9}$ = 7.4 Hz, C8-H); 1.84 (m, 2H, C9-H); 1.38 to 1.21 (m, 14H, C10-H to C16-H); 0.88 (t, 3H, $^{3}J_{H17\text{-}H16}$= 6.7 Hz, C17-H). ^{13}C NMR ($CDCl_3$) δ 170.7 (C=O); 142.8 (C); 133.1 (CH); 132.6 (CH); 126.5 (C); 126.1 (CH); 124.0 (CH); 32.4 (CH_2); 31.8 to 28.2 (C9 to 15, CH_2); 22.6 (CH_2); 14.1 (CH_3). HRMS calculated mass for $C_{17}H_{26}O_2NaS$ ($M+Na^+$) 317.15457; found m/z 317.15442. IR υ_{max} 3385 (O-H); 2929 (-C-H); 1677 (C=O); 1483 (C=C aromatic) cm^{-1}.

Synthesis of 2-((3-ethoxy-3-oxopropyl)thio)benzoic acid (1g).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 77 mg of a light yellow solid (isolated yield: 78%). ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, 1H, $3J_{H2\text{-}H3}$ = 7.2 Hz, $^{4}J_{H2\text{-}H4}$ = 0.7 Hz, Ar2-H); 7.52 (dt, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz, $^{4}J_{H4\text{-}H2}$ = 0.7 Hz, Ar4-H); 7.38 (d, 1H, $^{3}J_{H5\text{-}H4}$ = 8.0 Hz, Ar5-H); 7.22 (t, 1H, $^{3}J_{H3\text{-}H4}$ = 7.7 Hz, Ar3-H); 4.18 (c, 2H, $^{3}J_{H11\text{-}H12}$ = 7.2 Hz, C11-H); 3.24 (t, 2H, $^{3}J_{H8\text{-}H9}$ = 7.6 Hz, C8-H); 2.72 (t, 2H, $^{3}J_{H9\text{-}H8}$ = 7.7 Hz, C9-H); 1.28 (t, 2H, $^{3}J_{H12\text{-}H11}$ = 7.3 Hz, C12-H). ^{13}C NMR ($CDCl_3$) δ 171.7 (C=O); 170.3 (C=O); 141.3 (C); 133.2 (CH); 133.3 (CH); 132.6 (C); 126.7 (CH); 126.1 (CH); 61.0 (CH_2); 33.3 (CH_2); 27.2 (CH_2); 14.2 (CH_3). HRMS calculated mass for $C_{12}H_{15}O_4S$ ($M+H^+$) 255.06856; found m/z 255.06851. IR υ_{max} 3134 (O-H); 2952 (-C-H); 1732, 1715 and 1697 (C=O); 1444 (C=C aromatic) cm^{-1}.

Synthesis of 2-((3-methylbut-2-en-1-yl)thio) benzoic acid (1h).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 63 mg of a light yellow solid (isolated yield: 72%). ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, 1H, $^{3}J_{H2\text{-}H3}$ = 7.2 Hz, $^{4}J_{H2\text{-}H4}$ = 0.7 Hz, Ar 2 -H); 7.49 (dt, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz, $^{4}J_{H4\text{-}H2}$ = 0.7 Hz, Ar4-H); 7.37 (d, 1H, $^{3}J_{H5\text{-}H4}$ = 8.0 Hz, Ar5-H); 7.22 (t, 1H, $^{3}J_{H3\text{-}H4}$ = 7.7 Hz, Ar3-H); 5.33 (t, 2H, $^{3}J_{H9\text{-}H8}$ = 7.6 Hz, C9-H); 3.57 (d, 2H, $^{3}J_{H8\text{-}H9}$ = 7.6 Hz, C8-H); 1.74 (s, 3H C11-H); 1.67 (s, 3H, C12-H). ^{13}C NMR (MeOD) δ 170.0 (C=O); 143.2 (C); 138.2 (C); 133.2 (CH); 132.3 (CH); 129.9 (C); 127.8 (CH); 125.0 (CH); 119.8 (CH); 31.5 (CH_2); 25.8 (CH_3); 17.9 (CH_3). HRMS calculated mass for $C_{12}H_{15}O_2S$ ($M+H^+$) 223.07873; found m/z 223.07859. IR υ_{max} 3361 (O-H); 2953 (=CH-); 2926 (-C-H); 1672 (C=O); 1487 (C=C aromatic) cm^{-1}.

Synthesis of (E)-2-((3,7-dimethylocta-2,6-dien-1-yl)thio)benzoic acid (1i).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 160 mg of a light yellow solid (isolated yield: 88%). ^{1}H NMR ($CDCl_3$) δ 8.13 (dd, 1H, $^{3}J_{H2\text{-}H3}$ = 7.2 Hz, $^{4}J_{H2\text{-}H4}$ = 0.7 Hz, Ar2-H); 7.48 (dt, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz, $^{4}J_{H4\text{-}H2}$ = 0.7 Hz, Ar4-H); 7.35 (d, 1H, $^{3}J_{H5\text{-}H4}$ = 8.0 Hz, Ar5-H); 7.20 (t, 1H, $^{3}J_{H3\text{-}H4}$ = 7.7 Hz, Ar3-H); 5.34 (t, 1H, $^{3}J_{H9\text{-}H8}$ = 7.5 Hz, C9-H); 5.07 (m, 1H, C13-H); 3.59 (d, 2H, $^{3}J_{H8\text{-}H9}$ = 7.6 Hz, C8-H); 2.06 (m, 4H, C11-H and C12-H); 1.70 (s, 3H, C17-H); 1.67 (s, 3H C16-H); 1.60 (s, 3H, C15-H). ^{13}C NMR ($CDCl_3$) δ 170.5 (C=O); 142.6 (C); 141.4 (C); 133.2 (CH); 133.3 (CH); 132.6 (C); 131.8 (C); 127.1 (CH); 126.1 (CH); 124.4 (CH); 123.8 (CH); 117.7 (CH); 117.7 (CH); 39.3 (CH_2); 31.2 (CH_2); 26.4 (CH_2); 25.7 (CH_3); 17.7 (CH_3); 16.3 (CH_3). HRMS calculated mass for $C_{17}H_{22}O_2SNa$ ($M+Na^+$) = 313.12327; found m/z 313.12332. IR υ_{max} 3350 (O-H); 2972 (=CH-); 2912 (-C-H); 1691 (C = O); 1462 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)thio)benzoic acid (1j). Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 69 mg of a light yellow solid (isolated yield: 79%). ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, 1H, $^{3}J_{H2\text{-}H3}$ = 7.5 Hz, $^{4}J_{H2\text{-}H4}$ = 1.0 Hz, Ar 2 -H); 7.48 (t, 1H, $^{3}J_{H4\text{-}H5}$ = 7.2 Hz, Ar4-H); 7.36 (d, 1H, $^{3}J_{H5\text{-}H4}$ = 7.8 Hz, Ar5-H); 7.22 (t, 1H, $^{3}J_{H3\text{-}H4}$= 7.5 Hz, Ar3-H); 5.34 (t; 1H, $^{3}J_{H9\text{-}H8}$= 7.6 Hz, C9-H); 5.08 (m, 2H, C13-H and C17-H); 3.59 (d, 2H, $^{3}J_{H8\text{-}H9}$= 7.6 Hz, C8-H); 2.15 to 1.92 (m, 10H, C11-H, C12-H, C15-H and C16-H); 1.68 (s, 6H, C19-H and C22-H); 1.60 (s, 6H, C20-H and C21-H). ^{13}C NMR ($CDCl_3$) δ 170.0 (C=O); 142.0 (C); 141.5 (C); 135.4 (C); 133.0 (CH); 133.0 (CH); 132.5 (C); 131.3 (C); 127.5 (CH); 127.2 (C); 124.6 (CH); 124.4 (CH); 123.7 (CH); 117.7 (CH); 39.6 (CH_2); 39.3 (CH_2); 31.4 (CH_2); 26.7 (CH_2); 26.3

(CH_2); 25.7 (CH_3); 17.7 (CH_3); 16.4 (CH_3); 16.0 (CH_3). HRMS calculated mass for $C_{22}H_{30}O_2NaS$ ($M+Na^+$) 381.18587; found m/z 381.18582. IR υ_{max} 3361 (O-H); 2955 (C=CH-); 2927 (-C-H); 1680 (C=O); 1487 (C=C aromatic) cm^{-1}.

Synthesis of (E)-2-((3,7,11,15-tetramethylhexadec-2-en-1-yl)thio)benzoic acid (1k).

Following the general reaction conditions for S-alkylated thiosalicylic acid synthesis, the reaction was worked up and purified to afford 120 mg of a light yellow solid (isolated yield: 85%). ^1H NMR ($CDCl_3$) δ 8.13 (dd, 1H, $^3J_{H2\text{-}H3}$ = 7.2 Hz, $^4J_{H2\text{-}H4}$ = 0.7 Hz, Ar2-H); 7.48 (t, 1H, $^3J_{H4\text{-}H5}$ = 7.2 Hz, Ar4-H); 7.36 (d, 1H, $^3J_{H5\text{-}H4}$ = 7.9 Hz, Ar5-H); 7.20 (t, 1H, $^3J_{H3\text{-}H4}$ = 7.5 Hz, Ar3-H); 5.32 (t, 1H, $^3J_{H9\text{-}H8}$ = 7.6 Hz, C9-H); 3.59 (d, 2H, $^3J_{H8\text{-}H9}$ = 7.4 Hz, C8-H); 2.01 (m, 2H, C11-H); 1.67 (s, 3H, C27-H); 1.59 to 0.99 (m, 19H, C12-H to C22-H); 0.85 (t, 12H, ^3J = 6.7 Hz, C23-H to C26-H). ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O); 142.0 (C); 141.9 (C); 133.0 (CH); 132.6 (CH); 132.6 (C); 127.2 (CH); 126.9 (CH); 124.4 (CH); 117.7 (CH); 39.3 (CH_2); 39.4 (CH_2); 37.4 to 36.6 (CH_2); 32.8 (CH); 32.7 (CH); 31.3 (CH_2); 28.0 (CH); 25.1 to 24.5 (CH_2); 22.7 (CH_3); 22.6 (CH_3); 19.7 (CH_3); 19.7 (CH_3); 16.2 (CH_3). HRMS calculated mass for $C_{27}H_{44}O_2SNa$ ($M+Na^+$) 455.29542; found m/z 455.29543. IR υ_{max} 3550 (O-H); 2953 (= CH-); 2926 (-C-H); 1681 (C = O); 1462 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-cyclohexyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2a).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 45 mg of a light yellow solid (isolated yield: 84%). ^1H NMR ($CDCl_3$) δ 8.13 (dd, 1H, $^3J_{H2\text{-}H3}$= 7.3 Hz, $^4J_{H2\text{-}H4}$= 0.9 Hz, Ar2-H); 7.48 (m, 3H, Ar4-H, Ar5-H, C10triazole-H); 7.19 (m, 1H, Ar3-H); 4.45 (m, 1H, C11-H); 4.29 (s, 2H, C8-H); 2.27 to 1.21 (m, 10H, C12-H to

C16-H). ^{13}C NMR ($CDCl_3$) δ 170.3 (C=O); 144.3 (C); 139.3 (C); 133.3 (CH); 132.6 (CH); 131.0 (C); 126.1 (CH); 124.8 (CH); 124.6 (CH); 60.3 (CH); 33.4 (CH_2); 33.4 (CH_2); 25.1 (CH_2); 25.0 (CH_2). HRMS calculated mass for $C_{16}H_{19}O_2N_3SNa$ ($M+Na^+$) 340.10902; found m/z 340.10898. IR υ_{max} 3501 (O-H); 2929 (-C-H); 1691 (C=O); 1454 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2b).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 44 mg of a light yellow solid (isolated yield: 80%). ^{1}H NMR ($CDCl_3$) δ 8.05 (d, 1H, $^3J_{H2\text{-}H3}$= 7.2 Hz, Ar2-H); 7.55 (s, 1H, C10triazole-H); 7.48 to 7.10 (m, 8H, aromatic carbons); 5.50 (s, 1H, C11-H) and 4.29 (s, 2H, C8-H). ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O); 144.3 (C); 139.2 (C); 133.3 (CH); 132.6 (CH); 131.0 (C); 129.9 (C); 128.7 to 128.0 (CH); 126.1 (CH); 124.8 (CH); 54.1 (CH_2); 27.7 (CH_2). HRMS calculated mass for $C_{17}H_{15}O_2N_3SNa$ ($M+Na^+$) 348.07772; found m/z 348.07781. IR υ_{max} 3450 (O-H); 2924 (C-H); 1687 (C=O); 1485 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-(3-phenylpropyl)-1H-1,2,3-triazol-4-yl)methyl)thio) benzoic acid (2c).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 53 mg of a light yellow solid (isolated yield: 88%). ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1H, $^3J_{H2\text{-}H3}$= 7.0 Hz Ar2-H); 7.50 to 7.08 (m, 8H, aromatic carbons); 7.44 (s, 1H, C10triazole-H); 4.29 (s, 2H, C8-H); 4.27 (t, 2H, $^3J_{H11\text{-}H12}$= 7.3 Hz, C11-H); 2.57 (t, 2H, $^3J_{H13\text{-}H12}$= 7.5 Hz, C13-H); 2.19 (q, 2H, $^3J_{H12\text{-}H13}$= 7.5 Hz, C12-H). ^{13}C NMR ($CDCl_3$) δ 170.2 (C=O); 144.3 (C); 140.2 (C); 139.2 (C); 133.3 (CH); 132.6 (CH); 131.0 (C); 129.9 (C); 128.8 to 128.0 (CH); 126.1 (CH); 124.8 (CH); 49.6 (CH_2); 32.4 (CH_2); 31.5 (CH_2); 27.7 (CH_2). HRMS calculated mass for $C_{19}H_{19}O_2N_3SNa$ ($M+Na^+$) 376.10902; found m/z 376.10988. IR υ_{max} 3388 (O-H); 2926 (-C-H); 1690 (C=O); 1484 (C=C aromatic) cm^{-1}.

Synthesis of (E)-2-(((1-cinnamyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2d).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 51 mg of a light yellow solid (isolated yield: 86%). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, $^{3}J_{H2\text{-}H3}$= 7.7 Hz, Ar 2 -H); 7.57 (s, 1H, C10triazole-H); 7.47 to 7.10 (m, 8H, aromatic protons); 6.62 (d, 1H, $^{3}J_{H13\text{-}H12}$= 14.9 Hz, C13-H); 6.26 (m, 1H, C12-H); 5.06 (d, 2H, $^{3}J_{H11\text{-}H12}$ = 6.6 Hz, C11-H); 4.31 (s, 2H, C8-H). ^{13}C NMR ($CDCl_3$) δ 170.6 (C=O); 144.5 (C); 141.0 (C); 135.5 (CH); 133.2 (CH); 135.4 (C); 132.3 to 124.4 (CH); 132.3 (C); 122.3 (CH); 121.1 (CH); 52.4 (CH_2); 27.6 (CH_2). HRMS calculated mass for $C_{19}H_{18}O_2N_3S$ ($M + H^+$) 352.11142; found m/z 352.11130. IR υ_{max} 3315 (O-H); 3926 (-C-H); 1672 (C=O); 1487 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-octyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2e).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 46 mg of a light yellow solid (isolated yield: 78%). ^{1}H NMR ($CDCl_3$) δ 8.09 (d, 1H, $^{3}J_{H2\text{-}H3}$= 8.1 Hz, Ar2-H); 7.49 (s, 1H, C10triazole-H); 7.45 to 7.42 (m, 2H, Ar4-H, Ar5-H); 7.18 (m, 1H, Ar3-H); 4.32 (s, 2H, C8-H); 4.27 (t, 2H, $^{3}J_{H11\text{-}H12}$= 7.3 Hz, C11-H); 1.84 (q, $^{3}J_{H12\text{-}H13}$= 6.3 Hz, C12-H); 1.23 (m, 10H, C13-H to C17-H); 0.86 (t, 3H, $^{3}J_{H18\text{-}H17}$ = 6.7 Hz, C18-H). ^{13}C NMR ($CDCl_3$) δ 170.7 (C=O); 144.4 (C); 141.1 (C); 133.2 (CH); 132.3 (CH); 126.9 (C); 126.1 (CH); 124.4 (CH); 122.3 (CH); 50.6 (CH_2); 31.7 to 22.6 (CH_2); 14.0 (CH_3). HRMS calculated mass for $C_{18}H_{25}O_2N_3SNa$ ($M+Na^+$) 370.15597; found m/z 376.15597. IR υ_{max} 3550 (O-H); 2929 (-C-H); 1682 (C = O); 1488 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-decyl-1H-1,2,3-triazol-4-yl)metyl)thio)benzoic acid. (2f).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 51 mg of a light yellow solid (isolated yield: 88%). ^{1}H NMR ($CDCl_3$) δ 8.08 (d,

1H, $^{3}J_{H6\text{-}H5}$= 7.6 Hz, C6-H); 7.48 (s, 1H, C10triazol-H); 7.45 to 7.43 (m, 2H, C3-H, C4-H); 7.20 (m, 1H, C5-H); 4.31 (s, 2H, C8-H); 4.27 (t, 2H, $^{3}J_{H11\text{-}H12}$= 7.3 Hz, C11-H); 1.84 (q, $^{3}J_{H12\text{-}H13}$= 6.8 Hz, C12-H); 1.24 (m, 14H, C13-H to C19-H); 0.87 (t, 3H, $^{3}J_{H19\text{-}H20}$= 6.7 Hz, C20-H). ^{13}C NMR ($CDCl_3$) δ 170.3 (C=O); 144.3 (C); 140.8 (C); 133.2 (CH); 132.3 (CH); 126.5 (C); 126.5 (CH); 124.6 (CH); 122.2 (CH); 50.5 (CH_2); 31.8 (CH_2); 30.2 (CH_2); 29,4 to 28,9 (CH_2); 27.5 (CH_2); 26.4 (CH_2); 22.7 (CH_2); 14.1 (CH_3). HRMS calculated mass for $C_{20}H_{30}O_2N_3S$ ($M+H^+$) 376.2053; found m/z 376.2053.

Synthesis of 2-(((1-(3-ethoxy-3-oxopropyl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2g). Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 158 mg of a light yellow solid (isolated yield: 91%). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, $^{3}J_{H2\text{-}H3}$= 7.6 Hz, Ar2-H); 7.59 (s, 1H, C10triazole-H); 7.45 (m, 2H, Ar4-H and Ar5-H); 7.21 (m, 1H, Ar3-H); 4.59 (t; 1H, $^{3}J_{H11\text{-}H12}$= 7.2 Hz, C11-H); 4.28 (s, 2H, C8-H); 4.12 (c, 2H, $^{3}J_{H14\text{-}H15}$= 7.1 Hz, C14-H); 2.92 (t, 2H, $^{3}J_{H12\text{-}H11}$= 6.5 Hz, C12-H); 1.21 (t, 3H, $^{3}J_{H15\text{-}H14}$= 7.1 Hz, C15-H). ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O); 169.8 (C=O); 144.2 (C); 140.7 (C); 133.2 (CH); 132.3 (CH); 127.1 (C); 126.6 (CH); 124.7 (CH); 123.3 (CH); 61.3 (CH_2); 45.7 (CH_2); 34.6 (CH_2); 27.5 (CH_2); 14.1 (CH_3). HRMS calculated mass for $C_{15}H_{17}O_4N_3SNa$ ($M+Na^+$) 358.08320; found m/z 358.08324. IR υ_{max} 3520 (O-H); 2929 (-C-H); 1715 (C=O); 1691 (C=O), 1454 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-(3-methylbut-2-en-1-yl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2h). Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 140 mg of a light yellow solid (isolated yield: 89%). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, $^{3}J_{H2\text{-}H3}$ = 7.6 Hz, Ar2-H; 7.54 (m, 2H, Ar4-H and Ar5-H); 7.52 (s, 1H, C10-triazol-H);

7.21 (m, 1H, Ar3-H); 5.45 (m, 1H, C12-H); 5.00 (d, 2H, $^{3}J_{H11\text{-}H12}$= 7.2 Hz, C11-H); 4.27 (s, 2H, C8-H); 1.83 (s, 3H, C14-H); 1.80 (s, 3H, C15-H). ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O); 144.2 (C); 140.7 (C); 139.8 (C); 133.2 (CH); 132.3 (CH); 127.1 (C); 126.6 (CH); 124.7 (CH); 123.3 (CH); 116.2 (CH); 48.1 (CH_2); 27.5 (CH_2); 25.7 (CH_3); 18.1 (CH_3). HRMS calculated mass for $C_{15}H_{17}O_2N_3SNa$ ($M+Na^+$) 326.09337; found m/z 326.09336. IR υ_{max} 3427 (O-H); 2955 (-C= H); 1695 (C=O), 1457 (C=C aromatic) cm^{-1}.

Synthesis of the acid 2-(((1-(3,7-dimethylocta-2,6-dien-1-yl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2i).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 162 mg of a light yellow solid (isolated yield: 84%). ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1H, $^{3}J_{H2\text{-}H3}$= 7.6 Hz, Ar2-H); 7.59 (s, 1H, C10triazole-H); 7.44 (m, 2H, Ar4-H and Ar5-H); 7.20 (m, 1H, Ar3-H); 5.44 (t, 1H, $^{3}J_{H4\text{-}H3}$= 7.4 Hz, C12-H); 5.05 (m, 1H, C16-H); 5.00 (d, 2H, $^{3}J_{H3\text{-}H4}$= 7.1, Hz, C11-H); 4.28 (s, 2H, C8-H); 2.15 (m, 4H, C14-H and C15-H); 1.83 (s, 3H, C20Z-H); 1.78 (s, 3H, C20E-H); 1.68 (s, 3H, C19-H); 1.60 (s, 3H, C18-H). ^{13}C NMR ($CDCl_3$) δ 170.5 (C=O); 144.1 (C); 140.7 (C); 133.0 (CH); 139.8 (C); 132.3 (CH); 132.2 (C); 127.1 (C); 126.6 (CH); 124.7 (CH); 123.3 (CH); 123.3 (CH); 116.2 (CH); 116.0 (CH); 48.1 (CH_2); 47.9 (CH_2); 39.9 (CH_2); 32.1 (CH_2); 27.6 (CH_2); 26.1 (CH_2); 25.7 (CH_3); 23.4 (CH_3); 17.7 (CH_3); 16.5 (CH_3). HRMS calculated mass for $C_{20}H_{25}O_2N_3SNa$ ($M+Na^+$) 394.15597; found m/z 394.15607. IR υ_{max} 3432 (O-H); 2961 (=CH-); 2926 (-C-H); 1672 (C=O); 1487 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-((6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2j).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 205 mg of a light yellow solid (isolated yield: 90%). ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1H, $^{3}J_{H2\text{-}H3}$= 7.5 Hz, Ar2-H); 7.61 and 7.60 (s, 1H, C10triazole-H); 7.45 (m, 2H, Ar4-H and Ar5-H); 7.20 (m, 1H, Ar3-H); 5.37 (t, 1H, $^{3}J_{H12\text{-}H11}$= 7.3 Hz, C12-H); 5.05 (m, 2H, C16-H and C20-H); 4.90 (d, 2H, $^{3}J_{H11\text{-}H12}$= 7.1 Hz, C11-H); 4.28 (s, 2H, C8-H); 2.20 to 1.80 (m, 8H, C14-H, C15-H, C18-H and C19-H); 1.83 (s, 3H, C25*Z*-H); 1.78 (s, 3H, C25*E*-H); 1.67 (s, 3H, C22-H); 1.60 (s, 6H, C23-H and C24-H). ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O); 144.2 (C); 140.7 (C); 139.9 (C); 136.6 (C); 136.0 (C); 133.2 (CH); 132.3 (CH); 131.5 (C); 127.1 (C); 126.6 (CH); 124.7 (CH); 124.1 (CH); 123.3 (CH); 123.1 (CH); 116.0 (CH); 48.1 (CH_2); 39.7 (CH_2); 39.4 (CH_2); 32.1 (CH_2); 27.6 (CH_2); 26.2 (CH_2); 26.2 (CH_2); 25.7 (CH_3); 23.5 (CH_3); 17.7 (CH_3); 16.6 (CH_3); 16.0 (CH_3). HRMS calculated mass for $C_{25}H_{33}O_2N_3SNa$ ($M+Na^+$) 462.21857; found m/z 462.21851. IR υ_{max} 3361 (O-H); 2961 (=CH-); 2926 (-C-H); 1693 (C=O); 1487 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-(3,7,11,15-tetramethylhexadec-2-en-1-yl)-1H-1,2,3-triazole-4-yl)methyl)thio)benzoic acid (2k).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 230 mg of a light yellow solid (isolated yield: 83%). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, $^{3}J_{H2\text{-}H3}$ = 7.8 Hz, Ar2-H); 7.48 (m, 3H, Ar4-H, Ar5-H and C10triazole-H); 7.20 (m, 1H, Ar3-H); 5.37 (t; 1H, $^{3}J_{H12\text{-}H11}$= 7.2 Hz, C12-H); 4.91 (d, 2H, $^{3}J_{H12\text{-}H11}$= 7.2 Hz, C11-H); 4.29 (s, 2H, C8-H); 2.05 (m, 2H, C14-H); 1.74 (s, 3H, C30-H); 1.59 to 0.99 (m, 19H, C12-H to C22-H); 0.85 (t, 12H, ^{3}J= 6.7 Hz, C23-H, C24-H, C25 -H and C26-H). ^{13}C NMR ($CDCl_3$) δ 170.2 (C=O);

144.3 (C); 144.1 (C); 144.0 (C); 141.1 (C); 133.2 (CH); 132.3 (CH); 126.9 (C); 126.4 (CH); 124.6 (CH); 121.7 (CH); 117.7 (CH); 116.4 (CH); 48.1 (CH_2); 47.9 (CH_2); 39.8 (CH_2); 39.4 (CH_2); 37.4 (CH_2); 36.9 to 36.7 (CH_2); 32.8 (CH); 32.3 (CH); 27.9 (CH); 27.6 (CH); 25.4 to 24.5 (CH_2); 22.7 (CH_3); 22.6 (CH_3); 19.7 (CH_3); 19.7 (CH_3); 19.7 (CH_3); 16.2 (CH_3). HRMS calculated mass for $C_{30}H_{47}O_2N_3SNa$ ($M+Na^+$) 536.32812; found m/z 536.32801. IR υ_{max} 3402 (O-H); 2958 (=CH-); 2925 (-C-H); 1688 (C=O); 1481 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1- (2-ethoxy-2-oxoethyl) -1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2l). Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 50 mg of a light yellow solid (isolated yield: 92%). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, $^3J_{H2\text{-}H3}$= 7.6 Hz, Ar2-H); 7.65 (s, 1H, C10triazole-H); 7.44 (m, 2H, Ar4-H and Ar5-H); 7.20 (m, 1H, Ar3-H); 5.08 (s; 1H, C11-H); 4.31 (s, 2H, C8-H); 4.21 (c, 2H, $^3J_{H13\text{-}H14}$= 7.1 Hz, C13-H); 1.24 (t, 3H, $^3J_{H14\text{-}H13}$= 7.1 Hz, C14-H). ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O); 169.8 (C=O); 144.2 (C); 140.7 (C); 133.2 (CH); 132.3 (CH); 127.1 (C); 126.6 (CH); 124.7 (CH); 123.3 (CH); 63.4 (CH_2); 50.9 (CH_2); 34.6 (CH_2); 27.5 (CH_2); 14.1 (CH_3). HRMS calculated mass for $C_{14}H_{17}O_4N_3SNa$ ($M+Na^+$) 344.06755; found m/z 344.06768. IR υ_{max} 3344 (O-H); 2930 (-C-H); 1732 (C=O); 1693 (C=O), 1444 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-hexadecyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2m).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 63 mg of a light yellow solid (isolated yield: 81%). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, $^3J_{H2\text{-}H3}$= 8.2 Hz, Ar2-H); 7.47 (s, 1H, C10triazole-H); 7.45 to 7.42 (m, 2H, Ar4-H and Ar5-H); 7.18 (m, 1H, Ar3-H); 4.32 (s, 2H, C8-H); 4.26 (t, 2H, $^3J_{H11\text{-}H12}$= 7.1 Hz, C11-H); 1.84 (m,

2H, C12-H); 1.23 (m, 24H, C13-H to C25-H); 0.85 (t, 3H, $^{3}J_{H26-H25}$= 6.5 Hz, C26-H). ^{13}C NMR ($CDCl_3$) δ 170.5 (C=O); 144.5 (C); 141.1 (C); 133.2 (CH); 132.3 (CH); 127.2 (C); 126.1 (CH); 124.4 (CH); 122.3 (CH); 50.6 (CH_2); 32.1 to 22.0 (CH_2); 14.1 (CH_3). HRMS calculated mass for $C_{26}H_{41}O_2N_3SNa$ ($M+Na^+$) 482.28117; found m/z 482.28121. IR υ_{max} 3443 (O-H); 2924 (-C-H); 1693 (C=O); 1456 (C=C aromatic) cm^{-1}.

Synthesis of 2-(((1-tridecyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2n).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 37 mg of a light yellow solid (isolated yield: 55%). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1H, $^{3}J_{H6-H5}$= 7.6 Hz, Ar6–H); 7.47 (s, 1H, C10triazol-H); 7.46 to 7.44 (m, Ar-3, Ar-4); 7.21 (m, 1H, Ar5-H); 4.30 (s, 2H, C8-H); 4.27 (t, 2H, $^{3}J_{H11-H12}$= 7.3 Hz, C11-H); 1.84 (q, 2H, $^{3}J_{H6-H5}$= 6.8 Hz, C12-H); 1.25 (m, 20H, C13-H to C22-H); 0.87 (t, 3H, $^{3}J_{H6-H5}$= 6.7 Hz, C23-H). ^{13}C NMR ($CDCl_3$) δ 169.6 (C=O); 144.2 (C); 140.5 (C); 133.1 (CH); 132.2 (CH); 127.2 (C); 126.8 (CH); 124.8 (CH); 122.1 (CH); 50.5 (CH_2); 31.9 (CH_2); 30.1 (CH_2); 29,6 to 28,9 (CH_2); 27.7 (CH_2); 26.4 (CH_2); 22.7 (CH_2); 14.1 (C23, CH3). HRMS calculated mass for $C_{21}H_{18}O_2N_3S$ ($M+H^+$) 418.2523; found m/z 418.2520.

Synthesis of 2-(((1-Phenylethyl-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2o).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 56 mg of a light yellow solid (isolated yield: 94%). ^{1}H NMR ($CDCl_3$) δ 8.10 (dd, 1H, $^{3}J_{H6-H5}$=7.8 Hz, $^{4}J_{H6-H4}$=1.3 Hz, Ar6-H); 7.45 (dt, 1H, $^{4}J_{H4-H6}$=1.3 Hz, Ar4-H); 7.40 (d, 1H, $^{2}J_{H3-H4}$=7.2 Hz, Ar3-H); 7.25 (s, 1H, C10triazol-H); 7.22 to 7.18 (m, 4H, Ar5-H, Ar15-H, Ar16-H, Ar17-H); 7.02 to 6.99 (m, 2H, Ar14-H, Ar18-H); 4.52 (t, 2H, $^{3}J_{H11-H12}$=7.2 Hz, C11-H); 4.27 (s, 2H, C8-H); 3.15 (t, 2H, $^{3}J_{H12-H11}$=7.2 Hz, C12-H). ^{13}C NMR ($CDCl_3$) δ 170.6 (C=O);

144.1 (C); 141.2 (C); 136.8 (C); 133.3 (CH); 132.3 (CH); 128,8 to 127,1 (CH); 126.7 (C); 126.0 (CH); 124.4 (CH); 122.8 (CH); 51.9 (CH_2); 36.6 (CH_2); 27.1 (CH_2). HRMS calculated mass for $C_{18}H_{18}O_2N_3S$ ($M+H^+$) 340.1114; found m/z 376.1125.

Synthesis of 2-(((1-(naphthalen-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzoic acid (2p).

Following the general reaction conditions for CuAAC synthesis, the reaction was worked up and purified to afford 20 mg of a light yellow solid (isolated yield: 33%). ^{1}H NMR (DMSO-d_6) δ 8.15 (s, 1H, C10triazol-H); 7.92 to 7.87 (m, 4H, Ar6-H, Ar14-H, Ar18-H, Ar21-H); 7.80 (s, 1H, Ar17-H); 7.56 to 7.47 (m, 4H, Ar3-H, Ar4-H, Ar19-H, Ar20-H); 7.40 (d, 1H, $^3J_{H13-H14}$ = 7.8 Hz, Ar13-H); 7.20 (t, 1H, $^3J_{H6-H5}$=7.3 Hz, Ar5-H); 5.73 (s, 2H, C11-H); 4.26 (s, 2H, C8-H). ^{13}C NMR (DMSO-d_6) δ 167.4 (C=O); 143.3 (C); 140.5 (C); 133.5 (C); 132.7 (C); 132.4 (C); 132.3 (CH); 130.9 (CH); 128.4 (C); 127.8 (CH); 127.6 (CH); 127.6 (CH); 126.7 (CH); 126.5 (CH); 126.4 (CH); 125.7 (CH); 125.6 (CH); 124.0 (CH); 123.7 (CH); 52.9 (CH_2); 26.1 (CH_2). HRMS calculated mass for $C_{21}H_{18}O_2N_3S$ ($M+H^+$) 376.1114; found m/z 376.1107.

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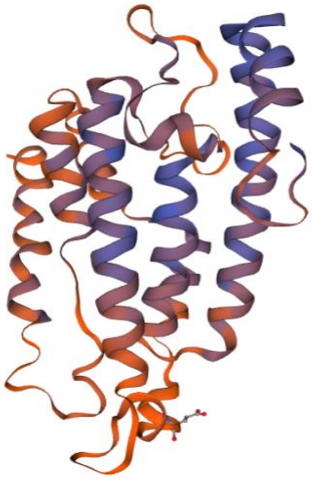

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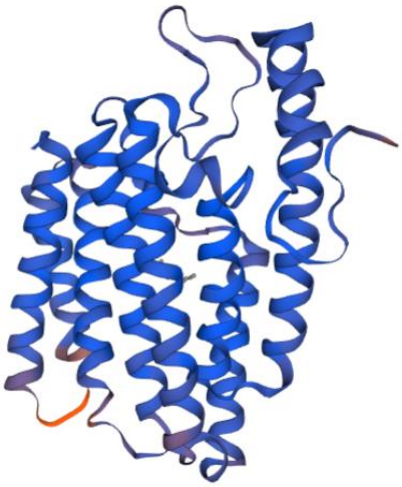
QMEAN = -3.86



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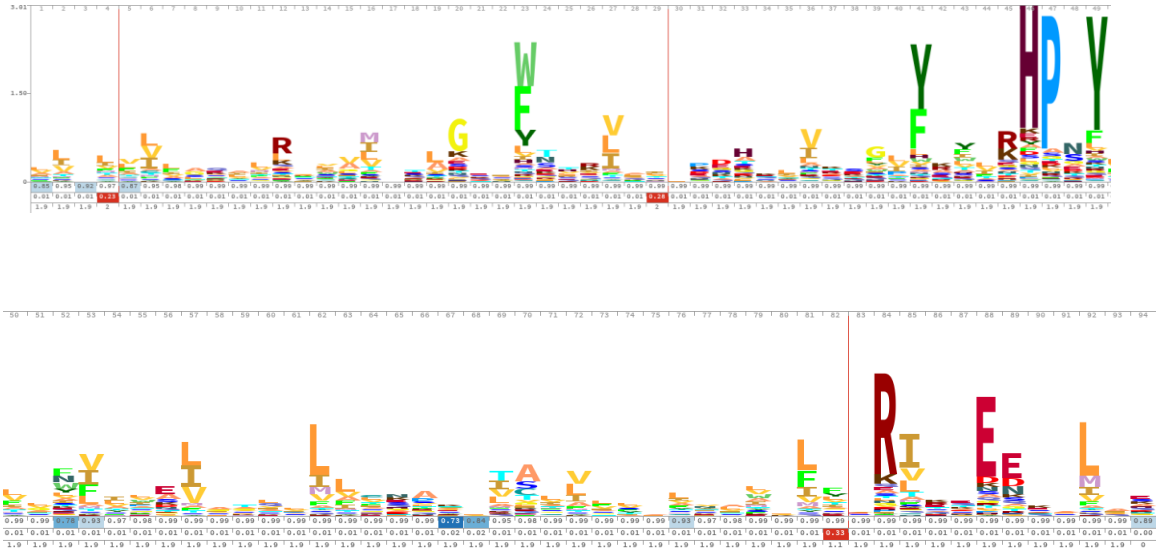
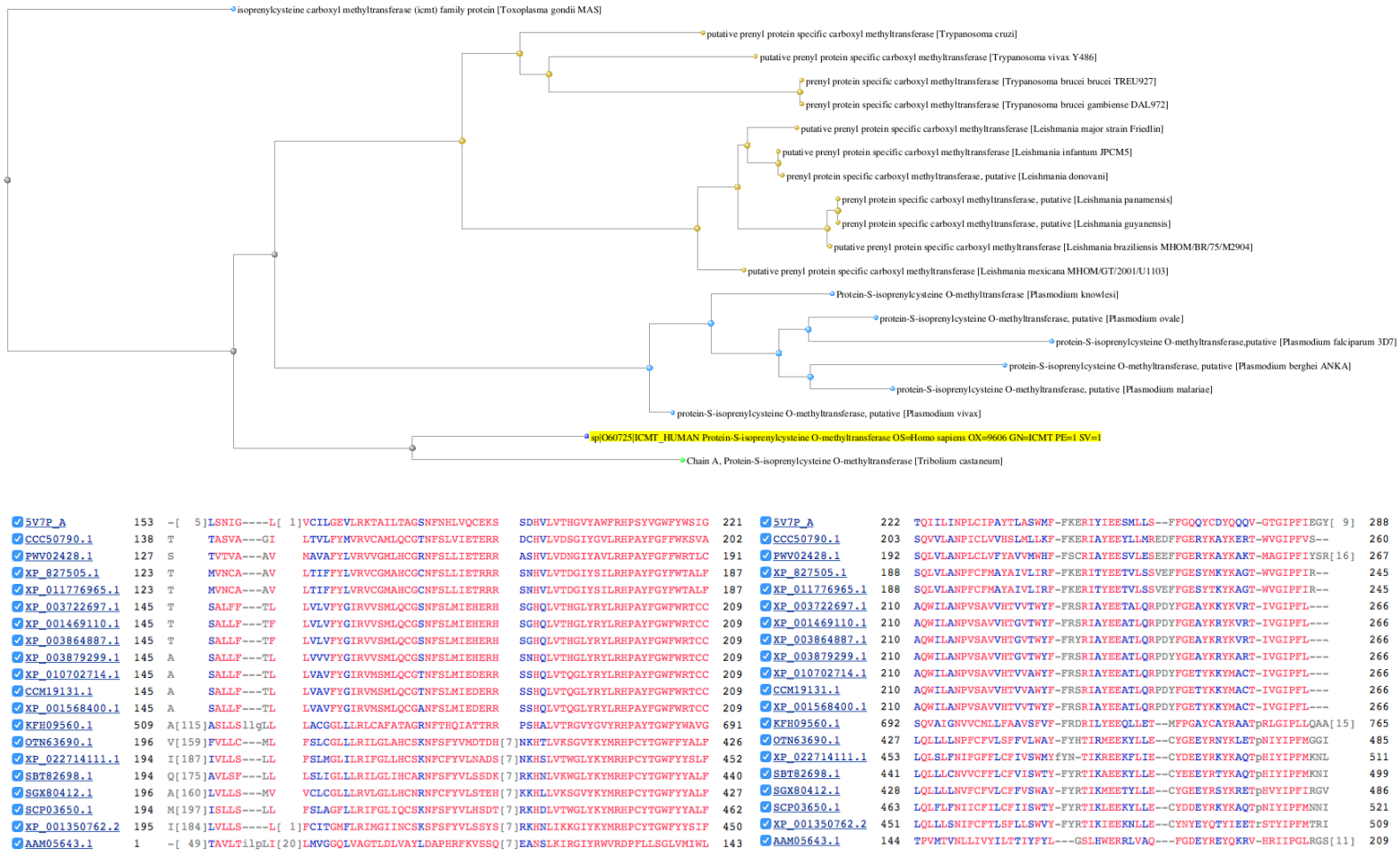


Figure S1. Top: ICMT structure homology-modelling to *Pf*-ICMT and *Hs*-ICMT.[1] In both cases, X-ray structure of ICMT (*Tribolium castaneum*) was used as a template.[2] **Bottom:** Hidden Markov models (HMMs) to sequence alignment of several ICMTs (including mammals, Apicomplexans and Trypanosomatidae orthologs). HMMs can be used to convert multiple sequence alignments into position-specific scoring systems and they are sophisticated and powerful statistical models, very well suited to searching databases for homologous sequences. In this case, members of the ICMT family of proteins have a characteristic and highly conserved dominance towards the C-terminus.

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PWV02428.1      127  S     TVTVA---AV    MAVAFYLVRVVGMLHCGRNFSLLIETERR   ASHVLVDNGIYAVLRHPAYFGFWRTLC  191
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AAM05643.1      144  TPVMTVNLLIVYILTTIYFYL---GSLHWERRLVAQ---FGDEYREYQKRV-HRIIPGLRGS[11]  209
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Figure S2. Top: Phylogenetic tree of ICMTs. Comparison between human, apicomplexans and trypanosomatids structures. Also included are the ICMTs of *Methanosarcina acetivorans* and *Tribolium castaneum* (the only two ICMTs with crystallographic structures reported). **Bottom:** Multiple sequence alignment of C-Terminus (ICMT domain).

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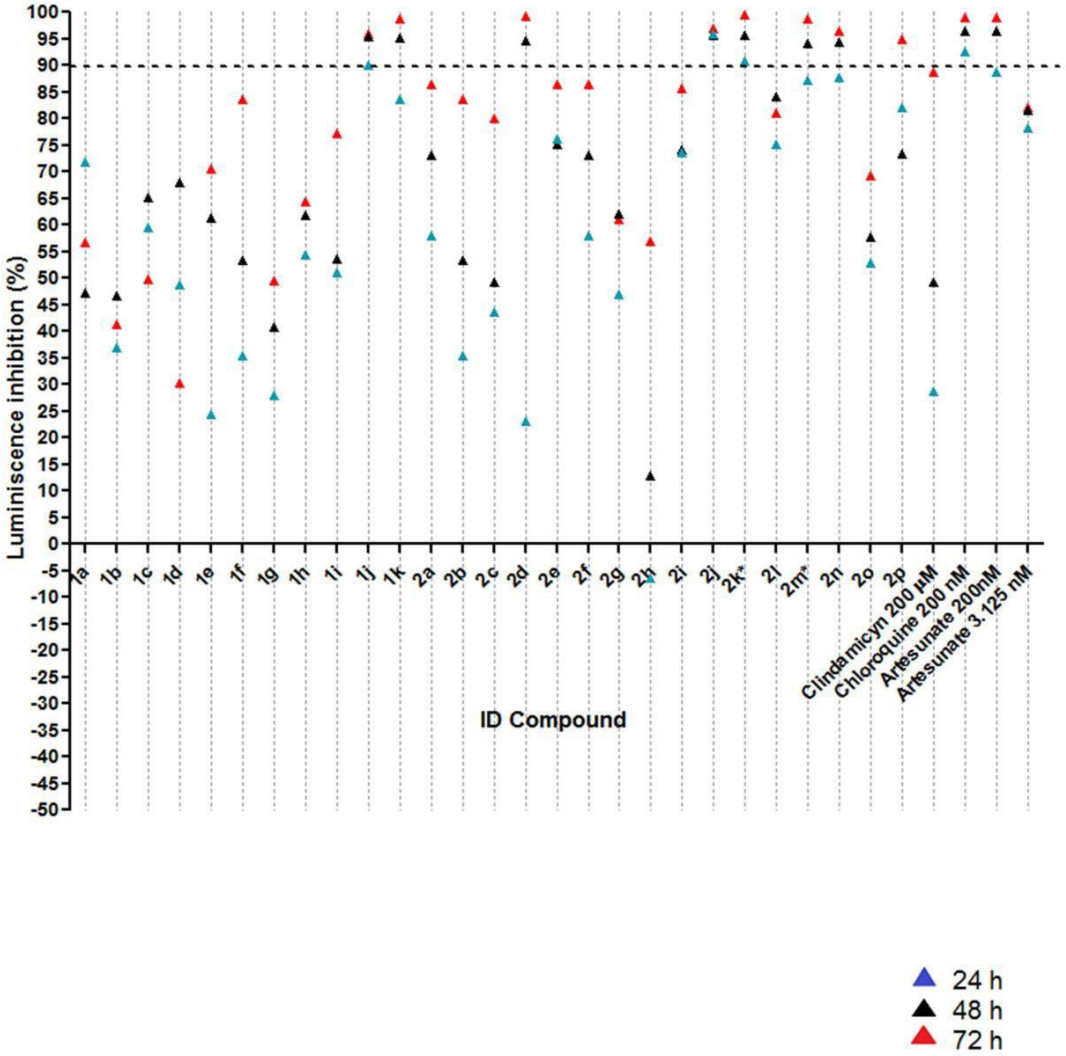


Figure S3. All tested compounds inhibition percentage in function of an untreated control at 24, 48 and 72 h. FTS and its analogues were tested at 200 µM or 100 µM, when is indicated (*). Antimalarial drugs quality controls include 200 µM clindamycin, 200 nM for both artesunate and chloroquine as a supraletal controls, and 3.125 nM artesunate as a subletal control. Each point is the average value of three experiments, each one with three technical replicates.

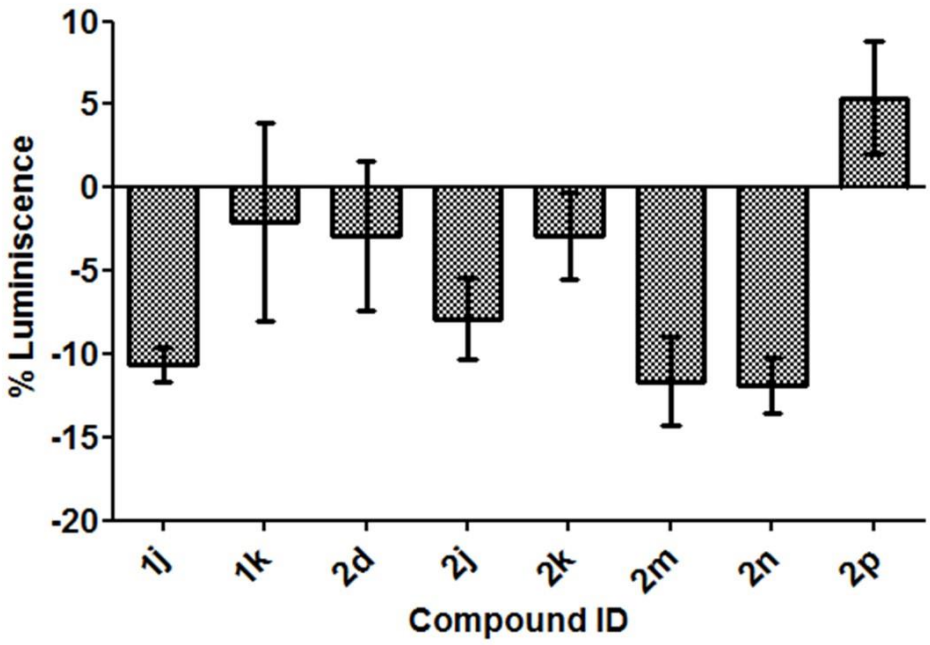
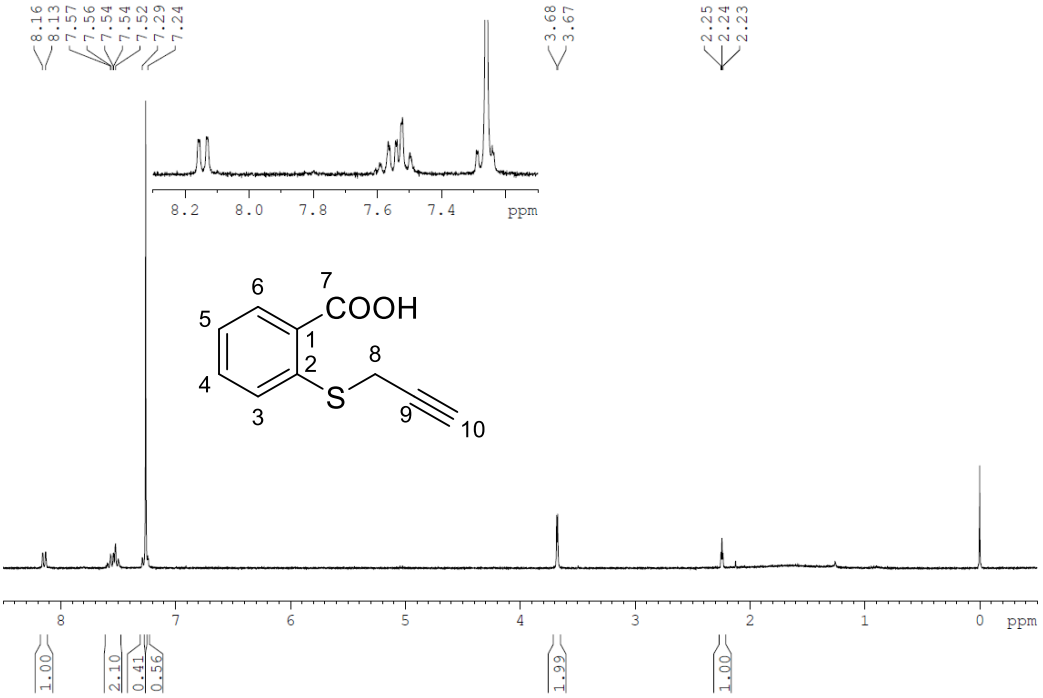


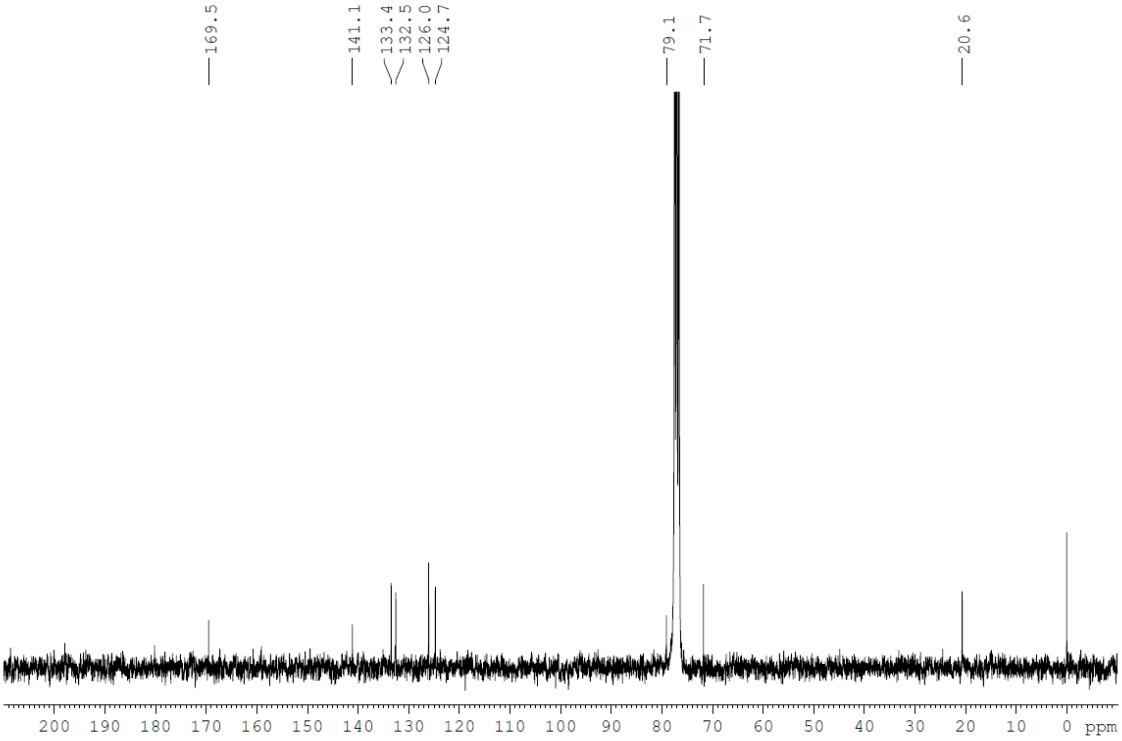
Figure S4. Percentage of luminiscence emitted at 200 μM concentration for each compound in parasite lysate from unsynchronized cultures (parasitemia 1%, hematocrit 2%) relative to an untreated control.

Table S1. Artesunate IC_{50} values and robust analysis for *P. falciparum* 3D7 and nLuc transfected *P. falciparum* studied by nLuc and fluorescent DNA staining methodologies.

	Artesunate IC_{50} (nM)	Z_{value} (SD)	R^2 (SD)
DNA staining (3D7 *P. falciparum*)	1.717 (1.64-1.79)	0.74 (0.06)	0.99 (0.02)
DNA staining (nLuc transfected *P. falciparum*)	1.588 (1.45-1.71)	0.72 (0.07)	0.98 (0.03)
nLuc (nLuc transfected *P. falciparum*)	1.74 (1.70-1.73)	0.99 (0.04)	0.99 (0.03)

Spectral data of Compound 1





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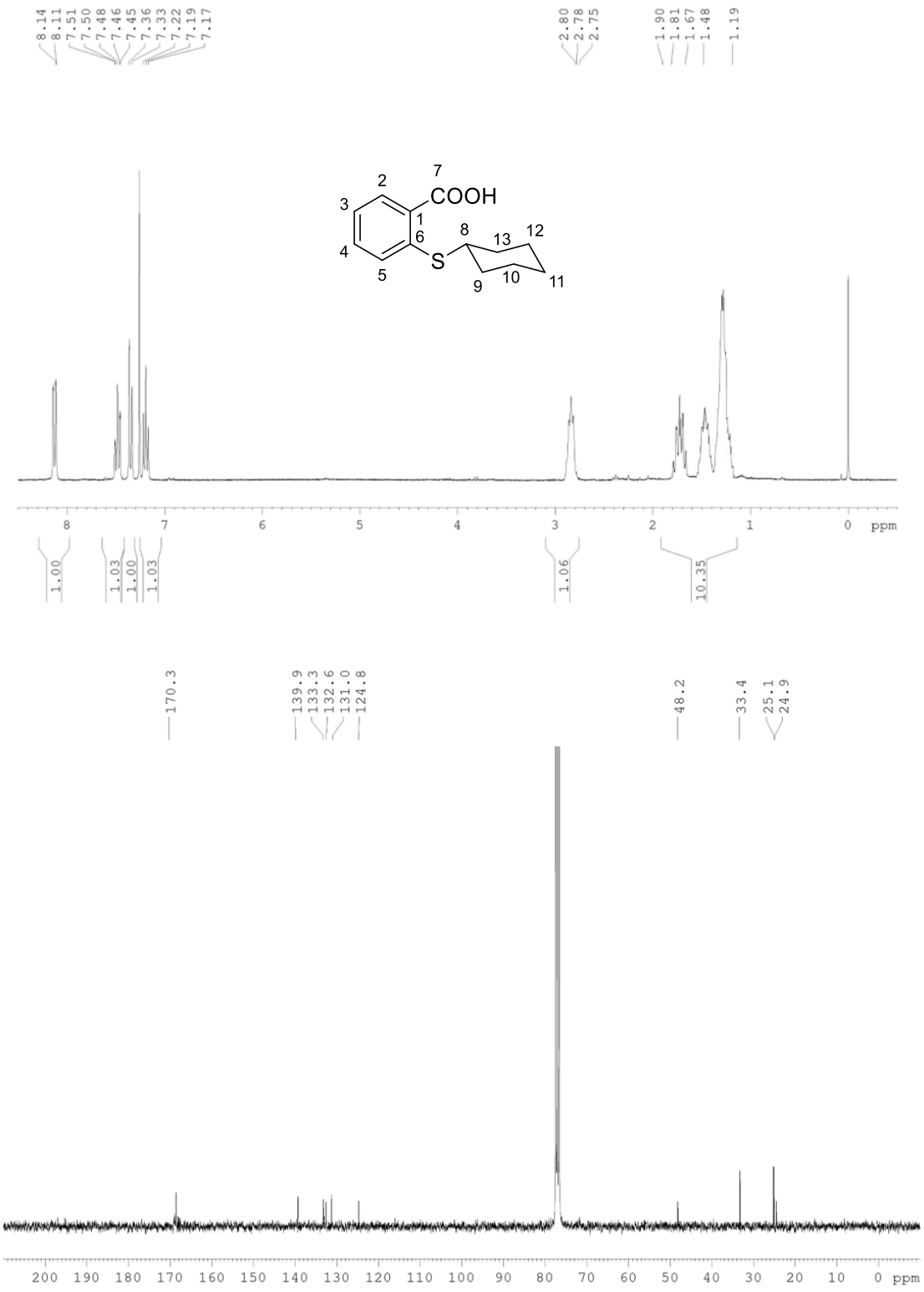

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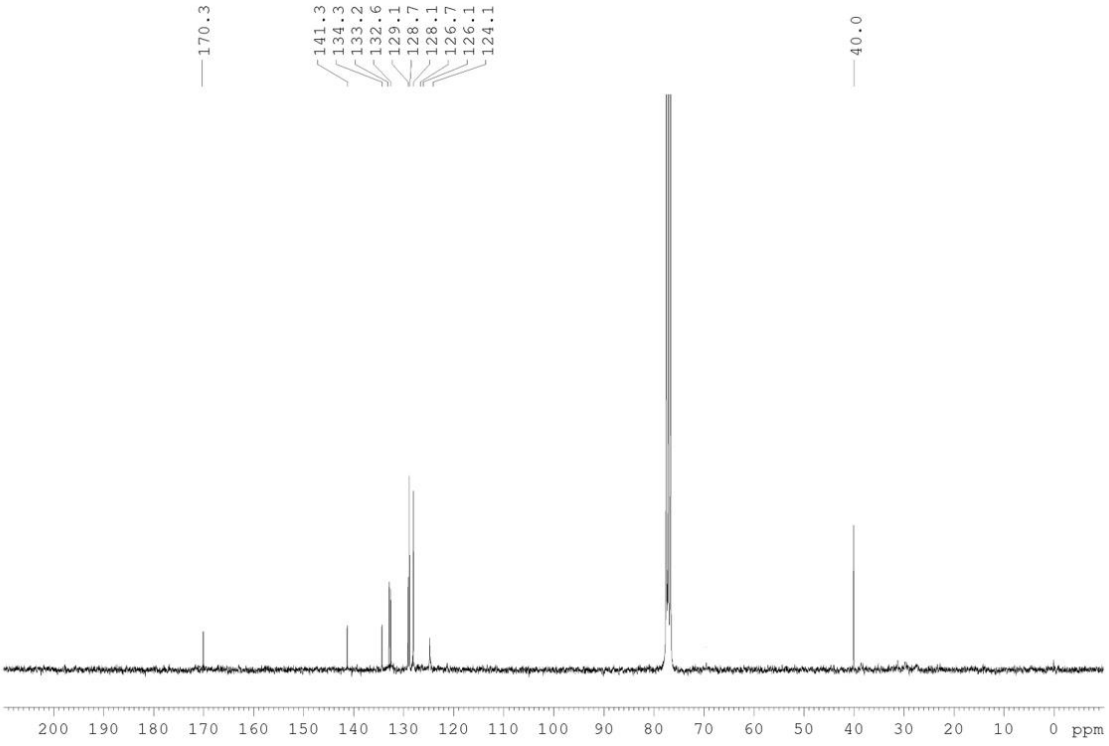

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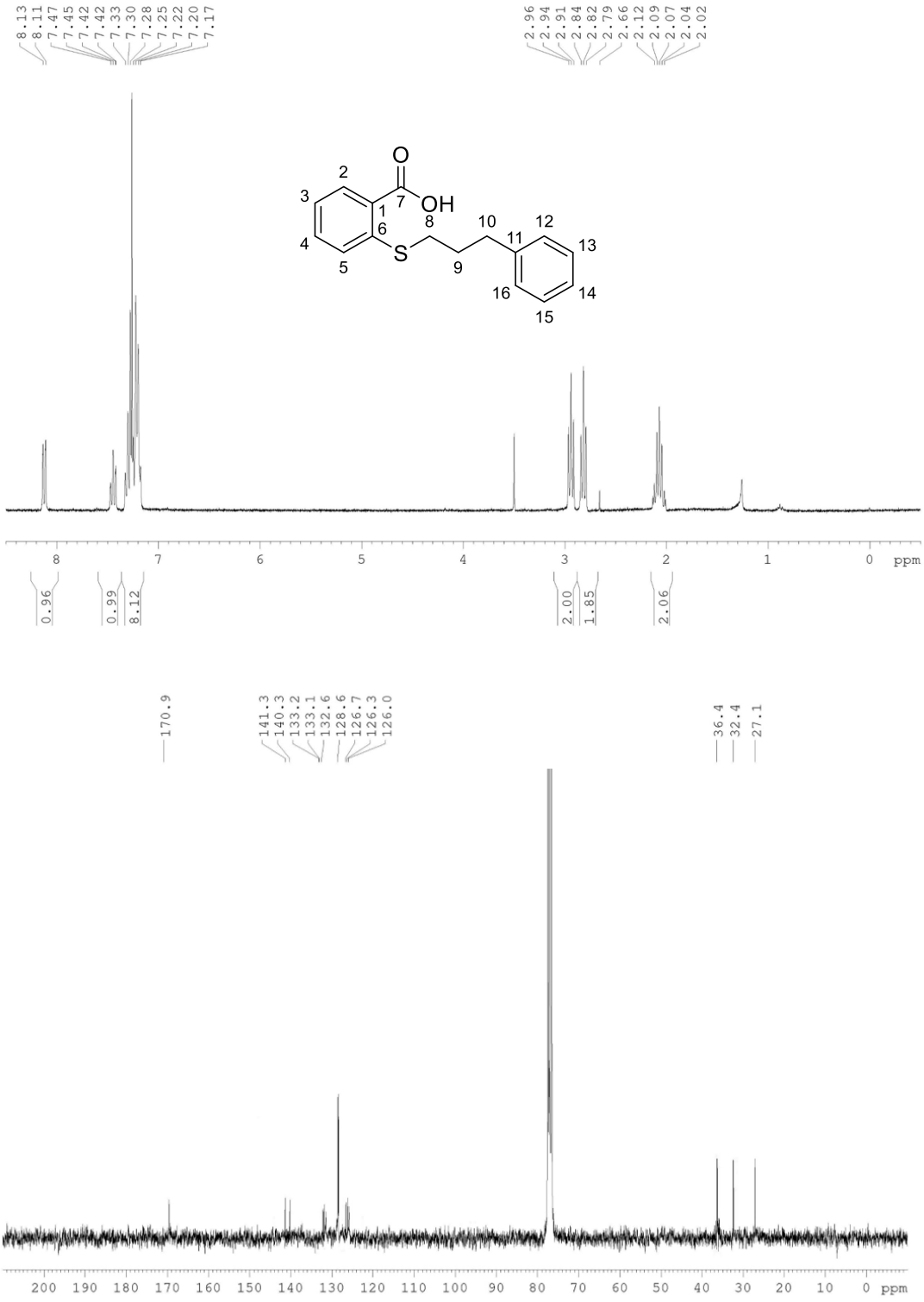

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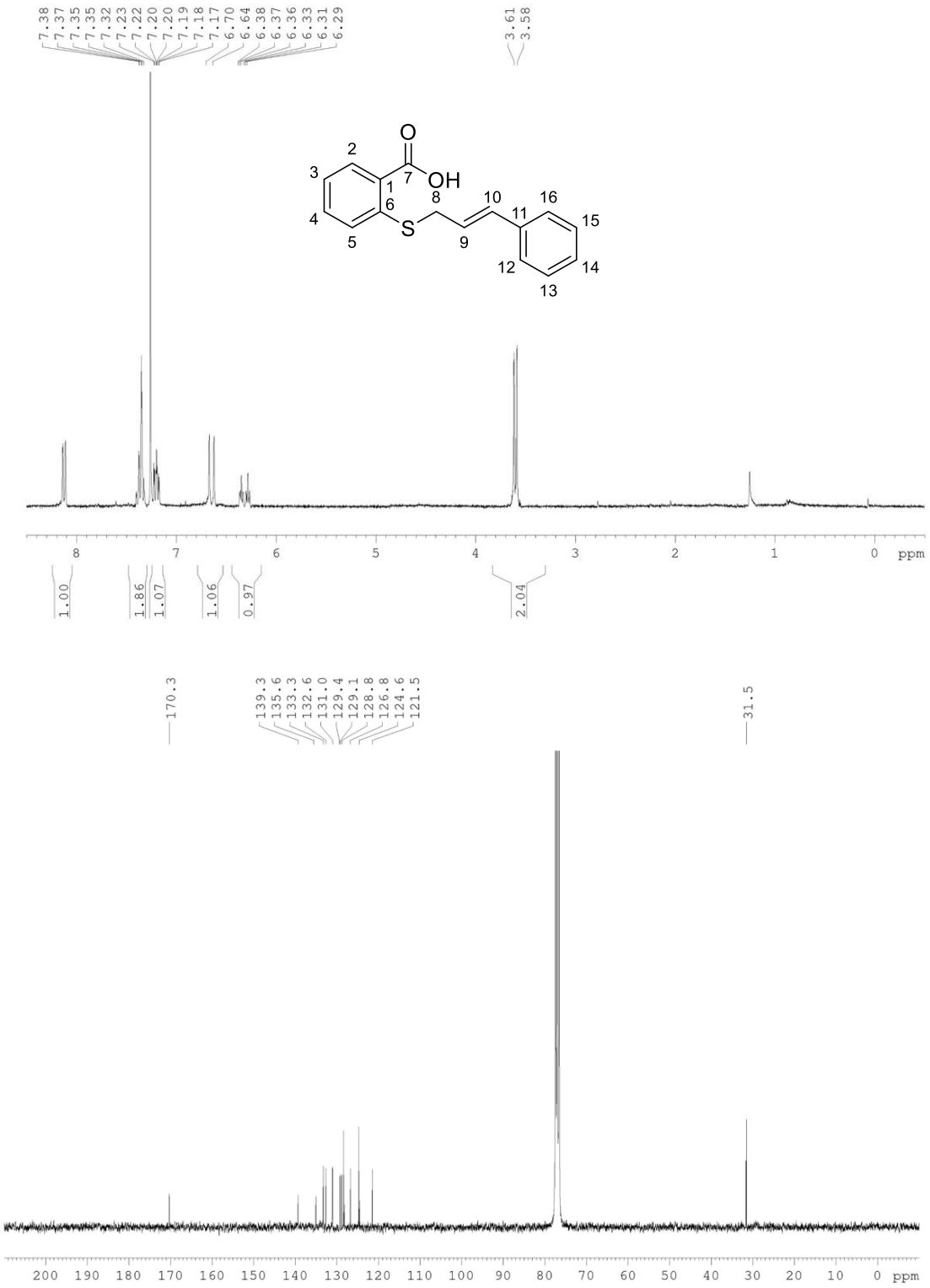

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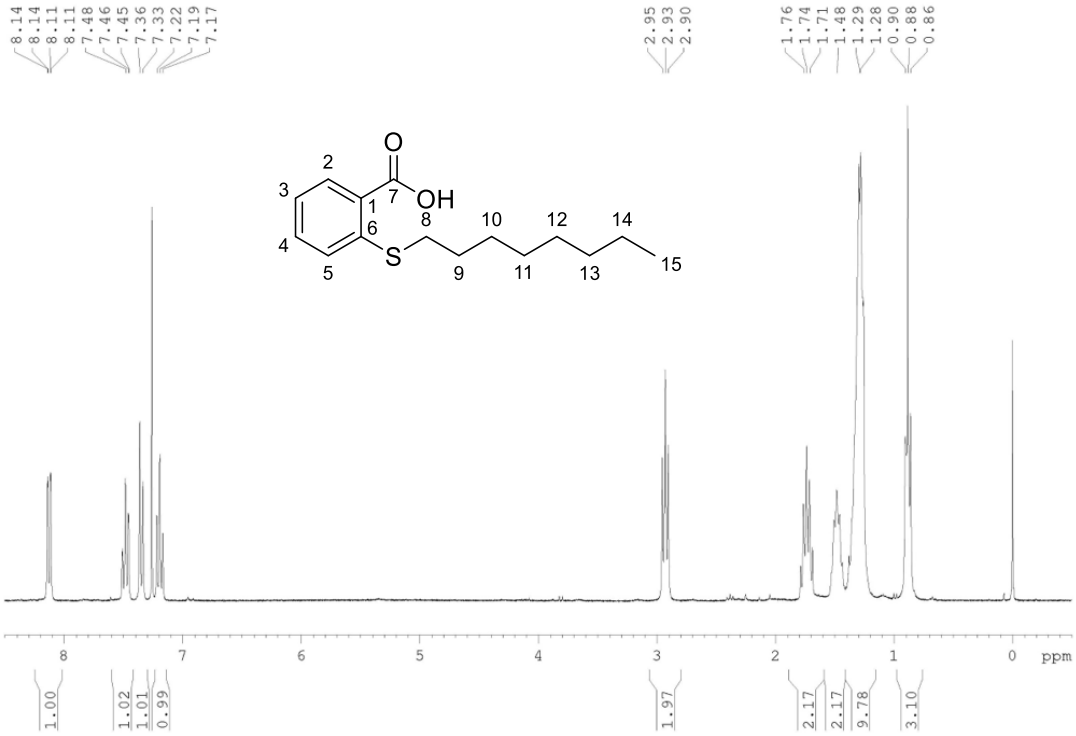

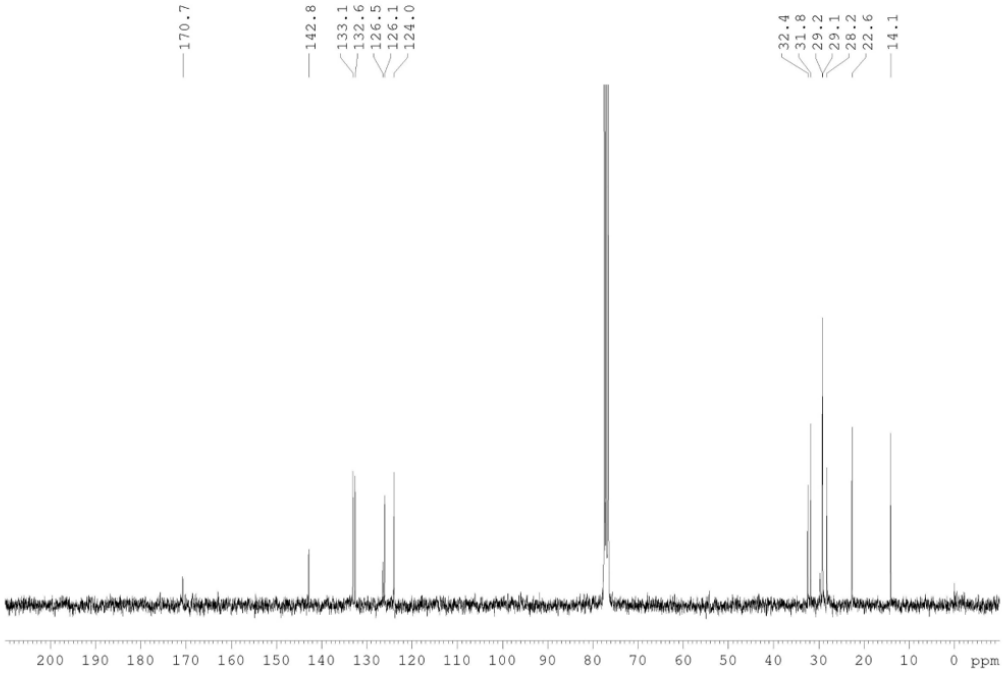

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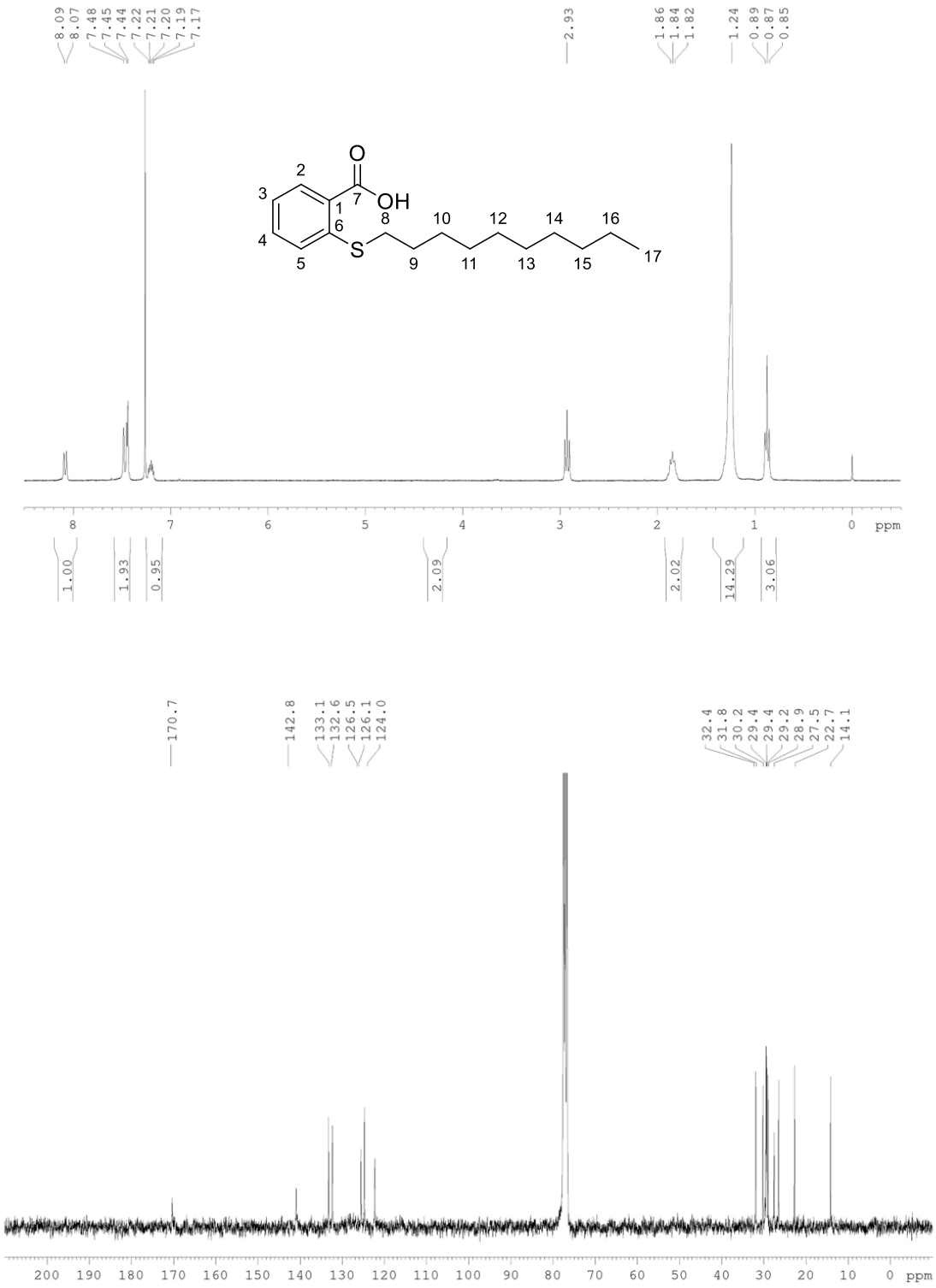

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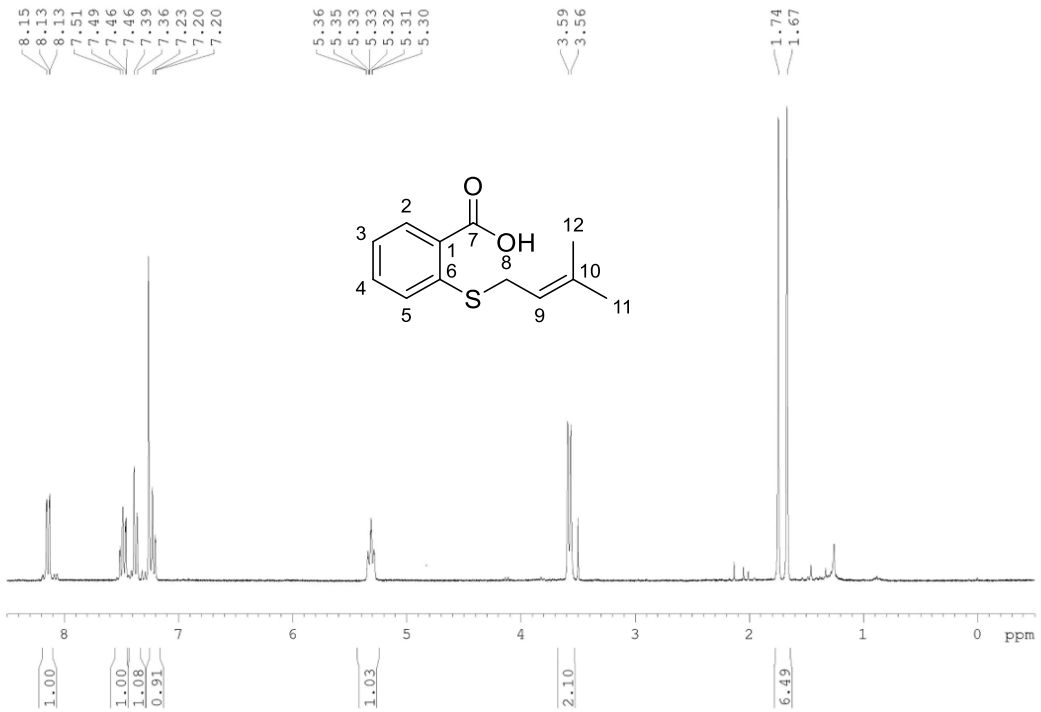
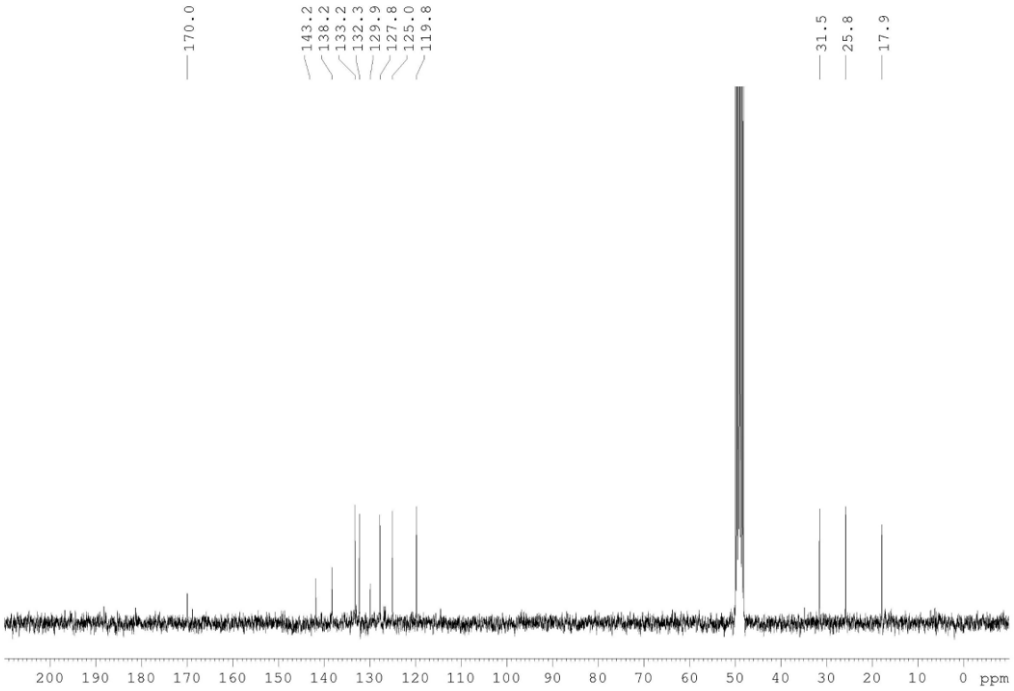
Spectral data of Compound 1h





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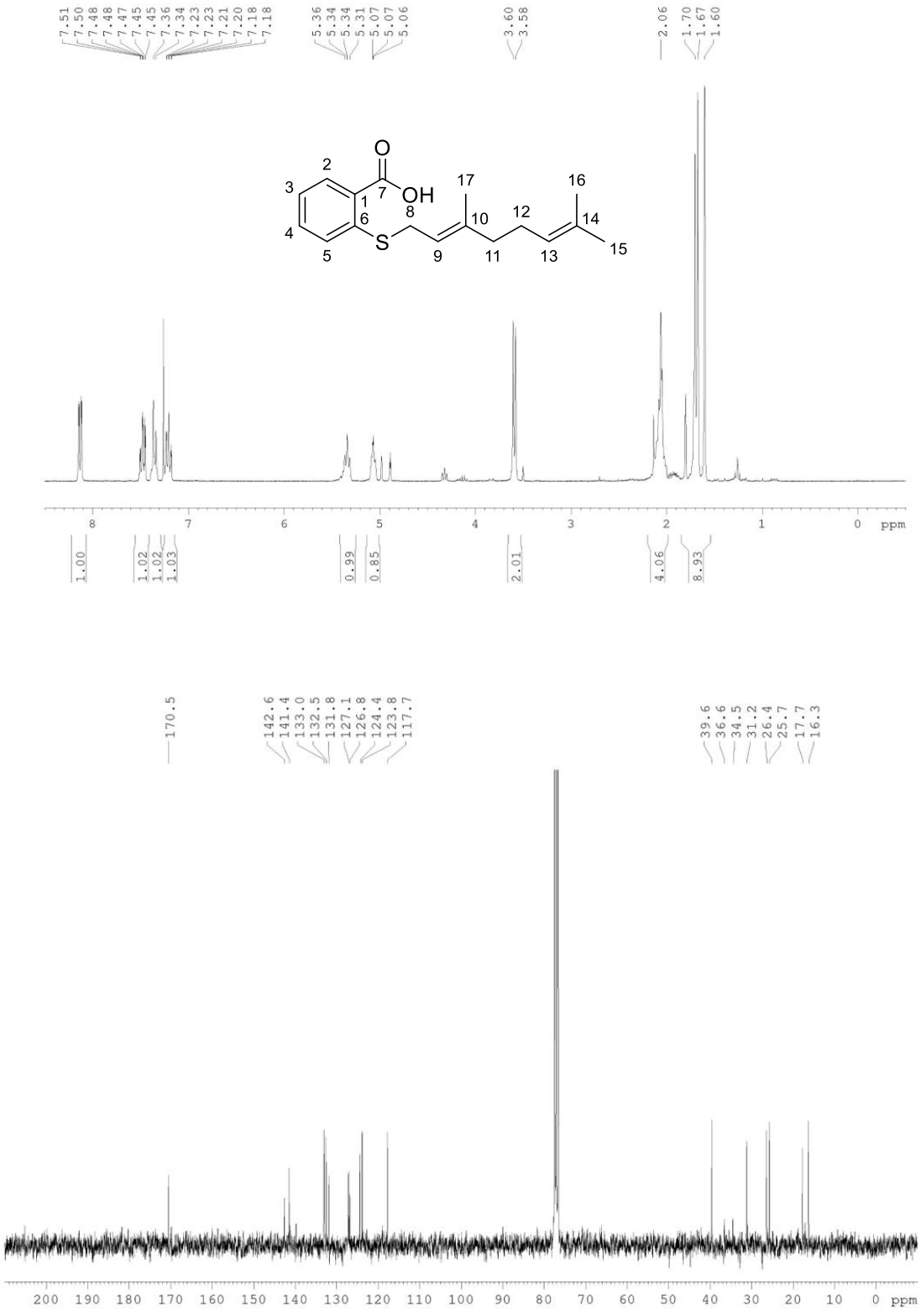

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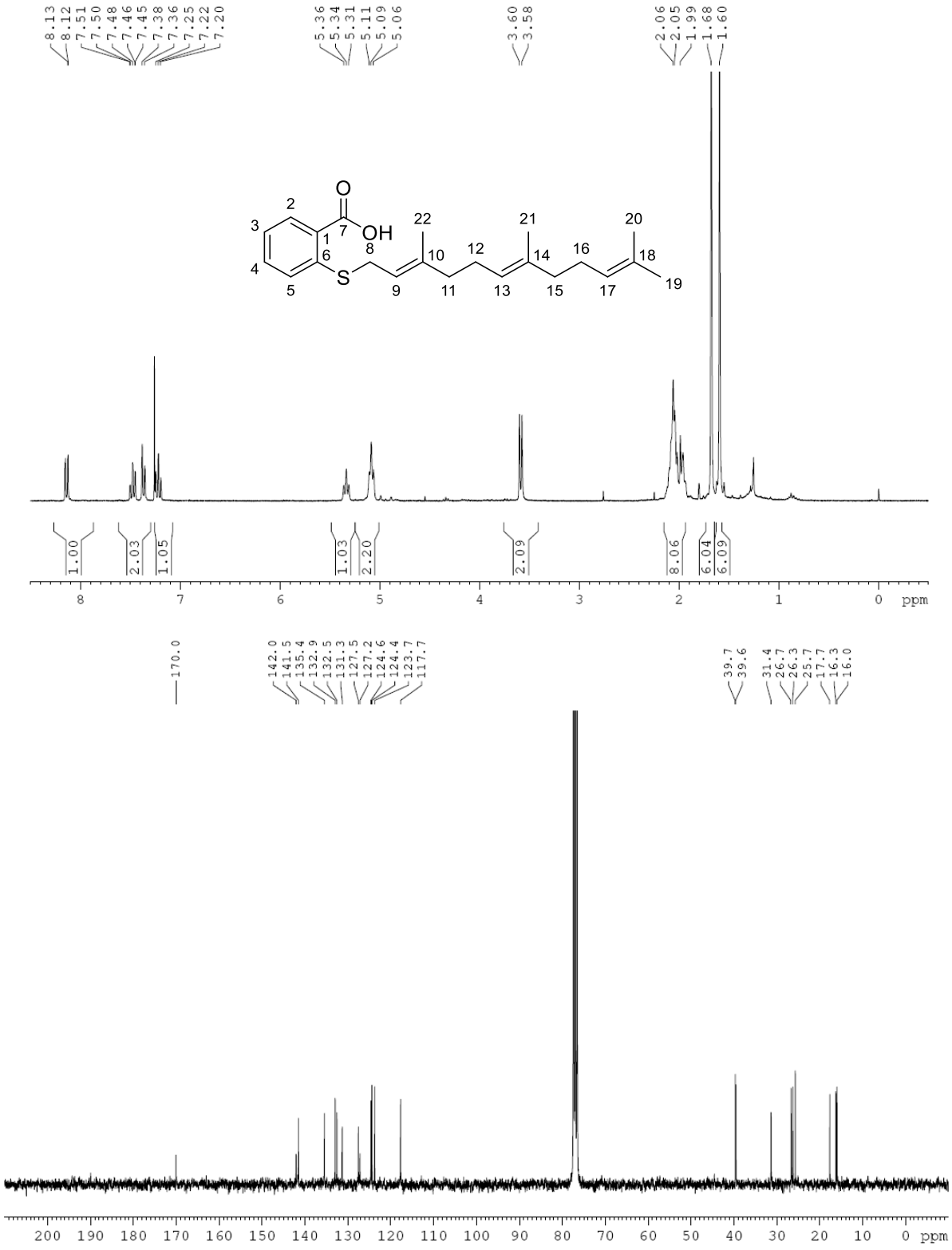

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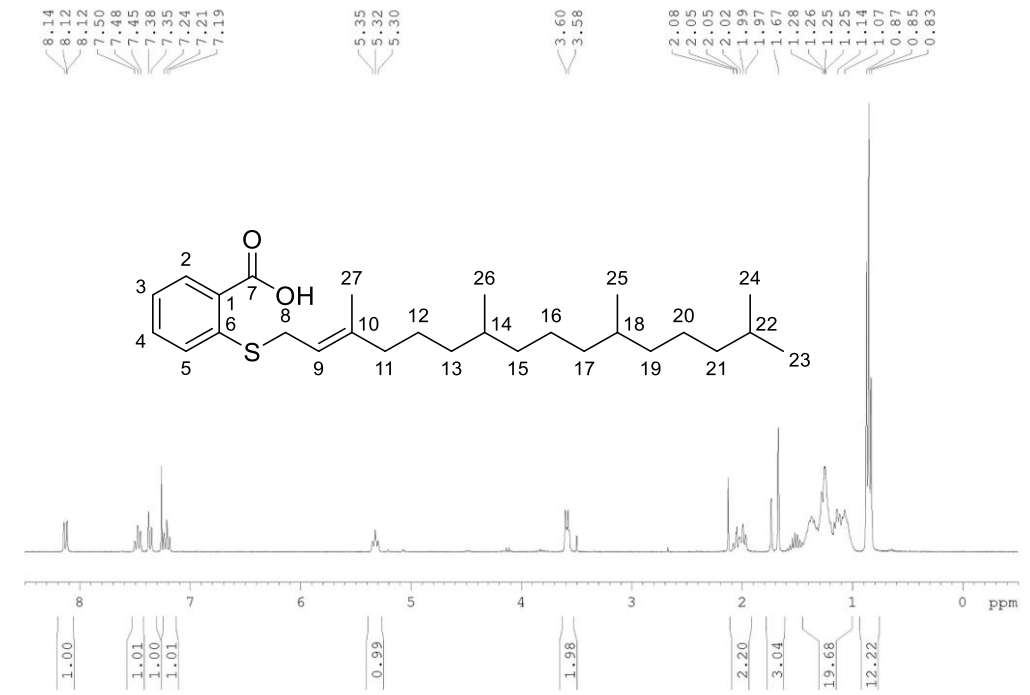

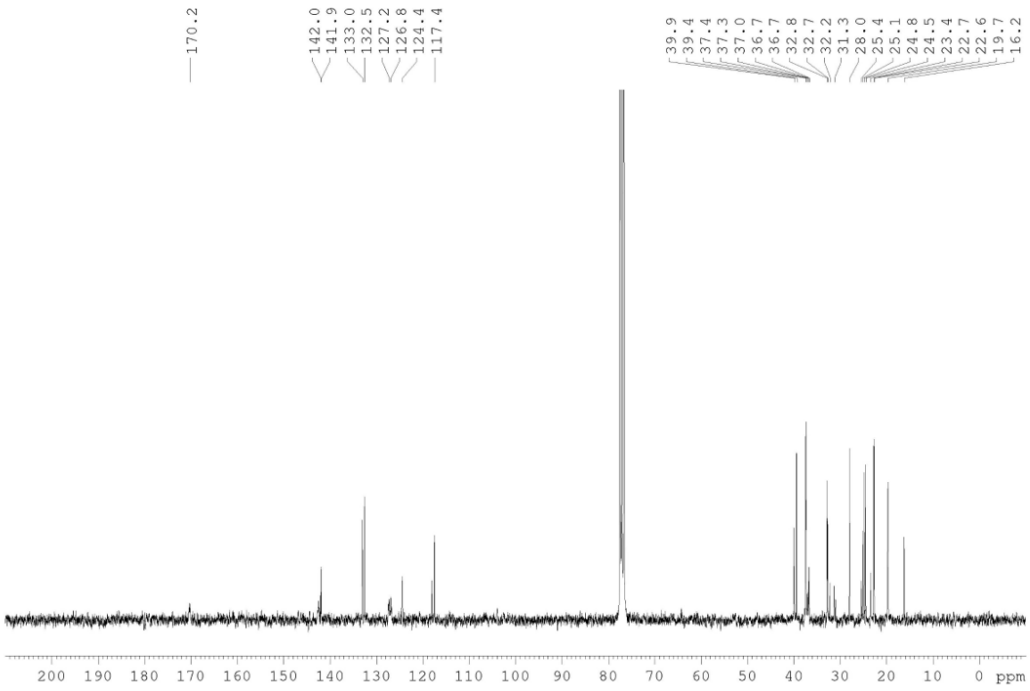

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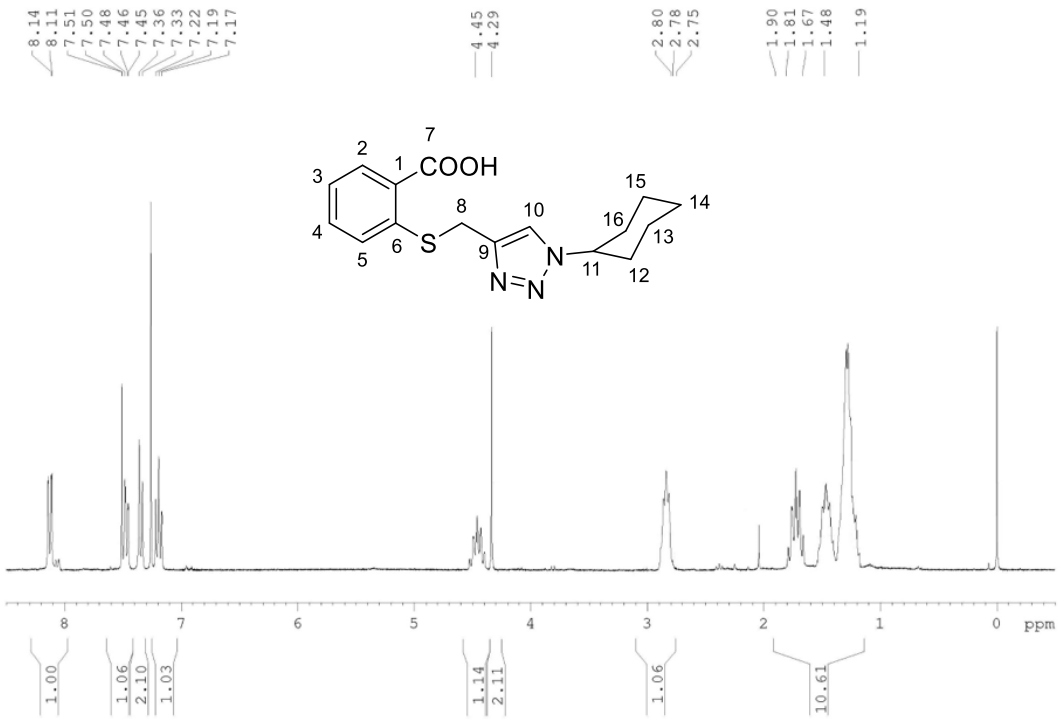
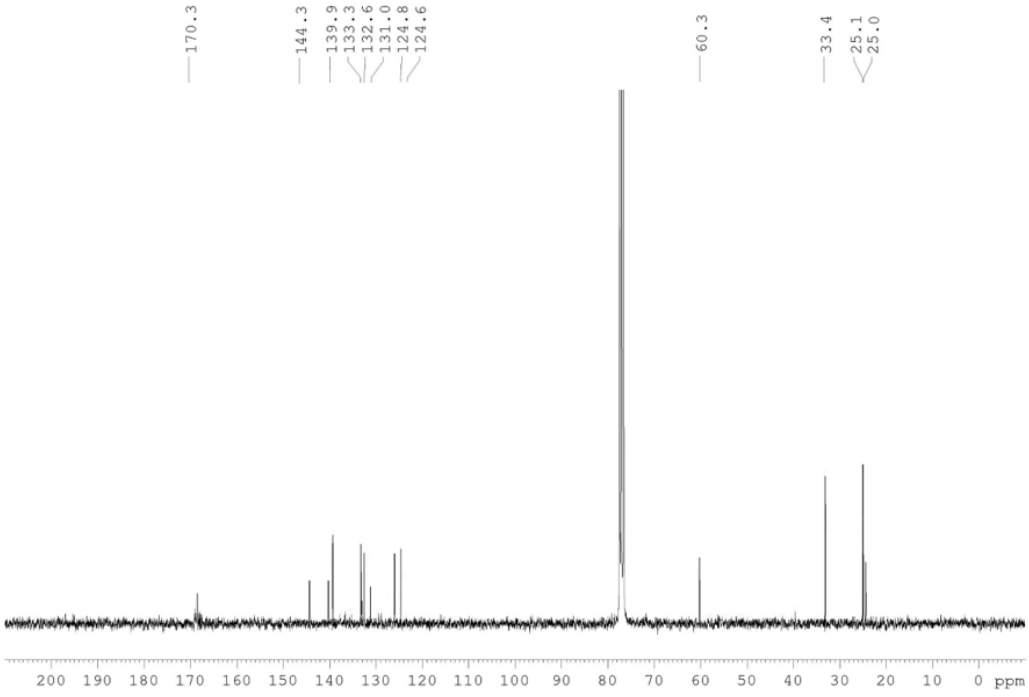
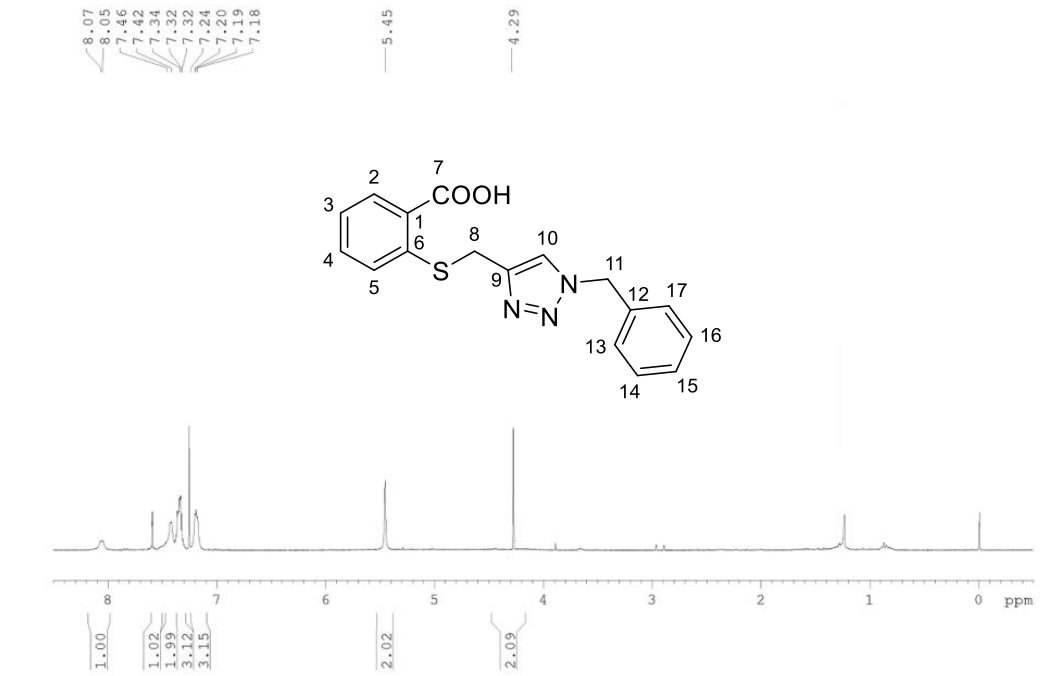
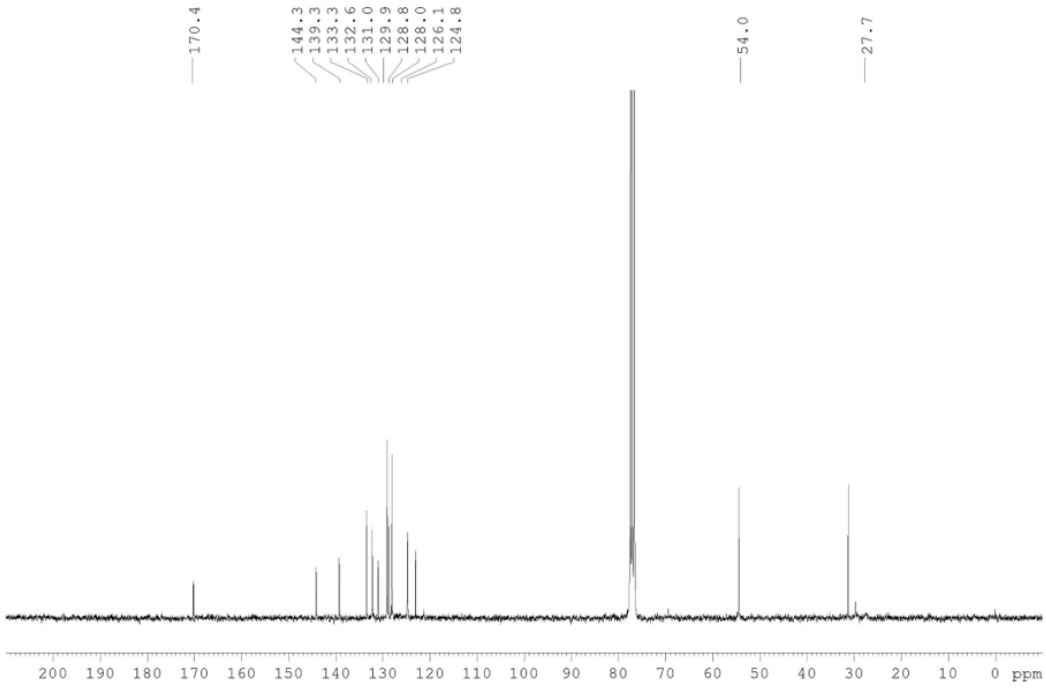


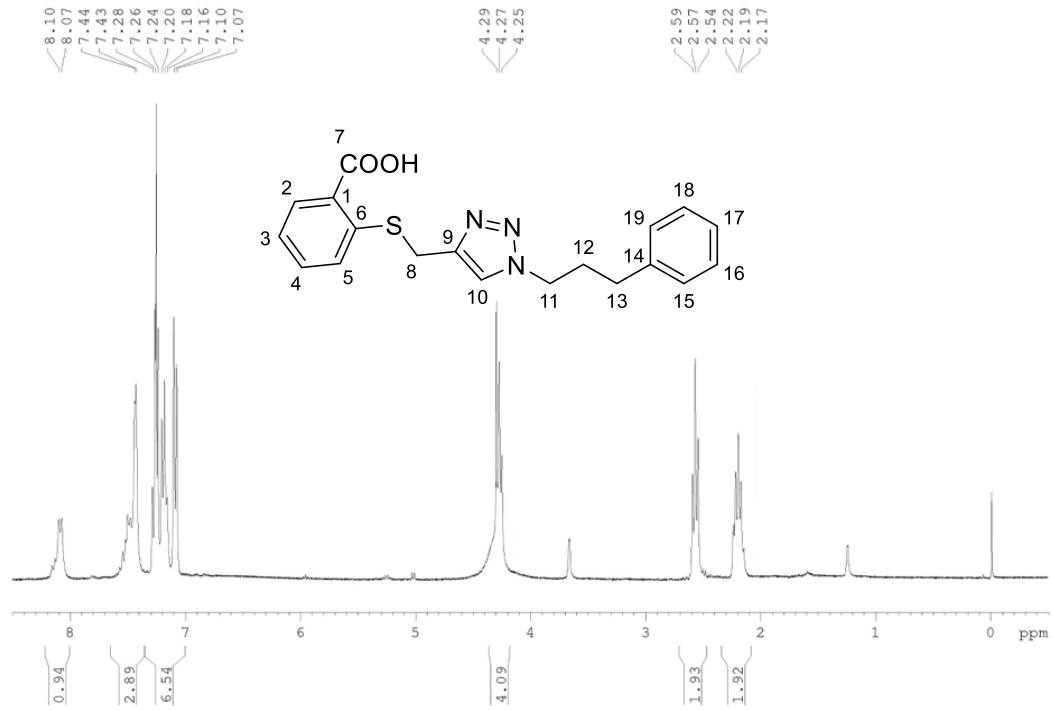


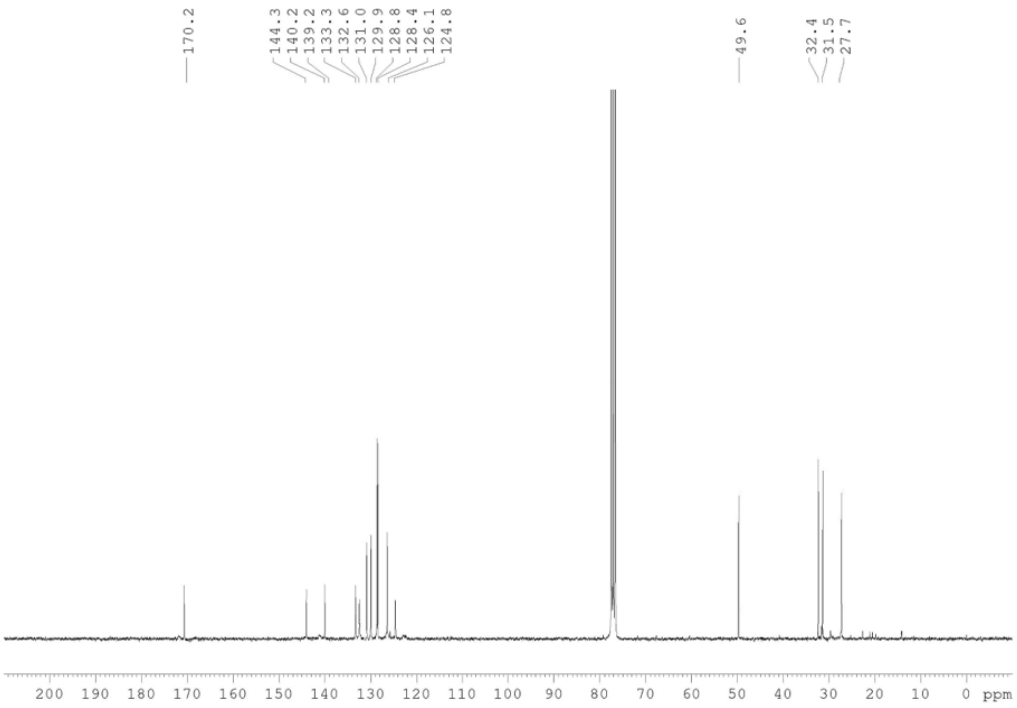
Spectral data of Compound 2b



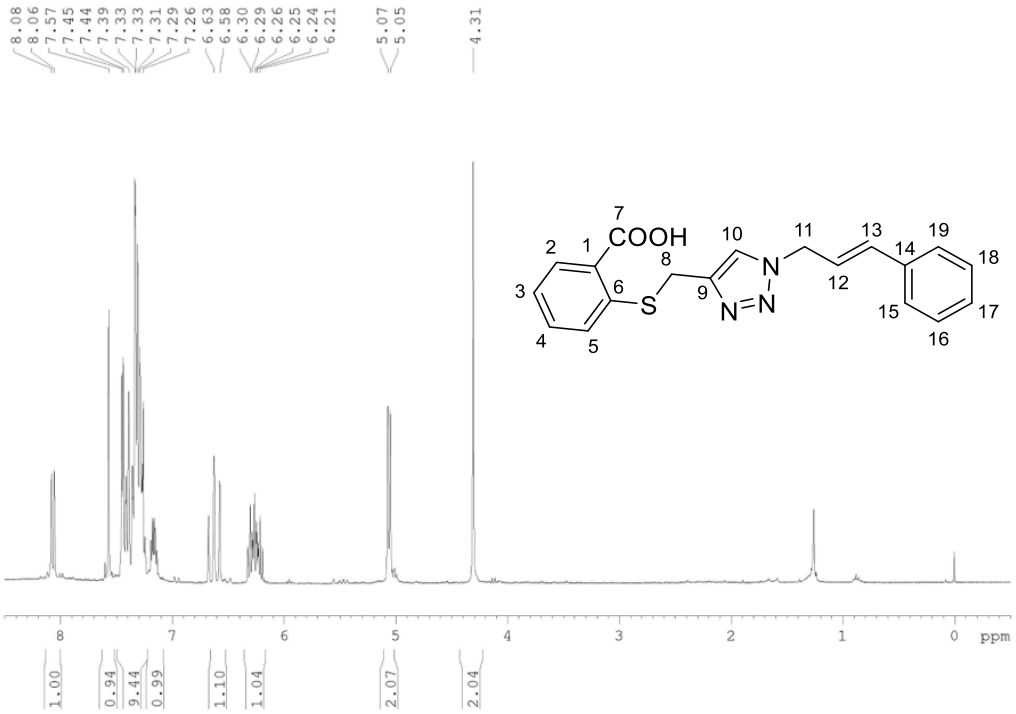


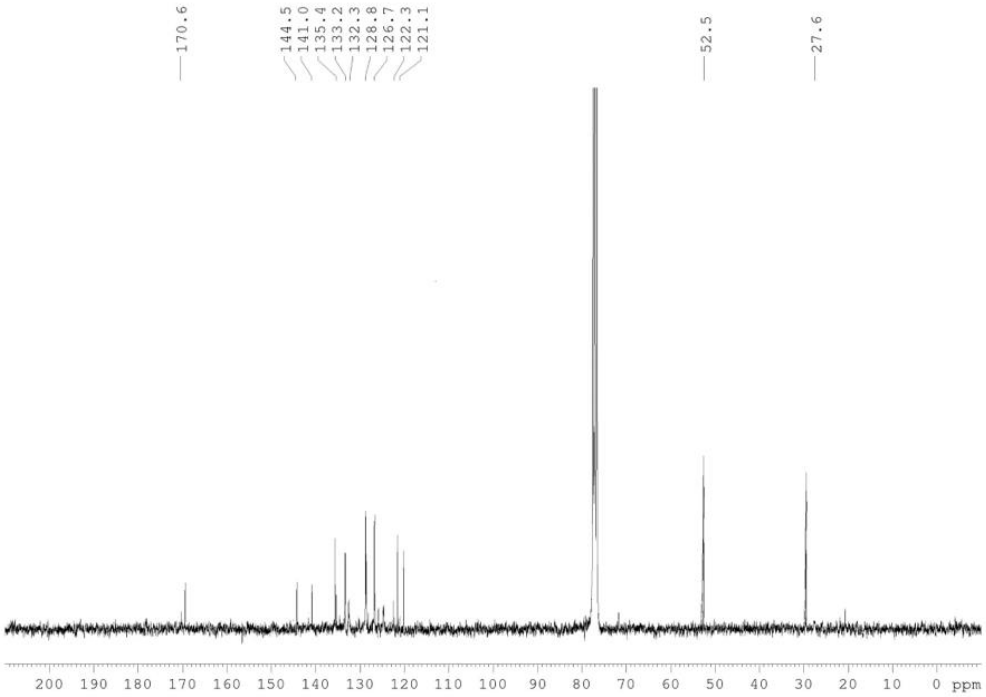
Spectral data of Compound 2c



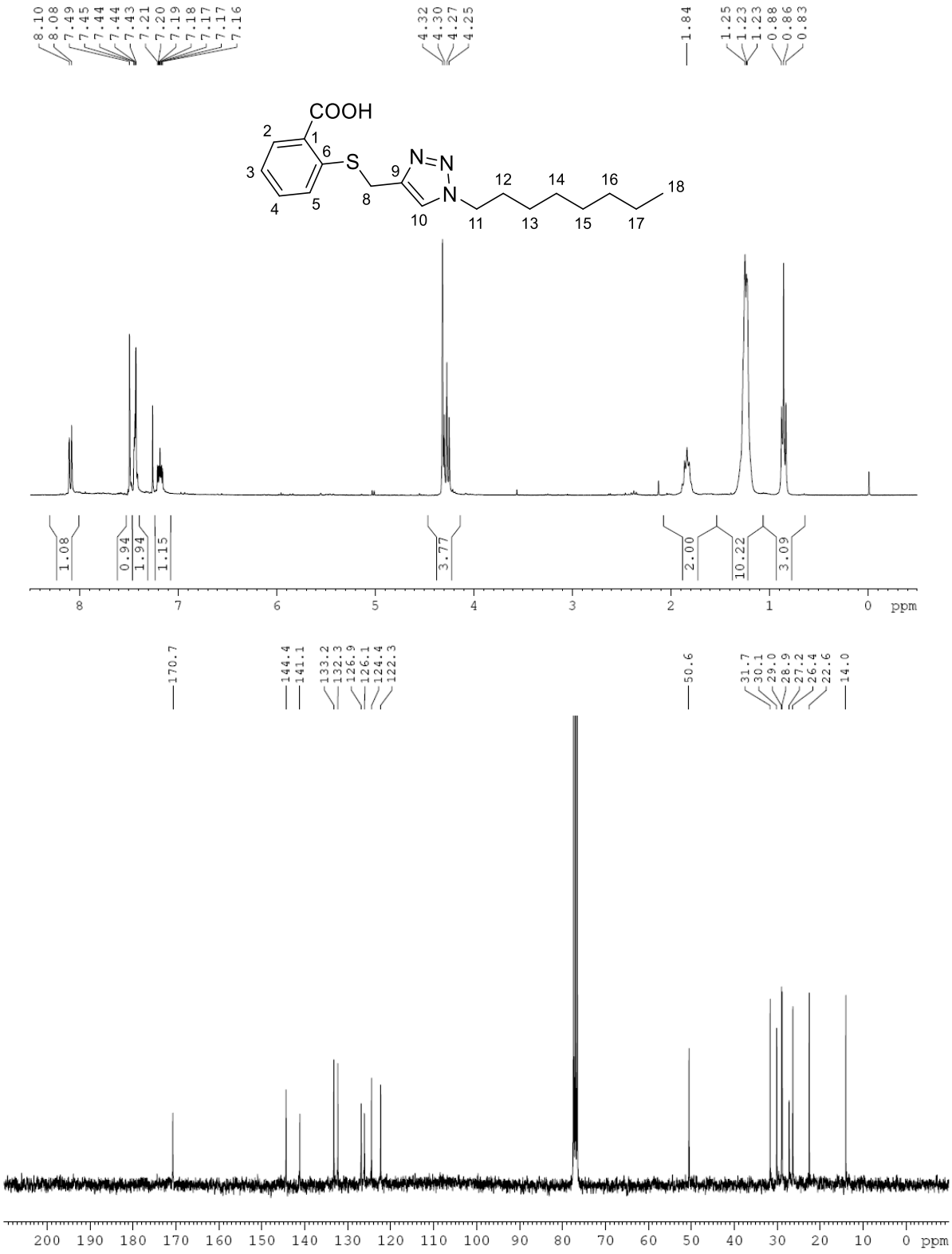


Spectral data of Compound 2d

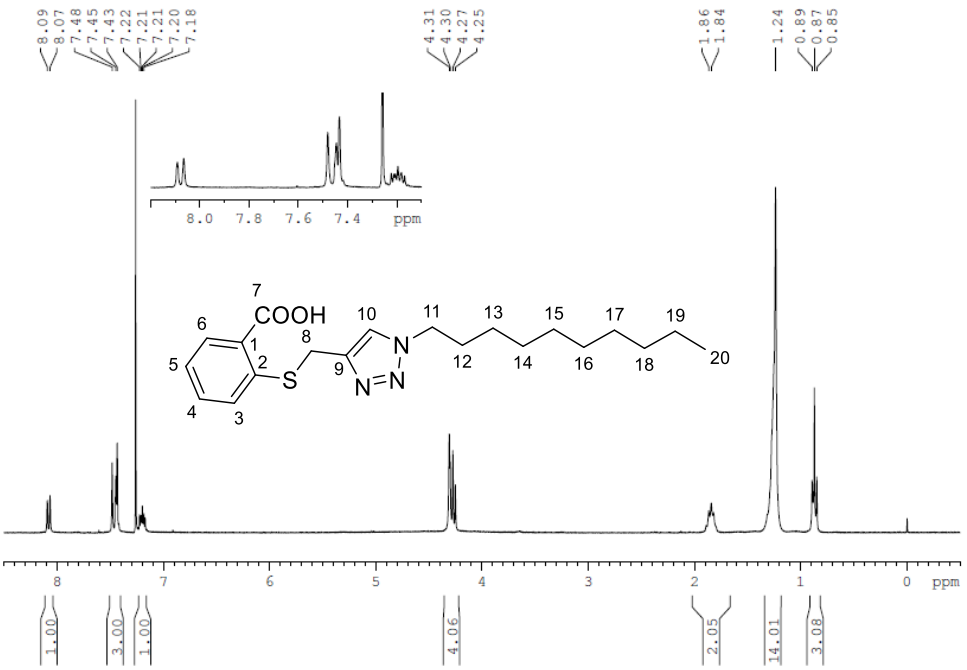


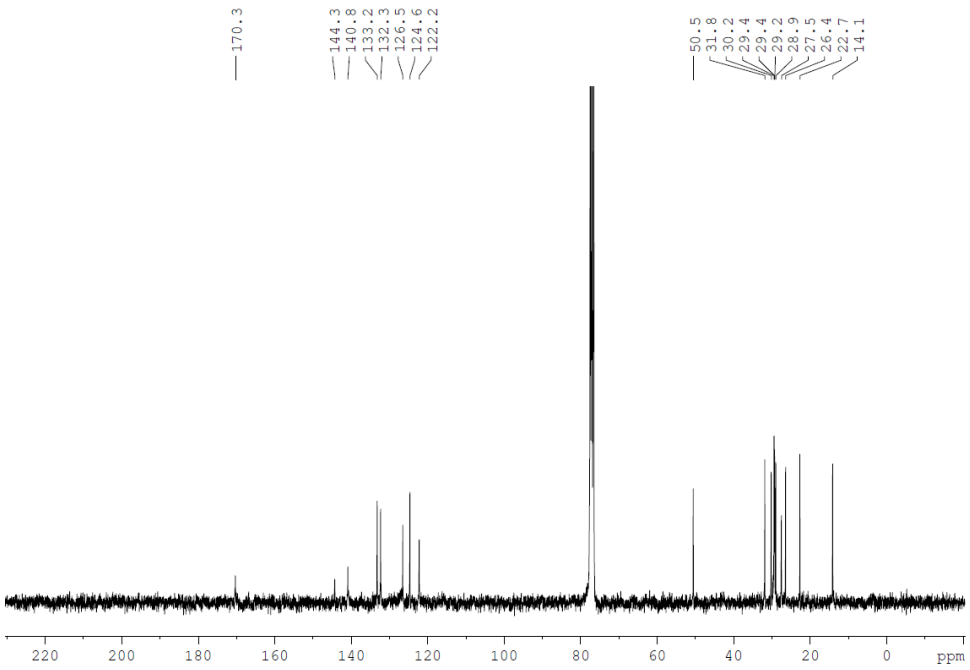


Spectral data of Compound 2e

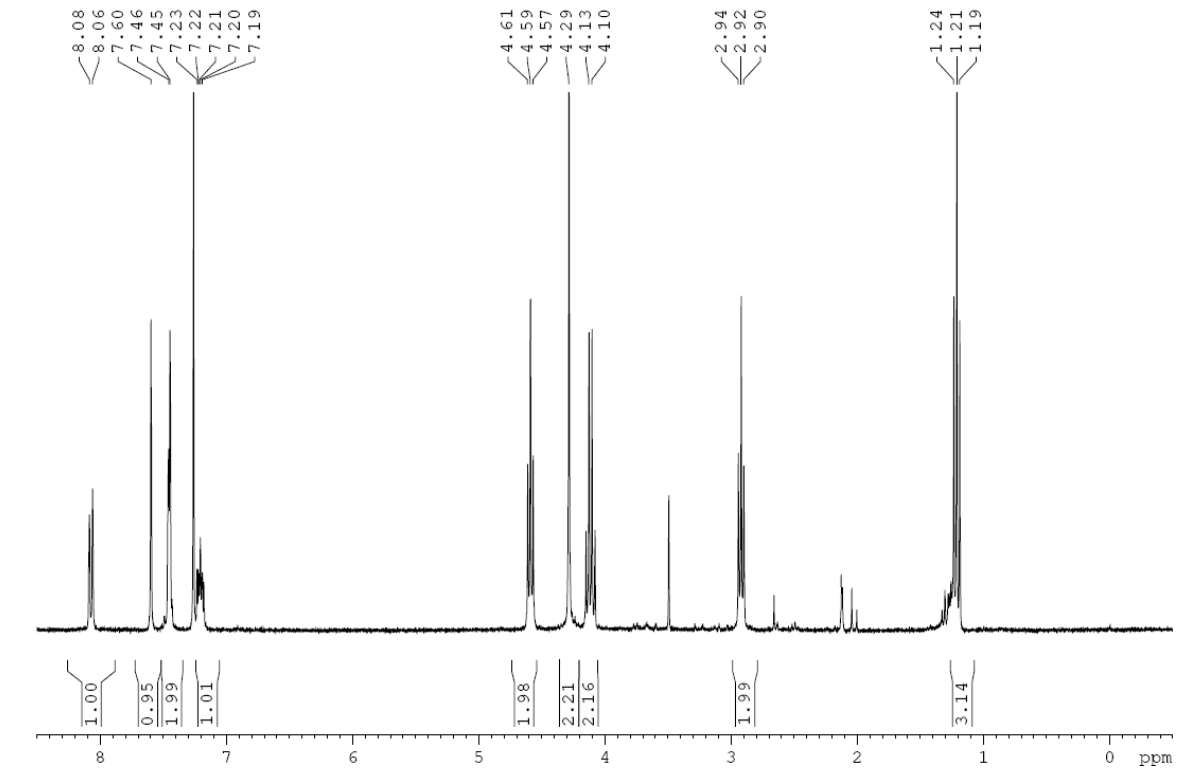


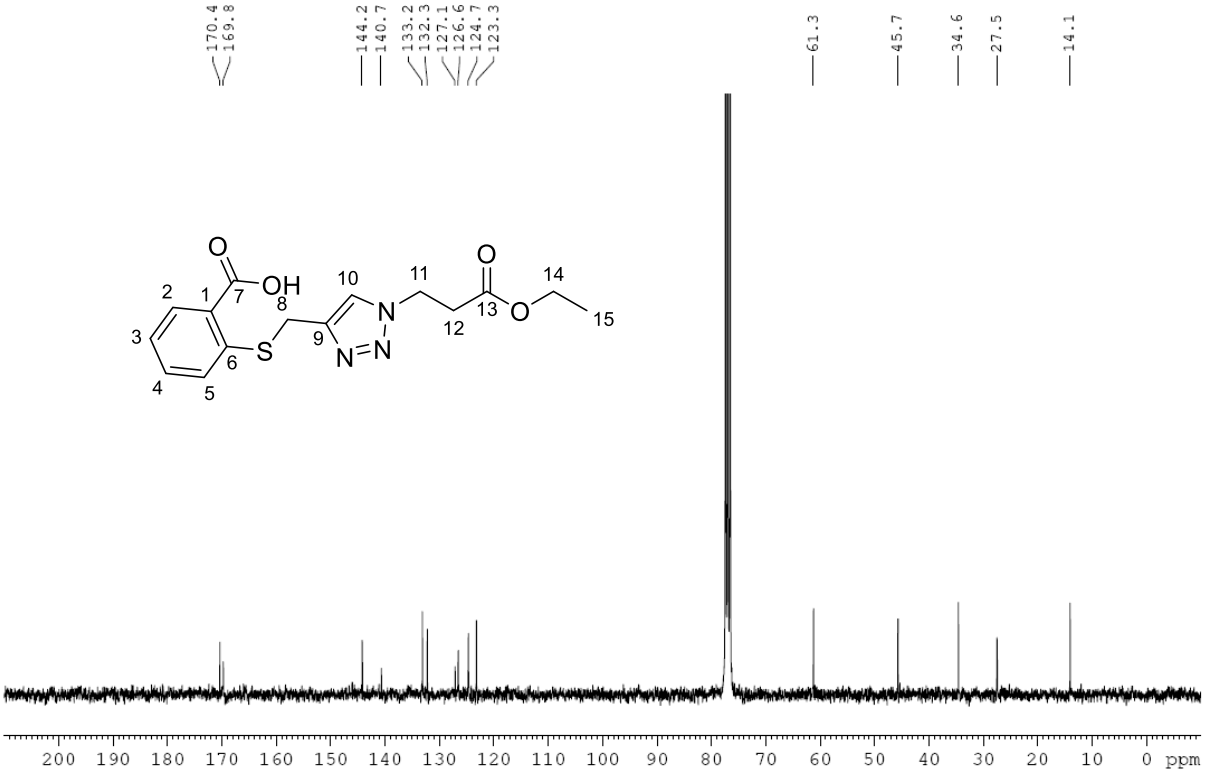
Spectral data of Compound 2f



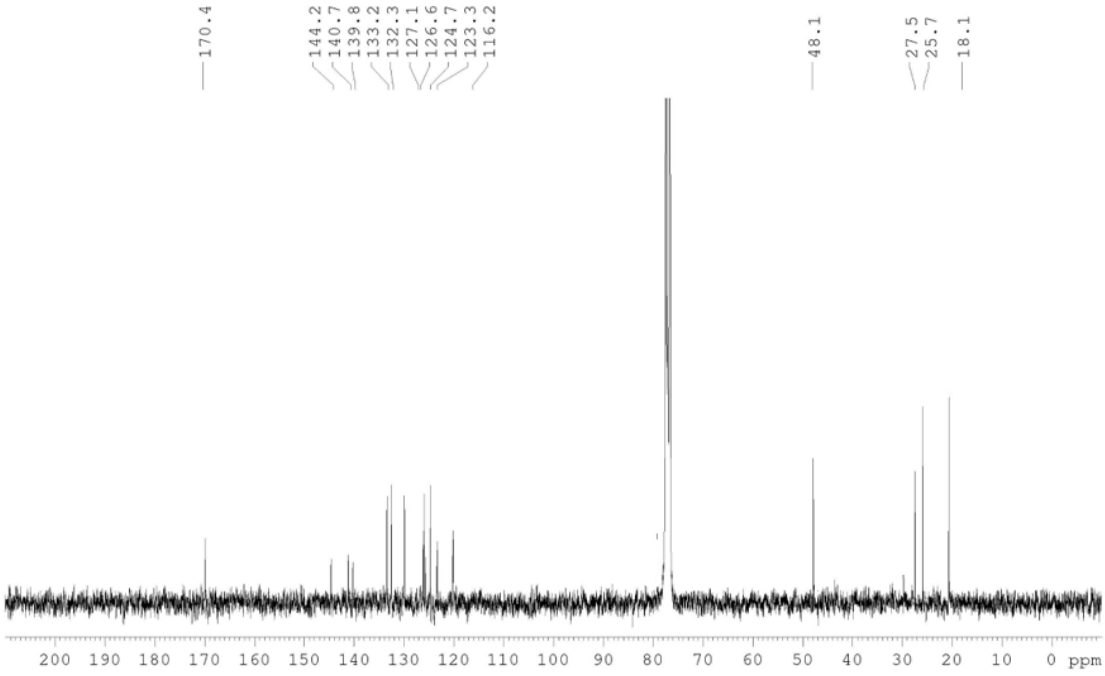


Spectral data of Compound 2g

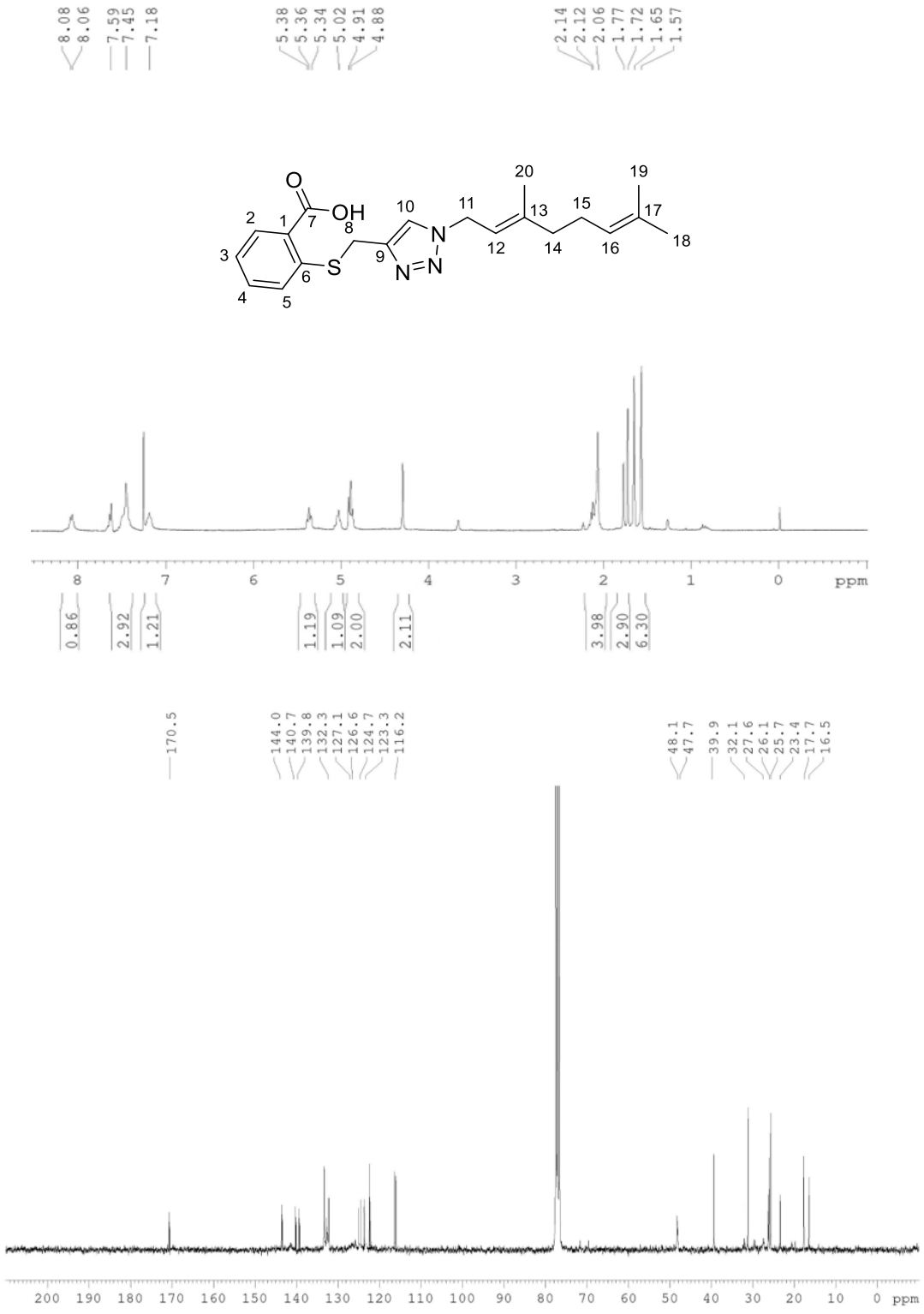




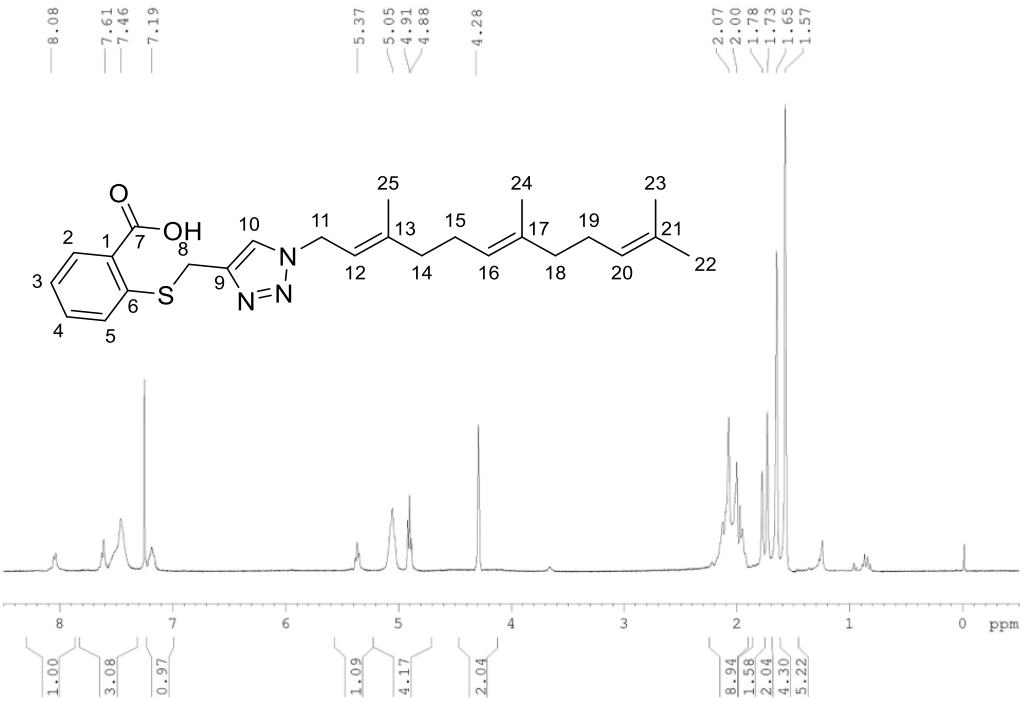
Spectral data of Compound 2h

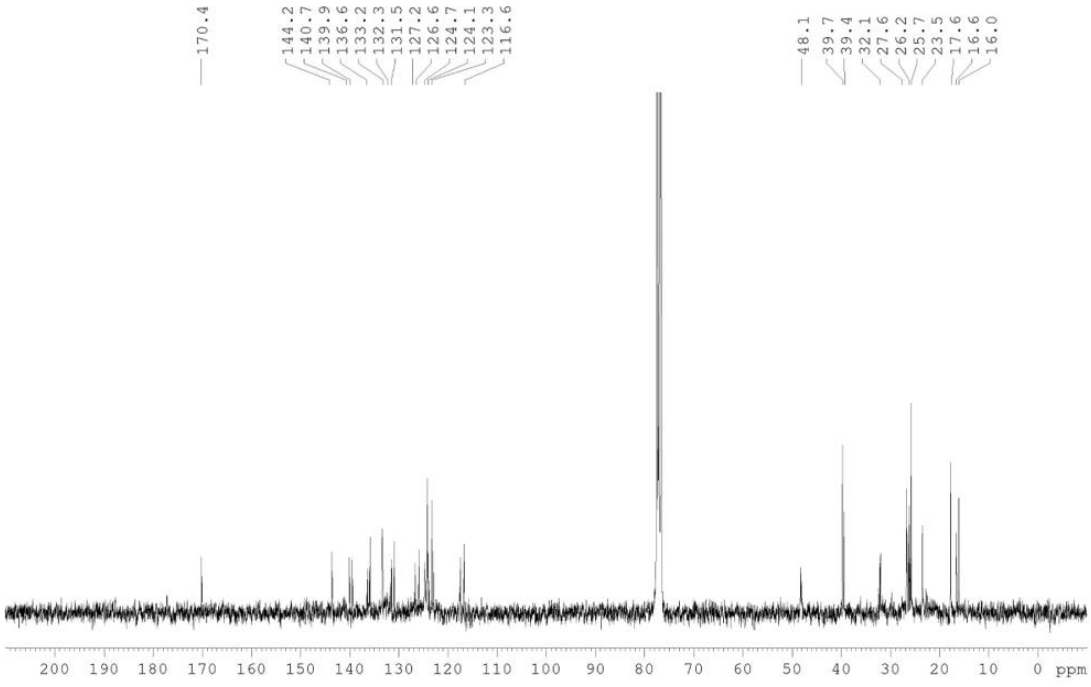


Spectral data of Compound 2i



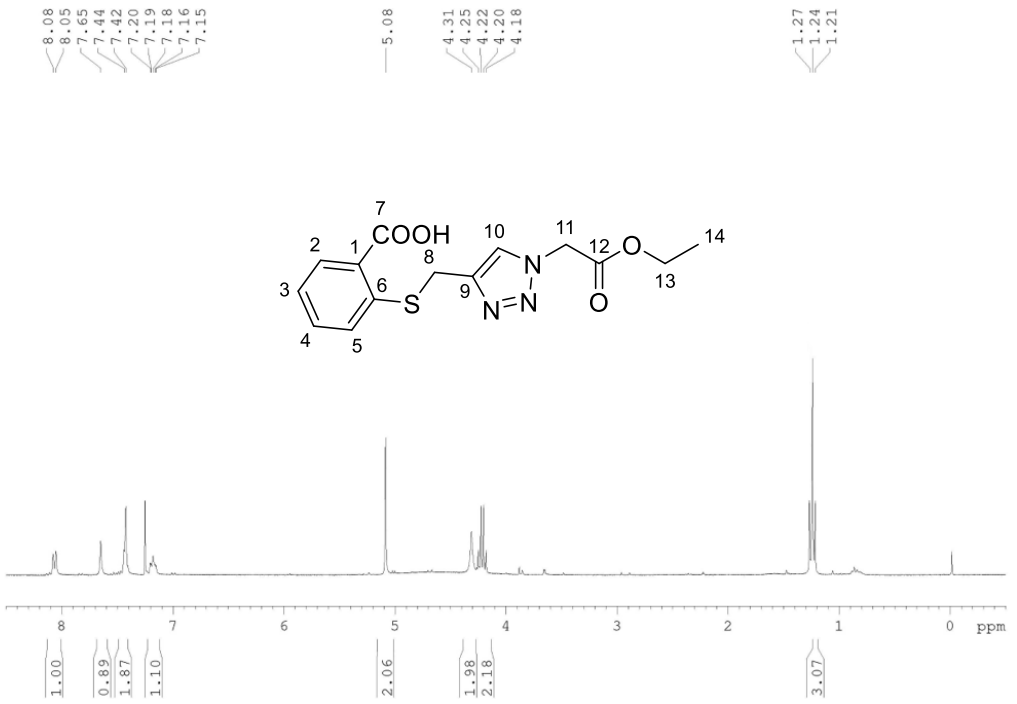
Spectral data of Compound 2j

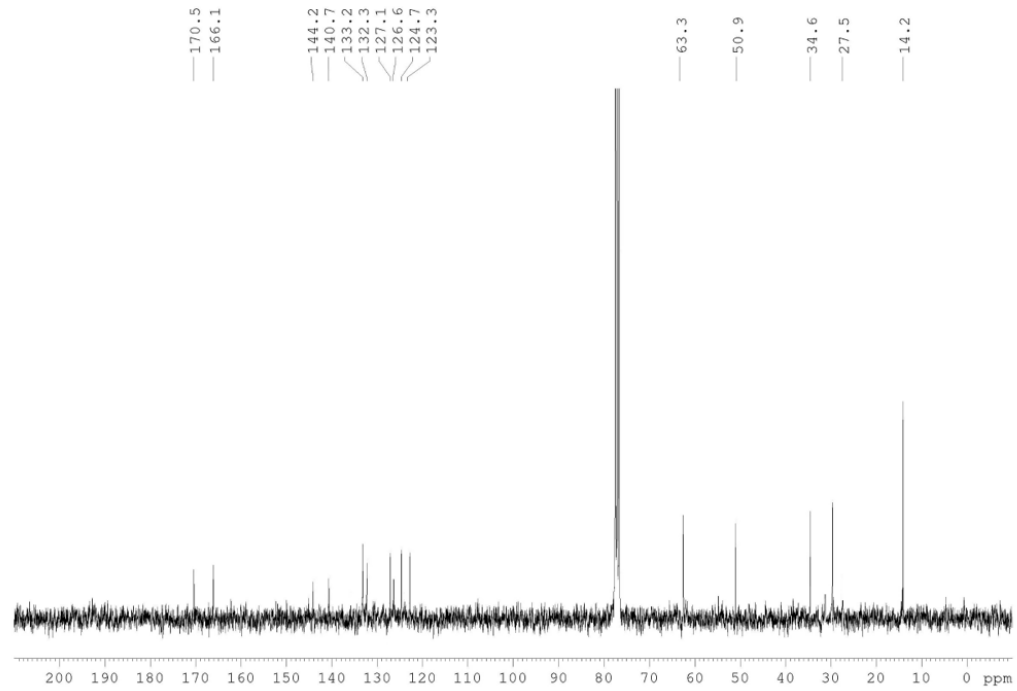




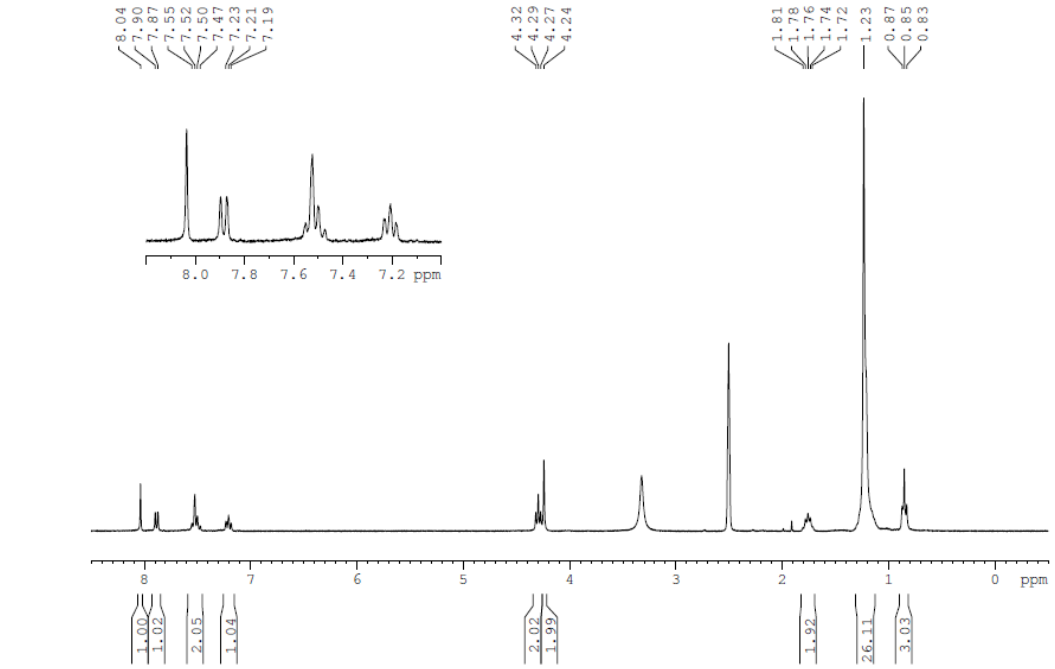
Spectral data of Compound 2k

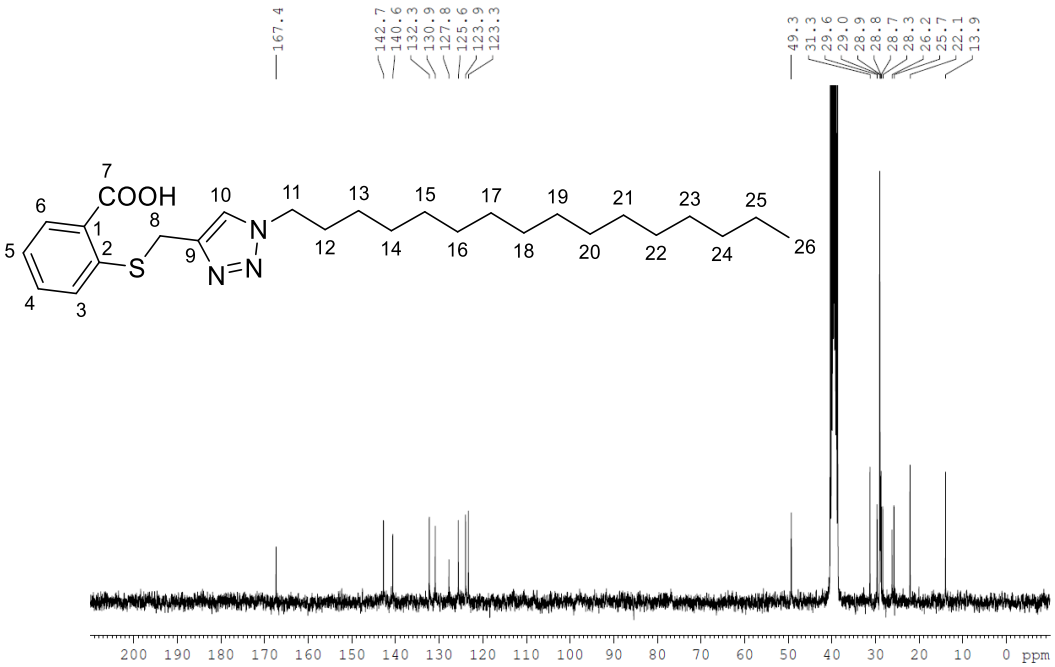
Spectral data of Compound 2l



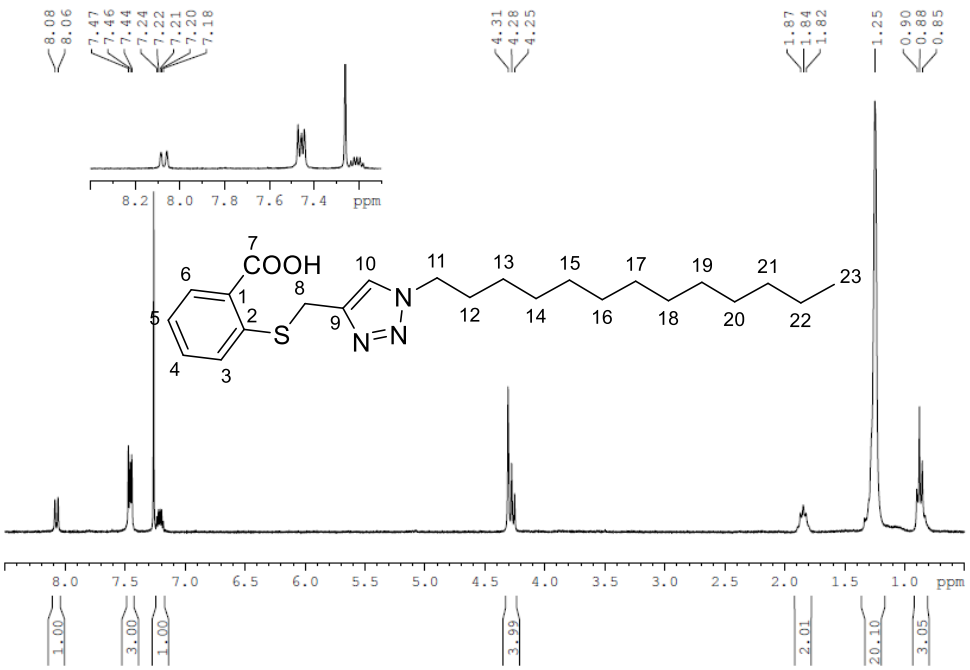


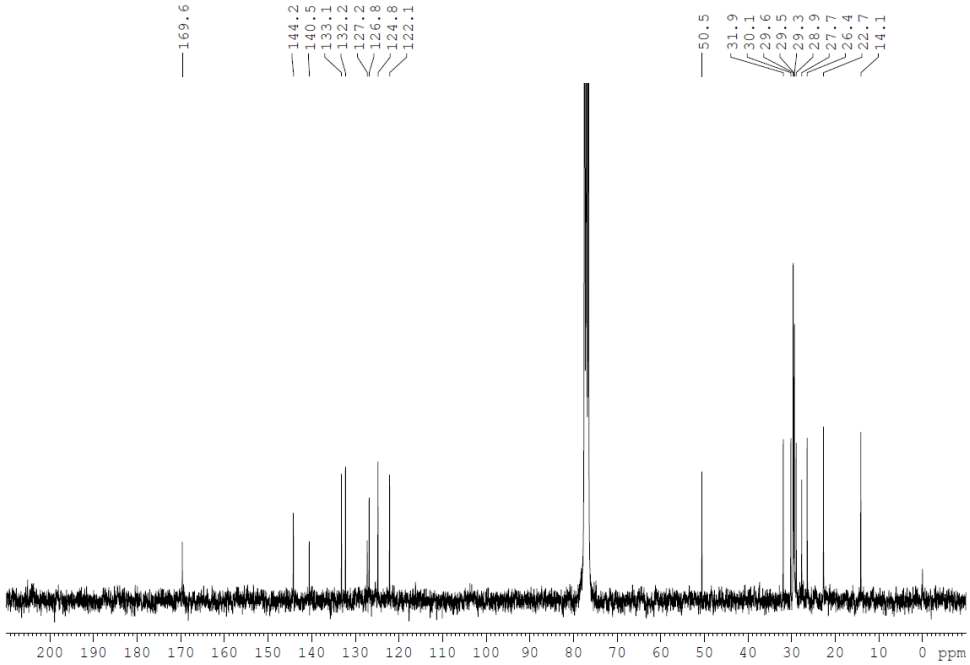
Spectral data of Compound 2m



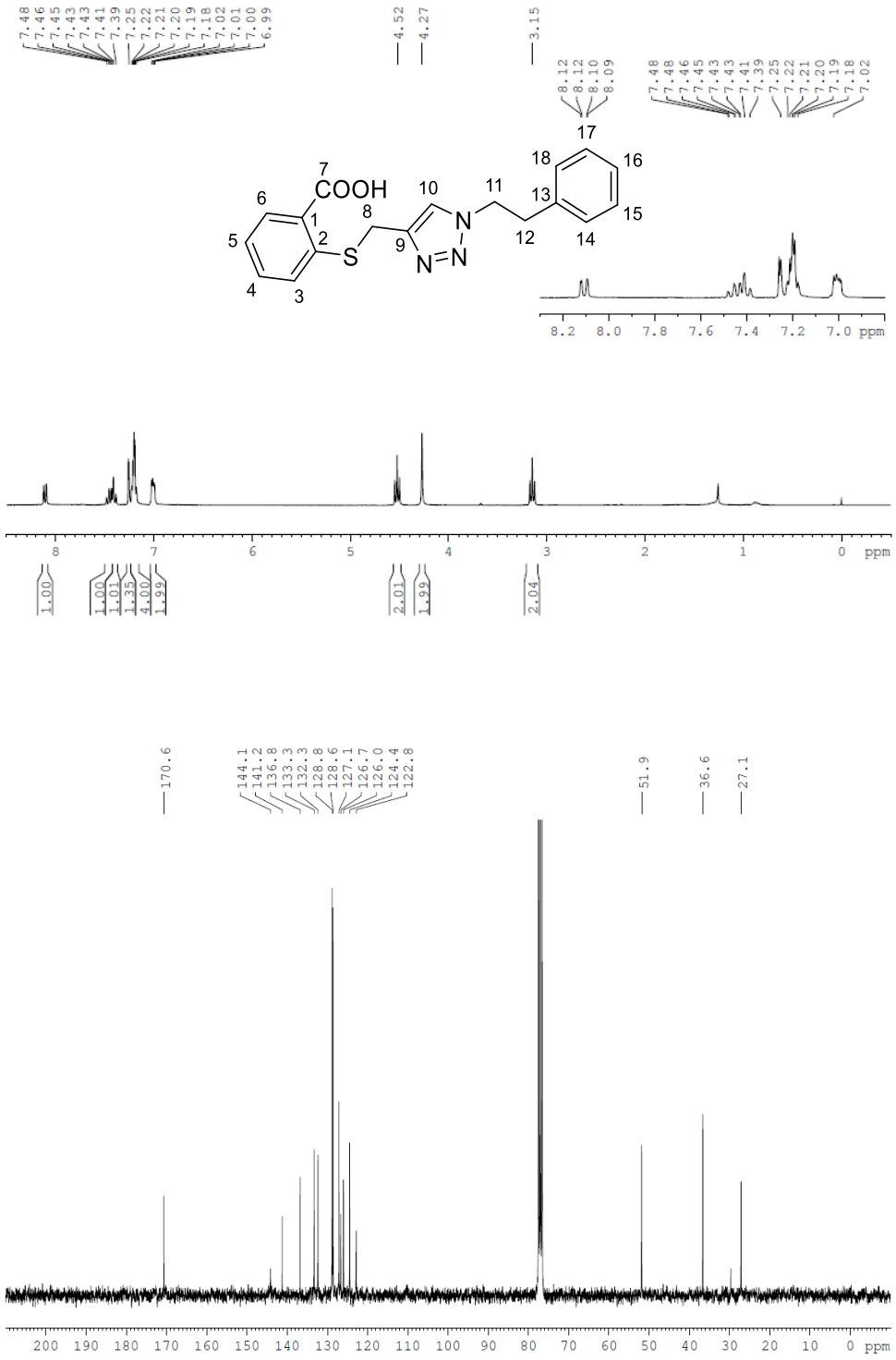


Spectral data of Compound 2n





Spectral data of Compound 2o



Spectral data of Compound 2p