Supplementary Information

Discovery of Lipoic acid-4-phenyl-1H-pyrazole Hybrids as Novel Bifunctional ROCK Inhibitors with Antioxidant Activity

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Contents

General information

Reagents and solvents were purchased from commercial sources and were used without further purification unless stated. The progress of the reactions was monitored by thin-layer chromatography on a glass plate coated with silica gel with fluorescent indicator (GF254) and visualized with UV light or by treatment with phosphomolybdic acid (PMA) or ninhydrin. Flash chromatography was performed on silica gel (200-300 mesh) using solvents as indicated. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance spectrometer 400 at 400 and 100 MHz respectively. Chemical shifts are given in ppm (δ) referenced to $CDCl_3$ with 7.26 for ^{1}H and 77.10 for ^{13}C, and to *d*6-DMSO with 2.50 for ^{1}H and 4.90 for ^{13}C. In the case of multiplet, the signals are reported as intervals. Signals are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are expressed in hertz. High-resolution mass spectrometric data (HRMS) were collected on a Shimadzu LCMS-IT-TOF mass spectrometer. The purity of all final compounds was determined by Agilent 1260 HPLC system using an Eclipse XDB-C18 column. In HPLC conditions, flow rate was set at 1 mL/min, and gradient elution was uesd 70%MeOH/H_2O with 0.1% TFA for 15mins.

HPLC-grade acetonitrile and methanol purchased from Merck (Darmstadt, Germany) were used for HPLC analysis. Dullbecco's modified Eagle's medium

(DMEM), and fetal bovine serum (FBS) were purchased from Gibico-BRL (Grand Island, NY, USA). 3-(3, 4- dimehylthiazol-2-yl)-2, 5-diphenyl-tetrazolium bromide (MTT), and all other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA) unless stated.

Synthesis and characterization

General procedure A to synthesize 1-8: The synthesis of compound 6 was exemplified here.

To a solution of 2-(dimethylamino)ethanol (1.15 mL, 11.48 mmol) in THF (30 mL) at 0 ℃ was added NaH (60%, 636.31 mg, 15.91 mmol). After stirring for 20 min, the mixture was allowed to room temperature and stirred overnight. The solvent was removed by rotary evaporation and the residue was added addition of saturated aq. $NaHCO_3$ and then extracted with EtOAc（20 ml × 3）. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the crud 2-(5-bromo-2-nitrophenoxy)-N,N-dimethylethanamine (18*6) as a brown oil (2.97 g, 90.4%).

To a mixture of crude 18*6 (300.00 mg, 1.04 mmol), pyridine-4-boronic acid pinacol ester (234.05 mg, 1.14 mmol), $Pd[P(Ph)_3]_4$ (23.98 mg, 20.75 μmol) and K_2CO_3 (573.61 mg, 4.15 mmol) in a sealed tube, a mixed solvent (toluene/H_2O/EtOH=7/2/1, 9 ml) were then injected under Argon and the mixture was stirred at 100 ℃ for 8h. After cooling to room temperature, the solvent was removed

by rotary evaporation and the residue was added addition of water and extracted with EtOAc（15 ml × 3）. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (MeOH/DCM 1/30-1/20) to give N,N-dimethyl-2-(2-nitro-5-(pyridin-4-yl)phenoxy)ethanamine (19*6) as a brown-orange solid (311.00 mg, 100%).

To a solution of 19*6 (155 mg, 539.48 μmol) in MeOH (5 ml) was added Raney nickel (20 mg) and Hydrazine (200 ul), the reaction mixture was stirred at rt for 3h. The mixture was filtered, and the filtrate was evaporated by rotary evaporation to give 2-(2-(dimethylamino)ethoxy)-4-(pyridin-4-yl)aniline (20*6) as a brown solid (140 mg, 100%).

To a solution of 20*6 (140.00 mg, 544.05 μmol), LA (123.48 mg, 598.45 μmol) and DIEA (269.75 μl, 1.63 mmol) in DMF (5 ml) was added HATU (268.92 mg, 707.26 μmol) and the solution was stirred at rt overnight. After the solvent was removed by rotary evaporation, saturated aq. $NaHCO_3$ was added and then extracted with EtOAc (15 ml × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered, the filtrate was concentrated and the residue was purified by flash chromatography on silica gel (MeOH/DCM 1/50-1/20) to give compound 6.

General Procedure B to synthesize 9-16: The synthesis of compound 14 was exemplified here.

To a mixture of crude 18*6 (300.00 mg, 1.04 mmol), 1-Boc-4-pyrazoleboronic acid pinacol ester (305.22 mg, 1.04 mmol), $PdCl_2$(dppf) (75.92 mg, 103.76 μmol) and Cs_2CO_3 (676.15 mg, 2.08 mmol) in a sealed tube, a mixed solvent (dioxane/H2O =10/1, 6ml) were then injected under Argon and the mixture was stirred at 70 ℃ for 6h. After cooling to room temperature, the solvent was removed by rotary evaporation and the residue was added addition of water and extracted with EtOAc（15 ml × 3）. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered, the filtrate was concentrated and the residue was purified by flash chromatography on silica gel (MeOH/DCM 1/50-1/20) to give tert-butyl 4-(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)-1H-pyrazole-1-carboxylate (21*14) as a white solid (249.00 mg, 63.8%).

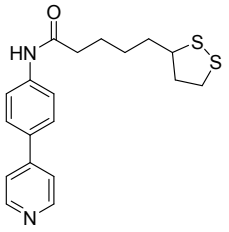
To a solution of 21*14 (360.00 mg, 956.41 μmol) in MeOH (8 ml) was added 10%Pd/C, the reaction mixture was stirred at rt under H_2 balloon atmosphere for 1h. The mixture was filtered, and the filtrate was evaporated by rotary evaporation to give tert-butyl -(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)-1H-pyrazole-1-carboxylate (22*14) as a brown solid (320.00 mg, 96.6%) .

To a solution of 22*14 (228.00 mg, 658.15 μmol), LA (176.53 mg, 855.60 μmol) and DIEA (375.37 mg, 987.23 μmol) in DMF (2 ml) was added HATU (326.32 μl, 1.97 mmol) and the solution was stirred at rt overnight. After the solvent was removed by rotary evaporation, saturated aq. $NaHCO_3$ was added and then extracted with EtOAc (15ml × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered, the filtrate was concentrated and the residue was

purified by flash chromatography on silica gel (MeOH/DCM 1/50-1/20) to give tert-butyl4-(4-(5-(1,2-dithiolan-3-yl)pentanamido)-3-(2-(dimethylamino)ethoxy)phenyl)-1H-pyrazole-1-carboxylate (23*14) as a brown-orange solid (200.00 mg, 56.8%).

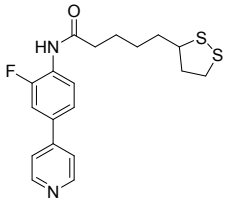
To a solution of 23*14 in DCM (2 mL) was injected TFA (0.4 mL) at rt. The mixture was stirred at rt for 2h and concentrated under a reduced pressure to remove TFA, then saturated aq. $NaHCO_3$ was added and the aqueous phase was extracted with DCM (15 ml × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated and the residual solid was purified by flash chromatography on silica gel (MeOH/DCM 1/20) to give 14 as a faint yellow solid.

5-(1,2-dithiolan-3-yl)-N-(4-(pyridin-4-yl)phenyl)pentanamide (1):



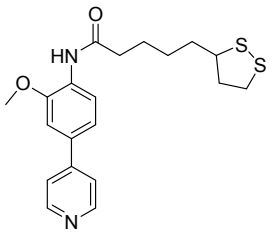
Similar to the General Procedure A, 1 was obtained as a faint yellow solid at 52% yield for three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.7 Hz, 2H), 7.96 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 5.2 Hz, 2H), 3.64 – 3.49 (m, 1H), 3.22 – 3.04 (m, 2H), 2.53 – 2.33 (m, 3H), 1.90 (dt, *J* = 19.7, 6.8 Hz, 1H), 1.84 – 1.62 (m, 4H), 1.61 – 1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 150.1, 147.7, 139.2, 133.4, 127.6, 121.3, 120.2, 56.4, 40.3, 38.5, 37.4, 34.7, 28.9, 25.2. ESI-HRMS for $[C_{19}H_{23}N_2OS_2]^+$, calcd: 359.1246; found: 359.1232. Purity: 100%.

5-(1,2-dithiolan-3-yl)-N-(2-fluoro-4-(pyridin-4-yl)phenyl)pentanamide (2):



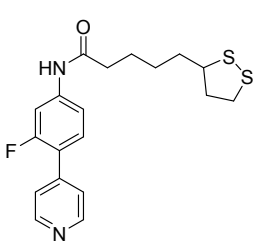
Similar to the General Procedure A, 2 was obtained as a faint yellow solid at 32.8% yield for three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 6.0 Hz, 2H), 8.48 (t, J = 8.2 Hz, 1H), 7.51 – 7.35 (m, 5H), 3.66 – 3.53 (m, 1H), 3.25 – 3.06 (m, 2H), 2.57 – 2.37 (m, 3H), 1.93 (td, J = 13.6, 6.9 Hz, 1H), 1.87 – 1.72 (m, 4H), 1.62 – 1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 152.7, 150.3, 149.3, 145.5 (d, J = 1.8 Hz), 133.0 (d, J = 7.5 Hz), 126.3, 126.2, 122.1 (d, J = 3.0 Hz), 121.1, 120.1, 112.3, 112.1, 55.3, 39.2, 37.5, 36.4, 33.6, 27.8, 24.1. ESI-HRMS for $[C_{19}H_{22}FN_2OS_2]^+$, calcd: 377.1158; found: 377.1151. Purity: 99%.

5-(1,2-dithiolan-3-yl)-N-(2-methoxy-4-(pyridin-4-yl)phenyl)pentanamide (3) :



Similar to the General Procedure A, 3 was obtained as a faint yellow solid at 22% yield for three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, J = 4.5, 1.6 Hz, 2H), 8.50 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 7.47 (dd, J = 4.5, 1.6 Hz, 2H), 7.29 – 7.23 (m, 1H), 7.11 (d, J = 1.8 Hz, 1H), 3.97 (s, 3H), 3.64 – 3.52 (m, 1H), 3.24 – 3.06 (m, 2H), 2.54 – 2.39 (m, 3H), 1.97 – 1.85 (m, 2H), 1.83 – 1.69 (m, 4H), 1.60 – 1.47 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 170.0, 149.2, 147.1, 147.0, 132.3, 127.7, 120.3, 119.0, 107.3, 55.4, 54.9, 39.3, 37.5, 36.7, 33.7, 27.8, 24.2. ESI-HRMS for $[C_{20}H_{25}N_2O_2S_2]^+$, calcd: 389.1352; found: 389.1350. Purity: 99%.

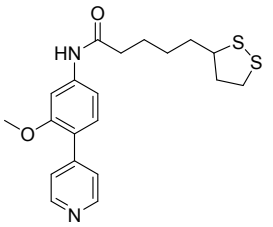
5-(1,2-dithiolan-3-yl)-N-(3-fluoro-4-(pyridin-4-yl)phenyl)pentanamide (4):



Similar to the General Procedure A, 4 was obtained as a faint yellow solid at 45.2% yield for three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H),

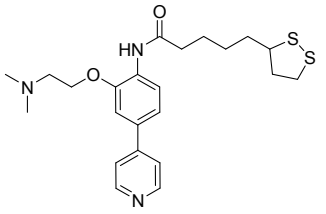
8.63 (d, J = 5.8 Hz, 2H), 7.68 (d, J = 12.9 Hz, 1H), 7.47 (d, J = 4.7 Hz, 2H), 7.40 (t, J = 8.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 3.59 – 3.48 (m, 1H), 3.21 – 3.02 (m, 2H), 2.46 – 2.36 (m, 3H), 1.87 (td, J = 13.6, 6.9 Hz, 1H), 1.81 – 1.61 (m, 4H), 1.56 – 1.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 161.3, 158.8, 149.7, 143.5, 140.8, 140.6, 130.3 (d, J = 4.3 Hz), 123.5 (d, J = 3.7 Hz), 121.1, 121.0, 115.6, 108.1, 107.8, 56.4, 40.3, 38.5, 37.3, 34.6, 28.9, 25.2. ESI-HRMS for $[C_{19}H_{22}FN_2OS_2]^+$, calcd: 377.1152; found: 377.1136. Purity: 98%.

5-(1,2-dithiolan-3-yl)-N-(3-methoxy-4-(pyridin-4-yl)phenyl)pentanamide (5):



Similar to the General Procedure A, 5 was obtained as a yellow solid at 78.8% yield for three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.78 (s, 1H), 7.65 (s, 1H), 7.47 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 1H), 6.96 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.84 (s, 3H), 3.58 (td, *J* = 12.7, 6.4 Hz, 1H), 3.26 – 3.06 (m, 2H), 2.51 – 2.39 (m, 3H), 1.91 (dt, *J* = 19.7, 6.9 Hz, 1H), 1.84 – 1.69 (m, 4H), 1.58 – 1.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 157.2, 149.2, 146.2, 140.3, 130.5, 124.2, 122.9, 111.7, 103.4, 56.4, 55.6, 40.3, 38.5, 37.4, 34.7, 28.9, 25.2. ESI-HRMS for $[C_{20}H_{25}N_2O_2S_2]^+$, calcd: 389.1352; found: 389.1342. Purity: 99%.

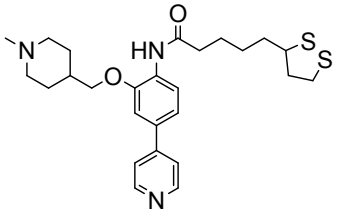
N-(2-(2-(dimethylamino)ethoxy)-4-(pyridin-4-yl)phenyl)-5-(1,2-dithiolan-3-yl)pentanamide (6):



A faint yellow solid at 67.8% yield for four steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.54 (dd, J = 4.5, 1.6 Hz, 2H), 8.40 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 4.5, 1.6 Hz, 2H), 7.24 (dd, J = 8.5, 2.0 Hz, 1H), 7.14 (d, J = 2.0 Hz,

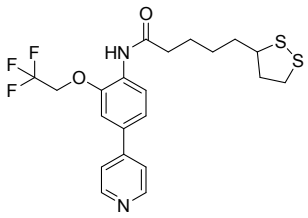
1H), 4.12 (t, J = 5.2 , 2H), 3.57 – 3.48 (m, 1H), 3.17 – 2.99 (m, 2H), 2.63 (t , J = 5.2 , 2H), 2.41 – 2.34 (m, 3H), 2.29 (s, 6H), 1.85 (td, J = 13.8, 7.0 Hz, 1H), 1.76 – 1.62 (m, 4H), 1.53 – 1.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 149.1, 147.0, 146.8, 132.2, 130.0, 120.2, 112.1, 67.0, 57.0, 55.4, 44.2, 39.2, 37.5, 36.2, 33.7, 28.0, 24.3. ESI-HRMS for $[C_{23}H_{32}N_3O_2S_2]^+$, calcd: 446.1930; found: 446.1929. Purity: 99%.

5-(1,2-dithiolan-3-yl)-N-(2-((1-methylpiperidin-4-yl)methoxy)-4-(pyridin-4-yl)phenyl)pentanamide (7)：



Similar to the General Procedure A, 7 was obtained as a brown yellow solid at 64.8% yield for four steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.6 Hz, 2H), 8.48 (d, J = 8.0 Hz, 1H), 7.81 (s, 1H), 7.47 (d, J = 4.7 Hz, 2H), 7.10 (s, 1H), 3.99 (d, J = 5.6 Hz, 2H), 3.64 – 3.53 (m, 1H), 3.22 – 3.08 (m, 2H), 3.02 – 2.91 (m, 3H), 2.50 – 2.42 (m, 3H), 2.33 (s, 3H), 2.08 – 1.97 (m, 6H), 1.89 – 1.82 (m, 4H), 1.58 – 1.51 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 150.2, 148.2, 147.5, 133.4, 128.7, 121.4, 120.2, 120.0, 109.4, 73.2, 56.4, 55.2, 46.2, 40.3, 38.5, 37.8, 35.2, 34.7, 29.0, 28.9, 25.3. ESI-HRMS for $[C_{26}H_{36}N_3O_2S_2]^+$, calcd: 486.2243; found: 486.2234. Purity: 98%.

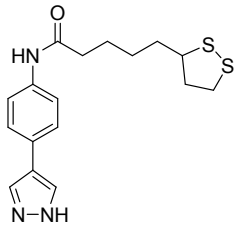
5-(1,2-dithiolan-3-yl)-N-(4-(pyridin-4-yl)-2-(2,2,2-trifluoroethoxy)phenyl)pentanamide (8):



Similar to the General Procedure A, 8 was obtained as a white solid at 40.4% yield for four steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 4.9 Hz, 2H), 8.52 (d, J = 8.3 Hz, 1H), 7.73 (s, 1H), 7.45 (d, J = 5.2 Hz, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.13 (s, 1H), 4.52 (dd, J = 15.7, 7.8 Hz, 2H), 3.69 – 3.52 (m, 1H), 3.29 –

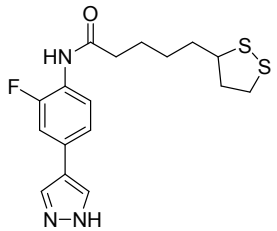
3.04 (m, 2H), 2.59 – 2.37 (m, 3H), 1.92 (dt, J = 19.7, 6.8 Hz, 1H), 1.88 – 1.67 (m, 4H), 1.64 – 1.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 149.3, 146.2, 145.2, 132.7, 128.2, 123.5, 121.2, 120.7, 120.2, 120.1, 109.7, 66.5, 66.1, 65.8, 65.4, 55.3, 39.2, 37.5, 36.7, 33.7, 27.8, 24.1. ESI-HRMS for $[C_{21}H_{24}F_3N_2O_2S_2]^+$, calcd: 457.1226; found: 457.1225. Purity: 99%.

N-(4-(1H-pyrazol-4-yl)phenyl)-5-(1,2-dithiolan-3-yl)pentanamide (9)：



Similar to the General Procedure B, 9 was obtained as a white solid at 5.6% yield for four steps. ^{1}H NMR (400 MHz, DMSO) δ 12.81 (s, 1H), 9.86 (s, 1H), 7.97 (s, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 3.74 – 3.56 (m, 1H), 3.26 – 3.05 (m, 2H), 2.41 (td, J = 12.5, 6.3 Hz, 1H), 2.30 (t, J = 7.3 Hz, 2H), 1.87 (dt, J = 19.7, 6.8 Hz, 1H), 1.77 – 1.55 (m, 4H), 1.46 – 1.37 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 170.9, 137.2, 127.7, 125.3, 120.9, 119.4, 56.1, 38.1, 36.2, 34.1, 28.3, 24.9. ESI-HRMS for $[C_{17}H_{22}N_3OS_2]^+$, calcd: 348.1199; found: 348.1195. Purity: 97%.

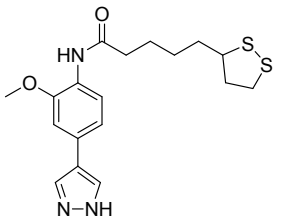
5-(1,2-dithiolan-3-yl)-N-(2-fluoro-4-(1H-pyrazol-4-yl)phenyl)pentanamide(10):



Similar to the General Procedure B, 10 was obtained as a faint yellow solid at 7% yield for four steps. ^{1}H NMR (400 MHz, DMSO) δ 12.94 (s, 1H), 9.60 (s, 1H), 8.06 (s, 2H), 7.77 (t, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 12.3, 1.8 Hz, 1H), 7.38 (dd, J = 8.3, 1.5 Hz, 1H), 3.62 (td, J = 12.3, 6.2 Hz, 1H), 3.22 – 3.05 (m, 2H), 2.45 – 2.31 (m, 3H), 1.87 (dq, J = 13.5, 6.8 Hz, 1H), 1.75 – 1.52 (m, 4H), 1.48 – 1.33 (m, 5H). ^{13}C NMR (100 MHz, DMSO) δ 171.4, 155.4, 152.9, 130.4 (d, J = 7.6 Hz),

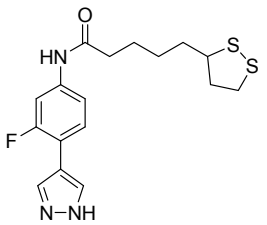
124.7, 123.7, 123.6, 120.6 (d, J = 2.8 Hz), 120.0 (d, J = 1.9 Hz), 111.9, 111.7, 56.1, 38.1, 35.5, 34.1, 28.2, 24.9. ESI-HRMS for $[C_{17}H_{21}FN_3OS_2]^+$, calcd: 366.1105; found: 366.1098. Purity: 97%.

5-(1,2-dithiolan-3-yl)-N-(2-methoxy-4-(1H-pyrazol-4-yl)phenyl)pentanamide (11):



Similar to the General Procedure B, 11 was obtained as a white solid at 14.3% yield for four steps. ^{1}H NMR (400 MHz, DMSO) δ 12.90 (s, 1H), 9.02 (s, 1H), 8.34 – 7.76 (m, 3H), 7.23 (s, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 3H), 3.62 (td, *J* = 12.5, 6.2 Hz, 1H), 3.26 – 3.06 (m, 2H), 2.47 – 2.32 (m, 3H), 1.87 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.77 – 1.50 (m, 4H), 1.48 – 1.33 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 171.6, 150.5, 129.7, 125.8, 122.9, 121.7, 117.3, 108.6, 56.7, 56.2, 38.6, 36.3, 34.6, 28.8, 25.5. ESI-HRMS for $[C_{18}H_{24}N_3O_2S_2]^+$, calcd: 378.1304; found: 378.1306. Purity: 99%.

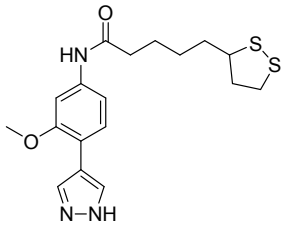
5-(1,2-dithiolan-3-yl)-N-(3-fluoro-4-(1H-pyrazol-4-yl)phenyl)pentanamide (12):



Similar to the General Procedure B, 12 was obtained as a faint yellow solid at 15.3% yield for four steps. ^{1}H NMR (400 MHz, DMSO) δ 13.00 (s, 1H), 10.08 (s, 1H), 7.98 (s, 2H), 7.73 – 7.57 (m, 2H), 7.28 (dd, J = 8.5, 1.8 Hz, 1H), 3.67 – 3.56 (m, 1H), 3.24 – 3.06 (m, 2H), 2.47 – 2.37 (m, 1H), 2.33 (dd, J = 18.4, 11.0 Hz, 2H), 1.87 (td, J = 13.4, 6.8 Hz, 1H), 1.74 – 1.52 (m, 4H), 1.46 – 1.35 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 171.8, 159.9, 157.4, 139.0, 138.9, 128.3 (d, J = 5.9 Hz), 115.5 (d, J = 2.1 Hz), 115.4, 115.3, 115.1 (d, J = 1.8 Hz), 107.0, 106.7, 56.6, 38.6,

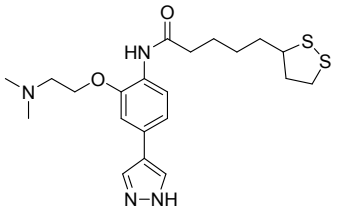
36.7, 34.6, 28.8, 25.2. ESI-HRMS for $[C_{17}H_{21}FN_3OS_2]^+$, calcd: 366.1105; found: 366.1090. Purity: 98%.

5-(1,2-dithiolan-3-yl)-N-(3-methoxy-4-(1H-pyrazol-4-yl)phenyl)pentanamide (13):



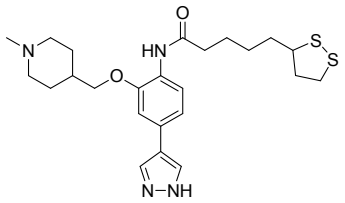
Similar to the General Procedure B, 13 was obtained as a orange solid at 4.3% yield for four steps. ^{1}H NMR (400 MHz, DMSO) δ 12.78 (s, 1H), 9.89 (s, 1H), 7.96 (s, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.15 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.82 (s, 3H), 3.67 – 3.57 (m, 1H), 3.23 – 3.07 (m, 2H), 2.41 (dt, *J* = 18.7, 6.3 Hz, 1H), 2.30 (t, *J* = 7.3 Hz, 2H), 1.87 (td, *J* = 13.5, 6.8 Hz, 1H), 1.75 – 1.54 (m, 4H), 1.46 – 1.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 171.0, 155.4, 138.4, 127.0, 116.8, 116.2, 111.2, 102.7, 56.1, 55.2, 38.1, 36.3, 34.1, 28.3, 24.8. ESI-HRMS for $[C_{18}H_{24}N_3O_2S_2]^+$, calcd: 378.1304; found: 378.1301. Purity: 98%.

N-(2-(2-(dimethylamino)ethoxy)-4-(1H-pyrazol-4-yl)phenyl)-5-(1,2-dithiolan-3-yl)pentanamide (14):



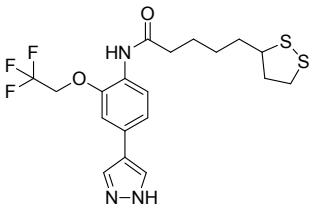
A faint yellow solid at 16.1% yield for four steps. ^{1}H NMR (400 MHz, DMSO) δ 12.89 (s, 1H), 9.34 (s, 1H), 8.14 (s, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 4.16 (t, *J* = 4.8 Hz, 2H), 3.71 – 3.53 (m, 1H), 3.22 – 3.11 (m, 2H), 2.63 (t, *J* = 4.8 Hz, 2H), 2.46 – 2.38 (m, 1H), 2.38 – 2.30 (m, 2H), 2.27 (s, 6H), 1.87 (dt, *J* = 19.2, 6.5 Hz, 1H), 1.80 – 1.50 (m, 4H), 1.50 – 1.30 (m, 2H).^{13}C NMR (100 MHz, DMSO) δ 171.3, 149.4, 136.9, 129.6, 127.5, 125.9, 122.5, 121.5, 118.5, 112.3, 68.3, 58.0, 56.6, 55.4, 45.7, 38.6, 36.6, 34.7, 28.8, 25.5. ESI-HRMS for $[C_{21}H_{31}N_4O_2S_2]^+$, calcd: 435.1883; found: 435.1883. Purity: 99%.

5-(1,2-dithiolan-3-yl)-N-(2-((1-methylpiperidin-4-yl)methoxy)-4-(1H-pyrazol-4-yl)phenyl)pentanamide (15):



Similar to the General Procedure B, 15 was obtained as a white solid at 24.6% yield for four steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.2 Hz, 1H), 7.80 (s, 2H), 7.73 (s, 1H), 7.09 (dd, J = 8.3, 1.7 Hz, 1H), 6.97 (d, J = 1.7 Hz, 1H), 3.96 (d, J = 5.9 Hz, 2H), 3.64 – 3.52 (m, 1H), 3.24 – 3.08 (m, 2H), 3.06 – 2.96 (m, 2H), 2.46 – 2.40 (m, 3H), 2.36 (s, 3H), 2.15 – 2.05 (m, 3H), 1.95 – 1.83 (m, 4H), 1.79 – 1.71 (m, 3H), 1.63 – 1.52 (m, 4H). ^{13}C NMR (100 MHz, CDCl3) δ 170.8, 147.6, 131.0, 128.3, 126.3, 122.5, 120.5, 118.5, 108.7, 73.1, 56.4, 55.2, 46.1, 40.3, 38.5, 37.7, 35.2, 34.7, 29.7, 28.9, 25.4. ESI-HRMS for $[C_{24}H_{35}N_4O_2S_2]^+$, calcd: 475.2196; found: 475.2179. Purity: 99%.

N-(4-(1H-pyrazol-4-yl)-2-(2,2,2-trifluoroethoxy)phenyl)-5-(1,2-dithiolan-3-yl)pentanamide (16)



Similar to the General Procedure B, 16 was obtained as a white solid at 8.7% yield for four steps. ^{1}H NMR (400 MHz, DMSO) δ 12.91 (s, 1H), 9.01 (s, 1H), 8.09 (s, 2H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.40 (s, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 4.81 (d, *J* = 8.6 Hz, 2H), 3.68 – 3.60 (m, 1H), 3.25 – 2.98 (m, 2H), 2.46 – 2.22 (m, 3H), 1.96 – 1.80 (m, 1H), 1.80 – 1.52 (m, 4H), 1.49 – 1.36 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 171.7, 149.7, 130.7, 125.9, 125.8, 125.2, 123.1, 121.2, 119.2, 111.2, 66.6, 66.3, 65.9, 65.6, 56.6, 38.6, 36.3, 34.7, 28.7, 25.5. ESI-HRMS for

$[C_{19}H_{23}F_3N_3O_2S_2]^+$, calcd: 446.1178; found: 446.1161. Purity: 98%.

Cell Culture HT22 cells were maintained in DMEM supplemented with 10% (v/v) fetal bovine serum and incubated at 37 ℃ under 5% CO_2. Test compounds were dissolved in DMSO and diluted in DMEM supplemented with 10% (v/v) FBS. The final concentration of DMSO in the medium was less than 0.01% (vol/vol) which showed no influence on cell growth.

MTT assay To study the neuroprotective effects of tested compounds, HT22 cells were seeded in 96-well plates at a density of 4×10^3 in triplicate cultures and incubated overnight. Cells were pretreated with tested compounds or the vehicle DMSO for 30 min followed with / without 2 mM glutamate for 24 h. 10 μL of 5 mg/mL MTT was added to each well and cells were incubated for 2 h at 37 °C. To dissolved purple formazan crystal, 100 μL DMSO was carefully added to replace the medium. After vigorously shaking for 15 min at 37°C, the absorbance at 570 nm was measured using a microculture plate reader (Bio-Tek, USA).

Kinase activity assay Kinase inhibition by tested compounds were evaluated by a fluorescence resonance energy transfer based Z'-LYTE kinase assay kit following our described protocols[1]. The IC_{50} value of compound 15 for inhibition of ROCK 1/2 kinases to determine the selectivity of 15 between ROCK1 and ROCK2 was carried out by SelectScreen® Kinase Profiling Services (Life Technologies). Measurements were performed using a Km app Z'-LYTE assay (Assay ID: 784, 787) in duplicates at each concentration (10 points were detected, Fig. S1).

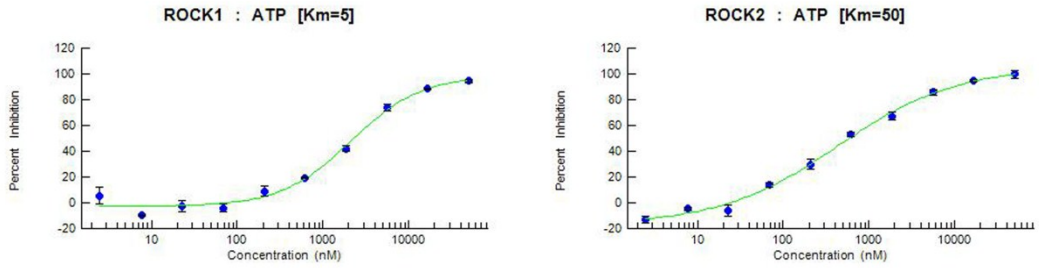


Fig. S1 Dose response data for ROCK inhibition by compound 15.

PAMPA-BBB assay Prediction of the brain penetration of compounds was evaluated using a parallel artificial membrane permeation assay (PAMPA) and porcine brain lipid (Avanti Polar Lipids) in a similar manner as our previously described[1].

Table S1 Permeability (Pe×10^{-6} cm s^{-1}) in the PAMPA-BBB assay for the selected compounds and their predicted penetration into the CNS.

Comp.	*Permeability* (*P_e*×10^{-6} cm s^{-1})	Prediction	Comp.	*Permeability* (*P_e*×10^{-6} cm s^{-1})	Prediction
1	3.69±0.05	CNS+/-	9	2.93±0.09	CNS+/-
2	12.3±0.83	CNS+	10	7.65±0.17	CNS+
3	NT[a]	-	11	NT[a]	-
4	7.71±1.31	CNS+	12	4.78±0.62	CNS+
5	9.15±0.65	CNS+	13	12.23±0.25	CNS+
6	12.87±0.98	CNS+	14	6.72±0.70	CNS+
7	8.78±0.79	CNS+	15	5.70±0.48	CNS+
8	13.26±0.33	CNS+	16	13.49±0.49	CNS+

[a]NT, not tested (insoluble in the buffer).

Table S2 Ranges of Permeability of PAMPA-BBB Assays (P_e, 10^{-6} cm s^{-1})[2]

Compounds of high BBB permeation (CNS+)	P_e >4.7
Compounds of uncertain BBB permeation (CNS+/-)	4.7> P_e >1.8
Compounds of low BBB permeation (CNS-)	P_e <1.8

Measurement of intracellular ROS HT22 cells were grown in Corning 96-well plates at a cell density 4 × 10^3 cells/well. After overnight attachment, cells were

pretreated with 15, LA or the vehicle control DMSO for 30 min and then incubated with / without 2 mM glutamate for 10 h. Cells were washed twice with phosphate-buffered saline (PBS) and then incubated with 10 μM non-fluorescent dye DHE in serum-free medium for 30 min at 37 ℃ in the dark. Cells were subsequently washed twice with PBS, photographed and analyzed by a high content system (ArrayScanVTI, Thermo Fisher). Values were expressed as a percentage of the fluorescence relative to the vehicle control.

Glutathione (GSH) assay kit Intracellular GSH concentration was tested by a GSH assay kit (48 T, Nanjing Jiancheng, China). By reacting with dithiobisnitrobenzoicacid, reduced GSH could form a yellow compound, which is quantifiable at 405 nm and reflect the content of the reduced GSH indirectly. In brief, after treatment, whole-cell lysate was prepared and tested according to manufacturer's instructions. All GSH values were normalized to per μg protein of each sample.

Rat aorta assay Male Sprague-Dawley (SD) rats (200 ± 20 g) were supplied by the Center of Experimental Animals, Sun Yat-sen University (Guangzhou, China, Certificate No.SCXK 20110029). The rats were housed in standard cages under controlled temperature conditions of 21 ℃ with free access to food and water until 12 h prior to experiments. The vasorelaxant effects were examined by a rat thoracic aorta assay. Briefly, animals were anesthetized with 0.1% sodium pentobarbital (50 mg/kg). The thoracic aorta was quickly isolated and cleaned of fat and adherent connective tissue. Aortic rings 2–3 mm in length were prepared and mounted horizontally in 5

mL organ bath containing the Krebs–Henseleit (K-H) solution at 37 ℃, bubbled with 95% O_2 and 5% CO_2. The ring was allowed to equilibrate for 30min under 2 g resting tension. Then, KCl (60 mM) was used to induce a similar sustained contraction of thoracic aorta rings with a peak tension in each group. Following, fasudil, compound 15 were cumulatively added into the organ bath in 15min intervals respectively. DMSO was also added into the bath as a control. The contractile responses were expressed as a percentage of the responses following and before the application of the testing compounds. Results are expressed as mean ± S.D. Statistical analysis was performed with repeated measures of the ANOVA. Differences were accepted as statistically significant at P values < 0.05.

Molecular docking In order to understand the interactions between 15 and ROCK2 in the active site in detail, a Molecular Operating Environment (MOE 2010) (Chemical Computing Group Inc, Montreal, Quebec, Canada) was used for molecular docking. 15 was constructed using the builder module and were energy minimized using Force Field MMFF94x and saved as MDB file. The crystal structure of ROCK2 with fasudil was downloaded from the protein data bank (PDB ID: 2F2U), water molecules were removed, and one of the chain was deleted as the ROCK2 is a dimer. The residual crystal structure was prepared using ligX with the the default parameters of MOE [gradient: 0.1, Force Field: MMFF94X]. Define 5Å radius around the bound inhibitor (fasudil) in the crystal structure as active site. The prepared ligand structure was flexibly docked into the ROCK2 binding site, triangle matcher as the placement methodology, LondonΔG as scoring methodology, Forcefield Refinement was

selected and dock calculations was run automatically. The obtained 30 conformations were generated and stored in database, the best conformation was analyzed for the binding interaction.

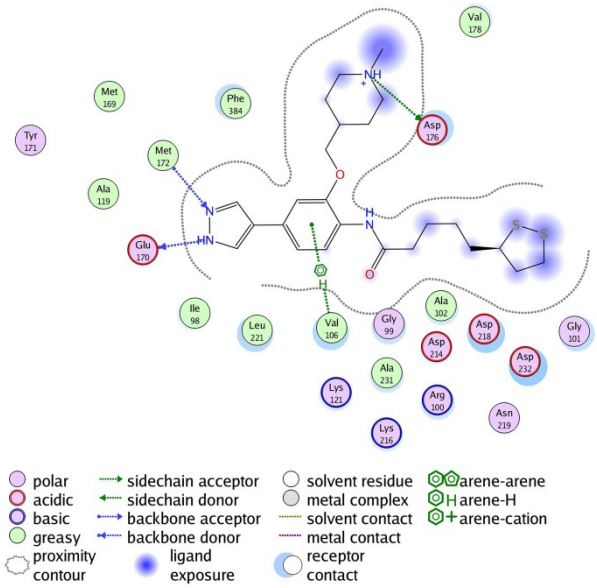


Fig. S2 2D representation of the binding mode of 1**5** in ROCK-II (2F2U).

Statistical analysis All quantitative data and experiments described in this study were repeated at least three times. Data were presented as mean ± S.D. of multiple independent experiments. Statistics were analyzed with one-way ANOVA followed by a least significant difference test (Graphpad Prism 5.0 software (US)). Statistical difference was considered at $P < 0.05$.

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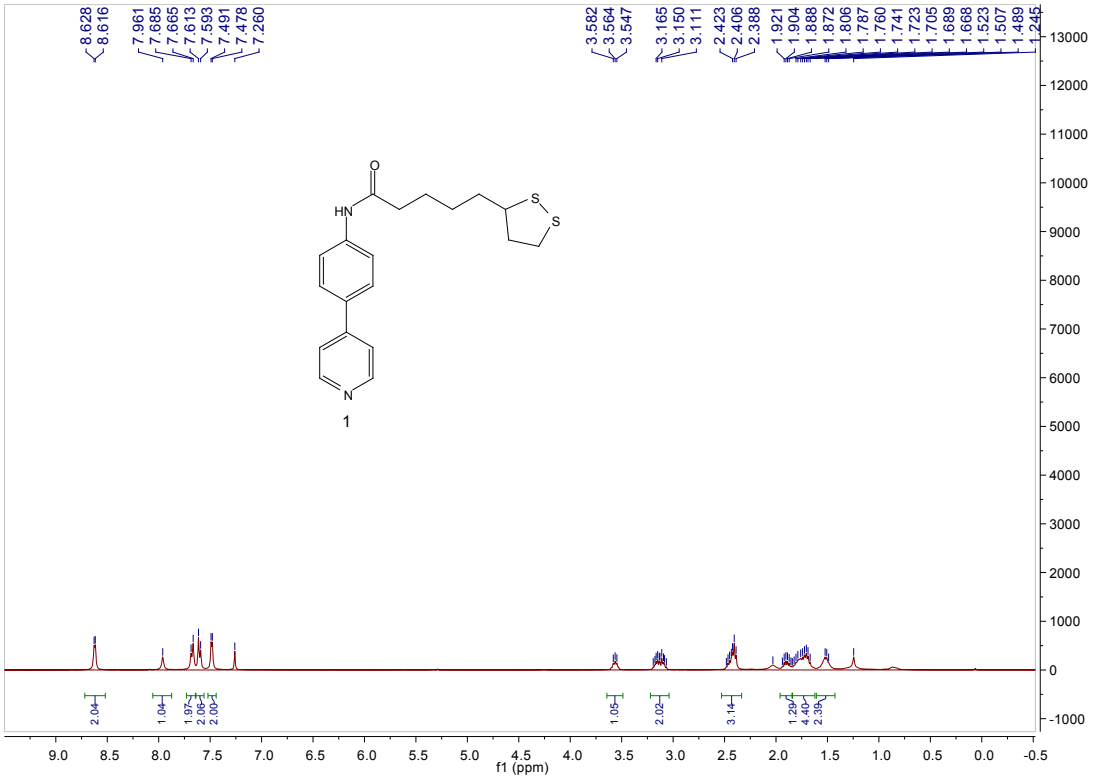
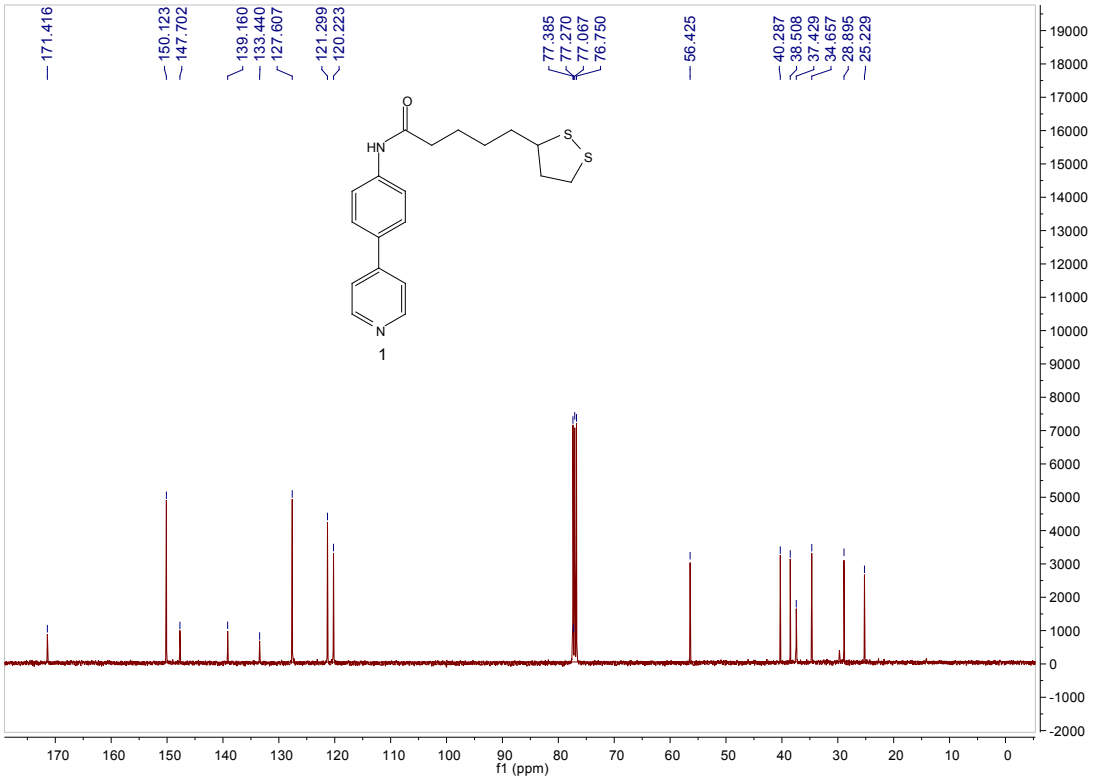
2. Z. Wang, Y. Wang, B. Wang, W. Li, L. Huang and X. Li, *Journal of medicinal chemistry*, 2015, **58**, 8616-8637.

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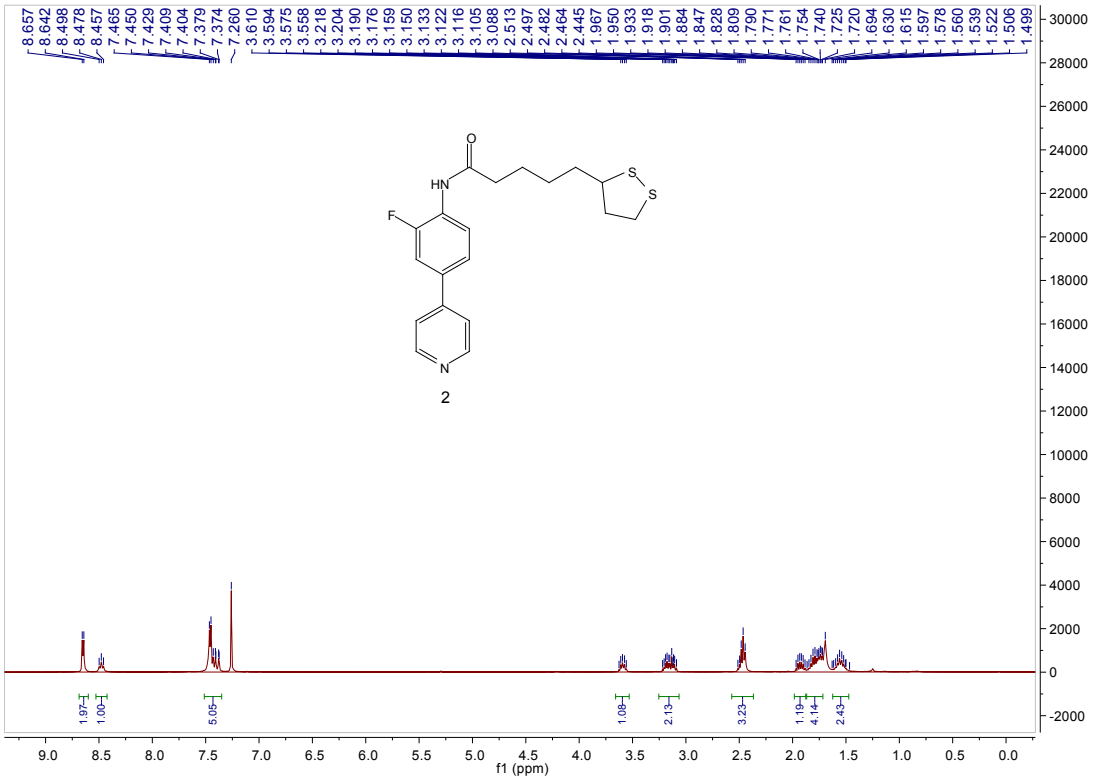
f1 (ppm)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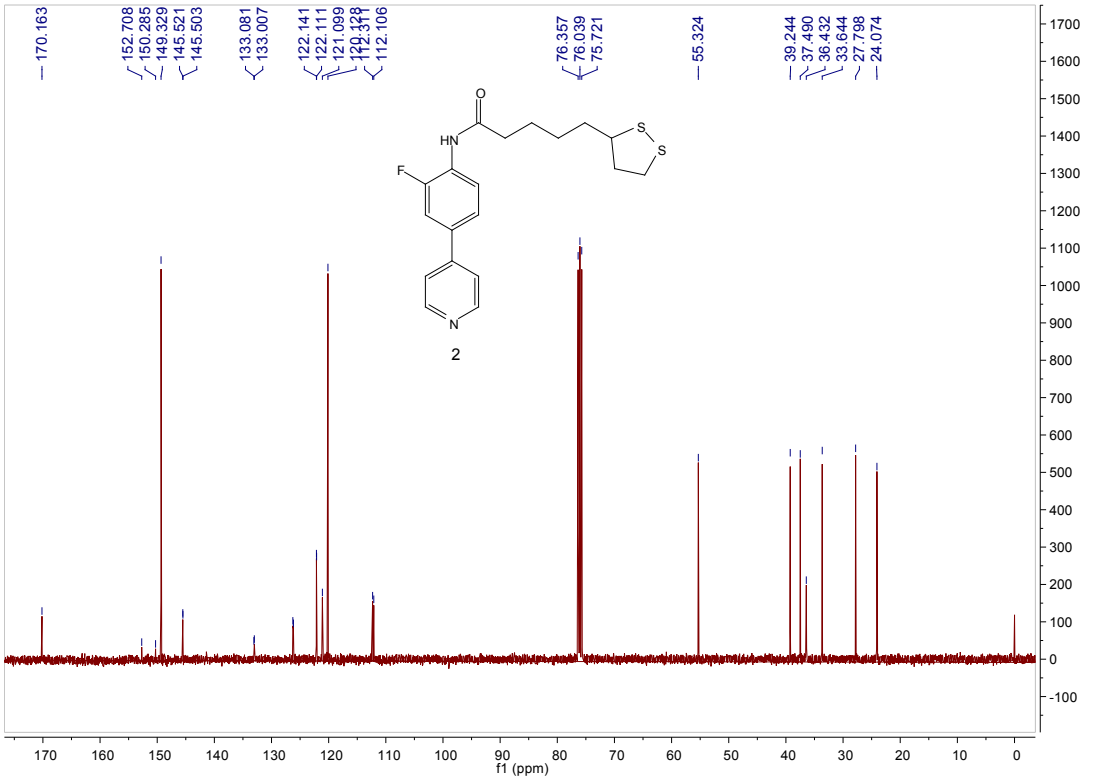
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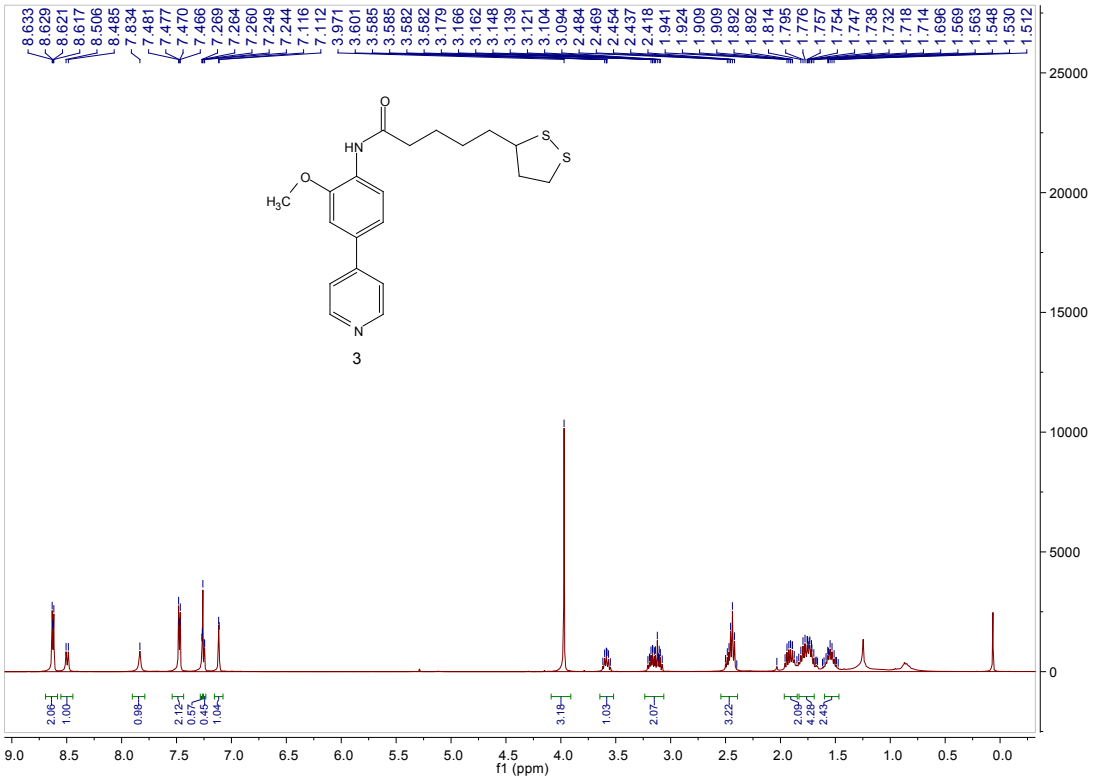
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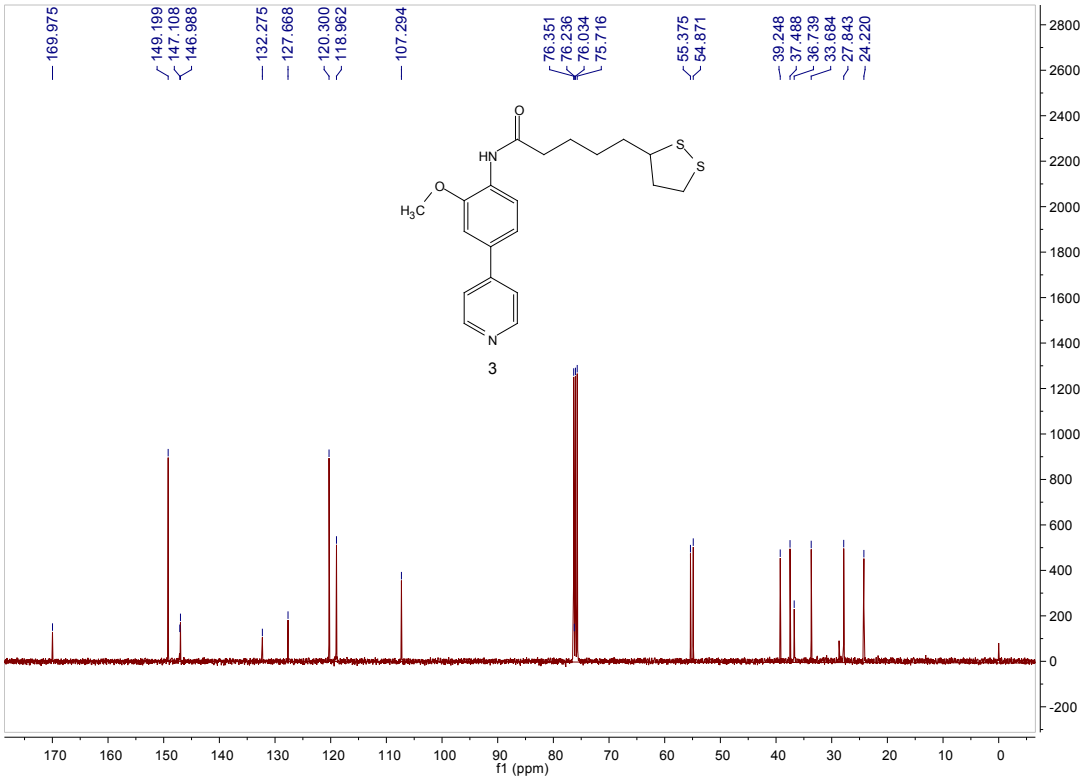
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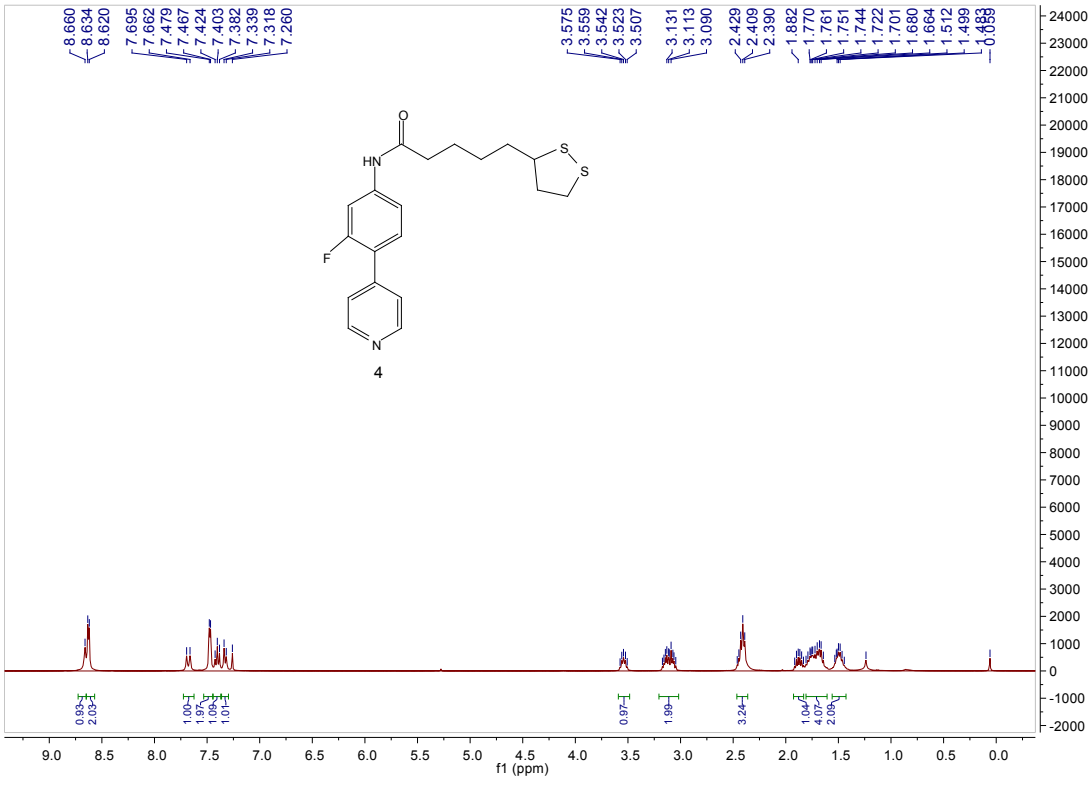
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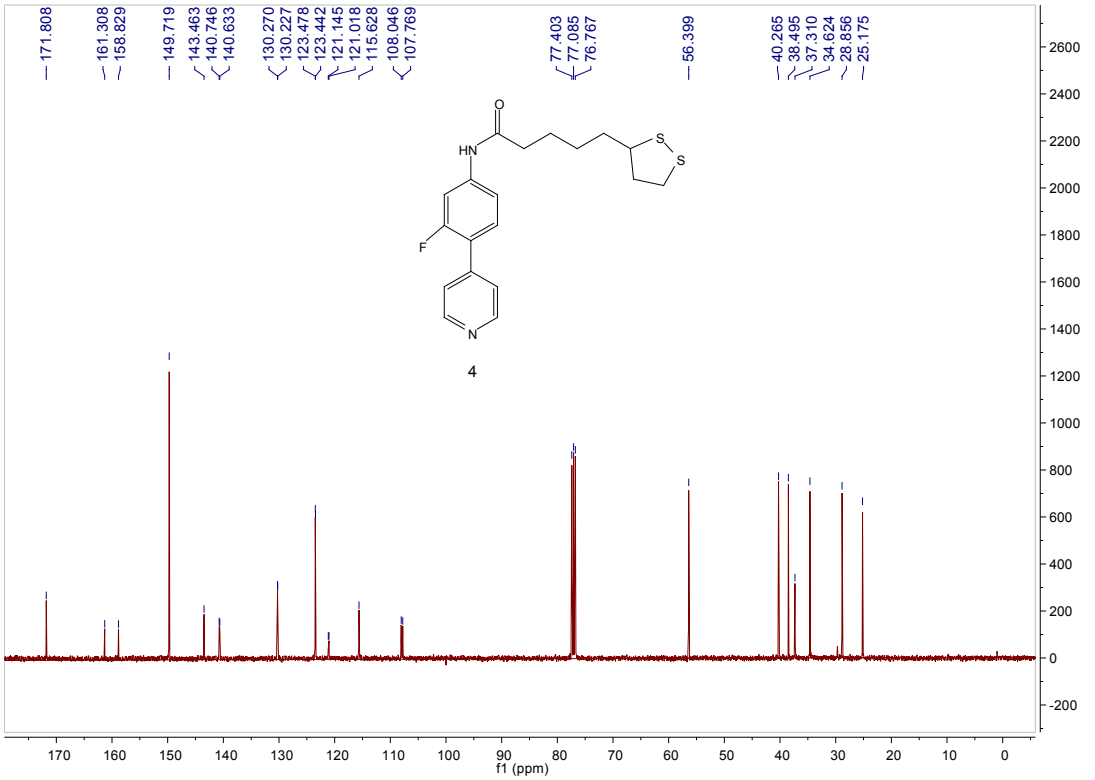
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HN
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S
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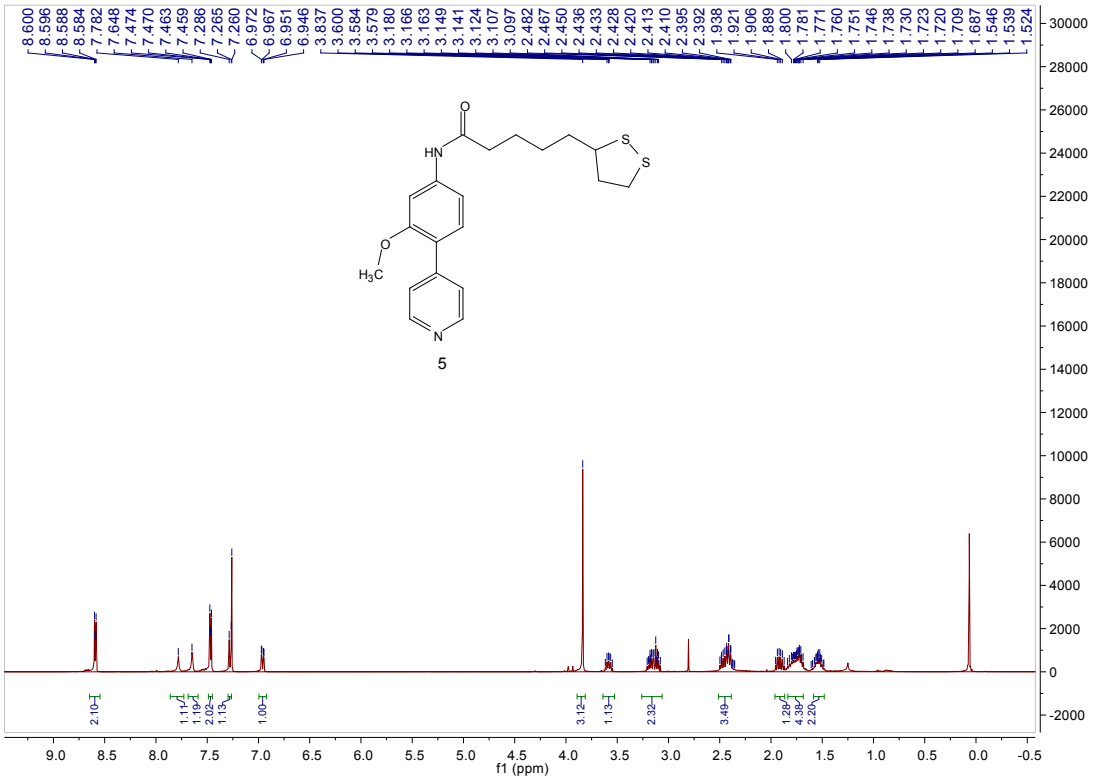
F
N
f1 (ppm)

4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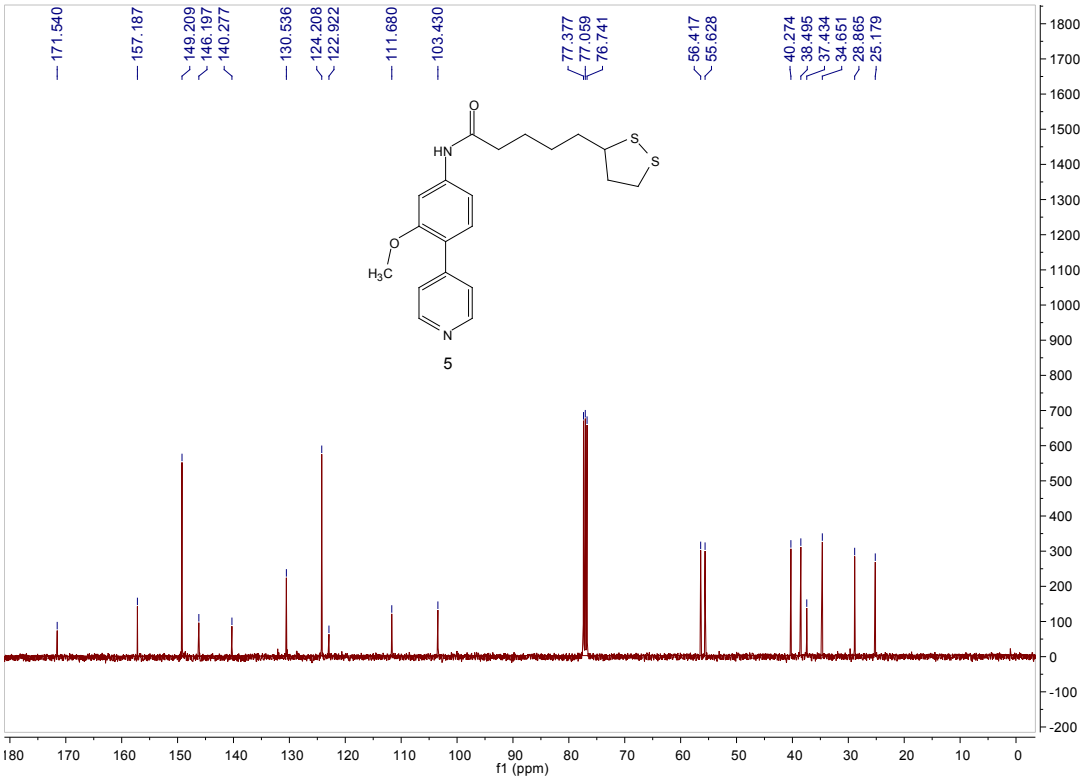
8.588
8.584
7.782
7.648
7.474
7.470
7.463
7.459
7.286
7.265
7.260
6.972
6.967
6.951
6.946
3.837
3.600
3.584
3.579
3.180
3.166
3.163
3.149
3.141
3.124
3.107
3.097
2.482
2.467
2.450
2.436
2.433
2.428
2.420
2.413
2.410
2.395
2.392
1.938
1.921
1.906
1.889
1.800
1.781
1.771
1.760
1.751
1.746
1.738
1.730
1.723
1.720
1.709
1.687
1.546
1.539
1.524
HN
O
S
S
O
H3C
N
f1 (ppm)

5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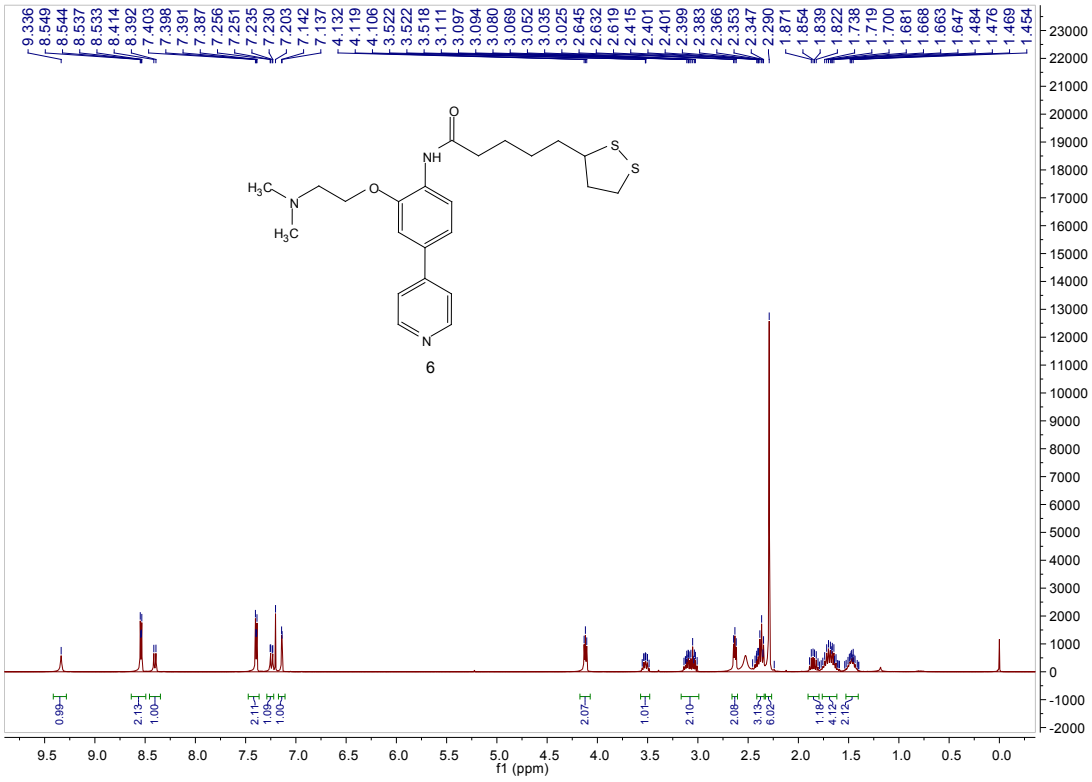
157.187
149.209
146.197
140.277
130.536
124.208
122.922
111.680
103.430
77.377
77.059
76.741
56.417
55.628
40.274
38.495
37.434
34.651
28.865
25.179
HN
O
S
S
O
H3C
N
f1 (ppm)

5


9.336
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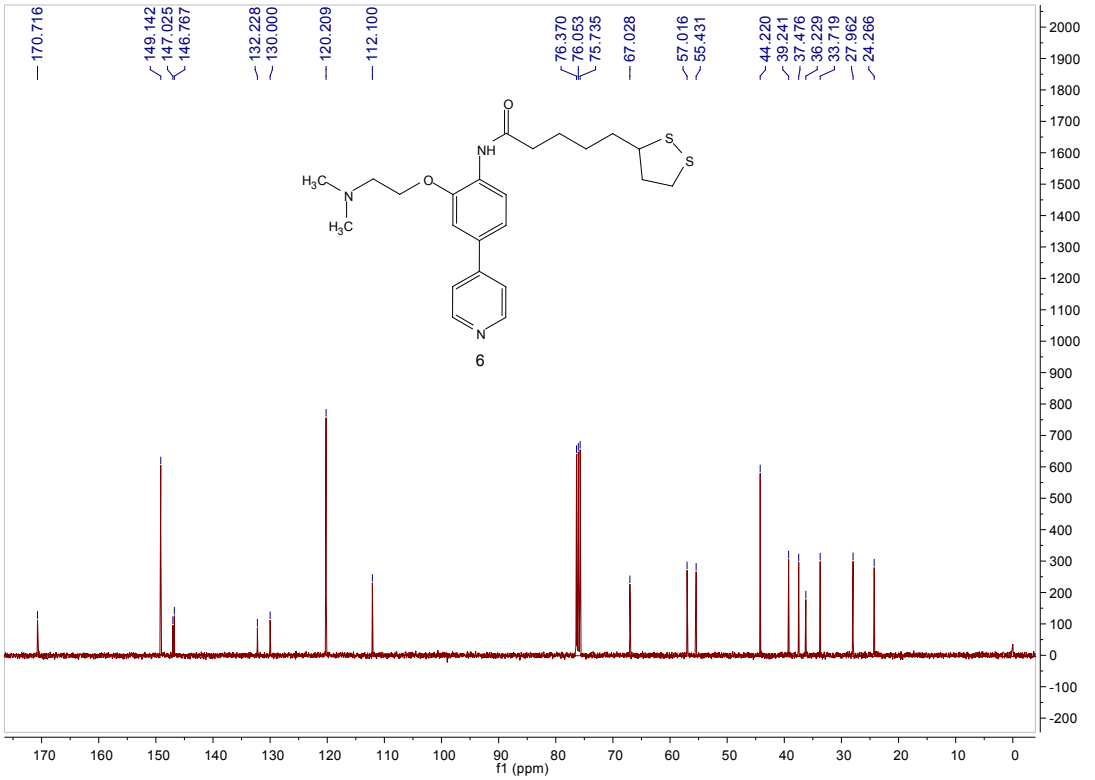
8.544
8.537
8.533
8.414
8.392
7.403
7.398
7.391
7.387
7.256
7.251
7.235
7.230
7.203
7.142
7.137
4.132
4.119
4.106
3.522
3.522
3.518
3.111
3.097
3.094
3.080
3.069
3.052
3.035
3.025
2.645
2.632
2.619
2.415
2.401
2.401
2.399
2.383
2.366
2.353
2.347
2.290
1.871
1.854
1.839
1.822
1.738
1.719
1.700
1.681
1.668
1.663
1.647
1.484
1.476
1.469
1.454
NH
O
S
S
H3C
N
H3C
O
N
0.99
2.13
1.00
2.11
1.08
1.00
2.07
1.01
2.10
2.08
3.13
6.02
1.19
4.12
2.12
f1 (ppm)

6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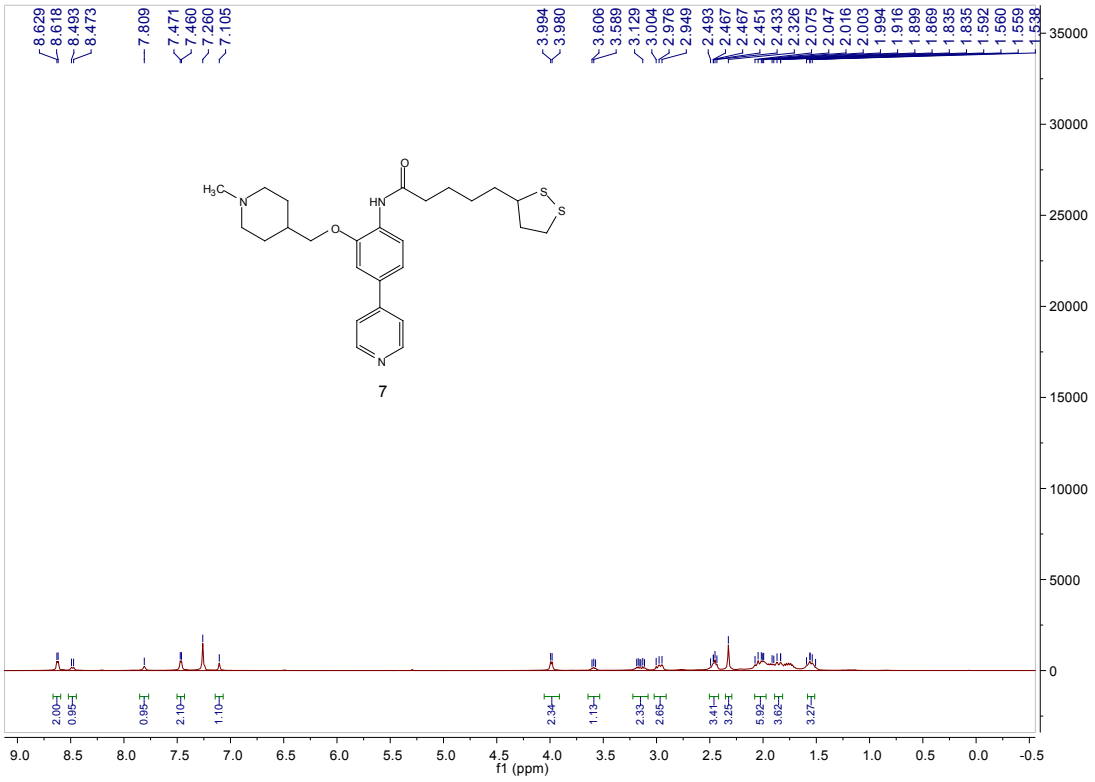
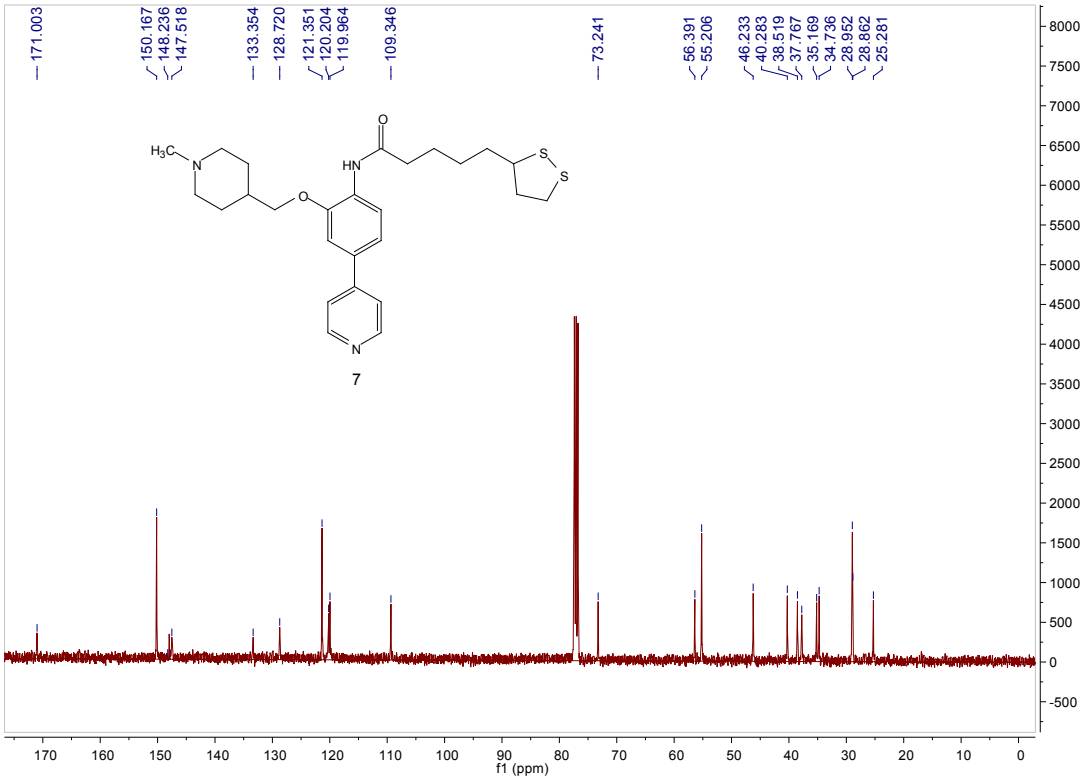
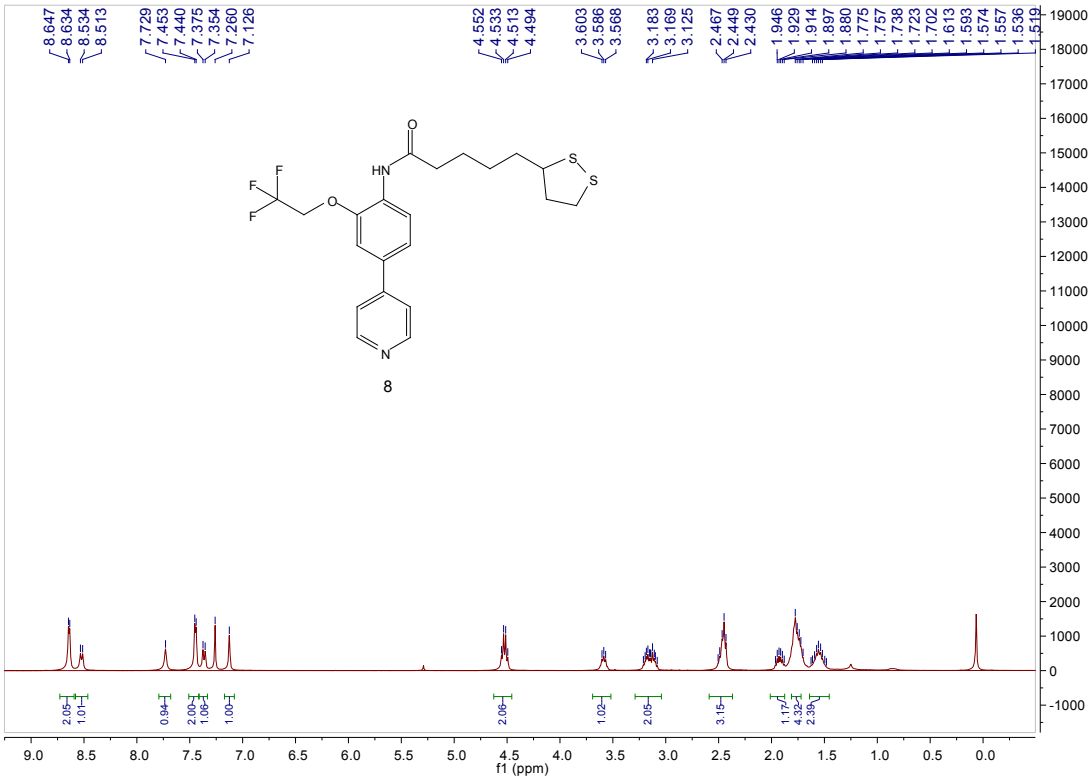
149.142
147.025
146.767
132.228
130.000
120.209
112.100
76.370
76.053
75.735
67.028
57.016
55.431
44.220
39.241
37.476
36.229
33.719
27.962
24.266
6
f1 (ppm)

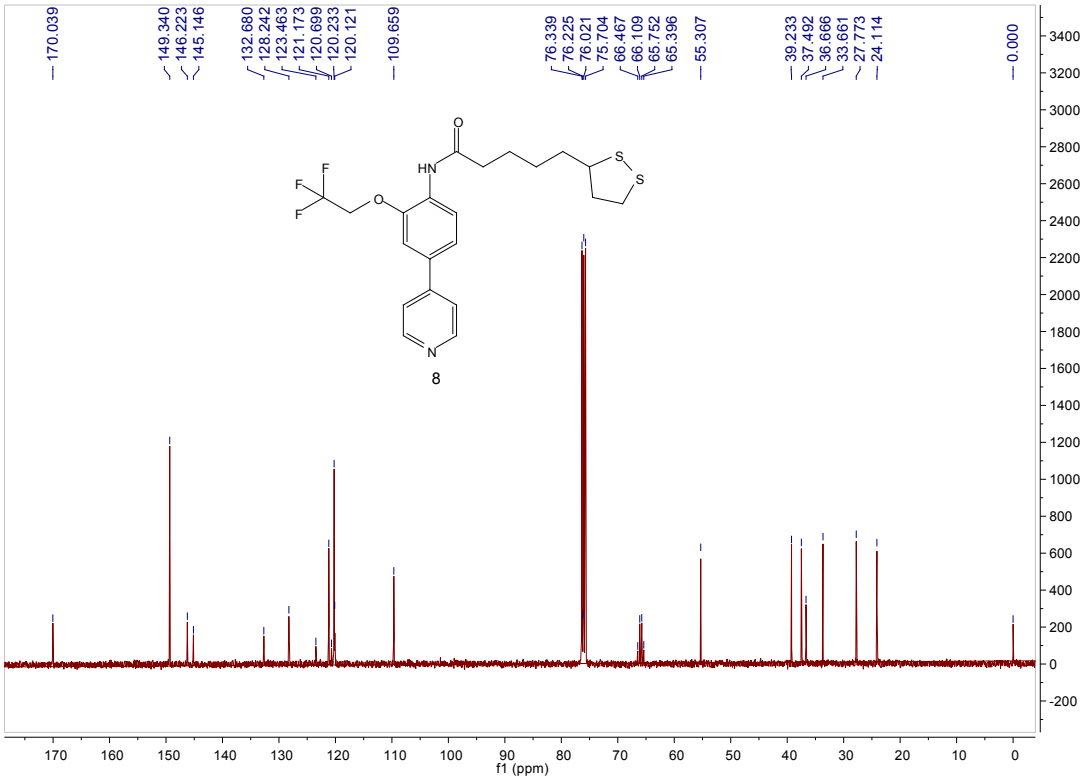

8.629
8.618
8.493
8.473
7.809
7.471
7.460
7.260
7.105
3.994
3.980
3.606
3.589
3.129
3.004
2.976
2.949
2.493
2.467
2.467
2.451
2.433
2.326
2.075
2.047
2.016
2.003
1.994
1.916
1.899
1.869
1.835
1.835
1.592
1.560
1.559
1.538
7
f1 (ppm)


171.003
150.167
148.236
147.518
133.354
128.720
121.351
120.204
119.964
109.346
73.241
56.391
55.206
46.233
40.283
38.519
37.767
35.169
34.736
28.952
28.862
25.281
f1 (ppm)

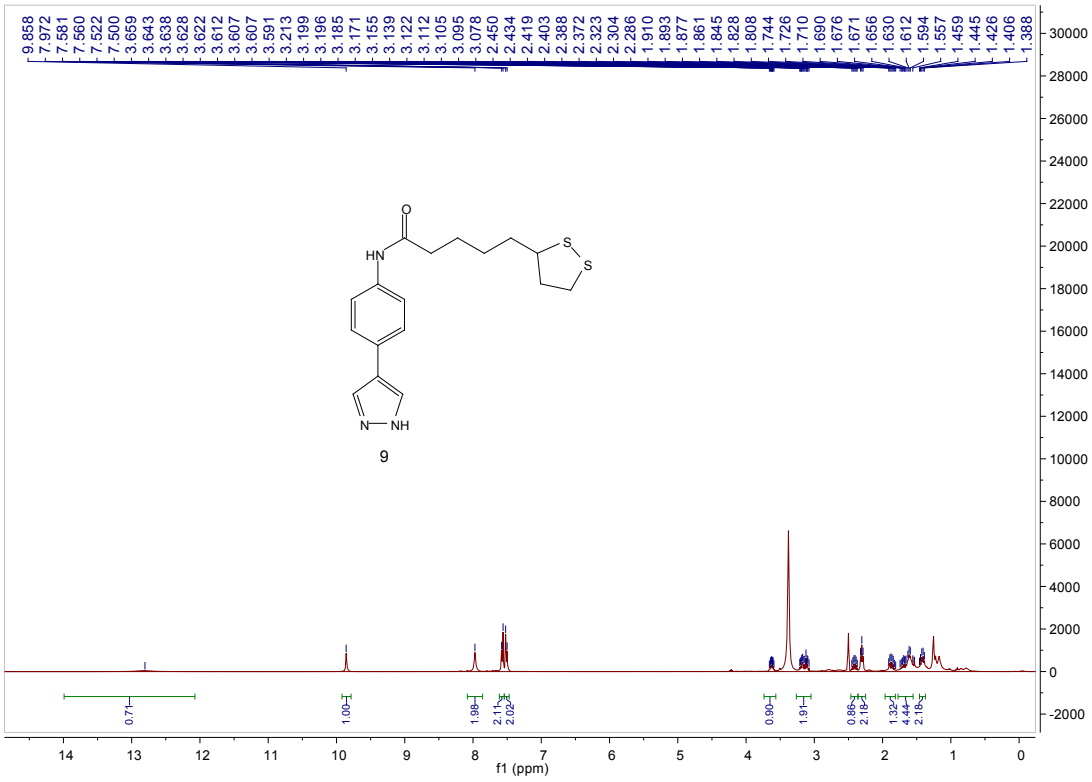
7


8.647
8.634
8.534
8.513
7.729
7.453
7.440
7.375
7.354
7.260
7.126
4.552
4.533
4.513
4.494
3.603
3.586
3.568
3.183
3.169
3.125
2.467
2.449
2.430
1.946
1.929
1.914
1.897
1.880
1.775
1.757
1.738
1.723
1.702
1.613
1.593
1.574
1.557
1.536
1.519
f1 (ppm)

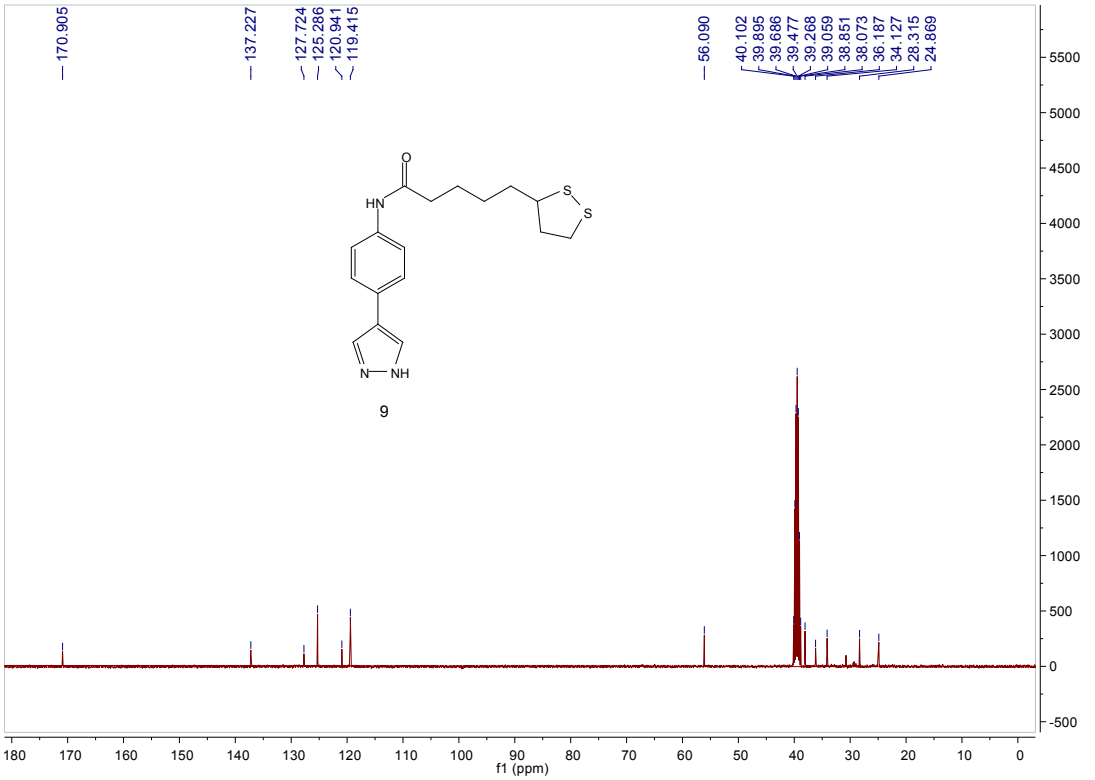
8


170.039
149.340
146.223
145.146
132.680
128.242
123.463
121.173
120.699
120.233
120.121
109.659
76.339
76.225
76.021
75.704
66.467
66.109
65.752
65.396
55.307
39.233
37.492
36.666
33.661
27.773
24.114
0.000
f1 (ppm)

8


9.858
7.972
7.581
7.560
7.522
7.500
3.659
3.643
3.638
3.628
3.622
3.612
3.607
3.607
3.591
3.213
3.199
3.196
3.185
3.171
3.155
3.139
3.122
3.112
3.105
3.095
3.078
2.450
2.434
2.419
2.403
2.388
2.372
2.323
2.304
2.286
1.910
1.893
1.877
1.861
1.845
1.828
1.808
1.744
1.726
1.710
1.690
1.676
1.671
1.656
1.630
1.612
1.594
1.557
1.459
1.445
1.426
1.406
1.388
0.71
1.00
1.98
2.11
2.02
0.90
1.91
0.86
2.18
1.32
4.44
2.18
f1 (ppm)

9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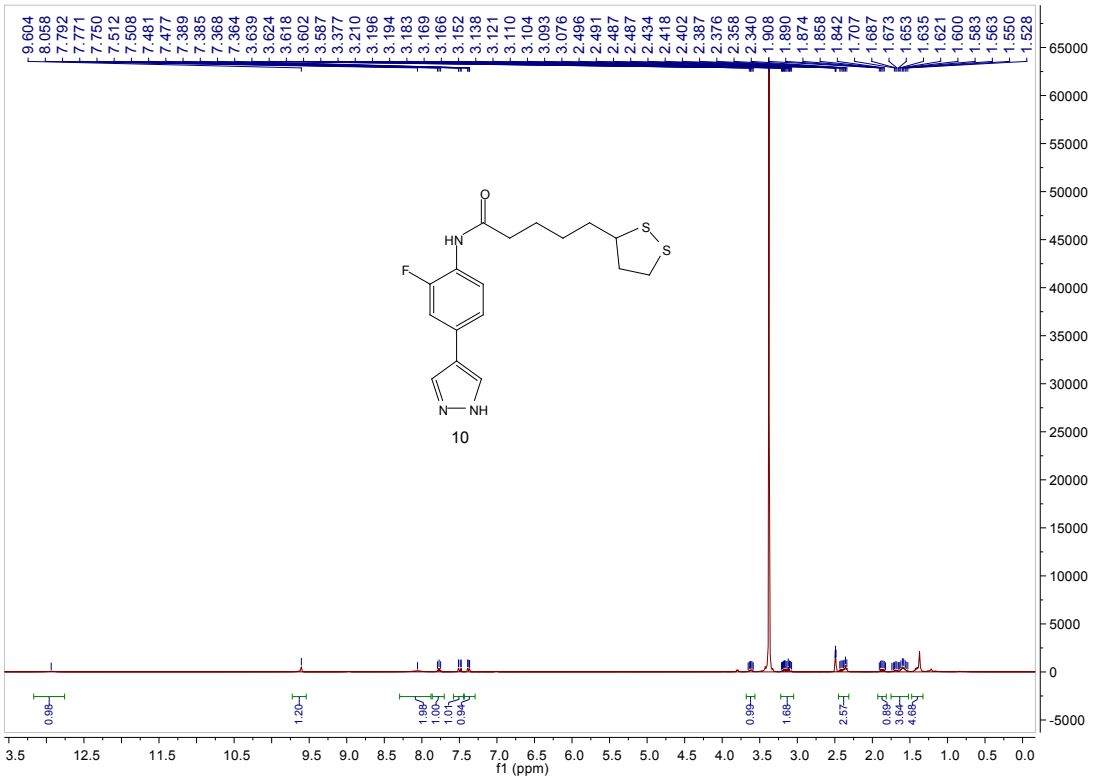
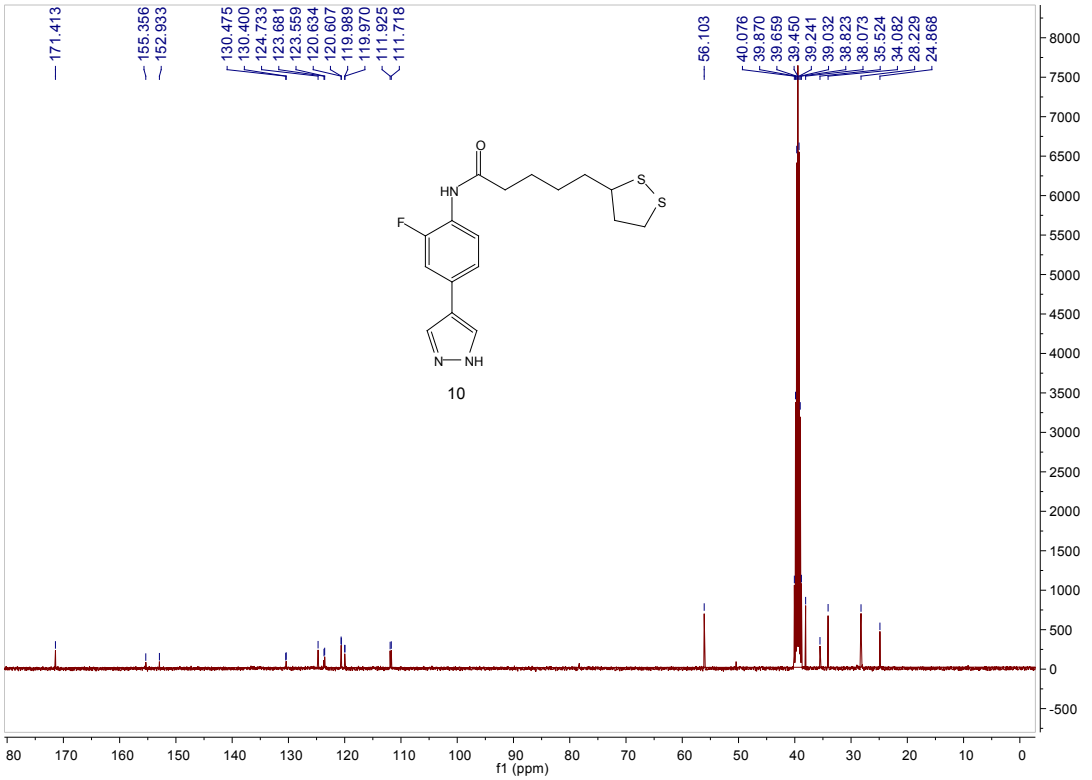
137.227
127.724
125.286
120.941
119.415
56.090
40.102
39.895
39.686
39.477
39.268
39.059
38.851
38.073
36.187
34.127
28.315
24.869
O
HN
S
S
N
NH
f1 (ppm)

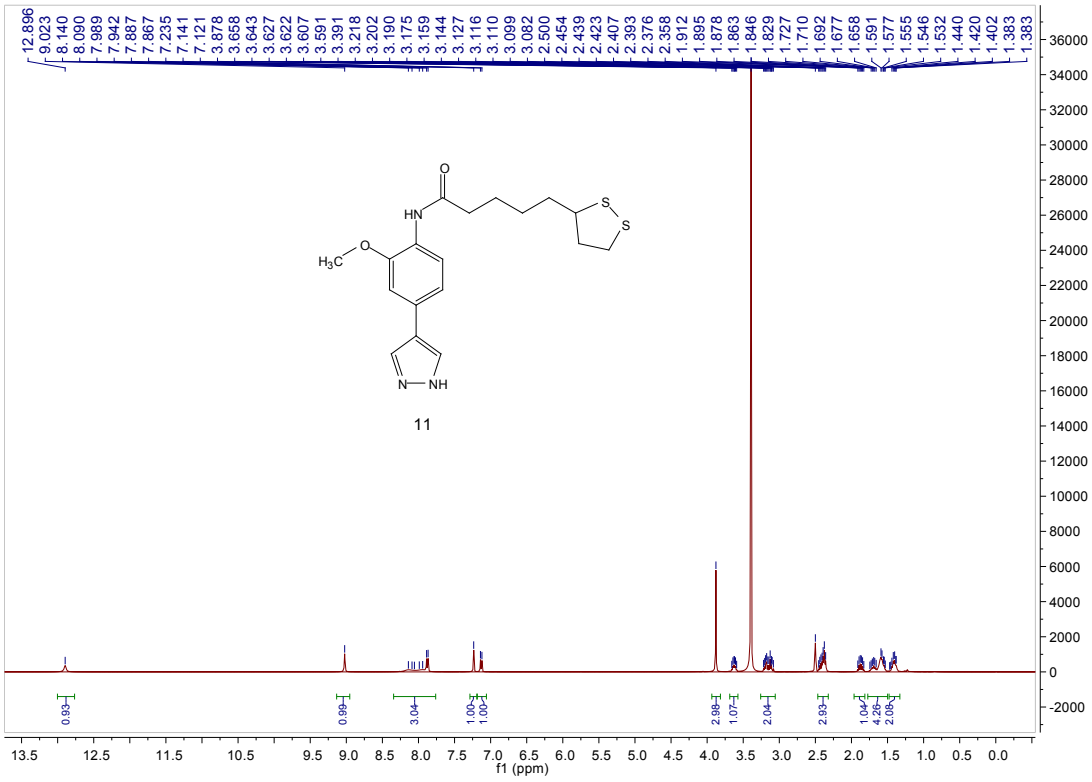
9


9.604
8.058
7.792
7.771
7.750
7.512
7.508
7.481
7.477
7.389
7.385
7.368
7.364
3.639
3.624
3.618
3.602
3.587
3.377
3.210
3.196
3.194
3.183
3.169
3.166
3.152
3.138
3.121
3.110
3.104
3.093
3.076
2.496
2.491
2.487
2.487
2.434
2.418
2.402
2.387
2.376
2.358
2.340
1.908
1.890
1.874
1.858
1.842
1.707
1.687
1.673
1.653
1.635
1.621
1.600
1.583
1.563
1.550
1.528
O
HN
F
S
S
N
NH
0.99
1.20
1.98
1.04
1.01
0.94
0.99
1.68
2.57
0.89
3.84
4.66
f1 (ppm)

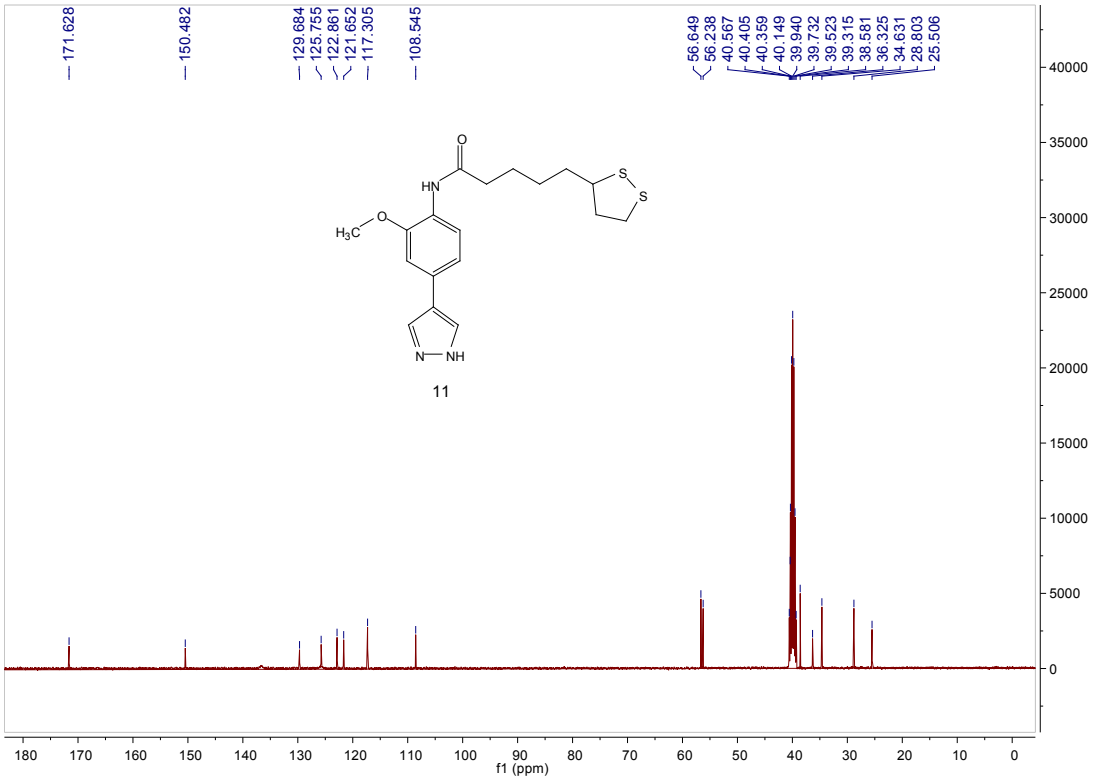
10

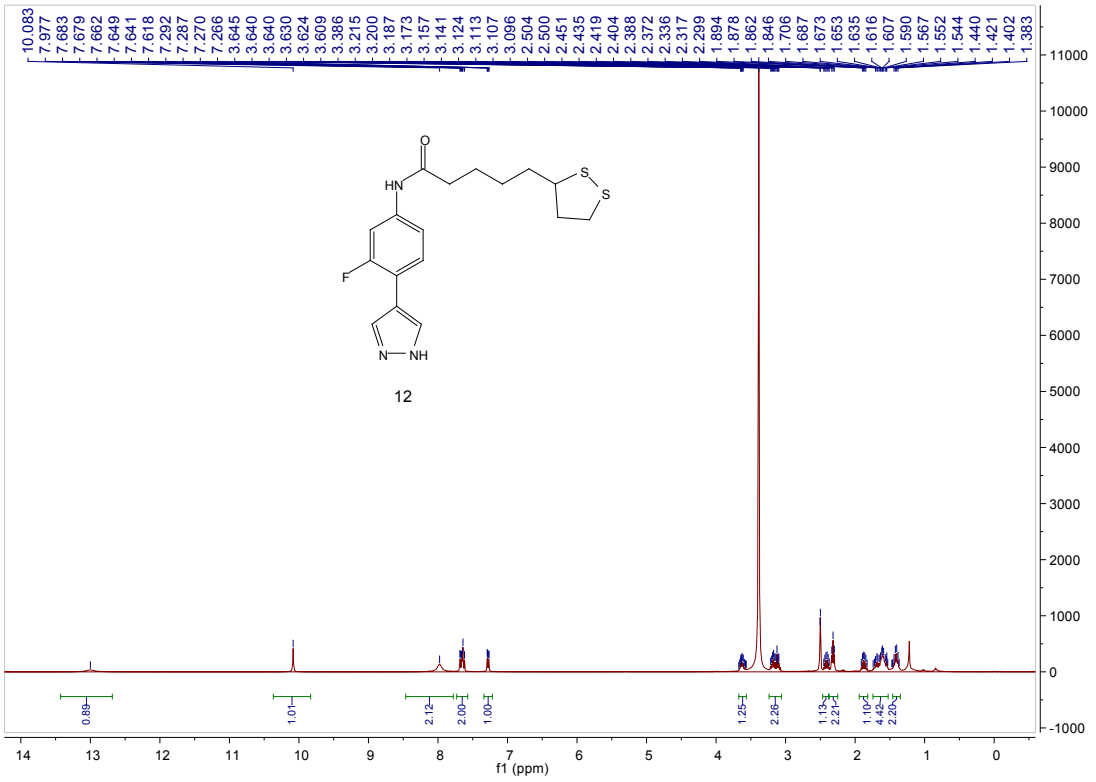

171.413
155.356
152.933
130.475
130.400
124.733
123.681
123.559
120.634
120.607
119.989
119.970
111.925
111.718
56.103
40.076
39.870
39.659
39.450
39.241
39.032
38.823
38.073
35.524
34.082
28.229
24.868
O
HN
S
S
F
N
NH
f1 (ppm)

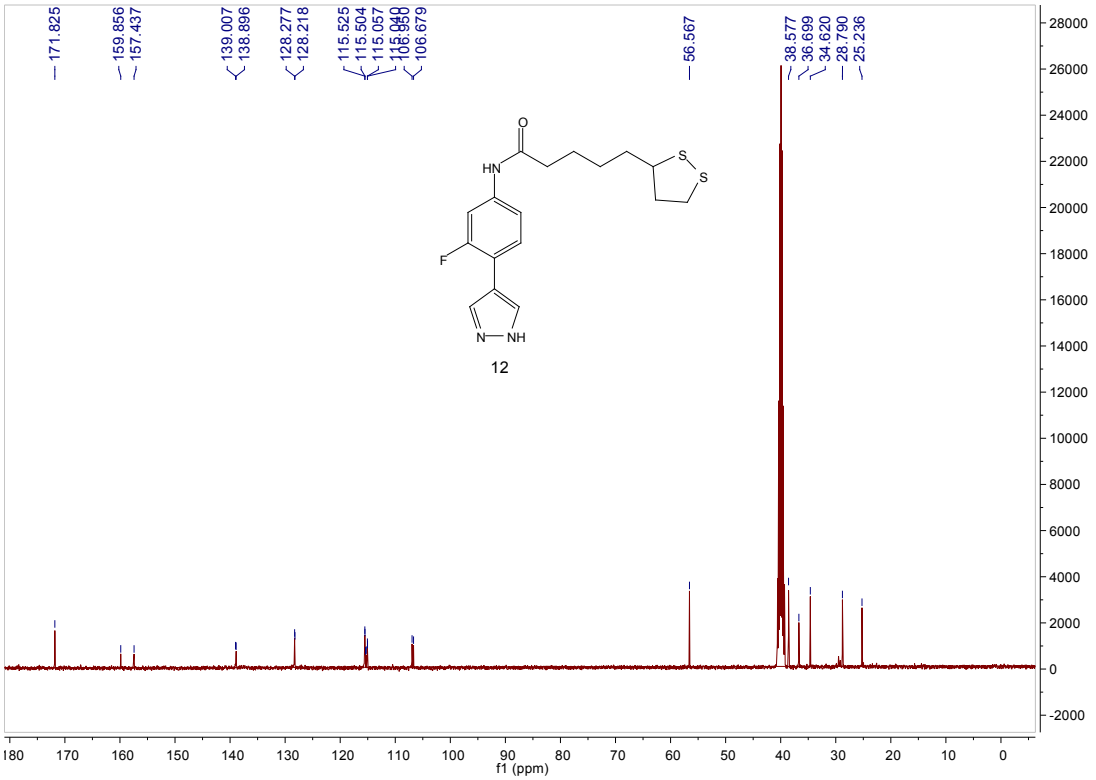
10

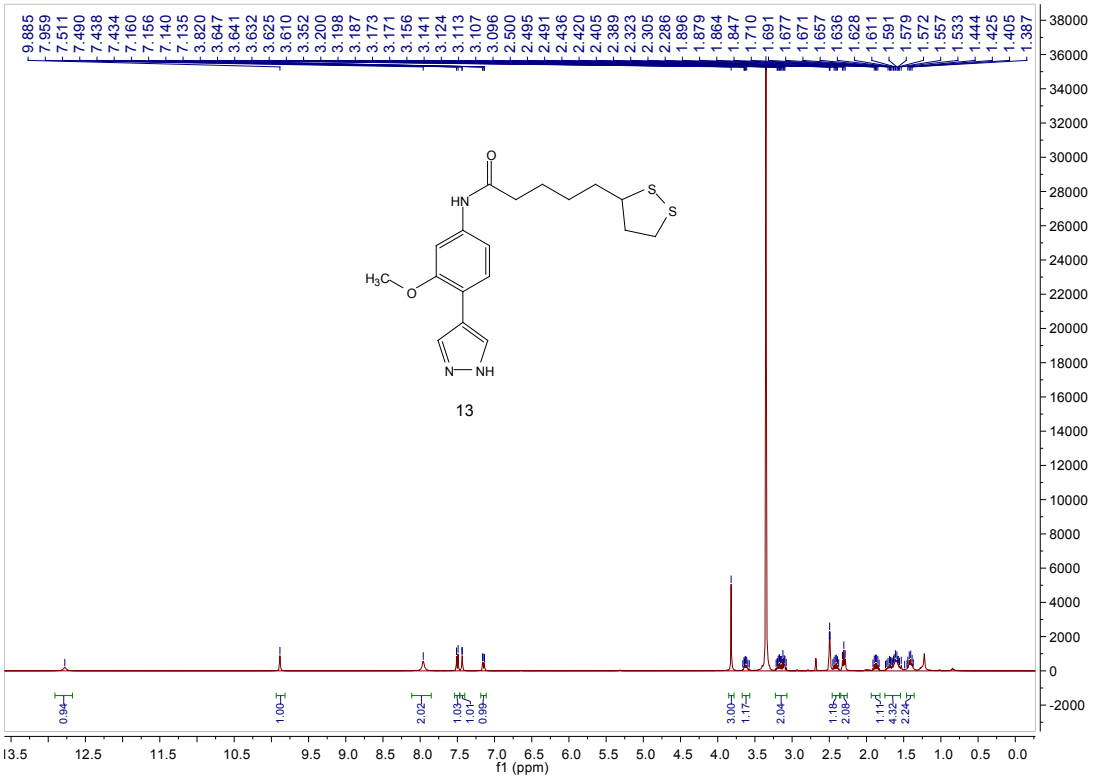

12.896
9.023
8.140
8.090
7.989
7.942
7.887
7.867
7.235
7.141
7.121
3.878
3.658
3.643
3.627
3.622
3.607
3.591
3.391
3.218
3.202
3.190
3.175
3.159
3.144
3.127
3.116
3.110
3.099
3.082
2.500
2.454
2.439
2.423
2.407
2.393
2.376
2.358
1.912
1.895
1.878
1.863
1.846
1.829
1.727
1.710
1.692
1.677
1.658
1.591
1.577
1.555
1.546
1.532
1.440
1.420
1.402
1.383
O
HN
S
S
H3C
O
N
NH
0.93
0.99
3.04
1.00
1.00
2.98
1.07
2.04
2.93
1.04
4.26
2.06
f1 (ppm)

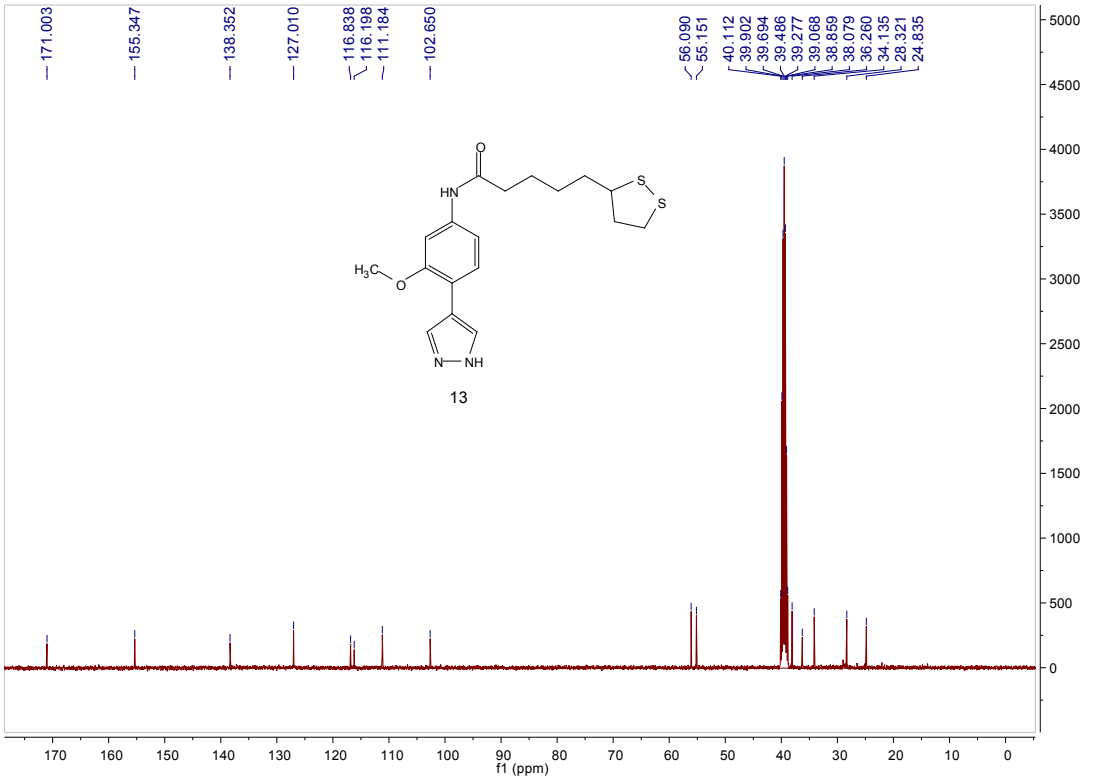
11


171.628
150.482
129.684
125.755
122.861
121.652
117.305
108.545
56.649
56.238
40.567
40.405
40.359
40.149
39.940
39.732
39.523
39.315
38.581
36.325
34.631
28.803
25.506
O
HN
S
S
H3C
O
N
NH
11
f1 (ppm)


10.083
7.977
7.683
7.679
7.662
7.649
7.641
7.618
7.292
7.287
7.270
7.266
3.645
3.640
3.640
3.630
3.624
3.609
3.386
3.215
3.200
3.187
3.173
3.157
3.141
3.124
3.113
3.107
3.096
2.504
2.500
2.451
2.435
2.419
2.404
2.388
2.372
2.336
2.317
2.299
1.894
1.878
1.862
1.846
1.706
1.687
1.673
1.653
1.635
1.616
1.607
1.590
1.567
1.552
1.544
1.440
1.421
1.402
1.383
O
HN
S
S
F
N
NH
12
0.89
1.01
2.12
2.00
1.00
1.25
2.26
1.13
2.21
1.10
4.42
2.20
f1 (ppm)


171.825
159.856
157.437
139.007
138.896
128.277
128.218
115.525
115.504
115.057
106.679
56.567
38.577
36.699
34.620
28.790
25.236
O
HN
S
S
F
N
NH
12
f1 (ppm)


9.885
7.959
7.511
7.490
7.438
7.434
7.160
7.156
7.140
7.135
3.820
3.647
3.641
3.632
3.625
3.610
3.352
3.200
3.198
3.187
3.173
3.171
3.156
3.141
3.124
3.113
3.107
3.096
2.500
2.495
2.491
2.436
2.420
2.405
2.389
2.323
2.305
2.286
1.896
1.879
1.864
1.847
1.710
1.691
1.677
1.671
1.657
1.636
1.628
1.611
1.591
1.579
1.572
1.557
1.533
1.444
1.425
1.405
1.387
O
HN
S
S
H3C
O
N
NH
13
0.94
1.00
2.02
1.03
1.01
0.99
3.00
1.17
2.04
1.18
2.08
1.11
4.32
2.24
f1 (ppm)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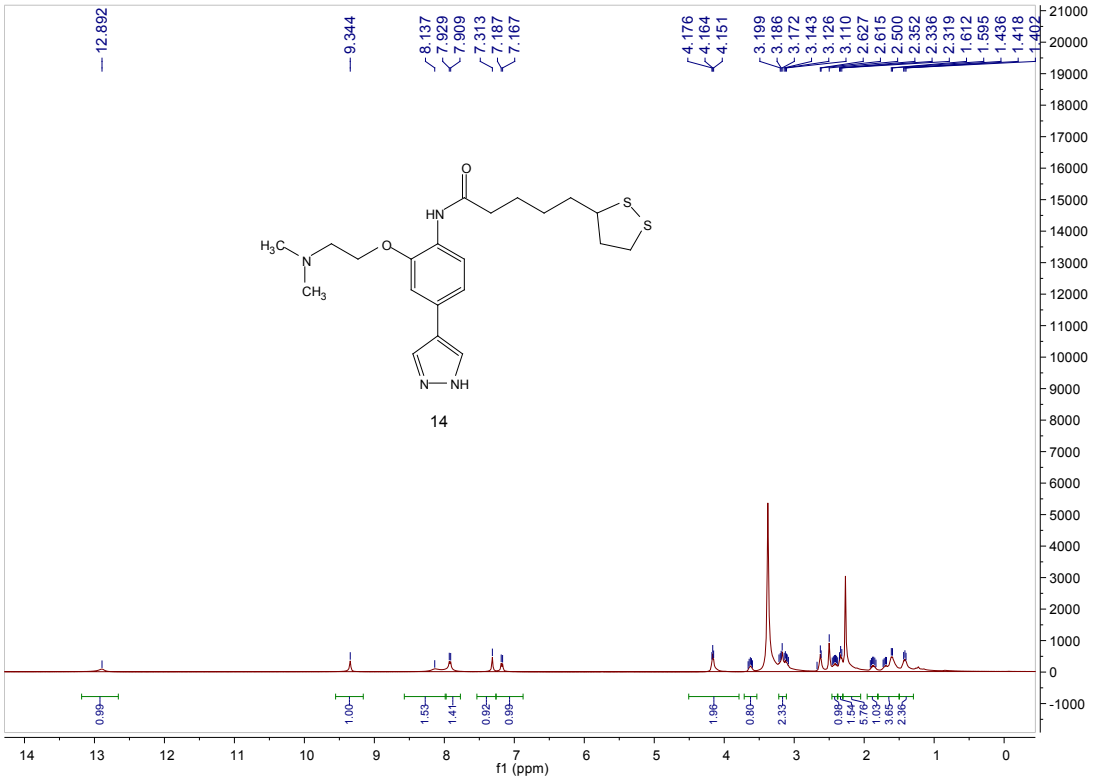
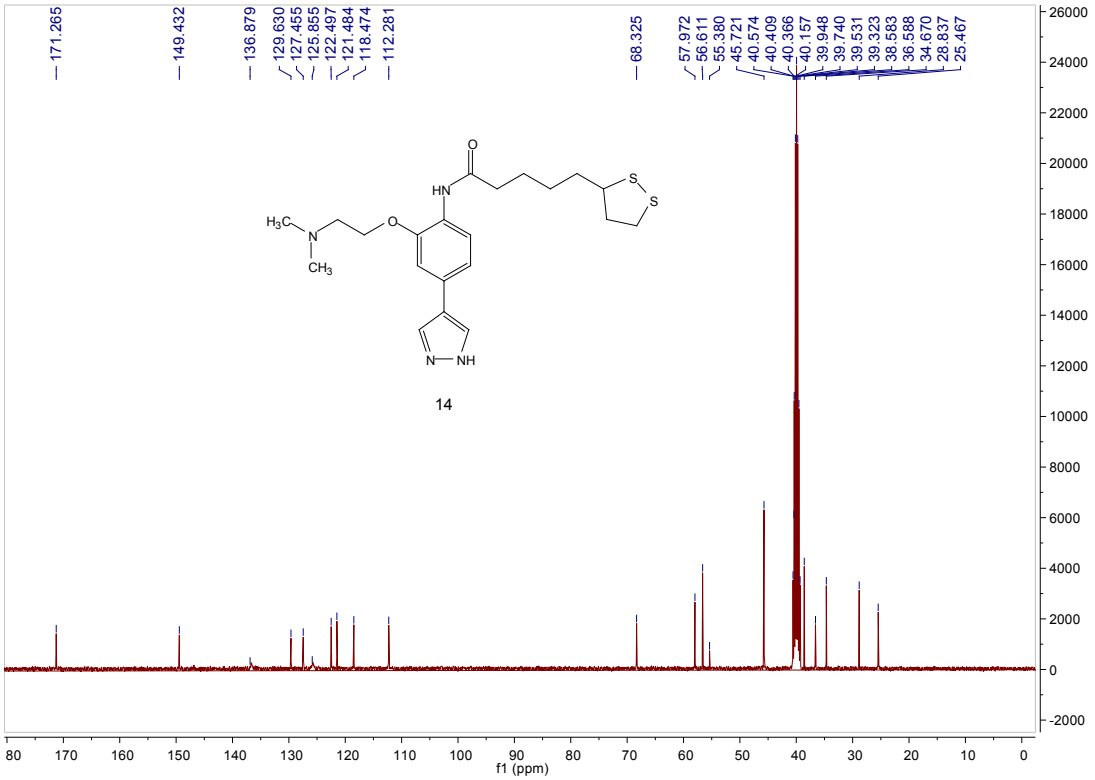
155.347
138.352
127.010
116.838
116.198
111.184
102.650
56.090
55.151
40.112
39.902
39.694
39.486
39.277
39.068
38.859
38.079
36.260
34.135
28.321
24.835
HN
O
S
S
H3C
O
N
NH
f1 (ppm)

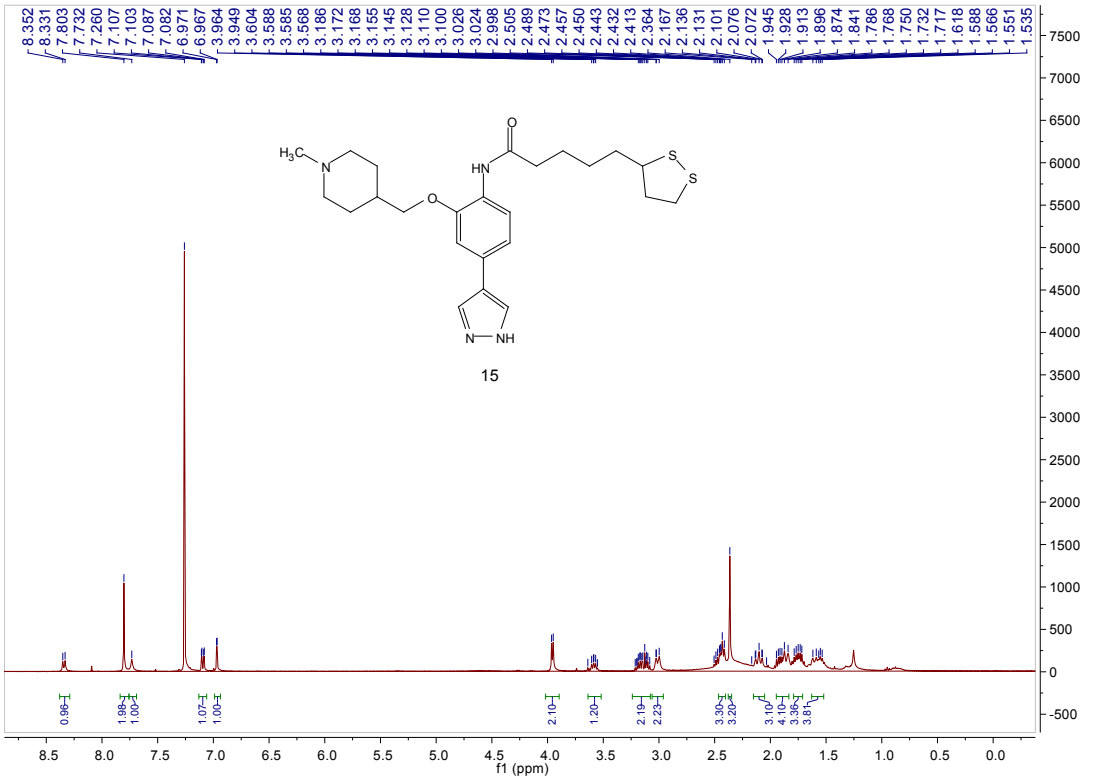
13


12.892
9.344
8.137
7.929
7.909
7.313
7.187
7.167
4.176
4.164
4.151
3.199
3.186
3.172
3.143
3.126
3.110
2.627
2.615
2.500
2.352
2.336
2.319
1.612
1.595
1.436
1.418
1.402
HN
O
S
S
H3C
N
CH3
O
N
NH
0.99
1.00
1.53
1.41
0.92
0.99
1.96
0.80
2.33
0.98
1.54
5.70
1.03
3.65
2.36
f1 (ppm)

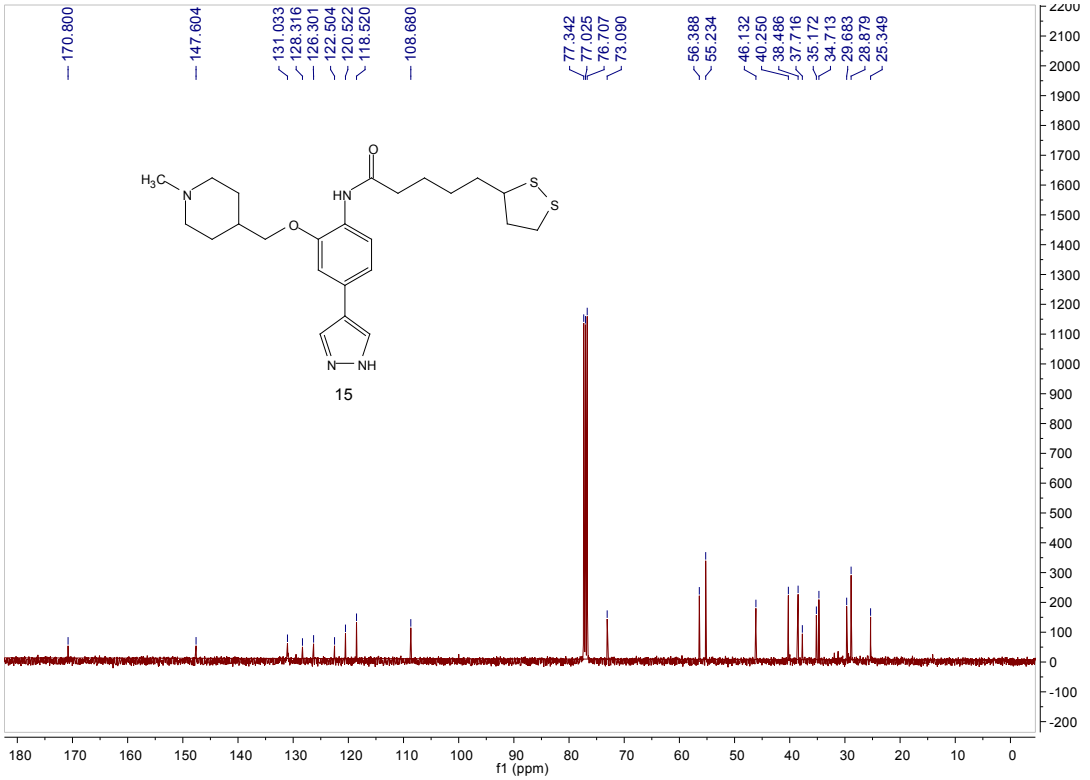
14

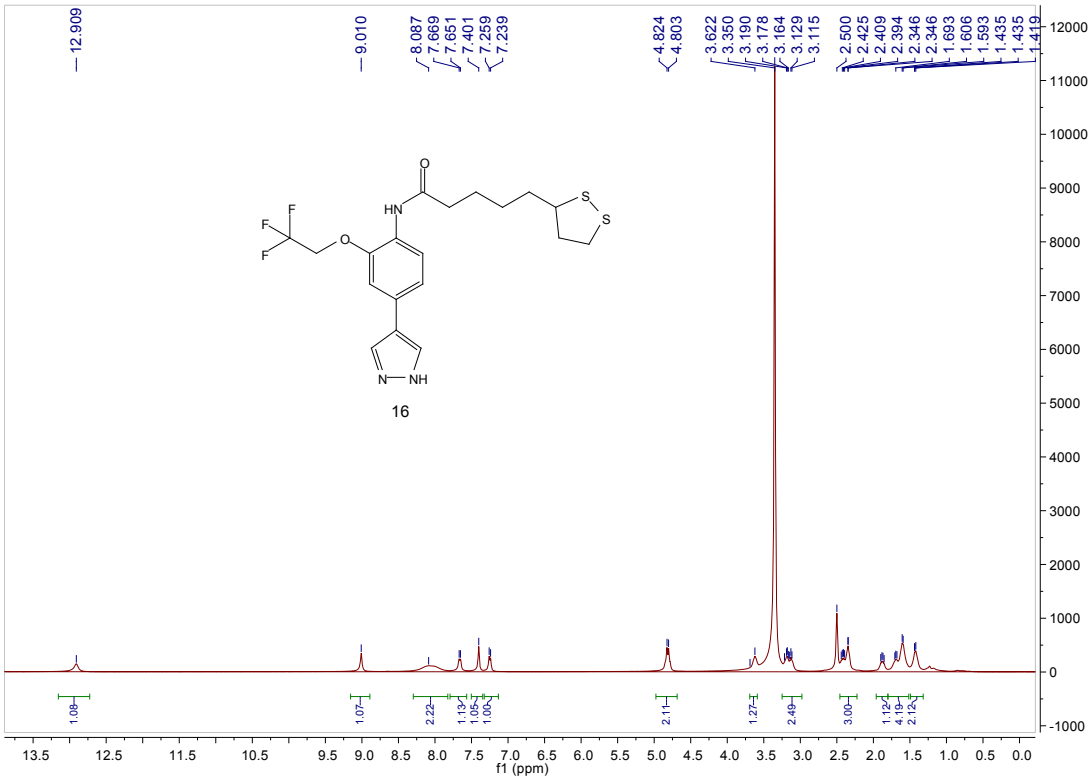

171.265
149.432
136.879
129.630
127.455
125.855
122.497
121.484
118.474
112.281
68.325
57.972
56.611
55.380
45.721
40.574
40.409
40.366
40.157
39.948
39.740
39.531
39.323
38.583
36.588
34.670
28.837
25.467
f1 (ppm)

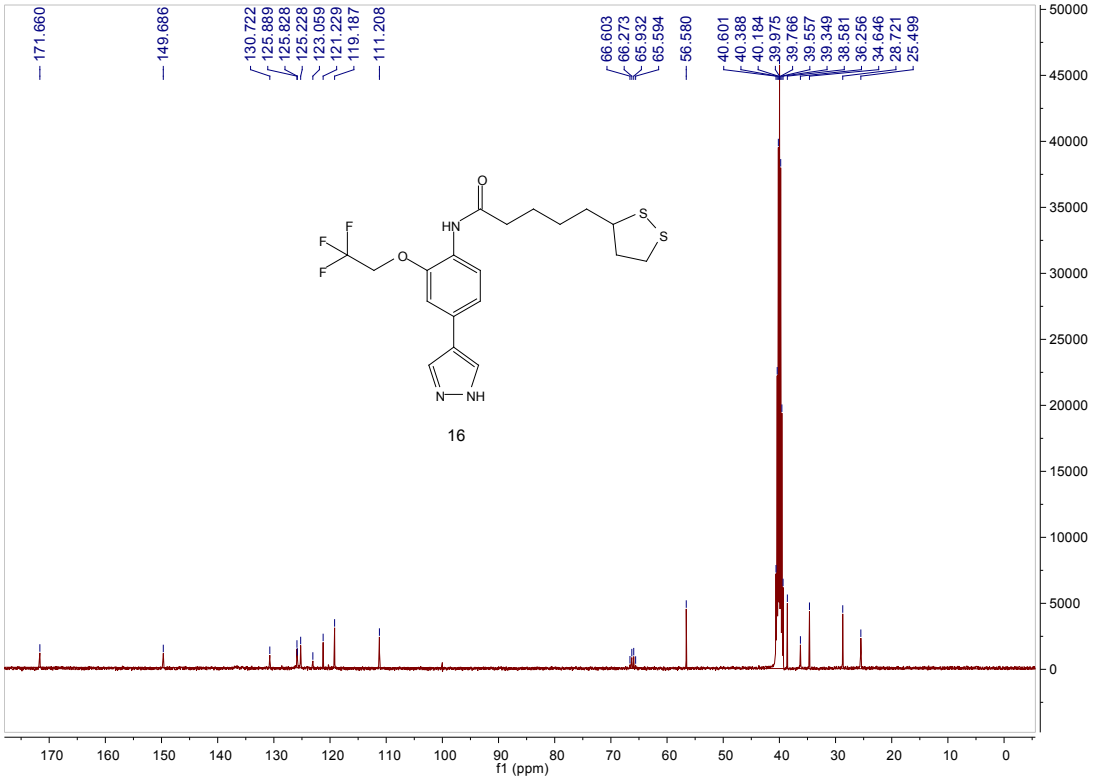
14


8.352
8.331
7.803
7.732
7.260
7.107
7.103
7.087
7.082
6.971
6.967
3.964
3.949
3.604
3.588
3.585
3.568
3.186
3.172
3.168
3.155
3.145
3.128
3.110
3.100
3.026
3.024
2.998
2.505
2.489
2.473
2.457
2.450
2.443
2.432
2.413
2.364
2.167
2.136
2.131
2.101
2.076
2.072
1.945
1.928
1.913
1.896
1.874
1.841
1.786
1.768
1.750
1.732
1.717
1.618
1.588
1.566
1.551
1.535
0.96
1.98
1.00
1.07
1.00
2.10
1.20
2.19
2.23
3.30
3.20
3.10
4.10
3.36
3.81
f1 (ppm)

15


170.800
147.604
131.033
128.316
126.301
122.504
120.522
118.520
108.680
77.342
77.025
76.707
73.090
56.388
55.234
46.132
40.250
38.486
37.716
35.172
34.713
29.683
28.879
25.349
15
f1 (ppm)


12.909
9.010
8.087
7.669
7.651
7.401
7.259
7.239
4.824
4.803
3.622
3.350
3.190
3.178
3.164
3.129
3.115
2.500
2.425
2.409
2.394
2.346
2.346
1.693
1.606
1.593
1.435
1.435
1.419
16
f1 (ppm)


171.660
149.686
130.722
125.889
125.828
125.228
123.059
121.229
119.187
111.208
66.603
66.273
65.932
65.594
56.580
40.601
40.388
40.184
39.975
39.766
39.557
39.349
38.581
36.256
34.646
28.721
25.499
O
HN
S
S
F
F
F
O
N
NH
16
f1 (ppm)