Supporting Information

Synthesis of 2-amino-9*H*-chromeno[2,3-*d*]thiazol-9-ones with Anti-inflammatory Activity *via* Cascade Reactions of 2-amino-3 iodochromones with Amines and Carbon Disulfide

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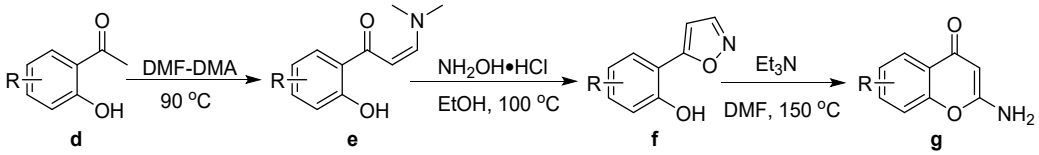
1. General information

Unless otherwise noted, all solvents and other reagents were commercially available and used without further purification. All reagents were weighed and handled under air at room temperature. The all commercial reagents were purchased from TCI, Sigma-Aldrich, Adamas-beta chemistry and Energy Chemical of the highest purity grade. Thin layer chromatography (TLC) employed glass 0.15-0.2 mm silica gel plates. NMR spectra were recorded on a Varian-MERCURY Plus-400 NMR spectrometer, a Brucker AVANCE III 500 NMR spectrometer, or a Brucker AVANCE III 600 NMR spectrometer and mass spectra (HRMS) were recorded on Micromass Ultra Q-TOF (ESI). The peaks were internally referenced to TMS (0.00 ppm) or residual undeuterated solvent signal.

1.1 General procedure for the synthesis of 2-amino-3-iodo-4*H*-chromen-4-ones (GP1)

1.1.1 General procedure for the synthesis of 2-amino-4*H*-chromen-4-ones (GP1.1)



Step 1

To a 50 mL round-bottom flask was added the 1-(2-hydroxyphenyl)ethan-1-ones (**d**, 10 mmol) and *N*, *N*-dimethylformamide dimethyl acetal (20 mL) in sequence. The mixture was then heated to 90 ℃ with stirring for 2 h. Cool the reaction to room temperature after the reation was complete detected by TLC. The solvent was removed in vacuo to obtain the crude intermediates 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-ones (**e**). The product **e** was used for the next step without further purification.

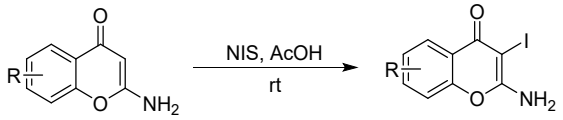
Step 2

To a 50 mL round-bottom flask was added the intermediate **e** obtained from step 1, hydroxylamine hydrochloride (12 mmol), and anhydrous ethanol (20 mL) in sequence. The mixture was then heated to 90 ℃ with stirring for 1 h. Cool the reaction to room temperature after the reaction was complete detected by TLC. The solvent was removed in vacuo, and the solid was washed with water repeatedly. The residue was then dried under vacuum to give the crude intermediates 2-(isoxazol-5-yl)phenols **f.**

Step 3

To a 50 mL round-bottom flask was added the intermediate **f** (10 mmol), *N, N*-dimethylformamide (20 mL), and triethylamine (20 mmol) in sequence. The mixture was then heated to 150 ℃ with stirring for 6 to 12 h. Until the reaction was complete detected by TLC, cool the reaction to room temperature. The solvent was then concentrated in vacuum, and the solid was washed with water to obtain the crude 2-amino-4*H*-chromen-4-ones **g**. The crude products were recrystallized with methanol to obtain pure intermediates **g**.

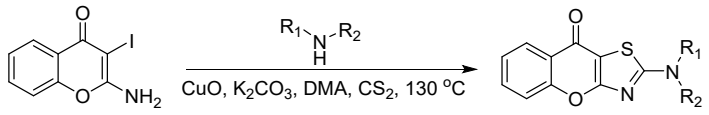
1.1.2 General procedure for the synthesis of 2-amino-3-iodo-4*H*-chromen-4-ones (GP1.2)



g **a**

To a 50 mL round-bottom flask was added the 2-amino-4*H*-chromen-4-ones **g** (6 mmol), NIS (7.2 mmol), and acetic acid (20 mL) successively. The mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous sodium carbonate (50 mL) and saturated aqueous sodium thiosulfate (50 mL) after the reaction was complete detected by TLC. Extracted the aqueous layer with ethyl acetate (50 mL × 3), and combined the organic phase. The mixture was dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate) to give 2-amino-3-iodo-4*H*-chromen-4-ones **a**.

1.2 General procedure for the synthesis of 2-amino-9*H*-chromeno[2, 3-*d*]thiazol-9-ones (GP2)



a **c**

To a 10 mL pressure tube was added *N, N*-dimethylacetamide (2.5 mL), amines (1.05 mmol), and CS_2 (0.7 mmol) in sequence. Then, added the 2-amino-3-iodine-chromones (**a**, 0.35 mmol), CuO (0.35 mmol), and K_2CO_3 (1.05 mmol) to the mixture. The mixture was then heated to 130 ℃ with stirring for 1 h. After the reaction was cooled to room temperature, the solvent was removed in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol or petroleum ether/dichloromethane) to give the compounds **c**.

1.3 General procedure for the anti-inflammatory activity test

Materials

MTT and LPS were purchased from Sigma-Aldrich (St. Louis, MO, USA). ELISA kits for mouse IL-6 and TNF-α were acquired from eBioscience (San Diego, CA, USA) and IL-1β was bought from Thermo Fisher Scientific (Waltham, MA, USA).

Cell culture

The murine adherent macrophage cell line RAW264.7 cells were procured from American Type Culture Collection (ATCC, Manassas, VA, USA) and cultured in DMEM medium (Meilunbio, China, Dalian) supplemented with 10% fetal bovine serum (FBS) (HyClone, Logan, UT) and 1% streptomycin/penicillin at 37 ℃ in a humified atmosphere containing 5% CO_2.

Cells viability assay

MTT assay was performed to assess cell viability, RAW264.7 cells (1×10^6 cells/mL) were seeded in triplicate in 96-well culture plates and incubated overnight at 37℃. The cells were then treated with or without the indicated concentrations of compounds and incubated for 48 h. After removing the culture medium, MTT solution (5 mg/mL) was added to each well. The MTT-formazan crystals

were dissolved in dimethyl sulfoxide (DMSO) and the absorbance of each well was measured at 570 nm using a microplate reader (Molecular Devices, Sunnyvale, CA, USA).

Cytokines measurement

RAW264.7 cells (1×10^6 cells/mL) were seeded in 96-well plates and incubated overnight at 37℃. The cells were then treated with LPS (10 μg/ml) in the presence or in the absence of various concentrations of compounds for 48 h. After incubation, the supernatants were harvested and the level of cytokines was determined in supernatant by using TNF-α, IL-6 ELISA kits, and IL-1β on the basis of manufacturer's instructions.

Immunoblotting

RAW264.7 cells were seeded at 2×10^6 cells/well in 6-well plates overnight. The cells were treated with LPS (1μg/ml) in the presence of or absence of YCH-3031 at the concentrations of 50, 10, and 2 μM for 12 h. Cells were lysed using sodium dodecyl sulfate (SDS) sample buffer (Beyotime, Shanghai, China) containing protease inhibitor cocktail (Roche Life Science, Mannheim, Germany) and the protein concentrations were detected using the BCA protein assay kit (Thermo Fisher Scientific, Waltham, MA). Equal amounts of protein were separated by 10% SDS-PAGE and transferred onto nitrocellulose membranes. After blocking the membranes with 5% BSA, membranes were incubated overnight at 4℃ with antibodies phospho-IκBα, phospho-JNK, JNK, NF-κB p65, phospho-NF-κB p65 (Cell Signaling Technology, Beverly, Massachusetts) and GAPDH (KangChen, Biotechnology, China). The signals were visualized using Super-Signal West Pico PLUS Chemiluminescent Substrate (Thermo Fisher Scientific) and detected using a ChemiDoc MP Imaging System (Bio-Rad). The protein on the film was quantified by gray analysis using Image J software.

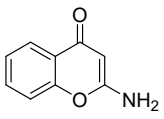
Statistical analysis

Statistical analyses were conducted by GraphPad Prism 8.4.0 (GraphPad Software Inc., CA, USA). One-way analysis of variance (ANOVA) with Dunnett's multiple comparisons test was applied for multi-group comparisons.

2 Characterization data of the products

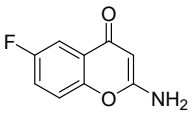
2.1 Characterization data of 2-amino-4H-chromen-4-ones

The following compounds were synthesized based on the literature[1, 2] that has been previously reported.



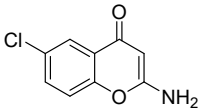
2-amino-4*H*-chromen-4-one

g1



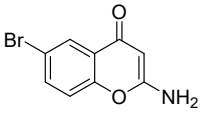
2-amino-6-fluoro-4*H*-chromen-4-one

g26



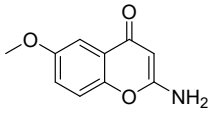
2-amino-6-chloro-4*H*-chromen-4-one

g30



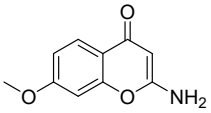
2-amino-6-bromo-4*H*-chromen-4-one

g31



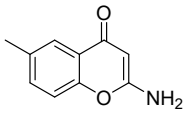
2-amino-6-methoxy-4*H*-chromen-4-one

g32



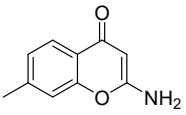
2-amino-7-methoxy-4*H*-chromen-4-one

g33



2-amino-6-methyl-4*H*-chromen-4-one

g35

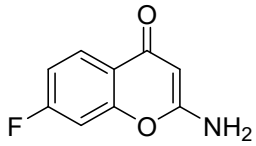


2-amino-7-methyl-4*H*-chromen-4-one

g36

The following compounds were prepared according to **GP1.1.** The yield is the total yield from step1 to step3.

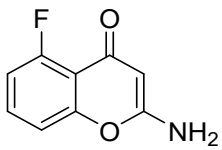
2-amino-7-fluoro-4*H*-chromen-4-one



g27

Yellow solid. Yield = 63%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (dd, *J* = 8.8, 6.6 Hz, 1H), 7.57 (s, 2H), 7.28 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.20 (td, *J* = 8.7, 2.4 Hz, 1H), 5.16 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.54, 164.93, 163.64 (d, *J* = 248.6 Hz), 153.91 (d, *J* = 13.4 Hz), 126.81 (d, *J* = 10.5 Hz), 119.85 (d, *J* = 2.5 Hz), 112.21 (d, *J* = 22.3 Hz), 103.59 (d, *J* = 25.9 Hz), 84.54. HRMS (EI) calculated for $[C_9H_6FNO_2]^+$ (M^+), requires m/z 179.0377, found m/z 179.0376.

2-amino-5-fluoro-4*H*-chromen-4-one

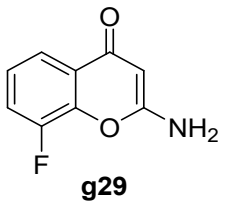


g28

Claybank solid. Yield = 32%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56 (d, *J* = 7.2 Hz, 1H), 7.48 (s, 2H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.08 (t, *J* = 9.7 Hz, 1H), 5.09 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.11, 163.74, 159.58 (d, *J* = 259.5 Hz), 154.35 (d, *J* = 4.8 Hz), 132.14 (d, *J* = 10.9 Hz), 112.71 (d, *J* = 4.0 Hz),

112.56 (d, *J* = 9.9 Hz), 111.72 (d, *J* = 21.2 Hz), 85.79. HRMS (EI) calculated for $[C_9H_6FNO_2]^+$ (M^+), requires m/z 179.0377, found m/z 179.0371.

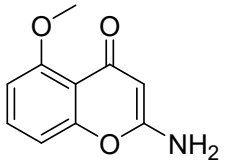
2-amino-8-fluoro-4*H*-chromen-4-one



g29

Claybank solid. Yield = 59%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.71 – 7.67 (m, 1H), 7.55 (ddd, *J* = 11.1, 8.1, 1.6 Hz, 1H), 7.31 (td, *J* = 8.0, 4.6 Hz, 1H), 5.21 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.27 (d, *J* = 2.7 Hz), 164.29, 149.43 (d, *J* = 248.6 Hz), 141.28 (d, *J* = 10.7 Hz), 125.08, 124.09 (d, *J* = 6.8 Hz), 119.78 (d, *J* = 3.4 Hz), 118.01 (d, *J* = 16.9 Hz), 85.05. HRMS (EI) calculated for $[C_9H_6FNO_2]^+$ (M^+), requires m/z 179.0377, found m/z 179.0376.

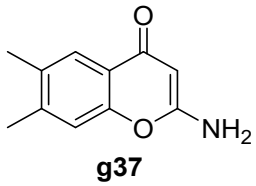
2-amino-5-methoxy-4*H*-chromen-4-one



g34

Yellow solid. Yield = 63%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (t, *J* = 8.3 Hz, 1H), 7.16 – 7.11 (m, 2H), 6.91 – 6.83 (m, 2H), 4.99 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 175.04, 162.95, 158.95, 155.43, 132.09, 112.82, 108.80, 107.36, 86.35, 56.00. MS (ESI) calculated for $[C_{10}H_{10}NO_3]^+$ ($M+H^+$), requires m/z 192.1, found m/z 192.1**.**

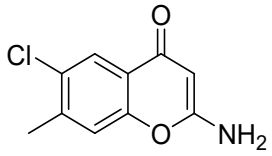
2-amino-6, 7-dimethyl-4*H*-chromen-4-one



g37

White solid. Yield = 60%.^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (s, 1H), 7.35 (s, 2H), 7.14 (s, 1H), 5.11 (s, 1H), 2.30 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.62, 164.66, 151.64, 141.40, 132.72, 124.55, 120.63, 116.64, 84.90, 19.55, 18.80. HRMS (EI) calculated for $[C_{11}H_{11}NO_2]^+$ (M^+), requires m/z 189.0784, found m/z 189.0775.

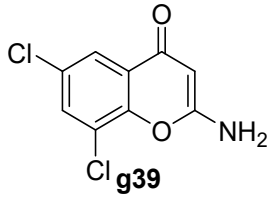
2-amino-6-chloro-7-methyl-4*H*-chromen-4-one



g38

Brown solid. Yield = 61%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.78 (s, 1H), 7.58 (s, 2H), 7.40 (s, 1H), 5.15 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.11, 164.90, 151.61, 139.98, 129.38, 123.99, 122.38, 118.93, 84.80, 19.77. MS (ESI) calculated for $[C_{10}H_9ClNO_2]^+$ (M+H$^+$), requires m/z 210.0, found m/z 210.1.

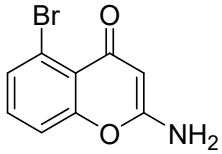
2-amino-6, 7-dichloro-4*H*-chromen-4-one



g39

Brown solid. Yield = 54%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 2.6 Hz, 1H), 7.87 (s, 2H), 7.77 (d, J = 2.6 Hz, 1H), 5.22 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.13, 164.66, 147.74, 131.54, 128.74, 125.43, 122.94, 121.80, 85.01. MS (ESI) calculated for $[C_9H_6Cl_2NO_2]^+$ (M+H$^+$), requires m/z 230.0, found m/z 230.0.

2-amino-5-bromo-4*H*-chromen-4-one



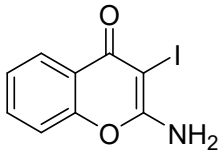
g40

Brown solid. Yield = 50%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (s, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 5.16 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.73, 161.24, 154.01, 132.64, 131.39, 118.95, 116.90, 116.66, 58.92. MS (ESI) calculated for $[C_9H_7BrNO_2]^+$ (M+H$^+$), requires m/z 240.0, found m/z 240.0.

2.2 Characterization data of 2-amino-3-iodo-4*H*-chromen-4-ones

The following compounds were prepared according to **GP1.2**

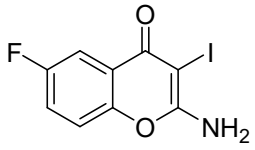
2-amino-3-iodo-4*H*-chromen-4-one



a1

Yellow solid. Yield = 93%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.88 (s, 2H), 7.64 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.40 (d, *J* = 3.9 Hz, 1H), 7.39 – 7.35 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.23, 162.35, 152.33, 132.60, 125.09, 124.78, 119.51, 116.11, 57.66. HRMS (ESI) calculated for $[C_9H_7INO_2]^+$ ($M+H^+$), requires m/z 287.9516, found m/z 287.9516.

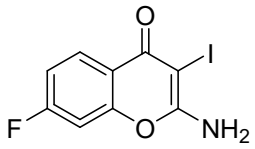
2-amino-6-fluoro-3-iodo-4*H*-chromen-4-one



a26

Yellow solid. Yield = 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (s, 2H), 7.43 – 7.33 (m, 1H), 7.30 – 7.22 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.49, 162.57, 158.63 (d, *J* = 242.3 Hz), 148.66, 120.82 (d, *J* = 7.1 Hz), 120.12 (d, *J* = 25.2 Hz), 118.63 (d, *J* = 8.3 Hz), 110.11 (d, *J* = 24.1 Hz), 57.44. ^{19}F NMR (376 MHz, DMSO-d_6) δ -116.66. HRMS (ESI) calculated for $[C_9H_6FINO_2]^+$ ($M+H^+$), requires m/z 305.9422, found m/z 305.9423.

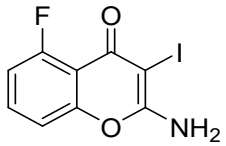
2-amino-7-fluoro-3-iodo-4*H*-chromen-4-one



a27

Yellow solid. Yield = 86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (dd, *J* = 8.9, 6.6 Hz, 1H), 7.93 (s, 2H), 7.32 (dd, *J* = 9.4, 2.4 Hz, 1H), 7.24 (td, *J* = 8.7, 2.4 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.59, 164.03 (d, *J* = 249.5 Hz), 162.58, 153.18 (d, *J* = 13.6 Hz), 127.60 (d, *J* = 10.6 Hz), 116.61, 112.89 (d, *J* = 22.5 Hz), 103.46 (d, *J* = 26.2 Hz), 57.20. ^{19}F NMR (376 MHz, DMSO-d_6) δ -87.14 – -122.70 (m). HRMS (ESI) calculated for $[C_9H_6FINO_2]^+$ ($M+H^+$), requires m/z 305.9422, found m/z 305.9421.

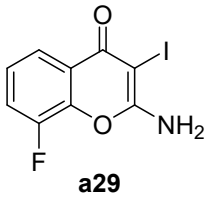
2-amino-5-fluoro-3-iodo-4*H*-chromen-4-one



a28

Yellow solid. Yield = 84%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 2H), 7.63 (td, *J* = 8.4, 5.6 Hz, 1H), 7.23 (dt, *J* = 8.4, 1.1 Hz, 1H), 7.15 (ddd, *J* = 11.2, 8.2, 1.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.34, 161.74, 159.03 (d, *J* = 260.6 Hz), 153.55 (d, *J* = 4.0 Hz), 132.87 (d, *J* = 10.7 Hz), 112.52 (d, *J* = 3.9 Hz), 112.04 (d, *J* = 21.1 Hz), 109.45 (d, *J* = 10.1 Hz), 58.79. ^{19}F NMR (376 MHz, DMSO-d_6) δ -113.02. HRMS (ESI) calculated for $[C_9H_6FINO_2]^+$ ($M+H^+$), requires m/z 305.9422, found m/z 305.9417.

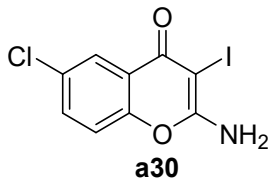
2-amino-8-fluoro-3-iodo-4*H*-chromen-4-one



a29

Yellow solid. Yield = 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 2H), 7.72 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.62 (ddd, *J* = 11.0, 8.1, 1.5 Hz, 1H), 7.35 (td, *J* = 8.0, 4.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.43, 161.91, 149.21 (d, *J* = 249.0 Hz), 140.74 (d, *J* = 10.8 Hz), 124.74 (d, *J* = 6.9 Hz), 121.70, 120.44 (d, *J* = 3.8 Hz), 118.65 (d, *J* = 16.8 Hz), 57.91. ^{19}F NMR (376 MHz, DMSO-d_6) δ -134.87. HRMS (ESI) calculated for $[C_9H_6FINO_2]^+$ ($M+H^+$), requires m/z 305.9422, found m/z 305.9414.

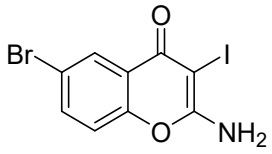
2-amino-6-chloro-3-iodo-4*H*-chromen-4-one



a30

Yellow solid. Yield = 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 – 7.95 (m, 2H), 7.84 (s, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 8.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 170.05, 162.52, 150.95, 132.33, 128.98, 124.13, 120.82, 118.57, 57.60. HRMS (ESI) calculated for $[C_9H_6ClINO_2]^+$ ($M+H^+$), requires m/z 321.9126, found m/z 321.9127.

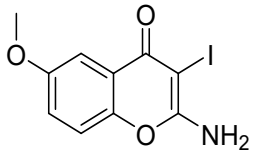
2-amino-6-bromo-3-iodo-4*H*-chromen-4-one



a31

Yellow solid. Yield = 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 2H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.79 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.99, 162.48, 151.37, 135.13, 127.20, 121.17, 118.85, 116.88, 57.54. HRMS (ESI) calculated for $[C_9H_6BrINO_2]^+$ ($M+H^+$), requires m/z 365.8621, found m/z 365.8608.

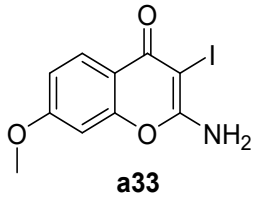
2-amino-3-iodo-6-methoxy-4*H*-chromen-4-one



a32

Yellow solid. Yield = 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 2H), 7.35 (s, 1H), 7.32 (s, 1H), 7.20 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.15, 162.36, 156.05, 146.78, 120.54, 120.17, 117.53, 106.37, 57.68, 55.63. HRMS (ESI) calculated for $[C_{10}H_9INO_3]^+$ ($M+H^+$), requires m/z 317.9622, found m/z 317.96.17.

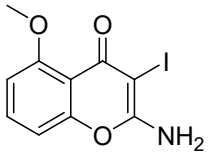
2-amino-3-iodo-7-methoxy-4*H*-chromen-4-one



a33

Yellow solid. Yield = 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, *J* = 8.8 Hz, 1H), 7.74 (s, 2H), 6.96 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.08, 162.66, 162.27, 153.85, 126.52, 113.18, 112.83, 99.71, 57.00, 55.86. HRMS (ESI) calculated for $[C_{10}H_9INO_3]^+$ ($M+H^+$), requires m/z 317.9622, found m/z 317.96.23.

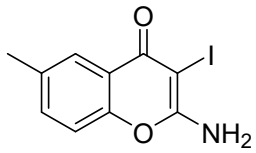
2-amino-3-iodo-5-methoxy-4*H*-chromen-4-one



a34

Yellow solid. Yield = 81%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 – 7.53 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 8.2, 2.1 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.54, 160.98, 158.36, 154.41, 132.67, 109.61, 108.27, 107.54, 59.89, 56.13. HRMS (ESI) calculated for $[C_{10}H_9INO_3]^+$ (M+H$^+$), requires m/z 317.9622, found m/z 317.9626.

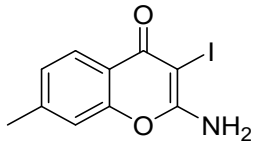
2-amino-3-iodo-6-methyl-4*H*-chromen-4-one



a35

Yellow solid. Yield = 86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 2H), 7.72 (d, *J* = 2.2 Hz, 1H), 7.46 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.32, 162.35, 150.60, 134.16, 133.46, 124.69, 119.25, 115.95, 57.78, 20.38. HRMS (ESI) calculated for $[C_{10}H_9INO_2]^+$ (M+H$^+$), requires m/z 301.9672, found m/z 301.9668.

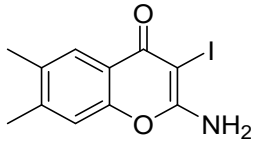
2-amino-3-iodo-7-methyl-4*H*-chromen-4-one



a36

Yellow green solid. Yield = 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, *J* = 7.6 Hz, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.27, 162.27, 152.45, 143.31, 125.96, 124.95, 117.29, 115.95, 57.51, 21.06. HRMS (ESI) calculated for $[C_{10}H_9INO_2]^+$ (M+H$^+$), requires m/z 301.9672, found m/z 301.9675.

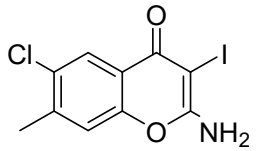
2-amino-3-iodo-6, 7-dimethyl-4*H*-chromen-4-one



a37

Brown solid. Yield = 83%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (s, 2H), 7.66 (s, 1H), 7.18 (s, 1H), 2.31 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.34, 162.20, 150.78, 142.27, 133.34, 124.94, 117.28, 116.29, 57.67, 19.65, 18.80. HRMS (ESI) calculated for $[C_{11}H_{11}INO_2]^+$ (M+H$^+$), requires m/z 315.9829, found m/z 315.9821.

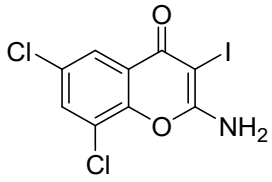
2-amino-6-chloro-3-iodo-7-methyl-4*H*-chromen-4-one



a38

Brown solid. Yield = 89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 2H), 7.81 (s, 1H), 7.44 (s, 1H), 2.42 (s, 3H).^{13}C NMR (126 MHz, DMSO-d_6) δ 170.16, 162.42, 150.81, 140.75, 129.66, 124.39, 118.85, 118.61, 57.32, 19.87. HRMS (ESI) calculated for $[C_{10}H_8ClINO_2]^+$ (M+H$^+$), requires m/z 335.9283, found m/z 335.9279.

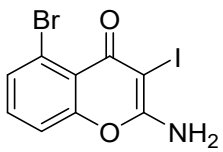
2-amino-6, 8-dichloro-3-iodo-4*H*-chromen-4-one



a39

Brown solid. Yield = 85%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 2H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.49, 162.14, 147.11, 131.96, 128.85, 123.28, 121.75, 121.55, 57.64. HRMS (ESI) calculated for $[C_9H_3INO_2]^-$ (M-H$^-$), requires m/z 353.8591, found m/z 353.8587.

2-amino-5-bromo-3-iodo-4*H*-chromen-4-one



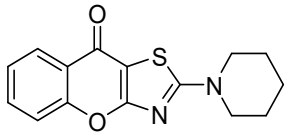
a40

Brown solid. Yield = 87%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (s, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.64, 161.14, 153.92, 132.55, 131.29, 118.85, 116.80, 116.57, 58.81. HRMS (EI) calculated for $[C_9H_5BrINO_2]^+$ (M$^+$),

requires m/z 364.8543, found m/z 364.8543.

2.3 Characterization data of 2-amino-9H-chromeno[2, 3-*d*]thiazol-9-ones

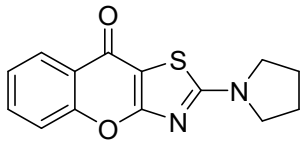
2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c1

White solid prepared according to **GP2** using the starting materials **a1** and piperidine. Yield = 81%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 3.64 (s, 4H), 1.78 – 1.66 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.47, 170.75, 164.99, 154.17, 132.67, 125.45, 124.74, 122.75, 117.70, 103.49, 49.47, 25.20, 23.80. HRMS (ESI) calculated for $[C_{15}H_{15}N_2O_2S]^+$ ($M+H^+$), requires m/z 287.0849, found m/z 287.0854.

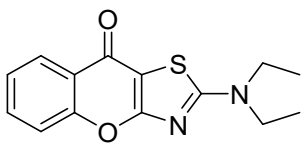
2-(pyrrolidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c2

White solid prepared according to **GP2** using the starting materials **a1** and pyrrolidine. Yield = 55%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.62 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.37 (m, 1H), 3.75 (s, 2H), 3.39 (s, 2H), 2.12 (s, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.95, 168.49, 165.03, 154.27, 132.75, 125.58, 124.83, 122.78, 117.81, 103.94, 49.92, 25.74. HRMS (ESI) calculated for $[C_{14}H_{13}N_2O_2S]^+$ ($M+H^+$), requires m/z 273.0692, found m/z 273.0691.

2-(diethylamino)-9*H*-chromeno[2, 3-*d*]thiazol-9-one

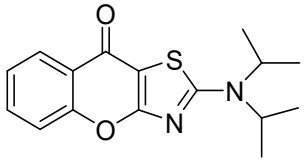


c3

Brown solid prepared according to **GP2** using the starting materials **a1** and diethylamine. Yield = 65%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 6.8 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 6.9 Hz, 1H), 3.62 (s, 4H), 1.33 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ

169.70, 169.17, 164.49, 153.59, 133.24, 125.11, 124.64, 122.05, 117.93, 102.18, 28.47, 11.60. HRMS (ESI) calculated for $[C_{14}H_{15}N_2O_2S]^+$ ($M+H^+$), requires m/z 275.0849, found m/z 275.0857.

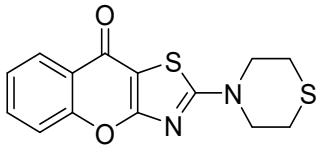
2-(diisopropylamino)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c4

Brown solid prepared according to **GP2** using the starting materials **a1** and diisopropylamine. Yield = 53%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.61 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 7.0 Hz, 1H), 4.03 – 3.94 (m, 2H), 1.45 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (201 MHz, DMSO-d_6) δ 169.06, 168.58, 164.35, 153.63, 133.19, 125.07, 124.64, 122.12, 117.97, 101.14, 39.99, 19.42. HRMS (ESI) calculated for $[C_{16}H_{19}N_2O_2S]^+$ ($M+H^+$), requires m/z 303.1162, found m/z 303.1164.

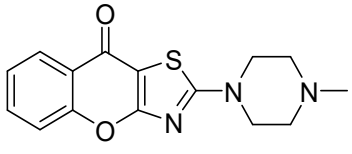
2-thiomorpholino-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c5

White solid prepared according to **GP2** using the starting materials **a1** and thiomorpholine. Yield = 41%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 7.9 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 4.00 (s, 4H), 2.82 – 2.73 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.52, 171.08, 164.73, 154.36, 133.06, 125.67, 125.05, 122.79, 117.88, 104.18, 51.22, 26.91. HRMS (ESI) calculated for $[C_{14}H_{13}N_2O_2S_2]^+$ ($M+H^+$), requires m/z 305.0413, found m/z 305.0416.

2-(4-methylpiperazin-1-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one

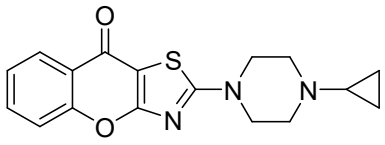


c6

Pale yellow solid prepared according to **GP2** using the starting materials **a1** and 1-methylpiperazine. Yield = 34%.^{1}H NMR (400 MHz, Methanol-d_4) δ 8.17 (d, *J* = 7.9, 1.7 Hz, 1H), 7.76 (t, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 3.82 – 3.70 (m, 4H), 2.61 (t, *J* = 5.2 Hz, 4H), 2.37 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 173.47, 172.73, 167.14, 155.69, 134.66, 126.35,

125.98, 123.32, 119.03, 104.67, 54.81, 49.57, 46.01. HRMS (ESI) calculated for $[C_{15}H_{16}N_3O_2S]+$ ($M+H^+$), requires m/z 302.0958, found m/z 302.0956.

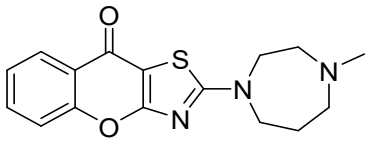
2-(4-cyclopropylpiperazin-1-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one



c7

Light red solid prepared according to **GP2** using the starting materials **a1** and 1-cyclopropylpiperazine. Yield = 55%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.64 (ddd, *J* = 8.6, 7.0, 1.8 Hz, 1H), 7.52 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.42 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.74 – 3.57 (m, 4H), 2.77 (t, *J* = 5.2 Hz, 4H), 1.74 – 1.68 (m, 1H), 0.56 – 0.42 (m, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.80, 171.05, 164.93, 154.37, 132.94, 125.67, 124.97, 122.85, 117.87, 104.05, 52.31, 48.17, 38.40, 6.23. HRMS (ESI) calculated for $[C_{17}H_{18}N_3O_2S]+$ ($M+H^+$), requires m/z 328.1114, found m/z 328.1117.

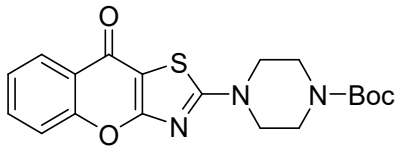
2-(4-methyl-1, 4-diazepan-1-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one



c8

Pale yellow solid prepared according to **GP2** using the starting materials **a1** and 1-methyl-1, 4-diazepane. Yield = 31%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.16 (d, J = 8.1, 1.7 Hz, 1H), 7.76 (t, J = 8.7, 7.0, 1.7 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 4.16 – 3.86 (m, 2H), 3.77 – 3.44 (m, 2H), 2.97 – 2.74 (m, 2H), 2.72 – 2.66 (m, 2H), 2.41 (s, 3H), 2.21 – 1.92 (m, 2H). ^{13}C NMR (126 MHz, Trifluoroacetic acid-d_4) δ 179.15, 173.31, 169.21, 156.13, 139.12, 129.94, 126.40, 120.37, 106.17, 59.30, 59.08, 52.96, 47.25, 46.88, 25.55. HRMS (ESI) calculated for $[C_{16}H_{18}N_3O_2S]+$ ($M+H^+$), requires m/z 316.1114, found m/z 316.1115.

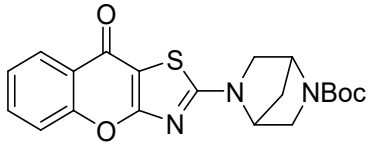
tert-butyl 4-(9-oxo-9*H*-chromeno[2, 3-*d*]thiazol-2-yl)piperazine-1-carboxylate



c9

White solid prepared according to **GP2** using the starting materials **a1** and tert-butyl piperazine-1-carboxylate. Yield = 64%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 3.65 (s, 4H), 3.59 (s, 4H), 1.46 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.94, 171.13, 164.68, 154.44, 154.39, 133.09, 125.70, 125.06, 122.78, 117.91, 104.29, 80.98, 47.97, 42.90, 28.49. HRMS (ESI) calculated for $[C_{19}H_{22}N_3O_4S]^+$ ($M+H^+$), requires m/z 388.1326, found m/z 388.1335.

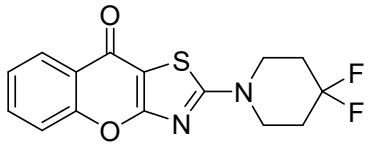
tert-butyl-5-(9-oxo-9*H*-chromeno[2, 3-*d*]thiazol-2-yl)-2, 5-diazabicyclo[2, 2, 1]heptane-2-carboxylate



c10

White solid prepared according to **GP2** using the starting materials **a1** and tert-butyl 2, 5-diazabicyclo[2.2.1]heptane-2-carboxylate. Yield = 67%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 5.21 – 4.52 (m, 2H), 3.67 – 3.40 (m, 4H), 2.09 – 1.99 (m, 2H), 1.52 – 1.38 (m, 9H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.00, 169.09, 164.83, 154.34, 154.04, 133.02, 125.71, 125.04, 122.75, 117.88, 104.23, 80.65, 61.43, 57.95, 56.9, 52.8, 37.8, 28.56. HRMS (ESI) calculated for $[C_{20}H_{22}N_3O_4S]^+$ ($M+H^+$), requires m/z 400.1326, found m/z 400.1329.

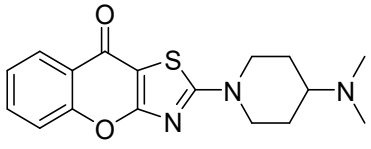
2-(4, 4-difluoropiperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c11

White solid prepared according to **GP2** using the starting materials **a1** and 4, 4-difluoropiperidine. Yield = 80%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.26 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.66 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.43 (td, *J* = 7.6, 7.1, 1.1 Hz, 1H), 3.84 (t, *J* = 5.9 Hz, 4H), 2.17 (tt, *J* = 12.9, 6.0 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.78 (d, *J* = 42.4 Hz), 163.99, 153.82, 132.61, 124.84 (d, *J* = 72.7 Hz), 122.16, 120.28, 118.35, 117.34, 104.13, 44.81, 32.86 (t, *J* = 24.1 Hz). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -98.38 (d, *J* = 14.4 Hz). HRMS (ESI) calculated for $[C_{15}H_{13}F_2N_2O_2S]^+$ ($M+H^+$), requires m/z 323.0660, found m/z 323.0668.

2-(4-(dimethylamino)piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one

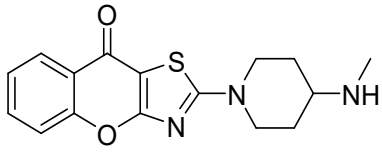


c12

White solid prepared according to **GP2** using the starting materials **a1** and *N, N*-dimethylpiperidin-4-amine. Yield = 68%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.63 (ddd, *J* =

8.6, 7.2, 1.7 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.37 (m, 1H), 4.30 – 4.09 (m, 2H), 3.31 – 3.18 (m, 2H), 2.56 – 2.45 (m, 1H), 2.32 (s, 6H), 1.98 – 1.95 (m, 2H), 1.72 – 1.58 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.48, 170.99, 165.00, 154.32, 132.88, 125.60, 124.93, 122.82, 117.84, 103.97, 61.20, 47.64, 41.78, 27.76. HRMS (ESI) calculated for $[C_{17}H_{20}N_3O_2S]^+$ ($M+H^+$), requires m/z 330.1271, found m/z 330.1276.

2-(4-(methylamino)piperidin-1-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one

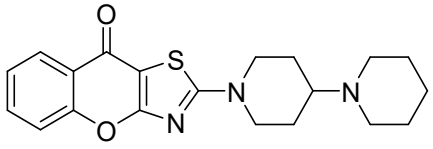


c13

First, yellow solid tert-butyl methyl(1-(9-oxo-9H-chromeno[2, 3-*d*]thiazol-2-yl)piperidin-4-yl)carbamate was prepared according to GP2 using the starting materials **a1** and tert-butyl methyl(piperidin-4-yl)carbamate. The solid was then added to a hydrochloric acid 1, 4-dioxane solution (4 M, 10 mL) and stirred for 2 h at room temperature. After the reaction was complete, the mixture was concentrated under vacuo to dryness. Then methanol (10 mL) and sodium bicarbonate (1.75 mmol) were added to the residue. The mixture was stirred for 0.5 h at room temperature and then the solvent was removed in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol) to give the compound **c13**.

White solid. Yield = 43%. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.42 – 7.34 (m, 2H), 3.91 (s, 2H), 3.34 (t, *J* = 11.9 Hz, 1H), 3.15 (s, 2H), 2.65 (s, 3H), 2.22 – 2.15 (m, 2H), 1.68 – 1.56 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.90, 169.78, 164.94, 154.12, 133.81, 125.65, 125.13, 122.53, 118.45, 103.05, 63.26, 54.86, 32.47, 29.82. HRMS (ESI) calculated for $[C_{16}H_{18}N_3O_2S]$+ ($M+H^+$), requires m/z 316.1114, found m/z 316.1116.

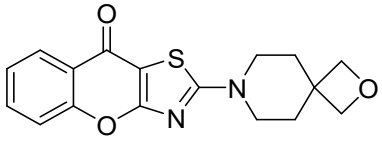
2-([1, 4'-bipiperidin]-1'-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one



c14

Pale yellow prepared according to **GP2** using the starting materials **a1** and 1, 4'-bipiperidine. Yield = 65%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.65 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1H), 7.51 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.42 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 4.28 (s, 2H), 3.24 (t, *J* = 12.8 Hz, 2H), 2.99 (s, 1H), 2.87 – 2.75 (m, 4H), 2.24 (d, *J* = 12.6 Hz, 2H), 1.91 – 1.73 (m, 6H), 1.61 – 1.48 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.36, 169.30, 164.53, 153.65, 133.33, 125.18, 124.66, 122.08, 117.98, 102.57, 60.58, 49.63, 40.11, 26.78, 25.89, 24.27. HRMS (ESI) calculated for $[C_{20}H_{24}N_3O_2S]$+ ($M+H^+$), requires m/z 370.1584, found m/z 370.1585.

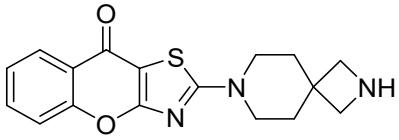
2-(2-oxa-7-azaspiro[3.5]nonan-7-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one



c15

Yellow prepared according to **GP2** using the starting materials **a1** and 2-oxa-7-azaspiro[3.5]nonane. Yield = 30%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.2, 1.5 Hz, 1H), 7.65 (t, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 4.52 (s, 4H), 3.67 – 3.59 (m, 4H), 2.05 (t, *J* = 6.9, 4.7 Hz, 4H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.68, 171.05, 164.87, 154.36, 133.01, 125.67, 125.02, 122.82, 117.88, 104.07, 80.94, 45.70, 38.68, 33.91. HRMS (ESI) calculated for $[C_{17}H_{17}N_2O_3S]+$ ($M+H^+$), requires m/z 329.0954, found m/z 329.0952.

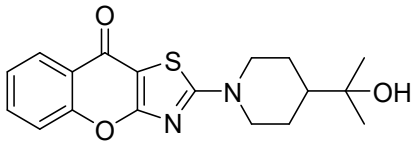
2-(2, 7-diazaspiro[3.5]nonan-7-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one



c16

First, yellow solid tert-butyl 7-(9-oxo-9*H*-chromeno[2, 3-d]thiazol-2-yl)-2, 7-diazaspiro[3.5]nonane-2-carboxylate was prepared according to **GP2** using the starting materials **a1** and tert-butyl 2, 7-diazaspiro[3.5]nonane-2-carboxylate. The resulting solid was then added to a hydrochloric acid 1, 4-dioxane solution (4 M, 10 mL) and stirred for 2 h at room temperature. After the reaction was complete, the mixture was concentrated under vacuo to dryness. Then methanol (10 mL) and sodium bicarbonate (1.75 mmol) were added to the residue. The mixture was stirred for 0.5 h at room temperature and then the solvent was removed in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol) to give the compound **c16**.
White solid. Yield = 27%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.17 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.78 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.61 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.51 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.97 (s, 4H), 3.76 – 3.71 (m, 4H), 2.06 (t, 4H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 173.28, 172.70, 167.13, 155.66, 134.71, 126.40, 125.97, 123.30, 119.02, 104.62, 56.20, 46.16, 37.76, 34.56. HRMS (ESI) calculated for $[C_{17}H_{18}N_3O_2S]+$ ($M+H^+$), requires m/z 328.1114, found m/z 328.1117.

2-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one

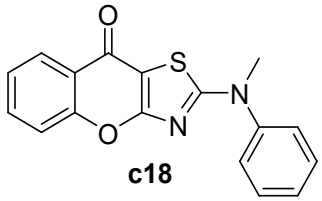


c17

Pale yellow prepared according to **GP2** using the starting materials **a1** and 2-(piperidin-4-yl)propan-2-ol. Yield = 56%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.15 (d, *J* = 7.9, 1.7 Hz, 1H), 7.75 (t, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 4.57 – 3.89 (m, 2H), 3.22 (t, 2H), 2.02 – 1.94 (m, 2H), 1.65 (tt, *J* = 12.2, 3.2 Hz, 1H), 1.52 – 1.37 (m, 2H), 1.19 (s, 6H). ^{13}C NMR

(126 MHz, Methanol-d_4) δ 172.94, 172.52, 167.44, 155.60, 134.52, 126.28, 125.92, 123.34, 118.98, 104.21, 72.49, 49.63, 47.90, 27.47, 26.86. HRMS (ESI) calculated for $[C_{18}H_{21}N_2O_3S]$+ ($M+H^+$), requires m/z 345.1267, found m/z 345.127.

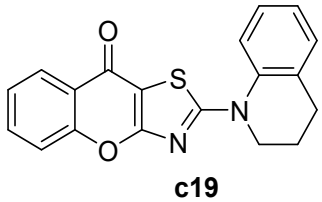
2-(methyl(phenyl)amino)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c18

White solid prepared according to **GP2** using the starting materials **a1** and N-methylaniline. Yield = 50%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.67 – 7.59 (m, 1H), 7.60 – 7.47 (m, 3H), 7.45 – 7.33 (m, 4H), 3.64 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.56, 171.22, 164.50, 154.39, 143.82, 132.95, 130.56, 128.93, 125.90, 125.61, 124.92, 122.78, 117.90, 104.85, 40.98. HRMS (ESI) calculated for $[C_{17}H_{12}N_2NaO_2S]^+$ ($M+Na^+$), requires m/z 331.1628, found m/z 331.1628.

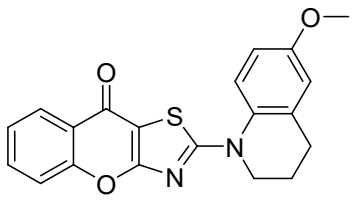
2-(3, 4-dihydroquinolin-1(2*H*)-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c19

White solid prepared according to **GP2** using the starting materials **a1** and 1, 2, 3, 4-tetrahydroquinoline. Yield = 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.65 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.45 – 7.38 (m, 1H), 7.29 (td, *J* = 8.2, 1.8 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.19 – 7.13 (m, 1H), 4.05 (t, *J* = 6.3 Hz, 2H), 2.82 (t, *J* = 6.4 Hz, 2H), 2.09 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.39, 170.35, 163.96, 154.51, 138.63, 133.09, 131.81, 129.40, 127.11, 125.96, 125.67, 124.94, 122.85, 121.70, 117.95, 104.03, 49.55, 27.22, 23.44. HRMS (ESI) calculated for $[C_{19}H_{15}N_2O_2S]^+$ ($M+H^+$), requires m/z 335.0849, found m/z 335.0846.

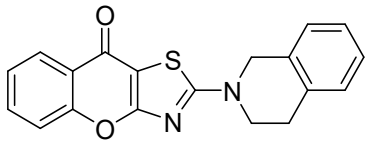
2-(6-methoxy-3, 4-dihydroquinolin-1(2*H*)-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c20

White solid prepared according to **GP2** using the starting materials **a1** and 6-methoxy-1, 2, 3, 4-tetrahydroquinoline. Yield = 58%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.64 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.39 (m, 1H), 6.82 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.75 (d, *J* = 2.8 Hz, 1H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.08 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.29, 170.56, 164.19, 157.47, 154.48, 133.60, 133.00, 131.87, 125.65, 124.91, 123.08, 122.90, 117.92, 114.59, 112.08, 103.83, 55.64, 49.35, 27.39, 23.43. HRMS (ESI) calculated for $[C_{20}H_{17}N_2O_3S]^+$ ($M+H^+$), requires m/z 365.0954, found m/z 365.0958.

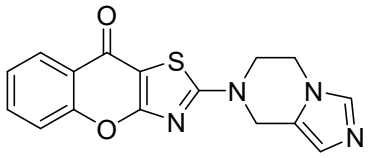
2-(3, 4-dihydroisoquinolin-2(1*H*)-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c21

White solid prepared according to **GP2** using the starting materials **a1** and 1, 2, 3, 4-tetrahydroisoquinoline. Yield = 49%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 – 8.26 (m, 1H), 7.69 – 7.63 (m, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.22 (m, 2H), 4.83 (s, 2H), 3.97 – 3.80 (m, 2H), 3.08 (t, *J* = 5.9 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.22, 171.06, 164.78, 154.34, 134.03, 132.92, 128.57, 127.60, 127.16, 126.51, 125.65, 124.94, 122.80, 117.86, 103.95, 49.49, 28.58. HRMS (ESI) calculated for $[C_{19}H_{15}N_2O_2S]^+$ ($M+H^+$), requires m/z 335.0849, found m/z 335.0856.

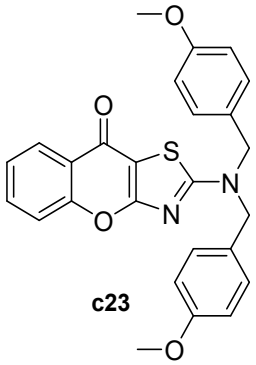
2-(5, 6-dihydroimidazo[1, 5-a]pyrazin-7(8*H*)-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one



c22

White solid prepared according to **GP2** using the starting materials **a1** and 5, 6, 7, 8-tetrahydroimidazo[1, 5-a]pyrazine. Yield = 59%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.68 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.55 (d, 1H), 7.45 (t, 1H), 7.13 (d, *J* = 1.3 Hz, 1H), 6.96 (d, *J* = 1.4 Hz, 1H), 4.92 (s, 2H), 4.26 – 4.22 (m, 4H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.57, 171.33, 164.22, 154.48, 138.72, 133.35, 129.26, 125.81, 125.23, 122.72, 118.75, 118.00, 105.17, 47.20, 45.00, 43.41. HRMS (ESI) calculated for $[C_{16}H_{13}N_4O_2S]$+ ($M+H^+$), requires m/z 325.0754, found m/z 325.0757.

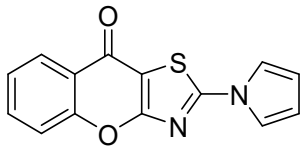
2-(bis(4-methoxybenzyl)amino)-9*H*-chromeno[2, 3-d]thiazol-9-one



c23

White solid prepared according to **GP2** using the starting materials **a1** and bis(4-methoxybenzyl)amine. Yield = 43%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06 (d, *J* = 7.9, 1.8 Hz, 1H), 7.78 (t, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.24 (m, 4H), 6.96 – 6.90 (m, 4H), 4.99 – 4.54 (m, 4H), 3.74 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 171.20, 169.40, 163.89, 158.99, 153.67, 133.39, 129.75, 129.36, 125.17, 124.69, 122.00, 118.00, 114.16, 103.04, 55.11, 40.11. HRMS (ESI) calculated for [$C_{26}H_{23}N_2O_4S$]+ (M+H$^+$), requires m/z 459.1373, found m/z 459.1377.

2-(1*H*-pyrrol-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one

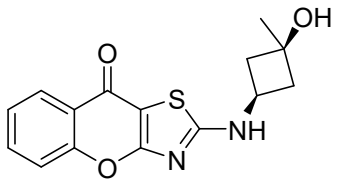


c24

To a 10 mL pressure tube was added *N, N*-dimethylacetamide (2.5 mL), pyrrole (1.05 mmol), CS_2 (0.7 mmol) and sodium hydroxide (1.05 mmol) in sequence. The mixture was stirred at room temperature for 3 h and **a1** (0.35 mmol) and CuO (0.35 mmol) was added. The mixture was then heated to 130 ℃ with stirring for 1 h. After the reaction was cooled to room temperature, the solvent was removed in vacuo. The residue was purified by flash chromatography (petroleum ether/dichloromethane) to give the compound **c24**.

Tawny solid prepared according to **GP2** using the starting materials **a1** and 1H-pyrrole. Yield = 38%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.75 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.43 (t, *J* = 2.3 Hz, 2H), 6.44 (t, *J* = 2.3 Hz, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.41, 164.07, 161.97, 154.17, 133.41, 125.28, 124.82, 121.82, 119.31, 117.58, 113.86, 108.21. HRMS (ESI) calculated for [$C_{14}H_9N_2O_2S$]+ (M+H$^+$), requires m/z 269.0379, found m/z 269.038.

2-(((1s, 3s)-3-hydroxy-3-methylcyclobutyl)amino)-9*H*-chromeno[2, 3-d]thiazol-9-one



c25

Step1

To a 50 mL round-bottom flask was added the tert-butyl ((1s, 3s)-3-hydroxy-3-methylcyclobutyl)carbamate (2.5 mmol) and dichloromethane (20 mL) and trifluoroacetic acid (5 mL) in sequence. The mixture was stirred at room temperature for 4 h. Remove the solvent in vacuo to give (1s, 3s)-3-amino-1-methylcyclobutan-1-ol trifluoroacetate. The intermediate was used for next step without further purification.

Step2

To a 50 mL round-bottom flask was added the trifluoroacetate prepared from step1, ethanol (20 mL) and 4-methoxybenzaldehyde (2.5 mmol, 1 eq) in sequence. The mixture was stirred at room temperature for 16 h and the sodium triacetoxyborohydride (7.5 mmol) was added. Remove the solvent in vacuo after the reation was complete detected by TLC. The residue was purified by flash chromatography (dichloromethane/methanol) to give the intermediate (1s, 3s)-3-((4-methoxybenzyl)amino)-1-methylcyclobutan-1-ol. White solid. Yield = 72%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (d, *J* = 2.1 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 3.78 – 3.74 (m, 5H), 3.15 (p, *J* = 7.6 Hz, 1H), 2.38 – 2.28 (m, 2H), 2.26 – 2.16 (m, 2H), 1.26 (s, 3H). MS (ESI) calculated for $[C_{13}H_{20}NO_2]$+ ($M+H^+$), requires m/z 222.1, found m/z 222.0.

Step3

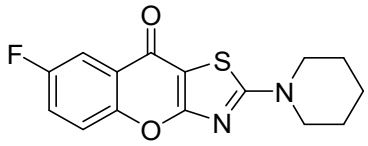
Use the **GP2** to give the intermediate 2-(((1s, 3s)-3-hydroxy-3-methylcyclobutyl)(4-methoxybenzyl)amino)-9*H*-chromeno[2, 3-*d*]thiazol-9-one.

Step4

To a 50 mL round-bottom flask was added the intermediate prepared from step3 and trifluoroacetic acid (10 mL) in sequence. The mixture was stirred at room temperature for 24 h and remove the solvent in vacuo. A saturated sodium carbonate solution was added to the residue to adjust the pH at 10-12. Extracted the aqueous layer with ethyl acetate (50 mL × 3), and combined the organic phase. The mixture was dried with anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol) to give the compound **c25**.

White solid. Yield = 32% (step3 to step4). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.76 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 4.14 – 3.72 (m, 1H), 2.65 – 2.56 (m, 2H), 2.20 – 2.10 (m, 2H), 1.40 (s, 3H). ^{13}C NMR (201 MHz, Trifluoroacetic acid-d_4) δ 175.21, 172.16, 166.85, 156.28, 138.83, 129.90, 126.95, 120.14, 119.96, 103.46, 71.20, 46.49, 45.21, 27.11. HRMS (ESI) calculated for $[C_{15}H_{15}N_2O_3S]$+ ($M+H^+$), requires m/z 303.0798, found m/z 303.0796.

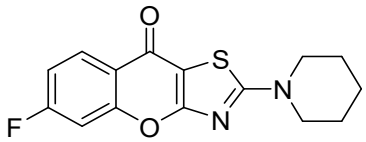
7-fluoro-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c26

Pale yellow solid prepared according to **GP2** using the starting materials **a26** and piperidine. Yield = 52%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.46 (dd, *J* = 9.1, 4.2 Hz, 1H), 7.33 – 7.28 (m, 1H), 3.63 (s, 4H), 1.74 – 1.69 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.57, 169.73 (d, *J* = 2.1 Hz), 165.31, 159.43 (d, *J* = 245.5 Hz), 150.23 (d, *J* = 2.0 Hz), 124.14 (d, *J* = 7.2 Hz), 120.42 (d, *J* = 25.2 Hz), 119.56 (d, *J* = 8.1 Hz), 110.69 (d, *J* = 24.3 Hz), 103.30, 49.58, 25.25, 23.82. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -116.24. HRMS (ESI) calculated for $[C_{15}H_{14}FN_2O_2S]^+$ ($M+H^+$), requires m/z 305.0755, found m/z 305.0763.

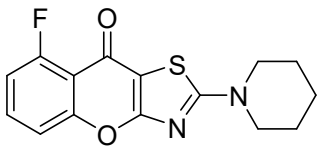
6-fluoro-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c27

Pale yellow solid prepared according to **GP2** using the starting materials **a27** and piperidine. Yield = 33%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (dd, *J* = 8.8, 6.3 Hz, 1H), 7.17 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.15 – 7.09 (m, 1H), 3.64 (s, 4H), 1.74 – 1.71 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.44, 169.90, 165.09, 164.98 (d, *J* = 253.2 Hz), 155.04 (d, *J* = 13.2 Hz), 127.65 (d, *J* = 10.3 Hz), 119.56 (d, *J* = 2.6 Hz), 113.12 (d, *J* = 22.4 Hz), 104.63 (d, *J* = 25.8 Hz), 103.27, 49.49, 25.16, 23.75. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -84.14 – -119.55 (m). HRMS (ESI) calculated for $[C_{15}H_{14}FN_2O_2S]^+$ ($M+H^+$), requires m/z 305.0755, found m/z 305.0760.

8-fluoro-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-d]thiazol-9-one

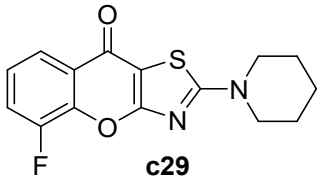


c28

Pale yellow solid prepared according to **GP2** using the starting materials **a28** and piperidine. Yield = 19%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 – 7.50 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.82 – 3.47 (m, 4H), 1.76 – 1.72 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.66, 169.34, 164.15, 160.95 (d, *J* = 263.3 Hz), 155.50 (d, *J* = 3.9 Hz), 132.55 (d, *J* = 10.9 Hz), 113.87 (d, *J* = 4.2 Hz), 113.28 (d, *J* = 10.1 Hz), 112.30 (d, *J* = 21.3 Hz), 104.54, 49.63, 25.31, 23.90. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -112.38 – -112.71 (m). HRMS (ESI) calculated for

$[C_{15}H_{14}FN_2O_2S]+$ (M+H$^+$), requires m/z 305.0755, found m/z 305.0754.

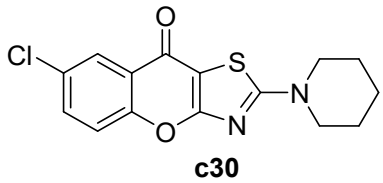
5-fluoro-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c29

Pale yellow solid prepared according to **GP2** using the starting materials **a29** and piperidine. Yield = 45%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.39 (ddd, *J* = 9.9, 8.0, 1.6 Hz, 1H), 7.31 (td, *J* = 8.0, 4.5 Hz, 1H), 3.66 (s, 4H), 1.74 – 1.71 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.63, 169.86 (d, *J* = 2.7 Hz), 164.67, 151.08 (d, *J* = 252.7 Hz), 142.84 (d, *J* = 11.5 Hz), 124.93, 124.44 (d, *J* = 6.6 Hz), 120.51 (d, *J* = 3.8 Hz), 118.83 (d, *J* = 16.8 Hz), 103.90, 49.61, 25.29, 23.86. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -133.05. HRMS (ESI) calculated for $[C_{15}H_{14}FN_2O_2S]^+$ (M+H$^+$), requires m/z 305.0755, found m/z 305.0760.

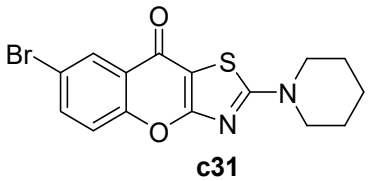
7-chloro-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c30

White solid prepared according to **GP2** using the starting materials **a30** and piperidine. Yield = 63%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.18 (d, *J* = 2.6 Hz, 1H), 7.54 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.42 (d, *J* = 8.9 Hz, 1H), 3.64 (s, 4H), 1.77 – 1.68 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.63, 169.42, 165.20, 152.51, 132.74, 130.67, 125.03, 123.94, 119.37, 103.59, 49.88, 25.28, 23.84. HRMS (ESI) calculated for $[C_{15}H_{14}ClN_2O_2S]^+$ (M+H$^+$), requires m/z 321.0459, found m/z 321.0465.

7-bromo-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one

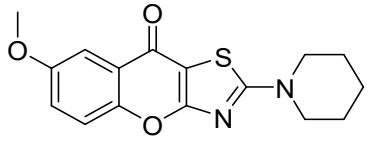


c31

White solid prepared according to **GP2** using the starting materials **a31** and piperidine. Yield = 50%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 2.5 Hz, 1H), 7.68 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 3.65 (s, 4H), 1.76 – 1.71 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.67, 169.33, 165.20, 153.01, 135.58, 128.21, 124.33, 119.68, 118.14, 103.62, 49.56, 25.30, 23.86. HRMS (ESI)

calculated for $[C_{15}H_{14}BrN_2O_2S]^+$ (M+H$^+$), requires m/z 364.9954, found m/z 364.9959.

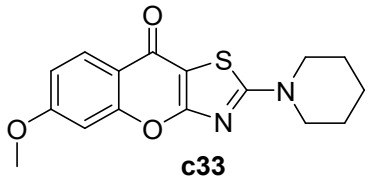
7-methoxy-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c32

White solid prepared according to **GP2** using the starting materials **a32** and piperidine. Yield = 58%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 3.1 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.19 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.89 (s, 3H), 3.64 (s, 4H), 1.76 – 1.69 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.44, 170.73, 165.13, 156.73, 148.83, 123.39, 122.09, 119.05, 105.54, 103.39, 56.06, 49.56, 25.29, 23.91. HRMS (ESI) calculated for $[C_{16}H_{17}N_2O_3S]^+$ (M+H$^+$), requires m/z 317.0954, found m/z 317.0953.

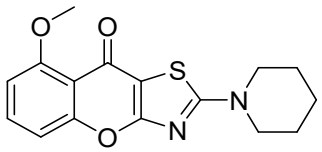
6-methoxy-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c33

White solid prepared according to **GP2** using the starting materials **a33** and piperidine. Yield = 49%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 8.8 Hz, 1H), 6.99 – 6.93 (m, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 3.88 (s, 3H), 3.63 (s, 4H), 1.74 – 1.68 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.35, 170.78, 164.84, 163.45, 155.92, 126.83, 116.59, 113.12, 103.14, 101.02, 55.87, 49.49, 25.27, 23.92. HRMS (ESI) calculated for $[C_{16}H_{17}N_2O_3S]^+$ (M+H$^+$), requires m/z 317.0954, found m/z 317.0962.

8-methoxy-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one

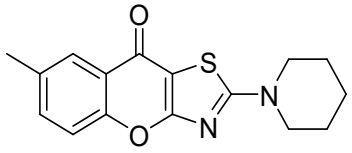


c34

White solid prepared according to **GP2** using the starting materials **a34** and piperidine. Yield = 54%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (t, *J* = 8.3 Hz, 1H), 7.10 – 7.02 (m, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 3.95 (s, 3H), 3.60 (s, 4H), 1.74 – 1.64 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.41, 171.11, 163.21, 159.88, 156.55, 132.59, 113.24, 110.24, 106.84, 105.06, 56.58, 49.37, 25.22, 23.85. HRMS (ESI) calculated for $[C_{16}H_{17}N_2O_3S]^+$ (M+H$^+$), requires m/z 317.0954, found m/z 317.0957.

HRMS (ESI) calculated for $[C_{16}H_{17}N_2O_3S]^+$ (M+H$^+$), requires m/z 317.0954, found m/z 317.09.

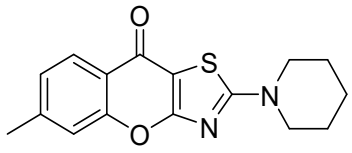
7-methyl-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c35

White solid prepared according to **GP2** using the starting materials **a35** and piperidine. Yield = 72%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 2.2 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 3.63 (s, 4H), 2.44 (s, 3H), 1.74 – 1.69 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.49, 171.02, 165.08, 152.48, 134.70, 133.83, 125.02, 122.44, 117.51, 103.54, 49.52, 25.27, 23.89, 20.99. HRMS (ESI) calculated for $[C_{16}H_{17}N_2O_2S]^+$ (M+H$^+$), requires m/z 301.1005, found m/z 301.1015.

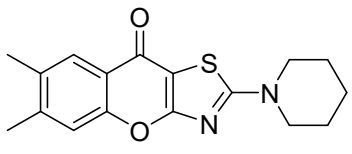
6-methyl-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c36

White solid prepared according to **GP2** using the starting materials **a36** and piperidine. Yield = 60%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.07 (m, 1H), 7.26 (d, *J* = 3.4 Hz, 1H), 7.19 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.66 – 3.57 (m, 4H), 2.45 (s, 3H), 1.72 – 1.68 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.46, 170.95, 164.93, 154.39, 143.94, 126.17, 125.26, 120.49, 117.62, 103.38, 49.47, 25.25, 23.86, 21.79. HRMS (ESI) calculated for $[C_{16}H_{17}N_2O_2S]^+$ (M+H$^+$), requires m/z 301.1005, found m/z 301.1011.

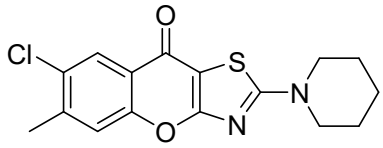
6, 7-dimethyl-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c37

Pale yellow solid prepared according to **GP2** using the starting materials **a37** and piperidine. Yield = 56%. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.25 (s, 1H), 3.64 (s, 4H), 2.37 (s, 3H), 2.34 (s, 3H), 1.74 – 1.70 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 171.43, 171.19, 164.93, 152.76, 142.94, 133.90, 125.32, 120.52, 118.04, 103.41, 49.50, 25.30, 23.93, 20.44, 19.39. HRMS (ESI) calculated for $[C_{17}H_{19}N_2O_2S]^+$ (M+H$^+$), requires m/z 315.1162, found m/z 315.1116.

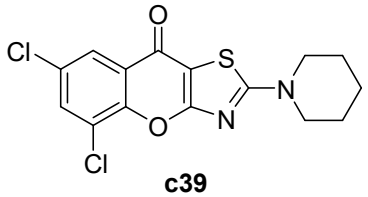
7-chloro-6-methyl-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c38

Pale yellow solid prepared according to **GP2** using the starting materials **a38** and piperidine. Yield = 58%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.33 (s, 1H), 3.63 (s, 4H), 2.47 (s, 3H), 1.91 – 1.39 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.54, 169.64, 165.05, 152.43, 141.64, 131.28, 125.26, 121.96, 119.60, 103.36, 49.66, 25.28, 23.87, 20.79. HRMS (ESI) calculated for $[C_{16}H_{16}ClN_2O_2S]^+$ ($M+H^+$), requires m/z 335.0616, found m/z 335.0618.

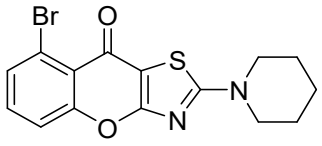
5, 7-dichloro-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c39

Yellow solid prepared according to **GP2** using the starting materials **a39** and piperidine. Yield = 30%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 2.6 Hz, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 3.68 (s, 4H), 1.78 – 1.70 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.79, 168.61, 165.10, 148.65, 132.83, 130.44, 125.03, 123.90 (d, *J* = 2.5 Hz), 103.81, 49.69, 25.36, 23.87. HRMS (EI) calculated for $[C_{15}H_{12}O_2N_2Cl_2S]^+$ (M^+), requires m/z 353.9983, found m/z 353.9991.

8-bromo-2-(piperidin-1-yl)-9*H*-chromeno[2, 3-*d*]thiazol-9-one



c40

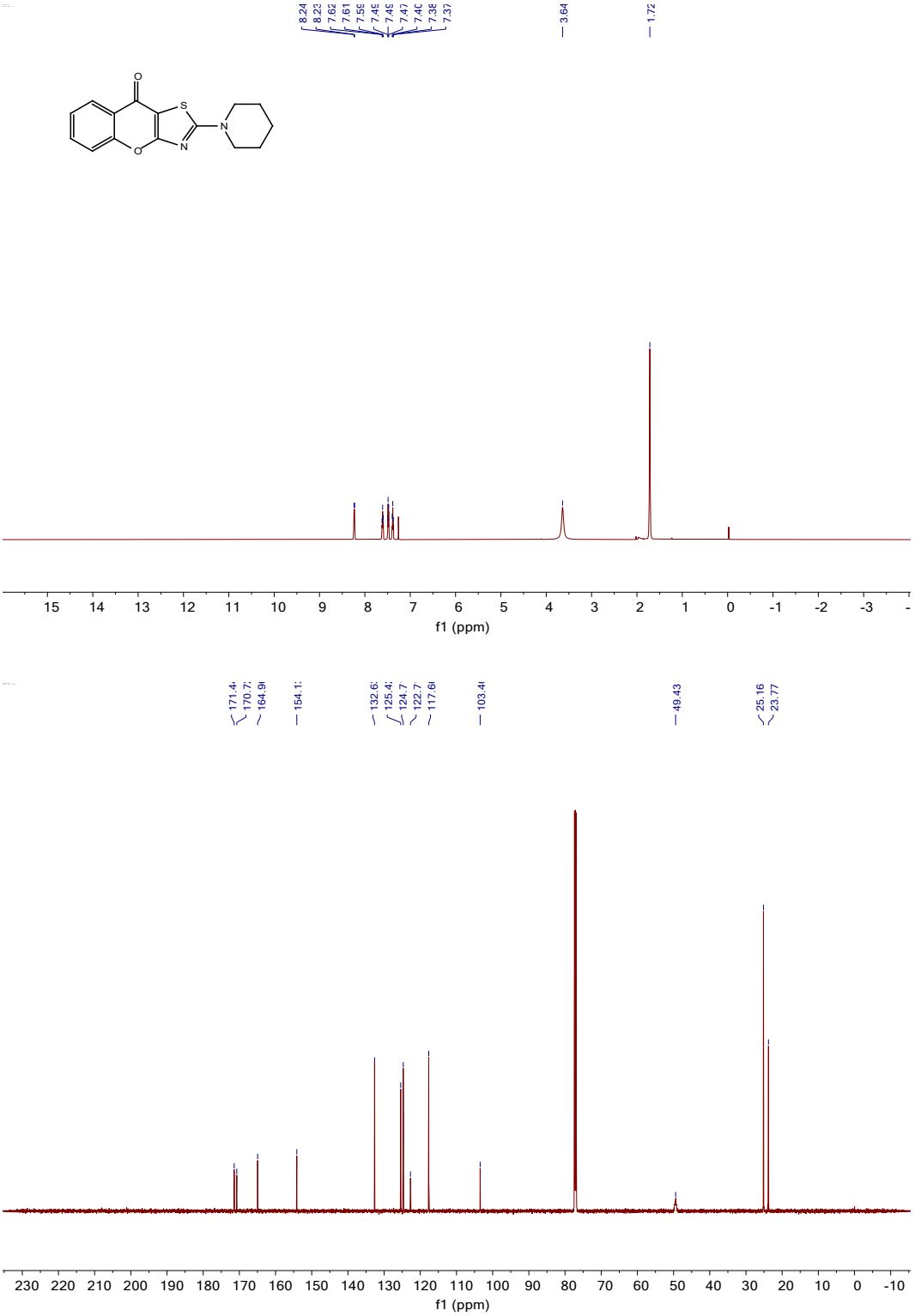
White solid prepared according to **GP2** using the starting materials **a40** and piperidine. Yield = 23%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.38 (t, *J* = 8.1 Hz, 1H), 3.65 (s, 4H), 1.75 – 1.71 (m, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.22, 169.11, 162.97, 155.39, 131.59, 131.45, 119.82, 119.70, 117.42, 104.25, 49.04, 24.69, 23.26. HRMS (ESI) calculated for $[C_{15}H_{14}BrN_2O_2S]$+ ($M+H^+$), requires m/z 364.9954, found m/z 364.9952.

3. Reference

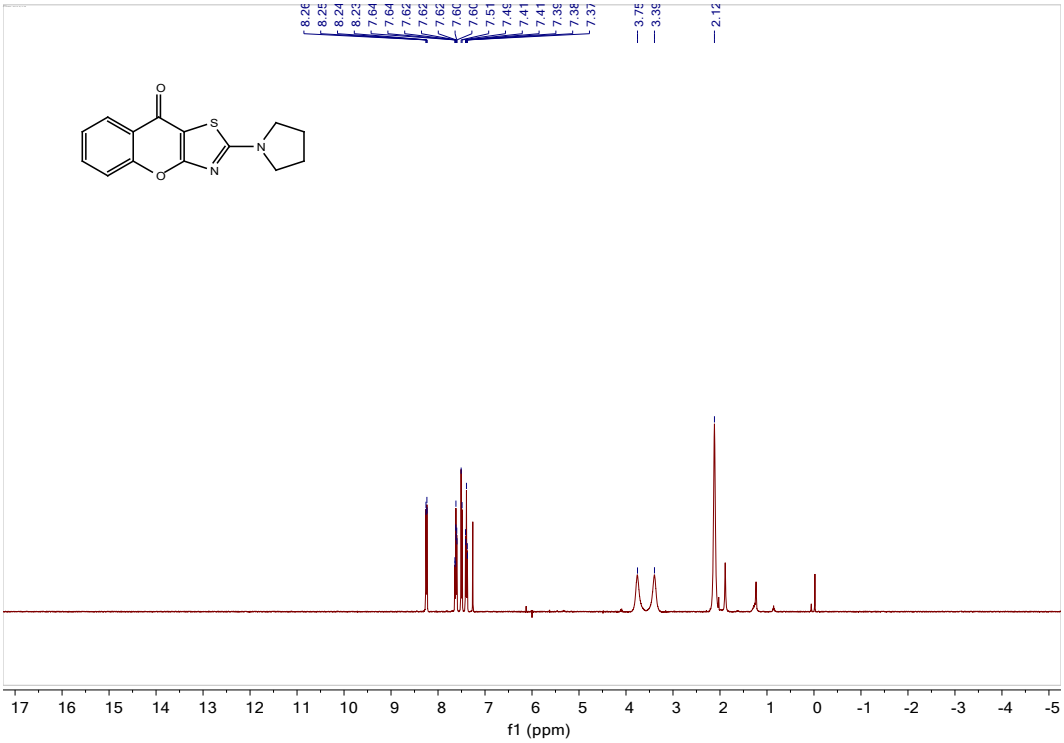
1. P. Tong, Z. Sun, S. Wang, Y. Zhang and Y. Li, *J. Org. Chem.*, 2019, **84**, 13967-13974.
2. C. Bandyopadhyay, T. Ghosh and S. Saha, *Synthesis*, 2005, **2005**, 1845-1849.

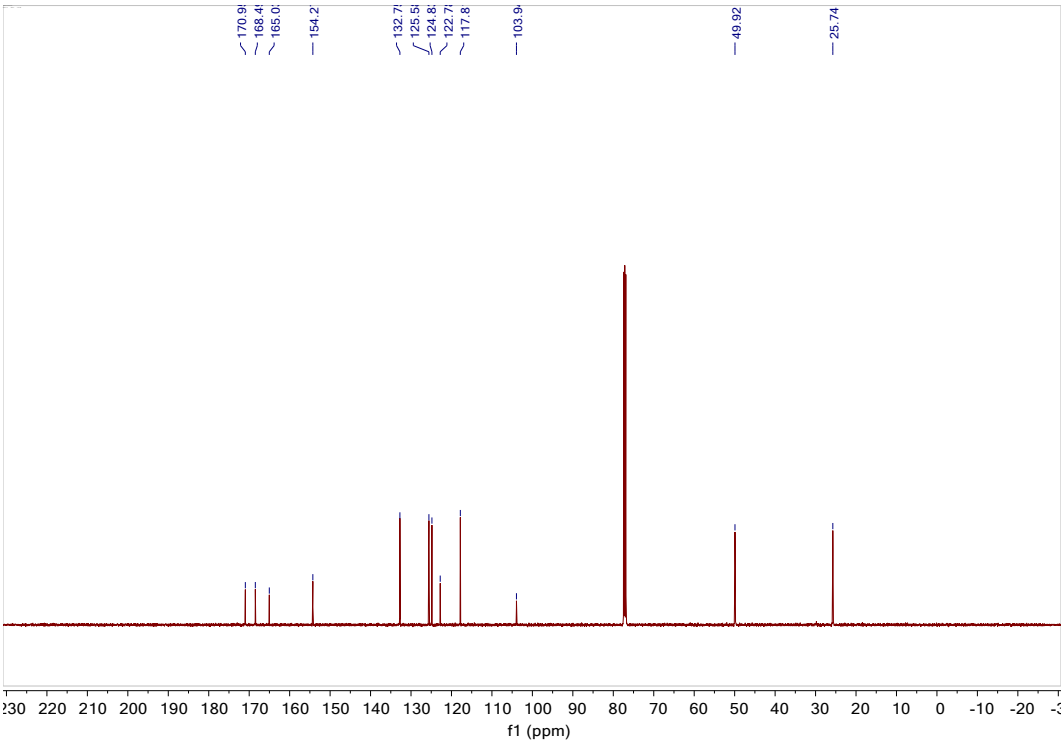
Copies of ^{1}H, ^{13}C, and ^{19}F NMR Spectra

^{1}H NMR and ^{13}C NMR of compound **c1**

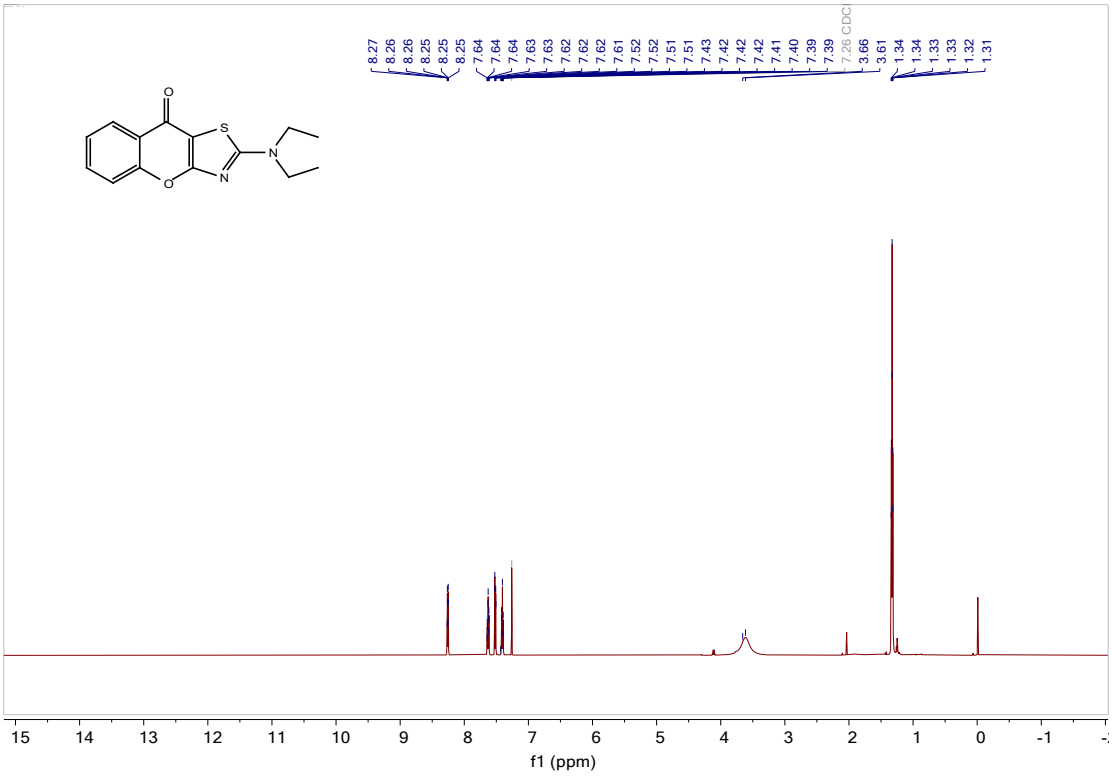


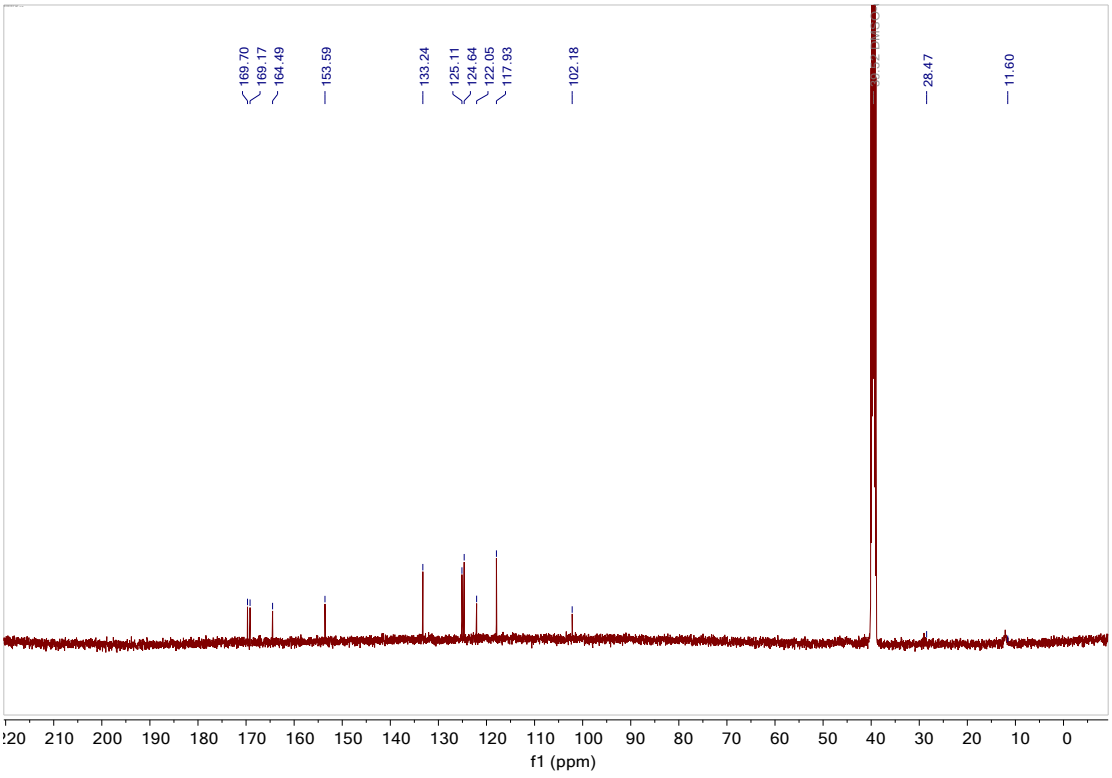
^{1}H NMR and ^{13}C NMR of compound **c2**



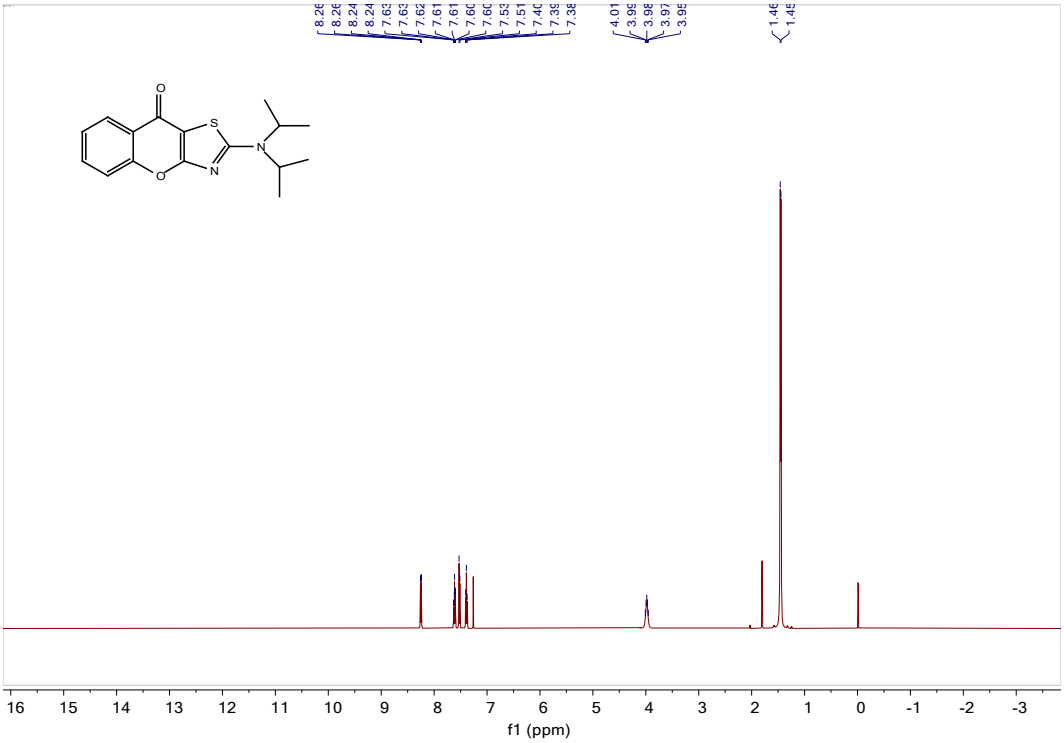


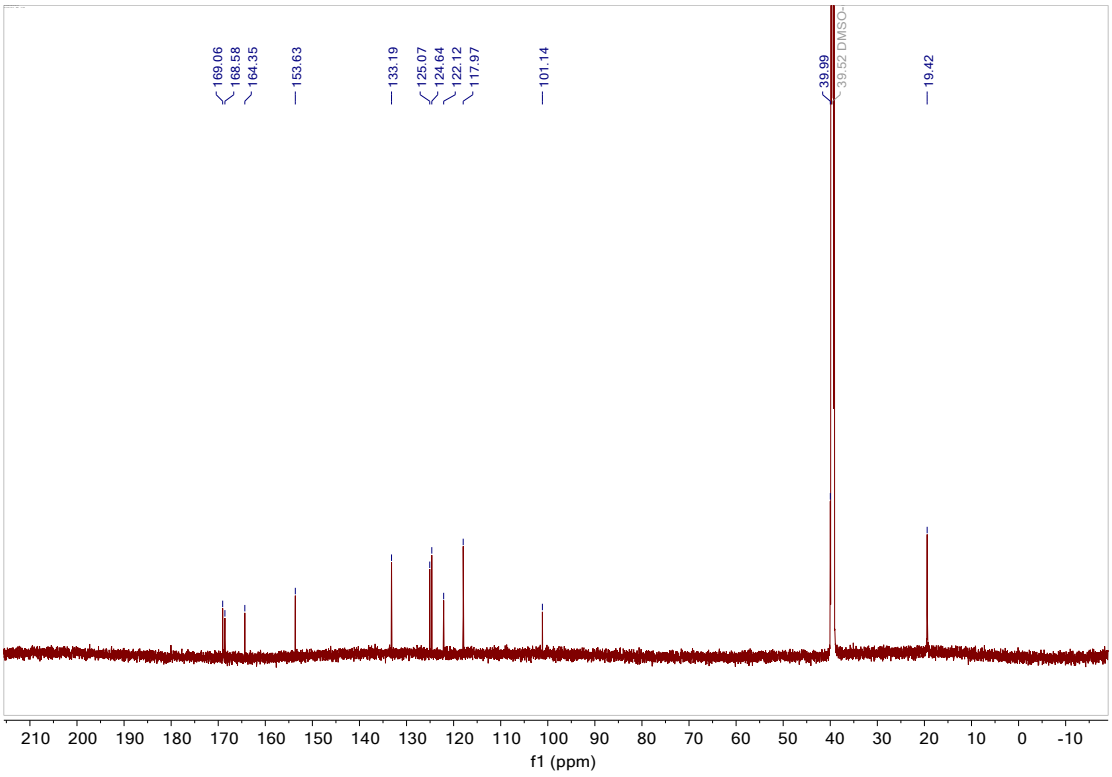
^{1}H NMR and ^{13}C NMR of compound **c3**



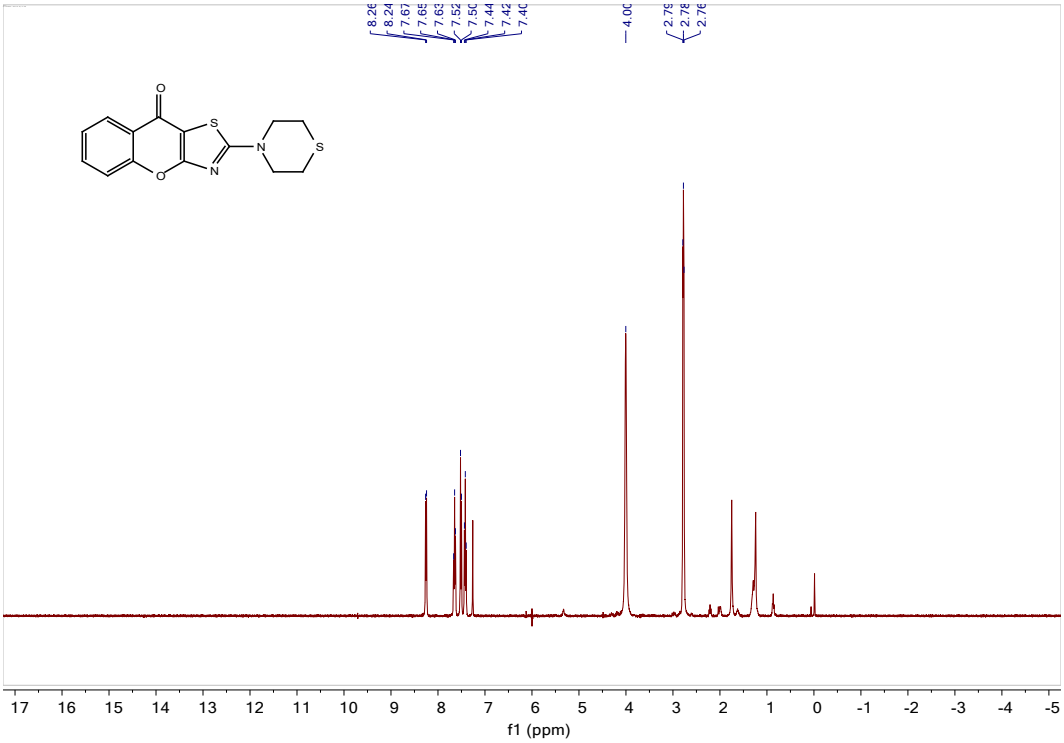


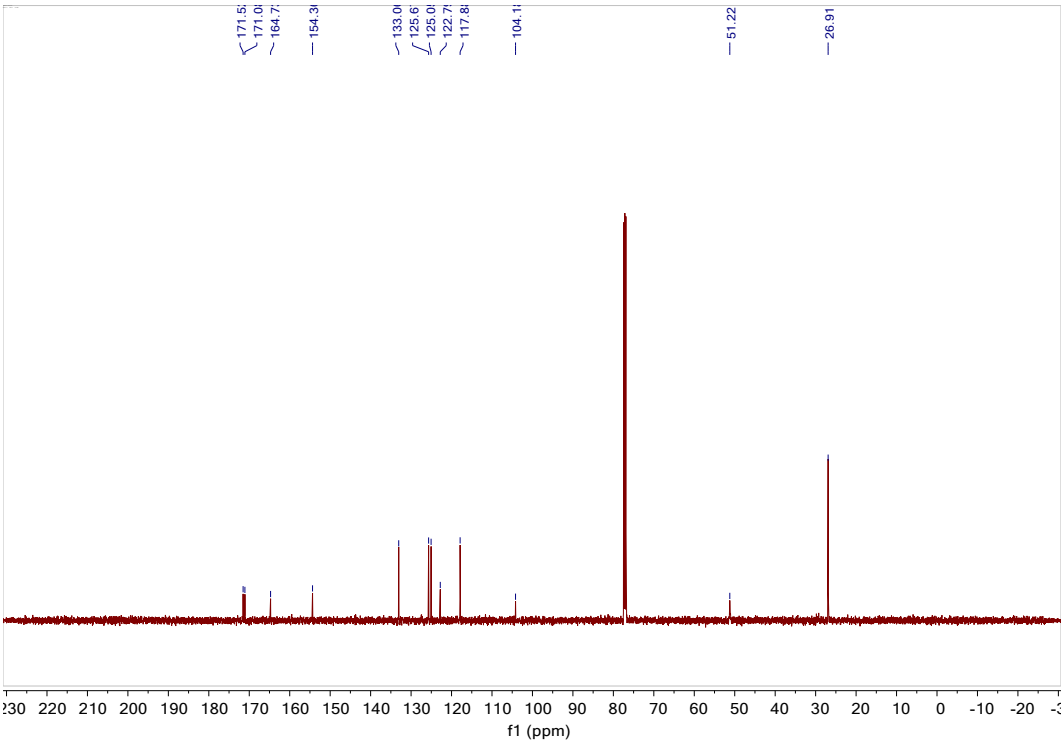
^{1}H NMR and ^{13}C NMR of compound **c4**



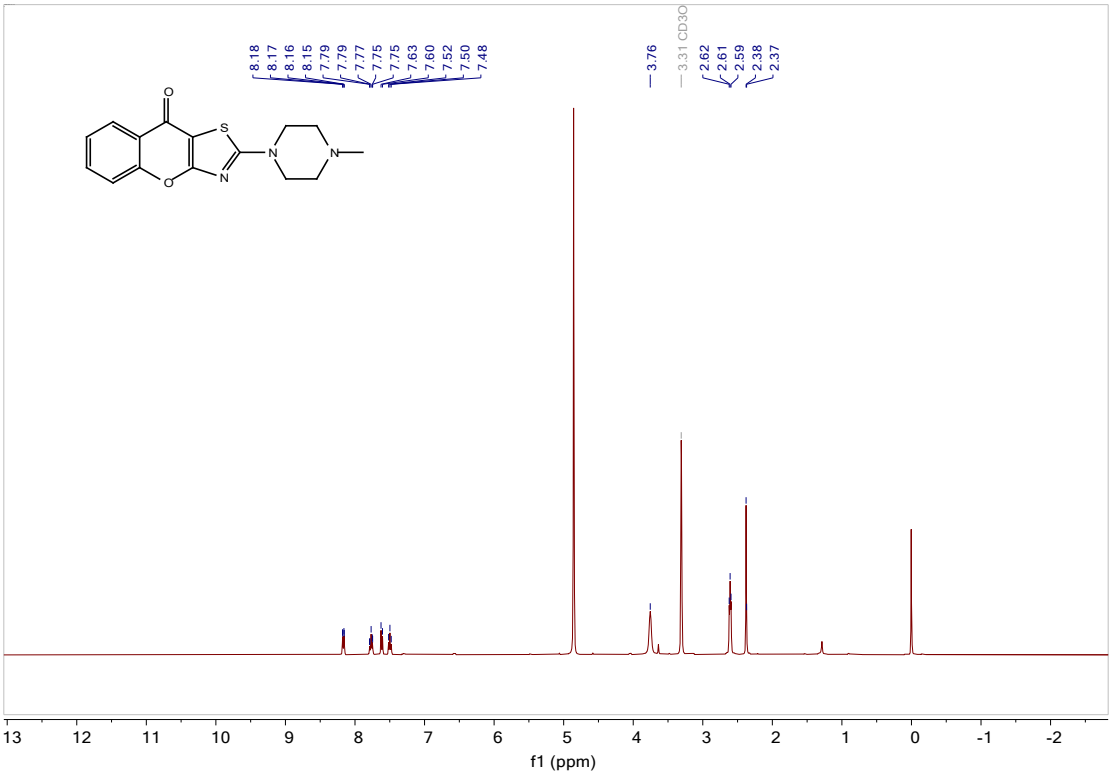


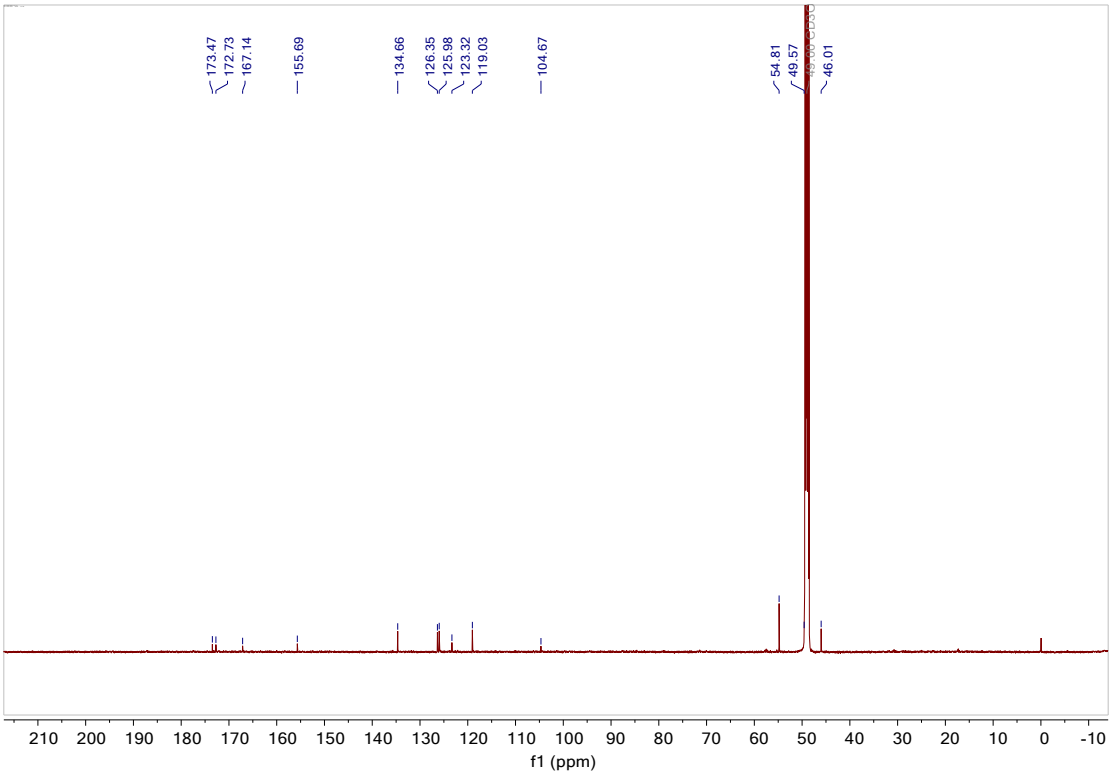
^{1}H NMR and ^{13}C NMR of compound **c5**



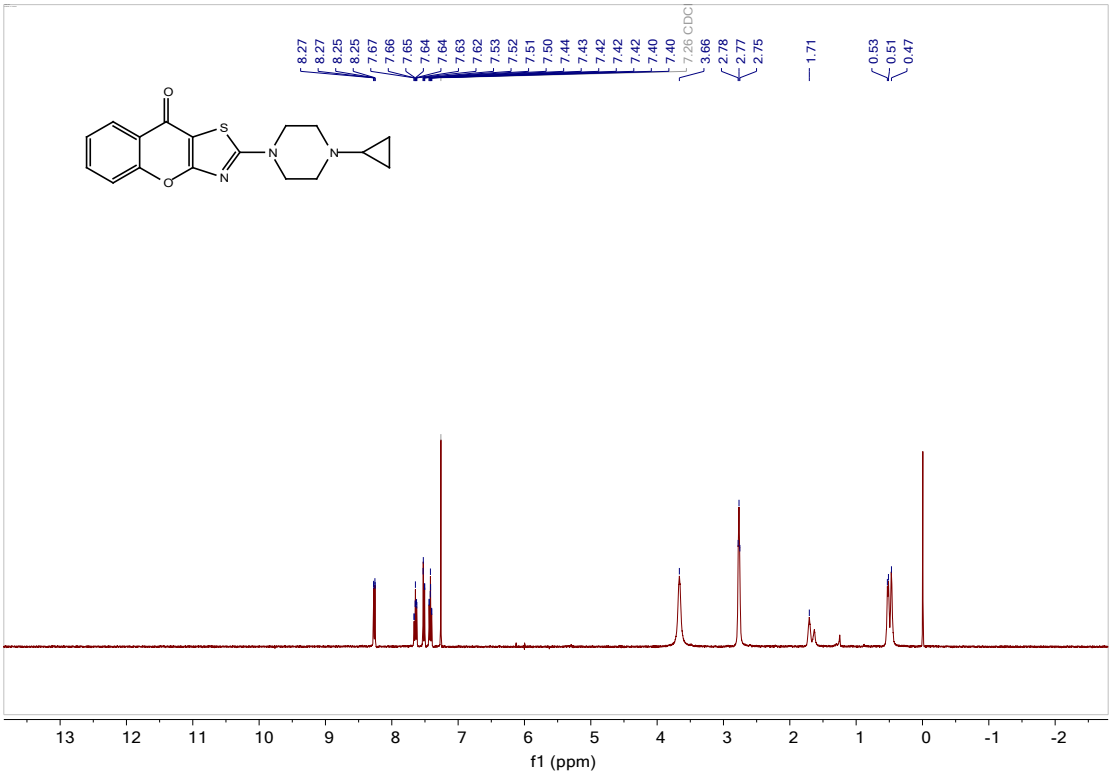


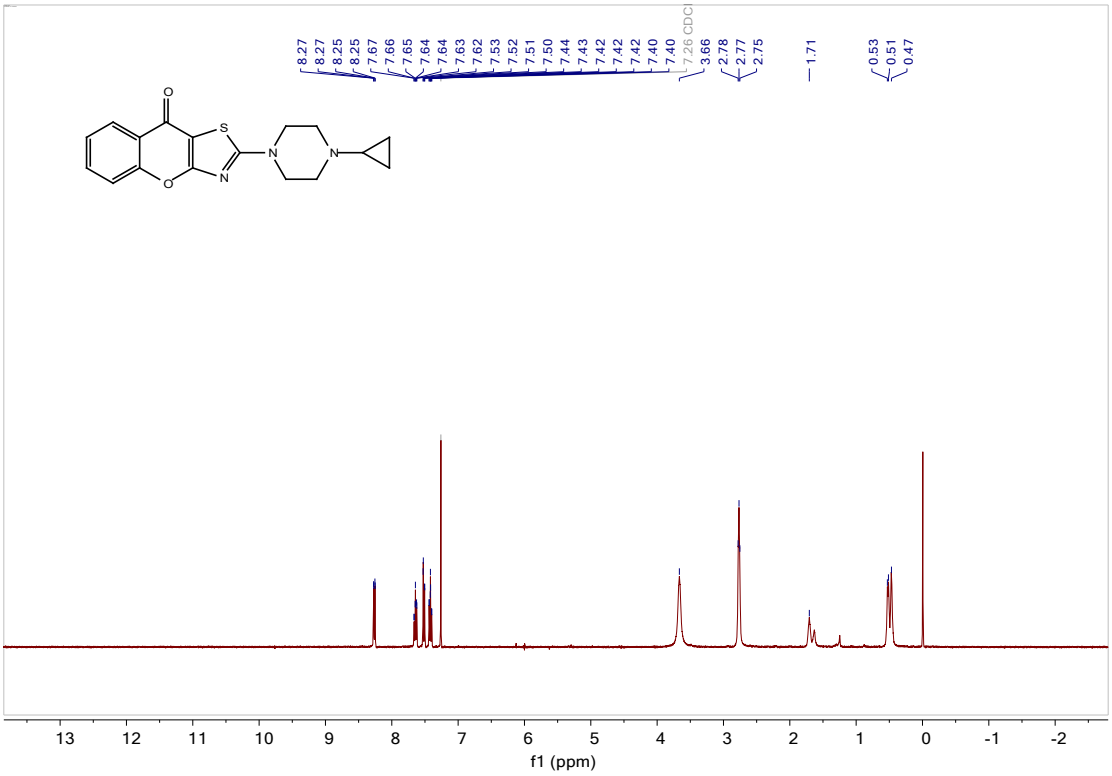
^{1}H NMR and ^{13}C NMR of compound **c6**



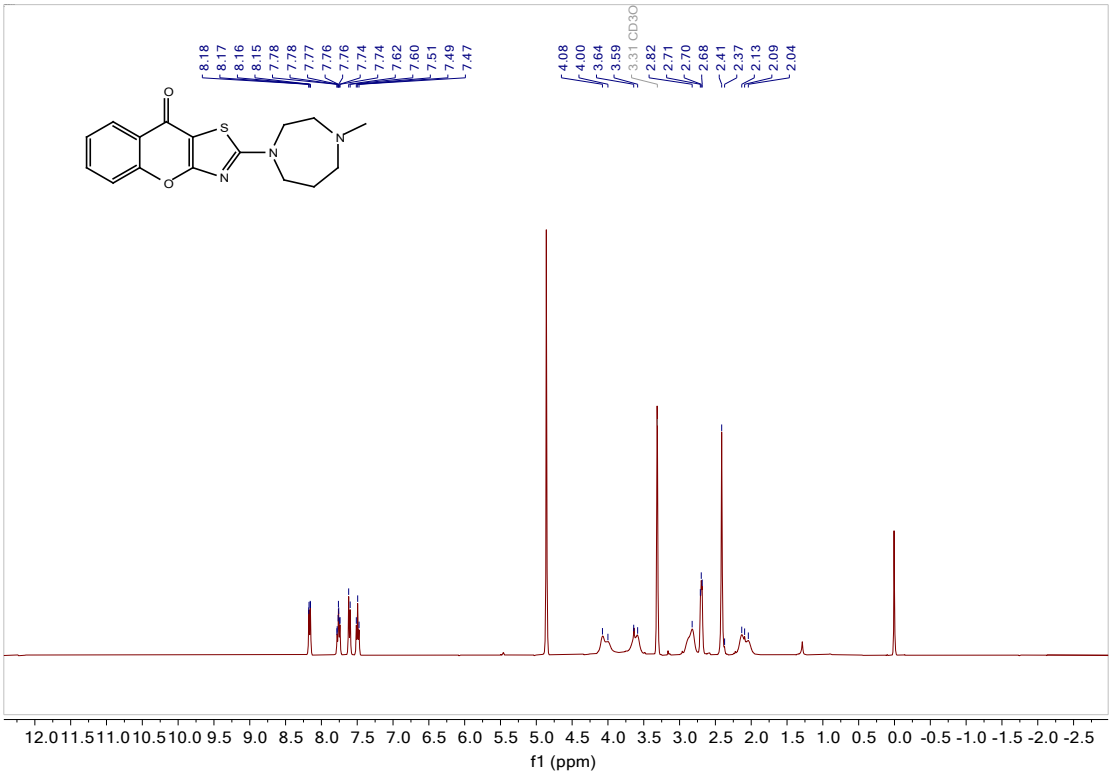


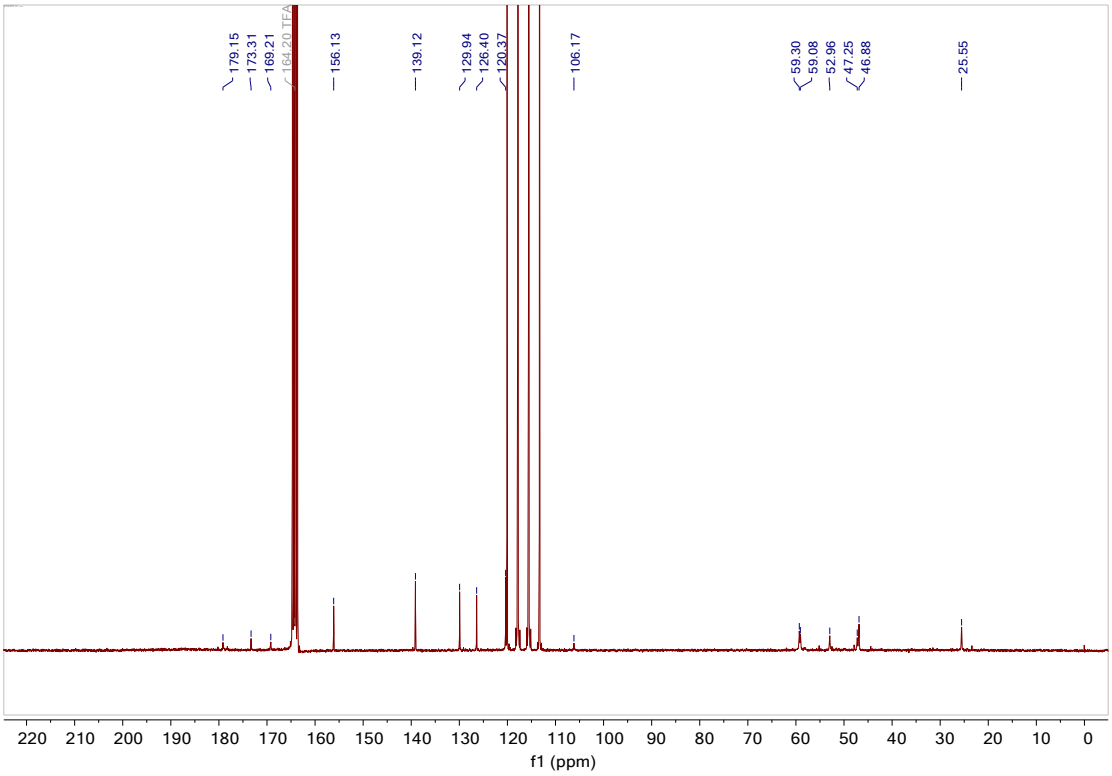
^{1}H NMR and ^{13}C NMR of compound **c7**



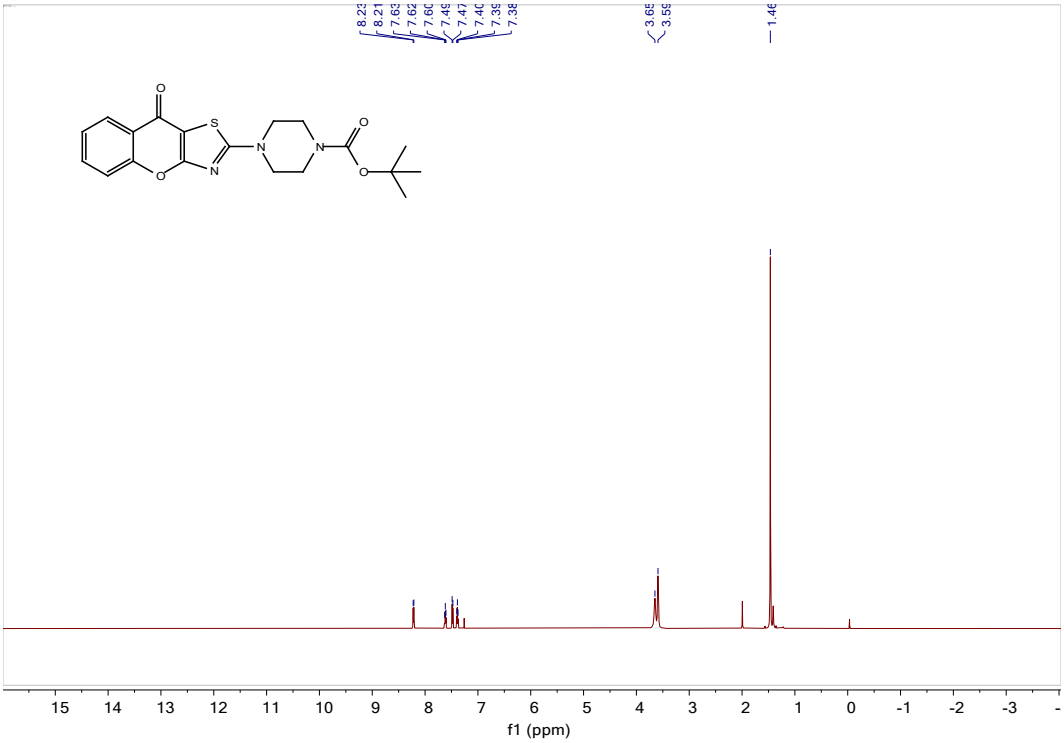


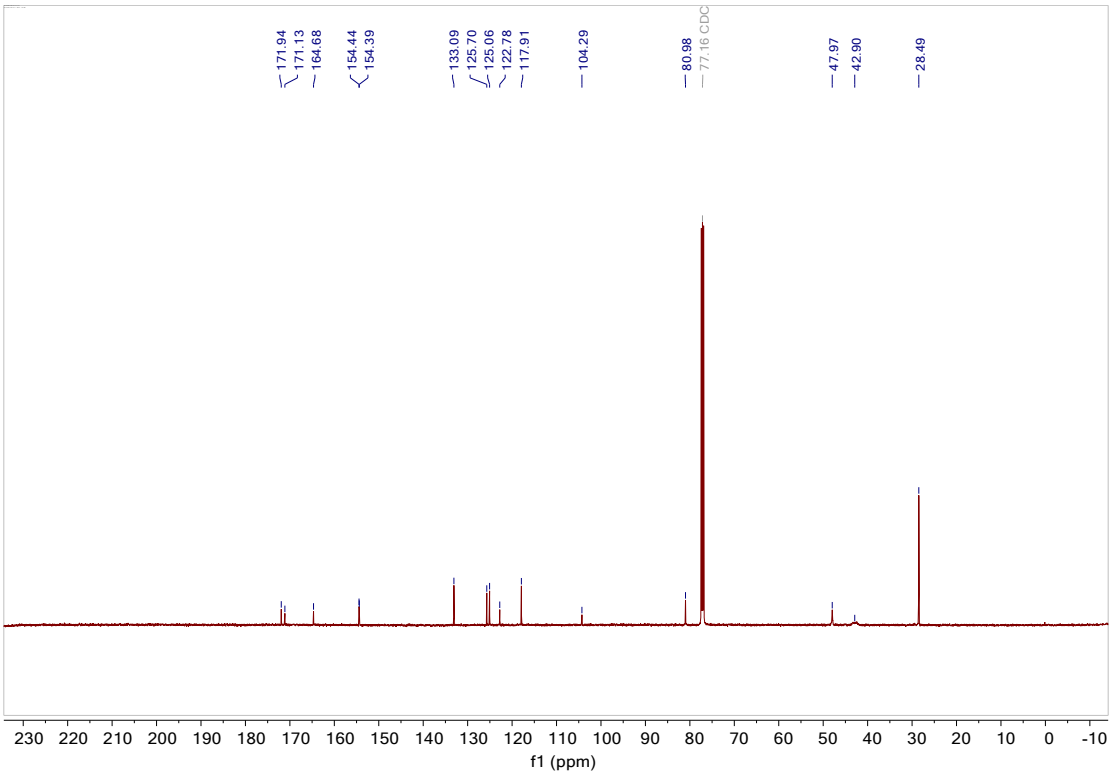
^{1}H NMR and ^{13}C NMR of compound **c8**



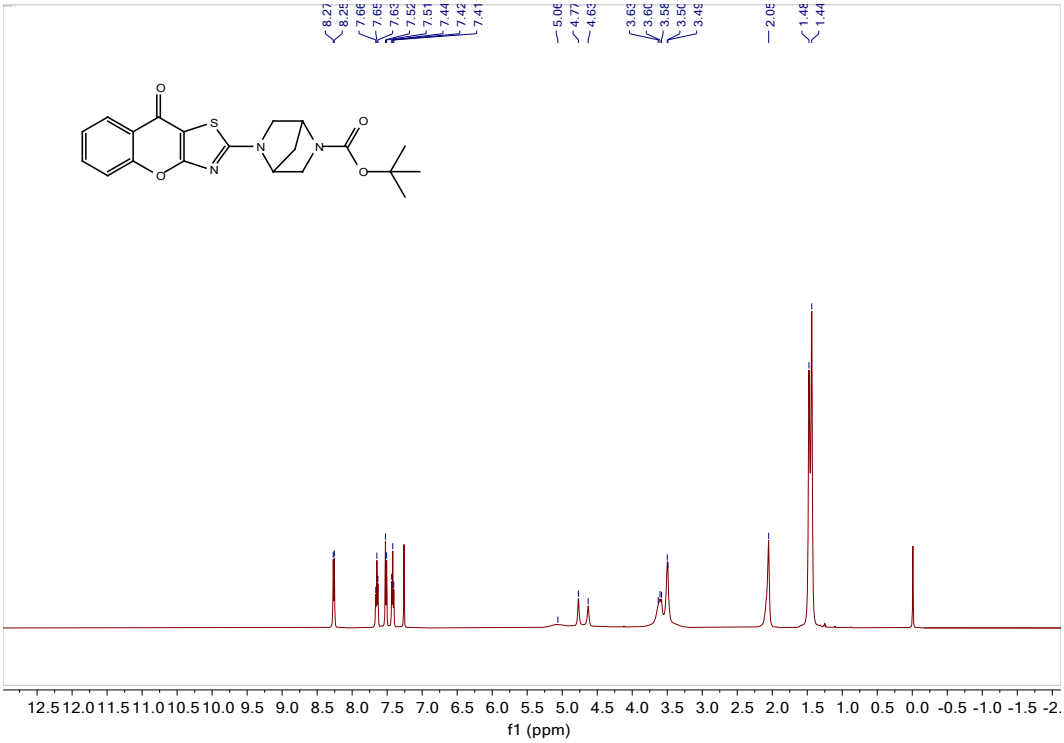


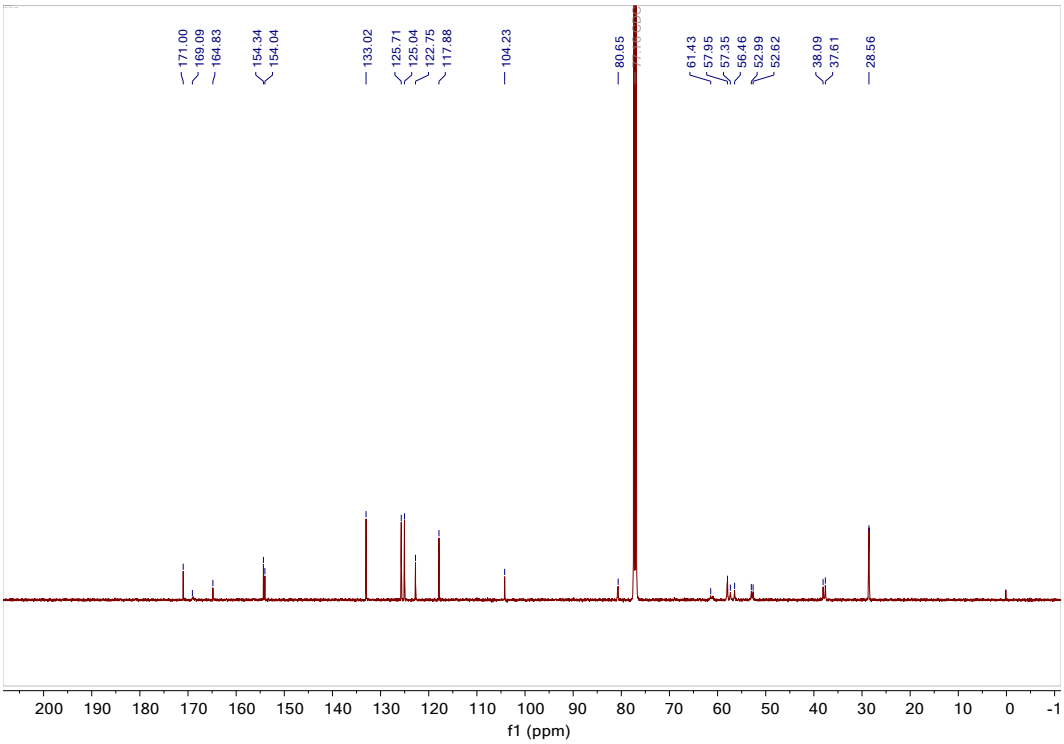
^{1}H NMR and ^{13}C NMR of compound **c9**



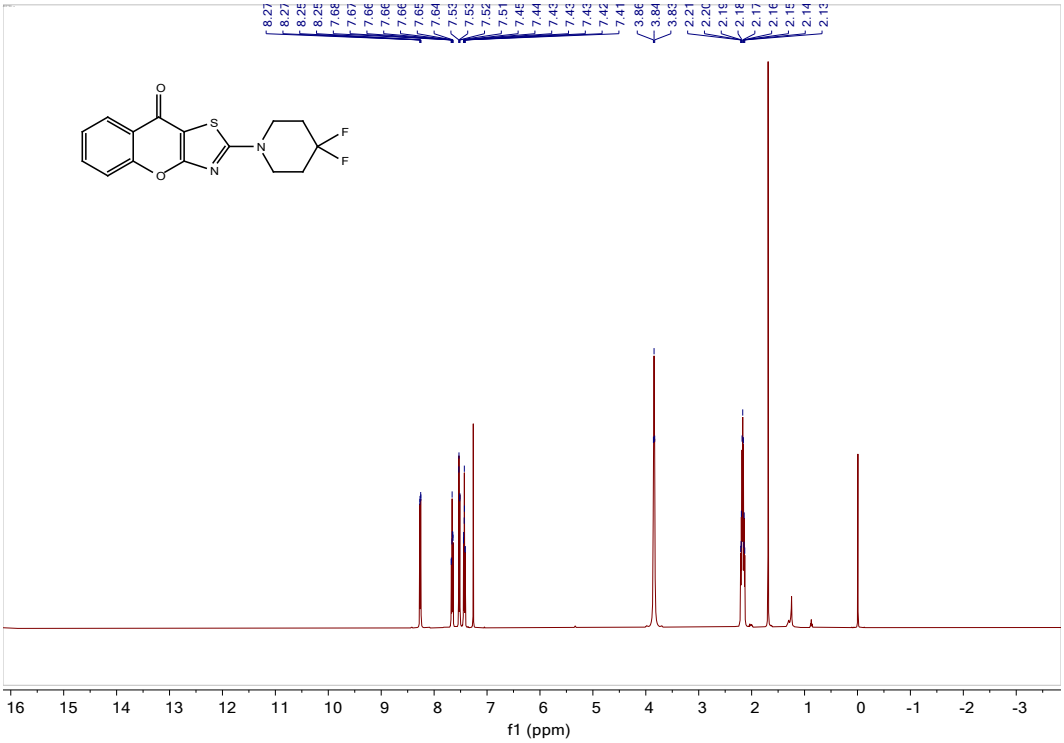


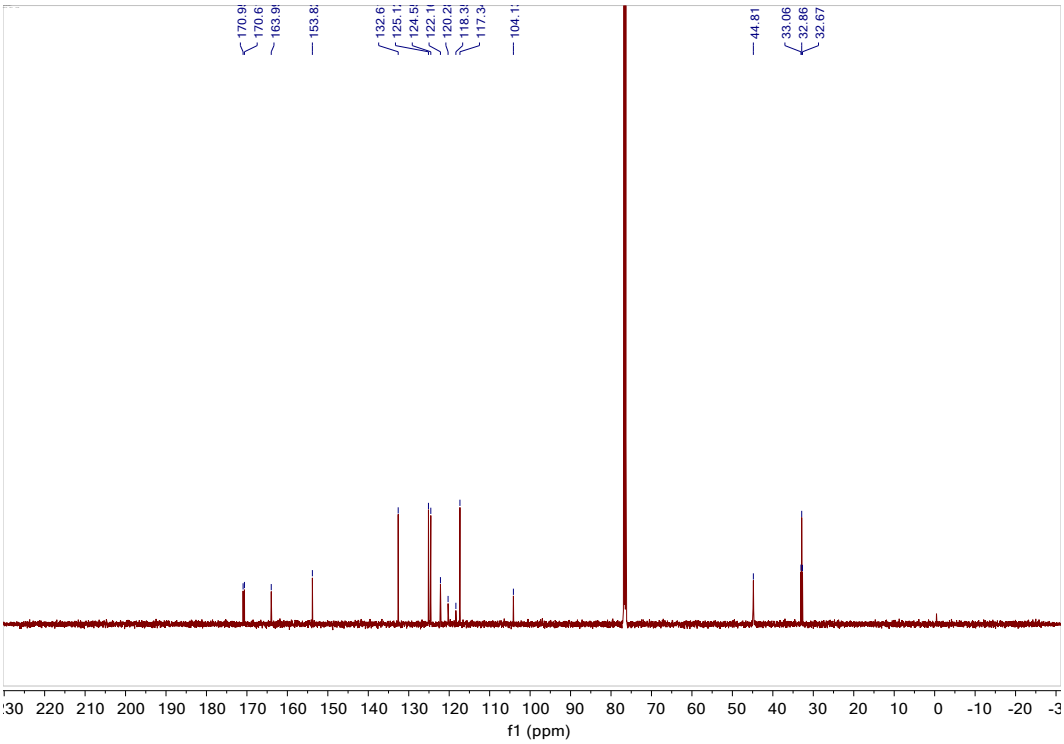
^{1}H NMR and ^{13}C NMR of compound **c10**



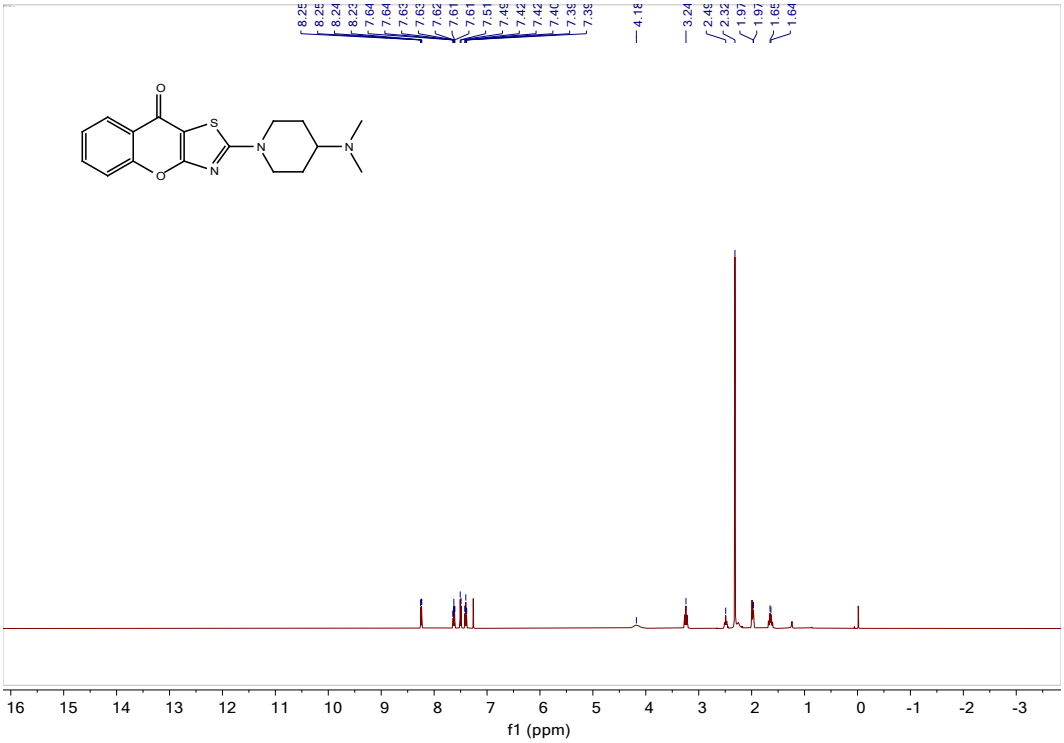


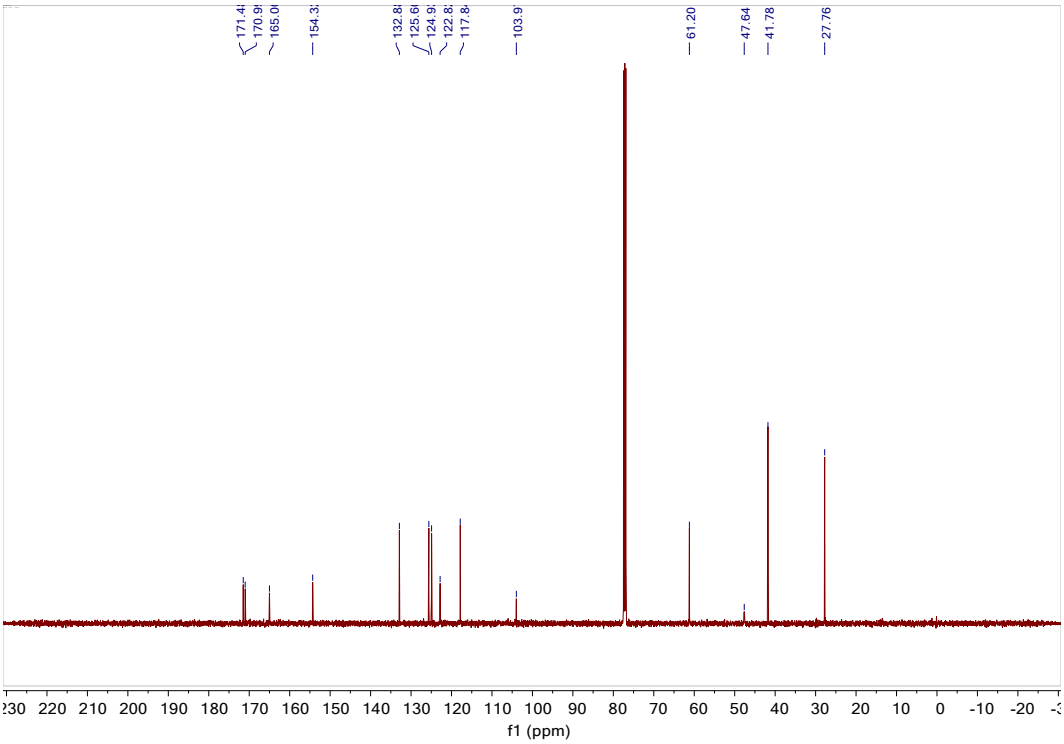
^{1}H NMR and ^{13}C NMR of compound **c11**



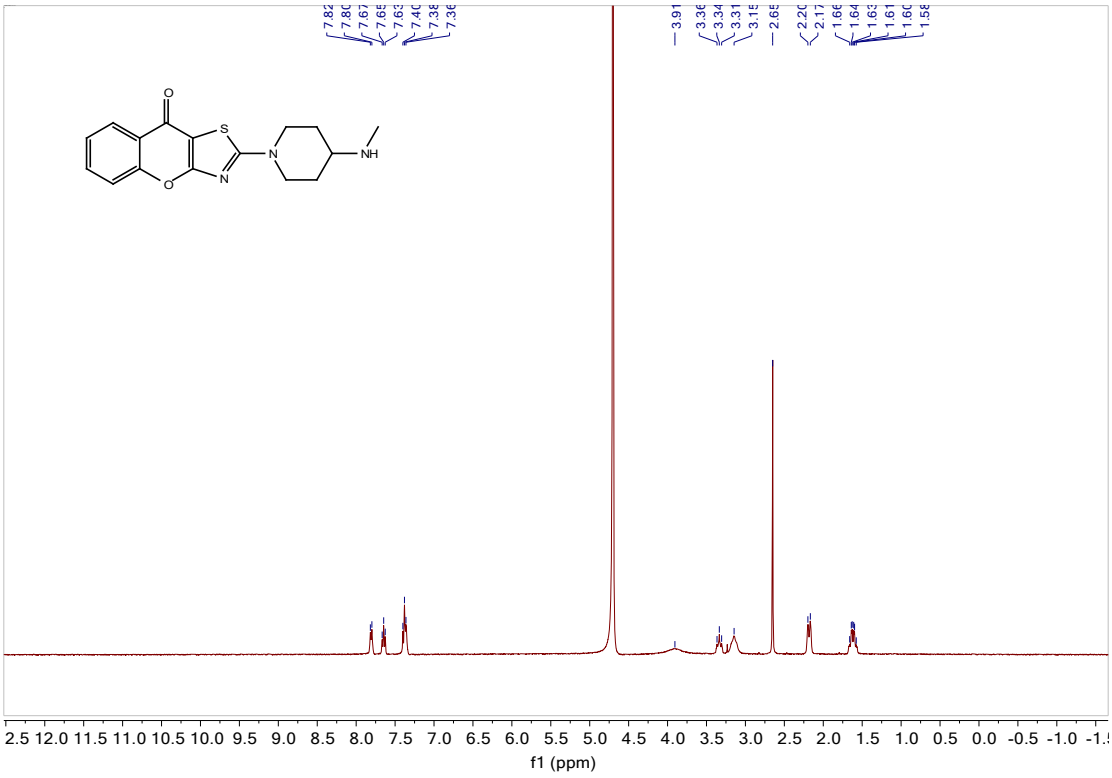


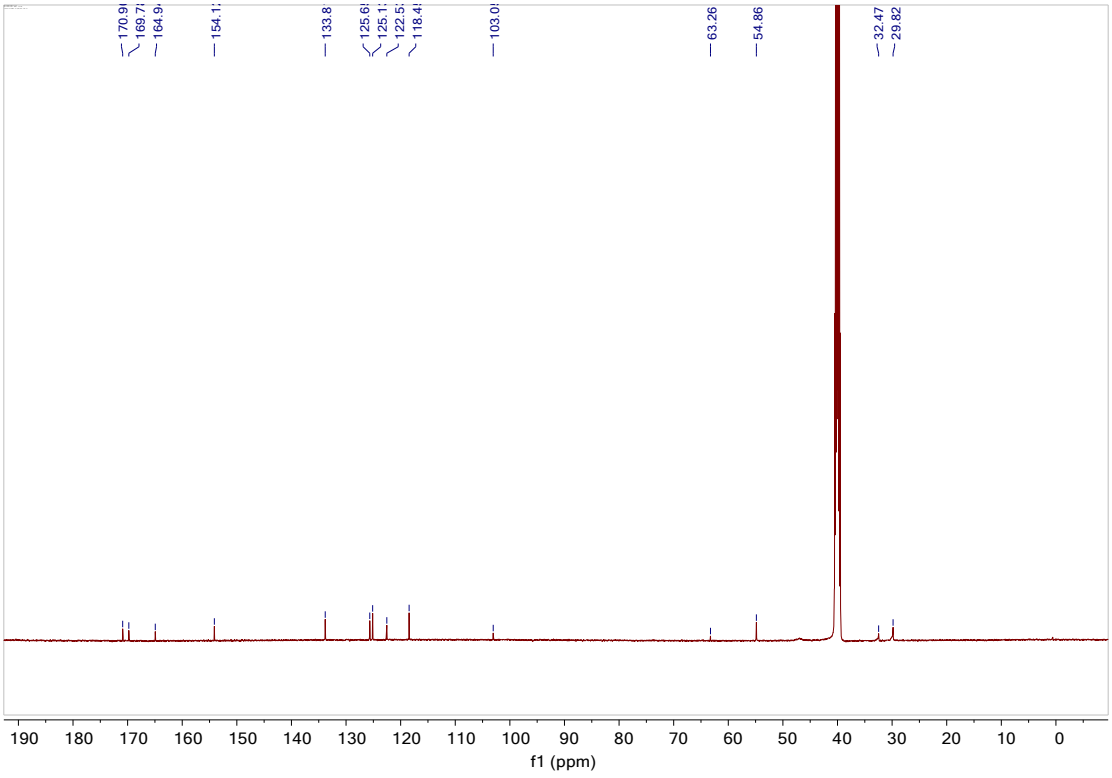
^{1}H NMR and ^{13}C NMR of compound **c12**



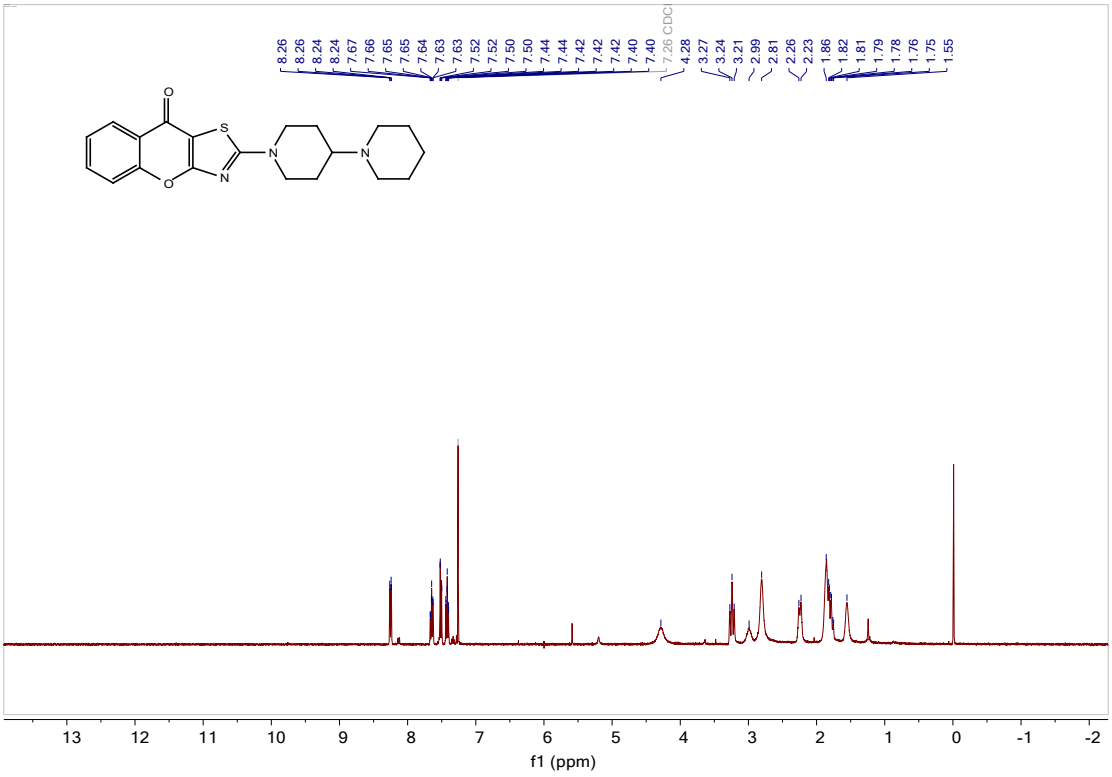


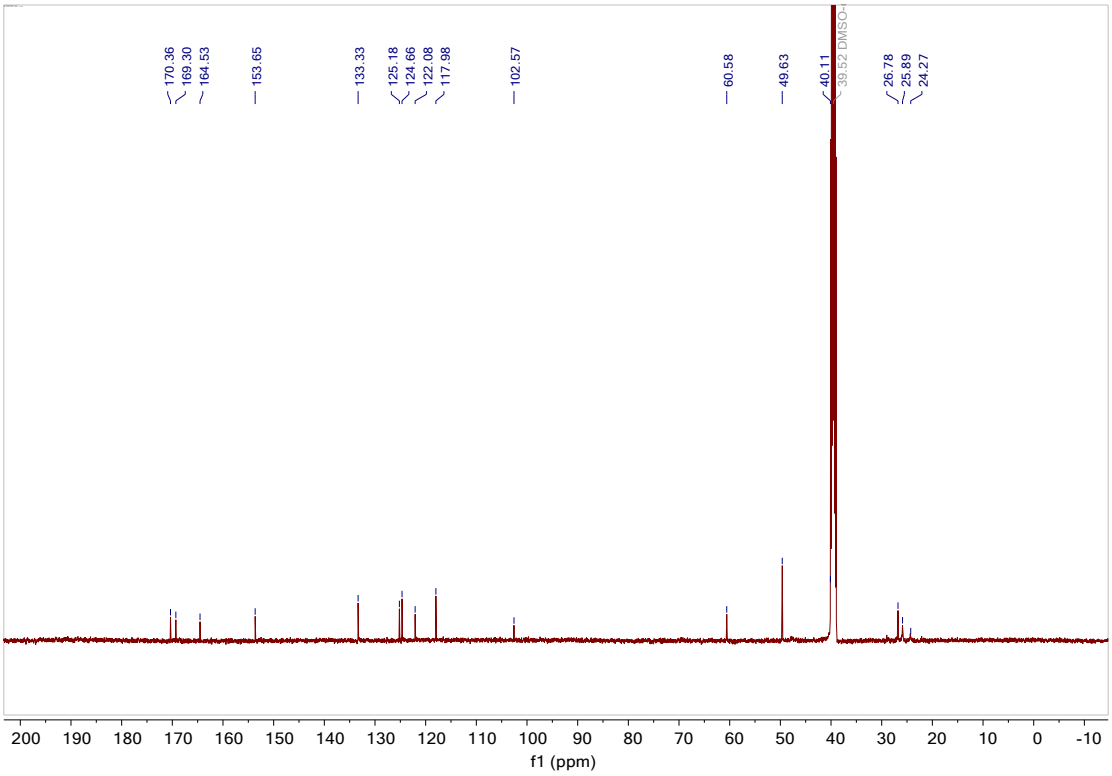
^{1}H NMR and ^{13}C NMR of compound **c13**



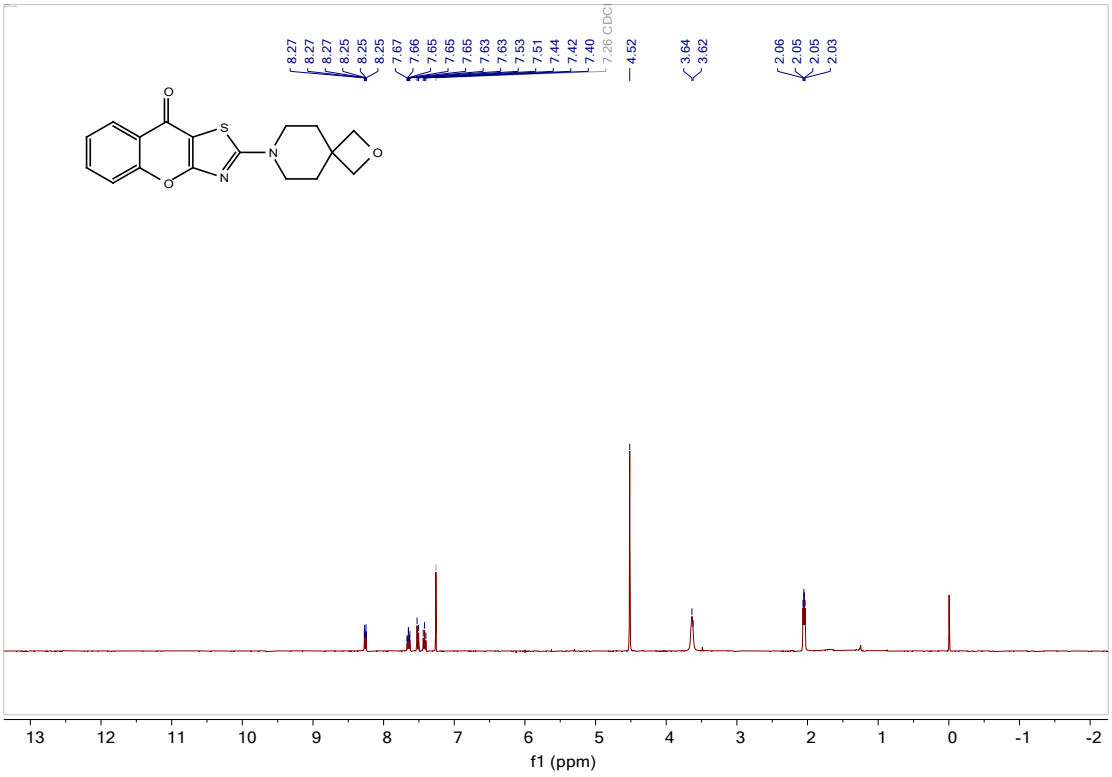


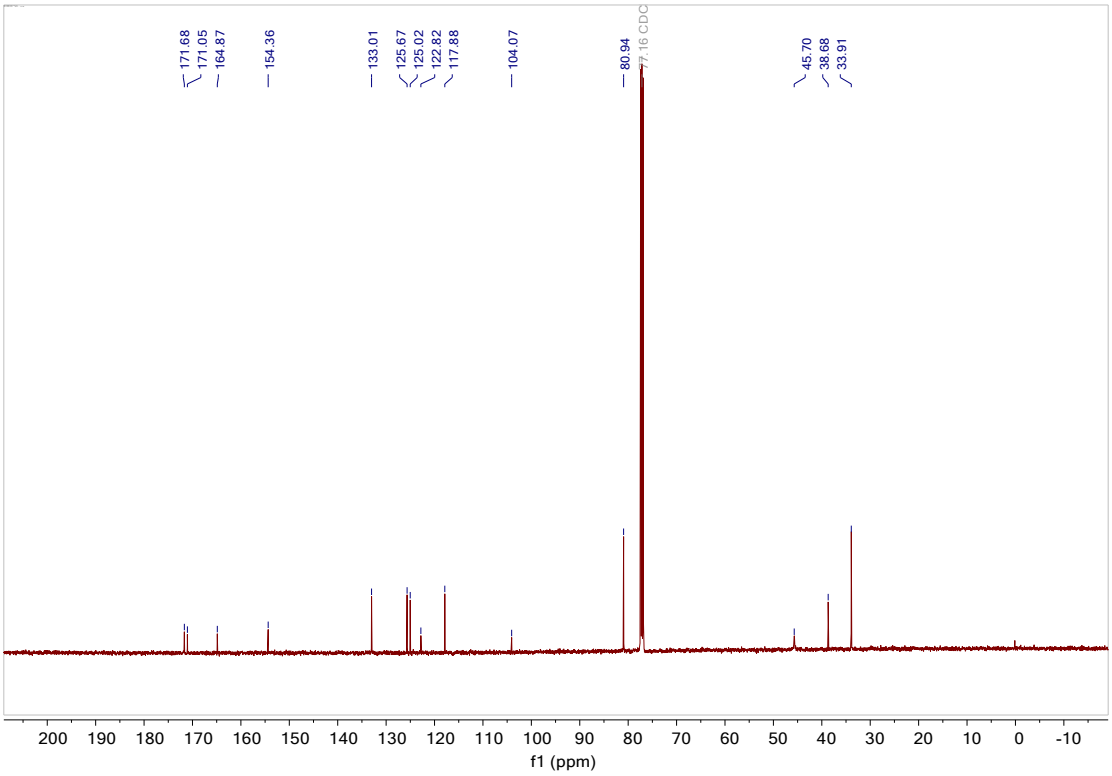
^{1}H NMR and ^{13}C NMR of compound **c14**



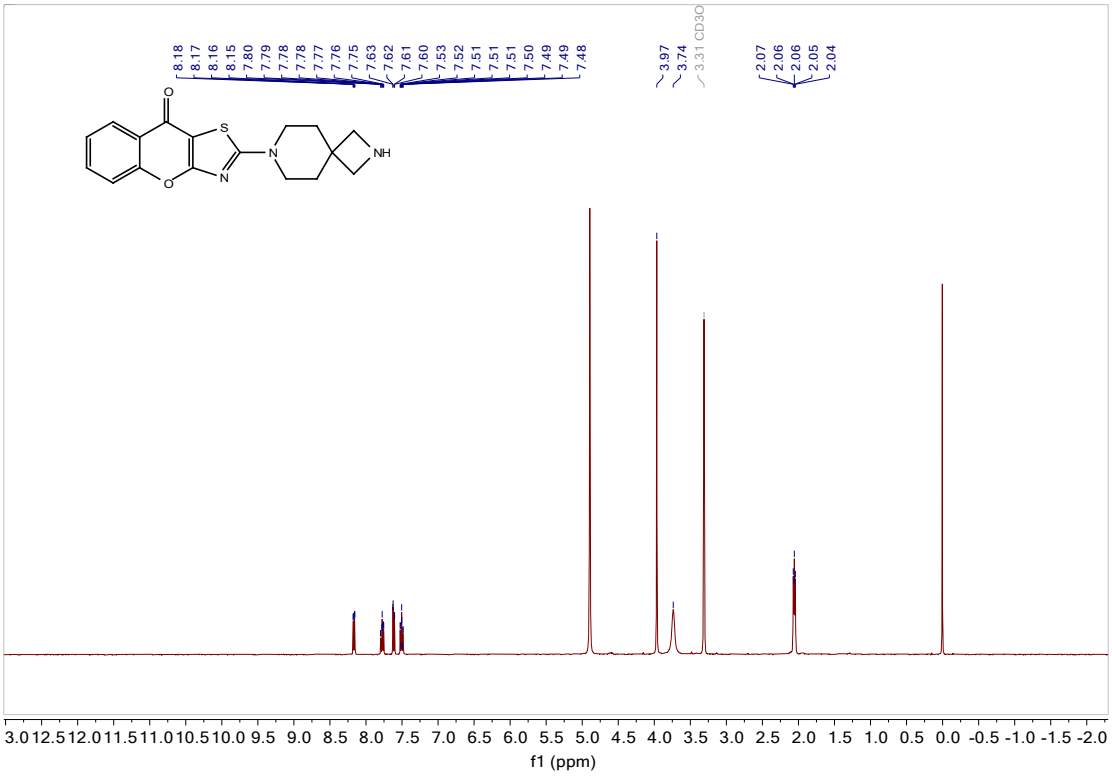


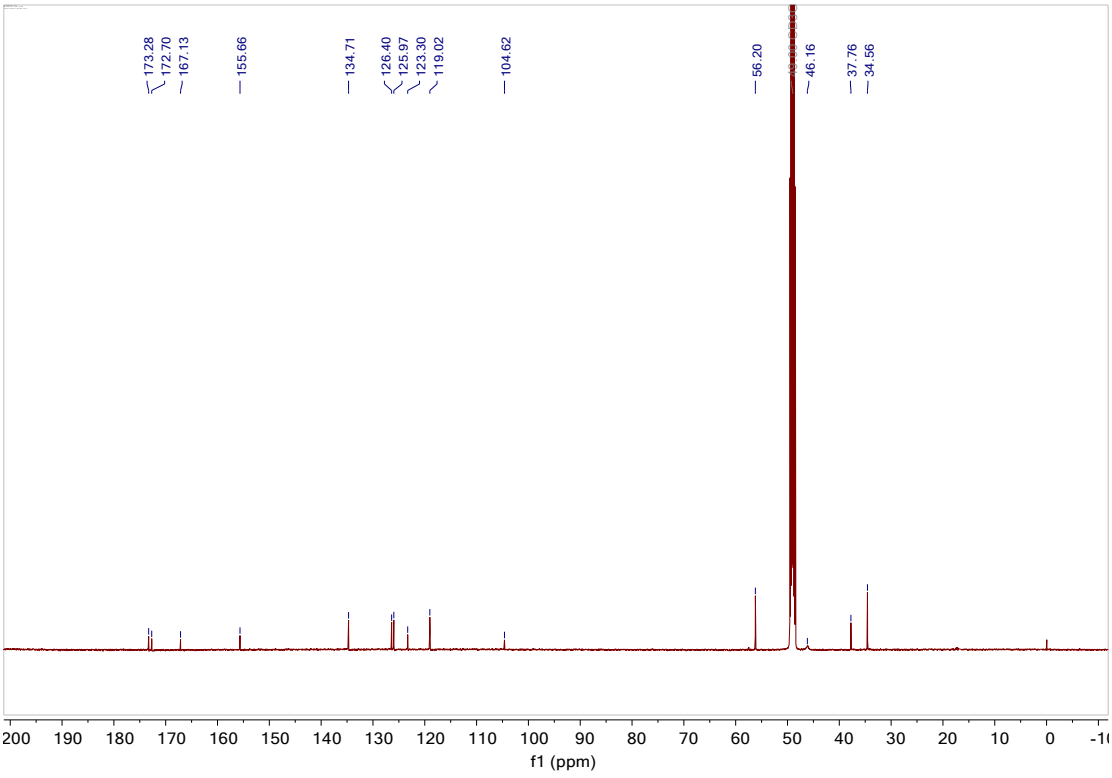
^{1}H NMR and ^{13}C NMR of compound **c15**



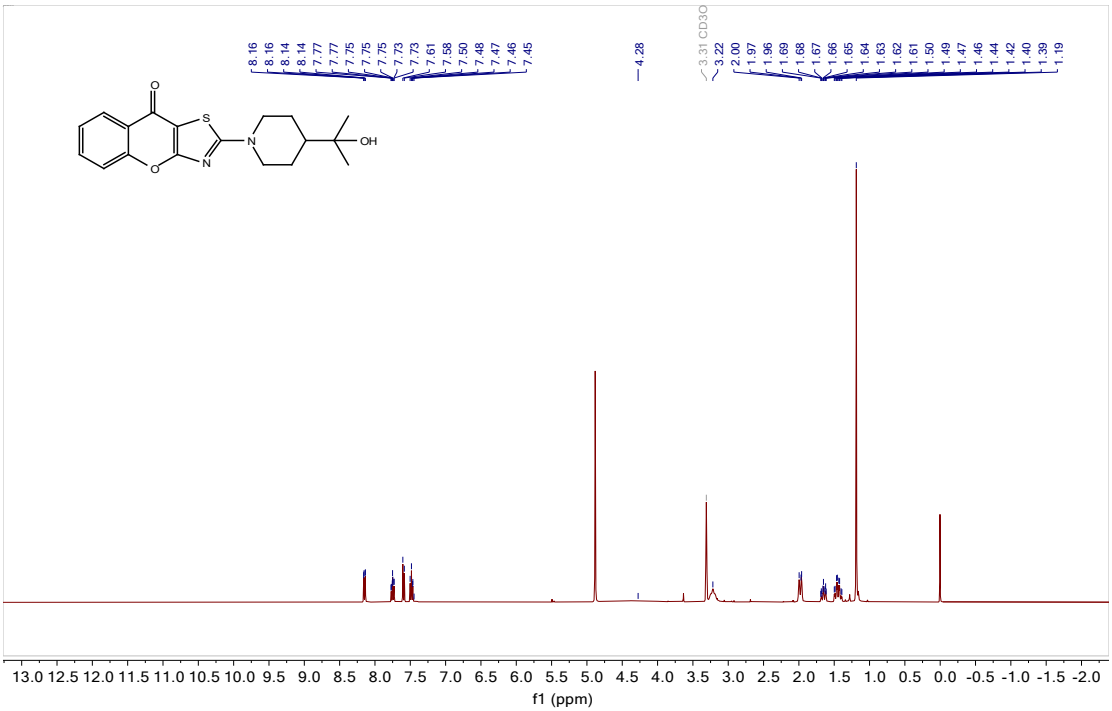


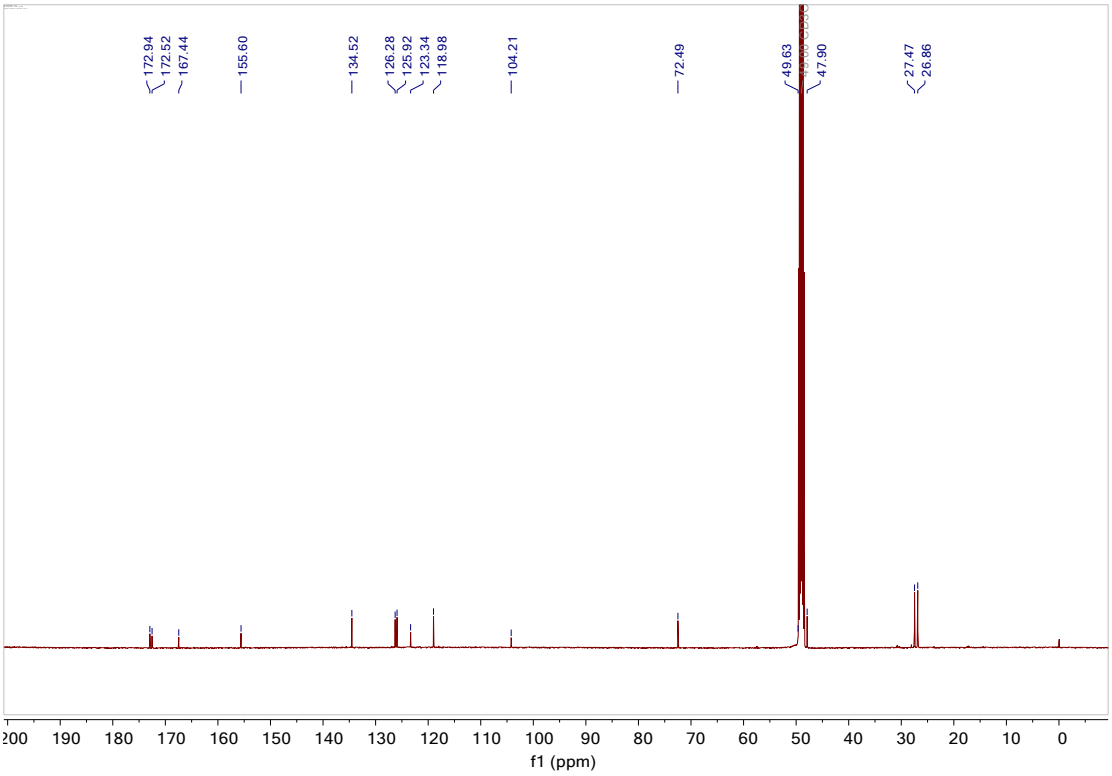
^{1}H NMR and ^{13}C NMR of compound **c16**



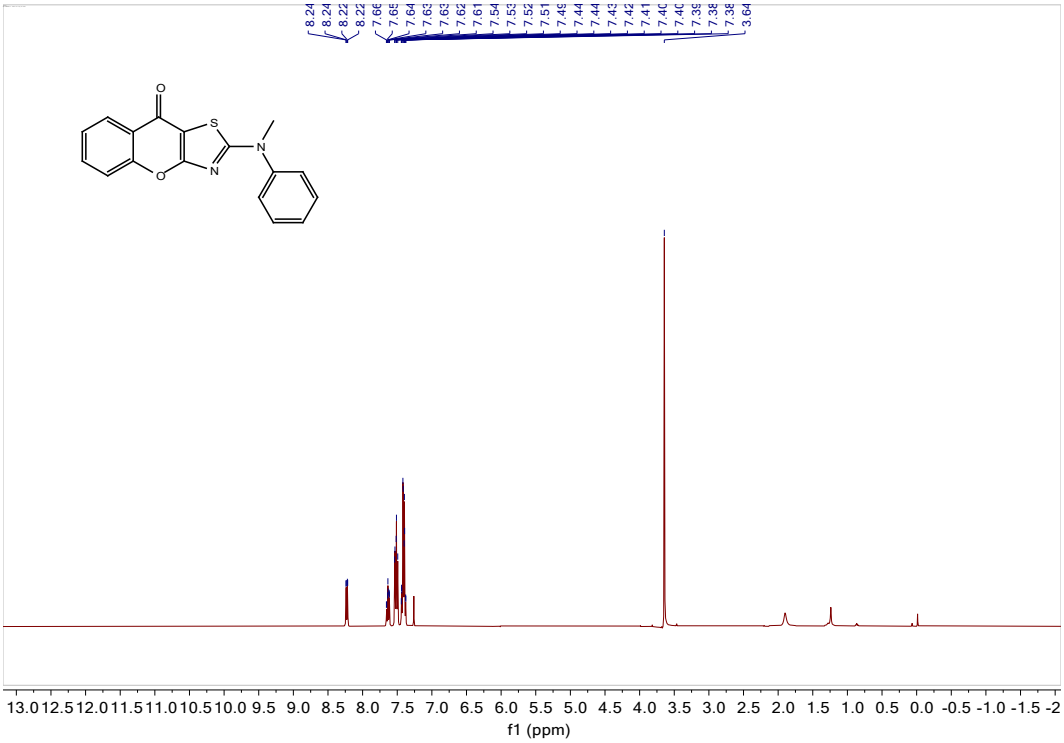


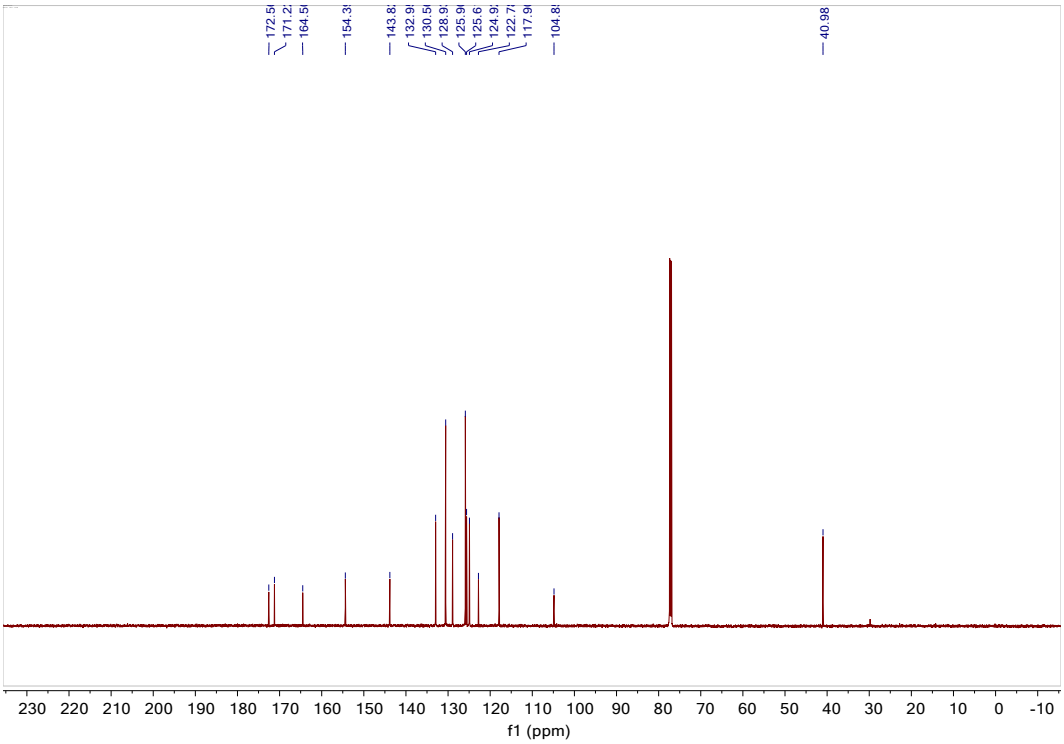
^{1}H NMR and ^{13}C NMR of compound **c17**



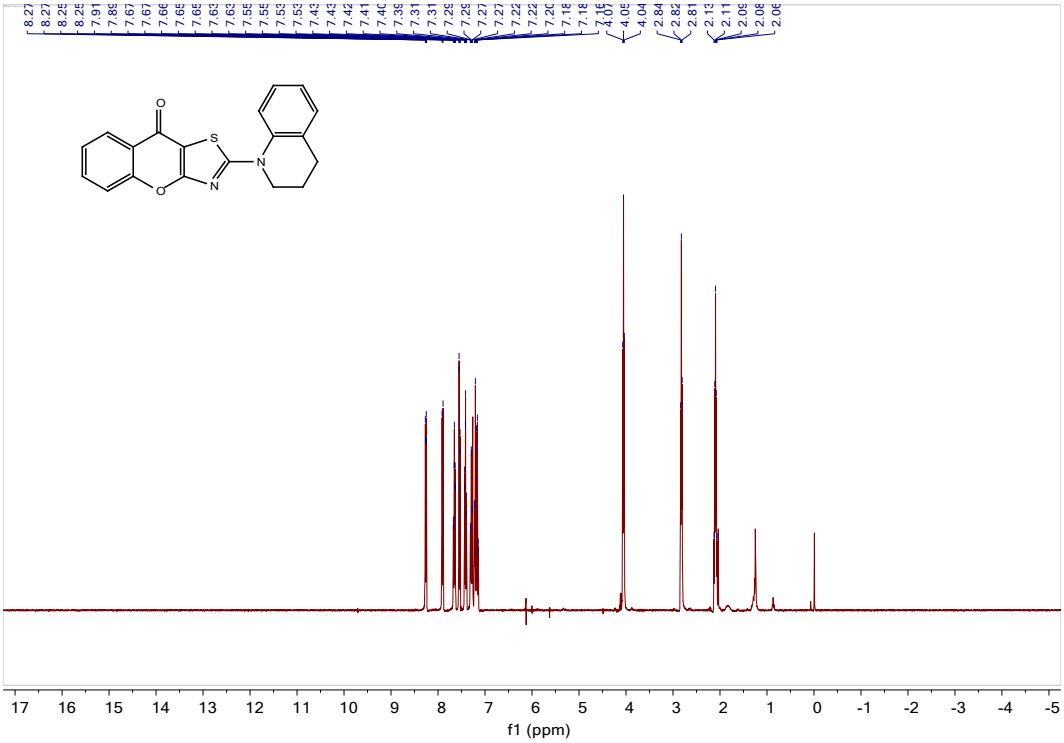


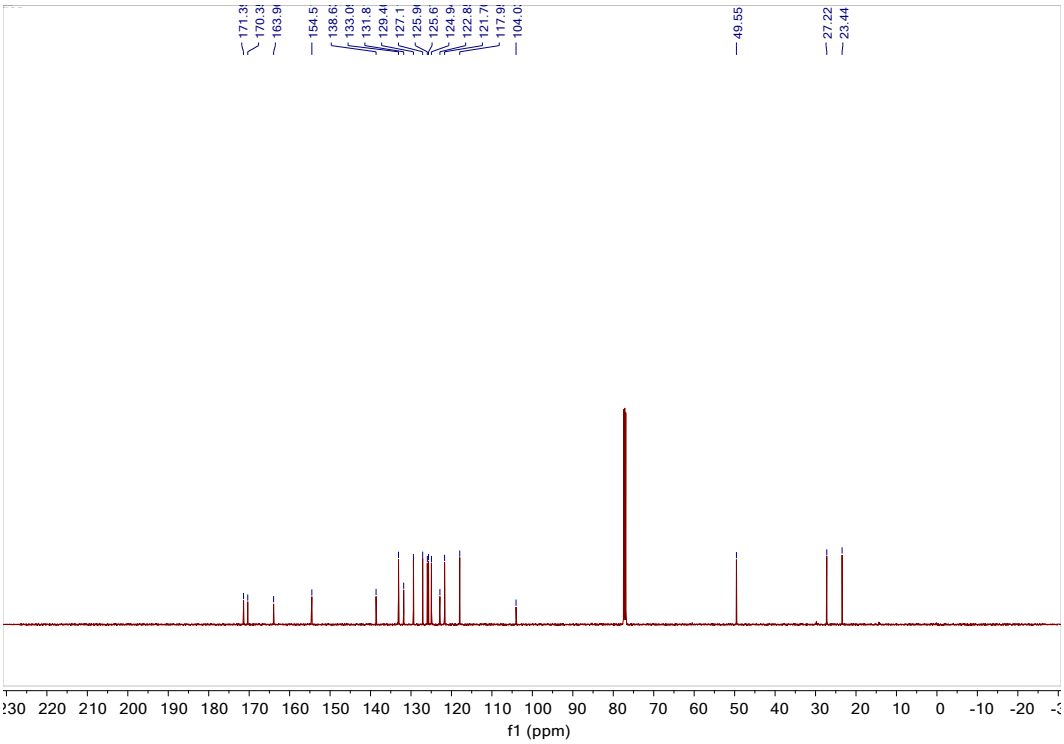
^{1}H NMR and ^{13}C NMR of compound **c18**



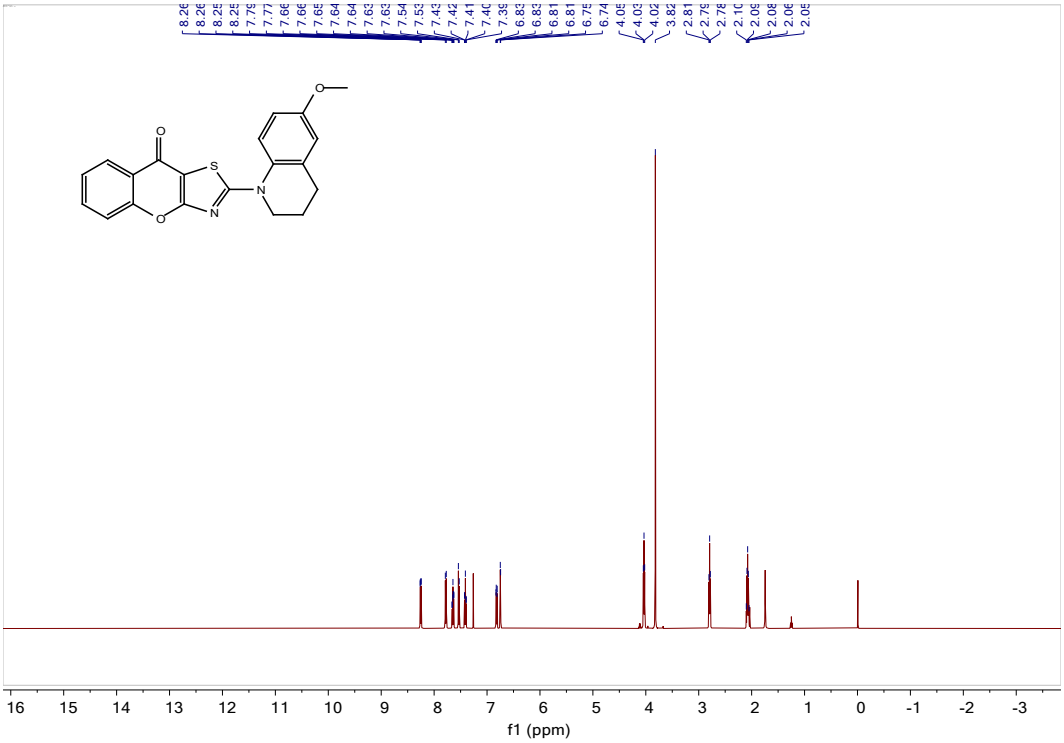


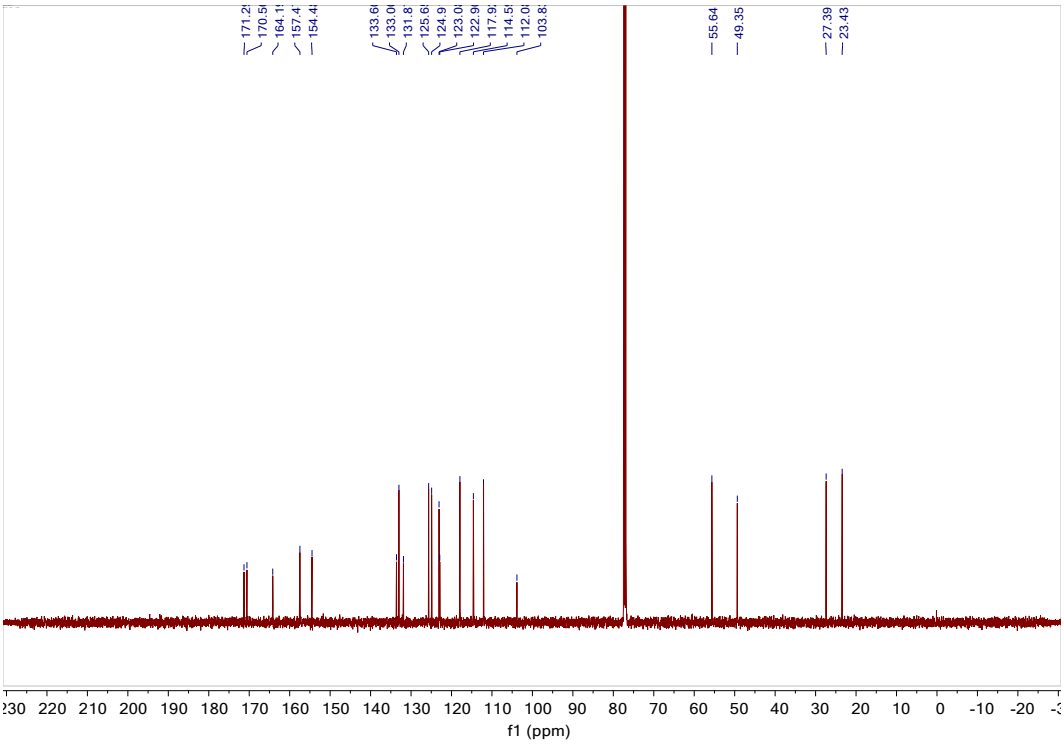
^{1}H NMR and ^{13}C NMR of compound **c19**



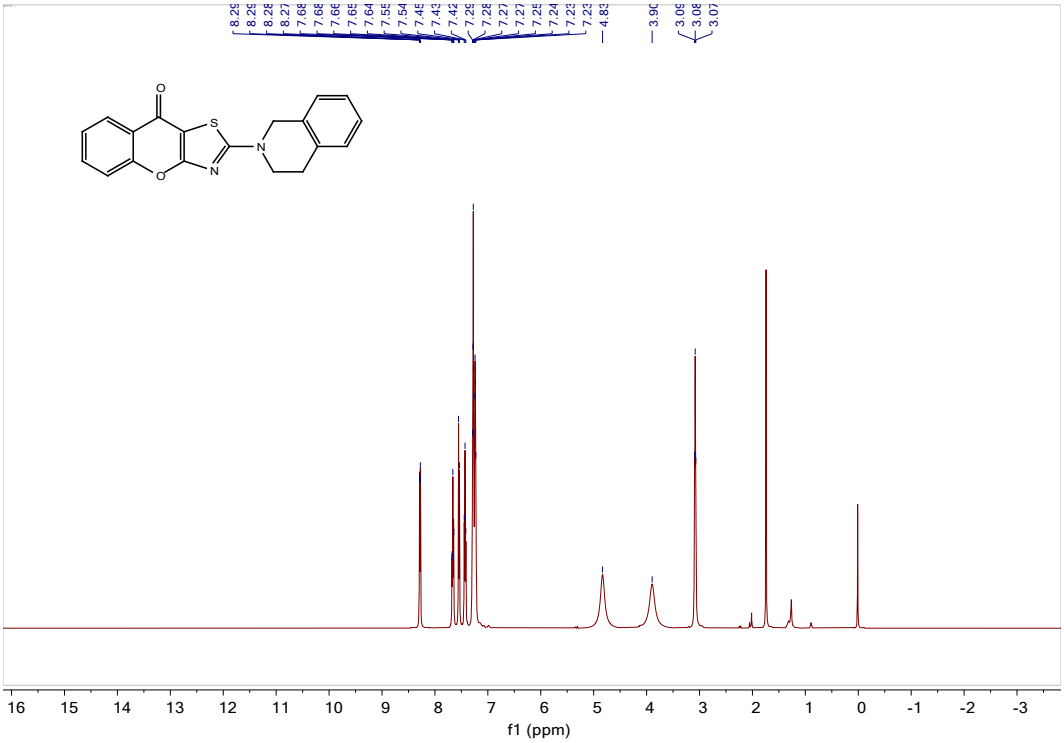


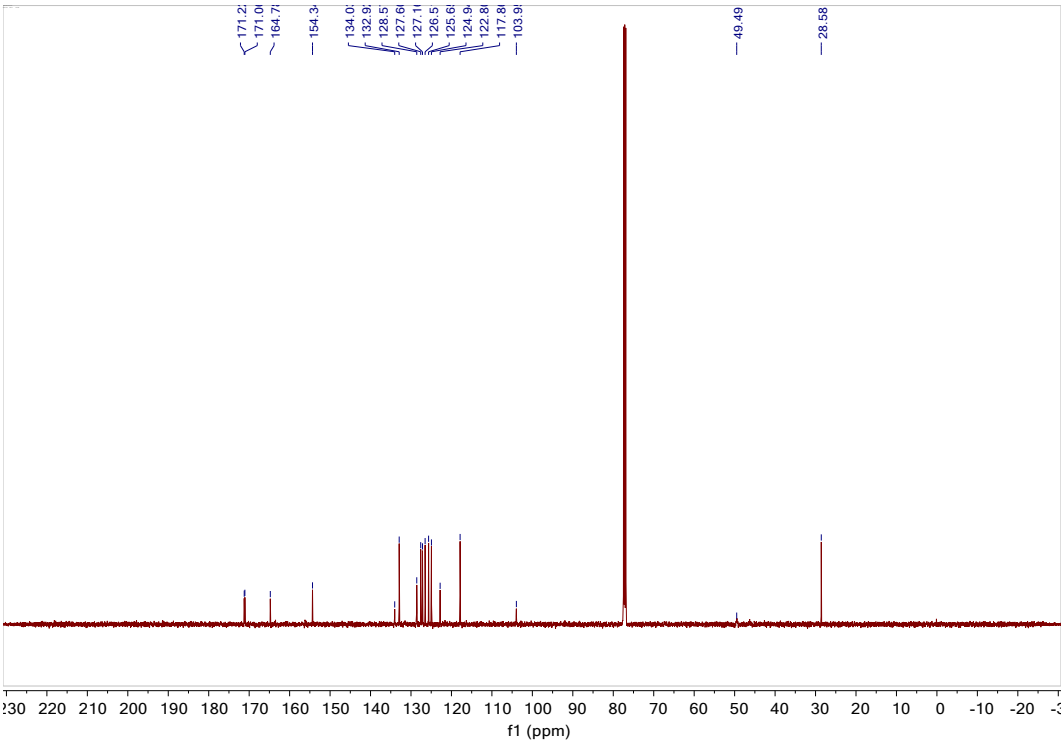
^{1}H NMR and ^{13}C NMR of compound **c20**



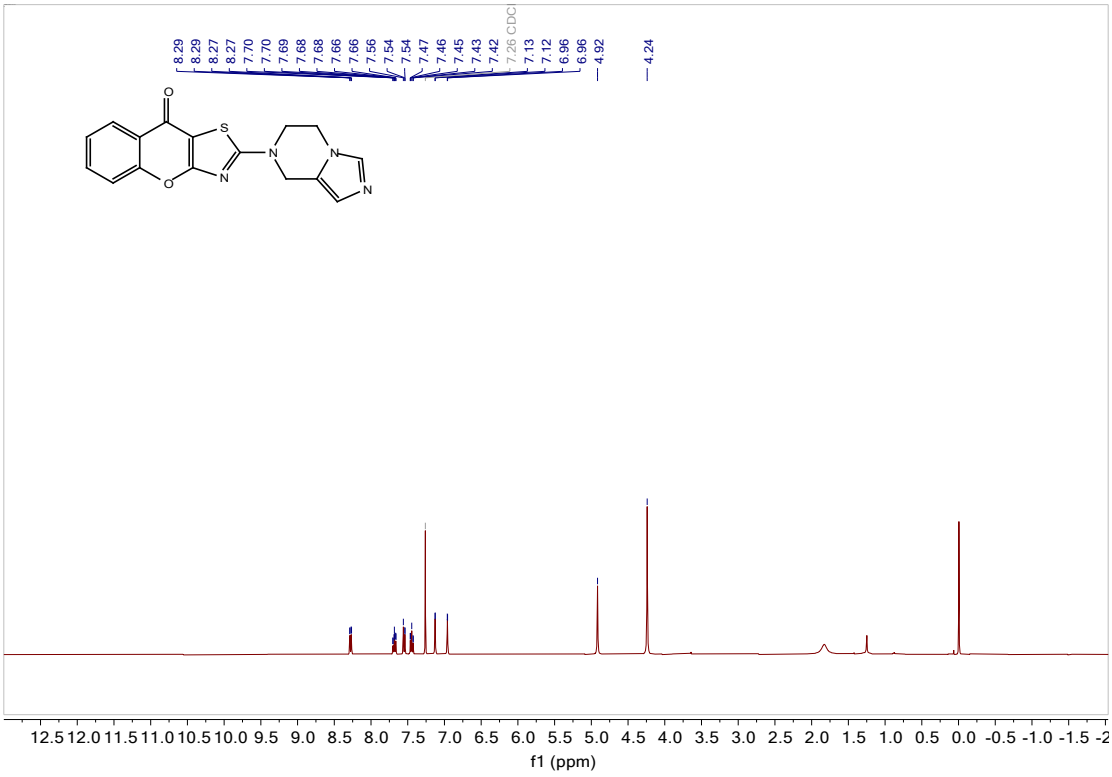


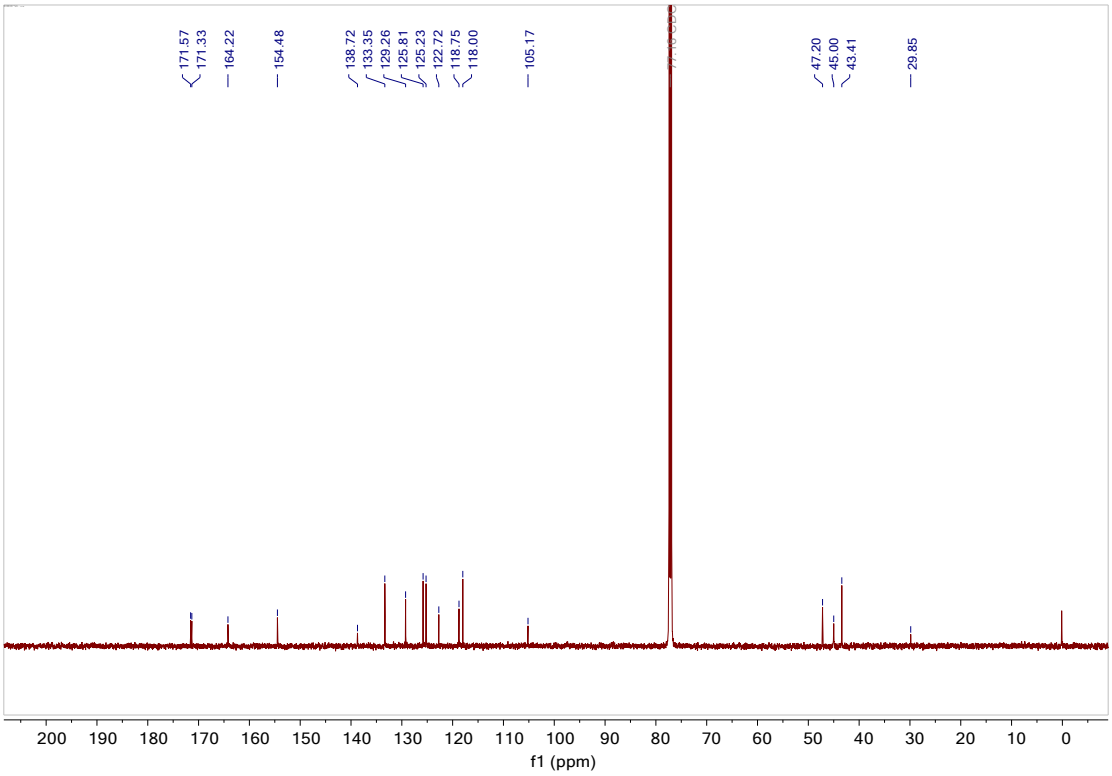
^{1}H NMR and ^{13}C NMR of compound **c21**



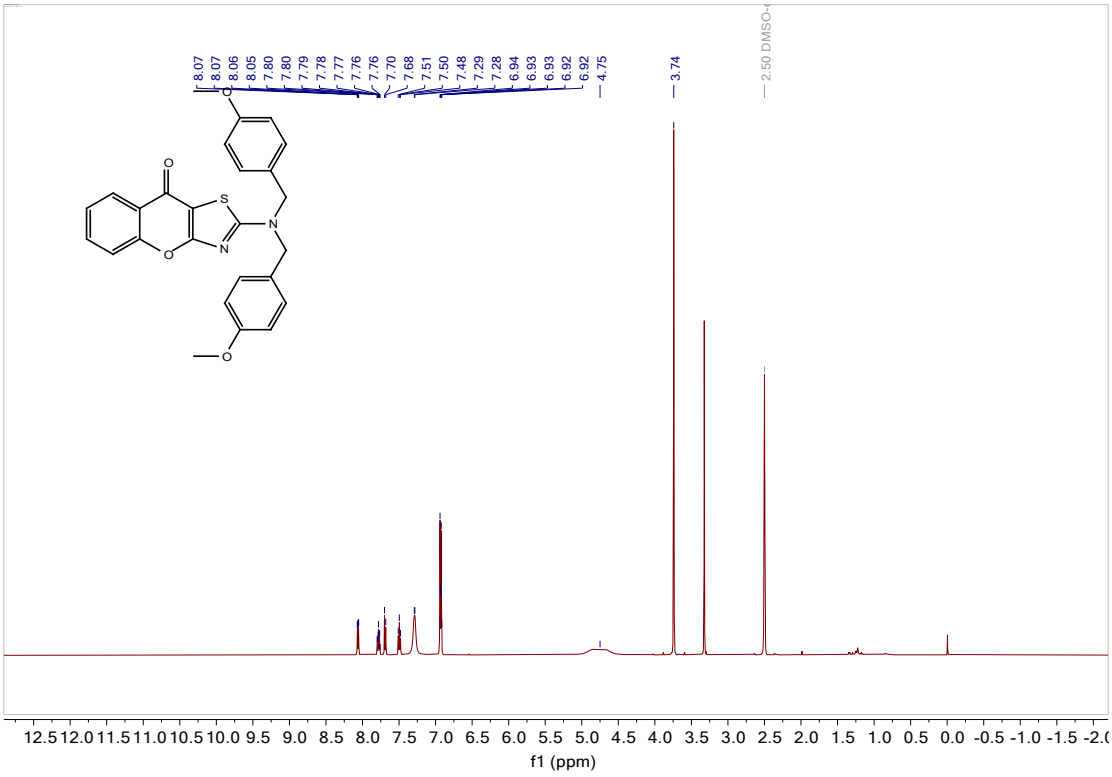


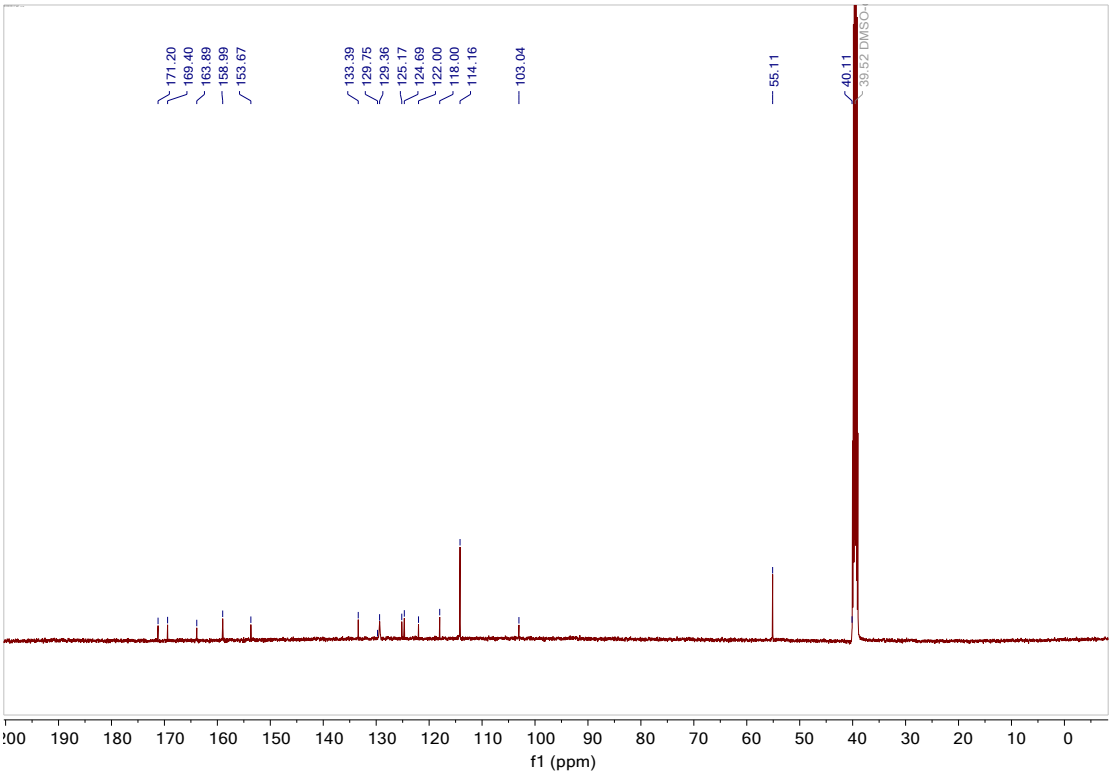
^{1}H NMR and ^{13}C NMR of compound **c22**



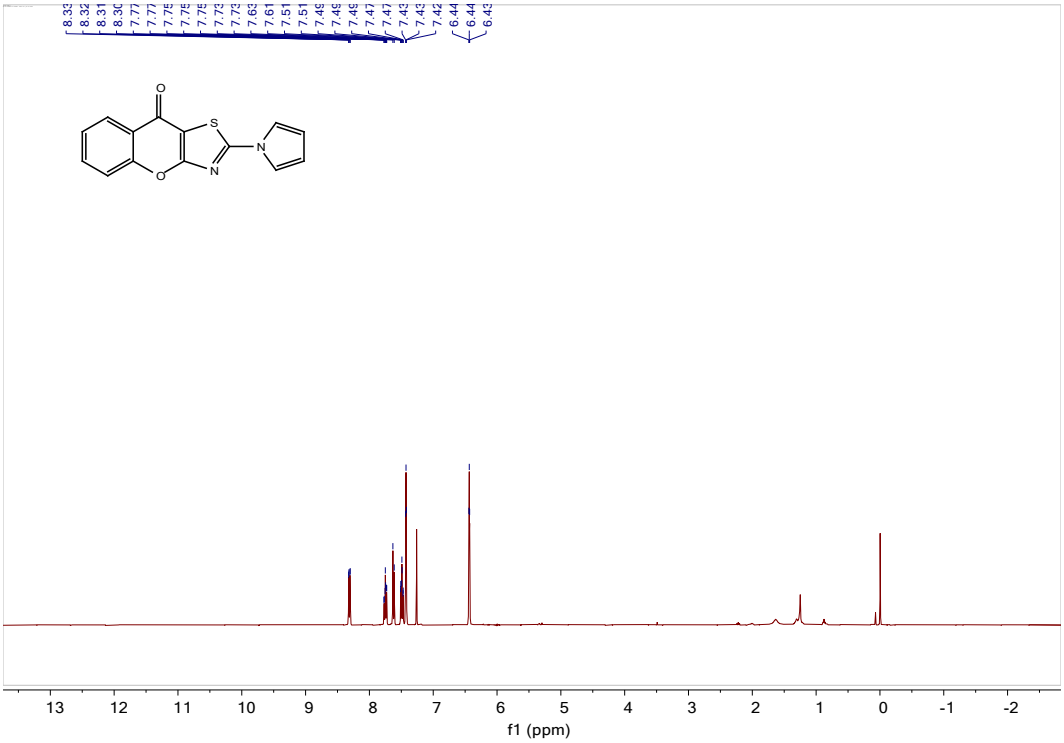


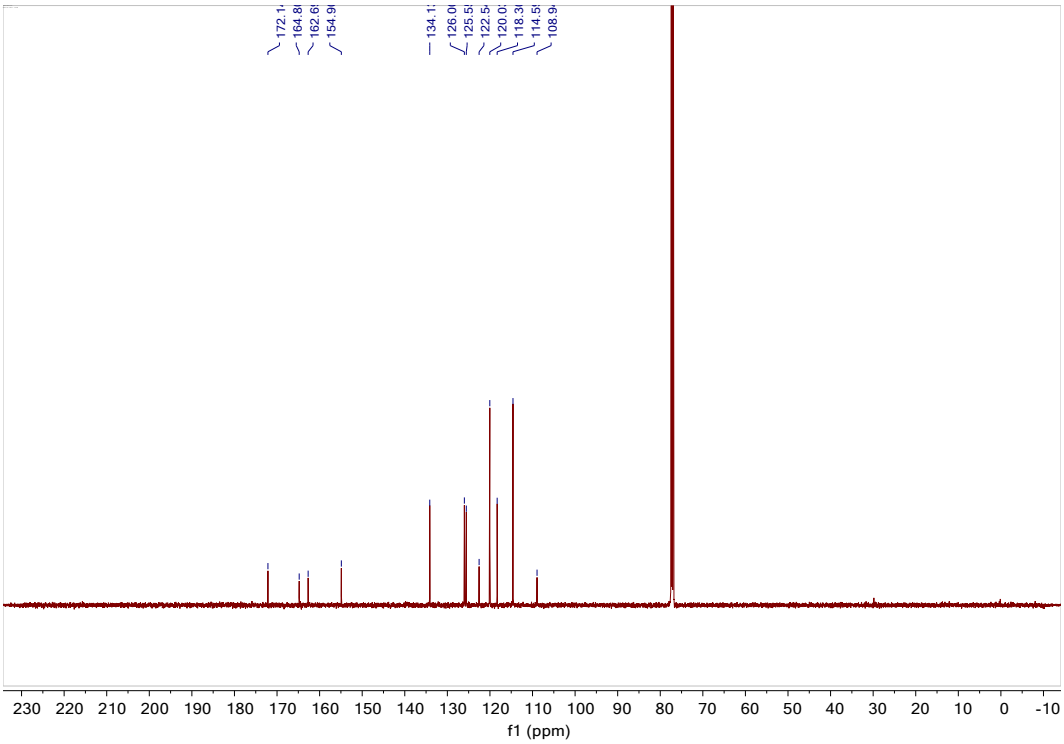
^{1}H NMR and ^{13}C NMR of compound **c23**



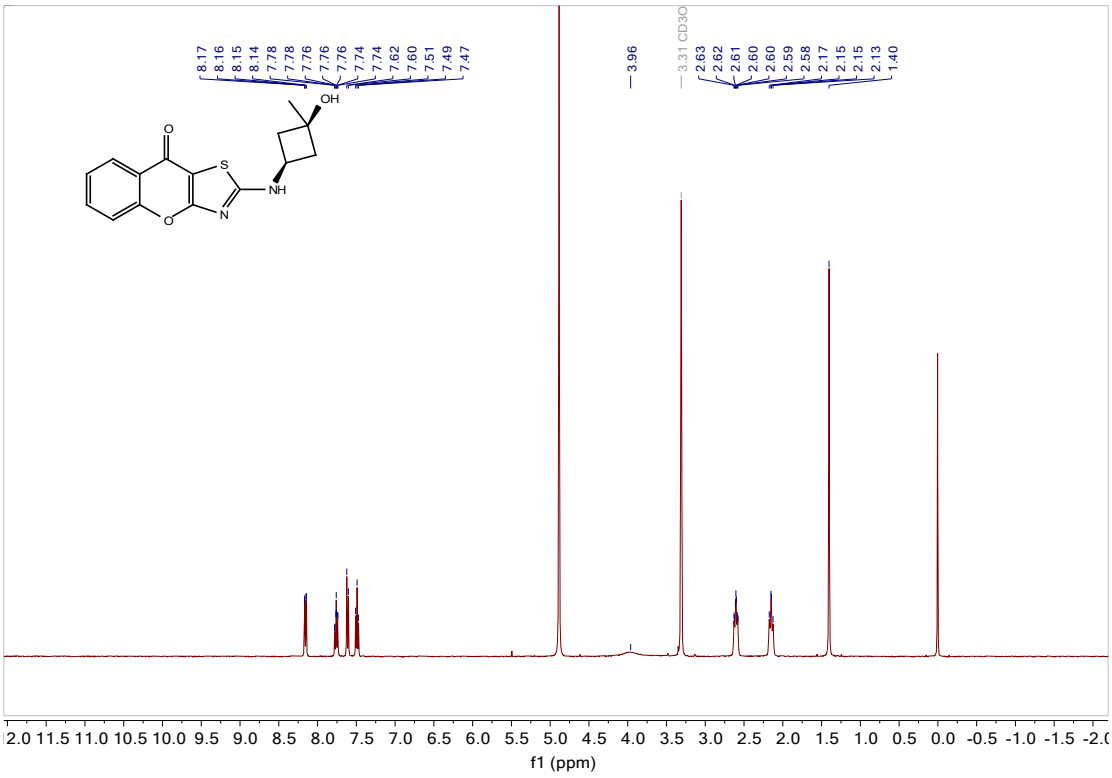


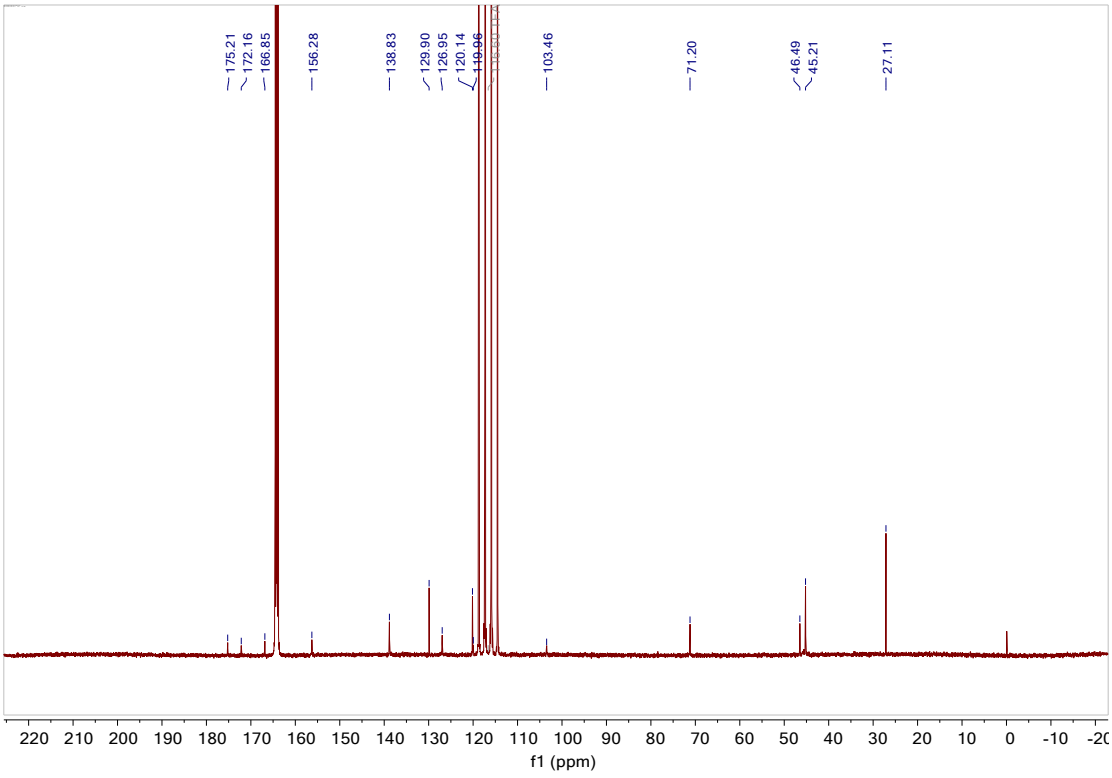
^{1}H NMR and ^{13}C NMR of compound **c24**



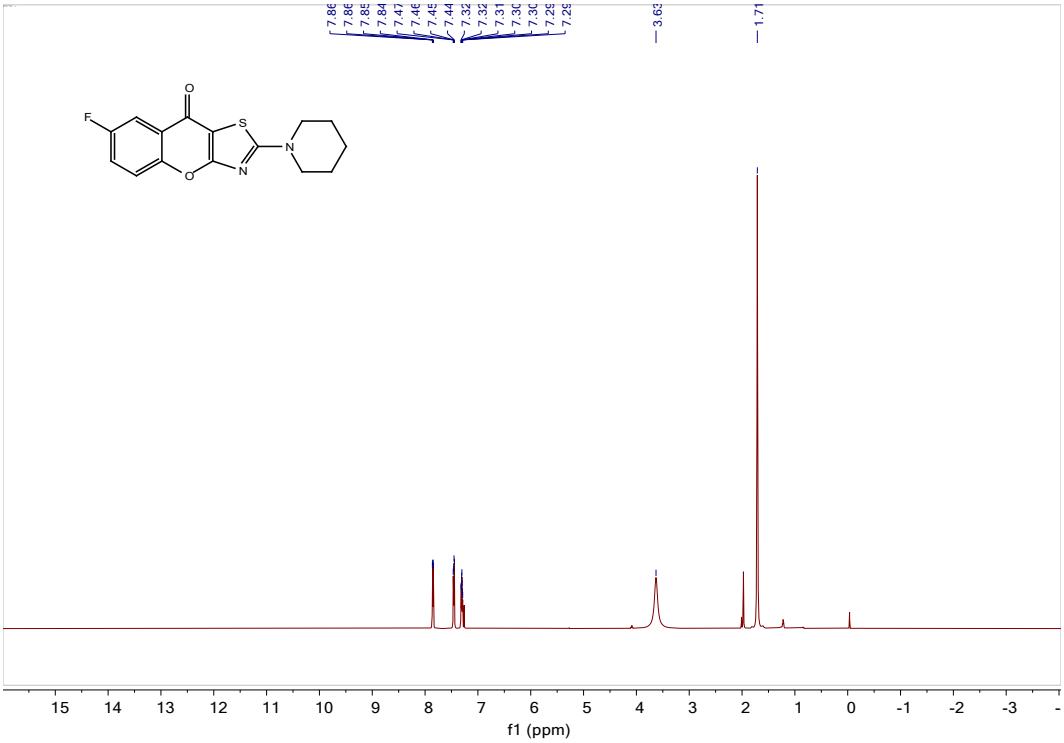


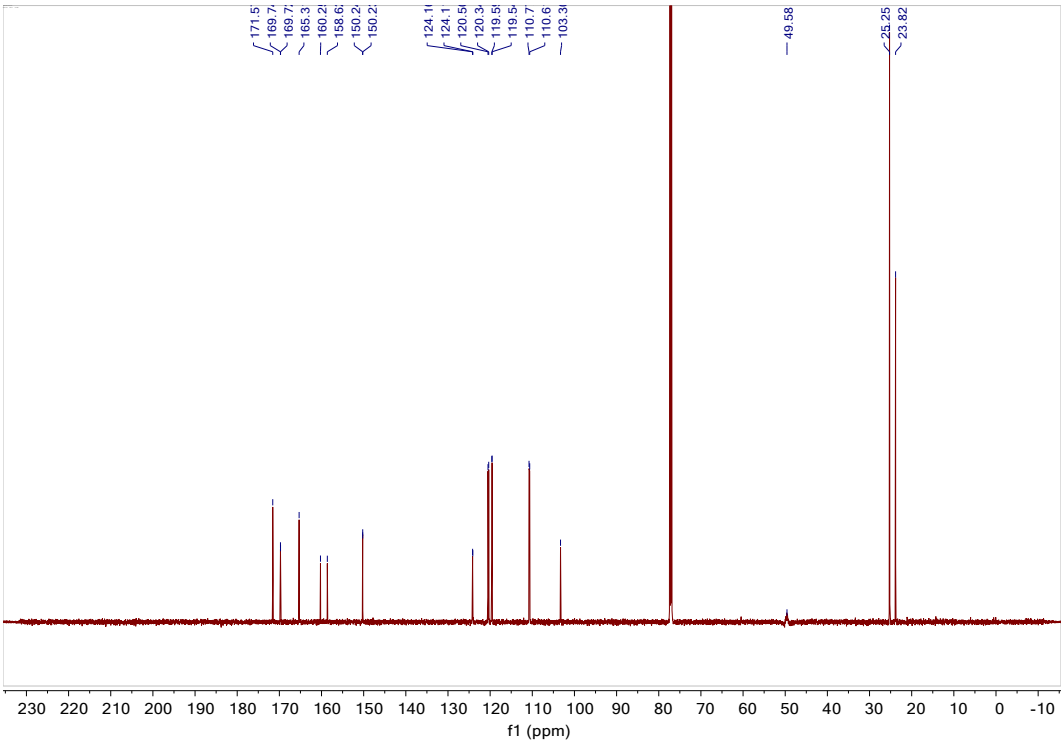
^{1}H NMR and ^{13}C NMR of compound **c25**

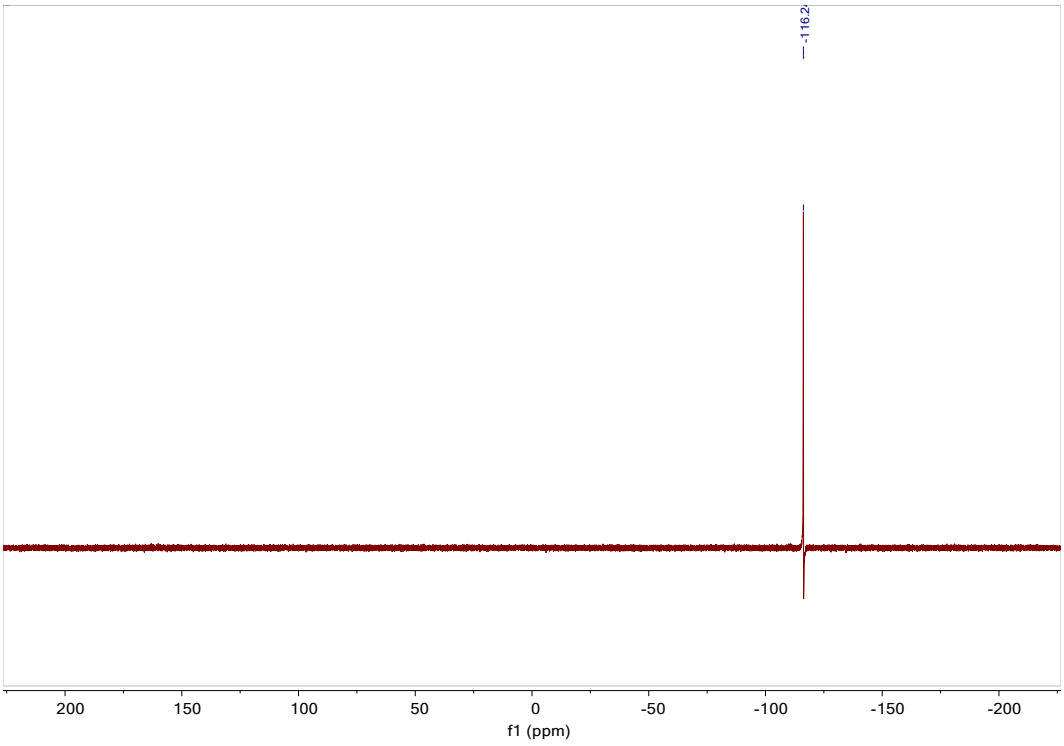




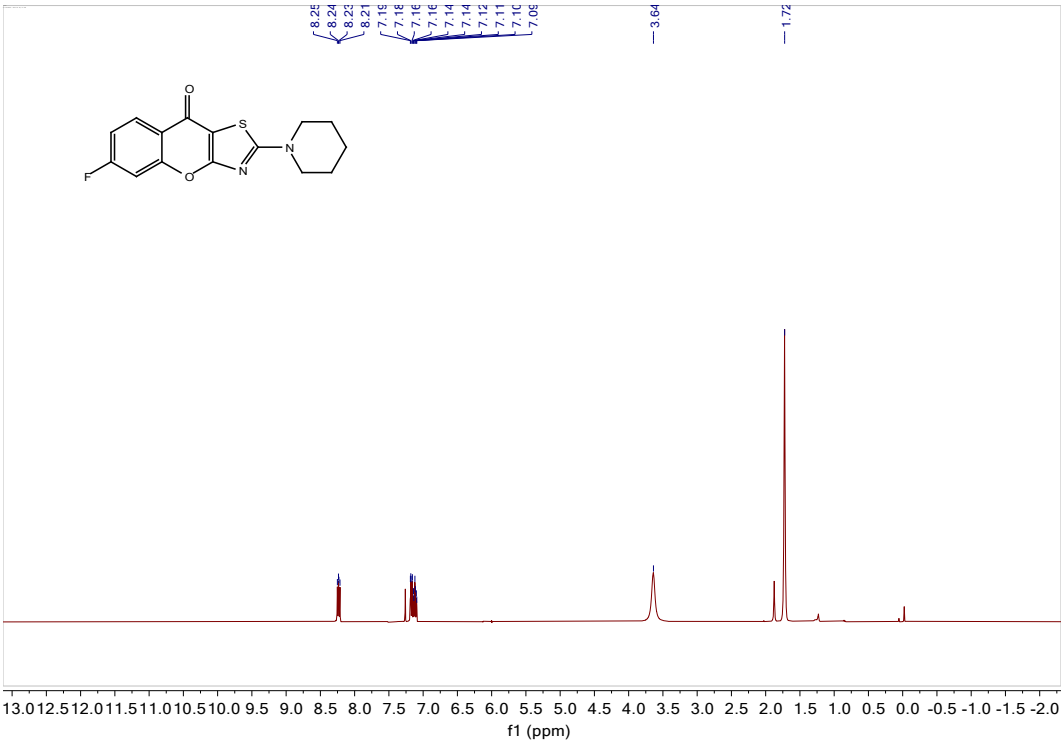
^{1}H NMR, ^{13}C NMR, and ^{19}F of compound **c26**

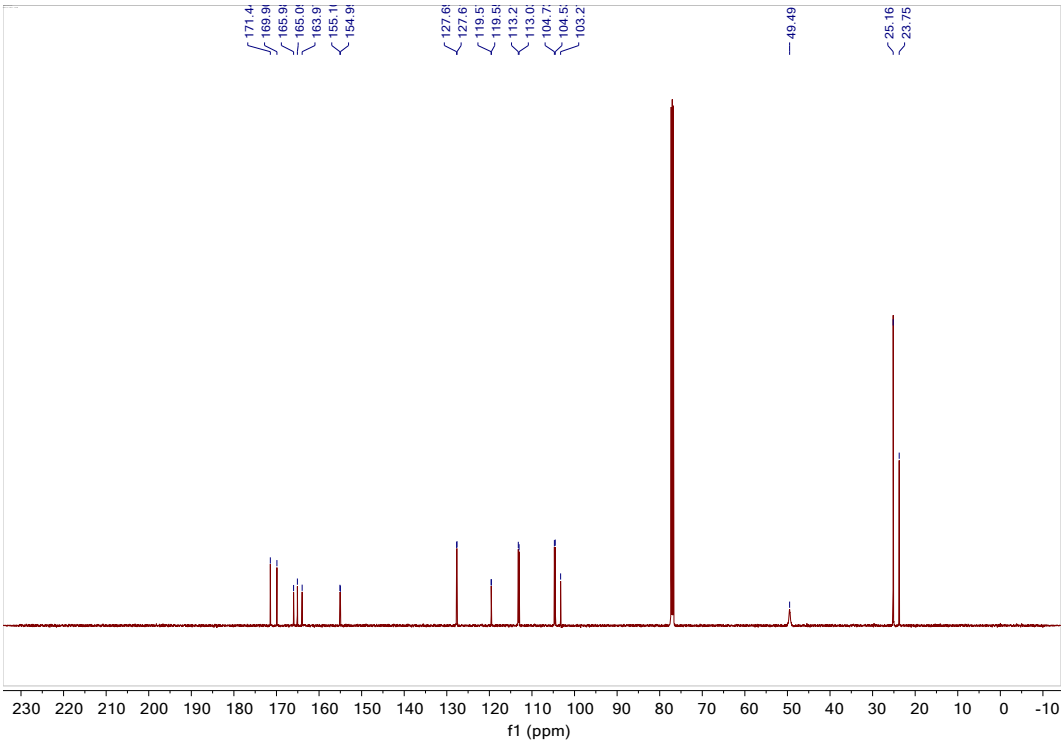


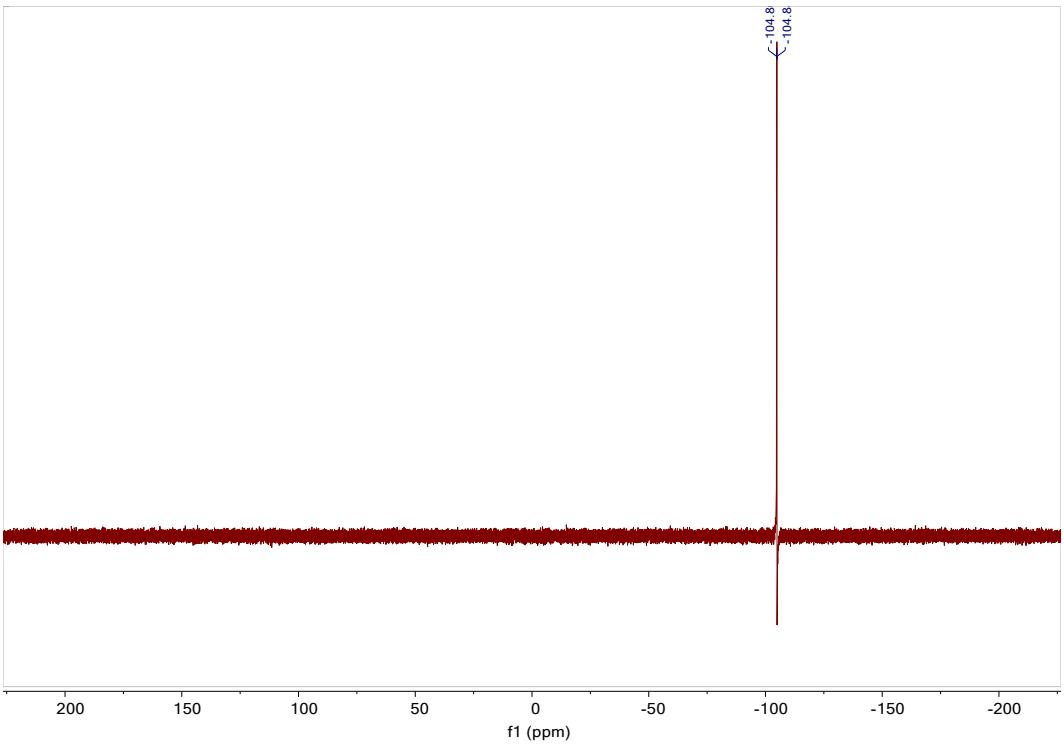




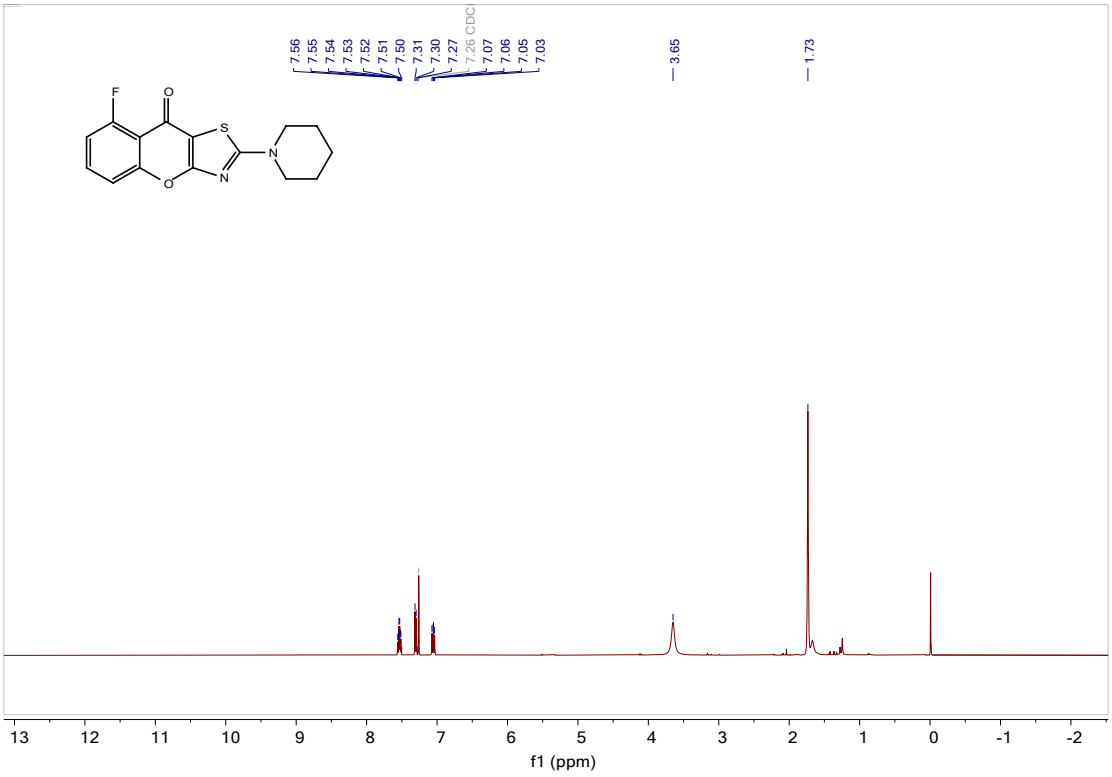
^{1}H NMR, ^{13}C NMR, and ^{19}F of compound **c27**

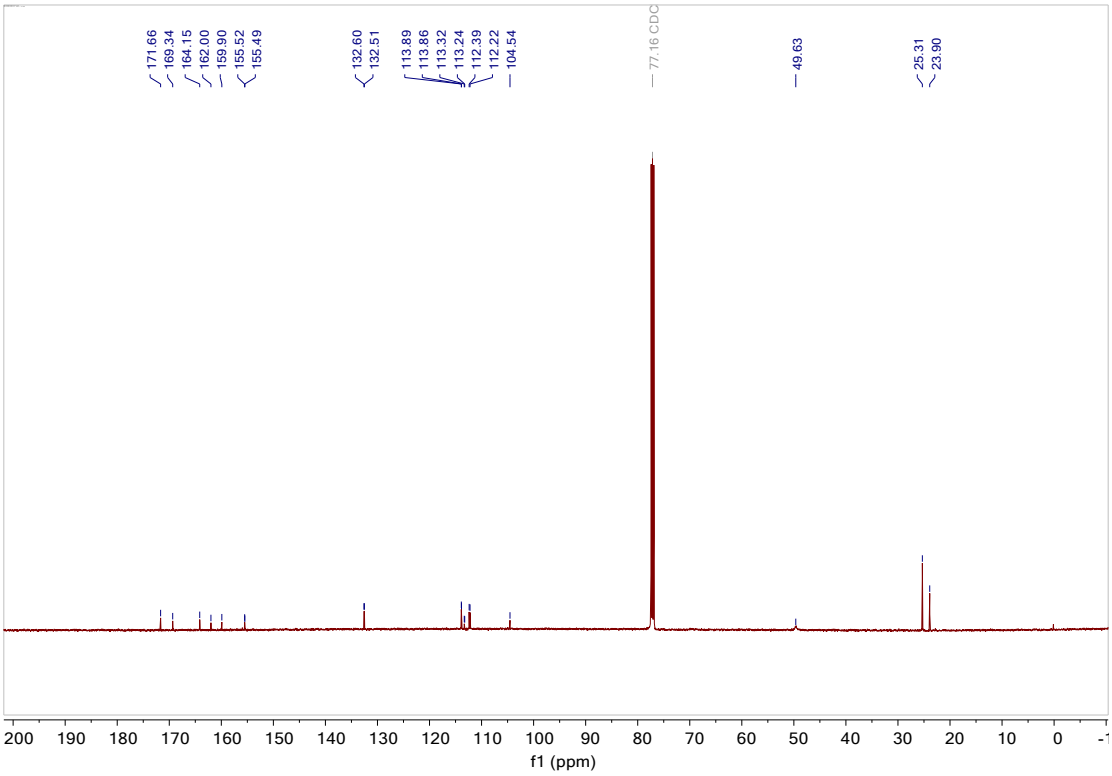


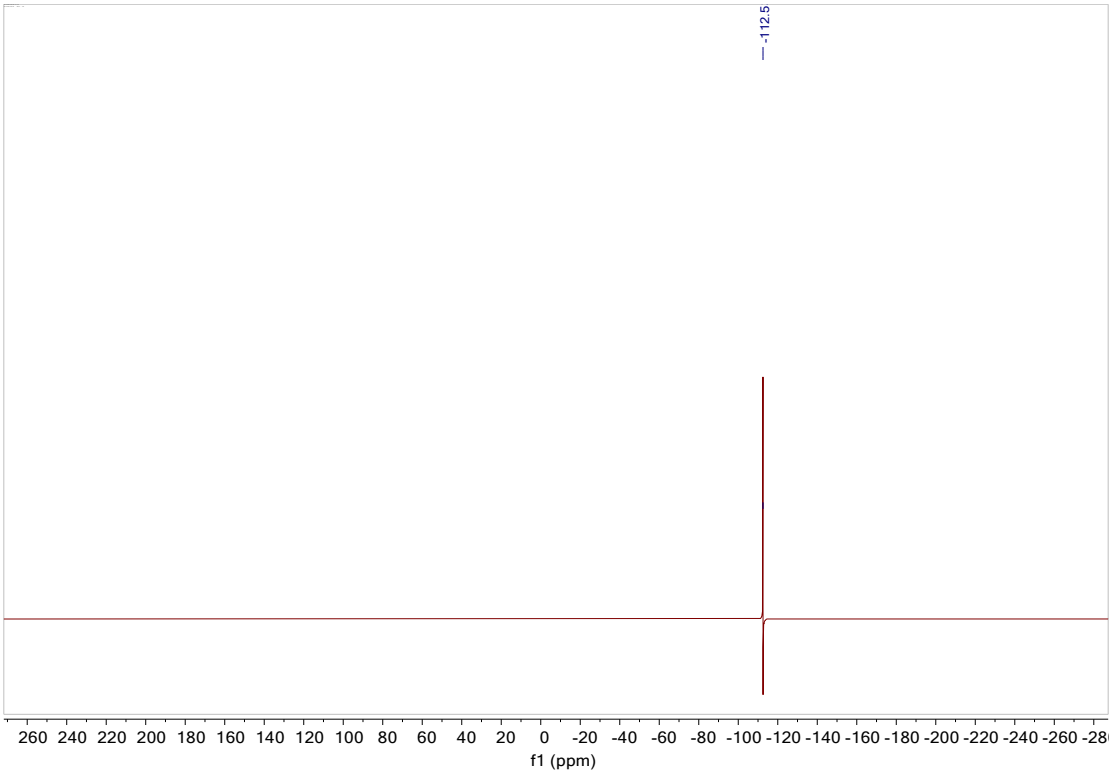

171.4
169.9
165.9
165.0
163.9
155.1
154.9
127.6
127.6
119.5
119.5
113.2
113.0
104.7
104.5
103.2
49.49
25.16
23.75
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


-104.8
-104.8
200 150 100 50 0 -50 -100 -150 -200
f1 (ppm)

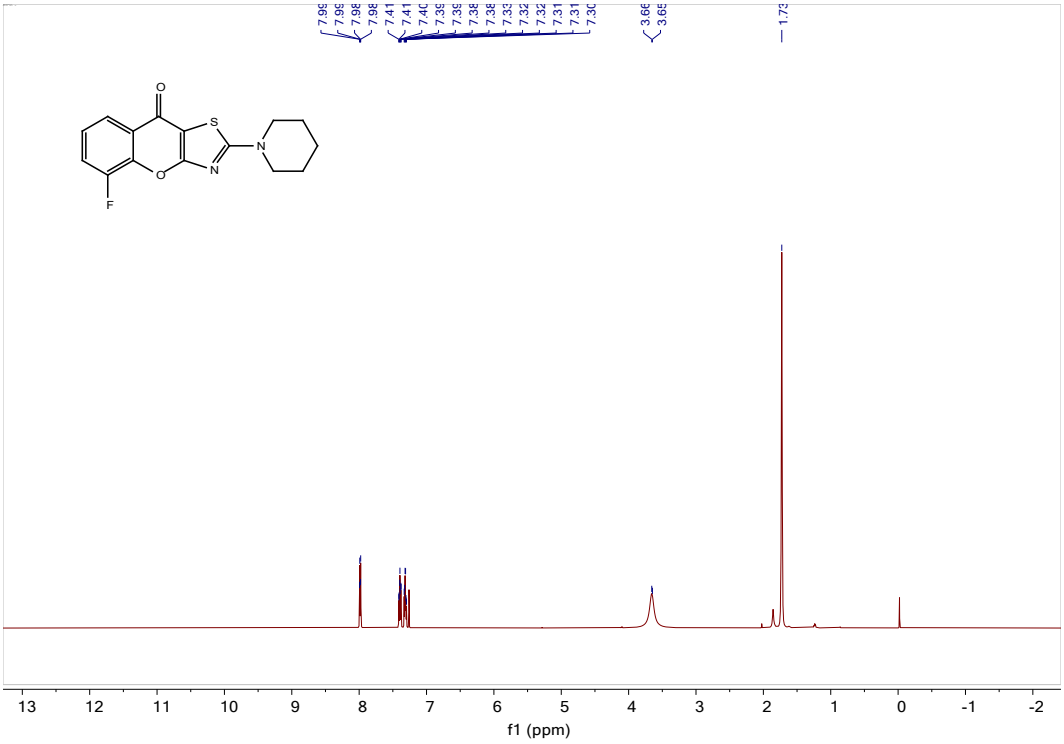
^{1}H NMR, ^{13}C NMR, and ^{19}F of compound **c28**

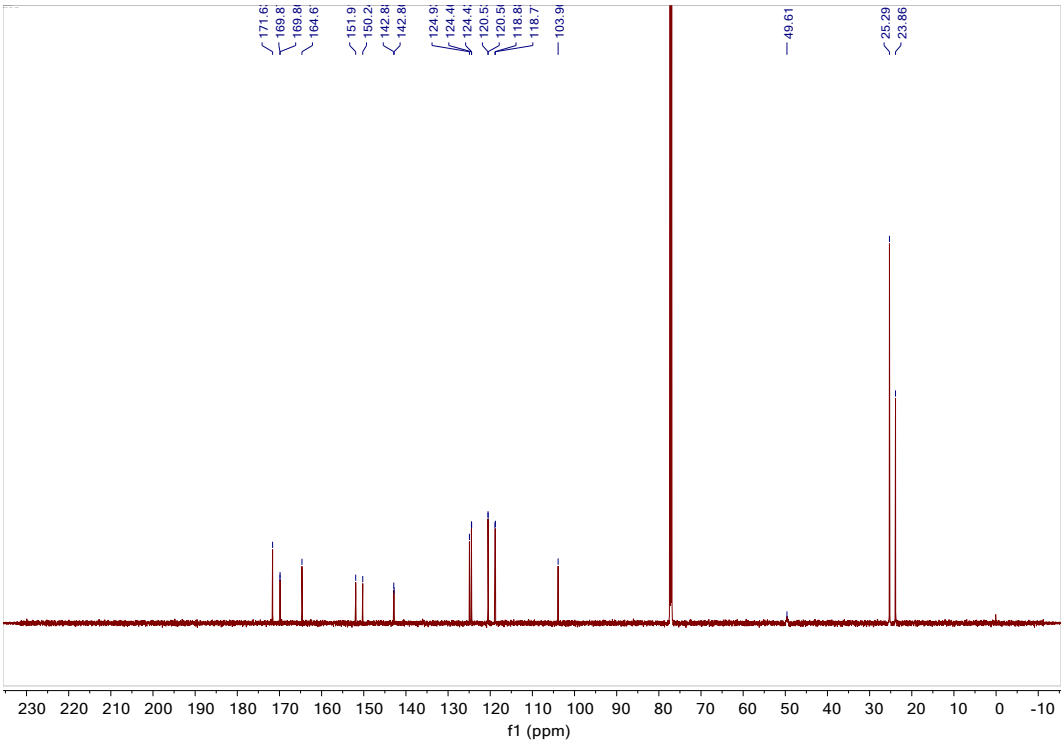


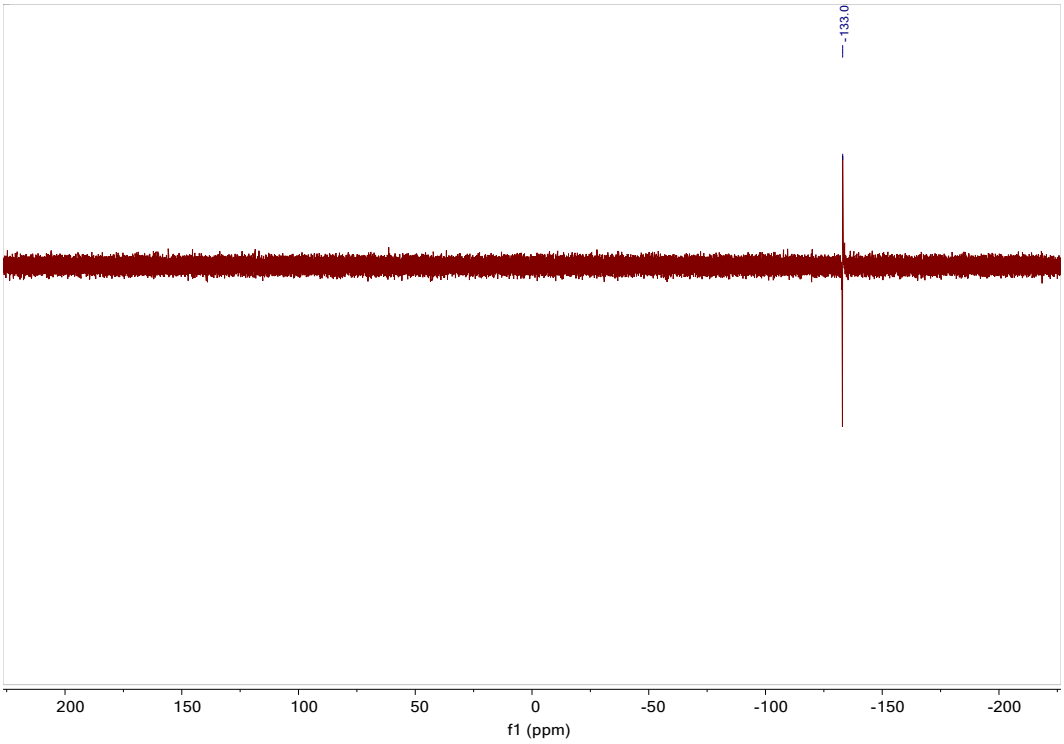




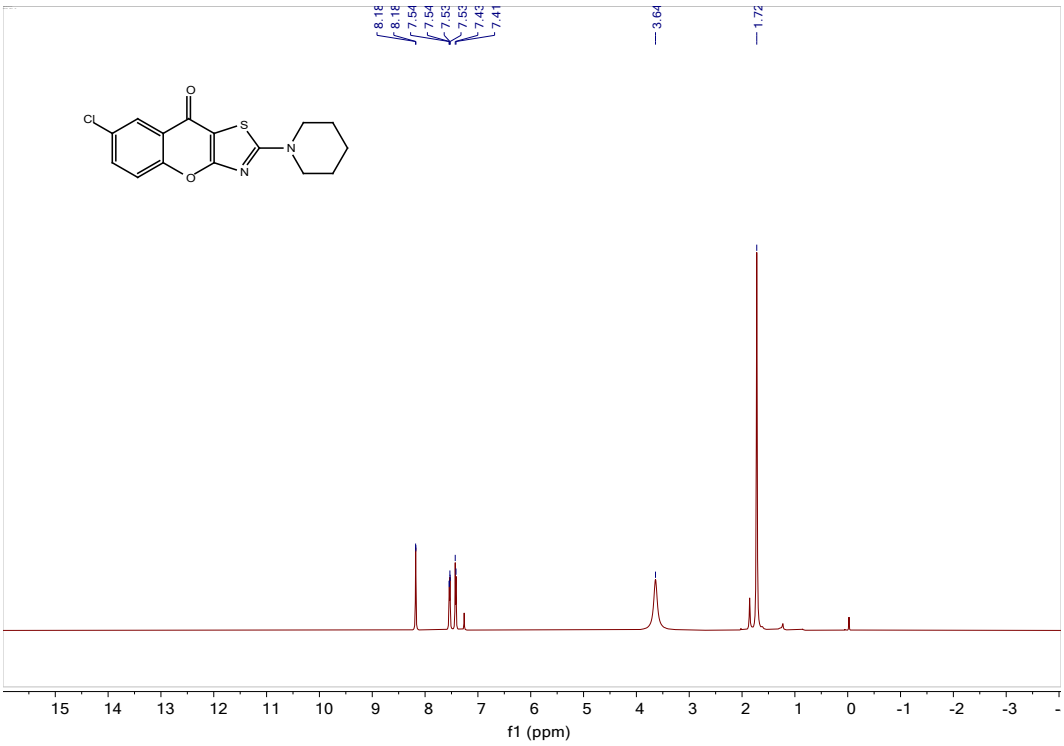
^{1}H NMR, ^{13}C NMR, and ^{19}F of compound **c29**

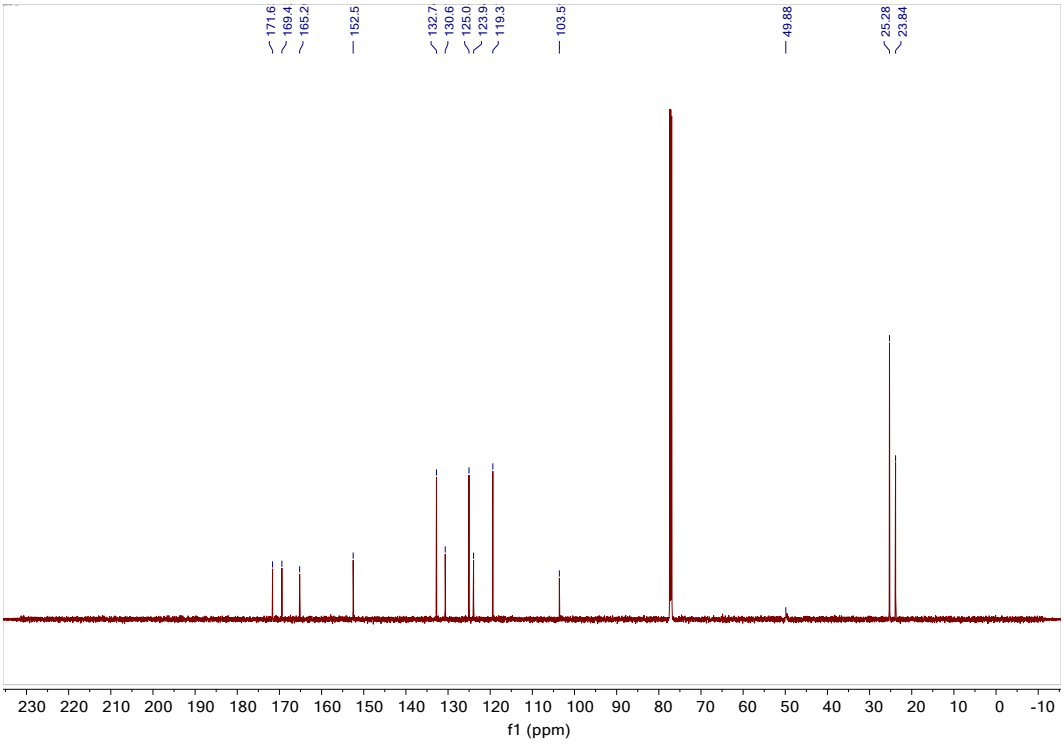



171.6
169.8
169.8
164.6
151.9
150.2
142.8
142.8
124.9
124.4
124.4
120.5
120.5
118.8
118.7
103.9
49.61
25.29
23.86
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

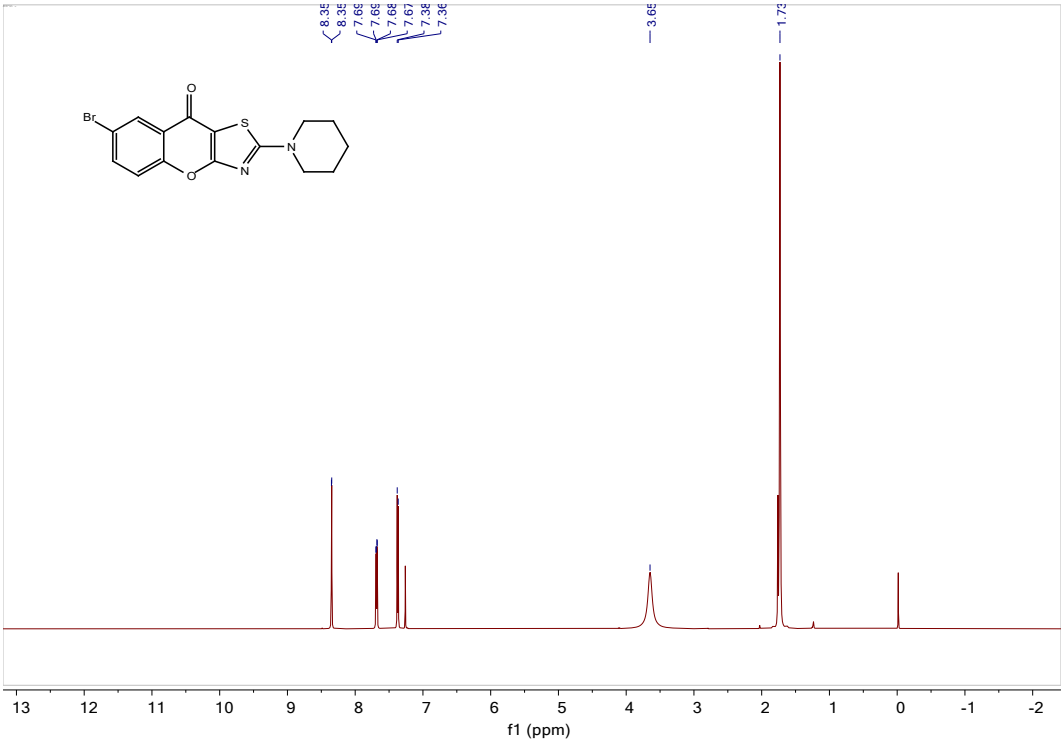

-133.0
200 150 100 50 0 -50 -100 -150 -200
f1 (ppm)

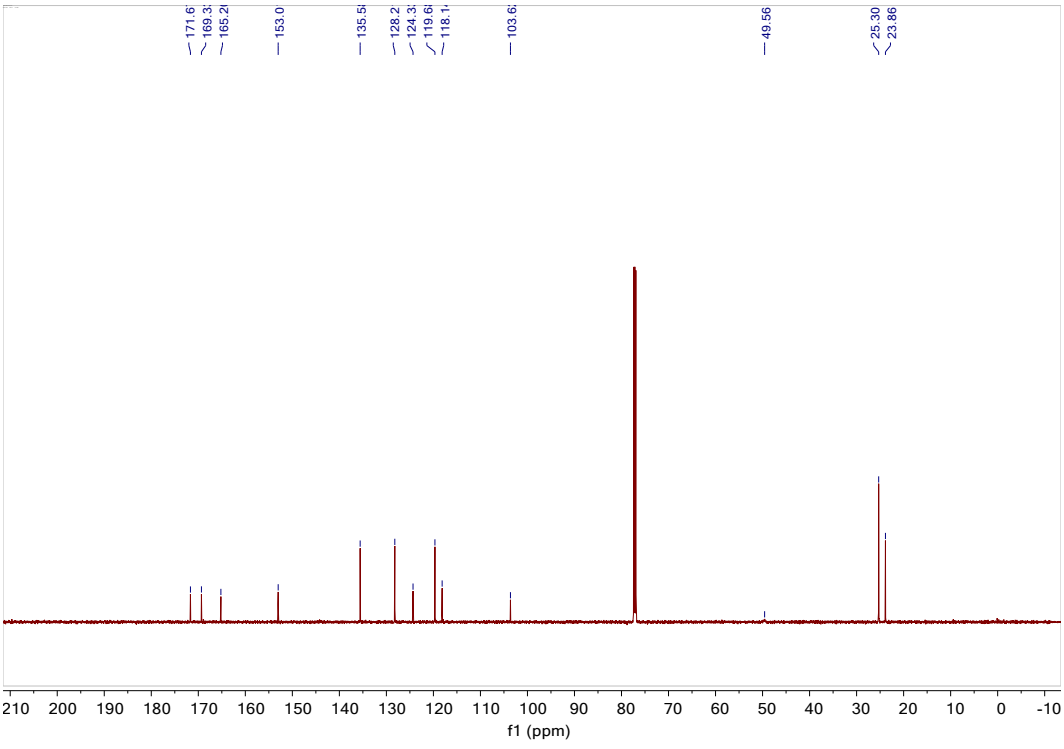
^{1}H NMR and ^{13}C NMR of compound **c30**



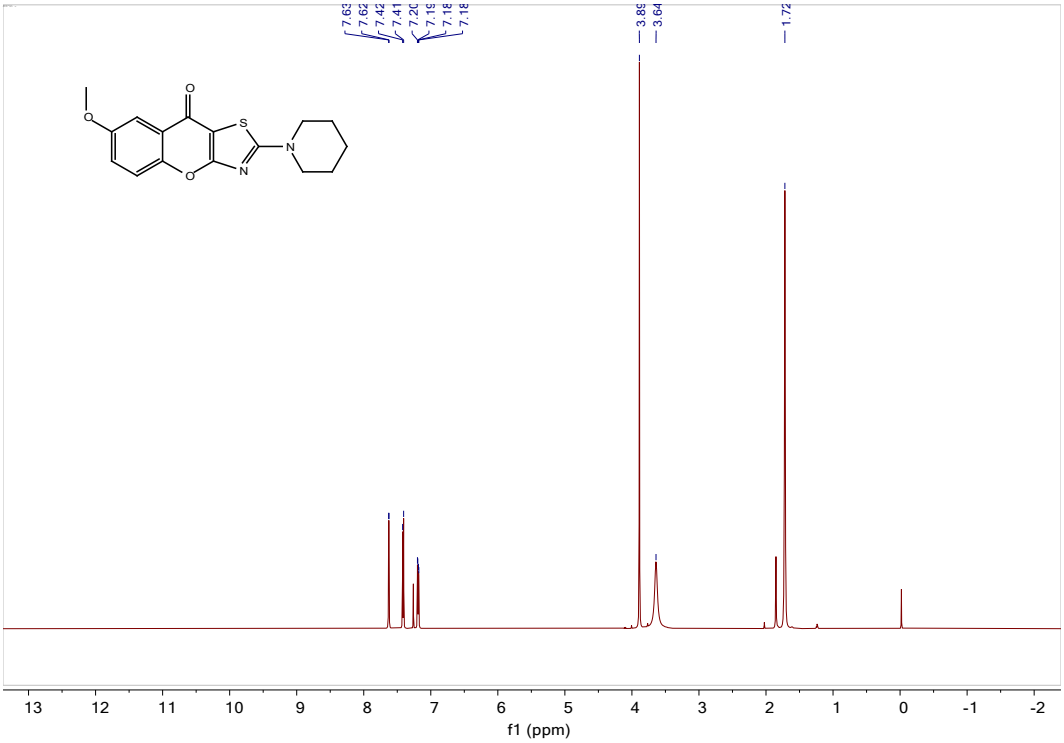


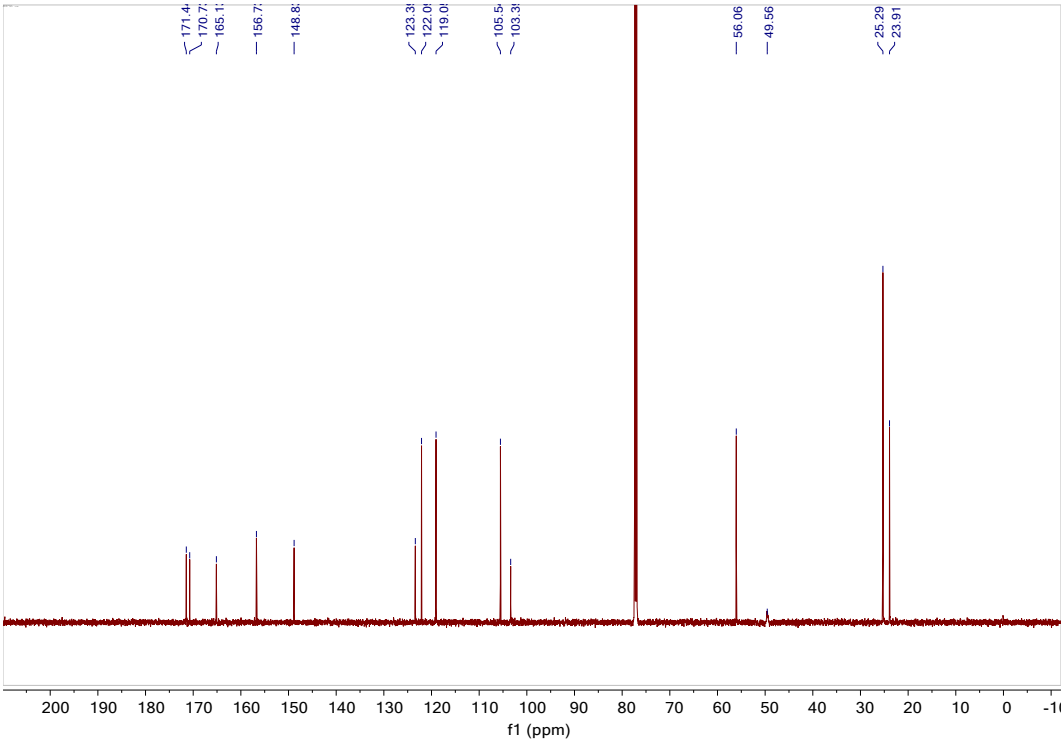
^{1}H NMR and ^{13}C NMR of compound **c31**



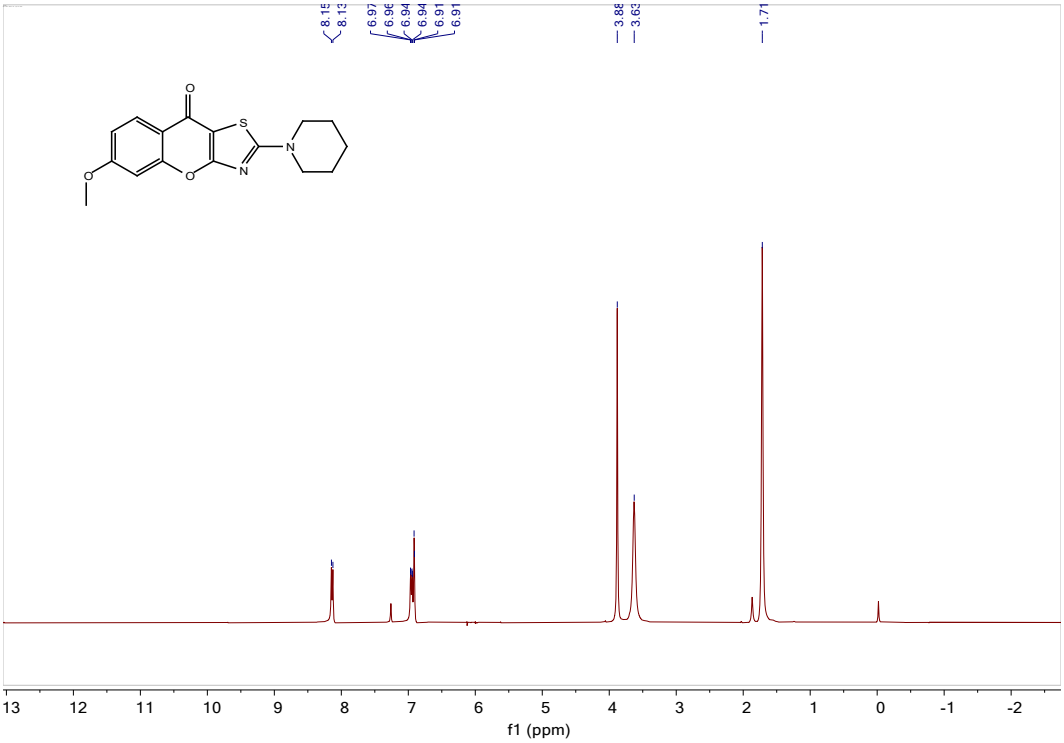


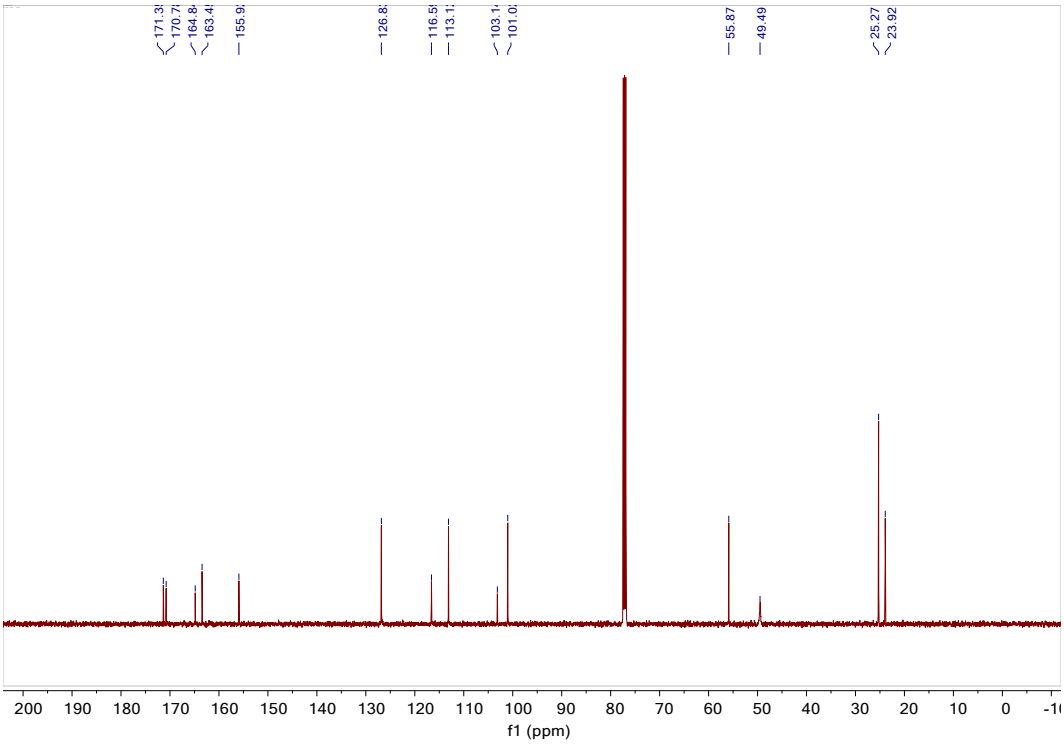
^{1}H NMR and ^{13}C NMR of compound **c32**



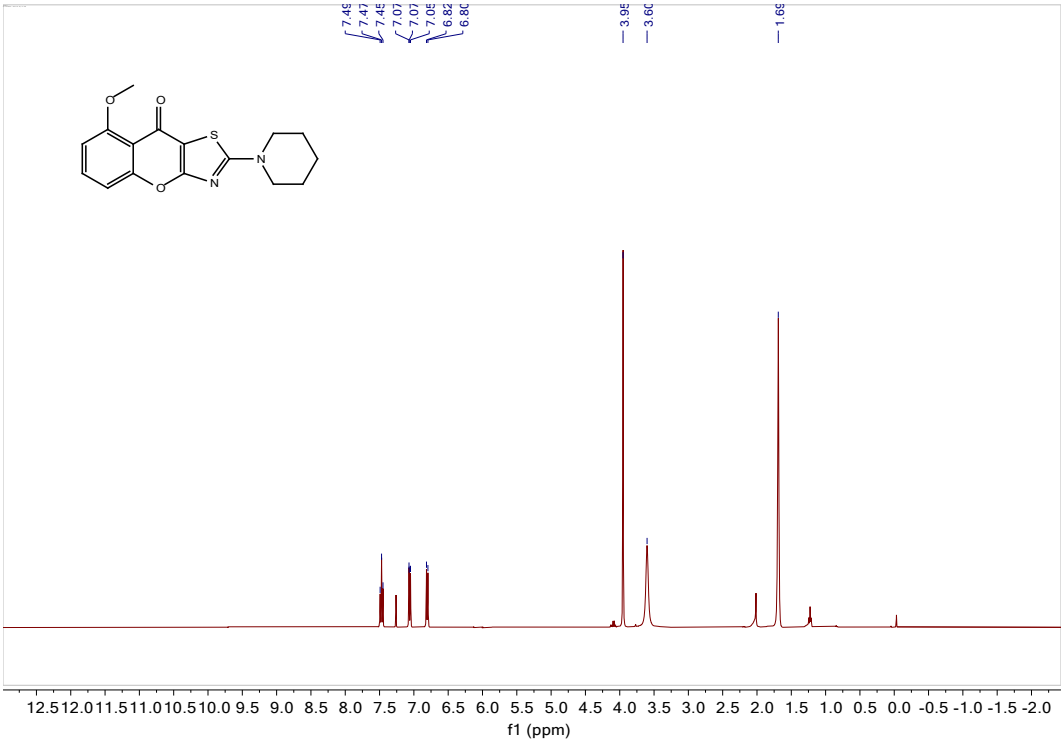


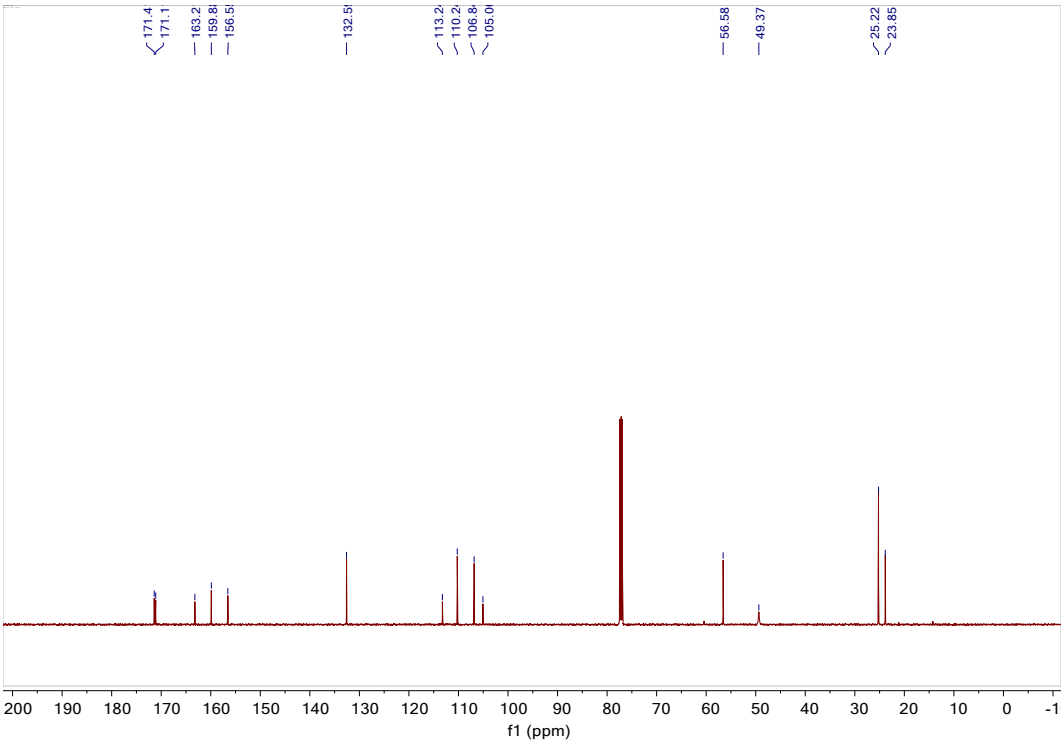
^{1}H NMR and ^{13}C NMR of compound **c33**



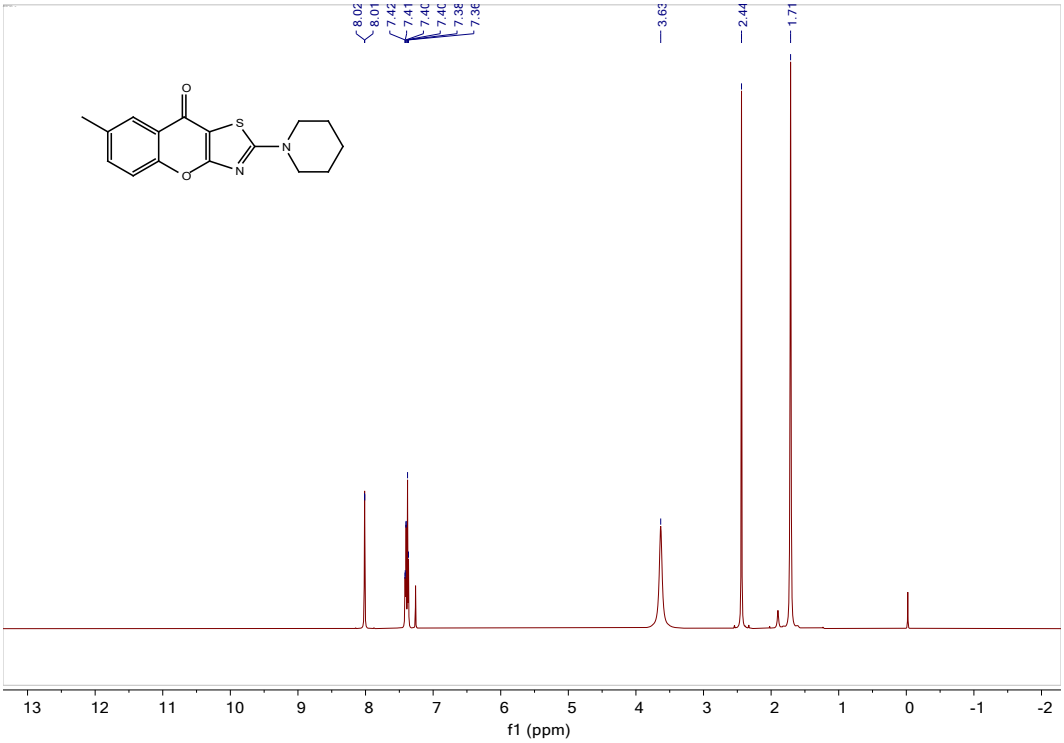


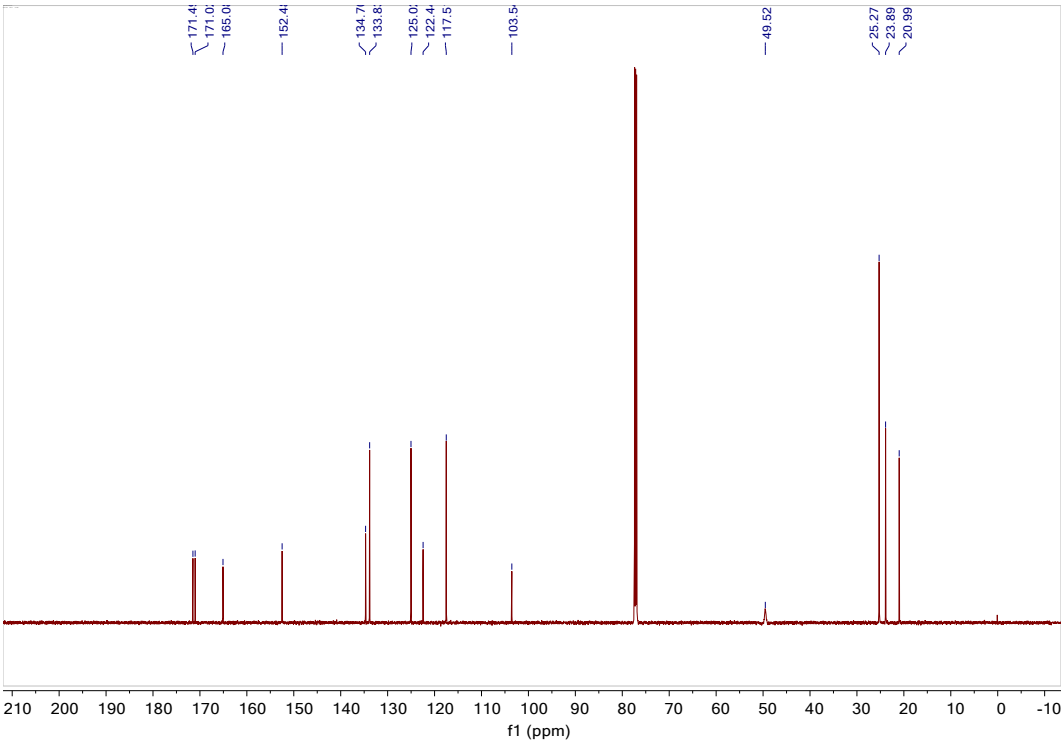
^{1}H NMR and ^{13}C NMR of compound **c34**



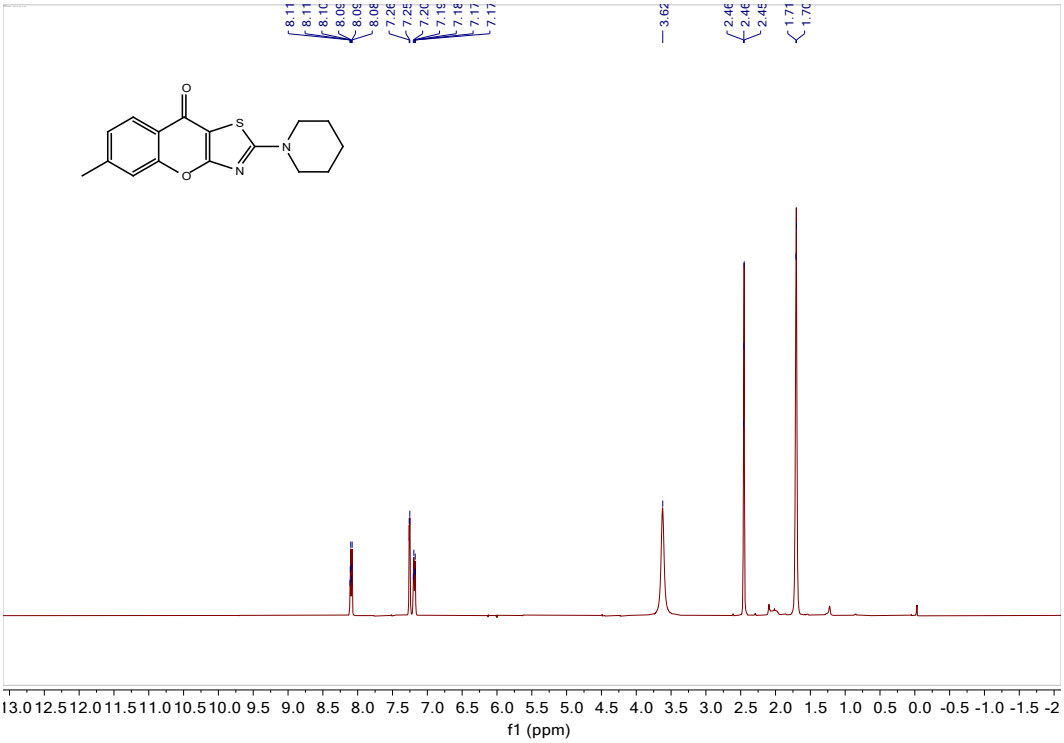


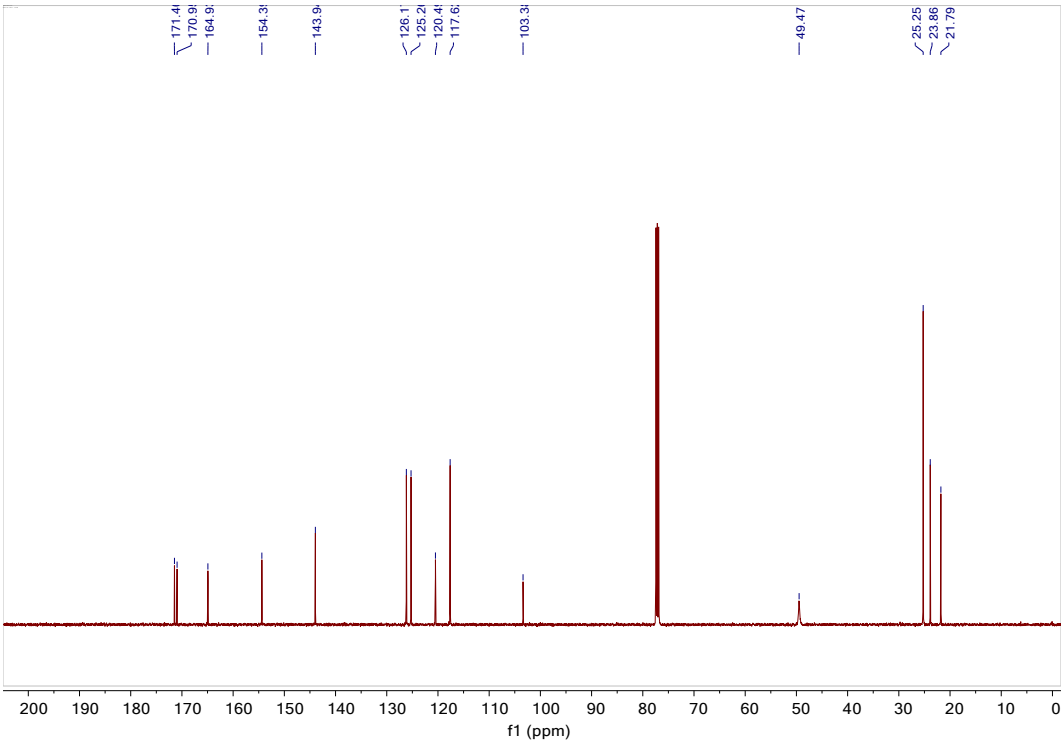
^{1}H NMR and ^{13}C NMR of compound **c35**



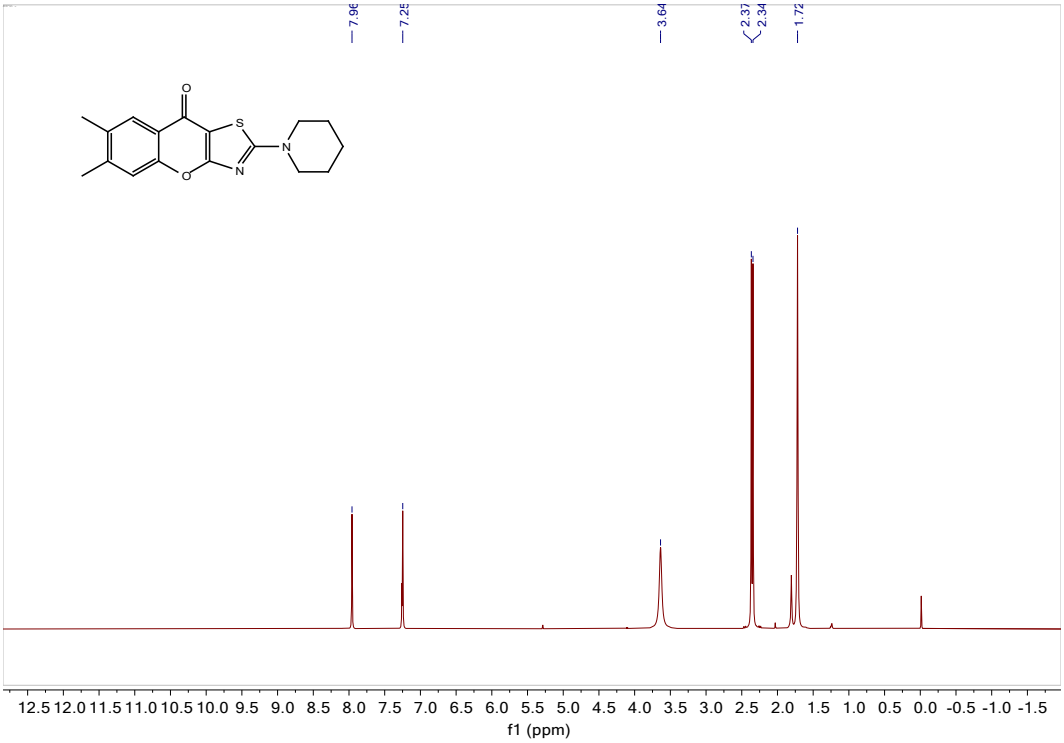


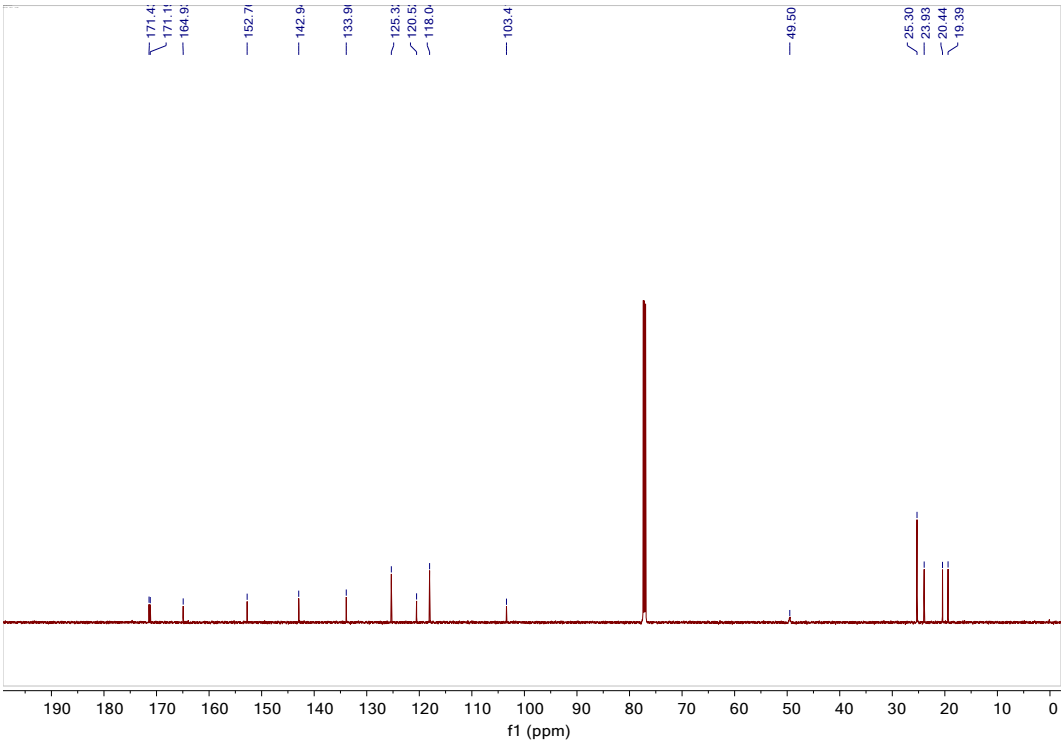
^{1}H NMR and ^{13}C NMR of compound **c36**



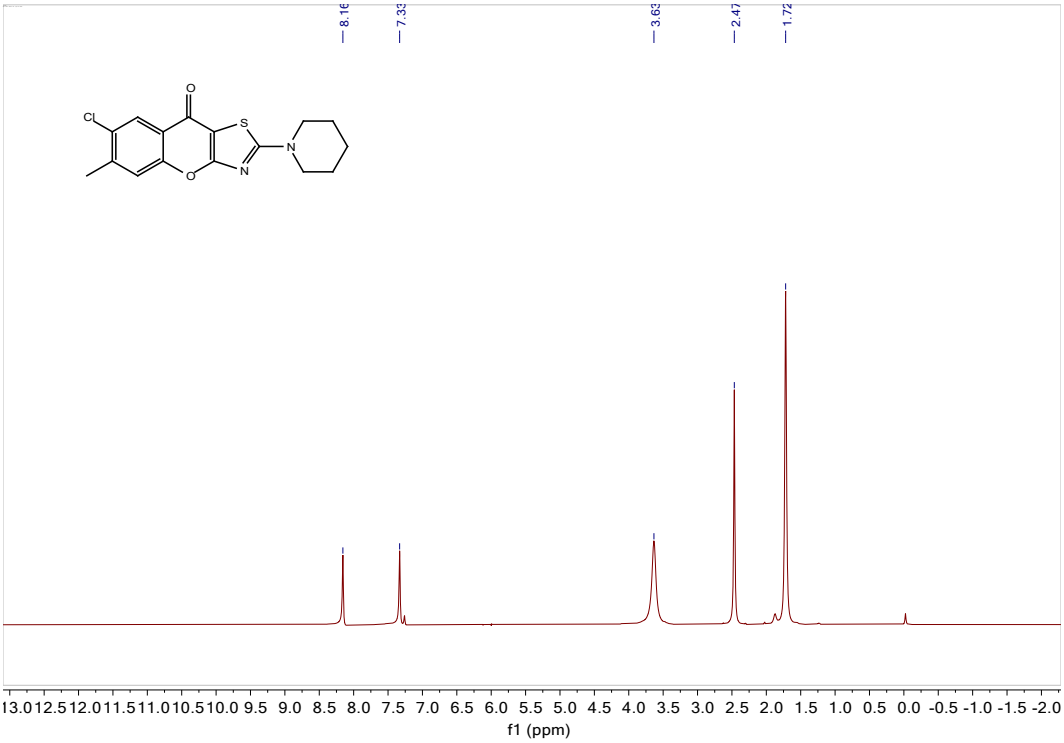


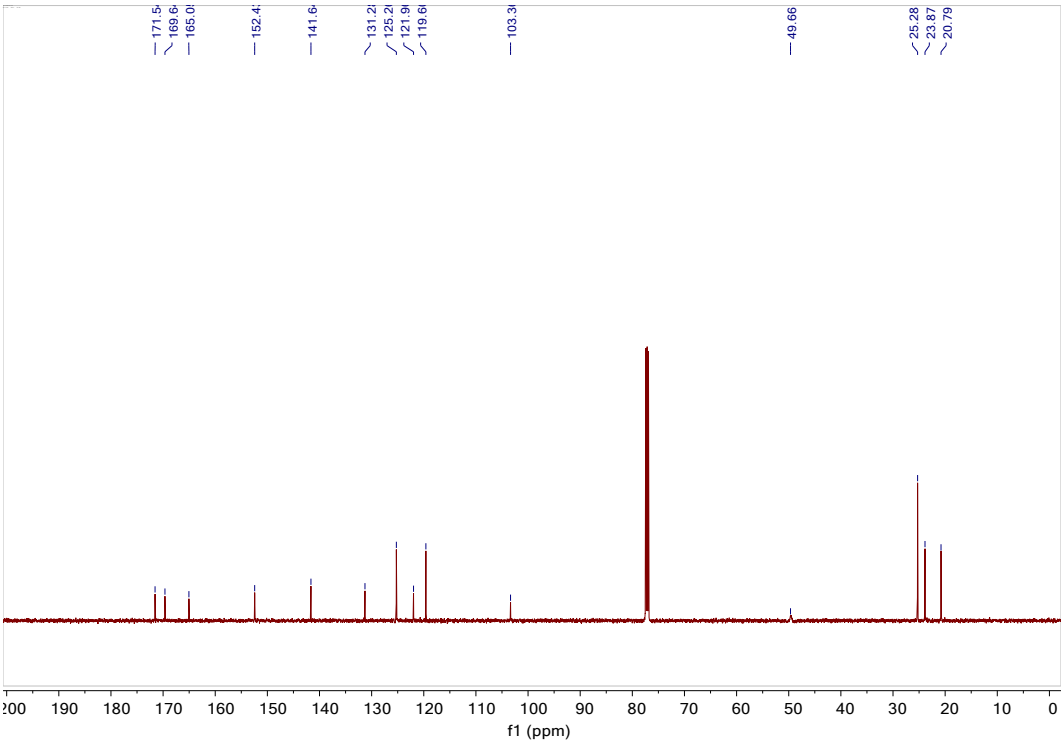
^{1}H NMR and ^{13}C NMR of compound **c37**



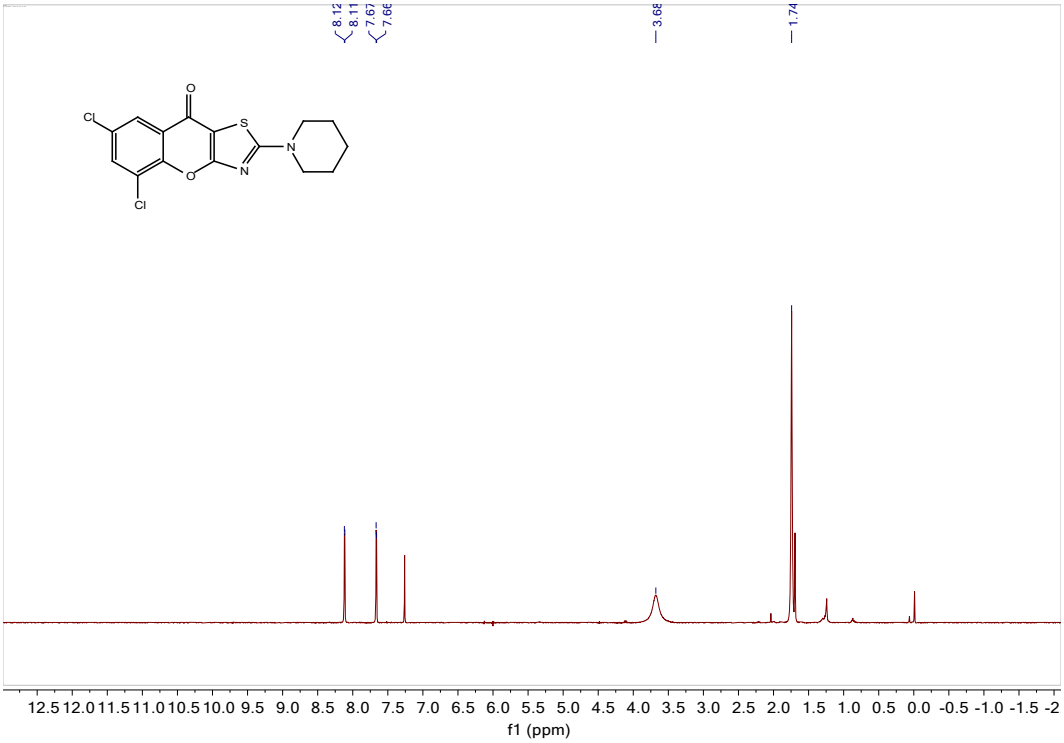


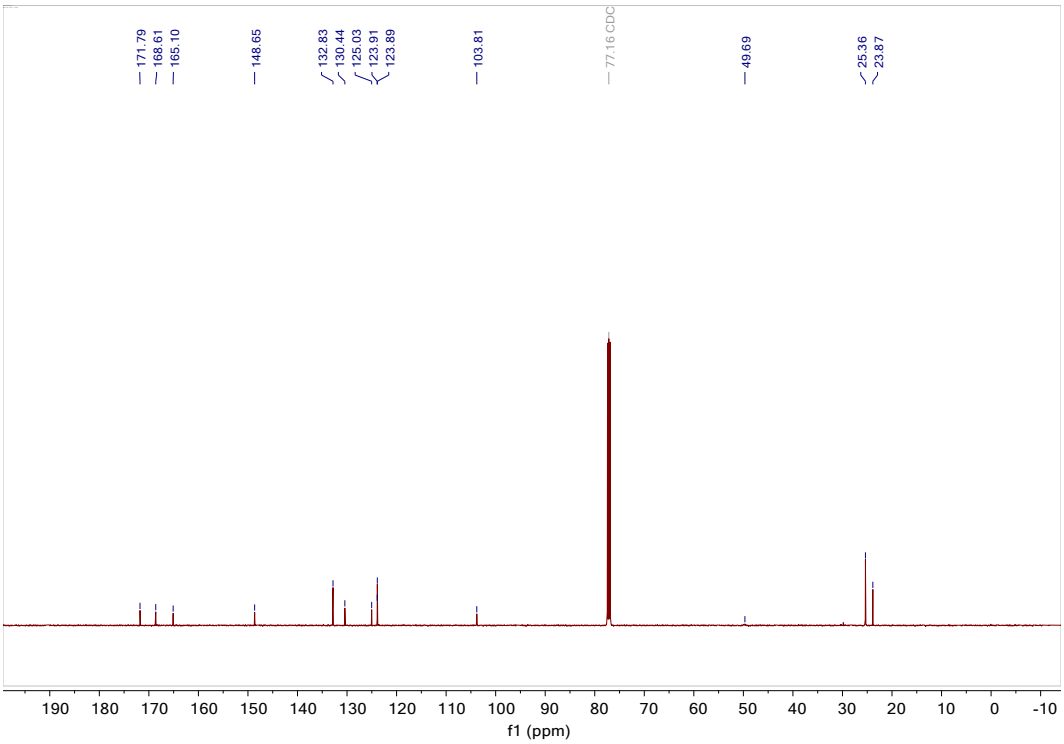
^{1}H NMR and ^{13}C NMR of compound **c38**



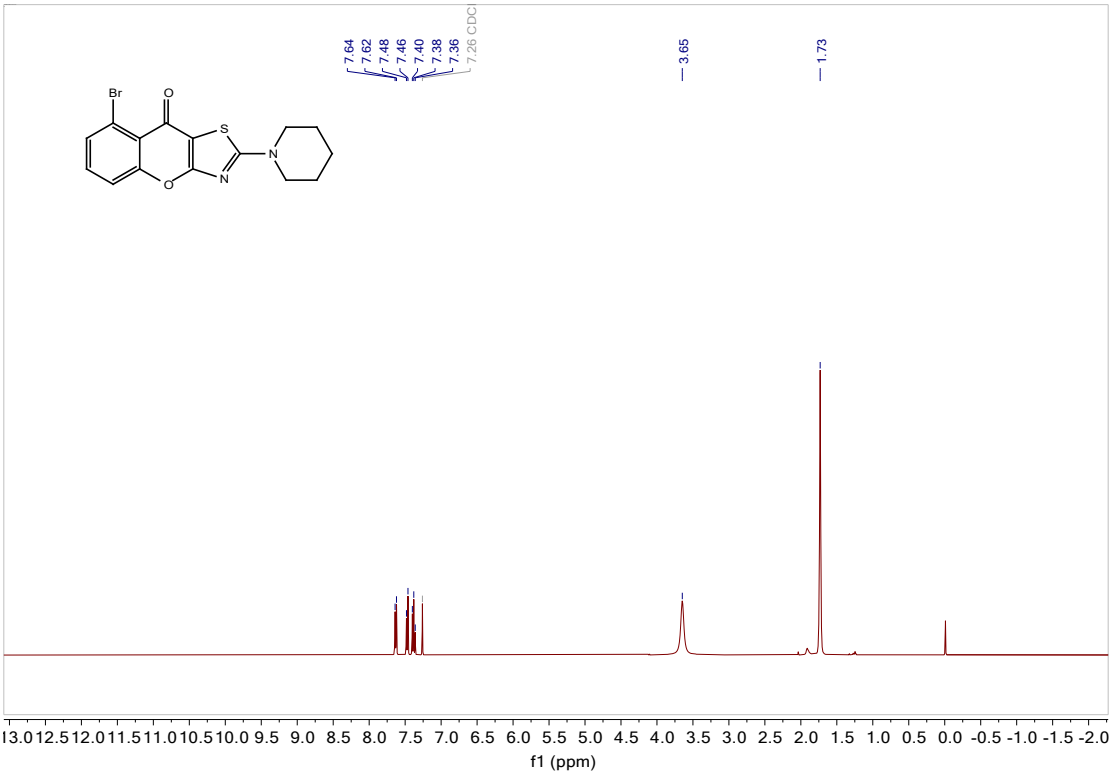


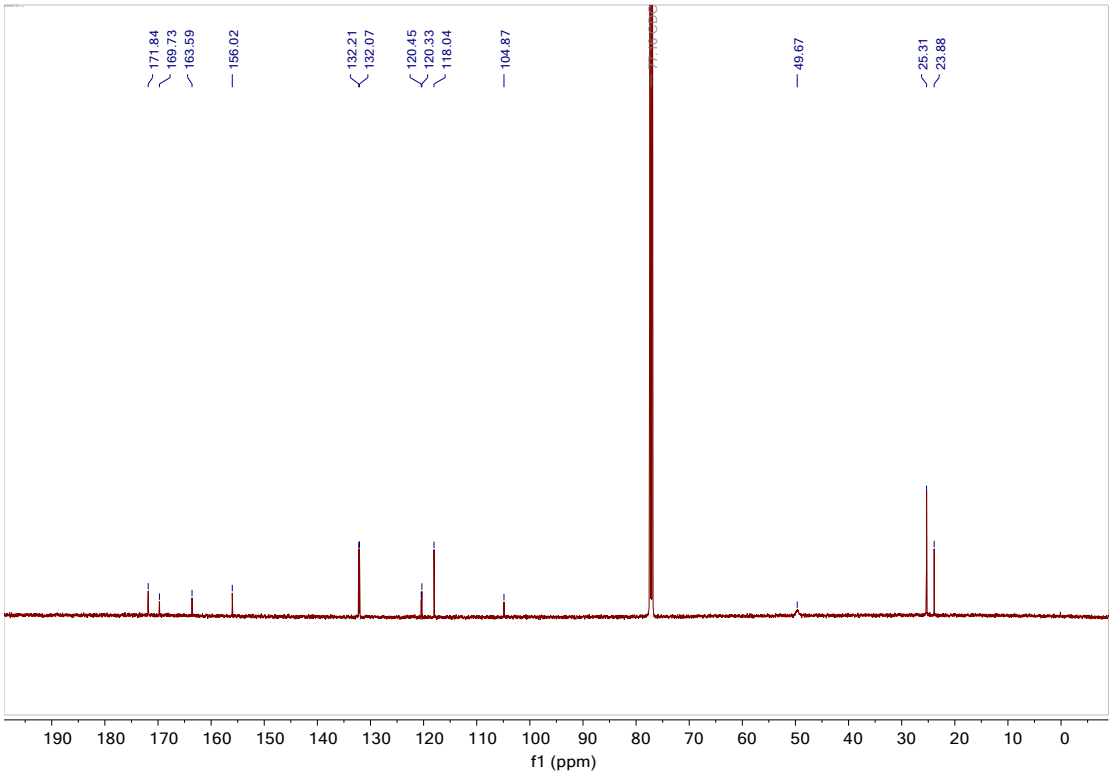
^{1}H NMR and ^{13}C NMR of compound **c39**



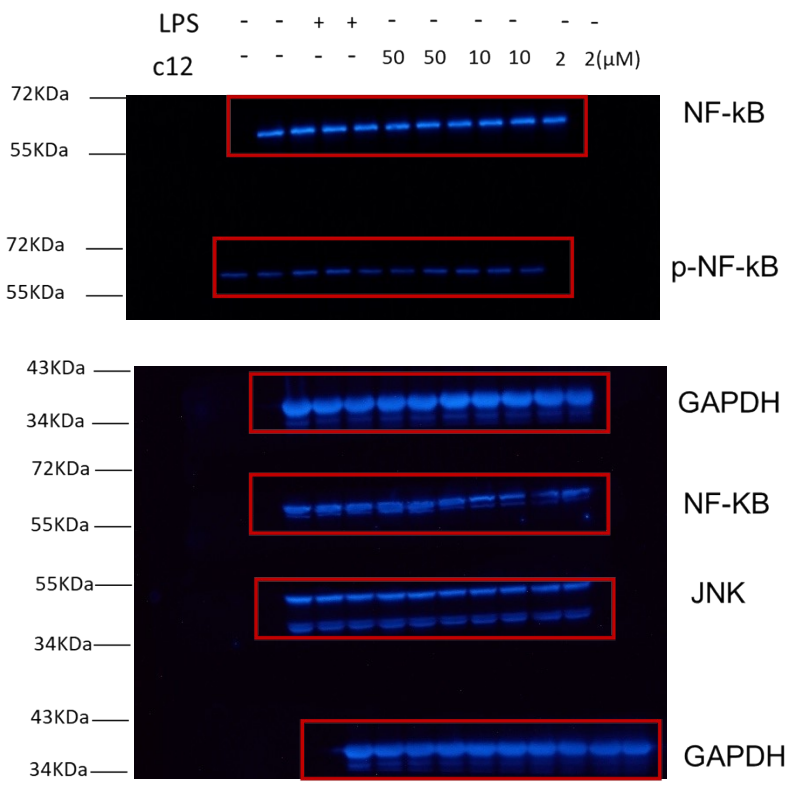


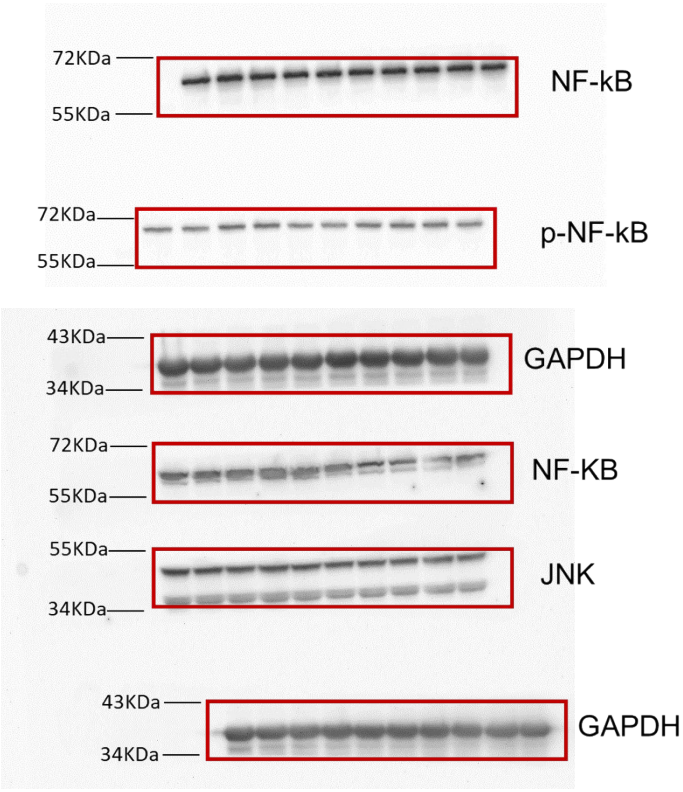
^{1}H NMR and ^{13}C NMR of compound **c40**

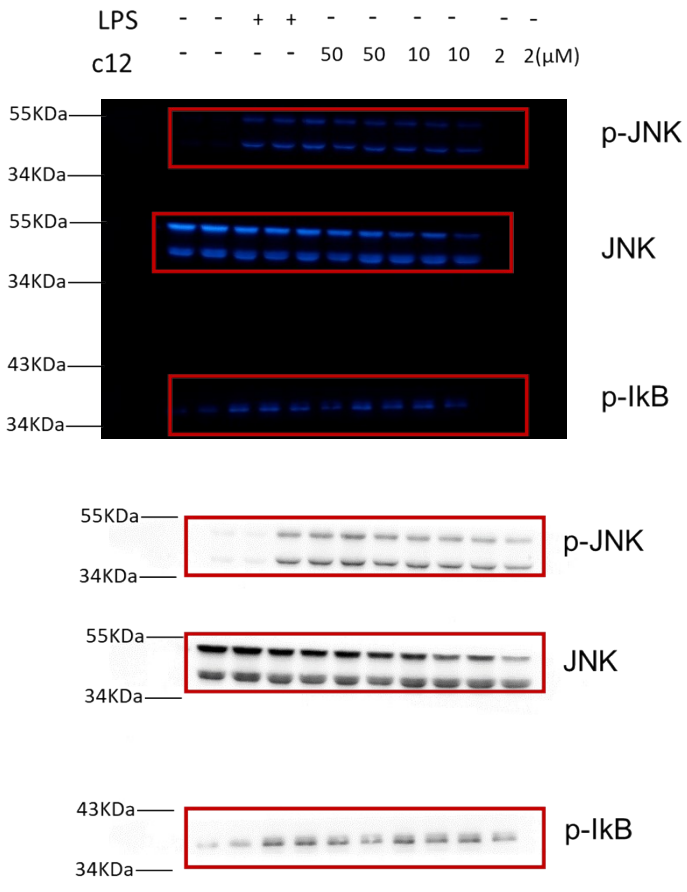




Raw data of western blots






LPS - - + + - - - - - -
c12 - - - - 50 50 10 10 2 2(μM)
55KDa
34KDa
55KDa
34KDa
43KDa
34KDa
p-JNK
JNK
p-IkB

55KDa
34KDa
p-JNK
55KDa
34KDa
JNK
43KDa
34KDa
p-IkB