Streamlining squaramide synthesis using a sustainable and versatile paper-based platform

Antonella Ilenia Alfano,[a,$] Panagiota M. Kalligosfyri,[b,$] Valerio Baia,[a]
Margherita Brindisi,[a,*,#] Stefano Cinti [b,*,#]

[a]SPOTS-Lab, Department of Pharmacy (DoE 2023-2027), University of Naples Federico II, via D. Montesano 49, 80131, Naples, Italy;

[b] UniNanobiosensors, Department of Pharmacy (DoE 2023-2027), University of Naples Federico II, via D. Montesano 49, 80131, Naples, Italy;

[$] = co-first authors;

= co-last authors

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General materials and methods

Unless otherwise stated, all solvents were purchased from Sigma-Aldrich and used without further purification. Also, unless otherwise stated, all substrates and reagents were purchased from Zentek or Sigma-Aldrich and used as received.

Paper-based platform preparation

For the reaction's performance, 2-cm diameter discs were designed and printed onto a Whatman No.1 chromatography filter paper. These filter discs, serving as the reaction platform, were subsequently wax-printed with the ColorQube 8580 office printer (Xerox, USA). The wax printed on the Whatman filter paper was pretreated at 100°C for 1 min to facilitate the penetration of the wax-based ink into the pores of the filter paper. This step was crucial for creating completely insulated hydrophilic areas, which facilitated the deposition of reagents and allowed precise control of liquid handling.

Reaction set up and conditions

The 2-cm filter discs were inserted into a designated 3D-printed support (Figure S1), produced via the 3D-printer Creality Ender-3 V2 Neo (Shenzhen Creality 3D Technology, Shenzhen, China), providing stability and enabling easy handling of the paper-based platform. The desired amounts of the reagents, as thoroughly described below, were added onto the filter disc. The mixture was gently pipetted five times to ensure proper mixing. The reaction was completed within 5 min at room temperature, under the fume hood, and the final product was left to dry for subsequent characterization and/or purification.

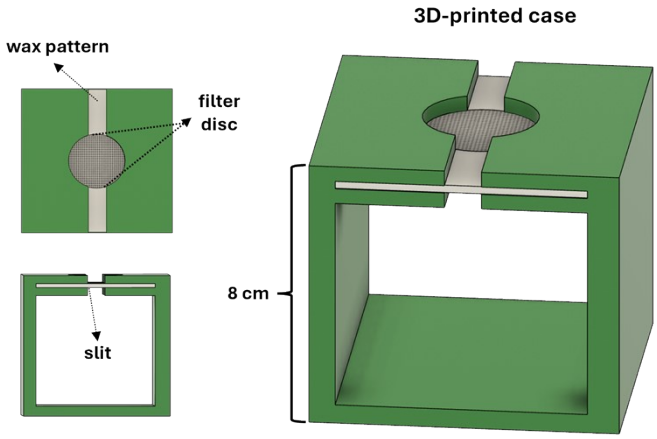


Figure S1: The 3D-printed case served as the platform for the reaction on the paper-based platform. The device included a slit to facilitate the handling of the filter disc. The paper platform consisted of a wax pattern, i.e. hydrophobic area, for liquid control and the deposition of the reagents and a circle pattern, i.e. hydrophilic area, where the reaction was performed.

Reaction monitoring and product characterization

Reaction monitoring was determined by integration of the diode array UV trace of ultra-performance liquid chromatography (UPLC) chromatograms, acquired on a Waters PDA UPLC system coupled with a single quadrupole. Analysis was conducted on a Acquity UPLC® BEH C18 column (2.1 mm x 50 mm), using H_2O/MeCN as gradient containing 0.1% formic acid (FA). The elution gradient was performed according to the following conditions: 0 - 0.10 min, isocratic on 5% phase B; 0.10 – 2.60 min, linear gradient from 5 to 100% B; 2.60 – 2.90 min, isocratic on 100% B; 2.90 – 3.00 min, linear gradient to 5% B; 3.00 – 3.50 min, isocratic on 5% B for column recondition. The separation parameters were as follows: column temperature was set at 40 °C, inject volume was 10 µL, the flow rate was set at 0.800 mL/min.

^{1}H-NMR , ^{13}C and ^{19}F spectra were recorded on 400 and 700 MHz instruments and are reported relative to the residual solvent: DMSO-d_6 (δ2.50 ppm). A weighed amount of analyte (about 5.0–10.0 mg) was dissolved in 600 µL of deuterated dimethyl sulfoxide (DMSO-d_6). The mixture was transferred into a 5 mm NMR tube and the spectra were acquired on a Bruker Advance 400 MHz and 700 MHz spectrometer by using the residual signal of the deuterated solvent as internal standard. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q) and broad (br); the values of chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hertz (Hz). NMR data were processed with MestreNova (Version 8.1.1, Mestrelab Research).

General experimental protocols

General procedure A:

A solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) in 280 µL of EtOH/H_2O 1:1 was prepared (0.5 M). Once total solubility was achieved, the solution was deposited on the 2 cm filter disc. Then, the amine (0.28 mmol, 2 equiv.) was added dropwise onto the filter disc (Figure S6A). After 5 min at room temperature, the reaction was completed and the ratio was calculated using UPLC chromatograms, on a Waters PDA UPLC system coupled with a single quadrupole. The completely dried product was removed from the filter disc without further purification step, unless mentioned below, and directly analysed with NMR showing total conversion of S.M. and > 90% of purity, unless otherwise specified. Each compound was weighed on the analytical balance to obtain the final yield.

Scale up experimental setup (Figure 2): For the scale up experiment, the general procedure A was followed. The reaction volume was ten-fold increased. Accordingly, the surface area of the filter paper disc, serving as the reaction platform, was increased approximately tenfold, resulting in a modification of the disc diameter from 2 cm to 6 cm. The 3D-printed housing was also used in this procedure to ensure the stability of the paper-based synthesis platform. This demonstrates that the paper-based platform is both scalable and customizable.

General procedure B:

A solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) in 230 µL of EtOH/H_2O 1:1 was prepared (0.6 M). Once total solubility was achieved, the solution was deposited on the 2 cm filter disc. Then, the amine (0.28 mmol, 2 equiv.) was dissolved in 50 µL and was added dropwise onto the filter disc. After 5 min at room temperature, the reaction was completed and the ratio was calculated using UPLC chromatograms, on a Waters PDA UPLC system coupled with a single quadrupole. The completely dried product was removed from the filter disc without further purification step, unless mentioned below, and directly analysed with NMR showing total conversion of S.M. and > 90% of purity, unless otherwise specified. All the paper containing the compounds were left under the fume hood overnight. By the following day, the solvent had completely evaporated or been absorbed, and the compounds were ready to be transferred into vials, without efforts. Each compound was then weighed on the analytical balance to obtain the final yield.

General procedure C:

A solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) in 280 µL of EtOH/H_2O 1:1 was prepared (0.5 M). Once total solubility was achieved, the solution was deposited on the 2 cm filter disc.

Then, the aniline (0.14 mmol, 1 equiv.) was added dropwise onto the filter disc. After 5 min at room temperature under the fume hood, the monomer was left to react and was analysed using UPLC chromatograms, on a Waters PDA UPLC system coupled with a single quadrupole. Upon completion of the analysis, the subsequent step involved adding 200 µL of EtOH/H_2O 1:1 to solubilize the initial product, followed by the dropwise addition of the amine (0.14 mmol, 1 equiv.). After 5 min at room temperature under the fume hood, the reaction was completed. The final dried product was removed from the filter disc without further purification step, unless mentioned below, and directly analysed with NMR showing > 90% of purity, unless otherwise specified. All the paper containing the compounds were left under the fume hood overnight. By the following day, the solvent had completely evaporated or been absorbed, and the compounds were ready to be transferred into vials, without efforts. Each compound was then weighed on the analytical balance to obtain the final yield.

General procedure D:

A solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) in 280 µL of EtOH/H_2O 1:1 was prepared (0.5 M). Once total solubility was achieved, the solution was deposited on the 2 cm filter disc. Then, the aniline (0.14 mmol, 1 equiv.) was added dropwise onto the filter disc. After 5 min at room temperature under the fume hood, the monomer was left to react and was analysed using UPLC chromatograms, on a Waters PDA UPLC system coupled with a single quadrupole. 21qwzUpon completion of the analysis, the subsequent step involved adding 200 µL of EtOH/H_2O 1:1 was added to solubilize the initial product and followed by the dropwise addition of the amine dissolved in 50 µL of EtOH/H_2O (0.14 mmol, 1 equiv.). After 5 min at room temperature under the fume hood the reaction was completed. The final dried product was removed from the filter disc and directly analysed with NMR showing > 90% of purity, unless otherwise specified. After 5 min at room temperature under the fume hood, the reaction was completed. The final dried product was removed from the filter disc without further purification step, unless mentioned below, and directly analysed with NMR showing > 90% of purity, unless otherwise specified. All the paper containing the compounds were left under the fume hood overnight. By the following day, the solvent had completely evaporated or been absorbed, and the compounds were ready to be transferred into vials, without efforts. Each compound was then weighed on the analytical balance to obtain the final yield.

Optimization tables

Screening conditions for the optimization in batch (polyester vial) of compound **3a** with diethyl squarate

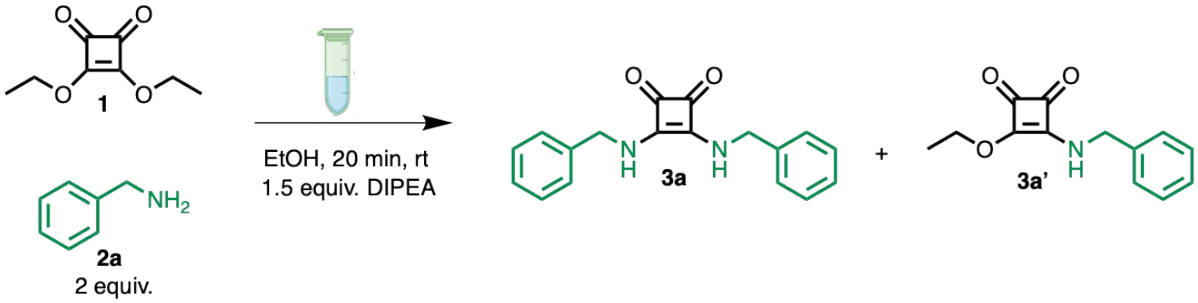


Table S1: [a] Reaction conditions: **1** (0.014 mmol), **2a** (2 equiv.) EtOH (0.5 M), 25 °C, 20 min. [b] Calculated by UPLC analysis integrating the area of the peaks.

Entry[a]	Deviation from the above conditions	Ratio 3a : 3a'[b]
1	none	95:5
2	1 min	42:58
3	5 min	62:38
4	1 min, 40 °C	42:58
5	5 min, 40 °C	85:15
6	20 min, 40 °C	97:3
7	1 min, 70 °C	64:35
8	5 min, 70 °C	95:5
9	20 min, 70 °C	90:10
10	20 min, 70 °C, NaOH	14:0
11	20 min, 70 °C, no base	88:6
12	5 min, EtOH/H_2O 1:1, NaOH	5:4
13	5 min, EtOH/H_2O 1:1, no base	88:12
14	30 min, no base	67:2
15	1 min, H_2O, no base	54:36
16	5 min, H_2O, no base	77:4

Optimization of reaction's solvent

The reaction in the polyester vial/batch was performed in EtOH as reported previously.[1,2] However, due to the use of the paper-based material, the percentage of EtOH, in water, was investigated to provide enough EtOH in the reaction, ensure compatibility with the filter paper and introduce a more sustainable approach for the synthesis of squaramides-based compounds. Different percentages of EtOH in water, ranging from 40-100%, were tested using a red dye to improve the visualization and interpretation of the results. 300 µL of solvent were deposited on the filter disc and after 5 minutes the image was obtained using a smartphone. The images were processed, in terms of diameter calculation, via the open-access ImageJ tool. The percentage of spread was calculated using the formula:

$$\frac{(Diameter\ of\ the\ drop\ at\ each\ percentage - Diameter\ of\ the\ filter\ disc)}{Diameter\ of\ the\ filter\ disc} \times 100\%$$

As shown in the histogram (Figure S2), a 50% solvent, i.e. EtOH: H2O 1:1, was chosen as optimal because the spread of the drop was under 10%, and the drop was normally deposited on the filter paper. As observed in the histogram and in the inset images, at solvent concentrations higher than 50%, the drop spread significantly. In fact at the higher percentage, i.e. 100% EtOH, the drop spread beyond the hydrophobic area of the paper. Finally even though the measurements were performed in triplicates the standard error was higher when higher EtOH% was tested due to the random spread of the drop.

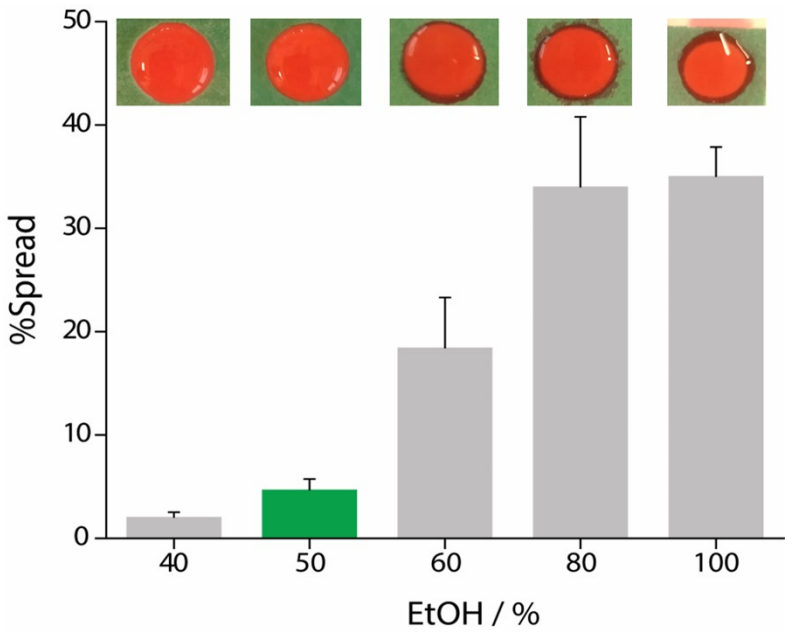


Figure S2: Percentages of drop spread for various percentages of EtOH. The inset images correspond to the percentages of EtOH.

Screening conditions for the filter paper optimization for compound **3a**

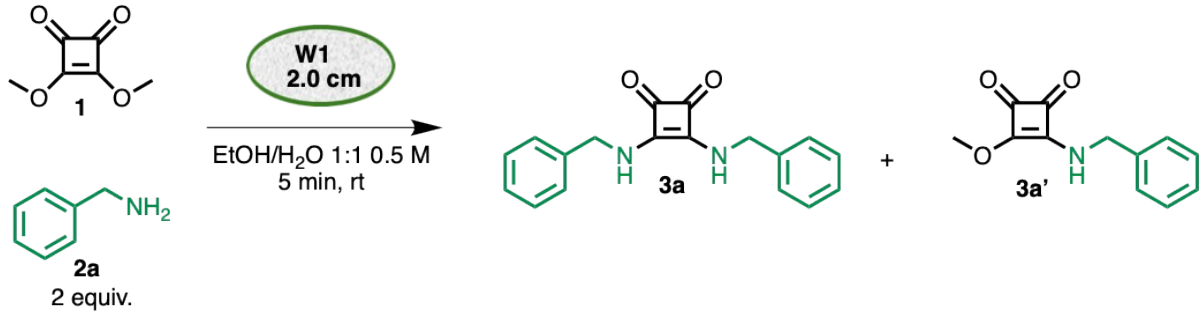


Table S2: [a] Reaction conditions: **1** (0.14 mmol), **2a** (2 equiv.) EtOH / H_2O 1:1 (0.5 M), 2.0 cm W1, 25 °C, 5 min. [b] Calculated by UPLC analysis integrating the area of the peaks. [c] 3,4-diethoxy-3-cyclobutene-1,2-dione is used. [d] 0.014 mmol scale (2 mg). [e] same ratio using 3,4-dimethoxy-3-cyclobutene-1,2-dione.

Entry	Deviation from the above conditions	Ratio 3a : 3a'[b]
1	**none**	97:3
2[c,d]	0.8 cm paper, 1M	90:10[e]
3	1.0 cm paper, 1M	68:32
4	1.2 cm paper, 1M	63:35
5	2.0 cm paper, 1M	92:6

Characterization of the paper-based platform

To investigate how the paper-based platform interacts with the reaction components, we performed microscopic analysis using an Exacta Optech microscope equipped with a Euromex Scientific Camera (Exacta Labcenter SpA, Italy). Images were taken before the reaction and after the reaction, once the paper-based platform had dried and the final product had been removed. After the completion of the reaction and product removal, which was achieved without significant effort as the dried product formed cracks that allowed it to detach easily from the paper-based platform and be transferred into a vial, no significant damage, swelling, or structural changes were observed under the microscope or by the naked eye, as shown in Figure S3. Some residual particles were observed on the platform after the reaction (Figure S3B, D).

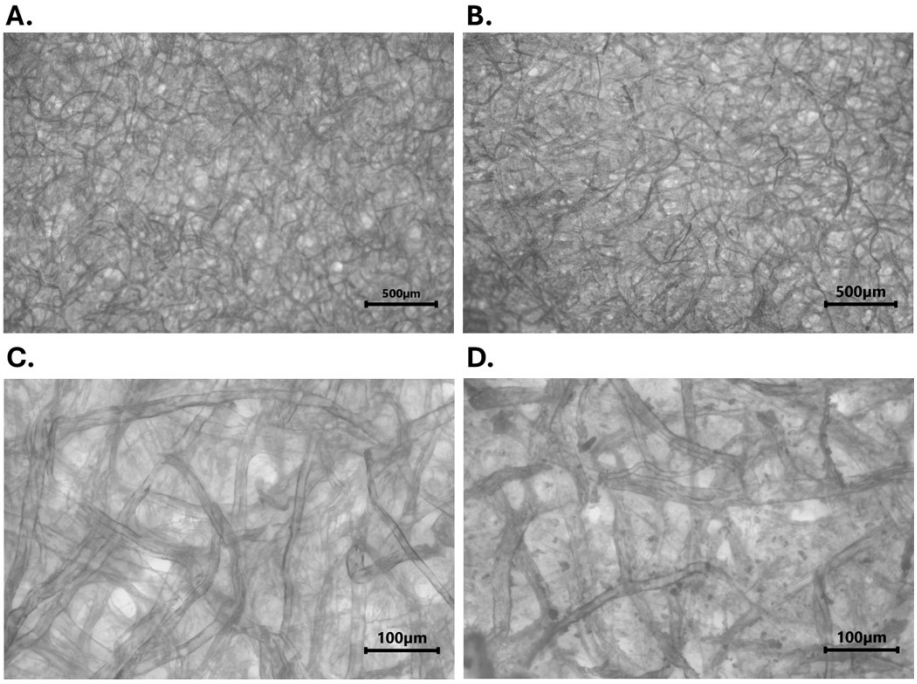


Figure S3: Microscope images of the paper-based platform before (A, C) and after the reaction and product removal (B, D) at two different scales: 500 µm and 100 µm.

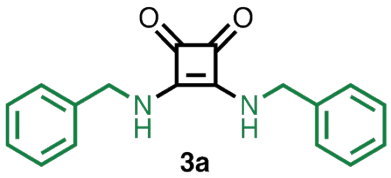
Additionally, we performed image analysis using ImageJ, the open-source, freely distributable image processing tool (https://imagej.net/ij/index.html), to calculate the fibers' width. This approach allowed us to correlate fiber swelling with potential damage. The results showed that there was no significant damage or swelling of the fibers in the paper-based platform. In fact, the analysis revealed no notable changes in the dimensions of the paper's structure. The measurements were conducted at a 100 µm scale, by randomly selecting 40 fiber widths across the images that were analyzed. The average fiber width was then calculated based on these measurements.

Table S3: The paper-based platform characterized before and after the reaction and compared in terms of fiber width.

Paper-based platform	Min width (µm)	Max width (µm)	Average width (µm)
before reaction	5.5	52.0	21.0
after product removal	9.0	54.4	21.2

Characterization data

3a: 3,4-bis(benzylamino)cyclobut-3-ene-1,2-dione



3a

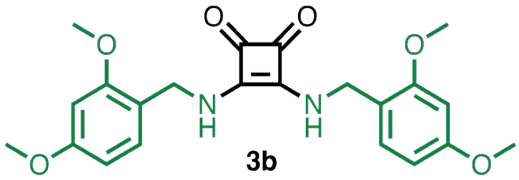
Following the general procedure A, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 30.8 µL of benzylamine (0.28 mmol, 2 equiv.), 40 mg (97% yield) of **3a** were obtained as white solid. The same reaction was also performed on 1.14 mmol scale, furnishing 93% yield. The spectroscopic data are in line with those previously reported in literature.[3,4]

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.72 (s broad, 2H), 7.39 – 7.34 (m, 5H), 7.32 – 7.27 (m, 5H), 4.71 (d, *J* = 6.4 Hz, 4H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 182.64 (2 C), 167.54 (2 C), 138.93 (2 C), 128.64 (4 CH), 127.49 (4 CH), 127.41 (2 CH), 46.80 (2 CH_2).

MS (ES+) calc for $C_{18}H_{16}N_2O_2$ 293.1 $(M+H)^+$, found 293.1 $(M+H)^+$.

3b: 3,4-bis((2,4-dimethoxybenzyl)amino)cyclobut-3-ene-1,2-dione



3b

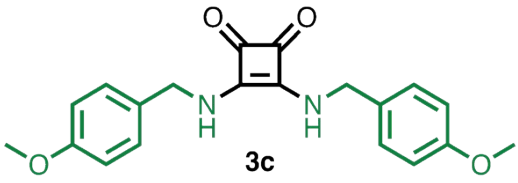
Following the general procedure A, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 42 µL of 2,4-dimethoxy benzylamine (0.28 mmol, 2 equiv.), 48 mg (84% yield) of **3b** were obtained as white solid. The product was obtained after a purification step that involved 1-min vortexing in 1.5 mL of methanol, followed by centrifugation at 8000 g for 10 min; it was then precipitated and dried at room temperature for further analysis. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.49 (s broad, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 2.4 Hz, 2H), 6.50 (dd, *J* = 8.3, 2.4 Hz, 2H), 4.58 (d, *J* = 6.1 Hz, 4H), 3.79 (s, 6H), 3.75 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 182.82 (2 C), 167.90 (2 C), 160.88 (2 C), 158.47 (2 C), 130.28 (2 C), 119.17 (2 CH), 105.02 (2 CH), 99.01 (2 CH), 56.01 (2 CH_3), 55.73 (2 CH_3), 42.55 (2 CH_2).

MS (TOES+) calc for $C_{22}H_{24}N_2O_6$ 413.1634 $(M+H)^+$, found 413.3310 $(M+H)^+$.

3c: 3,4-bis((4-methoxybenzyl)amino)cyclobut-3-ene-1,2-dione



3c

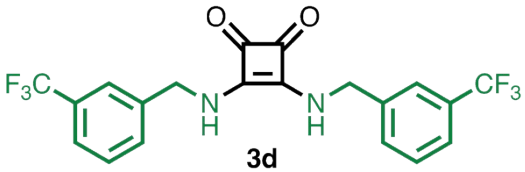
Following the general procedure A, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 36.5 µL of 4-dimethoxy benzylamine (0.28 mmol, 2 equiv.), 38 mg (78% yield) of **3c** were obtained as white solid. The product was obtained performing a purification step that involved 1-min vortexing in 1.5 mL of methanol, followed by centrifugation at 8000 g for 10 min; it was then precipitated and dried at room temperature for further analysis. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (s, 2H), 7.23 (d, J = 8.6 Hz, 4H), 6.91 (d, J = 8.6 Hz, 4H), 4.61 (s, 4H), 3.73 (s, 6H).

^{13}C NMR (176 MHz, DMSO) δ 183.01 (2 C), 159.11 (2 C), 131.35 (2 C) 129.29 (4 CH), 114.49 (4 CH), 55.57 (2 CH_3), 46.74 (2 CH_2).

MS (ES+) calc for $C_{20}H_{20}N_2O_4$ 353.1 $(M+H)^+$, found 353.2 $(M+H)^+$.

3d: 3,4-bis((3-(trifluoromethyl)benzyl)amino)cyclobut-3-ene-1,2-dione



3d

Following the general procedure A, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 40.2 µL of 3-trifluoromethyl benzylamine (0.28 mmol, 2 equiv.), 58 mg (97% yield) of **3d** were obtained as white solid. This compound is new and no previously spectroscopic data have been reported.

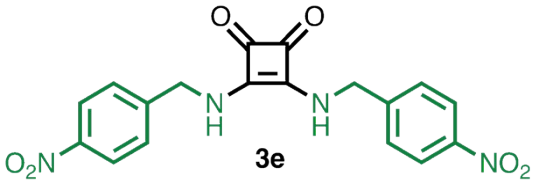
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 2H), 7.70 – 7.64 (m, 4H), 7.61 (d, *J* = 6.9 Hz, 4H), 4.80 (d, *J* = 7.0 Hz, 4H).

^{19}F NMR (377 MHz, DMSO-d_6) δ -60.89.

^{13}C NMR (101 MHz, DMSO-d_6) δ 182.79 (2 C), 167.64 (2 C), 140.48 (2 C), 131.64 (2 CH), 129.76 (CH) 129.45 (q, *J* =83 MHz, 2 C), 125.51 (q, *J* = 308 MHz, CF_3) 124.03 (2 CH), 124.12 (CH), 124.17 (2 CH), 46.21 (2 CH_2).

MS (ES+) calc for $C_{20}H_{14}F_6N_2O_2$ 429.0 $(M+H)^+$, found 429.1 $(M+H)^+$.

3e: 3,4-bis((4-nitrobenzyl)amino)cyclobut-3-ene-1,2-dione



3e

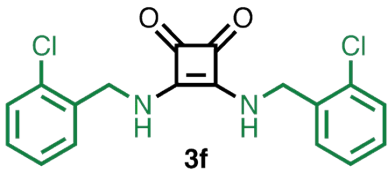
Following the general procedure B, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 42.6 mg of 4-nitro benzylamine (0.28 mmol, 2 equiv.), 43 mg (81% yield) of **3e** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 8.9 Hz, 4H), 7.58 (d, *J* = 8.5 Hz, 4H), 4.85 (s, 4H).

^{13}C NMR (101 MHz, DMSO) δ 183.33 (2 C), 168.22 (2 C) 147.33 (2 C), 147.22 (2 C), 129.03 (2 CH), 124.26 (2 CH), 46.57 (2 CH_2).

MS (ES+) calc for $C_{18}H_{14}N_4O_6$ 383.0 $(M+H)^+$, found 383.1 $(M+H)^+$.

3f: 3,4-bis((2-chlorobenzyl)amino)cyclobut-3-ene-1,2-dione



3f

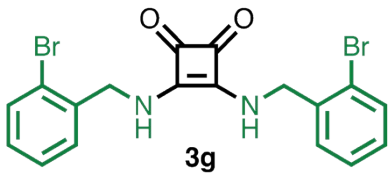
Following the general procedure A, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 33.8 µL of 2-chloro benzylamine (0.28 mmol, 2 equiv.), 47 mg (93% yield) of **3f** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (700 MHz, DMSO-d_6) δ 7.78 (s broad, 2H), 7.49 (dd, *J* = 6.7, 2.5 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.37 (q, *J* = 5.7 Hz, 4H), 4.82 (d, *J* = 6.3 Hz, 4H).

^{13}C NMR (176 MHz, DMSO-d_6) δ 183.07 (2 C), 168.01 (2 C), 136.34 (2 C), 132.89 (2 C), 130.06 (2 CH), 129.96 (4 CH), 128.14 (2 CH), 45.71 (2 CH_2).

MS (ES+) calc for $C_{18}H_{14}Cl_2N_2O_2$ 361.0 $(M+H)^+$, found 361.0 $(M+H)^+$.

3g: 3,4-bis((2-bromobenzyl)amino)cyclobut-3-ene-1,2-dione



3g

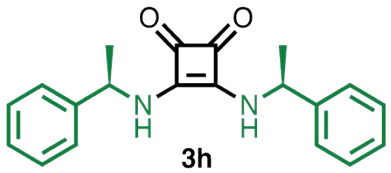
Following the general procedure B, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 52.1 mg of 2-bromo benzylamine (0.28 mmol, 2 equiv.), 55 mg (88% yield) of **3g** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.81 (s broad, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.43 (dd, *J* = 7.8, 6.6 Hz, 4H), 7.32 – 7.26 (m, 2H), 4.81 (d, *J* = 6.4 Hz, 4H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 183.17 (2 C), 168.04 (2 C), 137.96 (2 CH), 133.21 (2 CH), 130.24 (2 CH), 128.70 (2 CH), 123.21 (2 CH), 47.67 (2 CH_2).

MS (ES+) calc for $C_{18}H_{14}Br_2N_2O_2$ 448.9 $(M+H)^+$, found 448.9 $(M+H)^+$.

3h: 3-(((*R*)-1-phenylethyl)amino)-4-(((S)-1-phenylethyl)amino)cyclobut-3-ene-1,2-dione



3h

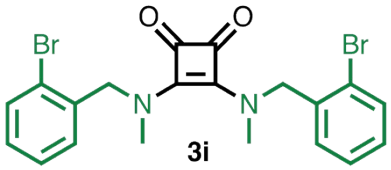
Following the general procedure A, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 34 µL of *(R)*-1-phenylethan-1-amine (0.28 mmol, 2 equiv.), 41 mg (93% yield) of **3h** were obtained as white solid. The spectroscopic data are in line with those previously reported in literature.[5]

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.69 (s, 2H), 7.40 – 7.31 (m, 8H), 7.31 – 7.26 (m, 2H), 5.20 (s, 2H), 1.52 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 182.27 (2 C), 166.89 (2 C), 143.58 (2 C), 128.65 (4 CH), 127.35 (2 CH), 126.00 (4 CH), 52.67 (2 CH_2), 22.98 (2 CH_3).

MS (ES+) calc for $C_{20}H_{20}N_2O_2$ 321.1 $(M+H)^+$, found 321.1 $(M+H)^+$.

3i: 3,4-bis((2-bromobenzyl)(methyl)amino)cyclobut-3-ene-1,2-dione



3i

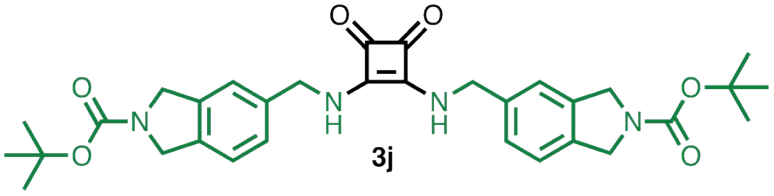
Following the general procedure A, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 41.2 µL of 1-(2-bromophenyl)-*N*-methylmethanamine (0.28 mmol, 2 equiv.), 42 mg (64% yield) of **3i** were obtained as white solid. The product was obtained performing a purification step that involved 1-min vortexing in 1.5 mL of methanol, followed by centrifugation at 8000 g for 10 min; it was then precipitated and dried at room temperature for further analysis. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.07 (d, *J* = 7.8 Hz, 2H), 7.87 – 7.80 (m, 4H), 7.70 (td, *J* = 7.5, 2.2 Hz, 2H), 5.33 (s, 4H), 3.47 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 183.20 (2 C), 169.06 (2 C), 134.92 (2 C), 133.00 (2 CH), 129.73 (2 CH), 129.38 (2 CH), 128.20 (2 CH), 122.00 (2 C), 55.67 (2 CH_2), 40.20 (2 CH_3).

MS (ES+) calc for $C_{20}H_{18}Br_2N_2O_2$ 476.9 $(M+H)^+$, found 477.0 $(M+H)^+$.

3j: di-*tert*-butyl 5,5'-(((3,4-dioxocyclobut-1-ene-1,2-diyl)bis(azanediyl))bis(methylene))bis(isoindoline-2-carboxylate)



3j

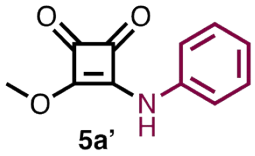
Following the general procedure B, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol) and 69.44 mg of *tert*-butyl 5-(aminomethyl)isoindoline-2-carboxylate (0.28 mmol, 2 equiv.), 69 mg (87% yield) of **3j** were obtained as yellow solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.75 (s broad, 2H), 7.30 – 7.17 (m, 6H), 4.70 (d, *J* = 6.5 Hz, 4H), 4.59 (t, *J* = 8.0 Hz, 8H), 1.45 (d, *J* = 8.9 Hz, 18H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 182.63 (2 C), 167.52 (2 C), 153.57 (C), 153.49 (C), 137.64 (C), 137.12 (C), 135.32 (C), 134.89 (C), 133.33 (2 C), 127.89 (2 CH), 127.42 (2 CH), 122.00 (2 CH), 78.90 (2 C), 51.88 (CH_2), 51.70 (CH_2), 50.46 (CH_2), 50.40 (CH_2), 44.63 (2 CH_2), 28.22 (6 CH_3).

MS (ES+) calc for $C_{32}H_{38}N_4O_6$ 575.2 $(M+H)^+$, found 575.1 $(M+H)^+$.

5a': 3-methoxy-4-(phenylamino)cyclobut-3-ene-1,2-dione



5a'

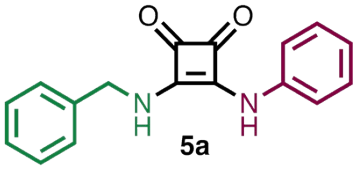
Following the general procedure C, using 20 mg of dimethyl squarate (0.14 mmol) and 12.7 µL of aniline, (0.14 mmol, 1 equiv.), 28 mg (99% yield) of **5a'** were obtained as white solid. The spectroscopic data are in line with those previously reported in literature. [6,7]

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.75 (s, 1H), 7.35 (d, *J* = 4.9 Hz, 4H), 7.11 (p, *J* = 4.3 Hz, 1H), 4.38 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 183.93 (C), 178.74 (C), 169.19 (C), 164.07 (C), 137.92 (C), 129.09 (3 CH), 124.07 (CH), 119.57 (CH), 60.53 (CH_3).

MS (ES+) calc for $C_{11}H_9NO_3$ 204.0 $(M+H)^+$, found 204.0 $(M+H)^+$.

5a: 3-(benzylamino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



5a

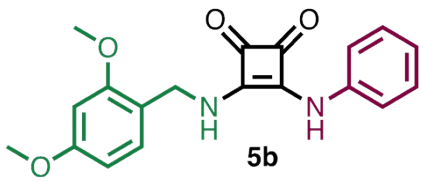
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 15.3 µL of benzylamine (0.14 mmol, 1 equiv.), 37 mg of **5a** (97 % yield) were obtained as white solid. The spectroscopic data are in line with those previously reported in literature.[8]

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.63 (s, 1H), 8.00 (s, 1H), 7.45 – 7.38 (m, 6H), 7.33 (t, *J* = 7.9 Hz, 3H), 7.02 (t, *J* = 7.3 Hz, 1H), 4.82 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 184.01 (C), 180.36 (C), 168.83 (C), 163.77 (C), 138.95 (C), 138.54 (C), 129.34 (2 CH), 128.74 (2 CH), 127.68 (2 CH), 127.62 (2 CH), 122.67 (2 CH), 118.01 (CH), 47.21 (C).

MS (ES+) calc for $C_{17}H_{14}N_2O_2$ 279.1 $(M+H)^+$, found 279.1 $(M+H)^+$.

5b: 3-((2,4-dimethoxybenzyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



5b

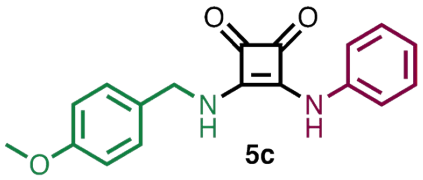
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 21 µL of benzylamine (0.14 mmol, 1 equiv.), 44.5 mg (95% yield) of **5b** were obtained as white solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.63 (s, 1H), 8.00 (s, 1H), 7.45 – 7.38 (m, 6H), 7.33 (t, *J* = 7.9 Hz, 3H), 7.02 (t, *J* = 7.3 Hz, 1H), 4.82 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 184.01 (C), 180.36 (C), 168.83 (C), 163.77 (C), 138.95 (C), 138.54 (C), 129.34 (2 CH), 128.74 (2 CH), 127.68 (2 CH), 127.62 (2 CH), 122.67 (2 CH), 118.01 (CH), 56.10 (CH_3), 55.77 (CH_3), 47.21 (C).

MS (ES+) calc for $C_{19}H_{18}N_2O_4$ 339.1 $(M+H)^+$, found 339.0 $(M+H)^+$.

5c: 3-((4-methoxybenzyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



5c

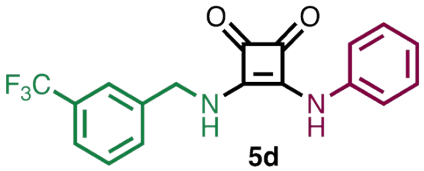
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 18.2 µL of 4-methoxy benzylamine (0.14 mmol, 1 equiv.), 36 mg (83% yield) of **5c** were obtained as white solid. The product was obtained performing a purification step that involved 1-min vortexing in 1.5 mL of methanol, followed by centrifugation at 8000 g for 10 min; it was then precipitated and dried at room temperature for further analysis. The spectroscopic data are in line with those previously reported in literature.[9]

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.60 (s broad, 1H), 7.94 (s broad, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.33 (t, *J* = 8.6 Hz, 4H), 7.04 – 6.99 (m, 1H), 6.97 – 6.93 (m, 2H), 4.74 (d, *J* = 5.1 Hz, 2H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 184.04 (C), 180.25 (C), 168.71 (C), 163.71 (C), 158.81 (C), 138.98 (C), 130.38 (C), 129.34 (2 CH), 129.17 (2 CH), 122.64 (C), 117.98 (2 CH), 114.12 (2 CH), 55.14 (CH_3), 46.70 (CH_2).

MS (ES+) calc for $C_{18}H_{16}N_2O_3$ 309.1 $(M+H)^+$, found 309.0 $(M+H)^+$.

5d: 3-(phenylamino)-4-((3-(trifluoromethyl)benzyl)amino)cyclobut-3-ene-1,2-dione



5d

Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 18.2 µL of 4-methoxy benzylamine (0.14 mmol, 1 equiv.), 47 mg (98% yield) of **5d** were obtained as white solid. This compound is new and no previously spectroscopic data have been reported.

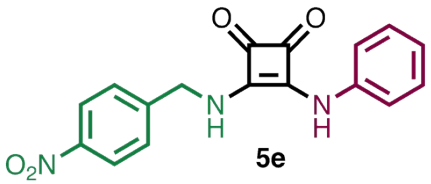
^{1}H NMR (400 MHz, DMSO) δ 9.69 (s, 1H), 8.04 (s, 1H), 7.78 (s, 1H), 7.72 – 7.68 (m, 2H), 7.66 – 7.61 (m, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 2H), 7.06 – 7.00 (m, 1H), 4.91 (d, *J* = 6.4 Hz, 2H).

^{19}F NMR (377 MHz, DMSO-d$_6$) -61.04

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 184.03 (C), 180.59 (C), 168.82 (C), 164.01 (C), 140.08 (C), 138.88 (C), 131.88 (2CH), 129.41 (q, *J* = 31.5 MHz, C), 129.33 (CH), 125.52 (q, *J* = 269.3 MHz, CF_3), 124.33 (CH), 124.24 (CH), 120.11 (2 CH), 118.15 (2 CH).

MS (ES+) calc for $C_{18}H_{13}F_3N_2O_2$ 347.0 $(M+H)^+$, found 347.0 $(M+H)^+$.

5e: 3-((4-nitrobenzyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



5e

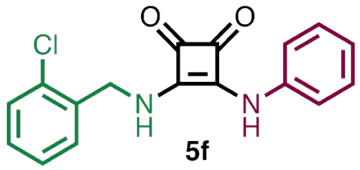
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 21.3 mg of 4-nitro benzylamine (0.14 mmol, 1 equiv.), 37 mg (81% yield) of **5e** were obtained as yellow solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO) δ 9.75 (s, 1H), 8.26 (d, *J* = 6.8 Hz, 2H), 8.09 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.07 – 7.02 (m, 1H), 4.96 (d, *J* = 6.5 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 181.20 (2 C), 164.60 (2 C), 147.33 (C), 146.99 (C), 139.31 (C), 129.84 (2 CH), 129.57 (CH), 129.04 (2 CH), 124.34 (2 CH), 123.31 (CH), 118.66 (CH), 46.91 (CH_2).

MS (ES+) calc for $C_{17}H_{13}N_3O_4$ 324.0 $(M+H)^+$, found 324.1 $(M+H)^+$.

5f: 3-((2-chlorobenzyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



5f

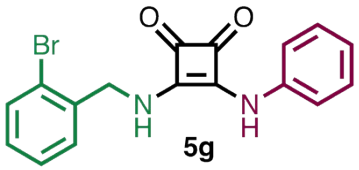
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 16.9 µL of 2-chloro benzylamine (0.14 mmol, 1 equiv.), 41 mg (95% yield) of **5f** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO) δ 9.70 (s, 1H), 8.01 (s, 1H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.06 – 6.99 (m, 1H), 4.91 (d, *J* = 6.3 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 183.82 (C), 180.52 (C), 168.90 (C), 163.88 (C), 138.91 (C), 135.63 (C), 132.48 (CH), 129.89 (CH), 129.68 (CH), 129.53 (CH), 129.36 (CH), 127.72 (CH), 122.74 (C), 118.07 (2 CH), 45.22 (CH_2).

MS (ES+) calc for $C_{17}H_{13}ClN_2O_2$ 313.0 $(M+H)^+$, found 313.0 $(M+H)^+$.

5g: 3-((2-bromobenzyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



5g

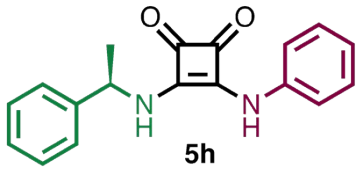
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.), 26 mg of 2-bromo benzylamine (0.14 mmol, 1 equiv.), 42 mg (85% yield) of **5g** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s broad, 1H), 8.00 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.38 – 7.27 (m, 4H), 7.03 (t, *J* = 7.3 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 184.31 (C), 181.03 (C), 169.37 (C), 164.37 (C), 139.38 (C), 137.67 (C), 133.26 (CH), 130.38 (2 CH), 129.84 (2 CH), 128.76 (CH), 123.27 (C), 118.56 (2 CH), 48.03 (CH_2).

MS (ES+) calc for $C_{17}H_{13}BrN_2O_2$ 357.0 $(M+H)^+$, found 358.9 $(M+H)^+$.

5h: *(R)*-3-(phenylamino)-4-((1-phenylethyl)amino)cyclobut-3-ene-1,2-dione



5h

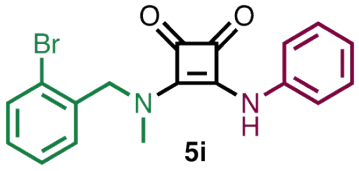
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 17.8 µL of *(R)*-1-phenylethan-1-amine (0.14 mmol, 1 equiv.), 39.5 mg (99% yield) of **5h** were obtained as white solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.58 (s broad, 1H), 8.08 (s broad, 1H), 7.46 – 7.37 (m, 6H), 7.38 – 7.31 (m, 3H), 7.03 (tt, *J* = 7.3, 1.2 Hz, 1H), 5.30 (p, *J* = 7.0 Hz, 1H), 1.61 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 183.60 (C), 180.27 (C), 168.28 (C), 163.75 (C), 143.14 (C), 138.95 (C), 129.40 (2 CH), 128.76 (2 CH), 127.55 (CH), 126.07 (3 CH), 122.68 (2 CH), 53.18 (CH), 23.01 (CH_3).

MS (ES+) calc for $C_{18}H_{16}N_2O_2$ 293.1 $(M+H)^+$, found 293.1 $(M+H)^+$.

5i: 3-((2-bromobenzyl)(methyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



5i

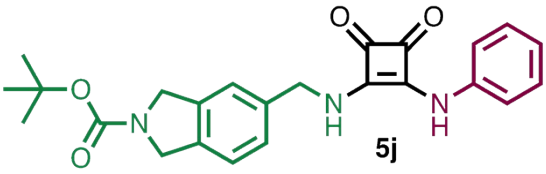
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 20.6 µL of 1-(2-bromophenyl)-*N*-methylmethanamine (0.14 mmol, 1 equiv.), 48.5 mg (95% yield) of **5i** were obtained as white solid. The product was obtained performing a purification step that involved 1-min vortexing in 1.5 mL of methanol, followed by centrifugation at 8000 g for 10 min; it was then precipitated and dried at room temperature for further analysis. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.53 (s broad, 1H), 7.69 (d, *J* = 9.5 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.33 – 7.29 (m, 3H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.05 (tt, *J* = 6.9, 1.3 Hz, 1H), 4.98 (s, 2H), 3.14 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 185.60 (C), 181.54 (C), 170.60 (C), 164.43 (C), 139.23 (C), 138.39 (C), 133.55 (CH), 130.46 (2 CH), 129.89 (CH_3), 129.05 (CH), 128.76 (CH), 124.55 (CH), 123.58 (C), 123.32 (CH), 120.78 (CH), 120.04 (CH), 61.01 (CH_2).

MS (ES+) calc for $C_{18}H_{15}BrN_2O_2$ 371.0 $(M+H)^+$, found 371.1 $(M+H)^+$.

5j: *tert*-butyl-5-(((3,4-dioxo-2-(phenylamino)cyclobut-1-en-1-yl)amino)methyl)isoindoline-2-carboxylate



5j

Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.8 µL of aniline (0.14 mmol, 1 equiv.) and 34.7 mg of 1-(2-bromophenyl)-*N*-methylmethanamine, 49 mg of **5j** (84% yield) were obtained as white solid. This compound is new and no previously spectroscopic data have been reported.

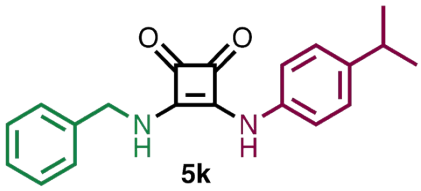
^{1}H NMR (700 MHz, DMSO-d$_6$) δ 9.62 (s broad, 1H), 7.98 (s broad, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 3H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 2H), 4.66 (d, *J* = 8.6 Hz, 2H), 4.61 (d, *J* = 18.4 Hz, 2H), 1.46 (s, 9H).

^{13}C NMR (176 MHz, DMSO-d$_6$) δ 183.85 (C), 180.39 (C), 168.86 (C), 163.78 (C), 153.61 (C), 153.51 (C), 138.94 (C), 137.77 (C), 137.26 (C), 135.49 (CH), 135.14 (CH), 132.94 (CH), 129.37 (2 CH), 128.04 (CH), 122.71 (CH), 118.01 (CH), 78.96 (C), 51.84 (d, *J* = 33.1 Hz, CH_2), 50.48 (d, *J* = 15.3 Hz, CH_2), 45.03 (d, *J* = 7.6 Hz, CH_2), 28.16 (3 CH_3).

δ 51.84 (d, *J* = 33.1 Hz), 50.48 (d, *J* = 15.3 Hz).

MS (ES+) calc for $C_{24}H_{25}N_3O_4$ 420.1 $(M+H)^+$, found 420.1 $(M+H)^+$.

5k: 3-(benzylamino)-4-((4-isopropylphenyl)amino)cyclobut-3-ene-1,2-dione



5k

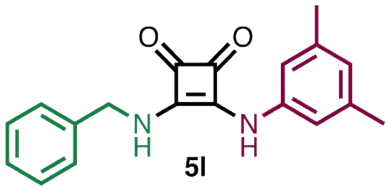
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 19.1 µL of 4-isopropylaniline (0.14 mmol, 1 equiv.) and 15.3 µL of benzylamine (0.14 mmol, 1 equiv.), 36 mg (82% yield) of **5k** were obtained as white solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.57 (s, 1H), 7.95 (s, 1H), 7.41 – 7.38 (m, 4H), 7.35 – 7.30 (m, 3H), 7.20 (d, *J* = 8.6 Hz, 2H), 4.81 (d, *J* = 6.3 Hz, 2H), 1.19 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 183.77 (C), 180.42 (C), 168.63 (C), 163.85 (C), 142.93 (C), 138.52 (C), 136.70 (C), 128.76 (3 CH), 127.71 (2 CH), 127.63 (2CH), 127.11 (2 CH), 118.18 (2 C), 47.19 (CH_2), 32.79 (CH), 23.94 (2 CH_3)

MS (ES+) calc for $C_{20}H_{20}N_2O_2$ 321.1 $(M+H)^+$, found 321.1 $(M+H)^+$.

5l: 3-(benzylamino)-4-((3,5-dimethylphenyl)amino)cyclobut-3-ene-1,2-dione



5l

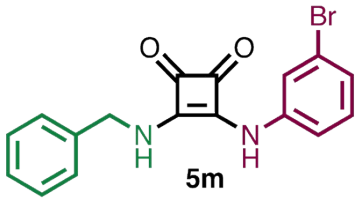
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 17.4 µL of 3,5-dimethylaniline (0.14 mmol, 1 equiv.) and 15.3 µL of benzylamine (0.14 mmol, 1 equiv.), 43 mg (97% yield) of **5l** were obtained as white solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.54 (s, 1H), 7.93 (s, 1H), 7.41 – 7.36 (m, 4H), 7.35 – 7.30 (m, 1H), 7.01 (s, 2H), 6.67 (s, 1H), 4.81 (d, J = 6.3 Hz, 2H), 2.23 (s, 6H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 184.48 (C), 180.91 (C), 169.13 (C), 164.34 (C) 139.20 (C), 139.00 (C), 138.96 (C), 129.22 (C), 128.16 (2 CH), 128.09 (3 CH), 124.86 (CH), 116.35 (2 CH), 47.65 (CH_2), 21.56 (2 CH_3).

MS (ES+) calc for $C_{19}H_{18}N_2O_2$ 306.1 $(M+H)^+$, found 307.0 $(M+H)^+$.

5m: 3-(benzylamino)-4-((3-bromophenyl)amino)cyclobut-3-ene-1,2-dione



5m

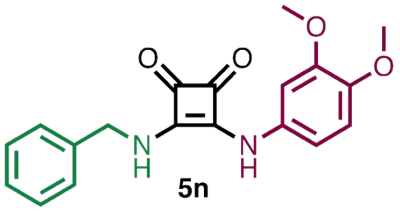
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 15.2 µL of 3-bromoaniline (0.14 mmol, 1 equiv.) and 15.3 µL of benzylamine (0.14 mmol, 1 equiv.), 26 mg (52% yield) of **5m** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.74 (s, 1H), 8.04 (s, 1H), 7.79 (s, 1H), 7.41 (d, *J* = 2.8 Hz, 1H), 7.40 (s, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.27 (m, 2H), 7.19 (dt, *J* = 6.3, 1.9 Hz, 1H), 4.82 (d, *J* = 6.1 Hz, 2H).

^{13}C NMR (176 MHz, DMSO-d$_6$) δ 184.77 (C), 180.82 (C), 169.49 (C), 163.68 (C), 141.06 (C), 138.80 (C), 131.72 (CH), 129.23 (3 CH), 128.18 (2 CH), 128.14 (C), 125.56 (CH), 121.01 (CH), 117.35 (CH), 47.71 (CH_2).

MS (ES+) calc for $C_{17}H_{13}BrN_2O_2$ 357.0 $(M+H)^+$, found 357.0 $(M+H)^+$.

5n: 3-(benzylamino)-4-((3,4-dimethoxyphenyl)amino)cyclobut-3-ene-1,2-dione:



5n

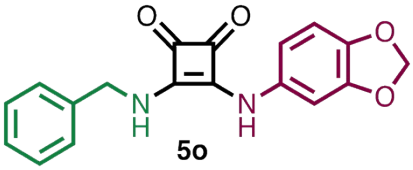
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 21.5 mg of 3,4-dimethoxyaniline (0.14 mmol, 1 equiv.) and 15.3 µL of benzylamine (0.14 mmol, 1 equiv.), 46 mg (98% yield) of **5n** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.56 (s, 1H), 7.89 (s, 1H), 7.40 – 7.38 (m, 3H), 7.35 – 7.29 (m, 2H), 7.25 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.81 (d, *J* = 6.1 Hz, 2H), 3.74 (s, 3H), 3.71 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 183.38 (C), 180.68 (C), 168.44 (C), 163.71 (C), 149.32 (C), 144.77 (C), 138.58 (C), 132.55 (C), 128.72 (3 CH), 127.66 (2 CH),, 112.66 (CH), 109.69 (CH), 103.61 (CH), 55.83 (CH_3), 55.40 (CH_3), 47.17 (CH_2).

MS (ES+) calc for $C_{17}H_{13}BrN_2O_2$ 357.0 $(M+H)^+$, found 357.0 $(M+H)^+$.

5o: 3-(benzo[d][1,3]dioxol-5-ylamino)-4-(benzylamino)cyclobut-3-ene-1,2-dione



5o

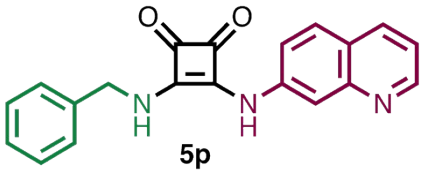
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 19 mg of benzo[d][1,3]dioxol-5-amine (0.14 mmol, 1 equiv.) and 15.3 µL of benzylamine (0.14 mmol, 1 equiv.), 27 mg (60% yield) of **5o** were obtained as yellowish solid. The product was obtained performing a purification step that involved 1-min vortexing in 1.5 mL of methanol, followed by centrifugation at 8000 g for 10 min; it was then precipitated and dried at room temperature for further analysis. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.55 (s broad, 1H), 7.91 (s broad, 1H), 7.41 – 7.36 (m, 4H), 7.34 – 7.29 (m, 1H), 7.23 (d, *J* = 10.9 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.3, 2.3 Hz, 1H), 5.99 (s, 2H), 4.79 (d, *J* = 6.2 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 183.47 (C), 180.49 (C), 168.49 (C), 163.61 (C), 147.89 (C), 143.03 (C), 138.52 (C), 133.54 (C), 128.76 (3 CH), 127.69 (2 CH), 108.51 (CH), 108.25 (CH), 101.38 (CH_2), 101.23 (CH), 47.20 (CH_2).

MS (ES+) calc for $C_{18}H_{14}N_2O_4$ 323.0 $(M+H)^+$, found 323.2 $(M+H)^+$.

5p: 3-(benzylamino)-4-(quinolin-7-ylamino)cyclobut-3-ene-1,2-dione



5p

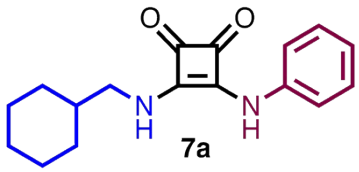
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 20 mg of quinolin-7-amine (0.14 mmol, 1 equiv.) and 15.3 µL of benzylamine (0.14 mmol, 1 equiv.), 45 mg (98% yield) of **5p** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.33 (s, 1H), 8.59 (d, *J* = 6.0 Hz, 1H), 8.24 (d, *J* = 5.6 Hz, 1H), 7.97 (d, *J* = 5.9 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 4H), 7.34 (td, *J* = 5.1, 2.8 Hz, 1H), 4.86 (d, *J* = 6.3 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 185.20 (C), 180.48 (C), 169.45 (C), 163.98 (C), 152.70 (CH), 142.98 (C), 138.43 (2 C), 132.74 (CH), 128.77 (3 CH), 127.77 (CH), 127.66 (CH), 127.53 (CH), 122.96 (CH), 120.66 (C), 114.77 (2 CH), 47.23 (CH_2)

MS (ES+) calc for $C_{20}H_{15}N_3O_2$ 330.1 $(M+H)^+$, found 330.1 $(M+H)^+$.

7a: 3-((cyclohexylmethyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



7a

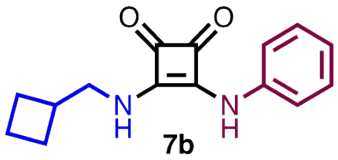
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline, (0.14 mmol, 1 equiv.) and 18 µL of (0.14 mmol, 1 equiv.), 39 mg (99% yield) of **7a** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s broad, 1H), 7.66 (s broad, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 3.46 (d, *J* = 13.2 Hz, 2H), 1.70 (d, *J* = 9.9 Hz, 4H), 1.62 (d, *J* = 12.4 Hz, 1H), 1.54 – 1.47 (m, 1H), 1.25 – 1.18 (m, 2H), 1.18 – 1.10 (m, 1H), 0.95 (q, *J* = 11.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 183.97 (C), 180.10 (C), 169.43 (C), 163.36 (C), 139.08 (C), 129.37 (2 CH), 122.54 (CH), 117.90 (2 CH), 49.68 (CH_2), 38.74 (CH), 29.65 (2 CH_2), 25.90 (CH_2), 25.26 (2 CH_2).

MS (ES+) calc for $C_{17}H_{20}N_2O_2$ 285.1 $(M+H)^+$, found 285.1 $(M+H)^+$.

7b: 3-((cyclobutylmethyl)amino)-4-(phenylamino)cyclobut-3-ene-1,2-dione:



7b

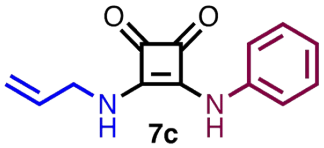
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline, (0.14 mmol, 1 equiv.) and 13.5 µL of cyclobutylmethanamine (0.14 mmol, 1 equiv.), 31 mg (88% yield) of **7b** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.65 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 2H), 7.05 – 6.99 (m, 1H), 3.64 (t, *J* = 6.8 Hz, 2H), 2.60 – 2.51 (m, 1H), 2.07 – 1.98 (m, 2H), 1.91 – 1.82 (m, 2H), 1.78 – 1.69 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 184.49 (C), 180.58 (C), 169.75 (C), 163.91 (C), 139.49 (C), 129.88 (CH), 129.57 (CH), 123.06 (CH), 120.04 (CH), 118.42 (CH), 48.91 (CH_2), 36.09 (CH), 25.05 (2 CH_2), 18.19 (CH_2).

MS (ES+) calc for $C_{15}H_{16}N_2O_2$ 257.1 $(M+H)^+$, found 275.1 $(M+H)^+$.

7c: 3-(allylamino)-4-(phenylamino)cyclobut-3-ene-1,2-dione



7c

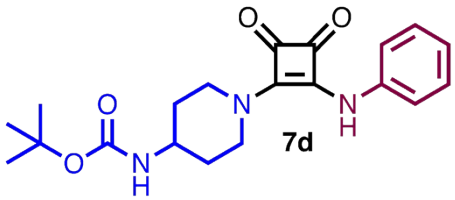
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline, (0.14 mmol, 1 equiv.) and 10.5 µL of allylamine (0.14 mmol, 1 equiv.), (40% UPLC yield), **7c** were obtained as yellowish solid. The final product was a mix of 7c and the monomer 5a'. For further recovery of the separate products, a chromatography column should be performed. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (700 MHz, DMSO) δ 9.65 (s broad, 1H), 7.75 (s broad, 1H), 7.35 (s, 4H), 7.03 (t, *J* = 7.4 Hz, 1H), 5.98 (td, *J* = 10.7, 5.1 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.20 (d, *J* = 10.3 Hz, 1H), 4.25 (s, 2H).

^{13}C NMR (101 MHz, DMSO) δ 184.38 (C), 180.91 (C), 169.62 (C), 164.22 (C), 139.47 (C), 135.59 (CH), 129.82 (2 CH), 123.11 (CH), 118.49 (2CH), 116.89 (CH_2), 46.23 (CH_2).

MS (ES+) calc for $C_{13}H_{12}N_2O_2$ 229.0 $(M+H)^+$, found 229.1 $(M+H)^+$.

7d: tert-butyl (1-(3,4-dioxo-2-(phenylamino)cyclobut-1-en-1-yl)piperidin-4-yl)carbamate



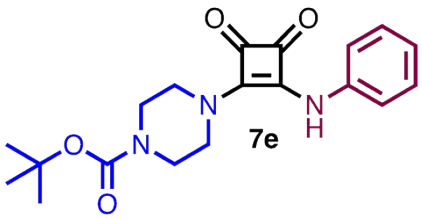
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline (0.14 mmol, 1 equiv.) and 28 mg of *tert*-butyl piperidin-4-ylcarbamate (0.14 mmol, 1 equiv.), 49 mg (96% yield) of **7d** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.49 (s, 1H), 7.33 – 7.28 (m, 2H), 7.20 (d, *J* = 6.5 Hz, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 4.21 (s, 2H), 3.54 (s, 2H), 3.26 (s, 1H), 1.84 (d, *J* = 13.3 Hz, 2H), 1.48 (d, *J* = 9.0 Hz, 2H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d$_6$)) δ 185.87 (C), 181.40 (C), 168.43 (C), 163.78 (C), 155.26 (C), 139.27 (C), 129.04 (2 CH), 123.46 (CH), 120.66 (2 CH), 78.21 (C), 46.59 (CH), 46.49 (2 CH_2), 32.34 (2 CH_2), 28.72 (3 CH_3).

MS (ES+) calc for $C_{20}H_{25}N_3O_4$ 372.1 $(M+H)^+$, found 372.3 $(M+H)^+$.

7e: tert-butyl 4-(3,4-dioxo-2-(phenylamino)cyclobut-1-en-1-yl)piperazine-1-carboxylate:



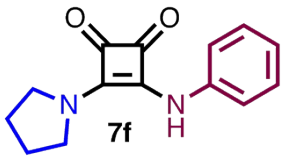
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline, (0.14 mmol, 1 equiv.), 26 mg of *tert*-butyl piperazine-1-carboxylate (0.14 mmol, 1 equiv.), 32 mg (65% yield) of **7e** were obtained as yellowish solid. The spectroscopic data are in line with those previously reported in literature. [10]

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.52 (s, 1H), 7.31 (m, 2H), 7.22 (dd, *J* = 8.7, 1.2 Hz, 2H), 7.08 – 7.04 (m, 1H), 3.76 – 3.67 (m, 4H), 3.47 (dd, *J* = 7.0, 3.5 Hz, 4H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 185.15 (C), 181.25 (C), 168.01 (C), 163.52 (C), 153.67 (C), 138.72 (C), 128.65 (2 CH), 123.14 (CH), 79.42 (2 CH), 60.55 (4 CH_2), 28.01 (3 CH_3).

MS (ES+) calc for $C_{19}H_{23}N_3O_4$ 358.1 $(M+H)^+$, found 358.1 $(M+H)^+$.

7f: 3-(phenylamino)-4-(pyrrolidin-1-yl)cyclobut-3-ene-1,2-dione:



7f

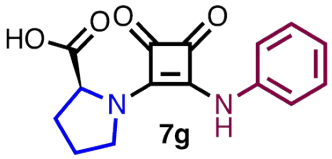
Following the general procedure C, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline, (0.14 mmol, 1 equiv.) and 11.5 µL of pyrrolidine (0.14 mmol, 1 equiv.), 55% UPLC yield), **7f** were obtained as yellowish solid. The final product was a mix of 7f and the monomer 5a'. For further recovery of the separate products, a chromatography column should be performed. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (700 MHz, DMSO-d_6) ^{1}H NMR (700 MHz, DMSO) δ 9.27 (s, 1H), 7.32 – 7.27 (m, 4H), 7.04 – 7.00 (m, 1H), 3.78 (t, *J* = 6.9 Hz, 4H), 1.92 – 1.87 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 185.33 (C), 180.37 (C), 167.74 (C), 163.69 (C), 139.05 (C), 128.60 (3 CH), 122.73 (CH), 119.87 (CH), 48.52 (2 CH_2), 24.54 (2 CH_2).

MS (ES+) calc for $C_{14}H_{14}N_2O_2$ 243.1 $(M+H)^+$, found 243.1 $(M+H)^+$.

7g: (3,4-dioxo-2-(phenylamino)cyclobut-1-en-1-yl)-L-proline



7g

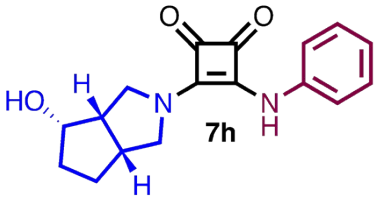
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline (0.14 mmol, 1 equiv.), 16.1 mg of proline (0.14 mmol, 1 equiv.) and 28.5 µL of 4M KOH for pH adjustment (0.12 mmol, 0.85 equiv), 29 mg (72% yield) of **7g** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.52 (s, 1H), 9.26 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.27 (ddd, *J* = 9.7, 7.7, 2.2 Hz, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 4.29 (dd, *J* = 7.9, 3.0 Hz, 1H), 3.88 (dt, *J* = 10.8, 7.6 Hz, 1H), 3.63 (ddd, *J* = 11.6, 7.7, 4.4 Hz, 1H), 2.27 (ddt, *J* = 11.4, 7.2, 3.6 Hz, 1H), 2.02 (dt, *J* = 11.6, 7.9 Hz, 1H), 1.84 (qt, *J* = 6.8, 3.7 Hz, 1H), 1.76 (dt, *J* = 11.7, 8.1 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 184.11 (C), 180.64 (C), 172.75 (C), 169.15 (C), 164.95 (C), 140.31 (C), 128.98 (2 CH), 121.58 (CH), 118.11 (2 CH), 65.08 (CH), 48.61 (CH_2), 28.21 (CH_2), 24.55 (CH_2).

MS (ES+) calc for $C_{15}H_{14}N_2O_4$ 287.0 $(M+H)^+$, found 287.0 $(M+H)^+$.

7h: 3-((3a*S*,4*S*,6a*R*)-4-hydroxyhexahydrocyclopenta[c]pyrrol-2(1H)-yl)-4-(phenylamino)cyclobut-3-ene-1,2-dione



7h

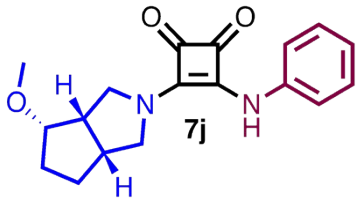
Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline (0.14 mmol, 1 equiv.) and 17.8 mg of (3a*S*,4*S*,6a*R*)-octahydrocyclopenta[*c*]pyrrol-4-ol (0.14 mmol, 1 equiv.), 39 mg (91% yield) of **7i** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.32 (s, 1H), 7.29 (d, J = 5.2 Hz, 4H), 7.05 – 6.99 (m, 1H), 4.14 – 4.03 (m, 2H), 3.94 (dd, J = 11.4, 7.9 Hz, 2H), 3.71 (dd, J = 11.8, 8.3 Hz, 2H), 3.61 (d, J = 11.1 Hz, 1H), 2.76 – 2.65 (m, 2H), 1.84 – 1.75 (m, 1H), 1.75 – 1.66 (m, 1H), 1.65 – 1.56 (m, 1H), 1.48 (dtd, J = 11.1, 6.7, 3.8 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 185.32 (C), 180.36 (C), 167.34 (C), 163.45 (C), 139.07 (C), 128.60 (2 CH), 122.68 (CH), 119.83 (2 CH), 72.16 (CH), 55.63 (CH_2), 48.59 (CH), 46.92 (CH_2), 40.91 (CH), 34.32 (CH_2), 28.05 (CH_2).

MS (ES+) calc for $C_{17}H_{18}N_2O_3$ 299.1 $(M+H)^+$, found 299.1 $(M+H)^+$.

7j: 3-((3a*S*,4*S*,6a*R*)-4-methoxyhexahydrocyclopenta[c]pyrrol-2(1H)-yl)-4-(phenylamino)cyclobut-3-ene-1,2-dione:



7j

Following the general procedure D, using 20 mg of 3,4-dimethoxy-3-cyclobutene-1,2-dione (0.14 mmol), 12.7 µL of aniline (0.14 mmol, 1 equiv.) and 26 mg (3a*S*,4*S*,6a*R*)-4-methoxyoctahydrocyclopenta[*c*]pyrrole (0.14 mmol, 1 equiv.), 28 mg (64% yield) of **7j** were obtained as yellowish solid. This compound is new and no previously spectroscopic data have been reported.

^{1}H NMR (700 MHz, DMSO-d$_6$) δ 9.36 (d, J = 13.8 Hz, 1H), 7.31 – 7.27 (m, 4H), 7.03 (t, J = 6.9 Hz, 1H), 3.93 (t, J = 9.8 Hz, 2H), 3.77 (d, J = 6.5 Hz, 2H), 3.65 – 3.56 (m, 1H), 3.22 (s, 3H), 2.89 – 2.84 (m, 1H), 2.73 (dt, J = 8.5, 4.4 Hz, 1H), 1.80 – 1.74 (m, 2H), 1.65 (td, J = 7.4, 4.1 Hz, 1H), 1.43 (td, J = 8.2, 4.8 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d$_6$) δ 185.24 (C), 180.49 (C), 167.40 (C), 163.57 (C), 139.01 (C), 128.60 (2 CH), 122.78 (CH), 119.95 (2 CH), 82.44 (CH), 56.81 (CH_2), 55.44 (CH_3), 48.24 (CH), 44.70 (CH_2), 40.39 (CH), 29.66 (CH_2) 27.57 (CH_2).

MS (ES+) calc for $C_{18}H_{20}N_2O_3$ 313.1 $(M+H)^+$, found 313.1 $(M+H)^+$.

Unsuccessful synthesis

The figure below presents some of the unsuccessful compounds. The failure of these reactions was attributed to several factors, including: the poor solubility of the starting materials, the unsuitability of the reaction solvent, which reduced both the reaction rate and solubility upon mixing, and the intrinsic properties of the starting materials, such as high viscosity and hydrophobicity. Even when diluted, these properties caused the compounds to spread on the filter disc, bypassing the hydrophobic barriers. Additionally, the reactivity of the compounds themselves contributed to the lack of success in these reactions.

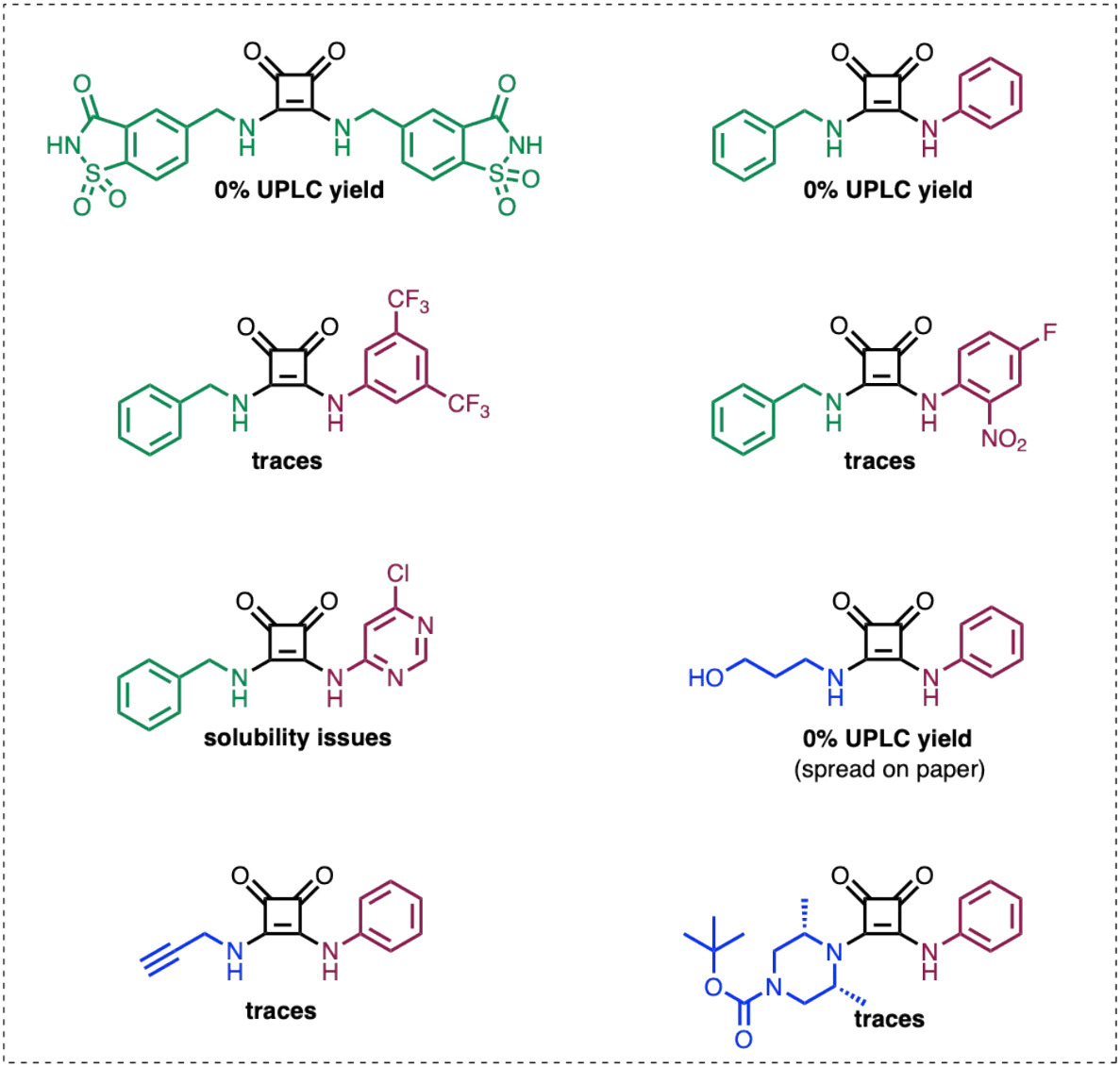


Figure S4: Unsuccessful synthesis of compounds.

Green metrics calculation

The green metrics were thoroughly calculated also for the monomer product 5a' and the asymmetric dimer 5a as shown in Figure S4 and Figure S5.. respectively.

Green metrics – Monomer

$$\text{Atom economy (\%)} = \frac{\text{Molecular weight of the desired product}(s)}{\text{molecular weight of all reactants}} \times 100 = \frac{203.19}{142.09+93.13} \times 100 = 86\%$$

$$\text{Atom efficiency (\%)} = (\%\ \text{yield of product} \times \%\text{atom economy}) \times 100 = (99\% \times \%86) \times 100 = 85\%$$

$$\text{Carbon efficiency (\%)} = \frac{\text{Moles of product (s)} \times \text{no. of carbons in product}(s)}{\sum \text{moles of reactants} \times \text{no.of carbons of reactants}} \times 100 = \frac{0.14 \times 11}{(0.14 \times 6)+(0.14 \times 6)} \times 100 = 92\%$$

$$\text{Reaction Mass efficiency (\%)} = \frac{\text{Mass of isolated product}(s)}{\text{Mass of all reactants}} \times 100 = \frac{28}{20+13} \times 100 = 86\%$$

Reactant 1	3,4-dimethoxy-3-cyclobutene-1,2-dione **(1)**	0.020 g	0.14 mmol	MW 142.11
Reactant 2	aniline	0.013 g	0.14 mmol	MW 93.13
Solvent	EtOH/H_2O	0.11 g /0.14 g	2.3 mmol /7.7 mmol	MW 46.06 / 18.01
Product (99% yield)	3-methoxy-4-(phenylamino)cyclobut-3-ene-1,2-dione **(5a')**	0.028 g	0.14 mmol	MW 203.19

$$\text{E-factor} = \frac{\text{Total waste (g)}}{\text{Total product (g)}} = \frac{(0.11+0.14+0.02+0.013)-0.028}{0.028} = 9.1\ g_{waste}/g_{product}$$

Figure S5: Green metrics components detailed calculation for the monomer **5a'**.

Green metrics – Asymmetric dimer

$$\text{Atom economy (\%)} = \frac{\text{Molecular weight of the desired product}(s)}{\text{molecular weight of all reactants}} \times 100 = \frac{264.28}{142.09+93.1+107.15} \times 100 = 77\%$$

$$\text{Atom efficiency (\%)} = (\%\ \text{yield of product} \times \%\text{atom economy}) \times 100 = (96\% \times \%77) \times 100 = 74\%$$

$$\text{Carbon efficiency (\%)} = \frac{\text{Moles of product (s)} \times \text{no. of carbons in product}(s)}{\sum \text{moles of reactants} \times \text{no.of carbons of reactants}} \times 100 = \frac{0.14 \times 11}{(0.14 \times 6)+(0.14 \times 6)+(0.14 \times 6)} \times 100 = 91\%$$

$$\text{Reaction Mass efficiency (\%)} = \frac{\text{Mass of isolated product}(s)}{\text{Mass of all reactants}} \times 100 = \frac{37.3}{20+15+13} \times 100 = 78\%$$

Reactant 1	3,4-dimethoxy-3-cyclobutene-1,2-dione **(1)**	0.020 g	0.14 mmol	MW 142.11
Reactant 2	Benzylamine **(2a)**	0.015 g	0.14 mmol	MW 107.15
Reactant 3	aniline	0.013 g	0.14 mmol	MW 93.13
Solvent	EtOH/H_2O	0.188 g /0.14 g	4 mmol /13.3 mmol	MW 46.06 / 18.01
Product (96% yield)	3-(benzylamino)-4-(phenylamino)cyclobut-3-ene-1,2-dione **(5a)**	0.0373 g	0.14 mmol	MW 264.28

$$\text{E-factor} = \frac{\text{Total waste (g)}}{\text{Total product (g)}} = \frac{(0.11+0.14+0.020+0.015+0.078+0.10+0.013)-0.028}{0.028} = 11.8\ g_{waste}/g_{product}$$

Figure S6: Green metrics components detailed calculation for the asymmetric dimer **5a**.

The three model compounds namely the symmetric dimer **3a**, the monomer **5a'** and the asymmetric dimer **5a** were evaluated in the green metrics scale and compared to other similar synthesized compounds. The comparison between our sustainable approach and the reported works are presented in the Table below.

Table S4: Green metrics were calculated for the symmetric dimer **(3a)**, monomer **(5a')**, and asymmetric dimer **(5a)** and compared with those of other reported methods where green metrics were also evaluated.

Product yield	Atom Economy (%)	Atom Efficiency (%)	Carbon Efficiency (%)	Reaction Mass Efficiency (%)	E-factor (g_{waste} / $g_{product}$)	EcoScale (out of 100)	REF
Symmetric Dimer							
87	74	64	67	63	46.84	76.5	[3]
59	67	40	49	47	570	61.5	[4]
97	**82**	**79**	**90**	**80**	**6.5**	**88.5**	**This work**
Monomer							
74	70	52	89	89	24.37	71	[6]
85	73	62	11	11	233.54	63.5	[7]
99	**86**	**85**	**92**	**86**	**9.1**	**89.5**	**This work**
Asymmetric dimer							
96	**77**	**74**	**91**	**78**	**11.8**	**88**	**This work**

EcoScale calculation

The EcoScale calculation is an essential component of green metrics in organic synthesis, offering a quantitative evaluation of a reaction's environmental impact and efficiency. This calculation is performed by summing individual penalties assigned to various reaction parameters, as reported previously.[11] For the given reaction, penalties were attributed as follows: yield penalty of 1.5, cost of components penalty of 5 (considering the prices of dimethyl squarate and benzylamine), safety penalty of 5, and no penalties for technical setup, temperature/time, or workup/purification. With an ideal reaction scoring 100, the EcoScale value for this synthesis was calculated as 88.5 (100 - 11.5), categorizing it as excellent (>75). This result underscores the reaction's alignment with green chemistry principles, balancing high yield, reasonable costs, and minimal environmental and operational impact.

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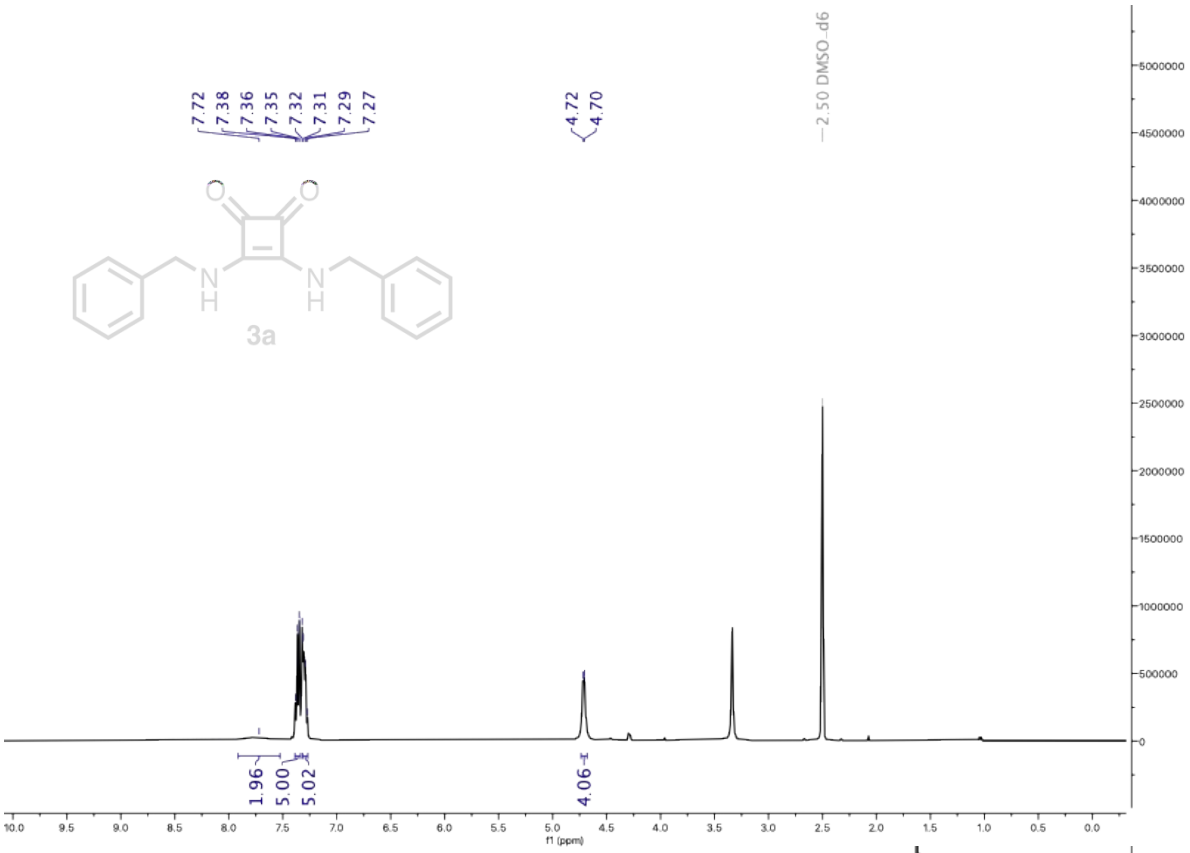
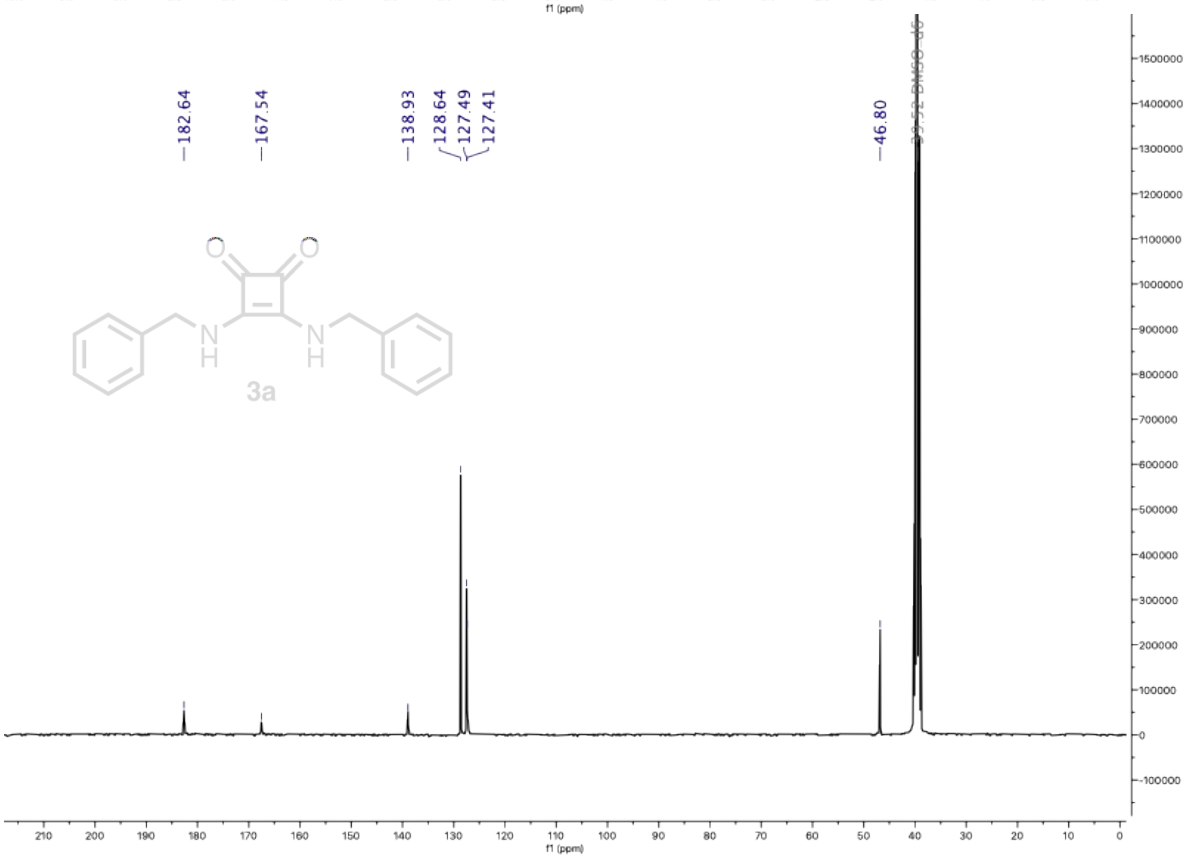
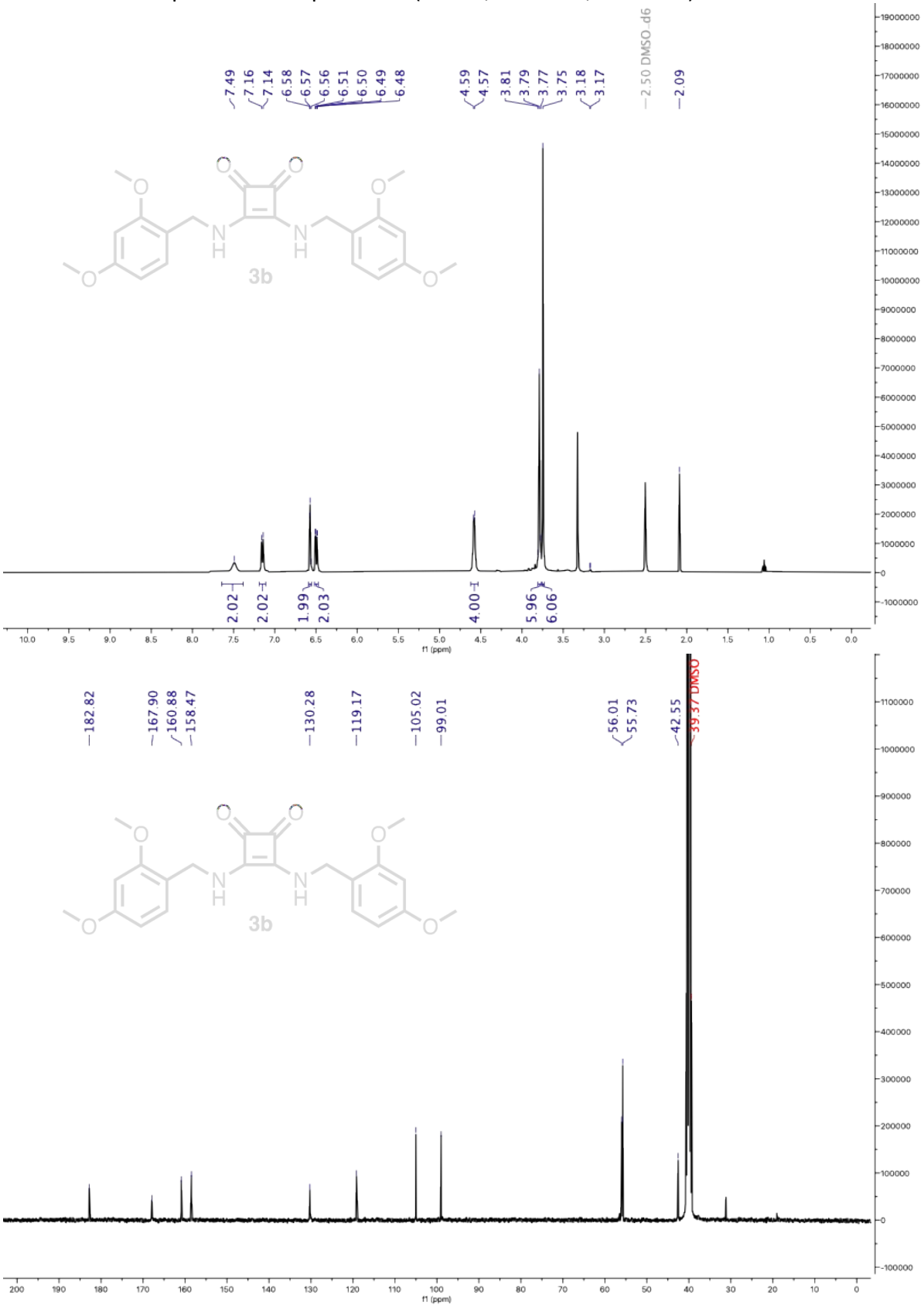
Copies of NMR Spectra

^{1}H and ^{13}C NMR spectra of compound **3a** (DMSO, 400 MHz, 101 MHz)

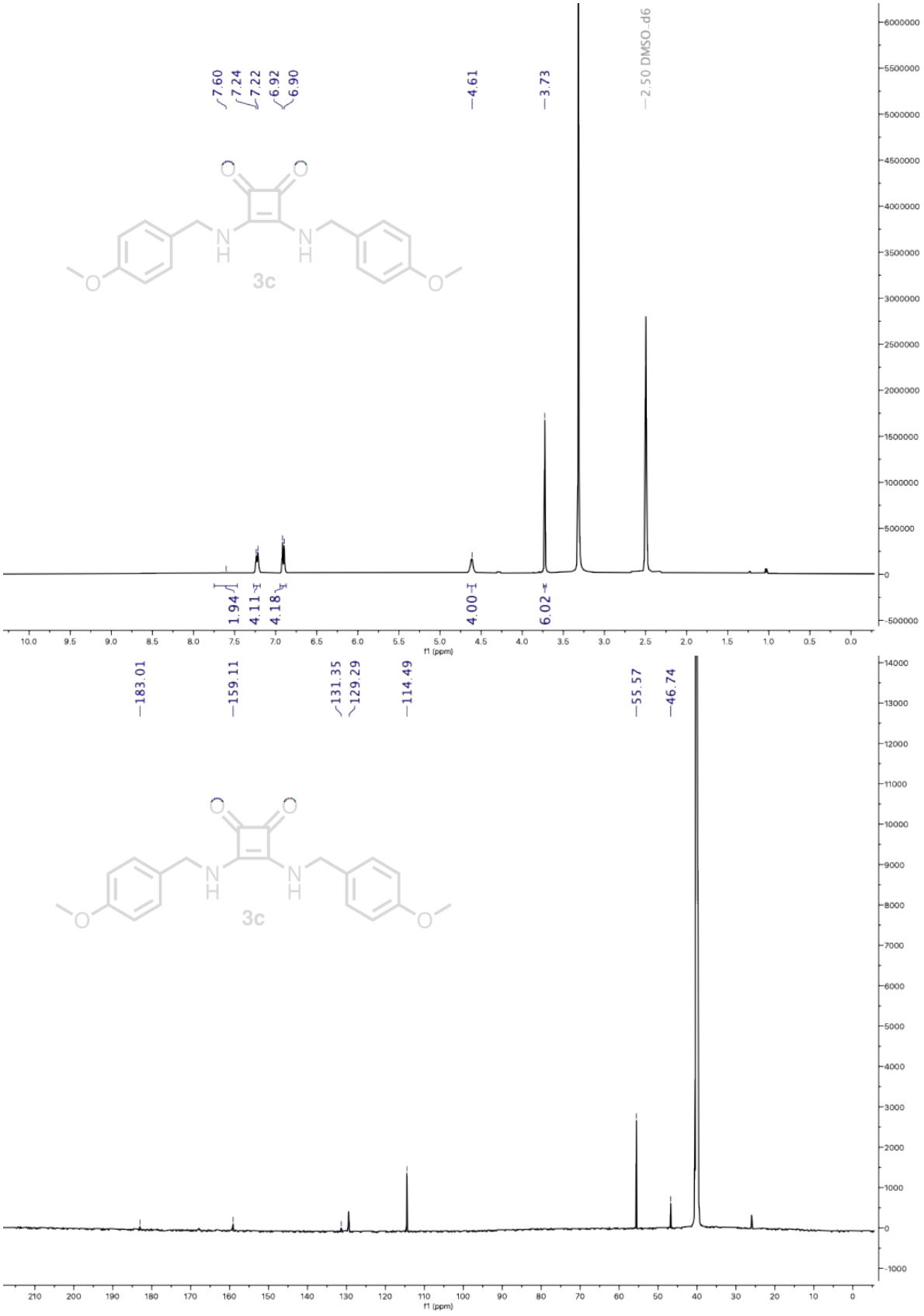




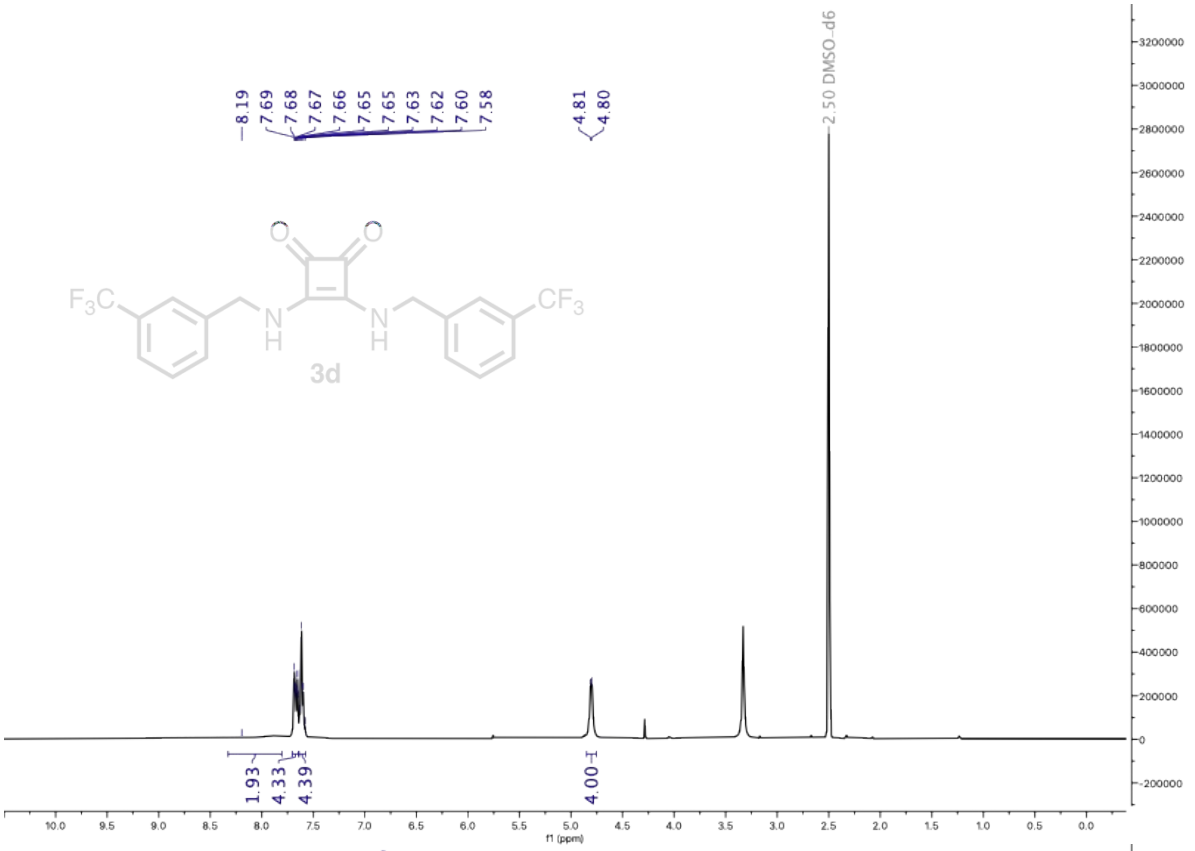
^{1}H and ^{13}C NMR spectra of compound **3b** (DMSO, 400 MHz, 101 MHz)

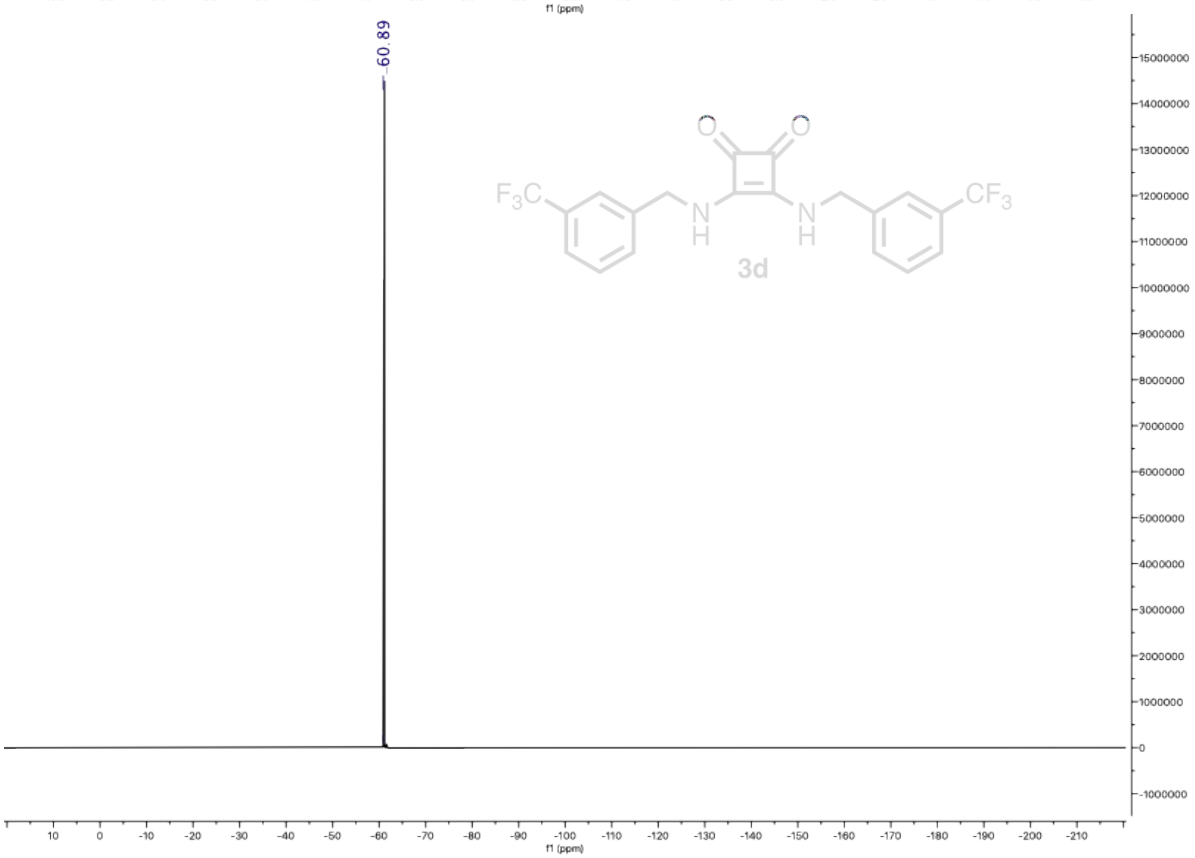


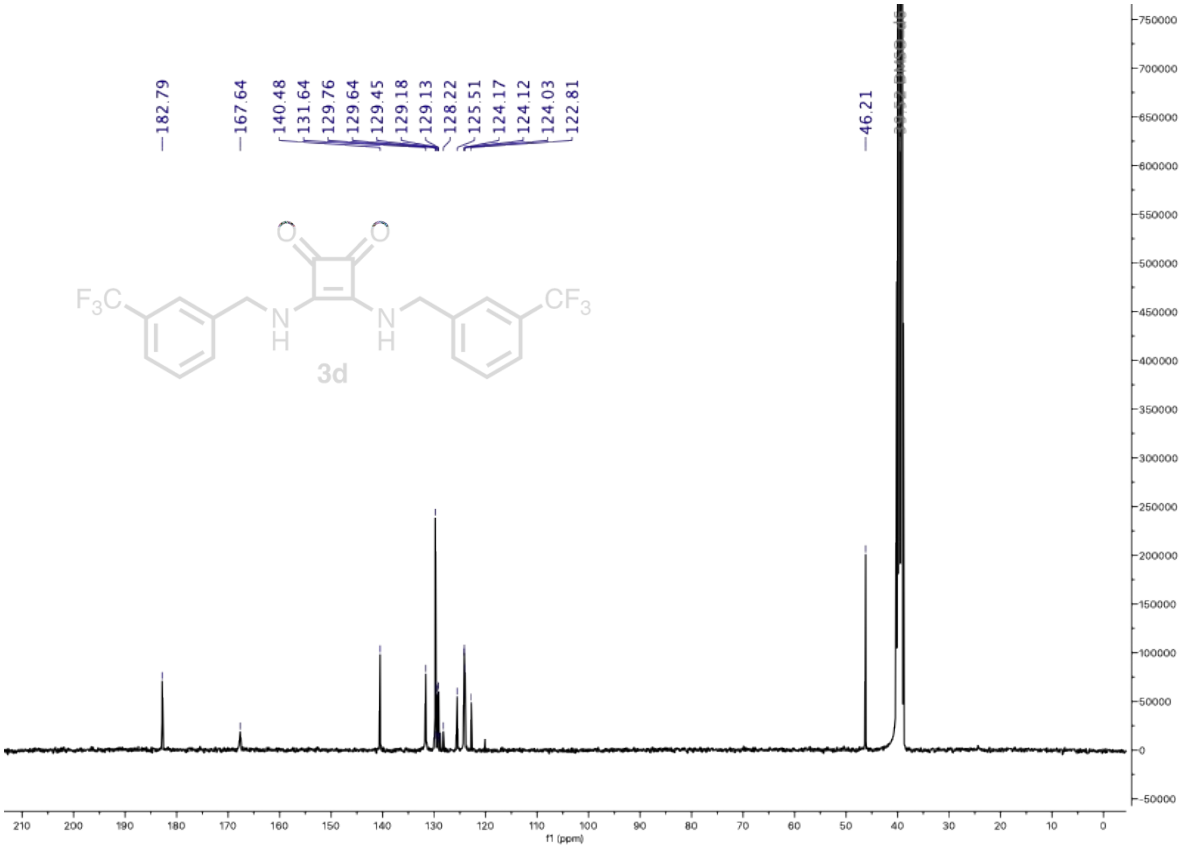
^{1}H and ^{13}C NMR spectra of compound **3c** (DMSO, 400 MHz, 176 MHz)



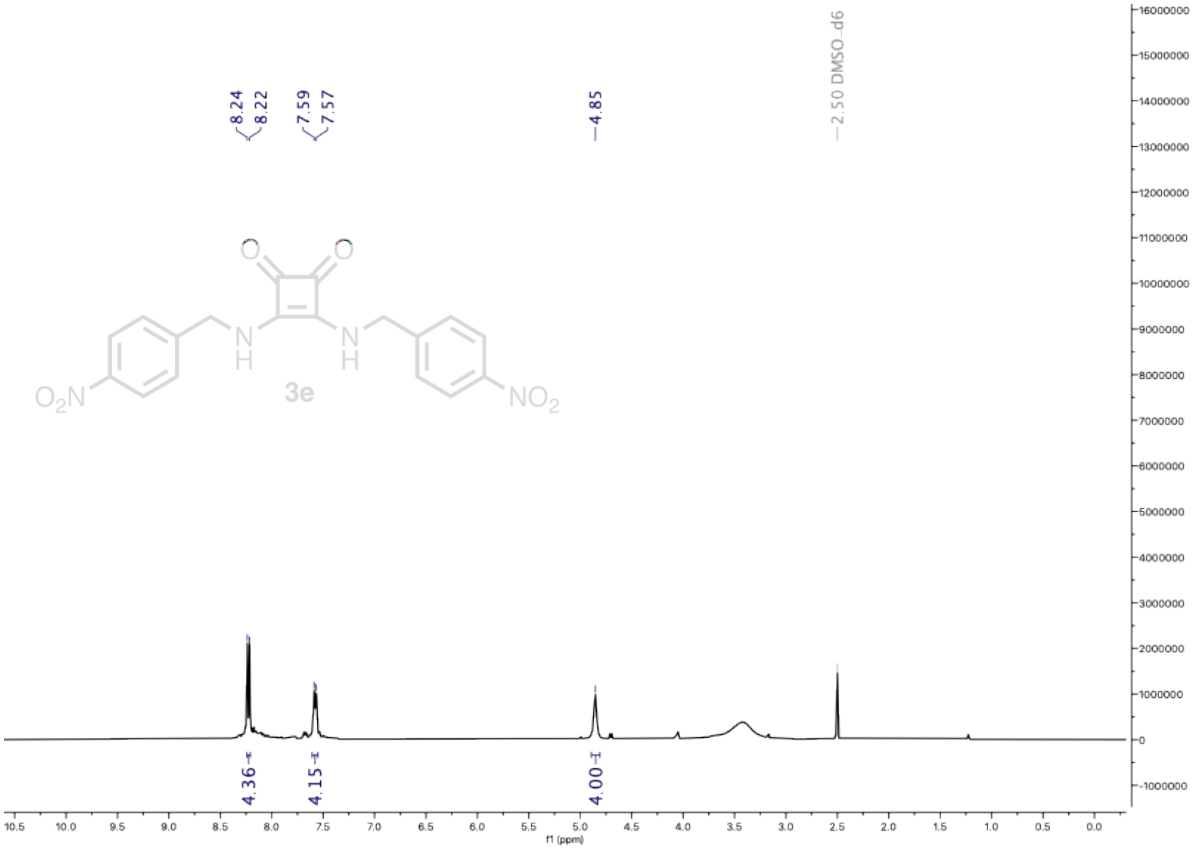
^{1}H, ^{19}F and ^{13}C NMR spectra of compound **3d** (DMSO, 400 MHz, 377 MHz, 101 MHz)


8.19
7.69
7.68
7.67
7.66
7.65
7.55
7.63
7.62
7.60
7.58
4.81
4.80
2.50 DMSO-d6
1.93
4.33
4.39
4.00
f1 (ppm)
3d

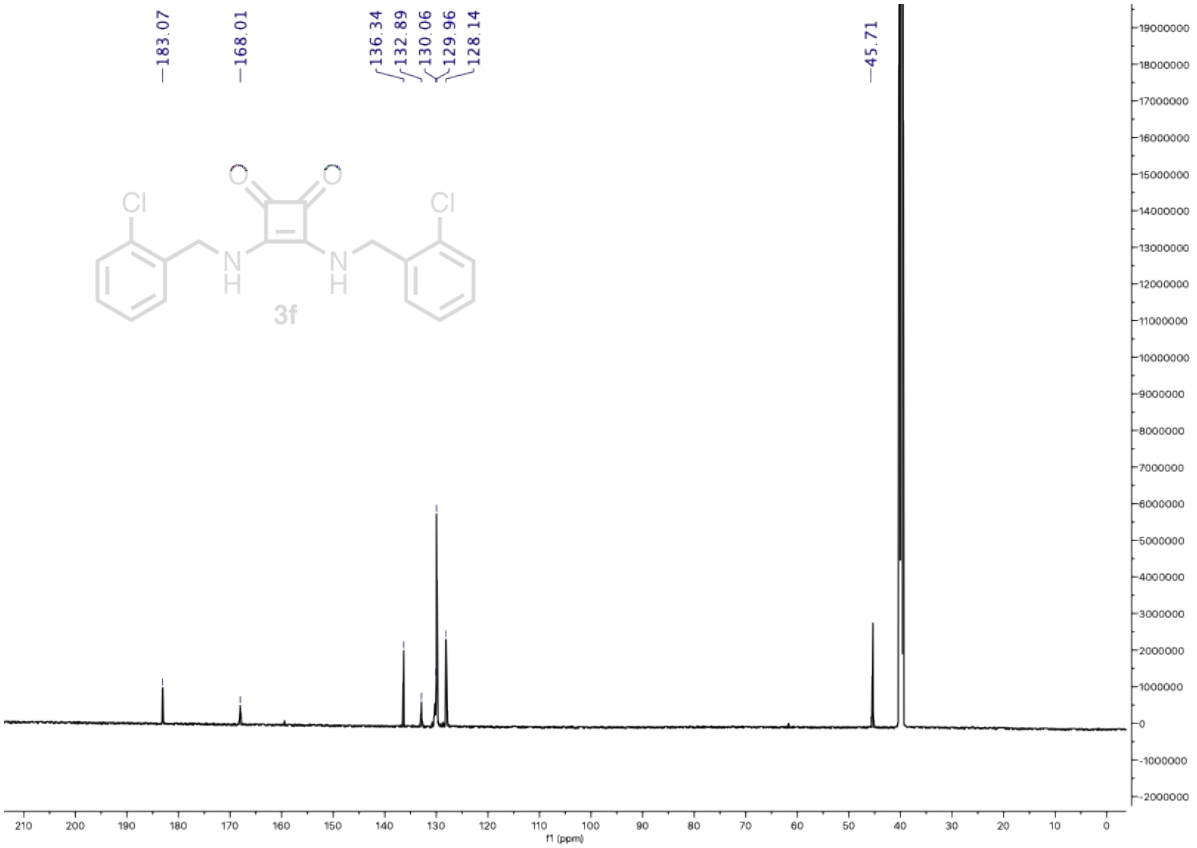

-60.89
f1 (ppm)
3d



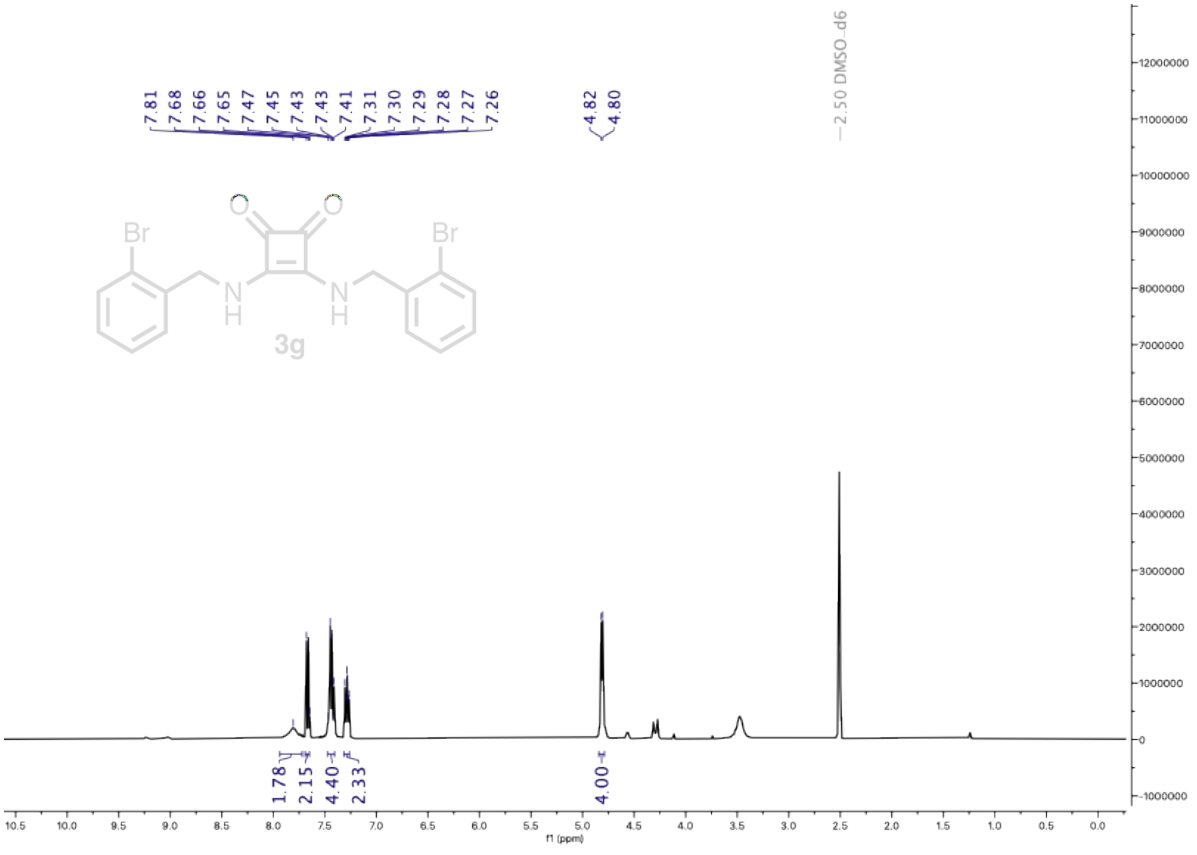
^{1}H and^{13}C NMR spectra of compound **3e** (DMSO, 400 MHz, 176 MHz)

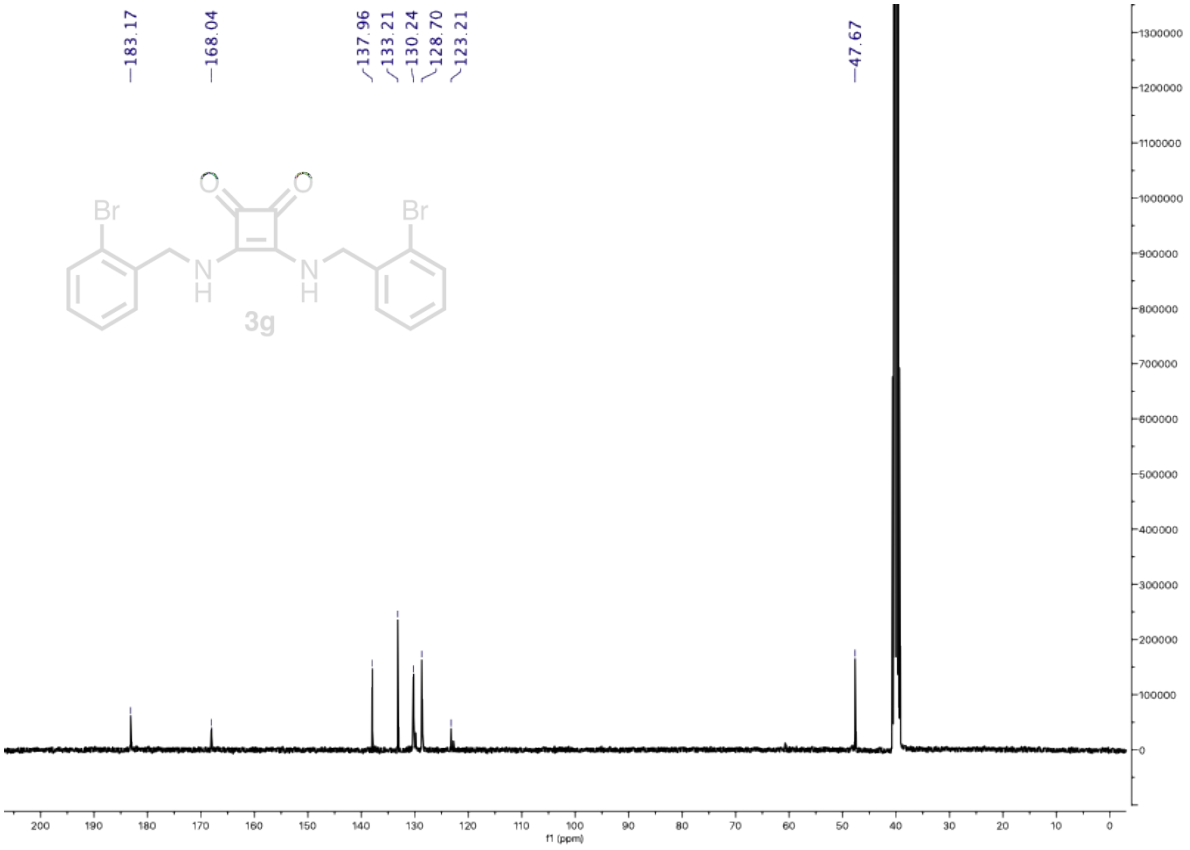


^{1}H and ^{13}C NMR spectra of compound **3f** (DMSO, 700 MHz, 176 MHz)

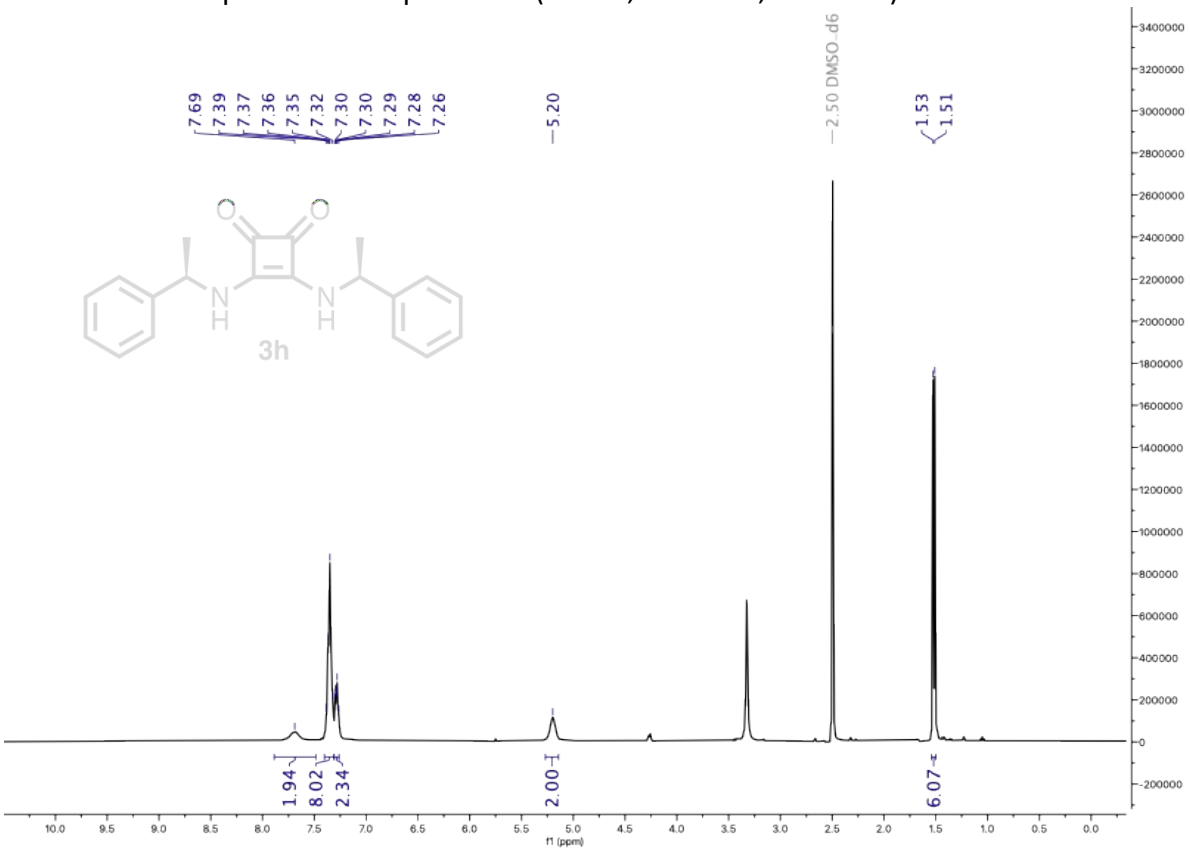


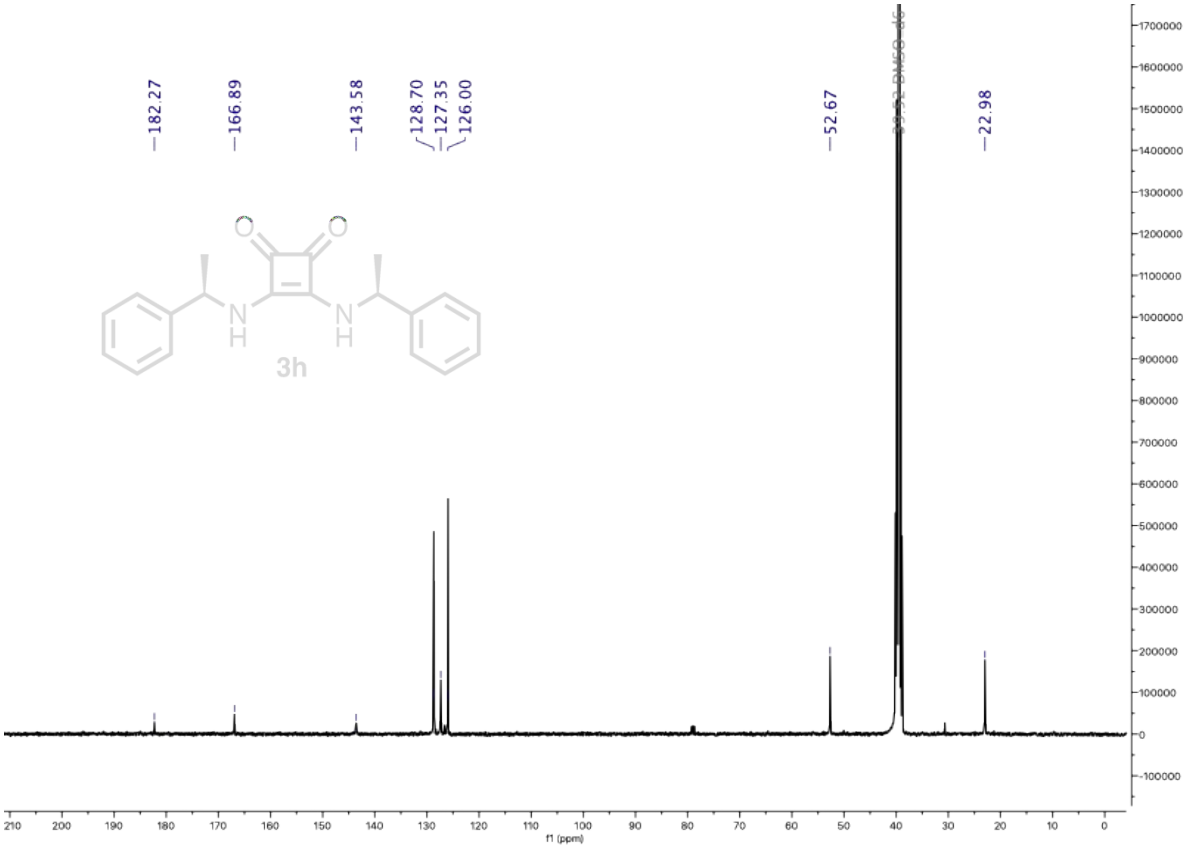
^{1}H and ^{13}C NMR spectra of compound **3g** (DMSO, 700 MHz, 176 MHz)



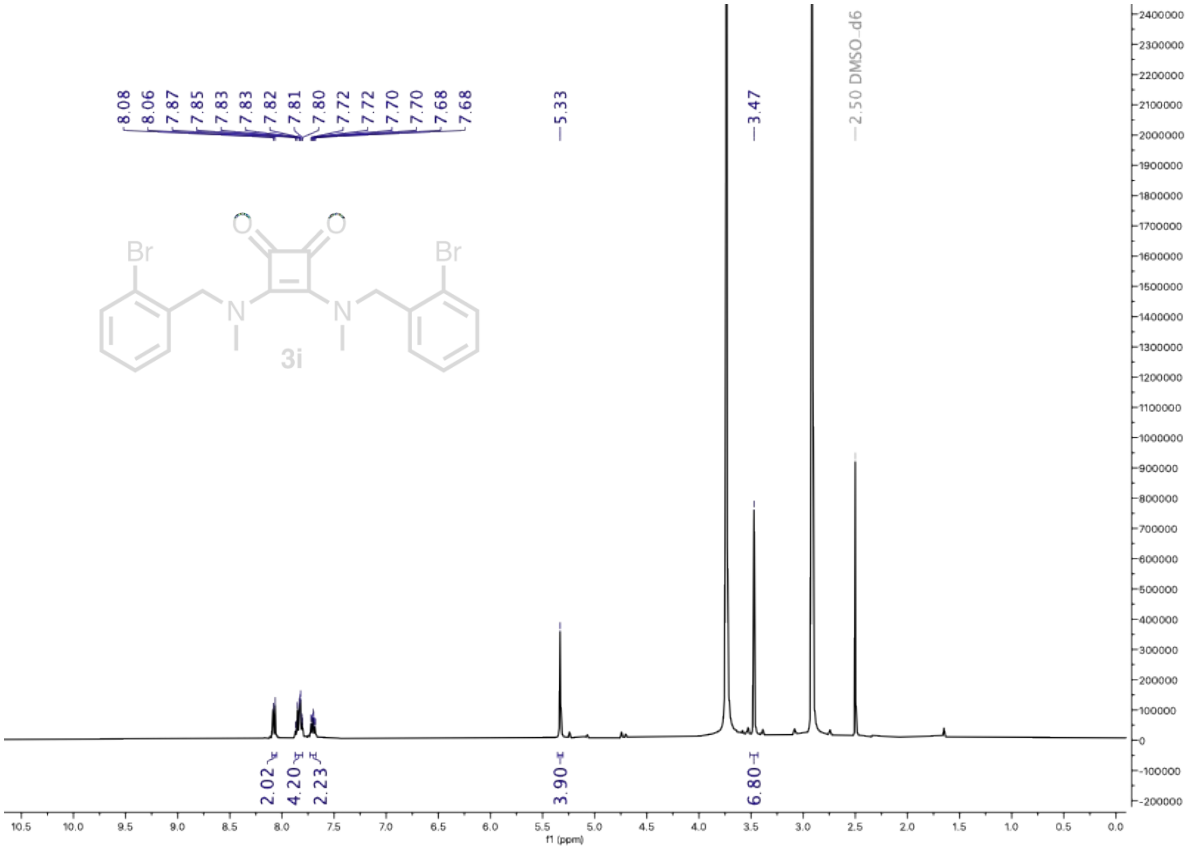


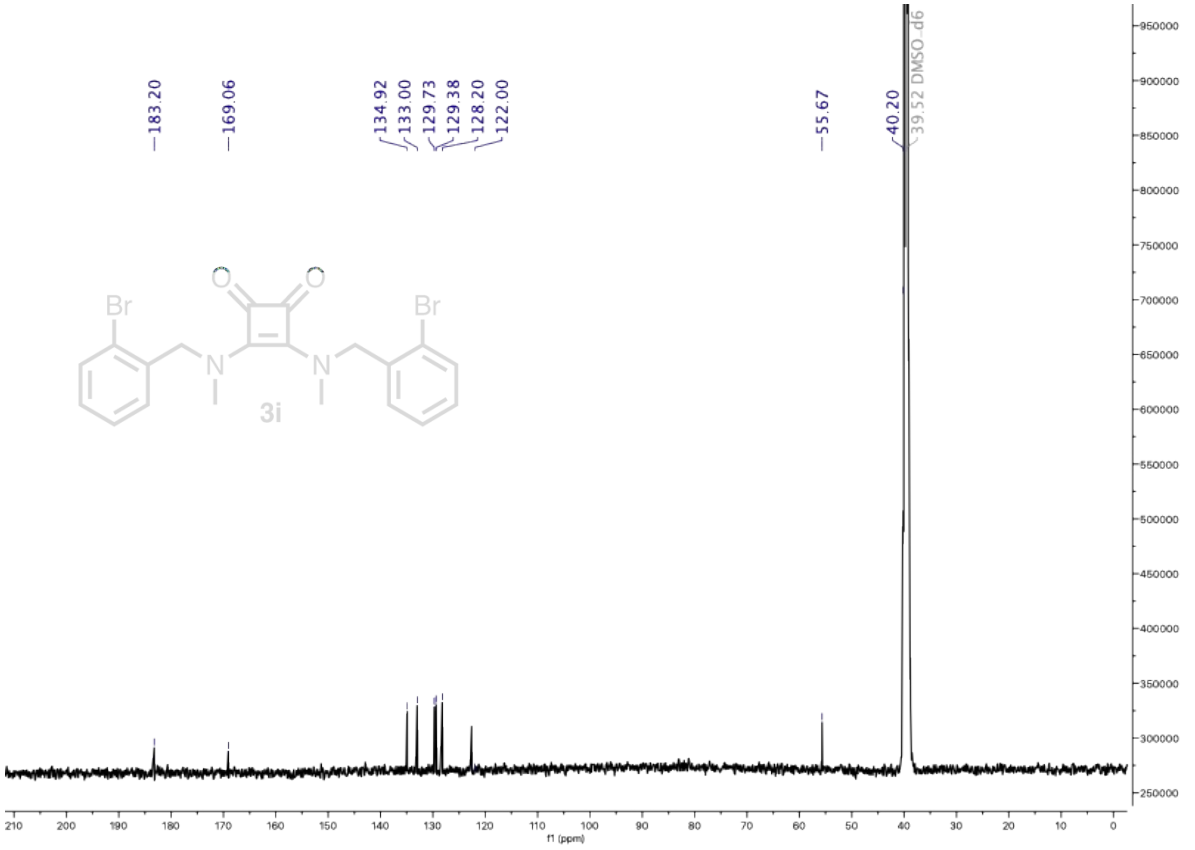
^{1}H and ^{13}C NMR spectra of compound **3h** (DMSO, 400 MHz, 101 MHz)



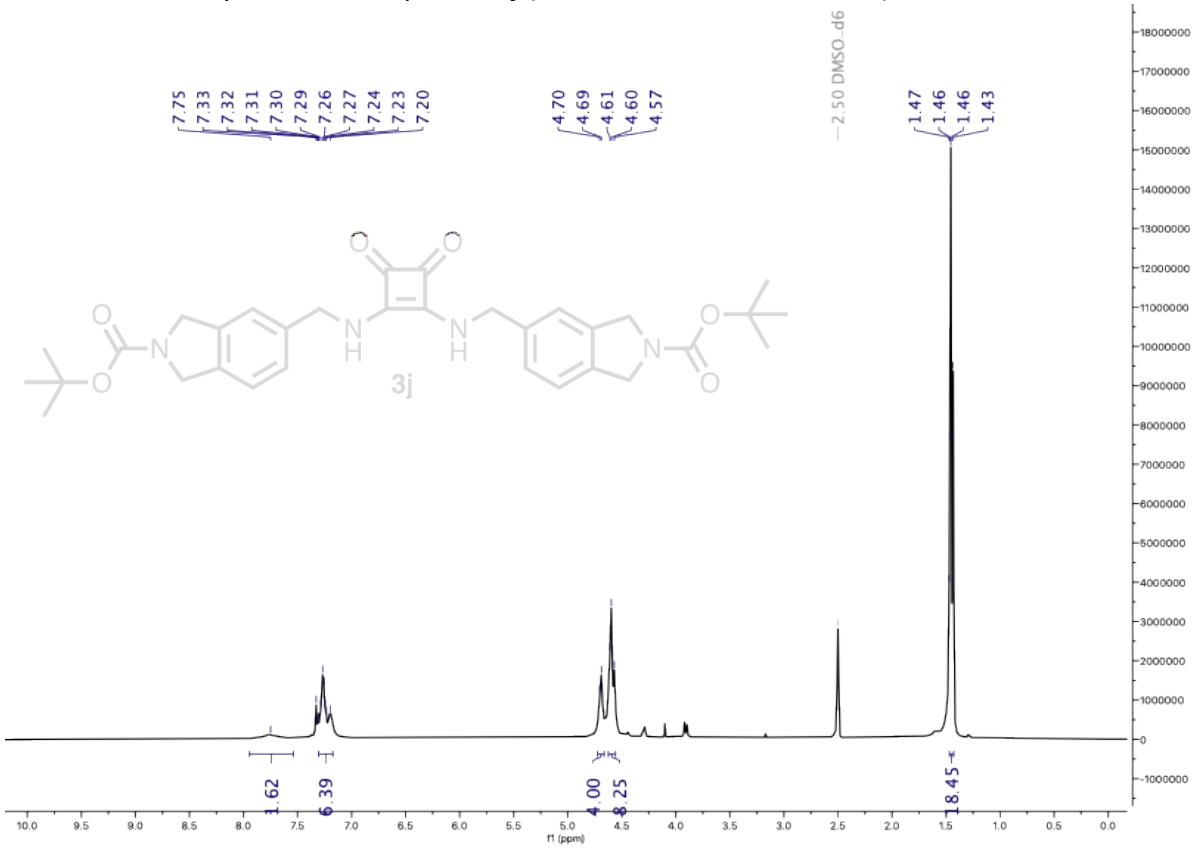


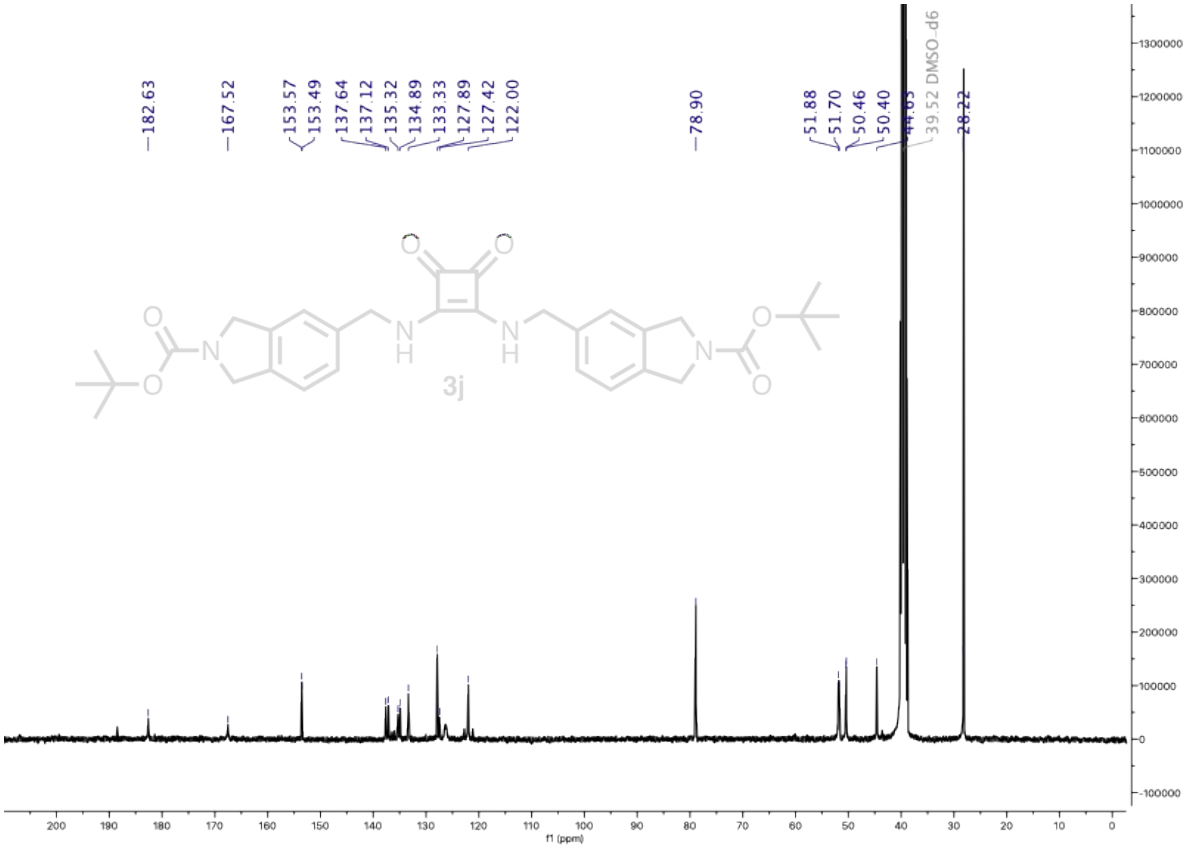
^{1}H and ^{13}C NMR spectra of compound **3i** (DMSO, 400 MHz, 101 MHz)



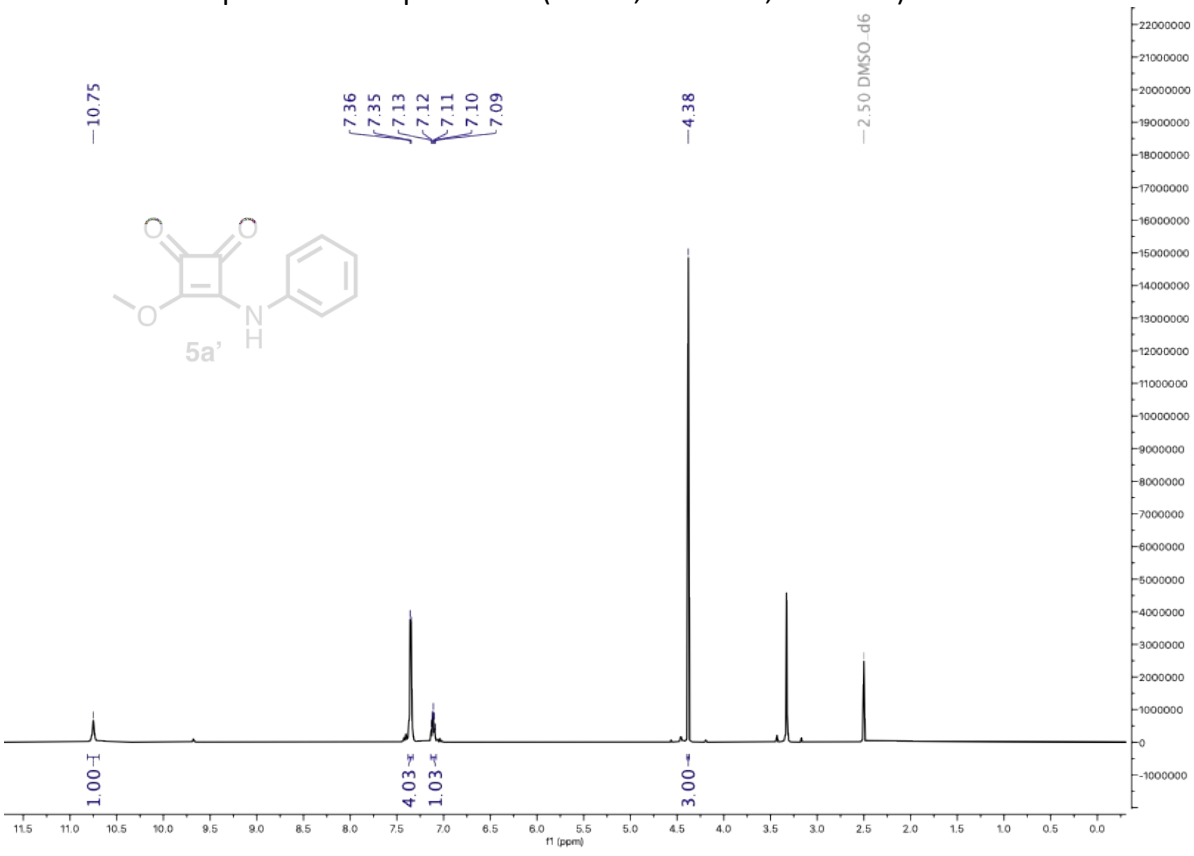


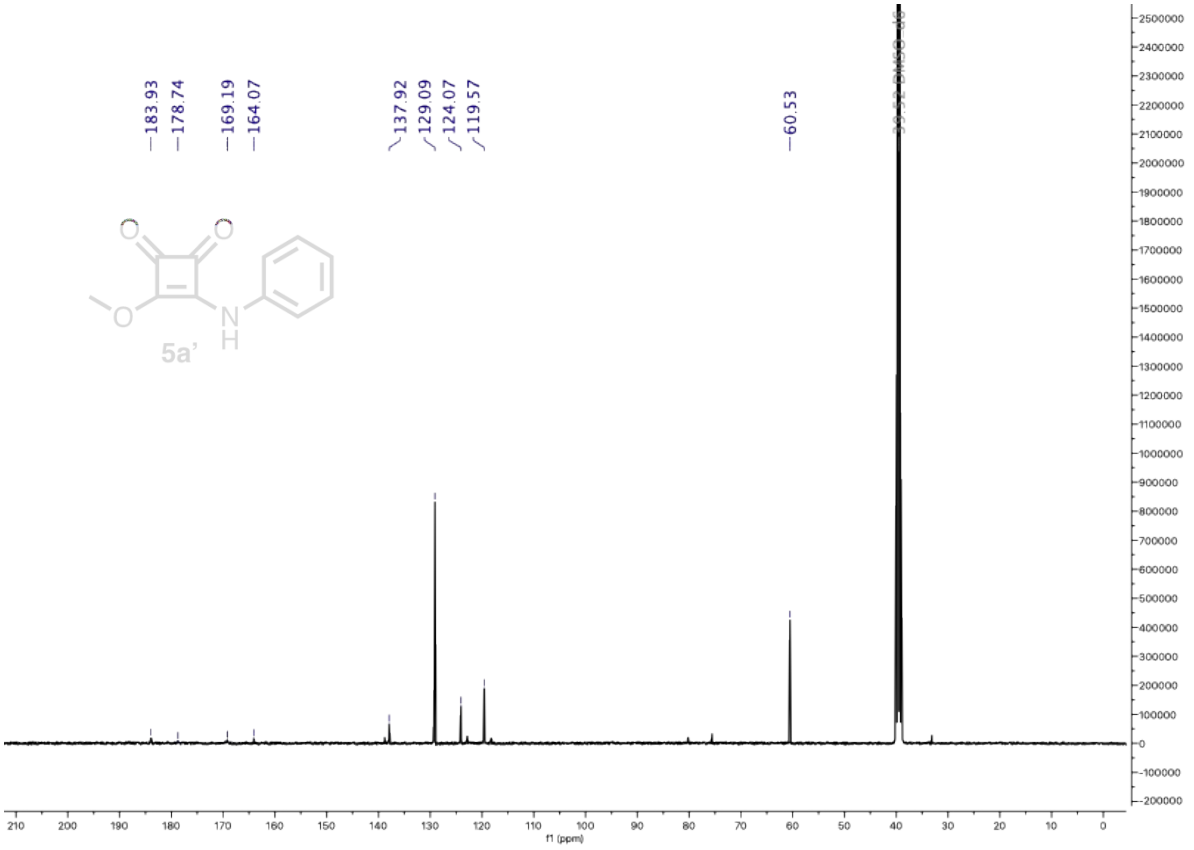
^{1}H and ^{13}C NMR spectra of compound **3j** (DMSO, 400 MHz, 101 MHz)



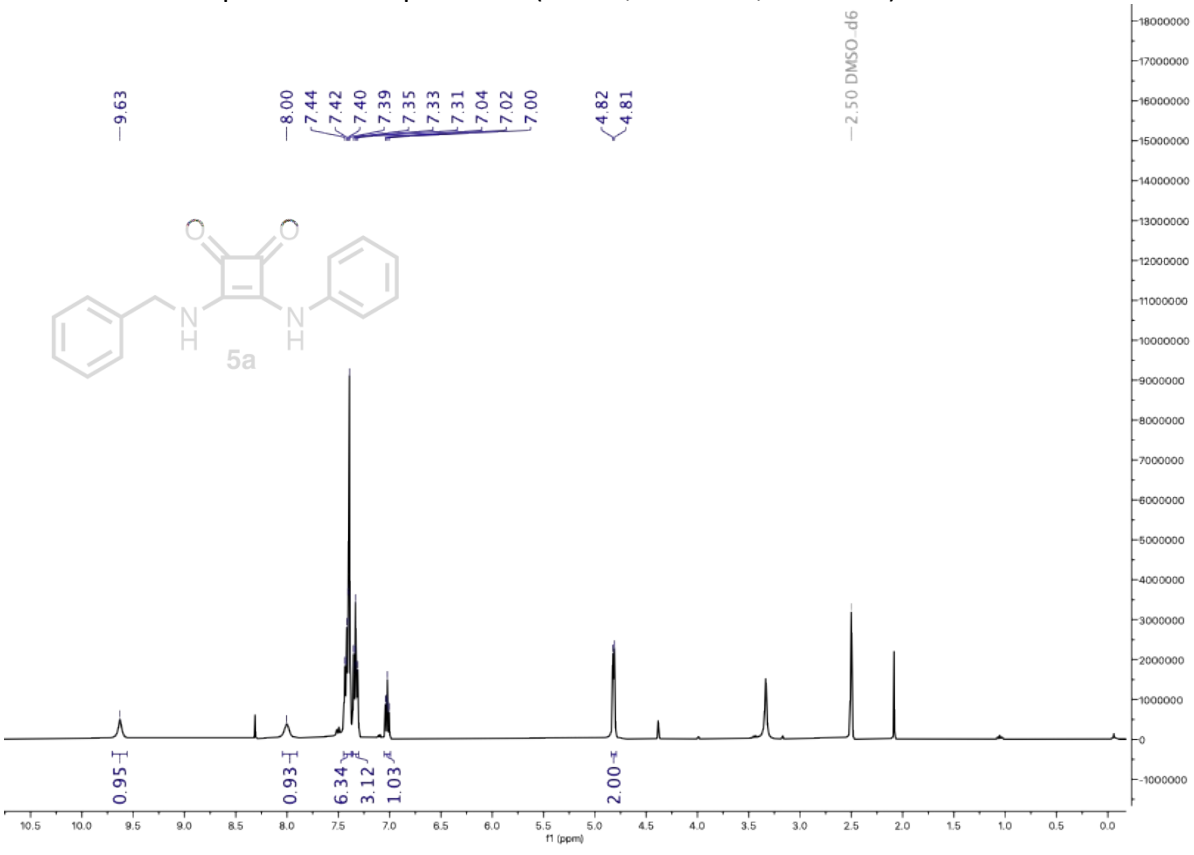


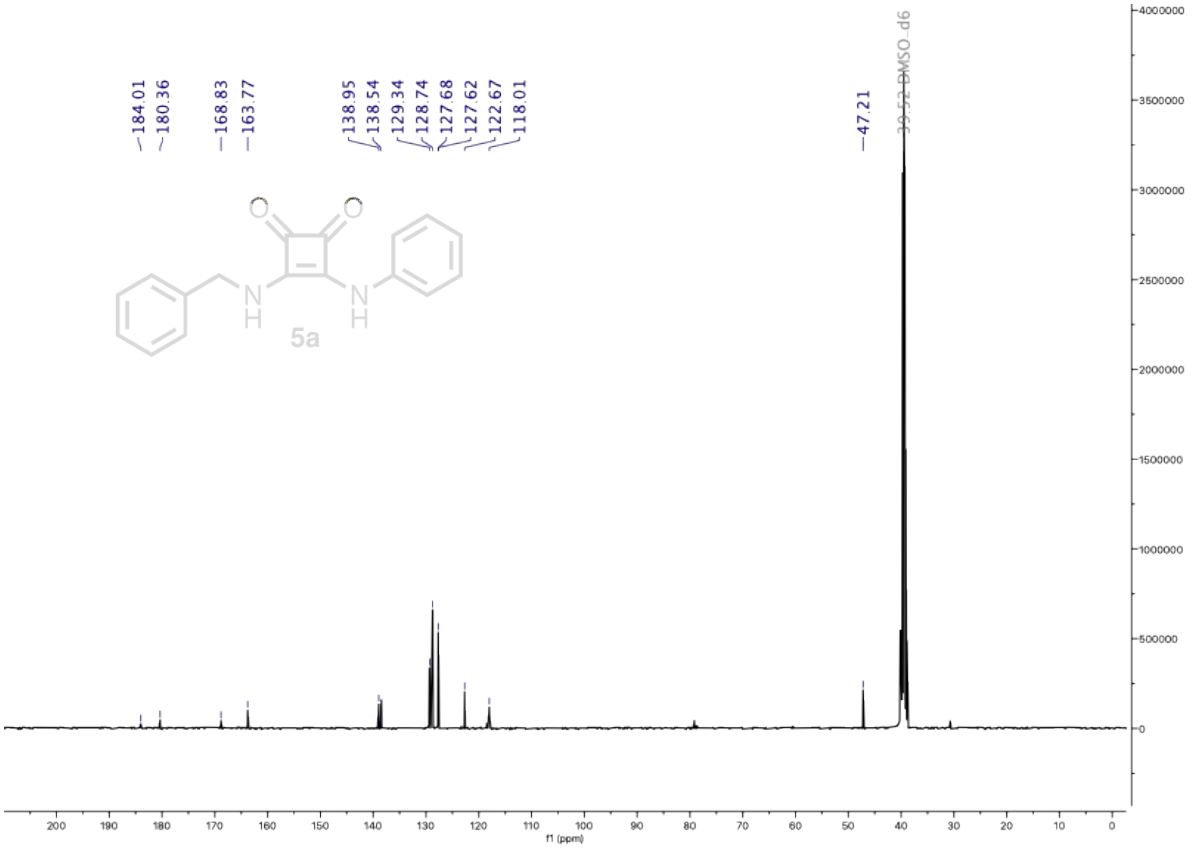
^{1}H and ^{13}C NMR spectra of compound **5a'** (DMSO, 400 MHz, 101 MHz)



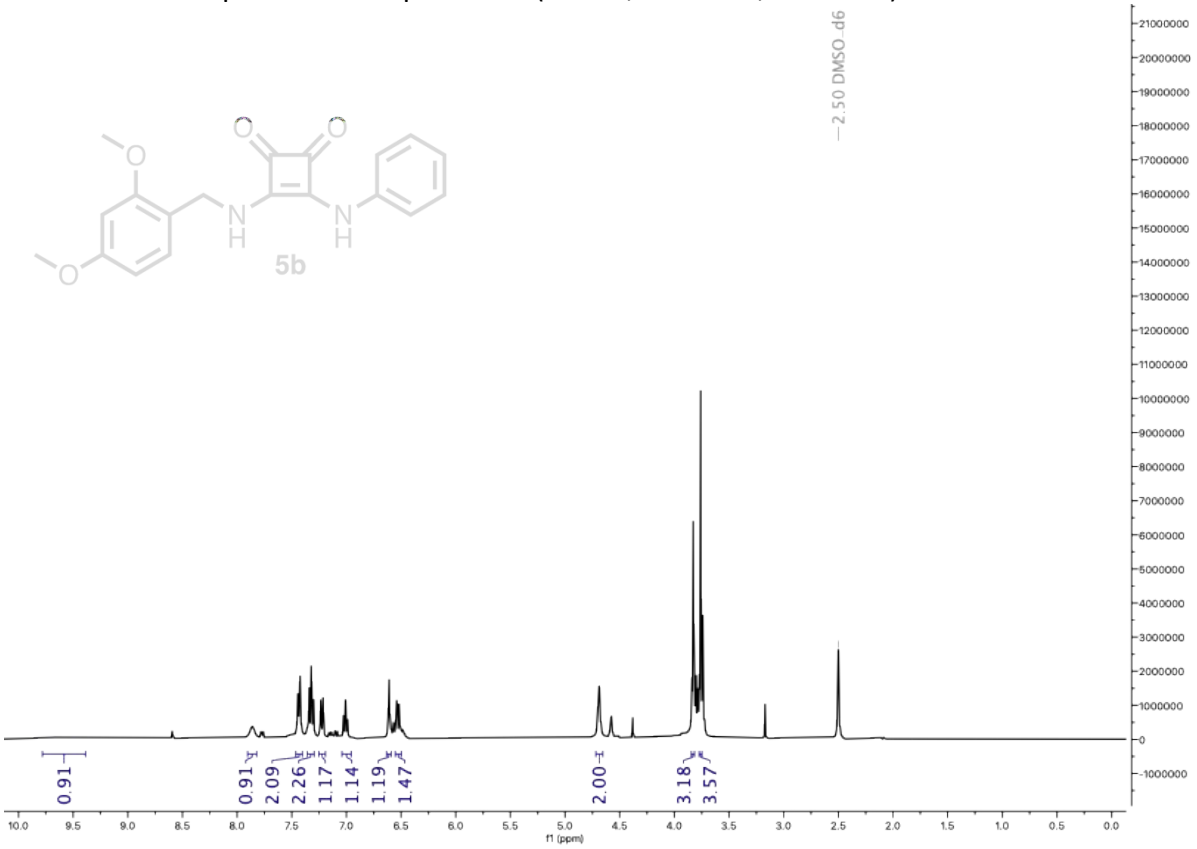


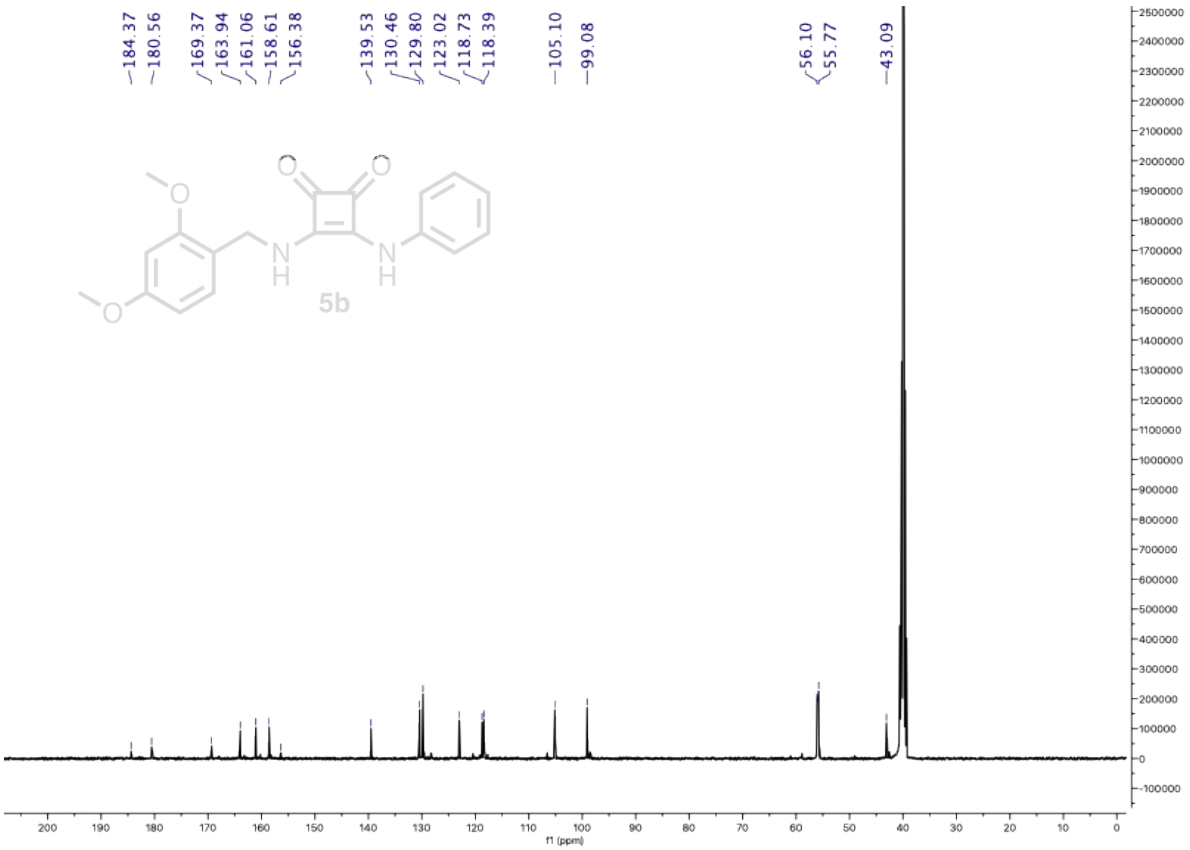
^{1}H and ^{13}C NMR spectra of compound **5a** (DMSO, 400 MHz, 101 MHz)



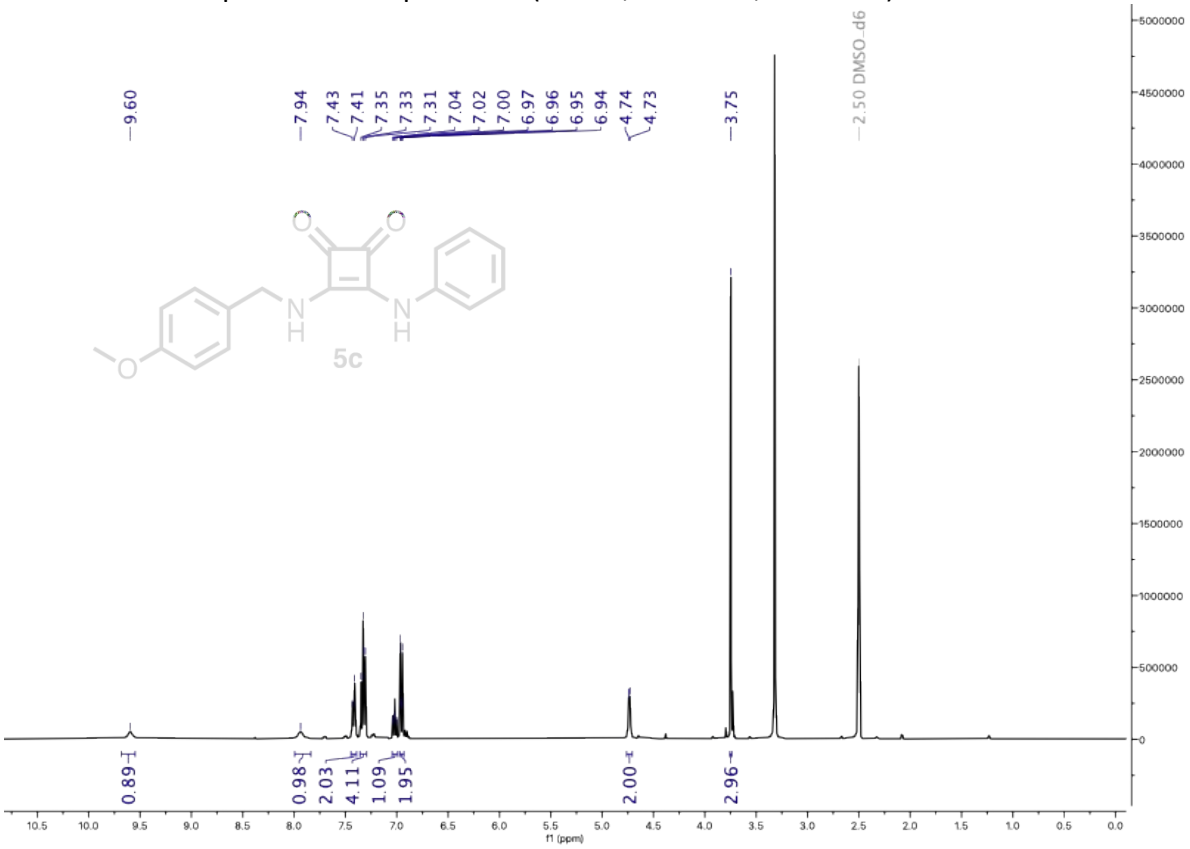


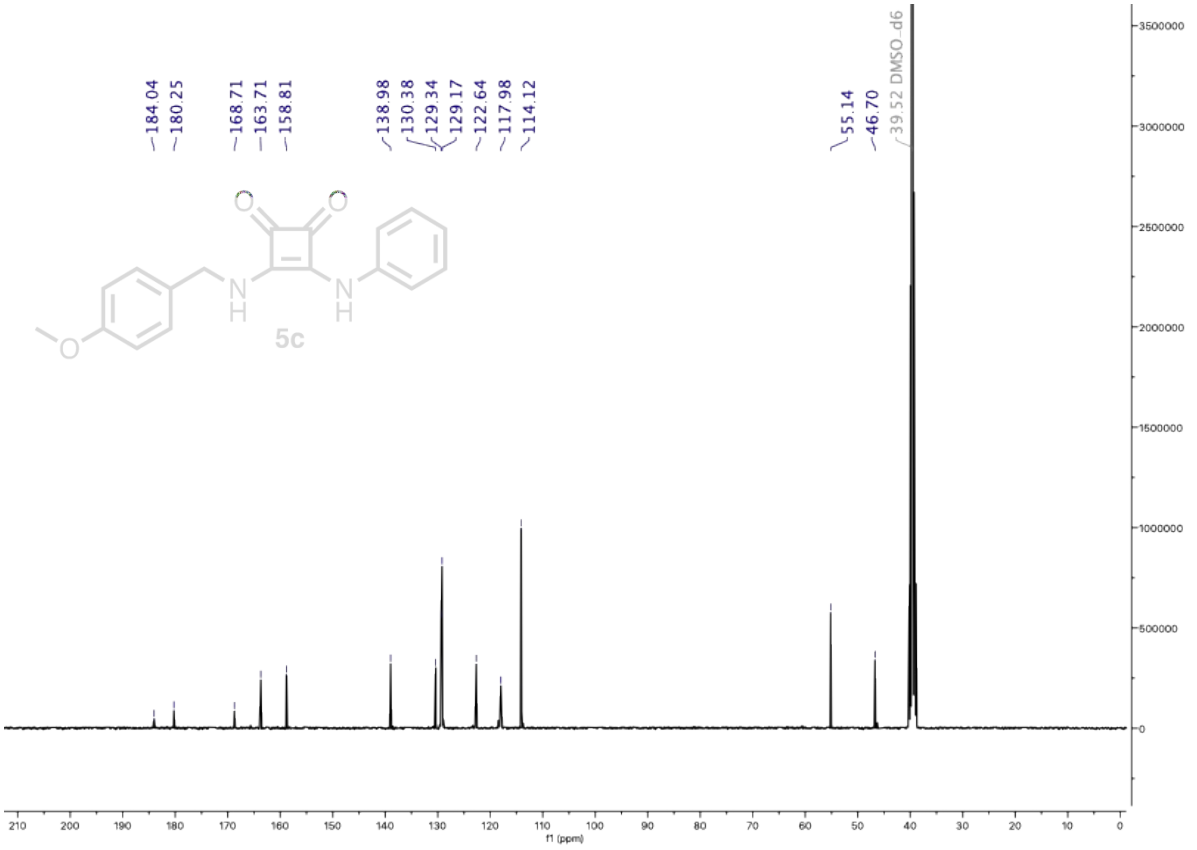
^{1}H and^{13}C NMR spectra of compound **5b** (DMSO, 400 MHz, 101 MHz)



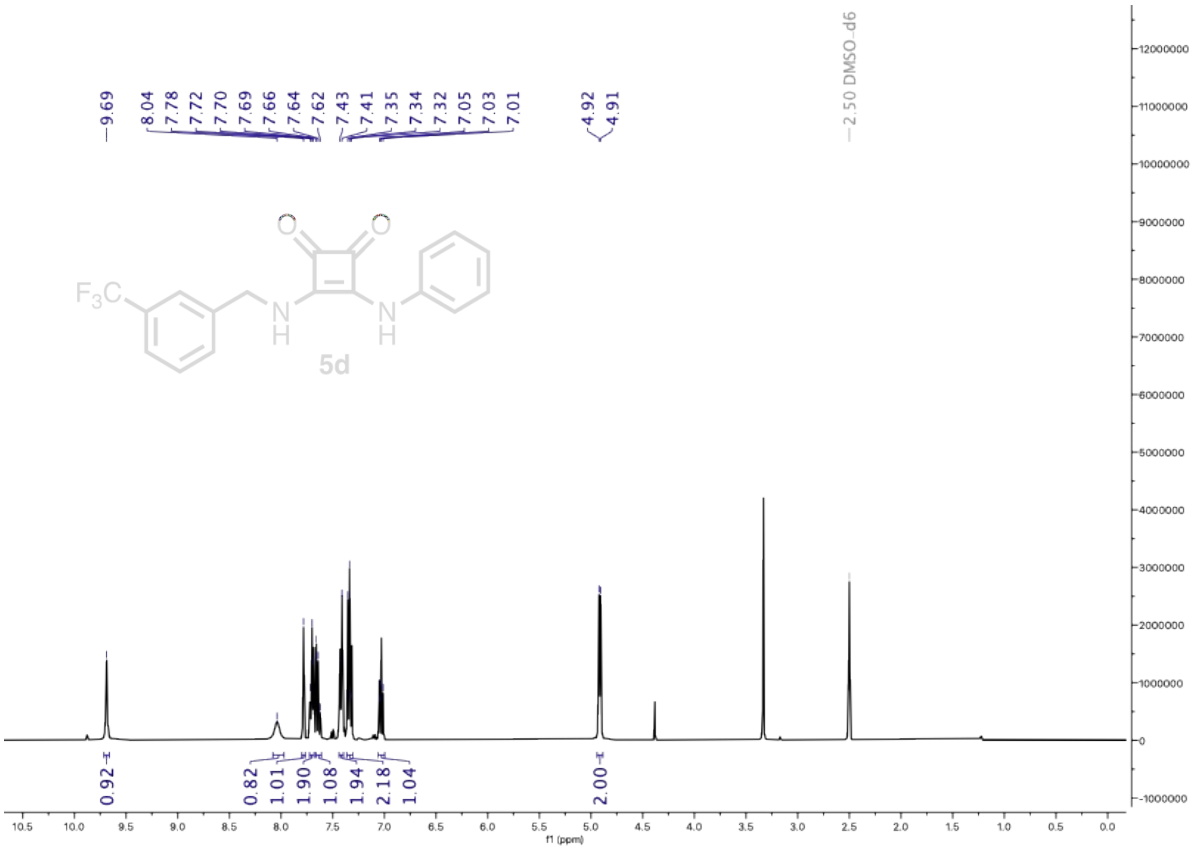


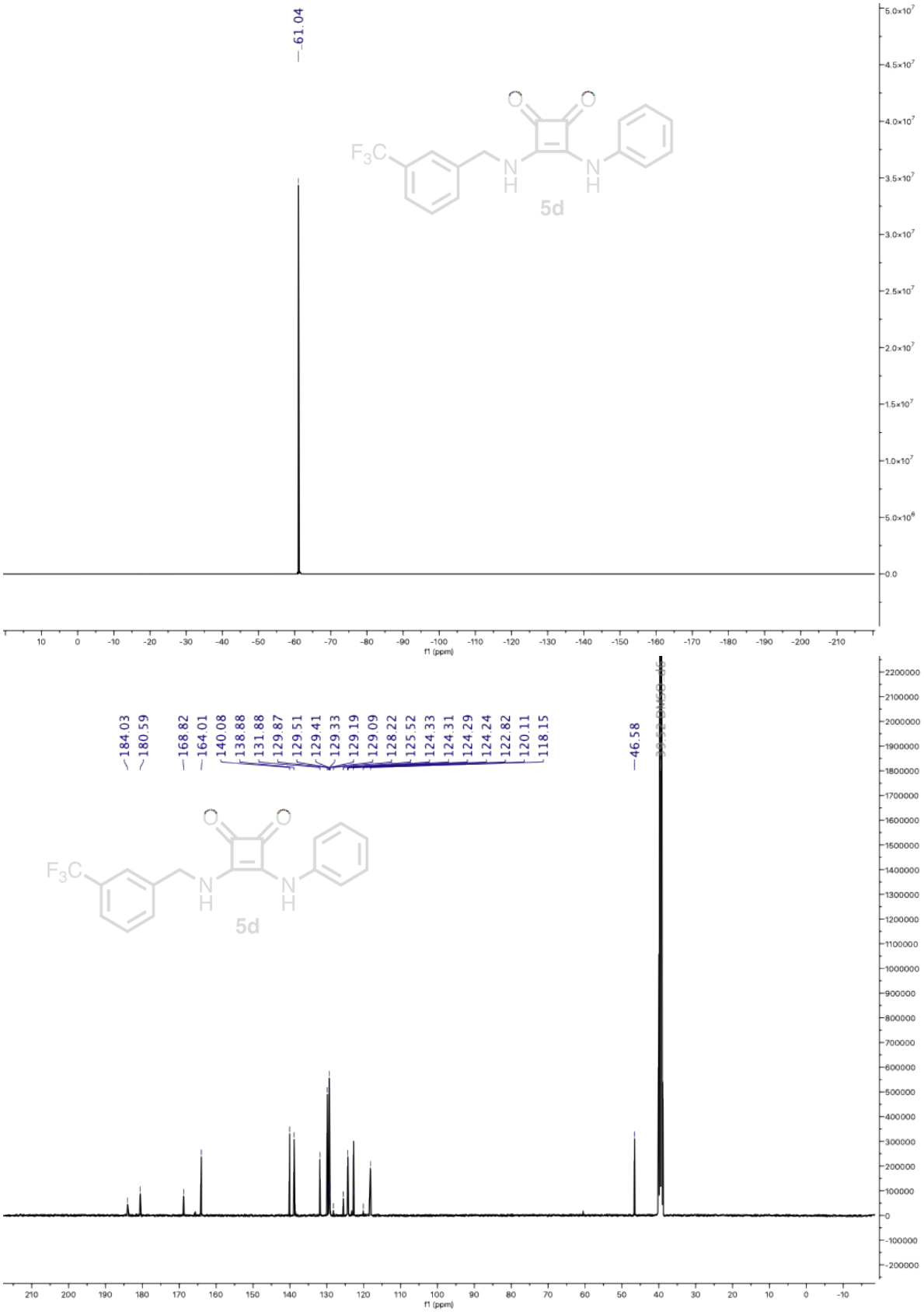
^{1}H and ^{13}C NMR spectra of compound **5c** (DMSO, 400 MHz, 101 MHz)



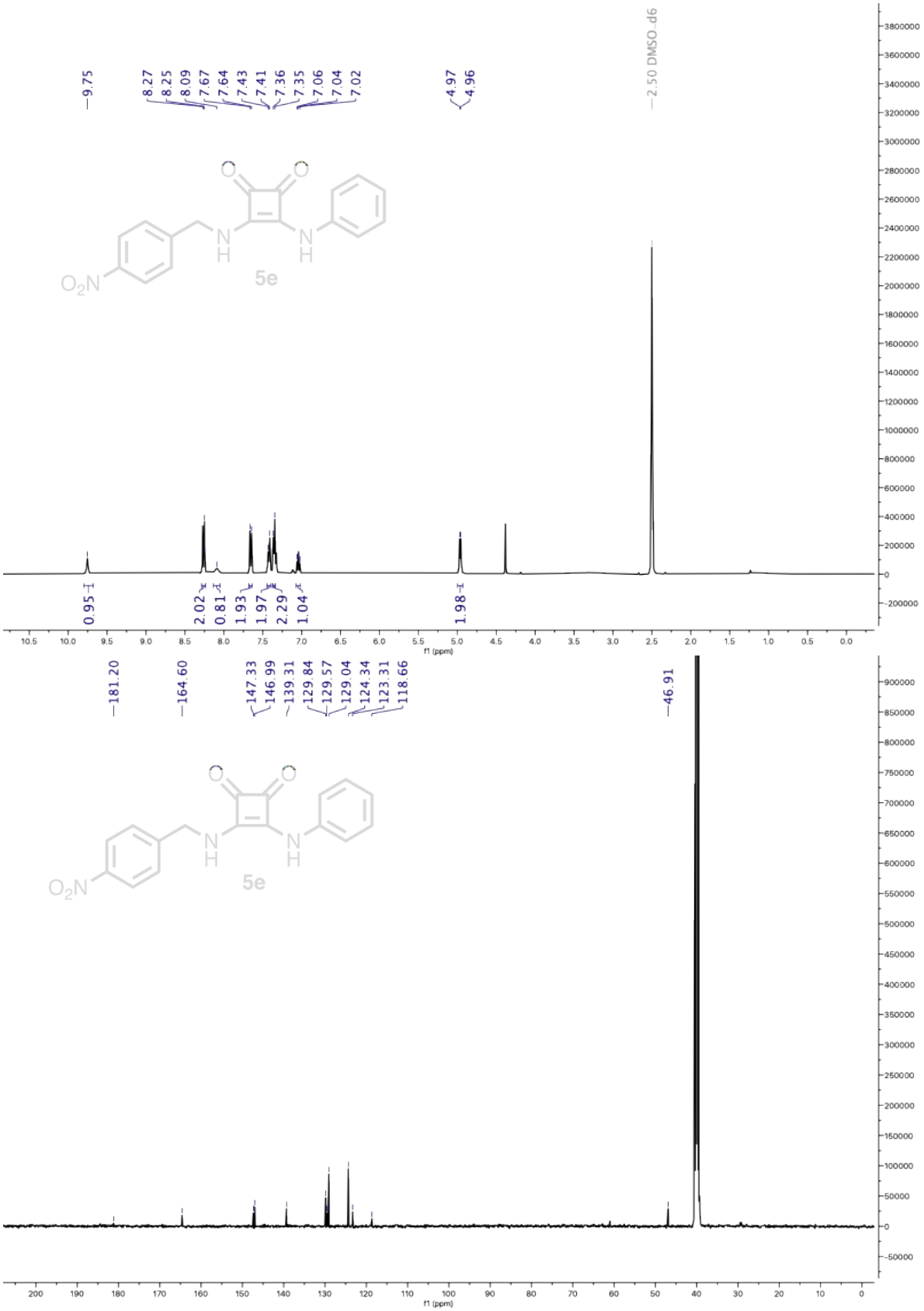


^{1}H, ^{19}F and^{13}C NMR spectra of compound **5d** (DMSO, 400 MHz, 377 MHz, 101 MHz)

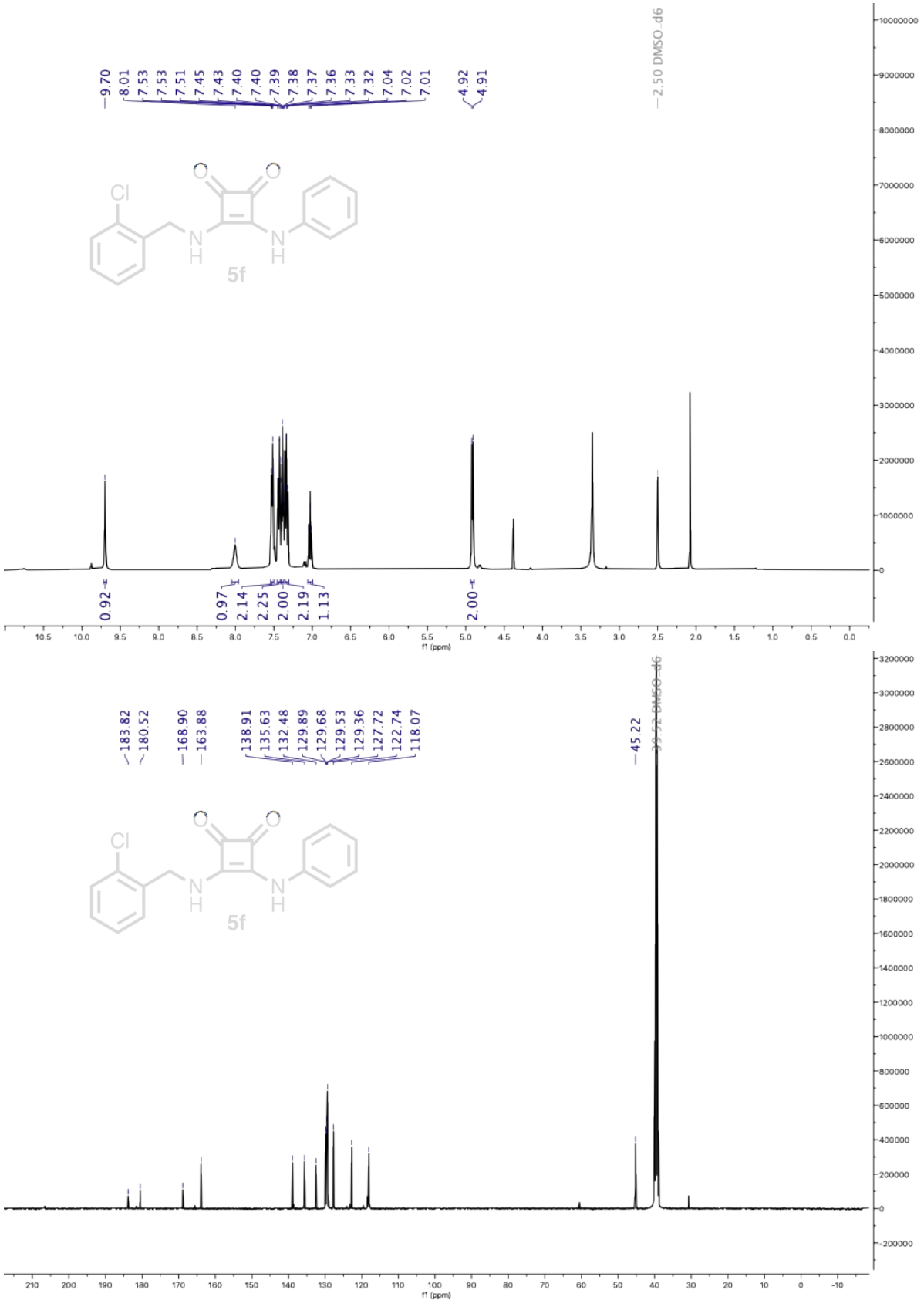




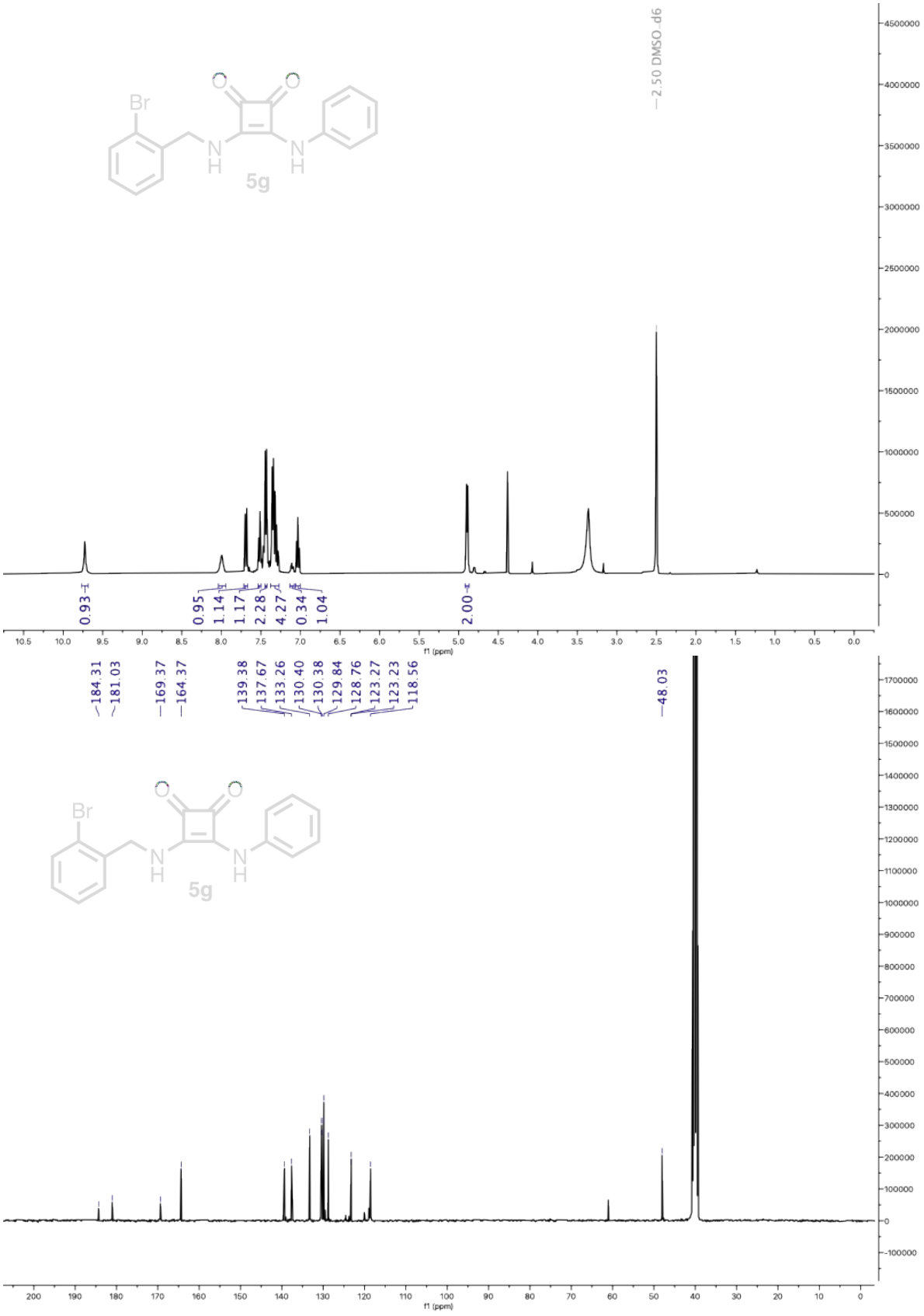
^{1}H and ^{13}C NMR spectra of compound **5e** (DMSO, 400 MHz, 101 MHz)



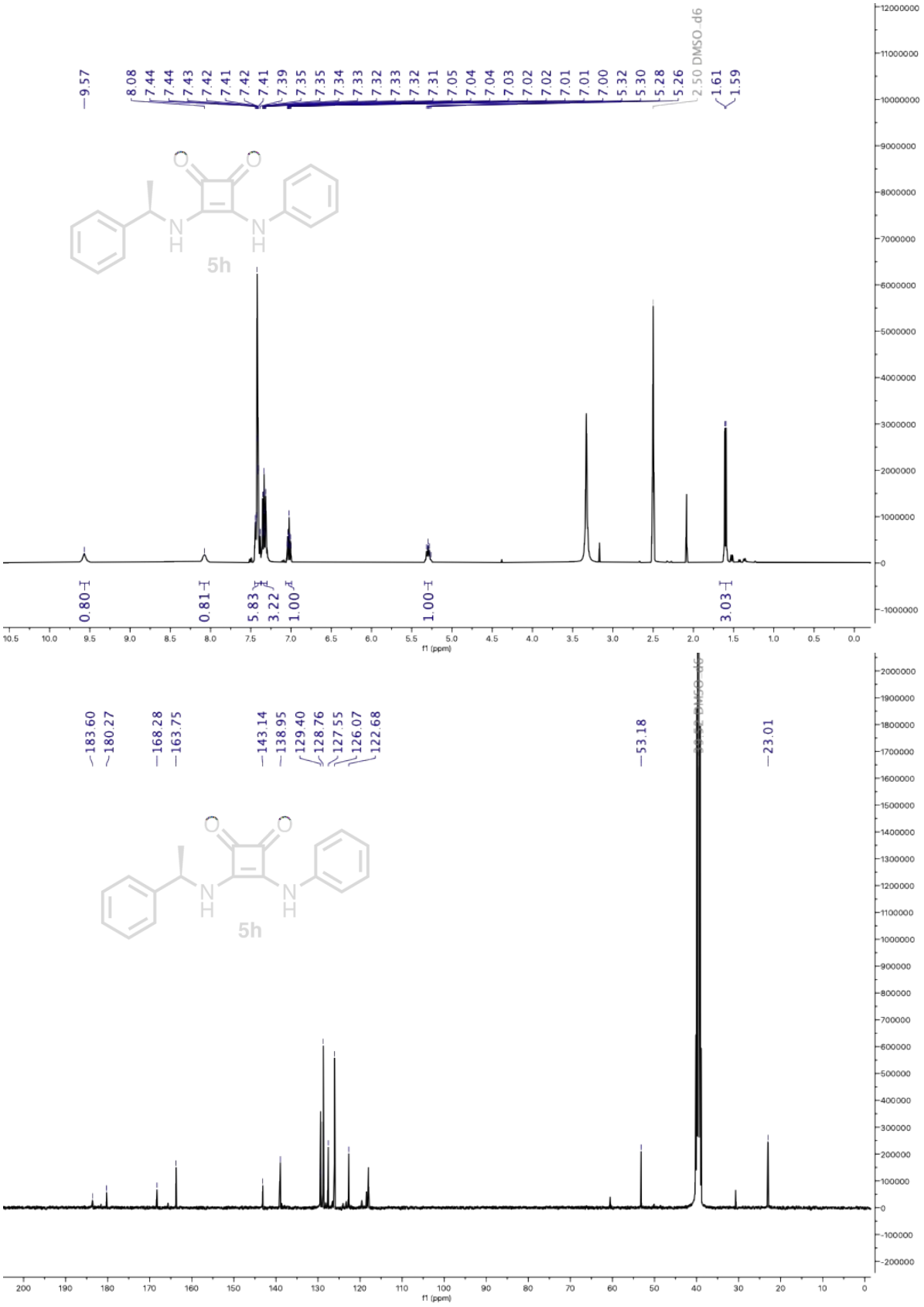
^{1}H and ^{13}C NMR spectra of compound **5f** (DMSO, 400 MHz, 101 MHz)



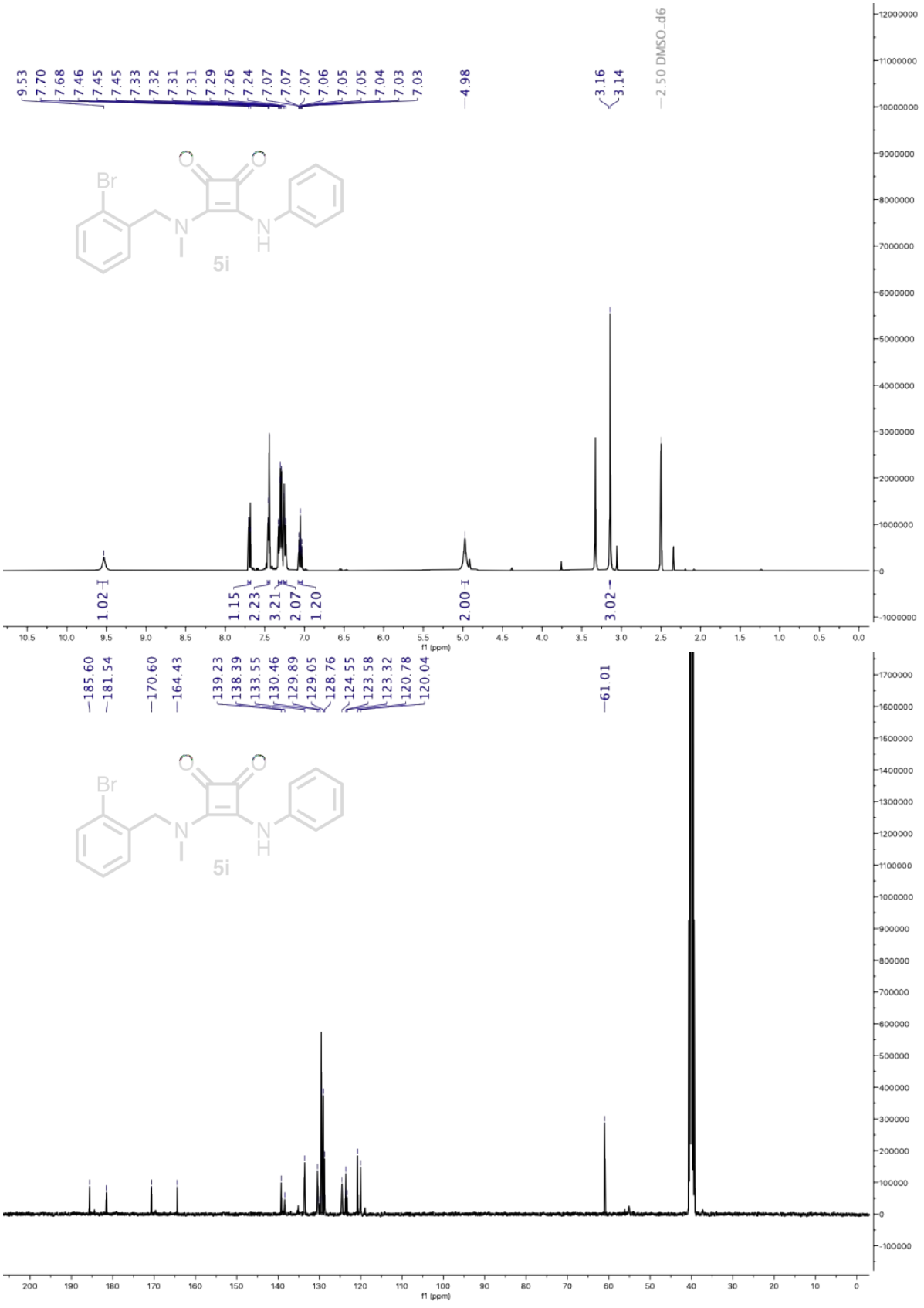
^{1}H and ^{13}C NMR spectra of compound **5g** (DMSO, 400 MHz, 101 MHz)



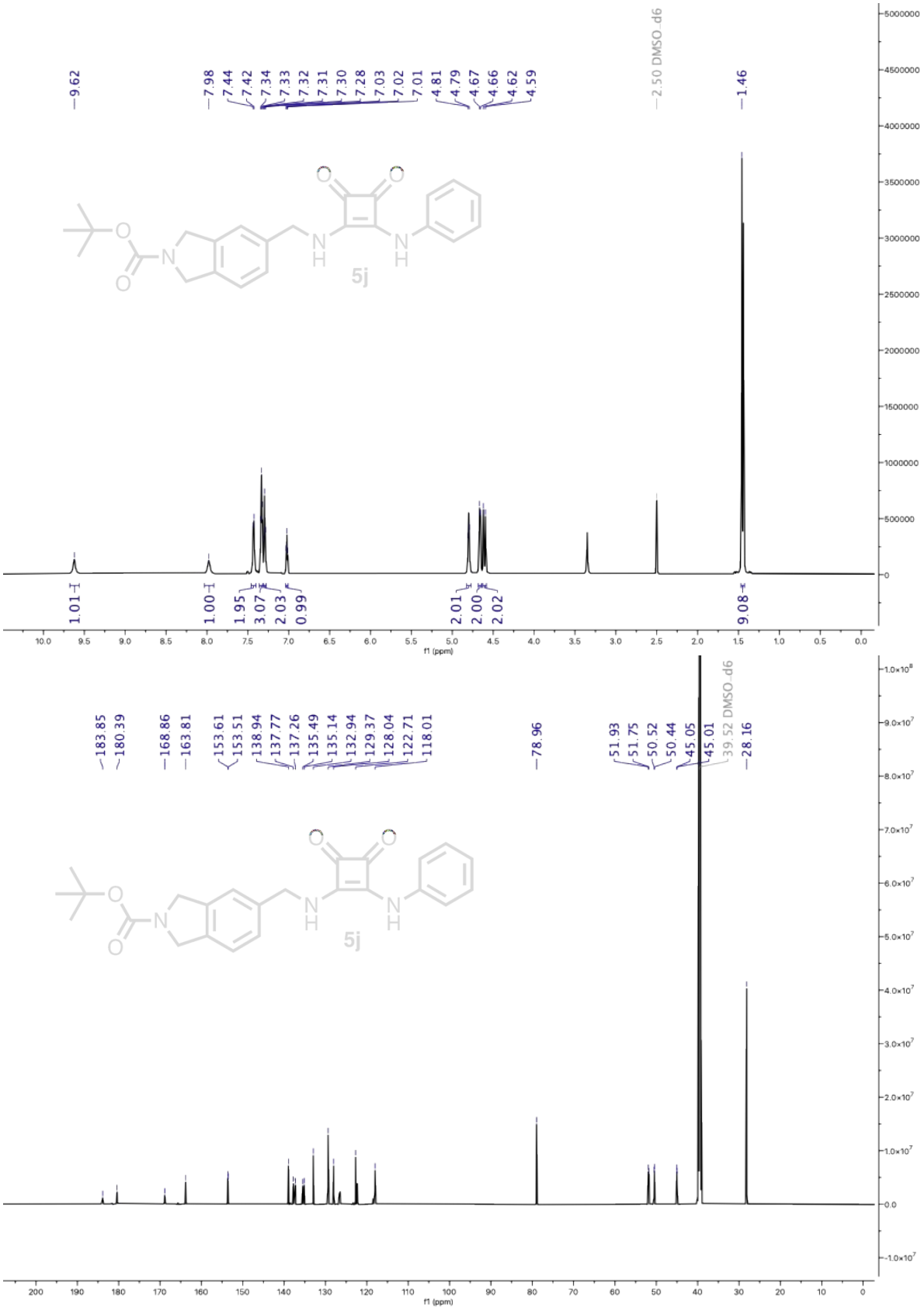
^{1}H and^{13}C NMR spectra of compound **5h** (DMSO, 400 MHz, 101 MHz)



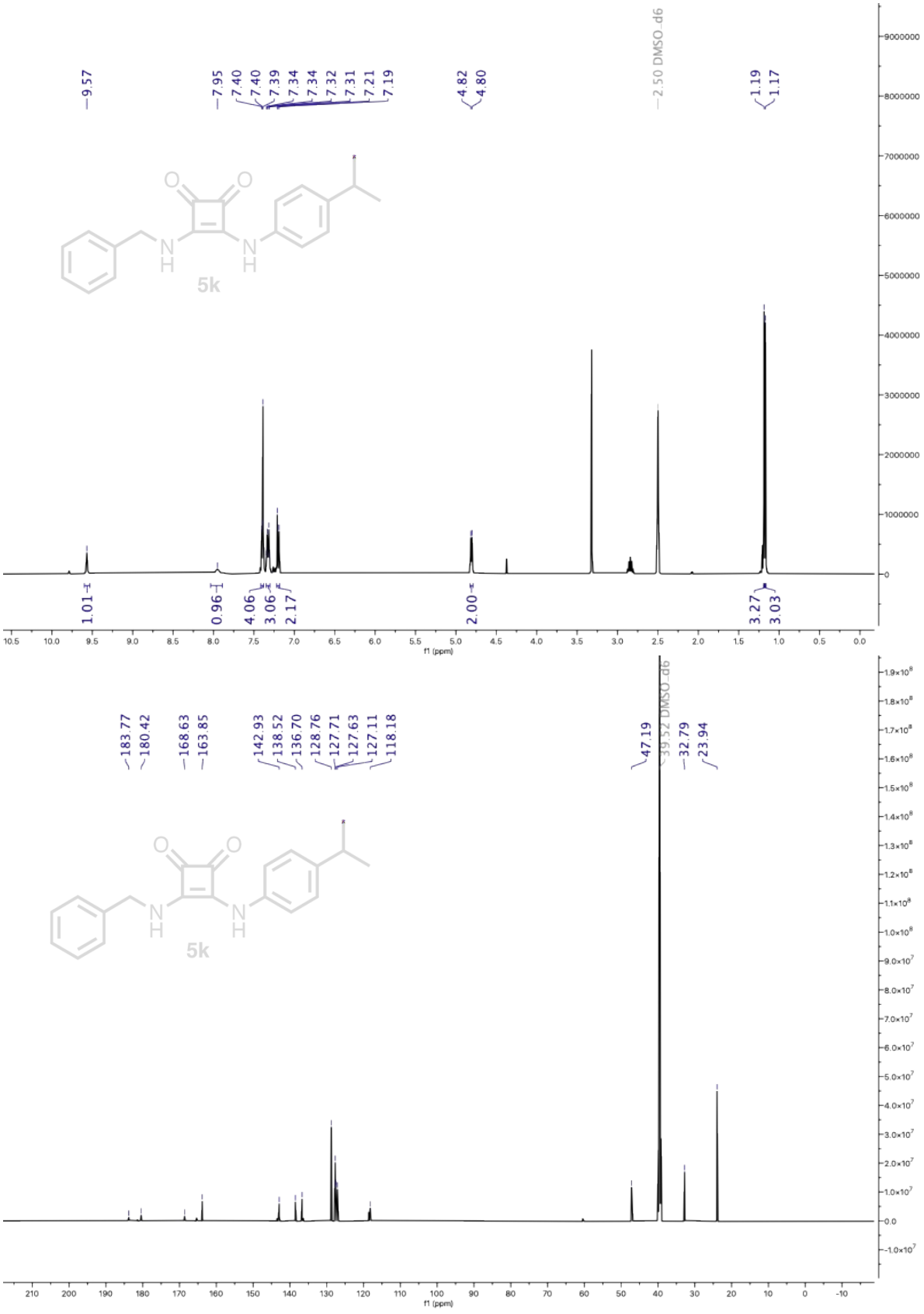
^{1}H and ^{13}C NMR spectra of compound **5i** (DMSO, 400 MHz, 101 MHz)



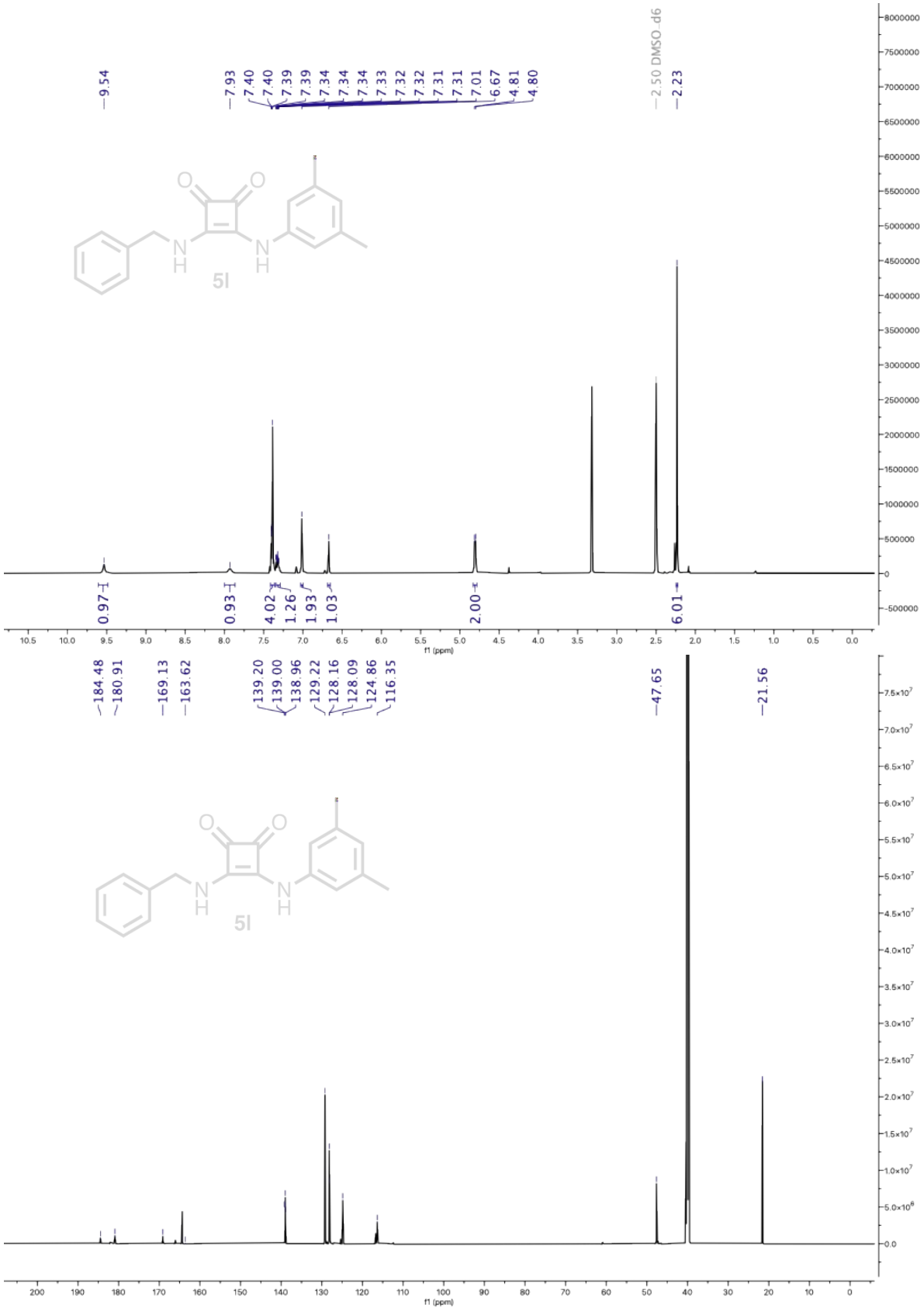
^{1}H and ^{13}C NMR spectra of compound **5j** (DMSO, 700 MHz, 176 MHz)



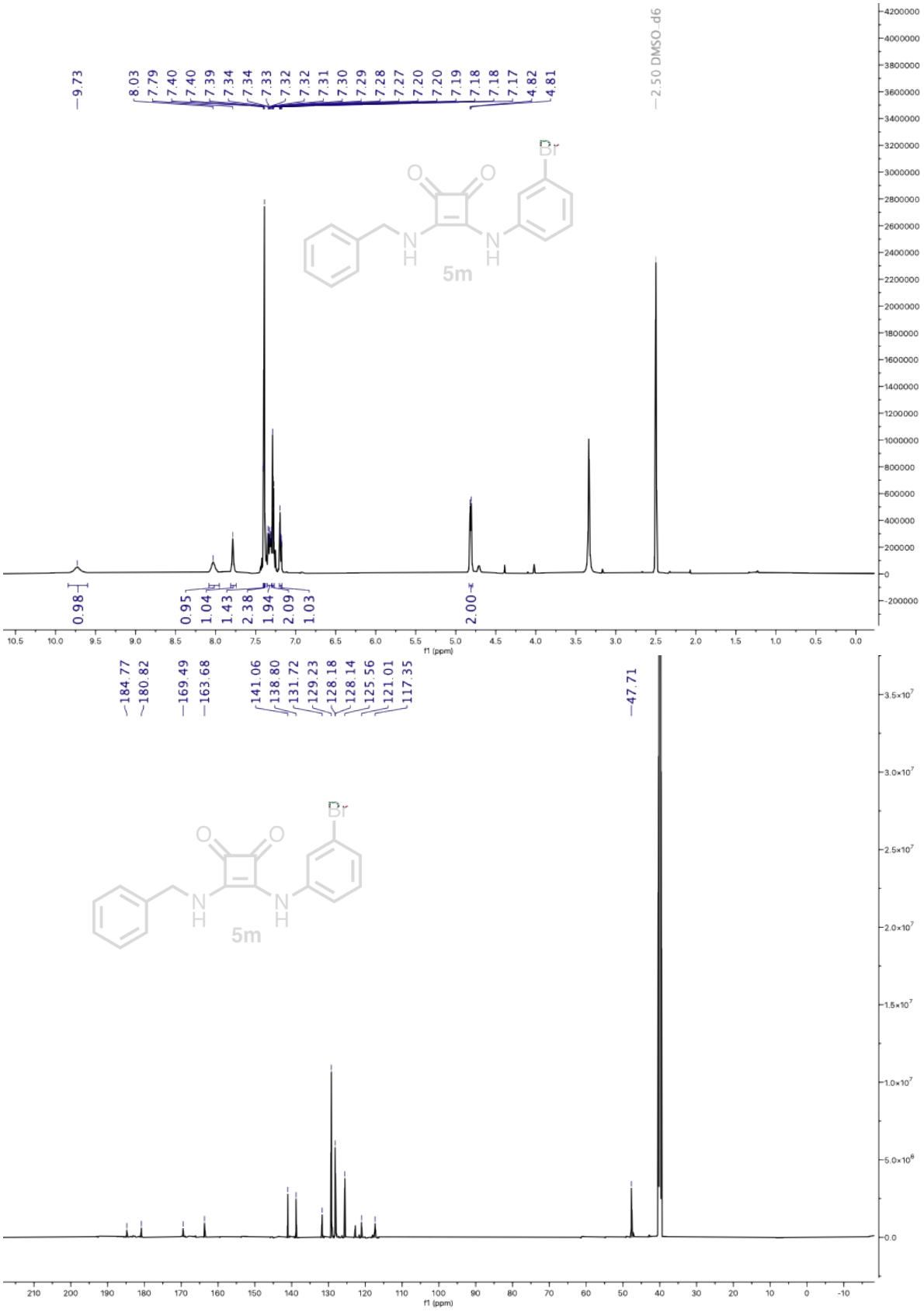
^{1}H and ^{13}C NMR spectra of compound **5k** (DMSO, 700 MHz, 176 MHz)



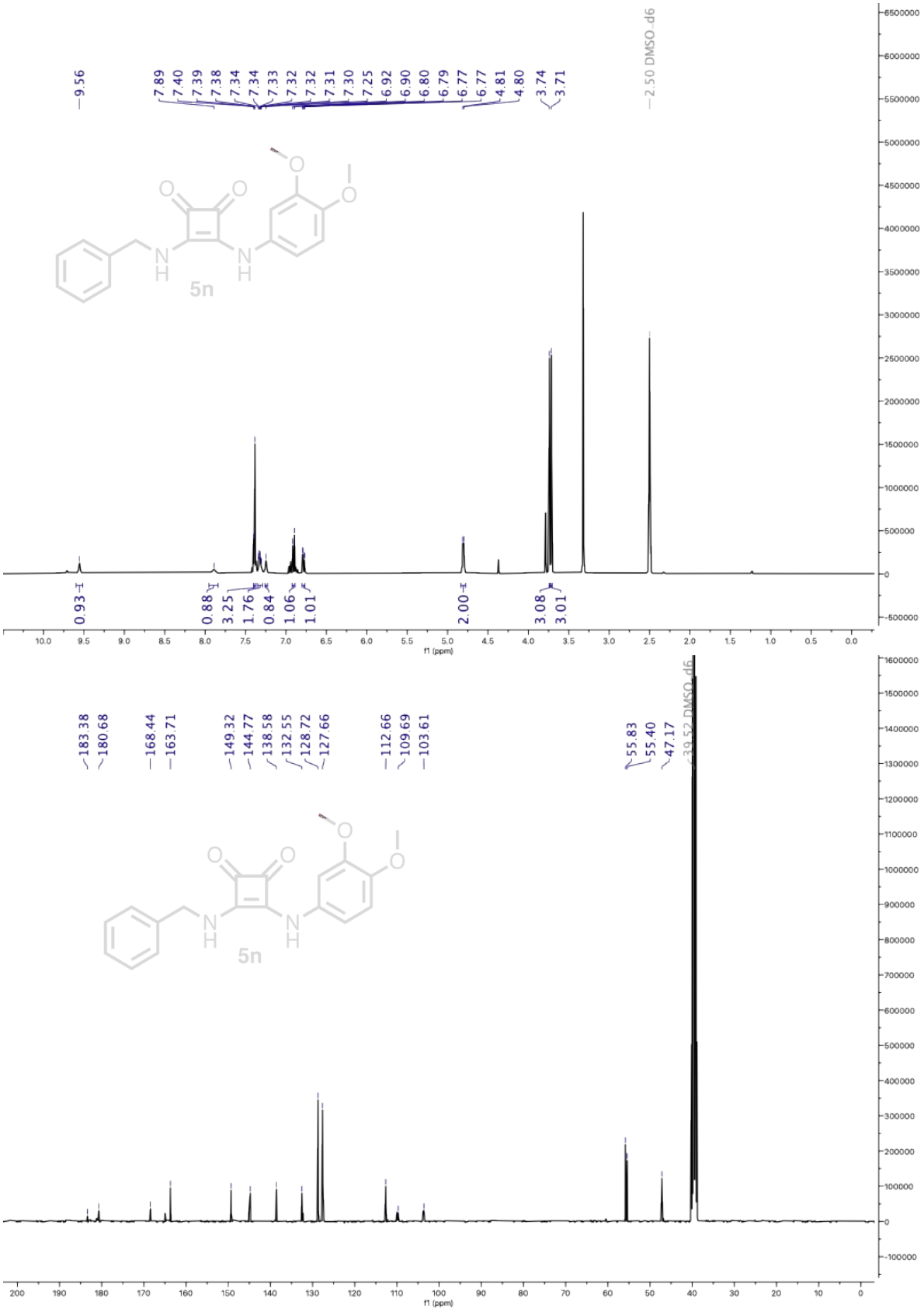
^{1}H and ^{13}C NMR spectra of compound **5l** (DMSO, 700 MHz, 176 MHz)



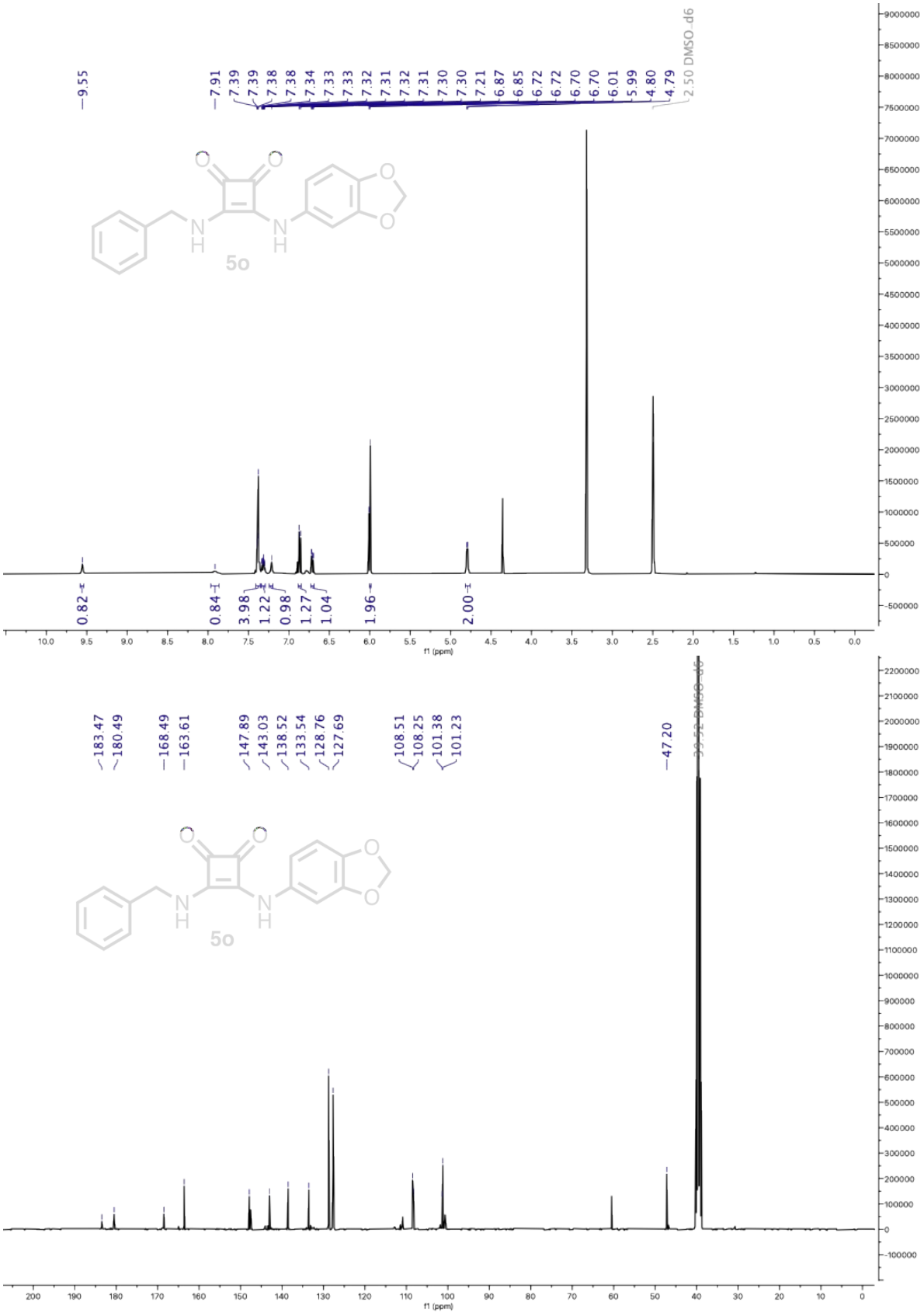
^{1}H and ^{13}C NMR spectra of compound **5m** (DMSO, 400 MHz, 176 MHz)



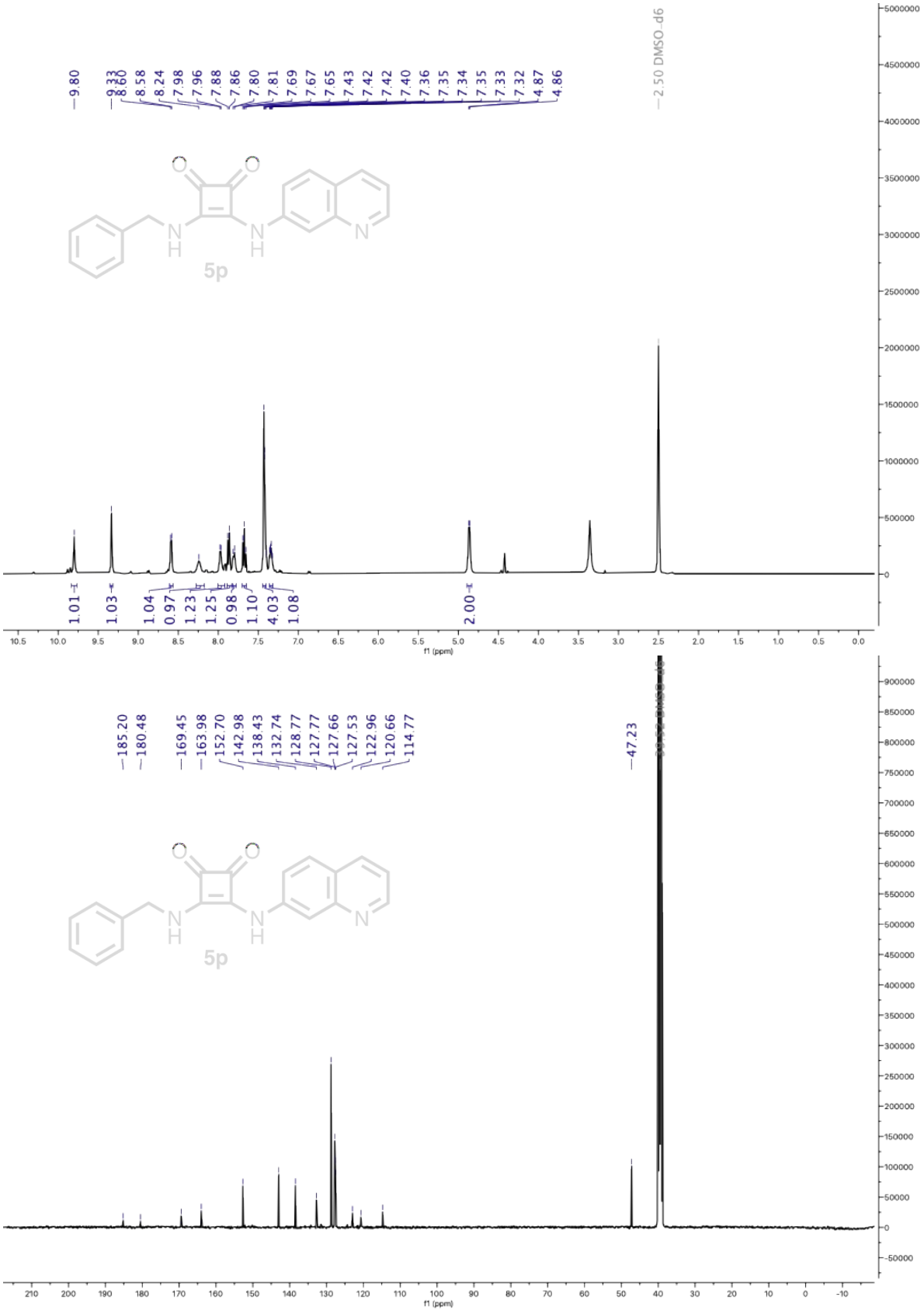
^{1}H and ^{13}C NMR spectra of compound **5n** (DMSO, 400 MHz, 101 MHz)



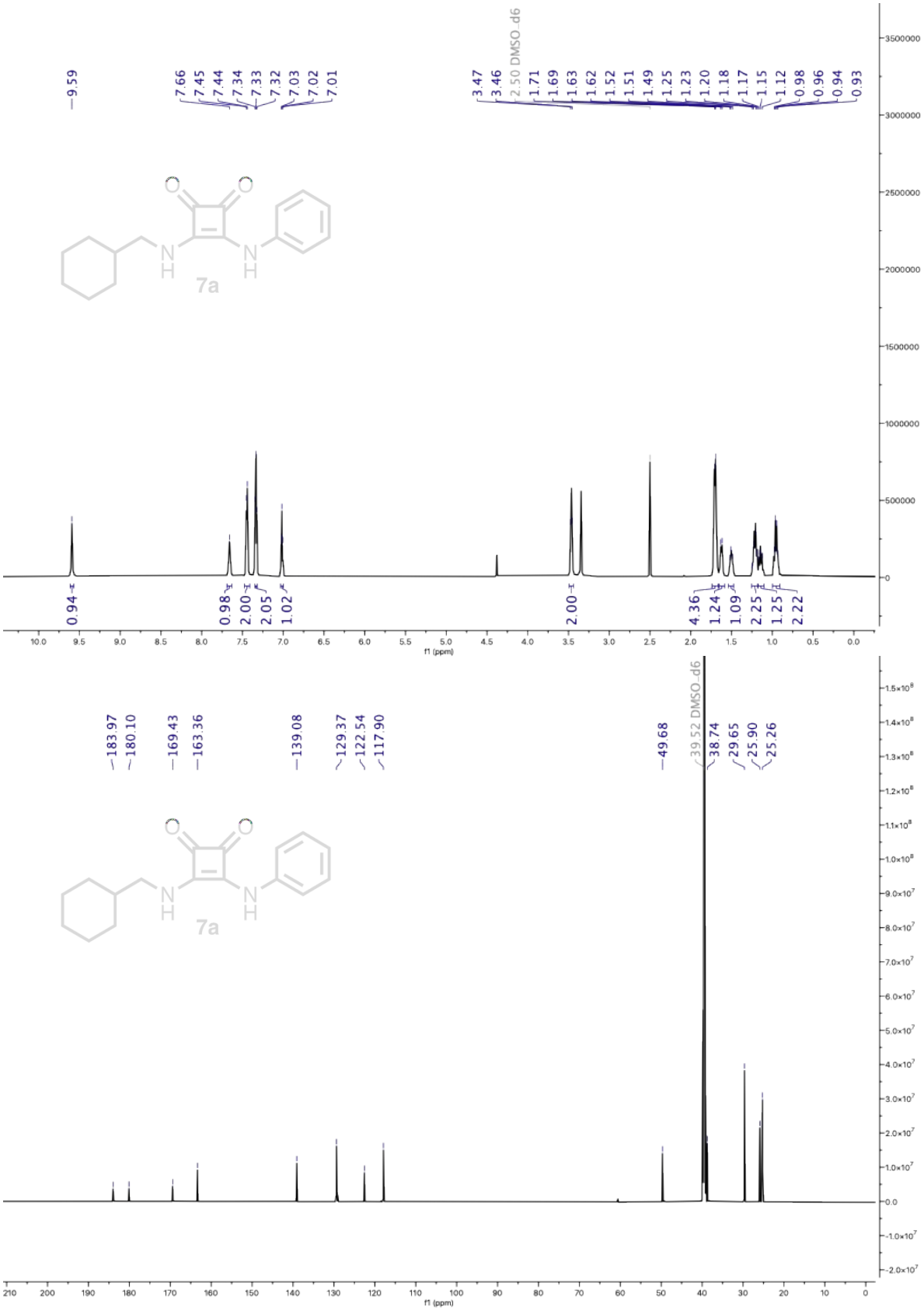
^{1}H and ^{13}C NMR spectra of compound **5o** (DMSO, 400 MHz, 101 MHz)



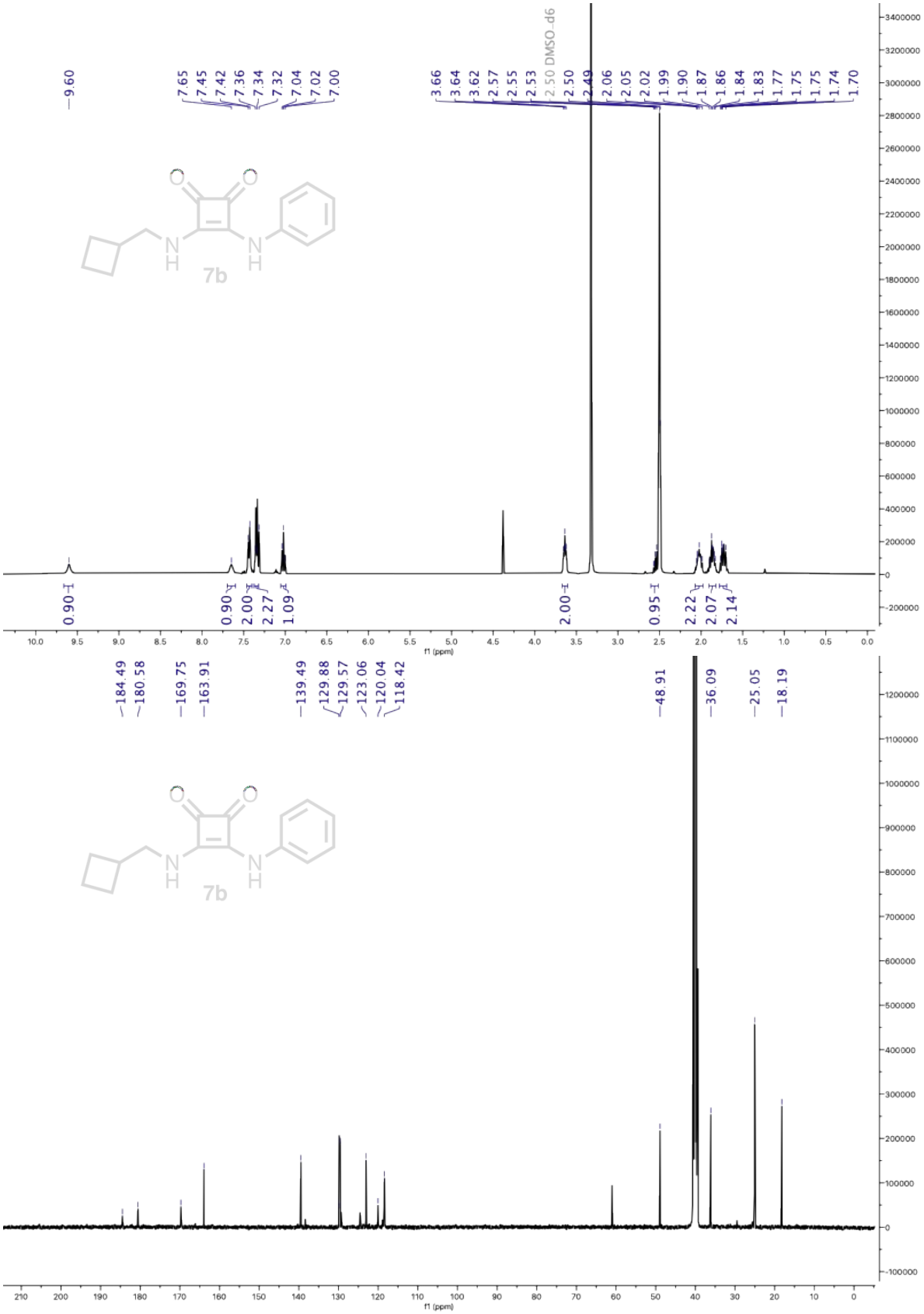
^{1}H and ^{13}C NMR spectra of compound **5p** (DMSO, 400 MHz, 101 MHz)



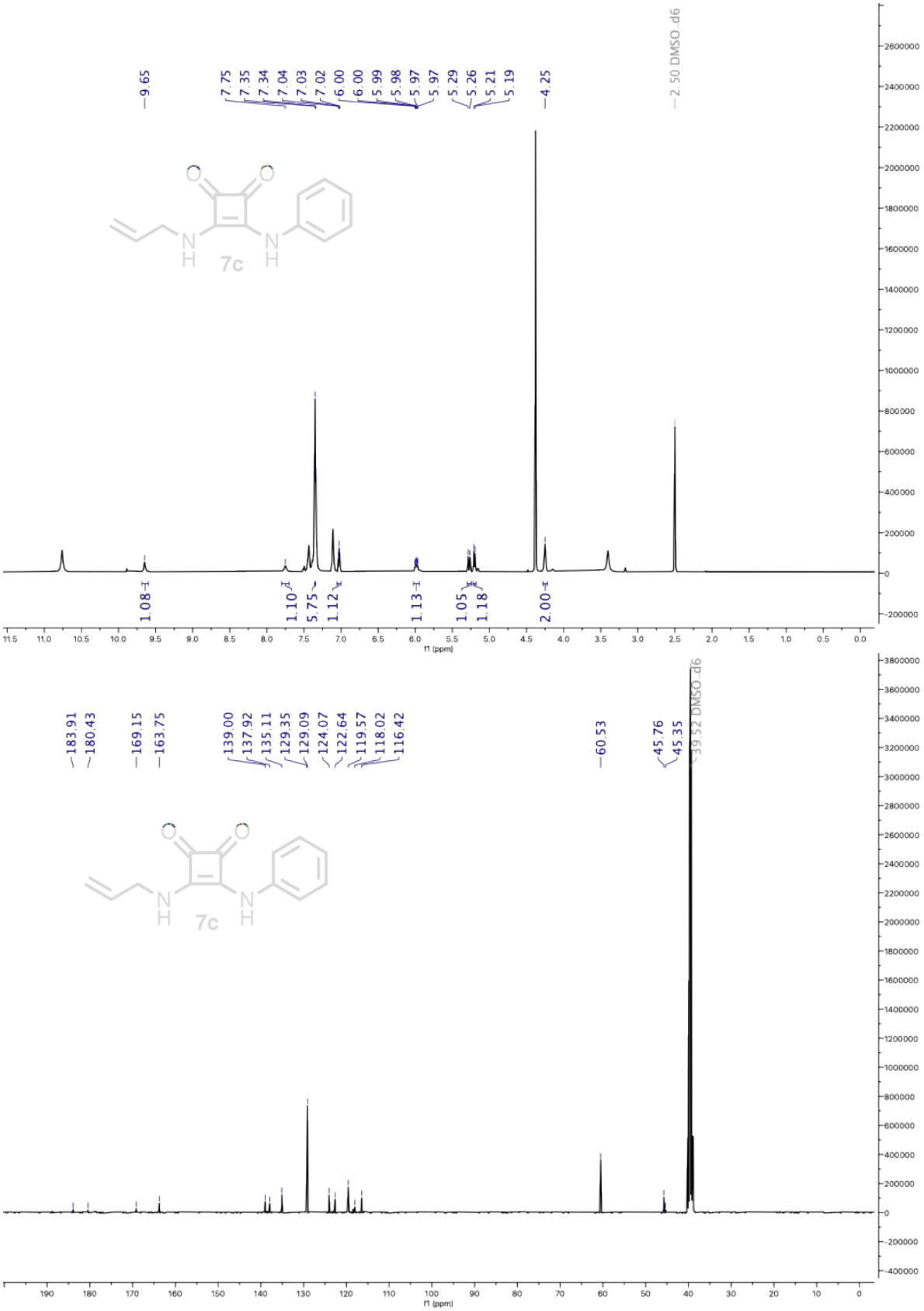
^{1}H and ^{13}C NMR spectra of compound **7a** (DMSO, 700 MHz, 176 MHz)



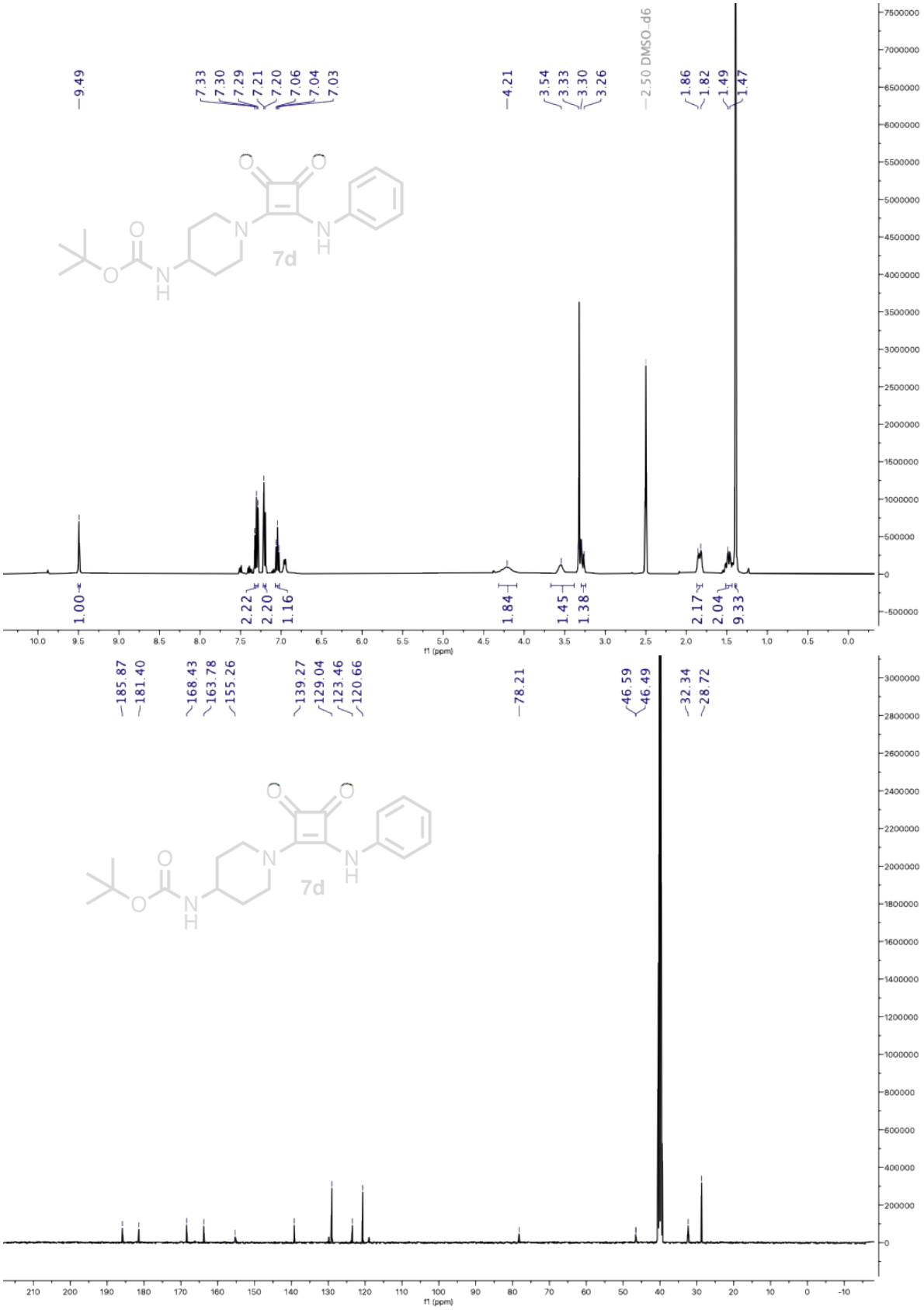
^{1}H and ^{13}C NMR spectra of compound **7b** (DMSO, 400 MHz, 101 MHz)



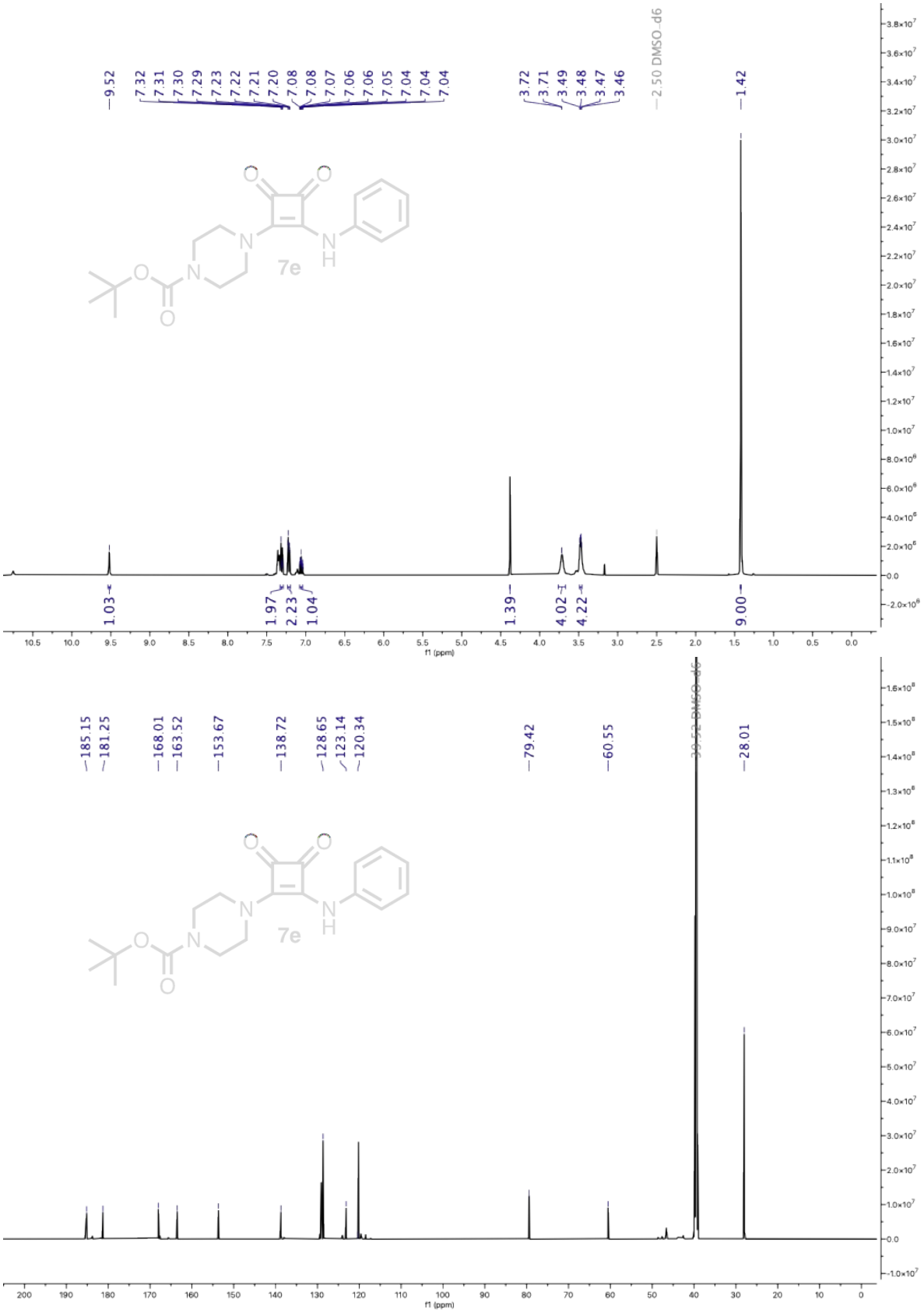
^{1}H and ^{13}C NMR spectra of compound **7c** (DMSO, 700 MHz, 176 MHz)



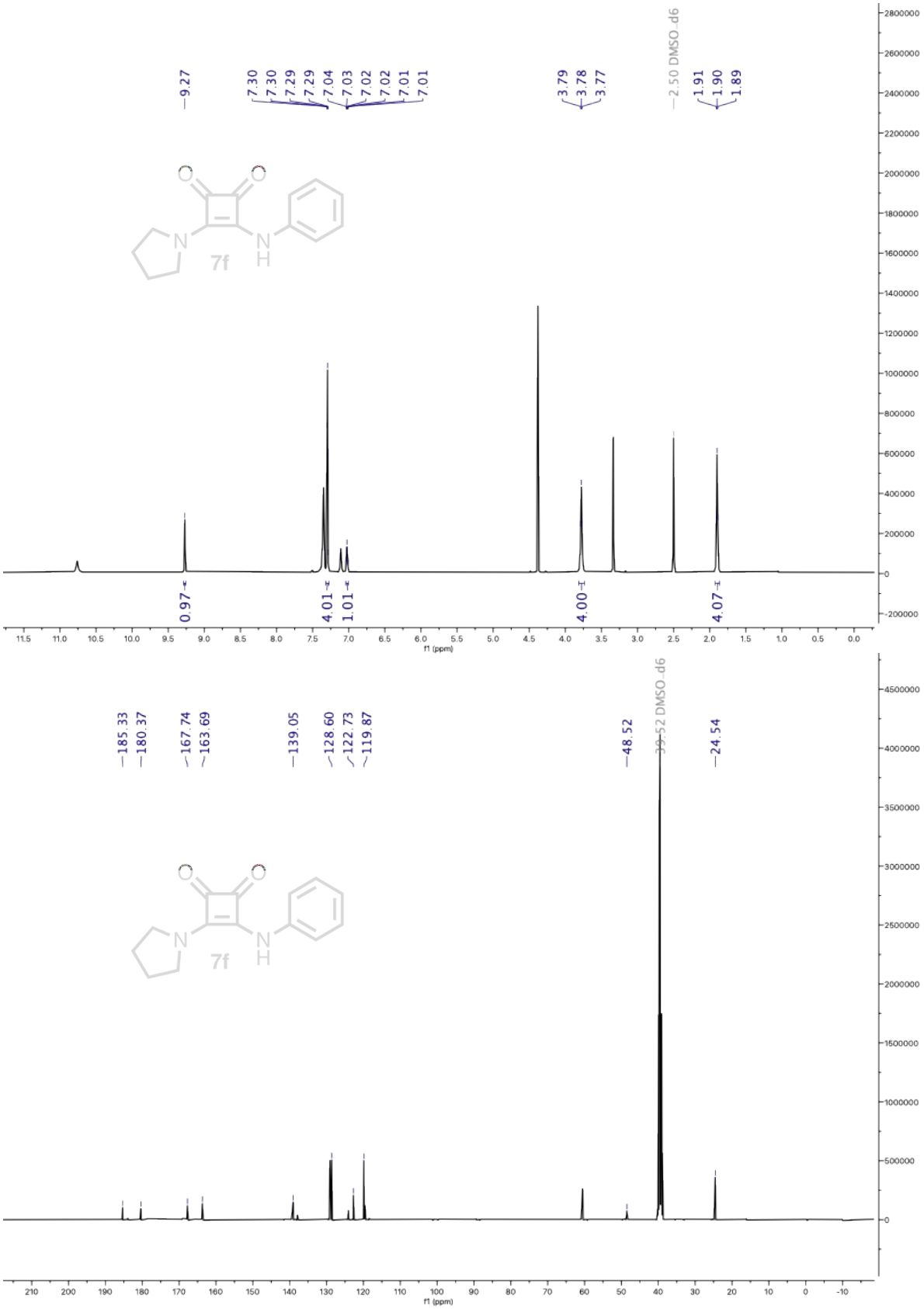
^{1}H and ^{13}C NMR spectra of compound **7d** (DMSO, 700 MHz, 176 MHz)



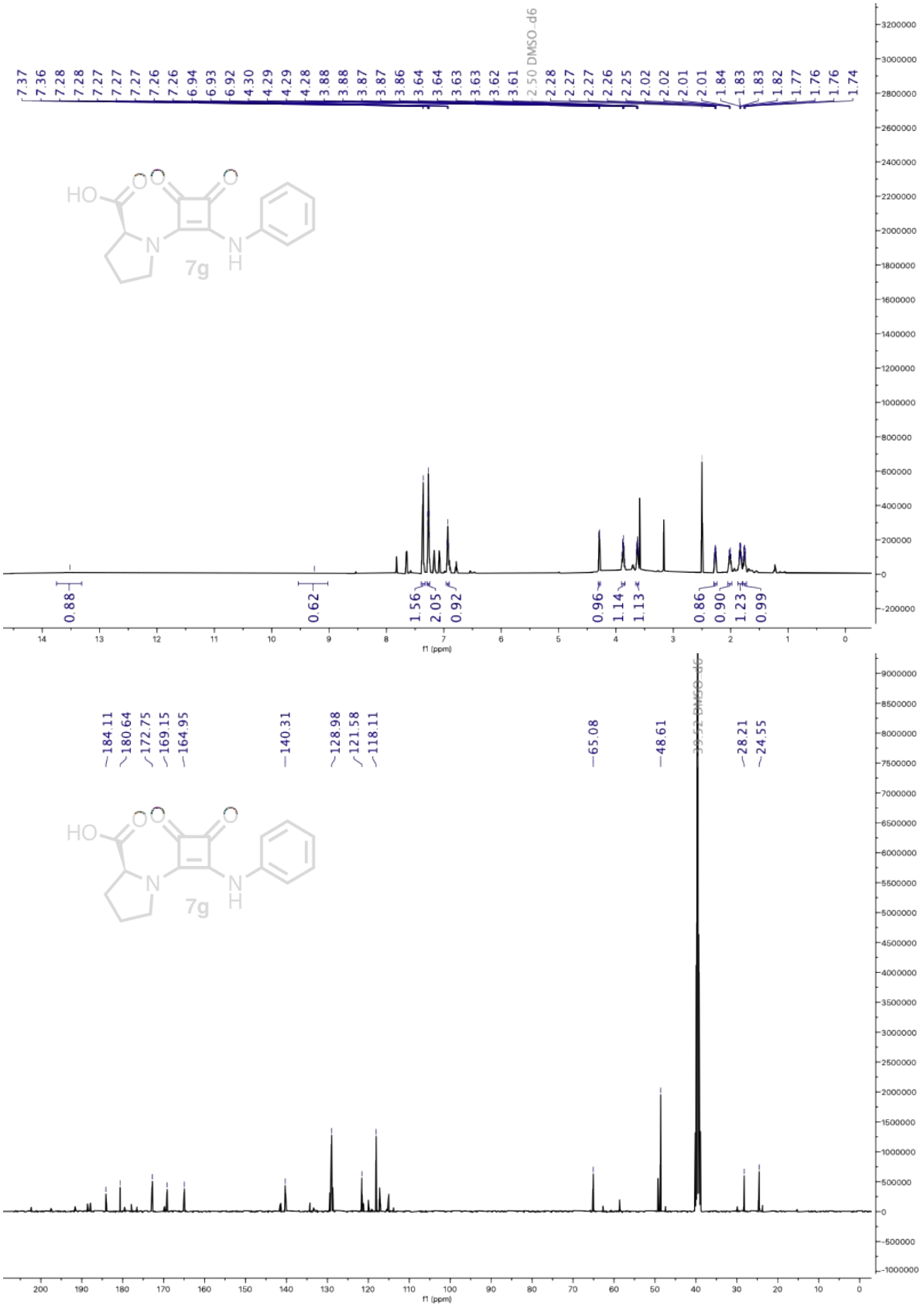
^{1}H and ^{13}C NMR spectra of compound **7e** (DMSO, 700 MHz, 176 MHz)



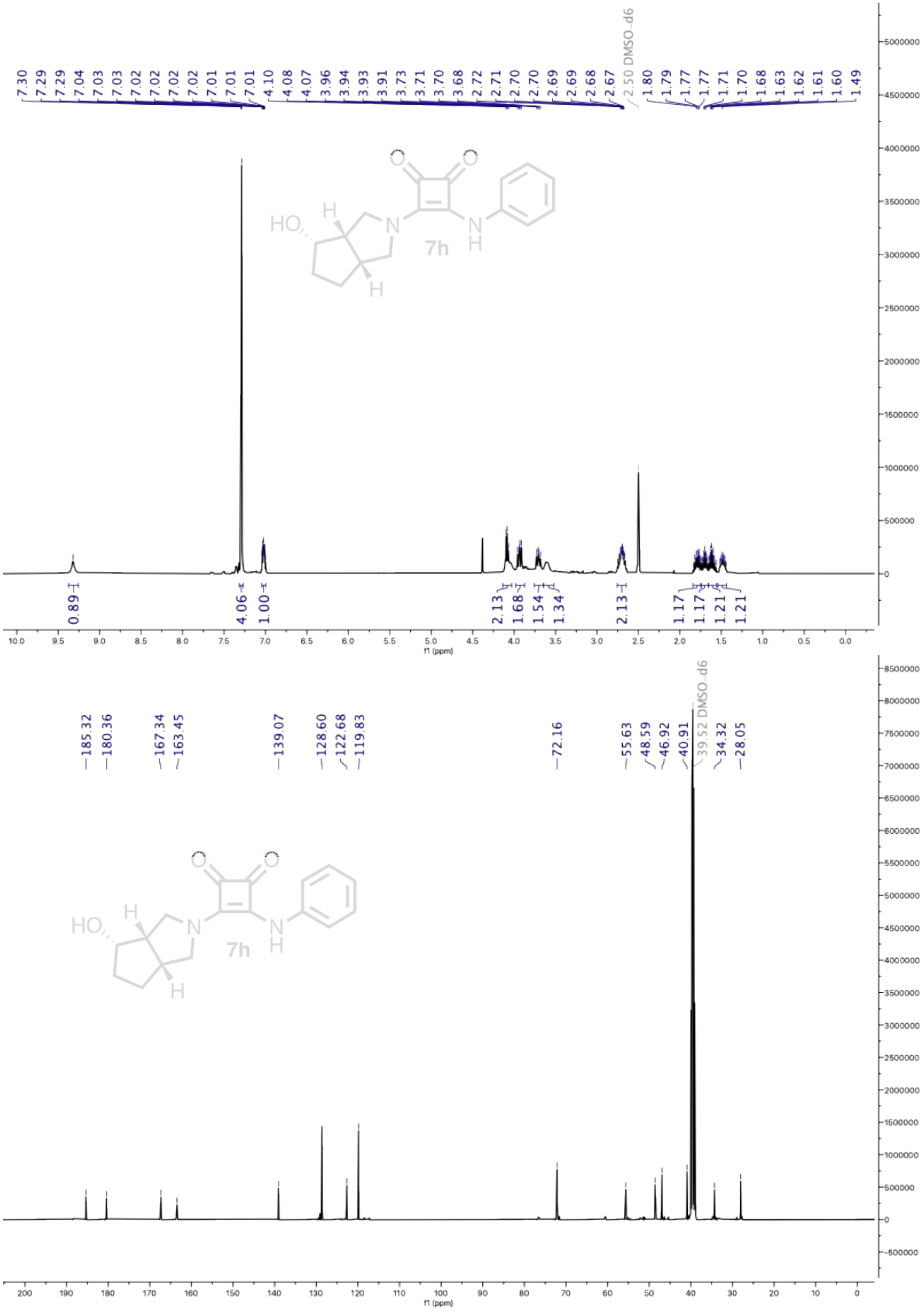
^{1}H and ^{13}C NMR spectra of compound **7f** (DMSO, 700 MHz, 176 MHz)



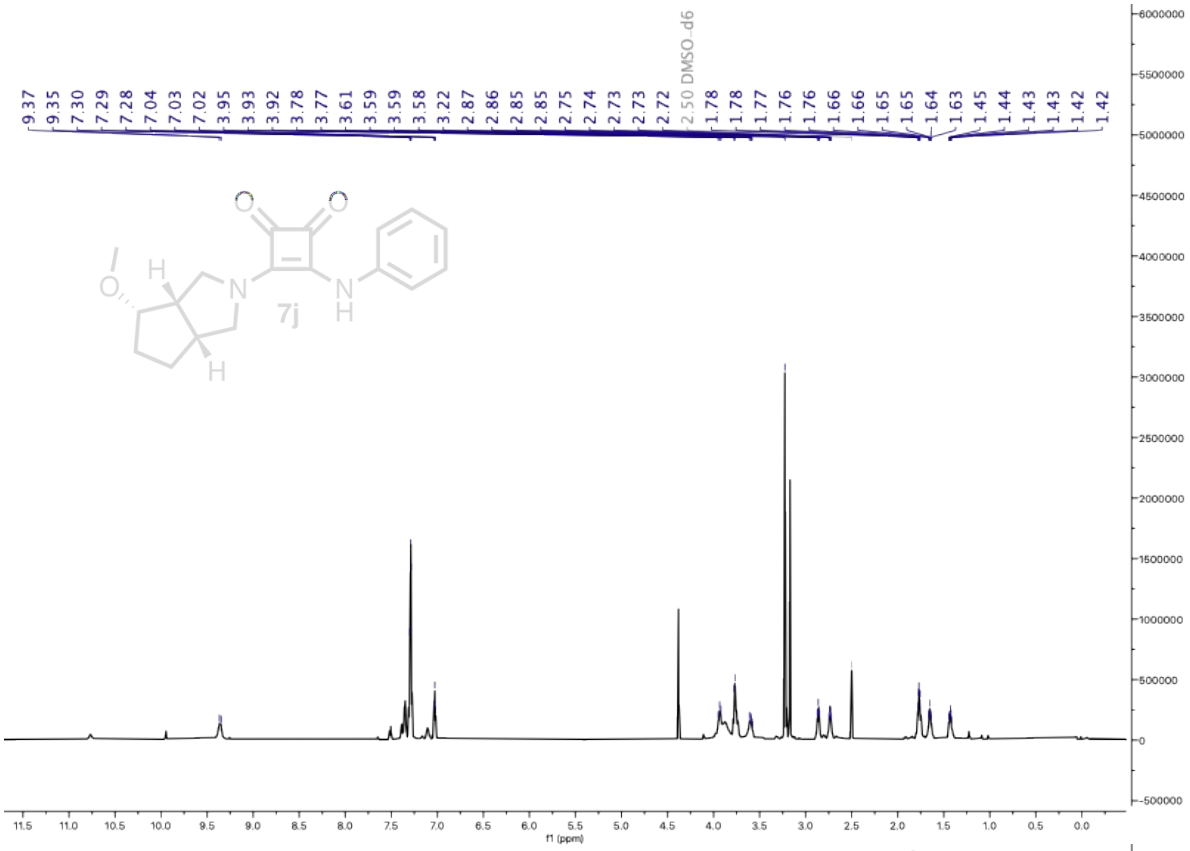
^{1}H and ^{13}C NMR spectra of compound **7g** (DMSO, 400 MHz, 101 MHz)

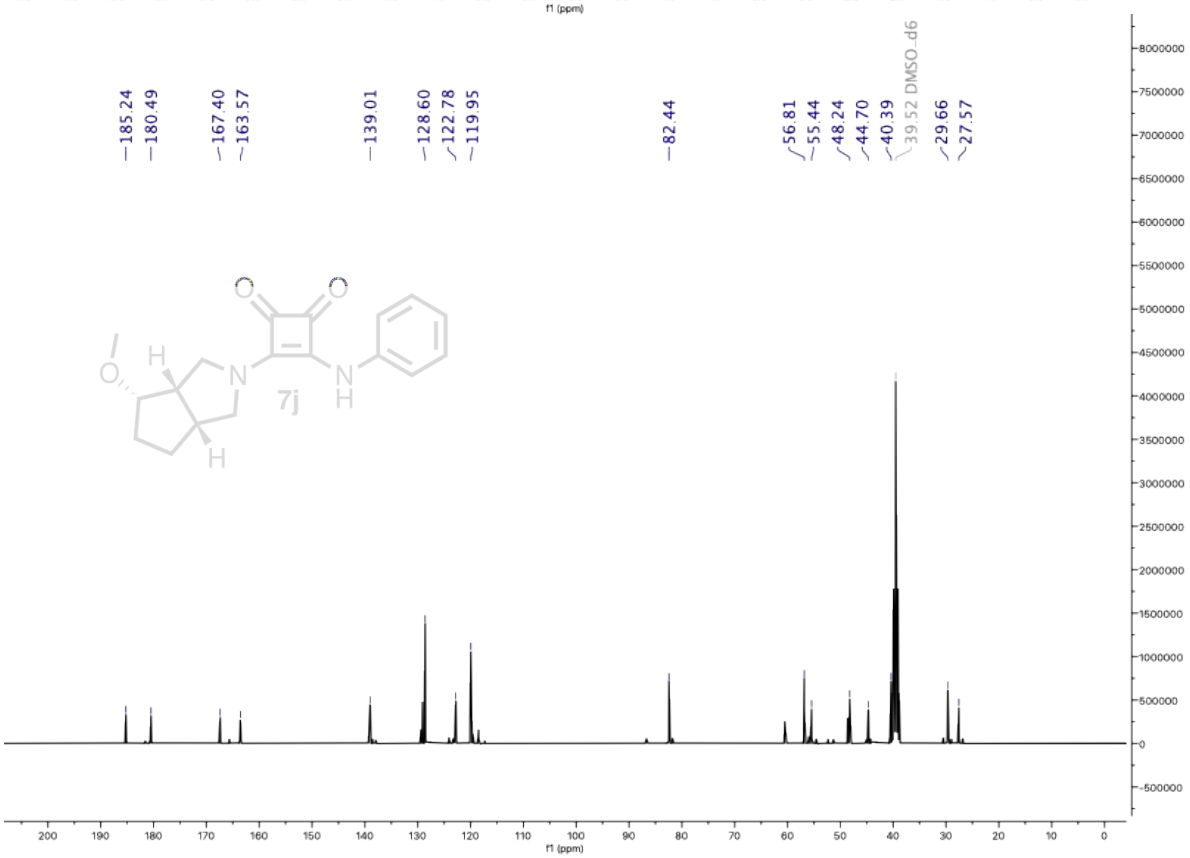


^{1}H and ^{13}C NMR spectra of compound **7h** (DMSO, 400 MHz, 101 MHz)

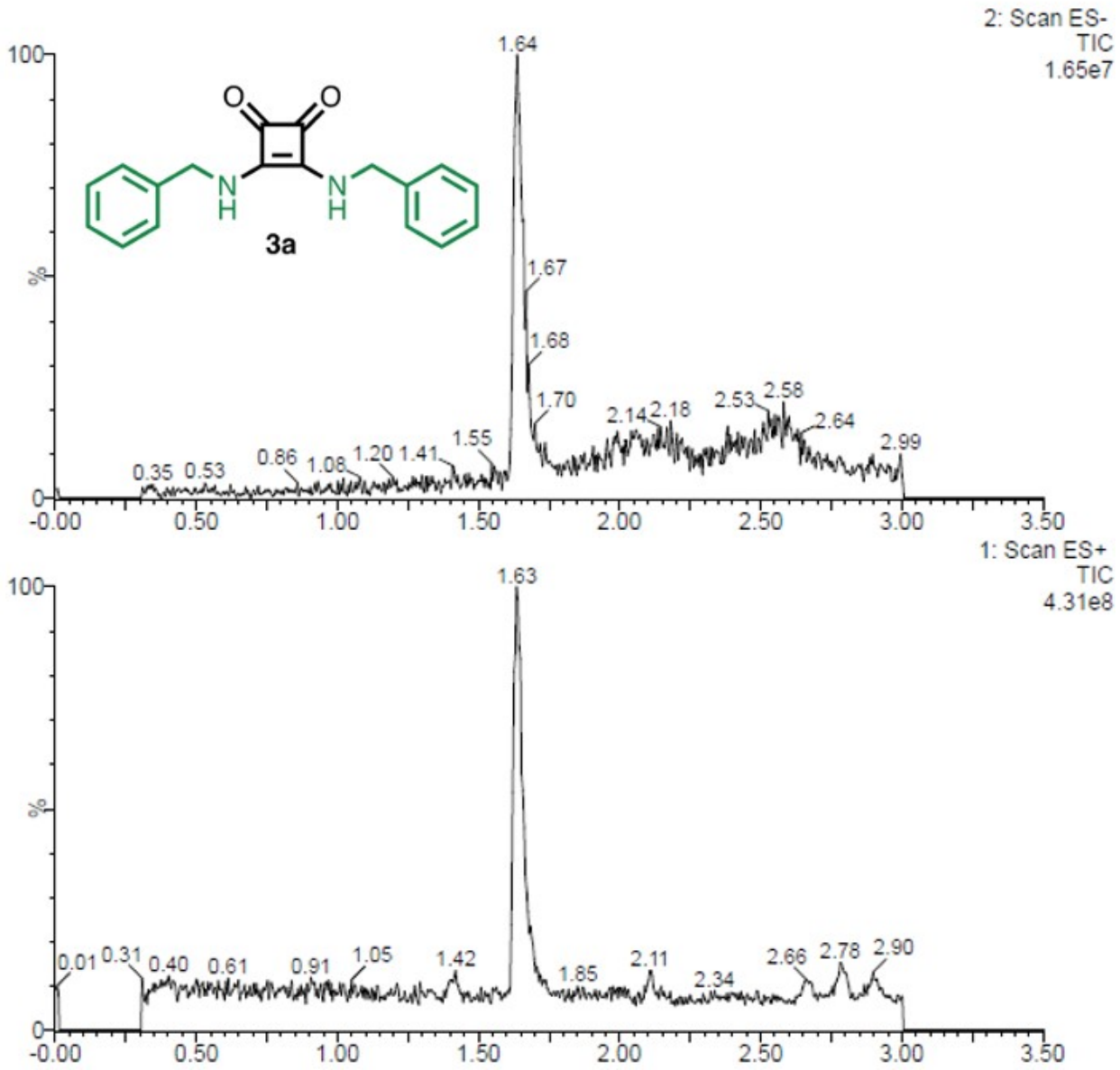


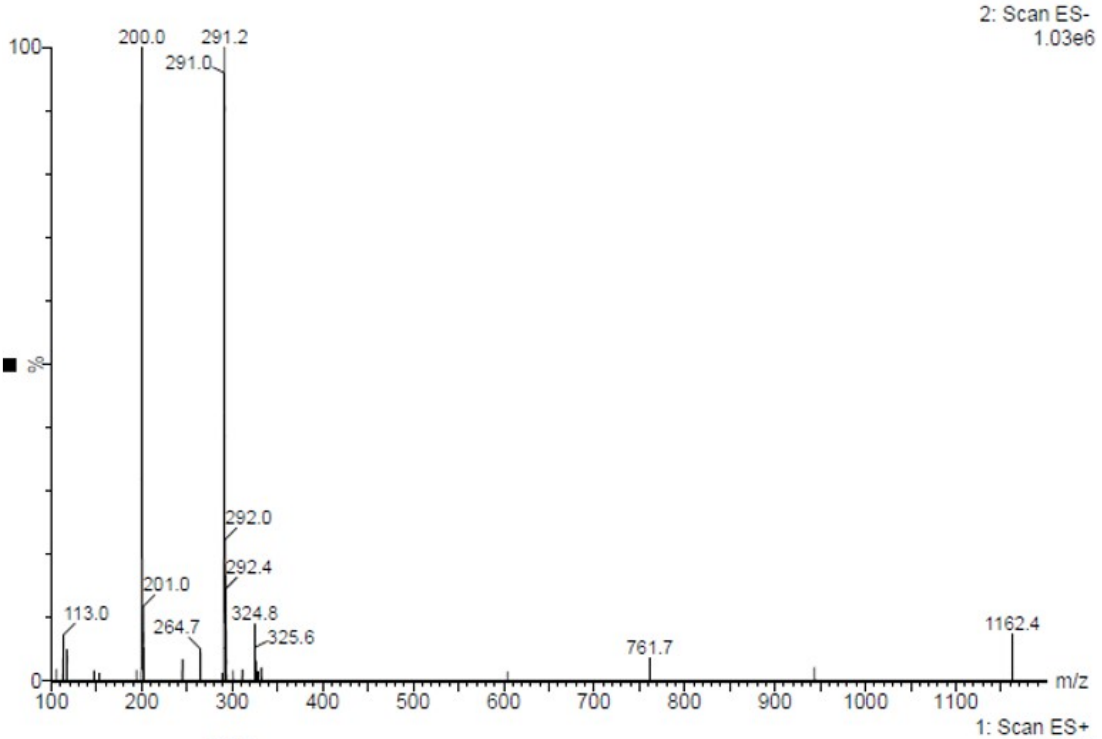
^{1}H and ^{13}C NMR spectra of compound **7j** (DMSO, 700 MHz, 101 MHz)

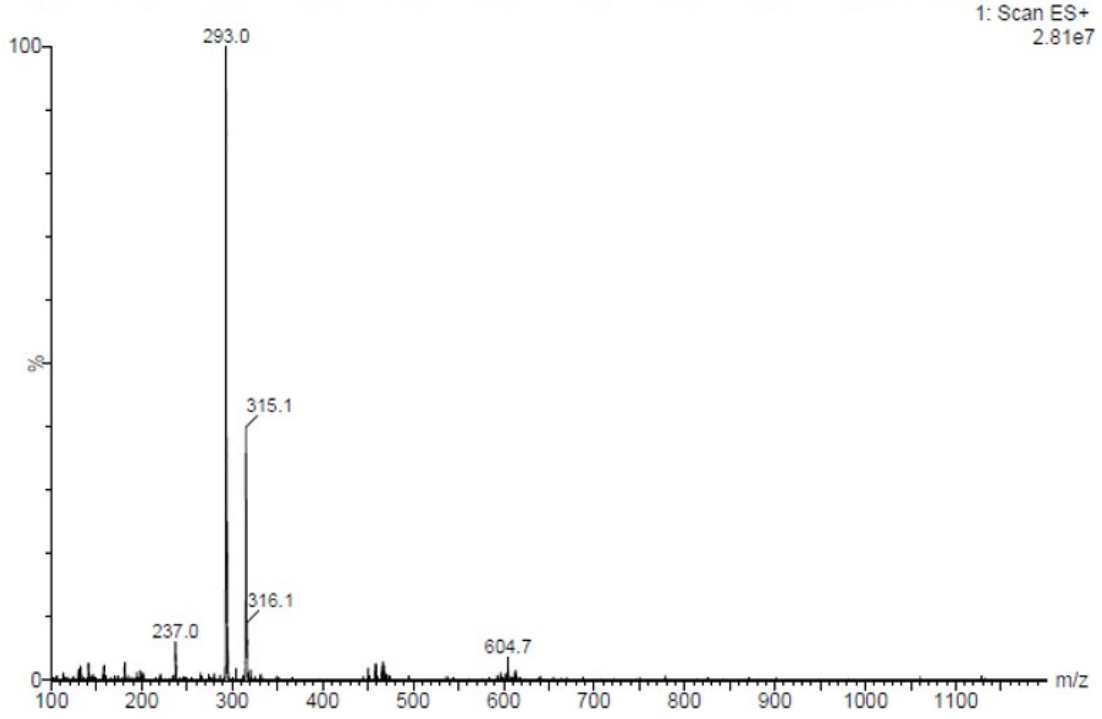

9.37
9.35
7.30
7.29
7.28
7.04
7.03
7.02
3.95
3.93
3.92
3.78
3.77
3.61
3.59
3.59
3.58
3.22
2.87
2.86
2.85
2.75
2.74
2.73
2.73
2.72
2.50 DMSO_d6
1.78
1.78
1.77
1.76
1.76
1.66
1.66
1.65
1.65
1.64
1.63
1.45
1.44
1.43
1.43
1.42
1.42
7j
f1 (ppm)


185.24
180.49
167.40
163.57
139.01
128.60
122.78
119.95
82.44
56.81
55.44
48.24
44.70
40.39
39.52 DMSO_d6
29.66
27.57
7j
f1 (ppm)

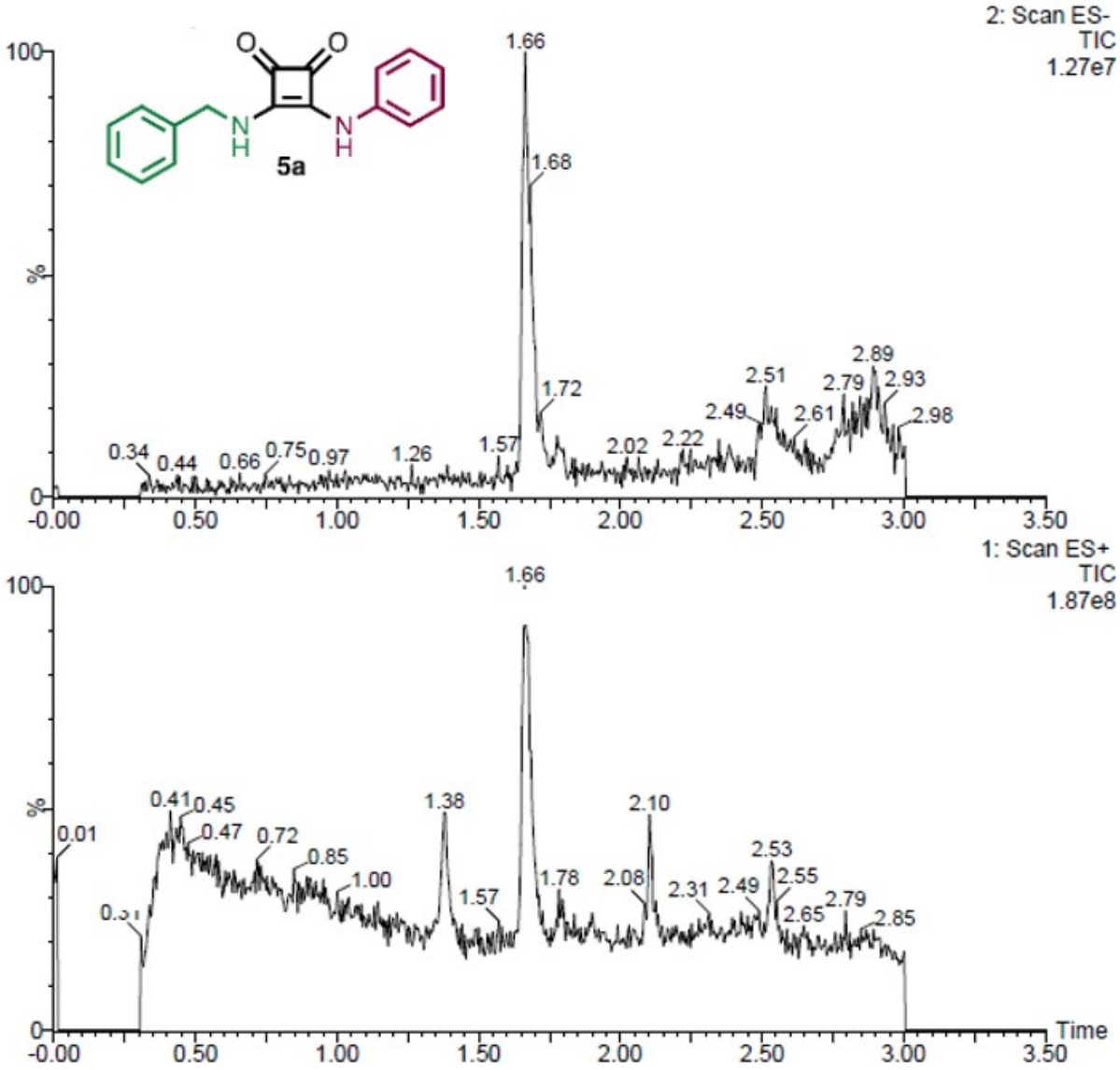
Copies of UPLC-MS chromatogram and MS spectra

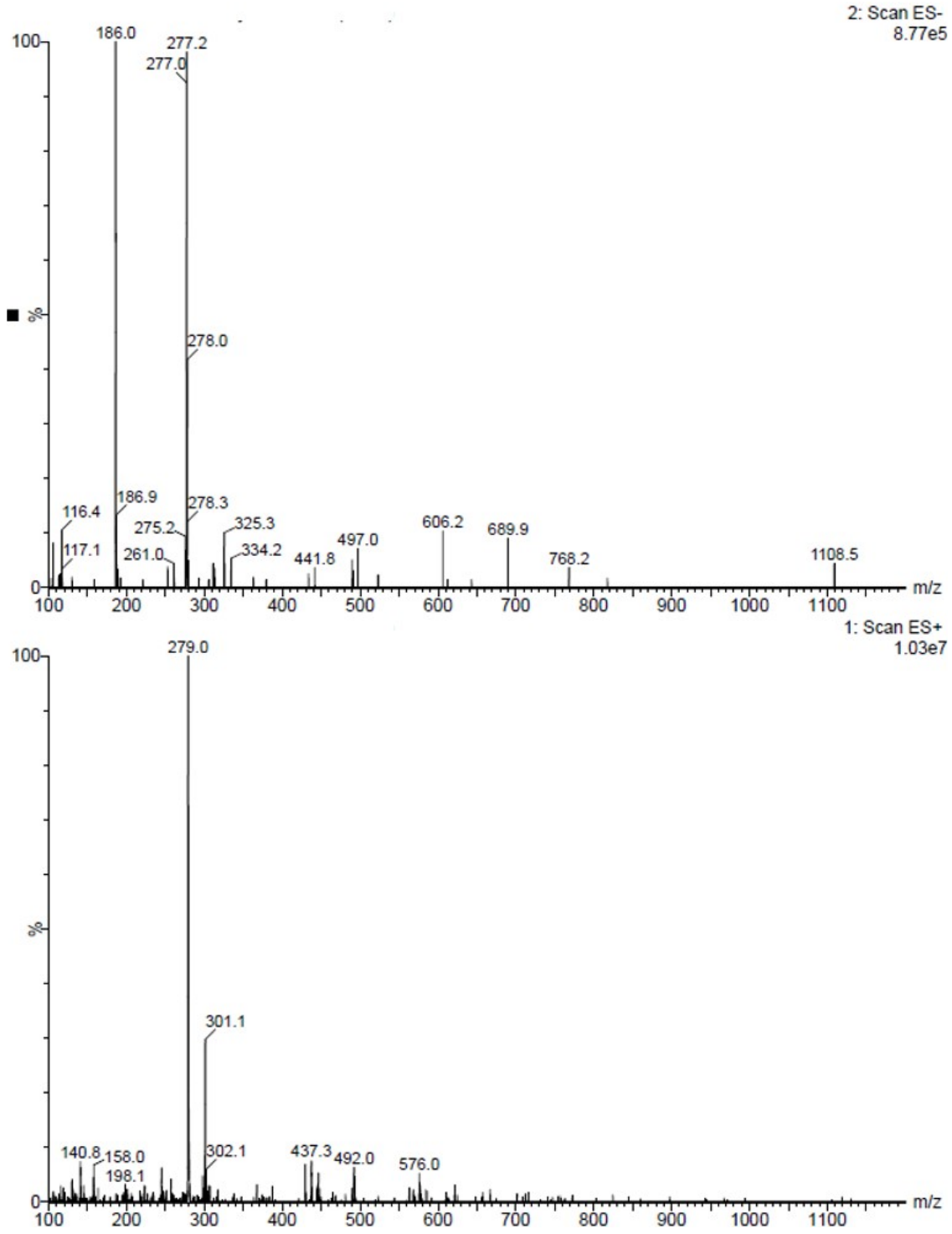



2: Scan ES-
1.03e6
100
%
0
200.0
291.2
291.0
292.0
292.4
201.0
113.0
264.7
324.8
325.6
761.7
1162.4
100
200
300
400
500
600
700
800
900
1000
1100
m/z

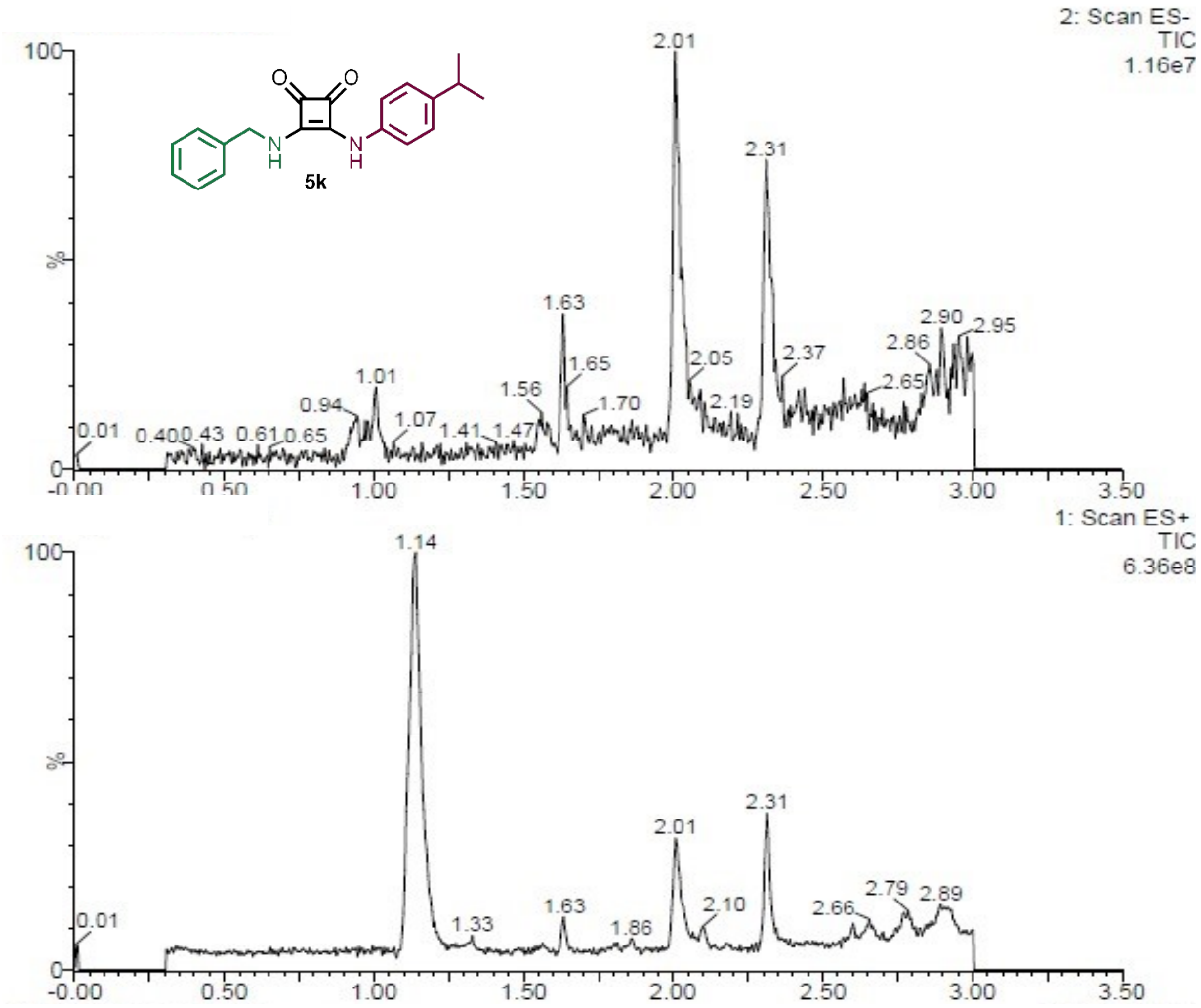

1: Scan ES+
2.81e7
100
%
0
293.0
315.1
316.1
237.0
604.7
100
200
300
400
500
600
700
800
900
1000
1100
m/z

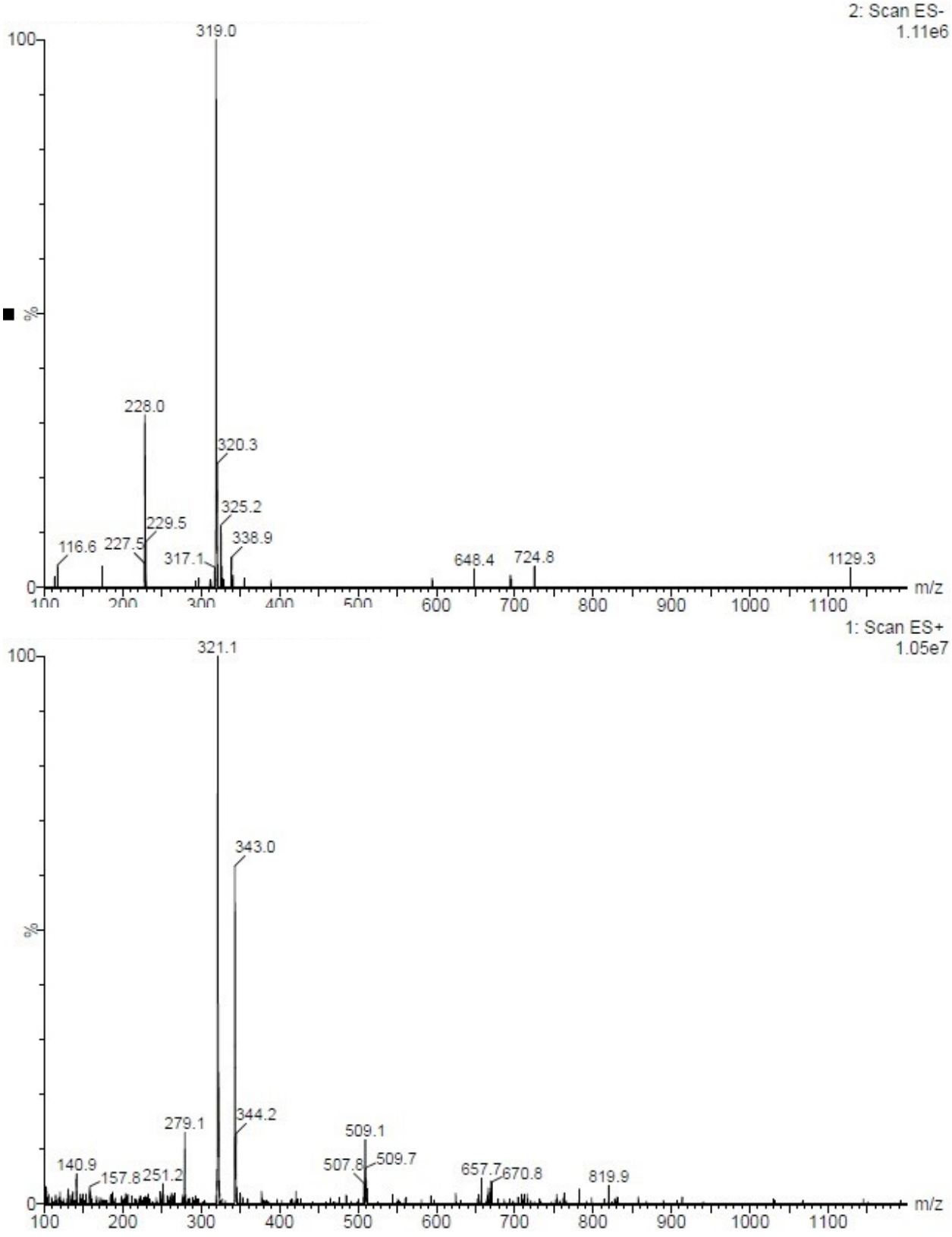
UPLC-MS chromatogram and MS spectra of compound **3a**



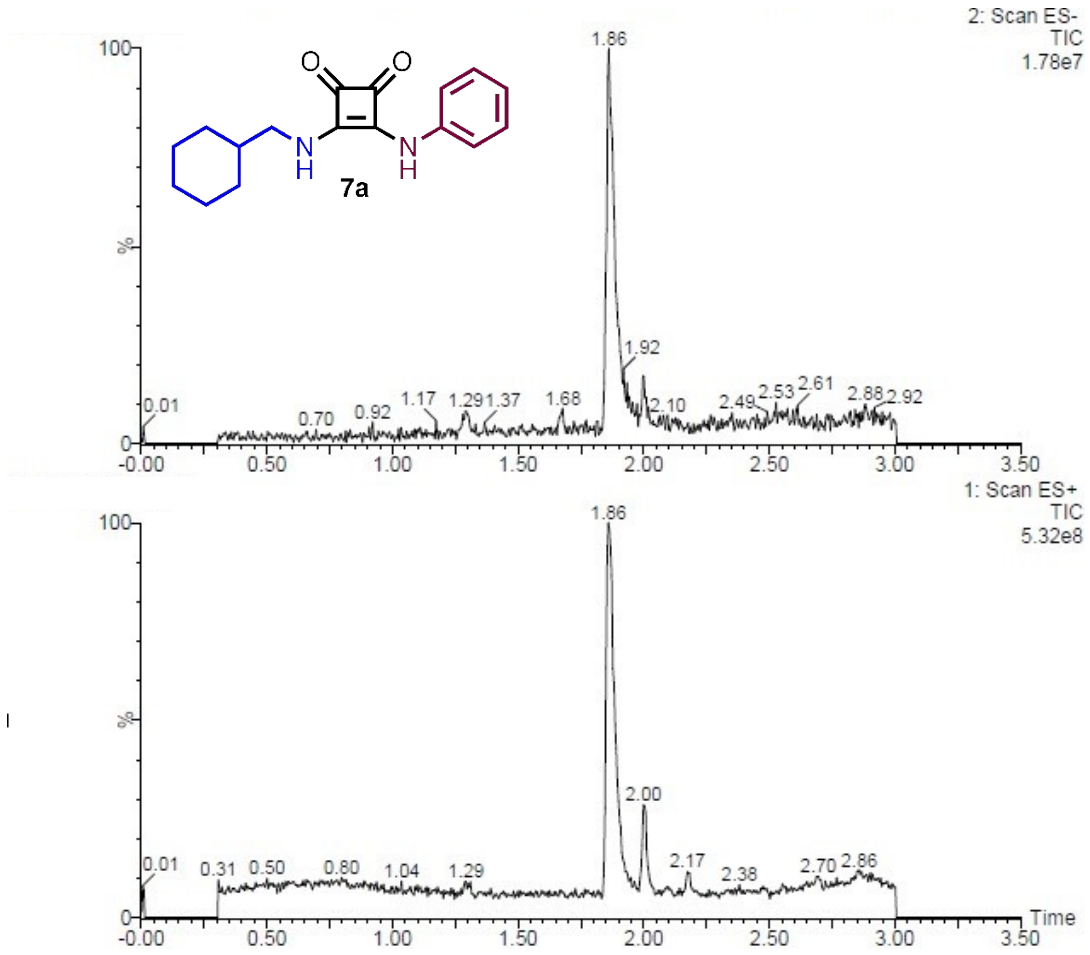


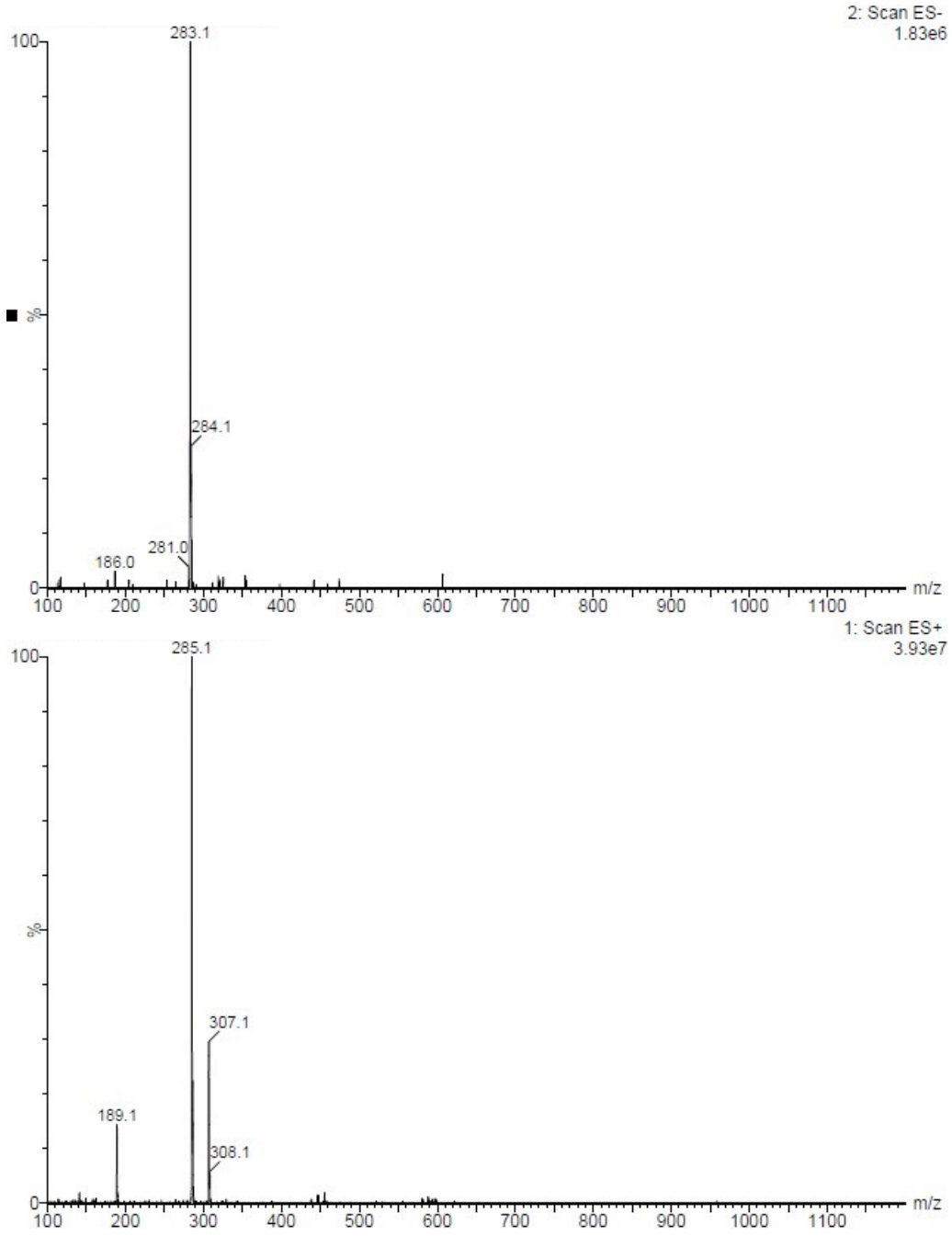
UPLC-MS chromatogram and MS spectra of compound **5a**


2: Scan ES-
TIC
1.16e7
100
%
0
5k
2.01
2.31
1.63
1.65
2.90
2.95
2.86
2.37
2.05
1.01
1.56
2.65
0.94
1.07
2.19
1.70
0.01
0.40
0.43
0.61
0.65
1.41
1.47
-0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
1: Scan ES+
TIC
6.36e8
100
%
0
1.14
2.01
2.31
0.01
1.33
1.63
1.86
2.10
2.66
2.79
2.89
-0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50



UPLC-MS chromatogram and MS spectra of compound **5k**


2: Scan ES-
TIC
1.78e7
100
%
0
1.86
1.92
0.01
0.70
0.92
1.17
1.29
1.37
1.68
2.10
2.49
2.53
2.61
2.88
2.92
-0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
7a
1: Scan ES+
TIC
5.32e8
100
%
0
1.86
2.00
0.01
0.31
0.50
0.80
1.04
1.29
2.17
2.38
2.70
2.86
Time
-0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50



UPLC-MS chromatogram and MS spectra of compound **7a**